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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 36 practice-changing clinical trials whose results were announced between 2014 and April 2020. 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)**

    - NRG Oncology CC001—In people with brain metastases eligible for Whole Brain radiation (WBRT), this phase III trial showed that hippocampal avoidance WBRT (HA-WBRT) plus memantine resulted in less deterioration in executive function, learning, and memory compared to standard WBRT plus memantine.

    - 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 study found that for women with hormone receptor (HR)-positive, 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)**

  - 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 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-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, which is part of the Cancer Immunotherapy Trials Network (CITN). In December 2018, the drug received accelerated approval from the FDA for this cancer.