Efficacy and Immune Activation with PEGylated human IL-10 (AM0010) in Combination with an anti-PD1 in Advanced NSCLC - Update

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Background

At therapeutic concentrations, AM0010 stimulates the cytotoxicity, survival and proliferation of intratumoral antigen activated CD8+ T cells in pre-clinical cancer models and in patients. AM0010 activates antigen stimulated CD8 T cells while PD-1 inhibits them. This provides the rationale for combining AM0010 and an anti-PD1. AM0010 monotherapy induced durable objective responses in ocular melanoma and renal cell cancer. AM0010 alone or in combination with chemotherapy and anti-PD-1 has been well tolerated in this Phase 1 basket trial.

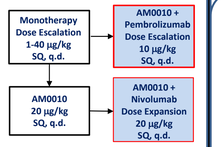
Study Design and Eligibility

AM0010
- 9 pts. with metastatic NSCLC were treated with AM0010 (20µg/kg SQ, q.d.) (7 pts. were evaluable for tumor response)

AM0010 + Pembrolizumab
- 5 pts. with advanced NSCLC treated with AM0010 (10µg/kg SQ, q.d.) and pembrolizumab (2mg/kg, IV q3wk).

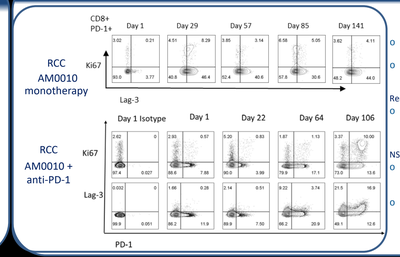
AM0010 + Nivolumab
- 29 pts. with advanced NSCLC treated with AM0010 (20µg/kg daily SQ, q.d.) and nivolumab (3mg/kg, IV q2wk).

Tumor responses were measured according to irRC criteria.



Key Eligibility in AM0010 + Nivolumab Expansion Cohort
- Advanced NSCLC with progression on prior platinum based regimen, no prior anti-PD-1/PD-L1 containing therapy.
- Excluded prior Guillain-Barré syndrome and neuro-inflammatory diseases
- Allowed all other autoimmune diseases (example RA, Crohn's disease, psoriasis)

AM0010 induces Invigoration of Exhausted CD8+ T cells



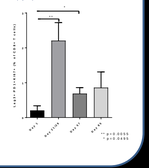
NSCLC - AM0010 + Pembrolizumab

- T cell activation / exhaustion analysis
- Comparison of pretreatment baseline (Day 1) with on-treatment samples

Renal cell cancer (left panel)
- Comparison of AM0010 and AM0010+pembrolizumab in a RCC patient on AM0010 monotherapy, compared to AM0010 + anti-PD-1

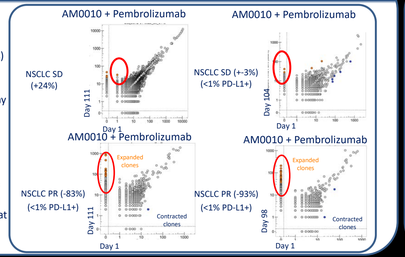
NSCLC (right panel)
- NSCLC treated with AM0010 + pembrolizumab (right panel, n=4)
- AM0010 and AM0010 + anti-PD-1 induces sustained expansion and invigoration of PD1+ Lag-3+ CD8+ T cells

Lag3+ PD1+ KI67+ CD8+ T cells



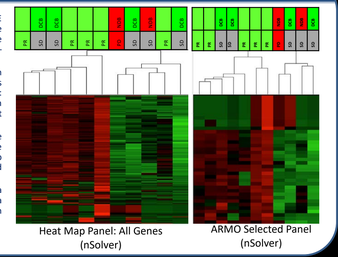
Clonal T cell Expansion correlates with Tumor Response

- T cell clonality analysis from peripheral blood by TCRb deep sequencing (Adaptive Biotechnologies)
- Comparison of on-treatment samples with pretreatment baseline (Day 1); NSCLC (PD-L1<1%+)
  - ➢ Expansion of novel T cells continues throughout the treatment
  - ➢ Sustained expansion of "newly expanded T cell clones (not detectable at Day 1) correlates with objective responses



Immune Signature Correlates with Response

- Archival tumor tissues (FFPE slides) were analyzed for immune related mRNAs using the PanCancer Immunoprofiling – (Nanostring)
- Analysis of all mRNAs led to an incomplete separation of patients with durable clinical benefit (DCB: CR/PR or SD>6 months) from patients with no durable benefit (NDB)
- Using a selected set of immune related mRNAs allows to separate patients with DCB on Nivolumab + AM0010 from patients who had NDB.
- Patients with an DCB had a different mRNA signature with a higher expression of certain mRNAs .



AM0010 - Mechanism of Action (Background cont.)

- IL-10 is anti-inflammatory and at higher concentrations and continuous exposure leads to the activation and expansion of antigen activated CD8+ T cells
- Tumor antigen recognition by CD8+ T cells (TCR) induces the IL-10 receptor on CD8+ T cells
- IL-10 activates CD8+ T cells ("Cytotoxic License")
- PEG-IL-10 induces phosphorylation of the STAT1 and STAT3 in CD8+ T cells. This leads to increased cytotoxicity, proliferation and survival of CD8+ T cells and the persistence of antigen activated intratumoral CD8+ T cells

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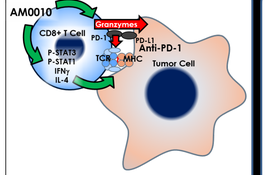
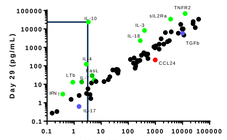
PEG-IL-10 treatment in preclinical tumor models with large tumors induced tumor rejection and the establishment of anti-tumor immune memory. (Mumm Cancer Cell 2011; Emmerich Cancer Res 2012).

In a large Phase 1 study, 144 patients with advanced solid tumors have been treated with **AM0010 monotherapy**.
AM0010 Monotherapy increased Th1 cytokine and the products of cytotoxic T cells in the serum of patients.

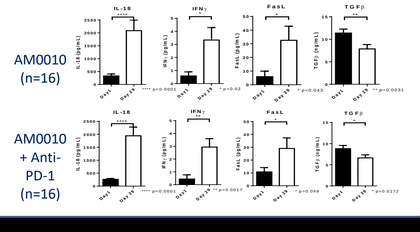


AM0010 Induced Serum Cytokines



Serum cytokines measured with Luminex.
● increased ≥2 fold; ● decreased ≥2 fold; ● Th17

Th1 Cytokines Changes with AM0010 or AM0010+ Pembrolizumab (RCC patients)



Results

AM0010 / AM0010 + anti-PD-1 in NSCLC Patients

- A cohort of 34 NSCLC pts. was fully enrolled on AM0010 (10-20µg/kg SC, q.d.) and pembrolizumab (2mg/kg, q3wk IV; n=5) or nivolumab (3mg/kg, q2wk IV; n=29).
- Pts had a median of 2 prior therapies (range 1-3).
- The median follow-up is 14.9 mo (range 5.6-23.2) for the nivolumab and 28.2 mo (26.5-30.3) for the pembrolizumab subgroup. Tumor responses were assessed by irRC.
- 20 patients were analyzed for PD-L1 expression (22C3), 60% had <1%, 15% had 1-49% and 25% had >50% PD-L1+ tumor cells.
- Immune responses were measured by analysis of serum cytokines (Luminex), activation of blood derived T cells (FACS) and peripheral T cell clonality (TCR sequencing).

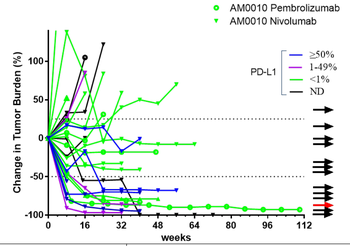
	AM0010 Monotherapy 2mg (20 µg/kg) N=9	AM0010 1mg (10 µg/kg) + Pembrolizumab N=5	AM0010 2mg (20 µg/kg) + Nivolumab N=29
Median Age, years (range)	58 (44, 68)	74 (56, 80)	62 (40, 84)
Sex, n (%)			
Male	2 (22%)	4 (80%)	14 (48%)
Female	7 (78%)	1 (20%)	15 (52%)
ECOG Performance Status, n (%)			
0	3 (33%)	0 (0%)	8 (25%)
1	6 (66%)	5 (100%)	21 (75%)
Histology type, n (%)			
Squamous	0	2 (40%)	4 (14%)
Non-squamous	9 (100%)	3 (60%)	24 (83%)
Unknown	0	0	1 (3%)
Prior Therapy, median (range)	3 (1-7)	2 (0-5)	2 (1-3)

AM0010 / AM0010 + anti-PD-1 in NSCLC Safety Profile

	Grade 1/2			Grade 3/4		
AM0010 dose	10 µg/kg	20 µg/kg		10 µg/kg	20 µg/kg	
System Organ Class Preferred Term	pembro n=5	mono n=9	nivo n=29	pembro n=5	mono n=9	nivo n=29
Blood and lymphatic system disorders						
Anaemia		3 (33.3)	5 (17.2)	3 (60.0)	2 (22.2)	5 (17.2)
Thrombocytopenia	1 (20.0)	2 (22.2)	1 (3.4)	3 (60.0)	3 (33.3)	5 (17.2)
General disorders and administration site conditions						
Chills		1 (11.1)	3 (10.3)			
Fatigue	3 (60.0)	1 (11.1)	3 (10.3)	1 (20.0)	2 (22.2)	5 (17.2)
Pyrexia		3 (33.3)	7 (24.1)			2 (6.9)
Injury, poisoning and procedural complications, Investigations						
Injection site reaction			2 (6.9)			
INR increased		1 (11.1)	4 (13.8)			
Platelet count decreased			3 (10.3)	1 (20.0)		1 (3.4)
Metabolism and nutrition disorders						
Decreased appetite	3 (60.0)		3 (10.3)			
Hypertriglyceridemia	1 (20.0)	1 (11.1)	3 (10.3)			3 (10.3)
Hypoalbuminaemia			3 (33.3)			
Musculoskeletal and connective tissue disorders						
Arthralgia			3 (10.3)			
Myalgia		3 (33.3)	3 (10.3)			
Nervous system disorders						
Headache		2 (22.2)	3 (10.3)			
Peripheral sensory neuropathy			2 (6.9)			
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (20.0)		2 (6.9)		1 (11.1)	
Pneumonitis	2 (40.0)					1 (3.4)
Skin and subcutaneous tissue disorders						
Dry Skin		1 (11.1)	2 (6.9)			
Pruritus	2 (40.0)	2 (22.2)	2 (6.9)			
Rash		3 (33.3)	6 (20.7)			1 (3.4)
Rash maculo-papular	2 (40.0)	1 (11.1)	3 (10.3)	1 (20.0)		2 (6.9)

Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE v4.02, (>1 event & 5% in at least one cohort); no G5 event were observed.

Combination of AM0010 and anti-PD-1

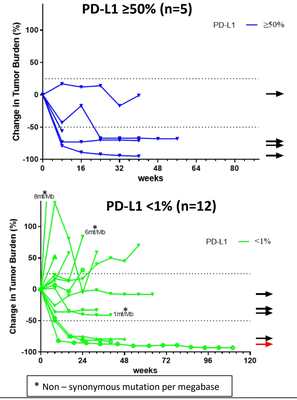


Disease	Treatment Combo	ORR by PD-L1 status (%) All	<1% PD-L1+	1-49% PD-L1+	≥ 50% PD-L1+
NSCLC	**AM0010 + anti-PD-1 mAbs**	36.4% (n=27)	25 %	50.0%	80.0%
	Pembrolizumab (Garon, NEJM; 2015)	19.4%	9.1%	15.6%	43.9%

A cohort of 9 NSCLC pts. were enrolled on AM0010 (20µg/kg SQ, q.d.).

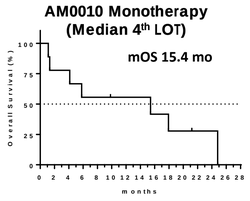
A cohort of 34 NSCLC pts. was enrolled on AM0010 (10-20µg/kg SQ, q.d.) + pembrolizumab (2mg/kg, q3wk IV; n=5) or nivolumab (3mg/kg. q2wk, IV; n=29).

Combination of AM0010 and anti-PD-1

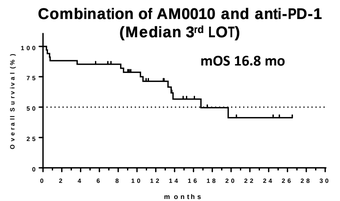


* Non – synonymous mutation per megabase

AM0010 Monotherapy (Median 4th LOT)



Combination of AM0010 and anti-PD-1 (Median 3rd LOT)



Summary of Results

- **AM0010 + anti–PD-1 is well tolerated in NSCLC**
  - No increase or exacerbation of autoimmune toxicities
  - Recommended Phase2/3 dose is 10 µg/kg, SQ, q.d. in combination with an anti-PD-1.
- **CD8+ T cell invigoration and clonal expansion of novel T cells confirms the activation of an essential MOA for immune therapy of cancer**
- **The ORR and durability of responses regardless of PD-L1 expression suggests an efficacious combination for phase 2/3 studies.**
- **Preliminary PFS and OS findings are encouraging.**

Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR (%)	ORR (%)	mPFS (Months)	mOS (Months)
NSCLC	**AM0010** (n=7/9)[1]	3 (1-7)	57%	–	1.7	15.4[3]
	AM0010 + pembrolizumab (n=5/5)[2]	2 (0-5)	100%	40%	10.9	NR[4]
	AM0010 + nivolumab (n=22/29)	2 (1-3)	82%	8 (36.4%)	NR[5]	NR[5]
	Anti-PD-1 mAb (e.g. Pembrolizumab) (Garon NEJM 2015)	1	41%	19.4%	3.0[6]	9.3[6]

(1) 5 of 5 patients tested are PD-L1 negative
(2) 4 of 4 patients tested are PD-L1 negative
(3) Final data
(4) Study in progress. Numbers as of August 11, 2017. 60% alive, median follow-up 28.2 months (range 26.5-30.3)
(5) Study in progress. Numbers as of August 11, 2017. Median follow-up 14.9 months (range 5.6-23.2)
(6) Data set at NEJM 2015, previously treated patients
NR Not reached

Information

SPONSOR

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; Brahmer et al., NEJM 2015

CONTACT INFORMATION

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