Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

REFERENCE

1. Romee R, Cooley S, Berrien-Elliott MM, *et al*. First-in-human phase 1 clinical study of the IL-15 superagonist complex ALT-803 to treat relapse after transplantation. *Blood* 2018;**131**(23):2515-2527.

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802 RAMUCIRUMAB PLUS ATEZOLIZUMAB IN PATIENTS WITH STAGE IV NON-SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH IMMUNE CHECKPOINT BLOCKADE

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Background T-cell trafficking to the tumor is inhibited via vascular endothelial growth factor (VEGF)-mediated downregulation of important adhesion molecules on tumor-associated blood vessels and progression of disease on immune checkpoint blockers (ICBs) has been associated with decreased tumor-infiltrating immune cells.[1 2] We hypothesized that inhibiting VEGF signaling through its receptor, VEGFR2, would increase intratumoral T cells. Therefore we sought to evaluate the combination of ramucirumab, an anti-VEGF receptor 2 monoclonal antibody, and atezolizumab in patients with advanced-stage, non-small cell lung cancer (NSCLC) patients who have previously progressed on at least one line of ICB. Here, we report on the first twelve patients enrolled on trial.

Methods Advanced stage NSCLC patients with an ECOG performance status of ≤1 who had previously been treated with ICBs were eligible with no limitation on prior lines of ICB therapy. Patients with untreated brain metastasis, recent hemoptysis, gastrointestinal bleeding or perforation or fistula were excluded. The study was conducted with a two-stage MiniMax design. Peripheral blood and repeated biopsy, when feasible, were collected for correlative analysis.

Results Twelve patients were enrolled in the first stage of the trial. The median age was 68 (range 47-78), 10 of the patients are female, and 10 had non-squamous histology. Patients had an average of 3.5 prior lines of therapy and 1.6 lines of prior immunotherapy. Overall, treatment was well-tolerated with no grade 3 or 4 adverse events. The most common adverse events were grade 1 or 2 hypertension (35%), nausea (25%) and vomiting (25%). There were no objective responses and 11 patients (91%) achieved stable disease. The median progression-free survival is 3 months with 3 patients (25%) on trial for more than 12 months. The median overall survival (OS) at the time of the latest data cutoff on 9/15/20 is 11.5 months.

Conclusions The preliminary data from our study showed that combination of ramucirumab and atezolizumab is well-tolerated and associated with prolonged overall survival in a subset of heavily pretreated patients who progressed on prior ICB. The trial is still accruing patients and exploratory analyses are planned.

Ethics Approval The study was approved by the Washington University Institutional Review Board.

REFERENCES

1. Dirkx AE, oude Egbrink MG, Castermans K, *et al*. Anti-angiogenesis therapy can overcome endothelial cell anergy and promote leukocyte-endothelium interactions and infiltration in tumors. *FASEB J* 2006;**20**(6):621-630.
2. Herbst RS, Soria JC, Kowanetz M, *et al*. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014;**515**(7528):563-567.

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803 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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Background 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).[1] 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. 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 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. 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 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. 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). The combination of ENB-003 plus pembrolizumab was well tolerated in the first 2 cohorts of the ongoing Phase 1 trial in patients with advanced refractory solid tumors that are ETBR+. Best overall responses from the first 2 cohorts (n=6) demonstrates disease stabilization (SD) in 2 patients as well as a partial response (PR) in an ovarian cancer patient with ~60% reduction in target lesions.

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. Trial updates will be reported.

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

REFERENCE

1. Kandalaft L, Facciabene A, Buckanovich R, Coukos G. Endothelin B Receptor, a New Target in Cancer Immune Therapy. *Clin Cancer Res* 2009;**15**(14):4521-4528.

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804 A PHASE II STUDY OF THE ANTI-PROGRAMMED CELL DEATH-1 (PD-1) ANTIBODY PENPULIMAB IN PATIENTS WITH METASTATIC NASOPHARYNGEAL CARCINOMA (NPC) WHO HAD PROGRESSED AFTER TWO OR MORE LINES OF CHEMOTHERAPY

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Background NPC is rare but has a distinct geographic distribution, with a predominance in Southeast Asia. Favorable results with PD-1 inhibitors in NPC provide a strong rationale to investigate penpulimab in this disease. Penpulimab was engineered to eliminate FcγR binding and ADCC/ADCP completely,where ADCC/ADCP effects can induce T-cell apoptosis and clearance and then compromise anti-tumor activity. Penpulimab demonstrated a slower PD-1 antigen binding off-rate than marketed PD-1 antibodies, which result in better cellular activity and higher receptor occupancy. Penpulimab also showed numerous contacts with N58 glycosylation on the BC loop of PD-1 which could be an advantage to facilitate interaction of PD-1 antibody and may contribute to slower binding off-rate. These structural differentiations offer more robust biological effect and enhance anti-tumor activity of penpulimab.
Methods AK105-202 (NCT03866967) is a multicenter, single-arm, open-label study of penpulimab in metastatic NPC patients (pts) with disease progression after ≥2 prior lines of therapy including platinum-containing chemotherapy. All patients received penpulimab 200 mg q2w until progression or unacceptable toxicity. The primary endpoint was ORR based on RECIST v1.1 as assessed by an independent review committee (IRC). Key secondary endpoints included DCR, PFS, duration of response (DoR). Archived tissues were retrieved for the analysis of PD-L1 (Shuwen SAB-028). PD-L1 expression of tumor proportion score (TPS)≥50% was regarded as positive. Plasma Epstein-Barr virus DNA were obtained for biomarker correlative analysis.
Results As of 18 September 2020, the median follow-up was 7.9 months (range 0.9 to 16.9). The anti-tumor activity of penpulimab in the 111 pts with disease progression after ≥2 prior lines of therapy evaluable for efficacy (defined as pts who had an opportunity to be followed for at least 16 weeks and had measurable disease at baseline per RECIST v1.1) is shown in the table 1.

Treatment-related adverse events (TRAEs, including unlikely related) occurred in 79.2% of pts (≥G3 in 14.6% [19/130], treatment discontinuation in 3.1% [4/130]). Treatment-related SAEs occurred in 10.0% [13/130]. Most frequent TRAEs (≥10%) were fever (24.5%), hypothyroidism (24.6%), anemia (23.1%), ALT increased (17.0%) and WBC decreased (10.8%). Grade ≥3 TRAEs (≥2%) were hepatic function abnormal (2.3%) and anemia (2.3%).

Abstract 804 Table 1

	IRC-assessed (N=111)
Confirmed ORR [a], % (95% CI)	27.0% (19.0, 36.3)
ORR for PD-L1 positive[b]	39.5% (25.0, 55.6)
ORR for PD-L1 negative[b]	19.7% (10.9, 31.3)
DCR[c], % (95% CI)	49.5% (39.9, 59.2)
DoR, median (range), months	NR (0.95+ - 11.43+)
6mon- DoR, % (95% CI)	85.6% (52.5, 96.3)

a. Including 1 complete response and 29 partial response. At data cutoff, 90% of responders remained ongoing.
b.43 pts were PD-L1 positive (TPS≥50%) and 66 pts were PD-L1 negative (TPS<50%).
c. Including 1 ongoing response awaiting confirmation classified under SD.

Conclusions Penpulimab demonstrated encouraging anti-tumor activity and favorable safety profile in pts with disease progression after ≥2 prior lines of therapy. A higher proportion of objective responses was observed in NPC pts with PD-L1–positive tumors receiving penpulimab than those with PD-L1–negative tumors.

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805 SAFETY AND EMERGING EVIDENCE OF IMMUNE MODULATION OF THE LIVE BIOTHERAPEUTIC MRX0518 IN THE NEOADJUVANT SETTING FOR PATIENTS AWAITING SURGICAL REMOVAL OF SOLID TUMOURS

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Background The gut microbiome has emerged as a promising innovative therapeutic target for immune-stimulation treatment of solid tumours. MRx0518 is a novel, gut microbiome-derived oral live biotherapeutic. It has potent anti-tumorigenic efficacy in the preclinical setting including murine models of lung (LLC1), kidney (Renca) and breast (EMT6) cancer.[1] In these models, a significant reduction in tumour growth has been demonstrated, including induction of immunostimulatory responses with tumour infiltration of NK cells, CD8+ and CD4+ T-cells. MRx0518 is under investigation in various oncological settings, including in combination with immune checkpoint inhibitors (NCT03637803) and radiotherapy (NCT04193904).
Methods Treatment naïve patients were recruited from April 2019 to February 2020. Patients were eligible if they received a histologically confirmed diagnosis of cancer (solid tumours) scheduled for surgical resection. Patients received 1 capsule of MRx0518 (1x1010 to 1x1011 CFU) twice daily from