Carrefour Pathologie 2018

Molecular Pathology of Gastric Cancer

Novel insights and possible future applications

Fátima Carneiro
i3S/Ipatimup & Medical Faculty/ CHS João
Porto, Portugal

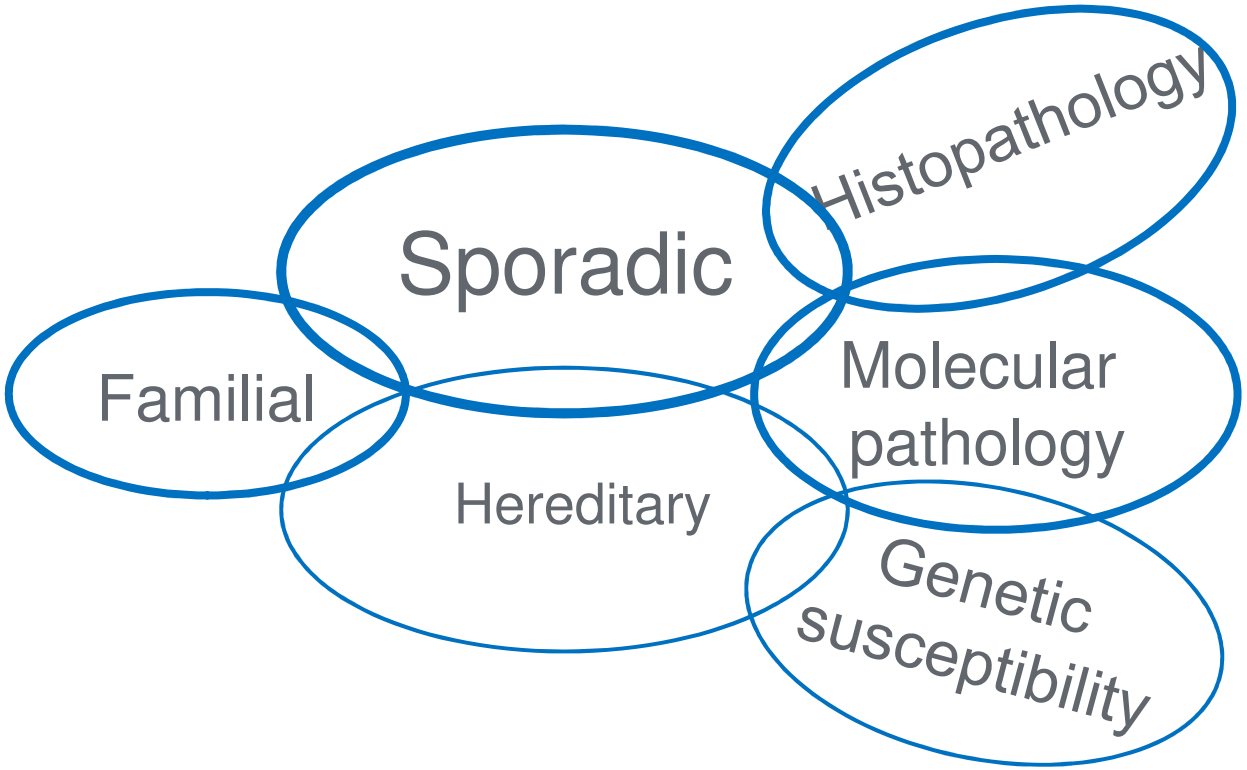
Outline

1. Major histological types of gastric cancer and the variants with clinical relevance (WHO 2018)

2. Major molecular classifications of gastric cancer

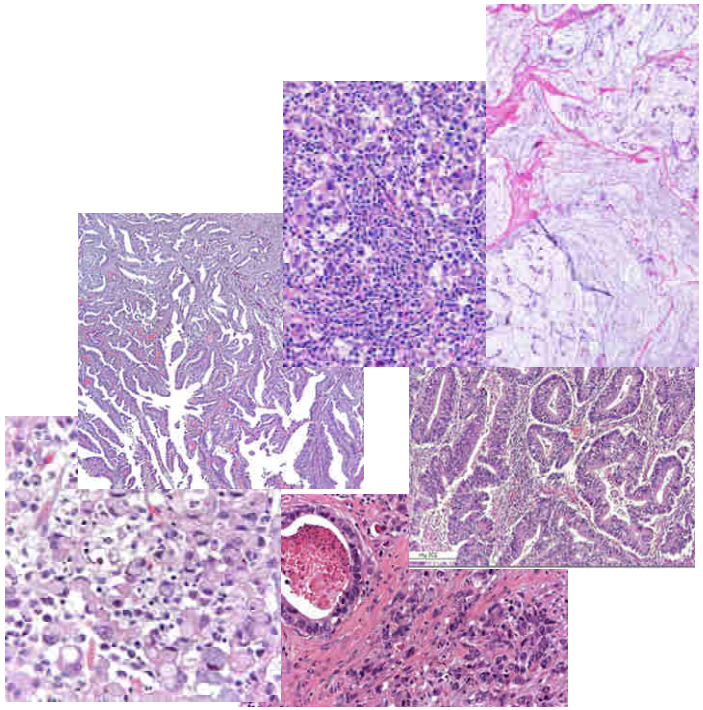
3. Molecular targets for therapy

Gastric Cancer

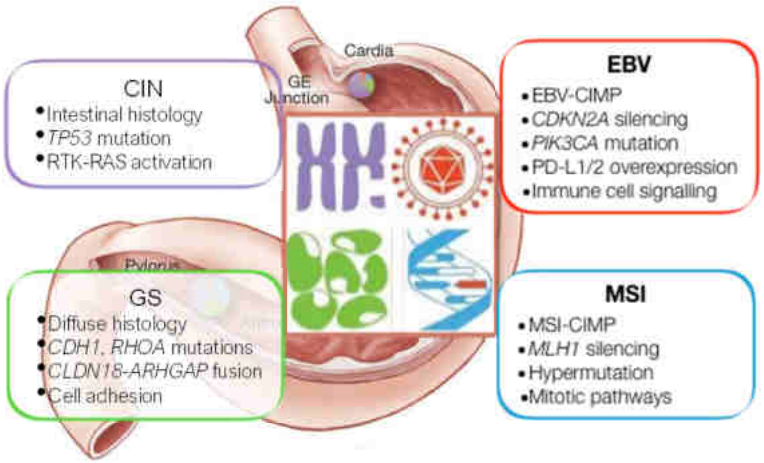


Gastric cancer

Morphological heterogeneity

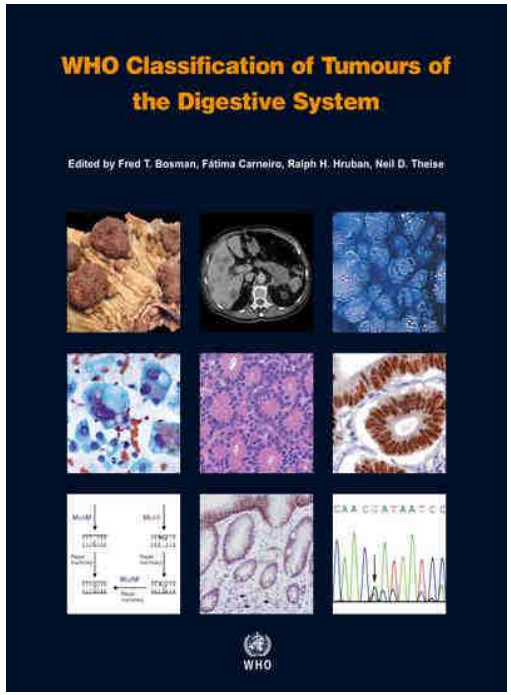


Molecular heterogeneity



Gullo I *et al* Pathobiology 2018; TCGA Nature 2014

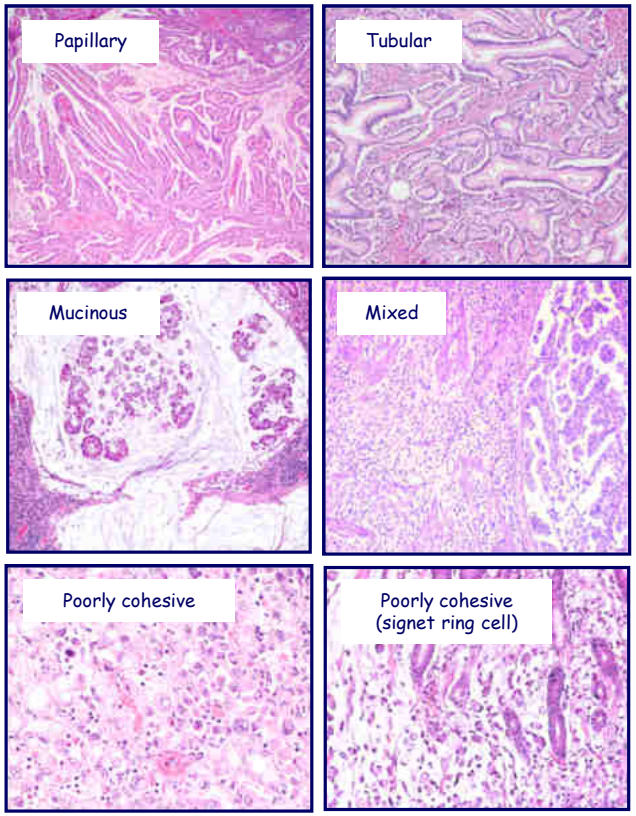
WHO Classification of Tumours of the Digestive System, 4th edition, 2010



WHO Classification of Gastric Carcinoma,4th edition, 2010

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori

ICD-O Code	
Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Poorly cohesive carcinoma	8490/3
(Signet-ring cell carcinoma and variants)	
Mixed carcinoma	8255/3



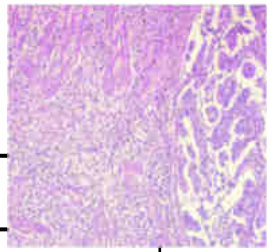
WHO-5th Edition –Editorial board

Histological classifications of gastric cancer

WHO, 5th edition

Laurén (1965)	**Nakamura** (1968)	**JGCA** (2017)	**WHO** (2018)
Intestinal	Differentiated	Papillary: pap Tubular 1, well-differentiated: tub1 Tubular 2, moderately-differentiated: tub2	Papillary Tubular, well-differentiated Tubular, moderately-differentiated
Indeterminate	Undifferentiated	Poorly 1 (solid type): por 1	Tubular, poorly-differentiated (solid)
Diffuse	Undifferentiated	Signet ring cell carcinoma (SRC): sig Poorly 2 (non-solid type): por2	Poorly cohesive, SRC type Poorly cohesive, NOS
Intestinal/diffuse/indeterminate	Differentiated/ Undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (*e.g.* por2>sig>tub2)	Mixed
Not defined	Not defined	**Special type:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type	**Histological variants:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid carcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type Micropapillary adenocarcinoma
*JGCA, Japanese Gastric Cancer Association {978-4-307-20375-3}. **Table prepared in collaboration with Prof. Ryoji Kushima, Japan			

Histological classifications of gastric cancer



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Histological classifications of gastric cancer

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JGCA, Japanese Gastric Cancer Association (2017)

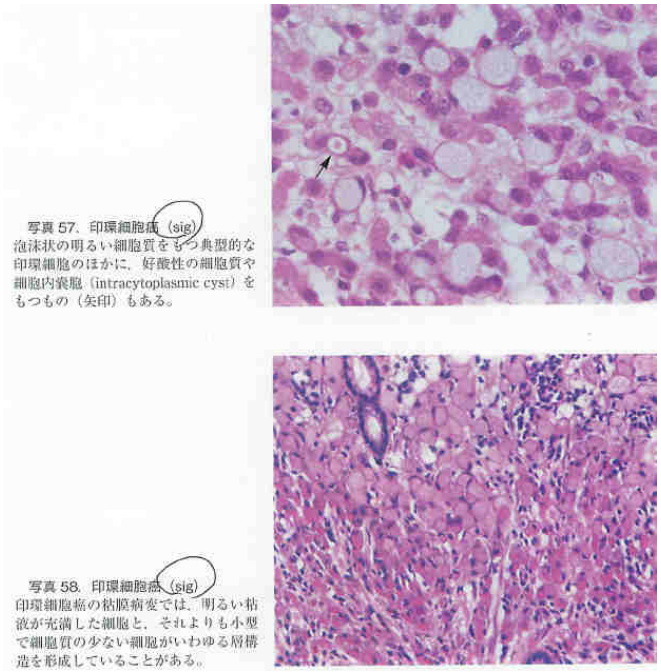


写真 57. 印環細胞癌（sig）
泡沫状の明るい細胞質をもつ典型的な印環細胞のほかに，好酸性の細胞質や細胞内嚢胞（intracytoplasmic cyst）をもつもの（矢印）もある。

写真 58. 印環細胞癌（sig）
印環細胞癌の粘膜病変では，明るい粘液が充満した細胞と，それよりも小型で細胞質の少ない細胞がいわゆる層構造を形成していることがある。

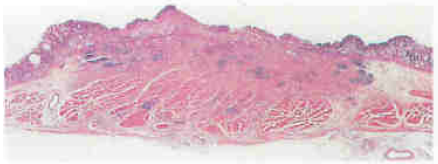


写真 54. 低分化腺癌：非充実型（por2）
ルーペ像。腫瘍は明瞭な腺巣をつくらず，線維形成を伴い，びまん性に増殖している。

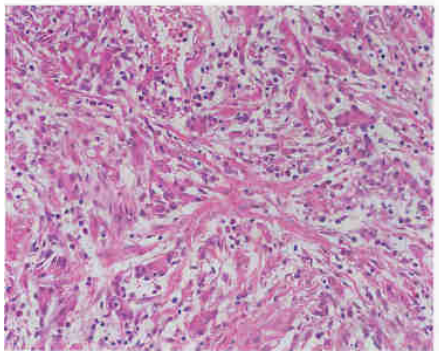


写真 55. 低分化腺癌：非充実型（por2）
腺房状，小索状あるいは孤在性になった癌細胞が，著明な線維形成を伴って増殖している。

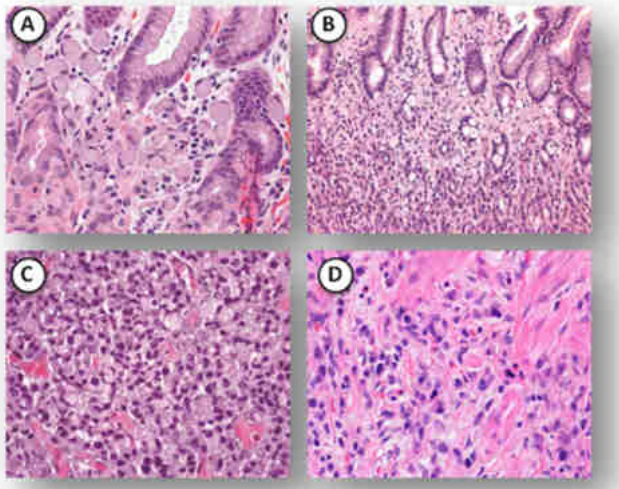
⇩ WHO classification (2018) ⇩

Poorly cohesive carcinoma, SRC

Poorly cohesive carcinoma, NOS

Poorly cohesive carcinoma: mutational signatures

Heterogeneity of poorly cohesive carcinoma



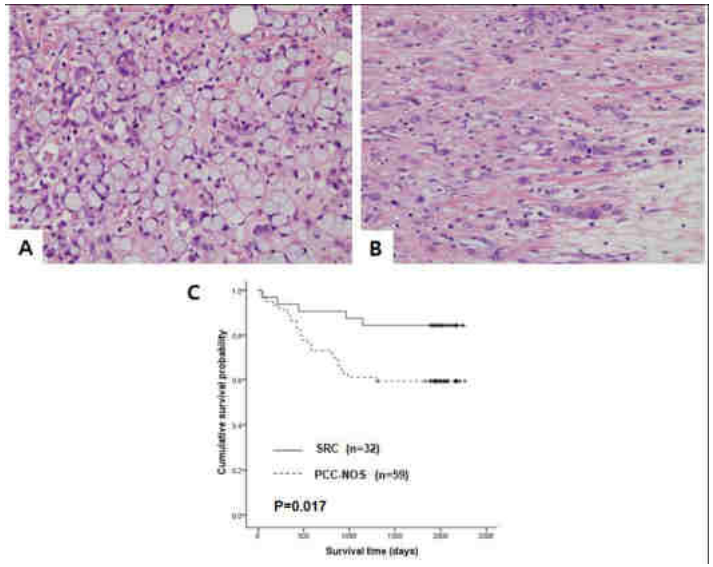
PCC-NOS :
TP53, BRAF, PI3CA,
SMAD4, and RHOA

Histopathology

Histopathology 2018, 72, 556–568. DOI: 10.1111/his.13383

Gastric poorly cohesive carcinoma: a correlative study of mutational signatures and prognostic significance based on histopathological subtypes

Chae H Kwon,[1,2] Young K Kim,[1,2] Sojeong Lee,[1,2] Ahrong Kim,[1,2] Hye J Park,[1,2] Yuri Choi,[1,2] Yeo J Won,[1,2] Do Y Park[1,2] & Gregory Y Lauwers[3]



Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma

Gastric Cancer
https://doi.org/10.1007/s10120-018-0868-0

SPECIAL ARTICLE

Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma

C. Mariette[1] · F. Carneiro[2] · H. I. Grabsch[3,4] · R. S. van der Post[5] · W. Allum[6] · Giovanni de Manzoni[7] on behalf of European Chapter of International Gastric Cancer Association

Poorly-Cohesive Carcinoma

- SRC (>90%)
- SRC/NOS (10% - 90%)
- NOS (<10%)

Histological classifications of gastric cancer

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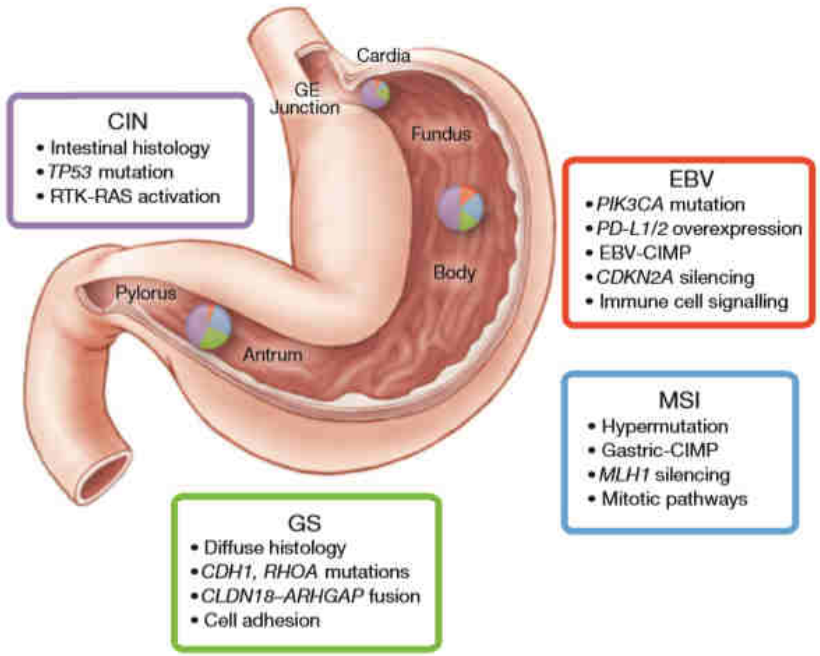
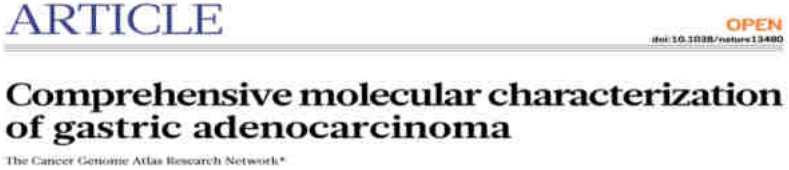
*JGCA, Japanese Gastric Cancer Association {978-4-307-20375-3}. **Table prepared in collaboration with Prof. Ryoji Kushima, Japan

Molecular classification of gastric cancer (TCGA)



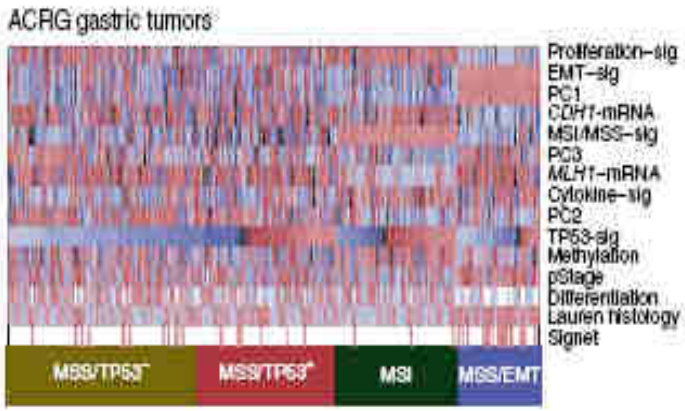

ARTICLE OPEN

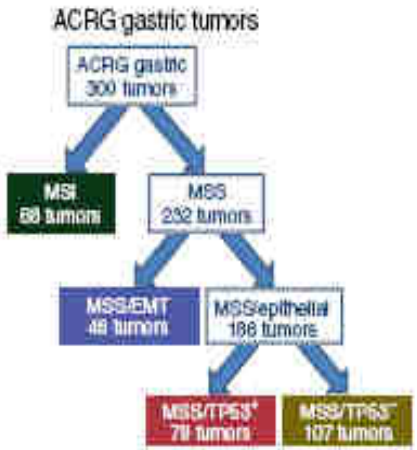
Comprehensive molecular characterization of gastric adenocarcinoma

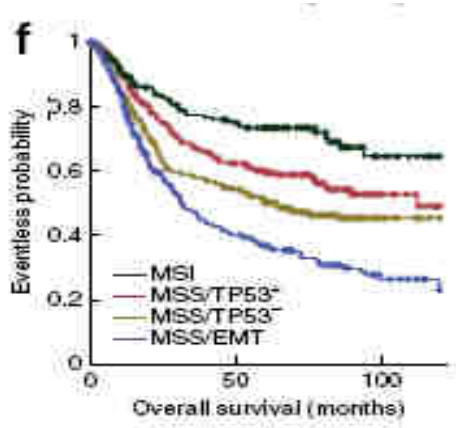
The Cancer Genome Atlas Research Network*

The Cancer Genome Atlas (TCGA) project; Nature 2014

Molecular classification of gastric cancer (ACRG)

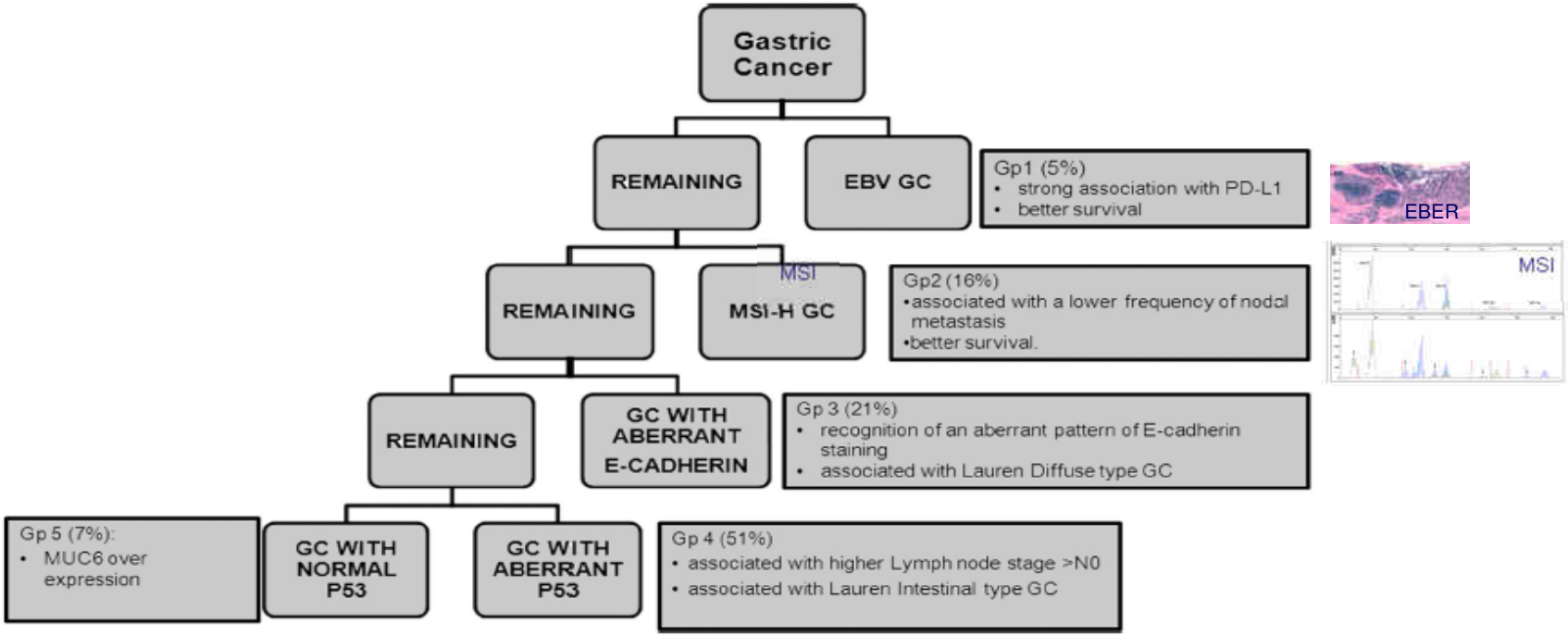






Asian Cancer Research Group.
Cristescu R *et al*: Nature Medicine 21; 449, 2015

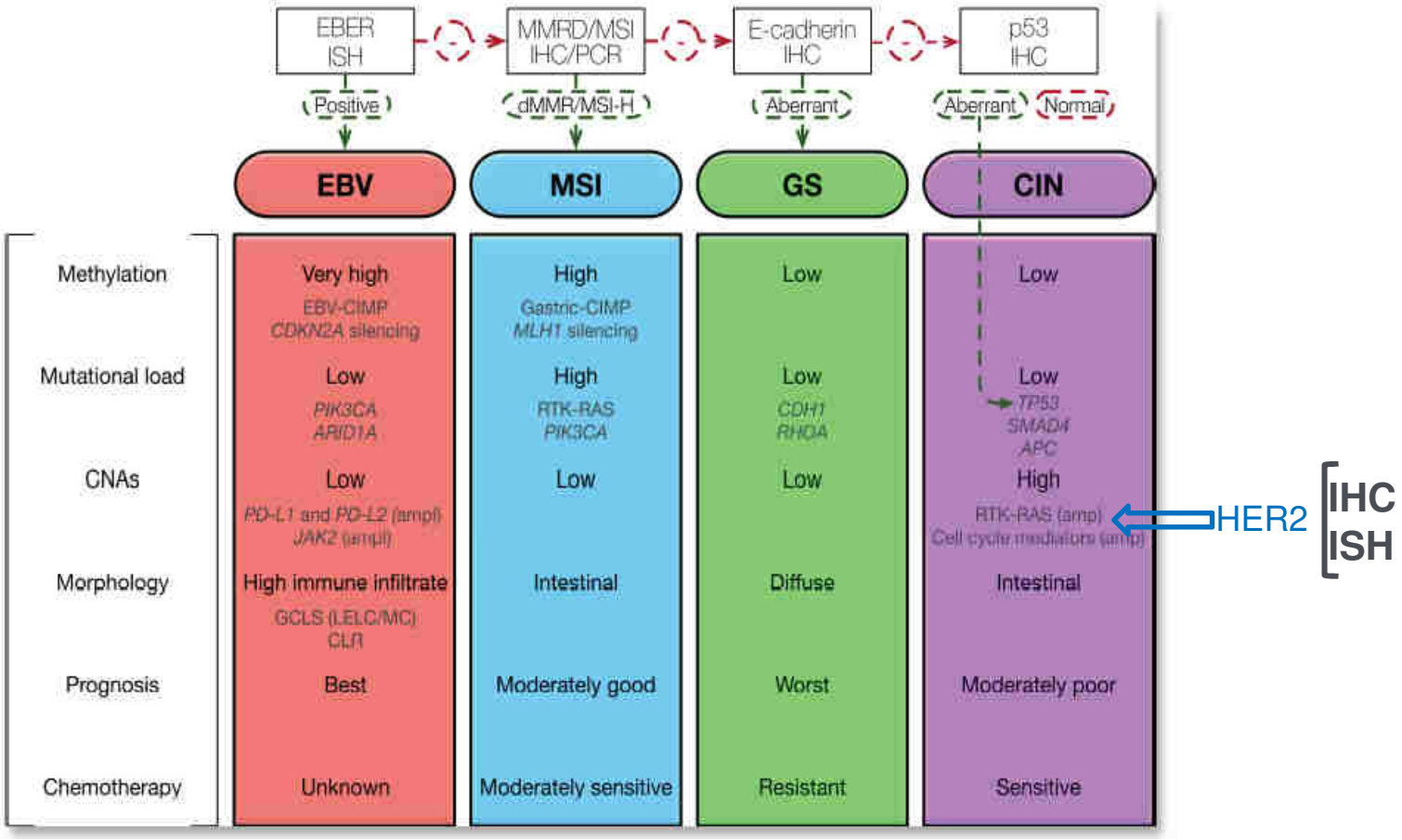
A protein and mRNA expression-based classification of gastric cancer



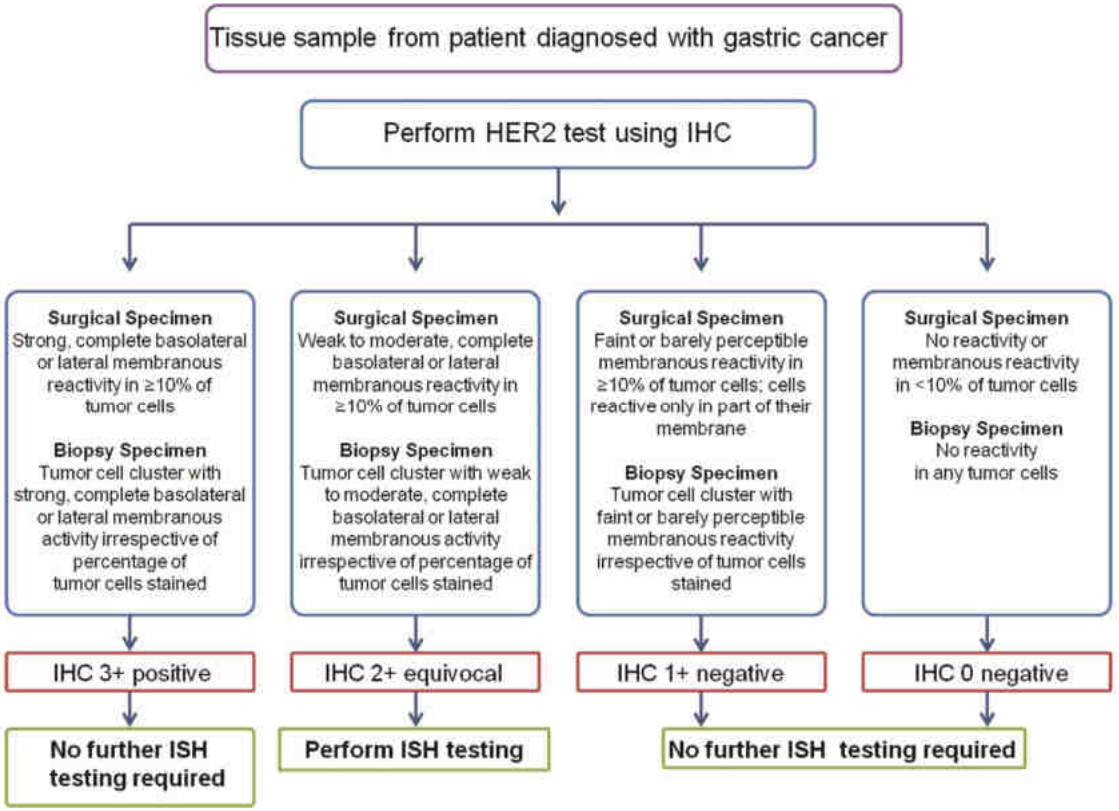
Setia M *et al*. Mod Pathol 29:772, 2016

Ahn S et al. Am J Surg Pathol 41:106, 2017

Molecular classification of gastric cancer

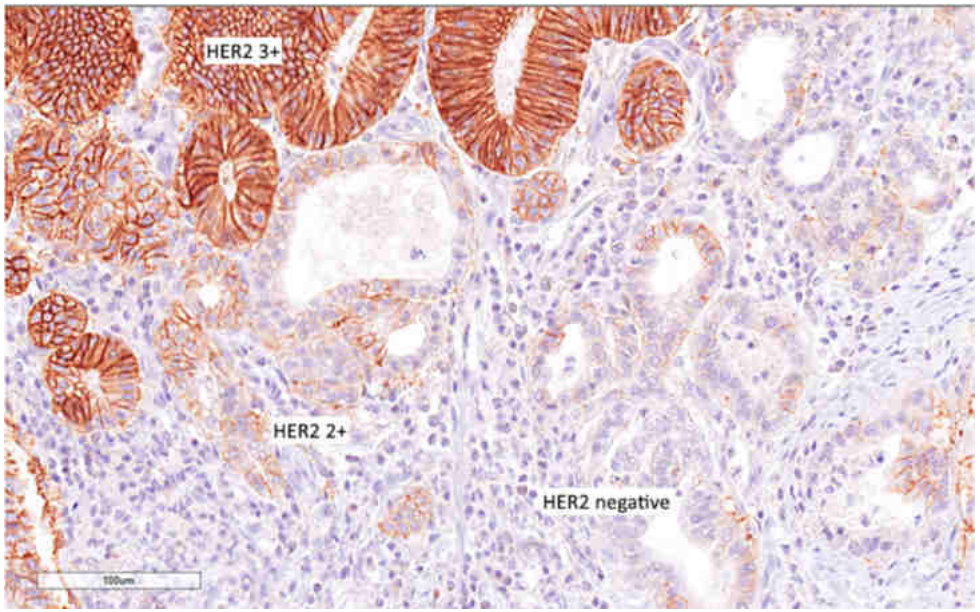


Evaluation of HER2 status

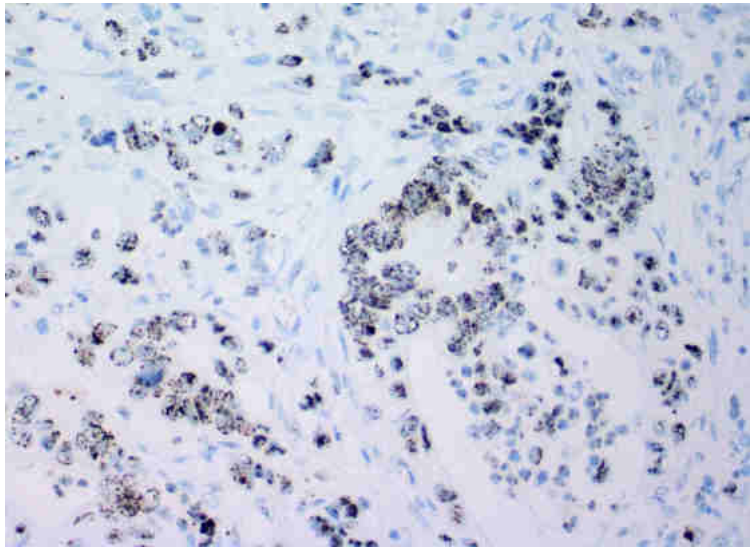


Evaluation of HER2 status

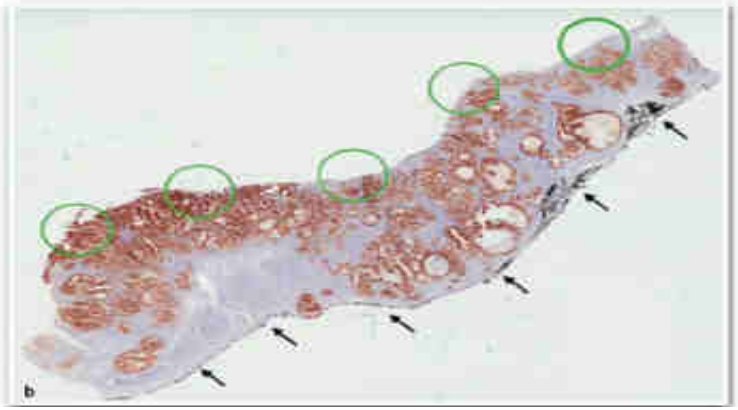
Immunohistochemistry

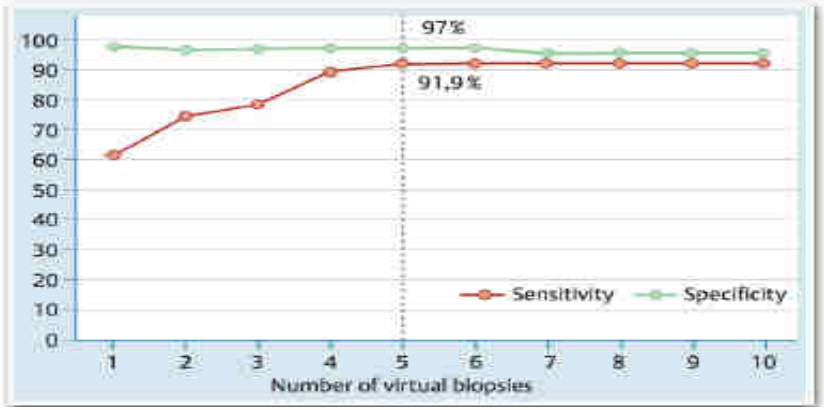


In situ hybridization



Minimum biopsy set for HER2 evaluation





Gastric Cancer
DOI 10.1007/s10120-015-0502-3

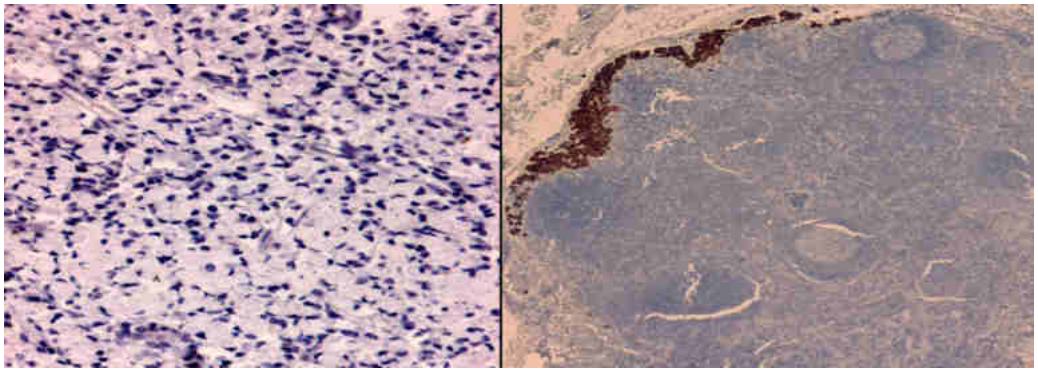
ORIGINAL ARTICLE

Five biopsy specimens from the proximal part of the tumor reliably determine HER2 protein expression status in gastric cancer

"Minimum biopsy set for HER2 evaluation in gastric and gastro-oesophageal cancer"
Endosc Int Open. 2015 Apr;3(2):E165-70
doi: 10.1055/s-0034-1391359

Tominaga N et al. Gastric Cancer 2016. doi: 10.1007/s10120-015-0502-3.

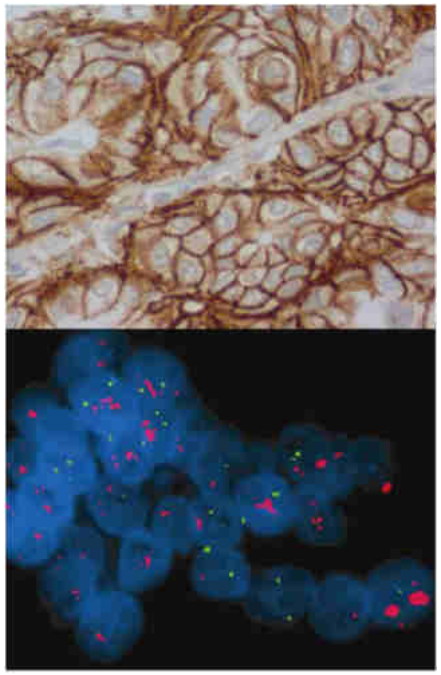
Differential expression of HER2 in gastric carcinoma and lymph node metastases



Putative impact on the therapeutic management and prognosis of the patients

Ieni A et al. Int J Mol Sci 2014. doi: 10.3390/ijms151222331

HER-2 in gastric carcinoma: prognostic and/or predictive factor



Prognostic factor

- YES (56%)
- NO (44%)

HER-2 amplification
in intestinal-type gastric carcinoma

⇩

Blood born metastases
Poor prognosis

David L *et al*; Mod Pathol 5:384, 1992
Barros-Silva J *et al*; Br J Cancer 100: 487,2009

Predictive factor

ToGA Trial

HER-2 overexpression in 22% of advanced gastric cancers; improved survival in patients treated with with trastuzumab

ASCO 2009 (LBA 4509)

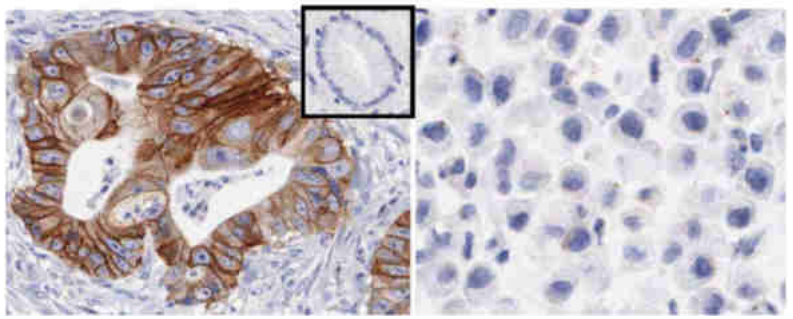
HER2 status in gastric cancer (prognostic and/or preditive factor?)

- HER2 expression is not related to gastric cancer patient prognosis and only a very small subgroup of intestinal type GC may potentially respond to HER2 targeting therapy.

Cellular Oncology 32 (2010) 57–65
DOI 10.3233/CLO-2009-0497
IOS Press

HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value – conclusions from 924 cases of two independent series

Heike Grabsch[a,*], Shivan Sivakumar[a], Sally Gray[b], Helmut E. Gabbert[c] and Wolfram Müller[d]



HER2 status in gastric cancer (prognostic and/or preditive factor?)

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Level of *HER2* Gene Amplification Predicts Response and Overall Survival in HER2-Positive Advanced Gastric Cancer Treated With Trastuzumab

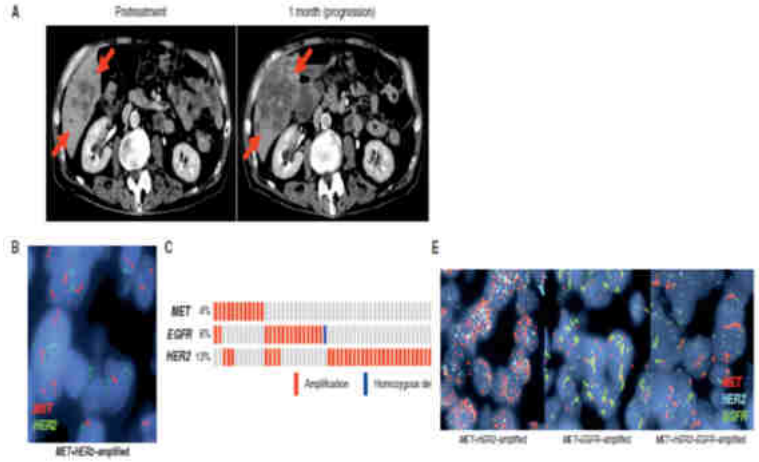
It is not only the quality but also the quantity

Resistance to HER2 targeted therapy in gastric cancer

- Patients initially respond to HER2 targeted therapy but eventually become resistant to treatment.
- Individual tumours with similar clinical stage have different clinical outcomes.

Putative causes

- Heterogeneity of HER2 expression
- Presence of ERBB2/EGFR co-amplification in the same tumour cells or even in the same tumour cells.
- HER2 copy number in ctDNA



Lee HE et.al. Eur J Cancer 2013; Kim J et al J Clin Invest 2014; Kwak EL et al Cancer Discov 2015; . Wang et al. Eur J Cancer 2018, 88: 92-100

Potential molecular targets in gastric cancer

Anti-EGFR

negative phase-3: EXPAND, REAL3

Lordick et al. Lancet Oncol 2013
Waddell et al. Lancet Oncol 2013

Anti-MET

negative phase-3: MetMab, RiloMet

Shah et al. ASCO 2015
Cunningham et al. ASCO 2015

anti-FGFR

preliminary phase-2: Shine

Bang et al. ASCO 2015

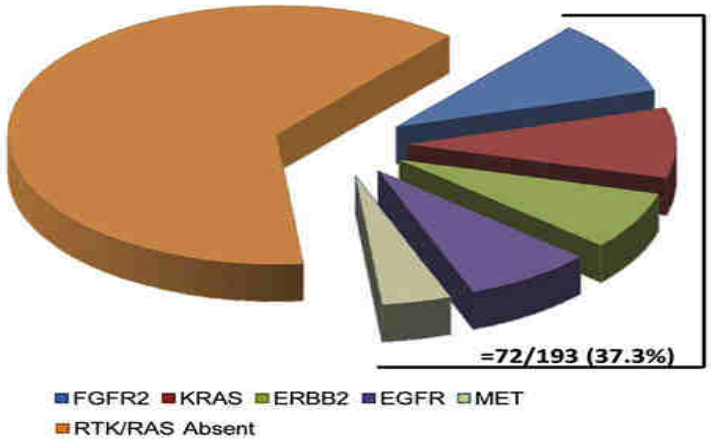
KRAS

non druggable (?)

HER2

positive phase-3: ToGA

Bang et al. Lancet 2010



Deng N, et al. *Gut* 2012;61:673-84

Actionable gene-based classification by NGS toward precision medicine

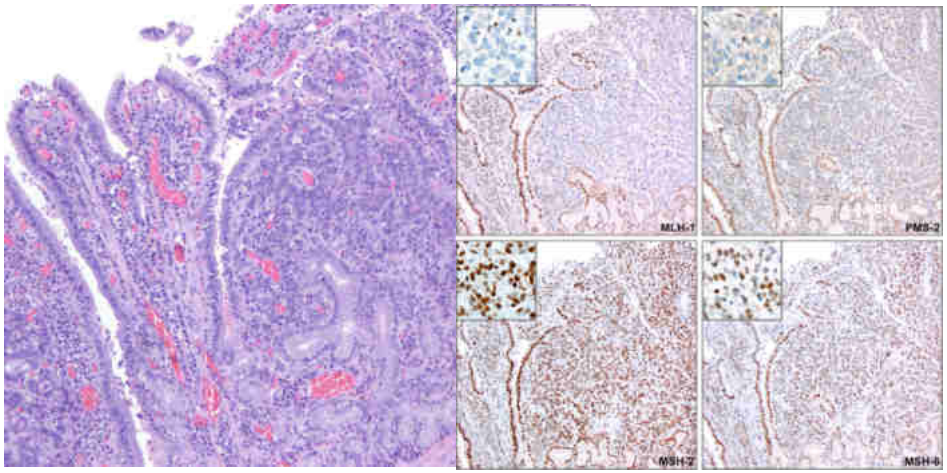
Table 1 Frequent gene alterations in 207 Japanese gastric cancers

Number	Mutation gene	Frequency	SCNA gene	Alteration	Frequency
1	*TP53*	53.1%	***ERBB2***	AMP	12.1%
2	*ARID1A*	15.9%	*CCNE1*	AMP	6.8%
3	*CDH1*	14.0%	***KRAS***	AMP	5.8%
4	***BRCA2***	10.6%	*ZNF217*	AMP	5.8%
5	*ARID1B*	10.1%	***CDKN2A***	DEL	5.3%
6	***ATM***	9.7%	***CDKN2B***	DEL	5.3%
7	***PIK3CA***	8.7%	*GATA4*	AMP	4.3%
8	*APC*	8.2%	*MYC*	AMP	2.4%
9	*ACVR2A*	7.2%	***CCND3***	AMP	1.9%
10	*CHD2*	6.3%	***CD274***	AMP	1.9%
11	*KMT2D*	6.3%	***CDK6***	AMP	1.9%
12	***RNF43***	5.8%	***EGFR***	AMP	1.9%
13	*EPHA2*	5.8%	***FGFR2***	AMP	1.9%
14	*TGFBR2*	5.3%	***JAK2***	AMP	1.9%
15	***FLCN***	4.3%	*GNAS*	AMP	1.9%
16	***PALB2***	4.3%	***CCND1***	AMP	1.4%
17	*PTPRT*	4.3%	***MET***	AMP	1.4%
18	*RAD50*	4.3%	*HSP90AB1*	AMP	1.4%
19	***BRCA1***	3.9%	*SMAD4*	DEL	1.4%
20	***STK11***	3.9%	*TEK*	DEL	1.4%

Genome Med. 2017;9. doi: 10.1186/s13073-017-0484-3

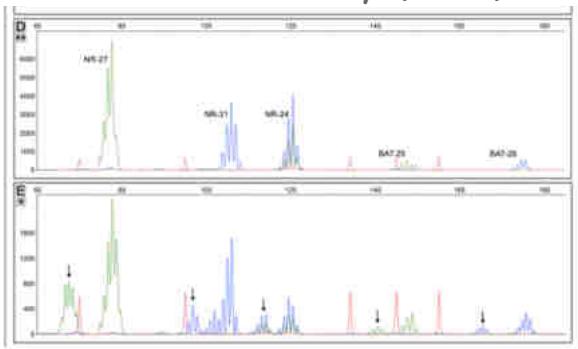
MSI in gastric carcinoma

Mismatch Repair Deficiency (MMRd)



(Immunohistochemistry)

Microsatellite Instability (MSI)



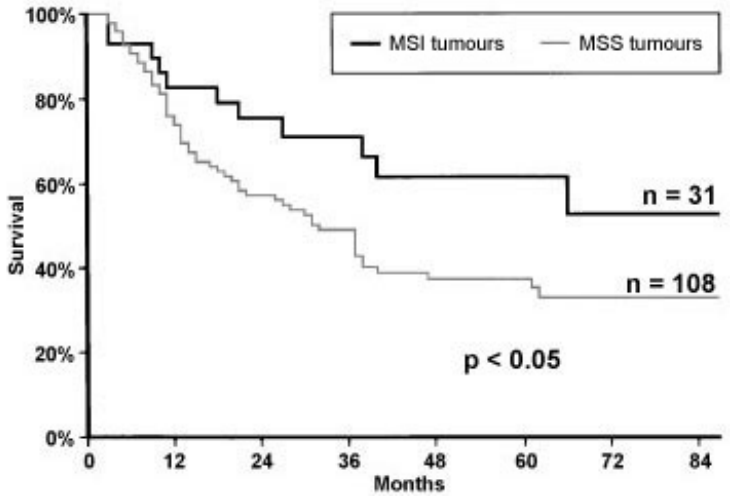
(Fluorescent Multiplex PCR)

Next Generation Sequencing (NGS)

- Instability signatures
- Instability burden
(correlation with overall survival)

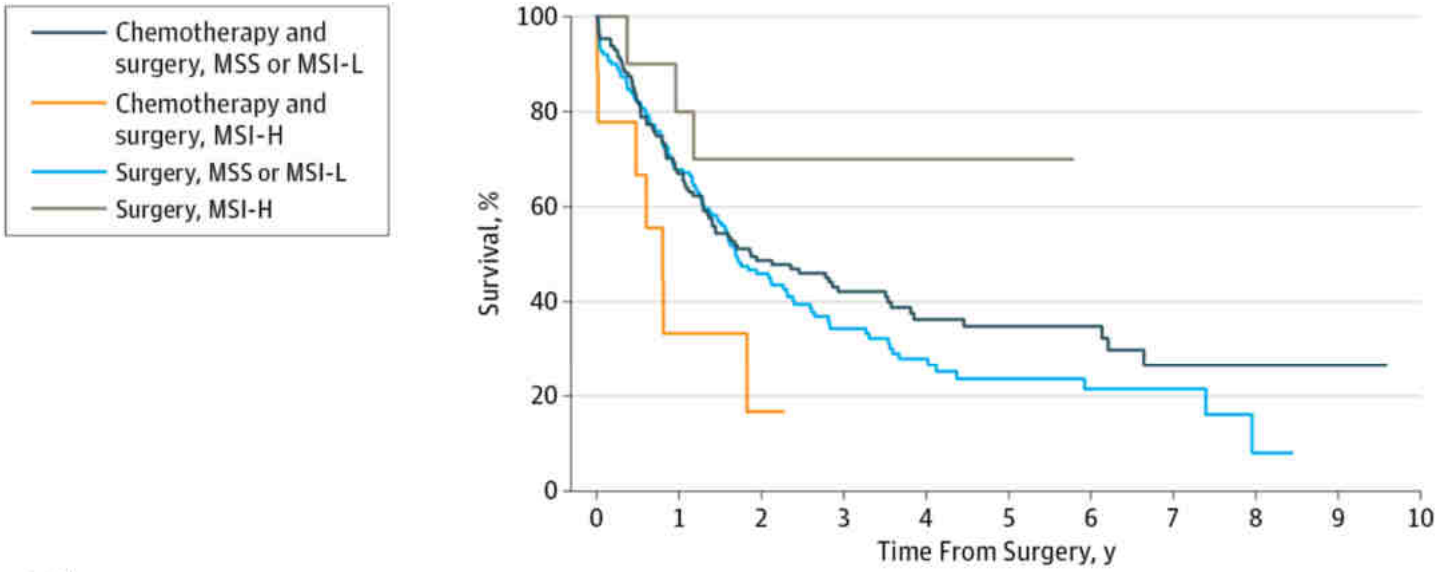
MSI in gastric carcinoma

Molecular marker of good prognosis in sporadic gastric cancer (caused by *hMLH1* promoter hypermethylation)



Survival of patients

MSI and Prognosis

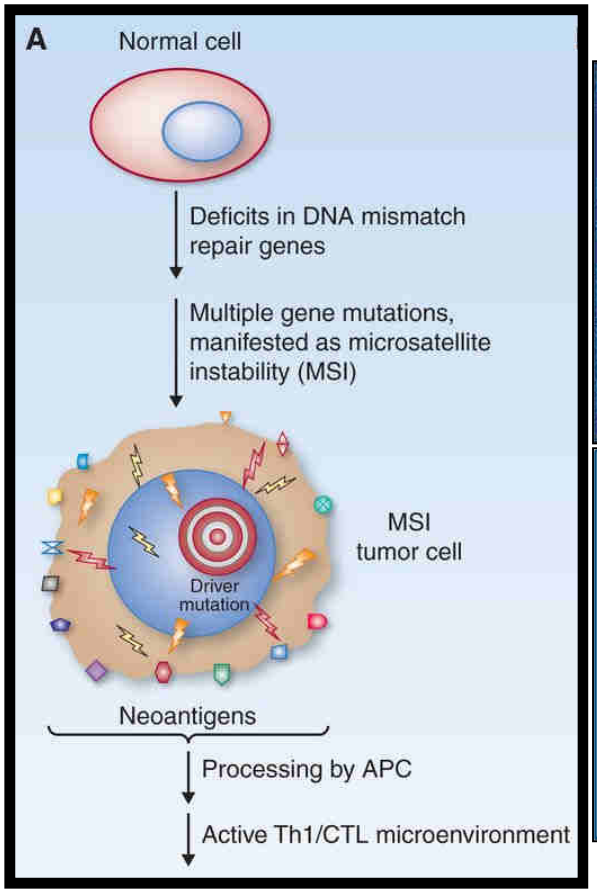


No. at risk

Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

JAMA Oncol. 3(9):1197, 2017. doi:10.1001/jamaoncol.2016.6762

MSI and immunotherapy



Science REPORTS

Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[3] George A. Fisher,[4] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[2,4] James R. Eshleman,[15] Bert Vogelstein,[1,2,4] Robert A. Anders,[1,2,15] Luis A. Diaz Jr.[1,2,3]†‡

The genomes of cancers deficient in mismatch repair (MMR) contain exceptionally high numbers of somatic mutations. In a proof-of-concept study, we previously showed that colorectal cancers with MMR deficiency were sensitive to immune checkpoint blockade with anti-PD-1 antibodies. We have expanded this study to now evaluate efficacy of PD-1 blockade in patients with advanced MMR-deficient cancers across 12 different tumor types. [...] These data support the hypothesis that the large proportion of mutant neoantigens in MMR-deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.

Science 28;357(6349), 2018; 409-413. doi: 10.1126/science.aan6733

Gastric cancer and immune checkpoint blockade

Predictive biomarkers

MSI-high *status*

Science REPORTS

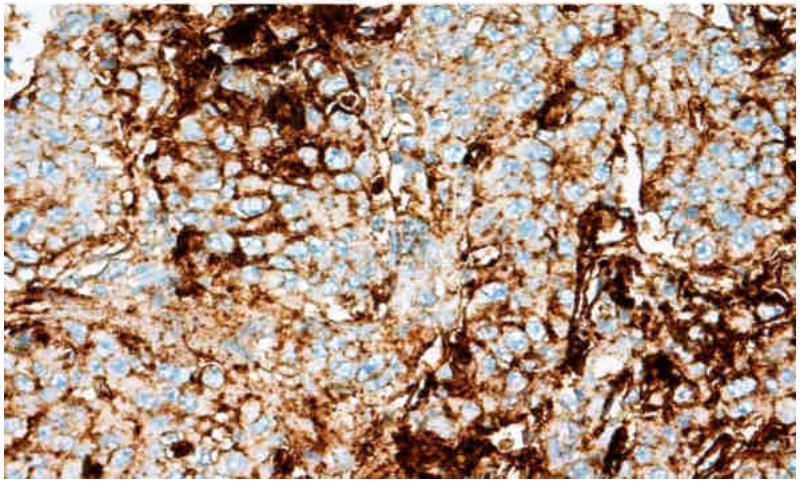
Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

PD-L1 expression

Original Article

Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer



Le DT et al Science 2017; Kulangara K Arch Pathol Lab Med. 2018; Kim ST Nat Med 2018

Gastric cancer and immune checkpoint blockade

Predictive biomarkers

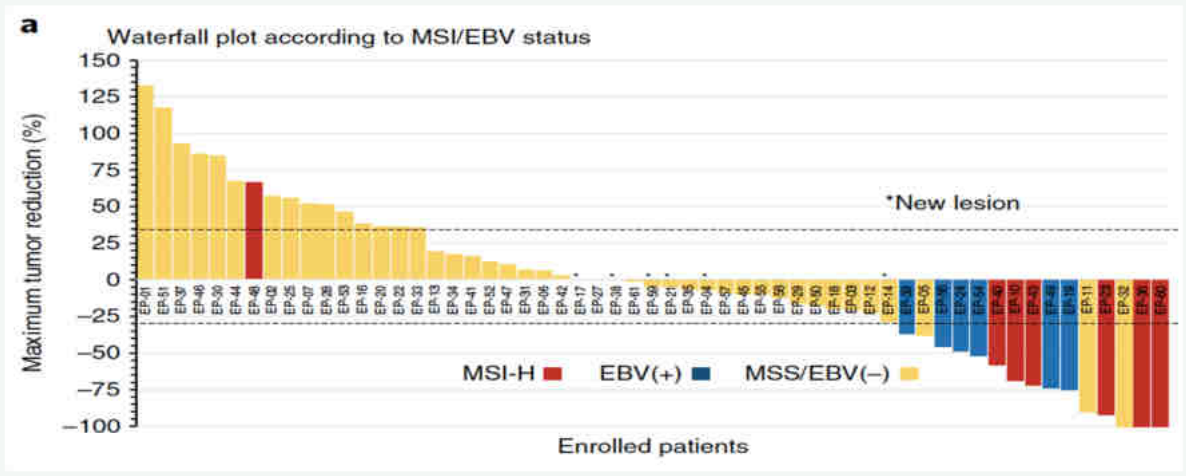
EBV+ and MSI-high *status*

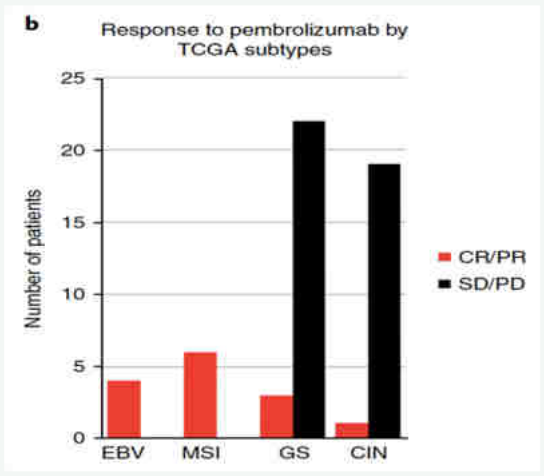
nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0101-z

Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer





Le DT et al Science 2017; Kulangara K Arch Pathol Lab Med. 2018; Kim ST Nat Med 2018

EBV infection and MSI in gastric cancer

International Journal of
Molecular Sciences

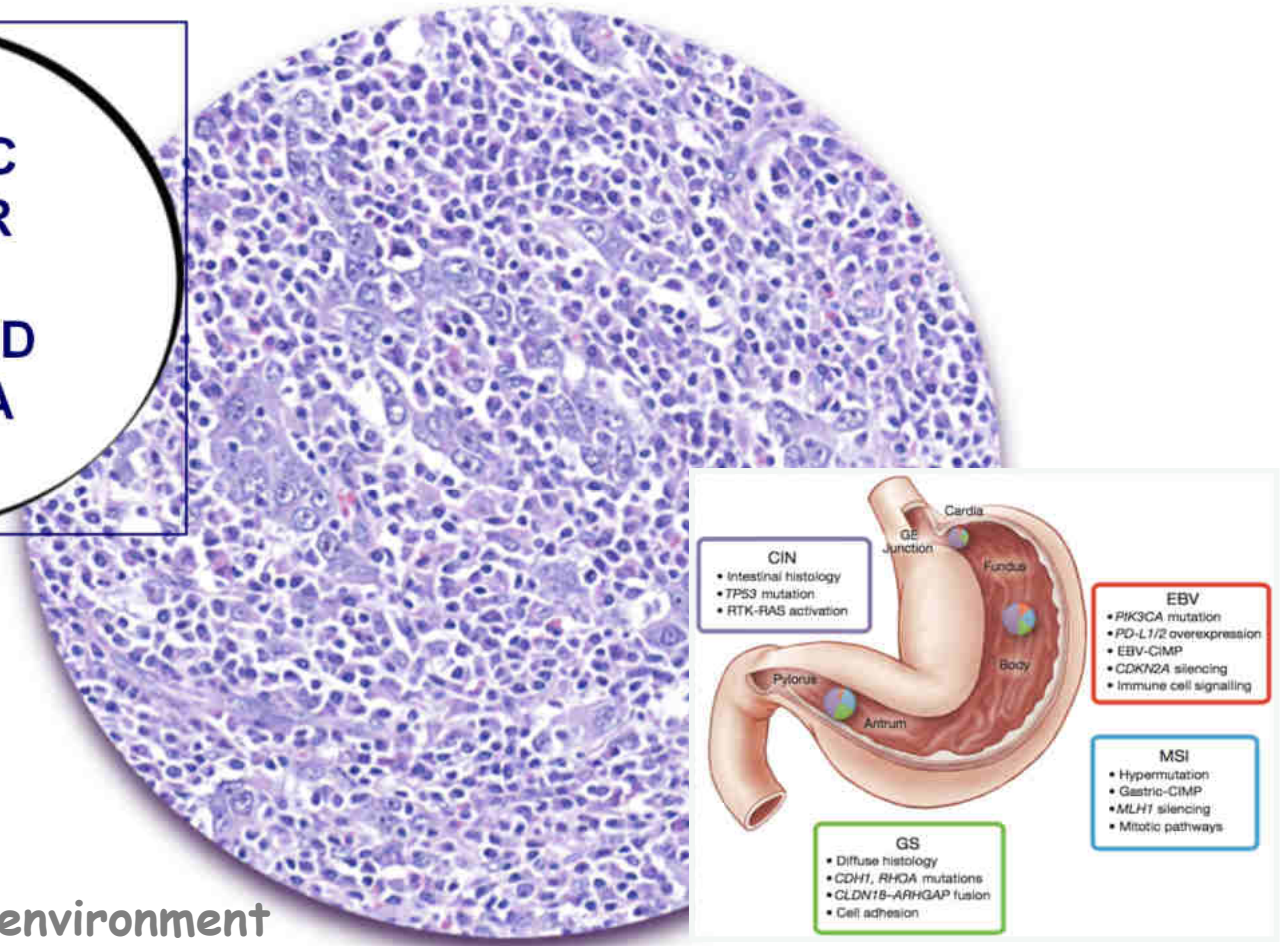
MDPI

Article

The Transcriptomic Landscape of Gastric Cancer: Insights into Epstein-Barr Virus Infected and Microsatellite Unstable Tumors

Irene Gullo [1,2,3,4], Joana Carvalho [3,4], Diana Martins [3,4], Diana Lemos [3,4], Ana Rita Monteiro [3,4], Marta Ferreira [3,4], Kakoli Das [5], Patrick Tan [5,6,7], Carla Oliveira [3,4], Fátima Carneiro [1,2,3,4] and Patrícia Oliveira [3,4,*]

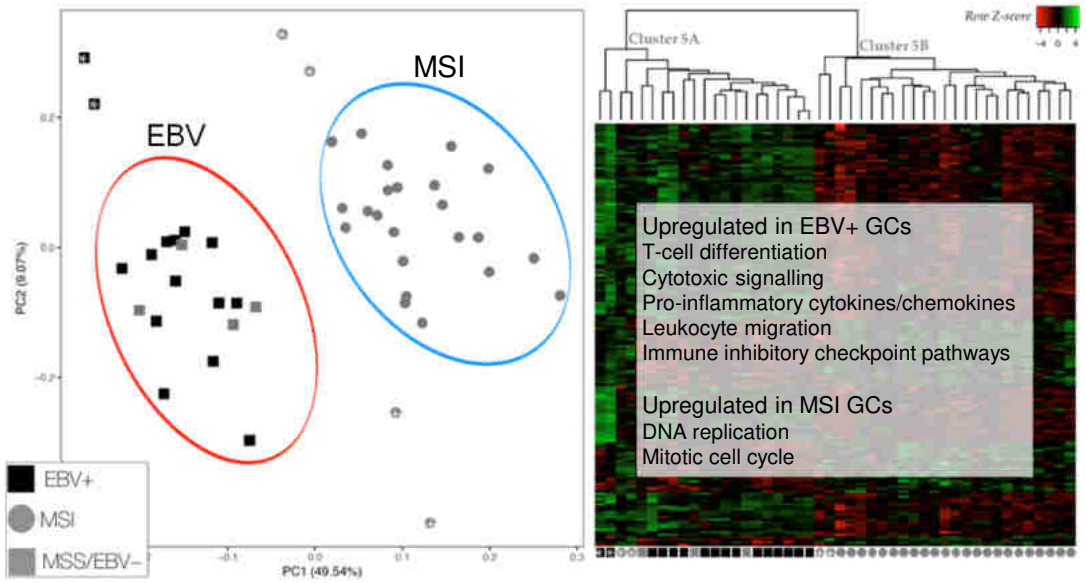
GASTRIC CANCER WITH LYMPHOID STROMA



The tumour microenvironment

EBV+ and MSI GCs displayed distinct transcriptomic signatures

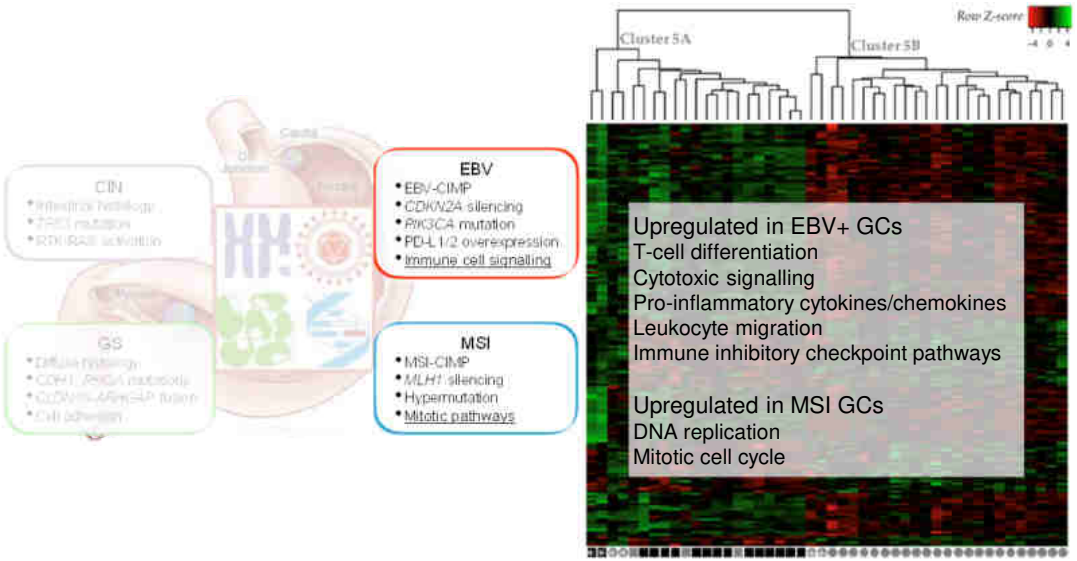
Unclustered analysis: differentially expressed (DE) genes



Gullo I et al: Int J Mol Sci, 2018

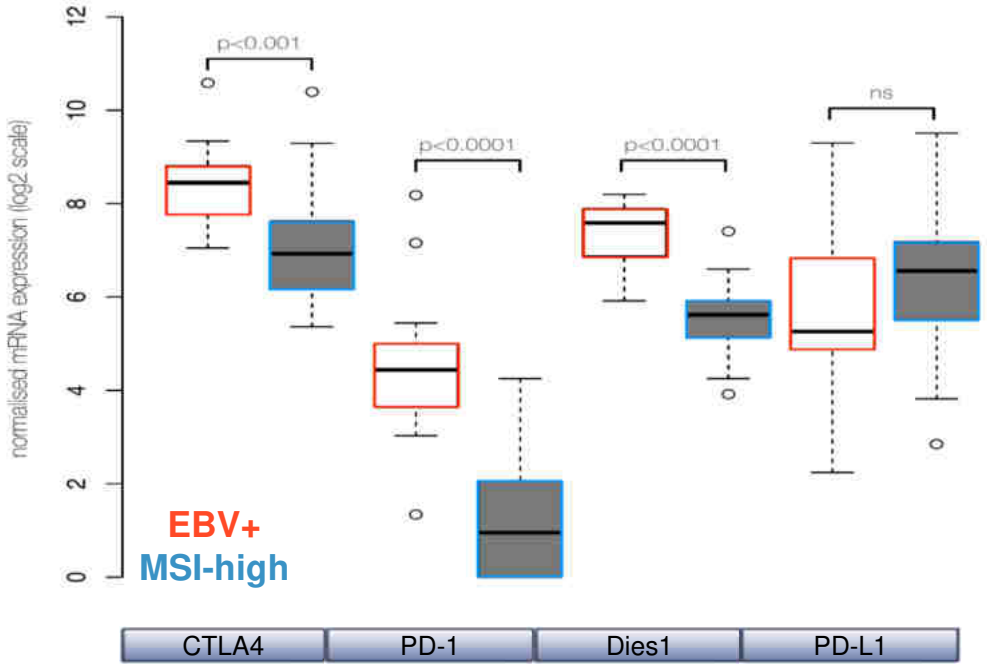
EBV+ and MSI GCs displayed distinct transcriptomic signatures

Unclustered analysis: differentially expressed (DE) genes

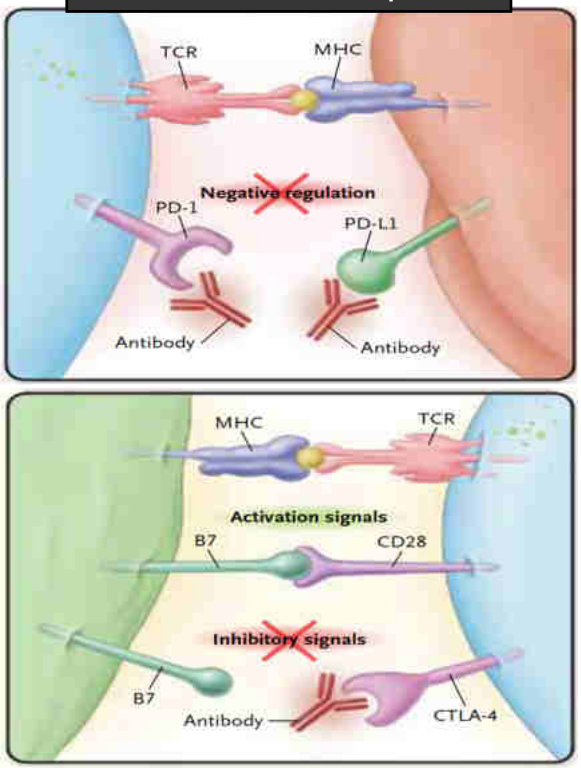


Gullo I et al: Int J Mol Sci, 2018

Immunotherapy targets in EBV and MSI gastric cancers



Combination immunotherapies



PD-L1 protein expression

- Cancer cells: No differences
- Immune cells: EBV+ showed higher expression than MSI-high *cases (p=0.0052)*

Ribas A et al NEJM 2012

Tumour types for which imune check point immunotherapies are FDA-approved

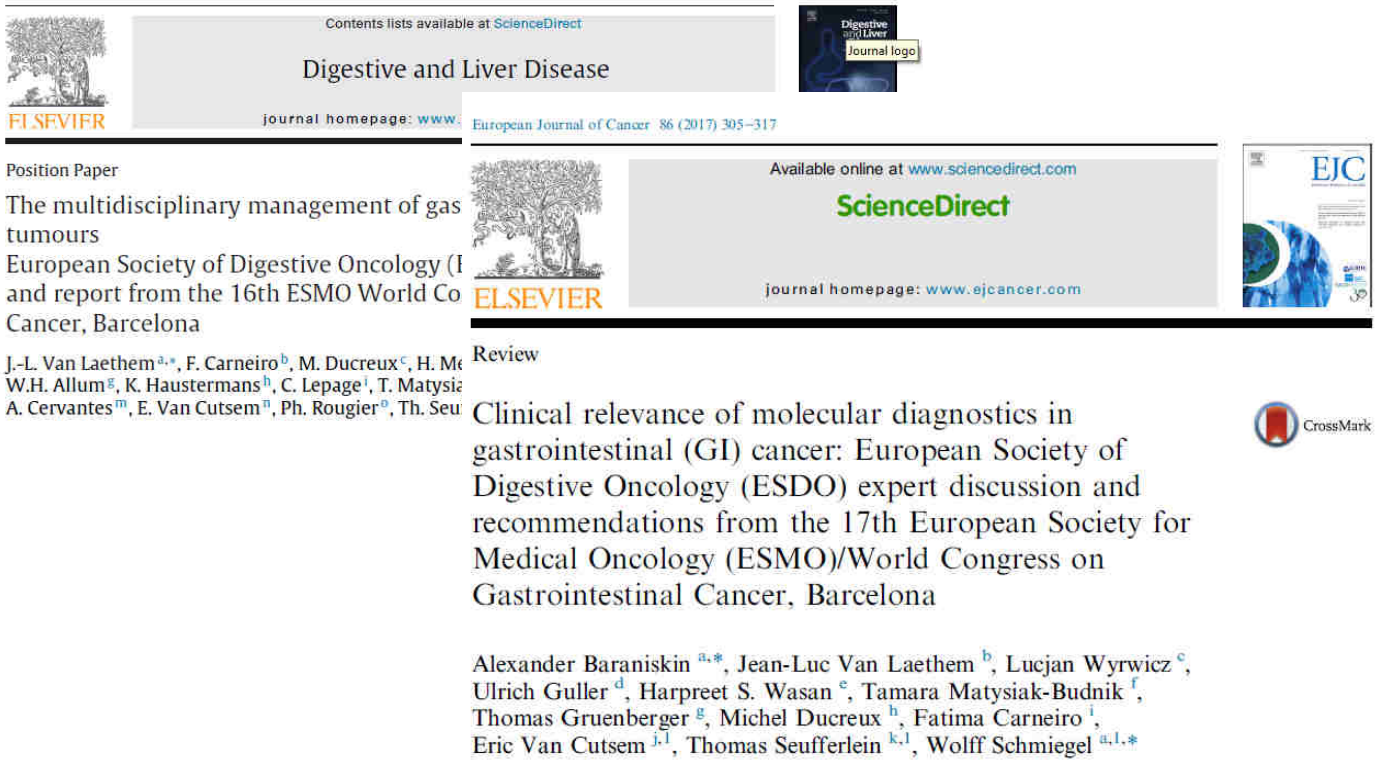
Tumor type	Therapeutic agent	FDA approval year
Melanoma	Ipilimumab	2011
Melanoma	Nivolumab	2014
Melanoma	Pembrolizumab	2014
Non-small cell lung cancer	Nivolumab	2015
Non-small cell lung cancer	Pembrolizumab	2015
Melanoma (BRAF wild-type)	Ipilimumab + nivolumab	2015
Melanoma (adjuvant)	Ipilimumab	2015
Renal cell carcinoma	Nivolumab	2015
Hodgkin lymphoma	Nivolumab	2016
Urothelial carcinoma	Atezolizumab	2016
Head and neck squamous cell carcinoma	Nivolumab	2016
Head and neck squamous cell carcinoma	Pembrolizumab	2016
Melanoma (any BRAF status)	Ipilimumab + nivolumab	2016
Non-small cell lung cancer	Atezolizumab	2016
Hodgkin lymphoma	Pembrolizumab	2017
Merkel cell carcinoma	Avelumab	2017
Urothelial carcinoma	Avelumab	2017
Urothelial carcinoma	Durvalumab	2017
Urothelial carcinoma	Nivolumab	2017
Urothelial carcinoma	Pembrolizumab	2017
MSI-high or MMR-deficient solid tumors of any histology	Pembrolizumab	2017
MSI-high, MMR-deficient metastatic colorectal cancer	Nivolumab	2017
Pediatric melanoma	Ipilimumab	2017
Hepatocellular carcinoma	Nivolumab	2017
Gastric and gastroesophageal carcinoma	Pembrolizumab	2017
Non-small cell lung cancer	Durvalumab	2018
Renal cell carcinoma	Ipilimumab + nivolumab	2018

James P. Allison and Tasuku Honjo

Discovery of cancer therapy by inhibition of negative immune regulation

Wei SC, Duffy CR, Allison JP. Cancer Discovery 2018. doi: 10.1158/2159-8290.CD-18-0367

Clinical relevance of molecular diagnosis



Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.

Position Paper

The multidisciplinary management of gas
tumours
European Society of Digestive Oncology (E
and report from the 16th ESMO World Co
Cancer, Barcelona

J.-L. Van Laethem [a,*], F. Carneiro [b], M. Ducreux [c], H. Me
W.H. Allum [g], K. Haustermans [h], C. Lepage [i], T. Matysia
A. Cervantes [m], E. Van Cutsem [n], Ph. Rougier [o], Th. Seu

European Journal of Cancer 86 (2017) 305–317

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Clinical relevance of molecular diagnostics in gastrointestinal (GI) cancer: European Society of Digestive Oncology (ESDO) expert discussion and recommendations from the 17th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer, Barcelona

Alexander Baraniskin [a,*], Jean-Luc Van Laethem [b], Lucjan Wyrwicz [c], Ulrich Guller [d], Harpreet S. Wasan [e], Tamara Matysiak-Budnik [f], Thomas Gruenberger [g], Michel Ducreux [h], Fatima Carneiro [i], Eric Van Cutsem [j,1], Thomas Seufferlein [k,1], Wolff Schmiegel [a,1,*]

Clinical relevance of molecular diagnosis

Brief summary of the recommendations.

Tumor entity	Molecular genetic marker	Recommendation
Oesophageal and gastric adenocarcinoma	HER2 status	Part of standard diagnostics
	HER2 status re-testing	For patients with metastatic or recurrent cancer when initially HER2-neg. or borderline low/1−2+/FISH negative
	Liquid biopsy in HER2-testing	Not enough data, not recommended in routine use
	MSI	Recommended for stage IV alone
	EBV in tissue	Not recommended in routine use
	PD-L1 expression	Not recommended in routine use
	FGFR expression/gene fusions	Not recommended in routine use
Esophageal SCC	Molecular diagnostic	No biomarkers are recommended in routine use

Baraniskin A et al. Eur J Cancer, 2017

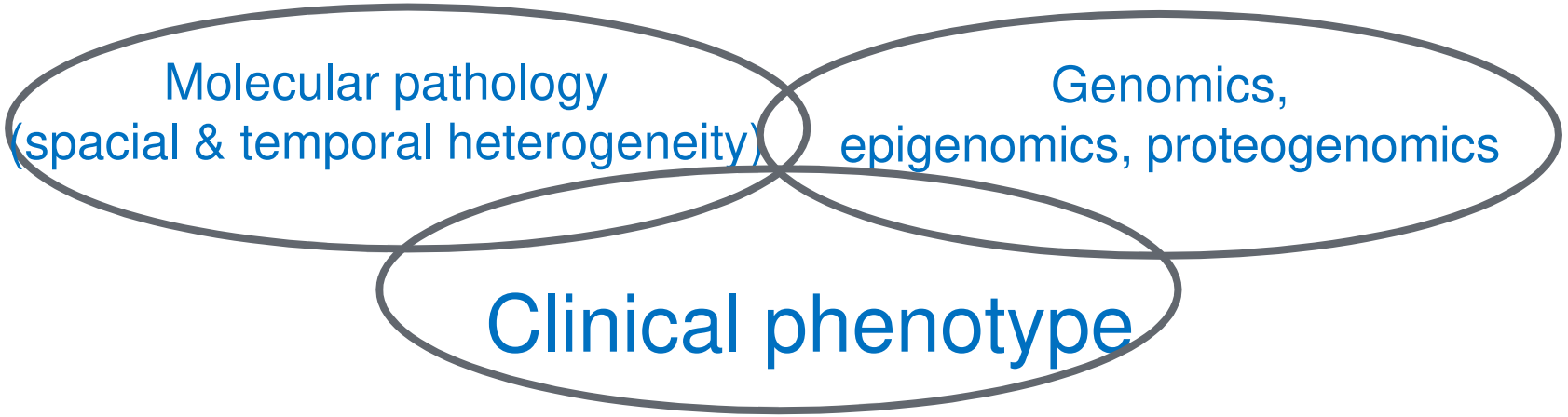
Take home lessons

1) Established predictive biomarkers, such as HER2 *(a*nti-HER2 therapy benefits patients with unresectable or metastatic/recurrent HER2-positive GC, and HER2 testing is used to predict potential therapy response)

2) Biomarkers partly established and/or under development such as:
   a. Receptor tyrosine kinases*;*
   b. MSI *status* and EBV infection;
   c. Biomarkers for cancer immunotherapy (Tumour mutational load, density of intratumoural CD8+ T cell infiltrates and PD-L1 expression);
   d. Two molecular subtypes (MSI-high and EBV + might be potential good candidates for immunotherapy targeting of the PD-L1/PD-1 axis).

Upfront molecular testing. Is it time yet?

Integrated Molecular Pathology



- Better understanding
- Translation to clinics

- Lloyd M et al: Pathology to enhance precision medicine in oncology: Lessons from landscape ecology. Adv Anat Pathol 22: 267, 2015
- Salto-Tellez M & Kennedy M:Integrated molecular pathology: the Belfast model. Drug Discovery Today 20: 1451, 2015

Thanks for your attention