HIGHLIGHTS AND KEY TAKEAWAYS FROM THE 2021 MPN ROUNDTABLE

MPN RESEARCH FOUNDATION
CHANGE YOUR PROGNOSIS

INTRODUCTION

In September 2019, the Myeloproliferative Neoplasm (MPN) Research Foundation (MPNRF) held a public, externally-led Patient-Focused Drug Development meeting. The objective was to capture specific needs from patients with MPNs and provide them with a forum to describe the impact of their disease, its associated symptoms and the burden of their disease on daily life. Additionally, patients provided their insights regarding current and emerging treatment options. The resultant *"The Voice of the Patient Report for Myeloproliferative Neoplasms"* was published in October 2021, which captured these findings.[1]

Subsequently, MPNRF hosted a two-day virtual roundtable with thought leaders in the field to further examine issues relevant to the MPN community, including disease detection and developing patient-centered clinical endpoints. This article highlights disease-specific background information, unmet needs identified in *The Voice of the Patient* Report, and key takeaways from portions of each day of the roundtable that may help to address unmet needs for patients with MPNs.

DAY 1 HIGHLIGHTS: OPPORTUNITIES FOR THE EARLY DETECTION OF MPN

The first day of the event featured presentations by the 2019 MPN Challenge recipients and introduced the 2021 Challenge recipients. As a highlight from day one, there was a keynote presentation titled, *Early Detection of MPN: Challenges and Opportunities*, led by Kelly Bolton, M.D., Ph.D., an assistant professor in the Oncology Division at the Washington University School of Medicine at St. Louis. This presentation set the stage for key areas of discussion during the second day roundtable panel discussions. Dr. Bolton focused on addressing the current use of assessment tools for early detection coupled with identifying patients at risk for developing MPNs and commented on the availability of safe and effective treatment options.

MPNs are chronic, progressive, rare blood cancers characterized by an overproduction of platelets, red blood cells or white blood cells, or increased bone marrow fibrosis. MPNs are classified into three subgroups: essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF). MPNs and some other hematologic malignancies can occur after expansion of mutant stem cell populations in a process called clonal hematopoiesis (CH). These mutant stem cells harbor somatic mutations in genes normally involved in regulating cell growth

KEY TAKEAWAYS

- Early identification of patients who are at high risk for developing myeloproliferative neoplasms (MPNs) was cited as a clinical need.
  - Early detection of clonal hematopoiesis, a precursor to developing MPNs, is possible using next-generation sequencing and blood count measurement.
- Clinicians noted a need for identifying high-risk populations (e.g., patients with primary solid tumors, especially breast cancer, patients receiving chemotherapy treatment and patients who have comorbidities such as cardiovascular disease and a history of thrombotic events). Identifying certain high-risk mutations in blood samples may also help with early detection of patients at risk for developing MPNs.
- There is a need for novel treatment options in the MPN treatment landscape to address the limitations of current FDA-approved treatment options.
  - Curative treatment options such as mutant stem cell directed therapy are needed, which is already a focus of interest for research and development. Clinicians need better tools to assess the development and expansion of malignant stem cell populations.
  - The clinical development of novel treatment options that target inflammation was cited as a viable future treatment approach in the MPN landscape.
  - Treatment should begin earlier in the disease process.
- Commonly used end points of total symptom score and spleen volume reduction in clinical trials for patients with MPNs could be expanded to include patient-focused outcome measures or modified to use different cutoff values, to help assess the potential clinical benefit of interventions.
  - Future clinical trial designs may benefit from incorporating several patient-centric end points, including fatigue, overall survival and progression-free survival in the myelofibrosis population and changes in blood counts and thrombotic event incidence for patients with essential thrombocythemia and polycythemia vera. Additional research is needed to understand the prognostic relevance of bone marrow fibrosis and mutant allele burden in patients with MPNs.

and proliferation (e.g., Janus kinase 2 [*JAK2*]), which result in abnormal activity of the encoded proteins (e.g., JAK2). The mutated cells exhibit increased proliferation and differentiation, cause inflammation and, over time, may lead to development of blood cancers such as MPNs. Harboring mutations in high-risk genes such as *TP53* or *IDH*, or having multiple mutations in high-risk genes, can confer a greater than 20-fold increased risk for blood cancer development. As there may be a several decades-long delay between the occurrence of CH and the development of MPNs, early detection of CH in patients at high risk for developing MPNs offers an important opportunity for early diagnosis, treatment initiation and improving health outcomes.

Four general requirements are necessary for effective cancer screening, and they are applicable to MPNs. First, proven and safe tests are needed to detect a pre-disease stage. Dr. Bolton noted that specific MPN-associated driver mutations can be detected by next-generation sequencing in blood samples from asymptomatic patients with CH. Some patients with CH, particularly those who harbor *JAK2* driver mutations, may have slight elevations in hemoglobin levels and platelet count, so obtaining blood counts may help identify patients at risk of disease.

Second, a latent or early symptomatic stage should be recognizable. As noted above, often a long latent stage between CH and the development of MPNs exists, but as a clinical challenge, patients with CH or early stages of MPNs may be asymptomatic.

Third, enough patients with latent disease must progress to symptomatic disease in order to design effective screening and intervention strategies. As MPNs are relatively rare and the absolute risk of a patient developing the disease is low, it is important to identify those at the highest risk of developing the disease. Patients with primary solid tumors (e.g., breast cancer) who are undergoing cytotoxic chemotherapy may be at increased risk of developing MPNs due to chemotherapy-related induction of secondary MPNs. For some patients with breast cancer who have the highest absolute risk of developing MPNs or other blood cancers, delaying chemotherapy could potentially decrease the incidence of these secondary cancers and improve patient outcomes. The development of clinical risk assessment tools, which could include individual risk factors (e.g., presence of cardiovascular disease or thrombosis) and combining specific mutational analyses, may be helpful to identify other patients who are at ultra-high risk of MPN development.

Finally, safe and effective treatments must be available for patients with the cancer in question. Dr. Bolton noted that for MPNs, currently available treatment options include JAK2 inhibitors, pegylated interferon alpha and hydroxyurea, but limitations with these treatments provide opportunities for continued research and development of novel strategies. Limited data are available to suggest that the JAK2 inhibitor, ruxolitinib, modifies the disease process. Therefore, MF disease progression after ruxolitinib treatment discontinuation is a significant unmet need. Additionally, although pegylated interferon has demonstrated efficacy for certain populations of patients with MPNs, a key limitation to its utility is the potential for intolerable treatment-related side effects (e.g., depression, fatigue, fever, nausea, vomiting).

Additional FDA-approved treatment options are needed, as current options are not able to completely control symptoms and prevent disease progression. The clinical development of novel treatment options that target inflammation was cited as a viable future treatment approach in the MPN landscape.

DAY 2 HIGHLIGHTS: ADVANCEMENTS IN DEFINING AND DEVELOPING PATIENT-FOCUSED CLINICAL END POINTS

The second day of the event included informative presentations summarizing the FDA guidance for incorporating patient-specific endpoints into clinical trials. Additionally, stakeholder discussions in both patient- and clinician-focused panels took place that aimed to identify potential future trial end points that are clinically meaningful to these patients and may help to address evidence gaps.

Starting in June 2018, the FDA published a four-part online guidance series for selection of patient-focused clinical outcome assessments, recognizing that patient input is an important part of drug development.[2] According to the FDA, clinical trial end points should adequately measure the clinical benefit of an intervention, which is defined as the positive, clinically meaningful effect of the intervention on how patients feel, function, and survive.

Landscape of Current MPN Clinical Trial End Points

John O. Mascarenhas, M.D., professor of medicine at the Icahn School of Medicine at Mount Sinai, described commonly used trial end points for patients with MPNs in a presentation titled, *Landscape of Current MPN Clinical End Points: A Gap Analysis*.

In patients with MF, several end points are included in clinical trials to assess the efficacy of investigational therapies regarding the improvement of common symptoms (e.g., anemia, splenomegaly [enlarged spleen]). A 50% or greater reduction in total symptom score (TSS) from baseline to a given prespecified timepoint in the trial is also a commonly used end point. The TSS is a validated 10-item instrument intended to measure patient-reported improvements in common MPN-associated symptoms. Clinical trials also often include measurements of transfusion independence and 35% or greater spleen volume

reduction (SVR). Splenomegaly is caused by extramedullary hematopoiesis (EMH), which is an accumulation of hematopoietic stem cells in organs outside of the bone marrow such as the spleen, and is common in patients with hematologic disorders such as MPNs. In patients with MF, high EMH activity and the presence of splenomegaly contribute to symptom severity and increased risk of complications (e.g., cardiovascular events, thrombosis). Therefore, SVR is thought to be a valid surrogate measure of disease and symptom control in clinical trials. Dr. Mascarenhas cited limitations with the commonly used SVR and TSS cutoff values; he noted that they may be too stringent and that less-pronounced changes may still lead to improvements in symptom burdens and quality of life for patients.

Whenever possible, future clinical trials should use overall survival (OS) as the primary end point, as OS is positively correlated with outcomes from several commonly used end points. Evidence from separate clinical trials demonstrated that patients who either achieved transfusion independence or greater than 50% SVR experienced a longer OS. The presence of bone marrow fibrosis (scarring), defined as abnormal deposition of reticulin and collagen-containing fibers in the bone marrow, is thought to contribute to MPN disease and symptom severity and may lead to poorer prognoses. High fibrosis grade indicates increased severity of fibrotic scarring. Fibrosis grade measurement is not yet considered to be a validated end point in clinical trials for patients with MPNs. In one study of imetelstat, a telomerase inhibitor, patients with a stable or improved fibrosis grade had a lower risk of death. Additional data are needed to elucidate the role of fibrosis in MPN pathogenesis and progression, and to determine whether decreased fibrosis severity leads to improved long-term patient outcomes.

ET and PV are heterogeneous diseases with uncertain prognoses and progression to MF. Specifically, patients with PV can have many causes of mortality such as thrombosis and leukemia. Compared with MF populations, fewer validated clinical trial end points, assessment tools and patient-focused outcomes exist for populations with ET and PV, especially those relating to thrombosis and progression. For example, the European LeukemiaNet (ELN) response criteria are commonly used in patients with PV; however, they are correlated with disease progression to MF and not thrombosis.

As a key area of needed development, potential trial end points to be explored for ET and PV populations can include blood counts and incidence of thrombotic events. Additionally, patients with high mutant allele burden (i.e., a high proportion of stem cells harboring MPN-associated driver mutations) generally have more severe symptoms and more aggressive disease. If new treatments are shown to decrease mutant allele burden compared with pretreatment levels and, as a result, delay or halt disease progression, this variable could be a valid surrogate measure of disease control.

CLINICIAN-FOCUSED PANEL ROUNDTABLE DISCUSSION: PRIORITIES FOR FUTURE MPN CLINICAL END POINTS

A clinician-focused roundtable explored key knowledge gaps and unmet needs, pros and cons of commonly measured clinical trial end points, and identified clinical outcomes that may be important to patients to include in future clinical trial designs. The panel included Dr. Mascarenhas; Ruben Mesa, M.D., UT Health San Antonio MD Anderson Cancer Center; Allison Moliterno, M.D., Johns Hopkins University Medical School; Catriona Jamieson, M.D., Ph.D., University of California, San Diego; Larry J. Bauer, R.N., M.S., Hyman, Phelps and McNamera, P.C. and Richard Winneker, Ph.D., Director of Scientific Strategies, MPNRF.

As echoed in Dr. Bolton's presentation on the previous day, panelists agreed that patients with MPNs should begin treatment earlier in the disease process instead of waiting for disease progression to occur. The ideal MPN care pathway should include strategies that are similar to those for patients with chronic myeloid leukemia who often begin treatment immediately after diagnosis and in whom molecular testing is used to guide decision-making.

Currently, no curative therapies exist for MPNs. Ideally, future therapies should improve both survival and patients' quality of life (i.e., how they feel and function). Clinicians stated that the availability of stem cell-directed therapy would be "game-changing" in the MPN treatment landscape. However, a key limitation to the development of this therapy was identified: panelists need better tools to understand how malignant stem cell populations develop and expand so that they may identify patients harboring high-risk molecular alterations soon after CH, in order to enable earlier MPN diagnosis and develop safe and effective treatments. Dr. Bolton had identified some potential strategies to address this unmet need in her presentation.

Regarding potential improvements in common clinical trial end points, a significant part of the discussion focused on the TSS and its use in conjunction with additional measures that could potentially be implemented as end points in future clinical trials. As Dr. Mascarenhas noted limitations with TSS in his presentation, panelists further supported that TSS should not be the only tool used in assessing symptom severity. They agreed that the cutoff value of 50% or more improvement is arbitrary, overly simplistic and does not capture the symptom improvements of each patient. For example, two patients may have the same TSS score, but a patient with a few very severe

symptoms can feel much worse than a patient with multiple minor symptoms. The TSS is a valuable and accurate tool that gives a patient the opportunity to provide information about their self-assessed symptom severity. Fatigue is the symptom that most commonly persists after treatment; therefore, patients might benefit from additional validated instruments for quantifying fatigue. The TSS should be used as a continuous variable and possibly integrated with other end points such as SVR and allele burden. In patients with MF who are being treated with fedratinib, clinicians should routinely monitor them for thiamine (vitamin B1) deficiency, and patients being treated with ruxolitinib should be monitored for John Cunningham virus reactivation as these adverse effects can cause or worsen symptoms.

Instead of OS, progression-free survival (PFS) was suggested as a primary end point with the rationale that OS is not an effective end point for most patients with chronic diseases such as MPNs. Identifying surrogate measures for estimating quality of life improvement and delaying or halting disease progression is a key area for the creation of additional end points in future trials. Potential surrogate end points include measuring bone marrow fibrosis or allele burden, but before these can be utilized, more validation studies are needed.

CONCLUSIONS

In addition to commonly used end points such as TSS and SVR, clinical trials for patients with MPNs should include other patient-focused end points that help to assess the clinical benefit of interventions. For patients with MF, fatigue, OS and PFS were among the panelists' suggested end points; for patients with ET, they identified platelet and white blood cell counts as potentially useful. Including allele burden and bone marrow fibrosis as trial end points may be clinically meaningful for patients with MPNs, but clinicians need better tools to understand how malignant stem cell populations develop and expand and how fibrosis contributes to progression and severity of MPNs. The uncertainty of disease progression concerns many patients with MPNs. Patients want to avoid disease progression, but question how it can be accurately measured in the context of clinical trials. Panelists expressed that patients with MPNs need new treatment options, especially curative ones, such as stem cell-directed therapy. Lastly, treatment also should begin earlier in the disease process. ■

REFERENCES

1. Voice of the Patient: a report on the first externally-led patient focused drug development meeting on myeloproliferative neoplasms (MPNs). MPN Research Foundation. Published November 18, 2021. Accessed January 6, 2022. https://www.mpnresearchfoundation.org/pfdd/
2. FDA patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making. The U.S. FDA website. Accessed January 6, 2022. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

MPN RESEARCH FOUNDATION
CHANGE YOUR PROGNOSIS