Efficacy of PEGylated Human IL-10 (AM0010) in Combination with anti-PD-1 Blockade in Patients (pts) with Metastatic Renal Cell Carcinoma (mRCC): A phase 1b Trial

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IL-10: Less Inflammation and More CD8+ Cytotoxicity

- **Humans (and mice) deficient in the IL-10R or IL-10 develop colitis and cancer**
  Glocker et al., NEJM 2009; Neven et al., Blood 2013
- IL-10 is produced by activated APCs and T cells
- IL-10 receptor is induced in CD8+ T cells upon antigen recognition
- IL-10 reduces inflammatory responses to bacterial products or tissue damage
  - Inhibition of inflammatory T cells (Th17) and macrophages (IL-12/23)
  - May decrease tumor associated inflammation
  - May sustain CD4+ T regulatory cells
- **IL-10 stimulates cytotoxicity and sustained proliferation of antigen activated CD8+ T cells**

- **Expression of IL-10 or treatment with PEGylated IL-10 leads tumor rejection in mice**
  - Mediated by CD8+ T cells
  - Increases activity of intratumoral CD8+ T cells
    - Granzymes, FasL
    - IFNγ
  - Increased MHC expression in the tumor
  - Amplification of tumor specific CD8+ T cells in the tumor and in the blood

Mumm et al., Cancer Cell 2011
Emmerich et al., Cancer Research 2012
Oft, Cancer Immunology Research 2014

AM0010 Ph1/Ph1b Basket Trial

- 353 patients enrolled
  - Monotherapy (n=144)
  - Chemo (n=98)
  - Anti-PD-1 (n=111)
- Enrollment completed

11/25/2013 – 9/12/2017

Monotherapy Dose Escalation (n=33)

Monotherapy Dose Expansion 10 Indications (n=111)

Combo-Therapy Dose Escalation 7 Chemo SOC (n=67)

- PDAC 2nd Line (n=21) FOLFOX + AM0010 → Sequoia - Phase 3 PDAC 2nd Line (n=566) FOLFOX + AM0010
- TNBC 1st/2nd Line (n=10) Gem/Carbo + AM0010

Combo-Therapy Dose Escalation with Anti-PD-1 Pembro (n=28) RCC (n=8)

- Melanoma ≥2nd Line (n=25) Anti-PD-1 Refractory Pembro + AM0010
- NSCLC ≥2nd Line (n=29) Nivo + AM0010
- RCC ≥2nd Line (n=29) Nivo + AM0010

Naing et al., JCO 2016

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AM0010 has Single Agent Activity and is Well Tolerated

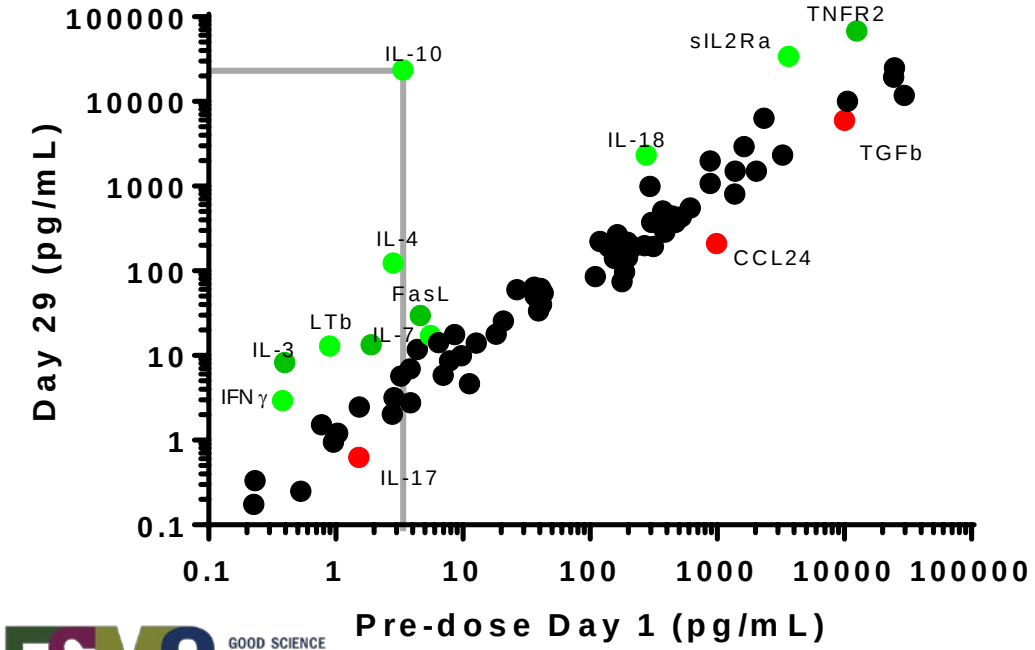
- **AM0010 is well tolerated** as a single agent (144 patients)
- **Compliance** (up to 2.5 years)
- TrAEs include thrombocytopenia, anemia, fatigue, fever
- **G3/4 TrAEs were reversible** (low discontinuation rate due to TrAEs)
  - Anemia (17%), thrombocytopenia (17%)
- **No auto-immune related TrAEs**, such as colitis, pneumonitis, hepatitis or endocrine disorders
- **AM0010 monotherapy has a 25% objective response rate (ORR) in RCC**, and durable responses in uveal melanoma and a CR in Cutaneous T cell lymphoma
- Durable responses for up to 2.5 years (uveal melanoma, RCC) and prolonged stable disease in CRC and PDAC

Naing et al., JCO 2016

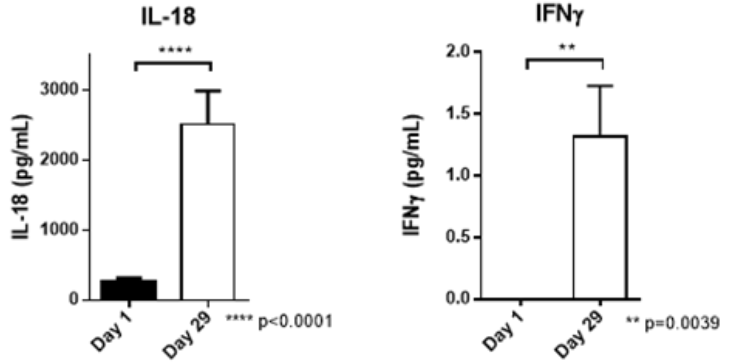
AM0010 Induces Systemic Th1/CD8+ T cell Immune Signature

- AM0010 is dosed to a serum level of ~2-10 x EC50 of AM0010
- AM0010 induced a reproducible immune activation signature in patients (serum cytokines)

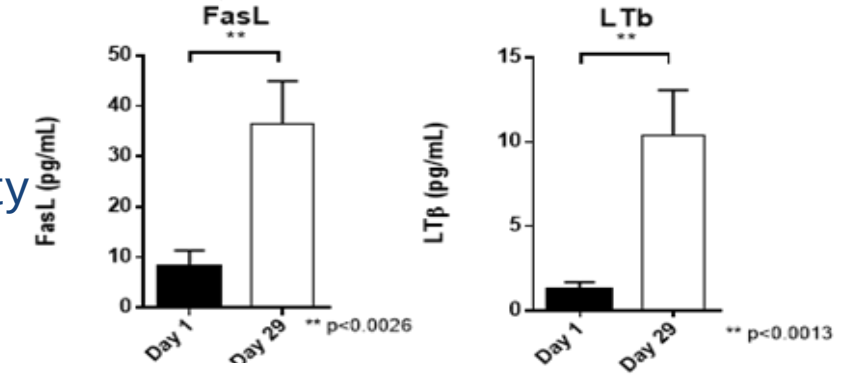
Serum cytokines: Pre-dose to Day 29
(20 µg/kg; n=30)



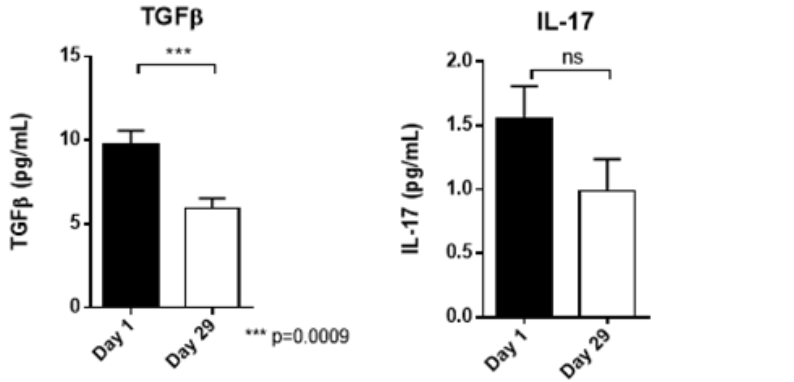
Th1



CD8+ activity



Inflammation



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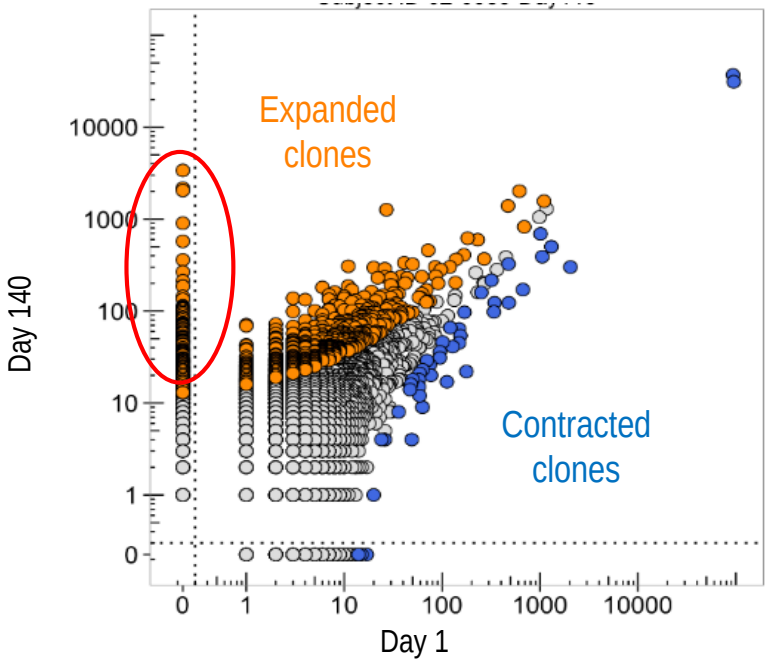
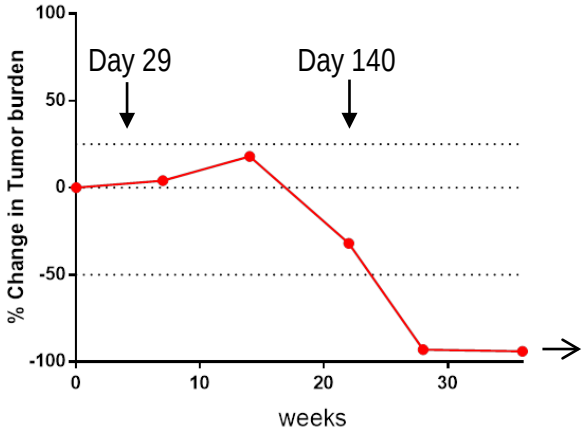
AM0010 Induces Previously Rare T-Cell Clones

- 100-800 T cell clones per patient expand more than 10 fold in the blood
- Expanding clones become 1-20% of the total T cell repertoire
- Many T cell clones were not detectable prior to treatment
- Number of expanding clones correlate with objective tumor response



Adaptive Biotechnologies



Renal Cell Carcinoma Patient

- Dose: 20 μg/kg AM0010
- 2 prior anti-angiogenic Therapies
- Patient continues on monotherapy (2.5y)

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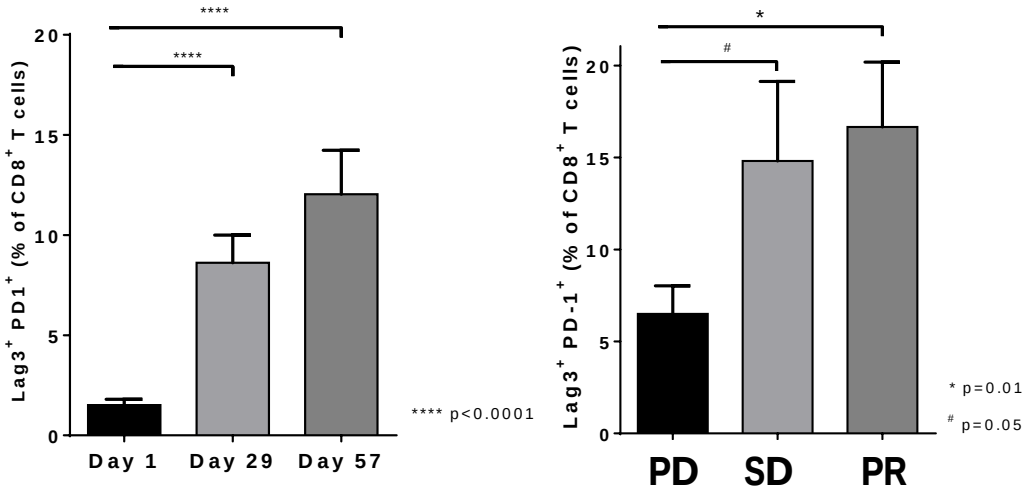
AM0010 Induces the Proliferation and Expansion of PD-1$^+$ Lag-3$^+$ CD8$^+$ T Cells

- PD-1+ Lag-3+ CD8+ T cells contain a high percentage of tumor specific T cells
  - Gros et al Nature Medicine 2016
- AM0010 induces the **proliferation** and **sustained expansion** of PD-1+ Lag-3+ CD8+ T cells in the blood
- Expansion of PD1+ Lag-3+ CD8+ T cells correlate with anti-tumor response

PD-1$^+$ Lag-3$^+$ CD8$^+$ T cells Expansion Correlates with Tumor Response



Percentage of PD-1+ Lag-3+ CD8+ T cells in the peripheral blood

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PEGylated IL-10 - Mechanism of Action

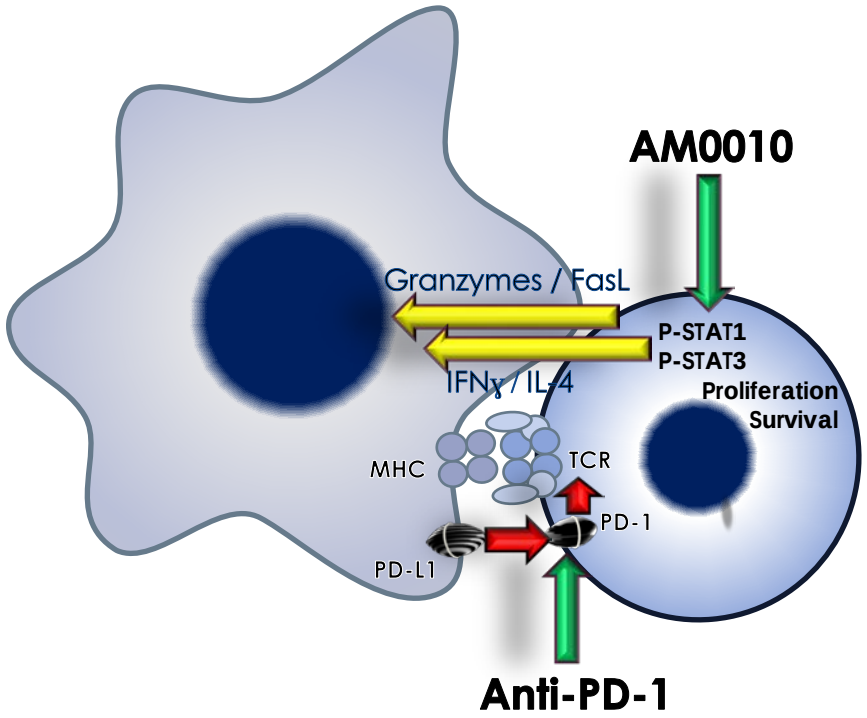
Without AM0010, CD8+ T cells recognize the tumor cell, become exhausted and undergo apoptosis

AM0010

- Tumor recognizing CD8+ T cells are activated and proliferate
- AM0010 inhibits CD8+ T cell apoptosis and induces Granzymes and FasL
- Granzyme and FasL induces tumor cell death

⇨ Rationale for AM0010 + anti-PD-1

- Increased TCR signal
- Blocks CD8+ T cell exhaustion and apoptosis
- Two complementary pathways activated



AM0010 + anti-PD-1 in RCC – Patients (anti-PD-1 naïve)

	Monotherapy 2mg (20 µg/kg) N=19	**AM0010 - 1mg / 2mg (10 / 20 µg/kg) + Pembrolizumab N=8 (+1*)**	**AM0010 - 1 mg / 2mg (10 / 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)
IMDC (intermediate - poor)	18 (95%)	8 (89%)	27(93%)
* 1 patient with prior AM0010 monotherapy was included in safety but not in efficacy analysis			

Treatment related Adverse Events - AM0010 + anti-PD-1

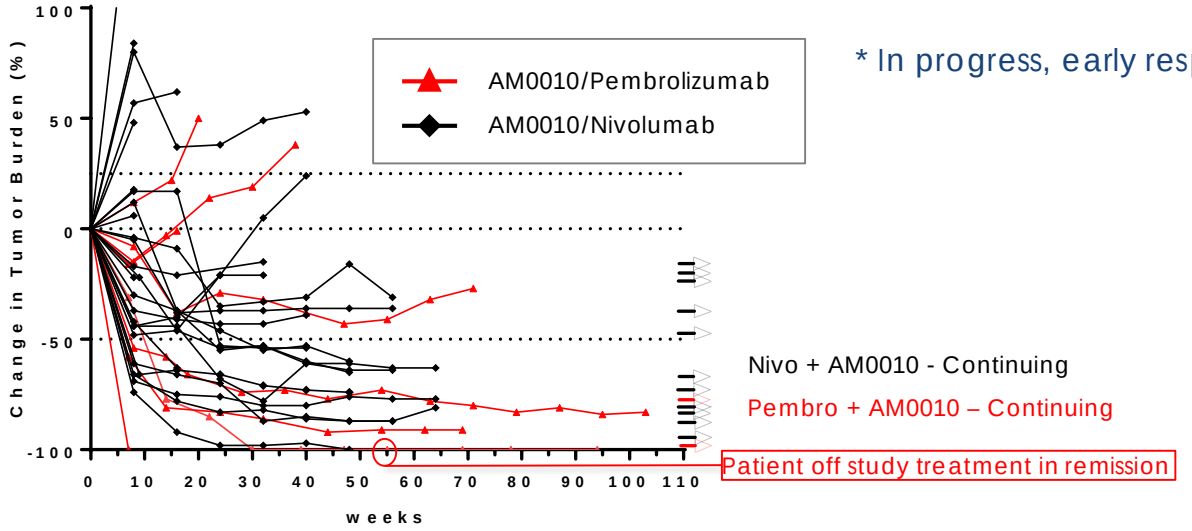
- AM0010 and anti-PD-1 is well tolerated (n=38 RCC)
  - pembrolizumab (2mg/kg, q3w) or nivolumab (3mg/kg, q2w)
- TrAEs were similar to single agents
- **No increase in frequency or severity of auto-immune related TrAEs compared to expected anti-PD-1 TrAEs**
- Anemia and thrombocytopenia mediated by macrophage mediated phagocytosis
  - IFNγ induced scavenger receptors
- G3/4 TrAEs were reversible
  - Anemia, thrombocytopenia, fatigue, ALT/AST increase, hypertriglyceridemia,
- **Very well tolerated at 10μg/kg AM0010**
- **3 of 6 patient at 10μg/kg AM0010 had an OR**
- **Ph2 dose for AM0010 + anti-PD-1 is 10μg/kg AM0010**

	Grade 1/2		Grade 3/4	
AM0010 Dose	10μg/kg	20μg/kg	10μg/kg	20μg/kg
Number of Patients	N=6	N=32	N=6	N=32
Anaemia	3 (50.0)	6 (18.8)		10 (31.3)
Histiocytosis haematophagic		1 (3.1)		1 (3.1)
Neutropenia	0 (0.0)	0 (0.0)	1 (16.7)	2 (6.3)
Splenomegaly		1 (3.1)		1 (3.1)
Thrombocytopenia	2 (33.3)	4 (12.5)		7 (21.9)
Chills		5 (15.6)		
Fatigue	4 (66.7)	11 (34.4)		1 (3.1)
Malaise		1 (3.1)		1 (3.1)
Night sweats	1 (16.7)	3 (9.4)		
Oedema		1 (3.1)		1 (3.1)
Pyrexia	1 (16.7)	11 (34.4)		
Alanine aminotransferase increased		4 (12.5)	1 (16.7)	1 (3.1)
Amylase increased		1 (3.1)		1 (3.1)
Aspartate aminotransferase increased		5 (15.6)	1 (16.7)	1 (3.1)
Decreased appetite	1 (16.7)	2 (6.3)		
Hyperglycaemia		3 (9.4)		
Hypertriglyceridaemia	2 (33.3)	5 (15.6)	1 (16.7)	5 (15.6)
Hypoalbuminaemia		2 (6.3)		
Arthralgia		5 (15.6)		
Myalgia		8 (25.0)		
Headache		5 (15.6)		
Pruritus		8 (25.0)	1 (16.7)	1 (3.1)
Rash	1 (16.7)	7 (21.9)		
Rash maculo-papular	1 (16.7)	6 (18.8)	1 (16.7)	

AM0010 + Anti-PD-1 in 2nd line RCC Patient (92% Poor to Intermediate risk)

Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	ORR (%)	CR (%)	mPFS (Months)	mOS (Months)
RCC	**AM0010** (n=16/19)	3 (0-7)	4 (25%)	–	1.9	9.8
	AM0010 + pembrolizumab (n=8/8) [1]	2 (0-5)	4 (50%)	2[4] (25%)	16.7	NR[2]
	AM0010 + nivolumab (n=26/29) [1]	1 (1-3)	10 (39%)	NR	NR[3]	NR[3]
	AM0010 + anti-PD-1 (n=34/37) [1]	2 (0-5)	14 (41%)	2[4]		
	Anti-PD-1 mAb (nivolumab) (Motzer et al., JCO 2014)	1	20-22%	1	2.7-4.2	25

(1) Study in progress. Numbers as of October 29, 2017. (2) Median follow-up 29.4 months (range 12.3-30.6); (3) Median follow-up 13.8 months (range 0.5-19.8); (4) 2 partial responses with 100% reduction in measurable disease; NR not reached



* In progress, early responses

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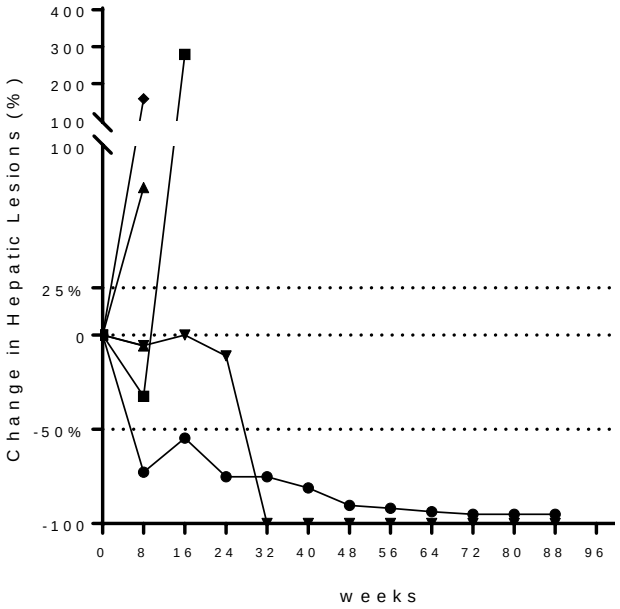
Liver Metastasis of RCC on AM0010 or AM0010 + Anti-PD-1

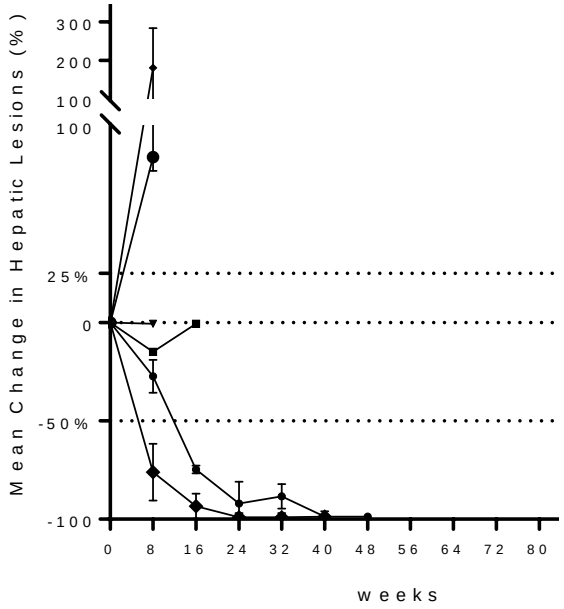
- Melanoma and NSCLC patients with liver metastasis have a lower overall response rate to immune checkpoint inhibition Tumeh et al. Cancer Imm. Res. 2017; Pillai et al ASCO 2017
- On AM0010, 2 of 6 patients with RCC metastases to the liver had reduction (> - 50%) of the liver metastasis
- On AM0010 + anti-PD-1, 2 of 6 patients with RCC liver metastasis had reduction (> - 50%) of the liver metastasis

AM0010 Monotherapy



Mean target liver lesions in RCC patients (n=5) on AM0010

AM0010 + anti-PD-1



Mean target liver lesions in RCC patients (n=6) on AM0010 + anti-PD-1

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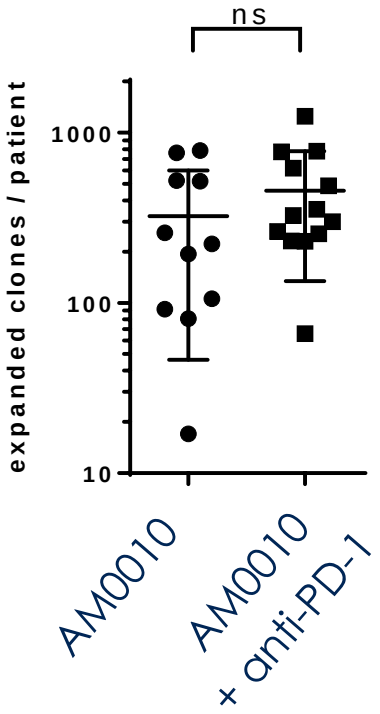
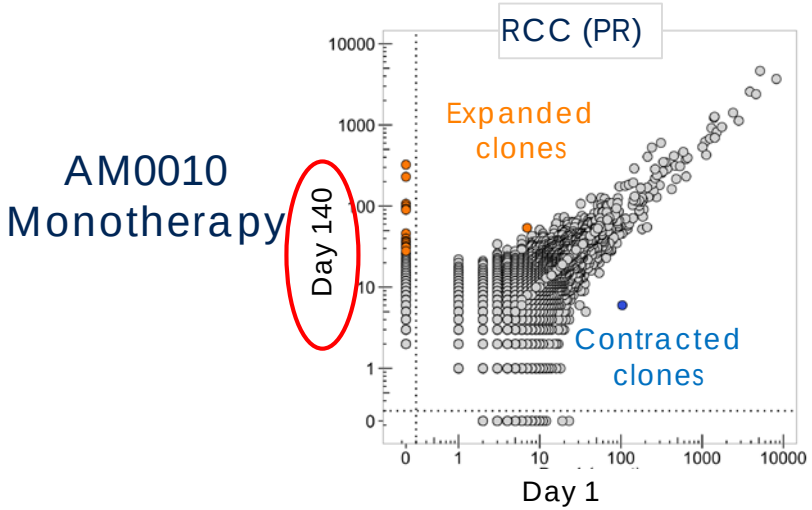
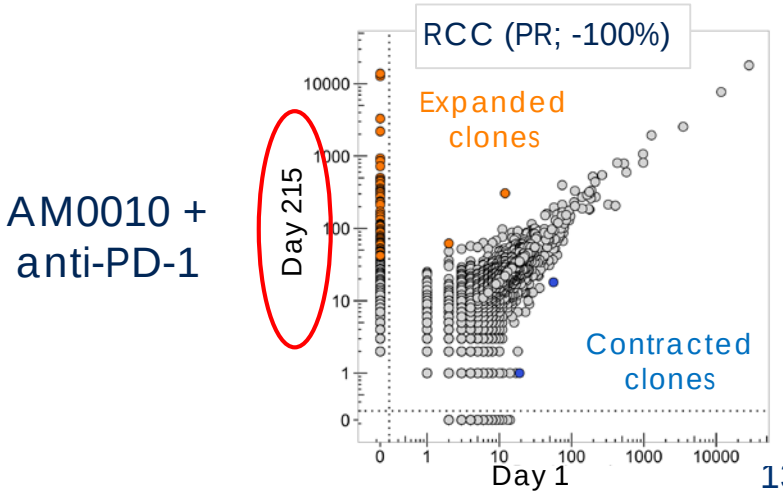
Sustained Clonal T cell Expansion in Response to AM0010 or AM0010 + anti-PD-1

- AM0010 + anti-PD-1 induces expansion of up to 1000 T cell clones per patient to expand more than 10x
- T cell clonal expansion continues throughout the treatment period

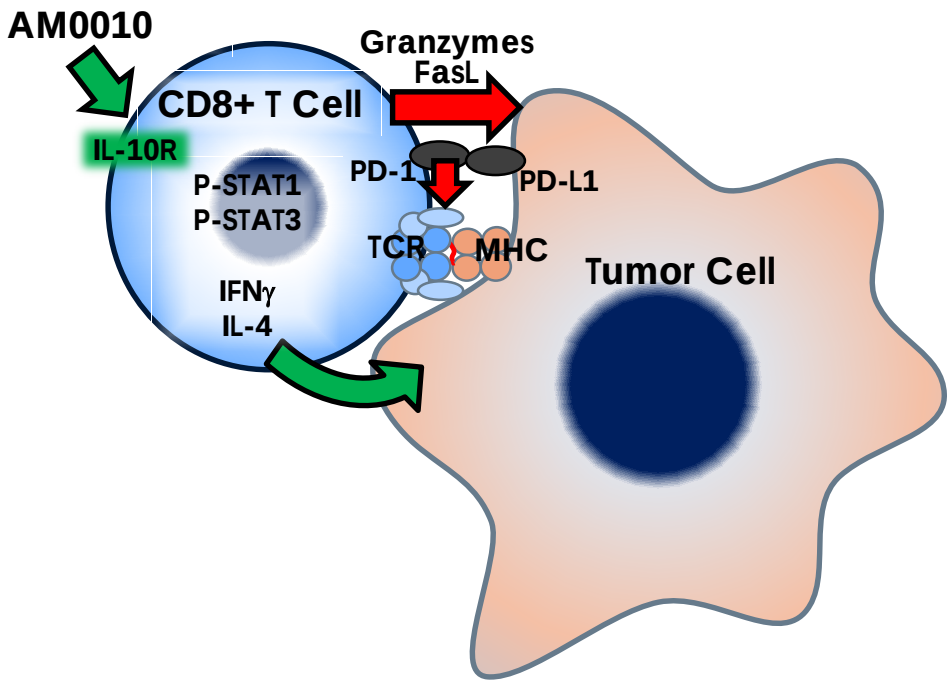






PEG-IL-10 in IO Therapy

- Tumor antigen recognition by CD8+ T cells (TCR) induces IL-10R and PD-1 on CD8+ T cells
  - PD-1 is a negative feedback ("Immune Checkpoint")
  - IL-10 activates antigen specific CD8+ T cells ("Cytotoxic License")
- AM0010 induces
  - Phospho-STAT3 in intratumoral CD8+ T cells
  - Accumulation of immune checkpoint positive CD8+ T cells (PD-1+ / Lag-3+)
  - Expansion of several hundred previously not detectable T cell clones / patient



- AM0010 induces objective tumor responses in monotherapy
  - 25% ORR in RCC
  - Long lasting response in RCC, ocular melanoma and CTCL (CR)

- AM0010 synergizes with anti PD-1
  - Tolerated with no significant increase in AE profile over either agent in monotherapy
  - ORR in RCC 41% (14 of 34 pts (2 CRs), 2x expected RR)

We want to thank all patients and their families!

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