ENB-003, an ETBR inhibitor, in combination with pembrolizumab for 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 (vodudeutentan) 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 refractory and platinum resistant ovarian cancer, chemoresistant pancreatic cancer, chemoresistant TNBC (triple negative breast cancer) and anti-PD1 resistant SCC (squamous cell carcinoma) of the head and neck

MATERIALS AND METHODS

Preclinical: For all studies, 6-8 week old female C57BL6 mice were implanted with tumor cells and dosing initiated when tumors were 50mm3-150mm3. ENB-003 was administered IV, unless otherwise indicated, 3X a week for a total of 6-9 doses Anti-PD1 was administered IP Q4D. For orthotopic studies, dosing was initiated 10 days after implantation.

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 refractory solid tumors. The part 1 3+3 dose escalation is enrolling subjects with ETBR+ tumors and includes 6 escalating doses of ENB-003 (ranging from 150ug-2000ug) in combination with a fixed dose of pembrolizumab (200mg). Pembrolizumab is administered once every 21-day cycle. ENB-003 is administered IV as a single agent during a 1-week monotherapy run-in, followed by combination therapy with pembrolizumab. ENB-003 was administered 3x per week for a total of 6 doses in odd numbered cycles for the first 5 cohorts and administered every cycle for the last and current cohort. The primary objective of part 1 is to assess safety and tolerability, the secondary objective is to evaluate anti-tumor effect (RECIST 1.1 , iRECIST and OS for PAC). Exploratory objectives are to examine biomarkers/ pharmacodynamics.

PRE-CLINICAL RESULTS

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, breast cancer and SCC (see Figures 1-4, data for bladder cancer, ovarian 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.

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 as a single agent 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

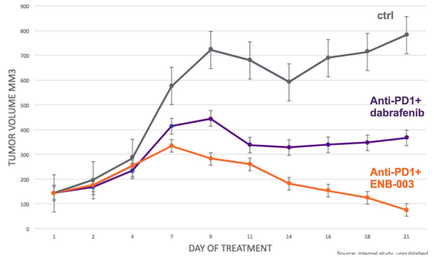
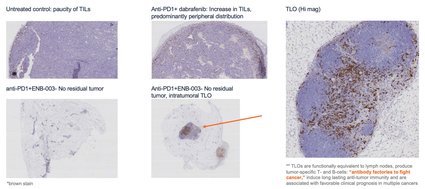


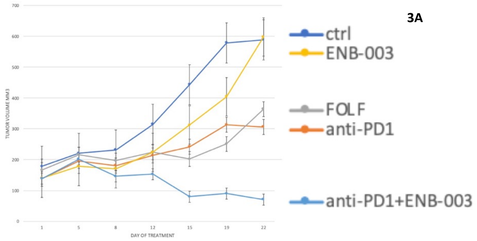
Fig. 2 ENB-003+ anti-PD1 eradicates melanoma tumors within 21 days, promotes robust CD8 infiltration and intratumoral TLO formation



PRE-CLINICAL RESULTS

Fig 3. ENB-003+ anti-PD1 combination is superior to standard of care FOLFIRINOX in a syngeneic pancreatic cancer model: Model= UN-KC-6141

3A. FOLFIRINOX treatment resulted in rapid outgrowth of drug resistant tumor whereas the combination of anti-PD1 plus ENB-003 resulted in ~50% tumor shrinkage at study termination. **3B.** No tumor growth was observed at 22 days with the ENB-003 +anti-PD1 combination when tumor cells were implanted orthotopically



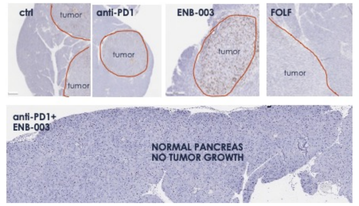
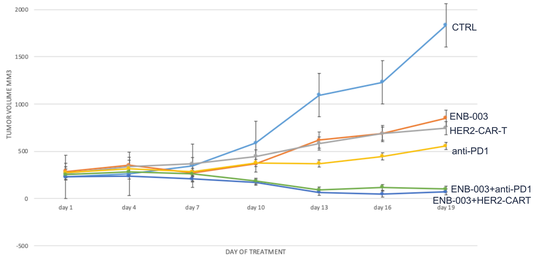


Fig 4. SC formulation of ENB-003 with single agent activity in syngeneic breast cancer model and eradicates 50% of tumors when combined with either HER2-CAR-T or anti-PD1 : model= 4T1-HER2

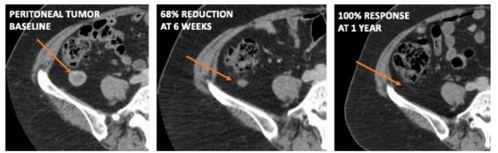


PHASE 1 CLINICAL RESULTS (ONGOING)

Clinical: The combination of ENB-003 plus pembrolizumab was well tolerated, with no additional toxicity caused by ENB-003 over the known toxicity profile of pembrolizumab. In the ongoing Phase 1B trial, best overall responses across 16 patients to date within our target indications demonstrate a DCR of 50% with one 95% partial response (PR) in a platinum refractory ovarian cancer patient (see Figure 5), disease stabilization (SD) in 7 patients and disease progression (PD) in 8 patients, and a 7-month SD was also observed in an anti-PD1 refractory HN-SCC in an early cohort. Plasma levels of ENB-003 were subtherapeutic across the first 5 cohorts. The drug IC50 was only achieved in the current (6th) cohort. All patients in the first 5 cohorts were ETBR+. To date, 2 ETBR+ (1 SD- 4TH line PAC with 7+ months OS; 1 PD) and 3 ETBR- patients (2 SD and 1 PD) have been enrolled in the 6th cohort.

Fig 5. The : ENB-003 + pembrolizumab combination resulted in a 95% reduction in tumor burden in a platinum refractory ovarian cancer patient that was durable out to a year. Serial CT scans and measurements of lesions are shown below. Of note:

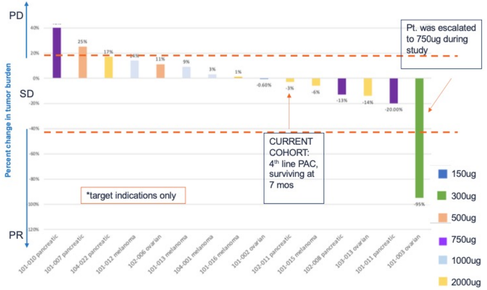
- The patient was PD-L1 negative and MSS (micro-satellite stable) making it unlikely that the response was solely due to the activity of pembrolizumab
- Historically, platinum refractory ovarian cancer patients do not respond to single agent anti-PD1
- MSI-H/dMMR ovarian cancer patients have a mPFS of ~2 months and maximum PFS of 6 months with single agent pembrolizumab



CT SCAN	BASELINE	6 WEEKS	12 WEEKS	24 weeks	36 weeks	52 weeks
Target lesions mm	36 52 25	17 21 25	14 14 8	0 12 6	0 8 0	0 6 0
Sum (mm)	113	63 (-44%)	36 (-68%)	18 (-84%)	8 (-93%)	6 (-95%)
Non-target lesions mm	2	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD	PD 1 of 2

PHASE 1 CLINICAL RESULTS (ONGOING)

Fig 6. Best response of target lesions in target indications



CONCLUSIONS

ETBRi is a novel approach to overcoming immunotherapy resistance. The combination of ENB-003 and pembrolizumab demonstrates robust preclinical proof of concept for enhancing immunotherapy efficacy such as anti-PD1 and CAR-T, across multiple cancer indications. In the clinic, the combination is well tolerated and is demonstrating promising early signals of anti-tumor efficacy. The best signals thus far have been observed in platinum refractory/ resistant ovarian cancer and chemoresistant pancreatic cancer. These data suggest that ETBR blockade is well tolerated, may expand the benefit of anti-PD1 in drug resistant solid tumors and warrants further study in subsequent trials.

Enrollment in the 6th cohort of the Phase 1 is ongoing and initiation of the Phase 2 trial is planned for H1 2023.

REFERENCES

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

ACKNOWLEDGEMENTS

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