GvHDHub

cGvHD

TCT 2019 | Pharmacodynamics and updated data from the phase IIa KD025-208 trial

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On 21 February 2019 at the 2019 TCT Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR in Houston, Texas, USA, Madan Jagasia from the Vanderbilt University Medical Center, presented updated data from the phase IIa KD025-208 study of patients with chronic graft versus host disease (cGVHD).

cGVHD is characterized by an imbalance between effector and regulatory arms of the immune system that results in overproduction of IL-17 and IL-21. A reduction in the regulatory T (Treg) cells limits the ability of the immune system to re-calibrate this pro-inflammatory environment. KD025 is an oral Rho kinase 2 (ROCK2) selective inhibitor. *In vitro* data demonstrate KD025 modulates immune homeostasis by shifting the Th17/Treg balance towards Treg.

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**
  - 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%)
  - Cohort 1: elevated GGT (18%), anemia (12%), hyperglycemia (12%)
  - Cohort 2: elevated GGT (19%), anemia, elevated ALT/AST
  - Cohort 3: hyperglycemia (12%)
  - Most common adverse events (AEs)
  - Most common grade > 3 AEs
  - 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 KD025 achieved responses with little toxicity. Responses are clinically meaningful with durability, reductions in CS doses and improvement in LSS score. PD data indicate KD025 may restore the Th17/Treg balance.

Based on this data presented at TCT 2019, KD025 is a promising therapy choice for cGvHD patients providing favorable clinical outcomes, while minimizing adverse events of high dose steroid therapy.

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 #36. 2019 Feb 21. 2019 TCT Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR, Houston, Texas, USA.