National Cancer Institute (NCI)
National Cancer Advisory Board (NCAB)
Subcommittee on Clinical Investigations

Gaithersburg Marriott Washingtonian Center
Gaithersburg, MD
11 June 2024
5:30–6:30 p.m. EDT

SUMMARY

Subcommittee Members

Dr. Nilofer S. Azad, Chair
Ms. Margaret Anne Anderson (absent)
Dr. Anna D. Barker
Dr. Howard J. Fingert
Dr. Christopher R. Friese
Dr. Amy B. Heimberger (absent)
Dr. Margaret Mooney, Executive Secretary
Dr. Ana Navas-Acien (absent)
Dr. Fred K. Tabung
Dr. Susan Thomas Vadaparampil (absent)
Dr. Ashani T. Weeraratna (absent)
Dr. Karen M. Winkfield

Other Participants

Dr. Chandrakanth Are, Board of Scientific Advisors (BSA)
Dr. Karen M. Basen-Engquist, BSA
Dr. John D. Carpten, Chair, NCAB
Dr. James H. Doroshow, NCI
Dr. H. Shelton Earp, BSA
Dr. Dorothy K. Hatsukami, BSA
Dr. Ana Maria Lopez, BSA
Ms. Anne Lubenow, NCI
Dr. Karen M. Mustian, BSA
Dr. W. Kimryn Rathmell, Director, NCI
Ms. Joy Wiszneauckas, NCI
Ms. Sally Paustian, The Scientific Consulting Group, Inc., Rapporteur

Welcome and Opening Remarks
Dr. Nilofer S. Azad, Professor of Oncology, Co-Director, Developmental Therapeutics Program, Co-Leader, Cancer Genetics and Epigenetics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University

Dr. Nilofer S. Azad, Subcommittee Chair, welcomed the participants to the NCAB Subcommittee on Clinical Investigations (Subcommittee) meeting. This Subcommittee is charged with providing feedback and oversight on clinical trials operated through NCI mechanisms. Dr. Azad commented that COVID-19 illuminated the need to conduct clinical trials more pragmatically to provide better enrollment and access, make the trials easier, and ensure that the budget goes further. These practical considerations make a difference in NCI's ability to open and enroll trials that represent the entire United States. Dr. Kimryn Rathmell, NCI Director, emphasized the need to deliver clinical knowledge to the right places and capture ideas while they are fresh.

New Effort/Model for Streamlining Clinical Trials—Pragmatica-Lung Trial
Dr. Margaret Mooney, Associate Director, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI

Dr. Margaret Mooney, Subcommittee Executive Secretary, provided an interim report on efforts to design a simpler pragmatic trial that can reach more patient communities while maintaining high data quality.

The NCI National Clinical Trials Network (NCTN) provides centralized support for trials focused on questions less likely to be studied commercially. A survey of key NCTN participants in 2022 showed that the highest levels of dissatisfaction were in the areas of enrollment of diverse populations and ensuring efficient activation and completion of trials. Funding also is at a level that does not compete favorably with industry trials.

The Pragmatica-Lung Treatment Trial uses a design that removes many barriers that prevent people from enrolling and provides ways to increase the diversity of participants. It was designed as an Investigational New Drug (IND) study for agents with known risk profiles and a new indication for non–small cell lung cancer (NSCLC). Pragmatica enrolls patients with advanced disease who have been previously treated and randomizes them to a standard-of-care treatment arm—which can be any approved standard of care chosen by the physician that is accepted under the National Comprehensive Cancer Network (NCCN) Guidelines or is U.S. Food and Drug Administration (FDA)–approved for advanced NSCLC—or an "experimental" treatment arm in which they are treated with a new combination of ramucirumab and pembrolizumab, provided by industry partners Eli Lilly & Co. and Merck. This study is based on a previous NCTN randomized phase 2 trial (S1800A) led by the SWOG NCTN Group that showed a trend toward a survival advantage with this drug combination.

The simplified trial design included reduced data collection and a primary endpoint of overall survival. Because the risk profile of these drugs was already well known, only streamlined toxicity data were collected. Allowing physicians to pick the standard of care broadened eligibility.

The timeline from when the proposal was first sent to the NCI Thoracic Malignancy Steering Committee for review to activation of the trial was 200 days (compared with the maximum phase 3 trial timeline of 540 days), and the protocol document was much shorter than usual. Concentrated efforts were made to implement a recruitment and retention plan, and a remote consent option instituted in response to COVID-19 was maintained as regular procedure for this trial. The informed consent document is also much shorter than usual. The launch of the trial was coordinated with a national and local communications plan, extensive patient retention plans, and patient educational materials. The trial target accrual goal was 700 patients within 24 months; 15 months into the trial, 72 percent of the target accrual goal had been accrued. An amendment to the study has been submitted that would increase the sample size to 800 patients, which would increase the power from 85 percent to 90 percent, with accrual still likely to complete within the timeline of 24 months.

Race and ethnicity of patients accrued is more diverse than the incidence by race and ethnicity shown in data collected by the Surveillance, Epidemiology, and End Results (SEER) Program for this cancer, showing that Pragmatica is achieving its goal of accruing a more diverse patient population. Although accrual of Hispanic/Latino patients is not as strong as accrual of patients of diverse races, percentages are close to those in SEER; the consent form already is available in Spanish, and further outreach efforts are being developed. This trial also has diverse accrual across ages, and rates of male and female participants are comparable to SEER incidence data. Although definitions of a "rural" location in the United States vary, about 20 percent of the patients accrued to the trial are considered to live in a rural location. Recruitment also is fairly evenly spread across NCI Community Oncology Research Program (NCORP) sites, NCTN Lead Academic Participating Sites (LAPS), and other rostered sites.

Discussion

When asked about next steps, Dr. Mooney explained that development of Pragmatica predated the Clinical Trials Investigation Unit, a partnership between NCI and the FDA to identify other areas in which this type of trial would be acceptable to the FDA for an IND trial evaluating new cancer treatments. Another trial in the adjuvant setting for patients with NSCLC that is IND-exempt is in

development with a similar design, and studies of other disease sites or duration of therapy could fit this approach. The FDA Oncology Center of Excellence (OCE) is supporting the "Project 5 in 5" that is a crowdsourcing initiative to identify five clinically relevant questions that could be answered through the use of pragmatic trials using FDA-approved oncology therapies over the next 5 years. Dr. Azar suggested involving task force leadership of the NCTN Groups and NCI Disease-Specific Steering Committees, who might be particularly well suited to identifying appropriate tumor types for study.

When asked what might account for the success in diverse recruitment, Dr. Mooney commented that NCI and NIH have worked for many years to improve diverse recruitment. Pragmatica built on those ongoing efforts to broaden eligibility criteria in line with recommendations from the American Society of Clinical Oncology, Friends of Cancer Research, and the FDA. The ability of physicians to choose the standard of care treatment made recruitment easier, and the recruitment and retention plan was emphasized. The advocate community also was involved, and the trial was publicized broadly. The streamlined data collection made participation easier for both patients and physicians, and telemedicine is being integrated.

Dr. Mooney clarified that demographic proportions of patients enrolled in NCTN trials have not been compared across different types of sites for this trial, but these differences generally have narrowed in the past 10 years, particularly given the need for academic centers as well as community sites to maintain diversity programs for grant funding. Data on the trajectory of improvement could be provided.

In response to a question about the cost of a trial per patient, Dr. Mooney explained that NCI NCTN has fixed rates based on trial complexity and IND status. Because this trial is under an IND—which is the highest funding level NCTN program provides—and the burden of participation on patient and research staff is much less, more sites might be willing to participate. This trial saves money in staff and physician time, which is particularly important given the difficulty of recruiting staff since the beginning of the COVID-19 pandemic. Dr. Mooney also commented that overall survival as an endpoint was a priority for the FDA for this study indication. Although cost savings for future versions of this trial cannot be predicted, Dr. Mooney noted that the FDA has proposed using other streamlined pathways for IND trials. Attendees noted that the time required to enroll patients in a trial affects survival rates.

In response to a question about competition with industry, Dr. Mooney explained that Eli Lilly & Co. and Merck were involved from the beginning of Pragmatica-Lung, which was based on the previous SWOG phase 2 trial for this drug combination.

When asked whether the interest level of the experimental arm should be considered a driving factor, Dr. Mooney agreed that an interesting research question is always a factor in trial success.

In response to a question about returning to patients later in the trial to collect more data such as quality-of-life data, Dr. Mooney explained that quality-of-life data must be collected throughout the course of the patient's enrollment on trial, and some patients do not survive long terms with advanced cancer and thus cannot provide data later. A pragmatic trial requires a trade-off in reducing data collection, and researchers must consider when collecting additional data is necessary. Subcommittee members pointed out that the previous phase 2 trial was less diverse, so that trial could not collect as much information on how these agents affected diverse patient populations.

Dr. Azar suggested that NCI could anticipate exciting agents that could be approved in the next few years and make plans for trials.

Dr. Mooney commented that NCTN precision medicine trials have used centralized laboratories to reduce turnaround times for patient participation when a biomarker is required for patient enrollment. Although NCI does not have significant data on how many participants leave trial because of long screening times,

staggered start times may be appropriate for some trials, and recruitment and retention plans were emphasized in Pragmatica-Lung.

Adjournment

Dr. Azad thanked the participants and adjourned the meeting at 6:31 p.m. EDT.

Dr. Nilofer S. Azad Chair	Date	Dr. Margaret Mooney Executive Secretary	Date