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Blood 142 (2023) 3247–3248

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Phase 1b Trial of Irak 1/4 Inhibition for Low-Risk Myelodysplastic Syndrome Refractory/Resistant to Prior Therapies: A Trial in Progress

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Background and Significance:
Chronic stimulation of both the interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) in myeloid progenitors is thought to promote a proinflammatory environment in the bone marrow that causes persistent cytopenia in patients with low-risk myelodysplastic syndrome (LR-MDS). The serine/threonine kinases IRAK1 and IRAK4 are critical for the signaling downstream of IL-1R and most TLRs that promotes production of proinflammatory cytokines and NLRP3 inflammasome-driven pyroptosis, leading to bone marrow inflammation and cell death. Therefore, inhibition of IRAK1/4 is a potential target for the treatment of LR-MDS by decreasing inflammation and cell death within the bone marrow, allowing for restoration of hematopoiesis.
R289 is a prodrug that is converted to the active drug R835 in the gastrointestinal (GI) tract. R835 is a potent and selective inhibitor of IRAK1 and IRAK4 kinases that inhibits TLR and IL-1R-dependent proinflammatory cytokine production in multiple cell types. *In vivo*, R835 blocks TLR4 and IL-1R-dependent systemic cytokine release in mice.
The safety and pharmacokinetic properties of R289/R835 were evaluated in a phase 1 study in healthy volunteers (Study C-906289-001). R289 was well tolerated with no serious or severe adverse events (AEs) reported. Most AEs were mild and transient; the most common AEs (mild/moderate) were headache and GI disturbance. Overall, the phase 1 trial results supported the further study of R289. An open-label phase 1b study to determine the tolerability and preliminary efficacy of R289 for patients with LR-MDS refractory to prior therapies is currently recruiting patients.
Study Design and Methods:
The R289 phase 1b study (NCT05308264) is an open label, single arm, multi-center study, which includes a dose escalation phase (up to 12 patients) and a dose expansion phase (up to 10 patients). Inclusion criteria for both phases will include patients ≥18 years with a definitive diagnosis of low-risk MDS (International Prognostic Scoring System-R ≤3.5) and ≤5% bone marrow myeloblasts. Patients must be relapsed or refractory/resistant or intolerant to prior MDS therapies. Exclusion criteria include prior MDS treatment(s) within 4 weeks of study treatment, clinically significant anemia (from iron deficiency, hemolysis, or GI bleeding), and chronic myelomonocytic leukemia.
Dose Escalation Phase: A 3+3 dose escalation design will be used to determine the maximum tolerated dose (MTD). An initial R289 dose of 250 mg qd, will be given orally, with or without food, progressing to 500 mg qd with dose limiting toxicity (DLT) assessed at both doses. The DLT evaluation period will be 28 days. After completion, patients not experiencing DLTs may remain at their respective dose levels as long as they demonstrate continued clinical benefit without toxicity.
Dose Expansion Phase: Up to 10 additional patients with LR-MDS will be enrolled, with R289 administered to all patients at a dose not exceeding the MTD determined in the dose escalation phase.
The primary endpoint of the study is safety and tolerability of R289, assessed by incidence of AEs, discontinuation/interruption of R289 due to AEs, and incidence of DLTs. Secondary endpoints include preliminary efficacy, assessed by red blood cell transfusion independence by Week 24 (% achieving ≥50% reduction in transfusions), and pharmacokinetics of R289. Change from baseline in plasma biomarkers, including C-reactive protein and TNFα, and bone marrow biomarkers will be assessed.
Statistical analyses will be primarily descriptive. Tabulations will be produced for disposition, demographics, disease characteristics, safety, pharmacokinetics, pharmacodynamics, and clinical activity. For analyses of clinical activity, such as proportion of patients with RBC transfusion independence, complete responder rate, overall response rate, and proportion of subjects with hematologic improvements, the summary will be produced separately for the dose escalation phase and dose expansion phase. For the dose escalation phase, data will be summarized by dose level and overall.
The trial is currently recruiting at 9 US sites. The study has enrolled 7 patients in the dose escalation phase.

Disclosures Garcia-Manero: *Bristol Myers Squibb:* Other: Medical writing support, Research Funding; *Genentech:* Research Funding; *AbbVie:* Research Funding. **Yan:** *Rigel Pharmaceuticals, Inc.:* Current Employment, Current equity holder in publicly-traded company.

https://doi.org/10.1182/blood-2023-172511