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Correlation Analyses of Imetelstat Exposure with Pharmacodynamic Effect, Efficacy and Safety in a Phase 2 Study of Patients with Higher-risk Myelofibrosis Refractory to Janus Kinase Inhibitor Identified Optimal Dosing Regimen for the Phase 3 Study

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Disclosure

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Background

- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm. Currently, there are no approved treatment options for patients who are relapsed after or refractory to (R/R) therapy with Janus kinase inhibitors (JAKi). Development of new therapies with a novel mechanism remains a significant area of unmet need.
- Imetelstat is a first-in-class telomerase inhibitor currently in clinical development for hematologic myeloid malignancies.
- IMbark (MYF2001; NCT02426086) was a 2-dose (9.4 mg/kg or 4.7 mg/kg IV every 3 weeks), randomized Phase 2 study of imetelstat in intermediate-2/high-risk MF patients R/R to prior JAKi treatment. Clinical activity and an acceptable safety profile were reported:
 - Rate of symptom response (total symptom score [TSS] reduction $\geq 50\%$) at Week 24 was 32.2% for the 9.4 mg/kg arm and 6.3% for the 4.7 mg/kg arm, respectively.¹
 - Median overall survival (OS) was 28.1 months (95% confidence interval [CI]: 22.8, 31.6) for the 9.4 mg/kg arm and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9) with an overall study follow up of 42 months.²
 - Dose-dependent on-target pharmacodynamic (PD) activity of imetelstat was observed, and it correlated with clinical responses and longer OS.³
 - Most common adverse events were cytopenias; the majority of grade 3/4 cytopenias resolved within 4 weeks without significant clinical consequences

1. Mascarenhas et al, ASH 2018 Oral Presentation (Abstract #685).

2. Mascarenhas et al, EHA 2020 (Abstract # EP1107).

3. Mascarenhas et al, EHA 2020 (Abstract # EP1098).



Objectives And Methods

Objective

To perform exposure-response analyses on the IMbark study to further evaluate the benefit/risk profile and justify 9.4 mg/kg every 21 days as the optimal dosing regimen for the planned Phase 3 study of imetelstat in refractory MF.

Methods:

- Imetelstat exposure was defined as average concentration (C_{avg}), calculated as the total cumulative area under the concentration curve after all imetelstat administrations divided by time. C_{avg} values from 107 subjects were grouped into 4 quartiles (Q1, Q2, Q3, and Q4) to represent different levels of imetelstat exposure regardless of the protocol-specified dose arm assignment. Q1 group included patients with lowest and Q4 with highest imetelstat exposure.
- Optimal PD effect of imetelstat was defined as $\geq 50\%$ reduction from baseline in telomerase activity (TA) or human telomerase reverse transcriptase (hTERT).
- The exposure-response relationships between imetelstat exposure quartiles and optimal PD effect, symptom response, OS, and safety parameters were assessed and summarized by comparing each exposure quartile.
- The Kaplan-Meier method was used to estimate the distribution of OS for each exposure quartile in the intent-to-treat population.



Results: Relationship Between Imetelstat Exposure and Dose

- Majority of patients in the 4.7 arm were in the Q1-Q2, the quartiles with low exposure and as expected. Only few were in higher exposure Q3 and Q4, and those were with dose escalation to 9.4 mg/kg during the study.
- Majority of patients in the 9.4 arm were in the higher exposure quartiles Q3 and Q4 as expected; those that were in Q1 and Q2 were the those with dose delay (D), reduction (R) or interruption (I) during the study.

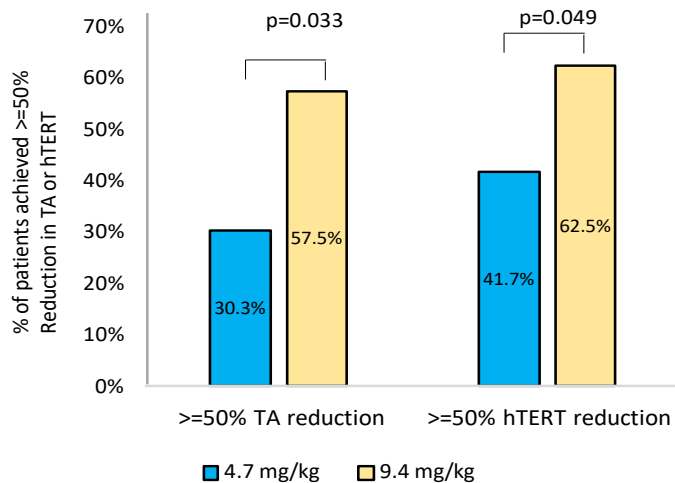
Summary of Imetelstat Median Concentrations in Each Exposure Quartile Group and Distribution by Dose Levels

Exposure (C _{avg}) Quartile	N	Median C _{avg} (µg/mL)	Minimum C _{avg} (µg/mL)	Maximum C _{avg} (µg/mL)	4.7 mg/kg, N (%)	9.4 mg/kg, N (%)
Q1 (lowest)	27	0.21	0.12	0.27	24 (89%)	3 (11%), all 3 with dose D/R/I
Q2	27	0.37	0.27	0.45	15 (56%), 5 had dose escalated to 9.4 mg/kg	12 (44%), 9 with dose D/R/I
Q3	27	0.6	0.45	0.72	8 (30%), 6 had dose escalated to 9.4 mg/kg	19 (70%), 12 with dose D/R/I
Q4 (highest)	26	0.96	0.73	2.22	1 (4%), 1 had dose escalated to 9.4 mg/kg	25 (96%), 16 with dose D/R/I

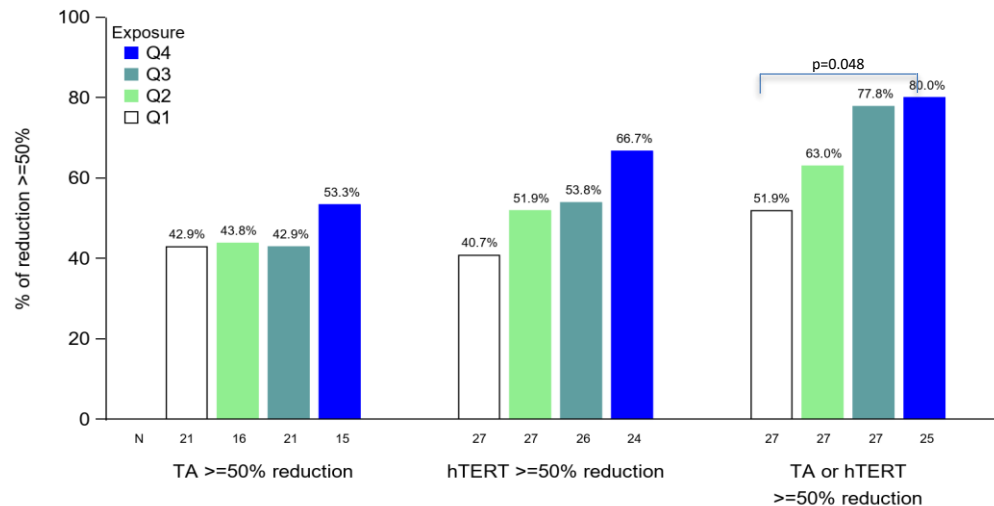


Dose- and Exposure-dependent Pharmacodynamic Effects

Significantly more subjects in the 9.4 mg/kg arm achieved optimal PD effect* compared to the 4.7 mg/kg arm



Significantly more subjects in the highest exposure quartile Q4 achieved optimal PD effect* compared to subjects in the lowest exposure quartile of Q1, indicating exposure-dependent on-target activity of imetelstat

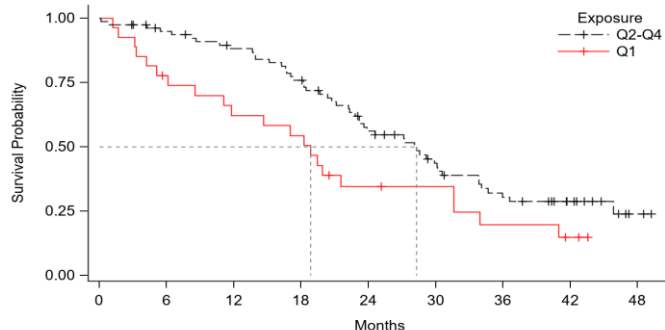
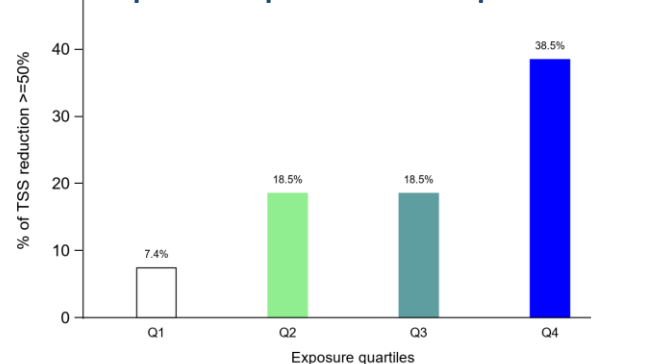


* Optimal PD effect: ≥50% reduction from baseline in TA or hTERT)



Imetelstat Exposure Correlated with Clinical Benefits

Exposure dependent TSS response* and OS



Months	0	6	12	18	24	30	36	42	48
Q2-Q4	80	72	65	56	39	27	18	11	2
Q1	27	20	16	14	8	7	4	2	

Higher survival rate correlated with higher exposure

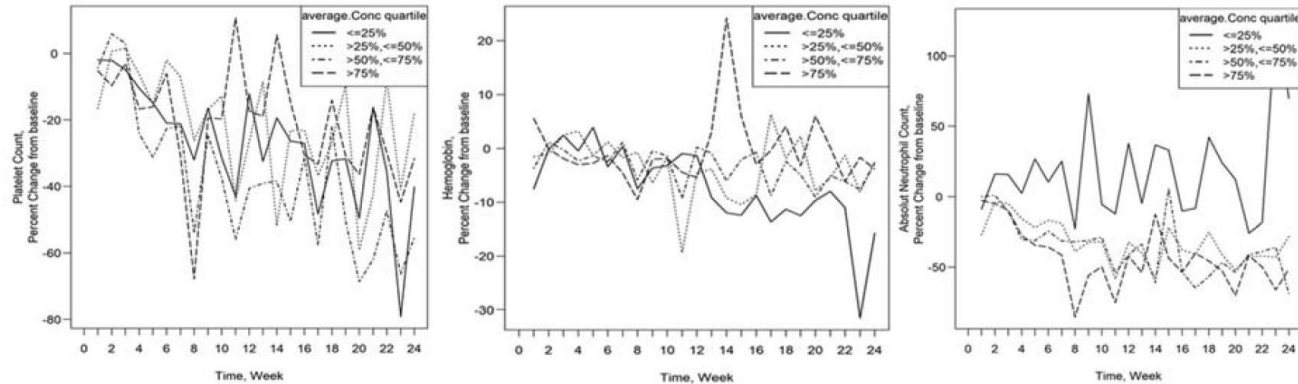
	Exposure Q1	Exposure Q2-Q4
Total number of subjects	27	80
Death	21 (77.8%)	50 (62.5%)
Censored	6 (22.2%)	30 (37.5%)
Duration of OS (Months)		
Median (95% CI)	18.9 (8.5, 31.6)	28.3 (22.8, 33.8)
Range	1.2, 43.6+	0.2, 49.2+
12-months survival rate (95% CI)	0.622 (0.411, 0.776)	0.882 (0.785, 0.937)
24-months survival rate (95% CI)	0.346 (0.172, 0.526)	0.562 (0.440, 0.667)
36-months survival rate (95% CI)	0.198 (0.066, 0.379)	0.304 (0.198, 0.418)
Hazard ratio (95% CI)		0.570 (0.341, 0.952)
Log-rank P value		0.0302

*Symptom response: $\geq 50\%$ total symptom score reduction at Week 24



Correlation Between Imetelstat Exposure and Safety

No apparent associations between imetelstat exposure quartiles and change of hematology values



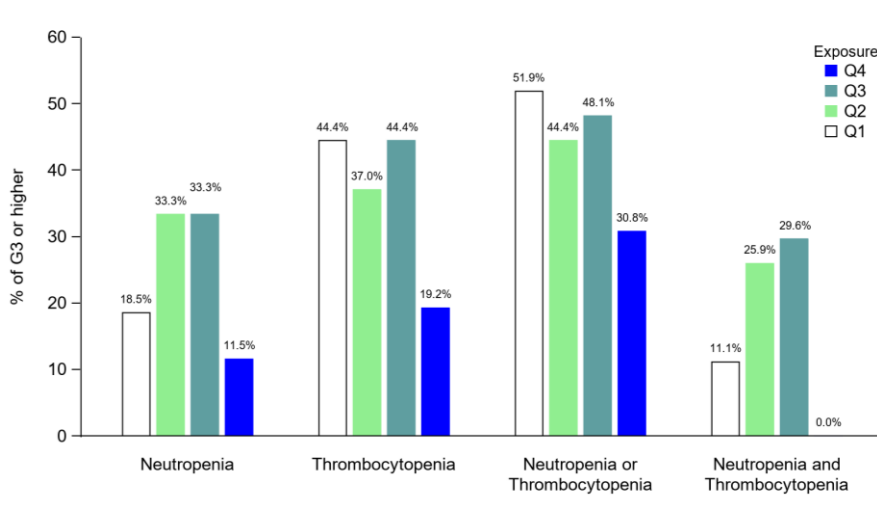
Exposure Q1: <=25%
Exposure Q2: >25%, <=50%
Exposure Q3: >50%, <=75%
Exposure Q4: >75%

Time Course of Mean Platelet Count, Hemoglobin Concentration, and Neutrophil Count Percent Change from Baseline by Exposure Quartile

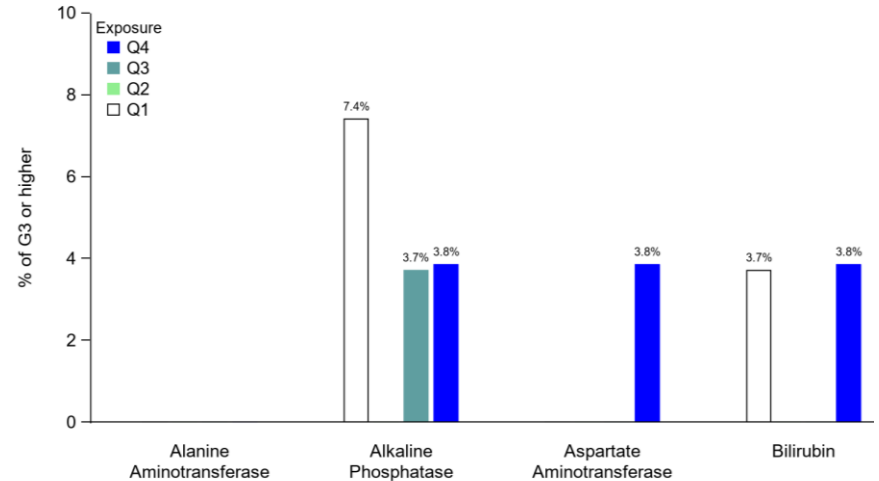


Correlation between Imetelstat Exposure and Safety

No apparent associations between imetelstat exposure quartiles and the proportions of patients with Grade ≥ 3 neutropenia and/or thrombocytopenia



Overall incidence of Grade ≥ 3 liver function lab test elevations was low, and there was no apparent association with exposure levels



Conclusions

- Imetelstat exposure correlated with the dose levels that subjects received, with the 9.4 mg/kg dose being associated with higher exposure.
- Dose- and exposure-dependent optimal PD effect of imetelstat was observed, indicating on target activity of imetelstat.
- Symptom response rates were 7.4%, 18.5%, 18.5%, and 38.5% for subjects with imetelstat exposure quartile Q1 (the lowest exposure), Q2, Q3, and Q4 (the highest exposure), respectively, indicating exposure-dependent clinical benefit.
- Exposure-dependent survival benefit was observed. Subjects in the 3 higher exposure quartiles (i.e. Q2-Q4) demonstrated a longer survival than those in the lowest exposure quartile group (Q1).
- There was no correlation between exposure quartiles and liver function lab test safety parameters or Grade ≥ 3 cytopenias.

In summary, the results from this exposure-response analyses indicated that 9.4 mg/kg and 4.7 mg/kg covered the therapeutic window of imetelstat in MF patients R/R to JAKi. Imetelstat 9.4 mg/kg treatment yielded higher exposure, leading to a higher rate of MF patients achieving the optimal PD effect, consistently better clinical benefits, and a similar safety profile as 4.7 mg/kg (Mascarenhas et al; ASH 2018 Abstract #685). This benefit/risk profile supports the 9.4 mg/kg dose every 21 days as the optimal dosing regimen for the upcoming imetelstat Phase 3 study in refractory MF (IMPactMF, NCT04576156).

