Overall Survival of Pegilodecakin (AM0010) with 5-FU/LV and Oxaliplatin (FOLFOX) in Metastatic Pancreatic Adenocarcinoma (PDAC)

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Background

The therapeutic options for 2nd line therapy PDAC remain unsatisfying with 5-FU/LV plus oxaliplatin or nal-irinotecan resulting in a mOS of 5-6 mo. PDAC has been largely refractory to immune-oncology approaches and CD8+ T cells are rare in most PDAC. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells. Immune activation, durable stable disease and a 1yr survival of 22.5% was seen in salvage PDAC patients (pts) receiving AM0010 alone. AM0010 has synergistic anti-tumor activity with 5-FU/LV or oxaliplatin in preclinical models. Here we report on the safety, efficacy and overall survival of AM0010 + FOLFOX as 2nd and later line treatment in PDAC pts.

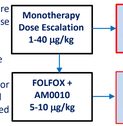
Study Design and Eligibility

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 response and 22 treated patients were analyzed for PFS/OS)

AM0010 + FOLFOX

PDAC pts progressing on a median of 2 prior therapies (range 1-5) were treated with AM0010 (5ug/kg SQ, qd) + FOLFOX (n=21). The safety population (n=25) included also 4 pts with prior oxaliplatin / 5-FU. Tumor responses were assessed with irRC. The survival population included all patients without prior platinum containing regimen. Biomarkers included the activation of blood derived T cells and peripheral T cell clonality. Pretreatment archival tissue samples were evaluated by IHC for tumor infiltration by CD8+ T cells and with whole exome sequencing and mRNA analysis..



Key Eligibility in AM0010 + FOLFOX PDAC Dose Expansion Cohort

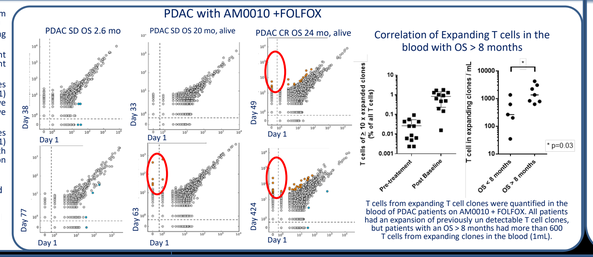
- PDAC with progression on prior gemcitabine containing regimen, no prior platinum
- Excluded prior Guillain-Barré syndrome and neuro-inflammatory diseases
- Allowed all other autoimmune diseases incl. RA, Crohn's disease, psoriasis
- Excluded anti-coagulants with T1/2 > 24h

Remodeling of the T cell Repertoire 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) 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

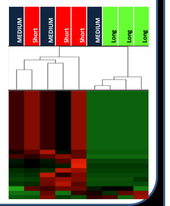
- More than 5 fold expanded
- More than 5 fold contracted



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 inflammation related mRNAs.

ARMO PDAC Selected Panel (nSolver)



Summary of Results

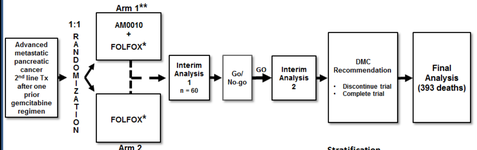
AM0010 + FOLFOX was well tolerated

- Tolerated on continuous dosing without autoimmune AEs
  - G3/4 anemia (44%) and thrombocytopenia (56%)
    - 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 43% 1-year survival.
- The magnitude of the expansion of previously rare T cell clones correlates with overall survival of the patients.

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)

N=566; global phase 3 study



* 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

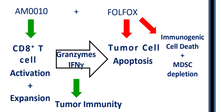
Interim Analysis 2
After 276 deaths
(70% of 393 deaths)

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

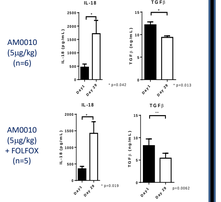
Endpoints
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, Safety

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).
- PEG-IL-10 and 5-FU or platinum compounds have at least additive anti tumor efficacy when combined in syngeneic mouse models of cancer.
- 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.

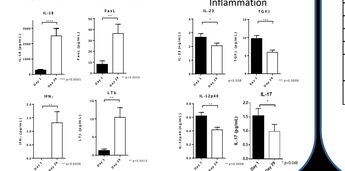


AM0010 induced immune activation is retained in Pancreatic cancer patients treated with AM0010 + FOLFOX



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

AM0010 + FOLFOX, was generally well tolerated. G3/4 TrAEs included thrombocytopenia (56%), anemia (44%), neutropenia (36%) and fatigue (12%). Most cytopenias had a short duration and reaching retreatment criteria within 2-5 days after dose interruption. Dosing AM0010 for 5 days followed by a 2 days dose holiday has avoided G3/4 cytopenias. As of 10/29/2017, 2 patients had remained on treatment for > 1 year. Of 19 evaluable pts, 2 had an irCR, 1 had irPR with 100% reduction in tumor burden, ORR is 15.8%, DCR is 74%. With median follow-up of 20.3 months (range 15.8,), mPFS was 2.6 mo, mOS was 10.2 mo, the 1-year survival was 43%. Transcriptional profiling and CD8+ T cells analysis in archival tumor tissue may identify patients with longer OS.

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)

Safety and Tolerability

Reduction of Neuropathy Compared to Historic Controls (treatment related and unrelated)

Study	Grade 1/2	Grade 3/4	Reference
OFF 2nd LOT	38.2%	4%	Oettle JCO 2014
FOLFOX 2nd LOT	44%	7%	Zaanan BMC 2014
FOLFOX 2nd LOT	NA	4.1%	Gill JCO 2016
AM0010 + FOLFOX	16%	0%	Current data

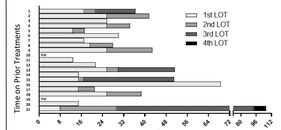
Treatment related adverse events – AM0010 / AM0010 + FOLFOX cohorts

Combination	Grade 1/2 mono	Grade 1/2 FOLFOX	Grade 3/4 mono	Grade 3/4 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)	4 (18.2)	11 (44.0)
Leukopenia		2 (8.0)	1 (4.5)	3 (12.0)
Neutropenia		3 (12.0)		9 (36.0)
Thrombocytopenia	6 (27.3)	5 (20.0)	7 (31.8)	14 (56.0)
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)		
Metabolism and nutrition disorders/Musculoskeletal and connective tissue disorders				
Decreased appetite	3 (13.6)	5 (20.0)		
Dehydration		1 (4.0)		1 (4.0)
Hypertriglyceridaemia	2 (9.1)	3 (12.0)		
Myalgia		2 (8.0)		
Nervous system disorders				
Dizziness	2 (9.1)	3 (12.0)		
Headache	2 (9.1)	1 (4.0)		
Neuropathy		3 (12.0)		
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)	

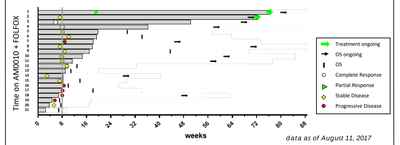
Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE v4.03, (>1 event / 5% in at least one cohort)

AM0010 + FOLFOX in PDAC

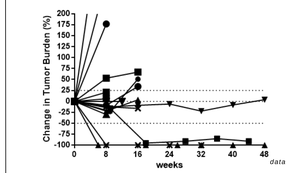
Time on Prior Therapies (n=21)



Time on Therapy - AM0010 + FOLFOX in PDAC (n=21)



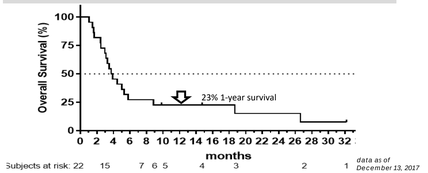
AM0010 + FOLFOX in PDAC – Tumor size (irRC)



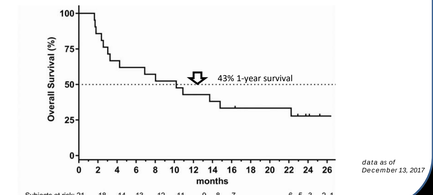
Treatment (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR (%)	ORR (%)	CR (%)	mPFS[3,5] (Months)	mOS[3,5] (Months)	1-year OS (%)	2-year OS (%)
AM0010 (n=15/22)[1]	3 (2-6)	53%[2]	0	0	1.7	3.8	23%	15%
AM0010 + FOLFOX[4] (n=19/21)	2 (1-5)	74%	16 %	11%	2.6	10.2	43%	28%

(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 October 29, 2017. 5 patients are still followed for survival status with more than 16 months overall survival.
(5) Numbers as of December 13, 2017

Overall survival of PDAC on AM0010



Overall survival of PDAC on AM0010 + FOLFOX



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