

# Brain Tumor Trials Collaborative

# NCI-CONNECT annual meeting

The inaugural [NCI-CONNECT \(Comprehensive Oncology Network Evaluating Rare CNS Tumors\)](#) Meeting was held in conjunction with the [Brain Tumor Trials Collaborative \(BTTC\)](#) Annual Meeting at the National Institutes of Health (NIH). The meetings on June 11-12, 2018, were hosted by the Neuro-Oncology Branch at the Center for Cancer Research (CCR), National Cancer Institute (NCI), and was the largest BTTC meeting to date with over 100 attendees.



The goal of the meetings were to bring together leaders in neuro-oncology clinical care, basic science and clinical research with advocacy partners in a collegial and collaborative environment to discuss [current](#) and future brain and spine tumor clinical trials. Attendees shared new clinical trial concepts that had both high levels of scientific merit and also incorporated measures of patient quality of life and outcomes. The aim is to help advance treatments for patients with malignant brain tumors, with a particular focus on rare tumors of the central nervous system.

An overview of each session and a summary of key findings from the meeting is provided below.

## Day 1: Monday, June 11

The first day focused on NCI-CONNECT, a new program supported by the Cancer Moonshot<sup>SM</sup>. This new program will use the existing and successful BTTC infrastructure and network for clinical trials. NCI-CONNECT aims to advance the understanding of rare adult central nervous system (CNS) cancers by establishing and fostering patient-advocacy-provider partnerships and networks to improve approaches to care and treatment.

Mark Gilbert, M.D., the Principal Investigator for the BTTC, Co-director of NCI-CONNECT and Chief of the Neuro-Oncology Branch at the NIH, welcomed attendees. He shared an overview of the [current open clinical trials](#) for patients with rare CNS cancers at the NIH and ways the BTTC network can [refer patients](#). One of these studies, the [Natural History Study](#), led by Terri Armstrong, Ph.D., ANP-BC, Co-director of NCI-CONNECT and Senior Investigator for the Patient Outcomes Program in the Neuro-Oncology Branch at the NIH, evaluates the natural history and collects specimens for patients with CNS cancers to better understand the disease and uncover areas for further research. Patients receive free care at the NIH if they're enrolled on a study, allowing patients and their families to focus on treatment instead of costs.



Dr. Armstrong shared plans to maximize data collection. Studies will collect DNA specimens from patients and caregivers. This will help improve the understanding of [outcomes and risk factors](#) associated with the occurrence of rare CNS tumors. Patients don't need to visit the NIH to take part in the study. Instead, they can participate at home by completing an online survey and submitting a saliva sample to be used for genetic testing.

Jill Barnholtz-Sloan, Ph.D., Professor at Case Western Reserve University School of Medicine, and Carol Kruchko, President and Chief Mission Officer of the [Central Brain Tumor Registry of the United States \(CBTRUS\)](#),

discussed how CBTRUS gathers and shares surveillance and epidemiology data and is the sole source in the United States for incidences for all primary CNS tumors. Knowing this data helps investigators design clinical, research, epidemiologic and survivorship trials and studies. They are currently working on a report with data on NCI-CONNECT's selected [12 rare CNS tumors](#). In the future, they plan to collect data based on the 2016 WHO classification and surveillance of biomarkers.

The morning continued with disease-focused discussions led by BTTC investigators to review current treatments and associated challenges, and then discuss treatment advances for the following tumor types in adults:

- High Grade Meningioma by Priscilla Brastianos, M.D., Massachusetts General Hospital
  - **Current treatment and challenges:** This session discussed the recent findings about the genomic alterations in meningioma genomes; they are simple and show clinically significant mutations. Investigators should consider if molecular classification could revolutionize treatment for meningiomas like it has in other CNS tumors and molecular biomarkers should be incorporated to diagnose and plan treatment.
  - Future trials should investigate targeted therapies.
- Midline Glioma by Brett Theeler, M.D., Walter Reed National Military Medical Center
  - **Current treatment and challenges:** Diffuse midline glioma H3K27M-mutant was a new subtype reported in 2016 by the World Health Organization. H3F3A is the most common histone mutations in adults and pediatric patients. There are four other mutations: TP53, ATRX, PPM1D, and ACVR1. Standard treatment includes: biopsy, adjuvant radiotherapy (depending on location) and low evidence of temozolomide's effectiveness. Patients have poor outcomes regardless of H3 mutation status.
  - Future trials should investigate the drug ONC201 dopamine D2 receptor antagonist as an immunotherapy for these tumors.



- Pleomorphic Xanthroastrocytoma (PXA) by Dr. Theeler
  - **Current treatment and challenges:** The first generation of BRAF inhibitors were used in PXAs. The BRAF inhibitor PLX8394 was studied in a phase I/II clinical trial for patients with rare CNS neoplasms and preliminary results were presented at American Society of Clinical Oncology 2018 meeting.
  - Future trials using BRAF inhibitors would need to be more inclusive in enrolling patients and investigators need to learn more about non-BRAF PXAs.
- Medulloblastoma by Marta Penas-Prado, M.D., The University of Texas MD Anderson Cancer Center
  - **Current treatment and challenges:** Adult data is far behind the pediatric data for medulloblastoma and there are few prospective trials. The optimal chemotherapy has shown to improve outcomes, but also cause many toxicities. Subgroups do not indicate survival.
  - Future trial designs would benefit from using optimal chemotherapy, radiation therapy, liquid biopsies, immune profiling and advanced images.
- Atypical Teratoid Rhabdoid Tumor (AT/RT) by Nicole Shonka, M.D., University of Nebraska Medical Center
  - **Current treatment and challenges:** AT/RT shows loss of function mutation in the INI1/SMARCB1 gene. There are three pediatric subgroups: ATRT-TYR, ATRT-SHH and ATRT-MYC and three molecular and epigenetic subgroups, but there is no subtype for adults. A tamoxifen injection inactivates the SMARCB1 gene in mouse models.
  - Future trials should use therapies designed for subgroups using specific pathways.
- Preclinical Models by Eric Holland, M.D., Ph.D., University of Washington



- **Current treatment and challenges:** For supratentorial ependymoma, researchers are using the RCAS/tv-a system to determine if the C11orf95 RELA fusion is enough. Results are challenging since only half of the mouse models develop a tumor. For comparisons of glioma in multiple species, they're generating various animal models to find a unifying theory of gliomas among mammals. Modeling IDH-mutant gliomas can be challenging because they have different immune status. Bilateral gliomas as an experimental paradigm model can be generated with different genetics to help researchers study local and systemic therapies and their interactions. The immune competent RCAS/

tva mouse models for brain tumors are ependymoma, medulloblastoma, PNET, AT/RT, DIPG, CNS sarcomas, ISH mutant gliomas and PXA. More molecular data on human disease is needed to be sure how similar mouse models are.

- Future trials should be a multi-arm concept and non-competing, as enrollment would be low with the rare population.

One of the key features of these disease-specific talks was that they led to focused discussions about these tumors including the implementation of molecular classifications and biomarkers to advance treatments and how to develop targeted therapy clinical trials. This was particularly important in tumor types where genetic mutations and subgroups have been identified. Investigators also discussed the need for collaboration and awareness to move trial designs forward.



Brittany Cordeiro, Advocacy Liaison and Navigator of NCI-CONNECT, led the advocacy breakout sessions, with NCI-CONNECT colleagues, Drs. Armstrong and Gilbert, and Kristin Odom, Communications Editor. The NCI-CONNECT advocacy partners are non-profit organizations that have agreed to facilitate engagement with patients with selected rare CNS tumors by sharing information about available clinical trials and information generated by NCI-CONNECT to educate patients. Advocate representatives from five non-profit organizations – the American Brain Tumor Association, Biden Cancer Initiative, CERN Foundation, International Brain Tumour Alliance and National Brain Tumor Society – attended the meeting. These sessions

included focused discussions on patient education and communications, clinical trial accrual, advocacy training and resources, and clinical care and treatment at the NIH.



In the afternoon, Dr. Armstrong shared information about the NIH tumor repository. Plans are underway to collect tumor samples with clinical history from patients with selected CNS tumors. The repository will allow researchers to more accurately classify CNS tumor types and predict outcomes. Data collected from the tumor repository will help scientists to predict which drugs, and combination of drugs, will have a therapeutic effect.

Later that afternoon, Christine Siegel, Nurse Practitioner, and Kiera Caffee and Tracy Ani, Patient Care Coordinators, in the Neuro-Oncology Branch at the NIH, shared how patients can be referred for neuro-oncology clinical care at the NIH. The Neuro-Oncology Branch clinical care team works together with patients' primary care physicians to ensure they receive the best treatment possible. Patients or physicians can contact [NCINOBRreferrals@mail.nih.gov](mailto:NCINOBRreferrals@mail.nih.gov) or call 1-866-251-9686 or 240-760-6010.

The first day of the meeting concluded with a discussion on multi-arm trial planning, led by Drs. Gilbert and Armstrong, and Tito Mendoza, Ph.D., and Ying Yuan, Ph.D., of MD Anderson Cancer Center. The meeting brought NCI-CONNECT advocacy partners together with neuro-oncology researchers and clinicians for the first time. The goal of this discussion was to allow investigators to hear the perspective of people who help patients find and participate in clinical trials and educate patients on treatment and care decisions. The NCI-CONNECT advocacy partners were a valuable addition to the conversation.



The day ended with an evening reception celebrating the 15 year anniversary of the BTTC and the [Head for the Cure Foundation](#).



## Day 2: Tuesday, June 12

Dr. Gilbert welcomed attendees to the BTTC meeting. The BTTC was created in 2003 as a network of medical centers with the expertise and the desire to participate in state-of-the-art clinical trials investigating new treatments for malignant brain tumors.

Caryn Steakley, Deputy Clinical Director of the CCR, shared her support of the BTTC as a stellar program in the NCI Intramural Research Program. The CCR at the NCI serves as the lead institution and coordinating center for the BTTC.

Michael Pollack, Ph.D., Supervisory Technology Transfer Specialist at the NCI, oversees the BTTC site agreements. Drs. Gilbert and Pollack discussed the status of current and legacy trials and agreements. Trial information is available online at [ccr.cancer.gov/Neuro-Oncology-Branch](http://ccr.cancer.gov/Neuro-Oncology-Branch).

The morning sessions for investigators continued with the following protocol concept ideas proposed to the group by BTTC investigators:

- Phase II Study of Trametinib and Trametinib plus Pembrolizumab in Recurrent Glioblastoma with Alterations in NF1  
Howard Colman, M.D., Huntsman Cancer Institute
- Enhanced Nanoliposomal Targeting of Glioblastoma by Combining BXQ350 and Bevacizumab  
Vinay Puduvalli, M.D., Ohio State University Wexner Medical Center
- Regorafenib in Glioblastoma: A Biomarker-driven Adaptive Design Clinical Trial  
David Cachia, M.D., Medical University of South Carolina



- Combination of PD-1 Inhibitor and IDO Inhibitor at First Progression in Surgically Accessible Recurrent Glioblastoma  
Jacob Mandel, M.D., Baylor College of Medicine
- Randomized Phase II Study of Temozolomide +Eflornithine (DFMO) Versus Temozolomide Alone After Radiation and Temozolomide for Newly Diagnosed Patients with Anaplastic Gliomas with IDH Mutation  
Howard Colman, M.D., Huntsman Cancer Institute

The [32 BTTC investigators](#) in attendance thoroughly discussed the trial concepts and showed enthusiasm for moving forward. The plan is to continue discussions on these proposals with the expectation that several will be fully developed into BTTC clinical trials. More information will be shared as those trial concepts progress.

Kenneth Aldape, M.D., Chief of the Laboratory of Pathology, and Eytan Ruppin, M.D., Ph.D., Chief of Data Science, both of CCR, NCI, at the NIH, discussed the concept of applying synthetic lethality, a concept where molecular testing of cancers reveal potential therapeutic targets that are unique because the likely partner that would lead to treatment resistance has been lost. Dr. Aldape explained that histology, or studying tumor tissue under a microscope, has its limits in classifying CNS tumors. And when there is difficulty in histology diagnosis, it's useful to genetically profile brain tumors. More, methylation patterns help define the cells of origin for CNS tumors, so DNA methylation profiling can also be used to classify brain tumors and help sort out biological differences. Dr. Ruppin further explained they're looking for actionable genetic mutations – events that transform normal cells to cancer cells – to target vulnerabilities particularly when loss of partner genes make the vulnerabilities even more likely to cause death of the cancer cells. The goal is to allow doctors to more accurately develop personalized therapies for patients.



Breakout sessions for research staff to learn more about the programmatic and clinical care details of BTTC clinical trials were led by the BTTC Coordinating Center team members at the NCI/NIH. The coordinating center team shared how they can prepare for the GBM Pembro HSPPC trial opening at the additional BTTC sites. Nurse Practitioner Christine Siegel discussed the care of patients on immunotherapy drugs, like pembrolizumab, BTTC Protocol Coordinator Jennifer Reyes shared an overview of the regulatory requirements for BTTC members to initiate the trial at their sites, Research Nurse Sonja Crandon gave an overview of an electronic survey given to study participants to assess how well they are doing, and BTTC Project Manager Katie Blackburn provided a demonstration of the tissue and blood collection kits for clinical trials.



The breakout sessions for research staff also included future clinical trial concepts. Nurse Practitioner Lisa Boris and Research Nurse Chrissy Bryla shared information on a proposed phase II trial using a drug called TG02, which has been shown to kill glioma cancer cells. The safety of the drug in combination with another chemotherapy drug is currently being evaluated in a [phase I trial](#) enrolling patients with recurrent anaplastic astrocytoma and glioblastoma at the NIH. NCI Research Analyst Elizabeth Vera, who focuses on patient outcomes, presented an overview of a proposed tissue repository study that would collect both tissue and clinical data from patients with rare

CNS tumors. The goal of the tissue repository study is to better understand the tumors and to develop clinical trials to target the tumors and improve patient care.

In conclusion, the NCI-CONNECT and BTTC Meetings were a great success. Attendees learned from other neuro-oncology experts and advocates, participated in invigorating discussions on current disease treatments and advances in the pipeline, and reviewed proposed clinical trials and thoroughly discussed new ideas and concepts for multi-arm clinical trials, all with the ultimate goal of improving therapies and outcomes for adult patients with brain and spine tumors.