A phase 1b single-arm study of bintrafusp alfa for the treatment of pretreated, locally advanced/unresectable or metastatic urothelial cancer

INTRODUCTION

Urothelial cancer
- UC is the most common histological type of bladder cancer (>90% of diagnoses!)
- Platinum-based CT is the 1L SOC in mUC for patients able to tolerate it
- Five PD-L1+ inhibitors have been approved in platinum-refractory or platinum-ineligible mUC, with ORRs of 18% to 23%12
- Low ORRs in this setting indicate an unmet need for improved outcomes

TGF-β
- Overexpression of TGF-β is significantly correlated with invasive UC and advanced cancer stage, while TGF-β activation is associated with immune exclusion of tumors10
- TGF-β signaling has been associated with resistance to PD-L1 inhibitors in patients with mUC10
- Lower TGF-β expression was associated with greater OS benefit withavelumab10
- Simultaneous inhibition of the TGF-β pathway in the TME and PD-L1 pathway in UC may:

Bintrafusp alfa
- Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-βRII receptor to function as TGF-β “trap” fused to a human IgG1 antibody blocking PD-L1 (Figure1).
- Bintrafusp alfa is designed to target tumors via colocalized, simultaneous blocking of 2 nonredundant immunosuppressive pathways (TGF-β and PD-L1), which may potentially improve clinical benefit in mUC10
- In 2 phase 1 trials (NCT020517396; NCT020969515), bintrafusp alfa demonstrated encouraging clinical activity and manageable safety profile in >670 patients with advanced solid tumors11-17
- This is the first study in which bintrafusp alfa is being evaluated in patients with UC.

Figure. Proposed mechanism of action of bintrafusp alfa

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Tumor cells are a major source of TGF-β to the TME.