Efficacy and Safety of PEGylated Human IL-10 (AM0010) in Combination with an anti-PD1 in Renal Cell Cancer

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Background

At therapeutic concentrations, AM0010 (Pegilodecakin) stimulates the cytotoxicity, survival and proliferation of CD8+ T cells. IL-10 receptors and PD-1 are expressed on activated and exhausted CD8+ T cells, providing a rationale for combining AM0010 and an anti-PD-1.

Partial tumor responses (PR) were observed in 4 of 16 patients with poor to intermediate risk RCC (ORR 25%) treated with AM0010 monotherapy.

In dose escalation, 4 of 8 RCC patients receiving AM0010 plus pembrolizumab in 3rd line of therapy, had a PR. The mPFS was 16.7 months.

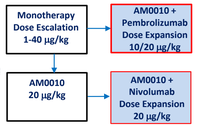
Study Design and Eligibility

AM0010

- 19 pts. with metastatic RCC were treated with AM0010 at 20µg/kg (16 pts. were evaluable for tumor response)

AM0010 + Nivolumab

- In this Phase 1b, 29 pts. with metastatic RCC were enrolled until Nov. 18 2016 on AM0010 (10 ug/kg daily SC) and nivolumab (3mg/kg, q2wk IV). 2 had favorable, 20 had intermediate and 4 had poor IMDC risk (3 were not available). Pts. had a median of 1 prior therapy (range 1-3). All pts. had received a VEGFR-TKI. Tumor responses were assessed following irRC. Immune responses were measured by analysis of serum cytokines, activation of blood derived T cells and peripheral T cell clonality.
- Tumor responses were measured according to irRC criteria.

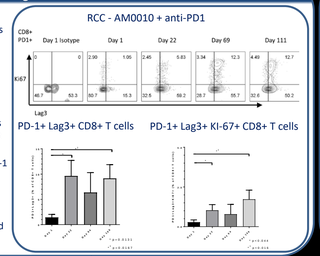


Key Eligibility in AM0010 + Nivolumab Dose Expansion Cohort

- Metastatic RCC with progression on prior gemcitabine containing regimen, no prior platinum
- Excluded prior Guillain-Barré syndrome and neuro-inflammatory diseases
- Allowed all other autoimmune diseases incl. RA, Crohn's disease, psoriasis

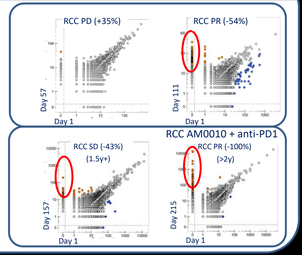
Sustained Invigoration of Exhausted CD8+ T cells

- T cell activation / exhaustion analysis
- FACS analysis of CD8+ T cells from peripheral blood mononuclear cell (PBMC)
- Comparison of on-treatment samples with pretreatment baseline (Day 1)
- AM0010 + anti-PD-1 increases the proliferation and expansion of exhausted CD8 T cells (also observed in AM0010 alone)



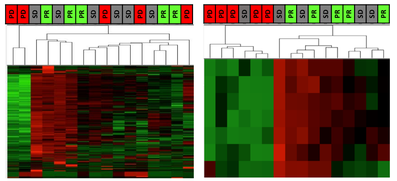
Clonal T cell Expansion correlates with Response

- T cell clonality analysis from peripheral blood (EDTA blood)
- TCRb deep sequencing (Adaptive Biotechnologies)
- Comparison of on-treatment samples with pretreatment baseline (Day 1)
- Expansion of "novel" T cell clones (not detectable at Day 1) appear to correlate with survival of RCC patients on AM0010 or AM0010 and anti-PD-1
- Sustained Expansion of novel T cell clones



Immune Signature Correlates with Tumor Response

- Archival tumor tissues (FFPE slides) were analyzed for immune related mRNAs using the PanCancer Immuneprofiling – (Nanostring)
- Analysis of all mRNAs revealed an in-complete separation of patients with partial response (PR) from patients with progressive disease (PD)
- Using a selected set of immune related mRNAs allows to separate RCC patients with a partial response on nivolumab + AM0010 from patients who had progressive disease.
- Patients with a partial response had a different mRNA expression profile than progressing patients.



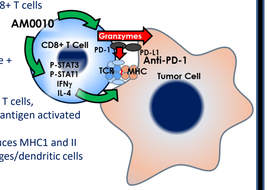
Heat Map Panel: All Genes (nSolver)

ARMO RCC Selected Panel (nSolver)

AM0010 - Mechanism of Action

Mechanism of Action of AM0010 + anti-PD-1

- 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 protects activated, Granzyme + CD8+ T cells - "Cytotoxic License"
- PEG-IL-10 induces cytotoxicity, proliferation and survival of CD8+ T cells, which leads to the persistence of antigen activated intratumoral CD8+ T cells
  - Increased IFNg secretion induces MHC1 and II on tumor cells and macrophages/dendritic cells



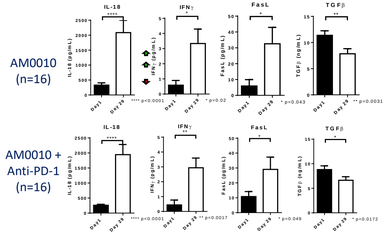
Preclinical Activity

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).

Phase 1 AM0010 Monotherapy

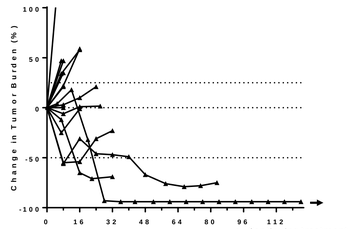
In a large Phase 1 study, 144 patients with advanced solid tumors have been treated with AM0010 monotherapy and 110 have received AM0010 in combination with an anti-PD-1 (pembrolizumab (n=52) or nivolumab (n=58)).

Serum Cytokines in RCC Patients Treated with AM0010 or AM0010 + Pembrolizumab



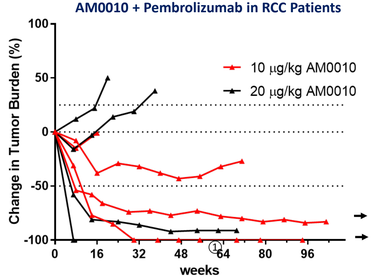
Background – AM0010 in RCC

AM0010 Monotherapy in RCC Patients



PR in 4 of 16 patients with poor to intermediate risk RCC (ORR 25%)

AM0010 + Pembrolizumab in RCC Patients



Results – AM0010 + Nivolumab or Pembrolizumab

AM0010 + anti-PD-1 - RCC Patient Characteristics

	Monotherapy 2mg (20 µg/kg) N=19	AM0010 - 1mg / 2mg (10 µg/kg / 20 µg/kg) + Pembrolizumab N=9	AM0010 2mg (20 µg/kg) + Nivolumab N=29
Median Age, years (range)	61 (22, 68)	54 (32, 75)	66 (36, 77)
Sex, n (%)			
Male	12 (63%)	6 (67%)	21 (72%)
Female	7 (37%)	3 (33%)	8 (28%)
ECOG Performance Status, n (%)			
0	11 (58%)	3 (33%)	9 (31%)
1	8 (42%)	6 (67%)	20 (69%)
Prior Therapy, median (range)	3 (0-7)	2 (0-5)	1 (1-3)

AM0010 + anti-PD-1 – TRAEs in RCC

Treatment related adverse events – AM0010 + pembrolizumab / nivolumab in RCC

	Grade 1/2				Grade 3/4			
AM0010 Dose	10µg/kg		20µg/kg		10µg/kg		20µg/kg	
	Pembro	Nivo	Pembro	Nivo	Pembro	Nivo	Pembro	Nivo
Number of Patients	N=5	N=1	N=4	N=28	N=5	N=1	N=4	N=28
Blood and lymphatic system								
Anaemia	2 (40.0)	1 (100)		6 (21.4)				10 (35.7)
Neutropenia					1 (20.0)		1 (25.0)	1 (3.6)
Thrombocytopenia	2 (40.0)			4 (14.3)			1 (25.0)	6 (21.4)
General disorders and administration site conditions								
Chills				5 (17.9)				
Fatigue	4 (80.0)		2 (50.0)	9 (32.1)				1 (3.6)
Night sweats		1 (100)		3 (10.7)				
Pyrexia		1 (100)	1 (25.0)	10 (35.7)				
Investigations								
Alanine aminotransferase increased				4 (14.3)		1 (100)	1 (25.0)	
Aspartate aminotransferase increased				5 (17.9)		1 (100)	1 (25.0)	
Platelet count decreased		1 (100)		9 (32.1)				2 (7.1)
Serum ferritin increased	1 (20.0)			3 (10.7)				
Metabolism and nutrition disorders								
Hypertriglyceridaemia	1 (20.0)	1 (100)		5 (17.9)	1 (20.0)			5 (17.9)
Musculoskeletal and connective tissue disorders								
Arthralgia			1 (25.0)	4 (14.3)				
Myalgia				8 (28.6)				
Nervous system disorders								
Headache				5 (17.9)				
Skin and subcutaneous tissue disorders								
Pruritus			2 (50.0)	6 (21.4)	1 (20.0)			1 (3.6)
Rash		1 (100)	1 (25.0)	6 (21.4)				
Rash maculo-papular	1 (20.0)		2 (50.0)	4 (14.3)	1 (20.0)			

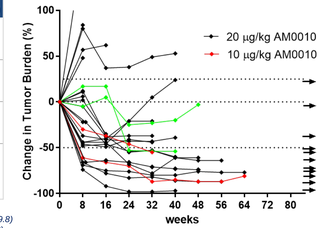
Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE, (>10% in total population or >5% in G3/4)
Patients in the AM0010+Pembro cohort received 10 or 20 mg/kg AM0010 daily and 2mg/kg Pembrolizumab every three weeks

Table: Efficacy of AM0010 or AM0010 + anti-PD-1 in RCC Patients

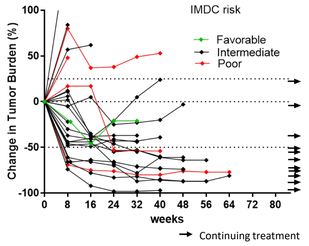
Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR n (%)	ORR (%)	CR (%)	mPFS (Months)	mOS (Months)
RCC	**AM0010** (n=16/19)	3 (0-7)	9 (56%)	4 (25%)	–	1.9	9.8[1]
	AM0010 + pembrolizumab (n=8/8)	2 (0-5)	8 (100%)	4 (50%)	2[4] (25%)	16.7	NR[2]
	AM0010 + nivolumab (n=26/29)	1 (1-3)	21 (81%)	10 (38.5%)	–	NR[3]	NR[3]
	Anti-PD-1 mAb (nivolumab) (Motzer et al., JCO 2014)	1	57-65%	20-22%	1	2.7-4.2	25

(1) Median follow-up 25.4 months (range 19.3-33.3)
(2) Study in progress. Numbers as of August 11, 2017. Median follow-up 26.75 months (range 12.3-29.8)
(3) Study in progress. Numbers as of August 11, 2017. Median follow-up 11.1 months (range 0.5-17.3)
(4) 2 partial responses with 100% reduction in measurable disease
NR not reached

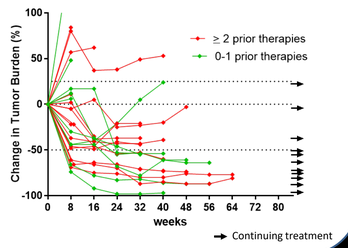
Tumor responses in RCC Patients on AM0010 + Nivolumab (≥2nd Line or Treatment)



Tumor responses in RCC Patients on AM0010 + Nivolumab with Intermediate to Poor Risk



Tumor responses in RCC Patients on AM0010 + Nivolumab 0-1 vs ≥2 Prior Therapies



Summary of Results

AM0010 + anti–PD-1 is well tolerated in RCC

- Recommended Phase2/3 dose is 10 µg/kg in combination with an anti-PD-1
- No exacerbation of autoimmune TrAEs observed in combination with anti-PD-1 antibodies

AM0010 +/- anti-PD-1 induces invigoration of CD8+ T cells and clonal expansion of novel T cells
mRNA analysis of the pretreatment immune microenvironment may correlate with tumor response. Further subpopulation analysis is in progress.

The preliminary clinical responses and the observed immune activation are encouraging and warrants further exploration of this combination in Phase 2 and 3 studies in RCC

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. Motzer et al NEJM 2015.

CONTACT INFORMATION

The pdf of this poster is 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