Phase 1/2 study using ENB-003, a first-in-class selective ETBRI, in combination with pembrolizumab in subjects with advanced refractory solid tumors

Sumayah Jamal, MD-PhD1, Adnan Nagrial, MD2, Anthony M. Joshua, MD3, Richard W. Eek, MD4

1ENB Therapeutics Inc, New York, NY, USA; 2Blacktown Cancer and Haematology Centre, Blacktown NSW, AUS; 3Kinghorn Cancer Centre, Darlinghurst, NSW, AUS; 4Border Medical Oncology Research Unit Albury NSW, AUS

INTRODUCTION

The endothelin B receptor (ETBRI) is upregulated in many types of cancer and is associated with poor overall survival and a paucity of TILs (Tumor infiltrating lymphocytes). The ETBRI provides a target for cancer therapy by mediating adhesion molecule downregulation in the tumor vasculature. Thus ETBRI expression may mediate resistance to immunomodulatory therapy. ENB-003 is a small molecule ETBRI (ETBRI inhibitory) which overcomes resistance to anti-PD1 across many cancer types in preclinical studies. Part 1 of this study seeks to evaluate the safety and tolerability of ENB-003 in combination with pembrolizumab in refractory advanced ETBR+ solid tumors. Part 2 of the study is an expansion cohort trial assessing the efficacy of ENB-003 in combination with pembrolizumab in anti-PD1 refractory melanoma, platinum resistant ovarian cancer and refractory pancreatic cancer.

METHODS

Preclinical: for all studies except the pancreatic model 6-8 week old female C57Bl6 mice were implanted with tumor cells and dosing initiated when tumors were 50mmx50mm. For the orthotopic pancreatic model, dosing was initiated 10 days after tumor implantation and tumors harvested and weighed at day 10 of the study. ENB-003 was administered weekly for a total of 6 doses (4 doses for the pancreatic study). Anti-PD1 was administered IP Q40. Clinical: Study ENB-003-101 (MK-3475-951) is a multicenter, Phase 1/2, open-label study of ENB-003 in combination with pembrolizumab in adult subjects with advanced solid tumors. The part 1 dose escalation is enrolling subjects with ETBR tumors and includes 5 doses of ENB-003 in combination with a fixed dose of pembrolizumab (200ug). Pembrolizumab is administered once every 21-day cycle. ENB-003 is administered iv as a sole agent during a 1 week monotherapy run-in, followed by combination therapy with pembrolizumab. ENB-003 is administered 3x per week for a total of 6 doses in 3q on numbered cycles. The primary objective of part 1 is to assess safety and tolerability, the secondary objective is to evaluate anti-tumor effect (iRECIST 1.1 and iRECIST). Exploratory objectives are to examine biomarkers/pharmacokinetics.

RESULTS

Preclinical: ENB-003, as a single agent and in combination with anti-PD1, was investigated in a variety of syngeneic preclinical models. ENB-003 enhanced the anti-tumor activity of anti-PD1 in anti-PD1 resistant models of melanoma, ovarian cancer, pancreatic cancer, bladder cancer and SCC (see Figures 1-4, data for bladder cancer and SCC not shown). For example, the combination of ENB-003 plus anti-PD1 in an anti-PD1 resistant melanoma model resulted in complete tumor eradication in 21 days as well as the formation of TILs (lymphoid lymph organ) – see Figure 1.2. Clinical: The combination of ENB-003 plus pembrolizumab was well tolerated, with no SAEs observed, in the first 2 cohorts of the ongoing Phase 1B trial in patients with advanced refractory solid tumors that are ETBR+. Best overall responses from the first 2 cohorts (iv+iv) demonstrates disease progression (PD) in 3 patients, disease stabilization (SD) in 2 patients as well as a partial response (PR) in an ovarian cancer patient with ‘>90% reduction in target lesions’ (see Figure 5). The 150ug cohort is substantial therapeutic but the 300ug dose is at the low end of the therapeutic window extrapolated from preclinical studies.

REFERENCES


ACKNOWLEDGEMENTS

Trial registration NCT04420227. This study was approved by an institutional Review Board at each investigational site.