



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

A Phase II study of modified docetaxel, cisplatin, and fluorouracil (mDCF) in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department: Yelena Y. Janjigian, MD Medicine: Gastrointestinal
Office: 646.888.4186
Fax: 646.888.4256
Email: janjigiy@mskcc.org

Co-Principal Investigator(s)/Department: David Kelsen, MD Medicine: Gastrointestinal

Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, NY 10021



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

A Phase II study of modified docetaxel, cisplatin, and fluorouracil (mDCF) in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department: Yelena Y. Janjigian, MD Medicine: Gastrointestinal
Office: 646.888.4186
Fax: 646.888.4256
Email: janjigiy@mskcc.org

Co-Principal Investigator(s)/Department: David Kelsen, MD Medicine: Gastrointestinal

Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, NY 10021



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Investigator(s)/Department:

| | |
|---------------------------------|------------------------------|
| Gary K. Schwartz, MD | Medicine: Melanoma/Sarcoma |
| David Ilson, MD PhD | Medicine: Gastrointestinal |
| Leonard Saltz, MD | Medicine: Gastrointestinal |
| Nancy Kemeny, MD | Medicine: Gastrointestinal |
| Diane Reidy-Lagunes, MD | Medicine: Gastrointestinal |
| Marinela Capanu, PhD | Epidemiology : Biostatistics |
| David D'Adamo, MD PhD | Medicine: Melanoma/Sarcoma |
| Ki Young Chung, MD | Medicine: Gastrointestinal |
| Neil H. Segal, MD, PHD | Medicine: Gastrointestinal |
| Kenneth Yu, MD | Medicine: Gastrointestinal |
| Maeve Lowery, MD | Medicine: Gastrointestinal |
| Rona D. Yaeger, MD | Medicine: Gastrointestinal |
| Andrew S. Epstein, MD | Medicine: Gastrointestinal |
| Geoffrey Y. Ku, MD | Medicine: Gastrointestinal |
| James Harding, MD | Medicine: Gastrointestinal |
| Anna Varghese, MD | Medicine: Gastrointestinal |
| Peter Maslak, MD | Medicine: Leukemia |
| Robert Lefkowitz, MD | Radiology |
| Marc Simmons, MD | Radiology |
| Heiko Schoder, MD | Radiology: Nuclear Medicine |
| Laura Tang, MD | Pathology |
| Ephraim Casper, MD | Medicine: All Networks |
| Sree Chalasani, MD | Medicine: Basking Ridge |
| Audrey Hamilton, MD | Medicine: Basking Ridge |
| Mila Gorsky, MD | Medicine: Basking Ridge |
| Magi Khalil, MD | Medicine: Basking Ridge |
| Han Xiao, MD | Medicine: Basking Ridge |
| Avni Desai, MD | Medicine: Commack |
| Marisa Siebel, MD | Medicine: Commack |
| Stefan Berger, MD | Medicine: Commack |
| Julie Fasano, MD | Medicine: Commack |
| John Fiore, MD | Medicine: Commack |
| Stuart Lichtman, MD | Medicine: Commack |
| Philip Schulman, MD | Medicine: Commack |
| Steven Sugarman, MD | Medicine: Commack |
| Arlyn Apollo, MD | Medicine: Mercy |
| Pamela Drullinsky, MD | Medicine: Mercy |
| Zoe Goldberg, MD | Medicine: Mercy |
| Kenneth Ng, MD | Medicine: Mercy |
| Tiffany Troso-Sandoval, MD | Medicine: Mercy |
| Michelle Boyar, MD | Medicine: Phelps |
| Philip Caron, MD | Medicine: Phelps |
| Nancy Mills, MD | Medicine: Phelps |
| Carolyn Wasserheit-Lieblich, MD | Medicine: Phelps |
| Stephanie Smith-Marrone, MD | Medicine: Phelps |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Consenting

Professional(s)/Department:

| | |
|---------------------------------|----------------------------|
| Yelena Y. Janjigian, MD | Medicine: Gastrointestinal |
| David P. Kelsen, MD | Medicine: Gastrointestinal |
| Gary K. Schwartz, MD | Medicine: Melanoma/Sarcoma |
| David Ilson, MD PhD | Medicine: Gastrointestinal |
| Leonard Saltz, MD | Medicine: Gastrointestinal |
| Nancy Kemeny, MD | Medicine: Gastrointestinal |
| Diane Reidy-Lagunes, MD | Medicine: Gastrointestinal |
| Kenneth Yu, MD | Medicine: Gastrointestinal |
| Maeve Lowery, MD | Medicine: Gastrointestinal |
| Rona D. Yaeger, MD | Medicine: Gastrointestinal |
| Andrew S. Epstein, MD | Medicine: Gastrointestinal |
| Geoffrey Y. Ku, MDDavid | Medicine: Gastrointestinal |
| D'Adamo, MD | Medicine: Melanoma/Sarcoma |
| Ki Young Chung, MD | Medicine: Gastrointestinal |
| Neil H. Segal, MD, PHD | Medicine: Gastrointestinal |
| James Harding, MD | Medicine: Gastrointestinal |
| Anna Varghese, MD | Medicine: Gastrointestinal |
| Ephraim Casper, MD | Medicine: All Networks |
| Sree Chalasani, MD | Medicine: Basking Ridge |
| Audrey Hamilton, MD | Medicine: Basking Ridge |
| Mila Gorsky, MD | Medicine: Basking Ridge |
| Magi Khalil, MD | Medicine: Basking Ridge |
| Han Xiao, MD | Medicine: Basking Ridge |
| Avni Desai, MD | Medicine: Commack |
| Marisa Siebel, MD | Medicine: Commack |
| Stefan Berger, MD | Medicine: Commack |
| Julie Fasano, MD | Medicine: Commack |
| John Fiore, MD | Medicine: Commack |
| Stuart Lichtman, MD | Medicine: Commack |
| Philip Schulman, MD | Medicine: Commack |
| Steven Sugarman, MD | Medicine: Commack |
| Arlyn Apollo, MD | Medicine: Mercy |
| Pamela Drullinsky, MD | Medicine: Mercy |
| Zoe Goldberg, MD | Medicine: Mercy |
| Kenneth Ng, MD | Medicine: Mercy |
| Tiffany Troso-Sandoval, MD | Medicine: Mercy |
| Michelle Boyar, MD | Medicine: Phelps |
| Philip Caron, MD | Medicine: Phelps |
| Nancy Mills, MD | Medicine: Phelps |
| Carolyn Wasserheit-Lieblich, MD | Medicine: Phelps |
| Stephanie Smith-Marrone, MD | Medicine: Phelps |

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|---|--|------------------|
| National Coordinating Investigator | Manish A. Shah, MD Office: 646.962.6200 Fax: 646.962.1607 Email: mas9313@med.cornell.edu | |
| | | |
| Collaborating Institution (s): | <u>PI Name and Contact Info</u> | <u>Site Role</u> |
| University of Pittsburgh Cancer Institute | <u>PI: Ronald G. Stoller, M.D.</u> University of Pittsburgh Cancer Institute Hillman Cancer Center 5115 Centre Avenue Pittsburgh, PA 15232 Ph: 412-692-4724 Fax: 412-648-6579 Email: stollerrg@upmc.edu | Data Collection |
| Queens Cancer Center | <u>PI: Margaret Kemeny, M.D.</u> Queens Cancer Center of Queens Hospital 82-68 164th Street New Building – Room A531 Jamaica, NY 11432 Ph: 718-883-4031 Fax: 718-883-6295 Email: kemenym@nychhc.org | Data Collection |
| Long Island Jewish Medical Center | <u>PI: Bhoomi Mehrotra, M.D.</u> Long Island Jewish Medical Center Division of Hematology/Oncology New Hyde Park, NY 11040 Ph: 718-470-8934 Fax: 718-470-0169 Email: mehrotra@lij.edu | Data Collection |
| University Hospital of Cleveland | <u>PI: Smitha Krishnamurthi, M.D.</u> Ireland Cancer Center/University Hosp. of Cleveland Case Medical Center 11100 Euclid Avenue Cleveland, OH 44106 Ph: 216-844-5413 Fax: 216-844- 5449 Email: smitha.krishnamurthi@case.edu | Data Collection |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|--|---|-----------------|
| Weill Medical College of Cornell University | <u>PI: Allyson J. Ocean, M.D.</u> Assistant Professor of Medicine New York Presbyterian Hospital - Weill Medical College of Cornell University Division of Hematology/Oncology 520 East 70th Street, Starr 365 New York, NY 10021 Ph: 212-746-2844 Fax: 212-746-6645 E-mail: ajo9001@med.cornell.edu | Data Collection |
| City of Hope | <u>PI: Vincent Chung, M.D. FACP</u> Assistant Professor City of Hope Comprehensive Cancer Center 1500 E. Duarte Rd. Duarte, CA 91010 Ph: 626-471-9200 Fax: 626-301-8233 E-mail: vchung@coh.org | Data Collection |
| Medical College of Wisconsin | <u>PI: Paul Ritch, M.D.</u> Professor of Medicine Medical College of Wisconsin 9200 W. Wisconsin Avenue Milwaukee, WI 53226 Ph: 414-805-4600 Fax: 414-805-6838 E-mail: pritch@mcw.edu | Data Collection |
| Piedmont Hospital Research Institute (PHRI) | <u>PI: Charles Henderson, M.D.</u> Piedmont Hospital Research Institute (PHRI) 95 Collier Rd., Suite 2075 Atlanta, GA 30309 Ph: 404-350-9853 Fax: 404-350-8407 E-mail: chenderson@phoc.com | Data Collection |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|-----------------------------|--|-----------------|
| Nebraska Cancer Specialists | <u>PI: Yungpo Bernard Su, M.D.</u> Nebraska Cancer Specialists Methodist Estabrook Cancer Center 8303 Dodge Street, Suite 250 Omaha, Nebraska 68114 Ph: 402.354.8124 Fax: 402.354.8127 E-mail: drs@onchemwest.com | Data Collection |
| Memorial Cancer Institute | <u>PI: Dr. Pablo Ferraro, M.D.</u> Memorial Cancer Institute 801 North Flamingo Road Pembroke Pines, FL 33025 Ph: (954)430-6868 Fax: (954)443-4747 E-mail: pferraro@mhs.net | Data Collection |



Table of Contents

| | | |
|------------|--|-----------|
| 1.0 | <i>PROTOCOL SUMMARY AND/OR SCHEMA</i> | 1 |
| 2.0 | <i>OBJECTIVES AND SCIENTIFIC AIMS</i> | 4 |
| 3.0 | <i>BACKGROUND AND RATIONALE</i> | 5 |
| 3.1 | SCOPE OF DISEASE AND ROLE OF CHEMOTHERAPY..... | 5 |
| 3.2 | COMBINATION CHEMOTHERAPY REGIMENS..... | 5 |
| 3.3 | IS THERE A “STANDARD” CHEMOTHERAPY REGIMEN?..... | 7 |
| 3.4 | SUMMARY OF CHEMOTHERAPY FOR GASTRIC/GEJ ADENOCARCINOMA..... | 12 |
| 3.5 | PROPOSAL | 13 |
| 3.5.1 | Modified DCF dose and schedule determination..... | 13 |
| 3.5.2 | Pharmacokinetic and Pharmacodynamic Considerations (MSKCC ONLY)..... | 17 |
| 3.5.3 | FDG-PET Response Assessment | 19 |
| 4.0 | <i>OVERVIEW OF STUDY DESIGN/INTERVENTION</i> | 22 |
| 4.1 | Design..... | 22 |
| 4.2 | Intervention..... | 23 |
| 5.0 | <i>THERAPEUTIC/DIAGNOSTIC AGENTS</i> | 24 |
| 5.1 | Docetaxel (TAXOTERE®)..... | 24 |
| 5.2 | CISPLATIN | 27 |
| 5.3 | FLUOROURACIL | 28 |
| 5.4 | LEUCOVORIN..... | 29 |
| 5.5 | TRASTUZUMAB | 30 |
| 5.6 | CONCOMITANT MEDICATIONS..... | 34 |
| 6.0 | <i>CRITERIA FOR SUBJECT ELIGIBILITY</i> | 36 |
| 6.1 | Subject Inclusion Criteria..... | 36 |
| 6.2 | Subject Exclusion Criteria..... | 38 |
| 7.0 | <i>RECRUITMENT PLAN</i> | 39 |
| 8.0 | <i>PRETREATMENT EVALUATION</i> | 40 |
| 9.0 | <i>TREATMENT/INTERVENTION PLAN</i> | 42 |
| 9.1 | CHEMOTHERAPY ADMINISTRATION..... | 42 |
| 9.2 | SUPPORTIVE CARE GUIDELINES | 44 |
| 9.3 | TREATMENT PARAMETERS, DOSE DELAYS AND MODIFICATIONS | 46 |
| 9.4 | CORRELATIVE STUDIES | 53 |



| | | |
|-------------|--|-----------|
| 10.0 | <i>EVALUATION DURING TREATMENT/INTERVENTION</i> | 56 |
| 10.1 | <i>FOR PARTICIPATING SITES</i> | 57 |
| 11.0 | <i>TOXICITIES/SIDE EFFECTS</i> | 58 |
| 11.1 | CISPLATIN | 58 |
| 11.2 | DOCETAXEL | 59 |
| 11.3 | FLUOROURACIL | 59 |
| 11.4 | LEUCOVORIN..... | 59 |
| 11.5 | TRASTUZUMAB | 59 |
| 11.6 | SUPPORTIVE MEDICATIONS | 59 |
| 12.1 | DEFINITIONS..... | 60 |
| 12.2 | EVALUATION OF TARGET LESIONS | 61 |
| 12.3 | EVALUATION OF NON-TARGET LESIONS | 61 |
| 12.4 | EVALUATION OF BEST OVERALL RESPONSE..... | 62 |
| 12.5 | GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE | 62 |
| 12.6 | CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE..... | 63 |
| 13.0 | <i>CRITERIA FOR REMOVAL FROM STUDY</i> | 63 |
| 13.1 | DURATION OF THERAPY / CRITERIA FOR REMOVAL FROM STUDY | 63 |
| 13.2 | OFF-STUDY EVALUATION | 64 |
| 14.0 | <i>BIOSTATISTICS</i> | 65 |
| 15.0 | <i>RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES</i> | 67 |
| 15.1 | RESEARCH PARTICIPANT REGISTRATION | 67 |
| 15.3 | RANDOMIZATION | 69 |
| 16.0 | <i>DATA MANAGEMENT ISSUES</i> | 69 |
| 16.1 | QUALITY ASSURANCE | 71 |
| 16.2 | DATA AND SAFETY MONITORING | 72 |
| 16.3 | ETHICAL AND ADMINISTRATIVE ISSUES | 73 |
| 16.4 | INSTITUTIONAL REVIEW BOARD APPROVAL | 73 |
| 17.0 | <i>PROTECTION OF HUMAN SUBJECTS</i> | 75 |
| 17.1 | PRIVACY..... | 76 |
| 17.2 | SERIOUS ADVERSE EVENT (SAE) REPORTING | 76 |
| 17.3 | SERIOUS ADVERSE EVENT REPORTING FOR OUTSIDE CENTERS..... | 79 |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

18.0 INFORMED CONSENT PROCEDURES..... 80

18.1 FOR PARTICIPATING SITES 80

19.0 REFERENCE(S) 81

20.0 APPENDICES..... 85



1.0 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Objectives

Primary:

- 1) To determine the efficacy of modified docetaxel, cisplatin, and fluorouracil (mDCF) (ARM A) and the efficacy of parent DCF with growth factor support (ARM B) in patients with unresectable or metastatic gastric or gastroesophageal junction(GEJ) adenocarcinoma as measured by 6 month progression free survival (PFS).

Secondary:

- 2) To establish the safety of mDCF and parent DCF with growth factor support in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 3) To observe other measures of efficacy of mDCF and parent DCF with growth factor support, including response rate, median PFS, overall and 1-year survival in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 4) To explore the association of early FDG-PET imaging with treatment efficacy.
- 5) To explore the differences in docetaxel pharmacology between both study arms.
- 6) To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.
- 7) To report the efficacy of mDCF with trastuzumab as measured by 6 month PFS amongst Her2 positive patients.
- 8) To report the safety profile of patients receiving mDCF and trastuzumab.

1.2 Eligibility

Patients with histologically confirmed metastatic or unresectable gastric or gastroesophageal junction adenocarcinoma are eligible for entry into this Phase II study. Patients may have received neoadjuvant and/or adjuvant chemotherapy or chemoradiotherapy. Patients may not have received previous chemotherapy containing cisplatin or docetaxel. Prior fluorouracil is allowed if more than 6 months have passed since the patient last received it. Patients must provide written informed consent prior to study enrollment.

Patients must be at least 18 years of age, and use birth control if male, or if female of childbearing age. Patients must have a Karnofsky performance status of greater than or equal to 70% (ECOG < 2), and be of sound mind to sign informed consent. Hematologic/ laboratory criteria for eligibility include: WBC $\geq 3000/\text{mm}^3$, ANC $\geq 1500/\text{mm}^3$, hemoglobin ≥ 9 g/dl, platelet count $\geq 100,000/\text{mm}^3$, serum creatinine ≤ 1.5 mg/dl. For patients with a serum creatinine of 1.2-1.5, their creatinine clearance must be at least 50 ml/min. Total serum bilirubin ≤ 1.5 , serum AST(SGOT)/ALT(SGPT) and ALK PHOS levels as per chart below:

| | AST or ALT: | | | |
|-----------------------|-------------|---------------------------|---------------------------|------------|
| ALK PHOS: | \leq ULN | $>1x$ but $\leq 1.5x$ ULN | $>1.5x$ but $\leq 5x$ ULN | $>5x$ ULN |
| \leq ULN | Eligible | Eligible | Eligible | Ineligible |
| $>1x$ but $\leq 2.5x$ | Eligible | Eligible | Ineligible | Ineligible |
| $>2.5x$ but $\leq 5x$ | Eligible | Ineligible | Ineligible | Ineligible |
| $>5x$ ULN | Ineligible | Ineligible | Ineligible | Ineligible |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients must have a PT (INR) ≤ 1.5 and a PTT ≤ 3 seconds above the upper limits of normal if they are not on anticoagulation. Women of childbearing potential must also have a negative pregnancy test. Biopsy confirmation of M1 disease is encouraged, unless the risk of such a procedure is significant, in which case confirmation by a 2nd imaging modality is required. Exclusions include patients with brain or central nervous system metastases, patients with significant co-morbidities including cardiac diseases, serious non-healing wound or ulcer, peripheral vascular disease or stroke, or significant hearing loss.

December 2009 Amendment

As of October 2009, trastuzumab plus chemotherapy is part of the NCCN standard treatment algorithm for the first line for advanced gastric/GEJ adenocarcinoma. This amendment is to allow patients who are Her2 positive to receive trastuzumab with mDCF. Her2 positive patients are defined as IHC 3+ for Her2 or FISH + (>2 HER2:CEP17). Biopsy samples (i.e. small tissue fragments) with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. $<10\%$, as per Hofmann et al¹ To receive trastuzumab, patients must have a baseline left ventricular ejection fraction of $\geq 50\%$. Her2 positive patients who receive trastuzumab will be considered as a separate cohort and independent cohort.

1.3 Treatment Plan

This will be a random assignment phase II study of two different administration schedules of docetaxel, cisplatin, and fluorouracil in patients with unresectable or metastatic gastric or GEJ adenocarcinoma. Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 OR 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg* | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments). Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments). Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter.

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

August 2010 Amendment:

Arm A has reached target accrual of 54 patients. Arm B remains closed due to toxicity. Her2 positive patients will be enrolled onto the Trastuzumab Cohort and will receive mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

1.4 Pharmacology and Pharmacodynamics (MSKCC patients only)

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4. Similarly, we hypothesize that inhibition of CYP3A4 by these anti-emetic agents would result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity.

Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 (15 min following the end of docetaxel infusion)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each of these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

March 2008 Addendum: On our initial pharmacokinetic analysis, we have observed that the clearance of docetaxel appears to be reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen. Based on this, we will expand our pharmacokinetic evaluation and examine additional docetaxel PK without cisplatin in up to 6 patients randomized to parent DCF who underwent cycle 1 docetaxel PK (when cisplatin was administered on day 1 as well). See section 9.4.3.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

1.5 Correlative Studies

A. One objective is to store pre-treatment paraffin embedded tumor tissue for future tissue based correlative studies. We will keep a tissue bank for these future immunohistochemistry based exploratory studies.

HER2 testing will be performed in all patients to better characterize HER2-positive gastric cancer in US patients. HER2 testing will be performed by the MSKCC diagnostic molecular laboratory on banked tumor specimens from the patients currently enrolled on the protocol and prospectively on all the patients screened for protocol participation. FISH is performed using FDA-approved ERBB2 (HER2/NEU) PathVysion assay probes and procedure (Abbott-Vysis). IHC staining is performed using FDA-approved anti-Her2/neu Ventana's PATHWAY rabbit monoclonal primary antibody (clone 4B5) directed against the internal domain of the c-erbB-2 oncoprotein (Her2).

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

B. Another objective is to evaluate the utility of FDG-PET/CT scans to monitor response to treatment. All patients will undergo a baseline staging FDG-PET/CT scan. A second PET scan will be performed during week 3:

ARM A: following the d 15 treatment, but before week 4 (eg during day 18, 19, or 20)

ARM B: once on either day 18, 19, or 20

We hypothesize that patients with a good PET/CT response will have RECIST evidence for response at their subsequent routine imaging time point and have an increased time to progression. Alternatively, patients with a bad PET/CT response will progress early. If successful, this would allow patients to minimize toxicity by minimizing exposure to ineffective therapy.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary:

- 1) To determine the efficacy of modified docetaxel, cisplatin, and fluorouracil (mDCF) (ARM A) and the efficacy of parent DCF with growth factor support (ARM B) in patients with unresectable or metastatic gastric or gastroesophageal junction(GEJ) adenocarcinoma as measured by 6 month progression free survival.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Secondary:

- 2) To establish the safety of mDCF and parent DCF with growth factor support in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 3) To observe other measures of efficacy of mDCF and parent DCF with growth factor support, including response rate, median PFS, overall and 1-year survival in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 4) To explore the association of early FDG-PET imaging with treatment efficacy.
- 5) To explore the differences in docetaxel pharmacology between both study arms.
- 6) To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.
- 7) To report the efficacy of mDCF with trastuzumab as measured by 6 month PFS amongst Her2 positive patients.
- 8) To report the safety profile of patients receiving mDCF and trastuzumab.

3.0 BACKGROUND AND RATIONALE

3.1 SCOPE OF DISEASE AND ROLE OF CHEMOTHERAPY

Gastric cancer is an aggressive neoplasm that is associated with an extremely poor prognosis. Median survival for metastatic or unresectable disease is approximately 8 to 10 months. On a global basis, cancer of the stomach is the third most prevalent malignancy worldwide, with 947,000 expected new cases in 2000, and the second leading cancer cause of death (734,000 deaths annually). [1]

Unfortunately, despite its enormous global impact, we have made little progress in the treatment of this disease. Conventional chemotherapy for metastatic gastric cancer remains palliative, with few patients ever demonstrating long term survival. Historically, most tumors develop rapid drug resistance and evidence of disease progression within a few months of initiation of therapy. However, palliative chemotherapy has a proven survival advantage over best supportive care for gastric cancer. Four randomized trials have all shown that patients assigned to receive best supportive care alone, even when allowed to receive chemotherapy at a later date, did significantly worse than those assigned to receive immediate chemotherapy (reviewed by Shah[2]).

3.2 COMBINATION CHEMOTHERAPY REGIMENS

The chemotherapeutic agents historically considered as active in this disease include fluorouracil, cisplatin, anthracyclines (doxorubicin and epirubicin), mitomycin C, and etoposide (reviewed previously[2, 3]). Single agent activity ranges with response rates from 10% to 20%, though the data are pooled from clinical trials performed in the 1960's and 1970's, and may be an overestimation of the true single agent activity as assessed by objective radiographic measurements.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Several combination regimens have been developed with the aims of improving overall response rates and duration of response. Table 1 summarizes the results of large random assignment studies involving these combination regimens. A three arm random assignment trial comparing ELF (etoposide, leucovorin, fluorouracil bolus), CF (cisplatin, fluorouracil infusion), and FAMTX (fluorouracil bolus, adriamycin, and high dose methotrexate) was reported by Vanhoefer, et al in 2000[4]. Overall response rates were notably low compared to previously reported phase II studies, ranging from 9% to 20% in the three arms, and survival was equally dismal at less than 7.2 months for each of the arms. These authors concluded that none of the regimens tested should be regarded as a standard treatment for metastatic or unresectable gastric cancer[4]. Another study compared CF, UFTM (uracil, tegafur, and mitomycin), and single agent 5-FU[5]. The CF regimen was associated with a modest, significant increase in progression free survival and response rate over 5-FU (3.9 mo and RR 34% vs. 1.9 mo and 11%, respectively). However, despite these improvements, overall survival was not improved with CF, with median and 1-year survival of 7.3 months and 29% respectively, compared with 7.1 months and 28% with 5-fluorouracil alone. Notably, approximately 50% of patients who were assigned to fluorouracil alone received cisplatin based therapy on progression in this study (personal communication, Ohtsu). These authors concluded that single agent fluorouracil should remain the reference standard regimen for advanced phase gastric cancer studies[5]. A similar conclusion was drawn by the authors of another random assignment study comparing EEP (etoposide, epirubicin, and cisplatin) vs. FEP (fluorouracil, epirubicin, and cisplatin). [6]

Table 1. Phase III clinical trials for gastric cancer using ‘older’ combination regimens (modified from Shah[2]).

| Reference | Disease | Treatment Regimen ¹ | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival | p value |
|--------------------|---------------------|--------------------------------|-----|--|-----------------------------|-----------------|---------|
| Tebbutt, 2002[7] | Esophagus + Gastric | PVI | 123 | 16.1% (9.5- 22.7%) | 22.5% (15.2-30%) | 6.3 mo | NS |
| | | PVI + MMC | 127 | 19.1% (12- 26.0%) | 18.4% (12-25.9%) | 5.3 mo | |
| Ohtsu, 2003[5] | Gastric | FU | 105 | 11.4% (6- 19.1%) | 28% | 7.1 mo | NS |
| | | FU + Cisplatin | 105 | 34.3% (25.3 - 44.2%) | 28% | 7.3 mo | |
| | | UFTM | 70 | 8.6% (3 – 18 %) | 16% | 6.0 mo | |
| Icli, 1998[6] | Gastric | EEP | 64 | 20.3%(12-59%) | 16 % ³ | 6.0 mo | NS |
| | | FEP | 67 | 15.3%(9- 59%) | 11 % ³ | 5.0 mo | |
| Vanhoefer, 2000[4] | Gastric | ELF | 132 | 9% (3.5-17.5%) | 28% | 7.2 mo | NS |
| | | CF | 134 | 20% (11 -30%) | 32% | 7.2 mo | |
| | | FAMTX | 133 | 12% (6-20.5%) | 33% | 6.7 mo | |

¹ Treatment Regimens: PVI = continuous infusion FU (300 mg/m²/d), MMC = mitomycin, EEP = etoposide, epirubicin, cisplatin, FEP = fluorouracil (bolus), epirubicin, cisplatin, CF = cisplatin, fluorouracil., UFTM = uracil, tegafur, mitomycin

² RR in evaluable patients, ³ 1-year survival estimated from Kaplan-Meier curves.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

3.3 IS THERE A “STANDARD” CHEMOTHERAPY REGIMEN?

Current or *modern* combination chemotherapy regimens have included prolonged infusional schedules of fluorouracil in combination with cisplatin and epirubicin (ECF), docetaxel, cisplatin and a 5 day fluorouracil infusion (DCF), and irinotecan based combinations both with cisplatin and with fluorouracil infusions. The data regarding these combination chemotherapy regimens are summarized in table 2 below. The overall efficacy as assessed by response rate, median and overall survival, and 1-year survival of these combination regimens appear to be improved over the combination chemotherapy regimens listed in table 1. However, as discussed below, specific issues surround each of these regimens that limit their general acceptability as a “standard” combination chemotherapy regimen for this disease.

Table 2. Recent studies for gastric cancer using modern regimens.

| Reference | Disease | Treatment Regimen ¹ | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival | p value |
|---|---|--------------------------------|-----|--|-----------------------------|--------------------------------------|-----------|
| <i>ECF based Phase III studies</i> | | | | | | | |
| Ross, 2002[8] | Esophagus + Gastric | ECF | 289 | 42.4% (37– 48%) | 40.2% (34– 46%) | 9.4 mo | NS |
| | | MCF | 285 | 44.1% (38– 50%) | 37.7% (27-38%) | 8.7 mo | |
| Webb, 1997[9, 10] | Esophagus + Gastric | ECF | 121 | 46% (37-55%) | 37% (28-45%) | 8.7 mo | p < 0.01 |
| | | FAMTX | 116 | 21% (13-28%) | 22% (15-29%) | 6.1 mo | |
| <i>DCF vs. CF phase III study</i> | | | | | | | |
| Ajani, 2003[11], Moiseyenko 2005[12] | Gastric + GEJ | DCF | 221 | 36.7% (30.3 – 43.4%) | 40.2% | 9.2 mo (8.38 – 10.58) | p = 0.02 |
| | | CF | 224 | 25.4% (19.9 – 31.7%) | 31.6% | 8.6 mo (7.16 – 9.46) | |
| <i>Irinotecan based studies (Note only the Dank is a phase III study)</i> | | | | | | | |
| Pooled results [13-15] | Esophagus + Gastric | Irinotecan/C isplatin | 105 | 48 % - 58% | | | |
| Pozzo et al. 2004[16] | Gastric + GEJ (Random assignment phase II) | Irinotecan/C isplatin | 56 | 32.1% (20.3 – 46%) ³ | 25.3% | 6.9 mo (5.55 - 8.67 mo) ⁴ | p = 0.002 |
| | | Irinotecan/F U infusion/ FA | 59 | 42.4 % (29.6 – 55.9%) ³ | 44.9% | 10.7 mo (8.02-14.62 mo) ⁴ | |
| Dank et al. 2005[17] | Gastric + GEJ | Irinotecan/F U infusion/ FA | 170 | 31.8% | | 9.0 mo (8.3 – 10.2 mo) | p = 0.53 |
| | | CF | 165 | 25.8% | | 8.7 mo (7.8 – 9.8 mo) | |

¹ Treatment Regimens: ECF = epirubicin, cisplatin, fluorouracil (continuous infusion), MCF = mitomycin, cisplatin, fluorouracil, DCF = docetaxel, cisplatin, fluorouracil, CF = cisplatin, fluorouracil.

² RR in evaluable patients. ³ Per protocol population, ⁴ Full analysis population

3.3.1 The ECF Regimen

The ECF regimen has recently been examined in two large random assignment studies (see table 2). First, ECF was compared with FAMTX, [10] with an update of the results recently reported by Waters, et al. [9] This study randomly assigned 274 patients (137 in each group) to receive ECF or FAMTX. ECF was associated with a better response rate (46% vs. 21%, p = 0.0002) and



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

an improvement in median survival (8.7 mo vs. 6.1 mo, $p = 0.0005$) when compared to FAMTX. However, this study was not generally accepted because of an apparent imbalance in the number of patients proceeding to surgery for locally advanced disease between the two arms.

The investigators then proceeded to examine ECF versus MCF (mitomycin, cisplatin, and infusional fluorouracil) in what is the largest random assignment study of chemotherapy in metastatic or unresectable esophagogastric cancer published to date[8]. This study randomly assigned 574 eligible patients with esophagus ($n=188$), gastroesophageal junction ($n=125$), or gastric cancers ($n=221$) to receive either ECF ($n=289$) or MCF ($n=285$). Response to therapy was equivalent (42.4% for ECF vs. 44.1% for MCF), as was survival (median survival 9.4 mo for ECF vs. 8.7 mo for MCF). Although ECF appeared to have greater toxicity, global quality of life scores were maintained in the ECF arm, whereas they fell in the MCF arm, suggesting that ECF was subjectively perhaps a more tolerable regimen[8]. Notably, the fluorouracil administration in the MCF arm was 50% higher ($300 \text{ mg/m}^2/\text{day}$) than in the ECF arm ($\text{FU } 200 \text{ mg/m}^2/\text{day}$) resulting in an imbalance between total fluorouracil administered between the two arms (net 42% higher with MCF, $p < 0.00001$). Although this study confirmed the activity of ECF in esophagogastric tumors, it also raises the question as to the role of epirubicin in a cisplatin-fluorouracil combination. The study also confirmed that the prognosis of patients with esophagogastric tumors not amenable to resection remains dismal (with median survival remaining less than 10 months).

3.3.2 Docetaxel Based Combination Therapy

Taxanes and taxane containing combinations have considerable activity in the treatment of gastric cancer. Although both paclitaxel and docetaxel have similar single agent response rates in the first line setting, occasional complete responses were reported with docetaxel. Both drugs have been examined with combination chemotherapy regimens with cisplatin, with associated improvements in response rates (ranging from 37% to 56%) and complete responses. [18, 19]

Based on the single agent and early combination activity observed with docetaxel-based therapy in upper gastrointestinal malignancies, docetaxel was examined in combination with cisplatin and fluorouracil (DCF) and compared with the 'standard' chemotherapy regimen of CF in a large random assignment phase III study (see table 2). [12]The results reported at ASCO 2005 demonstrate a significant improvement in time to progression (primary endpoint) with the docetaxel containing combination (5.6 vs. 3.7 months, $p=0.0004$) as well as an improvement in median and overall survival (median survival of 9.2 vs. 8.6 months, $p = 0.02$) with the addition of docetaxel to cisplatin + fluorouracil when compared with CF alone. At 6 months, 42.7% of the DCF-treated subjects had not progressed compared with 27.4% of the CF-treated subjects.

However, both DCF and CF was associated with significant toxicity (see table 3). Notably, in the DCF arm 82% of patients developed grade 3-4 neutropenia and 30% developed febrile neutropenia or a neutropenic infection. This is significantly more than the control arm of cisplatin and fluorouracil infusion in which 57% of patients developed grade 3-4 neutropenia, and 13.5% of patients developed febrile neutropenia or neutropenia with infection.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

For both arms, the majority of patients did not receive prophylactic growth factor support. Non-hematologic toxicity was considerable as well. In the DCF arm, 81% of patients developed a non-hematologic grade 3-4 adverse event, whereas in the CF arm, there was a similar high rate of grade 3-4 non-hematologic toxicity of 75.4%. Since both arms involved a 5 day infusion of fluorouracil, the grade 3-4 stomatitis rate was considerable (46% in DCF and 61% in CF). Other notable toxicity occurring in nearly half of the patients enrolled on the DCF arm include 47% developing grade 3-4 lethargy and 45% developing grade 3-4 diarrhea.

This toxicity spectrum is very similar to the toxicity we observed in an MSKCC phase II study of DCF (as originally prescribed) given as preoperative therapy for locally advanced gastric cancer (IRB 99-66, PI David Kelsen, MD). In this study, which was closed early due to toxicity, three out of the first 8 patients enrolled were unable to complete 2 cycles of preoperative DCF therapy due to significant treatment related toxicity. This suggests that the toxicity with the parent DCF regimen is significant, not only in patients with advanced, metastatic disease who may have been predicted to tolerate less aggressive therapy, but also in patients with locally advanced disease with less disease burden who generally are felt to tolerate treatment better.

Table 3. Toxicity of DCF and CF [12]

| Adverse Event | Grade 3-4 DCF | Grade 3-4 CF |
|--|------------------|-----------------|
| <i>Hematologic Toxicity</i> | | |
| Neutropenia | 82.3 | 56.8 |
| Febrile neutropenia or neutropenic infection | 30 | 13.5 |
| <i>Non-Hematologic Toxicity</i> | | |
| Neurosensory | 17 | 7 |
| Infection | 36 | 23 |
| Anorexia | 29 | 26 |
| Nausea | 35 | 42 |
| Vomiting | 33 | 42 |
| Lethargy | 47 | 40 |
| Diarrhea | 45 | 18 |
| Stomatitis | 46 | 61 |
| At least one grade 3-4 Adverse Event | 81.4 | 75.4 |
| <i>Deaths during treatment or within 30d of Tx</i> | 10.4 | 8.5 |

Overall, 41.2% of patients who received DCF required a dose reduction, and 47.5% of patients had a treatment related adverse event that led to a delay in treatment or dose reduction. The most common grade 3-4 side effects for the DCF arm included the following: lethargy, stomatitis, diarrhea, cancer pain, infection, nausea, vomiting, anorexia, and neuropathy. These toxicities were not considerably different than that experienced with cisplatin and fluorouracil infusion (CF). However, hematologic toxicity was considerable and significantly more with DCF than with CF. Specifically, 82.3% of patients who received DCF developed grade 3-4 neutropenia and 30% of patients developed febrile neutropenia or neutropenic infection. Notably, a portion



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

of patients (n = 41 or only 18.6% of the total study population) received prophylactic G-CSF. In this group, 63.4 % of patients developed grade 3-4 neutropenia and 12.2% of patients developed febrile neutropenia or neutropenic infection.

At this time, the question remains whether the toxicity attributable to the addition of docetaxel to CF will outweigh the modest observed improvement in survival. However, it is clear that docetaxel is an active chemotherapy agent in the treatment of this disease and that its addition to cisplatin and fluorouracil may confer a clinically important survival advantage. Based on these data, the FDA has recently approved the use of docetaxel with cisplatin and fluorouracil in the first line treatment setting for gastric and GEJ adenocarcinoma.

To capitalize on the potential survival advantage with docetaxel, efforts to reduce toxicity of the DCF regimen have been and are being pursued. These include substituting carboplatin for cisplatin, reducing FU to low-dose continuous infusion[20-22], or limiting the infusion of FU to 24 hours[23, 24] or 72 hours[25]. Unfortunately, these modifications are not clearly superior to the 'parent' DCF regimen. For example, the regimen developed by SAKK involves fluorouracil administered as a low dose continuous infusion at 300 mg/m²/day for 2 out of 3 weeks is furthest along in development. Although investigators observed approximate equivalent efficacy, they also noted approximate equivalent toxicity to the parent DCF regimen[22]. Specifically, they reported a 76% incidence of grade 3-4 neutropenia, 39% rate of febrile neutropenia, and a 44% rate of dose reductions/cycle.

Another study evaluated an alternative schedule of FU given weekly over 24 hours with leucovorin (the AIO schedule). [26] These investigators initiated a study combining this administration schedule of FU with cisplatin 50 mg/m² and docetaxel 50 mg/m² given every other week, and noted once again that more than 80% of patients required a dose reduction. They completed their phase II study with cisplatin and docetaxel at 40 mg/m² given every other week, and FU 24 hour infusion administered weekly and did notice a modest improvement in toxicity with a slight reduction in dose adjustments (62% of patients instead of over 80%). Notable grade 3/4 adverse events with this schedule included 20.4% neutropenia, 6.1% febrile neutropenia, 22.4% diarrhea, 8.2% nausea, 10.2% vomiting, and 18.4% fatigue. Although an apparent improvement over parent DCF, this schedule still was relatively toxic.

On the other hand, we are not aware of studies evaluating the combination of cisplatin and docetaxel with the de Gramont schedule of FU administration. This FU administration schedule is commonly used in colorectal cancer[27] with both irinotecan and oxaliplatin and is considered well tolerated and an improvement over bolus schedules and prolonged continuous infusion schedules of FU/LV administration. This FU administration schedule has been examined in upper GI cancers with oxaliplatin[28, 29] and is felt to be quite tolerable. Bouche et al examined the de Gramont administration schedule of FU with cisplatin 50 mg/m² in gastric and GEJ adenocarcinoma as well, and noted a slightly lower incidence of grade 3-4 neutropenia of 60%, similar rates of nausea/vomiting, and notably, a 0% incidence of grade 3-4 stomatitis[30]. This modest improvement in toxicity over cisplatin and 5-day infusion fluorouracil is particularly



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

encouraging in light of similar (or possibly slightly improved) efficacy over what is historically observed with cisplatin and 5-day infusional fluorouracil. Finally, although anecdotal, we (Dr. Shah and Dr. Kelsen) have personal experience with administering cisplatin and fluorouracil with the de Gramont schedule of FU administration and also find the regimen quite tolerable and as active.

3.3.3 Irinotecan based combination therapy

Recently, irinotecan based combinations have been evaluated in random assignment phase II and III clinical trials[16, 17, 30] (see table 2). The largest study is a random assignment phase III study involving 337 patients comparing irinotecan + fluorouracil (IF) versus cisplatin + fluorouracil (CF). [17] In this study, fluorouracil was administered weekly over 22 hours with leucovorin in the IF arm, and fluorouracil was administered as a continuous infusion over 5 days as is commonplace in the CF arm. There was no improvement in survival with IF (hazard ratio 1.08; 95%CI: 0.86-1.35), however this arm did appear to have a reduction in grade 3-4 toxicity. A second study performed by Bouche et al is a random assignment phase II study of irinotecan with fluorouracil and cisplatin with fluorouracil, using the De Gramont schedule of fluorouracil administration in both arms[30]. This study demonstrated similar results of approximate equal efficacy[30] with potentially less toxicity with irinotecan than with cisplatin.

3.3.4 Rationale for addition of trastuzumab to mDCF in HER2-positive gastric/GEJ adenocarcinoma patients.

Trastuzumab is a humanized monoclonal antibody (IgG1 isotype) directed against the extracellular region of HER2 that has been developed as a therapeutic modality for treating HER2-positive breast cancer. Trastuzumab is approved by the U.S. Food and Drug Administration (FDA) for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. Trastuzumab is also indicated as a single agent and in combination with paclitaxel for the treatment of patients with HER2-positive metastatic breast cancer. In these patients, the combination of trastuzumab plus paclitaxel results in improved response rate, time to disease progression, and overall survival compared with single-agent paclitaxel.

With the results of the recent phase III ToGA study, the benefit of trastuzumab in combination with cisplatin and fluoropyrimidine (CF) chemotherapy in HER2-positive metastatic gastric/GEJ adenocarcinoma has been established.² In this study, HER2-positive patients (FISH+ and/or IHC 3+) were randomly assigned to receive CF alone or with trastuzumab. Patients assigned to receive trastuzumab + CF had a significant improvement in overall survival (13.8 mo vs 11.1 mo, HR 0.74 [0.6-0.91], p = 0.0046). Trastuzumab is the first biological strategy to show a survival benefit in advanced GC. Based on these results, trastuzumab is now in the NCCN compendium for treatment of patients with HER2-positive advanced gastric cancer in combination with systemic chemotherapy.

This amendment is written to ensure that Her2 positive gastric cancer patients are able to receive trastuzumab with chemotherapy in the first line setting in gastric cancer. Notably, the ToGA study involved an acceptable standard two drug chemotherapy regimen to which the addition of



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

trastuzumab was randomly assigned. The rationale to incorporate trastuzumab in this study is to report the efficacy of a three drug gastric cancer regimen with trastuzumab amongst a cohort of Her2 positive patients.

3.3.5 HER2 testing in gastric/GEJ adenocarcinoma patients

Accurate HER2 testing is crucial for the successful application of trastuzumab in the clinical setting. In ToGA, HER2 positivity was defined using IHC published by Hofmann et al specifically for gastric cancer.¹ In a validation study of HER2 scoring in 168 gastric cancer resection specimens, Hofmann et al noted in gastric cancer a higher rate of tumor heterogeneity and incomplete basolateral membranous compared to breast cancer tumors. Hofmann et al investigated the application in gastric cancer of the testing methodologies commonly used to detect HER2 in breast cancer specimens and proposed a refined HER2 IHC scoring system suitable to score gastric cancer samples accurately and reproducibly. Most notably, according to the Hofmann criteria, biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e.<10%. (In Breast Cancer for example, IHC3+ requires a minimum of 30% IHC membranous staining.)

To determine if the breast ASCO/CAP guidelines for HER2 assessment can be used to accurately determine HER2 status in gastric cancer, we studied HER2 status of tumor specimens from 133 advanced gastric cancer patients undergoing treatment at MSKCC. HER2 IHC and FISH was performed for all specimens using ASCO/CAP guidelines and the Hofmann et al criteria. We found that HER2 in gastric cancer can be accurately evaluated using the breast cancer ASCO/CAP guidelines, with the exception that in small biopsy specimens with any cohesive HER2 IHC3+ or FISH+ clones should be considered HER2 positive. For the purposes of this protocol, patients that are IHC 1+ or 2+ will undergo FISH testing to confirm HER2 positivity. Patients with IHC 3+ or FISH+ (>2 HER2:CEP17) will be eligible to receive treatment with trastuzumab on study.

3.4 SUMMARY OF CHEMOTHERAPY FOR GASTRIC/GEJ ADENOCARCINOMA

A careful review of the data described above reveals that there is no consensus standard chemotherapy regimen for the first line treatment of unresectable or metastatic gastric/GEJ adenocarcinoma at this time. Although chemotherapy is better than best supportive care, we have observed little to no improvement in overall survival beyond 8-10 months in randomized controlled clinical trials examining several different combination treatments. Cisplatin and fluorouracil based therapy is most commonly used as the reference arm in these random assignment phase III studies, and as a component of the investigational arm in several of these random assignment phase III studies.

The addition of docetaxel to cisplatin and fluorouracil is superior to cisplatin and fluorouracil alone. Based on this, docetaxel has received FDA and European Union approval in combination with fluorouracil and cisplatin for the first line treatment of gastric and GEJ adenocarcinoma. However, the toxicity of this three drug regimen, although not significantly worse than cisplatin



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

and fluorouracil infusion alone, is still significant, and is the primary limitation of its widespread acceptance.

December 2009 Amendment

With the recent compendium listing of trastuzumab as part of the first line treatment of gastric cancer, trastuzumab is now indicated in the first line setting with combination chemotherapy for the treatment of advanced gastric/GEJ adenocarcinoma. Patients who are Her2 positive should receive standard combination chemotherapy with trastuzumab. Patients who receive trastuzumab will be considered as a separate and independent cohort from the primary analysis.

3.5 PROPOSAL

With recent FDA and European Union approval, a combination of docetaxel, cisplatin and fluorouracil is now an acceptable standard regimen for the first line treatment of gastric and gastroesophageal junction adenocarcinomas. However, the toxicity of the parent DCF regimen as originally prescribed has prevented its widespread acceptance and usage.

We therefore propose to evaluate two modifications of the parent DCF regimen in a random assignment phase II clinical trial. In ARM A, we propose a modified DCF schedule with the following specific modifications to parent DCF: (1) a de Gramont schedule for FU administration, (2) reduced bi-monthly doses of cisplatin and docetaxel, and (3) the administration of docetaxel and cisplatin on consecutive days instead of immediately following one another. See section 3.5.1 for detailed discussion for the rationale of the mDCF schedule.

In ARM B, we will examine parent DCF with prophylactic growth factor support. Recall that in the TAX325 study, patients who received prophylactic G-CSF had a significantly reduced incidence of grade 3-4 neutropenia and incidence of febrile neutropenia or neutropenia with infection.

With this study, we will establish the efficacy and tolerability of modified DCF and of parent DCF with growth factor support. If mDCF appears to maintain the efficacy of the parent DCF regimen with less toxicity, we will have established a new treatment regimen for this disease to which targeted agents can be examined.

December 2009 Amendment

Due to toxicity, Arm B is now closed to further accrual. Arm A will continue to enroll until target accrual. In addition, patients who are Her2 positive will receive trastuzumab with mDCF, in a separate, independent cohort.

August 2010 Amendment

We have reached target accrual in Arm A. Her2 positive patients will receive trastuzumab with mDCF, in a separate, independent cohort.

3.5.1 Modified DCF dose and schedule determination

The specific modifications to parent DCF that we have proposed include (1) a de Gramont schedule for FU administration, (2) reduced bi-monthly doses of cisplatin and docetaxel, and (3)



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

the administration of docetaxel and cisplatin on consecutive days instead of immediately following one another.

We believe that a modified FU administration schedule (bolus + 48 hour infusion of FU) will confer less toxicity than longer infusion schedules of FU currently in use (eg. 5 day infusion used in parent DCF) with similar efficacy. Several lines of evidence from gastric cancer studies support altering the FU schedule to a bolus + 48 hour infusion and to administering chemotherapy bi-monthly at reduced doses. The most convincing is from Bouche et al. that describes a three arm random assignment phase II study with each arm receiving LV5FU2[30]. LV5FU2 is the same FU administration schedule as we have proposed in this study (bolus + 48 hr infusion). In the Bouche study, Arm A was LF5FU2 alone, arm B was cisplatin 50 mg/m² with LV5FU2, and arm C was irinotecan + LV5FU2. The response rate and survival of LV5FU2 (arm A) is consistent with that reported for single agent FU[5]. In addition, the response rate and survival of arm B (Cisplatin + LV5FU2) is consistent with that reported for cisplatin and FU x 5 day infusion schedules[5, 11, 17]. Notably, the efficacy is maintained while keeping the relative dose intensity for cisplatin identical to the historical standard of cisplatin and fluorouracil 5-day infusion. Specifically when cisplatin is administered with the 5-day infusion of FU, it is given at 100 mg/m² every 4-weeks which yields a dose intensity of 25 mg/m²/week. When cisplatin is administered with LV5FU2, it is administered at 50 mg/m² every other week, which yields an equivalent dose intensity of 25mg/m²/week.

The table below describes the efficacy of cisplatin and infusional FU (control arms) as observed in 3 recent large phase III studies and of cisplatin + LV5FU2 as described in the Bouche et al study.

| Reference | Treatment Regimen | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival |
|---|------------------------------|-----|--|-----------------------------|---------------------------|
| Ajani, 2003[11], Moiseyenko 2005[12] | Cisplatin + Infusional FU | 224 | 25.4% (19.9 – 31.7%) | 31.6% | 8.6 mo (7.16 – 9.46) |
| Ohtsu, 2003[5] | Cisplatin + Infusional FU | 105 | 34.3% (25.3 - 44.2%) | 28% | 7.3 mo |
| Dank 2005[17] | Cisplatin + Infusional FU | 165 | 25.8% | | 8.7 mo (7.8 – 9.8 mo) |
| | | | | | |
| Bouche, 2004 [30] | Cisplatin + LV5FU2 | 44 | 27% (14% - 40%) | 43% | 9.5 mo (6.9 – 12.2 mo) |

The FU administration schedule (bolus + 48 hour, or LV5FU2) with bi-monthly cisplatin administration confers approximate equal efficacy with regard to response rate, 1-year survival, and median survival when compared to the traditional cisplatin + infusional FU x 5 day schedule.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

With regard to the question of equal or reduced toxicity, the table below summarizes the relevant toxicity comparison:

| Toxicity (Grade 3-4) | Cisplatin + LV5FU2 (Bouche et al) (n=44) | Cisplatin + 5-day FU Infusion (Moiseyenko et al) (n=224) |
|----------------------|---|---|
| Neutropenia | 61% | 57% |
| Febrile neutropenia | 18% | 14% |
| Nausea/vomiting | 23% | 42% |
| Diarrhea | 2% | 18% |
| Mucositis | 0% | 61% |

As shown, the toxicity of the bolus + 48 hour FU infusion and reduced bi-monthly administration of cisplatin schedule is significantly less toxic with regard to diarrhea, mucositis, nausea and vomiting. Neutropenia is approximately equivalent. Thus, because of approximate equal efficacy with considerably less toxicity, the proposed administration schedule is a significant improvement over the traditional cisplatin + 5-day FU infusion schedule. Finally, we also have experience with docetaxel and cisplatin administered with this fluorouracil administration schedule in several patients with upper GI malignancies and have found the regimen be both quite tolerable and active (Shah and Kelsen, personal communication). Based on these data above, we feel that administering fluorouracil as per the De Gramont schedule (bolus + 48 hour infusion) provides approximate equivalent efficacy to 5 day FU administration schedules. When coupled with less frequent dosing of cisplatin, the combination is associated with less toxicity.

With regard to the best dose of cisplatin and docetaxel when both drugs are administered together with fluorouracil, two gastric cancer studies provide additional support (Lorenzen described here and Oh described below). A phase II study by Lorenzen and colleagues was reported at the 2006 GI Cancer symposium (San Francisco, CA) in which docetaxel and cisplatin (50 mg/m² each) were administered every other week in combination with a 24 hour infusion of FU (2,000 mg/m² over 24 hours) which was administered weekly[26]. The investigators felt that the combination at those doses of cisplatin and docetaxel was still too toxic and amended their study to administer docetaxel and cisplatin at a reduced dose of 40 mg/m² every other week. With these lower doses (eg. the doses that we have proposed), the investigators reported approximately equal efficacy to parent DCF with slightly improved toxicity including grade 3-4 neutropenia 20% and nausea/vomiting 20%, thus supporting our proposal.

Finally, by separating the docetaxel and cisplatin, we believe we will have even less toxicity due, in part, to improving docetaxel clearance when compared to the combined administration. The rationale for this is that docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and the standard antiemetics used when giving cisplatin (eg. aprepitant and palonosetron) also are CYP3A4 inhibitors. Thus, by administering cisplatin on a different day from docetaxel, the clearance of docetaxel should improve, thus reducing toxicity. This will be examined in the parallel random assignment study in which one arm will be mDCF and the other



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

arm will be parent DCF in which the docetaxel and cisplatin are administered on the same day immediately following one another.

A recent phase II report of a Korean study of docetaxel + cisplatin + fluorouracil provides support for this hypothesis[31]. Specifically, in this phase II study, docetaxel was administered on day 1 (70 mg/m²), cisplatin was administered on days 2 and 3 (40 mg/m² each day), and fluorouracil was administered over 10 hours on days 1, 2 and 3. The regimen was repeated every 3 weeks and again demonstrated approximate equal efficacy to parent DCF. However most interestingly, the incidence of grade 3 or 4 toxicity including nausea, vomiting, diarrhea, leucopenia or neutropenia, and mucositis was each less than 10%, which is a remarkable improvement over the parent DCF regimen in which these toxicities were 40% or higher and 80% for grade 3-4 neutropenia. The investigators were unable to explain this reduced toxicity and hypothesized that it may be related to the Korean population of the study. Alternatively, a potential PK interaction between cisplatin anti-emetics and docetaxel may explain this improved toxicity.

The table below describes the relative dose intensity of the parent DCF (as scheduled and as actually delivered) and modified DCF:

| Modified DCF q other week | | | ARM B – Parent DCF q 3 weeks | | | |
|---------------------------|---------------------------|---|------------------------------|-------------------------------------|--|--|
| Drug | Dose (mg/m ²) | Dose Intensity (mg/m ² per wk) | Drug | Scheduled Dose (mg/m ²) | Dose Intensity (mg/m ² /wk) | Delivered Dose Intensity (mg/m ² /wk) |
| Docetaxel | 40 | 20 | Docetaxel | 75 | 25 | 22 |
| Cisplatin | 40 | 20 | Cisplatin | 75 | 25 | 22 |
| Leucovorin | 400 | X | | | | |
| Fluorouracil | 400 | X | Fluorouracil | 750 | X | X |
| Fluorouracil | 1000 | X | | | | |

As shown, the proposed dose of docetaxel and cisplatin in the modified DCF regimen represent 80% of the scheduled dose of the parent DCF regimen. However, the proposed dose is in fact 90% of the delivered dose of the parent regimen.

Thus, based on the data shown above, there is sufficient evidence from a number of sources to consider modified DCF as a reasonably safe and effective DCF regimen.

- (1) The bolus and 48 hour infusion schedule of FU is equivalent to the 5-day infusion schedule of FU but is associated with less toxicity.
- (2) Administering reduced bi-monthly doses of docetaxel and cisplatin with FU confers less toxicity also while maintaining efficacy. This toxicity profile may be further improved by administering docetaxel and cisplatin on different days due to a possible pharmacokinetic interaction between docetaxel and the delayed emesis regimen used for cisplatin.
- (3) The dose intensity of cisplatin and docetaxel in the proposed mDCF regimen is insignificantly different from what was delivered in the parent DCF regimen.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

3.5.2 Pharmacokinetic and Pharmacodynamic Considerations (MSKCC ONLY)

Two initial phase I studies examined the combination of docetaxel and cisplatin[32, 33]. Pronk and colleagues evaluated two schedules of administration: Schedule A administered cisplatin as a 3 hour infusion 3 hours following 1-hour docetaxel infusion ($D_{1\text{hour}} \rightarrow 3\text{hr break} \rightarrow C_{3\text{hour}}$), and Schedule B administered cisplatin over 3 hours one day prior to docetaxel ($C_{3\text{hour}}$ day 1 $\rightarrow D_{1\text{hour}}$ day 2). These investigators noted that there was a trend toward greater hematologic toxicity with schedule B where cisplatin is given prior to docetaxel. This is consistent with the previous data regarding the sequence of administration of cisplatin and paclitaxel[34], and may be related to higher DNA-adduct formation and intracellular accumulation of cisplatin in human leukocytes if given prior to the taxane[35]. Pronk noted no significant differences in the pharmacokinetic parameters of cisplatin and docetaxel with the two schedules examined in their study[32]. However, the authors did point out the 21 hour time interval between cisplatin and docetaxel in schedule B, and noted that when cisplatin precedes paclitaxel by 6 hours, paclitaxel clearance reduced by 25% [34]. The 2nd phase I study by Millward et al. administered cisplatin over 1 hour immediately following docetaxel 1 hour infusion[33]. They also noted no pharmacokinetic interactions. In addition, they also evaluated the Pronk schedule A sequence of $D_{1\text{hour}} \rightarrow 3\text{hr break} \rightarrow C_{3\text{hour}}$ and it appeared that in a small number of patients, there was increased toxicity when administering cisplatin 3 hours following docetaxel instead of immediately following docetaxel. Since these studies were published in 1997, the convention for virtually all subsequent evaluations involving the combination of docetaxel and cisplatin administered the drugs as described by Millward et al with docetaxel given over 1 hour and then followed immediately with cisplatin administered over 1 hour.

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem[36]. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4[37, 38]. Indeed, this inhibition results in reduced clearance of the concomitantly administered steroid, dexamethasone, resulting in the recommended reduced dose of dexamethasone when administered with aprepitant and palonosetron[39]. Similarly, inhibition of CYP3A4 by these anti-emetic agents could result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity. However, a recent evaluation demonstrated no significant role of aprepitant on the pharmacokinetics of docetaxel[40]. However, this study did not examine docetaxel metabolites. In one study, detection of the M4 docetaxel metabolite may indicate reduced docetaxel clearance and possibly increased myelosuppression[41].

In our experience, we have observed that the co-administration of docetaxel and cisplatin on the same day in combination with fluorouracil infusion is associated with significant nausea, vomiting, and delayed emesis – in particular, significantly more so than when either cisplatin or docetaxel is administered alone with the same fluorouracil schedule. Aprepitant and palonosetron may be used to prevent acute and delayed emesis from cisplatin. However, it may inadvertently result in reduced docetaxel clearance and increased docetaxel related toxicity, or if not the parent compound, possibly reduced clearance of a metabolite. We note that the anti-emetic drugs, aprepitant and palonosetron, are administered primarily for cisplatin associated



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

nausea and vomiting. Based on these findings, we have moved cisplatin to be administered 1-2 days following docetaxel in several patients treated with mDCF already. Interestingly, we have anecdotally (in approximately 10 patients) noted a considerable improvement in their tolerance to the mDCF, thus supporting this hypothesis and warranting its further evaluation.

To examine this further and more formally, we propose to evaluate the pharmacokinetics of docetaxel and its metabolites in approximately 10 patients in each arm. Recall that docetaxel and cisplatin in Arm B are both given on day 1, along with initiation of the 5 day fluorouracil infusion. We believe there will be a significant difference in docetaxel clearance in the two arms that may explain, in part, the significant toxicity of the parent DCF regimen.

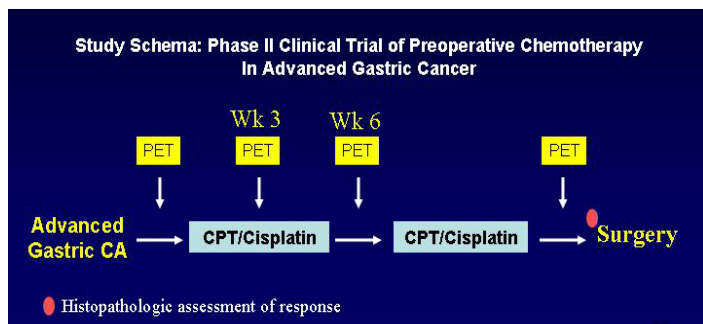
Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 (15 min following the end of docetaxel infusion)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

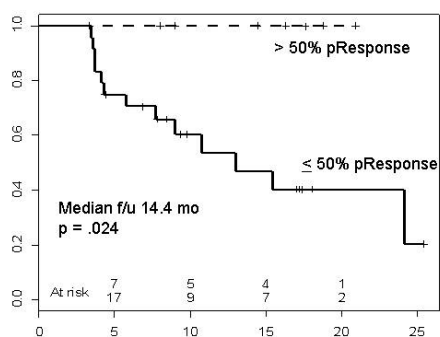
March 2008 Addendum: On our initial pharmacokinetic analysis, we have observed that the clearance of docetaxel appears to be reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen. Based on this, we will expand our pharmacokinetic evaluation and examine additional docetaxel PK without cisplatin in up to 6 patients randomized to parent DCF who underwent cycle 1 docetaxel PK (when cisplatin was administered on day 1 as well). See section 9.4.3.

3.5.3 FDG-PET Response Assessment



scans early in the treatment plan to predict treatment efficacy. Patients with high-risk

Pathologic Response as a Surrogate for Recurrence
(n = 32)



gastric cancer (preoperative stage T2N+, T3-T4, Nany, M0) were eligible. The study schema is provided in the figure below. Enrolled patients received preoperative chemotherapy with cisplatin 30 mg/m² and irinotecan 65 mg/m² during weeks 1, 2, 4, 5, 7, 8, 10, and 11, prior to surgical resection. FDG-PET/CT scans were performed prior to initiation of therapy, during week 3 and week 6 (day 15 and 35, respectively), and following completion of pre-operative therapy, prior to surgery. Thus far, 42 patients have enrolled on this phase II study with the following patient characteristics: median age 62 (range 25-83), male 29, KPS 90% (70%-90%).

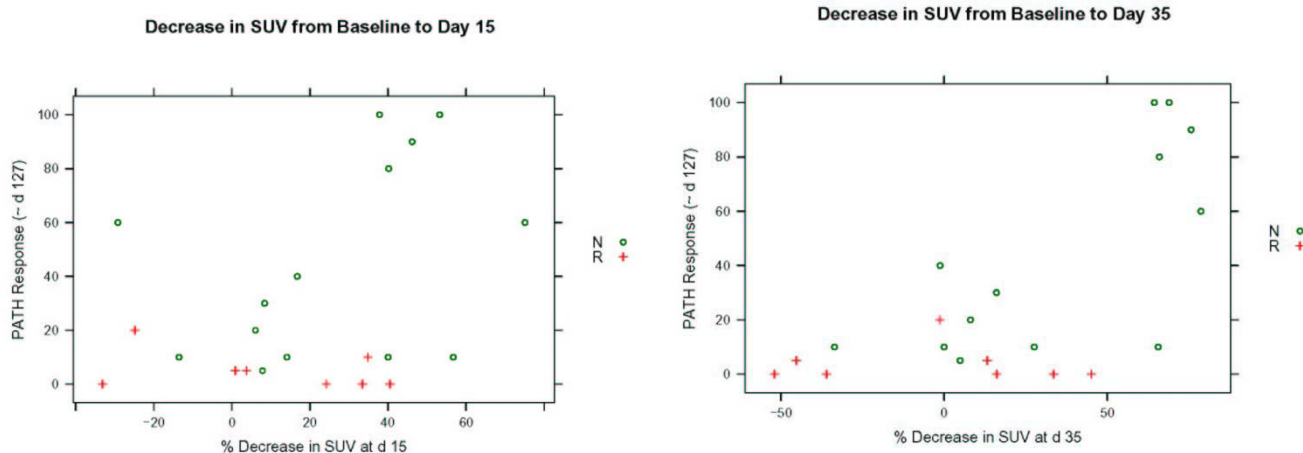
We first demonstrate that pathologic treatment response is a surrogate for treatment efficacy. Pathologic assessment of treatment response is assessed histologically, by visual assessment, based on the identification of residual cancer cells and on the extent of fibrosis[42]. In this system, a tumor regression grade (TRG) is established, and quantitated into five grades, ranging from TRG 1 (complete regression) to TRG 5 (complete absence of regressive changes). Response assessment is based on areas of tumor treatment effect that are characterized by the replacement of neoplastic tissue with fibrous tissue and scattered inflammatory cells. We have converted this grading system to a percent treatment response score from 0 to 100%, such that a TRG1 score has a 100% treatment response score, and a TRG5 has a treatment response of less than 10%. We evaluated the histopathologic response to treatment with disease free recurrence. 32 patients are evaluable thus far. Our median follow up period for these patients is 14 months and thus far, 13 patients (out of 32) have recurred. Based on this preliminary analysis, there is a significant correlation between pathologic response to therapy and disease free recurrence (see figure to the right). These data suggest that a 10% increase in pathologic response corresponds to a 49% risk reduction of recurrence (p = 0.013).



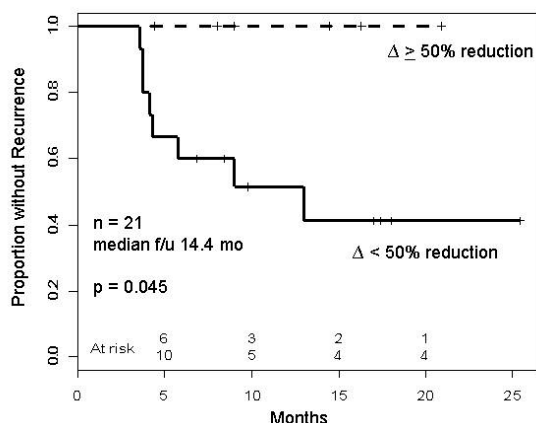
Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Next, we demonstrate the correlation between change in functional imaging and pathologic response. The two graphs below demonstrate the correlation between FDG-PET/CT response and pathologic response. It is important to point out that the FDG response assessment occurs at day 15 and at day 35, where one could potentially switch the chemotherapy regimen to alternative treatments in the hopes of improving response to therapy. Notably, the pathologic response assessment described above occurs at the time of surgical resection, approximately at day 127. At that time point, it is too late to switch therapy from ineffective therapy (eg. that associated with a minimal pathologic response to treatment) to a potentially more effective therapy. This is highlighted below by the pathologic response axis (y-axis on both graphs). Specifically, all of the patients who have recurred (red plus symbols) had a pathologic response of 20% or less. Knowing that one is destined for a poor pathologic response *a priori* would warrant a change in therapy with the hopes of improving this response. We have already demonstrated preliminary evidence that a poor pathologic response increases the probability of early recurrence, and certainly death from disease. With this in mind, the figures below demonstrate that with a high FDG response (eg. above 40% by day 15, or above 50% by day 35), the chance of achieving a high pathologic response to preoperative chemotherapy is quite high, whereas a lower FDG response is associated with a lesser degree of pathologic response and a higher chance of disease recurrence.



Correspondence between decrease in FDG SUV from baseline to on-treatment scan and pathologic response. In the graphs above, the open circles are patients who have not had a recurrence and the plus symbols represent patients who have had a recurrence.



These data support the fact that an early FDG-PET scan can predict response to chemotherapy that is identified histopathologically in the surgical resection specimen almost 3 months later. We then evaluated the association of FDG-PET response to recurrence and again found a strong and significant association (see figure to the left). This figure demonstrates the high correlation with FDG response (at day 35 in this case) and risk



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

of recurrence. A 50% or greater reduction in FDG-SUV by day 35 of the chemotherapy treatment plan is associated with an extremely low chance of disease recurrence, whereas a less than 50% reduction in FDG-SUV is associated with a significantly higher probability of disease recurrence ($p = 0.045$). Altogether, these data suggest that an early FDG-PET/CT scan, when compared with a baseline scan, may be predictive of response to preoperative chemotherapy as assessed by histopathologic response assessment and by disease free recurrence.

3.5.4 Discontinuation of chemotherapy after 6 months.

The study will allow for discontinuation of docetaxel, cisplatin, and/or fluorouracil at the discretion of the treating physician after having completed 6 months of chemotherapy. The rationale for this comes from a growing body of evidence that suggests that patients with solid tumor malignancies need not receive cytotoxic chemotherapy until disease progression. For example, in metastatic NSCLC, it is well accepted that 4 to 6 cycles of platinum based chemotherapy is a superior strategy as compared to maintenance chemotherapy (Pfister, JCO 2003). In metastatic colorectal cancer, the OPTIMOX1 study shows that intermittent dosing of oxaliplatin is less toxic and associated with an equivalent progression free survival and overall survival (Tournigand, JCO 2006). Similarly, in prostate cancer, patients who receive intermittent androgen ablation also demonstrate no evidence of decreased survival or time to progression, and did have a benefit of reduced toxicity (Calais Da Silva, ASCO 2006). Our primary endpoint is a landmark analysis of progression at 6 months. Allowing patients to discontinue cytotoxic therapy after 6 months does not interfere with our primary endpoint, and may reduce cumulative toxicity (particularly from docetaxel and cisplatin) without adversely affecting treatment efficacy.

3.5.5 Assessment of Quality of Life

The study will include an assessment of quality of life on both arms of the study at baseline, and periodically during the course of treatment. We will use the EORTC QLQ-C30 instrument to examine quality of life. This is a validated instrument that has been used in many large studies, including in gastric and gastroesophageal randomized studies (Aaronson, JNCI 1993; Glimelius, Ann Onc 1997; Ross, JCO 2002). We will administer the questionnaire at baseline, 6 weeks, 3 months, and 6, 9, and 12 months.

3.5.6 Volumetric CT Analysis of Response to Therapy (MSKCC only)

At MSKCC only and in collaboration with Larry Schwartz, MD, we will also initiate an exploratory volumetric CT analysis of Response to therapy. This study will make use of already acquired image data from this clinical trial. No additional human material or CT scans will be needed. The standard CT scan data (acquired either during PET/CT scanning or CT scanning) will be electronically transferred, via the hospital network, from the hospital PACS to the research PACS server, where patient identification information are de-identified. Volumetric CT will be used in an exploratory way to assess tumor response during therapy to compare with RECIST. The volumetric analysis, however, will not affect patient care and will not be communicated



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

to the patient or clinical investigator. To study effects of a wider range of slice thickness on the performance of the segmentation algorithms and reproducibility of tumor measurements, thinner section CT images will be reconstructed with CT raw data acquired for the radiographic assessment in the trial. The volumetric CT technique used in this study may be able to detect asymmetric or small change in tumor size at the level that may not be possible with the conventional uni-dimensional RECIST criteria.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a random assignment phase II study of two different administration schedules of docetaxel, cisplatin, and fluorouracil in patients with unresectable or metastatic gastric or GEJ adenocarcinoma. Patients may have received neoadjuvant and/or adjuvant chemotherapy or chemoradiotherapy. Patients may not have received previous chemotherapy containing cisplatin or docetaxel. Prior fluorouracil is allowed if more than 6 months have passed since the patient last received it. Patients must provide written informed consent prior to study enrollment.

At baseline, patients will require a full medical history and physical examination, including assessments of body weight, height, calculated body surface area, and vital signs (blood pressure, heart rate, respiratory rate, and temperature). Laboratory assessment will include CBC with differential, PT, PTT, comprehensive biochemical screening profile (which includes electrolytes, BUN, creatinine, AST, ALT, total bilirubin, total protein, albumin, alkaline phosphatase, and glucose), Ca, Mg, Phosphorus, LDH, and urinalysis. For females of childbearing potential, a serum pregnancy test is also required. Additional evaluation will include baseline ECG and a signed informed consent. CT scan of chest, abdomen, and pelvis will be performed in all patients and documentation of tumor measurement, in centimeters will be done. A baseline PET/CT scan will be performed as well for staging. In cases where there are multiple metastases, a representative sample of large masses, up to a total of five, will be chosen as the index lesions to be followed for a response, as per RECIST criteria. Measurable disease is not a requirement for study entry. Biopsy confirmation of M1 disease is encouraged, unless the risk of such a procedure is significant, in which case confirmation by a 2nd imaging modality is required (eg. PET/CT scan may be sufficient if tumor and metastases are both FDG avid).

December 2009 Amendment

As of October 2009, trastuzumab plus chemotherapy is part of the NCCN standard treatment algorithm for the first line for advanced gastric/GEJ adenocarcinoma. This amendment is to allow patients who are Her2 positive to receive trastuzumab with mDCF. Her2 positive patients are defined as FISH + and/or IHC 3+ for Her2. Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. <10%. FISH+ defined as >2 HER2:CEP17. To receive trastuzumab, patients must have a baseline left ventricular ejection fraction of $\geq 50\%$.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

4.2 Intervention

Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 or 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg * | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg.

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments).

Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments).

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

A given treatment may be moved +/- 14 days for specific administrative reasons, in particular clinic closure for holidays. Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter. Therapy will be administered in an outpatient setting, under the supervision of a physician and/or chemotherapy nurse, as is standard for chemotherapy administration at the treating institution.

Clinical evaluation: All assessments may be performed within one day of the planned treatment.

ARM A – Modified DCF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of cycle one (e.g. on day 1, day 15, and day 29 of cycle 1). In cycle 2 and all subsequent cycles, a physician evaluation (e.g. physical examination and toxicity assessment) will be performed prior to treatment on day 1 and day 29 treatments. Additional nurse or physician visits will be at the discretion of the treating physician. It is encouraged that an oncology nurse toxicity evaluation be performed prior to each treatment, especially if the patient is not assessed by a physician.

Patients treated with mDCF plus trastuzumab therapy should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain).

ARM B – Parent DCF with G-CSF



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of every cycle.

Laboratory evaluation:

ARM A – Modified DCF

On or within 1 day of the beginning of each cycle, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers will be performed. A CBC with differential and platelet count is required prior to each subsequent treatment (eg. day 15 and day 29). A BUN and Creatinine is required before the day 15 treatment (treatment #2), and a serum chemistry (electrolytes, BUN, Creatinine, glucose) is required before each day 29 treatment (#3). LFTs are required before each treatment (#1, #2 and #3) of cycle 1, and before treatment #1 and #3 for each subsequent cycle. Any patient with excessive LFTs abnormalities (see section 9.3) will require repeat LFTs prior to the next docetaxel administration.

ARM B – Parent DCF with G-CSF

On or within 1 day of the beginning of each treatment, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers are required.

Radiology evaluation: For both treatment arms, radiographic studies upon which tumor measurements were made will be repeated every cycle (six week intervals for most patients) for 6 cycles, and then after every two cycles of therapy (e.g. after cycles 1, 2, 3, 4, 5, 6, 8, 10, 12 etc.), to rule out progression of disease and to determine response for measurable disease.

Patients will remain on study until disease progression, patient withdrawal, unacceptable toxicity despite dose attenuation, or if the treating physician deems it is in the best interest of the patient following discussion with the principal investigator. Tolerability of this regimen will be determined from blood test results and toxicity assessment.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Docetaxel (TAXOTERE®)

For complete details, please see the package insert for further information.

5.1.1 Description

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is a white to almost-white powder with an empirical formula of



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

$C_{43}H_{53}N_{14}O_{14} \cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

5.1.2 Preparation and Administration

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing DOCETAXEL solutions. The use of gloves is recommended. Please refer to Handling and Disposal section.

If Docetaxel Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Docetaxel Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the Docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Docetaxel Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Docetaxel Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for DOCETAXEL 20 mg and DOCETAXEL 80 mg.

| Product | Diluent 13% (w/w) ethanol in water for injection Fill Range (mL) | Approximate extractable volume of diluent when entire contents are withdrawn (mL) | Concentration of the initial diluted solution (mg/mL docetaxel) |
|---------------------------|--|---|--|
| Taxotere® 20 mg/0.5 mL | 1.88 – 2.08 mL | 1.8 mL | 10 mg/mL |
| Taxotere® 80 mg/2 mL | 6.96 - 7.70 mL | 7.1 mL | 10 mg/mL |

A. Initial Diluted Solution

1. Docetaxel vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for Docetaxel 20 mg and approximately 7.1 mL for Docetaxel 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of Docetaxel Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted Docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted Docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded.

2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final Docetaxel dilution for infusion should be administered intravenously as a 30-minute to 60-minute infusion under ambient room temperature and lighting conditions.

Stability: Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared Docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

How Supplied: Docetaxel Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered as per institutional guidelines.

5.1.3 Source

For this study, locally obtained commercial supplies of Docetaxel should be used. Because commercial drug will be used, accounting for Docetaxel drug supplies is not specifically required in this study.

5.1.4 Safety Profile

Principal adverse effects include neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, ascites, mucositis, cardiac arrhythmias, hypotension, pleural effusion, peripheral neuropathy, rash, severe nail disorders (hypo or hyperpigmentation), onycholysis (loosening of the nails), alopecia, palmar-plantar dyserythroesthesia, hypersensitivity reaction, fatigue and fluid retention syndrome (may be irreversible).

5.2 CISPLATIN

For complete details, please see the package insert for further information.

5.2.1 Description

Cisplatin (cis-diaminedichloroplatinum, Platinol®) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis- position. Cisplatin binds to DNA bases and produces particular types of cisplatin-DNA lesions or adducts. The drug is supplied in 10 and 50 mg amber vials.

5.2.2 Preparation and Administration

ARM A: Cisplatin will be given on days 1, 15, and 29 of each cycle. The drug will be given at a dose of 40 mg/m² over 30 minutes on day 2 or 3 of each treatment.

ARM B: Cisplatin will be given on days 1 and 22 of each cycle. The drug will be given at a dose of 75 mg/m² over 60 minutes immediately following docetaxel administration.

Cisplatin is available in 100mg/100 ml solution vials. The solution is then further diluted into saline-based solutions (preferably 100-150 ml of 0.9% NaCL for intravenous administration). Before drug administration the patient should be given intravenous hydration with at least 500 ml of 5 % dextrose in normal saline (D5W) or normal saline over 1-2 hours. Aluminum needles should not be used. Patients will be advised to maintain an oral fluid intake of at least one (1) liter per meter squared on the day of treatment. This regimen may be adjusted as needed, e.g., for elderly persons.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

5.2.3 Source

For this study, locally obtained commercial supplies of Cisplatin should be used. Because commercial drug will be used, accounting for Cisplatin drug supplies is not specifically required in this study.

5.2.4 Safety Profile

Cumulative nephrotoxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia and hypotension may occur within minutes of cisplatin administration. Other side effects include anorexia, diarrhea, serum electrolyte disturbances (e.g., hyponatremia, hypomagnesemia), vascular toxicities (e.g., myocardial infarction, cerebrovascular accident etc.), neurotoxicity, peripheral neuropathy, autonomic neuropathy, muscle cramps, ocular toxicity (optic neuritis, papilledema, cerebral blindness), and hepatotoxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin.

5.3 FLUOROURACIL

For complete details, please see the package insert for further information.

5.3.1 Description

The chemical name of fluorouracil (FU) is 5-fluoropyrimidine-2,4(1H,3H)-dione. Fluorouracil is also known by other names 5-Fluorouracil; Fluorouracilo; Fluorouracilum; 5-FU; NSC-19893; Ro-2-9757; WR-69596. Its molecular formula is C₄H₃FN₂O₂; it has a molecular weight of 130.1. FU is a white to almost white, practically odorless, crystalline powder. It is sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and ether. A 1% solution has a pH of 4.5 to 5.0; the USP injection has a pH of 8.6 to 9.4 and the BP injection has a pH of 8.5 to 9.1. Fluorouracil is commercially available, and supplied in the U.S. by ICN pharmaceuticals, Lyphomed, Quad Pharmaceuticals, Baxter Healthcare, Abbott Laboratories, and as Adrucil® by Pharmacia & Upjohn.

5.3.2 Preparation and Administration

At our institution fluorouracil manufactured by Pharmacia & Upjohn (ADRUCIL®) is in use. It is supplied as a 50 mg/ml solution in vials of 50 ml and 100 ml. The appropriate volume is withdrawn into a syringe which is used for administration. No dilution is required. Filter ampules with aspiration needle (5µm). Compatible with D₅W, 0.9% NaCl, D₅LR. Fluorouracil will be administered as an intravenous push, usually over 1-2 minutes followed by a 48-hour intravenous continuous infusion (further dilution is not required). Ensure vein patency before administration



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Storage: Store at room temperature and protect from light. Dark yellow color indicates decomposition. Fluorouracil is stable in polypropylene syringes, and stable in PVC reservoirs for infusion pump usage for 12 days. Fluorouracil may adsorb to glass surfaces. It is stable in cellulose nitrate/acetate ester or Teflon filters.

5.3.3 Source

Locally obtained commercial supplies of Fluorouracil should be used. Because commercial drug will be used, accounting for Fluorouracil drug supplies is not specifically required in this study.

5.3.4 Safety Profile

Hematologic and gastrointestinal side effects are most frequently associated with fluorouracil. Hematologic toxicities of fluorouracil are leukopenia, granulocytopenia (9-14 days), thrombocytopenia (7-14 days), and anemia. Stomatitis, gastrointestinal ulceration and bleeding, and diarrhea are commonly seen gastrointestinal side effects of fluorouracil. Nausea and vomiting, effects on the skin including rashes and hyperpigmentation, alopecia, ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischemia have been reported. A complete listing of toxicities can be found in the fluorouracil package insert.

Drug Interactions

Allopurinol may decrease efficacy of fluorouracil. Leucovorin enhances cytotoxicity of fluorouracil by forming a more stable tertiary complex with thymidylate synthase.

5.4 LEUCOVORIN

Please see the package insert for complete details and further information.

5.4.1 Description

Leucovorin calcium is commercially available, and is a stable reduced formyl derivative and the active form of folic acid. The following products are available: Immunex (formally available from Lederle): 50 mg vial, 100 mg vial, 350 mg vial. Burroughs-Wellcome (Wellcovorin®): 100 mg vial. Chiron Therapeutics: 50 mg vial, and 100 mg vial.

5.4.2 Preparation and Administration

Leucovorin may be reconstituted with Bacteriostatic Water for Injection (BWI). Reconstitute 50 mg with 5 ml BWI, 100 mg vial with 10 ml BWI. Both of these will yield a solution of 10 mg/ml. Reconstitute 350 mg vial with 17 ml BWI to yield a solution of 20 mg/ml. Use bacteriostatic water only with doses < 10 mg/m². Leucovorin will be administered intravenously over 30 minutes prior to fluorouracil administration.

Storage: Unreconstituted vials are stored at room temperature and protected from light. The reconstituted 10 mg/ml or 20 mg/ml solution is stable for at least 7 days at room temperature.



5.4.3 Source

For this study, locally obtained commercial supplies of Leucovorin should be used. Because commercial drug will be used, accounting for leucovorin drug supplies is not specifically required in this study.

5.4.4 Safety Profile

The only adverse reaction for leucovorin is a rare report of allergic reactions to parenteral injections of leucovorin. This is extremely uncommon.

5.5 TRASTUZUMAB

Please see the package insert for complete details and further information.

5.5.1 Description

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay ($K_d = 5 \text{ nM}$) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of trastuzumab contains 400 mg of trastuzumab, 9.9 mg of L-histidine HCl, 6.4 mg of L-histidine, 400 mg of α, α -trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6.

5.5.2 Preparation, Administration, and Storage

Dosage

Trastuzumab will be administered on q2wk dosing schedule, with initial loading dose of 6 mg/kg as a 90 minute infusion, followed by trastuzumab 4 mg/kg q2wk, administered as a 30 minute infusion if the initial loading dose was well tolerated. Eligible HER2-negative patients will receive mDCF alone

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

Preparation

Use appropriate aseptic technique. Each vial of trastuzumab should be reconstituted with 20 mL of BWI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL trastuzumab. Immediately upon reconstitution with



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

BWFI, the vial of trastuzumab must be labeled in the area marked “Do not use after” with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). Trastuzumab which has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided.

Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. DEXTROSE (5%) SOLUTION SHOULD NOT BE USED. Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. Trastuzumab administration should precede chemotherapy administration. Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated subsequent doses of 4 mg/kg trastuzumab q2wk may be administered over 30 minutes. If chemotherapy is discontinued during the treatment phase, either because of completing a planned number of cycles of chemotherapy, or because of chemotherapy related toxicity, trastuzumab should be continued until disease progression or unacceptable toxicity related specifically to trastuzumab.

Trastuzumab should not be mixed or diluted with other rugs. Trastuzumab infusions should not be administered or mixed with Dextrose solutions.

Storage

Vials of trastuzumab are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. **DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.**

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted Trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

5.5.3 Source

Genentech will provide trastuzumab free of charge to the patient.

5.5.4 Safety Profile

Cardiac Dysfunction: Signs and symptoms of cardiac dysfunction were observed in a number of women who received trastuzumab alone or in combination with chemotherapy, most often anthracycline based treatment. Cardiac dysfunction was observed most frequently among patients who received trastuzumab plus AC chemotherapy (28%), compared with those who received AC alone (7%), trastuzumab plus paclitaxel (11%), paclitaxel alone (1%), or trastuzumab alone (7%). Severe disability or fatal outcome due to cardiac dysfunction was observed in ~1% of all patients. The signs and symptoms of cardiac dysfunction usually responded to treatment.

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or ECHO prior to entry into the study. Only patients with normal LVEF should be entered into this study. All should have regular cardiac monitoring throughout the study. It is suggested that the first evaluation occur 4 months after the initiation of trastuzumab therapy. During the course of trastuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

Management of Symptomatic Cardiac Changes. Patients who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides, as needed; HFSA guidelines). Consideration should be given to obtaining a cardiac consultation.

If the symptoms of CHF resolve with treatment, and cardiac function improves, Trastuzumab may be continued after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from Trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If Trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) is strongly recommended until cardiac function has normalized.

Management of Asymptomatic Decreases in LVEF. Trastuzumab may be continued in patients experiencing an asymptomatic absolute decrease in LVEF of <20 percentage points from baseline, when the ejection fraction remains within the imaging center's range of normal limits. Repeat measures of LVEF should be obtained using the methodology selected at baseline. Close follow-up of such patients is recommended. Patients with an asymptomatic absolute decrease in LVEF of >20 percentage points or an ejection fraction below the range of normal limits, should have trastuzumab held and be considered for treatment of incipient CHF as prescribed by the HFSA (e.g., ACE



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides, as needed; see HFSA guidelines). In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study to confirm an observed decline. Repeat measures of LVEF should be obtained using the same methodology selected at baseline. If trastuzumab has been discontinued for an asymptomatic decline in LVEF, a repeat measure of LVEF will be obtained in 1 month to determine if the decline has resolved.

If cardiac function improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from Trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO), using the methodology selected at baseline, is strongly recommended until cardiac function has normalized.

Infusion Associated Symptoms: During the first infusion with Trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Trastuzumab infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

Serious Infusion-Associated Events. Serious adverse reactions to Trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of Trastuzumab as indicated.

Hematologic Toxicity and Neutropenic Infections: In the clinical trials, an increased incidence of anemia was observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of trastuzumab therapy.

In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Secondary acute leukemia or myelodysplastic syndrome has been reported in 4 of approximately 1200 patients who participated in trastuzumab clinical trials. Patients treated with chemotherapeutic agents are known to be at increased risk for secondary leukemia. The observed incidence of leukemia among Trastuzumab treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer. Therefore, the contribution of Trastuzumab to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

Management of Hematologic Toxicities. Care should be taken to carefully monitor the patient's hematologic status throughout the course of the trial. Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists (ASCO) guidelines.

5.6 CONCOMITANT MEDICATIONS

5.6.1 Anticancer or experimental therapy

No other concurrent chemotherapy or anti-cancer therapy of any kind is permitted while the patient is receiving study treatment.

5.6.2 Hematopoietic Growth Factors

Colony-Stimulating Factor (G-CSF, GM-CSF):

ARM A

After cycle 1 (eg. 3 treatments of mDCF), the use of colony-stimulating factor is permitted at the discretion of the treating physician. However, the administration of G-CSF in a patient who has experienced neutropenia, or its therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, fever/neutropenia, etc. is recommended.

ARM B

Beginning with cycle 1, pegfilgrastim (Neulasta®) is given subcutaneous 6 mg on either day 8, 9, or 10 of every cycle. This is the preferred hematopoietic growth factor. Alternatively, filgrastim (Neupogen®) may be given by subcutaneous injection from day 10 to 17. The optimal dose is as follows:

Body weight \leq 60 kg: filgrastim 300 mcg subcut daily x 7 days

Body weight $>$ 60 kg: filgrastim 480 mcg subcut daily x 7 days

Epoetin alfa (Procrit® or Aranesp®):

Use of epoetin alfa is permitted at the discretion of the treating physician.

5.6.3 Antiemetics and Premedications



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

ARM A

The mDCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
evening - Dexamethasone 8 mg orally (pm)
- Day 3: *pre - Cisplatin* Dexamethasone 8 mg orally or IV
Palonosetron 250 mcg IVPB
Aprepitant 125 mg po
- Day 4 and 5: Dexamethasone 4 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

ARM B

The DCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
pre-Cisplatin - Palonosetron 250 mcg IVPB
Aprepitant 125 mg po

evening - Dexamethasone 8 mg orally (pm)
- Day 2 and 3: Dexamethasone 8 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

Both ARMS

For patients who have persistent nausea or vomiting with palonosetron, granisetron 2mg po or granisetron 1mg IV may be substituted prior to chemotherapy, and then granisetron 2 mg po may be continued on days 2 and 3. Metoclopramide 5-10 mg po every 4 hours and/or prochlorperazine 10 mg every 6 hours may be used as needed for nausea/vomiting,



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

and lorazepam may be used for anticipatory nausea/vomiting or anxiety related nausea/vomiting.

For patients who have no evidence of delayed emesis, the prophylaxis may be discontinued as tolerated as per the treating physician.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

This is a multicenter phase II study coordinated by Memorial Sloan-Kettering Cancer Center (MSKCC).

6.1 Subject Inclusion Criteria

1. Patients must have histologically or cytologically confirmed metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma. GEJ adenocarcinoma may be classified according to Siewert's classification type I, II, or III[43].
2. Histological documentation of local recurrence or metastasis is strongly encouraged, unless the risk of such a procedure outweighs the potential benefit of confirming the metastatic disease.
 - If no histologic confirmation, then the metastases or recurrence will require documentation by a 2nd radiographic procedure (eg. PET/CT scan or MRI in addition to the CT scan). If the imaging procedure does not confirm recurrent or metastatic disease, biopsy confirmation will be required.
3. Patients must have disease that can be evaluated radiographically. This may be measurable disease or non-measurable disease. Measurable disease is defined as that which can be measured in at least one dimension as ≥ 20 mm with conventional techniques, or ≥ 10 mm by high resolution imaging. Disease that is identified on radiology studies, but does not meet the criteria for measurable disease, is considered non-measurable— see section 12.1.1 for further details.
4. Patients may have received no prior chemotherapy for metastatic or unresectable disease. Patients may have received prior adjuvant therapy (chemotherapy and/or chemoradiation) if more than 6 months have elapsed between the end of adjuvant therapy and registration. Patients may not have received prior docetaxel or cisplatin.
5. Age 18 years or older.
6. Karnofsky performance status $\geq 70\%$ (ECOG performance status 0-1).
7. Peripheral neuropathy \leq grade 1



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

8. Hematologic (minimal values)

- White blood cell count $\geq 3000/\text{mm}^3$
- Absolute neutrophil count $\geq 1500 \text{ cells}/\text{mm}^3$
- Hemoglobin $\geq 9.0 \text{ g/dl}$
- Platelet count $\geq 100,000 / \text{mm}^3$

9. Hepatic (minimal values)

- Total bilirubin ≤ 1.5
- AST and ALT and Alkaline phosphatase must be within the eligible range as described by the table below. In determining eligibility, the more abnormal of the two values (AST or ALT) should be used. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

| | AST or ALT: | | | |
|------------------------------|-------------------|--|--|-------------------|
| ALK PHOS: | $\leq \text{ULN}$ | $>1x \text{ but } \leq 1.5x \text{ ULN}$ | $>1.5x \text{ but } \leq 5x \text{ ULN}$ | $>5x \text{ ULN}$ |
| $\leq \text{ULN}$ | Eligible | Eligible | Eligible | Ineligible |
| $>1x \text{ but } \leq 2.5x$ | Eligible | Eligible | Ineligible | Ineligible |
| $>2.5x \text{ but } \leq 5x$ | Eligible | Ineligible | Ineligible | Ineligible |
| $>5x \text{ ULN}$ | Ineligible | Ineligible | Ineligible | Ineligible |

10. Kidney function (minimal values)

serum creatinine $\leq 1.5 \text{ mg/dl}^*$

* if serum creatinine is 1.2-1.5 mg/dl, the creatinine clearance (either measured or calculated) must be 50 ml/min or greater.

11. The patient has a PT (INR) ≤ 1.5 and an PTT ≤ 3 seconds above the upper limits of normal if the patient is not on anticoagulation. If a patient is on full-dose anticoagulants, the following criteria should be met for enrollment:

- a. the patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or on stable dose of LMW heparin.
- b. the patient must not have active bleeding or pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels, known varices).

12. Women of childbearing potential have a negative pregnancy test.

13. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter.

14. Ability to understand informed consent and signing of written informed consent document prior to initiation of protocol therapy.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

15. Patients must have HER2-positive (FISH+ or IHC 3+) metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma to be eligible for trastuzumab. For the purposes of this protocol, FISH+ is defined as HER2:CEP17 ratio ≥ 2.0 . Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. $<10\%$. FISH+ defined as >2 HER2:CEP17. Note: Samples will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.
16. Patients who are receiving trastuzumab must have a left ventricular ejection fraction of $\geq 50\%$.

6.2 Subject Exclusion Criteria

1. Patients who have received previous chemotherapy for the treatment of metastatic or unresectable gastric or GEJ adenocarcinoma are ineligible. Patients who have received previous pre- or post-operative chemotherapy or chemoradiation are ineligible if therapy was completed less than 6 months prior to study registration. Patients must have recovered from adverse events from any previous therapy.
2. Patients who have received previous docetaxel or cisplatin.
3. Patients with a history of another neoplastic disease within the past three years, excluding basal cell carcinoma of the skin, cervical carcinoma in situ, or nonmetastatic prostate cancer.
4. Patients with brain or central nervous system metastases, including leptomeningeal disease.
5. Pregnant (positive pregnancy test) or breast feeding.
6. Serious, non-healing wound, ulcer, or bone fracture.
7. Significant cardiac disease as defined as:
unstable angina, New York Heart Association (NYHA) grade II or greater, congestive heart failure, history of myocardial infarction within 6 months
8. Evidence of bleeding diathesis or coagulopathy.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

9. History of a stroke or CVA within 6 months.
10. Clinically significant peripheral vascular disease.
11. Clinically significant hearing loss or ringing in the ears.
12. Patients with a history of severe hypersensitivity reaction to Taxotere® or other drugs formulated with polysorbate 80.
13. Inability to comply with study and/or follow-up procedures.
14. Patients with any other medical condition or reason, in that investigator’s opinion, makes the patient unstable to participate in a clinical trial.
15. For patients who are Her2 positive and will be treated on the trastuzumab + mDCF cohort, prior trastuzumab treatment is not allowed.
16. For patients who are Her2 positive and will be treated on the trastuzumab+mDCF cohort, left ventricular function <50%

7.0 RECRUITMENT PLAN

This study will be available to all patients seen at participating institutions who meet the eligibility criteria as outlined in section 6.0. Memorial Hospital is a referral center for this disease. In addition, the study will be placed on the MSKCC Website as well as available at the MSKCC satellite centers to maximize patient recruitment. Patients will be identified from medical oncology clinics for treatment of their disease.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study. The proposed study population is provided in the table below.

| Ethnic Category | Sex/ Gender | | | Total |
|--|-------------|-------|---------|-------|
| | Females | Males | Unknown | |
| Hispanic or Latino | 8 | 10 | | 18 |
| Not Hispanic or Latino | 28 | 62 | | 90 |
| Unknown | | | | |
| Ethnic Category: Total of all subjects | 36 | 72 | | 108 |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| Racial Category | | | | |
|---|----|----|--|-----|
| American Indian or Alaskan Native | 0 | 0 | | |
| Asian | 7 | 10 | | 17 |
| Black or African American | 4 | 8 | | 12 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | | |
| White | 23 | 52 | | 75 |
| More than one race | 0 | 0 | | 0 |
| Unknown | 2 | 2 | | 4 |
| Racial Category: Total of all subjects | 36 | 72 | | 108 |

Note, the results of the recent ToGA study demonstrate that for HER2 positive gastric cancer, patients have a survival benefit with the addition of trastuzumab to chemotherapy (see Sect 3.3.4). We are therefore amending the study to include a separate cohort of 35 patients who are Her2 positive to receive mDCF + trastuzumab (Trastuzumab cohort)

| Recruitment Expectations Per Site | |
|---|----|
| Memorial Sloan Kettering Cancer Center | 10 |
| City of Hope | 5 |
| University of Pittsburgh | 5 |
| Queens Cancer Center | 2 |
| Long Island Jewish Medical Center | 2 |
| University Hospital of Cleveland | 2 |
| Weill Medical College of Cornell University | 2 |
| Medical College of Wisconsin | 2 |
| Piedmont Hospital Research Institute (PHRI) | 2 |
| Nebraska Cancer Specialists | 2 |
| Memorial Cancer Institute | 1 |
| Total | 35 |

8.0 PRETREATMENT EVALUATION

To be completed within 14 days of starting therapy:

1. History and physical examination, including height, weight, calculated body surface area, vital signs, and performance status. See Appendix A for a conversion between Karnofsky and ECOG performance status.
2. Serum pregnancy test for all women of childbearing potential within 14 days of starting therapy. If the test result is positive, the patient will not be allowed to participate in this study.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

3. PA and lateral chest radiographs. Chest radiographs may be omitted if a baseline CT scan of the chest is available in the same time frame.
4. Routine urinalysis.
5. CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, coagulation studies, and tumor markers as they are available.
6. EORTC QLQ-C30 questionnaire.

To be completed within 30 days of starting therapy:

7. A 12-lead Electrocardiogram (ECG).
8. Documentation of all measurable or non-measurable disease parameters including radiographic imaging procedures within four weeks of study entry, and measurement of biochemical markers of disease (if applicable) within four weeks of study entry. The RECIST criteria as defined by CTEP (<http://ctep.info.nih.gov/Policies>) define measurable and non-measurable disease.
9. Signed informed consent for study participation.
10. Audiogram if clinically indicated.
11. CT scan of the chest, abdomen and pelvis.
12. Baseline PET/CT for staging.
July 2009 Addendum: Collaborating centers that are either not able to perform the PET/CT at baseline (i.e., denied authorization from insurance carriers) or have opted not to participate in the Week 3 PET/CT may forgo performing the scan at baseline.

To be completed at any time prior to starting therapy or during study:

13. Placement of a MediPort, Hickman catheter or similar indwelling catheter for administration of continuous infusional fluorouracil chemotherapy.
14. Paraffin stored tumor block or 15 unstained slides sent to MSKCC for planned future immunohistochemistry studies.
15. A baseline assessment of left ventricular ejection fraction (usually cardiac ECHO or MUGA scan).



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

9.0 TREATMENT/INTERVENTION PLAN

9.1 CHEMOTHERAPY ADMINISTRATION

Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 or 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg* | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg.

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments).

Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments).

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

A given treatment may be moved +/- 14 days for specific administrative reasons, in particular clinic closure for holidays. Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter. Therapy will be administered in an outpatient setting, under the supervision of a physician and/or chemotherapy nurse, as is standard for chemotherapy administration at the treating institution.

After 6 months of therapy, cisplatin, docetaxel, and/or fluorouracil may be discontinued at the discretion of the treating physician. Prior to discontinuing therapy, the treating physician will discuss in detail with the protocol PI. Patients without disease progression may resume chemotherapy at the discretion of the treating physician, or with progression if they had more than a 6 month treatment free interval.

Expected adverse events are described in Section 11.0. No investigational or commercial agents or therapies other than those described above may be administered with the intent to treat the patient's malignancy.

Clinical evaluation: All assessments may be performed within one day of the planned treatment.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

ARM A – Modified DCF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of cycle one (e.g. on day 1, day 15, and day 29 of cycle 1). In cycle 2 and all subsequent cycles, a physician evaluation (e.g. physical examination and toxicity assessment) will be performed prior to treatment on day 1 and day 29 treatments. Additional nurse or physician visits will be at the discretion of the treating physician. It is encouraged that an oncology nurse toxicity evaluation be performed prior to each treatment, especially if the patient is not assessed by a physician.

Patients treated with mDCF plus trastuzumab therapy should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain).

ARM B – Parent DCF with G-CSF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of every cycle.

Laboratory evaluation:

ARM A – Modified DCF

On or within 1 day of the beginning of each cycle, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, tumor markers. A CBC with differential and platelet count is required prior to each subsequent treatment (eg. day 15 and day 29). A BUN and Creatinine is required before the day 15 treatment (treatment #2), and a serum chemistry (electrolytes, BUN, Creatinine, glucose) is required before each day 29 treatment (#3). LFTs are required before each treatment (#1, #2 and #3) of cycle 1, and before treatment #1 and #3 for each subsequent cycle. Any patient with excessive LFTs abnormalities (see section 9.3) will require repeat LFTs prior to the next docetaxel administration.

ARM B – Parent DCF with G-CSF

On or within 1 day of the beginning of each treatment, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers are required.

Radiology evaluation: For both treatment arms, radiographic studies upon which tumor measurements were made will be repeated every cycle (six week intervals for most patients) for 6 cycles, and then after every two cycles of therapy (e.g. after cycles 1, 2, 3, 4, 5, 6, 8, 10, 12 etc.), to rule out progression of disease and to determine response for measurable disease.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients will remain on study until disease progression, patient withdrawal, unacceptable toxicity despite dose attenuation, or if the treating physician deems it is in the best interest of the patient following discussion with the principal investigator. Tolerability of this regimen will be determined from blood test results and toxicity assessment.

Cardiac evaluation: For patients who are Her2 positive and will be treated on the trastuzumab+mDCF cohort left ventricular function will be assessed with echocardiograms or MUGA every 12 weeks while on study.

A table of events to take place on this study is shown in section 10.0.

9.2 SUPPORTIVE CARE GUIDELINES

Concurrent supportive care is not restricted, including the use of narcotics for pain control and antiemetics and glucocorticoids for control of nausea, and antidiarrheal agents. Neither concurrent chemotherapy, immunotherapy, nor radiation therapy is permitted while on study.

Hematopoietic Growth Factors

Colony-Stimulating Factor (G-CSF, GM-CSF):

ARM A

Use of colony-stimulating factor is permitted at the discretion of the treating physician. However, the administration of G-CSF in a patient who has experienced neutropenia, or its therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, fever/neutropenia, etc. is recommended.

ARM B

Beginning with cycle 1, pegfilgrastim (Neulasta®) is given subcutaneous 6 mg on either day 8, 9, or 10 of every cycle. This is the preferred hematopoietic growth factor. Alternatively, filgrastim (Neupogen®) may be given by subcutaneous injection from day 10 to 17. The optimal dose is as follows:

Body weight \leq 60 kg: filgrastim 300 mcg subcut daily x 7 days

Body weight $>$ 60 kg: filgrastim 480 mcg subcut daily x 7 days

Epoetin alfa (Procrit® or Aranesp®):

Use of epoetin alfa is permitted at the discretion of the treating physician.

Antiemetics and Premedications

ARM A

The mDCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
evening - Dexamethasone 8 mg orally (pm)
- Day 3: *pre - Cisplatin* Dexamethasone 8 mg orally or IV
Palonosetron 250 mcg IVPB
Aprepitant 125 mg po
- Day 4 and 5: Dexamethasone 4 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

ARM B

The DCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
pre-Cisplatin - Palonosetron 250 mcg IVPB
Aprepitant 125 mg po

evening - Dexamethasone 8 mg orally (pm)
- Day 2 and 3: Dexamethasone 8 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

Both ARMS

For patients who have persistent nausea or vomiting with palonosetron, granisetron 2mg po or granisetron 1mg IV may be substituted prior to chemotherapy, and then granisetron 2 mg po may be continued on days 2 and 3. Metoclopramide 5-10 mg po every 4 hours and/or prochlorperazine 10 mg every 6 hours may be used as needed for nausea/vomiting, and lorazepam may be used for anticipatory nausea/vomiting or anxiety related nausea/vomiting.

For patients who have no evidence of delayed emesis, the prophylaxis may be discontinued as tolerated as per the treating physician.



9.3 TREATMENT PARAMETERS, DOSE DELAYS AND MODIFICATIONS

9.3.1 Treatment Parameters

1. Parameters for initiation of therapy (day 1) for cycle 1 are as follows:

- White blood cell count $\geq 3000/\text{mm}^3$
- Absolute neutrophil count $\geq 1500/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Hemoglobin ≥ 9.0 g/dl
- Creatinine ≤ 1.5 mg/dl
- Total Bilirubin ≤ 1.5 mg/dl

AST and ALT and Alkaline phosphatase must be within the treatment range as described by the table below. In determining acceptable levels for treatment, the more abnormal of the two values (AST or ALT) should be used. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

| | AST or ALT: | | | |
|---------------------|-------------|-------------------------|-------------------------|-----------|
| ALK PHOS: | \leq ULN | $>1x$ but $\leq 2x$ ULN | $>2x$ but $\leq 5x$ ULN | $>5x$ ULN |
| \leq ULN | Yes | Yes | Yes | No |
| $>1x$ but $\leq 3x$ | Yes | Yes | Yes | No |
| $>3x$ but $\leq 5x$ | Yes | Yes | No | No |
| $\geq 5x$ ULN | No | No | No | No |

2. Parameters for all subsequent treatments:

- Absolute Neutrophil count $\geq 1000/\text{mm}^3$
- Platelet count $\geq 75,000/\text{mm}^3$.
- Creatinine ≤ 1.8 mg/dl
 - for Creatinine > 1.8 mg/dl and
- Total bilirubin ≤ 1.5 (should be drawn prior to treatment on week 1, week 3, and week 5 of cycle 1 and again prior to treatment on week 1 and week 5 of every subsequent cycle beginning with cycle 2 (ie. minimum of every 4 weeks).)
 - For total bilirubin ≥ 1.5 but $\leq 2x$ ULN, docetaxel alone may be held.
 - For total bilirubin $\geq 2x$ ULN, hold all three drugs (docetaxel, cisplatin, fluorouracil)
- AST/ALT* and Alkaline Phosphatase as per table below (for docetaxel dosing):

| | AST or ALT: | | | |
|---------------------|-------------|-------------------------|-------------------------|-----------|
| ALK PHOS: | \leq ULN | $>1x$ but $\leq 2x$ ULN | $>2x$ but $\leq 5x$ ULN | $>5x$ ULN |
| \leq ULN | Full Dose | Full Dose | Full Dose | Hold |
| $>1x$ but $\leq 3x$ | Full Dose | Full Dose | Reduce Dose | Hold |
| $>3x$ but $\leq 5x$ | Full Dose | Reduce Dose | Hold | Hold |
| $>5x$ ULN | Hold | Hold | Hold | Hold |



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

** ARM A: LFTs should be drawn prior to treatment on week 1, week 3, and week 5 of cycle 1 and again prior to treatment on week 1 and week 5 of every subsequent cycle beginning with cycle 2 (ie. minimum of every 4 weeks). If LFTs are drawn prior to treatment on week 3, the above LFT treatment parameters must still be met. Both AST and ALT should be drawn. If LFTs are abnormal prior to any treatment, they should be drawn prior to the next docetaxel treatment. The more abnormal of the two values (AST or ALT) should be used in determining the dose of docetaxel.*

** ARM B: LFTs should be drawn prior to each 3-week cycle*

Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator. If above parameters are not met, hold until recovered, maximum 28 days, then retreat as per section 9.3.2 Dose Delays and Modifications. “Recovered” is defined as meeting the treatment parameters for #2 above with the exception that the ANC must be at least $1500/\text{mm}^3$ ($\text{ANC} \geq 1500/\text{mm}^3$).

9.3.2 Chemotherapy Dose Delays and Modifications

Chemotherapy will be held for grade 3 or 4 non-hematologic toxicity (with the exception of grade 3 electrolyte abnormalities) or for not meeting treatment parameters as described above on the day of treatment. If the toxicity has resolved and the patient meets treatment parameters but experienced interval toxicity, then for the purposes of determining dose reductions, the grade of toxicity should be that seen despite maximal medical management (i.e. intensive loperamide or tincture of opium for diarrhea). If multiple toxicities are seen the dose administered for a particular drug should be based on the most severe toxicity noted. In general, when multiple toxicities are experienced that can result in the dose reduction of multiple drugs, reducing multiple drugs at one time is the preferred approach. Treatment may resume when the toxicity has resolved to \leq grade 2, except as indicated below.

Generally, when therapy is held for chemotherapy related toxicity, all three drugs (cisplatin, docetaxel, and fluorouracil) will be held. For hepatotoxicity, docetaxel alone should be held (ie. Total bilirubin \geq ULN but \leq 2x ULN, and AST/ALT and Alkphos as per table above) and cisplatin and fluorouracil may continue without treatment delay. For an elevated creatinine or for ototoxicity (see below criteria), cisplatin alone may be held and the patient may continue with docetaxel and fluorouracil without treatment delay. If all three drugs are held for more than 4 weeks for toxicity, patients will be taken off study, unless there is a clinical benefit. If there is a clinical benefit, patients may be retreated at a lower dose after resolution of toxicity to \leq NCI-CTCAE v3.0 grade 2, except as indicated below. Cisplatin, docetaxel, and fluorouracil may each be dose attenuated, either in combination, or individually.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

ARM A: CHEMOTHERAPY DOSE ATTENUATION TABLE

| | Dose level 0 (mg/m ²) | Dose level -1 (mg/m ²) | Dose level -2 (mg/m ²) |
|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------|
| Docetaxel | 40 | 30 | 20 |
| Cisplatin | 40 | 30 | 20 |
| Fluorouracil (IVP)/ Leucovorin | 400/ 400 | 300/ 300 | 200/ 200 |
| Fluorouracil IVCI / day | 1000 | 800 | 600 |

ARM B: CHEMOTHERAPY DOSE ATTENUATION TABLE

| | Dose level 0 (mg/m ²) | Dose level -1 (mg/m ²) | Dose level -2 (mg/m ²) |
|-------------------------|-----------------------------------|------------------------------------|------------------------------------|
| Docetaxel | 75 | 60 | 50 |
| Cisplatin | 75 | 60 | 50 |
| Fluorouracil IVCI / day | 750 | 600 | 500 |

Dose attenuations will be based on toxicity as described below:

Neutropenia

- Docetaxel dose attenuation by one dose level may occur for any treatment delay due to neutropenia (i.e. ANC < 1000 /cc on a treatment day following Cycle 1 Week 1).
- For ARM A,, Neulasta or Neupogen (GCSF) should be given for subsequent treatments following any treatment delay due to neutropenia if a dose reduction is not required and not pursued. The recommended treatment is Neulasta 6 mg subcutaneously on day 3, day 4, or day 5 of the treatment cycle or neupogen (GCSF) for 3 to 5 days from day 9 to day 13.
- Grade 3 and Grade 4 neutropenia with recovery prior to next planned cycle do not require a dose attenuation in docetaxel with the following exceptions:
 - Grade 4, afebrile neutropenia ≥ 7 days
 - Grade 3 or 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period)
- Cisplatin and fluorouracil may be dose attenuated by one dose level at the treating physicians' discretion in addition to docetaxel dose attenuation, particularly with persistent delays due to neutropenia.

Thrombocytopenia

- For treatment delay due to thrombocytopenia (i.e. platelet count < 75,000/cc), reduce docetaxel by one dose level.
- For any platelet count of ≤ 50,000/cc, reduce docetaxel by one dose level.

Nausea/Vomiting

- Grade 1 nausea/vomiting does not require a dose reduction or treatment delay.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

- Grade 2 nausea/vomiting – hold treatment for 1 week. Reduce cisplatin by 1 dose level for persistent grade 2 nausea/ vomiting (eg. lasting for more than 5 days).
- For Grade 3 or 4 nausea/ vomiting, reduce cisplatin dose by one dose level. Docetaxel and fluorouracil may also be dose attenuated by one dose level at the treating physicians discretion.

Anorexia

- Grade 1 or 2 anorexia does not require a dose reduction
- For grade 3 or 4 anorexia, reduce cisplatin and docetaxel by one dose level.

Stomatitis

- If stomatitis is present on day 1 of any cycle, treatment should be held until the stomatitis has resolved.
- For ARM A:
 - If stomatitis is \leq grade 1 prior to treatment #2 or #3 of any cycle, treat at current dose.
 - For interval grade 2 stomatitis prior to treatment #2 or #3, reduce fluorouracil infusion by one dose level without treatment delay. For a subsequent grade 2 stomatitis event, reduce docetaxel by one dose level.
- For ARM B:
 - For interval grade 2 stomatitis that completely resolves prior to the next cycle, reduce fluorouracil infusion by one dose level without treatment delay. For a subsequent grade 2 stomatitis event, reduce docetaxel by one dose level.
- If Grade 3 or 4 stomatitis occurs at any time, hold chemotherapy until resolution to \leq grade 1, and then retreat with docetaxel and fluorouracil each reduced by one dose level.

Neurotoxicity

- If neuropathy \geq grade 2 is present on day 1 of any cycle, treatment should be held until neuropathy improves to \leq grade 1.
- For ARM A (treatment #2 and 3 of each cycle):
 - If neuropathy is \leq grade 1 on treatment #2 or #3 of any cycle, treat at current dose of all chemotherapy drugs.
 - If neuropathy is grade 2 on treatment #2 or #3, reduce docetaxel by one dose level and treat without delay.
- For ARM B (treatment #2 of each cycle):
 - If neuropathy is \leq grade 1 on treatment #2, treat at current dose of all chemotherapy drugs.
 - If neuropathy is grade 2 on treatment #2, reduce docetaxel by one dose level and treat without delay.
- For Grade 3 or 4 neuropathy, treatment should be held until neuropathy returns to grade \leq 1. Reduce cisplatin and docetaxel each by one dose level.

Kidney

- Serum creatinine must be \leq 1.5 mg/dl to initiate therapy



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- For each subsequent treatment, the serum creatinine must be ≤ 1.8 mg/dl to continue treatment at the current dose level.
- If serum creatinine is > 1.8 but ≤ 2 mg/dl, administer cisplatin at a single reduced dose level. A treatment delay is not required. Subsequent treatments may occur without further cisplatin dose attenuation if the serum creatinine remains stable at > 1.8 but ≤ 2 mg/dl.
- If serum creatinine is > 2.0 mg/dl, cisplatin will be held. Docetaxel and fluorouracil may be administered without treatment delay at the treating physicians discretion.
- Up to a 6-week treatment delay in cisplatin will be allowed. If the serum creatinine has not returned to less than 2.0 mg/dl within 6 weeks, then cisplatin will be discontinued.
- Patients should be euvolemic for the determination of serum creatinine.
- If the value of the serum creatinine is > 1.8 mg/dl the value may be confirmed by a second serum creatinine after hydration. Treatment may resume within the next day.
- Creatinine clearance will not be used for dose adjustments.

Diarrhea

- Grade 1 diarrhea dose not require treatment delay or dose reduction.
- For grade 2 diarrhea, hold treatment by 1 week.
- For grade 3 or 4 diarrhea, reduce fluorouracil by 1 dose level. Cisplatin may be dose reduced as well, at the treating physicians discretion.

Ototoxicity

- For grade 1 or 2 ototoxicity, no dose reduction in cisplatin is required.
- For grade 3 or 4 ototoxicity, hold cisplatin until it resolves to \leq grade 1, and then resume therapy with cisplatin dose reduced by one dose level.

Trastuzumab related cardiac dysfunction:

Symptomatic CHF

- Hold trastuzumab, refer to cardiology for treatment (e.g., ACE inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides).
- If the symptoms of CHF resolve with treatment, and cardiac function improves, trastuzumab may be continued after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction.
- If trastuzumab is restarted, cardiac function should be monitored with echocardiogram every cycle

Asymptomatic drop in LVEF

- Trastuzumab may be continued in patients experiencing an asymptomatic absolute decrease in LVEF of < 20 percentage points from baseline, when the ejection fraction remains $\geq 50\%$. Such patients should be monitored with echocardiograms every cycle.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Patients with an asymptomatic absolute decrease in LVEF of ≥ 20 percentage points or ejection fraction $< 50\%$, should have trastuzumab held. Consider cardiology referral for treatment of incipient CHF.
- If trastuzumab is discontinued for an asymptomatic decline in LVEF, a repeat echocardiogram will be obtained in 1 month to determine if the decline has resolved.
- If cardiac function improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction.

Hypersensitivity Reactions

- Trastuzumab treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.
- Docetaxel treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY

| Severity of Symptoms | Treatment Guidelines |
|--|--|
| <u>Mild</u> symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash | <ul style="list-style-type: none"> · consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete Taxotere infusion at the initial planned rate |
| <u>Moderate</u> symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg | <ul style="list-style-type: none"> · interrupt Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms · resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (eg. <i>infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, then finally, resume at the initial planned rate.</i>) · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, (eg. <i>infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, and finally, administer at the initial planned rate.</i>) |
| <u>Severe</u> symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema | <ul style="list-style-type: none"> · immediately discontinue Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed. |



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

| | |
|---|-------------------------------|
| Anaphylaxis (NCI CTCAE v. 3.0 grade 4 reaction) | NO FURTHER STUDY DRUG THERAPY |
|---|-------------------------------|

Fluid Retention

- There are no dose reductions for fluid retention.
- Patients developing new onset edema or ascites, progression of existing edema or ascites, or another sign of fluid retention (eg. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below:
 - Triamterene/hydrochlorothiazide one capsule po qd up to tid.
 - Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
 - If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.
- Further diuretic therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

Hyperlacrimation

- The following guidelines may be taken for patients experiencing clinically significant hyperlacrimation:
 - Dose reduction in fluorouracil treatment.
 - Withhold docetaxel treatment until resolution.
 - Frequent instillation of artificial tears.
 - Steroid ophthalmic solution starting the day before docetaxel administration in patients without a history of herpetic eye disease.
 - Ophthalmologist consult.

If a dose attenuation is required in any chemotherapy drug that is already at dose level -2, the other chemotherapy drugs may be reduced by one dose level instead. For cumulative toxicity, cisplatin, fluorouracil, leucovorin or docetaxel may be discontinued following discussion with the protocol principal investigator. If more than one grade 3 or 4 event occurred, then the chemotherapy to be dose attenuation should be that of the most severe toxicity.

For patients experiencing intolerable toxicity based on the treating physician's clinical assessment, individual chemotherapy doses may be attenuation following consultation with the Principal Investigator.



9.4 CORRELATIVE STUDIES

9.4.1 To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.

We plan to store pre-therapy paraffin embedded tumor tissue for future tissue based correlative studies. We will plan to examine this tissue bank by immunohistochemistry if markers for disease sensitivity or resistance to docetaxel based therapy is identified in ongoing trials. Any IHC studies performed will be selected for based on clinical significance, feasibility, and reproducibility, in conjunction with a reference pathologist (eg. Laura Tang, MD PhD). We will not require new tissue procurement for research purposes. Prior to tissue use, we will submit a proposal for approval by the MSKCC Human Tissue Utilization Committee.

HER2 testing will be performed in all patients to better characterize HER2-positive gastric cancer in US patients. HER2 testing will be performed by the MSKCC diagnostic molecular laboratory on banked tumor specimens from the patients currently enrolled on the protocol and prospectively on all the patients screened for protocol participation. FISH is performed using FDA-approved ERBB2 (HER2/NEU) PathVysion assay probes and procedure (Abbott-Vysis). IHC staining is performed using FDA-approved anti-Her2/neu Ventana's PATHWAY rabbit monoclonal primary antibody (clone 4B5) directed against the internal domain of the c-erbB-2 oncoprotein (Her2). Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. <10%. FISH+ defined as >2 HER2:CEP17.

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

9.4.2 FDG-PET Response Assessment

The primary aim of this correlative study is to examine the ability of an early FDG-PET/CT scan to predict treatment efficacy. By identifying patients who are progressing early, patients exposure to cytotoxic therapy that is of no therapeutic value can be limited and the associated toxicity can be reduced. As seen in patients who received preoperative chemotherapy, a significant drop from baseline in FDG uptake is associated with an improved pathologic treatment response and improved disease free survival (see Section 3.5.2). However, the challenge in patients with locally advanced, but potentially curable disease is that surgery does cure some patients. Thus, some patients who have a poor FDG-PET response, and an associated poor histopathologic tissue response, may still be cured with surgical resection of their tumor. However, for patients with metastatic or unresectable disease, this is not true. Specifically, we hypothesize that patients with a good FDG-PET response will have RECIST evidence of response at their routine imaging time point and have a longer time to disease progression, when



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

compared with patients with a poor FDG-PET response. If successful, we would be able to identify patients who are not benefiting from current therapy early, thereby allowing patients to minimize toxicity by minimizing exposure to ineffective therapy.

To examine this further, we will perform a 2nd FDG-PET/CT scan on patients with FDG-avid primary tumors. This 2nd scan will be performed during week 3 (following the day 15 treatment, but before week 4 of ARM A, and prior to the 2nd cycle of ARM B) at participating centers. The PET/CT scan is done with the patient fasting for about four to six hours, but water for hydration is allowed. Imaging starts about one hour after intravenous injection of a standard dose of F18-FDG (8 to 15 mCi). Oral CT contrast is also administered for better delineation of the stomach and GI tract.

Collaborating sites will specify at the time of study initiation if they will obtain the week 3 PET/CT scans on all patients who have informative PET/CT scans at baseline.

A low dose spiral CT is performed first, followed by acquisition of the PET images (emission scans only), of the neck, chest, abdomen and pelvis. The total radiation dose involved is about 1 rem (0.5 rem from the CT and 0.5 rem from the PET). Attenuation correction of the PET/CT images is then performed using the CT data. The final PET and CT image data sets are displayed on the fusion software for evaluation.

FDG-PET/CT Data Analysis: All images will be reviewed by a nuclear medicine physician independently and entered into separate data sheets. The PET/CT images will be reviewed in all standard planes (3-dimensional computer display) and a maximum intensity projection. The images will be reviewed together with the CT and the fusion images. Visual analysis of PET/CT data requires the definition of abnormal radiotracer uptake as being greater than background activity (on the attenuation corrected images) and outside of normal anatomic structures, which frequently exhibit various amount of FDG uptake (e.g., ureter, urinary bladder, bowel loops). Individual lesions will be graded on a scale of zero to four where 0 = definitely normal, 1 = probably benign, 2 = equivocal, 3 = probably malignant and 4 = definitely malignant. Semiquantitative analysis of tracer uptake, i.e. the standardized uptake value (SUV) will be done for lesions identified in the visual analysis by positioning of regions of interest (ROI) surrounding them. The SUV will then be calculated as below and entered into the data sheet (see Appendix D). The baseline SUV value for statistical analysis will be the maximum-pixel SUV detected of the primary tumor. $SUV_{BW} = \text{decay corrected activity (mCi/ml)} / \text{injected dose (mCi)} / \text{body weight (kg)}$

9.4.3 Pharmacology and Pharmacodynamics (MSKCC patients only)

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4. Similarly, we hypothesize that inhibition of CYP3A4 by these anti-emetic agents would result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 hours (15 min following the completion of docetaxel)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each of these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

Amendment March 2008:

In our initial pharmacokinetic analysis, we noted a suggestion of a difference in docetaxel pharmacokinetics when co-administered with cisplatin (Arm B) or without cisplatin (Arm A). Pharmacokinetic data are available preliminarily on 13 patients: 8 patients who were randomized to parent DCF (Arm B) in which cisplatin and docetaxel are co-administered on day 1, and 5 patients who were randomized to mDCF(Arm A) in which cisplatin is administered on day 3 and docetaxel is administered on day 1, and . In Arm B, when cisplatin is given concurrently with docetaxel, dose adjusted docetaxel PK are as follows:

AUC_{∞} 74.1 ng*hr/ml/mg/m²
CL 28.9 L/hr/m²
Vdss 27.8 L/m²
T_{1/2} 18.8 hr

When docetaxel is given on day 1 and cisplatin is given on day 3 (mDCF), dose adjusted docetaxel PK are as follows:

AUC_{∞} 46.1 ng*hr/ml/mg/m²
CL 38.1 L/hr/m²
Vd_{ss} 17.1 L/m²
T_{1/2} 12.1 hr

These results appear to demonstrate that the clearance of docetaxel is reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

We would like to expand on these initial findings. Specifically, in up to 6 patients randomized to the parent DCF arm (Arm B), in addition to performing docetaxel pharmacokinetics with cycle 1 treatment (as is already specified in the protocol), we would subsequently repeat docetaxel pharmacokinetics for a single cycle when cisplatin is not administered on the same day as docetaxel. For example, for a single subsequent cycle, we would plan to administer cisplatin on a later date (i.e. day 3) and repeat docetaxel pharmacokinetic sampling. Subsequent therapies would be as per protocol specification.

9.4.4 Volumetric CT Analysis of Response to Therapy

At MSKCC only and in collaboration with Larry Schwartz, MD, we will also initiate an exploratory volumetric CT analysis of Response to therapy. This study will make use of already acquired image data from this clinical trial. No additional human material or CT scans will be needed. The standard CT scan data (acquired either during PET/CT scanning or CT scanning) will be electronically transferred, via the hospital network, from the hospital PACS to the research PACS server, where patient identification information are de-identified. Volumetric CT will be used in an exploratory way to assess tumor response during therapy to compare with RECIST. The volumetric analysis, however, will not affect patient care and will not be communicated to the patient or clinical investigator. To study effects of a wider range of slice thickness on the performance of the segmentation algorithms and reproducibility of tumor measurements, thinner section CT images will be reconstructed with CT raw data acquired for the radiographic assessment in the trial. The volumetric CT technique used in this study may be able to detect asymmetric or small change in tumor size at the level that may not be possible with the conventional uni-dimensional RECIST criteria.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The table below describes the the study plan



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

TABLE 4. STUDY CALENDAR

| | Pre-Study | Cycle 1 | | | | | | Cycle 2 | | | | | | Cycle 3 (a) | Off Study (j) |
|--|-----------|---------|------|------|------|------|------|---------|------|------|------|------|------|-------------|---------------|
| | | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | → | |
| Day Number | | 1 | 8 | 15 | 22 | 29 | 35 | 42 | 49 | 56 | 63 | 70 | 77 | | |
| Informed consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Electrocardiogram | X | | | | | | | | | | | | | | |
| Pregnancy test (h) | X | | | | | | | | | | | | | | |
| Concomitant Meds | X | X | | | | | | X | | | | | | | X |
| Radiology (i) | X | | | | | | X | | | | | | X | | |
| FDG-PET/CT (m) | X | | | X | | | | | | | | | | | |
| Audiology Exam (k) | X | | | | | | | | | | | | | | |
| Tissue Collection | X | | | | | | | | | | | | | | |
| Coagulation | X | | | | | | | | | | | | | | |
| EORTC QLQ-C30 (n) | X | | | | | | X | | | | | | X | | |
| Pharmacology (l) | | X | | | | | | | | | | | | | X |
| ARM A - mDCF | | X | | X | | X | | X | | X | | X | | | X |
| Physical exam | X | X | | X | | X | | X | | | | X | | X | X |
| Toxicity check | X | X | | X | | X | | X | | X | | X | | X | X |
| Vital signs, Weight | X | X | | X | | X | | X | | X | | X | | X | X |
| Performance Status | X | X | | | | | | X | | | | | | X | X |
| CBC w/ diff, Plts | X | X | | X | | X | | X | | X | | X | | X | X |
| Serum chemistry (b) | X | X | | | | X | | X | | | | X | | X | X |
| BUN, Creatinine (c) | | | | X | | | | | | X | | | | | X |
| LFTs (d) | X | X | | X | | X | | X | | | | X | | X | X |
| Total protein, LDH, Alb, Ca, Mg, PO ₄ , tumor markers (e) | X | X | | | | | | X | | | | | | X | X |
| Echocardiogram/MUGA ^o | X | | | | | | | | | | | | X | | |
| ARB B - DCF + G-CSF | | X | | | X | | | X | | | X | | | X | |
| Physical exam | X | X | | X | | | | X | | | X | | | X | X |
| Toxicity check | X | X | | X | | | | X | | | X | | | X | X |
| Vital signs, Weight | X | X | | X | | | | X | | | X | | | X | X |
| Performance Status | X | X | | X | | | | X | | | X | | | X | X |
| CBC w/ diff, Plts | X | X | | X | | | | X | | | X | | | X | X |
| Comprehensive (g) | X | X | | X | | | | X | | | X | | | X | X |

^a Continues as per cycle 2, except the physical exam may be performed at the beginning of every cycle and as necessary and the toxicity check will be performed prior to the week 1 and 5 treatment of every subsequent cycle, and as needed.

^b Bicarbonate, BUN, chloride, creatinine, glucose, potassium, sodium

^d AST (SGOT), ALT (SGPT), Total Bilirubin, Alkaline Phosphatase. Any abnormal LFTs require repeat LFTs prior to subsequent docetaxel therapy. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

^{b, c, d, e, f, g} May be performed on or within 1 day of treatment ^o Tumor markers as available.

^g Comprehensive = serum chemistry + LFTs + total protein, LDH, alb, Ca, Mg, PO₄, and tumor markers as available.

^h For women of childbearing potential ⁱ Includes CT of the chest, abdomen and pelvis within 30 days and a PA and lateral chest x-ray unless a CT of the chest is available within 14 days of starting therapy. Tumor measurements are repeated after every cycle for the first 6 cycles and every 2 cycles thereafter. May be performed earlier at physician discretion. Radiologic documentation of progression is strongly recommended. ^j Patients will be monitored for overall survival following completion of study. Maybe performed by local physicians. ^k As clinically indicated, ^l Pharmacokinetic blood draws for MSKCC patients as per section 9.4.3. ^m FDG-PET/CT scans are performed at baseline, and again during week 3 (following treatment #2 in ARM A, before treatment #2 in ARM B), participating sites only. ⁿ EORTC QLQ-C30 is administered at baseline, 6 weeks, 3 months, 6 months, 9 months, and 12 months. ^o For patients receiving trastuzumab only, echocardiogram/MUGA will be done at baseline and every 12 weeks while on protocol.

10.1 FOR PARTICIPATING SITES



Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

Shipping of Specimen(s):

All sites should ship specimens to MSKCC Principal Investigator:
Yelena Y. Janjigian
Memorial Sloan-Kettering Cancer Center
300 E 66th Street BAIC 1033
New York, NY 10065

- Shipments should be batched.
- A copy of the pathology report and patient signed informed consent should be included with the shipment.
- At the time of shipment, a transmittal documenting patient ID and type of specimen sent should also be electronically submitted to janjigiy@mskcc.org and faxed to the Multicenter Core Project Coordinator (646-227-2482)
- Shipments will not be received on Saturday or Sunday

11.0 TOXICITIES/SIDE EFFECTS

11.1 CISPLATIN

Cumulative nephrotoxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia and hypotension may occur within minutes of cisplatin administration. Other side effects include anorexia, diarrhea, serum electrolyte disturbances (e.g., hyponatremia, hypomagnesemia), vascular toxicities (e.g., myocardial infarction, cerebrovascular accident etc.), renal insufficiency, neurotoxicity, peripheral neuropathy, autonomic neuropathy, muscle cramps, ocular toxicity (optic neuritis, papilledema, cerebral blindness), and hepatotoxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin. A complete list of toxicities can be found in the package insert.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

11.2 DOCETAXEL

Principal adverse effects include neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, ascites, mucositis, cardiac arrhythmias, hypotension, pleural effusion, peripheral neuropathy, rash, severe nail disorders (hypo or hyperpigmentation), onycholysis (loosening of the nails), alopecia, palmar-plantar dysesthesia, hypersensitivity reaction, fatigue and fluid retention syndrome (may be irreversible).

11.3 FLUOROURACIL

Hematologic and gastrointestinal side effects are most frequently associated with fluorouracil. Hematologic toxicities of fluorouracil are leukopenia, granulocytopenia (9-14 days), thrombocytopenia (7-14 days), and anemia. Stomatitis, gastrointestinal ulceration and bleeding, and diarrhea are commonly seen gastrointestinal side effects of fluorouracil. Nausea and vomiting, effects on the skin including rashes and hyperpigmentation, alopecia, ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischemia have been reported. A complete listing of toxicities can be found in the fluorouracil package insert.

11.4 LEUCOVORIN

The only adverse reaction for leucovorin is a rare report of allergic reactions to parenteral injections of leucovorin. This is extremely uncommon.

11.5 TRASTUZUMAB

Principal adverse effects include cardiac dysfunction, infusion associated symptoms, potentiation of chemotherapy related hematologic side effects. A complete listing of toxicities can be found in the trastuzumab package insert.

11.6 SUPPORTIVE MEDICATIONS

G-CSF: common side effects include nausea, vomiting, bone pain, injection site irritation and influenza-like illness. Rare side effects include vasculitis of the skin, and very rarely, acute respiratory distress syndrome and splenic rupture have been reported.

Decadron: with chronic use, common side effects include hypertension, atrophic skin, impaired skin healing, hypercortisolism and primary adrenocortical insufficiency, irritation of the GI tract, increased risk of infection, osteoporosis, cataracts or glaucoma, and depression or euphoria. Hyperglycemia is common even with single use.



12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients should be re-evaluated for response every cycle of chemotherapy, for the first 6 cycles of therapy. For patients remaining on therapy thereafter, patients are to be re-evaluated every 2 cycles of therapy. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response.

12.1 DEFINITIONS

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET, CT, MRI, x-ray) or as ≥ 10 mm with a high-resolution CT scan. All tumor measurements must be recorded in millimeters or decimal fractions of centimeters. A “high-resolution” CT scan is one in which images are recorded at least every 5 mm.

12.1.2 Non-Measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable. Stomach, GEJ, or esophageal wall thickening is considered non-measurable.

12.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

12.1.4 Non-target lesions

All other lesions (or sites of disease) that are not target lesions as defined in section 12.1.3 will be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are required when



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

feasible, since a patient may have progressive disease on the basis of larger non-target lesions. The presence or absence of each non-target lesion should be noted throughout follow-up.

12.2 EVALUATION OF TARGET LESIONS

Complete Response (CR): Disappearance of all target lesions. Endoscopy must be without evidence of tumor with negative cytologic brushings and esophageal biopsies. The patient must be free of all symptoms of cancer.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Positive washing, brushing or biopsy and/or residual tumor may still be evident on endoscopy and/or CT scan. No lesion may increase in size and no new lesion may appear.

Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

12.3 EVALUATION OF NON-TARGET LESIONS

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Non-Complete Response (non CR): Persistence of one or more non-target lesions or/ and maintenance of tumor marker level above the normal limits.

Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. (Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the reference radiologist (or study chair).

Note:

1. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
2. Cytology and histology: If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible. These techniques can be used to differentiate between PR and CR in rare cases (eg. residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for



response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

| Target Lesions | Non-Target Lesions | New Lesions | Overall response |
|----------------|--------------------|-------------|------------------|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

1. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
2. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.5 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

12.6 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation: The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 DURATION OF THERAPY / CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will receive at least one cycle of treatment. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression, defined as
 - (1) Appearance of a tumor > 1 cm in size at a new site, or
 - (2) Reappearance of a previously completely resolved measurable tumor or lesion, or
 - (3) An increase in tumor measurements (total longest diameter) > 20%.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- (4) New sites of or clinical progression in non-measurable sites of disease
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), including but not limited to
 - (1) grade 4 anaphylaxis
 - (2) grade 4 hypertension, hemorrhage, or symptomatic grade 4 venous thromboembolism
 - (3) any grade arterial thromboembolic event
 - (4) grade 4 proteinuria
 - (5) GI perforation or wound dehiscence (requiring medical or surgical therapy)
- Patient death,
- Patient decides to withdraw from the study or is lost to follow up, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be discontinued from the study if they exhibit any of the following:

- Dose limiting toxicity (not resolving) possibly, probably, or definitely attributable to the investigational agent: any Grade 3 or greater non-hematological event that does not recover to \leq grade 1. Nausea and vomiting will be dose limiting only if grade 3 despite adequate premedication. If a patient develops dose-limiting toxicity then the drug will be withheld until toxicity resolves to \leq grade 1, and restarted at a lower dose (Section 9.3).
- In addition, if a patient develops an adverse experience that the Investigator feels is severe enough to preclude further participation, the patient will be discontinued from the study and receive medical treatment as determined by the Investigator. The patient will remain under observation until the adverse experience is resolved.

Patients will be discontinued from the study if they exhibit any of the following:

- Lack of cooperation with the requirements of the study
- Intercurrent illness requiring medication not allowed by the protocol
- Withdrawal of consent

The patient's physician(s) are free to and should discontinue study treatment if this is believed to be in the patient's best interest. Furthermore, a patient is free to withdraw from study treatment and participation at any time for any reason. Full documentation of the reasons and circumstances of all patients who withdraw must be documented in the medical record and on the appropriate case report forms.

13.2 OFF-STUDY EVALUATION

- History and physical examination, including performance status and neurological exam.
- Laboratory: Complete blood counts and chemistry tests as required at baseline



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Tumor Measurements: Assessment of at least one measurable lesion (in appropriate patients) preferably by CT scan unless within 4 weeks of last measurements.
- Patients will be monitored for overall survival following completion of or removal from the study.

14.0 BIOSTATISTICS

The study will be an open-label random assignment phase II therapeutic clinical trial. The study population will be patients with histologically confirmed unresectable or metastatic gastric or gastroesophageal adenocarcinoma. Arm A will be modified DCF and ARM B will be 'parent' DCF with growth factor support.

The primary endpoint for both arms is progression free survival (PFS), as measured from the start of the treatment to the date of either documentation of disease progression or death. We will define progression of disease as per RECIST criteria. Patients with measurable disease and with evaluable radiographically but non-measurable disease will be eligible for study entry. As per RECIST criteria, any evidence of progression in non-measurable lesions, measurable lesions, or the development of new lesions, would qualify as disease progression. The 6 month progression free survival for 'parent' DCF is approximately 43% (see Section 3.3.2). Using this as a benchmark, we propose declaring each regimen comparable to parent DCF if the 6 months PFS exceeds 43%, and unworthy of further investigation if it is 26% or less. Each arm will be evaluated separately for this purpose. We will accrue 60 patients in each arm for a total study population of 120 patients. Anticipating a 10% inevaluable rate, with 54 evaluable patients enrolled in each arm we will be able to differentiate between 6 month PFS of 26% and 43% with type I and II error rates of 10% each (exact single stage binomial design) [44]. For each arm, the regimen is considered promising if 19 or more patients (out of 54) are progression free at 6 months. We will define "evaluable" patients as patients who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal within the first 6 months. We anticipate enrollment to be 8 patients/ month with completion of accrual in approximately 15 months.

Secondary endpoints of efficacy are response rate, median PFS, overall and 1 year survival. We anticipate that we will enroll approximately 40 patients with measurable disease in each arm, from which we can establish a response rate to within +/- 15%. This is consistent with most Phase II studies evaluating response. The median PFS will be estimated using the Kaplan-Meier method, and 95% confidence intervals will be based on the sign test [45]. The 1 year survival will be estimated using the Kaplan-Meier method, and Greenwood's formula will be used to calculate the standard error of the corresponding Kaplan Meier estimate and 95% confidence interval. Survival curves will be estimated using Kaplan-Meier methodology.

A secondary objective is to demonstrate improved toxicity profile of each regimen compared to parent DCF. It is reported that DCF has a grade 3-4 adverse event rate for non-hematologic toxicity exceeding 80%. We hypothesize that the modified De Gramont type of FU infusion and more frequent dosing of cisplatin and docetaxel (eg. ARM A) will be associated with less toxicity. Additionally, parent DCF administered growth factor support (eg. ARM B) will also be associated with less toxicity.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive grade 3 or 4 adverse events. We employ repeated significant testing with a constant significance level to monitor the grade 3/4 adverse event rate [46]. The table below provides a stopping boundary for this study based on an acceptable grade 3/4 adverse event rate of 50% and an unacceptable grade 3/4 adverse event rate of 70%. Using this boundary, if the true adverse event rate is 50% then the probability of stopping early is 5%. However, if the true toxicity rate is 70% then the probability of stopping early increases to 87%.

| | | | | |
|--------------------|----|--|----|-----------|
| Stop if we observe | 12 | grade 3 or 4 adverse events in the first | 15 | patients. |
| | 21 | | 30 | |
| | 30 | | 45 | |
| | 35 | | 54 | |

Grade 3 or 4 venous thromboembolic events will not be included for the purposes of this safety determination. We have previously demonstrated that the majority of these events are associated with minimal to no co-morbidity and are likely attributable to the disease and not the therapy[47].

Total accrual will be 108 evaluable patients with a 1:1 randomization. We will stratify based on center, disease (measurable vs. non-measurable), and location (gastric vs. GEJ).

December 2009 Amendment

Arm B will be closed because we met the above stopping rule. Specifically, we observed 22 grade 3-4 adverse events in the first 30 patients enrolled on Arm B. We note that there was a discrepancy between the two arms with regard to the rate of grade 3-4 thromboembolism (5 in Arm B, and 0 in Arm A). Because of this discrepancy, we included grade 3-4 venous thromboembolic events in the determination of the toxicity stopping rule. Notably, 16 patients in Arm B required admission due to toxicity in the first 3 months of protocol therapy. As a result of this unacceptable toxicity, the standard DCF + growth factor support arm will close.

As of October 23, 2009, 26 patients are evaluable for toxicity in Arm A (mDCF). We've observed 16 grade 3-4 adverse events attributable to treatment in the first 3 months, and 8 hospitalizations.

Note, the results of the recent ToGA study demonstrate that for Her2 positive gastric cancer, patients have a survival benefit with the addition of trastuzumab to chemotherapy (see Sect 3.3.4). We are therefore amending the study to include a separate cohort of 35 patients who are Her2 positive to receive mDCF + trastuzumab (Trastuzumab cohort)

Total patient accrual to this protocol is fixed at 120 patients. Arm B has closed with 31 patients enrolled in total. Arm A will remain with a target accrual of 54 eligible patients. For the remaining 35 patients, we will open a *Trastuzumab Cohort* in which Her2 positive patients with metastatic gastric/GEJ adenocarcinoma will receive mDCF + trastuzumab. With 35 HER2-positive patients, we will be able to differentiate between 6-month PFS of 43% and 64% with type I and II error rates of 10% each (exact single stage binomial design). The modified DCF

IRB
PB

Amended: 08/03/15



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

plus trastuzumab regimen will be considered promising if 19 or more Her2 positive patients (out of 35) are alive and progression free at 6 months.

For the *Trastuzumab Cohort*, we will employ a similar early stopping rule for safety, as we have done for Arm A and Arm B. The table below provides a stopping boundary for this study based on an acceptable grade 3/4 adverse event rate of 50% and an unacceptable grade 3/4 adverse event rate of 70%. Using this boundary, if the true adverse event rate is 50% then the probability of stopping early is 5%. However, if the true toxicity rate is 70% then the probability of stopping early increases to 87%.

| | | | | |
|--------------------|----|--|----|-----------|
| Stop if we observe | 12 | grade 3 or 4 adverse events in the first | 15 | patients. |
| | 21 | | 30 | |

For the FDG-PET/CT correlative study (section 9.4.2), the change between baseline and 2nd PET scan (change in SUV) will be correlated with response, time to tumor progression, and overall survival. These associations will be assessed using a t-test for response (comparing the means between responders and non-responders), and Cox regression for overall survival and time to tumor progression.

Another secondary objective is to explore the differences in docetaxel pharmacology between the two study arms. Serial blood draws will be performed in approximately 10 patients in each arm, as explained in section 9.4.3. Some patients in Arm B may have repeat docetaxel pharmacology tests without cisplatin administration. Standard pharmacokinetic parameters including C_{max}, T_{max}, and AUC will be estimated for each patient using non-compartmental methods, and a Wilcoxon rank sum test will be used to compare the distribution of levels for the two groups.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

All centers must register patients through MSKCC. No patient can be treated unless they are registered through MSKCC.

For MSKCC patients:

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

For Participating Centers:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center. Patient registration must be initiated at Memorial Sloan Kettering Cancer Center *within 48 hours of the patient signing the informed consent.*

To complete registration and enroll a patient from another institution, the study staff at that site must contact the Multicenter Core Project Coordinator to notify him/her of patient registration. The study staff then needs to fax registration/eligibility documents to the Multicenter Trials Core at MSKCC at 646-227-2482.

The following documents must be sent within 24 hours of informed consent form being signed for each enrollment:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

15.2 PROTOCOL PATIENT NUMBER

Once eligibility has been established and the patient is registered, the patient will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol patient number). This number is unique to the patient and must be written on all data and correspondence for the patient. This protocol patient number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.



15.3 RANDOMIZATION

After eligibility is established and immediately after consent is obtained and a patient number is assigned patients will be registered and randomized using the Clinical Research Database (CRDB). Patients will be 1:1 randomized to the two arms. Randomization will be accomplished by the method of random permuted block. We will stratify based on center, disease (measurable vs. non-measurable), and location (gastric vs. GEJ).

December 2009 Amendment

Due to excessive toxicity, Arm B has been closed. Patients will no longer be randomized between two arms of the study. Instead, patients will be assigned to Arm A. If they are Her2 positive and are eligible for trastuzumab, they will be assigned to the *Trastuzumab cohort*.

August 2010 Amendment

Arm B remains closed due to toxicity and target accrual has been reached for Arm A. Accordingly, eligibility criterion has been expanded to include Her2. Patients eligible under these criteria will be assigned to the *Trastuzumab cohort*.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database – CRDB). Source documentation will be available to support the computerized patient record. Standardized Case Report Forms (CRFs) that meet the requirements for MSKCC data reporting have been generated for this study. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by body system and to severity or toxicity grade. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.0.1 Data Management Requirements for Participating Sites

Data

Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Please see Appendix C for the data collection schedule that each participating center is expected to adhere to.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes but is not limited to:

- Baseline measures to assess pre-protocol disease status (ex. CT)
- Treatment records
- Grade 3-5 toxicities/adverse events
- Response designation

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should fax CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

FAX: To the attention of Multicenter Trials Core at **646-227-2482**

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to guidelines specified in Appendix A-C.

SAE Reporting:

Hospitalization requiring Serious Adverse Event Reporting must be reported within three calendar days.

Please see Section 17.2.1 regarding the requirements for SAE reporting.

Off-Study Requirements:

When a patient is taken off-study all CRFs with required source documentation are required to be sent to MSKCC not later than 14 calendar days after the off-study date. Failure to submit required forms in the timelines requested will result in suspension of accrual privileges at a given site until data is updated, and/or withholding of contract payments if applicable.

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

16.1 QUALITY ASSURANCE

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Site Auditing

Each site participating in the accrual of patients to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected patients records can be audited on-site at participating sites or (2) source documents for selected patients will be sent to MSKCC for audit. Audits will usually be determined by patient accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of Lead PI.

Audits will be conducted at least once shortly after initiation of patient recruitment at a site, and if possible, at the end or closeout of the trial at a site and during the trial if the trial lasts 3 or more years. At a minimum, audits will be conducted once a year or more frequently, if indicated. The number of patients audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timing and accuracy

A wrap-up session will be conducted at the outside site and preliminary findings will be discussed with the outside site PI and research team. The preliminary results will be sent to the MSKCC PI.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Each audit will be summarized and a final report will be sent to the PI at the audited participating institution within 30 days of the audit. The report will include a summary of findings, patient by patient case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating institution must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the outside site must be sent to the MSKCC IRB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites patient's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the outside sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent promptly upon request to MSKCC.

16.1.3 Adherence to the Protocol

The study will be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the patient requires alternative treatment. Any deviation from the protocol will be reported, explained and documented in the patient's medical record.

16.2 DATA AND SAFETY MONITORING

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: [http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20\(CRQA\)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf](http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf)

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (eg. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (eg. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

For Multicenter studies, standardized Case Report Forms (CRFs) have been generated from this study that meet the requirements of CTEP and MSKCC data reporting. A set of CRFs will be sent to each center (for photocopying and use) following local activation.

16.3 ETHICAL AND ADMINISTRATIVE ISSUES

The investigator will agree to personally conduct and supervise the proposed investigations according to recognized principles of good clinical practice (GCP).

16.4 INSTITUTIONAL REVIEW BOARD APPROVAL

This protocol and the informed consent form will be reviewed and approved by the IRB before the study is initiated. The Investigator is then responsible for informing the IRB of the completion of the study and will provide the IRB a final study status report. The Investigator/Study Coordinator will inform the IRB of all serious adverse events.

16.5 REGULATORY DOCUMENTATION

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

**IRB
PB**

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

16.5.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.5.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.5.3 Document maintenance

**IRB
PB**

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 7 years.

16.6 NONCOMPLIANCE

If a participating site is noncompliant with the data and regulatory requirements set forth in section 16.0 -16.5 accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 7.0.

Exclusion of Lactating or Pregant Women: Children have been excluded from this study. Gastric and GEJ adenocarcinoma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of the gastric tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications of treatment. The laboratory correlative studies and week 3 FDG-PET/CT scans will be performed without charge to the patient.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with metastatic gastric cancer alternative treatments may include other chemotherapy regimens as well as palliative radiation therapy, and/or surgery. At present, no specific chemotherapy regimen represents standard treatment for the disease. Patients may be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (eg, qualified monitors from MSKCC or collaborating institutions, the NCI, Sanofi-Aventis etc.), may review patients records and pathology slides, as required.

17.1 PRIVACY

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 SERIOUS ADVERSE EVENT (SAE) REPORTING

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

- Detailed text that includes the following information:
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

All adverse events, whether observed by the investigator, elicited from the patient, or volunteered by the patient, will be recorded. The MSKCC PI (Yelena Janjigian, MD) will report all SAE's to the MSKCC IRB and to Sanofi-Aventis Pharmaceuticals and Genentech via the CRDB AE report .

17.2.1 ADVERSE EVENT REPORTING DEFINITIONS

Adverse Event: An adverse event is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic functions, as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical trial, whether or not considered drug related. All of the following are to be considered adverse events:

- an exacerbation of a pre-existing condition.
- an intercurrent illness.
- any drug interaction.
- any event related to a concomitant medication.
- development of an abnormal laboratory value or a significant change from baseline in a laboratory value within the range of normal, considered by the investigator to be clinically important.
- an unexpected significant worsening of the cancer under treatment. Anticipated day-to-day fluctuations in the activity of the cancer or the anticipated progression of the cancer (other than death) should not be considered an adverse event.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" is that there is a reasonable possibility that the drug caused the adverse experience.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Life-threatening: A life-threatening adverse event implies an immediate risk of death from the reaction as it occurred. Life-threatening does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

ASSESSMENT OF SEVERITY

This study will utilize the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

ASSESSMENT OF RELATIONSHIP TO STUDY MEDICATION

The following definitions of relationship to study medication should be used in assessing the suspected causality of an adverse event:

- Definite: The adverse event is clearly related to the chemotherapy or investigational agent.
- Probable: The adverse event is likely related to the chemotherapy or investigational agent.
- Possible: The adverse event may be related to the chemotherapy or investigational agent.
- Unlikely: The adverse event is doubtfully related to the chemotherapy or investigational agent.
- Unrelated: The adverse event is clearly NOT related to the chemotherapy or investigational agent.

17.2.3 REPORTING ADVERSE EVENTS ASSOCIATED WITH TRASTUZUMAB (GENENTECH)

With the occurrence of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to or caused by trastuzumab. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to trastuzumab through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

Reporting Serious Adverse Events Associated With Trastuzumab

All SAEs that are serious and reasonably or probably related to the use of Trastuzumab (this applies to both expected and unexpected events) should faxed to:

Genentech Drug Safety Contact Line

Tele: 1-888-835-2555

Fax: (650) 225-4682/ (650) 225-4683

AND:

Study Coordination Center/Principal Investigator

Contact Information

AND:

IRB Contact information

**IRB
PB**

Amended: 08/03/15



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

17.2.4 SANOFI –AVENTIS REPORTING GUIDELINES

All SAEs are to be reported as soon as possible to Sanofi-Aventis. Reports by FAX should be sent to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department (908-231-4827), within 24 hours of receipt by investigator / sponsor. FAX transmission should include the following on the provided IIT SAE REPORT, fax cover form (Appendix E):

Reports by E-MAIL should be sent to: GPEmailbox@aventis.com , within 24 hours of receipt by investigator / sponsor. E-Mail transmission should include the following:

Investigator-Initiated (IIT #) study number: _____

Study Title: _____

Name of Principal Investigator: _____

17.3 SERIOUS ADVERSE EVENT REPORTING FOR OUTSIDE CENTERS

Responsibility of Participating Sites

Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within **3 calendar days**.

Participating sites should notify the MSKCC PI of any grade 5 event immediately.

Participating sites should use the SAE Report Template (appendix E) to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

PI: Yelena Y. Janjigian, MD

Tel: 646-888-4186

Email: janjigiy@mskcc.org

Multicenter Core Project Coordinator

Fax: 646-227-2482

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 [and to the funding entity as described in 17.2.3 and 17.2.4]
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 SAFETY REPORTS

IRB
PB

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

A note should be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCE(S)

1. Parkin, D.M., F.I. Bray and S.S. Devesa, *Cancer burden in the year 2000. The global picture*. European Journal of Cancer, 2001. 37(8): p. 4-66.
2. Shah, M.A. and G.K. Schwartz, *The Treatment of Metastatic Esophagus and Gastric Cancer*. Semin Oncol, 2004. 4: p. 574-587.
3. Janunger, K.G., L. Hafstrom, P. Nygren, et al., *A systemic overview of chemotherapy effects in gastric cancer*. Acta Onc., 2001. 40(2/3): p. 309-326.
4. Vanhoefer, U., P. Rougier, H. Wilke, et al., *Final Results of a Randomized Phase III Trial of Sequential High-Dose Methotrexate, Fluorouracil, and Doxorubicin Versus Etoposide, Leucovorin, and Fluorouracil Versus Infusional Fluorouracil and Cisplatin in Advanced Gastric Cancer: A Trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group*. J Clin Oncol, 2000. 18(14): p. 2648-2657.
5. Ohtsu, A., Y. Shimada, K. Shirao, et al., *Randomized phase III trial of fluorouracil versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205)*. J Clin Onc, 2003. 21(1): p. 54-9.
6. Icli, F., I. Celik, F. Aykan, et al., *A randomized phase III trial of etoposide, epirubicin, and cisplatin versus 5-fluorouracil, epirubicin, and cisplatin in the treatment of patients with advanced gastric carcinoma*. Cancer, 1998. 83: p. 2475-80.
7. Tebbutt, N.C., A. Norman, D. Cunningham, et al., *A multicentre, randomised phase III trial comparing protracted venous infusion (PVI) 5-fluorouracil with PVI plus mitomycin C in patients with inoperable oesophago-gastric cancer*. Ann Oncol, 2002. 13: p. 1568-75.
8. Ross, P., M. Nicolson, D. Cunningham, et al., *Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer*. J Clin Onc, 2002. 20: p. 1996-2004.
9. Waters, J.S., A. Norman, D. Cunningham, et al., *Long-term survival after epirubicin, cisplatin, and fluorouracil for gastric cancer: results of a randomized trial*. Br J Cancer, 1999. 80(1/2): p. 269-72.
10. Webb, A., D. Cunningham, J.H. Scarffe, et al., *Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer*. J of Clin Oncol, 1997. 15(1): p. 261-67.
11. Ajani, J.A., E. Van Cutsem, F.C. Moiseyenko, et al. *Docetaxel (D), cisplatin, 5-fluorouracil compared to cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naïve patients with metastatic or locally recurrent, unresectable gastric carcinoma: Interim results of a randomized phase III trial (V 325)*. in Proc Amer Soc Clin Onc. 2003. Chicago, IL.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

12. Moiseyenko, V.M., J.A. Ajani, S.A. Tjuladin, et al., *Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients (pts) with metastatic gastric adenocarcinoma.* Proc Am Soc Clin Oncol, 2005. 23: p. abs4002.
13. Ajani, J., J. Baker, P. Pisters, et al., *Irinotecan plus cisplatin in advanced gastric or gastroesophageal junction carcinoma.* Oncology (Huntingt), 2001. 15(3 Suppl 5): p. 52-4.
14. Boku, N., A. Ohtsu, Y. Shimada, et al., *Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer.* J of Clin Oncol, 1999. 17(1): p. 319-23.
15. Ilson, D., A.A. Forastier, M. Arquette, et al., *A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus.* Cancer J., 2000. 6(5): p. 316-23.
16. Pozzo, C., C. Barone, J. Szanto, et al., *Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study.* Ann Oncol, 2004. 15: p. 1773-1781.
17. Dank, M., J. Zaluski, C. Barone, et al., *Randomized phase 3 trial of irinotecan (CPT-11) + 5FU/folinic acid (FA) vs CDDP + 5FU in 1st line advanced gastric cancer patients.* Proc Am Soc Clin Oncol, 2005. 23: p. abs4003.
18. Roth, A., R. Maibach, G. Martinelli, et al., *Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology.* Ann Oncol, 2000. 11(3): p. 301-6.
19. Ridwelski, K., T. Gebauer, J. Fahlke, et al., *Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer.* Ann Oncol, 2001. 12(1): p. 47-51.
20. Roth, A.D., R. Maibach, N. Fazio, et al., *5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (Taxotere)-cisplatin in advanced gastric carcinoma: a phase I-II trial.* Ann Oncol, 2004. 5: p. 759-764.
21. Thuss-Patience, P., A. Kretschmar, M. Repp, et al., *Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study.* J Clin Onc, 2005. 23: p. 494-501.
22. Roth, A.D., R. Maibach, S. Falk, et al., *Docetaxel-cisplatin-5FU versus docetaxel-cisplatin versus epirubicin-cisplatin-5FU as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research (SAKK).* Proc Am Soc Clin Oncol, 2004. 22(14S): p. abs 4020.
23. Chen, L.-T., T.-W. Liu, C.-W. Wu, et al., *A phase I study of weekly docetaxel, 24-hour infusion of high-dose fluorouracil/leucovorin and cisplatin in patients with advanced cancer.* Oncology, 2002. 63: p. 239-47.
24. Constenla, M., R. Garcia-Arroyo, I. Lorenzo, et al., *Docetaxel, 5-fluorouracil, and leucovorin as treatment for advanced gastric cancer: results of a phase II study.* Gastric Cancer, 2002. 5: p. 142-47.
25. Park, S.R., J.H. Chun, Y.W. Kim, et al. *Phase II study of low-dose docetaxel/fluorouracil/cisplatin in metastatic gastric cancer.* in 2005 Gastrointestinal Cancers Symposium. 2005. Miami, FL.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

26. Lorenzen, S., J. Duyster, N. Weigert, et al. *Docetaxel (T) plus Cisplatin (P) and leucovorin (L)/5FU (F) in first line advanced gastric cancer and adenocarcinoma of the gastro-esophageal junction: First results of the phase II GASTRO-TAX-1 trial.* in 2006 *Gastrointestinal Cancers Symposium*. 2006. San Francisco, California: American Society of Clinical Oncology.
27. de Gramont, A., J.F. Bosset, C. Milan, et al., *Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study.* *J Clin Onc*, 1997. 15(2): p. 808-15.
28. Al-Batran, S.-E., A. Atmaca, S. Hegewisch-Becker, et al., *Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer.* *J Clin Onc*, 2004. 22(4): p. 658-63.
29. Kim, D.Y., J.H. Kim, S.-H. Lee, et al., *Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously-treated patients with advanced gastric cancer.* *Ann Oncol*, 2003. 14: p. 383-87.
30. Bouche, O., J.L. Raoul, F. Bonnetain, et al., *Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study - FCCD 9803.* *J Clin Onc*, 2004. 22(21): p. 4319-4328.
31. Oh, D.-Y., T.-Y. Kim, J.H. Kwon, et al., *Docetaxel + 5-fluorouracil + cisplatin 3-day combination chemotherapy as a first-line treatment in patients with unresectable gastric cancer.* *Jpn J Clin Oncol*, 2005. 35(7): p. 380-85.
32. Pronk, L.C., J.H.M. Schellens, A.S.T. Planting, et al., *Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors.* *J Clin Onc*, 1997. 15(3): p. 1071-1079.
33. Millward, M.J., J. Zalcberg, J.F. Bishop, et al., *Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small cell lung cancer.* *J Clin Onc*, 1997. 15(2): p. 750-58.
34. Rowinsky, E.K., M.R. Gilbert, W.P. McGuire, et al., *Sequences of taxol and cisplatin: a phase I and pharmacologic study.* *Journal of Clinical Oncology*, 1991. 9(9): p. 1692-703.
35. Ma, J., J. Verweij, A.S.T. Planting, et al., *Docetaxel and paclitaxel inhibit DNA-adduct formation and intracellular accumulation of cisplatin in human leukocytes.* *Cancer Chemother Pharmacol*, 1996. 37: p. 382-84.
36. TM, T., [package insert]. Bridgewater, NJ; Aventis Pharmaceuticals., 2005.
37. TM, A., [package insert]. Lugano, Switzerland: Helsinn Healthcare, 2003.
38. Oliver, I., *Aprepitant in antiemetic combinations to prevent chemotherapy-induced nausea and vomiting.* *Inter J. Clin Practice*, 2004. 58(2): p. 201-6.
39. McCrea, J.B. and e. al., *Effects of neurokinin 1 receptor antagonist on the pharmacokinetics of dexamethasone and methylprednisolone.* *Clin Pharmacol Ther*, 2003. 74: p. 17-24.
40. Nygren, P., K. Hande, K.J. Petty, et al., *Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients.* *Cancer Chemother Pharmacol*, 2005. 55: p. 609-616.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

41. Rosing, H., V. Lustig, L.J.C. van Warmerdam, et al., *Pharmacokinetics and metabolism of docetaxel administered as a 1-hour intravenous infusion*. *Cancer Chemother Pharmacol*, 2000. 45: p. 213-18.
42. Stein, H.J., M. Feith and J.R. Siewert, *Cancer of the esophagogastric junction*. *Surgical Oncology*, 2000. 9(1): p. 35-41.
43. Mandard, A.M., F. Dalibard, J.C. Mandard, et al., *Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: Clinicopathologic correlations*. *Cancer*, 1994. 73: p. 2680-86.
44. Chow, S.C., J. Shao and H. Wang, *Sample Size Calculations in Clinical Research*. 2003, New York: Marcell Dekker.
45. Brookmeyer, R. and Crowley, J., *A confidence interval for the median survival time*. *Biometrics*, 1982, 38: p. 29-41.
46. Siegmund, D., *Sequential Analysis: Tests and Confidence Intervals*. Springer Series in Statistics. 1985.
47. Shah, M.A., D. Ilson and D. Kelsen, *Thromboembolic Events In Gastric Cancer: High Incidence in Patients Receiving Irinotecan and Bevacizumab Based Therapy*. *J Clin Oncol*, 2005. 23(11): p. 2574-6.
48. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004 Jan 15;22(2):330-53. Epub 2003 Dec 22.
49. Maindrault-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, Mabro M, Artu P, Louvet C, De Gramont A. Optimox2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC). A GERCOR study. *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 3504
50. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, Svensson C, Enander LK, Linne T, Sellstrom H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 8:163-168, 1997
51. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85:365-376, 1993
52. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 16:139-144
53. Tournigand C, Cervantes A, Figuer A, et al: OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—A GERCOR study. *J Clin Oncol* 24:394-400, 2006
54. Ross P, Nicolson M, Cunningham D, et al: Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 20:1996-2004, 2002



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

55. Calais Da Silva FM, Bono A, Brausi M, Whelan P, Queimadelos A, Portillo J, Kirkali Z, Robertson C. Phase III intermittent MAB vs continuous MAB. *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 4513
56. Hofman M, Stoss O, Shi D, et al: Assessment of a Her2 scoring system for gastric cancer: results from a validation study. *Histopathology* 52:797-805., 2008
57. Van Cutsem E, Kang Y, Chung H, et al: Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol (Meeting Abstracts)* 27:LBA4509-, 2009
58. Marx AH, Tharun L, Muth J, et al: Her2 amplification is highly homogenous in gastric cancer. *Hum Pathol* 40:769-77., 2009

20.0 APPENDICES

Appendix A: KARNOFSKY / ECOG PERFORMANCE STATUS SCALES

Appendix B: TISSUE TRANSMITTAL SHEET

Appendix C: SERIOUS ADVERSE EVENT REPORT FORM FOR NON-MSKCC SITES

Appendix D: EORTC QLQ-C30



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Investigator(s)/Department:

| | |
|---------------------------------|------------------------------|
| Gary K. Schwartz, MD | Medicine: Melanoma/Sarcoma |
| David Ilson, MD PhD | Medicine: Gastrointestinal |
| Leonard Saltz, MD | Medicine: Gastrointestinal |
| Nancy Kemeny, MD | Medicine: Gastrointestinal |
| Diane Reidy-Lagunes, MD | Medicine: Gastrointestinal |
| Marinela Capanu, PhD | Epidemiology : Biostatistics |
| David D'Adamo, MD PhD | Medicine: Melanoma/Sarcoma |
| Ki Young Chung, MD | Medicine: Gastrointestinal |
| Neil H. Segal, MD, PHD | Medicine: Gastrointestinal |
| Kenneth Yu, MD | Medicine: Gastrointestinal |
| Maeve Lowery, MD | Medicine: Gastrointestinal |
| Rona D. Yaeger, MD | Medicine: Gastrointestinal |
| Andrew S. Epstein, MD | Medicine: Gastrointestinal |
| Geoffrey Y. Ku, MD | Medicine: Gastrointestinal |
| James Harding, MD | Medicine: Gastrointestinal |
| Anna Varghese, MD | Medicine: Gastrointestinal |
| Peter Maslak, MD | Medicine: Leukemia |
| Robert Lefkowitz, MD | Radiology |
| Marc Simmons, MD | Radiology |
| Heiko Schoder, MD | Radiology: Nuclear Medicine |
| Laura Tang, MD | Pathology |
| Ephraim Casper, MD | Medicine: All Networks |
| Sree Chalasani, MD | Medicine: Basking Ridge |
| Audrey Hamilton, MD | Medicine: Basking Ridge |
| Mila Gorsky, MD | Medicine: Basking Ridge |
| Magi Khalil, MD | Medicine: Basking Ridge |
| Han Xiao, MD | Medicine: Basking Ridge |
| Avni Desai, MD | Medicine: Commack |
| Marisa Siebel, MD | Medicine: Commack |
| Stefan Berger, MD | Medicine: Commack |
| Julie Fasano, MD | Medicine: Commack |
| John Fiore, MD | Medicine: Commack |
| Stuart Lichtman, MD | Medicine: Commack |
| Philip Schulman, MD | Medicine: Commack |
| Steven Sugarman, MD | Medicine: Commack |
| Arlyn Apollo, MD | Medicine: Mercy |
| Pamela Drullinsky, MD | Medicine: Mercy |
| Zoe Goldberg, MD | Medicine: Mercy |
| Kenneth Ng, MD | Medicine: Mercy |
| Tiffany Troso-Sandoval, MD | Medicine: Mercy |
| Michelle Boyar, MD | Medicine: Phelps |
| Philip Caron, MD | Medicine: Phelps |
| Nancy Mills, MD | Medicine: Phelps |
| Carolyn Wasserheit-Lieblich, MD | Medicine: Phelps |
| Stephanie Smith-Marrone, MD | Medicine: Phelps |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Consenting

Professional(s)/Department:

| | |
|---------------------------------|----------------------------|
| Yelena Y. Janjigian, MD | Medicine: Gastrointestinal |
| David P. Kelsen, MD | Medicine: Gastrointestinal |
| Gary K. Schwartz, MD | Medicine: Melanoma/Sarcoma |
| David Ilson, MD PhD | Medicine: Gastrointestinal |
| Leonard Saltz, MD | Medicine: Gastrointestinal |
| Nancy Kemeny, MD | Medicine: Gastrointestinal |
| Diane Reidy-Lagunes, MD | Medicine: Gastrointestinal |
| Kenneth Yu, MD | Medicine: Gastrointestinal |
| Maeve Lowery, MD | Medicine: Gastrointestinal |
| Rona D. Yaeger, MD | Medicine: Gastrointestinal |
| Andrew S. Epstein, MD | Medicine: Gastrointestinal |
| Geoffrey Y. Ku, MDDavid | Medicine: Gastrointestinal |
| D'Adamo, MD | Medicine: Melanoma/Sarcoma |
| Ki Young Chung, MD | Medicine: Gastrointestinal |
| Neil H. Segal, MD, PHD | Medicine: Gastrointestinal |
| James Harding, MD | Medicine: Gastrointestinal |
| Anna Varghese, MD | Medicine: Gastrointestinal |
| Ephraim Casper, MD | Medicine: All Networks |
| Sree Chalasani, MD | Medicine: Basking Ridge |
| Audrey Hamilton, MD | Medicine: Basking Ridge |
| Mila Gorsky, MD | Medicine: Basking Ridge |
| Magi Khalil, MD | Medicine: Basking Ridge |
| Han Xiao, MD | Medicine: Basking Ridge |
| Avni Desai, MD | Medicine: Commack |
| Marisa Siebel, MD | Medicine: Commack |
| Stefan Berger, MD | Medicine: Commack |
| Julie Fasano, MD | Medicine: Commack |
| John Fiore, MD | Medicine: Commack |
| Stuart Lichtman, MD | Medicine: Commack |
| Philip Schulman, MD | Medicine: Commack |
| Steven Sugarman, MD | Medicine: Commack |
| Arlyn Apollo, MD | Medicine: Mercy |
| Pamela Drullinsky, MD | Medicine: Mercy |
| Zoe Goldberg, MD | Medicine: Mercy |
| Kenneth Ng, MD | Medicine: Mercy |
| Tiffany Troso-Sandoval, MD | Medicine: Mercy |
| Michelle Boyar, MD | Medicine: Phelps |
| Philip Caron, MD | Medicine: Phelps |
| Nancy Mills, MD | Medicine: Phelps |
| Carolyn Wasserheit-Lieblich, MD | Medicine: Phelps |
| Stephanie Smith-Marrone, MD | Medicine: Phelps |

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|---|--|------------------|
| National Coordinating Investigator | Manish A. Shah, MD Office: 646.962.6200 Fax: 646.962.1607 Email: mas9313@med.cornell.edu | |
| | | |
| Collaborating Institution (s): | <u>PI Name and Contact Info</u> | <u>Site Role</u> |
| University of Pittsburgh Cancer Institute | <u>PI: Ronald G. Stoller, M.D.</u> University of Pittsburgh Cancer Institute Hillman Cancer Center 5115 Centre Avenue Pittsburgh, PA 15232 Ph: 412-692-4724 Fax: 412-648-6579 Email: stollerrg@upmc.edu | Data Collection |
| Queens Cancer Center | <u>PI: Margaret Kemeny, M.D.</u> Queens Cancer Center of Queens Hospital 82-68 164th Street New Building – Room A531 Jamaica, NY 11432 Ph: 718-883-4031 Fax: 718-883-6295 Email: kemenym@nychhc.org | Data Collection |
| Long Island Jewish Medical Center | <u>PI: Bhoomi Mehrotra, M.D.</u> Long Island Jewish Medical Center Division of Hematology/Oncology New Hyde Park, NY 11040 Ph: 718-470-8934 Fax: 718-470-0169 Email: mehrotra@lij.edu | Data Collection |
| University Hospital of Cleveland | <u>PI: Smitha Krishnamurthi, M.D.</u> Ireland Cancer Center/University Hosp. of Cleveland Case Medical Center 11100 Euclid Avenue Cleveland, OH 44106 Ph: 216-844-5413 Fax: 216-844- 5449 Email: smitha.krishnamurthi@case.edu | Data Collection |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|--|---|-----------------|
| Weill Medical College of Cornell University | <u>PI: Allyson J. Ocean, M.D.</u> Assistant Professor of Medicine New York Presbyterian Hospital - Weill Medical College of Cornell University Division of Hematology/Oncology 520 East 70th Street, Starr 365 New York, NY 10021 Ph: 212-746-2844 Fax: 212-746-6645 E-mail: ajo9001@med.cornell.edu | Data Collection |
| City of Hope | <u>PI: Vincent Chung, M.D. FACP</u> Assistant Professor City of Hope Comprehensive Cancer Center 1500 E. Duarte Rd. Duarte, CA 91010 Ph: 626-471-9200 Fax: 626-301-8233 E-mail: vchung@coh.org | Data Collection |
| Medical College of Wisconsin | <u>PI: Paul Ritch, M.D.</u> Professor of Medicine Medical College of Wisconsin 9200 W. Wisconsin Avenue Milwaukee, WI 53226 Ph: 414-805-4600 Fax: 414-805-6838 E-mail: pritch@mcw.edu | Data Collection |
| Piedmont Hospital Research Institute (PHRI) | <u>PI: Charles Henderson, M.D.</u> Piedmont Hospital Research Institute (PHRI) 95 Collier Rd., Suite 2075 Atlanta, GA 30309 Ph: 404-350-9853 Fax: 404-350-8407 E-mail: chenderson@phoc.com | Data Collection |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| | | |
|-----------------------------|--|-----------------|
| Nebraska Cancer Specialists | <u>PI: Yungpo Bernard Su, M.D.</u> Nebraska Cancer Specialists Methodist Estabrook Cancer Center 8303 Dodge Street, Suite 250 Omaha, Nebraska 68114 Ph: 402.354.8124 Fax: 402.354.8127 E-mail: drs@onchemwest.com | Data Collection |
| Memorial Cancer Institute | <u>PI: Dr. Pablo Ferraro, M.D.</u> Memorial Cancer Institute 801 North Flamingo Road Pembroke Pines, FL 33025 Ph: (954)430-6868 Fax: (954)443-4747 E-mail: pferraro@mhs.net | Data Collection |



Table of Contents

| | | |
|------------|--|-----------|
| 1.0 | <i>PROTOCOL SUMMARY AND/OR SCHEMA</i> | 1 |
| 2.0 | <i>OBJECTIVES AND SCIENTIFIC AIMS</i> | 4 |
| 3.0 | <i>BACKGROUND AND RATIONALE</i> | 5 |
| 3.1 | SCOPE OF DISEASE AND ROLE OF CHEMOTHERAPY..... | 5 |
| 3.2 | COMBINATION CHEMOTHERAPY REGIMENS..... | 5 |
| 3.3 | IS THERE A “STANDARD” CHEMOTHERAPY REGIMEN?..... | 7 |
| 3.4 | SUMMARY OF CHEMOTHERAPY FOR GASTRIC/GEJ ADENOCARCINOMA..... | 12 |
| 3.5 | PROPOSAL | 13 |
| 3.5.1 | Modified DCF dose and schedule determination..... | 13 |
| 3.5.2 | Pharmacokinetic and Pharmacodynamic Considerations (MSKCC ONLY)..... | 17 |
| 3.5.3 | FDG-PET Response Assessment | 19 |
| 4.0 | <i>OVERVIEW OF STUDY DESIGN/INTERVENTION</i> | 22 |
| 4.1 | Design..... | 22 |
| 4.2 | Intervention..... | 23 |
| 5.0 | <i>THERAPEUTIC/DIAGNOSTIC AGENTS</i> | 24 |
| 5.1 | Docetaxel (TAXOTERE®)..... | 24 |
| 5.2 | CISPLATIN | 27 |
| 5.3 | FLUOROURACIL | 28 |
| 5.4 | LEUCOVORIN..... | 29 |
| 5.5 | TRASTUZUMAB | 30 |
| 5.6 | CONCOMITANT MEDICATIONS..... | 34 |
| 6.0 | <i>CRITERIA FOR SUBJECT ELIGIBILITY</i> | 36 |
| 6.1 | Subject Inclusion Criteria..... | 36 |
| 6.2 | Subject Exclusion Criteria..... | 38 |
| 7.0 | <i>RECRUITMENT PLAN</i> | 39 |
| 8.0 | <i>PRETREATMENT EVALUATION</i> | 40 |
| 9.0 | <i>TREATMENT/INTERVENTION PLAN</i> | 42 |
| 9.1 | CHEMOTHERAPY ADMINISTRATION..... | 42 |
| 9.2 | SUPPORTIVE CARE GUIDELINES | 44 |
| 9.3 | TREATMENT PARAMETERS, DOSE DELAYS AND MODIFICATIONS | 46 |
| 9.4 | CORRELATIVE STUDIES | 53 |



| | | |
|-------------|--|-----------|
| 10.0 | <i>EVALUATION DURING TREATMENT/INTERVENTION</i> | 56 |
| 10.1 | <i>FOR PARTICIPATING SITES</i> | 57 |
| 11.0 | <i>TOXICITIES/SIDE EFFECTS</i> | 58 |
| 11.1 | CISPLATIN | 58 |
| 11.2 | DOCETAXEL | 59 |
| 11.3 | FLUOROURACIL | 59 |
| 11.4 | LEUCOVORIN..... | 59 |
| 11.5 | TRASTUZUMAB | 59 |
| 11.6 | SUPPORTIVE MEDICATIONS | 59 |
| 12.1 | DEFINITIONS..... | 60 |
| 12.2 | EVALUATION OF TARGET LESIONS | 61 |
| 12.3 | EVALUATION OF NON-TARGET LESIONS | 61 |
| 12.4 | EVALUATION OF BEST OVERALL RESPONSE..... | 62 |
| 12.5 | GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE | 62 |
| 12.6 | CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE..... | 63 |
| 13.0 | <i>CRITERIA FOR REMOVAL FROM STUDY</i> | 63 |
| 13.1 | DURATION OF THERAPY / CRITERIA FOR REMOVAL FROM STUDY | 63 |
| 13.2 | OFF-STUDY EVALUATION | 64 |
| 14.0 | <i>BIOSTATISTICS</i> | 65 |
| 15.0 | <i>RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES</i> | 67 |
| 15.1 | RESEARCH PARTICIPANT REGISTRATION | 67 |
| 15.3 | RANDOMIZATION | 69 |
| 16.0 | <i>DATA MANAGEMENT ISSUES</i> | 69 |
| 16.1 | QUALITY ASSURANCE | 71 |
| 16.2 | DATA AND SAFETY MONITORING | 72 |
| 16.3 | ETHICAL AND ADMINISTRATIVE ISSUES | 73 |
| 16.4 | INSTITUTIONAL REVIEW BOARD APPROVAL | 73 |
| 17.0 | <i>PROTECTION OF HUMAN SUBJECTS</i> | 75 |
| 17.1 | PRIVACY..... | 76 |
| 17.2 | SERIOUS ADVERSE EVENT (SAE) REPORTING | 76 |
| 17.3 | SERIOUS ADVERSE EVENT REPORTING FOR OUTSIDE CENTERS..... | 79 |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

18.0 INFORMED CONSENT PROCEDURES..... 80

18.1 FOR PARTICIPATING SITES 80

19.0 REFERENCE(S) 81

20.0 APPENDICES..... 85



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Objectives

Primary:

- 1) To determine the efficacy of modified docetaxel, cisplatin, and fluorouracil (mDCF) (ARM A) and the efficacy of parent DCF with growth factor support (ARM B) in patients with unresectable or metastatic gastric or gastroesophageal junction(GEJ) adenocarcinoma as measured by 6 month progression free survival (PFS).

Secondary:

- 2) To establish the safety of mDCF and parent DCF with growth factor support in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 3) To observe other measures of efficacy of mDCF and parent DCF with growth factor support, including response rate, median PFS, overall and 1-year survival in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 4) To explore the association of early FDG-PET imaging with treatment efficacy.
- 5) To explore the differences in docetaxel pharmacology between both study arms.
- 6) To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.
- 7) To report the efficacy of mDCF with trastuzumab as measured by 6 month PFS amongst Her2 positive patients.
- 8) To report the safety profile of patients receiving mDCF and trastuzumab.

1.2 Eligibility

Patients with histologically confirmed metastatic or unresectable gastric or gastroesophageal junction adenocarcinoma are eligible for entry into this Phase II study. Patients may have received neoadjuvant and/or adjuvant chemotherapy or chemoradiotherapy. Patients may not have received previous chemotherapy containing cisplatin or docetaxel. Prior fluorouracil is allowed if more than 6 months have passed since the patient last received it. Patients must provide written informed consent prior to study enrollment.

Patients must be at least 18 years of age, and use birth control if male, or if female of childbearing age. Patients must have a Karnofsky performance status of greater than or equal to 70% (ECOG < 2), and be of sound mind to sign informed consent. Hematologic/ laboratory criteria for eligibility include: WBC \geq 3000/mm³, ANC \geq 1500/mm³, hemoglobin \geq 9 g/dl, platelet count \geq 100,000/mm³, serum creatinine \leq 1.5 mg/dl. For patients with a serum creatinine of 1.2-1.5, their creatinine clearance must be at least 50 ml/min. Total serum bilirubin \leq 1.5, serum AST(SGOT)/ALT(SGPT) and ALK PHOS levels as per chart below:

| | AST or ALT: | | | |
|---------------------|-------------|-------------------------|-------------------------|------------|
| ALK PHOS: | \leq ULN | >1x but \leq 1.5x ULN | >1.5x but \leq 5x ULN | >5x ULN |
| \leq ULN | Eligible | Eligible | Eligible | Ineligible |
| >1x but \leq 2.5x | Eligible | Eligible | Ineligible | Ineligible |
| >2.5x but \leq 5x | Eligible | Ineligible | Ineligible | Ineligible |
| >5x ULN | Ineligible | Ineligible | Ineligible | Ineligible |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients must have a PT (INR) ≤ 1.5 and a PTT ≤ 3 seconds above the upper limits of normal if they are not on anticoagulation. Women of childbearing potential must also have a negative pregnancy test. Biopsy confirmation of M1 disease is encouraged, unless the risk of such a procedure is significant, in which case confirmation by a 2nd imaging modality is required. Exclusions include patients with brain or central nervous system metastases, patients with significant co-morbidities including cardiac diseases, serious non-healing wound or ulcer, peripheral vascular disease or stroke, or significant hearing loss.

December 2009 Amendment

As of October 2009, trastuzumab plus chemotherapy is part of the NCCN standard treatment algorithm for the first line for advanced gastric/GEJ adenocarcinoma. This amendment is to allow patients who are Her2 positive to receive trastuzumab with mDCF. Her2 positive patients are defined as IHC 3+ for Her2 or FISH + (>2 HER2:CEP17). Biopsy samples (i.e. small tissue fragments) with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. $<10\%$, as per Hofmann et al¹. To receive trastuzumab, patients must have a baseline left ventricular ejection fraction of $\geq 50\%$. Her2 positive patients who receive trastuzumab will be considered as a separate cohort and independent cohort.

1.3 Treatment Plan

This will be a random assignment phase II study of two different administration schedules of docetaxel, cisplatin, and fluorouracil in patients with unresectable or metastatic gastric or GEJ adenocarcinoma. Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 OR 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg* | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments). Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments). Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter.

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

August 2010 Amendment:

Arm A has reached target accrual of 54 patients. Arm B remains closed due to toxicity. Her2 positive patients will be enrolled onto the Trastuzumab Cohort and will receive mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

1.4 Pharmacology and Pharmacodynamics (MSKCC patients only)

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4. Similarly, we hypothesize that inhibition of CYP3A4 by these anti-emetic agents would result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity.

Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 (15 min following the end of docetaxel infusion)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each of these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

March 2008 Addendum: On our initial pharmacokinetic analysis, we have observed that the clearance of docetaxel appears to be reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen. Based on this, we will expand our pharmacokinetic evaluation and examine additional docetaxel PK without cisplatin in up to 6 patients randomized to parent DCF who underwent cycle 1 docetaxel PK (when cisplatin was administered on day 1 as well). See section 9.4.3.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

1.5 Correlative Studies

A. One objective is to store pre-treatment paraffin embedded tumor tissue for future tissue based correlative studies. We will keep a tissue bank for these future immunohistochemistry based exploratory studies.

HER2 testing will be performed in all patients to better characterize HER2-positive gastric cancer in US patients. HER2 testing will be performed by the MSKCC diagnostic molecular laboratory on banked tumor specimens from the patients currently enrolled on the protocol and prospectively on all the patients screened for protocol participation. FISH is performed using FDA-approved ERBB2 (HER2/NEU) PathVysion assay probes and procedure (Abbott-Vysis). IHC staining is performed using FDA-approved anti-Her2/neu Ventana's PATHWAY rabbit monoclonal primary antibody (clone 4B5) directed against the internal domain of the c-erbB-2 oncoprotein (Her2).

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

B. Another objective is to evaluate the utility of FDG-PET/CT scans to monitor response to treatment. All patients will undergo a baseline staging FDG-PET/CT scan. A second PET scan will be performed during week 3:

ARM A: following the d 15 treatment, but before week 4 (eg during day 18, 19, or 20)

ARM B: once on either day 18, 19, or 20

We hypothesize that patients with a good PET/CT response will have RECIST evidence for response at their subsequent routine imaging time point and have an increased time to progression. Alternatively, patients with a bad PET/CT response will progress early. If successful, this would allow patients to minimize toxicity by minimizing exposure to ineffective therapy.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary:

- 1) To determine the efficacy of modified docetaxel, cisplatin, and fluorouracil (mDCF) (ARM A) and the efficacy of parent DCF with growth factor support (ARM B) in patients with unresectable or metastatic gastric or gastroesophageal junction(GEJ) adenocarcinoma as measured by 6 month progression free survival.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Secondary:

- 2) To establish the safety of mDCF and parent DCF with growth factor support in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 3) To observe other measures of efficacy of mDCF and parent DCF with growth factor support, including response rate, median PFS, overall and 1-year survival in patients with unresectable or metastatic gastric or GEJ adenocarcinoma.
- 4) To explore the association of early FDG-PET imaging with treatment efficacy.
- 5) To explore the differences in docetaxel pharmacology between both study arms.
- 6) To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.
- 7) To report the efficacy of mDCF with trastuzumab as measured by 6 month PFS amongst Her2 positive patients.
- 8) To report the safety profile of patients receiving mDCF and trastuzumab.

3.0 BACKGROUND AND RATIONALE

3.1 SCOPE OF DISEASE AND ROLE OF CHEMOTHERAPY

Gastric cancer is an aggressive neoplasm that is associated with an extremely poor prognosis. Median survival for metastatic or unresectable disease is approximately 8 to 10 months. On a global basis, cancer of the stomach is the third most prevalent malignancy worldwide, with 947,000 expected new cases in 2000, and the second leading cancer cause of death (734,000 deaths annually). [1]

Unfortunately, despite its enormous global impact, we have made little progress in the treatment of this disease. Conventional chemotherapy for metastatic gastric cancer remains palliative, with few patients ever demonstrating long term survival. Historically, most tumors develop rapid drug resistance and evidence of disease progression within a few months of initiation of therapy. However, palliative chemotherapy has a proven survival advantage over best supportive care for gastric cancer. Four randomized trials have all shown that patients assigned to receive best supportive care alone, even when allowed to receive chemotherapy at a later date, did significantly worse than those assigned to receive immediate chemotherapy (reviewed by Shah[2]).

3.2 COMBINATION CHEMOTHERAPY REGIMENS

The chemotherapeutic agents historically considered as active in this disease include fluorouracil, cisplatin, anthracyclines (doxorubicin and epirubicin), mitomycin C, and etoposide (reviewed previously[2, 3]). Single agent activity ranges with response rates from 10% to 20%, though the data are pooled from clinical trials performed in the 1960's and 1970's, and may be an overestimation of the true single agent activity as assessed by objective radiographic measurements.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Several combination regimens have been developed with the aims of improving overall response rates and duration of response. Table 1 summarizes the results of large random assignment studies involving these combination regimens. A three arm random assignment trial comparing ELF (etoposide, leucovorin, fluorouracil bolus), CF (cisplatin, fluorouracil infusion), and FAMTX (fluorouracil bolus, adriamycin, and high dose methotrexate) was reported by Vanhoefer, et al in 2000[4]. Overall response rates were notably low compared to previously reported phase II studies, ranging from 9% to 20% in the three arms, and survival was equally dismal at less than 7.2 months for each of the arms. These authors concluded that none of the regimens tested should be regarded as a standard treatment for metastatic or unresectable gastric cancer[4]. Another study compared CF, UFTM (uracil, tegafur, and mitomycin), and single agent 5-FU[5]. The CF regimen was associated with a modest, significant increase in progression free survival and response rate over 5-FU (3.9 mo and RR 34% vs. 1.9 mo and 11%, respectively). However, despite these improvements, overall survival was not improved with CF, with median and 1-year survival of 7.3 months and 29% respectively, compared with 7.1 months and 28% with 5-fluorouracil alone. Notably, approximately 50% of patients who were assigned to fluorouracil alone received cisplatin based therapy on progression in this study (personal communication, Ohtsu). These authors concluded that single agent fluorouracil should remain the reference standard regimen for advanced phase gastric cancer studies[5]. A similar conclusion was drawn by the authors of another random assignment study comparing EEP (etoposide, epirubicin, and cisplatin) vs. FEP (fluorouracil, epirubicin, and cisplatin). [6]

Table 1. Phase III clinical trials for gastric cancer using ‘older’ combination regimens (modified from Shah[2]).

| Reference | Disease | Treatment Regimen ¹ | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival | p value |
|--------------------|---------------------|--------------------------------|-----|--|-----------------------------|-----------------|---------|
| Tebbutt, 2002[7] | Esophagus + Gastric | PVI | 123 | 16.1% (9.5- 22.7%) | 22.5% (15.2-30%) | 6.3 mo | NS |
| | | PVI + MMC | 127 | 19.1% (12- 26.0%) | 18.4% (12-25.9%) | 5.3 mo | |
| Ohtsu, 2003[5] | Gastric | FU | 105 | 11.4% (6- 19.1%) | 28% | 7.1 mo | NS |
| | | FU + Cisplatin | 105 | 34.3% (25.3 - 44.2%) | 28% | 7.3 mo | |
| | | UFTM | 70 | 8.6% (3 – 18 %) | 16% | 6.0 mo | |
| Icli, 1998[6] | Gastric | EEP | 64 | 20.3%(12-59%) | 16 % ³ | 6.0 mo | NS |
| | | FEP | 67 | 15.3%(9- 59%) | 11 % ³ | 5.0 mo | |
| Vanhoefer, 2000[4] | Gastric | ELF | 132 | 9% (3.5-17.5%) | 28% | 7.2 mo | NS |
| | | CF | 134 | 20% (11 -30%) | 32% | 7.2 mo | |
| | | FAMTX | 133 | 12% (6-20.5%) | 33% | 6.7 mo | |

¹ Treatment Regimens: PVI = continuous infusion FU (300 mg/m²/d), MMC = mitomycin, EEP = etoposide, epirubicin, cisplatin, FEP = fluorouracil (bolus), epirubicin, cisplatin, CF = cisplatin, fluorouracil., UFTM = uracil, tegafur, mitomycin

² RR in evaluable patients, ³ 1-year survival estimated from Kaplan-Meier curves.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

3.3 IS THERE A “STANDARD” CHEMOTHERAPY REGIMEN?

Current or *modern* combination chemotherapy regimens have included prolonged infusional schedules of fluorouracil in combination with cisplatin and epirubicin (ECF), docetaxel, cisplatin and a 5 day fluorouracil infusion (DCF), and irinotecan based combinations both with cisplatin and with fluorouracil infusions. The data regarding these combination chemotherapy regimens are summarized in table 2 below. The overall efficacy as assessed by response rate, median and overall survival, and 1-year survival of these combination regimens appear to be improved over the combination chemotherapy regimens listed in table 1. However, as discussed below, specific issues surround each of these regimens that limit their general acceptability as a “standard” combination chemotherapy regimen for this disease.

Table 2. Recent studies for gastric cancer using modern regimens.

| Reference | Disease | Treatment Regimen ¹ | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival | p value |
|---|---|--------------------------------|-----|--|-----------------------------|--------------------------------------|-----------|
| <i>ECF based Phase III studies</i> | | | | | | | |
| Ross, 2002[8] | Esophagus + Gastric | ECF | 289 | 42.4% (37– 48%) | 40.2% (34– 46%) | 9.4 mo | NS |
| | | MCF | 285 | 44.1% (38– 50%) | 37.7% (27-38%) | 8.7 mo | |
| Webb, 1997[9, 10] | Esophagus + Gastric | ECF | 121 | 46% (37-55%) | 37% (28-45%) | 8.7 mo | p < 0.01 |
| | | FAMTX | 116 | 21% (13-28%) | 22% (15-29%) | 6.1 mo | |
| <i>DCF vs. CF phase III study</i> | | | | | | | |
| Ajani, 2003[11], Moiseyenko 2005[12] | Gastric + GEJ | DCF | 221 | 36.7% (30.3 – 43.4%) | 40.2% | 9.2 mo (8.38 – 10.58) | p = 0.02 |
| | | CF | 224 | 25.4% (19.9 – 31.7%) | 31.6% | 8.6 mo (7.16 – 9.46) | |
| <i>Irinotecan based studies (Note only the Dank is a phase III study)</i> | | | | | | | |
| Pooled results [13-15] | Esophagus + Gastric | Irinotecan/C isplatin | 105 | 48 % - 58% | | | |
| Pozzo et al. 2004[16] | Gastric + GEJ (Random assignment phase II) | Irinotecan/C isplatin | 56 | 32.1% (20.3 – 46%) ³ | 25.3% | 6.9 mo (5.55 - 8.67 mo) ⁴ | p = 0.002 |
| | | Irinotecan/F U infusion/ FA | 59 | 42.4 % (29.6 – 55.9%) ³ | 44.9% | 10.7 mo (8.02-14.62 mo) ⁴ | |
| Dank et al. 2005[17] | Gastric + GEJ | Irinotecan/F U infusion/ FA | 170 | 31.8% | | 9.0 mo (8.3 – 10.2 mo) | p = 0.53 |
| | | CF | 165 | 25.8% | | 8.7 mo (7.8 – 9.8 mo) | |

¹ Treatment Regimens: ECF = epirubicin, cisplatin, fluorouracil (continuous infusion), MCF = mitomycin, cisplatin, fluorouracil, DCF = docetaxel, cisplatin, fluorouracil, CF = cisplatin, fluorouracil.

² RR in evaluable patients. ³ Per protocol population, ⁴ Full analysis population

3.3.1 The ECF Regimen

The ECF regimen has recently been examined in two large random assignment studies (see table 2). First, ECF was compared with FAMTX, [10] with an update of the results recently reported by Waters, et al. [9] This study randomly assigned 274 patients (137 in each group) to receive ECF or FAMTX. ECF was associated with a better response rate (46% vs. 21%, p = 0.0002) and



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

an improvement in median survival (8.7 mo vs. 6.1 mo, $p = 0.0005$) when compared to FAMTX. However, this study was not generally accepted because of an apparent imbalance in the number of patients proceeding to surgery for locally advanced disease between the two arms.

The investigators then proceeded to examine ECF versus MCF (mitomycin, cisplatin, and infusional fluorouracil) in what is the largest random assignment study of chemotherapy in metastatic or unresectable esophagogastric cancer published to date[8]. This study randomly assigned 574 eligible patients with esophagus ($n=188$), gastroesophageal junction ($n=125$), or gastric cancers ($n=221$) to receive either ECF ($n=289$) or MCF ($n=285$). Response to therapy was equivalent (42.4% for ECF vs. 44.1% for MCF), as was survival (median survival 9.4 mo for ECF vs. 8.7 mo for MCF). Although ECF appeared to have greater toxicity, global quality of life scores were maintained in the ECF arm, whereas they fell in the MCF arm, suggesting that ECF was subjectively perhaps a more tolerable regimen[8]. Notably, the fluorouracil administration in the MCF arm was 50% higher ($300 \text{ mg/m}^2/\text{day}$) than in the ECF arm ($\text{FU } 200 \text{ mg/m}^2/\text{day}$) resulting in an imbalance between total fluorouracil administered between the two arms (net 42% higher with MCF, $p < 0.00001$). Although this study confirmed the activity of ECF in esophagogastric tumors, it also raises the question as to the role of epirubicin in a cisplatin-fluorouracil combination. The study also confirmed that the prognosis of patients with esophagogastric tumors not amenable to resection remains dismal (with median survival remaining less than 10 months).

3.3.2 Docetaxel Based Combination Therapy

Taxanes and taxane containing combinations have considerable activity in the treatment of gastric cancer. Although both paclitaxel and docetaxel have similar single agent response rates in the first line setting, occasional complete responses were reported with docetaxel. Both drugs have been examined with combination chemotherapy regimens with cisplatin, with associated improvements in response rates (ranging from 37% to 56%) and complete responses. [18, 19]

Based on the single agent and early combination activity observed with docetaxel-based therapy in upper gastrointestinal malignancies, docetaxel was examined in combination with cisplatin and fluorouracil (DCF) and compared with the 'standard' chemotherapy regimen of CF in a large random assignment phase III study (see table 2). [12]The results reported at ASCO 2005 demonstrate a significant improvement in time to progression (primary endpoint) with the docetaxel containing combination (5.6 vs. 3.7 months, $p=0.0004$) as well as an improvement in median and overall survival (median survival of 9.2 vs. 8.6 months, $p = 0.02$) with the addition of docetaxel to cisplatin + fluorouracil when compared with CF alone. At 6 months, 42.7% of the DCF-treated subjects had not progressed compared with 27.4% of the CF-treated subjects.

However, both DCF and CF was associated with significant toxicity (see table 3). Notably, in the DCF arm 82% of patients developed grade 3-4 neutropenia and 30% developed febrile neutropenia or a neutropenic infection. This is significantly more than the control arm of cisplatin and fluorouracil infusion in which 57% of patients developed grade 3-4 neutropenia, and 13.5% of patients developed febrile neutropenia or neutropenia with infection.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

For both arms, the majority of patients did not receive prophylactic growth factor support. Non-hematologic toxicity was considerable as well. In the DCF arm, 81% of patients developed a non-hematologic grade 3-4 adverse event, whereas in the CF arm, there was a similar high rate of grade 3-4 non-hematologic toxicity of 75.4%. Since both arms involved a 5 day infusion of fluorouracil, the grade 3-4 stomatitis rate was considerable (46% in DCF and 61% in CF). Other notable toxicity occurring in nearly half of the patients enrolled on the DCF arm include 47% developing grade 3-4 lethargy and 45% developing grade 3-4 diarrhea.

This toxicity spectrum is very similar to the toxicity we observed in an MSKCC phase II study of DCF (as originally prescribed) given as preoperative therapy for locally advanced gastric cancer (IRB 99-66, PI David Kelsen, MD). In this study, which was closed early due to toxicity, three out of the first 8 patients enrolled were unable to complete 2 cycles of preoperative DCF therapy due to significant treatment related toxicity. This suggests that the toxicity with the parent DCF regimen is significant, not only in patients with advanced, metastatic disease who may have been predicted to tolerate less aggressive therapy, but also in patients with locally advanced disease with less disease burden who generally are felt to tolerate treatment better.

Table 3. Toxicity of DCF and CF [12]

| Adverse Event | Grade 3-4 DCF | Grade 3-4 CF |
|--|------------------|-----------------|
| <i>Hematologic Toxicity</i> | | |
| Neutropenia | 82.3 | 56.8 |
| Febrile neutropenia or neutropenic infection | 30 | 13.5 |
| <i>Non-Hematologic Toxicity</i> | | |
| Neurosensory | 17 | 7 |
| Infection | 36 | 23 |
| Anorexia | 29 | 26 |
| Nausea | 35 | 42 |
| Vomiting | 33 | 42 |
| Lethargy | 47 | 40 |
| Diarrhea | 45 | 18 |
| Stomatitis | 46 | 61 |
| At least one grade 3-4 Adverse Event | 81.4 | 75.4 |
| Deaths during treatment or within 30d of Tx | 10.4 | 8.5 |

Overall, 41.2% of patients who received DCF required a dose reduction, and 47.5% of patients had a treatment related adverse event that led to a delay in treatment or dose reduction. The most common grade 3-4 side effects for the DCF arm included the following: lethargy, stomatitis, diarrhea, cancer pain, infection, nausea, vomiting, anorexia, and neuropathy. These toxicities were not considerably different than that experienced with cisplatin and fluorouracil infusion (CF). However, hematologic toxicity was considerable and significantly more with DCF than with CF. Specifically, 82.3% of patients who received DCF developed grade 3-4 neutropenia and 30% of patients developed febrile neutropenia or neutropenic infection. Notably, a portion



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

of patients (n = 41 or only 18.6% of the total study population) received prophylactic G-CSF. In this group, 63.4 % of patients developed grade 3-4 neutropenia and 12.2% of patients developed febrile neutropenia or neutropenic infection.

At this time, the question remains whether the toxicity attributable to the addition of docetaxel to CF will outweigh the modest observed improvement in survival. However, it is clear that docetaxel is an active chemotherapy agent in the treatment of this disease and that its addition to cisplatin and fluorouracil may confer a clinically important survival advantage. Based on these data, the FDA has recently approved the use of docetaxel with cisplatin and fluorouracil in the first line treatment setting for gastric and GEJ adenocarcinoma.

To capitalize on the potential survival advantage with docetaxel, efforts to reduce toxicity of the DCF regimen have been and are being pursued. These include substituting carboplatin for cisplatin, reducing FU to low-dose continuous infusion[20-22], or limiting the infusion of FU to 24 hours[23, 24] or 72 hours[25]. Unfortunately, these modifications are not clearly superior to the 'parent' DCF regimen. For example, the regimen developed by SAKK involves fluorouracil administered as a low dose continuous infusion at 300 mg/m²/day for 2 out of 3 weeks is furthest along in development. Although investigators observed approximate equivalent efficacy, they also noted approximate equivalent toxicity to the parent DCF regimen[22]. Specifically, they reported a 76% incidence of grade 3-4 neutropenia, 39% rate of febrile neutropenia, and a 44% rate of dose reductions/cycle.

Another study evaluated an alternative schedule of FU given weekly over 24 hours with leucovorin (the AIO schedule). [26] These investigators initiated a study combining this administration schedule of FU with cisplatin 50 mg/m² and docetaxel 50 mg/m² given every other week, and noted once again that more than 80% of patients required a dose reduction. They completed their phase II study with cisplatin and docetaxel at 40 mg/m² given every other week, and FU 24 hour infusion administered weekly and did notice a modest improvement in toxicity with a slight reduction in dose adjustments (62% of patients instead of over 80%). Notable grade 3/4 adverse events with this schedule included 20.4% neutropenia, 6.1% febrile neutropenia, 22.4% diarrhea, 8.2% nausea, 10.2% vomiting, and 18.4% fatigue. Although an apparent improvement over parent DCF, this schedule still was relatively toxic.

On the other hand, we are not aware of studies evaluating the combination of cisplatin and docetaxel with the de Gramont schedule of FU administration. This FU administration schedule is commonly used in colorectal cancer[27] with both irinotecan and oxaliplatin and is considered well tolerated and an improvement over bolus schedules and prolonged continuous infusion schedules of FU/LV administration. This FU administration schedule has been examined in upper GI cancers with oxaliplatin[28, 29] and is felt to be quite tolerable. Bouche et al examined the de Gramont administration schedule of FU with cisplatin 50 mg/m² in gastric and GEJ adenocarcinoma as well, and noted a slightly lower incidence of grade 3-4 neutropenia of 60%, similar rates of nausea/vomiting, and notably, a 0% incidence of grade 3-4 stomatitis[30]. This modest improvement in toxicity over cisplatin and 5-day infusion fluorouracil is particularly



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

encouraging in light of similar (or possibly slightly improved) efficacy over what is historically observed with cisplatin and 5-day infusional fluorouracil. Finally, although anecdotal, we (Dr. Shah and Dr. Kelsen) have personal experience with administering cisplatin and fluorouracil with the de Gramont schedule of FU administration and also find the regimen quite tolerable and as active.

3.3.3 Irinotecan based combination therapy

Recently, irinotecan based combinations have been evaluated in random assignment phase II and III clinical trials[16, 17, 30] (see table 2). The largest study is a random assignment phase III study involving 337 patients comparing irinotecan + fluorouracil (IF) versus cisplatin + fluorouracil (CF). [17] In this study, fluorouracil was administered weekly over 22 hours with leucovorin in the IF arm, and fluorouracil was administered as a continuous infusion over 5 days as is commonplace in the CF arm. There was no improvement in survival with IF (hazard ratio 1.08; 95%CI: 0.86-1.35), however this arm did appear to have a reduction in grade 3-4 toxicity. A second study performed by Bouche et al is a random assignment phase II study of irinotecan with fluorouracil and cisplatin with fluorouracil, using the De Gramont schedule of fluorouracil administration in both arms[30]. This study demonstrated similar results of approximate equal efficacy[30] with potentially less toxicity with irinotecan than with cisplatin.

3.3.4 Rationale for addition of trastuzumab to mDCF in HER2-positive gastric/GEJ adenocarcinoma patients.

Trastuzumab is a humanized monoclonal antibody (IgG1 isotype) directed against the extracellular region of HER2 that has been developed as a therapeutic modality for treating HER2-positive breast cancer. Trastuzumab is approved by the U.S. Food and Drug Administration (FDA) for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. Trastuzumab is also indicated as a single agent and in combination with paclitaxel for the treatment of patients with HER2-positive metastatic breast cancer. In these patients, the combination of trastuzumab plus paclitaxel results in improved response rate, time to disease progression, and overall survival compared with single-agent paclitaxel.

With the results of the recent phase III ToGA study, the benefit of trastuzumab in combination with cisplatin and fluoropyrimidine (CF) chemotherapy in HER2-positive metastatic gastric/GEJ adenocarcinoma has been established.² In this study, HER2-positive patients (FISH+ and/or IHC 3+) were randomly assigned to receive CF alone or with trastuzumab. Patients assigned to receive trastuzumab + CF had a significant improvement in overall survival (13.8 mo vs 11.1 mo, HR 0.74 [0.6-0.91], p = 0.0046). Trastuzumab is the first biological strategy to show a survival benefit in advanced GC. Based on these results, trastuzumab is now in the NCCN compendium for treatment of patients with HER2-positive advanced gastric cancer in combination with systemic chemotherapy.

This amendment is written to ensure that Her2 positive gastric cancer patients are able to receive trastuzumab with chemotherapy in the first line setting in gastric cancer. Notably, the ToGA study involved an acceptable standard two drug chemotherapy regimen to which the addition of



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

trastuzumab was randomly assigned. The rationale to incorporate trastuzumab in this study is to report the efficacy of a three drug gastric cancer regimen with trastuzumab amongst a cohort of Her2 positive patients.

3.3.5 HER2 testing in gastric/GEJ adenocarcinoma patients

Accurate HER2 testing is crucial for the successful application of trastuzumab in the clinical setting. In ToGA, HER2 positivity was defined using IHC published by Hofmann et al specifically for gastric cancer.¹ In a validation study of HER2 scoring in 168 gastric cancer resection specimens, Hofmann et al noted in gastric cancer a higher rate of tumor heterogeneity and incomplete basolateral membranous compared to breast cancer tumors. Hofmann et al investigated the application in gastric cancer of the testing methodologies commonly used to detect HER2 in breast cancer specimens and proposed a refined HER2 IHC scoring system suitable to score gastric cancer samples accurately and reproducibly. Most notably, according to the Hofmann criteria, biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e.<10%. (In Breast Cancer for example, IHC3+ requires a minimum of 30% IHC membranous staining.)

To determine if the breast ASCO/CAP guidelines for HER2 assessment can be used to accurately determine HER2 status in gastric cancer, we studied HER2 status of tumor specimens from 133 advanced gastric cancer patients undergoing treatment at MSKCC. HER2 IHC and FISH was performed for all specimens using ASCO/CAP guidelines and the Hofmann et al criteria. We found that HER2 in gastric cancer can be accurately evaluated using the breast cancer ASCO/CAP guidelines, with the exception that in small biopsy specimens with any cohesive HER2 IHC3+ or FISH+ clones should be considered HER2 positive. For the purposes of this protocol, patients that are IHC 1+ or 2+ will undergo FISH testing to confirm HER2 positivity. Patients with IHC 3+ or FISH+ (>2 HER2:CEP17) will be eligible to receive treatment with trastuzumab on study.

3.4 SUMMARY OF CHEMOTHERAPY FOR GASTRIC/GEJ ADENOCARCINOMA

A careful review of the data described above reveals that there is no consensus standard chemotherapy regimen for the first line treatment of unresectable or metastatic gastric/GEJ adenocarcinoma at this time. Although chemotherapy is better than best supportive care, we have observed little to no improvement in overall survival beyond 8-10 months in randomized controlled clinical trials examining several different combination treatments. Cisplatin and fluorouracil based therapy is most commonly used as the reference arm in these random assignment phase III studies, and as a component of the investigational arm in several of these random assignment phase III studies.

The addition of docetaxel to cisplatin and fluorouracil is superior to cisplatin and fluorouracil alone. Based on this, docetaxel has received FDA and European Union approval in combination with fluorouracil and cisplatin for the first line treatment of gastric and GEJ adenocarcinoma. However, the toxicity of this three drug regimen, although not significantly worse than cisplatin



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

and fluorouracil infusion alone, is still significant, and is the primary limitation of its widespread acceptance.

December 2009 Amendment

With the recent compendium listing of trastuzumab as part of the first line treatment of gastric cancer, trastuzumab is now indicated in the first line setting with combination chemotherapy for the treatment of advanced gastric/GEJ adenocarcinoma. Patients who are Her2 positive should receive standard combination chemotherapy with trastuzumab. Patients who receive trastuzumab will be considered as a separate and independent cohort from the primary analysis.

3.5 PROPOSAL

With recent FDA and European Union approval, a combination of docetaxel, cisplatin and fluorouracil is now an acceptable standard regimen for the first line treatment of gastric and gastroesophageal junction adenocarcinomas. However, the toxicity of the parent DCF regimen as originally prescribed has prevented its widespread acceptance and usage.

We therefore propose to evaluate two modifications of the parent DCF regimen in a random assignment phase II clinical trial. In ARM A, we propose a modified DCF schedule with the following specific modifications to parent DCF: (1) a de Gramont schedule for FU administration, (2) reduced bi-monthly doses of cisplatin and docetaxel, and (3) the administration of docetaxel and cisplatin on consecutive days instead of immediately following one another. See section 3.5.1 for detailed discussion for the rationale of the mDCF schedule.

In ARM B, we will examine parent DCF with prophylactic growth factor support. Recall that in the TAX325 study, patients who received prophylactic G-CSF had a significantly reduced incidence of grade 3-4 neutropenia and incidence of febrile neutropenia or neutropenia with infection.

With this study, we will establish the efficacy and tolerability of modified DCF and of parent DCF with growth factor support. If mDCF appears to maintain the efficacy of the parent DCF regimen with less toxicity, we will have established a new treatment regimen for this disease to which targeted agents can be examined.

December 2009 Amendment

Due to toxicity, Arm B is now closed to further accrual. Arm A will continue to enroll until target accrual. In addition, patients who are Her2 positive will receive trastuzumab with mDCF, in a separate, independent cohort.

August 2010 Amendment

We have reached target accrual in Arm A. Her2 positive patients will receive trastuzumab with mDCF, in a separate, independent cohort.

3.5.1 Modified DCF dose and schedule determination

The specific modifications to parent DCF that we have proposed include (1) a de Gramont schedule for FU administration, (2) reduced bi-monthly doses of cisplatin and docetaxel, and (3)



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

the administration of docetaxel and cisplatin on consecutive days instead of immediately following one another.

We believe that a modified FU administration schedule (bolus + 48 hour infusion of FU) will confer less toxicity than longer infusion schedules of FU currently in use (eg. 5 day infusion used in parent DCF) with similar efficacy. Several lines of evidence from gastric cancer studies support altering the FU schedule to a bolus + 48 hour infusion and to administering chemotherapy bi-monthly at reduced doses. The most convincing is from Bouche et al. that describes a three arm random assignment phase II study with each arm receiving LV5FU2[30]. LV5FU2 is the same FU administration schedule as we have proposed in this study (bolus + 48 hr infusion). In the Bouche study, Arm A was LF5FU2 alone, arm B was cisplatin 50 mg/m² with LV5FU2, and arm C was irinotecan + LV5FU2. The response rate and survival of LV5FU2 (arm A) is consistent with that reported for single agent FU[5]. In addition, the response rate and survival of arm B (Cisplatin + LV5FU2) is consistent with that reported for cisplatin and FU x 5 day infusion schedules[5, 11, 17]. Notably, the efficacy is maintained while keeping the relative dose intensity for cisplatin identical to the historical standard of cisplatin and fluorouracil 5-day infusion. Specifically when cisplatin is administered with the 5-day infusion of FU, it is given at 100 mg/m² every 4-weeks which yields a dose intensity of 25 mg/m²/week. When cisplatin is administered with LV5FU2, it is administered at 50 mg/m² every other week, which yields an equivalent dose intensity of 25mg/m²/week.

The table below describes the efficacy of cisplatin and infusional FU (control arms) as observed in 3 recent large phase III studies and of cisplatin + LV5FU2 as described in the Bouche et al study.

| Reference | Treatment Regimen | n | Response Rate ² (95% CI) | 1-Year Survival (95% CI) | Median Survival |
|---|------------------------------|-----|--|-----------------------------|---------------------------|
| Ajani, 2003[11], Moiseyenko 2005[12] | Cisplatin + Infusional FU | 224 | 25.4% (19.9 – 31.7%) | 31.6% | 8.6 mo (7.16 – 9.46) |
| Ohtsu, 2003[5] | Cisplatin + Infusional FU | 105 | 34.3% (25.3 - 44.2%) | 28% | 7.3 mo |
| Dank 2005[17] | Cisplatin + Infusional FU | 165 | 25.8% | | 8.7 mo (7.8 – 9.8 mo) |
| Bouche, 2004 [30] | Cisplatin + LV5FU2 | 44 | 27% (14% - 40%) | 43% | 9.5 mo (6.9 – 12.2 mo) |

The FU administration schedule (bolus + 48 hour, or LV5FU2) with bi-monthly cisplatin administration confers approximate equal efficacy with regard to response rate, 1-year survival, and median survival when compared to the traditional cisplatin + infusional FU x 5 day schedule.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

With regard to the question of equal or reduced toxicity, the table below summarizes the relevant toxicity comparison:

| Toxicity (Grade 3-4) | Cisplatin + LV5FU2 (Bouche et al) (n=44) | Cisplatin + 5-day FU Infusion (Moiseyenko et al) (n=224) |
|----------------------|---|---|
| Neutropenia | 61% | 57% |
| Febrile neutropenia | 18% | 14% |
| Nausea/vomiting | 23% | 42% |
| Diarrhea | 2% | 18% |
| Mucositis | 0% | 61% |

As shown, the toxicity of the bolus + 48 hour FU infusion and reduced bi-monthly administration of cisplatin schedule is significantly less toxic with regard to diarrhea, mucositis, nausea and vomiting. Neutropenia is approximately equivalent. Thus, because of approximate equal efficacy with considerably less toxicity, the proposed administration schedule is a significant improvement over the traditional cisplatin + 5-day FU infusion schedule. Finally, we also have experience with docetaxel and cisplatin administered with this fluorouracil administration schedule in several patients with upper GI malignancies and have found the regimen be both quite tolerable and active (Shah and Kelsen, personal communication). Based on these data above, we feel that administering fluorouracil as per the De Gramont schedule (bolus + 48 hour infusion) provides approximate equivalent efficacy to 5 day FU administration schedules. When coupled with less frequent dosing of cisplatin, the combination is associated with less toxicity.

With regard to the best dose of cisplatin and docetaxel when both drugs are administered together with fluorouracil, two gastric cancer studies provide additional support (Lorenzen described here and Oh described below). A phase II study by Lorenzen and colleagues was reported at the 2006 GI Cancer symposium (San Francisco, CA) in which docetaxel and cisplatin (50 mg/m² each) were administered every other week in combination with a 24 hour infusion of FU (2,000 mg/m² over 24 hours) which was administered weekly[26]. The investigators felt that the combination at those doses of cisplatin and docetaxel was still too toxic and amended their study to administer docetaxel and cisplatin at a reduced dose of 40 mg/m² every other week. With these lower doses (eg. the doses that we have proposed), the investigators reported approximately equal efficacy to parent DCF with slightly improved toxicity including grade 3-4 neutropenia 20% and nausea/vomiting 20%, thus supporting our proposal.

Finally, by separating the docetaxel and cisplatin, we believe we will have even less toxicity due, in part, to improving docetaxel clearance when compared to the combined administration. The rationale for this is that docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and the standard antiemetics used when giving cisplatin (eg. aprepitant and palonosetron) also are CYP3A4 inhibitors. Thus, by administering cisplatin on a different day from docetaxel, the clearance of docetaxel should improve, thus reducing toxicity. This will be examined in the parallel random assignment study in which one arm will be mDCF and the other



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

arm will be parent DCF in which the docetaxel and cisplatin are administered on the same day immediately following one another.

A recent phase II report of a Korean study of docetaxel + cisplatin + fluorouracil provides support for this hypothesis[31]. Specifically, in this phase II study, docetaxel was administered on day 1 (70 mg/m²), cisplatin was administered on days 2 and 3 (40 mg/m² each day), and fluorouracil was administered over 10 hours on days 1, 2 and 3. The regimen was repeated every 3 weeks and again demonstrated approximate equal efficacy to parent DCF. However most interestingly, the incidence of grade 3 or 4 toxicity including nausea, vomiting, diarrhea, leucopenia or neutropenia, and mucositis was each less than 10%, which is a remarkable improvement over the parent DCF regimen in which these toxicities were 40% or higher and 80% for grade 3-4 neutropenia. The investigators were unable to explain this reduced toxicity and hypothesized that it may be related to the Korean population of the study. Alternatively, a potential PK interaction between cisplatin anti-emetics and docetaxel may explain this improved toxicity.

The table below describes the relative dose intensity of the parent DCF (as scheduled and as actually delivered) and modified DCF:

| Modified DCF q other week | | | ARM B – Parent DCF q 3 weeks | | | |
|---------------------------|---------------------------|---|------------------------------|-------------------------------------|--|--|
| Drug | Dose (mg/m ²) | Dose Intensity (mg/m ² per wk) | Drug | Scheduled Dose (mg/m ²) | Dose Intensity (mg/m ² /wk) | Delivered Dose Intensity (mg/m ² /wk) |
| Docetaxel | 40 | 20 | Docetaxel | 75 | 25 | 22 |
| Cisplatin | 40 | 20 | Cisplatin | 75 | 25 | 22 |
| Leucovorin | 400 | X | | | | |
| Fluorouracil | 400 | X | Fluorouracil | 750 | X | X |
| Fluorouracil | 1000 | X | | | | |

As shown, the proposed dose of docetaxel and cisplatin in the modified DCF regimen represent 80% of the scheduled dose of the parent DCF regimen. However, the proposed dose is in fact 90% of the delivered dose of the parent regimen.

Thus, based on the data shown above, there is sufficient evidence from a number of sources to consider modified DCF as a reasonably safe and effective DCF regimen.

- (1) The bolus and 48 hour infusion schedule of FU is equivalent to the 5-day infusion schedule of FU but is associated with less toxicity.
- (2) Administering reduced bi-monthly doses of docetaxel and cisplatin with FU confers less toxicity also while maintaining efficacy. This toxicity profile may be further improved by administering docetaxel and cisplatin on different days due to a possible pharmacokinetic interaction between docetaxel and the delayed emesis regimen used for cisplatin.
- (3) The dose intensity of cisplatin and docetaxel in the proposed mDCF regimen is insignificantly different from what was delivered in the parent DCF regimen.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

3.5.2 Pharmacokinetic and Pharmacodynamic Considerations (MSKCC ONLY)

Two initial phase I studies examined the combination of docetaxel and cisplatin[32, 33]. Pronk and colleagues evaluated two schedules of administration: Schedule A administered cisplatin as a 3 hour infusion 3 hours following 1-hour docetaxel infusion ($D_{1\text{hour}} \rightarrow 3\text{hr break} \rightarrow C_{3\text{hour}}$), and Schedule B administered cisplatin over 3 hours one day prior to docetaxel ($C_{3\text{hour}}$ day 1 $\rightarrow D_{1\text{hour}}$ day 2). These investigators noted that there was a trend toward greater hematologic toxicity with schedule B where cisplatin is given prior to docetaxel. This is consistent with the previous data regarding the sequence of administration of cisplatin and paclitaxel[34], and may be related to higher DNA-adduct formation and intracellular accumulation of cisplatin in human leukocytes if given prior to the taxane[35]. Pronk noted no significant differences in the pharmacokinetic parameters of cisplatin and docetaxel with the two schedules examined in their study[32]. However, the authors did point out the 21 hour time interval between cisplatin and docetaxel in schedule B, and noted that when cisplatin precedes paclitaxel by 6 hours, paclitaxel clearance reduced by 25% [34]. The 2nd phase I study by Millward et al. administered cisplatin over 1 hour immediately following docetaxel 1 hour infusion[33]. They also noted no pharmacokinetic interactions. In addition, they also evaluated the Pronk schedule A sequence of $D_{1\text{hour}} \rightarrow 3\text{hr break} \rightarrow C_{3\text{hour}}$ and it appeared that in a small number of patients, there was increased toxicity when administering cisplatin 3 hours following docetaxel instead of immediately following docetaxel. Since these studies were published in 1997, the convention for virtually all subsequent evaluations involving the combination of docetaxel and cisplatin administered the drugs as described by Millward et al with docetaxel given over 1 hour and then followed immediately with cisplatin administered over 1 hour.

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem[36]. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4[37, 38]. Indeed, this inhibition results in reduced clearance of the concomitantly administered steroid, dexamethasone, resulting in the recommended reduced dose of dexamethasone when administered with aprepitant and palonosetron[39]. Similarly, inhibition of CYP3A4 by these anti-emetic agents could result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity. However, a recent evaluation demonstrated no significant role of aprepitant on the pharmacokinetics of docetaxel[40]. However, this study did not examine docetaxel metabolites. In one study, detection of the M4 docetaxel metabolite may indicate reduced docetaxel clearance and possibly increased myelosuppression[41].

In our experience, we have observed that the co-administration of docetaxel and cisplatin on the same day in combination with fluorouracil infusion is associated with significant nausea, vomiting, and delayed emesis – in particular, significantly more so than when either cisplatin or docetaxel is administered alone with the same fluorouracil schedule. Aprepitant and palonosetron may be used to prevent acute and delayed emesis from cisplatin. However, it may inadvertently result in reduced docetaxel clearance and increased docetaxel related toxicity, or if not the parent compound, possibly reduced clearance of a metabolite. We note that the anti-emetic drugs, aprepitant and palonosetron, are administered primarily for cisplatin associated



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

nausea and vomiting. Based on these findings, we have moved cisplatin to be administered 1-2 days following docetaxel in several patients treated with mDCF already. Interestingly, we have anecdotally (in approximately 10 patients) noted a considerable improvement in their tolerance to the mDCF, thus supporting this hypothesis and warranting its further evaluation.

To examine this further and more formally, we propose to evaluate the pharmacokinetics of docetaxel and its metabolites in approximately 10 patients in each arm. Recall that docetaxel and cisplatin in Arm B are both given on day 1, along with initiation of the 5 day fluorouracil infusion. We believe there will be a significant difference in docetaxel clearance in the two arms that may explain, in part, the significant toxicity of the parent DCF regimen.

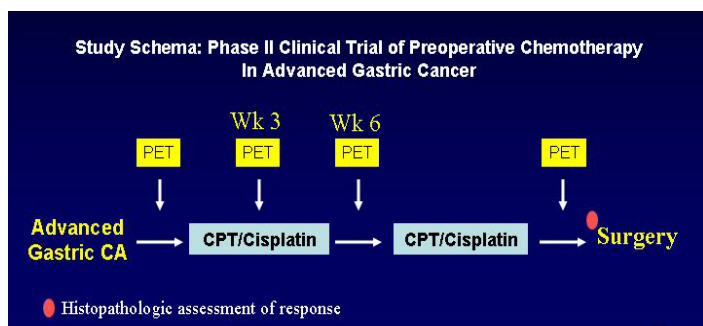
Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 (15 min following the end of docetaxel infusion)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

March 2008 Addendum: On our initial pharmacokinetic analysis, we have observed that the clearance of docetaxel appears to be reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen. Based on this, we will expand our pharmacokinetic evaluation and examine additional docetaxel PK without cisplatin in up to 6 patients randomized to parent DCF who underwent cycle 1 docetaxel PK (when cisplatin was administered on day 1 as well). See section 9.4.3.

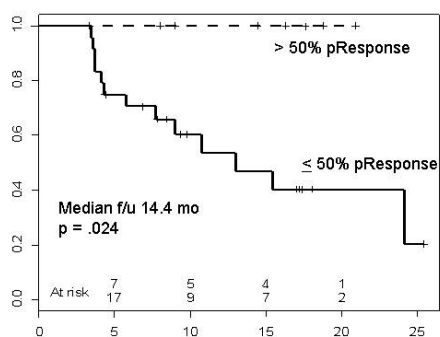
3.5.3 FDG-PET Response Assessment



We are interested in the utility of functional imaging to predict and monitor treatment response in gastric cancer. To begin to examine this question, we initiated an NCI sponsored phase II clinical trial of preoperative chemotherapy with irinotecan and cisplatin for locally advanced gastric cancer (NCI 5917). We planned to use functional imaging with FDG-PET/CT

scans early in the treatment plan to predict treatment efficacy. Patients with high-risk

Pathologic Response as a Surrogate for Recurrence
(n = 32)



gastric cancer (preoperative stage T2N+, T3-T4, Nany, M0) were eligible. The study schema is provided in the figure below. Enrolled patients received preoperative chemotherapy with cisplatin 30 mg/m² and irinotecan 65 mg/m² during weeks 1, 2, 4, 5, 7, 8, 10, and 11, prior to surgical resection. FDG-PET/CT scans were performed prior to initiation of therapy, during week 3 and week 6 (day 15 and 35, respectively), and following completion of pre-operative therapy, prior to surgery. Thus far, 42 patients have enrolled on this phase II study with the

following patient characteristics: median age 62 (range 25-83), male 29, KPS 90% (70%-90%).

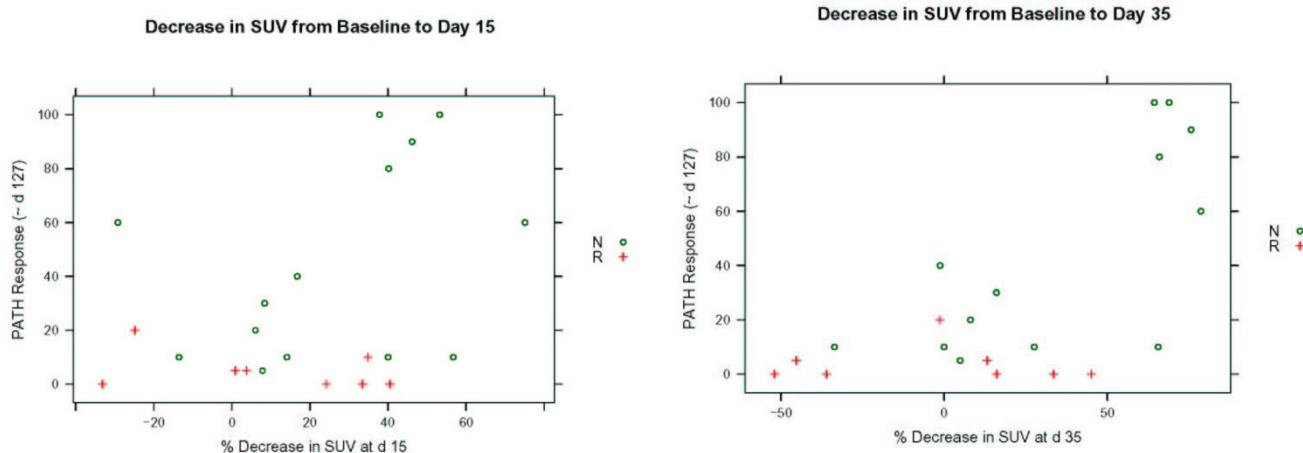
We first demonstrate that pathologic treatment response is a surrogate for treatment efficacy. Pathologic assessment of treatment response is assessed histologically, by visual assessment, based on the identification of residual cancer cells and on the extent of fibrosis[42]. In this system, a tumor regression grade (TRG) is established, and quantitated into five grades, ranging from TRG 1 (complete regression) to TRG 5 (complete absence of regressive changes). Response assessment is based on areas of tumor treatment effect that are characterized by the replacement of neoplastic tissue with fibrous tissue and scattered inflammatory cells. We have converted this grading system to a percent treatment response score from 0 to 100%, such that a TRG1 score has a 100% treatment response score, and a TRG5 has a treatment response of less than 10%. We evaluated the histopathologic response to treatment with disease free recurrence. 32 patients are evaluable thus far. Our median follow up period for these patients is 14 months and thus far, 13 patients (out of 32) have recurred. Based on this preliminary analysis, there is a significant correlation between pathologic response to therapy and disease free recurrence (see figure to the right). These data suggest that a 10% increase in pathologic response corresponds to a 49% risk reduction of recurrence (p = 0.013).



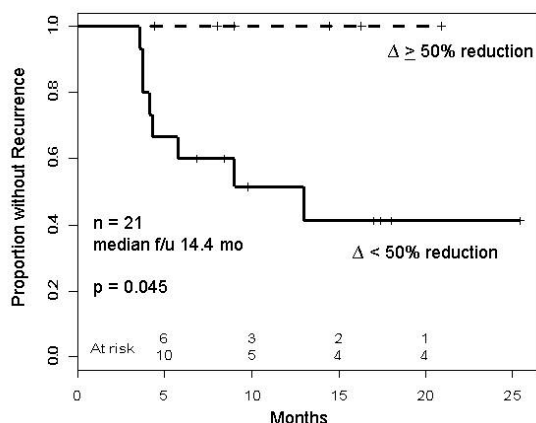
Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Next, we demonstrate the correlation between change in functional imaging and pathologic response. The two graphs below demonstrate the correlation between FDG-PET/CT response and pathologic response. It is important to point out that the FDG response assessment occurs at day 15 and at day 35, where one could potentially switch the chemotherapy regimen to alternative treatments in the hopes of improving response to therapy. Notably, the pathologic response assessment described above occurs at the time of surgical resection, approximately at day 127. At that time point, it is too late to switch therapy from ineffective therapy (eg. that associated with a minimal pathologic response to treatment) to a potentially more effective therapy. This is highlighted below by the pathologic response axis (y-axis on both graphs). Specifically, all of the patients who have recurred (red plus symbols) had a pathologic response of 20% or less. Knowing that one is destined for a poor pathologic response *a priori* would warrant a change in therapy with the hopes of improving this response. We have already demonstrated preliminary evidence that a poor pathologic response increases the probability of early recurrence, and certainly death from disease. With this in mind, the figures below demonstrate that with a high FDG response (eg. above 40% by day 15, or above 50% by day 35), the chance of achieving a high pathologic response to preoperative chemotherapy is quite high, whereas a lower FDG response is associated with a lesser degree of pathologic response and a higher chance of disease recurrence.



Correspondence between decrease in FDG SUV from baseline to on-treatment scan and pathologic response. In the graphs above, the open circles are patients who have not had a recurrence and the plus symbols represent patients who have had a recurrence.



These data support the fact that an early FDG-PET scan can predict response to chemotherapy that is identified histopathologically in the surgical resection specimen almost 3 months later. We then evaluated the association of FDG-PET response to recurrence and again found a strong and significant association (see figure to the left). This figure demonstrates the high correlation with FDG response (at day 35 in this case) and risk



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

of recurrence. A 50% or greater reduction in FDG-SUV by day 35 of the chemotherapy treatment plan is associated with an extremely low chance of disease recurrence, whereas a less than 50% reduction in FDG-SUV is associated with a significantly higher probability of disease recurrence ($p = 0.045$). Altogether, these data suggest that an early FDG-PET/CT scan, when compared with a baseline scan, may be predictive of response to preoperative chemotherapy as assessed by histopathologic response assessment and by disease free recurrence.

3.5.4 Discontinuation of chemotherapy after 6 months.

The study will allow for discontinuation of docetaxel, cisplatin, and/or fluorouracil at the discretion of the treating physician after having completed 6 months of chemotherapy. The rationale for this comes from a growing body of evidence that suggests that patients with solid tumor malignancies need not receive cytotoxic chemotherapy until disease progression. For example, in metastatic NSCLC, it is well accepted that 4 to 6 cycles of platinum based chemotherapy is a superior strategy as compared to maintenance chemotherapy (Pfister, JCO 2003). In metastatic colorectal cancer, the OPTIMOX1 study shows that intermittent dosing of oxaliplatin is less toxic and associated with an equivalent progression free survival and overall survival (Tournigand, JCO 2006). Similarly, in prostate cancer, patients who receive intermittent androgen ablation also demonstrate no evidence of decreased survival or time to progression, and did have a benefit of reduced toxicity (Calais Da Silva, ASCO 2006). Our primary endpoint is a landmark analysis of progression at 6 months. Allowing patients to discontinue cytotoxic therapy after 6 months does not interfere with our primary endpoint, and may reduce cumulative toxicity (particularly from docetaxel and cisplatin) without adversely affecting treatment efficacy.

3.5.5 Assessment of Quality of Life

The study will include an assessment of quality of life on both arms of the study at baseline, and periodically during the course of treatment. We will use the EORTC QLQ-C30 instrument to examine quality of life. This is a validated instrument that has been used in many large studies, including in gastric and gastroesophageal randomized studies (Aaronson, JNCI 1993; Glimelius, Ann Onc 1997; Ross, JCO 2002). We will administer the questionnaire at baseline, 6 weeks, 3 months, and 6, 9, and 12 months.

3.5.6 Volumetric CT Analysis of Response to Therapy (MSKCC only)

At MSKCC only and in collaboration with Larry Schwartz, MD, we will also initiate an exploratory volumetric CT analysis of Response to therapy. This study will make use of already acquired image data from this clinical trial. No additional human material or CT scans will be needed. The standard CT scan data (acquired either during PET/CT scanning or CT scanning) will be electronically transferred, via the hospital network, from the hospital PACS to the research PACS server, where patient identification information are de-identified. Volumetric CT will be used in an exploratory way to assess tumor response during therapy to compare with RECIST. The volumetric analysis, however, will not affect patient care and will not be communicated



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

to the patient or clinical investigator. To study effects of a wider range of slice thickness on the performance of the segmentation algorithms and reproducibility of tumor measurements, thinner section CT images will be reconstructed with CT raw data acquired for the radiographic assessment in the trial. The volumetric CT technique used in this study may be able to detect asymmetric or small change in tumor size at the level that may not be possible with the conventional uni-dimensional RECIST criteria.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a random assignment phase II study of two different administration schedules of docetaxel, cisplatin, and fluorouracil in patients with unresectable or metastatic gastric or GEJ adenocarcinoma. Patients may have received neoadjuvant and/or adjuvant chemotherapy or chemoradiotherapy. Patients may not have received previous chemotherapy containing cisplatin or docetaxel. Prior fluorouracil is allowed if more than 6 months have passed since the patient last received it. Patients must provide written informed consent prior to study enrollment.

At baseline, patients will require a full medical history and physical examination, including assessments of body weight, height, calculated body surface area, and vital signs (blood pressure, heart rate, respiratory rate, and temperature). Laboratory assessment will include CBC with differential, PT, PTT, comprehensive biochemical screening profile (which includes electrolytes, BUN, creatinine, AST, ALT, total bilirubin, total protein, albumin, alkaline phosphatase, and glucose), Ca, Mg, Phosphorus, LDH, and urinalysis. For females of childbearing potential, a serum pregnancy test is also required. Additional evaluation will include baseline ECG and a signed informed consent. CT scan of chest, abdomen, and pelvis will be performed in all patients and documentation of tumor measurement, in centimeters will be done. A baseline PET/CT scan will be performed as well for staging. In cases where there are multiple metastases, a representative sample of large masses, up to a total of five, will be chosen as the index lesions to be followed for a response, as per RECIST criteria. Measurable disease is not a requirement for study entry. Biopsy confirmation of M1 disease is encouraged, unless the risk of such a procedure is significant, in which case confirmation by a 2nd imaging modality is required (eg. PET/CT scan may be sufficient if tumor and metastases are both FDG avid).

December 2009 Amendment

As of October 2009, trastuzumab plus chemotherapy is part of the NCCN standard treatment algorithm for the first line for advanced gastric/GEJ adenocarcinoma. This amendment is to allow patients who are Her2 positive to receive trastuzumab with mDCF. Her2 positive patients are defined as FISH + and/or IHC 3+ for Her2. Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. <10%. FISH+ defined as >2 HER2:CEP17. To receive trastuzumab, patients must have a baseline left ventricular ejection fraction of $\geq 50\%$.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

4.2 Intervention

Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 or 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg * | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg.

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments).

Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments).

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

A given treatment may be moved +/- 14 days for specific administrative reasons, in particular clinic closure for holidays. Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter. Therapy will be administered in an outpatient setting, under the supervision of a physician and/or chemotherapy nurse, as is standard for chemotherapy administration at the treating institution.

Clinical evaluation: All assessments may be performed within one day of the planned treatment.

ARM A – Modified DCF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of cycle one (e.g. on day 1, day 15, and day 29 of cycle 1). In cycle 2 and all subsequent cycles, a physician evaluation (e.g. physical examination and toxicity assessment) will be performed prior to treatment on day 1 and day 29 treatments. Additional nurse or physician visits will be at the discretion of the treating physician. It is encouraged that an oncology nurse toxicity evaluation be performed prior to each treatment, especially if the patient is not assessed by a physician.

Patients treated with mDCF plus trastuzumab therapy should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain).

ARM B – Parent DCF with G-CSF



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of every cycle.

Laboratory evaluation:

ARM A – Modified DCF

On or within 1 day of the beginning of each cycle, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers will be performed. A CBC with differential and platelet count is required prior to each subsequent treatment (eg. day 15 and day 29). A BUN and Creatinine is required before the day 15 treatment (treatment #2), and a serum chemistry (electrolytes, BUN, Creatinine, glucose) is required before each day 29 treatment (#3). LFTs are required before each treatment (#1, #2 and #3) of cycle 1, and before treatment #1 and #3 for each subsequent cycle. Any patient with excessive LFTs abnormalities (see section 9.3) will require repeat LFTs prior to the next docetaxel administration.

ARM B – Parent DCF with G-CSF

On or within 1 day of the beginning of each treatment, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers are required.

Radiology evaluation: For both treatment arms, radiographic studies upon which tumor measurements were made will be repeated every cycle (six week intervals for most patients) for 6 cycles, and then after every two cycles of therapy (e.g. after cycles 1, 2, 3, 4, 5, 6, 8, 10, 12 etc.), to rule out progression of disease and to determine response for measurable disease.

Patients will remain on study until disease progression, patient withdrawal, unacceptable toxicity despite dose attenuation, or if the treating physician deems it is in the best interest of the patient following discussion with the principal investigator. Tolerability of this regimen will be determined from blood test results and toxicity assessment.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Docetaxel (TAXOTERE®)

For complete details, please see the package insert for further information.

5.1.1 Description

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is a white to almost-white powder with an empirical formula of



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

$C_{43}H_{53}N_{14}O_{14} \cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

5.1.2 Preparation and Administration

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing DOCETAXEL solutions. The use of gloves is recommended. Please refer to Handling and Disposal section.

If Docetaxel Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Docetaxel Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the Docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Docetaxel Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Docetaxel Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for DOCETAXEL 20 mg and DOCETAXEL 80 mg.

| Product | Diluent 13% (w/w) ethanol in water for injection Fill Range (mL) | Approximate extractable volume of diluent when entire contents are withdrawn (mL) | Concentration of the initial diluted solution (mg/mL docetaxel) |
|---------------------------|--|---|--|
| Taxotere® 20 mg/0.5 mL | 1.88 – 2.08 mL | 1.8 mL | 10 mg/mL |
| Taxotere® 80 mg/2 mL | 6.96 - 7.70 mL | 7.1 mL | 10 mg/mL |

A. Initial Diluted Solution

1. Docetaxel vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for Docetaxel 20 mg and approximately 7.1 mL for Docetaxel 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of Docetaxel Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted Docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted Docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded.

2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final Docetaxel dilution for infusion should be administered intravenously as a 30-minute to 60-minute infusion under ambient room temperature and lighting conditions.

Stability: Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared Docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

How Supplied: Docetaxel Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered as per institutional guidelines.

5.1.3 Source

For this study, locally obtained commercial supplies of Docetaxel should be used. Because commercial drug will be used, accounting for Docetaxel drug supplies is not specifically required in this study.

5.1.4 Safety Profile

Principal adverse effects include neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, ascites, mucositis, cardiac arrhythmias, hypotension, pleural effusion, peripheral neuropathy, rash, severe nail disorders (hypo or hyperpigmentation), onycholysis (loosening of the nails), alopecia, palmar-plantar dyserythroesthesia, hypersensitivity reaction, fatigue and fluid retention syndrome (may be irreversible).

5.2 CISPLATIN

For complete details, please see the package insert for further information.

5.2.1 Description

Cisplatin (cis-diaminedichloroplatinum, Platinol®) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis- position. Cisplatin binds to DNA bases and produces particular types of cisplatin-DNA lesions or adducts. The drug is supplied in 10 and 50 mg amber vials.

5.2.2 Preparation and Administration

ARM A: Cisplatin will be given on days 1, 15, and 29 of each cycle. The drug will be given at a dose of 40 mg/m² over 30 minutes on day 2 or 3 of each treatment.

ARM B: Cisplatin will be given on days 1 and 22 of each cycle. The drug will be given at a dose of 75 mg/m² over 60 minutes immediately following docetaxel administration.

Cisplatin is available in 100mg/100 ml solution vials. The solution is then further diluted into saline-based solutions (preferably 100-150 ml of 0.9% NaCL for intravenous administration). Before drug administration the patient should be given intravenous hydration with at least 500 ml of 5 % dextrose in normal saline (D5W) or normal saline over 1-2 hours. Aluminum needles should not be used. Patients will be advised to maintain an oral fluid intake of at least one (1) liter per meter squared on the day of treatment. This regimen may be adjusted as needed, e.g., for elderly persons.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

5.2.3 Source

For this study, locally obtained commercial supplies of Cisplatin should be used. Because commercial drug will be used, accounting for Cisplatin drug supplies is not specifically required in this study.

5.2.4 Safety Profile

Cumulative nephrotoxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia and hypotension may occur within minutes of cisplatin administration. Other side effects include anorexia, diarrhea, serum electrolyte disturbances (e.g., hyponatremia, hypomagnesemia), vascular toxicities (e.g., myocardial infarction, cerebrovascular accident etc.), neurotoxicity, peripheral neuropathy, autonomic neuropathy, muscle cramps, ocular toxicity (optic neuritis, papilledema, cerebral blindness), and hepatotoxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin.

5.3 FLUOROURACIL

For complete details, please see the package insert for further information.

5.3.1 Description

The chemical name of fluorouracil (FU) is 5-fluoropyrimidine-2,4(1H,3H)-dione. Fluorouracil is also known by other names 5-Fluorouracil; Fluorouracilo; Fluorouracilum; 5-FU; NSC-19893; Ro-2-9757; WR-69596. Its molecular formula is C₄H₃FN₂O₂; it has a molecular weight of 130.1. FU is a white to almost white, practically odorless, crystalline powder. It is sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and ether. A 1% solution has a pH of 4.5 to 5.0; the USP injection has a pH of 8.6 to 9.4 and the BP injection has a pH of 8.5 to 9.1. Fluorouracil is commercially available, and supplied in the U.S. by ICN pharmaceuticals, Lyphomed, Quad Pharmaceuticals, Baxter Healthcare, Abbott Laboratories, and as Adrucil® by Pharmacia & Upjohn.

5.3.2 Preparation and Administration

At our institution fluorouracil manufactured by Pharmacia & Upjohn (ADRUCIL®) is in use. It is supplied as a 50 mg/ml solution in vials of 50 ml and 100 ml. The appropriate volume is withdrawn into a syringe which is used for administration. No dilution is required. Filter ampules with aspiration needle (5µm). Compatible with D₅W, 0.9% NaCl, D₅LR. Fluorouracil will be administered as an intravenous push, usually over 1-2 minutes followed by a 48-hour intravenous continuous infusion (further dilution is not required). Ensure vein patency before administration



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Storage: Store at room temperature and protect from light. Dark yellow color indicates decomposition. Fluorouracil is stable in polypropylene syringes, and stable in PVC reservoirs for infusion pump usage for 12 days. Fluorouracil may adsorb to glass surfaces. It is stable in cellulose nitrate/acetate ester or Teflon filters.

5.3.3 Source

Locally obtained commercial supplies of Fluorouracil should be used. Because commercial drug will be used, accounting for Fluorouracil drug supplies is not specifically required in this study.

5.3.4 Safety Profile

Hematologic and gastrointestinal side effects are most frequently associated with fluorouracil. Hematologic toxicities of fluorouracil are leukopenia, granulocytopenia (9-14 days), thrombocytopenia (7-14 days), and anemia. Stomatitis, gastrointestinal ulceration and bleeding, and diarrhea are commonly seen gastrointestinal side effects of fluorouracil. Nausea and vomiting, effects on the skin including rashes and hyperpigmentation, alopecia, ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischemia have been reported. A complete listing of toxicities can be found in the fluorouracil package insert.

Drug Interactions

Allopurinol may decrease efficacy of fluorouracil. Leucovorin enhances cytotoxicity of fluorouracil by forming a more stable tertiary complex with thymidylate synthase.

5.4 LEUCOVORIN

Please see the package insert for complete details and further information.

5.4.1 Description

Leucovorin calcium is commercially available, and is a stable reduced formyl derivative and the active form of folic acid. The following products are available: Immunex (formally available from Lederle): 50 mg vial, 100 mg vial, 350 mg vial. Burroughs-Wellcome (Wellcovorin®): 100 mg vial. Chiron Therapeutics: 50 mg vial, and 100 mg vial.

5.4.2 Preparation and Administration

Leucovorin may be reconstituted with Bacteriostatic Water for Injection (BWI). Reconstitute 50 mg with 5 ml BWI, 100 mg vial with 10 ml BWI. Both of these will yield a solution of 10 mg/ml. Reconstitute 350 mg vial with 17 ml BWI to yield a solution of 20 mg/ml. Use bacteriostatic water only with doses < 10 mg/m². Leucovorin will be administered intravenously over 30 minutes prior to fluorouracil administration.

Storage: Unreconstituted vials are stored at room temperature and protected from light. The reconstituted 10 mg/ml or 20 mg/ml solution is stable for at least 7 days at room temperature.



5.4.3 Source

For this study, locally obtained commercial supplies of Leucovorin should be used. Because commercial drug will be used, accounting for leucovorin drug supplies is not specifically required in this study.

5.4.4 Safety Profile

The only adverse reaction for leucovorin is a rare report of allergic reactions to parenteral injections of leucovorin. This is extremely uncommon.

5.5 TRASTUZUMAB

Please see the package insert for complete details and further information.

5.5.1 Description

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay ($K_d = 5$ nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of trastuzumab contains 400 mg of trastuzumab, 9.9 mg of L-histidine HCl, 6.4 mg of L-histidine, 400 mg of α, α -trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6.

5.5.2 Preparation, Administration, and Storage

Dosage

Trastuzumab will be administered on q2wk dosing schedule, with initial loading dose of 6 mg/kg as a 90 minute infusion, followed by trastuzumab 4 mg/kg q2wk, administered as a 30 minute infusion if the initial loading dose was well tolerated. Eligible HER2-negative patients will receive mDCF alone

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

Preparation

Use appropriate aseptic technique. Each vial of trastuzumab should be reconstituted with 20 mL of BWI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL trastuzumab. Immediately upon reconstitution with



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

BWFI, the vial of trastuzumab must be labeled in the area marked “Do not use after” with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). Trastuzumab which has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided.

Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, USP. DEXTROSE (5%) SOLUTION SHOULD NOT BE USED. Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. Trastuzumab administration should precede chemotherapy administration. Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated subsequent doses of 4 mg/kg trastuzumab q2wk may be administered over 30 minutes. If chemotherapy is discontinued during the treatment phase, either because of completing a planned number of cycles of chemotherapy, or because of chemotherapy related toxicity, trastuzumab should be continued until disease progression or unacceptable toxicity related specifically to trastuzumab.

Trastuzumab should not be mixed or diluted with other rugs. Trastuzumab infusions should not be administered or mixed with Dextrose solutions.

Storage

Vials of trastuzumab are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. **DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.**

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted Trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

5.5.3 Source

Genentech will provide trastuzumab free of charge to the patient.

5.5.4 Safety Profile

Cardiac Dysfunction: Signs and symptoms of cardiac dysfunction were observed in a number of women who received trastuzumab alone or in combination with chemotherapy, most often anthracycline based treatment. Cardiac dysfunction was observed most frequently among patients who received trastuzumab plus AC chemotherapy (28%), compared with those who received AC alone (7%), trastuzumab plus paclitaxel (11%), paclitaxel alone (1%), or trastuzumab alone (7%). Severe disability or fatal outcome due to cardiac dysfunction was observed in ~1% of all patients. The signs and symptoms of cardiac dysfunction usually responded to treatment.

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or ECHO prior to entry into the study. Only patients with normal LVEF should be entered into this study. All should have regular cardiac monitoring throughout the study. It is suggested that the first evaluation occur 4 months after the initiation of trastuzumab therapy. During the course of trastuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

Management of Symptomatic Cardiac Changes. Patients who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides, as needed; HFSA guidelines). Consideration should be given to obtaining a cardiac consultation.

If the symptoms of CHF resolve with treatment, and cardiac function improves, Trastuzumab may be continued after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from Trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If Trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) is strongly recommended until cardiac function has normalized.

Management of Asymptomatic Decreases in LVEF. Trastuzumab may be continued in patients experiencing an asymptomatic absolute decrease in LVEF of <20 percentage points from baseline, when the ejection fraction remains within the imaging center's range of normal limits. Repeat measures of LVEF should be obtained using the methodology selected at baseline. Close follow-up of such patients is recommended. Patients with an asymptomatic absolute decrease in LVEF of >20 percentage points or an ejection fraction below the range of normal limits, should have trastuzumab held and be considered for treatment of incipient CHF as prescribed by the HFSA (e.g., ACE



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides, as needed; see HFSA guidelines). In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study to confirm an observed decline. Repeat measures of LVEF should be obtained using the same methodology selected at baseline. If trastuzumab has been discontinued for an asymptomatic decline in LVEF, a repeat measure of LVEF will be obtained in 1 month to determine if the decline has resolved.

If cardiac function improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from Trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO), using the methodology selected at baseline, is strongly recommended until cardiac function has normalized.

Infusion Associated Symptoms: During the first infusion with Trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Trastuzumab infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

Serious Infusion-Associated Events. Serious adverse reactions to Trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of Trastuzumab as indicated.

Hematologic Toxicity and Neutropenic Infections: In the clinical trials, an increased incidence of anemia was observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of trastuzumab therapy.

In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Secondary acute leukemia or myelodysplastic syndrome has been reported in 4 of approximately 1200 patients who participated in trastuzumab clinical trials. Patients treated with chemotherapeutic agents are known to be at increased risk for secondary leukemia. The observed incidence of leukemia among Trastuzumab treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer. Therefore, the contribution of Trastuzumab to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

Management of Hematologic Toxicities. Care should be taken to carefully monitor the patient's hematologic status throughout the course of the trial. Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists (ASCO) guidelines.

5.6 CONCOMITANT MEDICATIONS

5.6.1 Anticancer or experimental therapy

No other concurrent chemotherapy or anti-cancer therapy of any kind is permitted while the patient is receiving study treatment.

5.6.2 Hematopoietic Growth Factors

Colony-Stimulating Factor (G-CSF, GM-CSF):

ARM A

After cycle 1 (eg. 3 treatments of mDCF), the use of colony-stimulating factor is permitted at the discretion of the treating physician. However, the administration of G-CSF in a patient who has experienced neutropenia, or its therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, fever/neutropenia, etc. is recommended.

ARM B

Beginning with cycle 1, pegfilgrastim (Neulasta®) is given subcutaneous 6 mg on either day 8, 9, or 10 of every cycle. This is the preferred hematopoietic growth factor. Alternatively, filgrastim (Neupogen®) may be given by subcutaneous injection from day 10 to 17. The optimal dose is as follows:

Body weight \leq 60 kg: filgrastim 300 mcg subcut daily x 7 days

Body weight $>$ 60 kg: filgrastim 480 mcg subcut daily x 7 days

Epoetin alfa (Procrit® or Aranesp®):

Use of epoetin alfa is permitted at the discretion of the treating physician.

5.6.3 Antiemetics and Premedications



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

ARM A

The mDCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
evening - Dexamethasone 8 mg orally (pm)
- Day 3: *pre - Cisplatin* Dexamethasone 8 mg orally or IV
Palonosetron 250 mcg IVPB
Aprepitant 125 mg po
- Day 4 and 5: Dexamethasone 4 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

ARM B

The DCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
pre-Cisplatin - Palonosetron 250 mcg IVPB
Aprepitant 125 mg po

evening - Dexamethasone 8 mg orally (pm)
- Day 2 and 3: Dexamethasone 8 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

Both ARMS

For patients who have persistent nausea or vomiting with palonosetron, granisetron 2mg po or granisetron 1mg IV may be substituted prior to chemotherapy, and then granisetron 2 mg po may be continued on days 2 and 3. Metoclopramide 5-10 mg po every 4 hours and/or prochlorperazine 10 mg every 6 hours may be used as needed for nausea/vomiting,



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

and lorazepam may be used for anticipatory nausea/vomiting or anxiety related nausea/vomiting.

For patients who have no evidence of delayed emesis, the prophylaxis may be discontinued as tolerated as per the treating physician.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

This is a multicenter phase II study coordinated by Memorial Sloan-Kettering Cancer Center (MSKCC).

6.1 Subject Inclusion Criteria

1. Patients must have histologically or cytologically confirmed metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma. GEJ adenocarcinoma may be classified according to Siewert's classification type I, II, or III[43].
2. Histological documentation of local recurrence or metastasis is strongly encouraged, unless the risk of such a procedure outweighs the potential benefit of confirming the metastatic disease.
 - If no histologic confirmation, then the metastases or recurrence will require documentation by a 2nd radiographic procedure (eg. PET/CT scan or MRI in addition to the CT scan). If the imaging procedure does not confirm recurrent or metastatic disease, biopsy confirmation will be required.
3. Patients must have disease that can be evaluated radiographically. This may be measurable disease or non-measurable disease. Measurable disease is defined as that which can be measured in at least one dimension as ≥ 20 mm with conventional techniques, or ≥ 10 mm by high resolution imaging. Disease that is identified on radiology studies, but does not meet the criteria for measurable disease, is considered non-measurable— see section 12.1.1 for further details.
4. Patients may have received no prior chemotherapy for metastatic or unresectable disease. Patients may have received prior adjuvant therapy (chemotherapy and/or chemoradiation) if more than 6 months have elapsed between the end of adjuvant therapy and registration. Patients may not have received prior docetaxel or cisplatin.
5. Age 18 years or older.
6. Karnofsky performance status $\geq 70\%$ (ECOG performance status 0-1).
7. Peripheral neuropathy \leq grade 1



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

8. Hematologic (minimal values)

- White blood cell count $\geq 3000/\text{mm}^3$
- Absolute neutrophil count $\geq 1500 \text{ cells}/\text{mm}^3$
- Hemoglobin $\geq 9.0 \text{ g/dl}$
- Platelet count $\geq 100,000 / \text{mm}^3$

9. Hepatic (minimal values)

- Total bilirubin ≤ 1.5
- AST and ALT and Alkaline phosphatase must be within the eligible range as described by the table below. In determining eligibility, the more abnormal of the two values (AST or ALT) should be used. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

| | AST or ALT: | | | |
|------------------------------|-------------------|--|--|-------------------|
| ALK PHOS: | $\leq \text{ULN}$ | $>1x \text{ but } \leq 1.5x \text{ ULN}$ | $>1.5x \text{ but } \leq 5x \text{ ULN}$ | $>5x \text{ ULN}$ |
| $\leq \text{ULN}$ | Eligible | Eligible | Eligible | Ineligible |
| $>1x \text{ but } \leq 2.5x$ | Eligible | Eligible | Ineligible | Ineligible |
| $>2.5x \text{ but } \leq 5x$ | Eligible | Ineligible | Ineligible | Ineligible |
| $>5x \text{ ULN}$ | Ineligible | Ineligible | Ineligible | Ineligible |

10. Kidney function (minimal values)

serum creatinine $\leq 1.5 \text{ mg/dl}^*$

* if serum creatinine is 1.2-1.5 mg/dl, the creatinine clearance (either measured or calculated) must be 50 ml/min or greater.

11. The patient has a PT (INR) ≤ 1.5 and an PTT ≤ 3 seconds above the upper limits of normal if the patient is not on anticoagulation. If a patient is on full-dose anticoagulants, the following criteria should be met for enrollment:

- a. the patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or on stable dose of LMW heparin.
- b. the patient must not have active bleeding or pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels, known varices).

12. Women of childbearing potential have a negative pregnancy test.

13. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter.

14. Ability to understand informed consent and signing of written informed consent document prior to initiation of protocol therapy.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

15. Patients must have HER2-positive (FISH+ or IHC 3+) metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma to be eligible for trastuzumab. For the purposes of this protocol, FISH+ is defined as HER2:CEP17 ratio ≥ 2.0 . Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e. $<10\%$. FISH+ defined as >2 HER2:CEP17. Note: Samples will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.
16. Patients who are receiving trastuzumab must have a left ventricular ejection fraction of $\geq 50\%$.

6.2 Subject Exclusion Criteria

1. Patients who have received previous chemotherapy for the treatment of metastatic or unresectable gastric or GEJ adenocarcinoma are ineligible. Patients who have received previous pre- or post-operative chemotherapy or chemoradiation are ineligible if therapy was completed less than 6 months prior to study registration. Patients must have recovered from adverse events from any previous therapy.
2. Patients who have received previous docetaxel or cisplatin.
3. Patients with a history of another neoplastic disease within the past three years, excluding basal cell carcinoma of the skin, cervical carcinoma in situ, or nonmetastatic prostate cancer.
4. Patients with brain or central nervous system metastases, including leptomeningeal disease.
5. Pregnant (positive pregnancy test) or breast feeding.
6. Serious, non-healing wound, ulcer, or bone fracture.
7. Significant cardiac disease as defined as:
unstable angina, New York Heart Association (NYHA) grade II or greater, congestive heart failure, history of myocardial infarction within 6 months
8. Evidence of bleeding diathesis or coagulopathy.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

9. History of a stroke or CVA within 6 months.
10. Clinically significant peripheral vascular disease.
11. Clinically significant hearing loss or ringing in the ears.
12. Patients with a history of severe hypersensitivity reaction to Taxotere® or other drugs formulated with polysorbate 80.
13. Inability to comply with study and/or follow-up procedures.
14. Patients with any other medical condition or reason, in that investigator's opinion, makes the patient unstable to participate in a clinical trial.
15. For patients who are Her2 positive and will be treated on the trastuzumab + mDCF cohort, prior trastuzumab treatment is not allowed.
16. For patients who are Her2 positive and will be treated on the trastuzumab+mDCF cohort, left ventricular function <50%

7.0 RECRUITMENT PLAN

This study will be available to all patients seen at participating institutions who meet the eligibility criteria as outlined in section 6.0. Memorial Hospital is a referral center for this disease. In addition, the study will be placed on the MSKCC Website as well as available at the MSKCC satellite centers to maximize patient recruitment. Patients will be identified from medical oncology clinics for treatment of their disease.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study. The proposed study population is provided in the table below.

| Ethnic Category | Sex/ Gender | | | Total |
|--|-------------|-------|---------|-------|
| | Females | Males | Unknown | |
| Hispanic or Latino | 8 | 10 | | 18 |
| Not Hispanic or Latino | 28 | 62 | | 90 |
| Unknown | | | | |
| Ethnic Category: Total of all subjects | 36 | 72 | | 108 |



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

| Racial Category | | | | |
|---|----|----|--|-----|
| American Indian or Alaskan Native | 0 | 0 | | |
| Asian | 7 | 10 | | 17 |
| Black or African American | 4 | 8 | | 12 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | | |
| White | 23 | 52 | | 75 |
| More than one race | 0 | 0 | | 0 |
| Unknown | 2 | 2 | | 4 |
| Racial Category: Total of all subjects | 36 | 72 | | 108 |

Note, the results of the recent ToGA study demonstrate that for HER2 positive gastric cancer, patients have a survival benefit with the addition of trastuzumab to chemotherapy (see Sect 3.3.4). We are therefore amending the study to include a separate cohort of 35 patients who are Her2 positive to receive mDCF + trastuzumab (Trastuzumab cohort)

| Recruitment Expectations Per Site | |
|---|----|
| Memorial Sloan Kettering Cancer Center | 10 |
| City of Hope | 5 |
| University of Pittsburgh | 5 |
| Queens Cancer Center | 2 |
| Long Island Jewish Medical Center | 2 |
| University Hospital of Cleveland | 2 |
| Weill Medical College of Cornell University | 2 |
| Medical College of Wisconsin | 2 |
| Piedmont Hospital Research Institute (PHRI) | 2 |
| Nebraska Cancer Specialists | 2 |
| Memorial Cancer Institute | 1 |
| Total | 35 |

8.0 PRETREATMENT EVALUATION

To be completed within 14 days of starting therapy:

1. History and physical examination, including height, weight, calculated body surface area, vital signs, and performance status. See Appendix A for a conversion between Karnofsky and ECOG performance status.
2. Serum pregnancy test for all women of childbearing potential within 14 days of starting therapy. If the test result is positive, the patient will not be allowed to participate in this study.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

3. PA and lateral chest radiographs. Chest radiographs may be omitted if a baseline CT scan of the chest is available in the same time frame.
4. Routine urinalysis.
5. CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, coagulation studies, and tumor markers as they are available.
6. EORTC QLQ-C30 questionnaire.

To be completed within 30 days of starting therapy:

7. A 12-lead Electrocardiogram (ECG).
8. Documentation of all measurable or non-measurable disease parameters including radiographic imaging procedures within four weeks of study entry, and measurement of biochemical markers of disease (if applicable) within four weeks of study entry. The RECIST criteria as defined by CTEP (<http://ctep.info.nih.gov/Policies>) define measurable and non-measurable disease.
9. Signed informed consent for study participation.
10. Audiogram if clinically indicated.
11. CT scan of the chest, abdomen and pelvis.
12. Baseline PET/CT for staging.
July 2009 Addendum: Collaborating centers that are either not able to perform the PET/CT at baseline (i.e., denied authorization from insurance carriers) or have opted not to participate in the Week 3 PET/CT may forgo performing the scan at baseline.

To be completed at any time prior to starting therapy or during study:

13. Placement of a MediPort, Hickman catheter or similar indwelling catheter for administration of continuous infusional fluorouracil chemotherapy.
14. Paraffin stored tumor block or 15 unstained slides sent to MSKCC for planned future immunohistochemistry studies.
15. A baseline assessment of left ventricular ejection fraction (usually cardiac ECHO or MUGA scan).



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

9.0 TREATMENT/INTERVENTION PLAN

9.1 CHEMOTHERAPY ADMINISTRATION

Eligible patients will be randomly assigned to receive mDCF (ARM A) or parent DCF with growth factor support (ARM B) as follows:

| ARM A – Modified DCF | | | ARM B – Parent DCF with G-CSF | | |
|----------------------|---------------------------|--------------------------|-------------------------------|---------------------------|-------------------------|
| Drug | Dose (mg/m ²) | Schedule | Drug | Dose (mg/m ²) | Schedule |
| Docetaxel | 40 | Day 1 IVPB (60 min) | Docetaxel | 75 | Day 1 IVPB (60 min) |
| Leucovorin | 400 | Day 1 IVPB (30 min) | Cisplatin | 75 | Day 1 IVPB (60 min) |
| Fluorouracil | 400 | IVP day 1 | Fluorouracil | 750 | IVCI daily x 5 days |
| Fluorouracil | 1000 mg/m ² /d | IVCI daily x 2 days | Neulasta | 6 mg | subcut on d 8, 9, or 10 |
| Cisplatin | 40 | Day 2 or 3 IVPB (30 min) | or Neupogen | 300 or 480 mcg* | subcut x 7 d 10-17 |

* 300 mcg for weight ≤ 60 kg, 480 mcg for weight > 60 kg.

Arm A is repeated every 2 weeks, and a cycle will be considered 6 weeks (eg 3 treatments).

Arm B is repeated every 3 weeks, and a cycle will be considered every 6 weeks (eg 2 treatments).

December 2009 Amendment

We have met the early stopping rule for Arm B, parent DCF with growth factor support. Arm A will continue to accrue until target accrual of 54 patients. In addition, we will treat Her2 positive patients with mDCF + trastuzumab. Trastuzumab will be administered on an every 2 week dosing schedule, with an initial loading dose of 6 mg/kg over 90 minutes, followed by trastuzumab 4 mg/kg every 2 weeks over 30 minutes.

A given treatment may be moved +/- 14 days for specific administrative reasons, in particular clinic closure for holidays. Tumor assessments will be performed following the completion of every cycle for the first 6 cycles, and then every 2 cycles thereafter. Therapy will be administered in an outpatient setting, under the supervision of a physician and/or chemotherapy nurse, as is standard for chemotherapy administration at the treating institution.

After 6 months of therapy, cisplatin, docetaxel, and/or fluorouracil may be discontinued at the discretion of the treating physician. Prior to discontinuing therapy, the treating physician will discuss in detail with the protocol PI. Patients without disease progression may resume chemotherapy at the discretion of the treating physician, or with progression if they had more than a 6 month treatment free interval.

Expected adverse events are described in Section 11.0. No investigational or commercial agents or therapies other than those described above may be administered with the intent to treat the patient's malignancy.

Clinical evaluation: All assessments may be performed within one day of the planned treatment.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

ARM A – Modified DCF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of cycle one (e.g. on day 1, day 15, and day 29 of cycle 1). In cycle 2 and all subsequent cycles, a physician evaluation (e.g. physical examination and toxicity assessment) will be performed prior to treatment on day 1 and day 29 treatments. Additional nurse or physician visits will be at the discretion of the treating physician. It is encouraged that an oncology nurse toxicity evaluation be performed prior to each treatment, especially if the patient is not assessed by a physician.

Patients treated with mDCF plus trastuzumab therapy should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain).

ARM B – Parent DCF with G-CSF

Patients will have a history and physical examination and assessment of toxicities prior to each treatment of every cycle.

Laboratory evaluation:

ARM A – Modified DCF

On or within 1 day of the beginning of each cycle, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, tumor markers. A CBC with differential and platelet count is required prior to each subsequent treatment (eg. day 15 and day 29). A BUN and Creatinine is required before the day 15 treatment (treatment #2), and a serum chemistry (electrolytes, BUN, Creatinine, glucose) is required before each day 29 treatment (#3). LFTs are required before each treatment (#1, #2 and #3) of cycle 1, and before treatment #1 and #3 for each subsequent cycle. Any patient with excessive LFTs abnormalities (see section 9.3) will require repeat LFTs prior to the next docetaxel administration.

ARM B – Parent DCF with G-CSF

On or within 1 day of the beginning of each treatment, a CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, magnesium, phosphorus, albumin, total protein, LDH, and tumor markers are required.

Radiology evaluation: For both treatment arms, radiographic studies upon which tumor measurements were made will be repeated every cycle (six week intervals for most patients) for 6 cycles, and then after every two cycles of therapy (e.g. after cycles 1, 2, 3, 4, 5, 6, 8, 10, 12 etc.), to rule out progression of disease and to determine response for measurable disease.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Patients will remain on study until disease progression, patient withdrawal, unacceptable toxicity despite dose attenuation, or if the treating physician deems it is in the best interest of the patient following discussion with the principal investigator. Tolerability of this regimen will be determined from blood test results and toxicity assessment.

Cardiac evaluation: For patients who are Her2 positive and will be treated on the trastuzumab+mDCF cohort left ventricular function will be assessed with echocardiograms or MUGA every 12 weeks while on study.

A table of events to take place on this study is shown in section 10.0.

9.2 SUPPORTIVE CARE GUIDELINES

Concurrent supportive care is not restricted, including the use of narcotics for pain control and antiemetics and glucocorticoids for control of nausea, and antidiarrheal agents. Neither concurrent chemotherapy, immunotherapy, nor radiation therapy is permitted while on study.

Hematopoietic Growth Factors

Colony-Stimulating Factor (G-CSF, GM-CSF):

ARM A

Use of colony-stimulating factor is permitted at the discretion of the treating physician. However, the administration of G-CSF in a patient who has experienced neutropenia, or its therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, fever/neutropenia, etc. is recommended.

ARM B

Beginning with cycle 1, pegfilgrastim (Neulasta®) is given subcutaneous 6 mg on either day 8, 9, or 10 of every cycle. This is the preferred hematopoietic growth factor. Alternatively, filgrastim (Neupogen®) may be given by subcutaneous injection from day 10 to 17. The optimal dose is as follows:

Body weight \leq 60 kg: filgrastim 300 mcg subcut daily x 7 days

Body weight > 60 kg: filgrastim 480 mcg subcut daily x 7 days

Epoetin alfa (Procrit® or Aranesp®):

Use of epoetin alfa is permitted at the discretion of the treating physician.

Antiemetics and Premedications

ARM A

The mDCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
evening - Dexamethasone 8 mg orally (pm)
- Day 3: *pre - Cisplatin* Dexamethasone 8 mg orally or IV
Palonosetron 250 mcg IVPB
Aprepitant 125 mg po
- Day 4 and 5: Dexamethasone 4 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

ARM B

The DCF regimen has a high emetic potential. Additionally, the use of Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and may also decrease the incidence and severity of acute hypersensitivity reactions.

The recommended pre-medication and delayed emesis schedule for this study is as follows:

- Day prior to chemotherapy (day 0): Dexamethasone 8 mg orally in the pm
- Day of chemotherapy (day 1): *pre-Docetaxel -* Dexamethasone 8 mg orally
pre-Cisplatin - Palonosetron 250 mcg IVPB
Aprepitant 125 mg po

evening - Dexamethasone 8 mg orally (pm)
- Day 2 and 3: Dexamethasone 8 mg orally qd x 2d
Aprepitant 80 mg orally qd x 2d

Both ARMS

For patients who have persistent nausea or vomiting with palonosetron, granisetron 2mg po or granisetron 1mg IV may be substituted prior to chemotherapy, and then granisetron 2 mg po may be continued on days 2 and 3. Metoclopramide 5-10 mg po every 4 hours and/or prochlorperazine 10 mg every 6 hours may be used as needed for nausea/vomiting, and lorazepam may be used for anticipatory nausea/vomiting or anxiety related nausea/vomiting.

For patients who have no evidence of delayed emesis, the prophylaxis may be discontinued as tolerated as per the treating physician.



9.3 TREATMENT PARAMETERS, DOSE DELAYS AND MODIFICATIONS

9.3.1 Treatment Parameters

1. Parameters for initiation of therapy (day 1) for cycle 1 are as follows:

- White blood cell count $\geq 3000/\text{mm}^3$
- Absolute neutrophil count $\geq 1500/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Hemoglobin ≥ 9.0 g/dl
- Creatinine ≤ 1.5 mg/dl
- Total Bilirubin ≤ 1.5 mg/dl

AST and ALT and Alkaline phosphatase must be within the treatment range as described by the table below. In determining acceptable levels for treatment, the more abnormal of the two values (AST or ALT) should be used. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

| | AST or ALT: | | | |
|---------------------|-------------|-------------------------|-------------------------|-----------|
| ALK PHOS: | \leq ULN | $>1x$ but $\leq 2x$ ULN | $>2x$ but $\leq 5x$ ULN | $>5x$ ULN |
| \leq ULN | Yes | Yes | Yes | No |
| $>1x$ but $\leq 3x$ | Yes | Yes | Yes | No |
| $>3x$ but $\leq 5x$ | Yes | Yes | No | No |
| $\geq 5x$ ULN | No | No | No | No |

2. Parameters for all subsequent treatments:

- Absolute Neutrophil count $\geq 1000/\text{mm}^3$
- Platelet count $\geq 75,000/\text{mm}^3$.
- Creatinine ≤ 1.8 mg/dl
 - for Creatinine > 1.8 mg/dl and
- Total bilirubin ≤ 1.5 (should be drawn prior to treatment on week 1, week 3, and week 5 of cycle 1 and again prior to treatment on week 1 and week 5 of every subsequent cycle beginning with cycle 2 (ie. minimum of every 4 weeks).)
 - For total bilirubin ≥ 1.5 but $\leq 2x$ ULN, docetaxel alone may be held.
 - For total bilirubin $\geq 2x$ ULN, hold all three drugs (docetaxel, cisplatin, fluorouracil)
- AST/ALT* and Alkaline Phosphatase as per table below (for docetaxel dosing):

| | AST or ALT: | | | |
|---------------------|-------------|-------------------------|-------------------------|-----------|
| ALK PHOS: | \leq ULN | $>1x$ but $\leq 2x$ ULN | $>2x$ but $\leq 5x$ ULN | $>5x$ ULN |
| \leq ULN | Full Dose | Full Dose | Full Dose | Hold |
| $>1x$ but $\leq 3x$ | Full Dose | Full Dose | Reduce Dose | Hold |
| $>3x$ but $\leq 5x$ | Full Dose | Reduce Dose | Hold | Hold |
| $>5x$ ULN | Hold | Hold | Hold | Hold |



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

** ARM A: LFTs should be drawn prior to treatment on week 1, week 3, and week 5 of cycle 1 and again prior to treatment on week 1 and week 5 of every subsequent cycle beginning with cycle 2 (ie. minimum of every 4 weeks). If LFTs are drawn prior to treatment on week 3, the above LFT treatment parameters must still be met. Both AST and ALT should be drawn. If LFTs are abnormal prior to any treatment, they should be drawn prior to the next docetaxel treatment. The more abnormal of the two values (AST or ALT) should be used in determining the dose of docetaxel.*

** ARM B: LFTs should be drawn prior to each 3-week cycle*

Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator. If above parameters are not met, hold until recovered, maximum 28 days, then retreat as per section 9.3.2 Dose Delays and Modifications. “Recovered” is defined as meeting the treatment parameters for #2 above with the exception that the ANC must be at least $1500/\text{mm}^3$ ($\text{ANC} \geq 1500/\text{mm}^3$).

9.3.2 Chemotherapy Dose Delays and Modifications

Chemotherapy will be held for grade 3 or 4 non-hematologic toxicity (with the exception of grade 3 electrolyte abnormalities) or for not meeting treatment parameters as described above on the day of treatment. If the toxicity has resolved and the patient meets treatment parameters but experienced interval toxicity, then for the purposes of determining dose reductions, the grade of toxicity should be that seen despite maximal medical management (i.e. intensive loperamide or tincture of opium for diarrhea). If multiple toxicities are seen the dose administered for a particular drug should be based on the most severe toxicity noted. In general, when multiple toxicities are experienced that can result in the dose reduction of multiple drugs, reducing multiple drugs at one time is the preferred approach. Treatment may resume when the toxicity has resolved to \leq grade 2, except as indicated below.

Generally, when therapy is held for chemotherapy related toxicity, all three drugs (cisplatin, docetaxel, and fluorouracil) will be held. For hepatotoxicity, docetaxel alone should be held (ie. Total bilirubin \geq ULN but \leq 2x ULN, and AST/ALT and Alkphos as per table above) and cisplatin and fluorouracil may continue without treatment delay. For an elevated creatinine or for ototoxicity (see below criteria), cisplatin alone may be held and the patient may continue with docetaxel and fluorouracil without treatment delay. If all three drugs are held for more than 4 weeks for toxicity, patients will be taken off study, unless there is a clinical benefit. If there is a clinical benefit, patients may be retreated at a lower dose after resolution of toxicity to \leq NCI-CTCAE v3.0 grade 2, except as indicated below. Cisplatin, docetaxel, and fluorouracil may each be dose attenuated, either in combination, or individually.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

ARM A: CHEMOTHERAPY DOSE ATTENUATION TABLE

| | Dose level 0 (mg/m ²) | Dose level -1 (mg/m ²) | Dose level -2 (mg/m ²) |
|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------|
| Docetaxel | 40 | 30 | 20 |
| Cisplatin | 40 | 30 | 20 |
| Fluorouracil (IVP)/ Leucovorin | 400/ 400 | 300/ 300 | 200/ 200 |
| Fluorouracil IVCI / day | 1000 | 800 | 600 |

ARM B: CHEMOTHERAPY DOSE ATTENUATION TABLE

| | Dose level 0 (mg/m ²) | Dose level -1 (mg/m ²) | Dose level -2 (mg/m ²) |
|-------------------------|-----------------------------------|------------------------------------|------------------------------------|
| Docetaxel | 75 | 60 | 50 |
| Cisplatin | 75 | 60 | 50 |
| Fluorouracil IVCI / day | 750 | 600 | 500 |

Dose attenuations will be based on toxicity as described below:

Neutropenia

- Docetaxel dose attenuation by one dose level may occur for any treatment delay due to neutropenia (i.e. ANC < 1000 /cc on a treatment day following Cycle 1 Week 1).
- For ARM A,, Neulasta or Neupogen (GCSF) should be given for subsequent treatments following any treatment delay due to neutropenia if a dose reduction is not required and not pursued. The recommended treatment is Neulasta 6 mg subcutaneously on day 3, day 4, or day 5 of the treatment cycle or neupogen (GCSF) for 3 to 5 days from day 9 to day 13.
- Grade 3 and Grade 4 neutropenia with recovery prior to next planned cycle do not require a dose attenuation in docetaxel with the following exceptions:
 - Grade 4, afebrile neutropenia ≥ 7 days
 - Grade 3 or 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period)
- Cisplatin and fluorouracil may be dose attenuated by one dose level at the treating physicians' discretion in addition to docetaxel dose attenuation, particularly with persistent delays due to neutropenia.

Thrombocytopenia

- For treatment delay due to thrombocytopenia (i.e. platelet count < 75,000/cc), reduce docetaxel by one dose level.
- For any platelet count of ≤ 50,000/cc, reduce docetaxel by one dose level.

Nausea/Vomiting

- Grade 1 nausea/vomiting does not require a dose reduction or treatment delay.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

- Grade 2 nausea/vomiting – hold treatment for 1 week. Reduce cisplatin by 1 dose level for persistent grade 2 nausea/ vomiting (eg. lasting for more than 5 days).
- For Grade 3 or 4 nausea/ vomiting, reduce cisplatin dose by one dose level. Docetaxel and fluorouracil may also be dose attenuated by one dose level at the treating physicians discretion.

Anorexia

- Grade 1 or 2 anorexia does not require a dose reduction
- For grade 3 or 4 anorexia, reduce cisplatin and docetaxel by one dose level.

Stomatitis

- If stomatitis is present on day 1 of any cycle, treatment should be held until the stomatitis has resolved.
- For ARM A:
 - If stomatitis is \leq grade 1 prior to treatment #2 or #3 of any cycle, treat at current dose.
 - For interval grade 2 stomatitis prior to treatment #2 or #3, reduce fluorouracil infusion by one dose level without treatment delay. For a subsequent grade 2 stomatitis event, reduce docetaxel by one dose level.
- For ARM B:
 - For interval grade 2 stomatitis that completely resolves prior to the next cycle, reduce fluorouracil infusion by one dose level without treatment delay. For a subsequent grade 2 stomatitis event, reduce docetaxel by one dose level.
- If Grade 3 or 4 stomatitis occurs at any time, hold chemotherapy until resolution to \leq grade 1, and then retreat with docetaxel and fluorouracil each reduced by one dose level.

Neurotoxicity

- If neuropathy \geq grade 2 is present on day 1 of any cycle, treatment should be held until neuropathy improves to \leq grade 1.
- For ARM A (treatment #2 and 3 of each cycle):
 - If neuropathy is \leq grade 1 on treatment #2 or #3 of any cycle, treat at current dose of all chemotherapy drugs.
 - If neuropathy is grade 2 on treatment #2 or #3, reduce docetaxel by one dose level and treat without delay.
- For ARM B (treatment #2 of each cycle):
 - If neuropathy is \leq grade 1 on treatment #2, treat at current dose of all chemotherapy drugs.
 - If neuropathy is grade 2 on treatment #2, reduce docetaxel by one dose level and treat without delay.
- For Grade 3 or 4 neuropathy, treatment should be held until neuropathy returns to grade \leq 1. Reduce cisplatin and docetaxel each by one dose level.

Kidney

- Serum creatinine must be \leq 1.5 mg/dl to initiate therapy



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- For each subsequent treatment, the serum creatinine must be ≤ 1.8 mg/dl to continue treatment at the current dose level.
- If serum creatinine is > 1.8 but ≤ 2 mg/dl, administer cisplatin at a single reduced dose level. A treatment delay is not required. Subsequent treatments may occur without further cisplatin dose attenuation if the serum creatinine remains stable at > 1.8 but ≤ 2 mg/dl.
- If serum creatinine is > 2.0 mg/dl, cisplatin will be held. Docetaxel and fluorouracil may be administered without treatment delay at the treating physicians discretion.
- Up to a 6-week treatment delay in cisplatin will be allowed. If the serum creatinine has not returned to less than 2.0 mg/dl within 6 weeks, then cisplatin will be discontinued.
- Patients should be euvolemic for the determination of serum creatinine.
- If the value of the serum creatinine is > 1.8 mg/dl the value may be confirmed by a second serum creatinine after hydration. Treatment may resume within the next day.
- Creatinine clearance will not be used for dose adjustments.

Diarrhea

- Grade 1 diarrhea dose not require treatment delay or dose reduction.
- For grade 2 diarrhea, hold treatment by 1 week.
- For grade 3 or 4 diarrhea, reduce fluorouracil by 1 dose level. Cisplatin may be dose reduced as well, at the treating physicians discretion.

Ototoxicity

- For grade 1 or 2 ototoxicity, no dose reduction in cisplatin is required.
- For grade 3 or 4 ototoxicity, hold cisplatin until it resolves to \leq grade 1, and then resume therapy with cisplatin dose reduced by one dose level.

Trastuzumab related cardiac dysfunction:

Symptomatic CHF

- Hold trastuzumab, refer to cardiology for treatment (e.g., ACE inhibitors, angiotensin-II receptor blockers, β -blockers, diuretics, and cardiac glycosides).
- If the symptoms of CHF resolve with treatment, and cardiac function improves, trastuzumab may be continued after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction.
- If trastuzumab is restarted, cardiac function should be monitored with echocardiogram every cycle

Asymptomatic drop in LVEF

- Trastuzumab may be continued in patients experiencing an asymptomatic absolute decrease in LVEF of < 20 percentage points from baseline, when the ejection fraction remains $\geq 50\%$. Such patients should be monitored with echocardiograms every cycle.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Patients with an asymptomatic absolute decrease in LVEF of ≥ 20 percentage points or ejection fraction $< 50\%$, should have trastuzumab held. Consider cardiology referral for treatment of incipient CHF.
- If trastuzumab is discontinued for an asymptomatic decline in LVEF, a repeat echocardiogram will be obtained in 1 month to determine if the decline has resolved.
- If cardiac function improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction.

Hypersensitivity Reactions

- Trastuzumab treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.
- Docetaxel treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY

| Severity of Symptoms | Treatment Guidelines |
|--|--|
| <u>Mild</u> symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash | <ul style="list-style-type: none"> · consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete Taxotere infusion at the initial planned rate |
| <u>Moderate</u> symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg | <ul style="list-style-type: none"> · interrupt Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms · resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (eg. <i>infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, then finally, resume at the initial planned rate.</i>) · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, (eg. <i>infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, and finally, administer at the initial planned rate.</i>) |
| <u>Severe</u> symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema | <ul style="list-style-type: none"> · immediately discontinue Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed. |



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

| | |
|---|-------------------------------|
| Anaphylaxis (NCI CTCAE v. 3.0 grade 4 reaction) | NO FURTHER STUDY DRUG THERAPY |
|---|-------------------------------|

Fluid Retention

- There are no dose reductions for fluid retention.
- Patients developing new onset edema or ascites, progression of existing edema or ascites, or another sign of fluid retention (eg. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below:
 - Triamterene/hydrochlorothiazide one capsule po qd up to tid.
 - Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
 - If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.
- Further diuretic therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

Hyperlacrimation

- The following guidelines may be taken for patients experiencing clinically significant hyperlacrimation:
 - Dose reduction in fluorouracil treatment.
 - Withhold docetaxel treatment until resolution.
 - Frequent instillation of artificial tears.
 - Steroid ophthalmic solution starting the day before docetaxel administration in patients without a history of herpetic eye disease.
 - Ophthalmologist consult.

If a dose attenuation is required in any chemotherapy drug that is already at dose level -2, the other chemotherapy drugs may be reduced by one dose level instead. For cumulative toxicity, cisplatin, fluorouracil, leucovorin or docetaxel may be discontinued following discussion with the protocol principal investigator. If more than one grade 3 or 4 event occurred, then the chemotherapy to be dose attenuation should be that of the most severe toxicity.

For patients experiencing intolerable toxicity based on the treating physician's clinical assessment, individual chemotherapy doses may be attenuation following consultation with the Principal Investigator.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

9.4 CORRELATIVE STUDIES

9.4.1 To bank tumor biopsy material for future planned correlative studies for association with chemotherapy efficacy and survival.

We plan to store pre-therapy paraffin embedded tumor tissue for future tissue based correlative studies. We will plan to examine this tissue bank by immunohistochemistry if markers for disease sensitivity or resistance to docetaxel based therapy is identified in ongoing trials. Any IHC studies performed will be selected for based on clinical significance, feasibility, and reproducibility, in conjunction with a reference pathologist (eg. Laura Tang, MD PhD). We will not require new tissue procurement for research purposes. Prior to tissue use, we will submit a proposal for approval by the MSKCC Human Tissue Utilization Committee.

HER2 testing will be performed in all patients to better characterize HER2-positive gastric cancer in US patients. HER2 testing will be performed by the MSKCC diagnostic molecular laboratory on banked tumor specimens from the patients currently enrolled on the protocol and prospectively on all the patients screened for protocol participation. FISH is performed using FDA-approved ERBB2 (HER2/NEU) PathVysion assay probes and procedure (Abbott-Vysis). IHC staining is performed using FDA-approved anti-Her2/neu Ventana's PATHWAY rabbit monoclonal primary antibody (clone 4B5) directed against the internal domain of the c-erbB-2 oncoprotein (Her2). Biopsy samples with cohesive IHC3+ or FISH+ clones are considered HER2 positive irrespective of size, i.e.<10%. FISH+ defined as >2 HER2:CEP17.

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

9.4.2 FDG-PET Response Assessment

The primary aim of this correlative study is to examine the ability of an early FDG-PET/CT scan to predict treatment efficacy. By identifying patients who are progressing early, patients exposure to cytotoxic therapy that is of no therapeutic value can be limited and the associated toxicity can be reduced. As seen in patients who received preoperative chemotherapy, a significant drop from baseline in FDG uptake is associated with an improved pathologic treatment response and improved disease free survival (see Section 3.5.2). However, the challenge in patients with locally advanced, but potentially curable disease is that surgery does cure some patients. Thus, some patients who have a poor FDG-PET response, and an associated poor histopathologic tissue response, may still be cured with surgical resection of their tumor. However, for patients with metastatic or unresectable disease, this is not true. Specifically, we hypothesize that patients with a good FDG-PET response will have RECIST evidence of response at their routine imaging time point and have a longer time to disease progression, when



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

compared with patients with a poor FDG-PET response. If successful, we would be able to identify patients who are not benefiting from current therapy early, thereby allowing patients to minimize toxicity by minimizing exposure to ineffective therapy.

To examine this further, we will perform a 2nd FDG-PET/CT scan on patients with FDG-avid primary tumors. This 2nd scan will be performed during week 3 (following the day 15 treatment, but before week 4 of ARM A, and prior to the 2nd cycle of ARM B) at participating centers. The PET/CT scan is done with the patient fasting for about four to six hours, but water for hydration is allowed. Imaging starts about one hour after intravenous injection of a standard dose of F18-FDG (8 to 15 mCi). Oral CT contrast is also administered for better delineation of the stomach and GI tract.

Collaborating sites will specify at the time of study initiation if they will obtain the week 3 PET/CT scans on all patients who have informative PET/CT scans at baseline.

A low dose spiral CT is performed first, followed by acquisition of the PET images (emission scans only), of the neck, chest, abdomen and pelvis. The total radiation dose involved is about 1 rem (0.5 rem from the CT and 0.5 rem from the PET). Attenuation correction of the PET/CT images is then performed using the CT data. The final PET and CT image data sets are displayed on the fusion software for evaluation.

FDG-PET/CT Data Analysis: All images will be reviewed by a nuclear medicine physician independently and entered into separate data sheets. The PET/CT images will be reviewed in all standard planes (3-dimensional computer display) and a maximum intensity projection. The images will be reviewed together with the CT and the fusion images. Visual analysis of PET/CT data requires the definition of abnormal radiotracer uptake as being greater than background activity (on the attenuation corrected images) and outside of normal anatomic structures, which frequently exhibit various amount of FDG uptake (e.g., ureter, urinary bladder, bowel loops). Individual lesions will be graded on a scale of zero to four where 0 = definitely normal, 1 = probably benign, 2 = equivocal, 3 = probably malignant and 4 = definitely malignant. Semiquantitative analysis of tracer uptake, i.e. the standardized uptake value (SUV) will be done for lesions identified in the visual analysis by positioning of regions of interest (ROI) surrounding them. The SUV will then be calculated as below and entered into the data sheet (see Appendix D). The baseline SUV value for statistical analysis will be the maximum-pixel SUV detected of the primary tumor. $SUV_{BW} = \text{decay corrected activity (mCi/ml)} / \text{injected dose (mCi)} / \text{body weight (kg)}$

9.4.3 Pharmacology and Pharmacodynamics (MSKCC patients only)

Docetaxel is both a substrate and inhibitor of the cytochrome p450 enzyme CYP3A4, and its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, erythromycin, verapamil and diltiazem. Importantly, both aprepitant and palonosetron, recently approved anti-emetic agents for the treatment of acute and delayed nausea, are both inhibitors of CYP3A4. Similarly, we hypothesize that inhibition of CYP3A4 by these anti-emetic agents would result in reduced docetaxel metabolism, increased drug exposure, and potentially increased toxicity.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Pharmacokinetic blood draws will occur in patients enrolled at MSKCC only. We will perform serial blood draws in approximately 20 patients (10/ arm) at the following times:

1. 0.25 hours (15 min following initiation of docetaxel)
2. 0.75 hours (45 min following initiation of docetaxel)
3. 1 hour (end of docetaxel infusion)
4. 1.25 hours (15 min following the completion of docetaxel)
5. 2 hours
6. 4 hours
7. 6 hours
8. 8 hours
9. 24 hours

Additionally, on day 3, a CBC with differential and LFT's (AST, ALT, Alk Phos, total Bilirubin) will be drawn in each of these patients. For Arm A, these lab studies will be drawn prior to cisplatin administration.

Amendment March 2008:

In our initial pharmacokinetic analysis, we noted a suggestion of a difference in docetaxel pharmacokinetics when co-administered with cisplatin (Arm B) or without cisplatin (Arm A). Pharmacokinetic data are available preliminarily on 13 patients: 8 patients who were randomized to parent DCF (Arm B) in which cisplatin and docetaxel are co-administered on day 1, and 5 patients who were randomized to mDCF(Arm A) in which cisplatin is administered on day 3 and docetaxel is administered on day 1, and . In Arm B, when cisplatin is given concurrently with docetaxel, dose adjusted docetaxel PK are as follows:

AUC_{∞} 74.1 ng*hr/ml/mg/m²
CL 28.9 L/hr/m²
Vdss 27.8 L/m²
T_{1/2} 18.8 hr

When docetaxel is given on day 1 and cisplatin is given on day 3 (mDCF), dose adjusted docetaxel PK are as follows:

AUC_{∞} 46.1 ng*hr/ml/mg/m²
CL 38.1 L/hr/m²
Vd_{ss} 17.1 L/m²
T_{1/2} 12.1 hr

These results appear to demonstrate that the clearance of docetaxel is reduced when it is administered on day 1 with cisplatin (Arm B), and this is associated with an increased exposure to docetaxel. Conversely, when docetaxel is administered on day 1 and cisplatin is administered on day 3, docetaxel clearance appears to be higher and is associated with a lower AUC_{∞} . Recall that our hypothesis is that reduced clearance and higher exposure to docetaxel may be responsible for some of the increased toxicity observed with the parent DCF (Arm B) regimen.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

We would like to expand on these initial findings. Specifically, in up to 6 patients randomized to the parent DCF arm (Arm B), in addition to performing docetaxel pharmacokinetics with cycle 1 treatment (as is already specified in the protocol), we would subsequently repeat docetaxel pharmacokinetics for a single cycle when cisplatin is not administered on the same day as docetaxel. For example, for a single subsequent cycle, we would plan to administer cisplatin on a later date (i.e. day 3) and repeat docetaxel pharmacokinetic sampling. Subsequent therapies would be as per protocol specification.

9.4.4 Volumetric CT Analysis of Response to Therapy

At MSKCC only and in collaboration with Larry Schwartz, MD, we will also initiate an exploratory volumetric CT analysis of Response to therapy. This study will make use of already acquired image data from this clinical trial. No additional human material or CT scans will be needed. The standard CT scan data (acquired either during PET/CT scanning or CT scanning) will be electronically transferred, via the hospital network, from the hospital PACS to the research PACS server, where patient identification information are de-identified. Volumetric CT will be used in an exploratory way to assess tumor response during therapy to compare with RECIST. The volumetric analysis, however, will not affect patient care and will not be communicated to the patient or clinical investigator. To study effects of a wider range of slice thickness on the performance of the segmentation algorithms and reproducibility of tumor measurements, thinner section CT images will be reconstructed with CT raw data acquired for the radiographic assessment in the trial. The volumetric CT technique used in this study may be able to detect asymmetric or small change in tumor size at the level that may not be possible with the conventional uni-dimensional RECIST criteria.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The table below describes the the study plan



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

TABLE 4. STUDY CALENDAR

| | Pre-Study | Cycle 1 | | | | | | Cycle 2 | | | | | | Cycle 3 (a) | Off Study (j) |
|--|-----------|---------|------|------|------|------|------|---------|------|------|------|------|------|-------------|---------------|
| | | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | → | |
| Day Number | | 1 | 8 | 15 | 22 | 29 | 35 | 42 | 49 | 56 | 63 | 70 | 77 | | |
| Informed consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Electrocardiogram | X | | | | | | | | | | | | | | |
| Pregnancy test (h) | X | | | | | | | | | | | | | | |
| Concomitant Meds | X | X | | | | | | X | | | | | | | X |
| Radiology (i) | X | | | | | | X | | | | | | X | | |
| FDG-PET/CT (m) | X | | | X | | | | | | | | | | | |
| Audiology Exam (k) | X | | | | | | | | | | | | | | |
| Tissue Collection | X | | | | | | | | | | | | | | |
| Coagulation | X | | | | | | | | | | | | | | |
| EORTC QLQ-C30 (n) | X | | | | | | X | | | | | | X | | |
| Pharmacology (l) | | X | | | | | | | | | | | | | X |
| ARM A - mDCF | | X | | X | | X | | X | | X | | X | | | X |
| Physical exam | X | X | | X | | X | | X | | | | X | | X | X |
| Toxicity check | X | X | | X | | X | | X | | X | | X | | X | X |
| Vital signs, Weight | X | X | | X | | X | | X | | X | | X | | X | X |
| Performance Status | X | X | | | | | | X | | | | | | X | X |
| CBC w/ diff, Plts | X | X | | X | | X | | X | | X | | X | | X | X |
| Serum chemistry (b) | X | X | | | | X | | X | | | | X | | X | X |
| BUN, Creatinine (c) | | | | X | | | | | | X | | | | | X |
| LFTs (d) | X | X | | X | | X | | X | | | | X | | X | X |
| Total protein, LDH, Alb, Ca, Mg, PO ₄ , tumor markers (e) | X | X | | | | | | X | | | | | | X | X |
| Echocardiogram/MUGA ^o | X | | | | | | | | | | | | X | | |
| ARB B - DCF + G-CSF | | X | | | X | | | X | | | X | | | X | |
| Physical exam | X | X | | X | | | | X | | | X | | | X | X |
| Toxicity check | X | X | | X | | | | X | | | X | | | X | X |
| Vital signs, Weight | X | X | | X | | | | X | | | X | | | X | X |
| Performance Status | X | X | | X | | | | X | | | X | | | X | X |
| CBC w/ diff, Plts | X | X | | X | | | | X | | | X | | | X | X |
| Comprehensive (g) | X | X | | X | | | | X | | | X | | | X | X |

^a Continues as per cycle 2, except the physical exam may be performed at the beginning of every cycle and as necessary and the toxicity check will be performed prior to the week 1 and 5 treatment of every subsequent cycle, and as needed.

^b Bicarbonate, BUN, chloride, creatinine, glucose, potassium, sodium

^d AST (SGOT), ALT (SGPT), Total Bilirubin, Alkaline Phosphatase. Any abnormal LFTs require repeat LFTs prior to subsequent docetaxel therapy. Patients with alkaline phosphatase elevation secondary to the bony metastases rather than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.

^{b, c, d, e, f, g} May be performed on or within 1 day of treatment ^e Tumor markers as available.

^g Comprehensive = serum chemistry + LFTs + total protein, LDH, alb, Ca, Mg, PO₄, and tumor markers as available.

^h For women of childbearing potential ⁱ Includes CT of the chest, abdomen and pelvis within 30 days and a PA and lateral chest x-ray unless a CT of the chest is available within 14 days of starting therapy. Tumor measurements are repeated after every cycle for the first 6 cycles and every 2 cycles thereafter. May be performed earlier at physician discretion. Radiologic documentation of progression is strongly recommended. ^j Patients will be monitored for overall survival following completion of study. Maybe performed by local physicians. ^k As clinically indicated, ^l Pharmacokinetic blood draws for MSKCC patients as per section 9.4.3. ^m FDG-PET/CT scans are performed at baseline, and again during week 3 (following treatment #2 in ARM A, before treatment #2 in ARM B), participating sites only. ⁿ EORTC QLQ-C30 is administered at baseline, 6 weeks, 3 months, 6 months, 9 months, and 12 months. ^oFor patients receiving trastuzumab only, echocardiogram/MUGA will be done at baseline and every 12 weeks while on protocol.

10.1 FOR PARTICIPATING SITES



Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Tissue samples for HER2 testing will be processed locally in the laboratory of investigational sites. The results of local laboratory HER2 analysis will be required and sufficient to start the study treatment. The MSK laboratory will be used for subsequent confirmation of HER2 status. MSK pathology review will not be required to begin therapy on the protocol. Samples provided to the MSK laboratory must either be HER2 IHC slides, or if FISH confirmation is necessary, a paraffin block(s) of adequate size to allow if possible for at least 5 slides with cuts that are 5-microns thick or if a paraffin block is not available, then if possible at least 5 slides with cuts that are 5-microns thick will be acceptable. Archived or fresh tumor samples may be used.

Shipping of Specimen(s):

All sites should ship specimens to MSKCC Principal Investigator:
Yelena Y. Janjigian
Memorial Sloan-Kettering Cancer Center
300 E 66th Street BAIC 1033
New York, NY 10065

- Shipments should be batched.
- A copy of the pathology report and patient signed informed consent should be included with the shipment.
- At the time of shipment, a transmittal documenting patient ID and type of specimen sent should also be electronically submitted to janjigiy@mskcc.org and faxed to the Multicenter Core Project Coordinator (646-227-2482)
- Shipments will not be received on Saturday or Sunday

11.0 TOXICITIES/SIDE EFFECTS

11.1 CISPLATIN

Cumulative nephrotoxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea and vomiting. Ototoxicity, manifested by tinnitus and/or high frequency hearing loss, is significant. Anaphylactic like reactions to cisplatin have been reported. Facial swelling, bronchospasm, tachycardia and hypotension may occur within minutes of cisplatin administration. Other side effects include anorexia, diarrhea, serum electrolyte disturbances (e.g., hyponatremia, hypomagnesemia), vascular toxicities (e.g., myocardial infarction, cerebrovascular accident etc.), renal insufficiency, neurotoxicity, peripheral neuropathy, autonomic neuropathy, muscle cramps, ocular toxicity (optic neuritis, papilledema, cerebral blindness), and hepatotoxicity. Other rare side effects include cardiac abnormalities, hiccoughs, elevated serum amylase, rash and alopecia. Local soft tissue injury has been reported following extravasation of cisplatin. A complete list of toxicities can be found in the package insert.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

11.2 DOCETAXEL

Principal adverse effects include neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, ascites, mucositis, cardiac arrhythmias, hypotension, pleural effusion, peripheral neuropathy, rash, severe nail disorders (hypo or hyperpigmentation), onycholysis (loosening of the nails), alopecia, palmar-plantar dysesthesia, hypersensitivity reaction, fatigue and fluid retention syndrome (may be irreversible).

11.3 FLUOROURACIL

Hematologic and gastrointestinal side effects are most frequently associated with fluorouracil. Hematologic toxicities of fluorouracil are leukopenia, granulocytopenia (9-14 days), thrombocytopenia (7-14 days), and anemia. Stomatitis, gastrointestinal ulceration and bleeding, and diarrhea are commonly seen gastrointestinal side effects of fluorouracil. Nausea and vomiting, effects on the skin including rashes and hyperpigmentation, alopecia, ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischemia have been reported. A complete listing of toxicities can be found in the fluorouracil package insert.

11.4 LEUCOVORIN

The only adverse reaction for leucovorin is a rare report of allergic reactions to parenteral injections of leucovorin. This is extremely uncommon.

11.5 TRASTUZUMAB

Principal adverse effects include cardiac dysfunction, infusion associated symptoms, potentiation of chemotherapy related hematologic side effects. A complete listing of toxicities can be found in the trastuzumab package insert.

11.6 SUPPORTIVE MEDICATIONS

G-CSF: common side effects include nausea, vomiting, bone pain, injection site irritation and influenza-like illness. Rare side effects include vasculitis of the skin, and very rarely, acute respiratory distress syndrome and splenic rupture have been reported.

Decadron: with chronic use, common side effects include hypertension, atrophic skin, impaired skin healing, hypercortisolism and primary adrenocortical insufficiency, irritation of the GI tract, increased risk of infection, osteoporosis, cataracts or glaucoma, and depression or euphoria. Hyperglycemia is common even with single use.



12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients should be re-evaluated for response every cycle of chemotherapy, for the first 6 cycles of therapy. For patients remaining on therapy thereafter, patients are to be re-evaluated every 2 cycles of therapy. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response.

12.1 DEFINITIONS

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET, CT, MRI, x-ray) or as ≥ 10 mm with a high-resolution CT scan. All tumor measurements must be recorded in millimeters or decimal fractions of centimeters. A “high-resolution” CT scan is one in which images are recorded at least every 5 mm.

12.1.2 Non-Measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable. Stomach, GEJ, or esophageal wall thickening is considered non-measurable.

12.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

12.1.4 Non-target lesions

All other lesions (or sites of disease) that are not target lesions as defined in section 12.1.3 will be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are required when



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

feasible, since a patient may have progressive disease on the basis of larger non-target lesions. The presence or absence of each non-target lesion should be noted throughout follow-up.

12.2 EVALUATION OF TARGET LESIONS

Complete Response (CR): Disappearance of all target lesions. Endoscopy must be without evidence of tumor with negative cytologic brushings and esophageal biopsies. The patient must be free of all symptoms of cancer.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Positive washing, brushing or biopsy and/or residual tumor may still be evident on endoscopy and/or CT scan. No lesion may increase in size and no new lesion may appear.

Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

12.3 EVALUATION OF NON-TARGET LESIONS

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Non-Complete Response (non CR): Persistence of one or more non-target lesions or/ and maintenance of tumor marker level above the normal limits.

Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. (Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the reference radiologist (or study chair).

Note:

1. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
2. Cytology and histology: If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible. These techniques can be used to differentiate between PR and CR in rare cases (eg. residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for



response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

| Target Lesions | Non-Target Lesions | New Lesions | Overall response |
|----------------|--------------------|-------------|------------------|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

1. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
2. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.5 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

12.6 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation: The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 DURATION OF THERAPY / CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will receive at least one cycle of treatment. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression, defined as
 - (1) Appearance of a tumor > 1 cm in size at a new site, or
 - (2) Reappearance of a previously completely resolved measurable tumor or lesion, or
 - (3) An increase in tumor measurements (total longest diameter) > 20%.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- (4) New sites of or clinical progression in non-measurable sites of disease
- Intercurrent illness that prevents further administration of treatment,
 - Unacceptable adverse event(s), including but not limited to
 - (1) grade 4 anaphylaxis
 - (2) grade 4 hypertension, hemorrhage, or symptomatic grade 4 venous thromboembolism
 - (3) any grade arterial thromboembolic event
 - (4) grade 4 proteinuria
 - (5) GI perforation or wound dehiscence (requiring medical or surgical therapy)
 - Patient death,
 - Patient decides to withdraw from the study or is lost to follow up, or
 - General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be discontinued from the study if they exhibit any of the following:

- Dose limiting toxicity (not resolving) possibly, probably, or definitely attributable to the investigational agent: any Grade 3 or greater non-hematological event that does not recover to \leq grade 1. Nausea and vomiting will be dose limiting only if grade 3 despite adequate premedication. If a patient develops dose-limiting toxicity then the drug will be withheld until toxicity resolves to \leq grade 1, and restarted at a lower dose (Section 9.3).
- In addition, if a patient develops an adverse experience that the Investigator feels is severe enough to preclude further participation, the patient will be discontinued from the study and receive medical treatment as determined by the Investigator. The patient will remain under observation until the adverse experience is resolved.

Patients will be discontinued from the study if they exhibit any of the following:

- Lack of cooperation with the requirements of the study
- Intercurrent illness requiring medication not allowed by the protocol
- Withdrawal of consent

The patient's physician(s) are free to and should discontinue study treatment if this is believed to be in the patient's best interest. Furthermore, a patient is free to withdraw from study treatment and participation at any time for any reason. Full documentation of the reasons and circumstances of all patients who withdraw must be documented in the medical record and on the appropriate case report forms.

13.2 OFF-STUDY EVALUATION

- History and physical examination, including performance status and neurological exam.
- Laboratory: Complete blood counts and chemistry tests as required at baseline



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- Tumor Measurements: Assessment of at least one measurable lesion (in appropriate patients) preferably by CT scan unless within 4 weeks of last measurements.
- Patients will be monitored for overall survival following completion of or removal from the study.

14.0 BIOSTATISTICS

The study will be an open-label random assignment phase II therapeutic clinical trial. The study population will be patients with histologically confirmed unresectable or metastatic gastric or gastroesophageal adenocarcinoma. Arm A will be modified DCF and ARM B will be 'parent' DCF with growth factor support.

The primary endpoint for both arms is progression free survival (PFS), as measured from the start of the treatment to the date of either documentation of disease progression or death. We will define progression of disease as per RECIST criteria. Patients with measurable disease and with evaluable radiographically but non-measurable disease will be eligible for study entry. As per RECIST criteria, any evidence of progression in non-measurable lesions, measurable lesions, or the development of new lesions, would qualify as disease progression. The 6 month progression free survival for 'parent' DCF is approximately 43% (see Section 3.3.2). Using this as a benchmark, we propose declaring each regimen comparable to parent DCF if the 6 months PFS exceeds 43%, and unworthy of further investigation if it is 26% or less. Each arm will be evaluated separately for this purpose. We will accrue 60 patients in each arm for a total study population of 120 patients. Anticipating a 10% inevaluable rate, with 54 evaluable patients enrolled in each arm we will be able to differentiate between 6 month PFS of 26% and 43% with type I and II error rates of 10% each (exact single stage binomial design) [44]. For each arm, the regimen is considered promising if 19 or more patients (out of 54) are progression free at 6 months. We will define "evaluable" patients as patients who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal within the first 6 months. We anticipate enrollment to be 8 patients/ month with completion of accrual in approximately 15 months.

Secondary endpoints of efficacy are response rate, median PFS, overall and 1 year survival. We anticipate that we will enroll approximately 40 patients with measurable disease in each arm, from which we can establish a response rate to within +/- 15%. This is consistent with most Phase II studies evaluating response. The median PFS will be estimated using the Kaplan-Meier method, and 95% confidence intervals will be based on the sign test [45]. The 1 year survival will be estimated using the Kaplan-Meier method, and Greenwood's formula will be used to calculate the standard error of the corresponding Kaplan Meier estimate and 95% confidence interval. Survival curves will be estimated using Kaplan-Meier methodology.

A secondary objective is to demonstrate improved toxicity profile of each regimen compared to parent DCF. It is reported that DCF has a grade 3-4 adverse event rate for non-hematologic toxicity exceeding 80%. We hypothesize that the modified De Gramont type of FU infusion and more frequent dosing of cisplatin and docetaxel (eg. ARM A) will be associated with less toxicity. Additionally, parent DCF administered growth factor support (eg. ARM B) will also be associated with less toxicity.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive grade 3 or 4 adverse events. We employ repeated significant testing with a constant significance level to monitor the grade 3/4 adverse event rate [46]. The table below provides a stopping boundary for this study based on an acceptable grade 3/4 adverse event rate of 50% and an unacceptable grade 3/4 adverse event rate of 70%. Using this boundary, if the true adverse event rate is 50% then the probability of stopping early is 5%. However, if the true toxicity rate is 70% then the probability of stopping early increases to 87%.

| | | | | |
|--------------------|----|--|----|-----------|
| Stop if we observe | 12 | grade 3 or 4 adverse events in the first | 15 | patients. |
| | 21 | | 30 | |
| | 30 | | 45 | |
| | 35 | | 54 | |

Grade 3 or 4 venous thromboembolic events will not be included for the purposes of this safety determination. We have previously demonstrated that the majority of these events are associated with minimal to no co-morbidity and are likely attributable to the disease and not the therapy[47].

Total accrual will be 108 evaluable patients with a 1:1 randomization. We will stratify based on center, disease (measurable vs. non-measurable), and location (gastric vs. GEJ).

December 2009 Amendment

Arm B will be closed because we met the above stopping rule. Specifically, we observed 22 grade 3-4 adverse events in the first 30 patients enrolled on Arm B. We note that there was a discrepancy between the two arms with regard to the rate of grade 3-4 thromboembolism (5 in Arm B, and 0 in Arm A). Because of this discrepancy, we included grade 3-4 venous thromboembolic events in the determination of the toxicity stopping rule. Notably, 16 patients in Arm B required admission due to toxicity in the first 3 months of protocol therapy. As a result of this unacceptable toxicity, the standard DCF + growth factor support arm will close.

As of October 23, 2009, 26 patients are evaluable for toxicity in Arm A (mDCF). We've observed 16 grade 3-4 adverse events attributable to treatment in the first 3 months, and 8 hospitalizations.

Note, the results of the recent ToGA study demonstrate that for Her2 positive gastric cancer, patients have a survival benefit with the addition of trastuzumab to chemotherapy (see Sect 3.3.4). We are therefore amending the study to include a separate cohort of 35 patients who are Her2 positive to receive mDCF + trastuzumab (Trastuzumab cohort)

Total patient accrual to this protocol is fixed at 120 patients. Arm B has closed with 31 patients enrolled in total. Arm A will remain with a target accrual of 54 eligible patients. For the remaining 35 patients, we will open a *Trastuzumab Cohort* in which Her2 positive patients with metastatic gastric/GEJ adenocarcinoma will receive mDCF + trastuzumab. With 35 HER2-positive patients, we will be able to differentiate between 6-month PFS of 43% and 64% with type I and II error rates of 10% each (exact single stage binomial design). The modified DCF

IRB
PB

Amended: 08/03/15



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

plus trastuzumab regimen will be considered promising if 19 or more Her2 positive patients (out of 35) are alive and progression free at 6 months.

For the *Trastuzumab Cohort*, we will employ a similar early stopping rule for safety, as we have done for Arm A and Arm B. The table below provides a stopping boundary for this study based on an acceptable grade 3/4 adverse event rate of 50% and an unacceptable grade 3/4 adverse event rate of 70%. Using this boundary, if the true adverse event rate is 50% then the probability of stopping early is 5%. However, if the true toxicity rate is 70% then the probability of stopping early increases to 87%.

| | | | | |
|--------------------|----|--|----|-----------|
| Stop if we observe | 12 | grade 3 or 4 adverse events in the first | 15 | patients. |
| | 21 | | 30 | |

For the FDG-PET/CT correlative study (section 9.4.2), the change between baseline and 2nd PET scan (change in SUV) will be correlated with response, time to tumor progression, and overall survival. These associations will be assessed using a t-test for response (comparing the means between responders and non-responders), and Cox regression for overall survival and time to tumor progression.

Another secondary objective is to explore the differences in docetaxel pharmacology between the two study arms. Serial blood draws will be performed in approximately 10 patients in each arm, as explained in section 9.4.3. Some patients in Arm B may have repeat docetaxel pharmacology tests without cisplatin administration. Standard pharmacokinetic parameters including C_{max}, T_{max}, and AUC will be estimated for each patient using non-compartmental methods, and a Wilcoxon rank sum test will be used to compare the distribution of levels for the two groups.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

All centers must register patients through MSKCC. No patient can be treated unless they are registered through MSKCC.

For MSKCC patients:

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

For Participating Centers:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center. Patient registration must be initiated at Memorial Sloan Kettering Cancer Center *within 48 hours of the patient signing the informed consent.*

To complete registration and enroll a patient from another institution, the study staff at that site must contact the Multicenter Core Project Coordinator to notify him/her of patient registration. The study staff then needs to fax registration/eligibility documents to the Multicenter Trials Core at MSKCC at 646-227-2482.

The following documents must be sent within 24 hours of informed consent form being signed for each enrollment:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

15.2 PROTOCOL PATIENT NUMBER

Once eligibility has been established and the patient is registered, the patient will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol patient number). This number is unique to the patient and must be written on all data and correspondence for the patient. This protocol patient number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.



15.3 RANDOMIZATION

After eligibility is established and immediately after consent is obtained and a patient number is assigned patients will be registered and randomized using the Clinical Research Database (CRDB). Patients will be 1:1 randomized to the two arms. Randomization will be accomplished by the method of random permuted block. We will stratify based on center, disease (measurable vs. non-measurable), and location (gastric vs. GEJ).

December 2009 Amendment

Due to excessive toxicity, Arm B has been closed. Patients will no longer be randomized between two arms of the study. Instead, patients will be assigned to Arm A. If they are Her2 positive and are eligible for trastuzumab, they will be assigned to the *Trastuzumab cohort*.

August 2010 Amendment

Arm B remains closed due to toxicity and target accrual has been reached for Arm A. Accordingly, eligibility criterion has been expanded to include Her2. Patients eligible under these criteria will be assigned to the *Trastuzumab cohort*.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database – CRDB). Source documentation will be available to support the computerized patient record. Standardized Case Report Forms (CRFs) that meet the requirements for MSKCC data reporting have been generated for this study. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by body system and to severity or toxicity grade. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.0.1 Data Management Requirements for Participating Sites

Data

Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Please see Appendix C for the data collection schedule that each participating center is expected to adhere to.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes but is not limited to:

- Baseline measures to assess pre-protocol disease status (ex. CT)
- Treatment records
- Grade 3-5 toxicities/adverse events
- Response designation

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should fax CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

FAX: To the attention of Multicenter Trials Core at **646-227-2482**

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to guidelines specified in Appendix A-C.

SAE Reporting:

Hospitalization requiring Serious Adverse Event Reporting must be reported within three calendar days.

Please see Section 17.2.1 regarding the requirements for SAE reporting.

Off-Study Requirements:

When a patient is taken off-study all CRFs with required source documentation are required to be sent to MSKCC not later than 14 calendar days after the off-study date. Failure to submit required forms in the timelines requested will result in suspension of accrual privileges at a given site until data is updated, and/or withholding of contract payments if applicable.

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

16.1 QUALITY ASSURANCE

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Site Auditing

Each site participating in the accrual of patients to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected patients records can be audited on-site at participating sites or (2) source documents for selected patients will be sent to MSKCC for audit. Audits will usually be determined by patient accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of Lead PI.

Audits will be conducted at least once shortly after initiation of patient recruitment at a site, and if possible, at the end or closeout of the trial at a site and during the trial if the trial lasts 3 or more years. At a minimum, audits will be conducted once a year or more frequently, if indicated. The number of patients audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timing and accuracy

A wrap-up session will be conducted at the outside site and preliminary findings will be discussed with the outside site PI and research team. The preliminary results will be sent to the MSKCC PI.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Each audit will be summarized and a final report will be sent to the PI at the audited participating institution within 30 days of the audit. The report will include a summary of findings, patient by patient case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating institution must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the outside site must be sent to the MSKCC IRB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites patient's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the outside sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent promptly upon request to MSKCC.

16.1.3 Adherence to the Protocol

The study will be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the patient requires alternative treatment. Any deviation from the protocol will be reported, explained and documented in the patient's medical record.

16.2 DATA AND SAFETY MONITORING

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: [http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20\(CRQA\)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf](http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf)

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (eg. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (eg. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

For Multicenter studies, standardized Case Report Forms (CRFs) have been generated from this study that meet the requirements of CTEP and MSKCC data reporting. A set of CRFs will be sent to each center (for photocopying and use) following local activation.

16.3 ETHICAL AND ADMINISTRATIVE ISSUES

The investigator will agree to personally conduct and supervise the proposed investigations according to recognized principles of good clinical practice (GCP).

16.4 INSTITUTIONAL REVIEW BOARD APPROVAL

This protocol and the informed consent form will be reviewed and approved by the IRB before the study is initiated. The Investigator is then responsible for informing the IRB of the completion of the study and will provide the IRB a final study status report. The Investigator/Study Coordinator will inform the IRB of all serious adverse events.

16.5 REGULATORY DOCUMENTATION

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

**IRB
PB**

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

16.5.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.5.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.5.3 Document maintenance

**IRB
PB**

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 7 years.

16.6 NONCOMPLIANCE

If a participating site is noncompliant with the data and regulatory requirements set forth in section 16.0 -16.5 accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 7.0.

Exclusion of Lactating or Pregant Women: Children have been excluded from this study. Gastric and GEJ adenocarcinoma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of the gastric tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications of treatment. The laboratory correlative studies and week 3 FDG-PET/CT scans will be performed without charge to the patient.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with metastatic gastric cancer alternative treatments may include other chemotherapy regimens as well as palliative radiation therapy, and/or surgery. At present, no specific chemotherapy regimen represents standard treatment for the disease. Patients may be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (eg, qualified monitors from MSKCC or collaborating institutions, the NCI, Sanofi-Aventis etc.), may review patients records and pathology slides, as required.

17.1 PRIVACY

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 SERIOUS ADVERSE EVENT (SAE) REPORTING

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

- Detailed text that includes the following information:
 - o A explanation of how the AE was handled
 - o A description of the subject's condition
 - o Indication if the subject remains on the study
 - o If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

All adverse events, whether observed by the investigator, elicited from the patient, or volunteered by the patient, will be recorded. The MSKCC PI (Yelena Janjigian, MD) will report all SAE's to the MSKCC IRB and to Sanofi-Aventis Pharmaceuticals and Genentech via the CRDB AE report .

17.2.1 ADVERSE EVENT REPORTING DEFINITIONS

Adverse Event: An adverse event is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic functions, as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical trial, whether or not considered drug related. All of the following are to be considered adverse events:

- an exacerbation of a pre-existing condition.
- an intercurrent illness.
- any drug interaction.
- any event related to a concomitant medication.
- development of an abnormal laboratory value or a significant change from baseline in a laboratory value within the range of normal, considered by the investigator to be clinically important.
- an unexpected significant worsening of the cancer under treatment. Anticipated day-to-day fluctuations in the activity of the cancer or the anticipated progression of the cancer (other than death) should not be considered an adverse event.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" is that there is a reasonable possibility that the drug caused the adverse experience.



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

Life-threatening: A life-threatening adverse event implies an immediate risk of death from the reaction as it occurred. Life-threatening does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

ASSESSMENT OF SEVERITY

This study will utilize the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

ASSESSMENT OF RELATIONSHIP TO STUDY MEDICATION

The following definitions of relationship to study medication should be used in assessing the suspected causality of an adverse event:

- Definite: The adverse event is clearly related to the chemotherapy or investigational agent.
- Probable: The adverse event is likely related to the chemotherapy or investigational agent.
- Possible: The adverse event may be related to the chemotherapy or investigational agent.
- Unlikely: The adverse event is doubtfully related to the chemotherapy or investigational agent.
- Unrelated: The adverse event is clearly NOT related to the chemotherapy or investigational agent.

17.2.3 REPORTING ADVERSE EVENTS ASSOCIATED WITH TRASTUZUMAB (GENENTECH)

With the occurrence of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to or caused by trastuzumab. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to trastuzumab through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

Reporting Serious Adverse Events Associated With Trastuzumab

All SAEs that are serious and reasonably or probably related to the use of Trastuzumab (this applies to both expected and unexpected events) should faxed to:

Genentech Drug Safety Contact Line

Tele: 1-888-835-2555

Fax: (650) 225-4682/ (650) 225-4683

AND:

Study Coordination Center/Principal Investigator

Contact Information

AND:

IRB Contact information

**IRB
PB**

Amended: 08/03/15



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

17.2.4 SANOFI –AVENTIS REPORTING GUIDELINES

All SAEs are to be reported as soon as possible to Sanofi-Aventis. Reports by FAX should be sent to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department (908-231-4827), within 24 hours of receipt by investigator / sponsor. FAX transmission should include the following on the provided IIT SAE REPORT, fax cover form (Appendix E):

Reports by E-MAIL should be sent to: GPEmailbox@aventis.com , within 24 hours of receipt by investigator / sponsor. E-Mail transmission should include the following:

Investigator-Initiated (IIT #) study number: _____

Study Title: _____

Name of Principal Investigator: _____

17.3 SERIOUS ADVERSE EVENT REPORTING FOR OUTSIDE CENTERS

Responsibility of Participating Sites

Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within **3 calendar days**.

Participating sites should notify the MSKCC PI of any grade 5 event immediately.

Participating sites should use the SAE Report Template (appendix E) to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

PI: Yelena Y. Janjigian, MD

Tel: 646-888-4186

Email: janjigiy@mskcc.org

Multicenter Core Project Coordinator

Fax: 646-227-2482

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 [and to the funding entity as described in 17.2.3 and 17.2.4]
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 SAFETY REPORTS

IRB
PB

Amended: 08/03/15



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

A note should be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCE(S)

1. Parkin, D.M., F.I. Bray and S.S. Devesa, *Cancer burden in the year 2000. The global picture*. European Journal of Cancer, 2001. 37(8): p. 4-66.
2. Shah, M.A. and G.K. Schwartz, *The Treatment of Metastatic Esophagus and Gastric Cancer*. Semin Oncol, 2004. 4: p. 574-587.
3. Janunger, K.G., L. Hafstrom, P. Nygren, et al., *A systemic overview of chemotherapy effects in gastric cancer*. Acta Onc., 2001. 40(2/3): p. 309-326.
4. Vanhoefer, U., P. Rougier, H. Wilke, et al., *Final Results of a Randomized Phase III Trial of Sequential High-Dose Methotrexate, Fluorouracil, and Doxorubicin Versus Etoposide, Leucovorin, and Fluorouracil Versus Infusional Fluorouracil and Cisplatin in Advanced Gastric Cancer: A Trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group*. J Clin Oncol, 2000. 18(14): p. 2648-2657.
5. Ohtsu, A., Y. Shimada, K. Shirao, et al., *Randomized phase III trial of fluorouracil versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205)*. J Clin Onc, 2003. 21(1): p. 54-9.
6. Icli, F., I. Celik, F. Aykan, et al., *A randomized phase III trial of etoposide, epirubicin, and cisplatin versus 5-fluorouracil, epirubicin, and cisplatin in the treatment of patients with advanced gastric carcinoma*. Cancer, 1998. 83: p. 2475-80.
7. Tebbutt, N.C., A. Norman, D. Cunningham, et al., *A multicentre, randomised phase III trial comparing protracted venous infusion (PVI) 5-fluorouracil with PVI plus mitomycin C in patients with inoperable oesophago-gastric cancer*. Ann Oncol, 2002. 13: p. 1568-75.
8. Ross, P., M. Nicolson, D. Cunningham, et al., *Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer*. J Clin Onc, 2002. 20: p. 1996-2004.
9. Waters, J.S., A. Norman, D. Cunningham, et al., *Long-term survival after epirubicin, cisplatin, and fluorouracil for gastric cancer: results of a randomized trial*. Br J Cancer, 1999. 80(1/2): p. 269-72.
10. Webb, A., D. Cunningham, J.H. Scarffe, et al., *Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer*. J of Clin Oncol, 1997. 15(1): p. 261-67.
11. Ajani, J.A., E. Van Cutsem, F.C. Moiseyenko, et al. *Docetaxel (D), cisplatin, 5-fluorouracil compared to cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naïve patients with metastatic or locally recurrent, unresectable gastric carcinoma: Interim results of a randomized phase III trial (V 325)*. in Proc Amer Soc Clin Onc. 2003. Chicago, IL.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

12. Moiseyenko, V.M., J.A. Ajani, S.A. Tjuladin, et al., *Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients (pts) with metastatic gastric adenocarcinoma*. Proc Am Soc Clin Oncol, 2005. 23: p. abs4002.
13. Ajani, J., J. Baker, P. Pisters, et al., *Irinotecan plus cisplatin in advanced gastric or gastroesophageal junction carcinoma*. Oncology (Huntingt), 2001. 15(3 Suppl 5): p. 52-4.
14. Boku, N., A. Ohtsu, Y. Shimada, et al., *Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer*. J of Clin Oncol, 1999. 17(1): p. 319-23.
15. Ilson, D., A.A. Forastier, M. Arquette, et al., *A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus*. Cancer J., 2000. 6(5): p. 316-23.
16. Pozzo, C., C. Barone, J. Szanto, et al., *Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study*. Ann Oncol, 2004. 15: p. 1773-1781.
17. Dank, M., J. Zaluski, C. Barone, et al., *Randomized phase 3 trial of irinotecan (CPT-11) + 5FU/folinic acid (FA) vs CDDP + 5FU in 1st line advanced gastric cancer patients*. Proc Am Soc Clin Oncol, 2005. 23: p. abs4003.
18. Roth, A., R. Maibach, G. Martinelli, et al., *Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology*. Ann Oncol, 2000. 11(3): p. 301-6.
19. Ridwelski, K., T. Gebauer, J. Fahlke, et al., *Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer*. Ann Oncol, 2001. 12(1): p. 47-51.
20. Roth, A.D., R. Maibach, N. Fazio, et al., *5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (Taxotere)-cisplatin in advanced gastric carcinoma: a phase I-II trial*. Ann Oncol, 2004. 5: p. 759-764.
21. Thuss-Patience, P., A. Kretschmar, M. Repp, et al., *Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study*. J Clin Onc, 2005. 23: p. 494-501.
22. Roth, A.D., R. Maibach, S. Falk, et al., *Docetaxel-cisplatin-5FU versus docetaxel-cisplatin versus epirubicin-cisplatin-5FU as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research (SAKK)*. Proc Am Soc Clin Oncol, 2004. 22(14S): p. abs 4020.
23. Chen, L.-T., T.-W. Liu, C.-W. Wu, et al., *A phase I study of weekly docetaxel, 24-hour infusion of high-dose fluorouracil/leucovorin and cisplatin in patients with advanced cancer*. Oncology, 2002. 63: p. 239-47.
24. Constenla, M., R. Garcia-Arroyo, I. Lorenzo, et al., *Docetaxel, 5-fluorouracil, and leucovorin as treatment for advanced gastric cancer: results of a phase II study*. Gastric Cancer, 2002. 5: p. 142-47.
25. Park, S.R., J.H. Chun, Y.W. Kim, et al. *Phase II study of low-dose docetaxel/fluorouracil/cisplatin in metastatic gastric cancer*. in 2005 Gastrointestinal Cancers Symposium. 2005. Miami, FL.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

26. Lorenzen, S., J. Duyster, N. Weigert, et al. *Docetaxel (T) plus Cisplatin (P) and leucovorin (L)/5FU (F) in first line advanced gastric cancer and adenocarcinoma of the gastro-esophageal junction: First results of the phase II GASTRO-TAX-1 trial.* in 2006 *Gastrointestinal Cancers Symposium*. 2006. San Francisco, California: American Society of Clinical Oncology.
27. de Gramont, A., J.F. Bosset, C. Milan, et al., *Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study.* *J Clin Onc*, 1997. 15(2): p. 808-15.
28. Al-Batran, S.-E., A. Atmaca, S. Hegewisch-Becker, et al., *Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer.* *J Clin Onc*, 2004. 22(4): p. 658-63.
29. Kim, D.Y., J.H. Kim, S.-H. Lee, et al., *Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously-treated patients with advanced gastric cancer.* *Ann Oncol*, 2003. 14: p. 383-87.
30. Bouche, O., J.L. Raoul, F. Bonnetain, et al., *Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study - FCCD 9803.* *J Clin Onc*, 2004. 22(21): p. 4319-4328.
31. Oh, D.-Y., T.-Y. Kim, J.H. Kwon, et al., *Docetaxel + 5-fluorouracil + cisplatin 3-day combination chemotherapy as a first-line treatment in patients with unresectable gastric cancer.* *Jpn J Clin Oncol*, 2005. 35(7): p. 380-85.
32. Pronk, L.C., J.H.M. Schellens, A.S.T. Planting, et al., *Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors.* *J Clin Onc*, 1997. 15(3): p. 1071-1079.
33. Millward, M.J., J. Zalcberg, J.F. Bishop, et al., *Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small cell lung cancer.* *J Clin Onc*, 1997. 15(2): p. 750-58.
34. Rowinsky, E.K., M.R. Gilbert, W.P. McGuire, et al., *Sequences of taxol and cisplatin: a phase I and pharmacologic study.* *Journal of Clinical Oncology*, 1991. 9(9): p. 1692-703.
35. Ma, J., J. Verweij, A.S.T. Planting, et al., *Docetaxel and paclitaxel inhibit DNA-adduct formation and intracellular accumulation of cisplatin in human leukocytes.* *Cancer Chemother Pharmacol*, 1996. 37: p. 382-84.
36. TM, T., [package insert]. Bridgewater, NJ; Aventis Pharmaceuticals., 2005.
37. TM, A., [package insert]. Lugano, Switzerland: Helsinn Healthcare, 2003.
38. Oliver, I., *Aprepitant in antiemetic combinations to prevent chemotherapy-induced nausea and vomiting.* *Inter J. Clin Practice*, 2004. 58(2): p. 201-6.
39. McCrea, J.B. and e. al., *Effects of neurokinin 1 receptor antagonist on the pharmacokinetics of dexamethasone and methylprednisolone.* *Clin Pharmacol Ther*, 2003. 74: p. 17-24.
40. Nygren, P., K. Hande, K.J. Petty, et al., *Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients.* *Cancer Chemother Pharmacol*, 2005. 55: p. 609-616.



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-103 A(17)

41. Rosing, H., V. Lustig, L.J.C. van Warmerdam, et al., *Pharmacokinetics and metabolism of docetaxel administered as a 1-hour intravenous infusion*. *Cancer Chemother Pharmacol*, 2000. 45: p. 213-18.
42. Stein, H.J., M. Feith and J.R. Siewert, *Cancer of the esophagogastric junction*. *Surgical Oncology*, 2000. 9(1): p. 35-41.
43. Mandard, A.M., F. Dalibard, J.C. Mandard, et al., *Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: Clinicopathologic correlations*. *Cancer*, 1994. 73: p. 2680-86.
44. Chow, S.C., J. Shao and H. Wang, *Sample Size Calculations in Clinical Research*. 2003, New York: Marcell Dekker.
45. Brookmeyer, R. and Crowley, J., *A confidence interval for the median survival time*. *Biometrics*, 1982, 38: p. 29-41.
46. Siegmund, D., *Sequential Analysis: Tests and Confidence Intervals*. Springer Series in Statistics. 1985.
47. Shah, M.A., D. Ilson and D. Kelsen, *Thromboembolic Events In Gastric Cancer: High Incidence in Patients Receiving Irinotecan and Bevacizumab Based Therapy*. *J Clin Oncol*, 2005. 23(11): p. 2574-6.
48. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004 Jan 15;22(2):330-53. Epub 2003 Dec 22.
49. Maindrault-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, Mabro M, Artu P, Louvet C, De Gramont A. Optimox2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC). A GERCOR study. *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 3504
50. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, Svensson C, Enander LK, Linne T, Sellstrom H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 8:163-168, 1997
51. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85:365-376,1993
52. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 16:139-144
53. Tournigand C, Cervantes A, Figuer A, et al: OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—A GERCOR study. *J Clin Oncol* 24:394-400, 2006
54. Ross P, Nicolson M, Cunningham D, et al: Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 20:1996-2004, 2002



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 06-103 A(17)

55. Calais Da Silva FM, Bono A, Brausi M, Whelan P, Queimadelos A, Portillo J, Kirkali Z, Robertson C. Phase III intermittent MAB vs continuous MAB. *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 4513
56. Hofman M, Stoss O, Shi D, et al: Assessment of a Her2 scoring system for gastric cancer: results from a validation study. *Histopathology* 52:797-805., 2008
57. Van Cutsem E, Kang Y, Chung H, et al: Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol (Meeting Abstracts)* 27:LBA4509-, 2009
58. Marx AH, Tharun L, Muth J, et al: Her2 amplification is highly homogenous in gastric cancer. *Hum Pathol* 40:769-77., 2009

20.0 APPENDICES

Appendix A: KARNOFSKY / ECOG PERFORMANCE STATUS SCALES

Appendix B: TISSUE TRANSMITTAL SHEET

Appendix C: SERIOUS ADVERSE EVENT REPORT FORM FOR NON-MSKCC SITES

Appendix D: EORTC QLQ-C30