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**ENB-003, AN ETBR ANTAGONIST, IN COMBINATION WITH PEMBROLIZUMAB, SHOWS PROMISE IN MICROSATELLITE STABLE PLATINUM REFRACTORY/RESISTANT OVARIAN CANCER: DATA FROM THE ENBOLDEN-101 PHASE 1B STUDY**

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**Background** Endothelin B receptor (ETBR) expression in ovarian cancer is associated with a poor prognosis and tumors that lack tumor infiltrating lymphocytes.<sup>1</sup> ETBR expression prevents T-cell trafficking into tumors and ETBR blockade with an ETBR inhibitor (ETBRi) stimulates T-cell infiltration of tumors and enhances efficacy of a cancer vaccine in ovarian cancer models. Similarly, the ETBRi ENB-003 enhances the efficacy of anti-PD1 in ovarian cancer models. This Phase 1B study investigated the safety and efficacy of ENB-003 in combination with pembrolizumab in solid tumors refractory to standard of care therapies including ovarian cancer.

**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 6<sup>th</sup> 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.

**Results** No DLTs were 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). The DCR across all cohorts irrespective of ETBR status was 33% (2 PR, 8 SD, 20 PD). For microsatellite stable (MSS) platinum refractory/resistant ovarian cancer (OC) there was a 40% ORR and an 80% DCR across all cohorts (2 PR, 2 SD, 1 PD) with a trend for durable responses at higher doses of ENB-003. Responses included a 95% PR of 12-month duration in a primary platinum refractory MSS OC patient.

**Conclusions** MSS OC patients historically demonstrate poor response to single agent anti-PD1.ETBR blockade with ENB-003 may expand the therapeutic benefit to patients who are refractory or resistant to anti-PD1 therapy

**Acknowledgements** This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

**Trial Registration** NCT04205227

## REFERENCE

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**Ethics Approval** This study was approved by an institutional Review Board at each investigational site

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1527>