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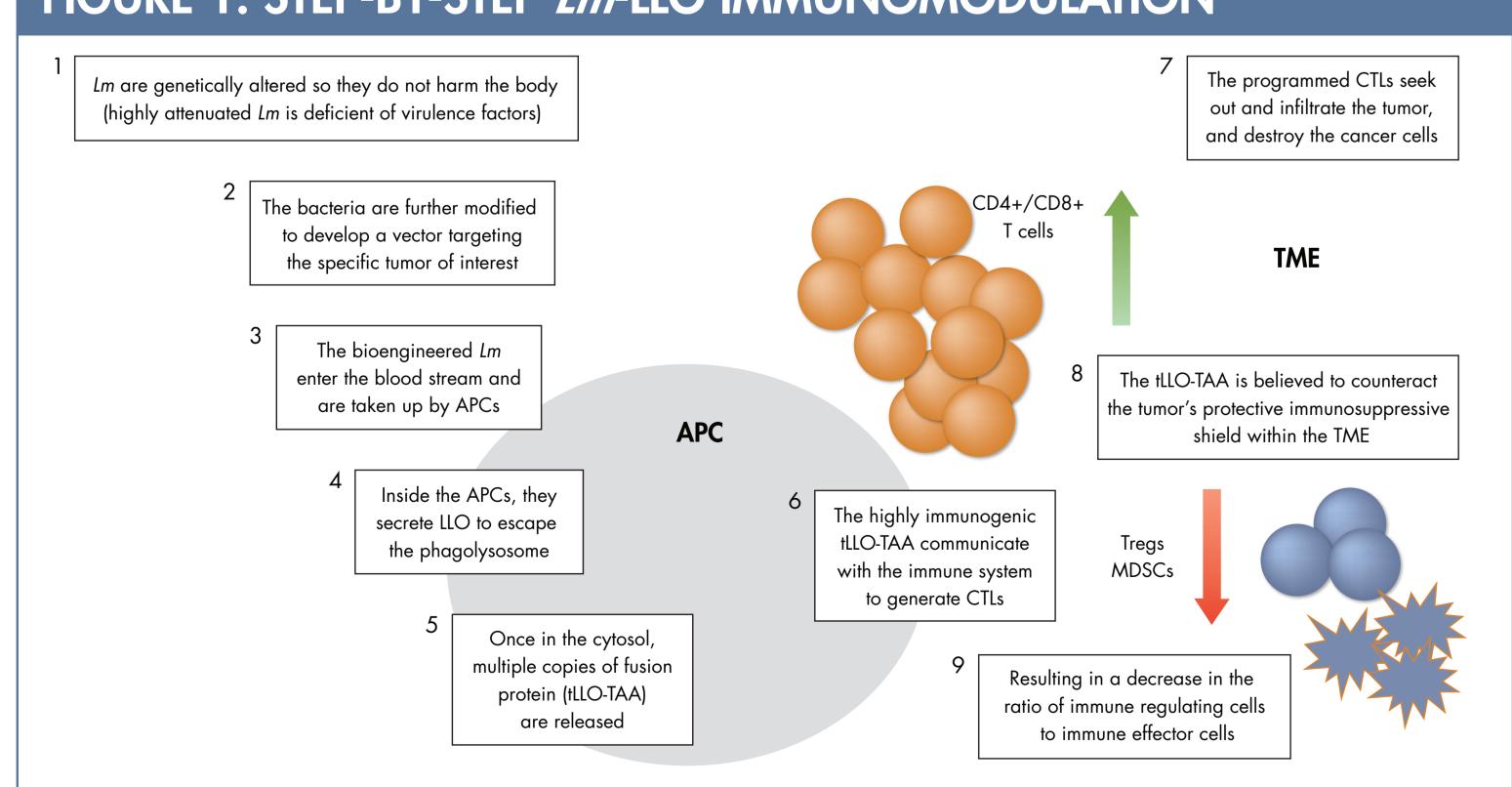
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INTRODUCTION

- Human epidermal growth factor receptor 2 (HER2) overexpression has been reported in a variety of cancers in addition to its well-established role in breast and gastric carcinomas.¹
- ADXS31-164 is a live, attenuated, bioengineered *Listeria monocytogenes* (*Lm*)-listeriolysin O (LLO) immunotherapy designed for the treatment of HER2-expressing cancers.²
- ADXS31-164 secretes an antigen-adjuvant fusion protein (tLLO-cHER2) consisting of a truncated fragment of LLO (tLLO) fused to the human cHER2, which is rapidly taken up by antigen-presenting cells (APCs), stimulating adaptive immunity and resulting in the generation of tumor-antigen-specific (HER2) cytotoxic T lymphocytes (CTLs).³
- *Lm*-LLO immunotherapies engineered to express specific tumor antigens stimulate both innate and adaptive tumor-specific immunity. They direct APCs to stimulate and activate the immune system and also reduce tumor immunosuppression in the tumor microenvironment by neutralizing regulatory T-cells (T regs) and myeloid-derived suppressor cells (MDSCs)⁴ (**Figure 1**)
- Preclinical studies with the ADXS31-164 immunotherapy showed antitumor activity versus control in HER2/neu-expressing transgenic mouse models.
- In FVB/N HER2/neu transgenic mice, ADXS31-164 reduced existing tumors and delayed the onset of spontaneous mammary tumors²
- In the same mouse model, ADXS31-164 also inhibited HER2/neu-expressing tumors in the brain²
- Thus, it is hypothesized that ADXS31-164 will generate a specific cellular immune response against HER2-expressing cells and overcome immunosuppressive or immunotolerant conditions in the tumor microenvironment.
- The present Phase 1b dose-escalation trial (NCT02386501) aims to determine the safety and tolerability and select a recommended Phase 2 dose (RP2D) of ADXS31-164 in patients with HER2-expressing solid tumors.

FIGURE 1. STEP-BY-STEP *Lm*-LLO IMMUNOMODULATION



APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; LLO, listeriolysin O; *Lm, Listeria monocytogenes*; MDSCs, myeloid-derived suppressor cells; TAA, tumor-associated antigen; tLLO, truncated LLO; TME, tumor microenvironment; Tregs, regulatory T cells.

OBJECTIVES

• The study objectives are outlined in **Table 1.**

TABLE 1. STUDY OBJECTIVES

Primary objective(s)

• Evaluate safety and tolerability of ADXS31-164

• Determine the RP2D of ADXS31-164

• Assess tumor response and PFS as a measure of antitumor activity of ADXS31-164 using RECIST v1.1 and irRECIST

• Describe and evaluate data from correlative

irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended

immunologic studies

METHODS

Exploratory objective

STUDY DESIGN

- Phase 1b, open-label, multicenter, multidose, dose-determining trial of ADXS31-164 in patients with HER2-expressing solid tumors.
- The targeted dose-limiting toxicity (DLT) rate for selection of the RP2D will be <33%
- DLTs include grade 4 hematologic toxicity, febrile neutropenia, prolonged grade 3 thrombocytopenia, any grade 3 or higher nonhematologic or prolonged laboratory value toxicity, or listeremia
- These toxicities will be considered dose limiting if judged by the investigator to be possibly, probably, or definitely related to the therapy
- The starting dose (Dose Level 1) for ADXS31-164 is 1×10^9 colony-forming units (CFU) every 3 weeks (Q3W) in a 12-week cycle.
- Dose escalations or de-escalations will follow a standard 3 + 3 design.
- Approximately 18 patients will be enrolled in the dose-escalating phase of the study
- In the absence of a grade 3 or 4 DLT in the 42-day DLT observation period, dose will be escalated to 5×10^9 CFU (Dose Level 2) and subsequently to 1×10^{10} CFU (Dose Level 3)
- Up to 4 expansion cohorts enrolling a maximum of 80 patients in total will be studied at the RP2D.
- Specific tumor types in these expansion cohorts may include patients with HER2-expressing breast and gastric cancers
- Tumor assessments will be performed at baseline, every 12 weeks (±1 week) after the first dose, and at the end of treatment/withdrawal.
- Treatment will be continued at the RP2D or a lower dose until a study discontinuation criterion is met, the patient has completed more than six months of study and at least one cycle of treatment post-complete response, or the patient has received 2 years of treatment.

STUDY TREATMENT

- ADXS31-164 infusions will be administered on day 1 of cycle 1. Subsequent infusions will be administered every 3 weeks.
- ADXS31-164 will be administered as a 60-minute intravenous (IV) infusion.
- Nonsteroidal anti-inflammatory drugs (NSAIDs; naproxen or ibuprofen), antihistamines, and antiemetics will be administered prophylactically to all patients and completed at least 30 minutes prior to each ADXS31-164 infusion.
- After the initial prophylactic treatments, if needed, a second dose of NSAID will be administered at approximately every 4 hours, while antiemetics will be administered every 8 hours on day 1 and day 2.
- A course of antibiotics 72 hours will be given after each ADXS31-164 infusion.

PATIENT ELIGIBILITY

• Key patient eligibility criteria are described in **Table 2.**

TABLE 2. KEY PATIENT ELIGIBILITY CRITERIA

Key inclusion criteria

Adult patients (≥18 years)

HER2 positivity to be determined by either IHC or FISH

- HER2-positive tumors include but are not limited to breast, bladder, pancreas, gastric, ovarian, osteosarcoma, NSCLC, SCCHN, and esophageal
- HER2 positivity will be defined as having at least 1+ positivity in 1% of the evaluable tumor cells as determined by IHC
- No additional testing is required if HER2 positivity has been previously ascertained by IHC or FISH. Local lab testing of HER2 is acceptable

Presence of histologic or cytologic diagnosis of locally advanced/metastatic HER2 solid tumors that have progressed or become intolerant to standard therapy or for which no standard therapy is available

Measurable and/or evaluable disease based on RECIST v1.1

ECOG PS ≤1

Adequate hematologic, hepatic, renal, and coagulatory functions

Key exclusion criteria

Has a Cardiac Functional Capacity of >1 (as per NY Heart Association) and LVEF below normal limits by institutional standards

Received prior anticancer chemotherapy, surgical treatment, or radiation therapy within ≤ 2 weeks prior to the first study treatment or has not recovered (ie, \leq grade 1 or at baseline) from AEs

Has known active central nervous system metastases and/or carcinomatous meningitis or an additional malignancy that is progressing or requires active treatment (except basal cell carcinoma/squamous cell carcinoma of the skin or progressing brain metastases requiring use of steroids for at least 7 days prior to trial treatment)

Diagnosed with immunodeficiency or received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days, or a monoclonal antibody (prior anti-HER2 acceptable) within 2 weeks prior to study day 1, or a live vaccine within 30 days of first trial dose

Has an active autoimmune disease requiring systemic treatment within the past 3 months or clinically severe autoimmune disease or has active infection requiring systemic therapy or is dependent on or currently receiving antibiotics which cannot be discontinued prior to dosing

Is currently dependent on, or has received within the past 4 weeks corticosteroids

Known contraindication/allergies to study antibiotics (amoxicillin, ampicillin, ciprofloxacin, erythromycin, gentamicin, penicillin, trimethoprim/sulfamethoxazole, and vancomycin) and to any component of the study drug formulation

Known history of listeriosis, or prior HER2 vaccine therapy, human immunodeficiency virus, and/or known active hepatitis B or C

AEs, adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; NY, New York; RECIST, Response Evaluation Criteria In Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck.

ENDPOINTS

Safety:

- AEs will be graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

- Efficacy:
- Tumor response will be measured by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and immune-related RECIST (irRECIST)⁵ criteria

- Kaplan-Meier curves will be produced for analysis of PFS

- Biomarkers (as a measure of immunologic response):
- Blood samples will be analyzed for circulating soluble markers of T-cell activation such as cytokines (IL-2, IL-6, IFN-gamma, TNF-alpha), and evaluated as potential pharmacodynamic biomarkers

STATISTICAL METHODS

Descriptive statistics will be used to summarize and evaluate the safety and tolerability of ADXS31-164.

- Summary statistics for continuous variables will include mean, standard deviation, median, and range
- Categorical variables will be presented as frequency counts and percentages
- Time-to-event variables will be summarized by Kaplan-Meier medians and survival plots
- Data analyses will be performed using Statistical Analysis System 9.2 (SAS 9.2) or higher.
- Safety analyses will be performed on the safety population, defined as all patients who receive at least 1 dose of study drug.
- Preliminary efficacy analysis will be performed on the efficacy population, defined as all patients who complete at least one cycle of ADXS31-164 treatment.

TRIAL STATUS

 The study is recruiting patients, and as of October 20, 2015, the study has enrolled 3 patients; the study is currently on clinical hold.

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