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 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 NCT03319940

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

Consent N/A

REFERENCE

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)

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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 ± 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 × 108 and 5 × 108 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 ± 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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Trial Registration NCT03847519

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

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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
abstracts

immune and clinical responses as well as safety in patients with 1st and 2nd line unresectable MPM.

Methods Eligible patients (experimental arm, n=20) received ONCOS-102 given intratumorally under CT or US guidance at a dose of 3 x 10 x 11 on Day 1, 4, 8, 36, 78 and 120 plus six cycles of SoC starting on Day 22. The control group (n=11) received only SoC. Imaging was done at baseline, Day 43–64 and 127–148. Patients were monitored regularly for immunological assessment including lesional biopsies (baseline and Day 36). Primary objective was safety and tolerability. Secondary objectives were immunological activation, ORR, PFS and OS as well as correlation between immunological activation and clinical outcome.

Results There were no safety concerns nor DLTs. In 1st line patients ORR/DCR was 30%/90% in the experimental group and 33%/83% in the control group. 2nd line patients had ORR/DCR of 11%/67% in the experimental group and 60%/80% in the control group. 12-month survival rate for the 1st line pts was 64% in the experimental group and 50% in the control group, PFS and OS are still to be reported. The treatment with ONCOS-102 induced strong upregulation of multiple genes associated with immune activation in tumor lesions. Profound innate and adaptive immune activation was observed in the experimental vs control group that was associated with better clinical outcome. In addition to an increase in intratumoral cytotoxic T-cells (10/15 pts), the treatment with ONCOS-102 resulted in polarization from M2 to M1 macrophages. An upregulation of PD-L1 was reported in 9/15 pts in the experimental group vs 2/5 pts in the control arm, highlighting the potential of ONCOS-102 as an immunosensitizing agent for combinatory therapies with checkpoint inhibitors.

Conclusions ONCOS-102 treated patients benefited from superior immune activation compared to patients receiving SoC with preliminary signals of clinical efficacy. Upregulation of adaptive immunity and cytotoxicity related gene expression, PD-L1 level and M2 to M1 macrophage polarization indicate that ONCOS-102 can induce a favourable TME modulation thus providing a scientific rationale for combination with check point inhibitors.

Trial Registration ClinicalTrials.gov NCT02879669

Ethics Approval This study was approved by the IRBs of all the sites in Madrid, Barcelona, Rennes and Poitiers.

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362 A PHII STUDY OF BEMCENTINIB, A FIRST-IN-CLASS SELECTIVE AXL KINASE INHIBITOR, IN COMBINATION WITH PEMBROLIZUMAB IN PTS WITH PREVIOUSLY-TREATED ADVANCED NSCLC: UPDATED CLINICAL & TRANSCRIPTOMIC ANALYSIS

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Background AXL is implicated in resistance to immunotherapy. Bemcentinib (BG324), a first-in-class, oral, selective and potent AXL kinase inhibitor, enhances checkpoint inhibitor (CPI) efficacy in preclinical models through tumor-immune mechanisms.

Methods BGBC008 is a PhII single-arm, 2-stage study with bemcentinib (200 mg/d) and pembrolizumab (200 mg q3wk) for previously-treated stage IV lung adenocarcinoma comprising 3 cohorts: chemotherapy-pretreated IO-naïve patients (Cohort-A), patients progressing on prior IO therapy (Cohort-B) or chemotherapy/pembrolizumab combination (Cohort-C). Primary endpoint was ORR according to RECIST1.1 with pre-defined criteria to proceed from the first to second stage in each cohort. Secondary endpoints included DCR, PFS, OS and safety. Exploratory endpoints include biomarker analysis and correlation with clinical endpoints, including composite (tumor and immune cell) cAXL score, PD-L1 TPS, and genome-wide mutational and transcriptome analysis.

Results As of July 2020, enrollment in Cohort-A and B (stage 1) is completed; a total of 66 NSCLC patients were dosed. Cohort-A (n=50) results were previously presented. All Cohort-B1 (n=16) patients received at least one prior line of therapy, the most recent including CPI; 4 patients had 1 and 12 had 2+ prior treatments. Of the Cohort-B1 patients, cAXL status was available for 13 patients: 8 cAXL-positive, 5 cAXL-negative. PD-L1 TPS was available for 13 patients: 5 TPS >50%, 5 TPS 1–49%, and 3 TPS <1%. Of patients who had previously undergone 1 line of CPI therapy (n=4), 75% were cAXL-positive and 25% were not evaluable for cAXL (median TPS of 20%). Patients who had previously undergone 2+ lines of therapy (n=12), 33% were cAXL-positive, 50% cAXL-negative, and 17% not evaluable for cAXL (median TPS of 50%). Of the treated pts, most common TEAEs (>25% of patients) were increased ALT (29%; 10% G3+), AST (29%; 5% G3+), and diaphorea (29%; 1% G3+). All cases of treatment-related transaminase increase were reversible and managed with concomitant administration of steroids and treatment interruption. Of the 15 radiologically-evaluable patients in Cohort-B1, 1 PR was observed; 6/7 (86%) cAXL-positive patients (1 PR, 5 SD) achieved clinical benefit while none was observed in cAXL negative patients. mPFS was 4.7mo in cAXL-positive and 1.9mo in cAXL-negative patients. Ongoing transcriptional analysis of pre-treatment biopsies revealed a distinct gene profile correlating with clinical benefit from bemcentinib + pembrolizumab combination treatment.

Conclusions Overall, bemcentinib in combination with pembrolizumab was well-tolerated and shows promising clinical activity in AXL-positive immunotherapy refractory disease. Updated survival and translation/biomarker data will be presented.

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Trial Registration NCT03184571

Ethics Approval This study was approved by all relevant institutions, including London Bridge Research Ethics Committee (UK), REC-South East (Norway), Drug Research Ethics Committee of the University Hospital Clinic of Barcelona (Spain), MCW/FH Institutional Review Board #4, Medical College of Wisconsin (USA).

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