Interim Results of an Ongoing Phase 1, Dose Escalation Study of MGA271 (Enoblituzumab), an Fc-optimized Humanized Anti-B7-H3 Monoclonal Antibody, in Patients with Advanced Solid Cancer

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  - Astra Zeneca/MedImmune
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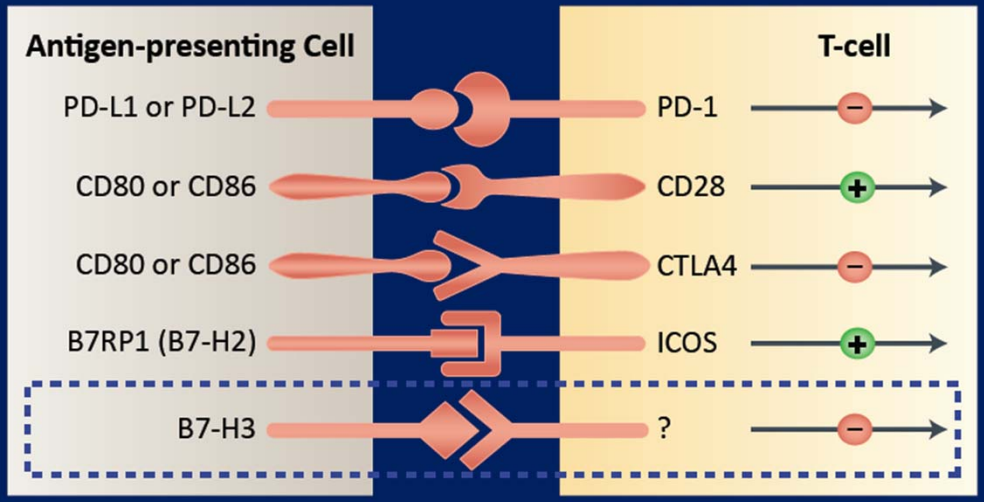
  - EMD Serono
- Speakers Bureau
  - BMS
  - Merck
- Stock Ownership: BioCytics, Lion Biotechnology, Juno Therapeutics, BlueBird Bio, Kite Pharma, ZioPharm Oncology

B7-H3 (CD276): Member of B7 Family of Immune Regulators



Adapted from Pardoll, et al., Nature, April 2012.

Immunosuppressive Role

- Expression on lung cancer cells and macrophages suppresses T-cell mediated anti-tumor immune response *(Chen 2013)*
- B7-H3-positive myeloid-derived suppressor cells found in tumor microenvironment *(Zhang 2015)*
- Crystal structure resolved: T-cell inhibitory domain mapped *(Vigdorovich 2013)*

Tumor Invasion and Metastatic Role

- Silencing reduces migration and invasion of melanoma and breast cancer cell lines *(Chen 2008)*
- Enhances metastatic potential of melanoma cells *(Tekle 2012)*

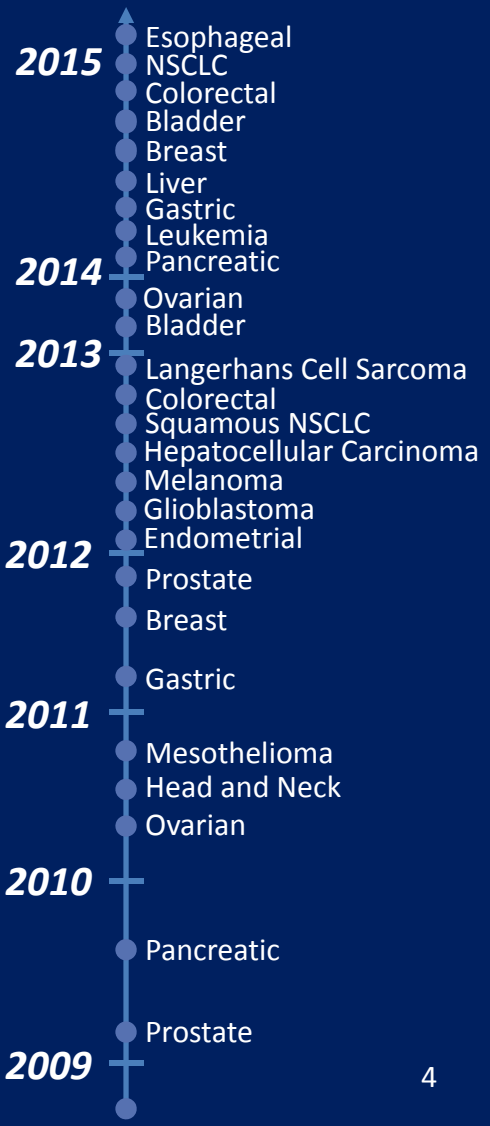
B7-H3: Tissue Expression and Prognosis

Fixed Tumor MicroArray	IHC Summary of Samples Screened			
	B7-H3 Positive		2+ or Above	
Lead Potential Indications:				
Head and Neck	19/19	100%	19/19	100%
Kidney Cancer	77 / 78	99%	75 / 78	96%
Lung Cancer	226/272	83%	211/272	78%
Breast Cancer	119/164	73%	115/164	70%
Prostate Cancer	88/99	89%	51/99	52%
Melanoma	66/70	94%	32/70	46%
Bladder	14/20	70%	9/20	45%
Other Potential Indications:				
Glioblastoma	65/66	98%	63/66	95%
Thyroid Cancer	34/35	97%	33/35	94%
Mesothelioma	41/44	93%	39/44	89%
Pancreas Cancer	69/78	88%	45/78	58%
Ovarian Cancer	59/79	75%	36/79	46%

B7-H3 Tissue Expression

- High level expression in a broad range of tumors
- Minimal expression on normal tissue
- Expressed on tumor neo-vasculature
- Correlation of high expression with advanced disease, presence of metastases and poor outcome

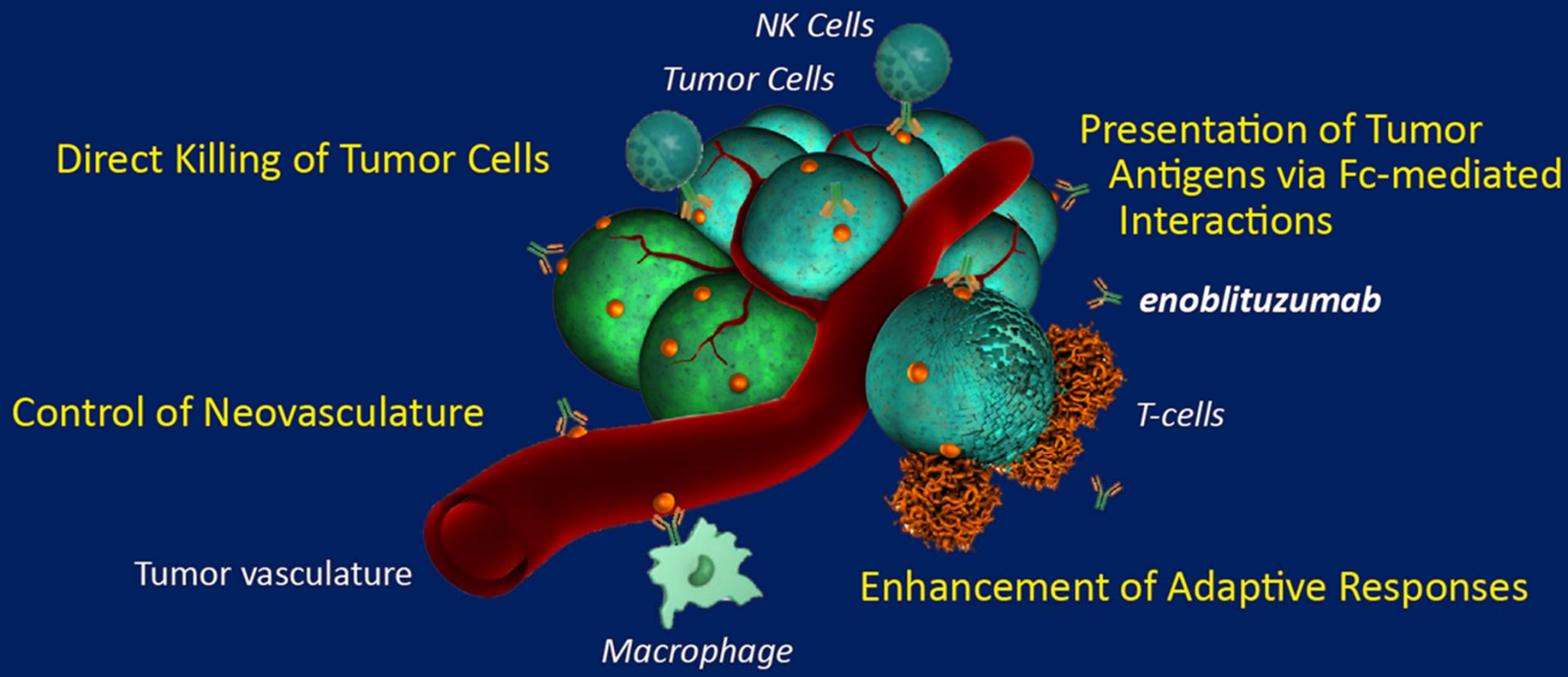
Timeline of selected B7-H3 articles in peer-reviewed publications



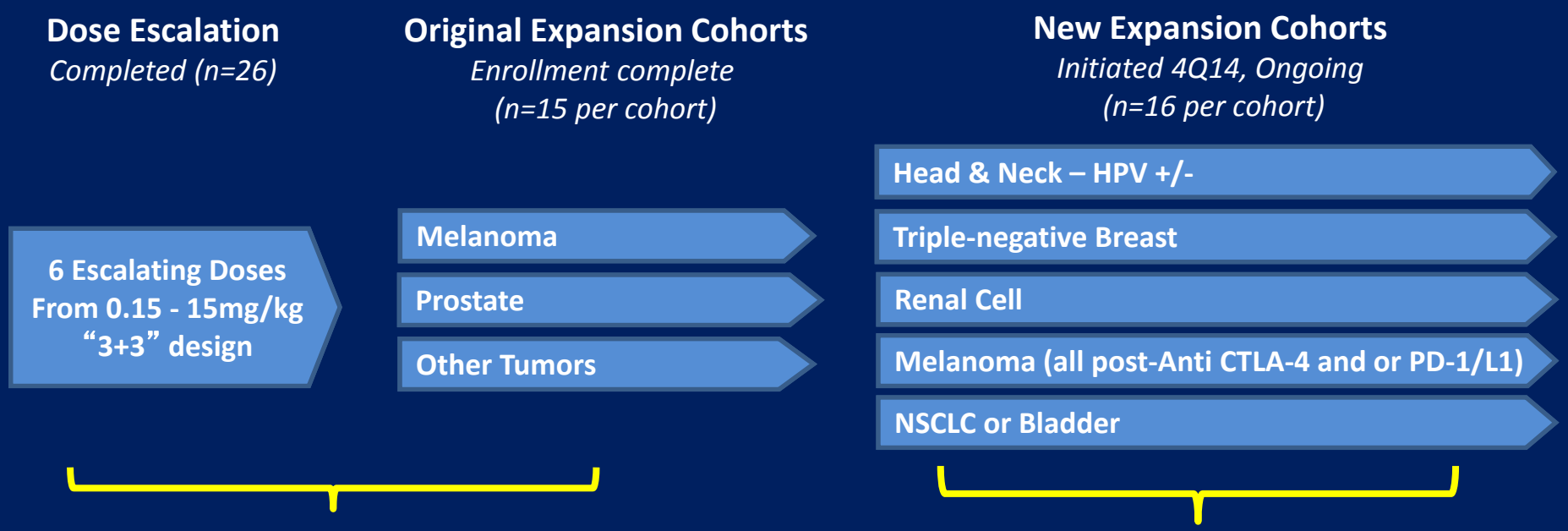
Enoblituzumab (MGA271, Anti-B7-H3 Antibody)

- Humanized IgG1 monoclonal antibody recognizing human B7-H3 with high affinity (KD ≈ 7 nM)
- Terminal Half Life ≈ 3 weeks
- Fc-optimized via mutation to enhance effector function (e.g., ADCC)
  - Increased affinity for activating Fcγ receptor (FcγRII, CD16A)
  - Decreased affinity for the inhibitory Fcγ receptor (FcγRIIB, CD32B)
- Once-weekly intravenous dosing
- Currently in clinical trials as monotherapy (described today) and in combination with checkpoint inhibitors including pembrolizumab and ipilimumab (see SITC Trials-In-Progress Poster Session)

Enoblituzumab
Potential Mechanisms of Action



Study Design: Ongoing Phase 1 Dose Escalation and Cohort Expansion



Original Study Design

- Cycle 1: dosing weekly x 4, then off x 4 weeks
- ≥ Cycle 2: dosing weekly x3, then off 1 week
- Standard RECIST for eval. & management
- Premed 10 mg dexamethasone, dose #1 & #2

New Trial Design

- Continuous weekly dosing for all cycles
- Management according to IR principles
- Evaluation by RECIST and irRECIST
- Premed 50-100mg hydrocortisone, dose #1 & #2

Study Objectives

- Primary Objective
  - Describe safety profile of enoblituzumab in patients with advanced cancer that expresses B7-H3 in tumor and/or tumor-associated vasculature
- Secondary Objectives
  - Determine Maximum Tolerated Dose or Maximum Administered Dose of enoblituzumab
  - Evaluate preliminary anti-tumor activity of enoblituzumab
  - Determine enoblituzumab pharmacokinetics/pharmacodynamics
- Exploratory Objectives
  - Evaluate and assess IHC diagnostic test for B7-H3 expression on tumor cells and tumor vasculature

Key Inclusion/Exclusion Criteria

Inclusion

- B7-H3 expression on tumor cells or tumor vasculature
  - ≥10% of tumor cells with 2 or 3+ IHC* staining or ≥ 25% of tumor vasculature having 2 or 3+ IHC staining
- Progressive disease during or following last treatment regimen
  - Up to 4 to 5 prior treatments allowed depending on tumor type
- Prior checkpoint inhibitor therapy allowed (mandated for melanoma)
- ECOG Performance Status ≤ 1
- Measurable disease by RECIST 1.1
  - Prostate cancer required measurable disease in new trial design
- Completed systemic anticancer therapy ≥ 28 days prior to enrollment

Exclusion

- ≥ Grade 3 autoimmune toxicity with prior immune checkpoint inhibitor
- Concurrent systemic steroids >10 mg/day of oral prednisone/equivalent
- Active brain metastases

*IHC: Immunohistochemistry with B7-H3 cell surface staining

Baseline Characteristics

Baseline Characteristics	Escalation n=26	Original Expansion n= 48	Additional Expansion n= 42	Total n= 116
Median age, (range), years	62 (42-77)	64 (26-88)	67 (24-83)	63 (24-88)
Male, no. (%)	17 (65)	33 (69)	28 (67)	78 (67)
Prior Cancer Therapy				
Median no. (range): Chemo and Immunotherapy	2 (1-5)	3 (0-8)	3 (0-5)	3 (0-8)
Prior Chemotherapy, no. (%)	21 (81)	34 (71)	37 (88)	92 (79)
Prior Immunotherapy, no. (%)	6 (23)	18 (38)	7 (17)	31 (27)
ECOG Performance Status, no. (%)				
0	16 (62)	20 (42)	10 (24)	46 (40)
1	10 (38)	28 (58)	32 (76)	70 (60)

Data as of September 21, 2015

Enoblituzumab-Related Adverse Events

- Acceptable safety profile
- No drug-related treatment discontinuation
- Mild-moderate infusion reactions readily managed with conventional supportive care including corticosteroids, decreased infusion rate

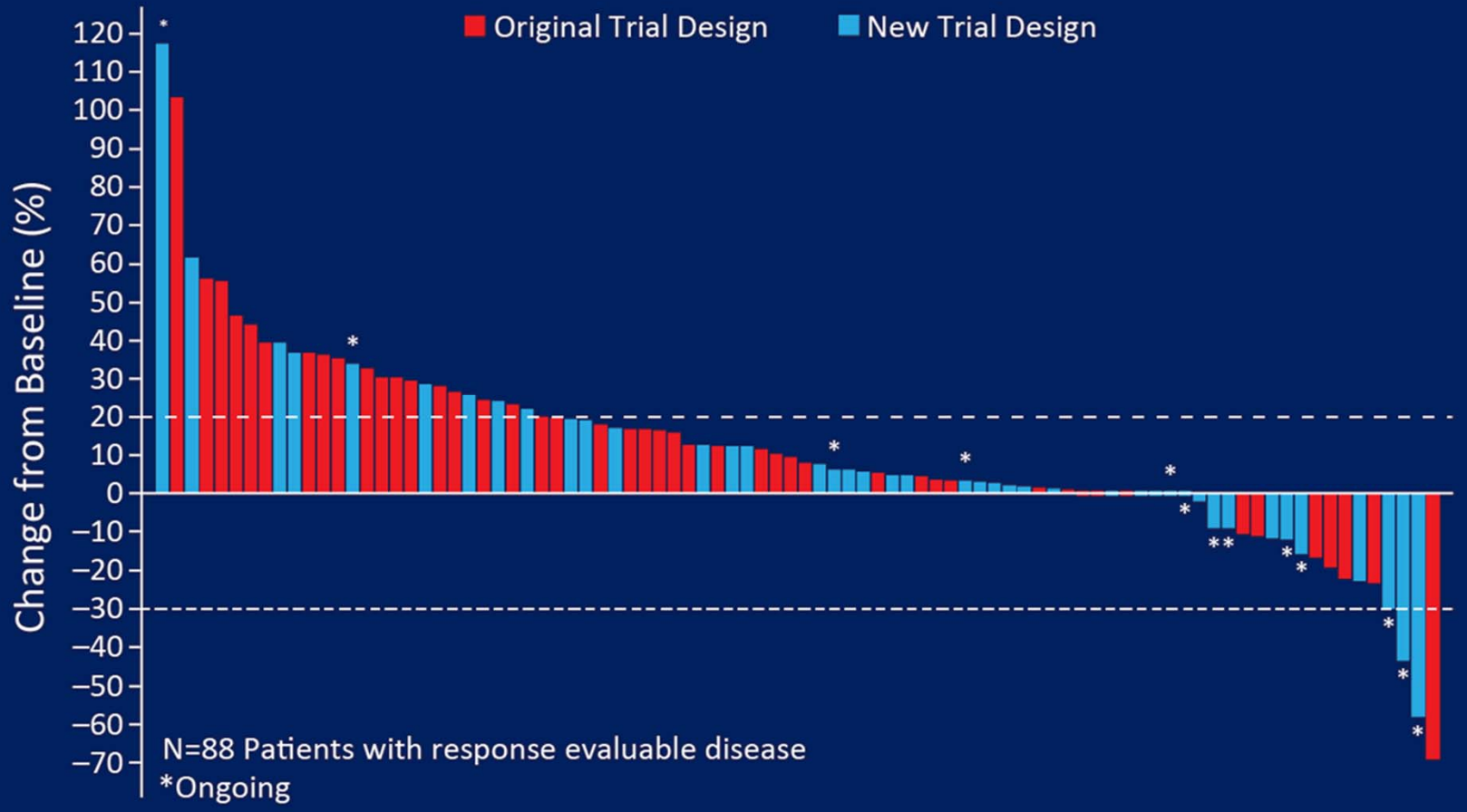
Drug-Related Adverse Event ≥10% of Patients	No. (%) of Patients			
	All Grades		Grades 3-4	
	Total Population (N=116)	New Study Design* (N=55)	Total Population (N=116)	New Study Design* (N=55)
Any adverse event	86 (74)	42 (76)	5 (4)	3(5)
Infusion related reaction/ cytokine release syndrome	39(34)	24 (44)	1(1)	1(2)
Fatigue	37 (32)	15 (27)	0	0
Nausea	22 (19)	14 (25)	0	0
Vomiting	15 (13)	10(18)	0	0

*New study design is continuous, uninterrupted weekly infusion of enoblituzumab with reduced steroid pre-med

Data as of September 21, 2015

Best Change in Target Lesion Size

All Response Evaluable Patients: Escalation and Expansion

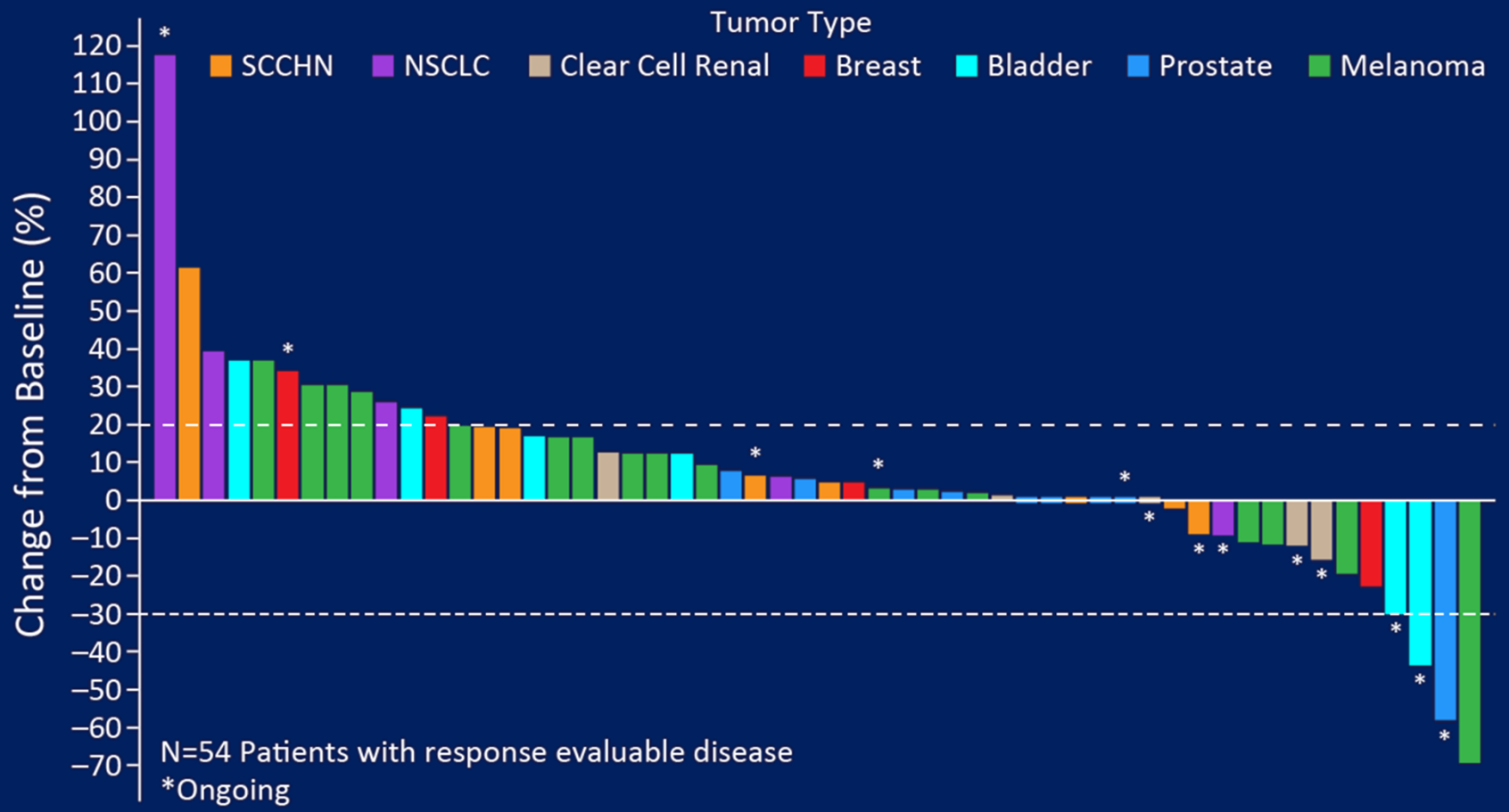


- Tumor regression at multiple dose levels (0.15mg/kg – 15mg/kg)
- Enrollment continues under new trial design: ≈ half of planned patients enrolled

Data as of September 21, 2015

Best Change in Target Lesion Size

Response Evaluable, Tumor-Specific Expansion Cohorts: 15 mg/kg
Cohorts: Melanoma, Prostate, TNBC, SCCHN, NSCLC, Bladder, RCC

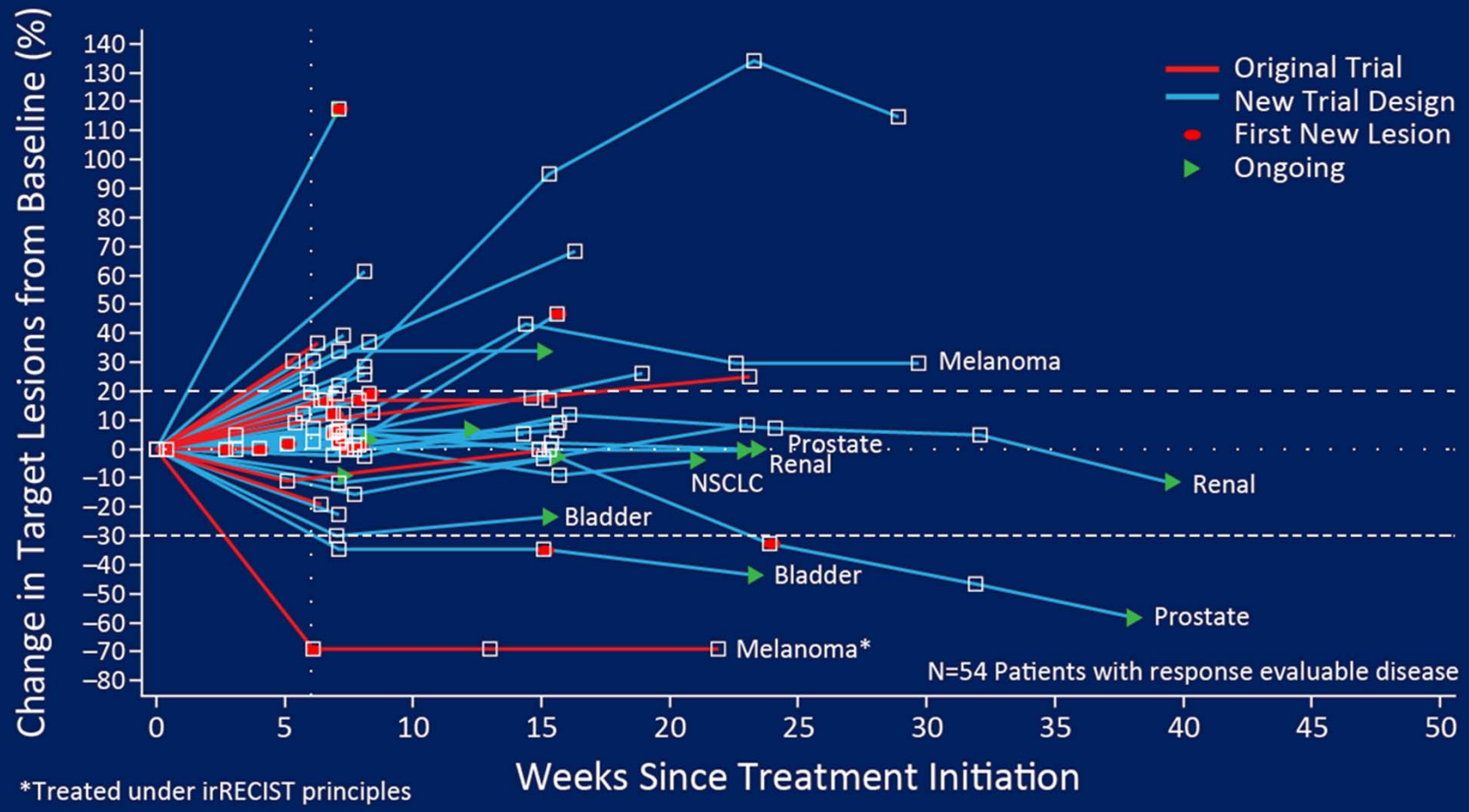


- Tumor regression observed in each disease cohort

Data as of September 21, 2015

Change in Target Lesion Size Over Time

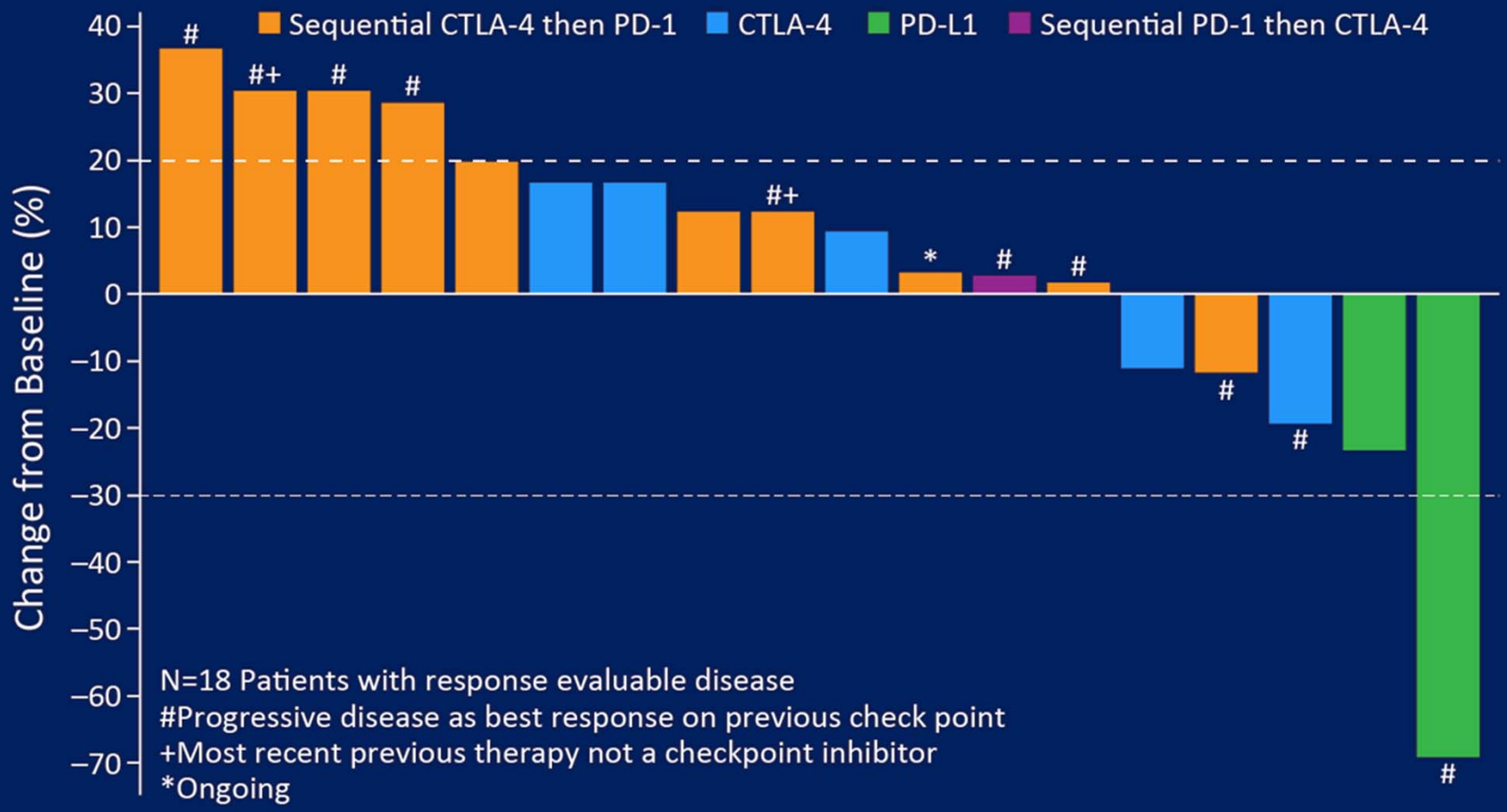
Response-Evaluable Tumor-Specific Expansion Cohorts: 15 mg/kg
Cohorts: Melanoma, Prostate, TNBC, SCCHN, NSCLC, Bladder, RCC



Data as of September 21, 2015

Best Change in Target Lesion Size: Melanoma

All patients are post-checkpoint inhibitor

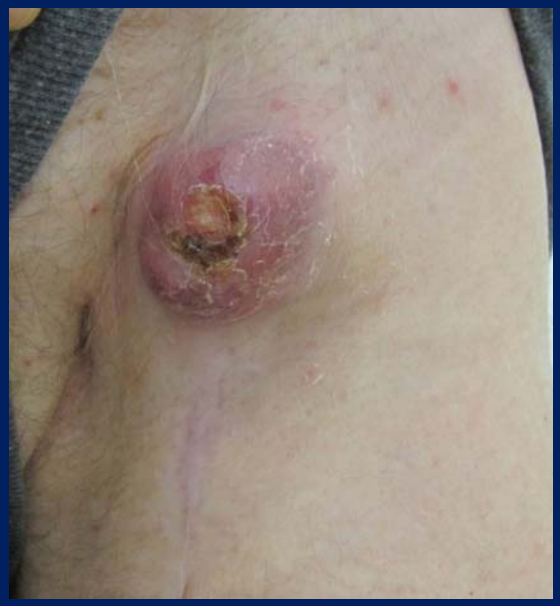
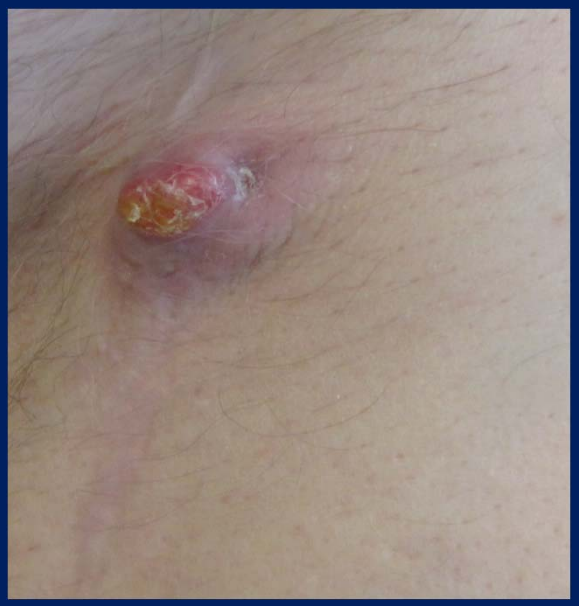
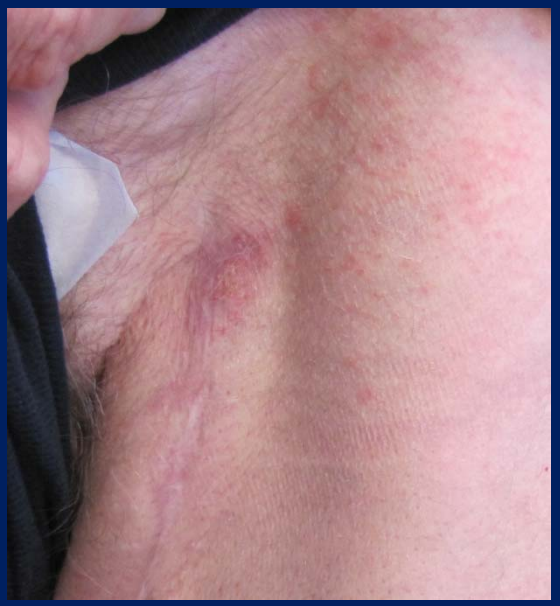


All but one patient treated 15mg/kg enoblituzumab

Data as of September 21, 2015

Metastatic Melanoma

73-year-old man previously progressed on Anti-PD-L1 And Trametinib

Pre-Treatment Baseline	Day 22 (3 *Doses* enoblituzumab - *15mg/kg)*	Day 98 (11 *Doses* enoblituzumab - *15mg/kg*)
		

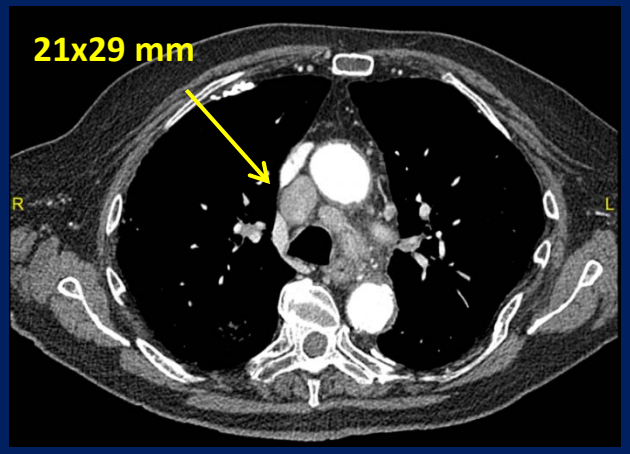
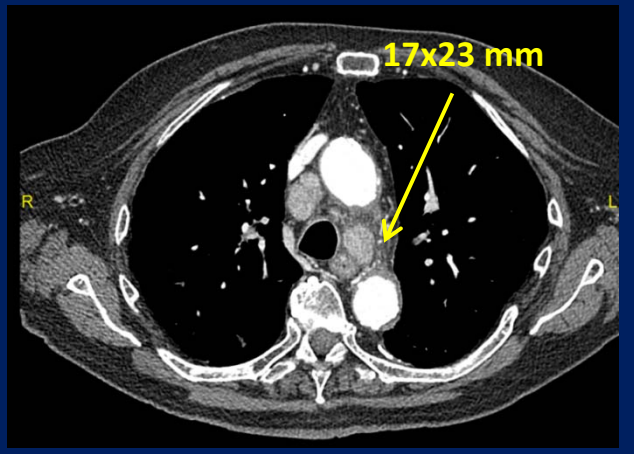
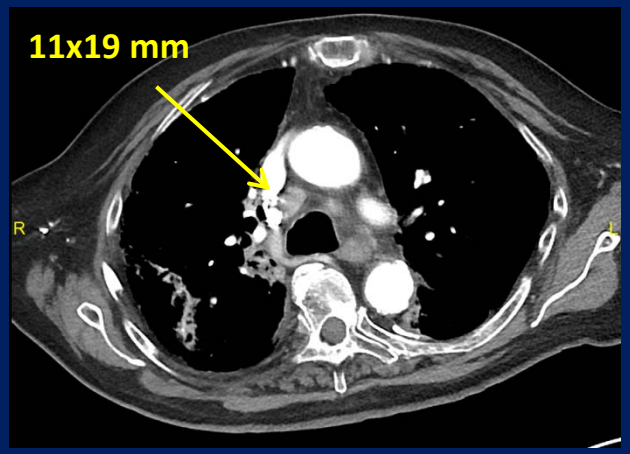
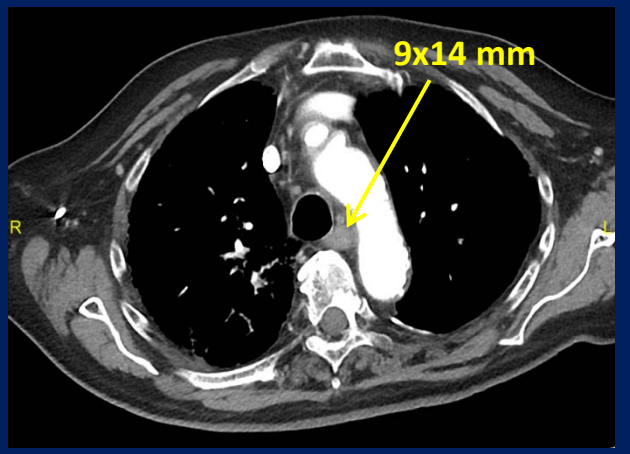
- Near complete regression of ulcerated 4 cm tumor in groin
- Regression of small pulmonary nodules on CT

Courtesy of Dr. Chmielowski at UCLA Jonsson Comprehensive Cancer Center

Data as of September 21, 2015

Metastatic Prostate Cancer

87-year-old man

	Right Paratracheal Lymph Node	Left Paratracheal Lymph Node
Pre-Treatment Baseline		
Day 287 34 Doses enoblituzumab (15mg/kg)		

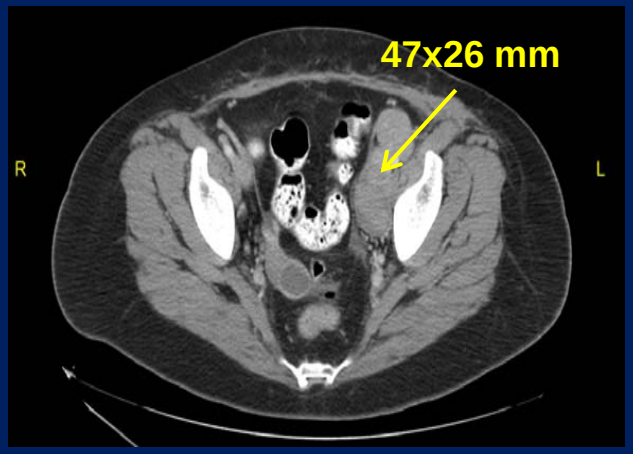
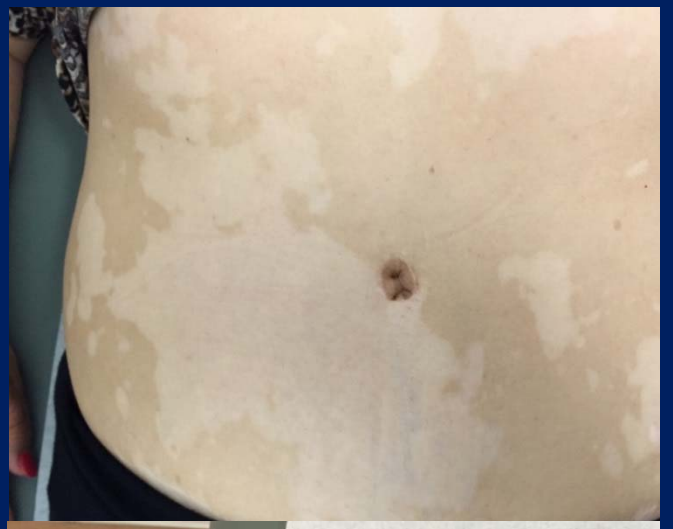
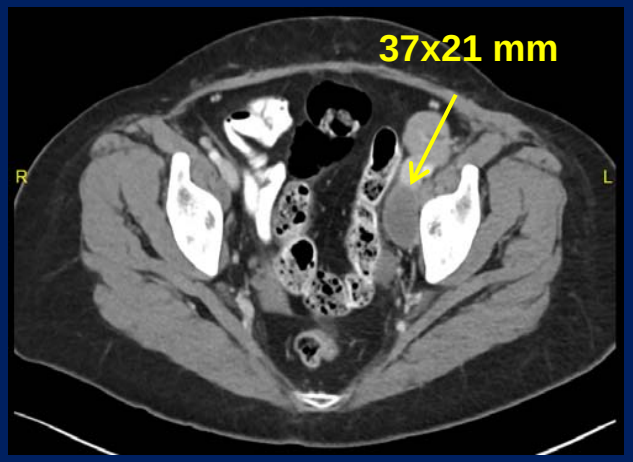
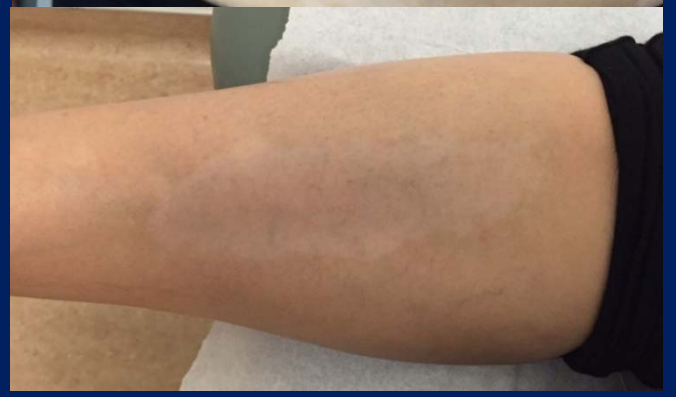
Patient remains on therapy after 11 months of treatment

Courtesy of Dr. Chmielowski at UCLA Jonsson Comprehensive Cancer Center

Data as of September 21, 2015

Vitiligo in Melanoma Patient with Progression on Prior Therapy with Checkpoint Inhibitors

52-year-old woman previously progressed on anti-CTLA-4 and anti PD-1

	Left Ext Iliac Lymph Node #1	Development of Vitiligo (Post-enoblituzumab)
Pre-Treatment Baseline		
Day 58 8 Doses enoblituzumab (15mg/kg)		

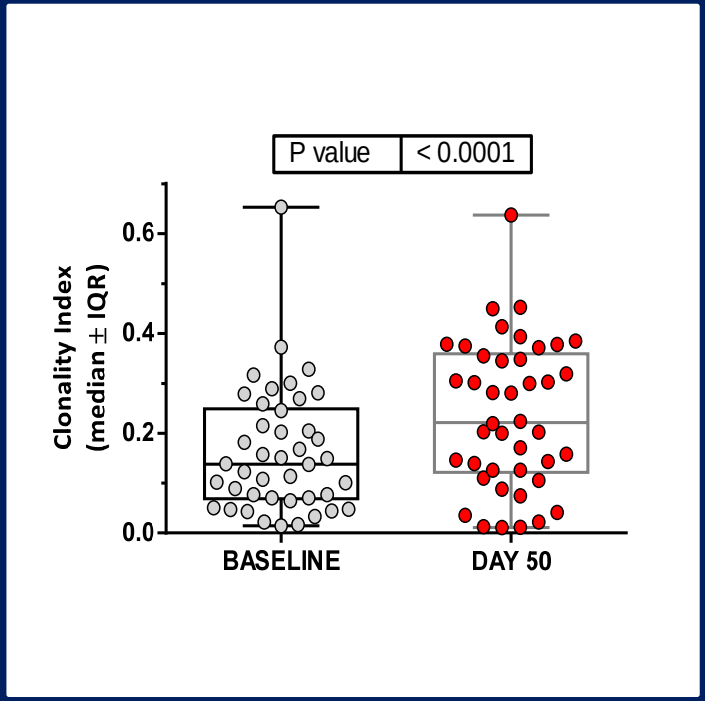
Courtesy of Dr. Chmielowski's patient at UCLA Jonsson Comprehensive Cancer Center

Data as of September 21, 2015

Increase in T-Cell Receptor Repertoire Clonality Following Enoblituzumab

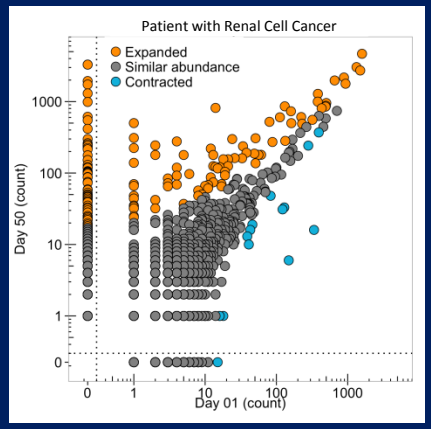
Evaluation of T-Cell Clonality in the Peripheral Blood

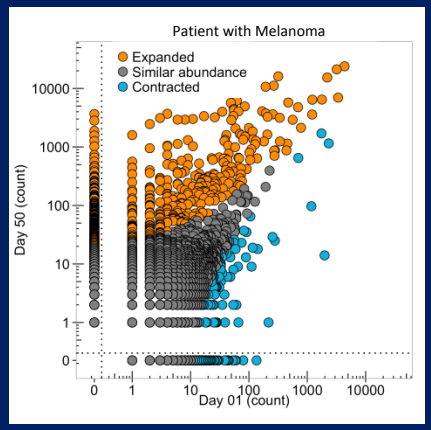
Population Clonality



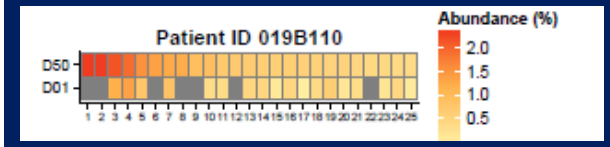
Baseline (Day 1) v D50 Post-treatment
(42 patients)

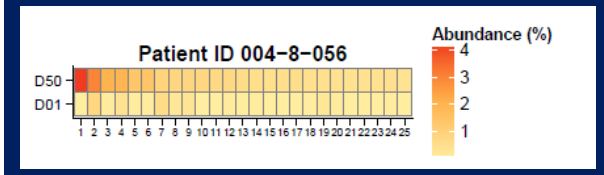
Clonality: 2 Patients with Tumor Shrinkage





Top 25 Clones at Day 50
Comparison to Baseline





Analyses performed in collaboration with Adaptive Biotechnologies

Conclusions from Ongoing Enoblituzumab CP-MGA271-01 Study

- Manageable and tolerable safety profile
  - No treatment related discontinuation
  - No severe immune mediated toxicity
- Preliminary anti-tumor activity in broad range of tumors
  - Post check-point inhibitor failure melanoma
  - New study design: management principles used in immune oncology
- Initial demonstration of T-cell modulation with enoblituzumab
- Interim results:
  - **Support continued evaluation of enoblituzumab monotherapy**
  - **Support evaluation of enoblituzumab in combination with check-point inhibitors: anti PD-1 and anti CTLA-4**

ACKNOWLEDGEMENTS

We thank all patients and their families

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  - Carolina BioOncology Institute, Huntersville, NC
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  - University of Pennsylvania/Abramson Cancer Center, Philadelphia, PA
  - Sarah Cannon Research Institute, Nashville, TN
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