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P1070 NAVITOCLAX MONOTHERAPY IN PATIENTS WITH MYELOFIBROSIS PREVIOUSLY TREATED WITH JAK-2 INHIBITORS: SAFETY AND TOLERABILITY

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background: Navitoclax is an oral, small-molecule inhibitor of anti-apoptotic B-cell lymphoma 2 family proteins (BCL-X_L, BCL-2, BCL-W) that is being evaluated in the ongoing, multicenter, multi-cohort, phase 2 trial (REFINE; NCT03222609). Previous results from REFINE Cohort 1a indicated that addition of navitoclax to ruxolitinib resulted in clinically meaningful outcomes with acceptable safety profile in patients with myelofibrosis (MF) with progression or suboptimal response to ruxolitinib monotherapy (Pemmaraju et al. *J Clin Oncol*. 2022).

Aims: To report preliminary safety results of navitoclax monotherapy (Cohort 2) in patients with suboptimal response to prior Janus kinase inhibitors (JAKis).

Methods: This phase 2, open-label trial in patients with MF enrolled patients into 4 cohorts according to JAKi experience; all patients provided informed consent. Patients in Cohort 2 had discontinued prior JAKi therapy and received navitoclax monotherapy orally at the starting dose of 100 mg/day (QD) or 200 mg QD if baseline platelet count was 75–150 × 10^9/L or >150 × 10^9/L, respectively. Eligible patients had previously received JAKi for ≥12 weeks, or ≥28 days with red blood cell transfusion dependence (≥2 units/month for 2 months) or with ≥ grade 3 adverse event (AE) of thrombocytopenia or anemia, while on JAKi; all patients had splenomegaly. The primary endpoint was spleen volume reduction of ≥35% (SVR_{35}) from baseline (BL) assessed centrally at Week 24. Secondary endpoints included change in grade of bone marrow fibrosis according to the European consensus grading system and anemia response as per International Working Group criteria. Exploratory endpoints included duration of response of SVR_{35} and overall survival. Safety and AEs were monitored throughout the study.

Results: As of Oct 4, 2021, 30 patients were enrolled and received navitoclax. A majority of patients were male (63%), median age was 68 years (range 55–84), with a median prior ruxolitinib exposure of 100 weeks (range 11–496). Fifteen patients (50%) had secondary MF, of which 8 patients (27%) had post–polycythemia vera MF and 7 patients (23%) had post-essential thrombocytopenia MF (**Table**). Fourteen patients (47%) started navitoclax at a dose of 100 mg QD and 16 patients (53%) started at 200 mg QD. The median follow-up time was 4.2 months (range 0.2–15.5). Median duration of navitoclax exposure was 9.4 weeks (range 0.1–67.1). Twenty-seven patients (90%) experienced ≥1 AE, the most common being: thrombocytopenia (n=16; 53%), diarrhoea (n=9; 30%), and nausea (n=8; 27%). Grade ≥3 AEs were experienced by 63% of patients, with thrombocytopenia (n=11; 37%) and anemia (n=7; 23%) being the most common. Three patients had serious AEs of dyspnea, hypoxia, and pulmonary hypertension. Navitoclax dose reductions and interruptions were experienced by 15 patients (50%) and 16 patients (53%), respectively. Three patients experienced AEs leading to navitoclax discontinuation (pulmonary hypertension, increased bilirubin, and low platelets; n=1 each). Eight patients discontinued navitoclax due to: AE (n=3), consent withdrawal (n=1), physician decision (n=1), disease relapse (n=1), and progressive disease (n=2). Two patients died

>30 days after the last dose of navitoclax. Details will be included in the presentation.

Image:

Table. Baseline demographic and clinical characteristics

Characteristics	Cohort 2 (navitoclax monotherapy) (N=30)	Cohort 1a (navitoclax and ruxolitinib) (N=34)
Age, median (range), years	68 (55–84)	68 (42–86)
Male	19 (63)	23 (68)
MF type		
Primary MF	14 (47)	16 (47)
Secondary MF	15 (50)	18 (53)
Post-PV	8 (27)	13 (38)
Post-ET	7 (23)	5 (15)
Response to prior ruxolitinib at screening		
Refractory	11 (37)	17 (52)
Relapsed	4 (13)	2 (6)
Disease progression	3 (10)	0
Intolerance	6 (20)	0
Other[a]	6 (20)	14 (42)
Unknown	0	1
Duration of prior ruxolitinib exposure, median (range), weeks	100 (11–496)	91 (19–391)
ECOG PS		
0	8 (27)	16 (47)
1	17 (57)	18 (53)
2	5 (17)	0
Spleen volume, median (range), cm^3	1646 (865–4044)	1695 (466–5047)
Hemoglobin		
<10 g/dL	19 (63)	11 (32)
≥10 g/dL	11 (37)	23 (68)
DIPSS at study entry		
Low	1 (3)	2 (6)
Intermediate-1	5 (17)	16 (47)
Intermediate-2	15 (50)	12 (35)
High	9 (30)	4 (12)

Data are n (%) unless otherwise specified.
[a]Included stable disease, PV progressed to MF, ET progressed to MF, not applicable, and other.
DIPSS, dynamic international prognostic scoring system; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

Summary/Conclusion: Navitoclax monotherapy in patients with MF after prior JAKi had a similar safety profile as previously reported in Cohort 1a. Efficacy analyses are underway to evaluate the activity of navitoclax monotherapy in patients with MF and will be available for the presentation.