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

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INTRODUCTION

The endothelin B receptor (ETBR) is upregulated in many types of cancer and is associated with poor overall survival and a paucity of TILs (tumor infiltrating lymphocytes). The ETBR prevents T-cell extravasation and tumor infiltration by a mechanism involving adhesion molecule downregulation in the tumor vasculature. Thus ETBR expression may mediate resistance to immunomodulatory therapy[1]. ENB-003 is a small molecule ETBRi (ETBR inhibitor) which overcomes resistance to anti-PD1 across multiple 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 basket 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 50mm3-150mm3. 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 3X a week for a total of 6 doses (4 doses for the pancreatic study). Anti-PD1 was administered IP Q4D.

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 odd numbered cycles. The primary objective of part 1 is to assess safety and tolerability, the secondary objective is to evaluate anti-tumor effect (RECIST 1.1 and iRECIST). Exploratory objectives are to examine biomarkers/ pharmacodynamics.

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 TLOs (tertiary lymphoid organs)- see Figures 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 (n=6) 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 ~60% reduction in target lesions (see Figure 5). The 150ug cohort is subtherapeutic while the 300ug dose is at the low end of the therapeutic window extrapolated from preclinical studies.

RESULTS

Fig. 1 ENB-003 overcomes anti-PD1 resistance in a syngeneic melanoma model and eradicates tumors within 21 days: The SM1 model does not respond to anti-PD1 but is demonstrated in the literature to have a partial response to the combination of anti-PD1+ dabrafenib. The aim of this study was to determine whether the combination of ENB-003+anti-PD1 was superior to this combination

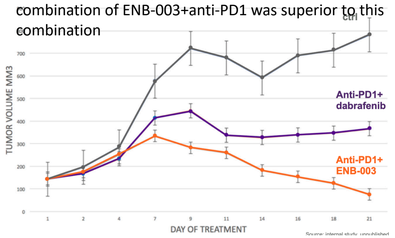


Fig. 2 ENB-003+ anti-PD1 eradicates melanoma tumors within 21 days, promotes robust CD8 infiltration and intratumoral TLO formation

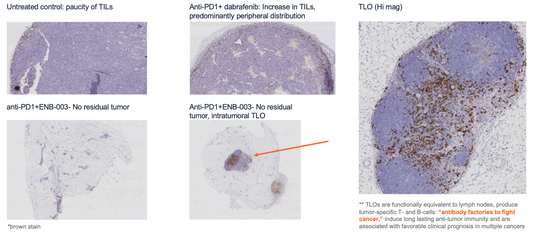


Fig. 3 ENB-003 overcomes anti-PD1 resistance in a syngeneic ovarian cancer model (ID8-VEGF)

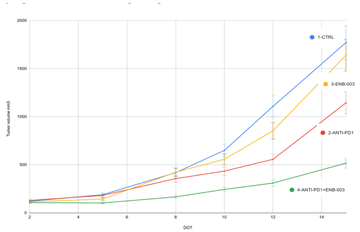


Fig. 4 ENB-003 enhances anti-PD1 response in a syngeneic orthotopic pancreatic cancer model (UNMC-6141)

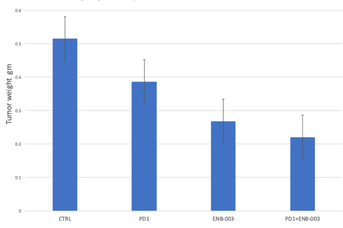
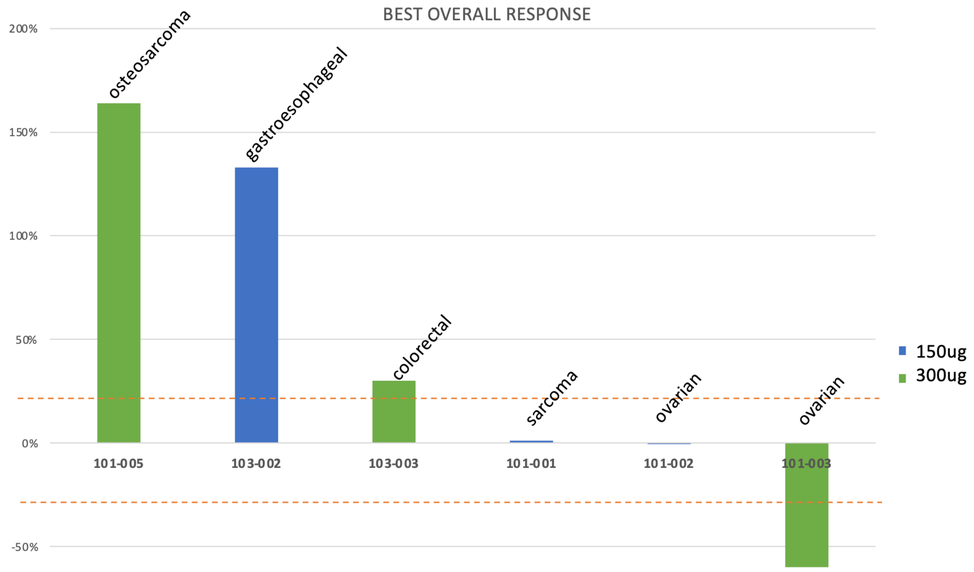


Fig. 5 BEST OVERALL TUMOR RESPONSES Ph1B: ENB-003+ PEMBROLIZUMAB

Design of the Phase 1B 3+3 dose escalation study: we are currently dosing at 500ug; CT scans pending



CONCLUSIONS

ETBRi is a novel approach to overcoming immunotherapy resistance. The combination of ENB-003 and pembrolizumab is well tolerated thus far and is demonstrating promising early signals of anti-tumor efficacy. The best signals thus far were observed in platinum resistant ovarian cancer patients, one of our target indications. These patients demonstrate <10% ORR to anti-PD1 as a single agent so the 60% PR is promising. Since the 150ug dose was subtherapeutic and the 300ug dose is at the low end of the extrapolated therapeutic window, we anticipate more robust responses as we dose escalate.

REFERENCES

1. Kandalaft, L. et al; Endothelin B Receptor, a New Target in Cancer Immune Therapy; Clin Cancer Res 2009;15(14): pg4521

ACKNOWLEDGEMENTS

Trial registration NCT04205227. This study was approved by an institutional Review Board at each investigational site.