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 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 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 retrieved for the analysis of PD-L1 (Shuwen SAB-028).

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 evaluation 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.

Abstract 804 Table 1

<table>
<thead>
<tr>
<th>ICR-assessed (N=111)</th>
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<tbody>
<tr>
<td>Confirmed ORR, % (95% CI):</td>
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<tr>
<td>ORR for PD-L1 positive</td>
</tr>
<tr>
<td>ORR for PD-L1 negative</td>
</tr>
<tr>
<td>DCR, % (95% CI):</td>
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</tbody>
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a. Including 1 complete response and 29 partial response. At data cutoff, 90% of respond- en 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 ID.

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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SAFETY AND EMERGING EVIDENCE OF IMMUNE MODULATION OF THE LIVE BIO THERAPEUTIC 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. 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...
inclusion until the day preceding surgery (maximum 28 days therapy). The primary study outcome is to evaluate safety and tolerability of MRx0518 monotherapy in treatment naïve patients. Additional exploratory outcomes including identifying surrogate biomarkers of efficacy, microbiome analysis, effect on metabolomic markers and identification of histological and genomic alterations in paired pre-treatment (diagnostic biopsy) and post-treatment (surgical specimen) samples.

Results In part A, 17 patients received treatment, across tumour groups including breast (n=8), prostate (n=4), uterine (n=3), melanoma (n=1) and bladder (n=1). MRx0518 was well tolerated by all, with no grade 3/4 CTCAE toxicity reported, no severe adverse effects or treatment discontinuations. All patients proceeded to surgery, however the COVID-19 pandemic delayed surgery in 3 cases.

Analysis of the first 5* patient paired samples utilising the NanoString Pan Cancer IO 360TM Gene Expression panel has demonstrated significant changes in gene expression profiles in 48 genes (p

Conclusions This study has demonstrated the safety and tolerability of the live biotherapeutic MRx0518 in treatment naïve cancer patients. Exploratory analyses of post-treatment samples has echoed preclinical observations of increased infiltration of immune cells following treatment and will undergo further validation. Part B will focus on investigating efficacy in a further 100 treatment naïve patients with a placebo-controlled arm.

Trial Registration NCT03934827

Ethics Approval The study was approved by East of England - Cambridge East Research Ethics Committee approval number 18/EE/0091.

REFERENCE
*Data analysis has been censored at 18/9/2020, further samples analysis is ongoing and will be updated.

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806 CHANGES IN T CELL CLONALITY IN AWARE-1 STUDY, A WINDOW-OF-OPPORTUNITY STUDY WITH ATEZOLIZUMAB AND THE ONCOCYTIC VIRUS PELAREOREP IN EARLY BREAST CANCER

Background A previous phase 2 study in metastatic breast cancer demonstrated a statistically significant improvement in overall survival (OS) in patients treated with pelareorep (pela) in combination with paclitaxel (PTX) versus PTX alone. Given that pela is an intravenously delivered immuno-oncolytic reovirus, we hypothesized that the OS benefit from pela + PTX may be attributed to an adaptive T cell response triggered by pela. To examine if pela can mediate the priming of an anti-tumor immune response, we are conducting together with the SOLTI group the AWARE-1 study (a window-of-opportunity study of pela in early breast cancer), which is currently enrolling and for which initial translational research results are presented.

Methods AWARE-1 is a window-of-opportunity study to evaluate the safety and effect of pela + atezolizumab on the tumor microenvironment (TME) in 38 women with early breast cancer. Patients are treated with pela on days 1, 2, 8, and 9, while atezolizumab is administered on day 3. Tumor biopsies are collected at diagnosis, day 3, and day ~21. Five cohorts will be examined: Cohort 1: HR+/HER2-neg (10 patients) receiving pelareorep + letrozole; Cohort 2: HR+/HER2-neg (10 patients) receiving pelareorep + letrozole + atezolizumab; Cohort 3: TNBC (6 patients) receiving pelareorep + atezolizumab; Cohort 4: HER2+/HR+ (6 patients) receiving pelareorep + trastuzumab + atezolizumab; Cohort 5: HER2+/HR- (6 patients) receiving pelareorep + trastuzumab + atezolizumab. The primary endpoint of the study is CeTIL score, a metric for quantifying the changes in tumor cellularity and infiltration of TILs, where an increase in CeTIL is associated with a favorable response to treatment. Tumor tissue is being examined for pela replication, and changes to the TME are being assessed by immunohistochemistry and T cell receptor sequencing (TCR-seq). Peripheral blood is also being examined by TCR-seq.

Results Detailed TCR-seq results from peripheral blood and tumor tissue are presented for the ten-patients enrolled into Cohort 1 who received pela and letrozole. In tumor tissue, T cell clonality increased in day 21 biopsies relative to baseline biopsies, with similar increases in T cell fraction (the number of T cells) in the majority of patients. In general, most of the tissue-expanded T cell clones were also seen in the peripheral blood.

Conclusions Overall, these preliminary data from cohort 1 of AWARE-1 demonstrate that pela mediates priming of a T cell-based immune response that occurs both systemically and within breast cancer tissue.

Trial Registration NCT04102618

Ethics Approval This study was approved by the Spanish Health Authority, protocol number 2018-003345-42.

REFERENCES