

HCC. Intensive peripheral immune-monitoring and longitudinal on-treatment tumor biopsies will focus on the role of the innate immune system, particularly Natural Killer cells, in anti-tumor responses.

Methods Patients with HCC (Childs Pugh A/B7; Barcelona Clinic Liver Cancer Stage B/C; ECOG 0/1; sorafenib-naïve or experienced) are being enrolled in a pilot study (Study Number UCDCRC/19/01) of tremelimumab at 2 dose levels (DL1 and DL2) in combination with durvalumab and TACE until disease progression (per irRECIST). DL1: tremelimumab (75 mg q28 days for 4 doses) and durvalumab (1500 mg q28 days). DL2: tremelimumab (300 mg in a single dose on day 1) and durvalumab (1500 mg q28 days). Subtotal TACE will be performed during study week 6 with the dose-limiting toxicity (DLT) evaluation period encompassing the first 8 weeks of the study. Primary endpoint is 6-month progression-free survival with secondary efficacy endpoints being safety, tolerability and overall survival. Exploratory objectives will evaluate changes in immune parameters in the tumor and peripheral blood of patients undergoing anti-CTLA4 therapy pre- and post-RFA or TACE. A major focus will be on the role of the innate immune system, particularly Natural Killer cells, in anti-tumor responses. Patients will be enrolled and treated at St Vincent's University Hospital in Dublin, Ireland. This study is currently open and actively recruiting.

Results N/A

Conclusions N/A

Trial Registration EudraCT Number 2019-002767-98

Ethics Approval St Vincent's University Hospital Research Ethics Committee Study Number UCDCRC/19/01.

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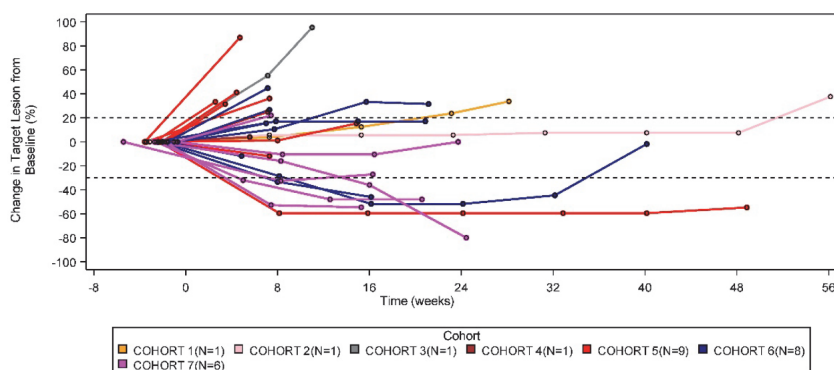
AMG 757, A HALF-LIFE EXTENDED BISPECIFIC T-CELL ENGAGER (BiTE®) IMMUNE THERAPY AGAINST DLL3 IN SCLC: PHASE 1 INTERIM RESULTS

¹Hossein Borghaei*, ²Michael Boyer, ³Melissa Johnson, ⁴Ramaswamy Govindan, ⁵Luis Paz-Ares Rodrigues, ⁶Fiona Blackhall, ⁷Rene Boosman, ⁸Stéphane Champiat, ⁹Horst-Dieter Hummel, ¹⁰W Victoria Lai, ¹¹Hibiki Udagawa, ¹²Anne Chiang, ¹³Afshin Dowlati, ¹⁴Christine Hann, ¹⁵Ravi Salgia, ¹⁶Everett Vokes, ¹⁷Mukul Minocha, ¹⁸Nooshin Hashemi-Sadraei, ¹⁹Aditya Shetty, ²⁰Marie-Anne Damiette Smit, ²¹Hui Yang, ²²Taofeek Owonikoko. ¹Fox Chase Cancer Center, Philadelphia, PA, USA; ²Chris O'Brien Lifecare, Camperdown, Australia; ³Sarah Cannon Research Institute, Tennessee, Nashville, TN, USA; ⁴Washington University Medical School, Saint Louis, MO, USA; ⁵Universidad Complutense and Ciberonc, Madrid, Spain; ⁶University of Manchester, Manchester, UK; ⁷The Netherlands Cancer Institute, Amsterdam, Netherlands; ⁸Paris-Saclay University, Villejuif, France; ⁹University Hospital Wuerzburg, Wuerzburg, Germany; ¹⁰Memorial Sloan Kettering Cancer Center, New York, NY, USA; ¹¹National Cancer Center Hospital East, Kashiwa, China; ¹²Yale School of Medicine, New Haven, CT, USA; ¹³University Hospitals Seidman Cancer Ctr, Cleveland, OH, USA; ¹⁴Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; ¹⁵City of Hope, Duarte, CA, USA; ¹⁶University of Chicago Medicine and Biolo, Chicago, IL, USA; ¹⁷Amgen Inc., Thousand Oaks, CA, USA; ¹⁸Emory University School of Medicine, Atlanta, GA, USA

Background Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand that is highly expressed in small cell lung cancer (SCLC) and minimally expressed in normal tissues.¹ AMG 757, a half-life extended BiTE® immune therapy, binds to DLL3 on tumor cells and CD3 on T cells, resulting in T cell-dependent killing of tumor cells. We report initial safety and efficacy from the ongoing phase 1 study of AMG 757 in patients with SCLC.

Methods AMG 757 was administered intravenously every two weeks (with/without step dose) at doses of 0.003–3.0 mg. Eligible patients had SCLC that progressed or recurred following ≥1 platinum-based regimen. Antitumor activity was assessed using modified RECIST 1.1. The study was approved by the Ethics Board at participating institutions.

Results As of 1 June 2020, safety and efficacy data are available for 31 patients enrolled at the first seven dose levels (DL) with median age, 63 (44–74) years; ECOG PS: 0–1,



Safety Analysis Set includes all subjects who received at least one dose of AMG 757.
N= Number of subjects with evaluable post-baseline assessment.

Abstract 359 Figure 1 Tumor shrinkage over time in response to AMG 757

n=30 (96.8%); median prior lines, 2.0 (1–6); and previous PD-1/PD-L1 treatment: n=12 (38.7%). Median treatment duration was 6.1 (0.1–59.4) weeks. Treatment-emergent adverse events (AEs) were reported for 30 (96.8%) patients. AMG 757-related AEs occurred in 25 (80.6%) patients, including 5 (16.1%) that were grade ≥ 3 and one (3.2%) grade 5 (pneumonitis in DL5 [0.3 mg]). Three AEs (dyspnea, pneumonitis, fatigue) led to treatment discontinuation. The most common AE was cytokine release syndrome (CRS), which was reported in 11 (35.5%) patients. CRS AEs were grade 1–2, consisted mainly of fever with/without hypotension, and occurred mostly within 24 hours of the first or second dose of AMG 757. CRS events were reversible, did not lead to treatment interruption or discontinuation, and were managed with supportive care, corticosteroids, and/or anti-IL 6 therapy. The MTD for AMG 757 has not yet been reached. AMG 757 exhibited dose proportional increase in exposures. Response to AMG 757 is shown (figure 1). Confirmed partial response was reported in 5 (16.1%) patients (1/12 [8.3%] in DL5, 1/8 [12.5%] in DL6, 3/7 [42.9%] in DL7), and stable disease in 8 (25.8%) of all treated patients. Most responses occurred after 8 weeks on treatment. All responders remain on treatment with duration of response ranging from 2.0+ to 7.4 months+.

Conclusions AMG 757 administered at a dose of up to 3 mg every two weeks has an acceptable safety profile and shows anti-tumor activity in patients with relapsed/refractory SCLC. Further dose escalation is ongoing.

Trial Registration NCT0319940

Ethics Approval The study was approved by the Ethics Board at participating institutions.

Consent N/A

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A PHASE 1 STUDY OF AN OFF-THE-SHELF, MULTI-NEOANTIGEN VECTOR (ADXS-503) ALONE AND IN COMBINATION WITH PEMBROLIZUMAB IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

¹Jonathan Goldman*, ²Thomas Stinchcombe, ³Gregory Gerstner, ⁴Missak Haigentz, ⁵Surya Vangala, ⁵Megan Parsi, ⁵Victor Kabala, ⁵Dinesh Simkhada, ⁶Andres Gutierrez, ⁷Suresh Ramalingam. ¹University of California Los Angeles, CA, Los Angeles, CA, USA; ²Duke University, Durham, NC, USA; ³Illinois Cancer Care, Peoria, IL, USA; ⁴Morristown Medical Center, Morristown, NJ, USA; ⁵Advaxis Inc, Princeton, NJ, USA; ⁶Advaxis Inc, Princeton, NJ, USA; ⁷Emory University, Atlanta, GA, USA

Background ADXS-503 (A503) is an off-the-shelf, attenuated *Listeria monocytogenes* (Lm)-based immunotherapy bioengineered to elicit potent T cell responses against 22 tumor antigens commonly found in NSCLC (i.e., 11 hotspot mutations and 11 tumor-associated antigens, TAAs). Pembrolizumab (Pembro) is a programmed death receptor-1 (PD-1)- blocking antibody approved for the treatment of advanced lung cancer. A503 and Pembro have complementary mechanisms of immune activation and reversal of immune tolerance.

Methods We conducted a phase 1 study of A503 \pm Pembro in patients (pts) with metastatic squamous or non-squamous NSCLC. In Part A, A503 alone has been tested at two dose

levels (i.e., 1×10^8 and 5×10^8 CFU) in pts refractory or intolerant to prior systemic therapy. In dose escalation Part B, A503 has been evaluated at the lower dose level (DL) in combination with Pembro within 6 weeks of presenting with disease progression per RECIST criteria v1.1. Part C dose expansion cohort with A503 + Pembro has started for first-line treatment in the metastatic setting. A503 \pm Pembro (200 mg) are infused by IV every 3 weeks until disease progression or limiting toxicity. Main endpoints include safety, tolerability and immune-correlative data.

Results Twelve patients have been treated: 7 in Part A, 4 in Part B-DL1 and 1 in Part C. No pts in Part A experienced dose-limiting toxicities at the 2 DLs tested. A503+ Pembro has also been well tolerated in 4 pts treated in Part B-DL1 and in one in Part C. No immune related AEs have been reported in Part B or Part C. Three evaluable pts in Part A achieved stable disease (SD). Of the three evaluable pts in Part B-DL1 one has achieved SD for 8 months and the second one a partial response for over 6 months; both of these patients had been on Pembro therapy for 2 years before enrollment. The 3rd pt showed progressive disease. ADXS-503 induced transient release of pro-inflammatory cytokines, activation of cytotoxic- and memory-CD8+ T cells against antigens in the construct and antigen spreading in peripheral blood across all cohorts. Preliminary data in on-therapy biopsies showed increased PD-L1 expression and decreased Treg cell counts. Part B -DL1 cohort has thus been expanded to further explore the potential reversal of Pembro resistance with ADXS-503 in these pts.

Conclusions ADXS-503 alone and in combination with Pembro has demonstrated a manageable safety profile and induction of antigen specific T cell responses. The potential effect of A503 to reverse resistance to Pembro is now being studied in an expansion cohort and this combination approach is also being evaluated in the first line treatment setting (Part C).

Ethics Approval This study was approved by all Institution's Ethics Board participating in the trial.

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A RANDOMISED OPEN-LABEL PHASE I/II STUDY ADDING ONCOS-102 TO PEMETREXED/CISPLATIN IN PATIENTS WITH UNRESECTABLE MALIGNANT PLEURAL MESOTHELIOMA – 12 MONTH ANALYSIS OF BIOMARKERS AND CLINICAL OUTCOMES

¹Magnus Jaderberg, ²Susana Cedres, ²Luis Paz-Ares*, ³Xavier Serres, ⁴Charles Ricordel, ²Nicolas Isambert, ²Santiago Ponce Aix, ¹Victor Levitsky, ¹Lukasz Kuryk, ¹Anne-Sophie Moller, ¹Sylvia Vethrus. ¹Research and Development, Oslo, Norway; ²Medical Oncology, Sevilla, Spain; ³Radiology, Barcelona, Spain; ⁴Pulmonology, Rennes, France

Background Malignant pleural mesothelioma (MPM) is a rare, aggressive malignancy without curative treatment. Majority of patients receive pemetrexed/cisplatin as standard of care (SoC). Median overall survival in unresectable disease is 12 months. ONCOS-102 is a granulocyte-macrophage colony stimulating factor (GM-CSF) expressing oncolytic adenovirus (Ad5/3-D24-GMCSF) with a unique ability to both prime and boost immune responses. The aim of the study was to assess