Regulated intratumoral expression of IL-12 in combination with cytotoxic agents as a strategy for the treatment of metastatic breast cancer

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Abstract

Tumor infiltration by lymphocytes is a critical component of effective immune responses against metastatic cancer. To this end, we have developed a novel approach, Ad×-RTS®-mIL-12, a vectorsial therapy based on the RheoSwitch Therapeutic System® (RTS®), to drive cytokine production in tumor infiltrating lymphocytes (TILs) through the administration of a dose-limiting cytotoxic agent. The Ad×-RTS®-mIL-12 gene is controlled by the RheoSwitch Therapeutic System® (RTS®), a synthetic molecular switch which is activated by a small molecule activator ligand, vRTS®. We have previously demonstrated a correlation between increased tumor IL-12 expression and increased tumor infiltration by TILs. We report here the results of a clinical study evaluating the safety, pharmacodynamics, and antitumor activity of the Ad×-RTS®-mIL-12 vector in patients with metastatic breast cancer.

Study Design

• Phase II, Randomized, Open-Label Study in Patients with Recurrent/Metastatic Breast Cancer and Hormone Sensitivity
• Intratumoral injection of Ad×-RTS®-mIL-12 on Day 1 of each cycle and oral vemurafenib (140 mg) for 7 days of each cycle

Primary Objectives

• Assess the safety and tolerability of vemurafenib + Ad×-RTS®-mIL-12 as monotherapy and in combination in subjects with recurrent and/or metastatic adenocarcinomas of the breast with accessible lesions
• Assess the efficacy of repeated cycles of intratumoral injections of Ad×-RTS®-mIL-12 with vemurafenib as monotherapy or in combination as measured by the 16-week progression-free survival rate

Secondary Objectives

• Estimate PFS by modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1
• Assess objective response rate (ORR) by mRECIST v1.1, duration of response and clinical benefit rate
• Evaluate pharmacodynamic tumor markers

Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a cytotoxic immune response against distant tumors

Inducible Gene Regulation: RheoSwitch Therapeutic System®

The Ad×-RTS®-mIL-12 gene is controlled by the RheoSwitch Therapeutic System® (RTS®), a synthetic molecular switch which is activated by a small molecule activator ligand, vRTS®. The RTS® system comprises a 2 component system: 1) the Switch Component, which is a recombinant protein that binds to the activated RTS® protein, and 2) the Inducible Promoter, which is a customizable promoter to which the Switch Component is attached. The Switch Component consists of a localized portion of mIL-12, a tail-activating portion that drives tumor-specific cytokine expression. The Ad×-RTS®-mIL-12 gene is controlled by the administration of an effective cytokine (mIL-12)

Chemotherapeutic Pretreatment Enhances Ad×-RTS®-mIL-12 Response

The Switch Component may be administered prior to the induction of the Inducible Promoter. The cytokine expressed by the Ad×-RTS®-mIL-12 vector may then be enhanced by the induction of the Inducible Promoter.

Patient Demographics, Prior therapies and Staging

Patient ID    Gender    Age    Disease Stage at Enrollment    Receptor Status    Number of Prior Systemic Treatments    Study Arm
105    female    38    Stage IV    Triple negative    4    Arm A
106    female    63    Stage IV    ER/PR - Positive    12    Arm A
107    female    70    Stage IV    ER/PR - Positive    12    Arm A
108    female    65    Stage IV    HER2 - Positive    4    Arm A
109    male    52    Stage IV    ER/PR - Positive    4    Arm A
110    female    74    Stage IV    HER2/Non-Recurrence    12    Arm A

Conclusions

• RTS® technology enables precise and controlled expression of IL-12 DNA. This facilitates exact control of dose and schedule
• Ad×-RTS®-mIL-12 - vemurafenib is biologically active as measured by on mechanism and on target toxicity in metastatic breast cancer and effects seen in ongoing melanoma studies.
• Preliminary monotherapy PFS rate too early to evaluate as only two patients have reached assessment timepoints
• All related AEs and SAEs reverse upon discontinuation of vemurafenib
• Recruitment is ongoing to refine dose, schedule, and optimal combination regimen

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