Phase 1 with PEGylated Recombinant Human IL-10 (AM0010) in Patients with Advanced Solid Tumors

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History and Rationale

- 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
- rIL-10 transiently lowered TNFα and IL-1 in patients (-50% only)
- Signs of efficacy observed but short T1/2 of rHuIL-10 eliminates its therapeutic potency
- Increased Granzymes and IFNγ were observed at higher doses (CD8+ T cell activity)

- ARMO BioSciences develops 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

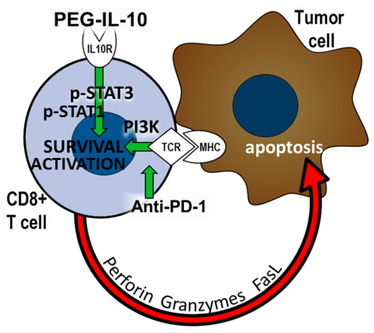
- In Ph1 clinical study as single agent and in combination with SOC chemo and anti-PD1 - To date >250 patients enrolled

Background

PEG-IL-10 - Immune Activation through Intra-tumoral CD8+ T cells

- CD8+ T cells require a T cell receptor signal (TCR) AND a confirmatory cytokine stimulation for activation and SURVIVAL in the tumor

- Tumor antigen recognition by CD8+ T cells (TCR) induces the IL-10 receptor and PD-1 on CD8+ T cells
  - IL-10 activates CD8+ T cells and provides positive feedback ("Cytotoxic License")
  - PD-1 inhibits the TCR signal in CD8+ T cells, provides negative feedback ("Immune Checkpoint")

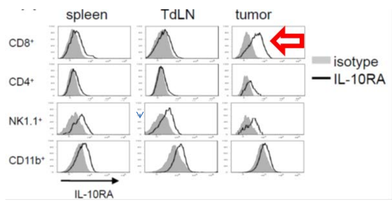


PEGylated IL-10 (AM0010) induces the activation and survival of intra-tumoral, tumor reactive CD8+ T cells through phosphorylation of the transcription factors STAT1 and STAT3. Pegylation of IL-10 ensures the activation of the essential survival pathway for the intra-tumoral CD8+ T cells to be activated without interruptions.

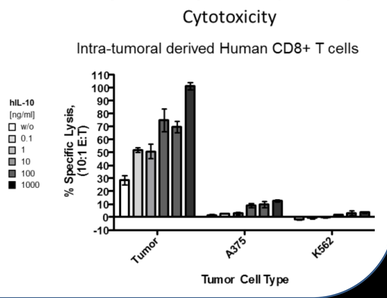
- The IL-10 receptor is highly expressed in intra-tumoral CD8+ T cells in mouse tumor models
- In-vitro treatment of human intra-tumoral CD8+ T cells with IL-10 increases their tumor specific cytotoxicity.

Treatment of preclinical tumor models with PEG-IL-10 induces tumor rejection and the long lasting anti-tumor immune memory.

IL-10R on CD8+ TILs (mouse)



IL-10 → Cytotoxicity of TILS (human)



Study Design

Study Design – Part A Monotherapy AM0010

- This is a phase 1, open-label, dose escalation study evaluating the preliminary clinical activity, tolerability and safety of AM0010 in patients with advanced solid tumors dosed daily subcutaneously (SC) (clinicaltrials.gov identifier NCT02009449)
- 3-6 patients were enrolled per cohort using the standard 3+3 dose-escalation (1, 2.5, 5, 10, 20 and 40 μg/kg)
- Disease specific escalation cohorts for the exploration of safety and efficacy were enrolled at the recommended phase 2 dose (RP2D) in monotherapy, 20μg/kg qd SC.

Study Design – Parts B-J: Combination therapy with Chemo-, Targeted- or Immuno-therapy

- Preclinical research and the conceptual convergence of the mechanism of action supports synergies between AM0010 and chemotherapies or anti-PD-1 immune checkpoint inhibitors (Conclusion and outlook)
- The maximal tolerated dose (MTD) is therefore explored in combination with a number of tumor therapies, including immune checkpoint inhibitors

Results

AM0010 Monotherapy Dose Escalation

- 5 patients (45%) treated at 20-40 μg/kg had disease control for at least 2 months
- 5 patients had mixed responses indicating anti-tumor activity
- 2 patients (20%) treated at 20-40 μg/kg had an objective response (PR); RCC and uveal melanoma
- 2 patients continue treatment at 18+ months (colorectal carcinoma, SD) and 12+ months (uveal melanoma, PR)

AM0010 Escalation - Clinical Activity

		AM0010 Phase 1 Dose Escalation	
Age	Median Range	64 39-82	
Prior Treatment	Median Range	4 1-11	
	Dose (μg/kg)	No. of Patients	Best Response (duration in mo.)
Escalation	1 2.5 5 10 20 40	4 6 6 6 6 5	1SD 1MXR (2) 1SD (18+) 2 MXR (2;2) 1PR (8), 2MXR (6;2) 1PR (10+)
	Total	33	2PR, 5MXR, 1SD (>18mo)
Tumor Histology	CRC Melanoma PC NSCLC RCC PanC OC	16 4 1 1 6 4 1	1SD (18+), 2MXR (2;2) 1PR (10+) , 1MXR (6) 1PR (8); 2MXR (2;2)
DCR (at first scan, % of all enrolled)	All Active dose (20-40μg/kg)	33% 45%	
ORR	20-40μg/kg	18%	

AM0010 Escalation – Patient Characteristics

Patient Characteristics		
Characteristic	No. of Patients	%
Sex		
Male	19	57.6
Female	14	42.4
Age, years		
Median	64	
Range	39-82	
Tumor histology		
Colorectal cancer	16	48.6
Renal cell carcinoma	6	18.2
Pancreatic cancer	4	12.1
Melanoma	4	12.1
Non-small-cell lung cancer	1	3
Ovarian cancer	1	3
Prostate cancer	1	3
ECOG PS		
0	18	54.5
1	15	45.5
Prior therapies		
Median	5	
Range	1-11	
Chemotherapy /Radiation therapy	30 / 3	
Immunotherapy	7	
Biologics /Targeted therapy	19 /15	

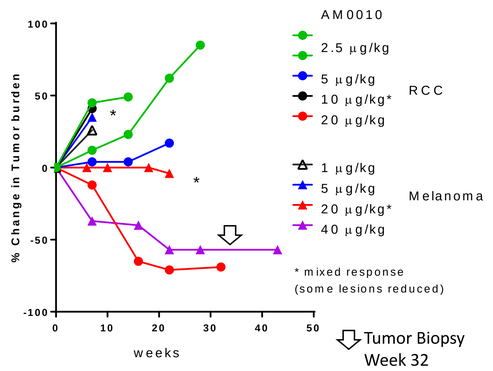
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

AM0010 Escalation - TrAEs

Cohort (μ g/kg)	1	2.5	5	10	20	40	1	2.5	5	10	20	40
n	4	6	6	6	6	5	4	6	6	6	6	5
Event	Grade 1-2						Grade 3-4					
Injection site reaction	7	3	3	2	1	2						
Pruritus			1	1	2							
Rash maculo-papular						1						
Anorexia	1	1	1	3	2	2						
Nausea	2	1	1	2	1							1
Vomiting	1	1	1									
Diarrhea			1	1		1						
Anemia		1	3		2	2	1			2	1	
Thrombocytopenia		1	1	2	3	4					1	
Headache	1				1	1						
Fever	1	1	2	1	3	2						
Flu like symptoms		1	1	1	1	1						
Chills			1		3	1						
Night sweats			1		1							
Fatigue		1	3	2	4	2						
Weakness												
Dyspnea												1
Transaminitis												1
Lipase increased												1

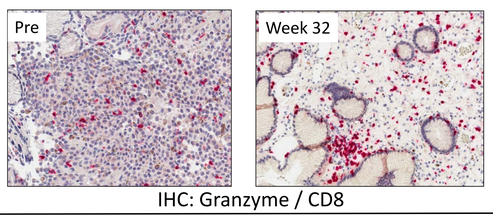
Table does not include events that occurred in less than three patients at grade 1-2 severity

AM0010 Escalation - Activity in RCC and Melanoma



Uveal Melanoma Lesions

- Uveal melanoma patient with stomach, peritoneal and lung lesions
- AM0010 monotherapy (40μg/kg)
- PR at 21 weeks
- Biopsy at week 32 indicates massive reduction of tumor cells with ongoing T cell activation

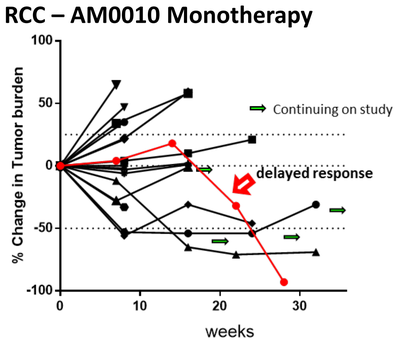


IHC: Granzyme / CD8

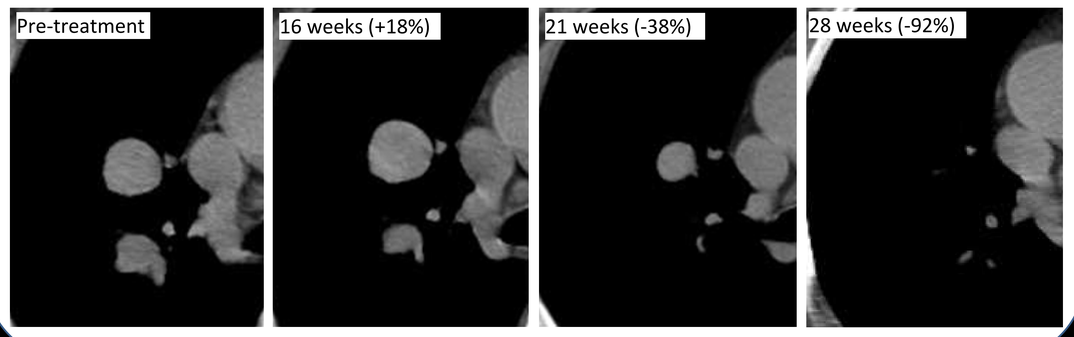
AM0010 Monotherapy RCC (20μg/kg) (n=16)

- 4 (25%) of 16 evaluable patients had a partial response
- 12 (75%) of 16 evaluable patients had at least stable disease
- Several patients discontinued despite early disease control
- 1 patients had a tumor reduction of -92% after 28 weeks of AM0010 despite initial slow tumor growth, reminiscent of an atypical immune related response. This may reflect on AM0010 mediated expansion of the adaptive CD8+ T cell repertoire.

RCC – AM0010 Monotherapy



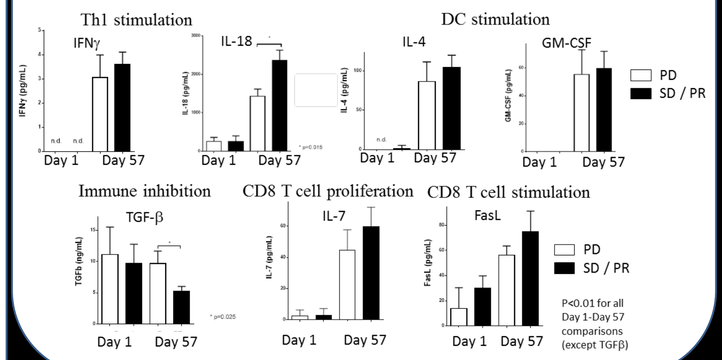
Delayed Response in RCC Patient treated with AM0010 (20 μg/kg)



Immune Activation by PEG-IL-10

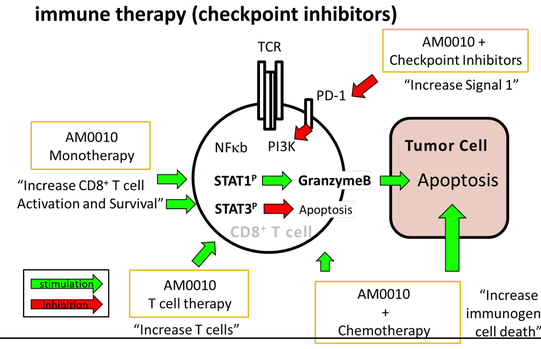
AM0010 single agent treatment (20μg/kg) induced a comprehensive immune signature in the serum of patients

Th1 cytokines	IFNγ , IL-18 ↑
Dendritic cell stimulation:	IL-4, GM-CSF ↑
Growth factor for memory CD8+ T cells	IL-7 ↑
CD8+ T cell activity	FasL ↑
Immune suppression	TGF-β ↓



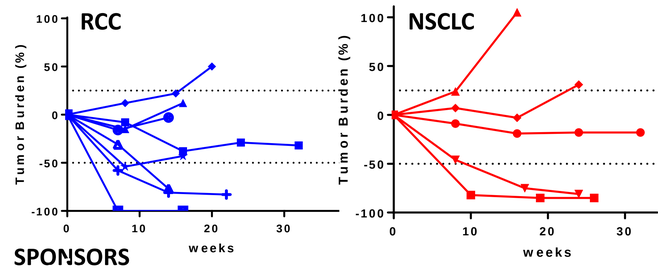
Conclusion and Outlook

- **Sustained Th1 / CD8+ T cell mediated immune activation**
  - Increase of activated tumor infiltrating CD8+ T cells
  - Increase of activated, PD-1+ CD8+ T cells
- **Well tolerated up to 18 months (CRC patient with SD)**
- **Durable Responses in melanoma, RCC**
  - 25% ORR in RCC (only advanced patients enrolled)
- **Durable SDs in subset of CRC, PDAC patients, encouraging mOS**
- **Supports the ongoing combination with chemo-, targeted and immune therapy (checkpoint inhibitors)**



AM0010 + Pembrolizumab - Methods & Preliminary Results

- 19 patients with immune sensitive tumor types (Melanoma, RCC, NSCLC) were enrolled for the treatment with PEG-IL-10 (10 or 20μg/kg qd) and Pembrolizumab (2mg/kg q3w).
- The combination was well tolerated at 10 and 20μg/kg AM0010 – no increase in irAEs
- RCC (n=8): ORR 50%, DCR 100% at 16 weeks
- NSCLC (n=5): ORR 40%, DCR 80% at 16 weeks



SPONSORS

AM0010 is being developed by ARMO BioSciences.

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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 available 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 phone: 1-650-779-5075