

8 intratumoral injections of CV8102 are being administered initially over a 12 week period, while patients benefiting from the single agent therapy may receive further treatment. In an initial dose escalation part the maximum tolerated dose and recommended phase 2 dose for subsequent cohort expansion will be defined.

Results As of September 16, 2020, 29 patients have been treated with CV8102 as a single agent (25-900 µg) and 21 patients have received CV8102 (25-900 µg) in combination with anti-PD-1 antibodies. Most frequent treatment related adverse events were mild to moderate fever, fatigue, chills and headache. One patient treated at the 900 µg single agent experienced a dose limiting toxicity (G3 transaminase increase in the context of G2 cytokine release syndrome).

Regression of injected and distant noninjected lesions was observed in several patients in the single agent and the anti-PD-1 combination cohorts. Updated safety and efficacy results will be presented.

Conclusions CV8102 showed an acceptable tolerability and preliminary evidence of clinical efficacy as single agent and in combination with anti-PD-1 antibodies.

Trial Registration NCT03291002

Ethics Approval The study was approved by the Central Ethics Committees in Tuebingen, Germany under 785/2016AMG1, in France under 19.05.17.64111, in Barcelona, Spain under the EudraCT number.

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.

REFERENCES

- Ziegler A, Ziedner C, Lienenklaus S, Spanier J, Trittel S, Riese P, Kramps T, Weiss S, Heidenreich R, Jasny E, Guzmán CA, Kallen KJ, Fotin-Mleczek M, Kalinke U. A new RNA-based adjuvant enhances virus-specific vaccine responses by locally triggering TLR- and RLR-dependent effects. *J Immunol* 2017;**198**(4):1595-1605. doi:10.4049/jimmunol.1601129
- Heidenreich R, Jasny E, Kowalczyk A, Lutz J, Probst J, Baumhof P, Scheel B, Voss S, Kallen KJ, Fotin-Mleczek M. A novel RNA-based adjuvant combines strong immunostimulatory capacities with a favorable safety profile. *Int J Cancer* 2015 Jul 15;**137**(2):372-84. doi: 10.1002/ijc.29402

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0800>

801

PRIME™ IL-15 (RPTR-147): PRELIMINARY CLINICAL RESULTS AND BIOMARKER ANALYSIS FROM A FIRST-IN-HUMAN PHASE 1 STUDY OF IL-15 LOADED PERIPHERALLY-DERIVED AUTOLOGOUS T CELL THERAPY IN SOLID TUMOR PATIENTS

¹Erika Hamilton, ²Sarah Nikiforow, ³Philip Bardwell*, ³Christine McInnis, ³Jeffrey Zhang, ⁴George Blumenschein, ⁵Mihaela Cristea, ⁶Keren Osman, ⁷Anthony Shields, ³Marlyane Motta, ³Sanela Bilic, ³Oliver Schoenborn-Kellenberger, ³James Rakestraw, ³Shawn Carey, ³Elena Geretti, ³Karsten Sauer, ³Tim Harris, ³Tap Maniar, ³Becker Hewes, ³Thomas Andresen, ³Jonathan Fitzgerald, ⁸Harriet Kluger. ¹Sarah Canon Research Institute, Nashville, TN, USA; ²Dana-Farber Cancer Institute, Boston, MA, USA; ³Repertoire Immune Medicines, Cambridge, MA, USA; ⁴MD Anderson, Houston, TX, USA; ⁵City of Hope, Duarte, CA, USA; ⁶Mount Sinai Medical Center, Cambridge, MA, USA; ⁷Karmanos Cancer Institute, Detroit, MI, USA; ⁸Yale, New Haven, CT, USA

Background RPTR-147 is a novel autologous non-genetically modified multi-clonal T cell product loaded with an IL15-Fc nanogel. The product was derived from rare peripherally-derived anti-tumor T cell clones that were primed against a multi-antigen cassette containing tumor associated antigens (TAA), known to be over-expressed in specific tumor types.

Abstract 801 Table 1 Summary of Patients

Tumor Type	Number of Patients
Melanoma	6
Non-Small Cell Lung Carcinoma	4
Renal Cell Carcinoma	2
Head & Neck	2
Appendiceal Carcinoma	1
Ovarian Carcinoma	1
Synovial Carcinoma	1

Tumor types for the 17 patients with advanced metastatic disease included in this clinical trial (NCT0381568)

We describe preliminary results from the ongoing first-in-human Phase 1 trial.

Methods Autologous anti-TAA T cells are generated with a proprietary dendritic cell priming process and then loaded with an IL15-Fc nanogel. TAAs used in cassette: PRAME, NY-ESO-1, SSX2, Survivin and WT1. Thawed RPTR-147 is delivered by infusion. Pre- and post-treatment biopsies were collected for biomarker analysis by immunohistochemistry (IHC) and transcriptome sequencing. Serial blood collections were obtained for measuring IL-15 pharmacokinetics and pharmacodynamic parameters including plasma cytokine levels and immunophenotyping by flow cytometry. T cell receptor sequencing (TCRSeq) was used to characterize the T cell repertoire from manufactured T cell product and the patient's blood.

Results Interim clinical and biomarker data from 17 patients with advanced metastatic disease refractory to SOC who received monthly infusions of 20-360 million cells/m², were reviewed (table 1). There were no dose-limiting toxicities and no evidence of cytokine-release syndrome. The 360M/m² dose contained 3X more IL15-Fc than the MTD of systemically administered IL15-Fc,¹ but produced less than a tenth of the systemic exposure to free IL15-Fc. Currently, 360M cells/m² is considered safe and well-tolerated. Further dose escalation is planned.

Matched evaluable biopsies were obtained in 7 patients. Tumor-infiltrating T cell lymphocytes was observed in 5 cases for CD8 T cells and 4 cases for CD4 T cells. A dose dependent increase in both inflammatory cytokines and NK & CD8 + T cells was observed, consistent with expected MOA and PK. TCRSeq analysis demonstrated that product specific T cell clones could be tracked in both patient's blood and tumor over time. Further analysis to decode the specificity of those cells and demonstrate that tumor antigen specific T cells can be found in patient's blood and tumor biopsies is ongoing.

Of the 17 patients who received RPTR-147 infusions 10 were noted to have stable disease (SD) and in 4 patients SD lasted > 6 months.

Conclusions Interim results with RPTR-147 have shown it to be well-tolerated and have a favorable safety profile. Dose-escalation is proceeding. Ongoing biomarker analysis will inform future clinical strategies in matching patients to an optimized PRIME IL-15 T cell product.

Trial Registration NCT03815682

Ethics Approval The study was approved by local institutional IRBs after acceptance of the IND by the FDA.

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.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0801>

802

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

Brett Herzog*, Saiama Waqar, Siddhartha Devarakonda, Jeffrey Ward, Ramaswamy Govindan, Daniel Morgensztern. *Washington University in St. Louis, Saint Louis, MO, USA*

Background T-cell trafficking to the tumor is inhibited via vascular endothelial growth factor (VEGF)-mediated down-regulation 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. Dirix 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.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0802>

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

¹Sumayah Jamal*, ²Adnan Nagrial, ³Anthony Joshua, ⁴Richard Eek, ¹Sumayah Jamal. ¹ENB Therapeutics Inc, New York, NY, USA; ²Blacktown Cancer and Haematology, Blacktown, Australia; ³Kinghorn Cancer Centre, Darlinghurst, Australia; ⁴Border Medical Oncology Research Unit, Albury, Australia

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.