

Overall and progression-free survival in patients treated with fedratinib as first-line myelofibrosis therapy and after prior ruxolitinib: results from the JAKARTA and JAKARTA2 trials

MPN-164

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Background

- Fedratinib (FEDR) is an oral, selective inhibitor of mutant and wild-type Janus kinase 2 (JAK2)
 - FEDR is approved in the United States, European Union, Canada, and elsewhere for treatment (Tx) of adult patients (pts) with primary or secondary myelofibrosis (MF), including pts previously treated with ruxolitinib (RUX)¹
- In the randomized, double-blind, phase 3 JAKARTA trial (NCT01437787), Tx with FEDR 400 mg/day significantly improved spleen volume and MF symptom severity vs. PBO at 24 weeks in pts with JAK-inhibitor-naïve MF
- Similarly, in the single, arm, phase 2 JAKARTA2 trial (NCT01523171), FEDR 400 mg/day (starting dose) improved spleen volume and symptom burden from baseline (BL) in pts with MF previously treated with RUX
- FEDR was placed on temporary clinical hold in Nov. 2013 due to suspected Wernicke encephalopathy (WE); the hold was later lifted but all FEDR clinical trials were halted and all pts discontinued FEDR Tx
- We assessed survival outcomes with FEDR 400 mg/day in JAKARTA and JAKARTA2

Objective

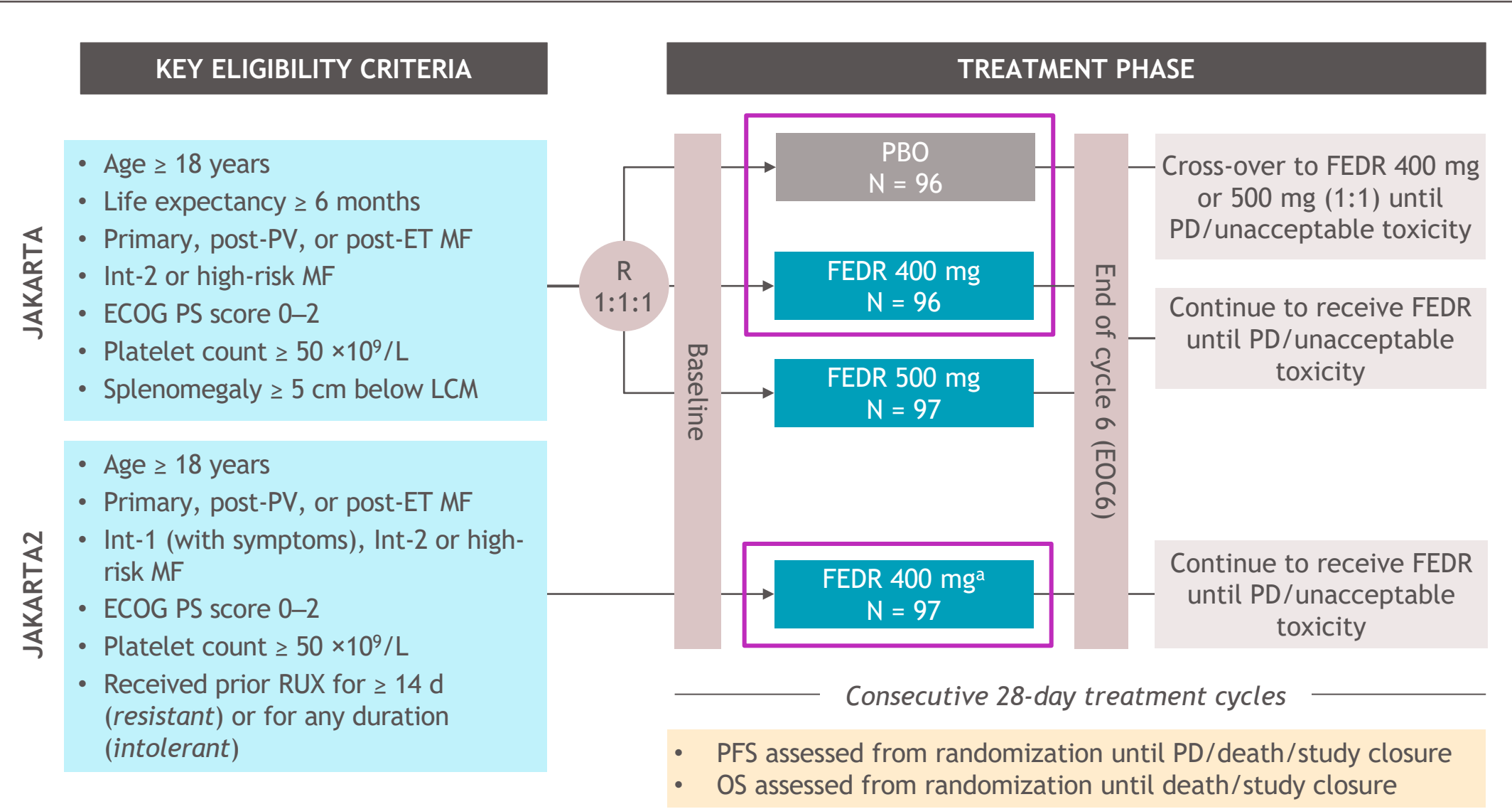
- Assess progression-free survival (PFS) and overall survival (OS) in pts treated with FEDR 400 mg/day in JAKARTA and JAKARTA2, and in PBO-randomized pts in JAKARTA

Methods

JAKARTA and JAKARTA2

- JAKARTA and JAKARTA2 study designs are shown in **Figure 1**
 - In JAKARTA, eligible pts were randomized 1:1:1 to FEDR 400 mg/day, FEDR 500 mg/day, or PBO
 - All pts in JAKARTA2 were assigned to receive FEDR 400 mg/day (starting dose)
 - Pts were to receive Tx for ≥ 6 continuous 4-week cycles (randomized Tx period). At the end of cycle 6 (EOC6)—or earlier in cases of progressive disease (PD)—pts initially randomized to PBO in JAKARTA could cross-over to receive FEDR until PD or unacceptable toxicity
- PFS was the time from randomization (JAKARTA) or first FEDR dose (JAKARTA2) until PD or death, and OS was the time from randomization or first dose until death. PFS and OS were estimated using Kaplan-Meier methods
 - In the absence of progression/death, PFS was censored at the date of the last valid assessment. Pts being followed for OS were censored at their last known alive date or time of clinical hold, whichever came later
- PFS was defined based on IWG-MRT criteria⁴:
 - Progressive splenomegaly: ≥ 25% increase in spleen volume from BL on MRI/CT
 - Leukemic transformation: bone marrow blast count ≥ 20% or occurrence of granulocytic sarcoma (chloroma)
 - Peripheral blood blast increase of ≥ 20% for ≥ 1 week
- Due to the clinical hold in 2013, both trials were terminated early and survival follow-up was stopped; Ongoing pts were censored at the time of the clinical hold
- These analyses included all pts who received FEDR 400 mg/day and pts in JAKARTA randomized to PBO (ITT analysis)
 - Importantly, PFS and OS results for pts in the JAKARTA PBO arm include time after crossover to FEDR

Figure 1. JAKARTA and JAKARTA2 key eligibility criteria and study designs



Results

Patients

- In JAKARTA, 96 pts were randomized to FEDR 400 mg/day and 96 were randomized to PBO
 - 71 pts (74%) in the PBO arm crossed-over to FEDR on-study
- 97 pts were enrolled in JAKARTA2 and received FEDR 400 mg/day (starting dose)
- Median Tx durations:
 - JAKARTA: FEDR 400, 62.1 weeks (range 1.0–91.9); PBO, 24.0 weeks (1.7–43.7)
 - JAKARTA2: 24.4 weeks (range 0.7–79.4)
- Study termination was the most common reason for Tx discontinuation in both trials (**Figure 2**)
- Key BL characteristics are shown in **Table 1**

Figure 2. Enrollment and disposition in JAKARTA (FEDR 400 and PBO) and JAKARTA2 (FEDR 400)

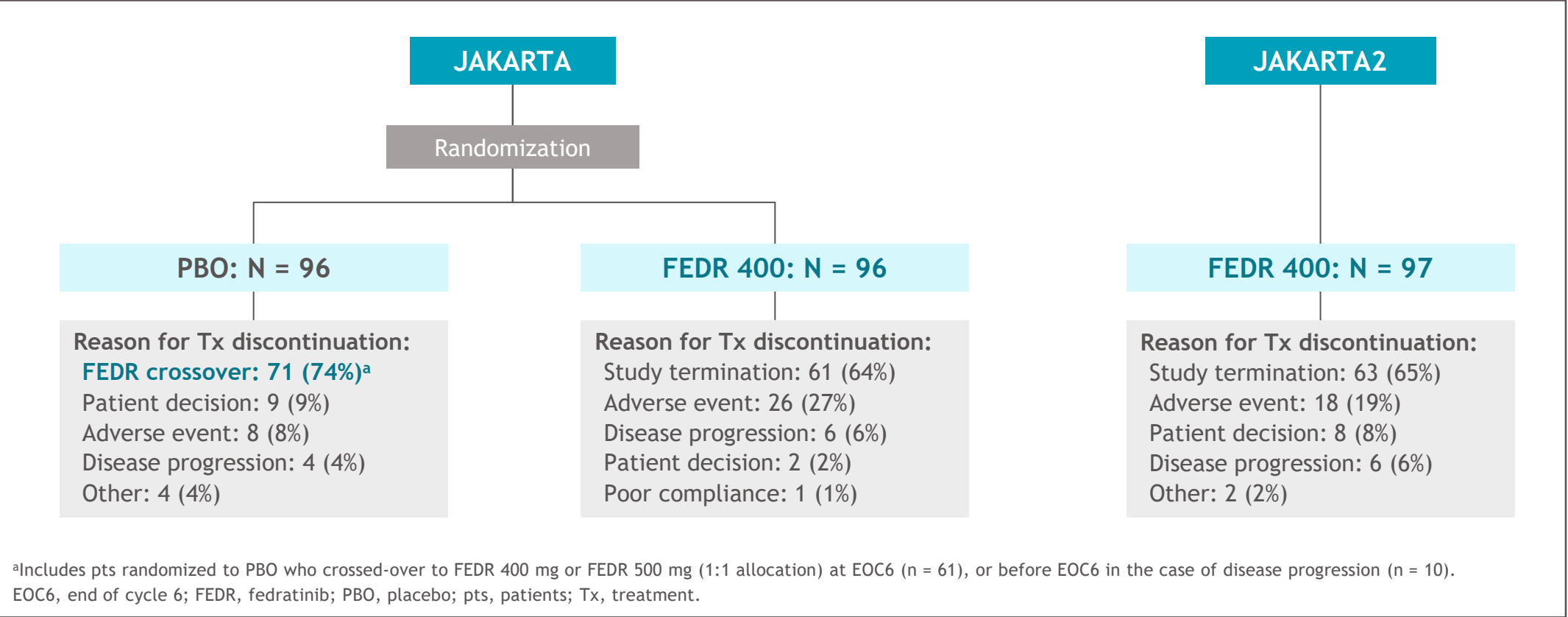


Table 1. Baseline characteristics

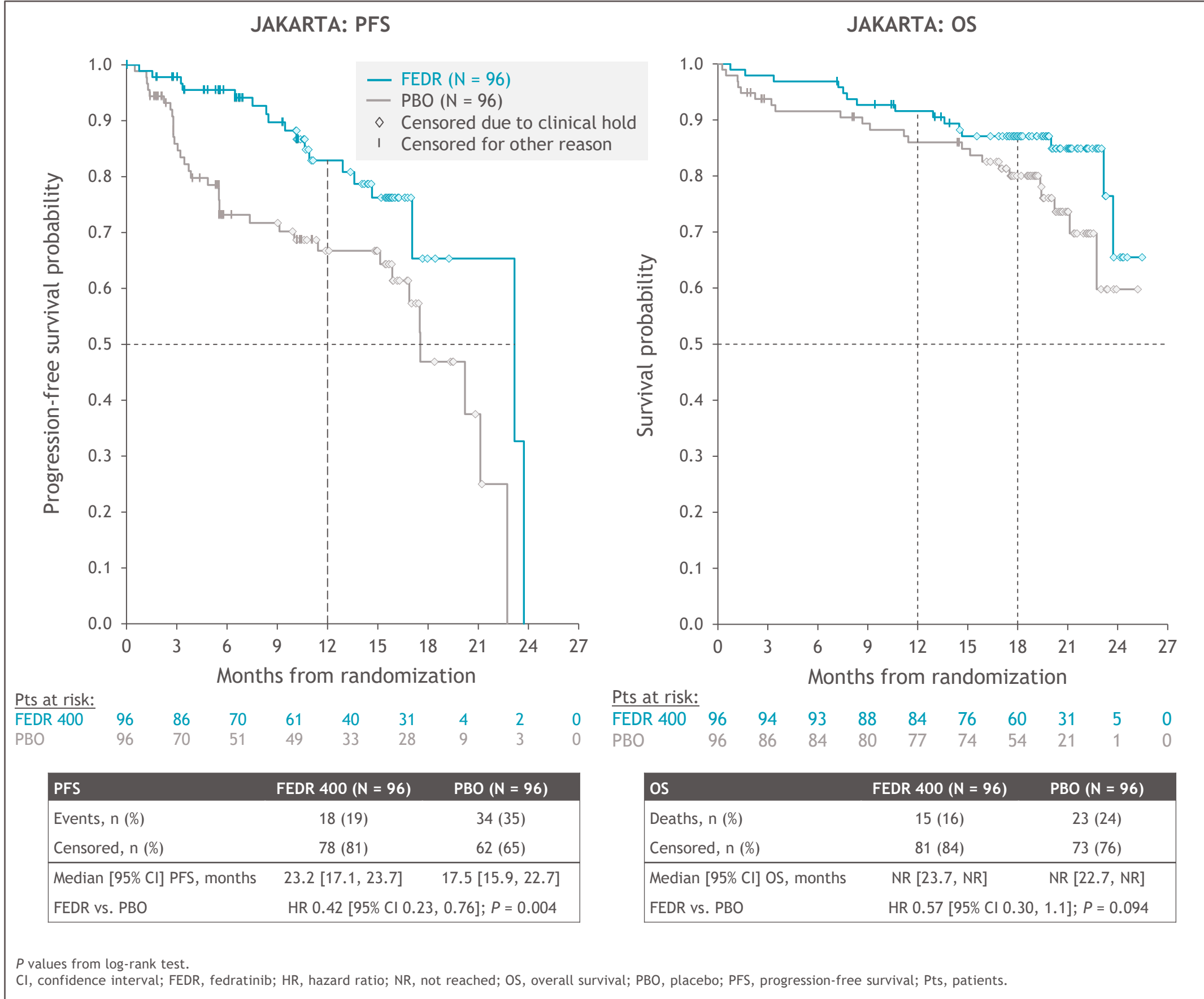
	JAKARTA		JAKARTA2
	PBO N = 96	FEDR 400 N = 96	FEDR 400 N = 97
Age, years, median (range)	66 (27–85)	63 (39–86)	67 (38–83)
MF setting, n (%)			
Primary	58 (60)	62 (65)	53 (55)
Post-PV	27 (28)	24 (25)	25 (26)
Post-ET	11 (11)	10 (10)	19 (20)
Risk status, n (%)			
Intermediate-1 with symptoms	NA	NA	16 (16)
Intermediate-2	46 (48)	57 (59)	47 (48)
High	50 (52)	39 (41)	34 (35)
ECOG PS score, n (%)			
0	31 (32)	41 (43)	26 (27)
1	56 (58)	47 (49)	45 (46)
2	8 (8)	8 (8)	23 (24)
Spleen volume, mL, median (range)	2660 (662–7911)	2652 (316–6430)	2893.5 (737–7815)
Spleen size by palpation, cm, median (range)	17 (5–40)	16 (5–40)	18 (5–36)
Prior hydroxyurea, n (%)	54 (56)	69 (72)	66 (68)
Platelets, 10 ⁹ /L, median (range)	187 (52–1075)	221 (31–1155)	147 (48–929)
Hemoglobin, g/dL, median (range)	10.1 (4.5–17.1)	10.7 (4.8–16.8)	9.8 (6.8–15.3)
MFSAF total symptom score, mean [SD]	14.7 [12.0]	17.6 [13.5]	20.7 [12.1]
Prior RUX duration, months, median (range)	NA	NA	10.7 (0.1–62.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; FEDR, fedratinib; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; PBO, placebo; PV, polycythemia vera; RUX, ruxolitinib; SD, standard deviation.

JAKARTA

- PFS was significantly prolonged with FEDR 400 vs. PBO (HR 0.42 [95% CI, 0.23–0.76]; $P = 0.004$) (**Figure 3**)
 - Median PFS from time of randomization was 5.7 months longer in the FEDR 400 arm vs. PBO: 23.2 vs. 17.5 months, respectively
 - 1-year PFS rate was 83% in the FEDR 400 arm and 67% in the PBO arm
- 80 pts (42%) were still being followed for PFS at the time of clinical hold
 - Median PFS follow-up: FEDR 400, 10.6 months; PBO, 9.1 months
- AML transformation was reported in 3 pts (3%) in the FEDR 400 arm and 2 pts (2%) in the PBO arm (based on adverse event [AE] reporting)
- Median OS was not reached (NR) in either Tx arm (HR 0.57 [95% CI, 0.30–1.10]; $P = 0.094$) (**Figure 3**)
 - Median OS follow-up: FEDR 400, 19.3 months; PBO, 18.8 months
 - 1-year survival rates were 92% and 86% in the FEDR 400 and PBO arms, respectively
- Overall, 139 pts (72%) were censored for OS at the time of clinical hold

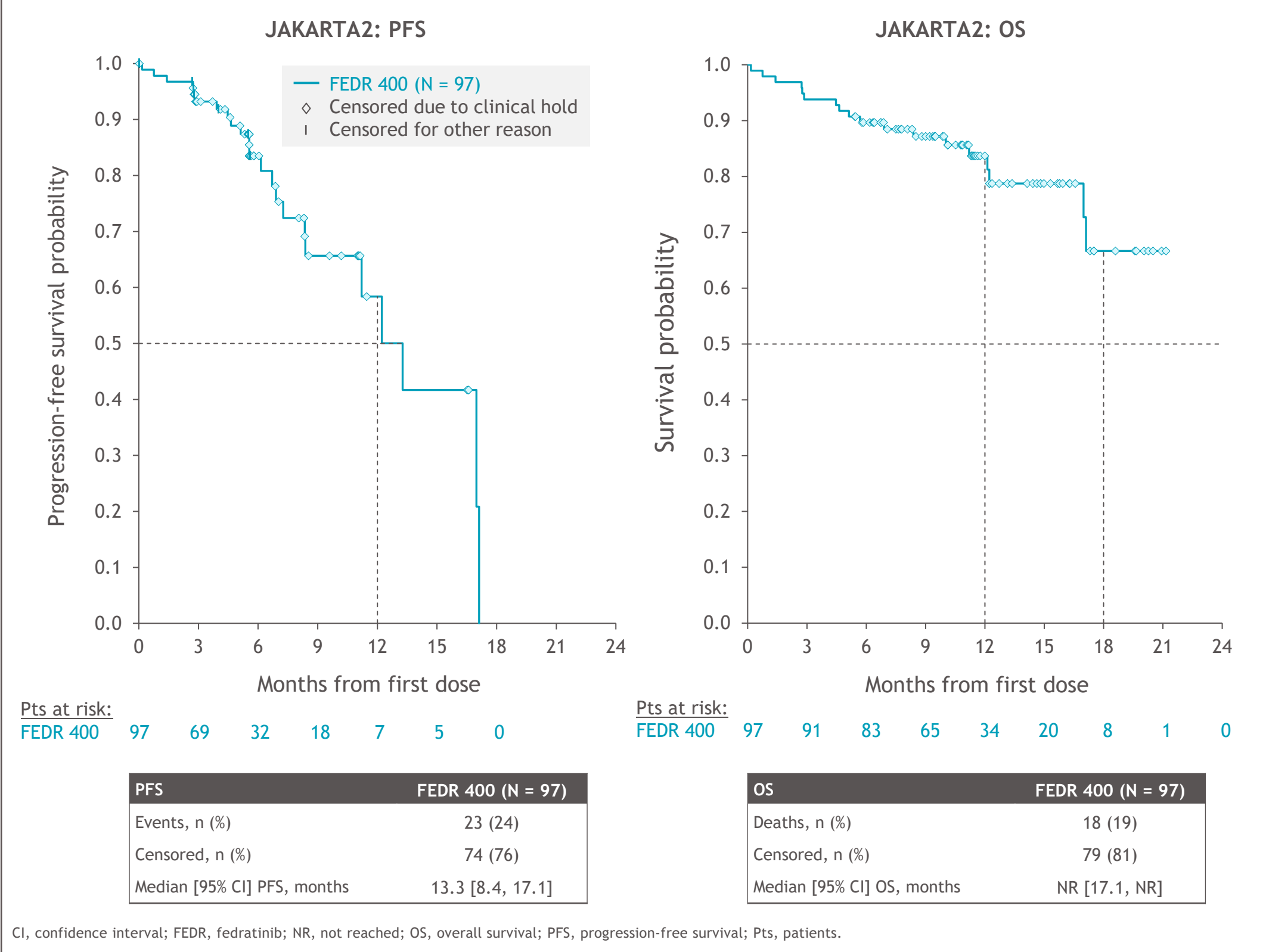
Figure 3. Progression-free and overall survival in JAKARTA



JAKARTA2

- Median PFS for all pts was 13.3 months from first dose [95% CI, 8.4–17.1] (**Figure 4**)
 - 1-year PFS rate was 59%
- 62 pts (64%) were still being followed for PFS at the time of the FEDR clinical hold
 - Median PFS follow-up: 5.6 months
- 2 pts (2%) experienced AML transformation (per AE reporting) during the JAKARTA2 Tx period
- Median OS was NR [95% CI, 17.1–NR] (**Figure 4**)
 - 1-year and 18-month OS rates were 84% and 67%, respectively
- 79 pts (81%) were censored for OS at the time of clinical hold
 - Median OS follow-up: 10.8 months

Figure 4. Progression-free and overall survival in JAKARTA2



Conclusions

- Substantial proportions of pts in JAKARTA and JAKARTA2 were still being followed for PFS and OS at the time of the FEDR clinical hold, resulting in heavy censoring and relatively short follow-up for both assessments
- In JAKARTA, FEDR showed to significantly reduce the risk of disease progression compared with PBO in pts with JAK-inhibitor-naïve MF
 - Separation of PFS and OS curves for FEDR and PBO in JAKARTA, despite FEDR Tx in the PBO arm after Tx crossover, suggests pts may derive greater benefit from early FEDR use
- For pts in JAKARTA2 treated with FEDR after prior RUX, median PFS, median OS, and 1-year survival rate compare favorably with outcomes after RUX discontinuation in pts included in a recent retrospective analysis of large healthcare databases⁵:

	FEDR 400–JAKARTA2	Mascarenhas et al ⁵
Median PFS	13.3 months	6.0 months
Median OS	Not reached	11.0 months
1-year OS rate	84%	47%

- Survival outcomes were favorable despite the impact of the FEDR clinical hold
- The ongoing FREEDOM (NCT03755518) and FREEDOM2 (NCT03952039) trials are further assessing survival with FEDR in pts with MF previously treated with RUX

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Acknowledgments

- These trials were originally supported by Sanofi S.A.; the current analyses were funded by Bristol Myers Squibb
- We thank the patients, families, co-investigators and all study personnel who participated in these trials
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Brian Kaiser and Sheila Truten of Medical Communication Company, Inc. (MEDCOMCO), funded by Bristol Myers Squibb