ENB Therapeutics

# ENB-003, an ETBR antagonist, in combination with pembrolizumab for refractory advanced solid tumors: Topline data from the ENBolden-101 Phase 1B study

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## KEY TAKEAWAYS

- The ENB-003 + pembrolizumab combination is well tolerated -no dose limiting toxicities (DLTs) across 6 dosing cohorts
- Promising preliminary efficacy signals with 33% disease control rate (DCR) across all cohorts
- Efficacy appears to correlate with endothelin B receptor (ETBR) expression: **83% DCR in ETBR-Hi patients** in cohort 6 (RP2D), 0% DCR in ETBR-Lo patients
- Platinum refractory/ resistant microsatellite stable (MSS) ETBR-Hi **ovarian cancer patients with 80% DCR** across all cohorts

## INTRO

- The endothelin B receptor (ETBR) prevents T-cell trafficking which may be required for anti-PD1 efficacy[1]
- The ETBR is expressed in more than 40% of cancers overall and expression correlates with cold tumors and poor survival[2,3]
- ETBR inhibitors (ETBRIs) enhance anti-PD1 efficacy across multiple tumor types in preclinical models
- This study aimed to investigate the safety and efficacy of the combination of pembrolizumab and ENB-003, an ETBRI, in patients refractory to anti-PD1 therapy or with MSS tumors that historically do not respond to single agent anti-PD1

## METHODS

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 enrolled 46 subjects and included 6 escalating doses of ENB-003 (ranging from 150ug-2000ug) in combination with a fixed dose of pembrolizumab (200mg). Pembrolizumab was administered once every 21-day cycle. ENB-003 was 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 6th cohort. The primary objective of part 1 was to assess safety and tolerability, secondary objectives included PFS, OS and ORR by RECIST 1.1 , iRECIST. Exploratory objectives are to examine biomarkers/ pharmacodynamics.

ETBR status determination: A validated immunohistochemical protocol was developed using Abcam anti-Endothelin B Receptor/ET-B [EPR2247] rabbit monoclonal antibody and OptiView DAB HIC Detection Kit on Ventana BenchMark Ultra Instrument. CD31 and Masson Trichrome counterstains were used to identify ETBR+ vasculature and stroma respectively. Patients in cohort 6 were designated as the preliminary training set to determine indication specific ETBR expression cutpoints based on ETBR expression in the TME and tumor response. Preliminary cutpoints, "ETBR-Hi", that were selected for future confirmation in the Phase 2 study were: Melanoma ≥25% (tumor), ovarian cancer>1% (tumor vasculature), pancreatic cancer ≥ 25% (tumor stroma). Because this data is from a training set, efficacy may be overestimated and thus should be interpreted with caution.

## RESULTS

**SAFETY**

- No DLTs observed across 6 dosing cohorts
- The most common treatment emergent adverse events irrespective of grade or causality included fatigue ( 28.2%), constipation (26.1% ), abdominal pain (26.1%), nausea (23.9%), anemia 17.4%, diarrhea (17.4%)
- Serious adverse events, grade 3 and above considered possibly related to pembrolizumab and/or ENB-003 include fatigue (n=4), diarrhea (n=3), dyspnea (n=3) constipation (n=2), rash (n=2)

**PK**

- Plasma levels of ENB-003 increased in a dose dependent fashion and the in vitro IC50 of ENB-003 was exceeded only with the 6th cohort (2000ug dose) which corresponds to where the therapeutic dose should occur
- The $T_{1/2}$ of ENB-003 at the 2000ug dose was ~90 minutes (~5X increase over the previous cohorts)
- 2000ug is the recommended Phase 2 dose (RP2D)

**EFFICACY*-**

- 15 patients with evaluable disease were enrolled in cohorts 1-5 (ENB-003 dose range 150ug-1000ug) and 15 patients with evaluable disease were enrolled in the 6th cohort (ENB-003 dose 2000ug)
- All patients enrolled in cohorts 1-5 were ETBR-Hi whereas in cohort 6 patients were enrolled irrespective of ETBR levels
- The dosing frequency for cohort 6 was doubled to 6 doses every 3 weeks from 6 doses every 6 weeks in cohort 1-5
- The DCR across all cohorts irrespective of ETBR status was 33% (1 PR, 9 SD, 20 PD)
- The DCR in ETBR-Hi patients was 33% in cohorts 1-5 (4 SD, 1 PR, 10 PD) and 83% in cohort 6 ( 5 SD, 1 PD)
- The DCR for ETBR-Lo patients in cohort 6 was 0% (9 PD)
- For MSS platinum R/R ovarian cancer there was an 80% DCR across all cohorts (1 PR, 3 SD, 1 PD) with a trend for durable responses at higher doses of ENB-003
  - 95% PR of 12-month duration in a platinum refractory MSS OC patient
- Clinical benefit was observed in an MSS PDAC patient refractory to standard of care chemotherapy and in anti-PD1 refractory melanoma and HNSCC patients with durable responses observed in all three patients

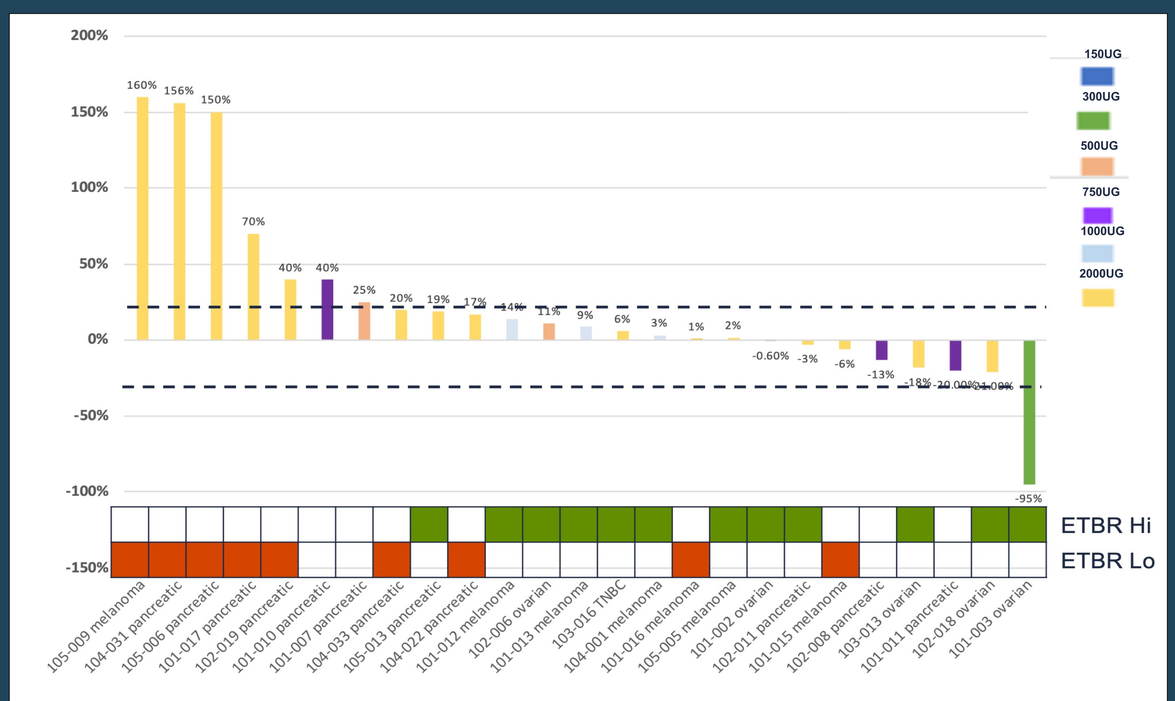
*sample size not powered for statistical significance



# ENB-003, an ETBR antagonist, in combination with pembrolizumab is well tolerated and preliminary efficacy may correlate with ETBR expression in advanced refractory solid tumors

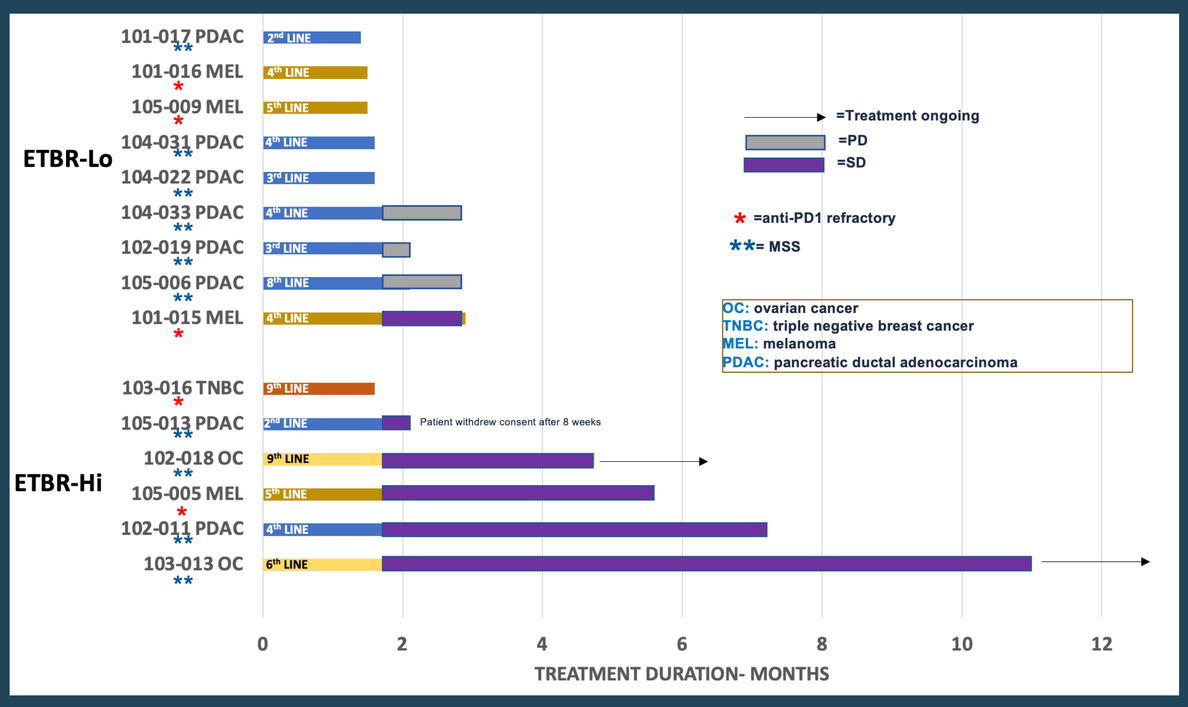
| TREATMENT EMERGENT ADVERSE EVENTS OCCURRING IN 10% OR MORE SUBJECTS IRRESPECTVE OF GRADE OR CAUSALITY (n=46) | n (%) | GRADE 3 OR HIGHER | POSSIBLY RELATED TO ENB-003 AND/OR PEMBROLIZUMAB |
|---|---|---|---|
| FATIGUE | 13 (28.2%) | 0 | 4 |
| CONSTIPATION | 12 (26.1%) | 0 | 2 |
| ABDOMINAL PAIN | 12 (26.1.%) | 4 | 1 |
| NAUSEA | 11 (23.9%) | 0 | 0 |
| ANEMIA | 8 (17.4%) | 1 | 1 |
| DIARRHEA | 8 (17.4%) | 0 | 3 |
| DYSPNEA | 7 (15.2%) | 3 | 3 |
| HYPONATREMIA | 6 (13.0%) | 2 | 0 |
| ASCITES | 5 (10.9%) | 1 | 0 |
| RASH | 5 (10.9%) | 0 | 2 |
| Vomiting | 5 (10.9%) | 1 | 1 |

## BEST RESPONSES-TARGET LESIONS




All cohorts- target indications, ETBR status indicated (%ETBR staining was not scored in 4 patients due to insufficient specimen)

## COHORT 6: DURABLE RESPONSES APPEAR TO CORRELATE WITH ETBR STATUS

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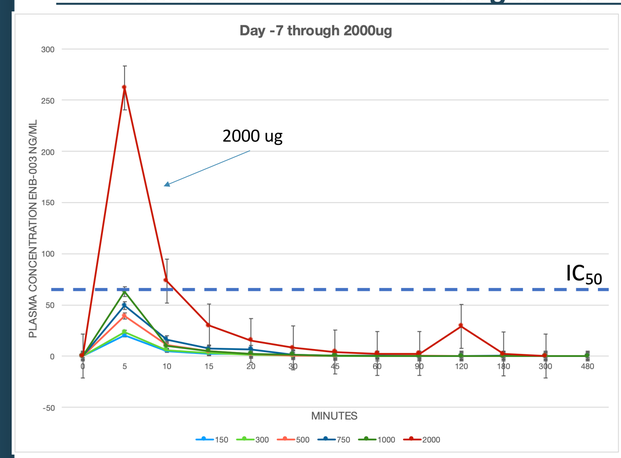
## PATIENT DEMOGRAPHICS

| | | Age Group | | Age Group | | Age Group | | Age Group | | ALL Age Groups Combined | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | 18-49 | | 50-63 | | 64-75 | | >/=75 | | | |
| | | M | F | M | F | M | F | M | F | M | F |
| Total | 46 | 2 | 2 | 11 | 10 | 7 | 8 | 3 | 3 | 23 | 23 |
| Caucasian | 36 | 0 | 2 | 10 | 7 | 6 | 5 | 3 | 3 | 19 | 17 |
| Asian | 7 | 1 | 0 | 0 | 3 | 1 | 2 | 0 | 0 | 2 | 5 |
| African American | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |

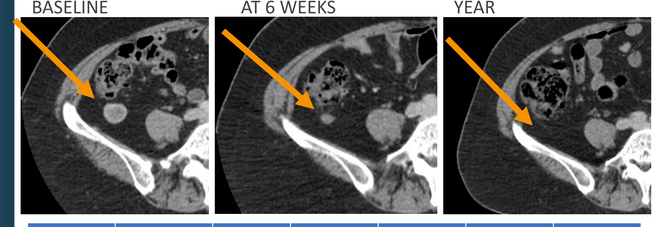
## PLASMA LEVELS OF ENB-003 EXCEEDED THE IC50 ONLY WITH THE 2000ug COHORT




The 2000 ug dose was the first dose in the dose escalation study where the therapeutic window was optimized by virtue of exceeding the IC50 for ENB-003. The T1/2 at this dose, which is the recommended Phase 2 dose, was ~90 minutes whereas the T1/2 in cohorts 1-5 was less than 20 minutes.

## SERIAL CT IMAGES FROM PLATINUM REFRACTORY MSS OVARIAN CANCER PATIENT WITH DURABLE 12 MONTH 95% PR

PERITONEAL TUMOR BASELINE | 68% REDUCTION AT 6 WEEKS | 100% RESPONSE AT 1 YEAR



| CT SCAN | BASELINE | 6 WEEKS | 12 WEEKS | 24 WEEKS | 36 WEEKS | 52 WEEKS |
|---|---|---|---|---|---|---|
| Target lesions mm | 36<br>52<br>25 | 17<br>21<br>25 | 14<br>14<br>8 | 0<br>12<br>6 | 0<br>8<br>0 | 0<br>6<br>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 |

## CONCLUSIONS

ETBRi is a novel approach to overcoming immunotherapy resistance. ENB-003 demonstrates robust preclinical proof of concept for enhancing anti-PD1 efficacy across multiple cancer indications. In the clinic, the combination is well tolerated and is demonstrating promising early signals of anti-tumor efficacy. The best efficacy signals thus far have been observed in patients expressing high levels of ETBR. Preliminary efficacy signals in platinum refractory/ resistant ovarian cancer are particularly encouraging and the therapeutic approach may also show promise in pancreatic cancer patients with TME stroma positive for ETBR. The data suggest that ETBR blockade with ENB-003 may expand the therapeutic benefit to patients who are refractory or resistant to anti-PD1 therapy. Initiation of the Phase 2 trial is planned for H1 2024 and will enroll MSS platinum refractory/platinum resistant ovarian cancer, MSS pancreatic cancer refractory to standard of care as well as and exploratory basket including the following anti-PD1 refractory indications : melanoma, HNSCC and TNBC.

## REFERENCES

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2. Brain Tumor Pathol (2015) 32:41–48
3. Br J Cancer. 2014 Feb 18; 110(4): 1027–1033

## AUTHOR AFFILIATIONS

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