# Presenter Disclosure Information

Martin Oft

The following relationships exist related to this presentation:

ARMO BioSciences, founder and employee

Cellular and Molecular Correlates to Anti PD-1 Responses

Anti-PD-1 response correlates with:

- High PD-L1 expression in the tumor
  - Garon et al NEJM 2014

- High tumor mutational burden (TMB)
  - Rizvi et al., Science 2015; Carbone et al. NEJM 2017

- High CD8+ T cells in the tumor
  - Tumeh et al., Nature 2014

- INFγ associated immune activation signature
  - Prat et al., Cancer Res. 2017; Ayers et al JCI 2017

- Absence of liver metastasis
  - Tumeh et al. Ca. Imm. Res. 2017; Pillai et al ASCO 2017

TMB	High	High	Low/medium	Low/medium
PD-L1	≥50%	1–49%	≥50%	1–49%
n =	16	31	41	70

Nivolumab
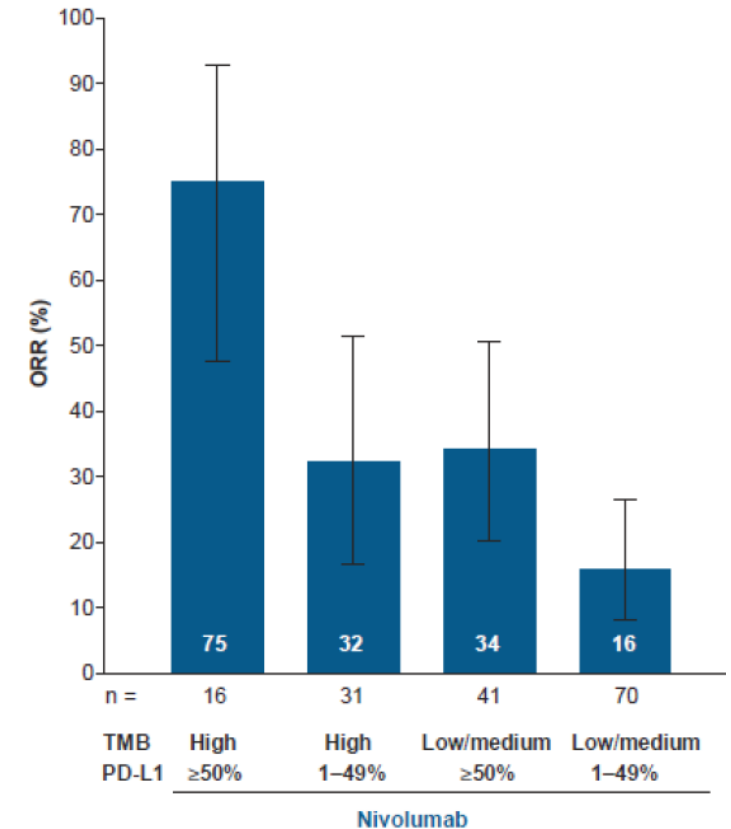
Carbone et al., NEJM 2017
Checkmate 026

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

Expanding the Reach of Immune Checkpoint Inhibition

Low neoantigen burden
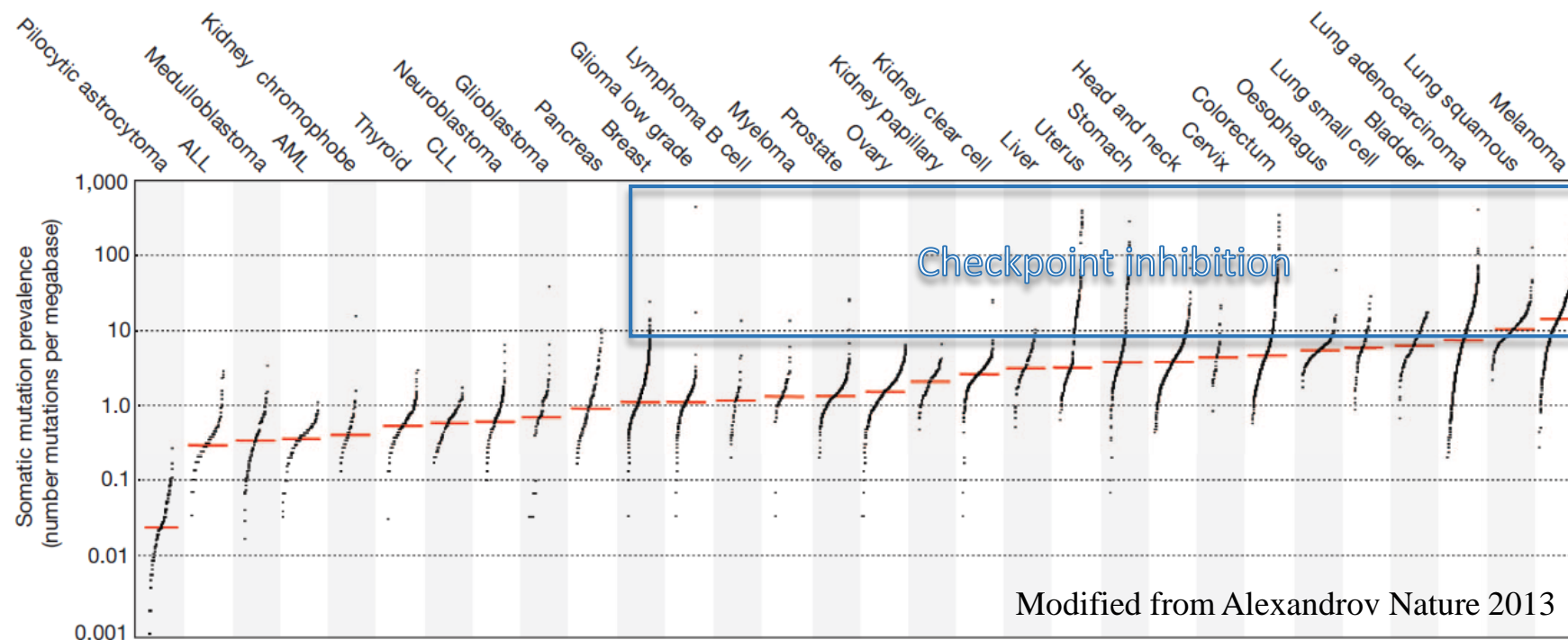➢ Rare neoantigen specific CD8+ T cells

Expand rare antigen specific CD8 T cells

Tumors with high neoantigen burden eventually escape ICIs
➢ T cell apoptosis (Immune desert)
➢ Inflammatory T cells (Th17/Tc17)
  - No granzyme / IFNγ expression

Increase survival factors for CD8+ T cells
Increase granzyme, IFNγ and MHCI expression

Modified from Alexandrov Nature 2013

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IL-10: Less Inflammation and More CD8$^+$ Cytotoxicity

- IL-10 is produced by activated T cells and APCs
- 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

> 1 pg/mL IL-10 (serum)

- IL-10 stimulates **cytotoxicity** and proliferation of **antigen activated CD8+ T cells** at higher concentrations

- **Humans (and mice) deficient in the IL-10R or IL-10 develop colitis and cancer**
    - Low infiltration of CD8+ T cells and absence of Granzymes
    Glocker et al., NEJM 2009; Neven et al., Blood 2013

- Overexpression of IL-10 or treatment of mouse tumor models with PEGylated IL-10 leads to **CD8+ T cell mediated rejection of large tumors** and rejection of metastases
    - Increases activity of intratumoral CD8+ T cells
        - Granzymes, FasL
        - IFNγ – MHC induction
    - Increased MHC expression in the tumor
    - Amplification of tumor specific CD8+ T cells in the tumor and in the blood
    - **Long lasting tumor immune memory**

> 1 ng/mL IL-10 (serum)

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

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ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

AM0010 (Pegilodecakin) 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)

Naing et al. JCO 2016

Monotherapy
Dose Expansion
10 Indications
(n=111)

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

Combo-Therapy
Dose Escalation
with Anti-PD-1
Nivo/Pembro
(n=28)

PDAC 2nd Line (n=21)
FOLFOX + AM0010

TNBC 1st/2nd Line (n=10)
Gem/Carbo + AM0010

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

Sequoia - Phase 3
PDAC 2nd Line (n=566)
FOLFOX + AM0010

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

AM0010 is Well Tolerated and has Single Agent Activity

- AM0010 is well tolerated as a single agent (144 patients)

- Excellent compliance (up to 2.5 years)

- TrAEs include thrombocytopenia, anemia, fatigue, fever, rash, LFT increase, and pruritus

- G3/4 TrAEs were reversible (low discontinuation rate due to TrAEs)

  - Anemia (17%), thrombocytopenia (17%)

- No durable auto-immune related TrAEs, such as colitis, pneumonitis, hepatitis or endocrine disorders

- AM0010 monotherapy induces objective responses in **RCC (25% ORR)**, uveal melanoma and a CR in Cutaneous T cell lymphoma

- Durable Responses up to 2.5 years (uveal melanoma, RCC) and prolonged stable disease in CRC and PDAC

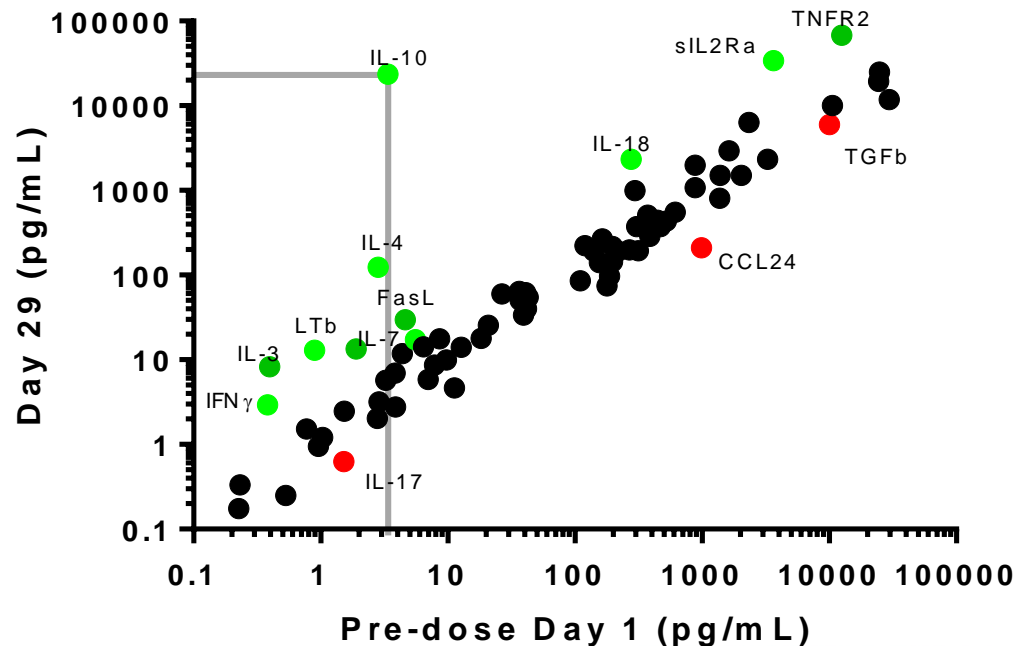- The selected MTD / Ph2 dose in monotherapy is 20 µg/kg

Naing et al. JCO 2016

AM0010 Induces Th1/CD8+ T cell Immune Signature

AM0010 Monotherapy

- AM0010 was dosed to a serum level of ~2-10 x EC50 of AM0010

- AM0010 induced a reproducible immune activation signature in patients (serum cytokines)
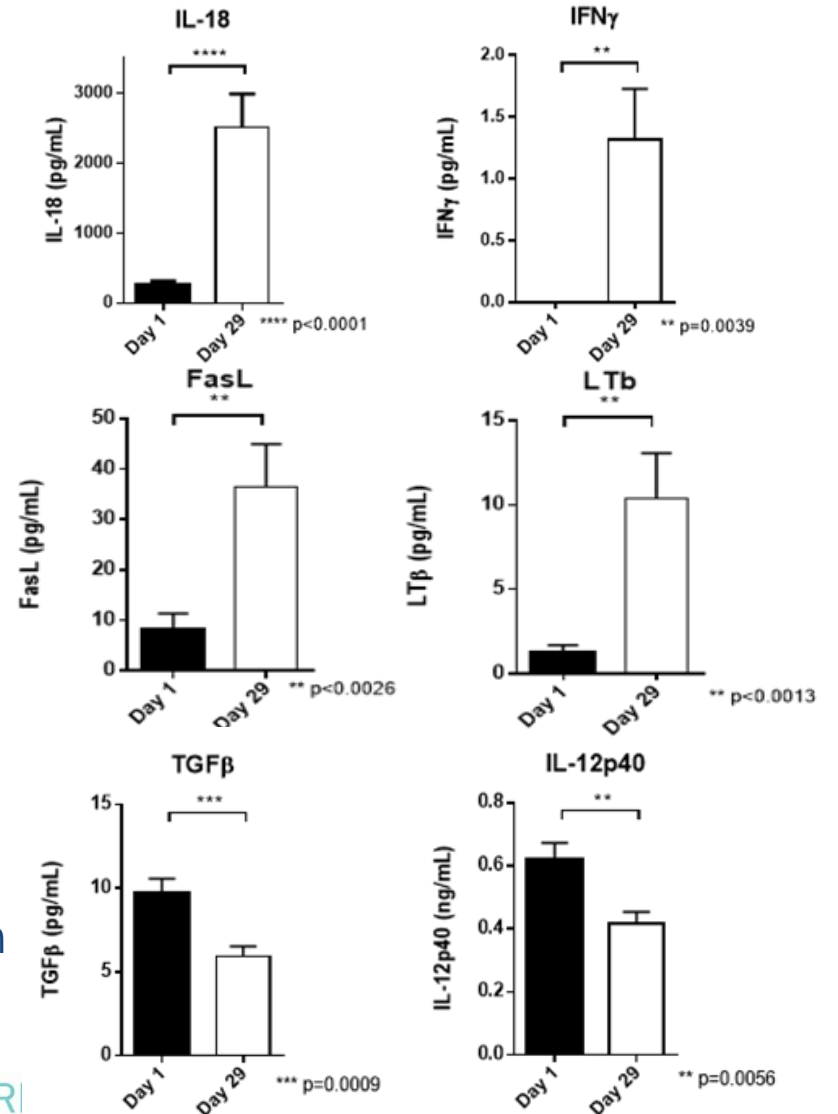
Serum cytokines: Pre-dose to Day 29
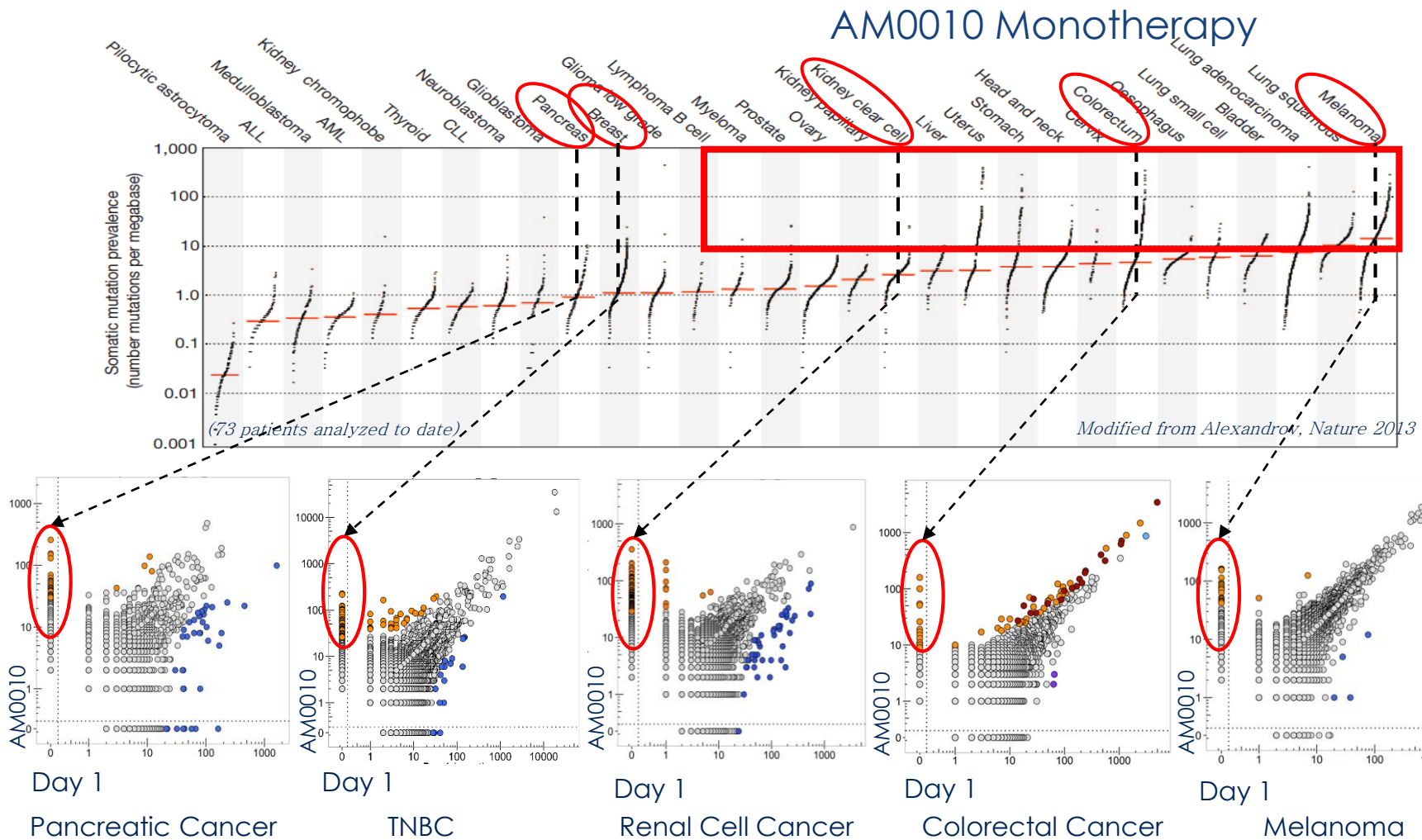(20 μg/kg; n=30)

Th1

CD8+ activity

Inflammation

Induction of Previously Rare T-Cell Clones Across Tumor Types

AM0010 Monotherapy

Expanding T cell Clones Correlate with Tumor response

(73 patients analyzed to date)

Modified from Alexandrov, Nature 2013

Day 1 — Pancreatic Cancer

Day 1 — TNBC

Day 1 — Renal Cell Cancer

Day 1 — Colorectal Cancer

Day 1 — Melanoma

$p = 0.0022$
$**[1]$ $p = 0.0043$
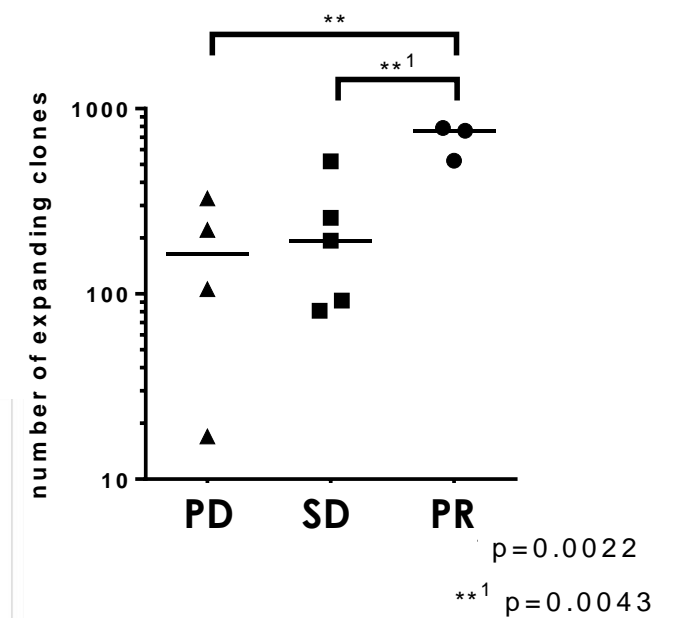
Absolute Number of ≥ 10x Expanded Unique T cell Clones (n / patient)

T cell clonal analysis by TCR deep sequencing; Adaptive Biotechnologies

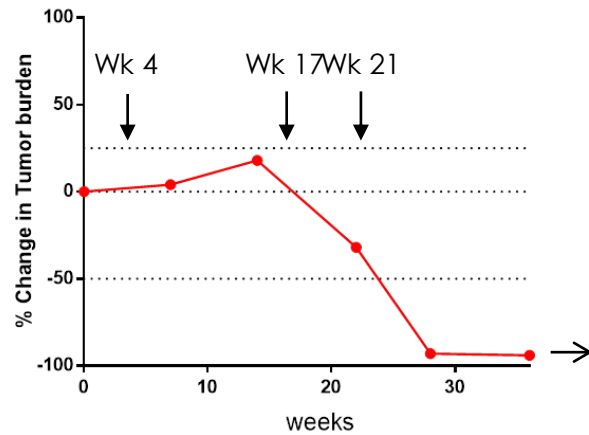# Proliferation and Expansion of PD-1$^+$ Lag-3$^+$ CD8$^+$ T Cells

AM0010 Monotherapy

Tumor Response (RCC)

Week 17   Week 21
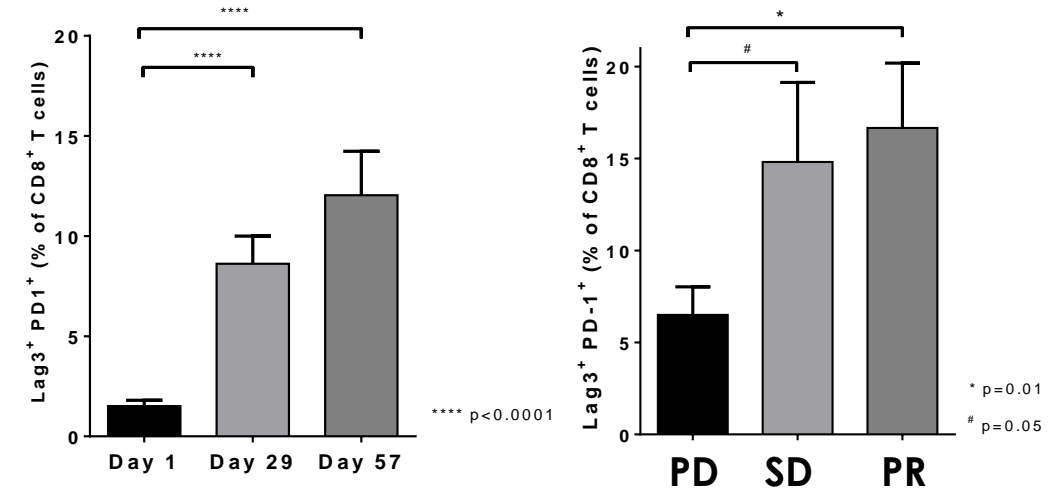
Lag-3$^+$ PD-1$^+$ CD8$^+$ T cell Expansion Correlates with Tumor Response

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

Percentage of Lag3$^+$ PD-1$^+$ cells of CD8$^+$ T cells in the peripheral blood during AM0010 Monotherapy

PEGylated IL-10 - Mechanism of Action

CD8+ T cells that recognize the tumor cell, become exhausted and undergo apoptosis, in the absence of a survival factor (IL-10)

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

- Two complementary pathways activated

➡ Rationale for AM0010 + Chemo

- Chemo induces immunogenic tumor cell death and AM0010 primes a sustained immune memory

AM0010

Granzymes / FasL

P-STAT1
P-STAT3
Proliferation
Survival

IFNγ / IL-4

MHC   TCR

PD-1

PD-L1

Chemo
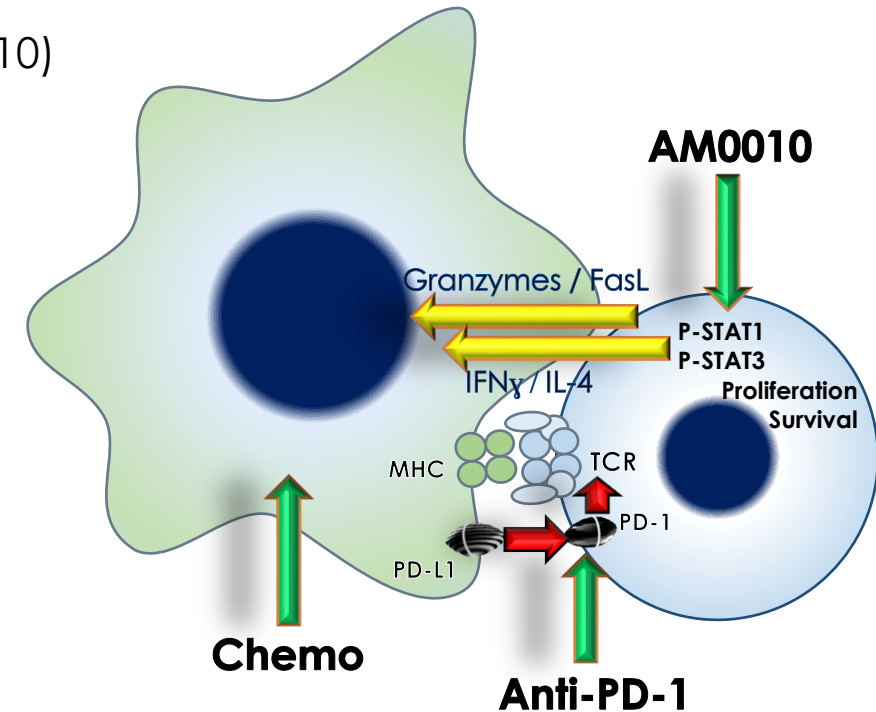
Anti-PD-1

➡ Sequoia - Phase 3
PDAC 2nd Line (n=566)
FOLFOX + AM0010

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 Risk (intermediate - poor)	18 (95%)	8 (89%)	27 (93%)
* 1 patient with prior AM0010 monotherapy, included in safety but not in efficacy analysis			

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

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 include thrombocytopenia, anemia, fatigue, fever, rash, pruritus

- Anemia and thrombocytopenia mediated by macrophage mediated phagocytosis
  - IFNγ induced scavenger receptors

- G3/4 TrAEs were reversible
  - Anemia, thrombocytopenia, fatigue, ALT/AST increase, hypertriglyceridemia,

- No increase in frequency or severity of auto-immune related TrAEs compared to expected anti-PD-1 TrAEs

- Very well tolerated at 10µg/kg AM0010

- 3 of 6 patient at 10µg/kg AM0010 had a PR/CR

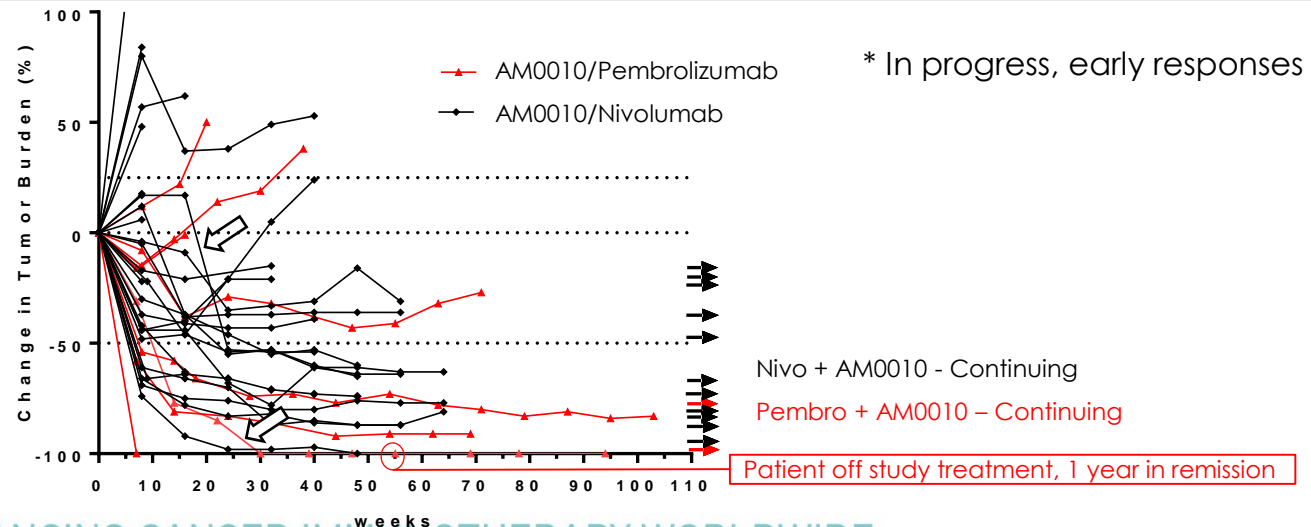- The selected MTD / Ph2 dose for AM0010 + anti-PD-1 is 10µg/kg AM0010

AM0010 Dose	Grade 1/2		Grade 3/4	
	10µg/kg	20µg/kg	10µg/kg	20µg/kg
Number of Patients	N=6	N=32	N=6	N=32
Blood and lymphatic system disorders				
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)
General disorders and administration site conditions				
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)		
Investigations				
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)
Metabolism and nutrition disorders				
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)		
Musculoskeletal and connective tissue disorders				
Arthralgia		5 (15.6)		
Myalgia		8 (25.0)		
Nervous system disorders				
Headache		5 (15.6)		
Skin and subcutaneous tissue disorders				
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 RCC (92% Poor to Intermediate risk)

AM0010 + Anti-PD-1 Shows Significant, Sustained Impact on Tumor Burden

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%)	11 (42%)[2]	NR	NR[3]	NR[3]
	AM0010 + anti-PD-1 (n=34/37)	2 (0-5)	29 (85%)	15 (44%) [1]	2[3]		
	Anti-PD-1 mAb (nivolumab) (Motzer et al., JCO 2014)	1	57-65%	20-22%	1	2.7-4.2	25

(1) ORR numbers as of 10/29/2017 (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


* In progress, early responses

Nivo + AM0010 - Continuing

Pembro + AM0010 – Continuing

Patient off study treatment, 1 year in remission

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

	AM0010 Monotherapy 2mg (20 µg/kg) N=9	AM0010 1mg (10 µg/kg) + Pembrolizumab N=5	AM0010 2mg (20 µg/kg) + Nivolumab N=29
Median Age, years (range)	58 (44, 68)	74 (56, 80)	62 (40, 84)
Sex, n (%)			
Male	2 (22%)	4 (80%)	14 (48%)
Female	7 (78%)	1 (20%)	15 (52%)
ECOG Performance Status, n (%)			
0	3 (33%)	0 (0%)	8 (25%)
1	6 (66%)	5 (100%)	21 (75%)
Histology type, n (%)			
Squamous	0	2 (40%)	4 (14%)
Non-squamous	9 (100%)	3 (60%)	24 (83%)
Unknown	0	0	1 (3%)
Prior Therapy, median (range)	3 (1-7)	2 (0-5)	2 (1-3)
PD-L1+ Status, n (%)	5 tested for PD-L1 <1% PD-L1+: n=5 (100%)	4 tested for PD-L1 <1% PD-L1+: n=4 (100%)	20 tested for PD-L1 (22C3) <1% PD-L1+: n=12 (60%) 1-49% PD-L1+: n=3 (15%) $\geq$50% PD-L1+: n=5 (25%)

AM0010 + Anti-PD-1 in NSCLC

| Disease	Treatment Combo (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR (%)	ORR (%)	mPFS (Months)	mOS (Months)
NSCLC	**AM0010** (n=7/9)[1]	3 (1-7)	57%	–	1.7	15.4[3]
	AM0010 + pembrolizumab (n=5/5)[2]	2 (0-5)	100%	2 (40%)	10.9	NR[4]
	AM0010 + nivolumab (n=22/29)	2 (1-3)	82%	9 (41%)[3]	NR[5]	NR[5]
	AM0010 + anti-PD-1 (n=27/34)	2 (0-5)	85%	11 (41%)[3]	NR[5]	NR[5]
	Anti-PD-1 (Pembrolizumab) (Garon NEJM 2015)	1	41%	19.4%	3.0[6]	9.3[6]

(1) 5 of 5 patients tested are PD-L1 negative; (2) 4 of 4 patients tested are <1% PD-L1+; (3) ORR numbers of 10/29/2017; (4) Study in progress. Numbers as of August 11, 2017. 60% alive, *median follow-up 28.4 months (range 26.5-30.3)* (5) Study in progress. Numbers as of August 11, 2017. Median follow-up 16.1 months (range 5.6-30.3); (6) Garon et al NEJM 2015, previously treated patients; NR:Not reached

● AM0010 Pembrolizumab
▼ AM0010 Nivolumab
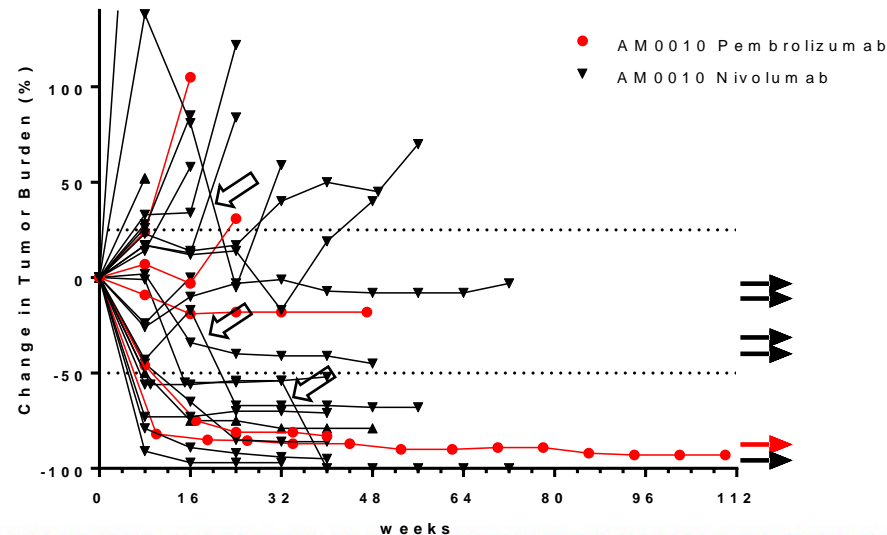
⇩ Biphasic response

AM0010 + Anti-PD-1 in NSCLC (PD-L1 Status)

| Disease	Treatment Combo	ORR by PD-L1 status (%)		
		<1% PD-L1+	1-49% PD-L1+	≥ 50% PD-L1+
NSCLC	AM0010 + anti-PD-1 mAbs (n=20 tested for PD-L1 status)	33 % (n=12)	67% (n=3)	80% (n=5)
	Pembrolizumab (Garon, NEJM; 2015)	9.1%	15.6%	43.9%
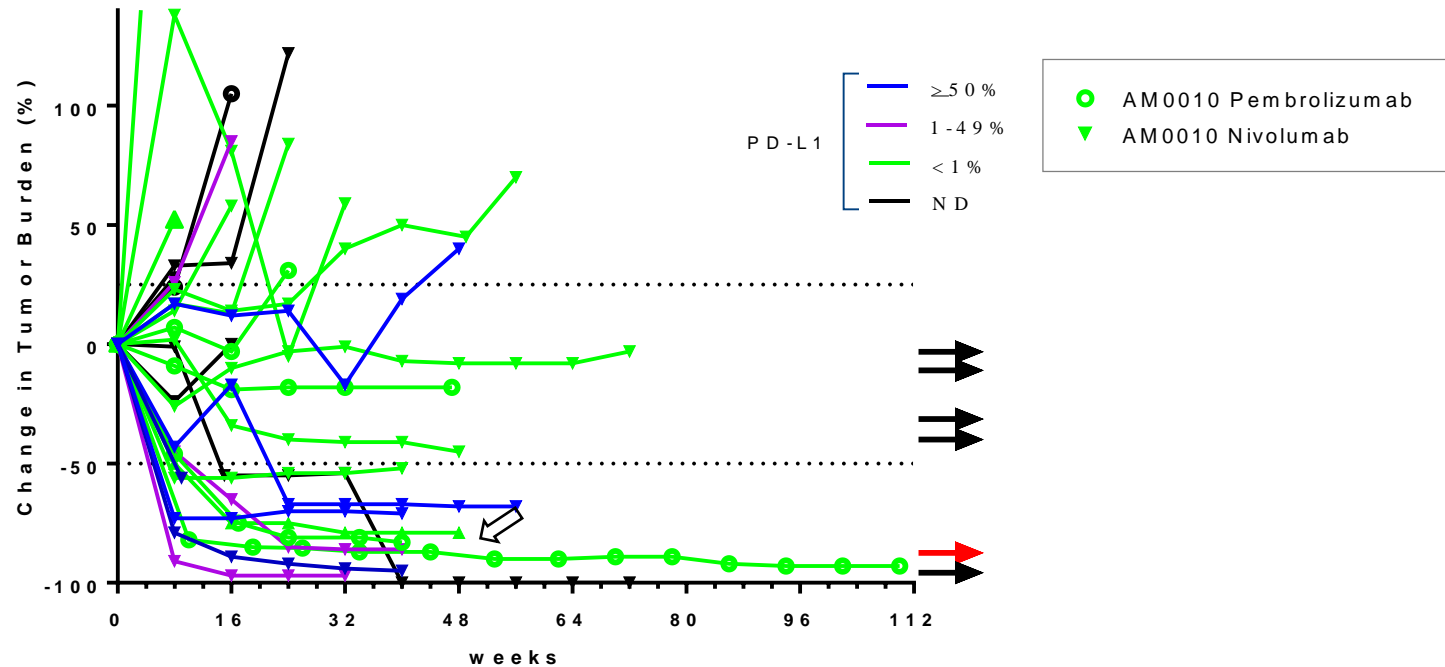
Liver Metastases of NSCLC on AM0010 + Anti-PD-1

- 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 + anti-PD-1, seven of nine patients with NSCLC metastases to the liver had a partial response

AM0010 + Pembrolizumab in PD-L1 neg. NSCLC
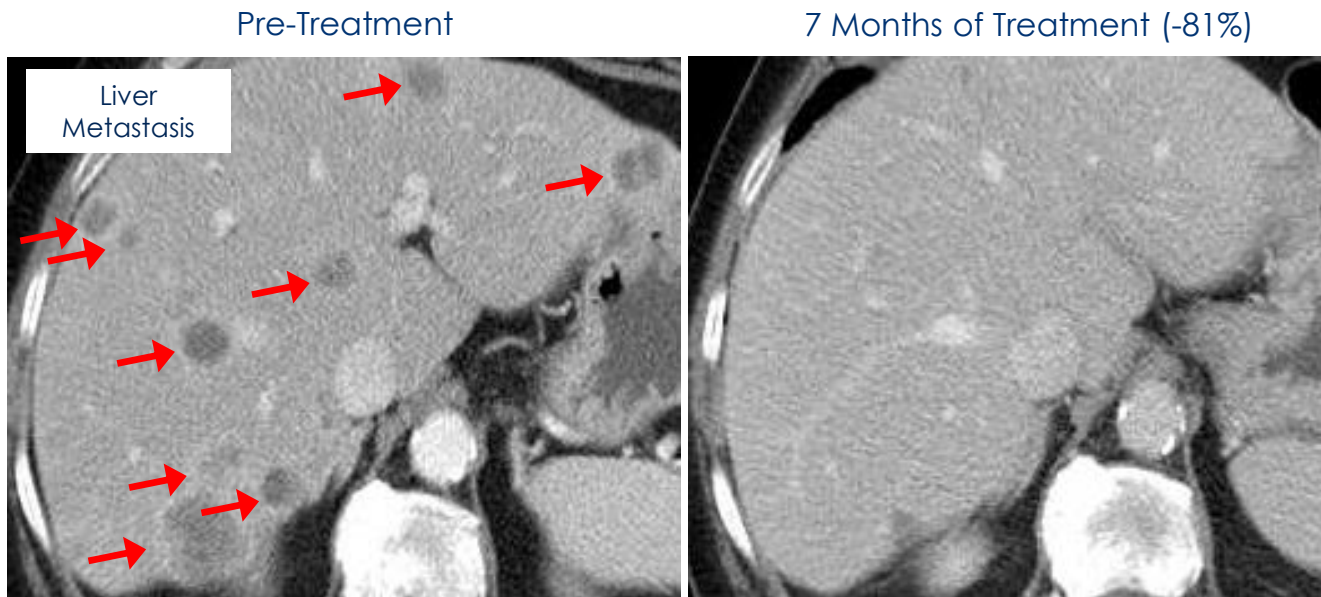
AM0010 + anti-PD1 Combination Reduces Measurable Liver Lesions

Pre-Treatment   7 Months of Treatment (-81%)


Liver Metastasis
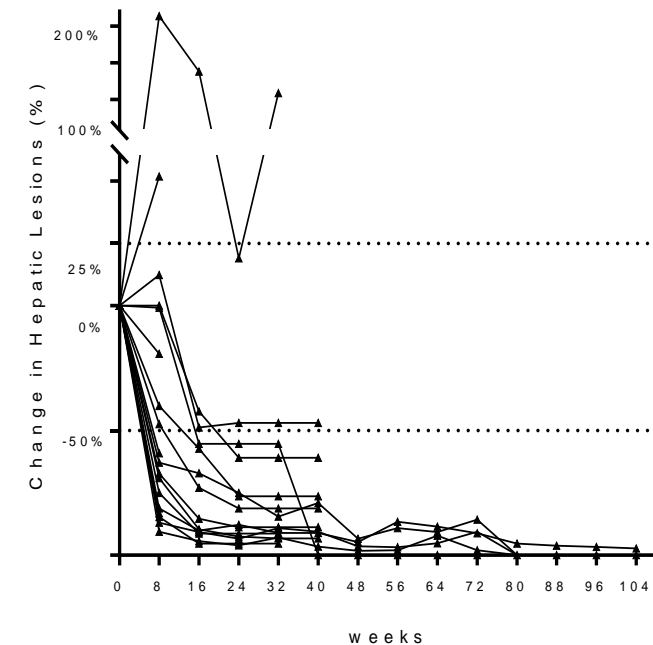
All measurable liver lesions in NSCLC patients on AM0010 + anti-PD-1 (n=18)

# AM0010 + Anti-PD-1 in NSCLC with Low to Intermediate Tumor Mutational Burden

- NSCLC patients with low or intermediate tumor mutational burden had a reduced response rate to nivolumab alone (n=23 of 111, 21%). Carbone et al. NEJM 2017
- Five of eight patients (62.5%) with low or intermediate TMB had a partial response on AM0010 + anti-PD-1

Disease	PD-L1+	Responses by TMB status (n=10)		
		Low (<100mut/Mb)	Medium (100-243mut/Mb)	High (>243mut/Mb)
NSCLC	PD-L1 0-49%	1 SD (n=1)	2 PR (n=3)	1 PR (n=2)
	PD-L1+ ≥ 50%	3 PR (n=4)		

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
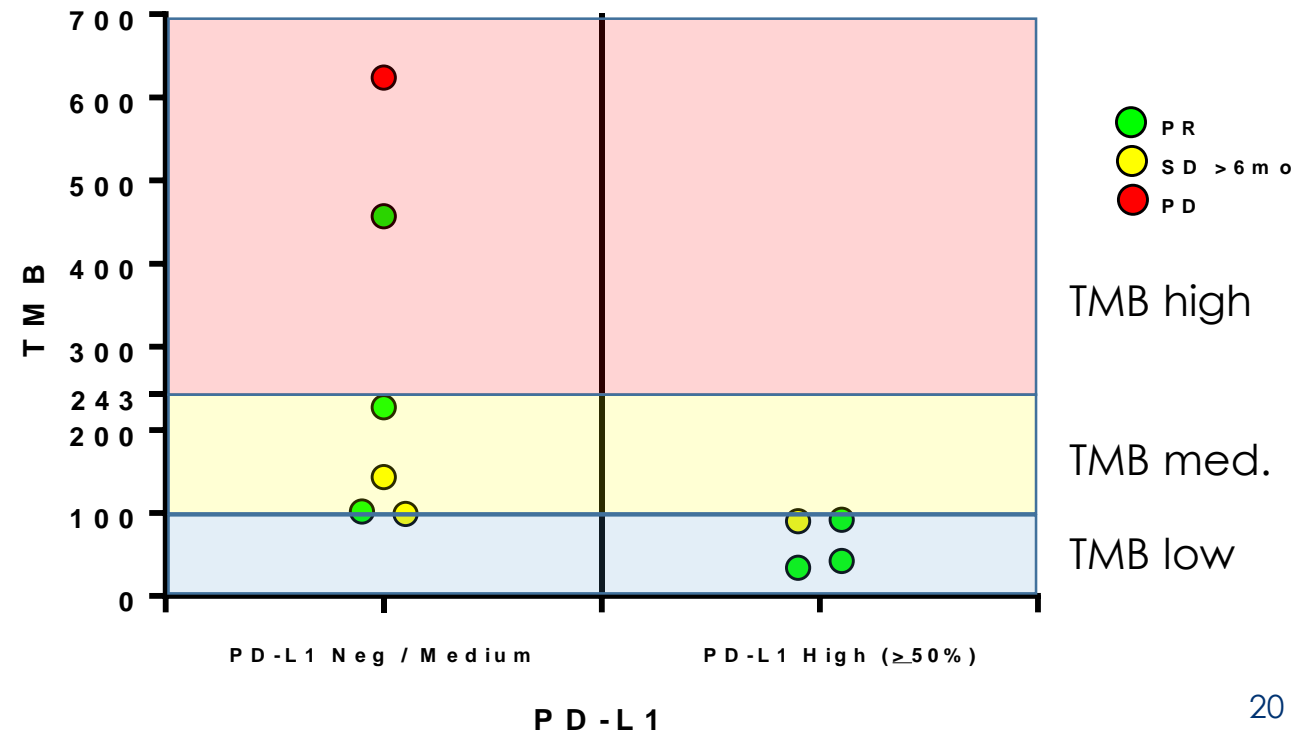
# AM0010 + Anti-PD-1in NSCLC (IFNγ associated GEP)

- Patients with a low IFNγ - associated gene expression profile have a reduced response rate to pembrolizumab
  (Prat et al., Cancer Res. 2017; Ayers et al., JCI 2017)

- Two patients (of five) with a low IFNγ - associated gene expression profile had a partial response on AM0010 + anti-PD-1, additional 2 had stable disease for more than 6 months
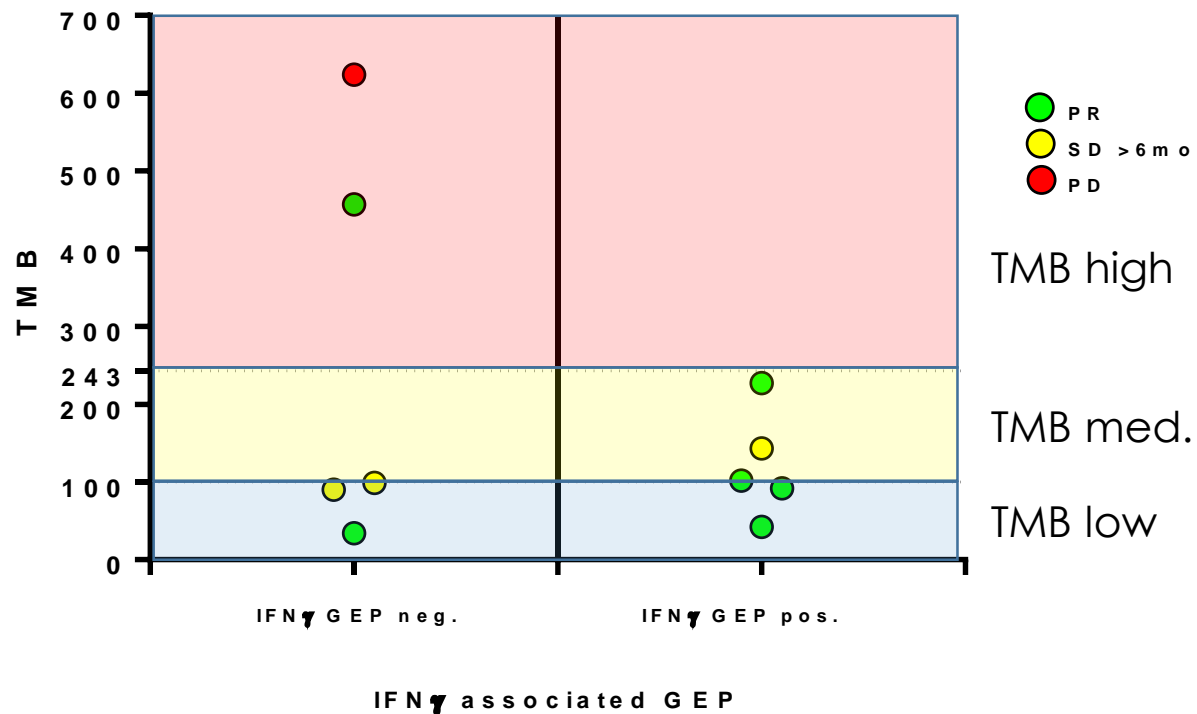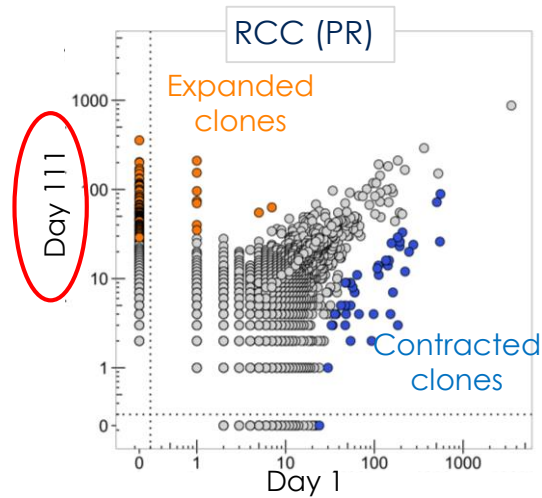

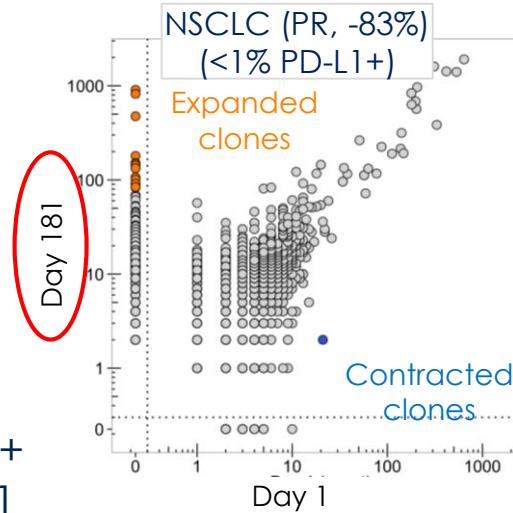IFNγ associated Gene Expression Profile
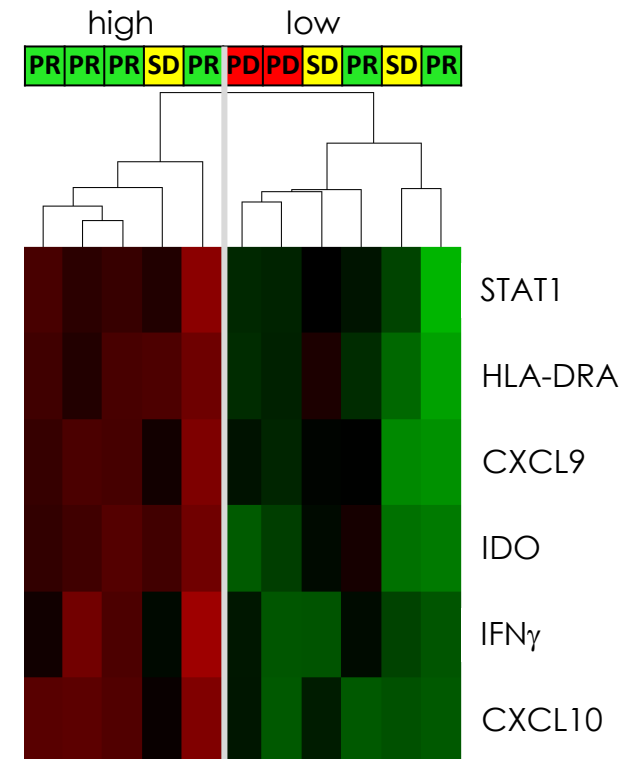
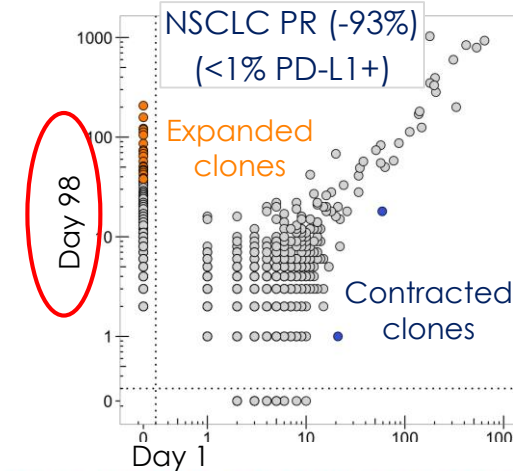# Sustainable Clonal T cell Expansion in Response to AM0010 or AM0010 + anti-PD-1
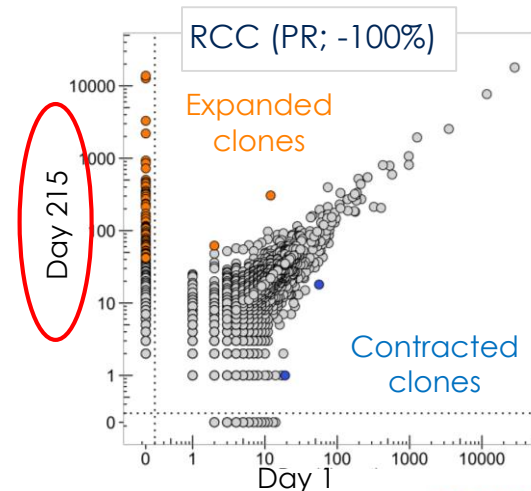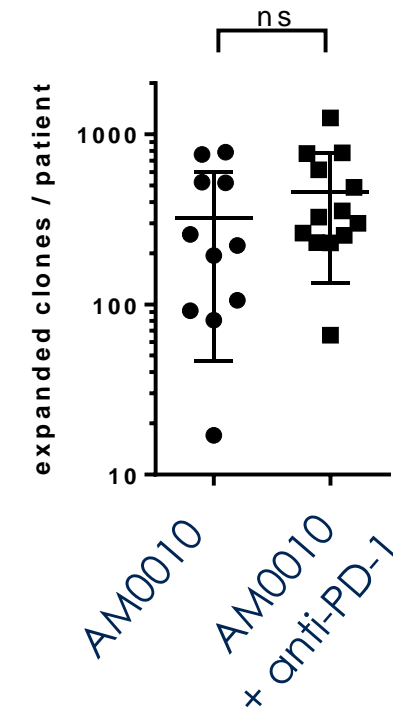

AM0010 Monotherapy

AM0010 + anti-PD-1

Absolute Number of >10x Expanding T cell clones

AM0010 (Pegilodecakin) 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 expands antigen activated CD8$^+$ T cells (cytotoxic license)
- AM0010 (Pegilodecakin) 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 44% (15 of 34 pts (2 CRs), 2x expected RR)
  - ORR in NSCLC 41% (11 of 27 pts, 2x expected RR)
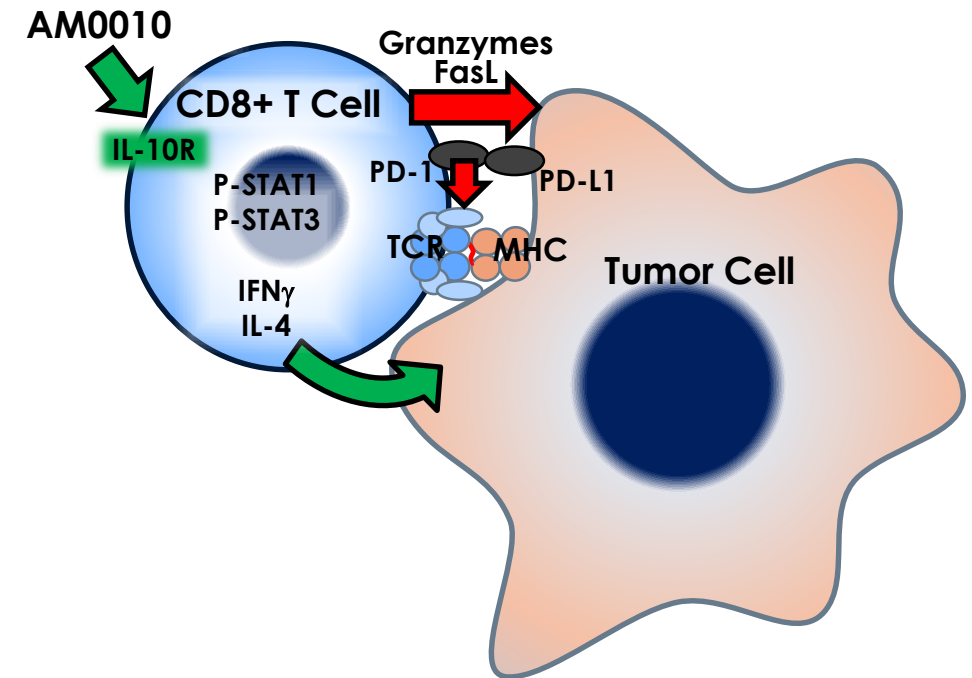
We want to thank all patients and their families!

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