ELSEVIER

Blood 142 (2023) 1828–1830

The 65th ASH Annual Meeting Abstracts

# POSTER ABSTRACTS

## 634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

### Oral Decitabine/Cedazuridine Is a Tolerable and Effective Ambulatory Regimen for Patients with Advanced Myeloproliferative Neoplasms

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**Background:** Treatment options are limited for patients (pts) with advanced myeloproliferative neoplasms (MPNs). Most pts become refractory to JAK2 inhibitor (JAKi) therapy by 3 years with subsequent survival of only 11-16 months.
Sequential treatment with chromatin-modifying agents including decitabine (D) can upregulate CXCR4 expression, correct abnormal trafficking of myelofibrosis (MF) stem cells, and eliminate *JAK2V617F+* MF stem and progenitor cells in preclinical models ( *Wang et al, Cancer Res 2019, Blood 2010).* Combination therapy with intravenous D and ruxolitinib (Rux) had a favorable effect on overall survival (OS) in a phase 2 study of MPN-accelerated/blast phase pts ( *Mascarenhas et al, Blood Adv 2020*) and prolonged survival in a cohort of DIPSS-plus high-risk MF pts ( *Bader et al, Leuk Res 2015*). Oral decitabine/cedazuridine (DC), therefore, represents an attractive ambulatory treatment option for pts with advanced MPNs.
**Methods:** We retrospectively reviewed the electronic health records of pts with advanced high-risk MF (AHR-MF) or MPN-accelerated phase (MPN-AP) seen at our institution that were treated with DC with or without a JAKi from 1/2021-7/2023. MPN-AP was defined by the presence of 10-19% blasts in peripheral blood/ bone marrow. AHR-MF was defined by the presence of 4-9% circulating blasts or 5-9% blasts in the bone marrow, and/or refractoriness to a JAKi.
**Results:** A total of 14 pts, 7 each with MPN-AP and AHR-MF, respectively received DC therapy (Table 1). Most pts (8/14 or 57%) were older than 75 years. All pts were classified as high risk/very high-risk (MIPPS70 plus v.2). Ten (71%) pts had one or more high molecular risk mutations ( *ASXL1, EZH2, SRSF2, IDH1/2, U2AF1*), with the most prevalent being *ASXL1* mutations in 8/14 (57%) pts. Other somatic mutations included *NF1, KRAS, NRAS, BRAF, GATA2, STAG2, DNMT3A and TET2* genes. Eight of the 14 pts (57%) had either an unfavorable or very high-risk karyotype (MIPSS70 plus v.2). Thirteen pts had previously failed JAKi therapy. The median number of cycles of DC therapy was 2 (range,1-6) and 4 (range,1-26) for MPN-AP and AHR-MF pts, respectively and 4/7 pts received a concurrent JAKi in each group. Two pts in AHR-MF cohort were successfully bridged to transplant. Two pts in the MPN-AP group discontinued treatment after cycle 1 due to neutropenic sepsis and progression to blast phase, respectively.
Among MPN-AP pts who received $\geq$ 2 cycles of DC, circulating blasts were reduced to $\leq$ 5% in 4/5 pts, normalization of thrombocytopenia and improvement in hemoglobin by $\geq$ 1.5 g/dl each occurred in 3/5 pts (Fig.1). In the AHR-MF cohort, 6/7 pts received $\geq$ 2 cycles of DC with elimination of circulating blasts in one pt. WBC and platelet count were effectively reduced in 4/4 and 2/2 pts with baseline WBC of >50x $10^3$/uL and platelet count >1000 x $10^3$/uL, respectively. Spleen size reduction was achieved in two pts with combination of DC + Rux who were previously refractory to a JAKi. One pt achieved complete resolution of palpable splenomegaly after 2 cycles of combination therapy.
The predominant treatment-related adverse event was neutropenic fever in three pts requiring hospitalization. DC cycle length was reduced from 5 to 3/28 days in 7/14 pts, which reduced the degree of therapy related neutropenia and anemia. Pts remained ambulatory during treatment except for hospitalizations related to neutropenic fever. With a median follow-up of 109 days (range, 28 days - 29 months), median OS has not been reached. Three pts in the MPN-AP cohort progressed to MPN-blast phase (BP), including two pts who only received one cycle of DC. Two pts with MPN-BP died after 28 and 68 days

of DC therapy, respectively. None of the AHR-MF pts progressed to MPN-AP/BP. The most durable response was observed in a pt who has received a total of 26 cycles of DC + Rux with stable disease for >2 years and loss of *BRAF* and *KRAS* mutations after 9 months of treatment.

**Conclusions:** DC therapy appears to be a well-tolerated and effective oral ambulatory regimen with clinically meaningful responses in elderly, transplant ineligible pts as well as a bridge to transplant in high-risk pts with advanced MPNs. The ease of outpatient administration significantly reduces pt treatment burdens and positively impacts their quality of life. These data provide a rationale for studying oral decitabine/cedazuridine +/- JAKi in a prospective manner, especially in pts with AHR-MF refractory to JAKi prior to evolution MPN-AP/BP.

**Disclosures Tremblay:** *Sierra Oncology:* Consultancy; *GSK:* Consultancy; *Cogent Biosciences:* Consultancy; *Astellas Pharma:* Research Funding; *Gilead:* Research Funding; *AbbVie:* Consultancy; *Novartis:* Consultancy; *CTI Biopharma:* Consultancy, Research Funding. **Mascarenhas:** *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; *Incyte, Novartis, Roche, Geron, GSK, Celgene/BMS, Kartos, AbbVie, Karyopharm, PharmaEssentia, Galecto, Imago, Sierra Oncology, Pfizer, MorphoSys, CTI Bio:* Consultancy; *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; *AbbVie, CTI BioPharma Corp, a Sobi company, Geron, GlaxoSmithKline, Imago, Incyte, Kartos, Kayropharm, MorphoSys, Novartis, Pfizer, PharmaEssentia, Sierra:* Consultancy; *GSK:* Honoraria. **Kremyanskaya:** *Protagonist Therapeutics, Inc.:* Consultancy, Research Funding. **Ginzburg:** *Protagonist Therapeutics, Inc.:* Consultancy, Research Funding. **Hoffman:** *Karyopharm:* Research Funding; *Kartos Abbvie:* Research Funding; *Curis:* Research Funding; *Dexcel Pharma:* Research Funding; *Summitomo:* Research Funding; *Dompe:* Patents & Royalties; *Silence Therapeutics:* Consultancy; *TD2:* Research Funding; *Cellinkos:* Consultancy; *Protagonist Therapeutics:* Consultancy.

**OffLabel Disclosure:** Oral decitabine-cedazuridine is FDA approved for previously treated and untreated, intermediate-high risk, de novo and secondary MDS and CMML. We report on its off-label use in advanced myeloproliferative neoplasms including MPN-accelerated phase.

https://doi.org/10.1182/blood-2023-178822

**Table 1. Baseline patient characteristics**

| | MPN-AP (N=7) | AHR- MF (N=7) |
|---|---|---|
| Age at starting oral decitabine/cedazuridine, Median (Range) in years | 77 (46-82) | 69 (60-85) |
| Initial MPN type | | |
| Pre-PMF | 4 (57%) | 0 (0%) |
| ET | 2 (29%) | 4 (57%) |
| PV | 0 (0%) | 3 (43%) |
| MF | 1 (14%) | 0 (0%) |
| Driver mutations | | |
| JAK2V617F | 4 (57%) | 4 (57%) |
| CALR | 2 (29%) | 2 (29%) |
| MPL | 0 | 1 (14%) |
| Triple Negative | 1 (14%) | 0 |
| Baseline counts (median, range) | | |
| White blood cell count ($10^3$/uL) | 16 (0.7-20.4) | 63.7 (9.9.-90.2) |
| Hemoglobin (g/dl) | 8.9 (4.3-10.3) | 8.9 (6.6-13.7) |
| Platelet count ($10^3$/uL) | 98 (1-1297) | 428 (37-1520) |
| Peripheral blood blast % | 11 (10-16) | 2 (2-6) |
| RBC- transfusion dependent | 3 (43%) | 1 (14%) |
| Platelet transfusion dependent | 1 (14%) | 0 |
| Baseline spleen size on palpation | 14 cm (0-20 cm) below costal margin | 11 cm (0-19 cm) below costal margin |
| Previous Splenectomy | 0 (0%) | 3 (43%) |
| Number of prior therapies | | |
| 0 | 1 (14%) | 0 (0%) |
| 1 | 2 (29%) | 1 (14%) |
| 2 | 2 (29%) | 4 (57%) |
| 3+ | 2 (29%) | 2 (29%) |

**Figure 1**

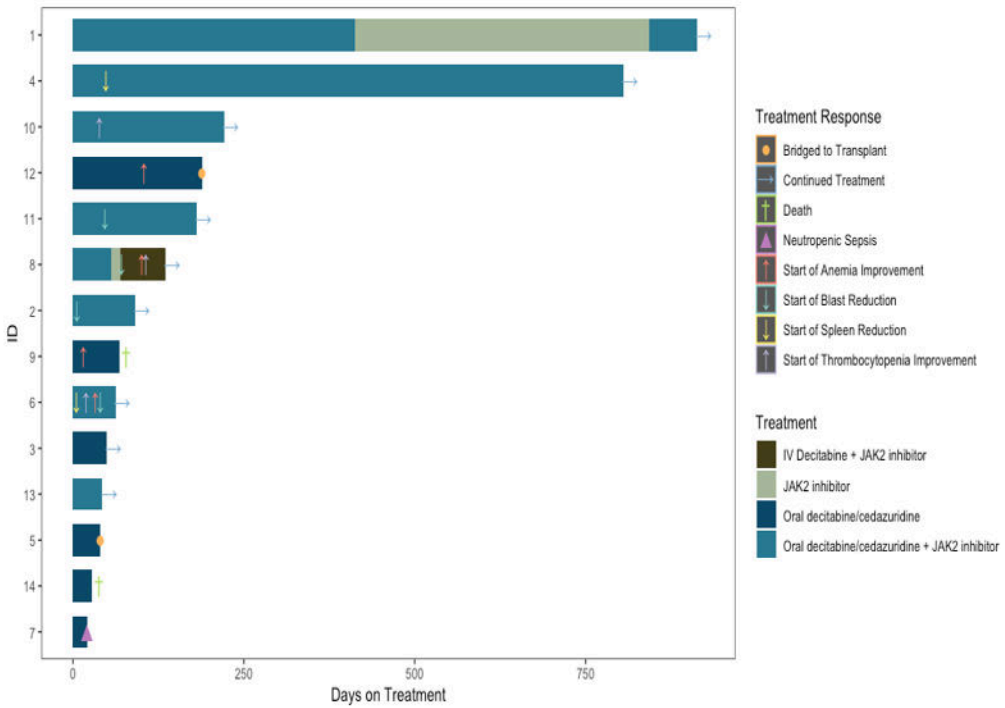


Fig. 1-Treatment response and survival in patients with advanced high-risk MF and MPN-accelerated phase treated with oral decitabine/cedazruridine +/- JAK inhibitor therapy.

**Figure 1**