Correlation Between IL-8 and TNF-Alpha and Overall Survival in Imetelstat-Treated Patients With Myelofibrosis Relapsed or Refractory to a Janus-Associated Kinase Inhibitor in the IMbark Trial

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Background

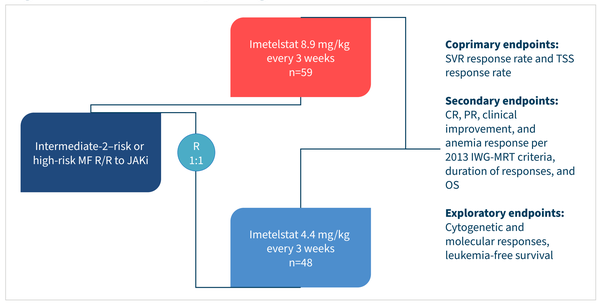
- The dysregulation of inflammatory cytokines plays a key role in the pathogenesis, progression, and clinical features of myelofibrosis (MF)[1,2]
- In particular, increased interleukin (IL)-8 and tumor necrosis factor alpha (TNF-α) have been associated with poor prognosis in patients with MF[1,3]
- In preclinical evaluations, treatment with the telomerase inhibitor, imetelstat, led to decreased expression of IL-8 in various tumor cell lines[4]
- In the Phase 2 IMbark trial (NCT02426086) of 2 dosing regimens, treatment with imetelstat showed a dose-related trend for clinical benefit, with improved overall survival (OS) in the higher dose arm compared with the lower dose arm, an acceptable safety profile, and potential disease-modifying activity in patients with intermediate-2–risk or high-risk MF relapsed or refractory (R/R) to Janus kinase inhibitor (JAKi) treatment[5,6]

This post hoc analysis evaluated the effect of imetelstat on proinflammatory cytokines and the impact on efficacy in patients from IMbark

Methods

- The study design for IMbark is presented in **Figure 1**. Patients were randomly assigned (1:1) to 4.4 mg/kg or 8.9 mg/kg imetelstat active dose (equivalent to 4.7 mg/kg or 9.4 mg/kg imetelstat sodium, respectively) by infusion every 3 weeks
- In this analysis, 21 cytokines were measured using Luminex® Multiplex Cytokine Assay Kits (R&D Systems, Inc.; Minneapolis, MN) in stored plasma samples collected at baseline and at weeks 12, 24, 36, and 48 of imetelstat treatment
- The correlation between percent change from baseline in cytokine levels and percent change in total symptom score (TSS) or spleen volume at each time point was evaluated using linear regression
- OS with imetelstat (any dose or by dose level) by baseline cytokine level was estimated using Kaplan-Meier; hazard ratio (HR) between cytokine levels was evaluated using Cox regression
- An unadjusted nominal *P* value from each test was reported

Figure 1. IMbark Study Design



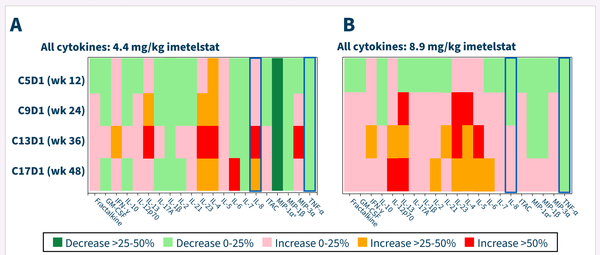
CR, complete remission; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; JAKi, Janus kinase inhibitor; OS, overall survival; PR, partial remission; R, randomized; R/R, relapsed or refractory; SVR, spleen volume reduction; TSS, total symptom score.

- For R/R status, patients must have had worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy either:
  - No reduction in spleen volume or size after 12 weeks of JAKi therapy
  - Worsening splenomegaly after starting JAKi, with documented spleen volume increase by 25% or increase in spleen size by palpation

Results

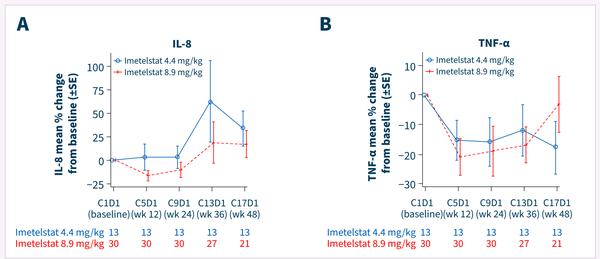
- A total of 43 out of 107 patients from IMbark who had plasma samples available for cytokine evaluation and quantifiable cytokine levels at baseline for ≥1 cytokine and ≥2 postbaseline assessments at 12 and 24 weeks were included in this analysis
- Of 21 cytokines analyzed, a consistent trend of dose-dependent reduction across time points was seen selectively with IL-8 and TNF-α levels (**Figure 2** and **Figure 3**)

Figure 2. Mean Percentage Change From Baseline in 21 Cytokines in Patients Treated With (A) 4.4 mg/kg Imetelstat or (B) 8.9 mg/kg Imetelstat Through Week 48



C, cycle; D, day; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; ITAC, interleukin-1 receptor-associated kinase 1; MIP, macrophage inflammatory protein; TNF-α, tumor necrosis factor alpha.
Note: A visit window of ±1 cycle was applied to derive cycles 5, 9, 13, and 17 for cytokine data, corresponding to weeks 12, 24, 36, and 48 (±3 weeks).
*Only 1 patient in the 4.4 mg/kg cohort and 4 patients in the 8.9-mg/kg cohort had detectable MIP-1α results.

Figure 3. Mean Percentage Change From Baseline in (A) IL-8 and (B) TNF-α Levels Through Week 48 in Patients Treated With Imetelstat

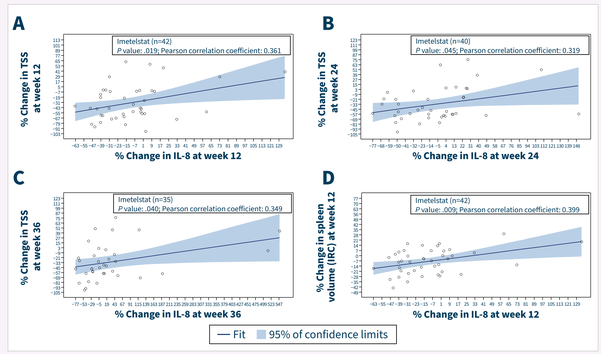


C, cycle; D, day; IL, interleukin; TNF-α, tumor necrosis factor alpha.
Note: A visit window of ±1 cycle was applied to derive cycles 5, 9, 13, and 17 for cytokine data, corresponding to weeks 12, 24, 36, and 48 (±3 weeks).

Response Outcomes

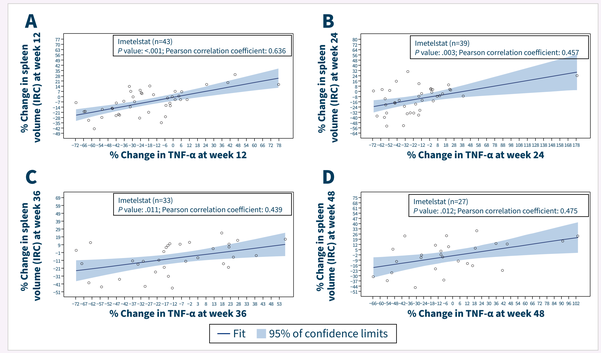
- Reductions from baseline in IL-8 levels with imetelstat (regardless of dose) at weeks 12, 24, and 36 were significantly correlated with reductions in TSS at the corresponding time points (correlation coefficients [CC] of 0.361 [*P*=.019], 0.319 [*P*=.045], and 0.349 [*P*=.040], respectively) and with spleen volume reduction (SVR) at week 12 (CC, 0.399; *P*=.009) (**Figure 4**)
  - The correlations between changes in IL-8 and in SVR at weeks 24 and 36 were not statistically significant (**not shown**)
- Reductions from baseline in TNF-α levels with imetelstat (regardless of dose) at weeks 12, 24, 36, and 48 were significantly correlated with SVR at the corresponding time points (CCs of 0.636 [*P*<.001], 0.457 [*P*=.003], 0.439 [*P*=.011], and 0.475 [*P*=.012], respectively) (**Figure 5**)
  - No statistically significant correlations between the changes in TNF-α and in TSS were observed (**not shown**)

Figure 4. Change in IL-8 From Baseline With Imetelstat Is Correlated With Change in TSS at Weeks (A) 12, (B) 24, and (C) 36, and With (D) Change in SVR at Week 12



IL, interleukin; IRC, independent review committee; SVR, spleen volume reduction; TSS, total symptom score.

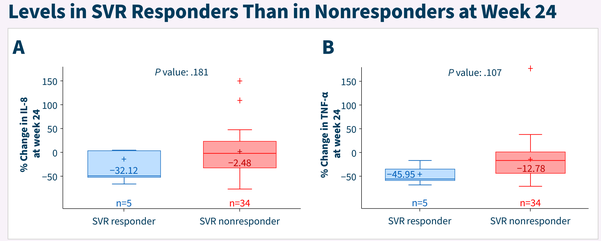
Figure 5. Change in TNF-α From Baseline With Imetelstat Is Correlated With Change in SVR at Weeks (A) 12, (B) 24, (C) 36, and (D) 48



IRC, independent review committee; SVR, spleen volume reduction; TNF-α, tumor necrosis factor alpha.

- Patients who achieved spleen response (≥35% SVR) at week 24 with imetelstat had mean reductions of 32% and 46%, respectively, in IL-8 and TNF-α levels at week 24; SVR nonresponders had mean reductions of 2% and 13%, respectively (**Figure 6**)

Figure 6. Greater Reduction From Baseline in (A) IL-8 and (B) TNF-α Levels in SVR Responders Than in Nonresponders at Week 24

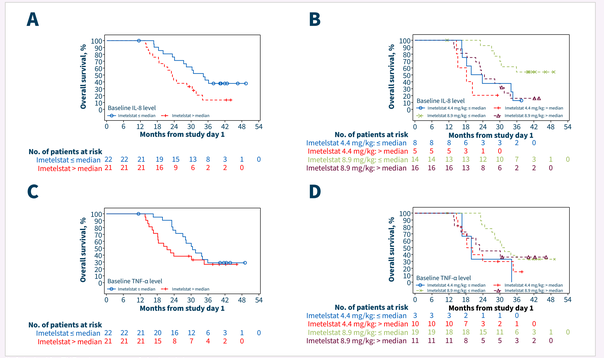


IL, interleukin; SVR, spleen volume reduction; TNF-α, tumor necrosis factor alpha.

Survival Outcomes

- Overall, patients with lower baseline IL-8 levels (defined as ≤ median level) had longer median OS with imetelstat compared with patients with higher baseline IL-8 levels (defined as > median level; HR [95% CI], 0.44 [0.21-0.93]; *P*=.03) (**Figure 7A**)
  - Among patients with higher baseline IL-8 levels, median OS (95% CI) was longer with 8.9 mg/kg imetelstat (24.1 months [18.4-31.6]) compared with 4.4 mg/kg imetelstat (18.2 months [14.7-not estimable]; HR [95% CI], 0.45 [0.14-1.48]; *P*=.18) (**Figure 7B**)
- Similar trends in OS were observed for TNF-α, but these were not statistically significant; patients with lower baseline TNF-α levels had longer median OS compared with patients with higher baseline TNF-α levels (HR [95% CI], 0.64 [0.31-1.31]; *P*=.21) (**Figure 7C**)
  - Among patients with higher baseline TNF-α levels, median OS (95% CI) was longer with 8.9 mg/kg imetelstat (22.8 months [13.9-not estimable]) compared with 4.4 mg/kg imetelstat (19.3 months [14.7-34.7]; HR [95% CI], 0.68 [0.24-1.88]; *P*=.45) (**Figure 7D**)

Figure 7. OS by (A) Baseline IL-8 Level, (B) Imetelstat Dose and Baseline IL-8 Level, (C) Baseline TNF-α Level, and (D) Imetelstat Dose and Baseline TNF-α Level



IL, interleukin; TNF-α, tumor necrosis factor alpha.

Conclusions

- In this post hoc analysis, imetelstat treatment was associated with dose-dependent reductions from baseline in IL-8 and TNF-α levels, which corresponded with reductions in TSS or spleen volume
- In a small number of patients with higher baseline IL-8 and TNF-α, 8.9 mg/kg imetelstat showed a longer survival benefit compared with 4.4 mg/kg imetelstat, despite the known association of elevated IL-8 and TNF-α with worse prognosis
- This hypothesis-generating, exploratory analysis identifies specific inflammatory cytokines reduced with imetelstat treatment and associated with reduction in spleen volume and symptoms that, together with previously presented data, suggest potential disease-modifying activity of imetelstat in MF
- Further confirmatory studies of imetelstat in MF are in progress

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