First-In-Human Phase I Study of Gatigostavim, A Novel Claudin 18.2/4-1BB Bispecific Antibody in Advanced Solid Tumors


**METHODS**

- **Network2018** is an open-label, first-in-human, phase 1 study of patients with advanced solid tumors utilizing the SysteomeXOptimal (SXM) design to evaluate the safety, tolerability, maximum tolerable dose (MTD), or maximum recommended dose (MRD) of Gatigostavim (GVT, pharmacokinetics (PK), pharmacodynamics (PD), recommend phase 2 dose (RP2D) based on preliminary efficacy of gatigostavim as monotherapy.

- **Dose escalation** started with the RP2D of gatigostavim (10 mg/kg) and escalated every 2 weeks (QW), and escalated up to 15 mg/kg over 4 different dose levels regardless of CLAUDIN18.2-presentation. Dose levels 1, 3, 10, and 15 mg/kg were explored to include an additional 6 patients each with CLAUDIN18.2-positive tumors. Each 6 patients were enrolled in a 2:1 (50%:50%) distribution on a 1-in-1 randomization of treatment group, defined as membranous expression of CLAUDIN18.2 and/or 1% of cells. An exploratory cohort of up to 30 patients with CLAUDIN18.2-positive GVE/CAR-T were evaluated in a separate, non-randomized phase 2a trial (RP2D) in mCRC or cholangiocarcinoma.

- **An exploratory cohort** will enroll up to 30 patients with CLAUDIN18.2-positive GVE/CAR-T.

- **A double-blind, placebo-controlled, phase 3 study** was conducted to evaluate the efficacy of gatigostavim compared to chemotherapy in patients with advanced gastric/GEJ adenocarcinoma (G1-2), advanced adenocarcinoma of the esophagus (AEO), esophageal squamous cell carcinoma (ESCC), or cholangiocarcinoma (CCA).

- **Clinical trial** of AUA 2020 for patients enrolled to the dose escalation and parallel dose escalation are described in two separate studies.

**RESULTS**

**Efficacy**

- Total of 16 subjects enrolled: 21 GC (20 CLAUDIN18.2+), 2 GGE (2 CLAUDIN18.2-), 14 PDAC (8 CLAUDIN18.2+), and 15 other various types (5 CLAUDIN18.2-).

- Of the 21 patients with CLAUDIN18.2-positive tumors were CLAUDIN18.2+; 20 patients were evaluable and closed at 8, 12, and 15 mg/kg. Partial response (PR) was observed in 3 out of 20 subjects that indicated 15 mg/kg (CLAUDIN18.2+ 1, 15+, 1+); 1, 15+, 1+; 11 mg/kg (CLAUDIN18.2+ 3, 15+, 1+); 11 mg/kg; 9 mg/kg (CLAUDIN18.2+ 2, 15+, 1+); 11 mg/kg; and 6 mg/kg (CLAUDIN18.2+ 1, 15+, 1+); 9 mg/kg; and 6 mg/kg.

- Stable disease (SD) was also observed in 4 out of 20 the evaluable patients. One patient had a PR on the first scan and subsequently withdrew from the study due to meeting criteria for SD.

- As additional PRs were observed in one patient with head and neck squamous cell carcinoma remaining 15 mg/kg, who remains on study at 230 days.

**Safety**

- No GVT was reported at 10 mg/kg, and NTD was not noted.

- The most commonly reported (≥20%) treatment-related adverse events (TAR) include Grade 1 or 2 nausea (23 of 32 subjects; vomiting (16%), fatigue (15%), and anemia (19%).

- The most severe (≥3%) experience at least Grade 3 TAR; No Grade 3 TARs occurred in more than 1 subject.

- Event rates of gastrointestinal AEs were generally after 14 days of treatment and recovered within 1 week, none led to drug withdrawal.

**Pharmacokinetics and Pharmacodynamics**

- Linear PK of gatigostavim was observed in all subjects with an apparent effective half-life of 5.5-7.6 days at a Q2W dose.

- At a 10 mg/kg Q2W, an individual dose after one cycle reached the target concentration (12 mg/L), derived from non-clinical pharmacokinetics studies and in vivo PK/TD study data.

- Bolusized and dose-dependent increase in soluble 4-1BB is observed with the highest induction of biomarker in the peripheral blood at 4.5 mg/kg and 12 mg/kg.

**CONCLUSIONS**

Gatigostavim monotherapy is safe and well-tolerated at up to 15 mg/kg in patients with advanced solid tumors. No DLT was observed and MTD was not reached.

Enrolling monotherapy safety was observed in heavily pre-treated GC, GEE, and EAC patients with a wide range of CLAUDIN18.2 expression, including low CLAUDIN18.2 tumors.

Linear PK profiles and dose-dependent anti-4-1BB induction without systemic changes in peripheral T cell activation or cytokine expression was observed with gatigostavim at 10-15 mg/kg administered every 2 weeks, including those who failed prior PD-L1 therapy.

Overall activity in 15 mg/kg CLAUDIN18.2-positive parallel dose escalation and 12 mg/kg dose escalation cohorts. Future development of gatigostavim in the treatment of third- and first-line GC, EAC, and DACC patients is planned.

**REFERENCES**

- GVE/CAR-T is the first-in-human CLAUDIN18.2-specific antibody designated as the 4-1BB chimeric antigen receptor (CAR) construct.

- Gatigostavim is a first-in-class bispecific antibody targeting CLAUDIN18.2 (CLCN18.2) and 4-1BB and with two key advantages:

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