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.

REFERENCES

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


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

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, TAAAs). 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 x 108 and 5 x 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-C8+ 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).

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