Clinical Pharmacology of Imetelstat, A First-In-Class Oligonucleotide Telomerase Inhibitor
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INTRODUCTION

- Imetelstat is a first-in-class telomerase inhibitor in development for the treatment of myeloid malignancies, including treatment of transfusion-dependent anemia in lower-risk myelodysplastic syndromes (LR-MDS).
- Imetelstat is a 13-mer N3-PS-5’-phosphorothioate oligonucleotide with a lipid tail to enhance cellular uptake2,14. It has a sequence complementing the telomerase specificity that binds with high affinity to the template region of the RNA component of human telomerase (Figure 1).
- Imetelstat and other oligonucleotide classes have structural similarities; however, the amino group for imetelstat is not antisense based, as it does not target mRNA of any gene. Instead, it acts as a classical active site enzyme inhibitor.
- Telomerase inhibition by imetelstat leads to loss of a malignant cell’s ability to maintain telomere length, resulting in inhibition of cell proliferation and death of malignant cells15,16.
- Nonclinical proof-of-concept studies for imetelstat correlated in vivo in xenograft mouse models and indicated that higher imetelstat doses were associated with greater plasma exposure and target engagement17-19.
- The IMbark Phase 2 randomized dose-finding study (NCT02460868)10. The IMerge Phase 3 study (NCT04576156) is ongoing to evaluate a potential role of imetelstat for transfusion-dependent anemia in lower-risk MDS at the proposed clinical dose of 7.5 mg/kg ∗.

METHODS

Evaluation of the clinical pharmacology properties of imetelstat to support its optimal use as a telomerase inhibitor for transfusion-dependent anemia in patients with LR-MDS at the proposed clinical dose of 7.5 mg/kg every 4 weeks (q4w) administered over 2 IV infusion.

ADME Properties

- AUC increases in more than dose proportional manner over the 0.4-11.7 mg/kg range.
- Little to no accumulation is observed following repeat doses (Figure 2).
- Imetelstat has moderate variability, with geometric mean (CV%) Cmax of 89 ± 22 µg/mL (27.2%) and AUC0-∞ of 554 ± 362 µg h/mL (43.4%) in MDS following a 7.5 mg/kg dose.
- Imetelstat is administered via IV infusion, and Tmax is observed at the end of infusion (Figure 2).

Distribution

- Human plasma protein binding is 94% in vitro.
- Imetelstat disposition studies demonstrate rapid distribution of imetelstat from plasma to tissues, with highest concentrations in bone marrow (site of action for myeloid malignancies), liver, kidney, and spleen.

Metabolism

- Like other oligonucleotides, imetelstat is likely metabolized into smaller fragments by nucleases in tissues and the bloodstream in vivo in xenograft mouse models and indicated that higher imetelstat concentrations were associated with greater plasma exposure and target engagement17-19.
- The clinical benefit of imetelstat in myelofibrosis (MF) was demonstrated in a statistically significant and clinically meaningful improvement in red blood cell transfusion independence over placebo and a manageable safety profile20,21.
- The clinical benefit of imetelstat in myelofibrosis (MF) was demonstrated in the IMbark Phase 2 randomized dose-finding study (NCT02460868)10. The IMerge Phase 3 study (NCT04576156) is ongoing to evaluate a potential role of imetelstat for transfusion-dependent anemia in lower-risk MDS at the proposed clinical dose of 7.5 mg/kg ∗.

RESULTS

CONCLUSIONS

- Imetelstat disposition properties were well characterized in support of the 7.5 mg/kg q4w dosing regimen in LR-MDS.
- No dose adjustments were recommended for sex, mild to moderate renal or hepatic impairment, age, or race.
- Body-weight-based dosing is supported by the popPK analysis. There are no clinically relevant drug-drug interactions for imetelstat.
- Based on integrated nonclinical and clinical assessments, an imetelstat dose level expressed in terms of imetelstat sodium (7.5 mg/kg) is unlikely to be the victim of DDIs mediated by CYP enzymes or drug transporters.
- Drug-drug interactions.
- Effect of Other Drugs on Imetelstat: Like other oligonucleotides 12,23, imetelstat is unlikely to be the victim of DDIs mediated by CYP enzymes or drug transporters.
- Effect of imetelstat on Other Drugs: No indication of cardiac toxicity in imetelstat-treated patients.
- No treatment-related clinical signs or effects on CNS and cardiac parameters were found in monkeys at ≥2.5×human Cmax.
- No effect of ADA on imetelstat PK, safety, or efficacy in LR-MDS.

REFERENCES