DKK1-01 in Combination with Tislelizumab and Chemotherapy as a First-line Therapy in Unselected Patients with Advanced Gastroesophageal Adenocarcinoma (GEA): DisTinGuish Trial

Background
- DisTinGuish Trials is a phase 2 trial with two parts.
- Part A is reported here.
- Part B evaluates second-line treatment with 300 or 600 mg DKN-01.

Preclinical Models
- DKN-01 activates innate immune response in preclinical models characterized by increased infiltration of NK cells and reduced MDSC function.
- DKN-01 suppresses anti-tumor immune responses through the downregulation of NK cell phagocytosis.
- DKK1 expression was associated with longer PFS (22.1 weeks vs 5.9 weeks).

Method
- Statistical significance was determined using the Wilcoxon rank sum test.
- Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Results
- Best Overall Response by DKK1 Expression
  - Tislelizumab + CAPOX vs CAPOX + Placebo: ORR: 50 vs 10
  - Median DoR and PFS were not reached.

Safety
- Most common DKN-01-related adverse events: fatigue, diarrhea, nausea, musculoskeletal disorder.
- Double-negative patients (DKK1-low and PD-L1 vCPS <5) overall (79% vs 67%) and in DKK1-high patients (100% vs 75%).

Conclusion
- DKN-01 + tislelizumab + CAPOX was well tolerated and has encouraging response rates as first-line treatment for advanced GEA.
- Improved ORR outcomes in the overall population compared to current standard of care in an unselected PD-L1-negative population.
- Efficacy driven by enhanced ORR in the DKK1-high patients, an aggressive subpopulation.
- Duration of response and progression-free survival data are not yet mature, expected in first half of 2022.

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References: