Antitumor Activity and Immune Correlates of PEG-IL-10 (AM0010) Alone or in Combination with Anti-PD-1

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Background and Purpose

- The success of and the durability of immune therapy of cancer is thought to depend on the activation and expansion of tumor reactive and infiltrating CD8+ T cells. The response to immune checkpoint blockade, depends on a pre-existing, CD8 T cell-rich tumor microenvironment. IL-10 stimulates the antigen mediated cytotoxicity, survival and proliferation of intra-tumoral CD8+ T cells and simultaneously dampens chronic inflammation. T cell receptor mediated activation of CD8 T cells induces the expression of IL-10 receptors on these cells. IL-10 activates with STAT3 an essential survival and proliferation signal in antigen activated CD8 T cells. This also provides a mechanistic rationale for combining AM0010 and anti-PD1 in the clinic. To evaluate the clinical activity, tolerability and anti-tumor activity of AM0010 alone or in combination with chemotherapy or immune checkpoint inhibitors a multi-basket phase 1 study was conducted. Additional disease specific expansion cohorts for the combination of AM0010 with FOLFOX in pancreatic cancer or with nivolumab in RCC or NSCLC are currently evaluated
- 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 of AM0010 in combination with Pembrolizumab.

Study Design and Eligibility

AM0010
- Continuous Daily Subcutaneous Injection
- 3+3 Dose Escalation
- Dose levels: 10 or 20 µg/kg

Pembrolizumab
- 2mg/kg every three weeks

Monotherapy Dose Escalation 1-40 µg/kg → Monotherapy Dose Expansion Cohort RCC 20 µg/kg

Pembrolizumab + AM0010 10-20 µg/kg → Pembrolizumab + AM0010 Dose Expansion 10 µg/kg

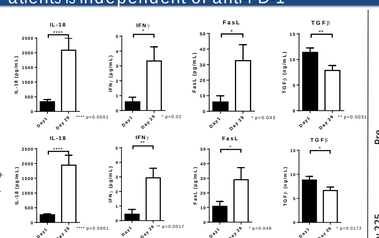
Key Eligibility in Pembrolizumab + AM0010 Cohorts
- Tumor types: Melanoma, RCC, NSCLC (no prior anti-PD1 or anti-PD-L1 allowed)
- Excluded prior Guillain-Barré syndrome and neuro-inflammatory diseases
- Allowed all other autoimmune diseases incl. RA, Crohn's disease, psoriasis

Immune Activation by PEG-IL-10 in Patients is independent of anti-PD-1

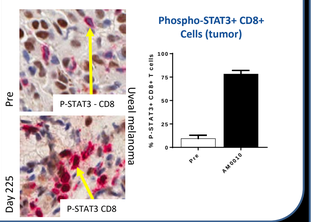
AM0010 - immune activation signature

- AM0010 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 ↓
- Th17 cytokines were reduced
- Other inflammatory cytokines were not significantly altered
- IL-10 immune activation signature is activated in all patients – with or without anti-PD-1
- AM0010 increases Phospho-STAT3 in tumor infiltrating CD8+ T cells

AM0010 (n=16) / AM0010 + Anti-PD-1 (n=16)



AM0010 Monotherapy induces Phospho-STAT3 in Intratumoral CD8+ T cells



Serum cytokine assays by Myriad RBM; IHC by Dr. Scott Rodig DFCI and Cr. Coya Tapiya MDACC; FACS analysis by Drs. Phil Wong, Jianda Yuan and Kong Shen, MSKCC

Conclusion and Outlook

Immune related TrAE occurred in the frequency and severity as expected from pembrolizumab monotherapy. The combination of AM0010 with pembrolizumab achieved objective responses (PR/CR) in 4 of 8 RCC pts and 2 of 5 NSCLC pts. Independent of the combination with anti-PD-1, AM0010 increased Th1 cytokines (IL-18, IFNγ, IL-7) in a dose dependent fashion. FasL and lymphotoxin beta - products of cytotoxic T cells - were also increased in the serum of AM0010 treated patients. In contrast, mediators of chronic inflammation, such as IL-23 and IL-17 and the immune suppressive cytokine TGFβ were reduced in the serum of patients. AM0010 increased the number and proliferation of PD1+ activated CD8 T cells while decreasing the proliferation of FoxP3+ Tregs and TGFβ in the blood (not shown). AM0010 induced de-novo oligoclonal expansion of T cell clones in the blood of patients without affecting total lymphocyte counts. This clonal expansion appeared not significantly enhanced and accelerated in patients treated with a AM0010 anti PD-1 combination. AM0010 also increased the number of tumor infiltrating Phospho-STAT3+ CD8+ T cells in tumors and the number of Granzyme+ PD1+ CD8+ T cells in tumor biopsies of treated patients.

Summary

- **Monotherapy and anti-PD-1 combination is well tolerated up to 24 or 18 months tested, respectively**
- **Sustained Th1 / CD8+ T cell mediated immune activation**
  - Increase in Th1 cytokines and products of CD8+ T cells
    - Not enhance by anti-PD-1
  - Increase of activated tumor infiltrating CD8+ T cells
  - Increase of activated, Lag-3+, PD-1+ CD8+ T cells
  - Expansion of rare, previously not detected T cell clones in the blood
    - Correlating with response
    - Not significantly enhanced by anti-PD-1

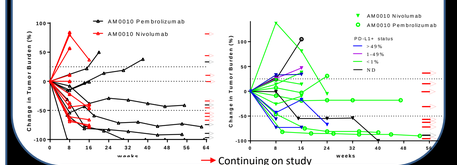
Conclusion

- AM0010 alone or in combination with anti-PD1 is well-tolerated. The clinical activity and the observed CD8+ T cell activation encourages the phase 2/3 studies of AM0010 in combination with anti-PD1 planned for early in 2017.

Outlook

RCC with AM0010 + Nivolumab or Pembrolizumab

NSCLC with AM0010 + Nivolumab or Pembrolizumab



Information

SPONSORS

AM0010 is being developed by ARMO BioSciences.

REFERENCES

1. Naing et al. JCO 2016; Mumm et al. Cancer Cell 2011; Emmerich et al. Cancer Research 2012
2. Fridman, Pages et al. NRI 2012; Oft. CIR 2014 (Reviews)
3. Garon et al. NEJM 2015; Motzer et al. JCO 2014

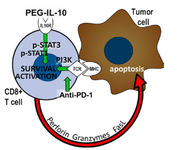
CONTACT INFORMATION

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 phone: 1-650-779-5075

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")

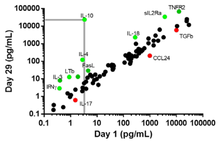


- AM0010 induces a Th1 and CD8+ T cell related immune signature
  - Increase of IFNγ, IL-18, TNFα, FasL, LTβ
  - Reduction of Th17 related cytokines IL-23, IL-17, TGFβ

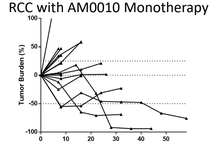
In a large Phase 1 study, 144 patients with advanced solid tumors have been treated with AM0010 monotherapy. Objective responses were observed in ocular melanoma, renal cell cancer (RCC) and lymphoma, prolonged disease stabilization has been observed in several additional indications, including H&NC,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

- PEG-IL-10 induces cytotoxicity, proliferation and survival of CD8+ T cells and the persistence of antigen activated intratumoral CD8+ T cells
  - Inhibition of Activation induced cell death in CD8+ T cells
  - Phosphorylation of STAT3 in CD8+ T cells

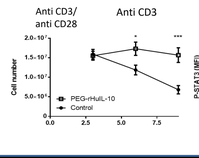
Immune Activation - AM0010 alone



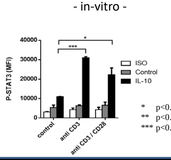
RCC with AM0010 Monotherapy



Activation induced cell death



Phospho-STAT3 in CD8+ T cells - in-vitro -



* p<0.05
** p<0.01
*** p<0.001

Results

AM0010 Monotherapy

- Patient self-administered daily doses of 20 µg/kg AM0010 SC.
- Grade3/4 TrAE were anemia (17%), thrombocytopenia (17%); Grade 2 TrAEs included fatigue (67%), rash (67%), fever (50%), chills (50%) and pruritis (33%).

AM0010 + anti-PD-1

- Patients self-administered daily doses of 20 µg/kg AM0010 SC, received Pembrolizumab 2 mg/kg q3w IV.

Treatment related adverse events – AM0010 + pembrolizumab cohorts

Combination	AM0010 - Pembro							
	Grade 1		Grade 2		Grade 3		Grade 4	
AM0010 Dose	10µg/kg	20µg/kg	10µg/kg	20µg/kg	10µg/kg	20µg/kg	10µg/kg	20µg/kg
Number of Patients	N=13	N=6	N=13	N=6	N=13	N=6	N=13	N=6
Hematopoietic AEs								
Anaemia	1 (8%)		3 (23%)	2 (33%)	2 (15%)	1 (17%)		
Neutropenia			1 (8%)		1 (7%)			
Thrombocytopenia	3 (23%)		3 (23%)		2 (15%)	1 (17%)		
Non-hematopoietic AEs								
Anorexia	3 (23%)	1 (17%)	3 (23%)					
Cough	2 (15%)							
Dehydration			2 (15%)					
Diarrhea	2 (15%)							
Dyspnea	2 (15%)		1 (8%)					
Fatigue	2 (15%)	2 (33%)	6 (46)	2 (33%)				
Fever		3 (50%)						
Hemoptysis					1 (7%)			
Injection site reaction	2 (15%)	2 (33%)						
Insomnia	1 (8%)							
Malaise							1 (17%)	
Nausea	1 (8%)	3 (50%)	1 (8%)					
Pneumonitis		1 (17%)	2 (15%)					
Pruritis	2 (15%)	2 (33%)	1 (8%)		1 (8%)			
Rash - generalized		2 (33%)		1 (17%)				
Rash - maculopapular	2 (15%)	2 (33%)	1 (8%)	1 (17%)	2(15%)			
Shortness of breath		1 (17%)		2 (33%)				
Weakness								
Lab values								
ALT / AST increase	1 (8%)					2 (33%)		
Hyperglycemia						1 (17%)		
Hypertriglyceridemia	2 (15%)		1 (8%)		1 (8%)	1 (17%)		
Hypokalemia					1 (8%)			
Hyponatremia					1 (8%)			

Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE; (1 event was not coded)
Patients in the AM0010+Pembro cohort received 10 or 20 µg/kg AM0010 daily and 2mg/kg Pembrolizumab every three weeks

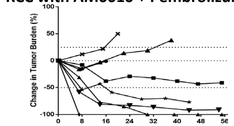
RCC AM0010 -/+ Pembrolizumab

- 15 patients with RCC treated with AM0010 alone at 20 µg/kg had disease evaluation
- 4 patients had a partial response (PR)
- 2 PRs had a late response
- The median progression free survival (mPFS) was 3 months
- 8 patients with RCC treated at 10 or 20 µg/kg AM0010 with Pembrolizumab (2mg/kg q3w) had disease evaluation
- 4 patients had an objective tumor response, 2 had a PR, 2 and a CR
- The median progression free survival was 9.95 months

NSCLC AM0010 -/+ Pembrolizumab

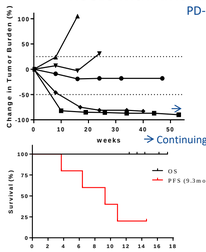
- 8 patients with NSCLC treated at 20 µg/kg AM0010 had a disease assessment (0 PR, 2 SD)
- Archival samples of 4 patients were analyzed for PD-L1 expression (all <1% PD-L1+)
- mOS was 15.4 months
- 5 patients with NSCLC treated at 10 or 20 µg/kg AM0010 with Pembrolizumab (2mg/kg q3w) had a disease assessment
- 2 patients had an objective tumor response, 2 had a SD (4 months)
- The median progression free survival was 9.3 months
- All patients are alive (observation period > 14 months)
- Archival samples of 4 patients (2 PR, 2 SD) were analyzed for PD-L1 expression
- All 4 samples were negative for PD-L1 (<1%) in both FDA approved assays

RCC with AM0010 + Pembrolizumab



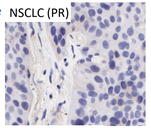
RCC	AM0010	AM0010 + Pembro
Objective responses	4 PR (n=15)	2 PR 2 CR (n=8)
ORR	27% (n=15)	50% (n=8)
mPFS (months)	3.0	9.95
mOS (months)	9.8	NR (>14)
Prior Therapies, median (range)	3 (0-7)	2.5 (0-4)

NSCLC with AM0010 + Pembrolizumab



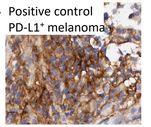
PD-L1 score: NA, <1%, <1%, <1%

NSCLC (PR)



Continuing on study

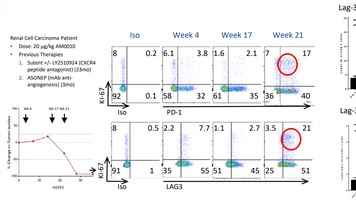
Positive control PD-L1+ melanoma



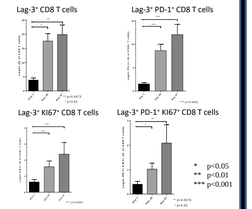
NSCLC	AM0010 (n=9)	AM0010 + Pembro
Objective responses	0 PR	2 PR (n=5)
ORR	0% (n=8)	40% (n=5)
mPFS (months)	1.8	9.3
mOS (months)	15.4	NR (>14)
Prior Therapies, median (range)	3 (1-6)	2 (0-5)
PD-L1 status < 1%; n (tested)	4 (4)	4 (4)

PD-1+ LAG-3+ KI-67+ CD8+ T cells in response to AM0010 Monotherapy

AM0010 monotherapy induces KI67+ PD-1+ / LAG3+ CD8+ T cells coinciding with tumor shrinkage

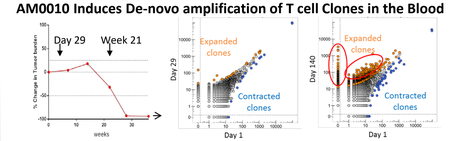


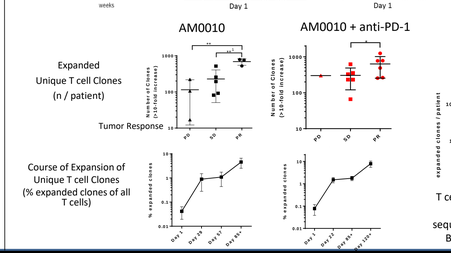
AM0010 monotherapy induces expansion of KI67+ PD-1+ LAG3+ CD8+ T cells



* p<0.05
** p<0.01
*** p<0.001

AM0010 Induces De-novo amplification of T cell Clones in the Blood





T cell clonal analysis by TCR deep sequencing; Adaptive Biotechnologies