A PHASE II STUDY OF THE ANTI-PROGRAMMED CELL DEATH-1 (PD-1) ANTIBODY PENPULIMAB IN PATIENTS WITH METASTATIC NASOPHARYNGEAL CARCINOMA (NPC) WHO HAD PROGGRESSED AFTER TWO OR MORE LINES OF CHEMOTHERAPY

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 effects 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, 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.

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 evaluable 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.

<table>
<thead>
<tr>
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<th>IRC-assessed (N=111)</th>
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<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>27.9% (19.0, 36.9)</td>
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<tr>
<td>ORR for PD-L1 positive</td>
<td>39.5% (25.0, 55.6)</td>
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<tr>
<td>ORR for PD-L1 negative</td>
<td>19.7% (10.9, 31.3)</td>
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<tr>
<td>DCR, % (95% CI)</td>
<td>49.5% (39.9, 59.2)</td>
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<tr>
<td>DoR, median (range, months)</td>
<td>NR (0.95 - 11.43)</td>
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<td>time: DoR, % (95% CI)</td>
<td>85.6% (52.5, 96.3)</td>
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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.
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 include identifying surrogate biomarkers of efficacy, microbiome analysis, effect on metabolic 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

**REFERENCES**


2. Data analysis has been censored at 18/9/2020, further samples analysis is ongoing and will be updated. http://dx.doi.org/10.1136/jitc-2020-SITC2020.0805

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**Changes in T Cell Clonality in Aware-1 Study, a Window-of-Opportunity Study with Atezolizumab and the Oncolytic Virus Palereorep 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 palereorep (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 palereorep + letrozole; Cohort 2: HR+/HER2-neg (10 patients) receiving palereorep + letrozole + atezolizumab; Cohort 3: TNBC (6 patients) receiving palereorep + atezolizumab; Cohort 4: HER2+/HR+ (6 patients) receiving palereorep + trastuzumab + atezolizumab; Cohort 5: HER2+/HR- (6 patients) receiving palereorep + trastuzumab + atezolizumab. The primary endpoint of the study is CelTIL score [2], a metric for quantifying the changes in tumor cellularity and infiltration of TILs, where an increase in CelTIL 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**


http://dx.doi.org/10.1136/jitc-2020-SITC2020.0806