EUROPEAN HEMATOLOGY ASSOCIATION

EHA2021 VIRTUAL

EP1077

PELABRESIB (CPI-0610) IMPROVED ANEMIA ASSOCIATED WITH MYELOFIBROSIS: INTERIM RESULTS FROM MANIFEST PHASE 2 STUDY

Topic: 16. Myeloproliferative neoplasms - Clinical

Keywords: Anemia, Hemoglobin, Myelofibrosis, Ruxolitinib

Srdan Verstovsek[1], Marina Kremyanskaya[2], John Mascarenhas[2], Moshe Talpaz[3], Claire Harrison[4], Raajit Rampal[5], Andrea Patriarca[6], Vikas Gupta[7], Nikki Granacher[8], Tim Somervaille[9], Gary Schiller[10], Mark Drummond[11], Linda Foltz[12], Jonathan Lambert[13], Witold Prejzner[14], Gozde Colak[15], Patricia Keller[15], James Shao[15], Katarina Luptakova[15], Ronald Hoffman[2], Prithviraj Bose[1], Alessandro Vannucchi[16]

[1] The University of Texas, MD Anderson Cancer Center, Houston, United States
[2] Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, United States
[3] The University of Michigan, Rogel Cancer Center, Ann Arbor, United States
[4] Guy's and St Thomas' Hospital, London, United Kingdom
[5] Memorial Sloan Kettering Cancer Center, New York, United States
[6] Azienda Ospedaliero Universitaria Maggiore della Carità di Novara SCDU Ematologia, Novara, Italy
[7] Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada
[8] Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium
[9] Manchester Institute, The University of Manchester, Manchester, United Kingdom
[10] David Geffen School of Medicine at UCLA, Los Angeles, United States
[11] Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom
[12] University of British Columbia, St. Paul's Hospital, Vancouver, Canada
[13] University College London Hospitals NHS Foundation Trust, London, United Kingdom
[14] Department of Hematology and Transplantology Medical University of Gdansk, Gdansk, Poland
[15] Constellation Pharmaceuticals, Cambridge, United States
[16] Azienda Ospedaliero Universitaria Careggi, Firenze, Italy

Background: Pelabresib (CPI-0610), a first-in-class, oral, small-molecule inhibitor of bromodomain and extraterminal domain (BET) proteins, has the potential to promote disease-modifying activity through altered gene regulation of key oncogenic, fibrotic, and inflammatory factors in the clonal disease cells of origin in myelofibrosis (MF). Furthermore, pelabresib promotes maturation and ex vivo differentiation of erythroid progenitors (Mertz, ASH 2020). Many MF patients (pts) treated with ruxolitinib (rux) develop worsening anemia and may become red blood cell (RBC) transfusion-dependent (TD) which represents a significant unmet medical need. Here we report improvement of anemia in advanced MF pts as evidenced by achievement of RBC-transfusion independence (TI) in TD pts or sustained mean hemoglobin (Hgb) increase of ≥1.5g/dL for 12 wks in non-transfusion dependent (non-TD) pts.

Aims: Evaluation of pelabresib monotherapy or as add-on to rux in advanced MF pts.

Methods: MANIFEST is an ongoing, open-label Phase 2 study. In Arm 1, pts that were refractory, intolerant or ineligible for JAKi were treated with pelabresib monotherapy. A washout of ≥2 wks since last systemic MF therapy was required. In Arm 2, pts receiving rux but not deriving adequate benefit were treated with pelabresib add-on to rux. Pts are stratified to cohorts 1A and 2A if they were TD (receiving ≥6U RBCs/12 wks) and into cohorts 1B and 2B as non-TD if they did not meet TD criteria. Primary endpoint was achievement of TI ≥12 wks in TD cohorts; ≥35% spleen volume reduction at wk 24 in non-TD cohorts.

Results: As of 29 Sep 2020, 19 TD pts and 27 non-TD pts were treated in Arm 1 (monotherapy). 76% of pts had baseline Hgb <10g/dL (Median: 9, range: 6-15). Median number of prior therapies was 2 (1-6). Median time since last rux dose in non-TD cohort was 9.2 mo (range 0.5-46 mo). In TD cohort, 21% (3/14) of pts achieved TI (median duration of transfusion-free period: 44 wk, range 32-50). In non-TD cohort, mean Hgb increase ≥ 1.5 g/dL sustained over a 12-wk transfusion-free period was achieved by 59.1% (13/22) of pts among which only 1 pt received rux within 4 months of study entry, suggesting the increase in Hgb was not a consequence of rebound

due to rux discontinuation.

In Arm 2, 52 TD pts and 26 non-TD pts were treated with pelabresib as add-on to rux. 76% of pts had baseline Hgb <10g/dL (median: 9, range: 6-13). In TD cohort, 36% (13/36) of pts achieved TI (median duration of transfusion-free period: 39 wk, range 18-148). 17.4 % (4/23) of non-TD pts had mean Hgb increase ≥ 1.5 g/dL sustained over a 12-wks transfusion-free period.

In pts with an anemia response, the observed Hgb improvement or achievement of TI has been generally associated with an increase in reticulocyte count and/or increased CD71+ progenitor cells in the bone marrow, suggesting a positive pelabresib effect on erythroid differentiation.

Pelabresib was generally well tolerated. The most common treatment emergent adverse events include diarrhea (46%, ≥Gr3: 4%), thrombocytopenia (40%, ≥Gr3: 22%), nausea (36%, ≥Gr3: 2%), asthenic conditions (32%, ≥Gr3: 2%), respiratory tract infections (32%, ≥Gr3: 4%), dysgeusia (26%, ≥Gr3: 1%) and cough (25%, no ≥Gr3).

Image:

Table 1	Monotherapy Non-TD (1B)	Add-on to rux Non-TD (2B)	Monotherapy TD (1A)	Add-on to rux TD (2A)
Mean Hgb increase of ≥1.5 over 12 wks[1,2]	59.1% (13/22)	17.4% (4/23)	-	-
Achievement of TI ≥12 wks[3]	-	-	21% (3/14)	36% (13/36)

[1]Patients are evaluable if they received ≥12wks of treatment; baseline: the latest Hgb assessment prior to C1D1
[2]Post-baseline mean Hgb increase of at least 1.5g/dL is required for any 12 wks RBC transfusion free period
[3]Patients are evaluable for achievement of transfusion independent (TI) ≥12 wks if they have been on treatment for at least 24 weeks by the data cutoff date or if they have been on treatment for at least 12 weeks by the data cutoff day and have achieved the conversion or would have failed to achieve the conversion by week 24

Summary/Conclusion: Pelabresib monotherapy was associated with a mean increase in Hgb ≥ 1.5 g/dL in majority of non-TD pts and conversion of one-fifth of TD pts to TI in heavily pretreated MF pts in Arm 1. Addition of pelabresib to rux in Arm 2 pts with suboptimal response on stable doses of rux resulted in mean increase in Hgb ≥ 1.5 g/dL in 17% of non-TD pts and conversion to TI in more than one-third of TD pts.

Abstract Book Citations: Authors, Title, HemaSphere, 2021;5:(S2):pages. Abstract Book, DOI: http://dx.doi.org/10.1097/HS9.0000000000000566