Efficacy, Safety and Immune Activation with PEGylated Human IL-10 (AM0010) plus FOLFOX in Metastatic Pancreatic Adenocarcinoma (PDAC)

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Background

Median overall survival on 2nd line therapy of PDAC with 5-FU/LV plus oxaliplatin or nal-irinotecan is 5-6 months. PDAC is refractory to immune therapies, the mutational burden of PDAC tumors is relatively low and tumor infiltrating CD8+ T cells are rare. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells and induced immune activation, durable stable disease and a 1yr survival of 22.5% in salvage PDAC pts. AM0010 (Pegilodecakin) has synergistic immune and anti-tumor activity with platinum and 5-FU in preclinical cancer models.

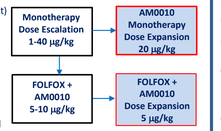
Study Design and Eligibility

AM0010

- 22 pts. with advanced pancreatic cancer (3rd-7th line of treatment) were treated at 20µg/kg AM0010 SC. q.d. (15 pts. were evaluable for tumor response and 22 treated patients were analyzed for PFS/OS)

AM0010 + FOLFOX

- A total of 25 pts. with advanced pancreatic cancer (2nd-6th line of treatment) were treated at AM0010 (5µg/kg) + FOLFOX
- Of those, a cohort of 21 pts. were treated in a phase 1b study
  - No prior platinum containing regimen,
  - 19 pts. were evaluable for tumor response and 21 were analyzed for PFS / OS
  - Tumor responses were measured according to irRC criteria.



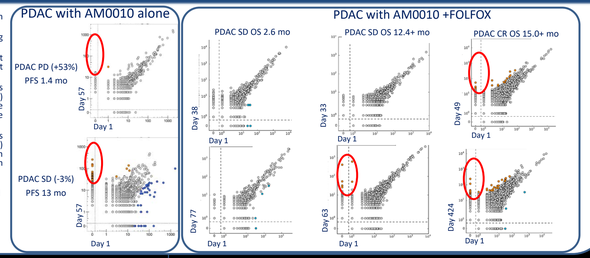
Key Eligibility in AM0010 + FOLFOX PDAC Dose Expansion Cohort

- PDAC 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
- Excluded anti-coagulants with T1/2 > 24h

Remodeling of the Peripheral T cell Repertoire correlates with Objective Tumor Response

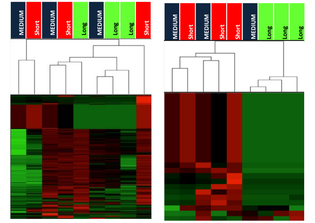
- T cell clonality analysis from peripheral blood (EDTA blood)
- TCRb deep sequencing (Adaptive Biotechnologies)
- Comparison of on-treatment samples with pretreatment baseline (Day 1)
- Expansion of novel T cell clones (not detectable at Day 1) correlate with objective response in immune sensitive cancers
- Expansion of novel T cell clones (not detectable at Day 1) appear to correlate with survival of PDAC patients on AM0010 + FOLFOX

Unique T cells clones in the blood
- More than 5 fold expanded
- More than 5 fold contracted



mRNA Profile Correlating with Survival

- Archival tumor tissues (FFPE slides) were analyzed for immune related mRNAs using the PanCancer Immunoprofiling – (Nanostring)
- Analysis of all mRNAs revealed an incomplete separation of patients with durable survival benefit ("Long OS; > 12 months) from patients who did not have a survival benefit
- Using a selected set of immune related mRNAs allows to separate patients with a long survival on FOLFOX + AM0010 from patients who had a short survival.
- Patients with a long survival had a low expression in several key immune related mRNAs.



Heat Map Panel: All Genes (nSolver)

ARMO PDAC Selected Panel (nSolver)

Summary of Results

AM0010 + FOLFOX was well tolerated

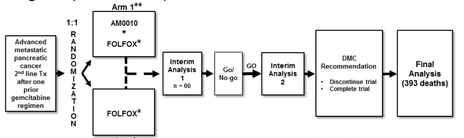
- Tolerated on continuous dosing without autoimmune AEs
  - G3/4 anemia (40%) and thrombocytopenia (52%)
    - Anemia and Thrombocytopenia were mitigated by 5 days on / 2 days off dosing schedule
    - No incidence of G3/4 anemia and thrombocytopenia and retained immune stimulation profile on the new dose schedule
  - Encouraging response rates, PFS and OS seen with combination with FOLFOX with some prolonged survival.
  - Preliminary data correlates immune activation with outcome

Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR (%)	ORR (%)	CR (%)	mPFS[3] (Months)	mOS[3,4] (Months)
PDAC	**AM0010** (n=15/22)[1]	3 (2-6)	53%[2]	0	0	1.7	3.8
	AM0010 + FOLFOX[4] (n=19/21)	2 (1-5)	74%	16%	11%	3.5	10.2

(1) N= number of evaluable patients/number of enrolled patients for ORR and DCR
(2) Based on 8 of 15 evaluable patients with SD at 2 months
(3) mPFS, mOS based on total enrolled patients
(4) Study in progress. Numbers as of August 11, 2017. Median follow-up 17.6 months (range 11.3, 21.3)

Enrolling :

Phase 3 study of AM0010 + FOLFOX vs FOLFOX as Second-line Therapy in Patients with Metastatic Pancreatic Cancer that has Progressed During or Following a First-Line Gemcitabine Containing Regimen (NCT02923921)



* Up to 12 cycles of FOLFOX
** Arm 1 in the absence of tumor progression may continue maintenance with AM0010 alone after completion of FOLFOX or FOLFOX intolerance

Interim Analysis 1
Aggregate PK exposure, safety, efficacy analysis

Interim Analysis 2
After 276 deaths (70% of 393 deaths)

Stratification
- Prior Gemcitabine or Prior Gemcitabine/nab-Paclitaxel
- North America vs. Europe vs. APAC

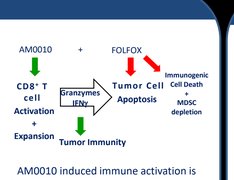
Endpoints
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, Safety

AM0010 - Mechanism of Action

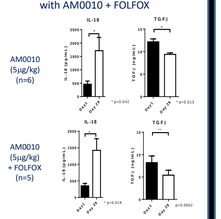
- IL-10 is anti-inflammatory and at higher concentrations and continuous exposure leads to the activation and expansion of antigen activated CD8+ T cells
- Tumor antigen recognition by CD8+ T cells (TCR) induces the IL-10 receptor on CD8+ T cells
- IL-10 activates CD8+ T cells ("Cytotoxic License")
-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

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**. Objective responses were observed in ocular melanoma, and in four of 16 patients with renal cell cancer (RCC). AM0010 induced a CR in a cutaneous T cell lymphoma and prolonged disease stabilization has been observed in several additional indications, including H&NC, PDAC and CRC.

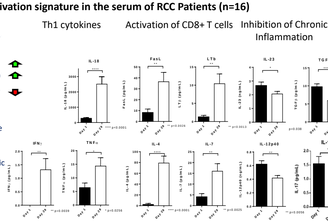


AM0010 induced immune activation is retained in Pancreatic cancer patients treated with AM0010 + FOLFOX



AM0010 - immune activation signature in the serum of RCC Patients (n=16)

- AM0010 (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
- Most other inflammatory cytokines were not significantly altered (83 tested)
- IL-10 immune activation signature is activated in all patients at the therapeutic dose and is more pronounced in responding patients

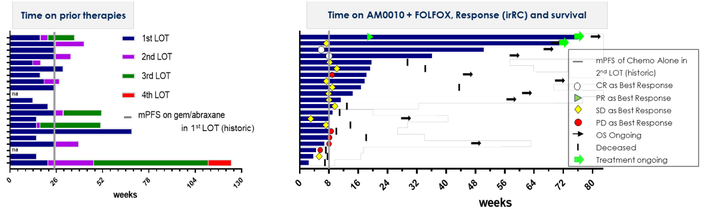


Results

AM0010 / AM0010 + FOLFOX in PDAC Patients

Patient Characteristics	AM0010 Monotherapy 2 mg (20 µg/kg) N=22	AM0010 + FOLFOX 0.5mg (5 µg/kg) N=25*
Median Age, years (range)	62 (34, 78)	66 (43, 85)
Sex, n (%)		
Male	14 (64%)	17 (68%)
Female	8 (36%)	8 (32%)
ECOG Performance Status, n (%)		
0	12 (55%)	9 (36%)
1	10 (45%)	16 (64%)
Prior Therapy, median (range)	3 (2-6)	2 (1-5)

* 21 patients in AM0010 FOLFOX expansion cohort (no- prior platinum containing regimen)



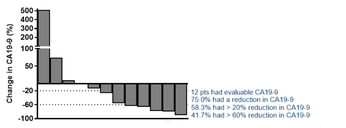
Treatment related adverse events – AM0010 / AM0010 + FOLFOX cohorts

	Grade 1/2		Grade 3/4	
Combination	mono	FOLFOX	mono	FOLFOX
System Organ Class Preferred Term	20 µg/kg n=22	5 µg/kg n=25	20 µg/kg n=22	5 µg/kg n=25
Blood and lymphatic system disorders				
Anaemia	7 (31.8)	5 (20.0)	3 (13.6)	11 (44.0)
Leukopenia		2 (8.0)	1 (4.5)	3 (12.0)
Neutropenia		3 (12.0)		9 (36.0)
Thrombocytopenia	6 (27.3)	6 (24.0)	7 (31.8)	13 (52.0)
Gastrointestinal disorders				
Abdominal pain		3 (12.0)		
Diarrhoea		2 (8.0)		
Nausea		11 (44.0)		1 (4.0)
Vomiting	1 (4.5)	5 (20.0)		1 (4.0)
General disorders and administration site conditions				
Asthenia	2 (9.1)			
Fatigue	5 (22.7)	15 (60.0)	2 (9.1)	3 (12.0)
Pyrexia	4 (18.2)	3 (12.0)		
Hepatobiliary disorders				
Cholangitis	2 (9.1)			
Investigations				
Lipase increased		2 (8.0)		
Platelet count decreased				2 (8.0)
Metabolism and nutrition disorders				
Decreased appetite	3 (13.6)	5 (20.0)		
Hypertriglyceridaemia	2 (9.1)	3 (12.0)		
Nervous system disorders				
Dizziness	2 (9.1)	3 (12.0)		
Headache	2 (9.1)	1 (4.0)		
Neuropathy peripheral		2 (8.0)		
Skin and subcutaneous tissue disorders				
Pruritus	2 (9.1)	1 (4.0)		
Rash	3 (13.6)	3 (12.0)		
Rash maculo-papular	2 (9.1)	1 (4.0)	1 (4.5)	

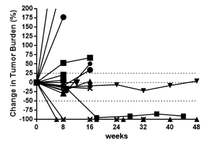
Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE v4.02, (>1 event / 5% in at least one cohort)

AM0010 + FOLFOX in PDAC; 3rd LOT (2nd-6th) (n=21)

AM0010 + FOLFOX in PDAC - Reduction in CA19-9

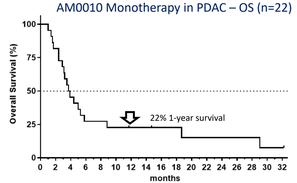


AM0010 + FOLFOX in PDAC – Tumor size (irRC)

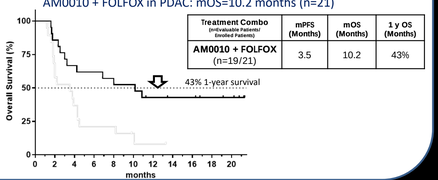


Overall survival of PDAC on AM0010 and AM0010 + FOLFOX

AM0010 Monotherapy in PDAC – OS (n=22)



AM0010 + FOLFOX in PDAC: mOS=10.2 months (n=21)

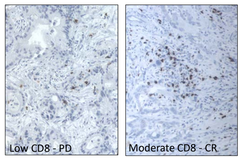


Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	mPFS (Months)	mOS (Months)	1 y OS (Months)
AM0010 + FOLFOX (n=19/21)	3.5	10.2	43%

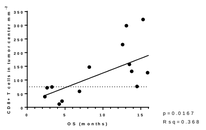
CD8+ T cell Infiltration in the Pre-treatment Tumor correlates with OS

IHC assessment of archival tumors for CD8. The number of CD8+ T cells in the tumor center prior to treatment correlates with overall survival of PDAC on AM0010 + FOLFOX

CD8+ T cells in PDAC - pretreatment



Correlation of pre-treatment CD8+ T cells mm^{-2} (tumor center) and Overall Survival



IHC and evaluation by Navneet Ratti and Dr. Hava Liberman, MD

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.Oettle et al., JCO 2014; Wang-Gillam et al., Lancet Onc. 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