NEUROFIBROMATOSIS CONSORTIUM

FISCAL YEAR 2021 REQUEST

We respectfully request $20 million for the Army's Neurofibromatosis (NF) Research Program (NFRP) in the FY2021 Department of Defense Appropriations bill.

NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM (NFCTC)

- The NF Clinical Trials consortium (NFCTC) was established in 2006 to develop and perform clinical trials for the treatment of NF complications in children and adults. The NFCTC was subsequently refunded in 2011 and again in 2016.

- The Consortium is composed of 25 clinical sites. Dr. Bruce Korf is the Principal Investigator and leads the Operations Center based at the University of Alabama at Birmingham (UAB). UAB serves as a clinical site and provides administrative, data management and statistical support to the NFCTC. Dr. Michael Fisher at Children's Hospital of Philadelphia chairs the Steering Committee.

- The NFCTC is funded by Department of Defense (DoD) through the Neurofibromatosis Research Program (NFRP), one of the Congressionally-Directed Medical Research Programs. The funding and collaboration with the DoD allows unique opportunities to partner with well-established NF Centers both nationally and internationally, pooling expertise and resources toward the common goal of new treatment opportunities and ultimately a cure for NF.

- The NFCTC has allowed its investigators to develop mature protocols through collaborative discussions with various disease and discipline committees, allowing for quicker turnaround of scientific reviews and regulatory approvals.

- The NFCTC has leveraged its collaboration with the DoD to work with pharmaceutical companies to acquire therapeutic agents and other organizations to assist in conducting additional trials. To date, the DoD investment in the NFCTC has yielded an additional $3.5 million of funding.

- The NFCTC has launched 14 studies and has 4 studies in development. More than 430 patients have been enrolled and treated. The NFCTC has published 12 peer-reviewed articles and has 7 additional manuscripts submitted or in preparation. Their work has generated 24 abstracts at scientific meetings and 36 invited talks.

CURRENT PARTICIPATING SITES

- The University of Alabama at Birmingham
- Children's Hospital Boston
- Massachusetts General Hospital
- Children's National Medical Center
- Children's Hospital Los Angeles
- Children's Hospital of Philadelphia
- Children's Hospital of Westmead (Sydney AU)
- Cincinnati Children's Medical Center
- Indiana University
- Mayo Clinic (Minnesota)
- National Cancer Institute
- New York University Medical Center
- University of Chicago
- University of Texas Southwestern (Dallas)
- University of Utah
- Washington University (St. Louis)
- Children's Healthcare of Atlanta
- Dana Farber Cancer Institute
- Johns Hopkins
- Lurie Children's Hospital of Chicago
- Memorial Sloan Kettering Cancer Center
- Murdoch Children's Research Institute (Melbourne AU)
- University of California Los Angeles
- University of Minnesota
- University of Pennsylvania

COMPLETED TRIALS

NF102 (STOPN), "A Phase II Study of the mTOR Inhibitor Sirolimus in NF1 Related Plexiform Neurofibromas." Dr. Brian Weiss of Cincinnati Children's Medical Center chaired this study. This primary objective of this study was to find out if sirolimus could stop or slow the growth of and/or shrink plexiform neurofibromas in patients with NF1. STOPN consisted of two strata: Stratum 1 recruited 46 evaluable participants with actively growing tumors, and Stratum 2 recruited 12 evaluable subjects with non-progressive tumors. This study yielded four publications. The results showed that sirolimus is well-tolerated in NF1 participants, prolongs the time to progression of growing tumors (stratum 1), but does not result in shrinkage of these tumors (stratum 2).

NF101 (STARS), "A Randomized Placebo-Controlled Study of Lovastatin in Children with NF1." Dr. Kathryn North chaired this study. STARS screened over 270 participants toward the goal of enrolling 128 evaluable. This study closed to enrollment with 125 evaluable participants. STARS was designed to determine whether Lovastatin could improve cognitive function in children with NF1. Participants were randomly assigned into one of two groups: lovastatin or a placebo control group (inactive substance). Lovastatin had no significant effect on primary outcomes of visual learning and attention; however, yielded important information that will inform subsequent trails, such as the reproducibility of cognitive endpoints and the impact ADHD symptoms on daily functioning. This study yielded four publications.

MPNST1, "SARC016 - Phase 2 Study of the mTOR Inhibitor Everolimus in combination with Bevacizumab in Patients with Sporadic and NF1 Related Refractory Malignant Peripheral Nerve Sheath Tumors (MPNST)" was conducted in collaboration with the Sarcoma Alliance for Research through Collaboration (SARC), with SARC serving as the Operations Center. Dr. Brigitte Widemann of the National Cancer Institute served as the Study Chair. A total of 25 patients were enrolled on this study. With a clinical benefit rate of 12% (3 out of 25 patients), the combination of everolimus and bevacizumab did not reach the study's target response rate and is not considered active in refractory MPNST. Results were published in the journal Sarcoma.

MPNST2, "SARC023 - Phase 1/2 Study of ganetespib in combination with sirolimus for refractory sarcomas and MPNST" was conducted in collaboration with SARC, with SARC serving as the Operations Center. Dr. AeRang Kim of Children's National Medical Center served as the Study Chair. The phase 1 portion enrolled 10 patients and identified the recommended dosing for phase 2 testing. The phase 2 portion enrolled 10 patients, but despite promising preclinical rationale and tolerability of the combination therapy, no responses were observed, and the study did not meet parameters for further evaluation in MPNST. Results were published in the journal Sarcoma.

COMPLETED ENROLLMENT AND STUDY ACTIVITIES

NF103 (RAD001), "A Phase II Study of RAD001 (Everolimus) for Children with NF1 and Chemotherapy-Refractory Radiographic Progressive Low-Grade Gliomas." Dr. Mark Kieran chaired this study. Novartis provided drug and funds for secondary pharmacokinetic and pharmacodynamics studies. The primary objective of the study was to learn if RAD001 is effective for low-grade gliomas in children with NF1. 23 participants were enrolled and yielded 22 evaluable for the primary objective. 68% of participants demonstrated a response, defined as either tumor shrinkage or arrest of tumor growth. A manuscript of results was submitted and is under review. The results are expected to be published in 2020.

NF105 (Adult Cohort), "A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Adolescents and Adults with NF1" Dr. Chie-Schin Shih from Indiana University Children's Hospital chaired this study. Exelixis provides drug for this study. This study is evaluating whether Cabozantinib shrinks plexiform neurofibromas in adolescents or adults with NF1. The study completed enrollment. 23 subjects enrolled, of which 21 are evaluable for toxicity and 19 are evaluable for response. Eight of 19 (42%) had a partial response to treatment. A manuscript of results was submitted and is under review.

The results are expected to be published in 2020. Since the results were encouraging in adolescents and adults, and the recommended pediatric dose of Cabozantinib was identified, the study was amended to add a separate stratum of pediatric patients (<16 years of age) (see below).

NF106, "A Phase 2 Trial of the MEK Inhibitor PD-0325901 in Adolescents and Adults with NF1-Associated Morbid Plexiform Neurofibromas" Dr. Brian Weiss from Cincinnati Children's Hospital Medical Center chairs this study. Pfizer, Inc. provides drug and funds for optional evaluations for this study. This study is evaluating whether PD-0325901 shrinks plexiform neurofibromas in adolescents or adults with NF1. This study has completed its planned enrollment of 19 evaluable subjects. Eight of 19 (42%) had a partial response to treatment. The study remains open for final data analysis. A manuscript is in preparation. The results are expected to be published in 2020.

NF104, "An Open-label, phase 2 study of bevacizumab in children and young adults with NF2 and progressive vestibular schwannomas that are poor candidates for standard treatment with surgery or radiation." Dr. Scott Plotkin of Massachusetts General Hospital chairs this study. Genentech provides drugs and funds for patient evaluations for this study. The trial enrolled patients aged 6 years or older with NF2 and vestibular schwannoma that are growing and causing hearing loss. The primary objective is to determine the hearing response rate at 24 weeks after treatment with bevacizumab. This study met recruitment and follow-up goals and is closed to enrollment. Nine of 22 (41%) subjects achieved a hearing response at 6 months (end of induction therapy). The induction therapy results were published in Journal of Clinical Oncology in 2019. A second manuscript evaluating the durability of hearing response to a lower dose maintenance regimen of bevacizumab is expected to be published in 2020.

TRIALS IN PROGRESS

NF107, "A Study of INFUSE Bone Graft ((recombinant human Bone Morphogenetic Protein-2/absorbable collagen sponge) in the treatment of Tibial Pseudarthrosis in NF1" Dr. Elizabeth Schorry of Cincinnati Children's Hospital Medical Center chairs this study. Medtronic provides the INFUSE device for this study. The goal of this trial is to determine if use of an osteogenic agent (rhBMP-2) applied as a collagen sponge (INFUSE) at the time of surgical treatment for tibial pseudarthosis will result in improved bone healing when compared to NF1 patients treated with the same surgical treatment but without BMP-2. Due to slow enrollment, the study closed to enrollment in 2019. There is currently one active patient on trial, and one manuscript in preparation for submission in 2020.

NF108, "Phase II Study of Binimetinib in Children and Adults with NF1 Plexiform Neurofibroma" Dr. Sabine Mueller of the University of California, San Francisco and Dr. Michael Fisher of Children's Hospital of Philadelphia co-chair this study. This is a collaboration with the Pacific Pediatric Neuro-Oncology Consortium (PNOC). Array BioPharma provides drug and funding for this study. The primary objective is to determine the response rate to binimetinib in children and adults with NF1 and inoperable plexiform neurofibromas. The study will enroll up to 25 participants in each of two cohorts: pediatric (1-17 years of age) and adult (18 years of age and older). The pediatric cohort has completed enrollment. The adult cohort is currently open for enrollment and should close to enrollment in 2020.

NF105 (Pediatric Cohort), "A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Patients with NF1 – Pediatric Cohort" Dr. Michael Fisher from The Children's Hospital of Philadelphia chairs this study. Exelixis provides drug and funding for this study. This phase 2 study is evaluating whether the targeted agent Cabozantinib shrinks plexiform neurofibromas in children with NF1 age 3-15 years. The study enrollment goal is 19 evaluable subjects. The study is open and is enrolling, and is expected to reach enrollment goals in 2020.

LGG, "Phase I/II Study of MEK 162 for Children with Low-Grade Gliomas and Other Ras/Raf/ERK Pathway Activated Tumors (LGG)" Dr. Nathan Robison from Children's Hospital Los Angeles chairs this study. Array BioPharma provides drug for this study. Once the phase 1 portion of the study was completed, a phase 2 portion with multiple strata opened. The NF1-

specific stratum was opened in 2018, with a goal of defining the response rate in children (1-18 years of age) with NF1-associated low grade gliomas. The study is open and is close to its enrollment goal of 20 evaluable participants.

MPNST3, "SARC031: Phase II Study MEK Inhibitor Selumetinib (AZD6244) in Combination with the mTOR Inhibitor Sirolimus for Patients with MPNST" This study is being conducted in collaboration with SARC, with SARC serving as the Operations Center. Dr. AeRang Kim serves as the Study Chair. The primary objective is to identify the clinical benefit rate for patients age 12 years or older with inoperable or recurrent high grade MPNST. The study opened to enrollment in 2019.

CLINICAL TRIALS OPENING IN 2020

NF110, "Phase 2 Clinical Trial of Crizotinib for Children and Adults with NF2 and Progressive Vestibular Schwannomas" – Dr. Matthias Karajannis from Memorial Sloan Kettering Cancer Center serves as the Study Chair. Crizotinib has multiple targets including MET, ROS, ALK and FAK. The primary objective is to estimate the objective volumetric response rate to crizotinib in children and adults with NF2 and vestibular schwannoma.

NF111, "Phase II Clinical Trial of poly-ICLC for Progressive Low-Grade Gliomas in Pediatric Patients with NF1" – Dr. Dolly Aguilera from Children's Healthcare of Atlanta serves as the Study Chair. Poly-ICLC is a biological response modifier with immuno-stimulatory properties. The primary objective is to evaluate the objective tumor response rate to poly-ICLC in pediatric patients with NF1 and progressive LGG.

NF112, "Phase 1/2 Trial of the MEK inhibitor selumetinib and bromodomain inhibitor AZD5153 with durvalumab, a PD-L1 antibody for sarcomas including MPNST" - This study is being conducted in collaboration with SARC, with the NFCTC serving as the Operations Center. Dr. AeRang Kim serves as the Study Chair. The primary objective of the phase 1 portion is to determine the safety, tolerability, pharmacokinetics and recommended doses of each agent in combination. The primary objective of the phase 2 portion is to determine the clinical benefit rate in adults with refractory MPNST.

Plexiform Neurofibroma Trial – The NFCTC Plexiform Neurofibroma Committee is planning a phase I/II study of Cabozantinib in combination with a MEK inhibitor for plexiform neurofibromas in adolescents and adults and with NF1. This will build on the successful NFCTC trials of each of these medications as single agents. This trial is in development.