Anti-tumor activity of PEGylated human IL-10 (AM0010) in patients with Pancreatic or Colorectal Cancer.

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Background and Purpose

- IL-10 was cloned at DNAX/Schering-Plough in 1989 – two functions
  - CSIF (cytokine synthesis inhibitory factor) - "anti-inflammatory"
  - B-TCGF (B cell derived T cell growth factor) - stimulates cytotoxic CD8+ T cells
- Schering-Plough sponsored several phase 3 studies with rHuIL-10 in immune mediated inflammatory diseases (Psoriasis, Crohn's disease, RA) and liver fibrosis
- rHuIL-10 transiently lowered TNFα and IL-1 in patients (-50% only)
- Signs of efficacy were observed but short T1/2 of rHuIL-10 limits its therapeutic efficacy
- Increased Granzymes and IFNγ were observed at higher doses (indicative of CD8+ T cell activity)
- ARMO BioSciences is developing AM0010, a PEGylated human IL-10 (PEG-rHuIL-10)
- High cure rate in animals with solid tumors and metastatic disease (PEG-IL-10 not rIL-10)
- Induces activation, proliferation and survival of intratumoral CD8+ T cells
- Expansion of tumor specific CD8+ T cells
- Treatment results in long-term "anti-tumor immune memory"
- Works in combination with chemotherapy

- In this Ph1 clinical study AM0010 was evaluated as single agent and in combination with SOC chemo and anti-PD-1
- Here we report on the cohorts with pancreatic cancer and CRC

Study Design and Eligibility

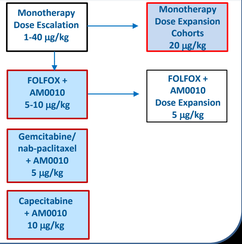
AM0010
- Continuous Daily Subcutaneous Injection
- 3+3 Dose Escalation

AM0010 + FOLFOX

AM0010 + Gemcitabine / nab-paclitaxel

AM0010 + Capecitabine

Key Eligibility in AM0010 Cohorts
- Tumor types: PDAC, CRC, Melanoma, RCC, NSCLC, other solid tumors
- Excluded prior Guillain-Barré syndrome and neuro-inflammatory diseases
- Allowed all other autoimmune diseases incl. RA, Crohn's disease, psoriasis

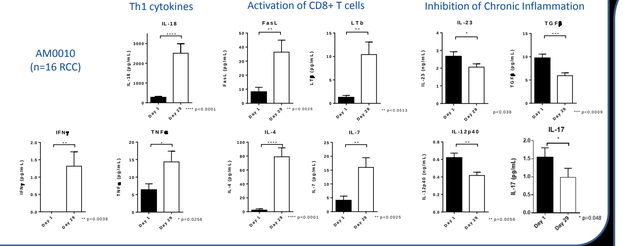


Immune Activation by PEG-IL-10 in Patients

AM0010 - immune activation signature in the serum

- AM0010 treatment (20µg/kg) induced a comprehensive immune signature in the serum of patients
  - Th1 cytokines — IFNγ , IL-18, TNFα
  - CD8+ T cell activity — FasL, LTb, IL-4, IL-7
  - Th17 cytokines / Immune suppression - TGF-β
- Other inflammatory cytokines were not significantly altered (96 tested)
- IL-10 immune activation signature is activated in all patients at the therapeutic dose and is more pronounced in responding patients
- IL-18 induction on Day 57 correlates with SD/PR vs. PD

Serum cytokine assays by Myriad RBM



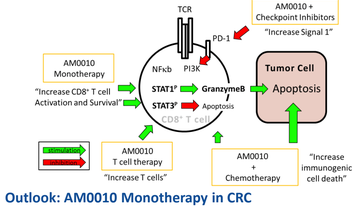
Summary and Outlook

Acceptable tolerability profile (up to 19.6 months)
- Tolerated on continuous dosing without autoimmune AEs
- Several patients are on AM0010 for more than one year including patients with PDAC for 13.5 mo, with melanoma for 19.6 mo., and with CRC for 19.4 mo.

Encouraging Efficacy Profile
- RCC (n=15): ORR 27%
- PDAC (n=17): DCR 47% at 8 weeks, reduction in CA19-9 in 47% of patients

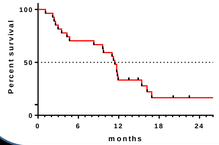
Sustained Th1 / CD8+ T cell mediated immune activation
- Increase of Th1 / CD8+ T cells centered immune signature
- Increase of activated tumor infiltrating CD8+ T cells
- Increase of proliferating, PD-1+ CD8+ T cells
- Oligoclonal expansion of novel T cells in systemic circulation

Mechanism Based Combinations with AM0010



Outlook: AM0010 Monotherapy in CRC

- CRC (n=27): mOS 11.4 mo;



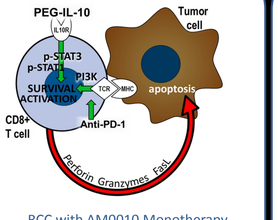
- mOS 11.4mo (ITT, 27 patients)
- Observation ≥ 11.4 months
- Patients had a median of 4 prior lines of treatment (2-7)
- 11 patient were in dose escalation cohorts (1-10µg/kg)
- 16 patient were treated at or above RP2D (20 or 40µg/kg)
- 7 patients had stable disease at 8 weeks (25 evaluable patients), 1 patient had SD for 19.4 months
- No objective responses were observed

Background: Mechanism of Action

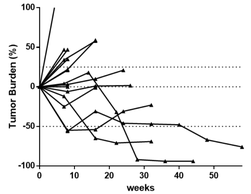
- Low levels of IL-10 are anti-inflammatory - high levels expand antigen activated CD8+ T cells
- Tumor antigen recognition by CD8+ T cells (TCR) induces PD-1 and the IL-10 receptor on CD8+ T cells
- IL-10 activates CD8+ T cells ("Cytotoxic License")
- PEG-IL-10 induces cytotoxicity, proliferation and survival of CD8+ T cells and the persistence of antigen activated intratumoral CD8+ T cells
  - Phosphorylation of the STAT1 and STAT3

In a large Phase 1 study, 144 patients with advanced solid tumors have been treated with AM0010 monotherapy. Objective responses were observed in ocular melanoma, renal cell cancer (RCC) and lymphoma, prolonged disease stabilization has been observed in several additional indications, including H&NC, PDAC and CRC.
Four of 15 patients with RCC had an objective response.

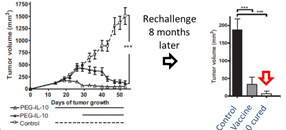
Treatment of preclinical tumor models with large tumors with PEG-IL-10 induced tumor rejection and the establishment of anti-tumor immune memory.
(Mumm et al. Cancer Cell 2011; Chan IJC 2016).



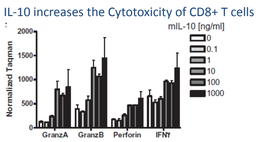
RCC with AM0010 Monotherapy



PEG-IL-10 induces Tumor Rejection and Immune Memory



IL-10 increases the Cytotoxicity of CD8+ T cells



CD8+ T cells, isolated from mouse spleens were cultured with increasing concentrations of IL-10 after anti CD3 stimulation. mRNA was analyzed by quantitative RT-PCR and indicates the increase of cytotoxicity mediating enzymes in response to IL-10 stimulation

Results

AM0010 Monotherapy in Pancreatic Cancer Patient
- 22 Patients with advanced pancreatic cancer (3rd-5th line of treatment) were enrolled at 20µg/kg
- 17 patients had a scan at 8 weeks

Treatment Related Adverse Events
- Most common TrAEs included fatigue (n=6; 27%), anemia (7; 32%), thrombocytopenia (7; 32%), fever (4; 18%)
- G3 TrAEs at 20µg/kg were anemia (2; 9%), fatigue (2; 9%) or thrombocytopenia (1; 4.5%)
- All G3/4 TrAEs were reversible and allowed AM0010 reintroduction
- Immune related TrAEs, such as colitis, pneumonitis or endocrine disorders were not observed

Treatment related Adverse Events – AM0010 Monotherapy – PDAC

Combination	AM0010			
Grade	Grade 1	Grade 2	Grade 3	Grade 4
AM0010 dose (n=22)	20 µg/kg (n(%))			
Hematopoietic AEs				
Anaemia	1 (4.5%)	4 (18%)	2 (9%)	
Thrombocytopenia	1 (4.5%)	5 (23%)		1 (4.5%)
Lymphocyte count decreased			1 (4.5%)	
White blood cell count decreased			1 (4.5%)	
Non-hematopoietic Aes				
Anorexia	1 (4.5%)			
Appetite loss/decrease	1 (4.5%)	1 (4.5%)		
Arthralgias		1 (4.5%)		
Chills	1 (4.5%)			
Cholangitis		2 (9%)		
Dizziness	2 (9%)			
Dry mouth	1 (4.5%)			
Fatigue	1 (4.5%)	3 (14%)	2 (9%)	
Fever	4 (18%)			
Flu like symptoms	2 (9%)			
Headaches	2 (9%)			
Injection site reaction	2 (9%)			
Pain			1 (4.5%)	
Petechia	1 (4.5%)			
Pneumonitis				
Pruritis	1 (4.5%)	1 (4.5%)		
Rash – generalized	2 (9%)	1 (4.5%)		
Rash - maculopapular	1 (4.5%)	1 (4.5%)	1 (4.5%)	
Tinnitus	1 (4.5%)			
Weakness	2 (9%)			
Lab values				
ALT / AST increase		1 (4.5%)		
Coagulopathy		1 (4.5%)		
Hypertriglyceridemia	1 (4.5%)	1 (4.5%)		
Hypokalemia	1 (4.5%)			

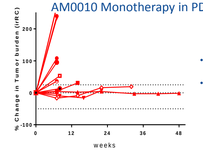
Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE, Patients in the AM0010 cohort received 20 µg/kg AM0010 daily

AM0010 anti-tumor activity in Pancreatic Cancer Patients

Pancreatic Cancer	AM0010 (µg/kg)	SD	PR	DCR (SD, PR at 8 wks)	mPFS
AM0010 (n=17; evaluable patients)	20	8	0	47%	1.7mo
AM0010 + FOLFOX (n=5)	2.5-10	4	1	100%	4.5mo
AM0010 + Gemcitabine / nab-paclitaxel (n=5)	5	4	1	100%	3.75mo
AM0010 + Capecitabine (n=5)	10	5	0	100%	2.1mo

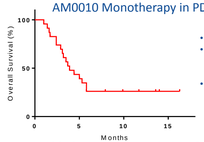
Chemotherapies were given following ASCO and NCNN guidelines, AM0010 was dosed daily

AM0010 Monotherapy in PDAC - Tumor response



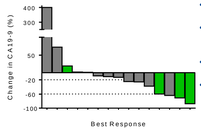
- 8 of 17 Patients had SD at 8 weeks
- 3 patients had SD at 16 weeks

AM0010 Monotherapy in PDAC - OS



- mOS 3.9mo (ITT, 22 patients)
- mOS 4.4 mo in patients who were at least 28 days on study (19)
- 6 of 22 patients (26%) had an OS > 8mo (8-16mo, all ongoing)

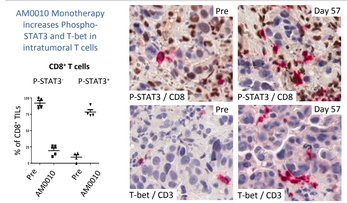
AM0010 Monotherapy in PDAC - Reduction in CA19-9



- 10 of 15 Patients had a reduction in CA19-9
- 7 of 15 patients had a reduction of CA19-9 >20%
- 4 patients had a CA19-9 reduction > 60%;
- 3 of those had an OS>9.9+ months

AM0010 Monotherapy activates T cell in PDAC CRC

AM0010 Monotherapy increases Phospho-STAT3 and T-bet in intratumoral T cells

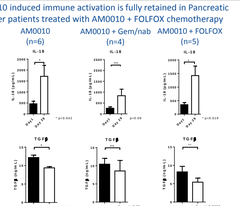


CRC patient on AM0010 Monotherapy (5 Patients tested)

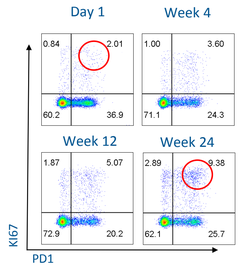
IHC by Dr. Scott Rodig DFCI and Cr. Coya Tapiya MDACC

Immune activation in AM0010 - FOLFOX

AM0010 induced immune activation is fully retained in Pancreatic cancer patients treated with AM0010 + FOLFOX chemotherapy

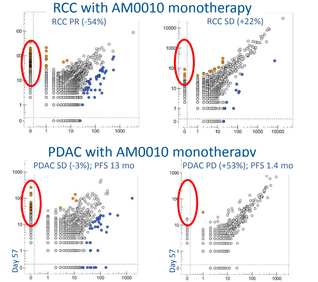


AM0010 Monotherapy increases PD1+ KI67+ CD8 T cells in responding PDAC patient



FACS analysis by Drs. Phil Wong, Jianda Yuan and Kong Shen, MSKCC

Remodelling of the peripheral T cells repertoire correlates with response



TCR clonal analysis by Adaptive Biotechnologies

Information

SPONSORS

AM0010 is being developed by ARMO BioSciences.

REFERENCES

1.Mumm et al. Cancer Cell 2011; Emmerich et al. Cancer Research 2012
2.Fridman, Pages et al. NRI 2012; Oft. CIR 2014 (Reviews)
3.Topalian, Hodi et al. NEJM 2012; Tumeh, Harview et al. Nature 2015

CONTACT INFORMATION

The pdf of this poster is at http://www.armobio.com/news-events/publications For more information on this trial, go to clinicaltrials.gov (NCT02009449) or contact martin.oft@armobio.com