ELSEVIER

Blood 142 (2023) 3195–3197

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Assessment of Minimal Clinically Important Difference in Patient-Reported Myelofibrosis-Associated Symptoms Using an Anchor-Based Analysis Based on MANIFEST Arm 3 Data

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Background

Myelofibrosis (MF) is a life-threatening hematologic neoplasm that can arise as a primary condition or as a progression from polycythemia vera or essential thrombocythemia. The MF Symptom Assessment Form (MFSAF) v4.0 is a seven-item questionnaire that assesses symptom severity from the patients' (pts) perspective. Each item is rated on a scale from 0 (Absent) to 10 (Worst Imaginable). The MFSAF Total Symptom Score (TSS) ranges from 0 to 70, with higher scores indicating worse symptoms.

A ≥50% reduction in TSS (TSS50) is a commonly used binary endpoint in clinical trials. However, the clinical meaningfulness of the dichotomization of response at 50% cutoff across the spectrum of responses remains uncertain. The relevance of considering TSS as a continuous endpoint in MF studies is assessed here to capture the full spectrum of symptom changes, enabling a potentially more accurate assessment of treatment effects.

Pelabresib (CPI-0610) is an investigational oral small-molecule BET inhibitor, while the Janus kinase inhibitors (JAKis) ruxolitinib or fedratinib are the current standard of care for intermediate- or high-risk pts with MF.InArm 3 of the Phase 2 MANIFEST trial of JAKi treatment-naïve pts with MF treated with pelabresib and ruxolitinib, 56% achieved TSS50 response at Week (Wk) 24.

Aims

This anchor-based analysis aims to determine the minimal clinically important difference (MCID) of change in TSS as a continuous endpoint, based on data from JAKi treatment-naïve pts with MF treated with pelabresib and ruxolitinib, to better evaluate the incremental clinical benefit of treatment effects.

Methods

Data from Arm 3 of the MANIFEST Phase 2 study of treatment-naïve pts with MF treated with pelabresib combined with ruxolitinib were used (July 29, 2022 data cut). Anchor-based methods compare the change in a scale-based outcome measure with that of an established patient-reported outcome (PRO). These methods are commonly used to establish the MCID, defined as the smallest difference in score that pts consider beneficial. In this analysis, the Patient Global Impression of Change (PGIC), a seven-point scale reflecting overall improvement compared with baseline (BL), was used as the anchor PRO. On the PGIC, pts rated their change from 'very much improved' to 'very much worse' (Table 1).

The relationship between TSS changes (percentage and absolute) at Wk 24 and PGIC categories was examined using correlation and graphical analyses. Linear and quantile regressions were applied to assess the impact of a one-point difference in

PGIC score on TSS change at Wk 24, adjusting for BL TSS score. Only pts with available TSS and PGIC data at Wk 24 were included, with no imputation for missing values.

Results

In Arm 3 of the MANIFEST trial, 78 of 84 pts treated with pelabresib and ruxolitinib had complete TSS data and PGIC at Wk 24. At BL, mean TSS was 16.4 (SD=8.4), and median TSS was 15.5 (range 2.0-38.3). A -58.8% and -7.7 median percentage and absolute reduction in TSS at Wk 24 was observed, respectively. For PGIC at Wk 24 (Table 1), only six pts (7.7%) scored in the three worsening PGIC categories. Percentage and absolute changes in TSS, and the percentage TSS50 responders for each PGIC category are shown in Table 1.

Linear regression demonstrated that a one-category increase in PGIC (indicating worsening) corresponded to an 11.89% increase (95% CI 3.12-20.65) in TSS (indicating worsening) at Wk 24. The quantile regression estimate for this relationship was 11.36% (3.53-19.19). For absolute change at Wk 24, a one-category increase in PGIC resulted in a 1.67 (range 0.74-2.60) increase in mean TSS, with a 1.87 (range 0.62-3.12) increase in median TSS.

Conclusion

Assuming a one-category change in the seven-category PGIC represents a clinically meaningful difference, the analyses suggest that the MCID in TSS for JAKi treatment-naïve pts with MF could be approximately 11-12% for percentage change from BL and approximately 1.5-2 points for absolute change from BL. These findings provide valuable guidance for assessing treatment outcomes and evaluating symptom improvements' clinical significance in this patient population. Further exploration of these findings requires larger data sets, which will be addressed in the forthcoming Phase 3 MANIFEST-2 study evaluating pelabresib and ruxolitinib versus placebo and ruxolitinib in JAKi treatment-naïve pts with MF.

Disclosures Mesa: *Leukemia & Lymphoma Society:* Membership on an entity's Board of Directors or advisory committees; *PharmaEssentia:* Research Funding; *AbbVie, CTI, Incyte, Sierra:* Consultancy, Honoraria, Research Funding; *Blueprint, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Novartis:* Consultancy, Honoraria. **Gupta:** *Novartis, BMS Celgene, Sierra Oncology, AbbVie, Constellation Biopharma, Pfizer, GSK Pharma, CTI Biopharma:* Consultancy; *BMS, Celgene, Roche, Abb Vie, Pfizer, Sierra Oncology, CTI Biopharma:* Membership on an entity's Board of Directors or advisory committees; *Novartis, BMS Celgene, GSK:* Honoraria; *Novartis, BMS Celgene, SMP Oncology, AbbVie, Constellation Biopharma, Pfizer, GSK Pharma, CTI Biopharma:* Consultancy; *GSK:* Other: Travel to EHA 2023 for invited talk at GSK sponsored MPN education session ; *BMS Celgene, Roche, AbbVie, Pfizer, Sierra Oncology, CTI Biopharma, GSK:* Other: Participation on a Data Safety Monitoring Board or Advisory Board. **Mascarenhas:** *Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Janssen, Kartos Therapeutics, Merck, Novartis, PharmaEssentia, Roche; Participated in consulting or advisory committees - AbbVie, Bristol Myers Squibb, Celgene, Constellation Pharmac:* Research Funding; *Incyte, Novartis, Roche, Geron, GSK, Celgene/BMS, Kartos, AbbVie, Karyopharm, PharmaEssentia, Galecto, Imago, Sierra Oncology, Pfizer, MorphoSys, CTI Bio:* Consultancy; *Bristol Myers Squibb, Celgene, Constellation Pharmaceuticals/MorphoSys, CTI BioPharma, Galecto, Geron, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, PharmaEssentia, Prelude Therapeutics, Pfizer, Merck, Roche, AbbVie, Kartos:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AbbVie, Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Novartis, Janssen, Kartos Therapeutics, Merck, PharmaEssentia, Roche:* Research Funding; *GSK:* Honoraria; *AbbVie, CTI BioPharma Corp, a Sobi company, Geron, GlaxoSmithKline, Imago, Incyte, Kartos, Kayropharm, MorphoSys, Novartis, Pfizer, PharmaEssentia, Sierra:* Consultancy. **Hobbs:** *Regeneron:* Current holder of *stock options* in a privately-held company, Other: Gabriella's spouse is currently employed by Regeneron; *AbbVie:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *GSK:* Consultancy, Honoraria; *Protagonist:* Consultancy, Honoraria; *Cogent:* Consultancy, Honoraria; *CTI:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *MorphoSys:* Consultancy, Honoraria; *Incyte:* Research Funding. **Kiladjian:** *Incyte Corporation:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *AOP Orphan Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *AbbVie, AOP Health, Bristol-Myers Squibb, GlaxoSmithKline, Incyte, Novartis, Pharmaessentia.:* Consultancy. **Kann:** *MorphoSys AG:* Current Employment. **Colak:** *Constellation Pharmaceuticals, a MorphoSys Company:* Current Employment. **Harrison:** *CTI:* Honoraria, Speakers Bureau; *AOP:* Honoraria, Speakers Bureau; *GSK:* Honoraria, Speakers Bureau; *Morphosys:* Honoraria, Speakers Bureau; *Novartis:* Honoraria, Research Funding, Speakers Bureau; *BMS:* Honoraria, Speakers Bureau; *Galecto:* Honoraria, Speakers Bureau; *Abbvie:* Honoraria, Speakers Bureau. **Dey:** *Constellation Pharmaceuticals, a MorphoSys Company:* Current Employment.

https://doi.org/10.1182/blood-2023-179924

Table 1: Change in TSS at Week 24 for each PGIC category

PGIC at Week 24	N (%)	Mean (%) Change in TSS From Baseline	Median (%) Change in TSS From Baseline	Mean (Abs) Change in TSS From Baseline	Median (Abs) Change in TSS From Baseline	TSS50 Responders (% in PGIC Category)
Very Much Improved	18 (23.1)	–78.1	–78.5	–12.0	–11.4	16 (88.9)
Much Improved	25 (32.1)	–53.0	–59.2	–9.2	–8.9	16 (64.0)
Minimally Improved	14 (17.9)	–16.9	–26.0	–4.0	–3.8	5 (35.7)
No Change	15 (19.2)	–25.7	–30.0	–4.9	–4.9	5 (33.3)
Minimally Worse	4 (5.1)	–46.9	–53.3	–7.1	–8.6	2 (50.0)
Much Worse	2 (2.6)	–58.4	–58.4	–14.9	–14.9	1 (50.0)
Very Much Worse	0	-	-	-	-	0

Abs, absolute; PGIC, Patient Global Impression of Change; TSS, total symptom score; TSS50, ≥50% reduction in TSS at Week 24.

Figure 1