Introduction

Enfortumab vedotin (EV) is an investigational antibody-drug conjugate (ADC) that is comprised of a Nectin-4 targeted monoclonal antibody (mAb) attached to a mitotic spindle-disrupting agent, monomethyl auristatin E (MMAE), via a protease- cleavable linker.

Nectin-4 is a cell adhesion protein highly expressed in several solid tumors, including bladder, breast, lung, and gastroesophageal cancers.

EV delivers MMAE to Nectin-4 positive cells, leading to cell cycle arrest and cell death.

Pharmacodynamic (PD) pharmacokinetic (PK) studies in dogs showed near-zero clearance of both the parental mAb and MMAE, and the pharmaco-kinetics of MMAE were similar in EV and non-binding ADC.

The PK profile of MMAE from EV was consistent across species, with a terminal phase half-life of 15.7 days in cynomolgus monkeys (Cynomolgus Monkeys, species: Macaca fascicularis, sex: Male, n = 3), and 7.6 days in healthy human volunteers (n = 12). The half-life of MMAE in cynomolgus monkeys and humans was consistent with previous studies in which the terminal phase half-lives ranged from 7.5-10.4 days.

EV was designed to have high specificity for Nectin-4, with results of an in vitro binding assay showing low binding of EV to a panel of negative tumor cells, but high binding to Nectin-4 positive T-24, T-24 Nectin-4, J82, and UM-UC-3 bladder cancer cell lines.

Additionally, EV induced the translocation or secretion of intracellular components to promote and sustain bystander effects in Nectin-4 negative cells.

EV induces the release of pro-inflammatory cytokines and upregulates genes coding for MHC-Class I and II, and the transporter associated with antigen presentation (TAP). Upregulation of differentially regulated genes was observed in EV treatment compared to untreated samples.

EV demonstrates the potential to turn "cold" tumors "hot" in bladder cancers by inducing immunogenic cell death and promoting immune cell recruitment at the tumor site.

Conclusions & Future Directions

- Beyond targeted antitumor activity, cytotoxic and bystander effects, the following antitumor mechanisms of action of enfortumab vedotin in urothelial cancer have been demonstrated:

  - The bystander effect activity supports clinical studies in heterogeneous Nectin-4-expressing tumors.
  - Induction of early hallmarks of immunogenic cell death result in the recruitment and upregulation of immune cells to bladder cancer models.
  - Potential to promote immune cell recruitment ("cold" tumor "hot") at the tumor site by a range of bladder cancer models.
  - Increased expression of HMACH-Class I and Class II to activate the adaptive immune system.
  - Future experiments include demonstrating the bystander activity of the combination of enfortumab vedotin and a PD-1/L1 inhibitor and examining mechanisms that may drive admissable responses.

- These data provide rationale for the clinical combination of enfortumab vedotin and a PD-1/L1 inhibitor, demonstrating drug synergy and immune cell recruitment.

- The Phase 1 dose-escalation and cohort A study was completed in an Asian population, and the Phase 3 study is ongoing in diverse populations. Further data are required to understand the impact of race and ethnicity on drug response.

- Additional mechanisms of action of enfortumab vedotin, an anti-Nectin-4 ADC demonstrating bystander effect and immunogenic cell death mechanisms in urothelial carcinoma

- Two Phase 3a clinical trials are anticipated: One for metastatic urothelial carcinoma (MUC) patients with Nectin-4 expressing primary tumors and the other in metastatic triple-negative breast cancer (MBC) patients with Nectin-4 expressing primary tumors.