A FIRST-IN-HUMAN STUDY OF PEGYLATED RECOMBINANT HUMAN IL-10 (AM0010), DAILY ADMINISTERED FOR FOUR MONTHS IN SELECTED ADVANCED SOLID TUMORS.

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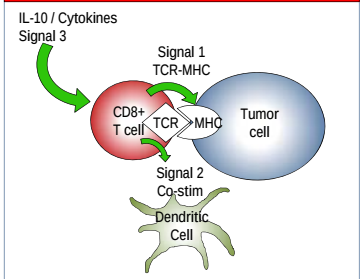
AM0010 - BACKGROUND

- Recent developments in cancer immunity have sparked the interest of scientists and clinicians, yielding novel and exciting immunotherapeutics.[1]
- AM0010 is a pegylated recombinant form of human IL-10 (PEG-rHuIL-10) that is being developed for the treatment of cancer.
- PEG-IL-10 increases and activates intra-tumoral CD8+ T cells (Fig. 2)[3].
- Intra-tumoral memory T cells correlate with survival in cancer patients[2].
- In preclinical studies, PEG-IL-10 induces the rejection of large tumors and the development of immunological memory against the tumor cells (Fig. 4).

Figure 1. Intra-tumoral CD8+ T cells require 3 signals for full activation

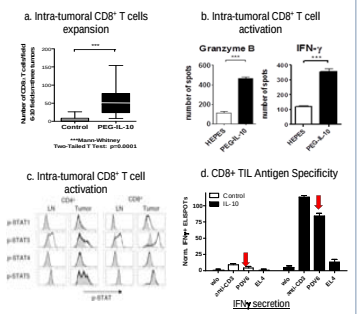


Signal 1 TCR stimulated by MHC and peptide on tumor cells
Signal 2 Co-stimulatory signals stimulated by T cell activation
Signal 3 Cytokine signal to induce the cytotoxic activation

Preclinical rationale

- PEG-IL-10 directly activates tumor specific CD8+ T cells.
- PEG-IL-10 increases IFNγ in the CD8+ T cell and MHC expression in the tumor.
- PEG-IL-10 induces tumor rejection and long lasting anti-tumor immune surveillance.

Figure 2. AM0010 activates CD8+ T cells in syngeneic mouse tumor models.



a. Increase of intra-tumoral CD8+ T cells
b. Increase of cytotoxic enzymes and IFNγ in intra-tumoral CD8+ T cells
c. Activation of STAT1 and STAT3 in intra-tumoral CD8+ T cells
d. Expansion of CD8+ T cells recognizing tumor cells

AM0010 / PEG-IL-10 Mechanism of Action

- Induces CD8+ T cell expansion via increased STAT3 phosphorylation (Fig. 2a,c)
- Activates CD8+ T cell via STAT1 phosphorylation (Fig. 2c)
- T cell activation increases Signal 2 via reduction of PD-1 expression
- Induces IFNγ in CD8+ T cells (Fig. 2b)
  - IFNγ induces MHC in tumor cells and dendritic cells (Signal 1) and induces co-stimulatory molecules on dendritic cells (Signal 2)
- Induces Granzymes in CD8+ T cells to kill tumor cells (Fig. 2b)

Figure 3. PEG-IL-10 treatment induces tumor rejection of mouse syngeneic colon carcinoma (CT26) and melanoma (M3)

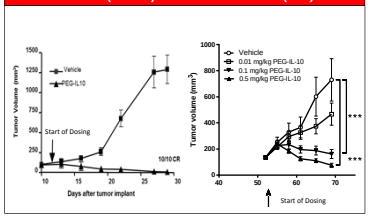
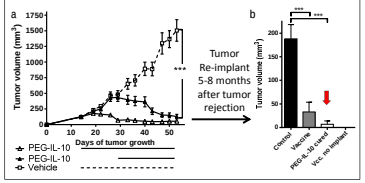


Figure 4. PEG-IL-10 induces tumor rejection and long lasting immune memory in a syngeneic mouse skin cancer model



AM0010 / PEG-IL-10

- Induces Tumor rejection in syngeneic mouse tumor models (Fig. 3, 4)
- PEG-IL-10 treated mice remain tumor free
- Immune memory mediates rejection of re-implanted tumor cells (without treatment; Fig. 4b ⬇)

STUDY OBJECTIVES

Primary

- To assess the safety, tolerability, maximum tolerated dose (MTD), and pharmacokinetics (PK) of AM0010

Secondary

- To assess the tumor response
- To evaluate anti-AM0010 antibodies

Exploratory Biomarkers

- Serum cytokines
- T and B cell responses to tumor associated antigens
- Immuno-profiling
- Immuno-score

ENDPOINTS

- Tumor Response will be assessed using the immune related response criteria (irRC) or the Prostate Cancer Working Group Criteria (PCWG2) for progression in bone
- Adverse Events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.02)

TRIAL DESIGN

- First-in-human, open-label, dose escalation study to evaluate the safety and tolerability of AM0010 in patients with advanced solid tumors dosed daily subcutaneously (SC) (clinicaltrials.gov identifier NCT02009449).

Figure 5. Trial Design

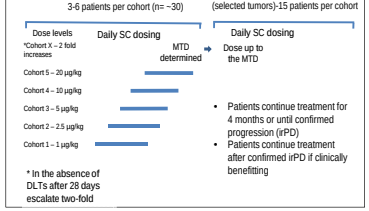
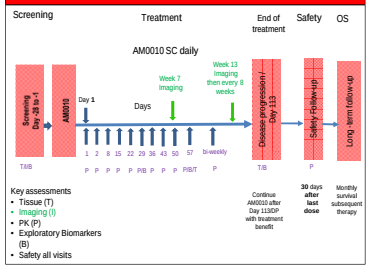


Figure 6. Trial Schema, Study Periods and Assessments



PATIENT ELIGIBILITY

Major inclusion criteria

- Advanced solid tumors; limited to melanoma, prostate, ovarian, renal, colorectal, pancreas, non-small cell lung cancer
- Life expectancy of >16 weeks

Major exclusion criteria

- Chronic inflammatory diseases of the peripheral and central nervous system
- Uncontrolled systemic fungal, bacterial, viral, or other infection
- Treatment with immune modulators including, but not limited to, anti-CTLA4, anti-PD1, anti-PDL1, systemic corticosteroids within 14 days
- History of a bleeding diathesis

TRIAL STATUS

- This study is open for enrollment at 4 sites in the United States
- As of May 22, 2014 22 patients have been enrolled in the Dose Escalation phase.
- Enrollment in Cohort 4 (10 µg/kg) has been completed without the MTD being reached.
- Cohort 5 (20 µg/kg) opened to enrollment in May 2014.

ACKNOWLEDGMENTS

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SPONSORS

AM0010 is being developed by ARMO BioSciences.

REFERENCES

1. Hodi, O'Day et al. 2010, Topalian, Hodi et al. 2012
2. Fridman, Pages et al. 2012
3. Mumm, Emmerich et al. 2011

CONTACT INFORMATION

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