# Immunologic and Objective Tumor Responses with PEGylated Human IL-10 (AM0010) + 5-FU / Oxaliplatin (FOLFOX) in Metastatic Pancreatic Adenocarcinoma

J. Randolph. Hecht[1], Aung Naing[2], Gerald S. Falchook[3], Manish Patel[4], Jeffrey R. Infante[5], Raid Aljumaily[6], Deborah J. Wong[1], Karen A. Autio[7], Zev A. Wainberg[1], Milind Javle[2], Johanna C. Bendell[5], Shubham Pant[2,6], Peter Van Vlasselaer[8], Gail L. Brown[8], Martin Oft[8], Kyriakos P. Papadopoulos[9].

[1]David Geffen School of Medicine at UCLA, Santa Monica, CA; [2]MD Anderson Cancer Center, Houston, CA [3]Sarah Cannon Research Institute at HealthONE, Denver, CO; [4]Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL; [5]Sarah Cannon Research Institute / Tennessee Oncology, PLLC, Nashville, TN; [6]Oklahoma University, Oklahoma City; [7]Memorial Sloan-Kettering Cancer Center, New York, NY; [8]ARMO Biosciences, Redwood City, CA; [9]START Center for Cancer Care, San Antonio, TX

## Background and Purpose

The benefit of adding nal-irinotecan or oxaliplatin to 5-FU in second-line therapy for PDAC is relatively small. In addition, PDAC has been refractory to immune therapies.

The success and the durability of immunotherapy in immune sensitive indications is thought to depend on the activation and expansion of intratumoral, tumor specific cytotoxic CD8+ T cells which are very low in the majority of PDAC. AM0010 stimulates the survival, expansion and cytotoxicity of intratumoral CD8+ T cells. Immune stimulation and prolonged stable disease in advanced PDAC patients (pts) with single agent AM0010 was recently presented. Treatment with platinum or 5-FU may activate immune responses to cancer. AM0010 has synergistic anti-tumor function with both, platinum and 5-FU in preclinical models. In this phase 1b clinical study, the efficacy of AM0010 in combination with FOLFOX was explored in patients with PDAC.

## Study Design and Eligibility

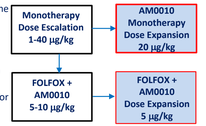
**AM0010**

- 22 pts. with advanced pancreatic cancer (3rd-7th line of treatment) were treated at 20µg/kg (15 pts. evaluable)

**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, 21 pts. were treated in a phase 1b (no prior platinum containing regimen, 19 pts. evaluable)

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

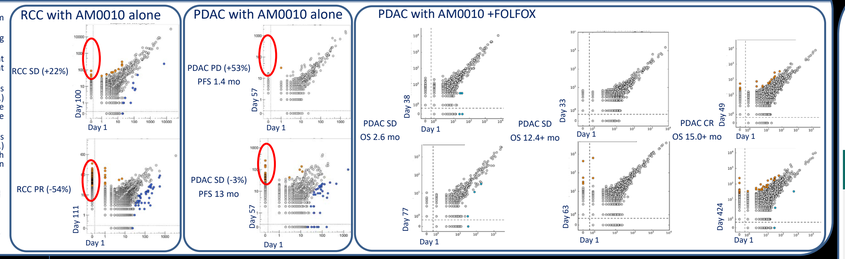
## Remodeling of the Peripheral T cell Repertoire correlates with Objective Tumor Response

- 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 patient on AM0010 + FOLFOX

Unique T cells clones in the blood

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

TCR clonal analysis by Adaptive Biotechnologies




## Summary and Outlook

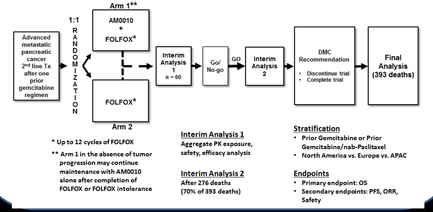
**AM0010 + FOLFOX has an acceptable tolerability profile**

- Tolerated on continuous dosing without autoimmune AEs
  - G3/4 anemia (36%) and thrombocytopenia (48%)
    - Anemia and Thrombocytopenia were mitigated by 5 days on – 2 days off dosing schedule
    - No incidence of G3/4 anemia and thrombocytopenia
    - Retained immune stimulation profile

| Disease | Treatment Combo (n=Evaluable Patients/ Enrolled Patients) | Prior Therapies Median (Range) | DCR n (%) | ORR (%) | CR (%) | mPFS (Months) | mOS (Months) |
|---|---|---|---|---|---|---|---|
| PDAC | AM0010@ (n=15/22)+ | 3 (2-6) | 8 (53%)* | 0 | 0 | 1.7& | 3.8& |
| | AM0010 + FOLFOX (n=19/21) | 2 (1-5) | 15 (79%) | 3 (16%) | 2# (11%) | 3.5& | NR$ |
| | FOLFOX (Zaanan et al BMC 2014) | 1 | 36% | 0 | 0 | 1.7 | 4.3 |

\+ N= number of evaluable patients/number of enrolled patients for ORR and DCR;
* Based on 8 of 15 evaluable patients had SD at 2 months
@ Median follow-up 23 months (18-30+)
& mPFS, mOS based on total enrolled patients
$ mOS not reached. Median follow-up 10.5 months (3.8-15.6+)
# 2 CRs
Data cut December 14 2016

**Enrolling ARTIST 1 (ARMO'1 Randomized Trial Inducing Stimulated T cells):**
**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)




## Information

### SPONSORS

AM0010 is being developed by ARMO BioSciences.

### REFERENCES

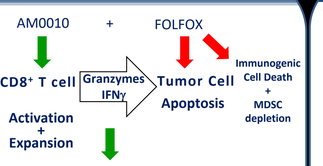
1.Naing et al JCO 2016; Mumm et al. Cancer Cell 2011; Emmerich et al. Cancer Research 2012
2.Fridman, Pages et al. NRI 2012; Oft. CIR 2014 (Reviews)
3.Topalian, Hodi et al. NEJM 2012; Tumeh, Harview et al. Nature 2015

### 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

## Background: Mechanism of Action

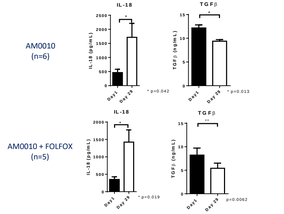
- IL-10 is anti-inflammatory and elevated concentrations and continuous exposure leads to the expansion of antigen activated CD8+ T cells
- Tumor antigen recognition by CD8+ T cells (TCR) induces the IL-10 receptor on CD8+ T cells
- IL-10 activates CD8+ T cells ("Cytotoxic License")
- PEG-IL-10 induces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




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

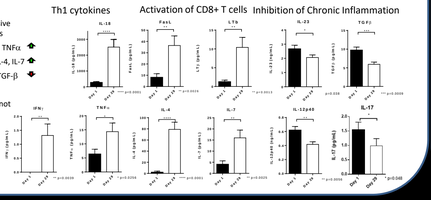
In a large Phase 1 study, 144 patients with advanced solid tumors have been treated with **AM0010 monotherapy**. Objective responses were observed in ocular melanoma, and in four of 15 patients with renal cell cancer (RCC). AM0010 induced a CR in a cutaneous T cell lymphoma and prolonged disease stabilization 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 + FOLFOX in Pancreatic Cancer Patients

Patient Characteristics

| | AM0010 Monotherapy 2 mg (20 µg/kg) N=22 | AM0010 0.5mg (5 µg/kg) + FOLFOX 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)

G3/4 TrAEs included thrombocytopenia (48%), anemia (36%) and neutropenia (32%). There was no significant bleeding or febrile neutropenia. 19 pts had a objective tumor response assessment; 2 CRs, 1 one PR and 12 SDs were observed. Eight remain on treatment, 2 for > 1 year. ORR was 16%, the DCR was 79%. The mPFS was 3.5 months.

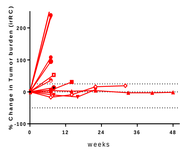
AM0010 increased serum Th1 cytokines and reduced mediators of chronic inflammation IL-23 and IL-17 and the immunosuppressive cytokine TGFβ. AM0010 increased the number and proliferation of PD1+ activated CD8+ T cells and induced de-novo oligoclonal expansion of T cell clones without affecting total lymphocyte counts.

Treatment Related Adverse Events

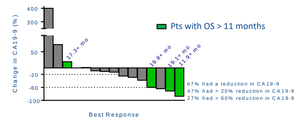
| | AM0010 Monotherapy | | | FOLFOX | | |
|---|---|---|---|---|---|---|
| | AM0010 5 µg/kg (N=1) | AM0010 20 µg/kg (N=22) | AM0010 40 µg/kg (N=1) | AM0010 2.5 µg/kg (N=2) | AM0010 5 µg/kg (N=25) | AM0010 10 µg/kg (N=2) |
| Grade[a] | n | 1-2 \| 3-4 | n | n | 1-2 \| 3-4 | n | 1-2 \| 3-4 | n |
| **MedDRA System Organ Class** | | | | | | | | |
| Preferred Term | | | | | | | | |
| Patients with at least one related serious TEAE | 1 | 0 | 8 | 10 | 0 | 1 | 1 | 1 | 5 | 20 | 0 | 2 |
| **Blood and lymphatic system disorders** | | | | | | | | |
| Thrombocytopenia | 0 | 0 | 6 | 7 | 1 | 0 | 1 | 0 | 5 | 12 | 0 | 2 |
| Anemia | 0 | 0 | 7 | 3 | 1 | 0 | 0 | 0 | 5 | 9 | 0 | 1 |
| Neutropenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 8 | 0 | 1 |
| Leukopenia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 1 |
| **General disorders and administration site conditions** | | | | | | | | |
| Fatigue | 1 | 0 | 5 | 2 | 0 | 0 | 2 | 0 | 13 | 3 | 1 | 0 |
| Pyrexia | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 0 | 3 | 0 | 0 | 0 |
| **Gastrointestinal disorders** | | | | | | | | |
| Nausea | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 11 | 1 | 0 | 0 |
| Vomiting | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 5 | 1 | 0 | 0 |
| Abdominal pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 |
| **Metabolism and nutrition disorders** | | | | | | | | |
| Decreased appetite | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 1 | 0 |
| Hypertriglyceridemia | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Hypokalemia | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

### AM0010 in Pancreatic Cancer

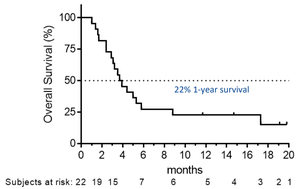
AM0010 Monotherapy in PDAC – Tumor size (irRC)




AM0010 Monotherapy in PDAC - Reduction in CA19-9

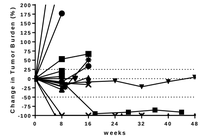



AM0010 Monotherapy in PDAC - OS

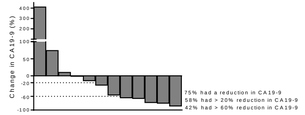



### AM0010 + FOLFOX in Pancreatic Cancer

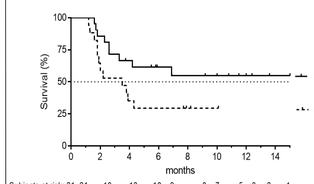
AM0010 + FOLFOX in PDAC – Tumor size (irRC)




AM0010 + FOLFOX in PDAC - Reduction in CA19-9




AM0010 + FOLFOX in PDAC – PFS / OS

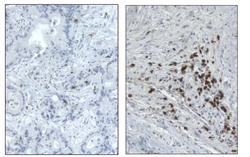



## Pre-treatment CD8+ T cell Infiltration correlates with OS

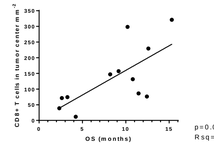
IHC assessment of archival tumors for CD8 and MHCI

The number of CD8+ T cells in the tumor center prior to treatment but not MHCI expression correlates with overall survival of PDAC on AM0010 - FOLFOX

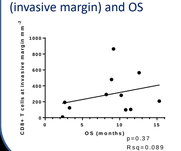
CD8+ T cells in PDAC - pretreatment



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




Correlation of CD8+ T cells mm$^{-2}$ (invasive margin) and OS




Correlation of MHC+ cells (% of tumor cells) and OS