852 **MODIFIED-EPITOPE-BASED VACCINE (OSE2101) COMBINED WITH ANTI-PD-1/IL-7V BISPECIFIC ANTIBODY SUSTAINS LONG-LASTING TUMOR SPECIFIC ANTIGEN MEMORY T CELL RESPONSE IN VIVO**

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Background OSE2101 is a cancer vaccine composed of 9 optimized epitopes of 5 different tumor-associated antigens (TAAs) CEA, p53, HER-2/neu, MAGE2, MAGE3 restricted to HLA-A2 combined with a universal helper T cell epitope (PADRE) characterized to induce a helper T lymphocyte (HTL) response. OSE2101 is designed to break self-tolerance and promotes tumor-specific cytotoxic-T lymphocytes (CTLs) against TAAs and Helper T Lymphocyte response. In phase III clinical trial, OSE2101 shown overall survival (OS) improvement compared with Chemotherapy (CT) (HR 0.59; p = 0.017) in patients with Non-Small Cell Lung Cancer after immunotherapy failure (ESMO 2021 #47LBA). At preclinical stage, OSE developed a BICKI®IL7v immunocytokine, anti PD-1 fused to IL7 mutein (IL7v) to reinvigorate $PD1^+$ $IL\text{-}7R^+$ tumor-specific T cells and sustain long-term response. IL-7 represents the main homeostatic cytokine, enhancing TCR repertoire diversity and favoring expansion/pro-survival of naïve and memory T cells. In this study, our goal was to evaluate the potential combination of OSE2101 and anti-PD-1/IL-7v to enhance frequency of anti-TAA tumor-specific cytotoxic-T lymphocytes.

Methods HLA-A2/DR1 KI mice were treated twice by OSE2101 injections (subcutaneous) +/- anti-PD-1/IL-7v. IFN-γ ELISPOT assay was used to measure CTL response in the spleen and bronchoalveolar-lavage at short (D28) and long-term (D49).

Results Phase II results showed that OSE2101 was able to induce a broad CTL and HTL responses in non-small cell lung cancer patients associated with clinical efficacy. In A2/DR1 transgenic mice, OSE2101 elicited a good CTL immunogenicity response in periphery but also induces lung-resident-memory T cell activation for a direct local anti-tumor efficacy. We next evaluated immunogenicity induced by combining with the Anti-PD-1/IL7v.

Anti PD-1/IL7v monotherapy efficiently antagonizes PD-1 receptor (pSHP-1) and CIS-delivers IL-7 cytokine to cis-potentiate PD-1+ tumor-specific T-cells. The bifunctional compound significantly sustains survival and proliferation of non-exhausted TCF1+ stem-like-memory T cells and demonstrated efficient monotherapy efficacy in orthotopic and ectopic mouse models by promoting long-term memory anti-tumor-T-cell response as evaluated by tumor-rechallenge model.

In A2DR1 immunogenicity model, the combination of OSE2101 + anti PD-1/IL7v treatment demonstrates significant higher peripheral, and lung resident tumor-specific-CTL response was observed as measured by IFNγ *ex-vivo* restimulation in both short-term or long-term models suggesting that Anti-PD-1 IL7v enhances OSE201 efficacy by favoring memory tumor-specific T cell.

Conclusions Our preclinical data support the potential benefit of combining modified-epitope-based Tedopi vaccine OSE2101 and anti-PD-1/IL7v immunocytokine to enhance magnitude and long-term maintenance of clonal anti-tumor-specific T cells.