279

Study Design of a Phase 3, Randomized, Open-Label, Multicenter Study to Evaluate Ruxolitinib Over BAT in Patients with Corticosteroid-Refractory Chronic Graft vs Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation (REACH-3)

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Background: Allogenic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for many patients with blood-related malignancies. Graft-versus-host disease (GvHD) is a major limitation for the success of allo-HSCT. Approximately, 40-50% of patients may develop SR-cGvHD, and the incidence is lower in children. About 50-60% of patients with moderate to severe cGvHD become corticosteroid refractory in ≤ 2 years after initial therapy and may need addition of another systemic therapy beyond corticosteroids and calcineurin inhibitor (CNI). Steroid-refractory cGvHD (SR-cGvHD) is associated with high morbidity and long-term mortality, as well as reduced quality of life, hence representing an unmet medical need. In a retrospective survey, ruxolitinib has demonstrated promising outcomes in patients with SR-cGVHD (Zeiser et al. 2015). Zeiser et al. also showed that ruxolitinib was generally well tolerated; CMV reactivation, rates of thrombocytopenia, and rate of underlying malignancy relapse are favorable when compared to published literature on the use of BAT (best available therapy) in patients with SR-cGvHD. REACH-3 is a prospective, phase 3 study investigating the efficacy of ruxolitinib as add-on therapy to corticosteroid therapy in patients with SR-cGVHD.
Methods: REACH-3 is a phase 3, randomized, open-label, multicenter study. Patients aged ≥ 12 years who underwent allo-HSCT, who have evidence of myeloid and platelet engraftment (absolute neutrophil count > 1000/mm^3 and platelets ≥ 25,000/mm^3) and have been diagnosed with moderate or severe cGvHD according to NIH Consensus Criteria (Jagasia et al, 2015), are eligible for inclusion. Patients are excluded if they have received prior JAK inhibitors for aGvHD except when they achieved complete response (CR) or partial response (PR) and have been off JAK inhibitor for ≥ 8 weeks prior to cycle 1 day 1, have failed prior SCT ≤ 6 months, or have overlap syndrome. Eligible patients will be randomized 1:1 to receive either ruxolitinib 10 mg orally twice daily or investigator-determined BAT. Patients randomized to the BAT arm are allowed to cross over to the ruxolitinib arm (Figure 1). Each patient will be treated and/or followed for a total of 3 years (39 cycles/156 weeks).

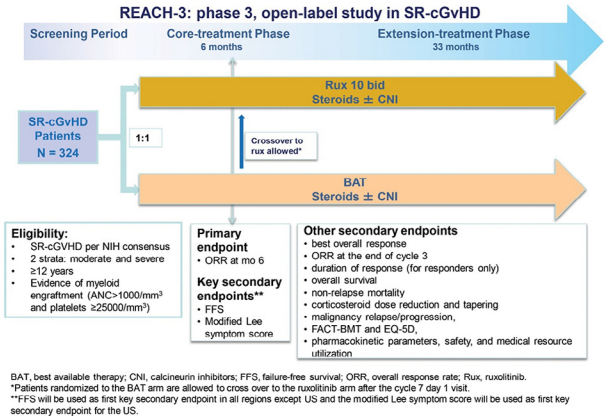

Figure 1. Study design.

The primary objective is to compare the efficacy of ruxolitinib vs BAT as assessed by overall response rate (ORR) at month 6. ORR is defined as the proportion of patients with CR or PR according to 2014 NIH response guideline (Lee et al, 2015). Overall 324 patients are planned to be enrolled to achieve 90% power for the ORR comparison (assuming odds ratio = 2.35). Failure-free survival and the modified Lee symptom score are key secondary endpoints. Please refer to figure for more details on end points.
Results/Conclusions: First patient was enrolled in June 2017. Enrollment is ongoing. Trial registered at ClinicalTrials.gov: NCT03112603.

280

Trial in Progress: Gravitas-301, a Randomized, Double-Blind Phase 3 Study of Itacitinib or Placebo with Corticosteroids (CS) for the First-Line Treatment of Patients with Acute Gvhd (aGVHD)

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Background: Approximately 50% of patients who receive allogeneic hematopoietic stem cell transplantation (aHSCT) for hematologic disorders develop aGVHD, a leading cause of nonrelapse mortality (NRM). There are currently no FDA-approved treatments for aGVHD; standard-of-care includes first-line treatment with CS. However, only a minority of patients experience sustained responses to CS, underscoring the need for improved treatments. Janus activated kinase (JAK), which is a transducer of signals from multiple cytokine receptors, has been implicated in GVHD pathogenesis. JAK inhibitors have demonstrated improvements in aGVHD outcomes while preserving the graft-versus-leukemia effect in preclinical models, and have shown preliminary clinical efficacy in patients with CS-refractory aGVHD. Itacitinib is a potent, selective JAK1 inhibitor that demonstrated an acceptable safety profile in a phase 1 study of patients with CS-naive and CS-refractory aGVHD. This report summarizes the study design for an ongoing phase 3 trial of first-line treatment with itacitinib in patients with aGVHD.
Methods: GRAVITAS-301 (NCT03139604) is a randomized, double-blind, placebo-controlled, multicenter, phase 3 study comparing the efficacy of itacitinib or placebo in