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cGvHD

ASH 2018 | Pharmacodynamics and updated data from the phase IIa KD025-208 trial

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KD025, a Rho-associated coiled-coil kinase 2 (ROCK2) inhibitor, was studied in a phase II trial (KD025-208, NCT02841995) in patients with chronic graft-versus-host disease (cGvHD). The previous results of this study, presented at the European Hematology Association 2018 Annual Meeting, have been reported by the GvHD Hub here. On Monday 3 December, an oral session was held and entitled: *722. Clinical Allogeneic Transplantation: Acute and Chronic GVHD, Immune Reconstitution: GVHD Treatment and Prevention Strategies* at the 60th American Society of Hematology (ASH) Annual Meeting, held in San Diego, California, from 1–4 December 2018. During this session, an oral abstract was presented by Madan Jagasia from Vanderbilt University Medical Center, Nashville, TN, USA. The title of the talk was: *602 KD025-208: A Phase 2a Study of KD025 for Patients with Chronic Graft Versus Host Disease (cGVHD) - Pharmacodynamics and Updated Results*.

Professor Jagasia began his talk by introducing the open-label, dose-escalation phase II study investigating KD025, an oral ROCK2-selective inhibitor, in patients with steroid-dependent or refractory cGVHD. KD025 may reduce inflammation and fibrosis in cGvHD by downregulating Tfh and Th17 cells as well as upregulating regulatory T cells. The key endpoints of the study included overall response rate, safety, and duration of response, response by organ system, and changes in corticosteroid and calcineurin inhibitor doses.

Patient characteristics

- In total, 54 patients with cGvHD involvement across all organ systems were enrolled and divided into three cohorts
  - Cohort 1, n = 17 patients (6 active)
  - Cohort 2, n = 16 patients (3 active)
  - Cohort 3, n = 21 patients (11 active)
- Median treatment duration
  - Cohort 1: 37 weeks
  - Cohort 2: 33 weeks
  - Cohort 3: 27 weeks
- Median age
  - Cohort 1: 50 years (range, 20-63)
  - Cohort 2: 55 years (range, 30-75)
  - Cohort 3: 46 years (range, 25-75)

- Median time cGvHD diagnosis prior to KD025 treatment:
  - Cohort 1: 25.9 months
  - Cohort 2: 15.8 months
  - Cohort 3: 20.3 months
- 67% of patients had received more than two prior lines of therapy
- 48% of patients had more than four organs involved
- Cohort 1 received 200 mg QD of KD025
- Cohort 2 received 200 mg BID of KD025
- Cohort 3 received 400 mg QD of KD025

Key findings

- Median treatment duration: 89 weeks in Cohort 1, 68 weeks in Cohort 2, and 34 weeks in Cohort 3
- Safety
  - Most common adverse events (AEs)
    - Cohort 1: elevated AST/ALT (35%), diarrhea (35%), nausea (35%) anemia (29%), elevated GGT (24%)
    - Cohort 2: upper respiratory tract infection (38%), elevated GGT (31%), anemia (25%), elevated AST/ALT (25%)
    - Cohort 3: fatigue (24%), nausea (24%), cough (24%), hyperuricemia (24%)
  - Most common grade > 3 AEs
    - Cohort 1: elevated GGT (18%), anemia (12%), hyperglycemia (12%)
    - Cohort 2: elevated GGT (19%), anemia, elevated ALT/AST
    - Cohort 3: hyperglycemia (12%)
  - Related serious adverse events in all cohorts: 0
- Overall response rate (ORR)
  - ORR in Cohort 1: 65% (11/17)
  - ORR in Cohort 2: 63% (10/16)
  - ORR in Cohort 3: 52% (11/21)
- Responses across organ systems
  - Complete responses (CRs) in upper GI, lower GI, esophagus, mouth, joints/fascia, skin, eyes and liver
  - Partial responses of the lung were observed in two patients
- Duration of response
  - Responses are durable with KD025
  - Rapid responses were observed, 75% of responders had a response at the first assessment (8 weeks)
- Corticosteroid and tacrolimus dose reduction

- Cohort 1: 73% (8/11) of responders and 83% (5/6) of non-responders achieved steroid dose reductions, and 67% of patients achieved tacrolimus dose reduction
- Cohort 2: 50% (5/10) of responders and 67% (4/6) of non-responders achieved dose reductions in steroid use, 83% of patients achieved tacrolimus dose reductions
- Cohort 3: 91% (10/11) of responders and 50% (5/10) of non-responders achieved dose reductions in steroid use, 45% of patients achieved tacrolimus dose reductions
- Seven patients completely discontinued steroid use

- Pharmacodynamics
  - KD025 may regulate immune homeostasis by restoring the TH17/Treg balance
  - Treg cells increased with KD025 treatment
  - TH17 cells decreased during therapy
  - These results are consistent with KD025 mechanism of action

Professor Jagasia concluded that KD025 "achieved clinically meaningful responses and it was well tolerated without treatment-related serious adverse events." Responses with KD025 are clinically meaningful because responses were durable, patients were able to reduce or even discontinue steroid therapy or other immunosuppressants, and symptoms clinically improved. Exploratory pharmacodynamics showed that KD025 decrease TH17 and increase Treg cells during therapy.

Based on this data presented at ASH 2018, KD025 is a promising therapy choice for cGvHD patients providing favorable clinical outcomes, while minimizing adverse events of high dose steroid therapy.

To listen to Professor Jagasia discussing this study click here.

Reference

1. Jagasia M. *et al*. KD025-208: A Phase 2a Study of KD025 for Patients with Chronic Graft Versus Host Disease (cGVHD) - Pharmacodynamics and Updated Results. Abstract #602. *ASH 60th Annual Meeting and Exposition*, December 2018, San Diego, CA.