Updated analysis of overall survival with imetelstat in relapsed/refractory myelofibrosis versus real-world data, and assessment of real-world treatment patterns

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Background

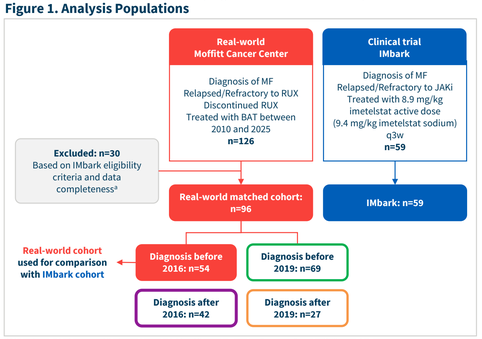
- Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by bone marrow fibrosis, splenomegaly, and anemia with nucleated and teardrop-shaped red blood cells[1-3]
  - The primary driver mutation in MF is in the *Janus kinase 2* (*JAK2*) gene
- The main goals of therapy are to reduce spleen volume, address symptoms, and improve survival[4]
  - Although allogeneic hematopoietic stem cell transplantation can be curative, it is associated with high morbidity and mortality[3]
  - JAK inhibitors (JAKi) are the current standard of care but have not been shown to modify the natural history of disease or prolong survival[3,4]
- Telomerase activity is upregulated and telomere length is short in patients with MF, regardless of *JAK2* mutation status, leading to investigations into telomerase as a therapeutic target[5-7]
- Imetelstat is a first-in-class telomerase inhibitor approved for the treatment of certain adult patients with low-risk to intermediate-1–risk myelodysplastic syndromes with transfusion-dependent anemia[8,9]
- In a previous analysis of the Phase 2 IMbark trial (NCT02426086), imetelstat showed significantly longer median overall survival (mOS) in patients with JAKi relapsed or refractory (R/R) intermediate-2–risk or high-risk MF versus closely matched real-world patients treated with best available therapy after the JAKi, ruxolitinib (hazard ratio [HR], 0.35; *P*=.0019)[10]
- The MF treatment landscape has changed considerably in the past 5 years, impacting the survival of patients who are R/R to ruxolitinib

Here, we present an updated survival analysis of IMbark patients versus a larger real-world patient cohort after extended follow-up and assess changes in real-world treatment patterns over this time period

Methods

- The updated real-world dataset included 126 patients who discontinued ruxolitinib and were subsequently treated with best available therapy at Moffitt Cancer Center between 2010 and 2025 (**Figure 1**)
  - To assess changes in real-world treatment patterns, baseline and disease characteristics and mOS of patients diagnosed before and after 2016 (cutpoint selected to match diagnosis period of IMbark population) and 2019 (year of fedratinib US approval) were compared
- To update the IMbark clinical trial versus real-world OS analysis, a closely matched cohort was identified using IMbark eligibility criteria, including patients diagnosed before 2016 who received ruxolitinib but were R/R (**Figure 1**)
  - For IMbark, OS was measured from time of JAKi discontinuation to death or censored at last known alive date
  - For the real-world analysis, OS was measured from time of JAKi discontinuation to death or censored at last follow-up
  - Propensity score approaches using average treatment effect for overlap population (ATO) or stabilized inverse probability treatment weighting (sIPTW) were implemented to adjust for baseline covariates and prognostic factors that could impact outcomes

Figure 1. Analysis Populations



BAT, best available therapy; JAKi, Janus kinase inhibitor; MF, myelofibrosis; q3w, every 3 weeks; RUX, ruxolitinib.
[a]Patients with baseline platelet <50×10⁹/L (n=28) or missing transfusion status (n=2) were removed.

Results

Updated OS Analysis of IMbark Versus Real-World Population

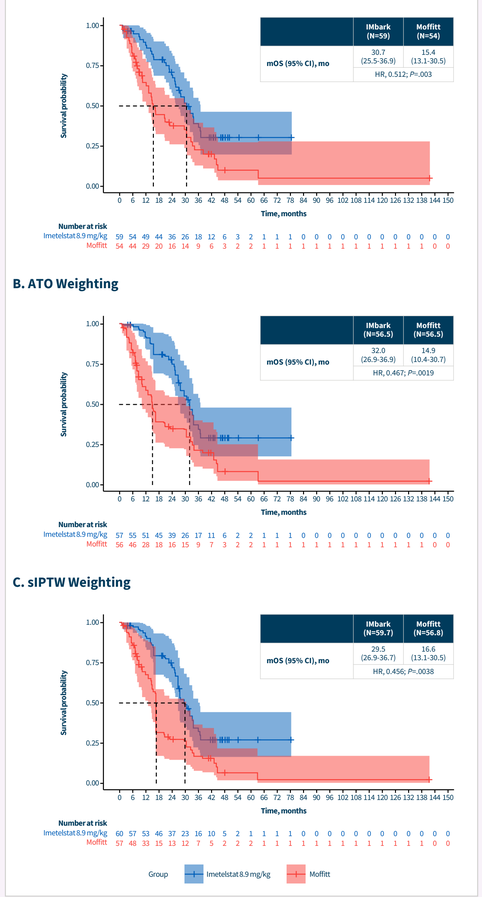
- Without adjustment, most baseline patient and disease characteristics were similar in the IMbark and Moffitt Cancer Center populations (**Table 1**)
  - An exception was Dynamic International Prognostic Scoring System risk score (*P*=.001)
- After ATO or sIPTW adjustment , standardized mean differences between populations across all key covariates were minimized (**Table 1**)
- With a median follow-up of 46.2 months for IMbark patients and 48.2 months for real-world patients, mOS (95% CI) was 30.7 months (25.5-36.9) with imetelstat in IMbark versus 15.4 months (13.1-30.5) with best available therapy in the real-world population (HR, 0.512; *P*=.003) per the unweighted analysis (**Figure 2A**)
  - Propensity-weighted analyses (ATO, sIPTW) had similar results (**Figure 2B-C**)

Table 1. IMbark and Real-World Baseline Patient and Disease Characteristics

	Before weighting		ATO weighting		sIPTW weighting	
	IMbark (N=59)	Moffitt (N=54)	IMbark (N=59.7)	Moffitt (N=56.8)	IMbark (N=56.5)	Moffitt (N=56.5)
Age,[a] mean (SD), y	66.5 (9.4)	68.3 (10.7)	67.6 (9.3)	68.5 (9.7)	67.1 (9.5)	67.1 (9.9)
	P=.350		*P*=.688		*P*=1.000	
Sex, n (%)						
Female	24 (40.7)	26 (48.1)	24.9 (41.6)	30.4 (53.5)	23.7 (41.9)	23.7 (41.9)
Male	35 (59.3)	28 (51.9)	34.8 (58.4)	26.4 (46.5)	32.8 (58.1)	32.8 (58.1)
	P=.543		*P*=.396		*P*=1.000	
MF subtype,[a] n (%)						
Primary	36 (61.0)	36 (66.7)	41.1 (68.9)	40.8 (71.9)	36.9 (65.3)	36.9 (65.3)
Post-ET	10 (16.9)	7 (13.0)	8.3 (13.9)	6.3 (11.1)	8.4 (14.8)	8.4 (14.8)
Post-PV	13 (22.0)	11 (20.4)	10.3 (17.2)	9.7 (17.0)	11.3 (19.9)	11.3 (19.9)
	P=.788		*P*=.908		*P*=1.000	
DIPSS score,[a] n (%)						
High	25 (42.4)	7 (13.0)	16.2 (27.1)	18.5 (32.6)	11.7 (20.6)	11.7 (20.6)
Int-1/2	34 (57.6)	47 (87.0)	43.5 (72.9)	38.3 (67.4)	44.8 (79.4)	44.8 (79.4)
	***P*=.001**		*P*=.717		*P*=1.000	
Platelets,[a] mean (SD), ×10⁹/L	212.2 (159.1)	208.3 (193.4)	199.5 (147.0)	200.1 (163.0)	205.4 (157.4)	205.4 (179.1)
	P=.908		*P*=.982		*P*=1.000	
Transfusion dependent,[a] n (%)	12 (20.3)	25 (46.3)	21.2 (35.6)	17.1 (30.1)	17.9 (31.6)	17.9 (31.6)
	P=.006		*P*=.655		*P*=1.000	
Time from diagnosis to RUX discontinuation, mean (SD), mo	54.3 (45.2)	77.0 (77.9)	53.7 (44.9)	58.7 (68.2)	60.3 (49.0)	60.3 (65.0)
	P=.059		*P*=.712		*P*=1.000	
RUX duration, mean (SD), mo	24.9 (17.8)	30.4 (42.5)	25.4 (17.0)	24.4 (36.1)	25.4 (17.5)	25.4 (36.3)
	P=.367		*P*=.871		*P*=1.000	
Presence of JAK biomarker,[a] n (%)						
0	25 (42.4)	17 (31.5)	18.8 (31.4)	24.5 (43.2)	17.8 (31.4)	17.8 (31.4)
1	32 (54.2)	36 (66.7)	39.4 (66.0)	31.2 (55.0)	37.3 (65.9)	37.3 (65.9)
2	2 (3.4)	1 (1.9)	1.5 (2.6)	1.0 (1.8)	1.5 (2.6)	1.5 (2.6)
	P=.392		*P*=.568		*P*=1.000	

ATO, average treatment effect for overlap population; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; PV, polycythemia vera; RUX, ruxolitinib; sIPTW, stabilized inverse probability treatment weighting.
[a]At time of informed consent for the IMbark population and at RUX discontinuation for the Moffitt Cancer Center population.

Figure 2. mOS for Imetelstat (IMbark) and BAT (Moffitt) (A) for Unweighted Analysis, (B) After ATO Weighting, and (C) After sIPTW Weighting



ATO, average treatment effect for overlap population; BAT, best available therapy; HR, hazard ratio; mOS, median overall survival; sIPTW, stabilized inverse probability treatment weighting.

Updated Treatment Patterns in a Real-World Setting

- Time from diagnosis to start of ruxolitinib and duration of ruxolitinib treatment were significantly shorter after 2016 versus before (**Table 2**)
  - Similar changes were observed after 2019 versus before
- Differences in the first therapy administered after ruxolitinib differed between those diagnosed before 2016 or 2019 and those diagnosed after 2016 or 2019 (**Table 3**)
- The mOS of patients diagnosed after 2016 and 2019 was significantly longer than for those diagnosed before these time points (**Figure 4**)

Table 2. Updated Real-World Baseline Patient and Disease Characteristics

	Before 2016 (N=54)	After 2016 (N=42)	Before 2019 (N=69)	After 2019 (N=27)
Age,[a] mean (SD), y	62.4 (12.4)	70.4 (11.2)	64.4 (12.1)	69.7 (12.9)
	***P*=.001**		*P*=.058	
Sex, n (%)				
Female	26 (48.1)	9 (21.4)	28 (40.6)	7 (25.9)
Male	28 (51.9)	33 (78.6)	41 (59.4)	20 (74.1)
	***P*=0.13**		*P*=.269	
MF subtype,[b] n (%)				
Primary	36 (66.7)	24 (57.1)	42 (60.9)	18 (66.7)
Post-ET	7 (13.0)	9 (21.4)	12 (17.4)	4 (14.8)
Post-PV	11 (20.4)	9 (21.4)	15 (21.7)	5 (18.5)
	P=.504		*P*=.870	
DIPSS score,[b] n (%)				
High	7 (13.0)	4 (9.5)	8 (11.6)	3 (11.1)
Int-1	15 (27.8)	7 (16.7)	16 (23.2)	6 (22.2)
Int-2	32 (59.3)	29 (69.0)	45 (65.2)	16 (59.3)
Low	0	2 (4.8)	0	2 (7.4)
	P=.217		*P*=.156	
Platelets,[b] mean (SD), ×10⁹/L	208.3 (193.4)	260.8 (263.4)	216.3 (196.3)	269.6 (292.0)
	P=.263		*P*=.303	
Transfusion dependent,[b] n (%)	25 (46.3)	24 (57.1)	35 (50.7)	14 (51.9)
	P=.396		*P*=1.000	
Time from diagnosis to RUX start, mean (SD), mo	46.7 (71.4)	10.5 (16.2)	39.7 (65.1)	8.2 (12.3)
	***P*=.002**		***P*=.015**	
Time from diagnosis to RUX discontinuation, mean (SD), mo	77.0 (77.9)	24.0 (20.7)	65.8 (72.9)	23.2 (18.3)
	***P*<.001**		***P*=.004**	
RUX duration, mean (SD), mo	30.4 (42.5)	13.5 (14.0)	26.1 (38.7)	15.0 (15.3)
	***P*=.015**		*P*=.151	
Transplant after RUX, n (%)	3 (5.6)	4 (9.5)	5 (7.2)	2 (7.4)
	P=.729		*P*=1.000	
Presence of JAK biomarker,[b] n (%)				
0	17 (31.5)	12 (28.6)	21 (30.4)	8 (29.6)
1	36 (66.7)	30 (71.4)	47 (68.1)	19 (70.4)
2	1 (1.9)	0	1 (1.4)	0
	P=.631		*P*=.815	

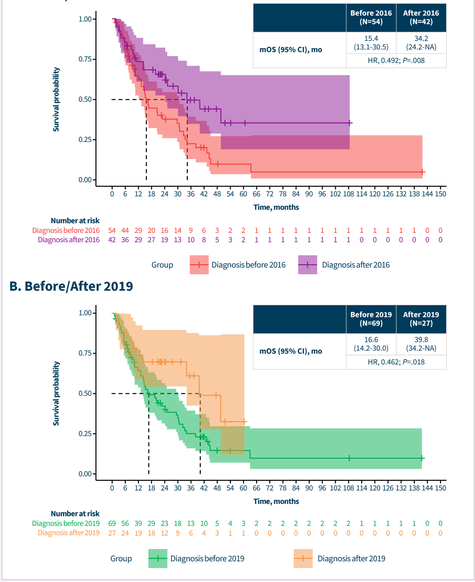
DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; PV, polycythemia vera; RUX, ruxolitinib.
[a]At diagnosis; [b]At time of RUX discontinuation.

Table 3. First Therapies After RUX in the Real-World Population

Agent, n (%)	Before 2016 (N=54)	After 2016 (N=42)	Before 2019 (N=69)	After 2019 (N=27)
Lenalidomide	8 (14.8)	3 (7.1)	10 (14.5)	1 (3.7)
Fedratinib	8 (14.8)	2 (4.8)	9 (13.0)	1 (3.7)
Thalidomide	7 (13.0)	6 (14.3)	9 (13.0)	4 (14.8)
Hydrea	5 (9.2)	6 (14.3)	6 (8.7)	5 (18.5)
Momelotinib	4 (7.4)	7 (16.7)	5 (7.2)	6 (22.2)
Luspatercept	1 (1.9)	1 (2.4)	1 (1.4)	1 (3.7)
Pacritinib	0	3 (7.1)	0	3 (11.1)
AHSCT	3 (5.6)	3 (7.1)	5 (7.2)	1 (3.7)
Observation	6 (11.1)	4 (9.5)	7 (10.1)	3 (11.1)
Supportive care	2 (3.7)	0	2 (2.9)	0
Other[a]	10 (18.5)	7 (16.7)	15 (21.7)	2 (7.4)

AHSCT, allogeneic hematopoietic stem cell transplantation; RUX, ruxolitinib.
[a]Other includes canakinumab trial, danazol, darbepoetin alfa, epoetin alfa, erythropoiesis-stimulating agent, calreticulin-CD3 bispecific antibody, peginterferon, splenic irradiation, unknown, and none.

Figure 4. mOS in the Real-World Population by Time of Diagnosis



HR, hazard ratio; mOS, median overall survival; NA, not available; RUX, ruxolitinib.

Discussion

- This updated post hoc analysis confirms a significantly more favorable mOS benefit with imetelstat versus best available therapy in patients with R/R MF and poor prognosis
  - These results are consistent with the previous report[10]
- A significant improvement in mOS in real-world patients after ruxolitinib over the last decade was also demonstrated, potentially due to shorter time from diagnosis to start of ruxolitinib or earlier switch to alternative JAKi or additional clinical trial options
- Evolving treatment patterns are key considerations for interpreting future clinical trial outcomes

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