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Title: Safety and immunogenicity of a personalized neoantigen-*Listeria* vaccine in cancer patients
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Abstract:

Background. Meaningful anti-tumor immunity in cancer patients (pts) has been associated with the presence of specific T cells directed at neoantigens, a class of unique peptides that arise from tumor-specific mutations. ADXS-NEO, a personalized *Listeria monocytogenes (Lm)*-based immunotherapy, is a bioengineered *Lm* that secretes an antigen-adjuvant fusion protein consisting of ≥ 20 unique (personal) neoantigens and a truncated fragment of listeriolysin O (tLLO), which has adjuvant properties. Preliminary safety and immunogenicity results from an ongoing phase 1 trial with ADXS-NEO are herein reported.

Methods. ADXS-NEO-02 is a phase 1 dose-escalation study of ADXS-NEO in subjects with metastatic microsatellite stable colon cancer (CRC), metastatic squamous histology head and neck cancer, and metastatic non-small cell lung cancer (NSCLC). Manufacturing of ADXS-NEO starts with whole exome sequencing of each pt-matched normal and tumor samples to detect genetic alterations in the coding regions of the genome followed by its production under GMP specifications. ADXS-NEO is infused intravenously every 3 weeks until disease progression or limiting toxicity. Main endpoints include safety, tolerability and immune-correlative data.

Results. The turnaround time for manufacturing ADXS-NEO has consistently been ≤ 8 weeks from biopsy to first dose. Two pts treated at $1X10^9$ CFU (dose level 1) experienced dose limiting toxicities (i.e., Gr 3 hypoxia ± Gr 3 hypotension) within 4 hours of completing the infusion of the second dose. These acute adverse events correlated with elevation of serum IL-6 and other cytokines, and both cases were manageable and reversible with tocilizumab and/or steroids. A dose de-escalation cohort was initiated at $1X10^8$ CFU, which has been found to be safe and tolerated by one pt. In these pts, ADXS-NEO induced: 1) activation and proliferation of CD4+ / CD8+ T cells; 2) neoantigen-specific T cell responses after 1 week of the initial priming dose and 3) antigen spreading and T cell responses to neoantigens not selected by algorithm.

Conclusions. ADXS-NEO at $1X10^9$ CFU was beyond the maximum tolerated dose but it was effective in eliciting a fast and broad anti-tumor immunity, including T cell responses to neoantigens and antigen spreading. Enrollment continues both in monotherapy and combination therapy arms with anti- PD-1/PD-L1 therapy, to define the recommended phase 2 dose.