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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 69 practice-changing clinical trials whose results were announced between 2014 and December 2022. 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-RTOG 1205 —The first and only trial to study re-irradiation in the management of recurrent GBM in a randomized trial, providing categorical level 1, practice-changing evidence that for appropriately selected GBM patients, re-irradiation added to salvage bevacizumab significantly prolongs progression free survival (3.8 vs. 7.1 months).

- E1910 — This study demonstrated that blinatumomab, a form of immunotherapy, improved survival in patients who had responded well to treatment and in whom the minimal residual disease test found no remaining evidence of disease. This reminds us that negative minimal residual test does not mean there is no disease, and more importantly, if it can be effectively targeted, patients may be cured.

- AHOD1331 —This was a randomized phase 3 study enrolling 600 patients with high-risk classical Hodgkin lymphoma, showing a 3-year EFS of 92.1% with Brentuximab vedotin (Bv) and chemotherapy (Bv-AVE-PC) and 82.5% with ABVE-PC ($P<0.001$). Toxicities were comparable by study arm and consistent with the myelosuppression of the AVE-PC chemotherapy backbone. Based on AHOD1331 results, the Food and Drug Administration approved brentuximab vedotin (Adcetris, Seagen, Inc.) in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide for pediatric patients 2 years of age and older with previously untreated high risk classical Hodgkin lymphoma.

- NRG RTOG 1112 —This randomized phase 3 trial demonstrated that the addition of SBRT to systemic therapy with sorafenib improved the survival of patients with advanced hepatocellular cancer. The is the first trial to demonstrate that the addition of local therapy in the form of SBRT is beneficial when added to systemic therapy for patients with advanced hepatocellular carcinoma.

- Olympia/NSABP-B-55 – This international trial showed that Olaparib therapy for one year after completion of standard neo/adjuvant therapy in patients with BRCA1/2-associated breast cancer improved outcomes.

- SWOG S1404 – This study compared adjuvant therapy with pembrolizumab to an active control arm of physician's choice of interferon alpha or ipilimumab and confirmed the benefit of pembrolizumab seen in placebo-controlled trials.

- SWOG S1512 – This was a phase II trial of neoadjuvant pembrolizumab in resectable desmoplastic melanoma, a rare subtype of melanoma. Pathologic complete response was noted in 55% of patients in the neoadjuvant resectable cohort, supporting the potential utility of neoadjuvant therapy in facilitating surgical resection.

- NRG-RTOG 9202, 9408, 9413, 9910, 0126 – NRG investigators analyzed clinical and digital histopathology data from five Phase III prostate cancer trials to develop and validate multimodal intelligence models (MMAI) that could outperform the National Comprehensive Cancer Network (NCCN) in the prediction of distant metastasis and other outcomes and found that the MMAI models could, in fact, stratify patients into risk groups that more accurately reflected their prognosis in comparison to NCCN risk groups.

- SWOG S1801 – This study compared a neoadjuvant treatment approach for melanoma with standard adjuvant therapy. Patients were randomized to either 3 doses of pembrolizumab, followed by surgery and then completion of one year of treatment, or surgery followed by one year of pembrolizumab. The study showed improvement in event-free survival with the neoadjuvant approach.

- AALL1331 – This phase 3 study evaluated the substitution of two courses of blinatumomab for two courses of intensive chemotherapy as consolidation therapy for children, adolescents, and young adults (AYA) with high- and intermediate-risk first relapse of B-ALL, with patients proceeding to allogeneic stem cell transplantation after consolidation therapy. The 2-year overall survival was 71.3% for the blinatumomab group vs 58.4% for the chemotherapy group (1-sided P=.02) and rates of serious adverse events were markedly lower for the blinatumomab arm compared to the intensive chemotherapy arm. The results establish pre-transplant consolidation therapy with two courses of blinatumomab as a new standard of care for pediatric and AYA patients high- and intermediate-risk first relapse B-ALL.

- 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 inhibitor-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.

- 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.

- 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).

- NSABP B42 – This trial assessed the efficacy of an additional 5 years of letrozole following 5 years of endocrine therapy that included an aromatase inhibitor. The trial did not show a significant improvement in disease-free survival with longer duration therapy in the full analysis population, highlighting the need for careful risk assessment in recommending extended adjuvant endocrine 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.

- NSABP B39/RTOG 0413 – This was the largest trial of accelerated partial breast irradiation vs whole breast irradiation and helped solidify the role of partial breast irradiation in early-stage breast cancer.

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

  - 10388 – Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to NETs that express somatostatin receptors (SSTRs). Radiolabeled somatostatin analogue Lutetium Lu 177 Dotatate (Lutathera) is a beta-emitting radionuclide, recently FDA approved for use in SSTR positive gastro-entero-pancreatic neuroendocrine tumors (GEPNETS) in the US based on the NETTER-1 Phase III trial. Despite favorable PFS and safety profile, the drug has limited cytoreductive capability with a 17% ORR. Ribonucleotide reductase (RNR) is the only enzyme responsible for conversion of ribonucleoside diphosphate to deoxyribonucleotide diphosphate (dNDP), the key building blocks for DNA synthesis. Triapine is an inhibitor of RNR. This study was a multicenter phase 1 dose escalation trial [using the Bayesian optimal interval design (BOIN)] of triapine in combination with fixed dose lutetium Lu 177 DOTATATE for well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) after the failure of at least one line of prior systemic cancer treatment with an expansion cohort at the recommended phase 2 dose (RP2D). The study found that the combination of triapine and Lu-177 DOTATATE was safe with preliminary efficacy signals, which will be further evaluated in ETCTN 10558, a randomized phase 2 study that is comparing the effectiveness of triapine and Lu-177 DOTATATE to Lu-177 DOTATATE alone.

- 10250 – This was a single-arm, multicenter, phase 2 trial evaluating olaparib+temozolomide in advanced uLMS pts with progression on ≥1 prior line. Pre-treatment (Pre) and on-treatment (On) biopsies were collected from 22 pts, and found that gene expression signatures for replicative stress showed borderline association with worse PFS. This trial also led to A092104, a phase 2/3 study in advanced uterine LMS after progression or prior chemotherapy, and also provided the dose and schedule for A021804 in pheochromocytoma.

- 10005 – The results of this clinical trial involving atezolizumab for the treatment of advanced alveolar soft part sarcoma (ASPS), as reported on the National Institutes of Health (NIH) website, showed that atezolizumab was effective in shrinking tumors and prolonging progression-free survival in patients with ASPS. The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) determined by an independent review committee using RECIST v1.1. ORR was 24% (95% CI: 13, 39). Of the 12 patients who experienced an objective response, 67% had a DOR of 6 months or more. These results led to the FDA approval of atezolizumab for the treatment of advanced ASPS providing a new treatment option for patients with this rare and aggressive type of cancer.

- 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.

- 9434 — This phase 1 trial led to NRG GY006, a randomized phase 2 comparison of triapine-cisplatin-radiotherapy to cisplatin-radiotherapy in a regionally advanced-stage uterine cervix cancer patient population, and led to orphan designation for triapine.

- 8348 —This Phase 1 trial led to 9825, a randomized phase 2 study of the combination cediranib and olaparib versus olaparib alone in ovarian cancer, which in turn led to three pivotal trials: one in platinum-sensitive (NRG GY004) ovarian cancer, one in in platinum-refractory (NRG GY005) ovarian cancer, and another trial NRG GY012, which is testing cediranib and olaparib in endometrial cancer. Studies Conducted by the Cancer Immunology Trials Network CITN)

- **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.