WM-NET: A NEW SOLUTION TO THE CLINICAL TRIAL CHALLENGES IN WM

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Becoming a participant in a clinical trial is a decision of utmost importance. After signing the consent form, the patient becomes a "participant," and the treating doctor becomes an "investigator." The relationship, therefore, changes to some degree. The investigator still acts and reacts, having the participant's best interest at hand, as is usually done between a physician and a patient. However, the actions and reactions in a clinical trial are delineated and guided by a protocol, or plan, guaranteeing that all participants be treated alike in a way that can be reproduced and shared with the rest of the world once the clinical trial results are published.

One of the purposes of a clinical trial is to evaluate a new agent or combination of agents that might (or might not) be safe and effective in treating a disease. Most of the time, previous laboratory or clinical studies using these investigational agents provide a preliminary, reasonable signal of efficacy that prompts our interest. However, there are still multiple unknowns. We do not know how effective the treatment is going to be. We do not know if an unknown side effect will be observed. Despite these unknowns, clinical trials are the most important way to advance the medical field. Without clinical trial participation, developing now-standard agents such as rituximab, bendamustine, proteasome inhibitors, BTK inhibitors, or BCL2 antagonists would have been impossible.

Clinical trial participants are usually "poked and probed" more often, as complete data are required to understand how the study treatment is benefiting (or not) the participant. Given these requirements and unknowns, some patients are not interested in participating in clinical trials, which is understandable. It is essential to note that the decision to participate in a clinical trial should be made after careful consideration of the pros and cons of standard approaches and with the understanding that participation is purely voluntary and can be stopped at any time.

Waldenström macroglobulinemia (WM) poses several challenges for developing clinical trials. As all of you know, WM is a rare disease, with a prevalence of less than 50,000 individuals yearly in the United States. Additionally, most WM patients are still treated in community health care settings with little or no knowledge of clinical trials. On the other hand, multiple clinical trials may be running concurrently and competing for the already rare patient who is a candidate for a clinical trial. An additional obstacle is that clinical trials are typically offered at single institutions, representing a high degree of travel, time, and financial commitment from participants.

Recently, a patient with WM came to see me in clinic. The patient was diagnosed 20 years ago and had received multiple lines of therapy. The disease had been well controlled on a BTK inhibitor for several years, but now the patient presented with evidence of disease progression causing fatigue and other symptoms. Given the extensive history of previous therapies, we discussed the limited treatment options available. We focused the discussion

Dr. Steven Treon, Newton Guerin, Dr. Tom Hoffmann, Dr. Jorge Castillo at the Cambridge, MA, meeting of the WM-NET.

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on clinical trials; this patient would have been an ideal candidate. Unfortunately, the patient felt a clinical trial in Boston would be too demanding. The patient lived alone and depended on friends for transportation. The trial required lab checks two days in a row for a few weeks, meaning the patient had to stay overnight in a hotel in Boston. The study was out of the question. If only a clinical trial were available closer to home.

At Dana-Farber Cancer Institute (DFCI), we have devised a way to address, at least in part, the issues mentioned above: the creation of WM-NET, a United States-based think tank aimed at designing and executing scientifically driven clinical trials and research projects to improve the lives of WM patients. We would start by convening a collaborative group of practicing clinician-researchers who can identify critical clinical questions and design studies to answer them. This network of clinical investigators would facilitate a more rapid translation of study results into practice. Additionally, a committed group of like-minded clinical investigators with a sustainable infrastructure to share information would allow for faster patient accrual into trials, facilitate bringing innovative trials closer to patients, encourage the participation of underrepresented populations, and provide leverage to negotiate with funding sources (such as pharmaceutical companies) to design clinically meaningful trials.

With the help of several strategic partners, such as the IWMF, and donors, such as the Brettschneider Family Fund, the Kaplan Family Fund, the Kissam Family Fund, the Siegel Family Fund, and the WMR Fund, we were able to secure funding to run WM-NET for five years. Over the following years, it is expected that WM-NET will activate clinical trials concurrently in multiple centers, accelerating

WM-NET current participating facilities

the access to novel agents. WM-NET will also be advised by the patient community and represented by members of the IWMF and by WM specialists outside of the United States.

In October 2023, clinician-researchers from 17 institutions gathered for the first WM-NET meeting in Cambridge, Massachusetts. During this three-day event, we discussed unmet needs in clinical trials, and different network members presented several innovative clinical trial concepts. The excitement for this initiative was evident. The highest interest was in developing limited-duration clinical trials using agents with novel mechanisms of action. The clinical trials should include cutting-edge genomic testing, biobanking, and quality-of-life assessments.

At the conclusion of the event, it was evident that much work is still needed, but the first WM-NET meeting was a decisive step in the right direction.

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