2022 **NF Conference Highlights**

Organized by Conference Co-Chairs **Thomas De Raedt, PhD**, (Children's Hospital of Philadelphia) and **Laura Papi, MD, PhD**, (University of Florence-Italy, Careggi University Hospital-Florence), this year's program was the first in-person meeting since 2019, with virtual gatherings since that time. The meeting focused on growing the NF scientific and clinical community, assessing what can be learned from other disease communities, and applying the best of those ideas to NF. In this way the field can facilitate new discoveries and accelerate the path from discovery to clinical benefit. This focus was represented by the invited keynote speakers from outside the NF field.

NF Clinical Care Symposium

The Clinical Care Symposium is a satellite half-day meeting specifically tailored to the NF and schwannomatosis clinical communities to address the current state of patient care, provide a forum for case studies, and to address other topics pertinent to running an NF clinic. This year's symposium was moderated by **Nicole Ullrich, MD, PhD**, and included updates on CTF's NF Clinic Network (NFCN), Clinical Care Advisory Board (CCAB), and the NF Registry, followed by additional topics and case presentations.

Scott Plotkin, MD, PhD, from Massachusetts General Hospital (MGH) and Chair of the CCAB, launched the symposium by recognizing the efforts of the group's NFCN subcommittee, which oversees the network that now includes 68 NFCN clinics, after over a decade of development by the CCAB and CTF. He mentioned other highlights of the work of the CCAB, including studying the effects of COVID-19 infection on people with NF, presenting monthly Virtual Case Conferences, and addressing the need for the delivery of guideline-concordant NF care.

Pierre Wolkenstein, MD, PhD, of Hopital Henri-Mondor in Paris, spoke about CTF-Europe's EU Clinical Care Advisory Board, which includes members from all over Europe. Its current focus is to provide complete, continuous NF medical education through a program called International NF Educational Resources, or **INFER**, which is creating a series of online medical lectures by leading NF experts and can be accessed live or as video recordings.

Following this, **Heather Radtke, MS, CGC**, manager of CTF's NF Clinic Network (NFCN), gave an overview of the network and its recent accomplishments. The network accepted its first two Canadian clinics this year, bringing the total of NFCN clinics to 68, which together saw nearly 20,000 patients last year. Ms. Radtke also described the NF Collective, a group of NF organizations from all over the U.S. who work together on ways to improve the lives of individuals with NF, under the medical direction of **David Viskochil, MD, PhD**, of the University of Utah. The Collective recently completed work on a "Transition to Adult Care" resource for young adults and their caregivers and is currently working on a Classrooms that Care Program to provide school educational activities that build empathy for those facing health challenges.

Pam Knight, MS, senior director of CTF's Clinical Program, reviewed the NF Registry and its progress over the last decade, during which membership grew to include 10,000 individuals. To date, the Registry has recruited patients for more than 60 clinical trials and research studies. Improvements underway will provide more precise metrics to allow CTF to improve outreach strategies, and enhance both recruitment effectiveness and the use of de-identified data for research.

Kaleb Yohay, MD, presented an updated version of his classic presentation, "Using a Business Plan Model for Funding Your Clinic," demonstrating his accounting-based approach to

Continued on page 16

Continued from page 8

capturing the financial value an NF clinic offers to its institution through referrals to surgery, radiology, laboratory services, consultation fees, and inpatient fees.

Next, **Jaishri Blakeley, MD**, director of the NF clinic at Johns Hopkins, shared the results of a study initiated in response to questions raised by the NF patient community about COVID-19 and how it might differentially affect their health. To understand more about the frequency and severity of COVID-19 in people with any form of NF, the CCAB collaborated with the NF Open Science Initiative (NF-OSI, part of Sage Bionetworks). Reassuringly, the analysis found that having NF does not appear to increase either the risk of COVID infection rates nor the risk of developing severe complications.

Gareth Evans, MD, chair of the U.K.'s nationally funded NF2-related schwannomatosis and schwannomatosis service at the University of Manchester, explored the potential impact of the new NF2 and SWN diagnostic criteria, and genetic testing through a case study of a patient with a solitary schwannoma. Because many of the diagnostic criteria include the presence of at least two tumors, a patient with one tumor will need additional evidence and testing for a diagnosis. Dr. Evans reported the prevalence of schwannoma-predisposition genes in people under 25 years old presenting with an apparently solitary schwannoma. Exon sequencing of *NF2*, *SMARCB1*, and *LZTR1* in these patients revealed that 19% of those in this cohort of 157 had a pathogenic variant in *NF2*, with 14% being mosaic. An *LZTR1* variant was found in 6%, *SMARCB1* in 4%, and no variant was detected in 70%.

Finally, the case conference portion of the program presented three case histories involving cutaneous neurofibroma. The cases were presented by **Carlos Romo, MD**, assistant professor at Johns Hopkins. Expert panel discussants included **Dr. Wolkenstein, Dr. Blakeley, Rox Anderson, MD**, a dermatologist and laser treatment researcher at Massachusetts General Hospital, and **Michelle Manahan, MD**, a plastic and reconstructive surgeon at Johns Hopkins University.

Emerging from the discussion were observations that cutaneous, subcutaneous, plexiform, and paraspinal tumors, while histologically similar, have different severities and prognoses, a fact that should be clearly communicated to the patient or parent. The panel discussed options other than electrodesiccation or surgical approaches for removing cutaneous neurofibromas, including innovative laser techniques. Developing clinical trials and potential treatments for cNF hold promise, the panel stated, but must confront difficulties with quantifying tumor burden, defining the goal (prevention or removal), and considering whether to use systemic or topical drugs.

OPENING KEYNOTE AND NEW OPPORTUNITIES

The official kick-off of the 2022 Children's Tumor Foundation NF Conference was a keynote given by **Nevan Krogan, PhD**, professor of cellular and molecular pharmacology at the University of California, San Francisco (UCSF). Dr. Krogan's scientific vision is to integrate data from various domains of genetics, biology, and proteomics to define new molecular networks that better describe diseases. The idea is that most diseases are not monogenic (caused by a pathogenic variant in one gene, i.e., *NF1* or *NF2*) but involve other key mutations, which need to be considered. This complex network uncovers previously unknown targets to exploit for drug discovery. Krogan's lab has tested this approach successfully by identifying new targets for breast, head, and neck cancer and applying the platform's power to interpret other cancer mutations. This approach to data integration was taken to combat SARS-CoV-2 infections and could be applied to NF and uncover new treatments or therapies.

At the end of his presentation, a key message was that pivotal discoveries are made only by collaborating and sharing data with no restrictions. The current incentive system for medical research is competitive in nature and self-restrictive. This precludes others from participating with new ideas, slowing down the collaboration process and limiting the number of solutions that could solve the problem.

The silver lining for COVID-19 was that it showed the world that if personal interests, bureaucratic issues, or regulatory hurdles are removed, collaboration can run at full speed and progress can be very fast. If it took only nine months to approve an emergency vaccine for COVID-19, why can 't we have the same output for other diseases? Why can't a network of researchers collaborate in the same way to solve cancer or NF or any other disease?

Opportunities for the Scientific Community in Basic and Clinical Science

Intending to incentivize collaboration, the conference co-chairs, **Thomas De Raedt, PhD**, and **Laura Papi, MD, PhD**, presented four opportunities after Dr. Krogan's talk to the scientific community. The session aimed at engaging the audience in active discussion and vote on the most appealing topic. CTF would then work to organize a follow-up workshop-style gathering focused on the opportunity that received the most votes. The four topics were:

1. State of the art preclinical testing
2. An NF cBioPortal instance: improving access to published data
3. Leveraging and learning from external consortia and networks
4. Artificial intelligence and machine learning in clinical care and research

A speaker introduced each topic and provided examples of other communities that created similar collaborations with clear benefits. At the end of the conference, opportunity number three won the most votes, reflecting an interest in creating a framework for successful collaboration by following other scientific communities' footprints.

Opportunities for the NF Community: Clinical Research

Laura Papi, MD, PhD, moderated the session. Her work is on the genetics of inherited tumor predisposition syndromes such as *NF2*-related schwannomatosis (NF2), schwannomatosis, and genetic predisposition to breast and colon cancers. Dr. Papi and her team are currently exploring the role of genetic modifiers in schwannomatosis.

Georgia Chenevix-Trench, PhD, chief of the cancer genetics lab at Queensland Institute of Medical Research-Berghofer, Brisbane, Australia, presented "CIMBA: Consortium of Investigators of Modifiers of BRCA1/2." With nearly 90 participating centers worldwide, CIMBA has collected a large number of samples with associated family history, DNA, pathology, survival data, and clinical history. It used genome-wide association studies (GWAS) and genotyping to search for candidate modifiers of breast and ovarian cancer in multiple-case families with BRCA1 or BRCA2. Two variants were found to influence breast cancer risk in BRCA1, and three variants were associated with breast cancer risk in BRCA2, which could influence medical management. Dr. Chevenix-Trench discussed how a similar approach might help explain the variable penetrance of NF and lead to identifying genetic biomarkers that may indicate the need for more frequent screening for those at higher risk. In the following months, CTF will work with the group of researchers who showed interest in creating a similar framework in NF to assess the next steps.

Eugene Jon Koay, MD, PhD, presented "Applications of Machine Learning and Radiomics for Pancreatic Cancer: Early Detection and Therapeutic Interventions." Dr. Koay is a physician-scientist at the University of Texas MD Anderson Cancer Center, where he leads the Cancer Physics and Engineering Laboratory Center. He discussed using artificial intelligence (AI) systems with image analysis to establish mathematical models in pancreatic cancer. These models could be applied to identify patient-specific parameters to enable early detection, predict treatment response to improve outcomes in this and other cancers, and provide a roadmap that NF researchers could follow. He described how his group uses the physical properties of the tumor revealed by imaging to use features such as morphology, cell proliferation and migration ratios, and perfusion defects in developing algorithms to predict tumor biology. This approach enables early detection and personalized treatments. The National Cancer Institute (NCI) Division of Cancer Prevention is building an image repository for team data science that can be used to build such algorithms.

A panel discussion with **Brigitte Widemann, MD,** National Cancer Institute; **Gareth Evans, MD,** University of Manchester, UK; and **Michael Fisher, MD,** Children's Hospital of Philadelphia, brought out the need to increase data sharing and aggregate information from biorepositories, both image and tissue, to have annotated samples for meaningful AI analysis.

KEYNOTE #2 AND TUMOR ATLAS SESSION

Imagine you could navigate and explore tumors the same way you explore google earth, sitting in front of your computer just moving and clicking around with your mouse. Imagine you could zoom in, visualize the most miniatured features, and see the connections between different elements and cells the same way you check countries, cities, and the roads that connect one place to another. The lab of **Sandro Santagata, MD, PhD**, Harvard University, has built visual maps of tumors that can be explored like Google Maps, at different scales and with a lot of information that describes how these complex tissues and cell networks function. Dr. Santagata explained that the tumor maps are not yet at the Google Earth level, but rather at the level of the first attempts at drawing an earth map back in the 15th century. Even still, the sophistication of such a great tool requires many researchers' work, open sharing of data, and extensive collaboration.
Taking this tool to the next level, the group is now implementing a 3D map that will allow the use of multiplexed tissue imaging to reveal the spatial biology of cancer. This will be obtained by layering different maps on the same spatial region. With these maps, researchers can uncover responses to treatment, predict outcomes, and better define the basic biology of tumors. Each layer is represented by a different data type (WGS, RNAseq, proteomic, metabolomic, etc.) that can be explored, analyzed, and connected with clinical features and outcomes, constituting a powerful tool to interpret complex interactions. The future is training pathologists and operating room personnel to collect tissue in a way that preserves its characteristics. Standard protocols must be defined for tissue procurement that must be followed by all who wish to collaborate and contribute their data to the atlas.

Following the inspiring presentation of Dr. Santagata, **Steve Angus, PhD**, from Indiana University and **Kathrin Bernt, MD**, from Children's Hospital of Philadelphia co-chaired the session on the NF1 tumor atlas. This session dove deep into the latest basic science discoveries in NF1, highlighting the complexity of this disease across the multiple tumor manifestations it can develop.

The first speaker, **Niousha Ahmari, PhD**, post-doc in the lab of Dr. Nancy Ratner at Cincinnati Children's Hospital, reported on studies highlighting the effect of SHP2 inhibitors, a class of compounds that increase the immune response in NF1 tumors. Previous MEK and SHP2 combo studies in mice showed no additive or synergistic effect of the two mechanisms, reporting no substantial difference in using single agents or the combination on tumor volume. Dissecting the mechanism of action, Dr. Ahmari showed evidence that tumors treated with SHP2 inhibitors significantly increased the accumulation of some T cells. T cells are part of the immune system and help protect the body from infection; when appropriately activated, T cells are effective in fighting cancer. In NF1 plexiforms, this effect could be exploited in combination

with immunotherapy as a strategy to activate T-cells to attack and shrink the neurofibromas.

Cutaneous Neurofibromas (cNF) are the most common NF1 tumor with 95% penetrance and a variable phenotype in patients. The lab of **Eduard Serra, PhD**, at Germans Trias i Pujol Research Institute (IGTP) in Barcelona, Spain, has studied the cellular mechanisms of cNF for years, unraveling critical effects that could be used to combat these tumors. In his report this year, the researchers learned that Schwann cells, the cells from which cNF develops, require a close interaction of different cell types to develop and proliferate cNF. Having reproduced such effects in the lab using cell co-cultures, they also identified a critical mechanism that could be disrupted, cause cell death, and reduce proliferation. Co-treatment of Ogerin, a small molecule inhibitor of GPR68 involved in the cAMP pathway, with selumetinib, an FDA-approved MEK inhibitor for the treatment of inoperable plexiform neurofibromas, induced the most striking effects in cell models of cNF. The results bode well for the future investigation of this new combination drug intervention in animal models of cNF that the group is planning to run.

David Gutmann, MD, PhD, from Washington University in St. Louis, reported interesting results that could impact NF1 optic pathway gliomas (OPG) treatment. OPG is the most common brain tumor in children with NF1. OPGs are low-grade gliomas that generally develop on the optic nerve and could affect vision and cause other morbidities. The latest research showed that a type of neuron called retinal ganglion cells that populate the optic nerve is involved in a series of complex mechanisms that regulate their excitability status and a cascade of events that ultimately sustain the growth of OPG tumors. The interruption of this mechanism of events using the drug Lamotrigine showed attenuation in OPG tumor progression, validating the researchers' hypothesis. Lastly, Dr. Gutmann reported an interesting observation that not all germline mutations are equal and that different *NF1* mutations have different effects on neuron-mediated glioma formation and growth. The development of OPG tumors could be specifically linked to the specific effect of that mutation on neurons.

GENE THERAPY SESSION

The gene therapy session began with an introductory talk by **Deeann Wallis, PhD**, from University of Alabama at Birmingham. Dr. Wallis presented an overview of the various gene therapy strategies at the DNA, RNA, and protein levels, and the pros and cons of each in the context of NF1.

Gary Brenner, MD, PhD, from Massachusetts General Hospital (MGH) presented a gene therapy strategy for schwannoma treatment that utilizes adeno-associated virus (AAV) delivery of the pro-apoptotic gene ASC. The AAV-ASC vector killed schwannoma cells very effectively with minimal toxicity, showed resolution of tumor-associated pain, and the efficacy was not altered by pre-existing AAV immunity.

Akiko Yoshinaga, PhD, from MGH presented a gene replacement approach for schwannoma therapy that involved the intratumoral injection of an AAV vector carrying the *NF2* gene. This vector restored merlin activity in cells lacking the *NF2* gene and suppressed schwannoma growth in mouse models, providing another potential gene therapy option for NF2.

The presentation by **Cameron Church** from University of Alabama at Birmingham focused on exon skipping using antisense oligonucleotides (ASO) as a therapeutic approach for NF1. Exon 52 of *NF1* gene was shown to be non-essential for *NF1* function and ASOs designed to skip mutated exon 52 restored *NF1* expression and Ras signaling. Thus, patients with mutations in *NF1* exon 52 can benefit from exon skipping therapy. The presentation by **Dr. Erik Westin, PhD**, also from University of Alabama at Birmingham, showed how delivery of nanoparticles encapsulating *NF1* cDNA into rat mammary gland tumors stopped tumor growth and also reduced tumor size, thus identifying *NF1* nanoparticles as another potential therapeutic strategy.

NF2 AND SCHWANNOMATOSIS SESSION

Long-Sheng Chang, PhD, from Nationwide Children's Hospital reported on "Orthotopic Xenograft Models and Potential Treatments for NF2-Deficient Meningiomas." In his presentation, Dr. Chang discussed the identification of eIF4A, an important target for tumor cell growth, that can be effectively inhibited by a new class of drugs showing potent growth-inhibitory activity on both NF1 and NF2 tumors. Initial experiments in NF1 MPNST and *NF2*-related SWN vestibular schwannoma and meningioma models (both in cells and animal models) showed promising activity for this class of compounds, reducing tumor growth and increasing DNA damage response and apoptosis, a method the body uses to get rid of unneeded or abnormal cells. These initial results still require more investigation to gather the necessary efficacy and safety evidence required by the FDA to initiate a clinical trial in humans.

Scott Plotkin, MD, PhD, from Massachusetts General Hospital, presented the revised diagnostic criteria and nomenclature for NF2 and schwannomatosis, a process involving worldwide experts in these diseases, including the patient community, and took about five years to complete. The previous criteria were established in 1995, and advancements in the knowledge of these diseases and the availability of genetic testing were two very important factors that triggered the scientific community to reassess the old criteria. With the updated nomenclature, schwannomatosis is now the recommended umbrella term for both NF2 and schwannomatosis since they share a genetic predisposition for schwannoma formation. Molecular analysis is clinically indicated for all patients suspected of schwannomatosis (except those with bilateral

vestibular schwannoma). The types of schwannomatosis are classified and referred to according to the specific gene variant. Neurofibromatosis type 2, or NF2 is now called "*NF2*-related schwannomatosis", and the general term for schwannomatosis is now specific to the gene variant identified, to include: *SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, schwannomatosis not otherwise specified (NOS), and schwannomatosis not elsewhere classified (NEC). Note that when referred to the gene, names are italicized, when referred to the gene product, or the protein produced by the gene, the names are not italicized

A retrospective study conducted by **Gareth Evans, MD,** from the University of Manchester, UK, of 266 *NF2*-related schwannomatosis (NF2) irradiated patients showed a significant increase in malignant progression or new primary malignancy developing in these patients. After years of anecdotal reports of malignant transformation for patients undergoing irradiation of their tumors, the study looked at data from 1969 until recent years to gather enough statistical significance to clarify this important evidence. Dr. Evans reported that the risk of developing malignancy or malignant progression in the *NF2-related SWN* population was 5-6%, a number that requires serious evaluation when considering such an approach, especially in the young population, as the risk is higher (up to 7.5%) in patients 25-years-old or younger.

Robert F. Hennigan, PhD, from Cincinnati Children's Hospital Medical Center, reported on recent advancements in understanding the NF2 protein function and its network of interactions with other molecules or proteins. This critical information allows us to gain insights into the consequences of its loss in developing *NF2*-related schwannomatosis (NF2). A protein called PIP2 regulates the tumor suppressor function of Merlin (NF2) and represents a mechanism to activate Merlin. This new interactor of the NF2 protein will be further investigated and could generate new hypotheses to enhance the tumor suppressor activity of Merlin. (https://doi.org/10.1101/2021.11.11.468247)

One of the hallmark features for all schwannomatoses, as well as NF1, is pain. Pain is highly variable among patients, puzzling researchers to understand the possible causes for such variation. **Sheila Mansouri, PhD**, from Princess Margaret Cancer Center, Toronto, Canada, presented the results of a study conducted to identify the molecular hallmarks of pain in schwannomatosis. This project, called **Synodos for Schwannomatosis**, analyzed a cohort of 165 tumors from 72 patients using a platform of genomic sequencing and analyses to correlate findings with clinical and molecular characteristics, uncover molecular mechanisms of pain in schwannomatosis and compare painful from non-painful tumor molecular profiles. The study unveiled that there are key genomic alterations in schwannomatosis and relative to non-syndromic schwannomatosis. It also showed key associations between pain and gender, tumor location, *LZTR1* mutation, and copy number variations. The significance of this study is that it will allow the testing of personalized therapeutic modalities for the treatment of pain depending on the patient's genetic makeup.

The session concluded with **Larry Sherman, PhD**, from Oregon Health and Science University, which reported on the protein SMARCB1 and its function in regulating the transcription of factors that directly mediate pain in schwannomatosis patients. In his findings, Dr. Sherman concluded that patients with *SMARCB1* compared to *LZTR1* mutations appear to experience different types of pain, likely through distinct mechanisms. Some schwannomatosis tumors secrete specific proteins called cytokines that are normally produced during inflammatory processes. Patients with *SMARCB1* mutations could benefit from pain relief by targeting IL6, a specific cytokine that plays a critical role in pain generation or progression. Targeting other secreted proteins that are common to Schwann cells could also be beneficial for pain relief, and further research is warranted in this field to characterize this approach better.

KEYNOTE #3 AND IMMUNOTHERAPY SESSION

The immunotherapy session began with a keynote lecture by **John Maris, MD**, from Children's Hospital of Philadelphia. The first half of Dr. Maris's talk focused on the discovery of the cell surface protein GPC2 as an oncoprotein in neuroblastoma and how it can be targeted by immune-based therapies such as antibody-drug conjugates and chimeric antigenic receptor (CAR) T cells. Both methods have shown strong efficacy with minimal toxicity in preclinical studies and have potential for development into clinical trials. Dr. Maris subsequently presented a novel strategy to recognize and target oncogenic proteins that are inside cancer cells and are typically not targetable. A new type of engineered CAR T cells called peptide-centric CARs (PC-CAR) were developed specifically to recognize a peptide from the *PHOX2B* gene implicated in neuroblastoma, and showed potent tumor killing. This technology has potential to significantly expand the immunotherapy field and make it available for more patients.

Antonio Iavarone, MD, from Columbia University Medical Center highlighted the differences in the tumor microenvironment of NF1 gliomas. He presented evidence for the presence of a low grade NF1 glioma subgroup that are 'high immune' type characterized by increased T lymphocytes, neoantigens, and other immune signatures. This category of low-grade glioma are potentially good candidates for immunotherapy.

KEYNOTE #4 AND PAIN SESSION

David Pang, MD from Guys' and St Thomas' Hospital NHS Trust, UK, gave a keynote lecture on NF and long term pain, highlighting the various receptors and biological pathways that are known to be involved in pain. He discussed how these receptors are being studied for NF and how pain can be influenced not only by these

biological pathways, but also psychological and social factors. NF pain could fit into a wider category of pain state called central sensitization state, whereby the pain's signaling is a hyperactive mode, and pain signals are being turned on despite the fact that no real injury exists.

Indeed, such hypersensitivity in *NF1* was also an important teaching of a talk by **Namrata Raut, PhD**, Cincinnati Children's Hospital, who demonstrated how *NF1* depletion in mice Schwann cells affects pain signaling independently from the presence of a tumor.

Frank Buono, PHD, of the Yale School of Medicine presented an ongoing trial co-funded by CTF which involves the use of the iCanCope mobile app as a tool to monitor and manage NF1-related pain through cognitive-behavioral therapy and mind-body alternative approaches. Such a tool could also find applications in NF2 and non-*NF2*-schwannomatosis pain.

A presentation on an ongoing clinical trial at Massachusetts General Hospital for pain in non-*NF2*-schwannomatosis by Jennifer Da highlighted the necessity to involve many different centers in order to reach a meaningful number of patients, as well as the need for deeper involvement of the patients in the design of such trials.

Lastly, **Angelica Sandstrom, PhD**, Massachusetts General Hospital, discussed the various brain imaging techniques that could be applied to study NF pain.

CLINICAL PLATFORM SESSION

Scott Plotkin, MD, PhD, from Massachusetts General Hospital provided interim results of brigatinib, a ALK tyrosine kinase inhibitor, in 20 *NF2*-related SWN patients with progressive tumors enrolled in the INTUITT-NF2 platform trial. Tumor shrinkage (>20% reduction in volume) was seen in 18% of 88 tumors. There was also a reduction in the growth rate of some tumors post-treatment, especially seen in non-vestibular schwannomas and meningiomas.
To optimize the accuracy and consistency of volumetric measure of optic pathway gliomas (OPG) between institutions and MRI manufacturers, a multi-center study using Quantitative Image Analysis in NF1-OPG was presented by **Robert Avery, DO**, from Children's Hospital of Philadelphia. The goal of this analysis will be to use automated volumetric MRI analysis to identify patients at low-risk of vision loss OPGs from patients at high risk of vision loss to guide clinical care and therapeutic clinical trials.

Amy Armstrong, MD, from Washington University provided a review of the phase 2 trial using cabozantinib for the treatment of NF1-associated progressive, clinically significant or inoperable plexiform neurofibroma in children. Of 21 patients, two (9.5%) showed a partial response of cabozantinib, and eight patients with progressive plexiforms before the study had stability of their plexiforms while on the trial. The researchers indicate that this may be a viable option for patients in cases where MEK inhibitors are not effective or tolerated.

A retrospective study looking at children on a selumetinib clinical trial for inoperable plexiform neurofibroma was provided by **Andrea Gross, MD** of the National Cancer Institute, (NCI). Of 49 evaluated children in the study, 33 (67%) had scoliosis and 38% of those had worsening of spine curvature while on treatment. Of seven subjects who had a spinal fusion during treatment, all had a large paraspinal plexiform with a majority having stable or partial response of the large adjacent plexiform neurofibroma during selumetinib treatment. The study did not support that treatment with selumetinib prevents the progression of scoliosis, even in patients with plexiforms that were responsive to selumetinib. However, given the limited numbers and methodology of the study, more investigation will be required to confirm these findings.

Pam Wolters, PhD, from National Institutes of Health discussed patient-reported outcome (PRO) measures of the phase II SPRINT trial to document the long-term clinical benefit of selumetinib in children with NF1 and inoperable plexiform neurofibromas. In a previous study, of 50 children on selumetinib for one year, 68% had partial response of their plexiform and a majority of these reported improvement in PRO measures including pain intensity, pain interference, and quality of life. The current study evaluates whether the PRO gains continued after the first year. The study found significant improvements in tumor pain intensity, pain interference, and quality of life that persisted over four years. Looking at qualitative data in 21 patients, a vast majority of children and their parents reported positive changes, especially with improved function, improved appearance, and decreased pain.

Longitudinal analysis of whole-body MRI (WBMRI) in NF1 was provided by **Eva Dombi, MD**, from the National Cancer Institute (NCI). Seventy-five patients enrolled in the NCI NF1 Natural History study were included in the analysis. At baseline, 71 of patients (95%) had plexiform neurofibroma involvement in at least one body region. Over time, an increase in tumor involvement was seen in 29 patients (39%), and 15 patients (20%) had neurofibroma burden regression. Patients with an increase in tumor involvement tended to be younger compared to those without an increase. Twenty-two patients developed new areas of tumor in previously unaffected body regions which were either distinct nodular lesions or nodular areas along major nerves, but the development of new bulky plexiform neurofibromas was not seen. It is important to note that the NCI study group was not representative of the general NF1 population.

To read more about the NF Conference, go to **nfconference.org**