December 2021

Selected Accomplishments from CTEP-Supported Clinical Trial Programs

The following clinical studies conducted in CTEP-supported clinical trial programs have provided significant findings that have advanced the treatment of cancer. Below is a brief compilation of 52 practice-changing clinical trials whose results were announced between 2014 and December 2021. The trials are presented under the CTEP-supported clinical trials program in which they were conducted.

• Studies Conducted by the National Clinical Trials Network (NCTN)

- EA6134, or DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing), tested initially giving patients with metastatic melanoma a combination of the immunotherapy drugs ipilimumab and nivolumab or a combination of the targeted therapies dabrafenib and trametinib. More of the patients treated first with immunotherapy drugs were alive at 2 years compared to patients treated first with the targeted therapy combination (72% versus 52%)—leading to early stoppage of the trial.

- GOG-0274/OUTBACK—The NRG Network Group collaborated in an international trial to find that adding chemotherapy to chemoradiation for locally advanced cervical cancer did not increase overall survival but did increase side effects—proving that more treatment is not better for this cancer, which is the leading cause of cancer death for women in many parts of the world.

- RxPonder (SWOG S1007)—The Rx for Positive Node, Endocrine Responsive Breast Cancer, or RxPONDER trial—a follow up to the TAILORx study, initially reported in 2018—was designed to assess whether patients with hormone receptor-positive (HR+) breast cancer and 1-3 positive lymph nodes with recurrence score of <25 benefit from the addition of chemotherapy to endocrine therapy. Among post-menopausal women, the international trial found no difference in disease-free survival in the study groups, meaning these women can be spared the chemotherapy. In premenopausal women, however, those who received chemotherapy and endocrine therapy had superior disease-free survival compared with those who received endocrine therapy alone. It is unknown whether this difference can be attributed to an actual benefit of chemotherapy, or whether this

may be due to the ovarian suppression induced by chemotherapy. Additional research is needed to explore whether treatment with medications that induce menopause given in combination with standard hormone therapy would have the same effect on risk of recurrence as that seen with chemotherapy in this study.

- GOG-0209—This report established carboplatin and paclitaxel as a standard of care treatment for recurrent or advanced endometrial cancer.

- AREN0534—This study of patients with bilaterally predisposed unilateral Wilms tumor defines a new treatment approach for these patients. This treatment approach includes standardized 2-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis, and histology-based postoperative therapy. Of these patients, who are at risk for end stage renal disease, 65% of them experienced preservation of renal parenchyma.

- Protocol 9177—This multicenter phase II study conducted by the NCTN in collaboration with the NIH Clinical Center demonstrated outcomes for patients with Burkitt lymphoma treated with dose-adjusted EPOCH-R that would be expected from the much more toxic and aggressive regimens used in the past. The doses are adjusted based on toxicity evaluations and blood counts to optimize the anti-lymphoma effect while balancing the toxicity. The dose-adjusted therapy was equally effective across all age groups and in both HIV-related and unrelated disease.

- S1320—Preclinical data suggested that intermittent dosing of dabrafenib and trametinib might decrease acquired resistance and result in better outcomes. S1320 assessed intermittent vs continuous dosing of these drugs in patients with BRAF-mutated advanced melanoma and showed superior progression-free survival among patients treated with the continuous dosing schedule.

- E2108—This Phase III study was designed to assess whether early local therapy to the intact breast prolongs survival in women who present with *de novo* metastatic breast cancer. The study found no improvement in progression-free or overall survival among women who received early local therapy.

- SWOG S1416—PARP-inhibitors are known to be effective treatment for patients with breast and ovarian cancer who carry germline *BRCA* mutations. This Phase II study showed that the combination of veliparib, a PARP-inhibitor, and cisplatin is

effective treatment for patients with BRCA-like tumors, which were defined as high homologous recombination deficiency (HRD) score, somatic BRCA mutation, or germline mutation in HR-pathway non-BRCA1/2 genes.

- NRG-GY004—This phase 3 trial examined the role of olaparib or olaparib+cediranib against physician's choice platinum doublet chemotherapy for women with recurrent PARP inhibitior-naïve platinum-sensitive ovarian cancer. The oral doublet of targeted agents, olaparib+cediranib, yielded similar progression-free survival to chemotherapy, across the full cohort, although not superior. It was superior to both chemotherapy and single agent olaparib in a subset analysis of women with BRCA1/2 mutation.

- ALTERNATE (A011106)—This study enrolled women with estrogen receptor-positive (ER+) breast cancer and randomized them to one of three endocrine treatments--anastrozole alone, fulvestrant alone, or the combination of anastrozole and fulvestrant. Patients underwent a mandatory biopsy after 4 weeks of treatment and those who had Ki-67 scores >10% at that time were recommended to switch to chemotherapy. Among those with Ki-67 scores ≤10%, the study showed no significant difference between the three treatment arms. Longer term follow-up is needed to conclude whether there is a difference between the treatments in terms of risk of recurrence or survival.

- Alliance A071401—Patients with progressive or recurrent meningiomas have limited treatment options. Given the predominance of NF2 mutations in meningiomas, GSK2256098, a FAK inhibitor, was evaluated and showed success in recurrent or progressive grade I-III meningiomas. This is the first study showing efficacy of genomically-determined treatment in meningiomas.

- AHEP0731—This trial of children with hepatoblastoma, who had complete resection at diagnosis, showed that good overall survival could be maintained with a 2-cycle chemotherapy course. This study also showed that, when possible, percutaneous liver biopsy was the best diagnostic approach because it had less risk than other biopsy methods of significant hemorrhage requiring transfusion.

- E1609—This Phase III study in patients with Stage III/IV resected melanoma compared adjuvant therapy with high-dose interferon to two different doses of ipilimumab--3 mg/kg and 10mg/kg. The currently-approved adjuvant ipilimumab dose of 10 mg/kg was not significantly superior to high-dose interferon, and was

more toxic than the 3mg/kg schedule. Patients treated with ipilimumab at 3 mg/kg had superior overall survival compared with those treatment with interferon, making it the treatment of choice for these patients.

- ARAR0331—This study reflects the largest prospective trial in childhood nasopharyngeal carcinoma exploring the use of induction chemotherapy (cisplatin and fluorouracil) and concurrent chemoradiotherapy (cisplatin alone). A radiation dose reduction was possible for patients responding to induction chemotherapy. Despite the more advanced presentation seen in children and adolescents, their outcomes seem to be superior to adults, as shown by population-based analyses and confirmed by this study.

- GOG-0281—Reporting final results at the 2019 meeting of the European Society for Medical Oncology, this study demonstrated superiority of trametinib in recurrent low grade serous ovarian cancer over physician's choice of treatment. Benefit was also observed for women who crossed over to trametinib.

- NRG RTOG 9601—This phase III trial demonstrated that addition of antiandrogen therapy (AAT) to salvage radiotherapy (SRT) improves clinical outcomes in prostate cancer patients with biochemical failure following radical prostatectomy. A follow-up transcriptome profiling of patients' tumors shows that a clinical-genomic risk score (GC) associates with survival benefit from AAT.

- ECOG 1912—The results from this randomized phase 3 trial completed in 2018 in those 18 to 70 years of age with chronic lymphocytic leukemia showed that treatment with ibrutinib and rituximab improved progression free and overall survival compared to standard therapy with fludarabine, cyclophosphamide, and rituximab.

- ANBL0531—This trial showed that therapy could be reduced for subsets of patients with intermediate-risk neuroblastoma using a biology-based and response-based algorithm to assign treatment duration while maintaining a 3-year overall survival of 94.9%.

- NRG RTOG 9402—Now 25 years since activation, this study evaluated chemoradiotherapy for anaplastic oligodendroglial tumors: Adding intensive procarbazine, lomustine, and vincristine (iPCV) to radiotherapy more than tripled progression-free survival and nearly doubled overall survival for patients with 1p19q co-deleted anaplastic tumors.

- ARST 0332—In this prospective study of pediatric patients and young adults, pre-treatment clinical features were used to effectively define treatment failure risk and to stratify young patients with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) for risk-adapted therapy. The risk stratification system used in this study will help clinicians plan risk-adapted therapy for patients younger than 30 years with NRSTS that optimizes the likelihood of cure while minimizing treatment exposures. The findings from this study will inform the standard of care while providing benchmark outcome data against which outcomes in the future clinical trials will be compared.

- NRG GOG-0213—Adding bevacizumab to standard chemotherapy for first recurrence platinum-sensitive ovarian cancer showed an overall survival benefit and led to the 2017 FDA licensing of bevacizumab for use in first recurrence of this cancer. Published in 2019, the results of the second study objective showed that secondary cytoreduction for women with first platinum-sensitive recurrence resulted in no better overall survival, changing practice away from surgery plus chemotherapy to chemotherapy alone.

- ARST09P1—This trial demonstrated that pediatric rhabdomyosarcoma patients in first relapse who were treated with temsirolimus in combination with vinorelbine and cyclophosphamide had a superior EFS than compared to the combination of chemotherapy with bevacizumab. As a result, temsirolimus is being studied in a randomized study with chemotherapy for newly diagnosed intermediate risk rhabdomyosarcoma (ARST1431).

- AREN0321—This trial showed that the outcome for stage I anaplastic Wilms tumor could be improved with the addition of radiation and doxorubicin to vincristine and dactinomycin. This yielded a 4-year overall survival of 100%. This defines a new standard treatment for this group of patients.

- ANBL0532—Standard of therapy became tandem myeloablative autologous stem cell transplant using peripheral blood stem cells for high-risk neuroblastoma.

- ALLIANCE A041202—The results from this randomized phase 3 trial completed in 2018 in those age 65 and older with chronic lymphocytic leukemia showed that treatment with ibrutinib improved progression free survival compared to standard treatment with bendamustine and rituximab.

- C10403—This intergroup study conducted in older adolescent and young adult patients with newly diagnosed acute lymphoblastic leukemia (ALL) successfully used a combination chemotherapy approach developed for children to improve outcome, setting a new standard of care for this population. This treatment now serves as the backbone for the ongoing randomized trial in the NCTN for newly diagnosed young adults with ALL (A041501).

- RTOG-1016—An interim analysis of data from this randomized, phase 3 clinical trial of patients with human papillomavirus (HPV)-positive oropharyngeal cancer found that treatment with radiation therapy and cetuximab is associated with worse overall and progression-free survival compared to the current standard treatment with radiation and cisplatin. The trial was designed to see if cetuximab with radiation would be less toxic than cisplatin with radiation without compromising survival for patients with the disease.

- TAILORx/PACCT-1—The Trial Assigning Individualized Options for Treatment (Rx), or TAILORx trial, showed no benefit from chemotherapy for 70 percent of women with the most common type of early stage breast cancer. The international study found that for women with hormone receptor-positive (HR+), HER2-negative, axillary lymph node–negative breast cancer, treatment with chemotherapy and hormone therapy after surgery is not more beneficial than treatment with hormone therapy alone.

- RTOG 0126—For patients with intermediate-risk prostate cancer, this randomized trial compared the efficacy of standard vs dose-escalated radiation therapy, which some clinicians were recommending and using without rigorous scientific evidence. Despite improvements in biochemical failure and distant metastases, dose escalation did not improve overall survival. High doses caused more late toxic effects and lower rates of salvage therapy.

- AALL0434—This largest-ever trial for children and adolescents with newly-diagnosed T-cell acute lymphoblastic leukemia (ALL) showed a disease-free survival rate exceeding 90 percent for patients who were randomized to receive high-dose methotrexate and nelarabine.

- E2211—Presented at ASCO 2018, this prospective, randomized phase 2 study showed that in patients with advanced pancreatic neuroendocrine tumors the combination of temozolomide and capecitabine improved progression-free survival and overall survival compared to temozolomide alone.

- AREN0534—This is the first prospective trial conducted in children with newly diagnosed bilateral Wilms tumors. COG investigators showed that with using a 3-drug preoperative chemotherapy regimen, followed by surgical resection within 12 weeks of diagnosis followed by histology-based postoperative therapy the overall EFS and survival was improved from the past. In addition, surgeons were able to preserve renal parenchyma as compared with historical controls. Based on this study, there is now a standard approach to bilateral Wilms tumors.

- CATNON RTOG 0834 (NRG)—International study showed that adjuvant temozolomide chemotherapy was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma.

- A091105 (also see NCI Press Release)—The results from this randomized, phase 3 clinical trial for patients with desmoid tumors or aggressive fibromatosis (DT/DF), which are rare tumors, showed that the multi-kinase inhibitor sorafenib tosylate (Nexavar) significantly extended progression-free survival compared with a placebo, making this drug a practice-changing approach for these patients.

- CALGB 10603—Midostaurin approved by FDA in 2017 for adult patients with newly diagnosed acute myeloid leukemia.

- ANBL1221—This randomized, phase 2 trial showed that relapsed and refractory neuroblastomas in children had a greater response to the combination of irinotecan-temozolomide-dinutuximab than to irinotecan-temozolomide-temsirolimus. This is a new standard of care for recurrent neuroblastoma. A pilot is underway to see if dinutuximab can be given with induction therapy for newly diagnosed high risk neuroblastoma patients.

- CALGB 100104—Provided critical contribution for the 2017 FDA approval for lenalidomide as maintenance therapy after autologous transplant for multiple myeloma.

- ECOG-ACRIN E3805—Docetaxel given at the beginning of androgen deprivation therapy for metastatic prostate cancer significantly increased overall survival.

- N0574—Among patients with 1 to 3 brain metastases, the use of stereotactic radiosurgery (SRS) alone, compared with SRS plus whole brain radiotherapy, resulted in less cognitive deterioration at 3 months. These findings suggest that for brain metastases amenable to radiosurgery, SRS alone may be a preferred strategy.

- A031203—The randomized Phase 2 trial of cabozantinib versus sunitinib in metastatic renal cell carcinoma (RCC) led to the pivotal METEOR trial. This comparison of cabozantinib to everolimus was the basis for the 2016 FDA approval of cabozantinib in patients with advanced renal cell carcinoma who had received prior anti-angiogenic therapy.

- ANBL0531—Standard of therapy became tandem myeloablative autologous stem cell transplant using peripheral blood stem cells for high-risk neuroblastoma.

- COG AALL0232—In pediatric patients with high-risk acute B cell lymphoblastic leukemia, event-free survival increased with the use dexamethasone (compared

with prednisone) and high-dose methotrexate (compared to an alternative way of administering methotrexate).

- CAN-NCIC-MA17R—In early-stage breast cancer, 10 years of aromatase inhibitor therapy improved disease-free survival when compared to five years of therapy.

- C106403—Intergroup study conducted in older adolescent and young adult patients with newly diagnosed acute lymphoblastic leukemia (ALL) successfully used a combination chemotherapy approach developed for children to improve outcome, setting a new standard of care for this population.

- **Studies Conducted by the Experimental Therapeutics Clinical Trials Network (ETCTN)**

- 9681—This Phase 1 study of cabozantinib and nivolumab in urothelial tumors created the foundation for the pivotal CHECKMATE-9ER study. Results from this study led to the 2021 FDA approval of cabozantinib and nivolumab for advanced renal cell carcinoma.

- 8799-SPRINT Trial—This trial established a new standard-of-care therapy for patients with NF1-related plexiform neurofibromas (PN). The trial assessed the MEK 1/2 inhibitor selumetinib and established that this agent can lead to durable tumor shrinkage and clinical benefit for children and adolescents suffering from symptomatic PN. In April 2020, selumetinib became the first FDA-approved therapy for this condition.

- 9673—First demonstration of anti-PD-1 drug (nivolumab) in squamous cell carcinoma of anal cancer which resulted in a change in National Comprehensive Cancer Network (NCCN) guidelines.

- 9825—Randomized Phase 2 study of combination cediranib and olaparib versus olaparib alone in ovarian cancer has led to three pivotal trials: one in platinum-sensitive (NRG GY004) and the other in platinum-refractory (NRG GY005) ovarian cancer; another trial also emerged—NRG GY012, which is testing cediranib and olaparib in endometrial cancer.

- **Studies Conducted by the Cancer Immunology Trials Network CITN)**

  - CITN-10—This Phase 2 trial demonstrating durable response to pembrolizumab in patients with advanced mycosis fungoides or Sézary syndrome led to the inclusion of pembrolizumab as a recommended therapy by the NCCN for cutaneous T-cell lymphomas (CTCL). It was the first study of any immune checkpoint inhibitor to demonstrate durable activity for CTCL.

  - CITN-12—First demonstration of safety of anti-PD-1 agent (pembrolizumab) in cancer patients with HIV infection, which has led to the recommendation for inclusion of HIV+ patients in immune-oncology trials.

  - CITN-09—First demonstration of activity of anti-PD-1 agent (pembrolizumab) in Merkel-cell carcinoma. PD-1 blockade with pembrolizumab in patients with advanced disease showed an objective response rate of 56 percent and a 67 percent rate of progression-free survival at 6 months in this Phase 2 study. In December 2018, the drug received accelerated approval from the FDA for this cancer.