The Evolution of Immune Checkpoint Inhibitors

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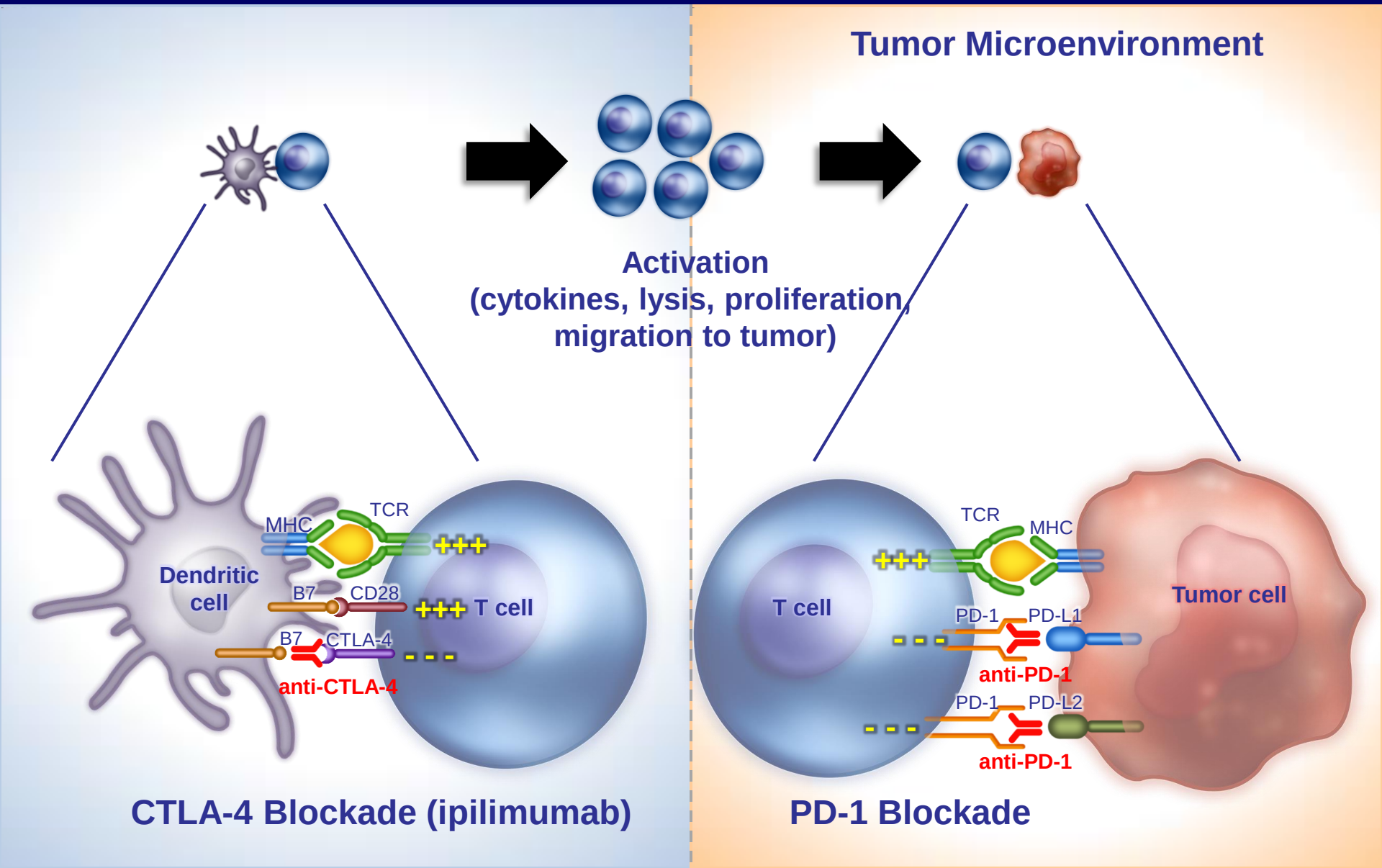
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

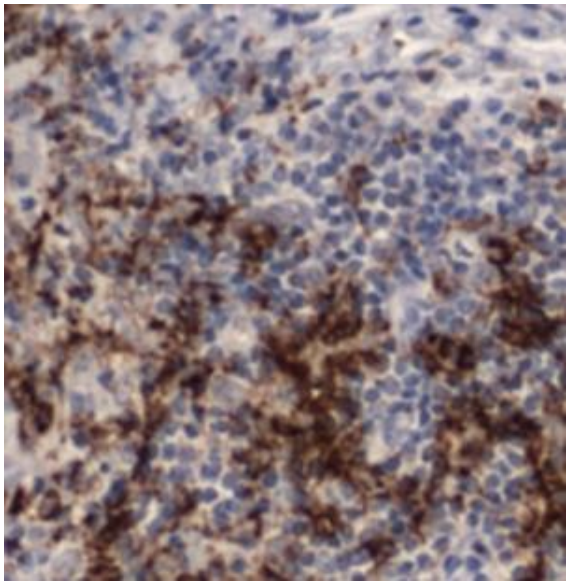
Advantages of Immunotherapy for Cancer Therapy

- **Specificity**
- **Memory**
- **Adaptability**

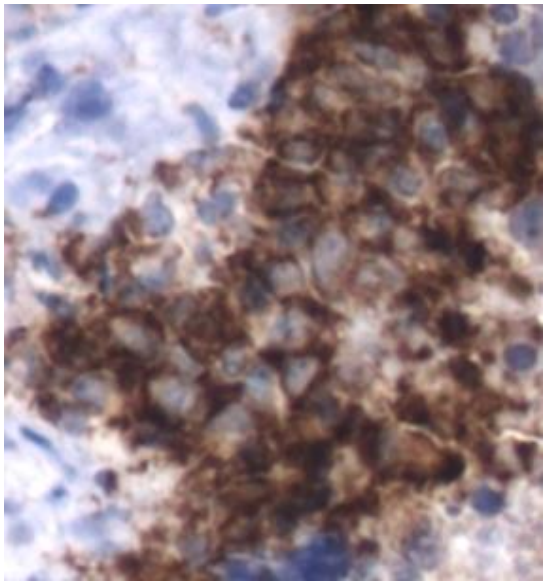
Blocking CTLA-4 and PD-1



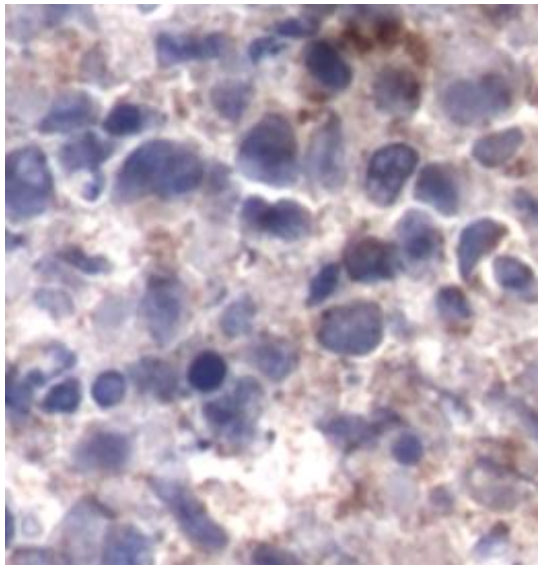
PD-L1 Immunohistochemistry (5H1)



A. PDL1 + tumor with TILS

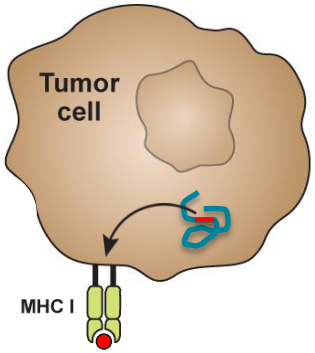


B. PDL1 + tumor

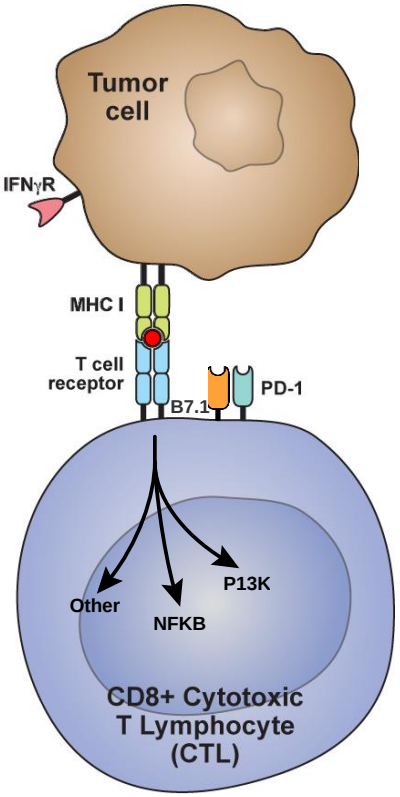


C. Control antibody

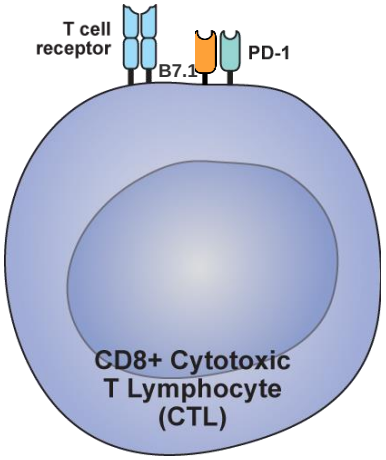
- **Which antibody**
- **Which cells**
- **Which tumor (heterogeneity)**
- **When in the course of a patient's disease course**



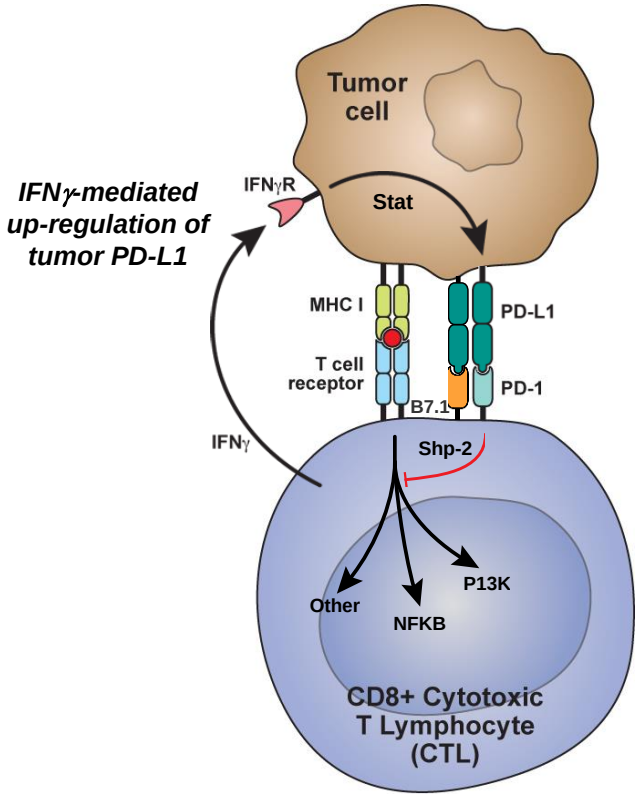
- Cancer cells develop many mutations that can make them appear foreign to the immune system



- T cells can recognize, attack and kill these “foreign” cancer cells



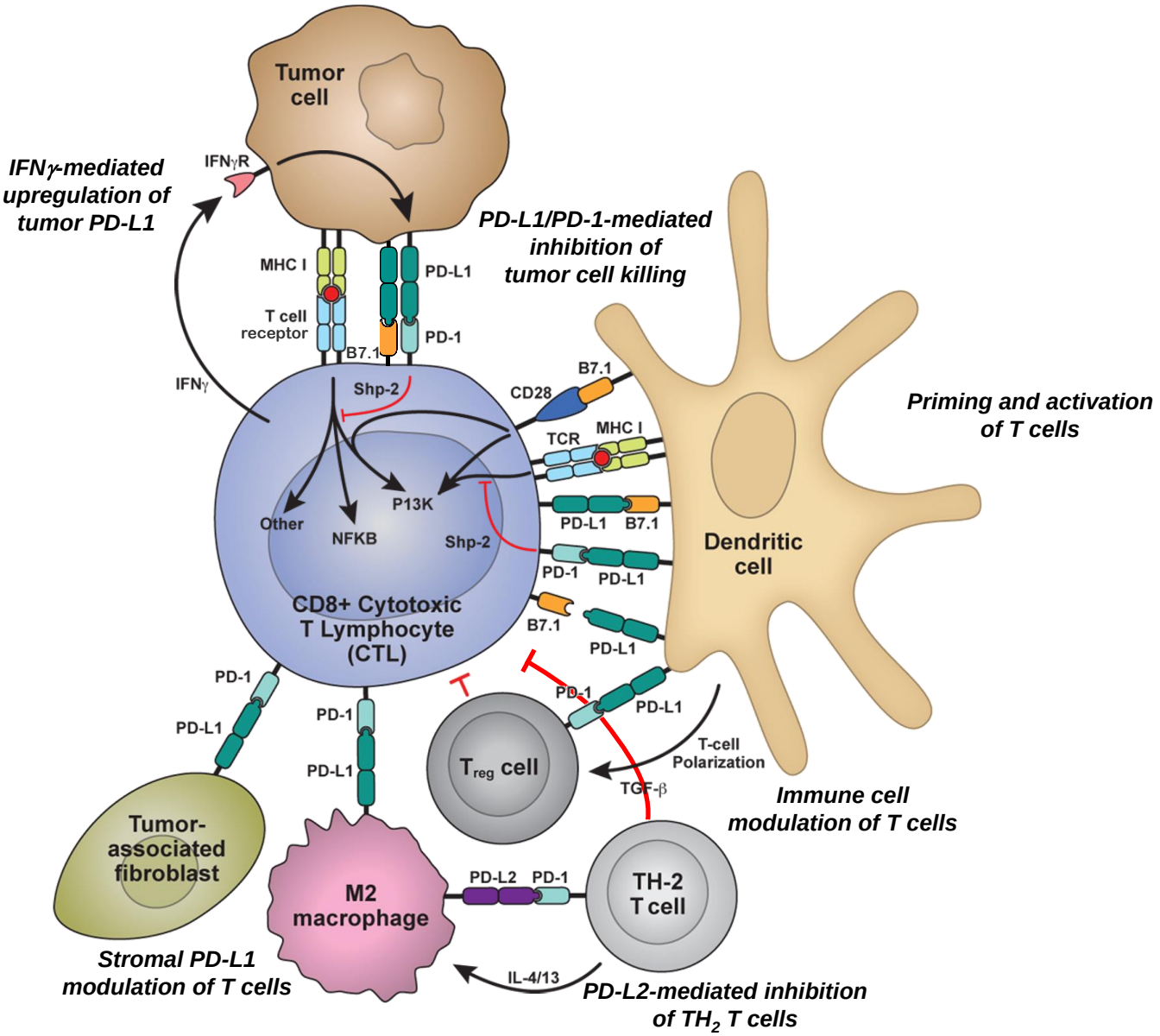
Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.



- Cancer cells can evade immune attack by expressing PD-L1

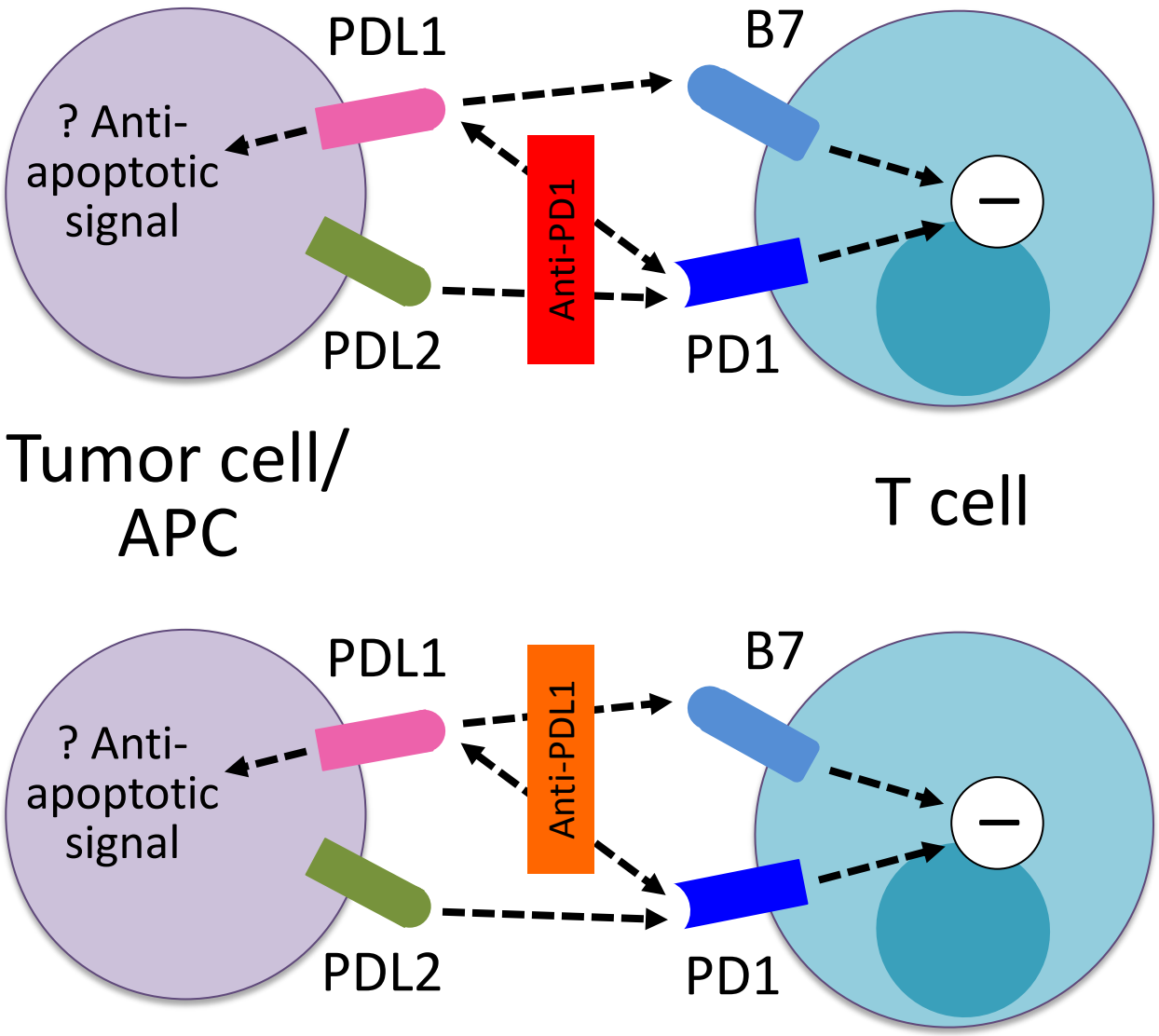
Adaptive Tumor Expression of PD-L1

Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.



PD-L1 plays an important role in dampening the anti-tumor immune response

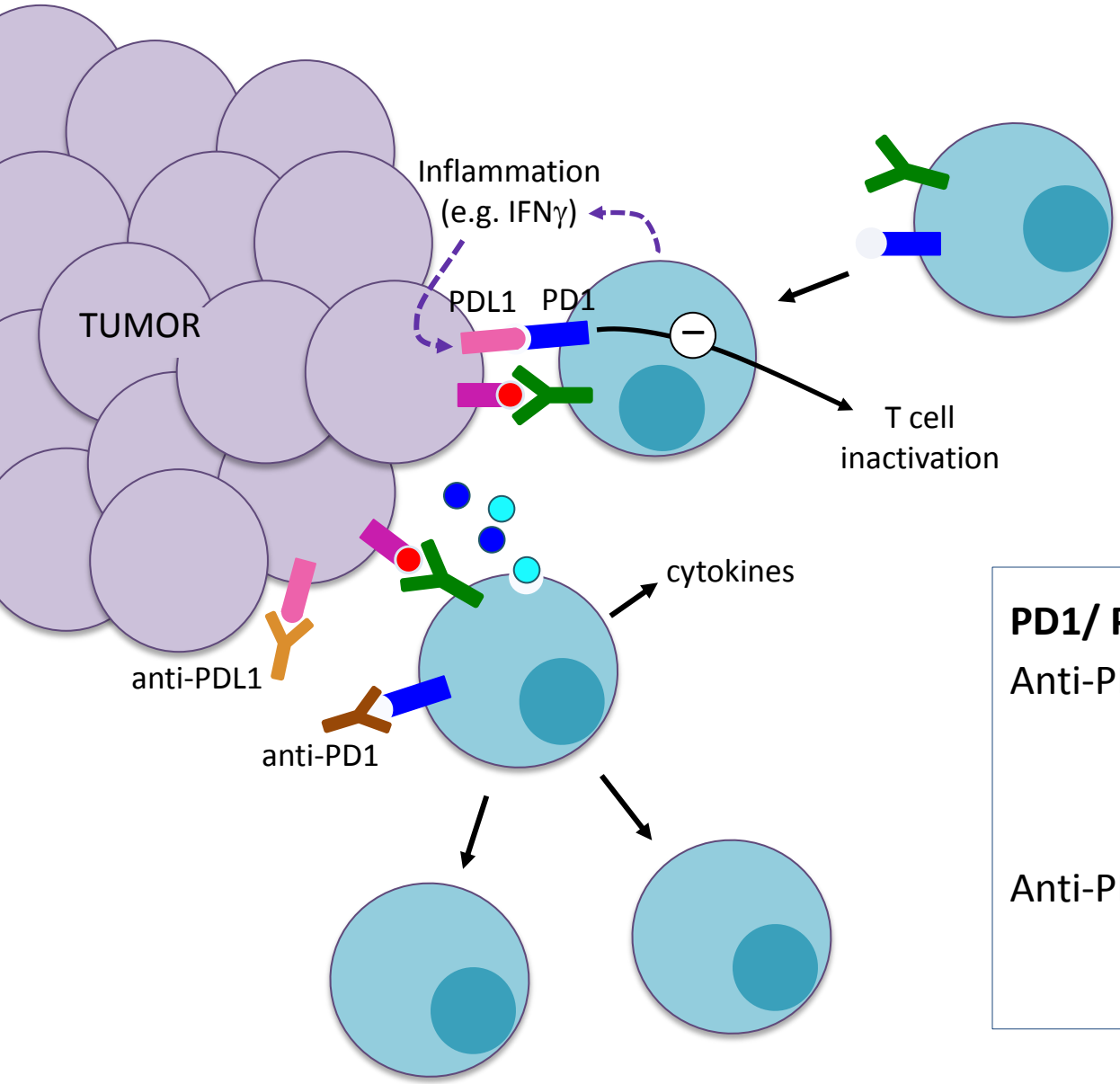
PD1 vs. PDL1 Blockade



Are there differences in Activity/Toxicity among agents

- **Binding Affinity**
- **Different targets**
- **Antibody Isotype (IgG4 vs IgG1 vs engineered)**
- **ADCC**
- **Anti PD1 vs anti PDl1**

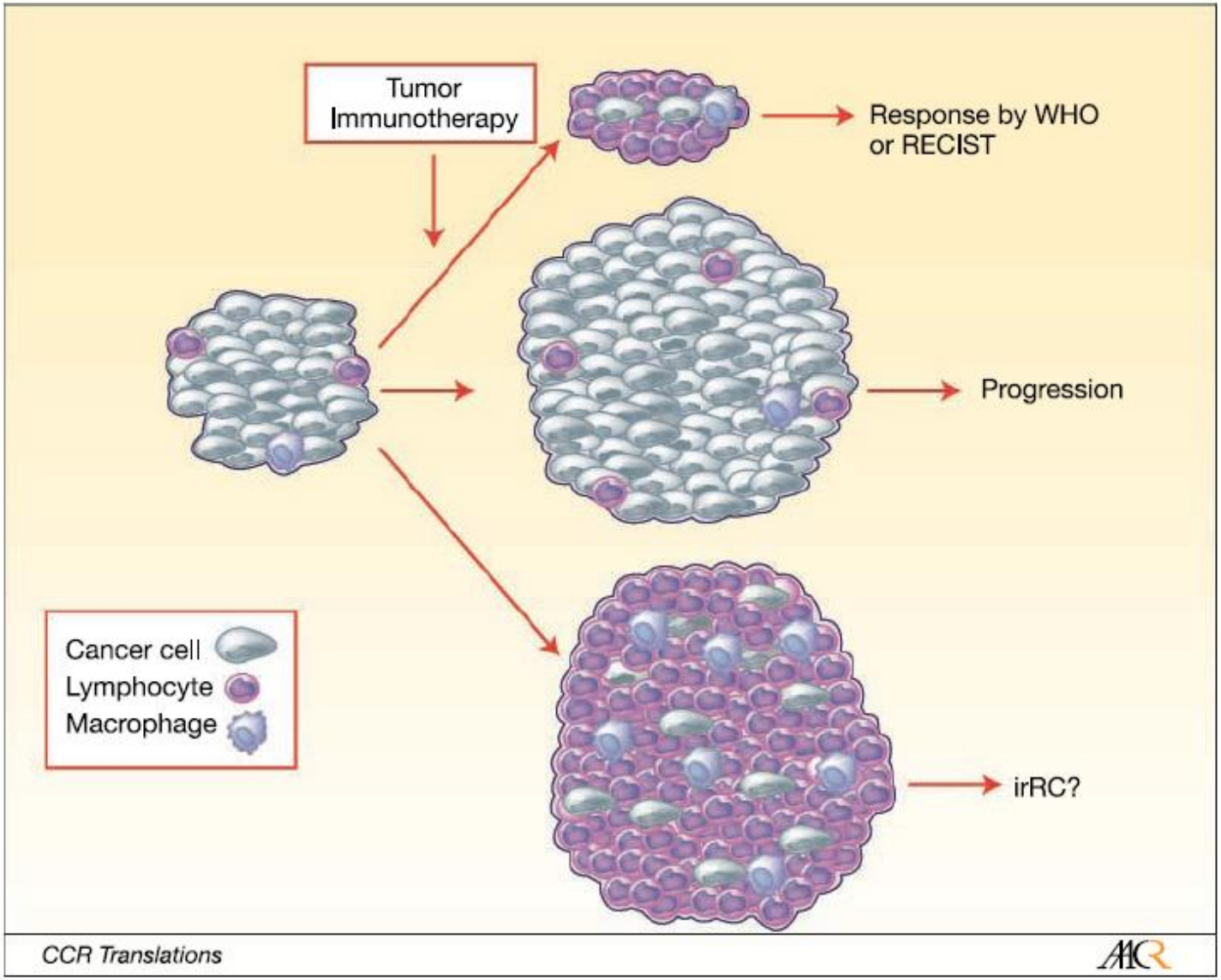
Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway



PD1/ PDL1 Blockade in Clinical Trials

Anti-PD1	BMS-936558
	MK3475
	CT-011
	AMP-224
Anti-PDL1	BMS-936559
	MPDL3280A
	MEDI4736

Tumor Volume Increase Due to Lymphocyte Infiltration



Ribas et al., Clin Cancer Res 2009; 15:7116–8

Cancer Immunotherapy Consortium

Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in Patients With Non-Small Cell Lung Cancer (NSCLC): Overall Survival and Long-term Safety in a Phase 1 Trial

Julie R. Brahmer,[1] Leora Horn,[2] Scott J. Antonia,[3] David R. Spigel,[4] Leena Gandhi,[5] Lecia V. Sequist,[6] Vindira Sankar,[7] Christoph M. Ahlers,[7] Georgia Kollia,[7] Ashok Gupta,[7] Scott Gettinger[8]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [4]Sarah Cannon Research Institute, Nashville, TN, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Bristol-Myers Squibb, Princeton, NJ, USA; [8]Yale Cancer Center, New Haven, CT, USA

*

Efficacy of Nivolumab Monotherapy in Patients (N=129) with NSCLC

Dose mg/kg	ORR[a,b] % (n/N)	Estimated Median DOR Weeks (Range)	Stable Disease Rate ≥24 Wks % (n/N)	Median PFS Months (95% CI)	Median OS Months (95% CI)
All doses	17.1 (22/129)	74.0 (6.1+, 133.9+)	10.1 (13/129)	2.3 (1.9, 3.7)	9.9 (7.8, 12.4)
1	3.0 (1/33)	63.9 (63.9, 63.9)	15.2 (5/33)	1.9 (1.8, 3.6)	9.2 (5.3, 11.1)
3	24.3 (9/37)	74.0 (16.1+, 133.9+)	8.1 (3/37)	1.9 (1.7, 12.5)	14.9 (7.3, NE)
10	20.3 (12/59)	83.1 (6.1+, 132.7+)	8.5 (5/59)	3.6 (1.9, 3.8)	9.2 (5.2, 12.4)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

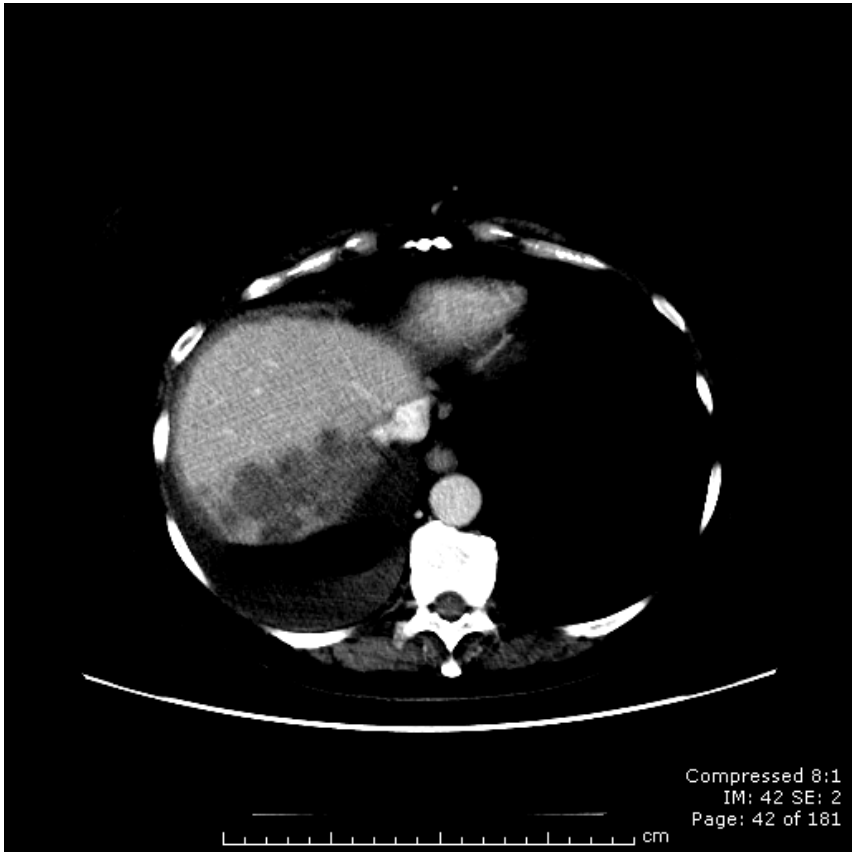
[a]Tumors and responses were assessed after each cycle per modified RECIST v1.0.

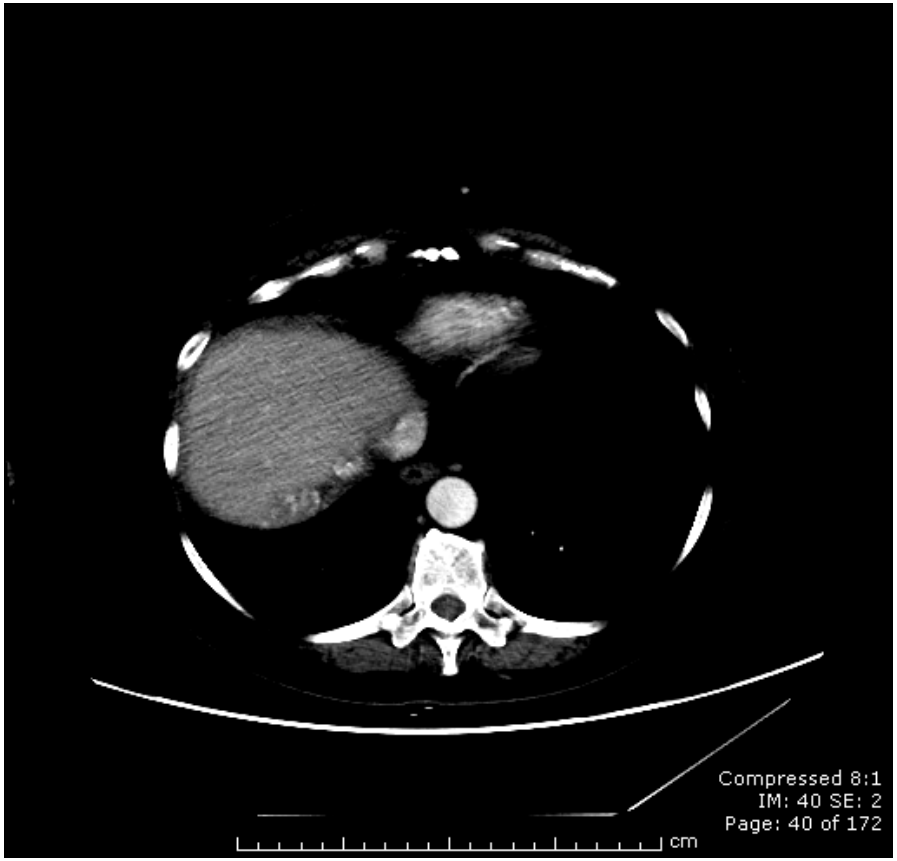
[b]All efficacy analyses based on data collected as of September 2013

- Durable responses were observed; responses are ongoing in 45% of patients (10/22)
- Higher ORRs observed at 3 and 10 mg/kg nivolumab doses relative to 1 mg/kg dose
- Rapid responses; 50% of patients (11/22) demonstrating response at first assessment (8 weeks)
- 7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response
- 6 patients with unconventional "immune-related" responses were not included as responders

Anti-PD-1 Therapy

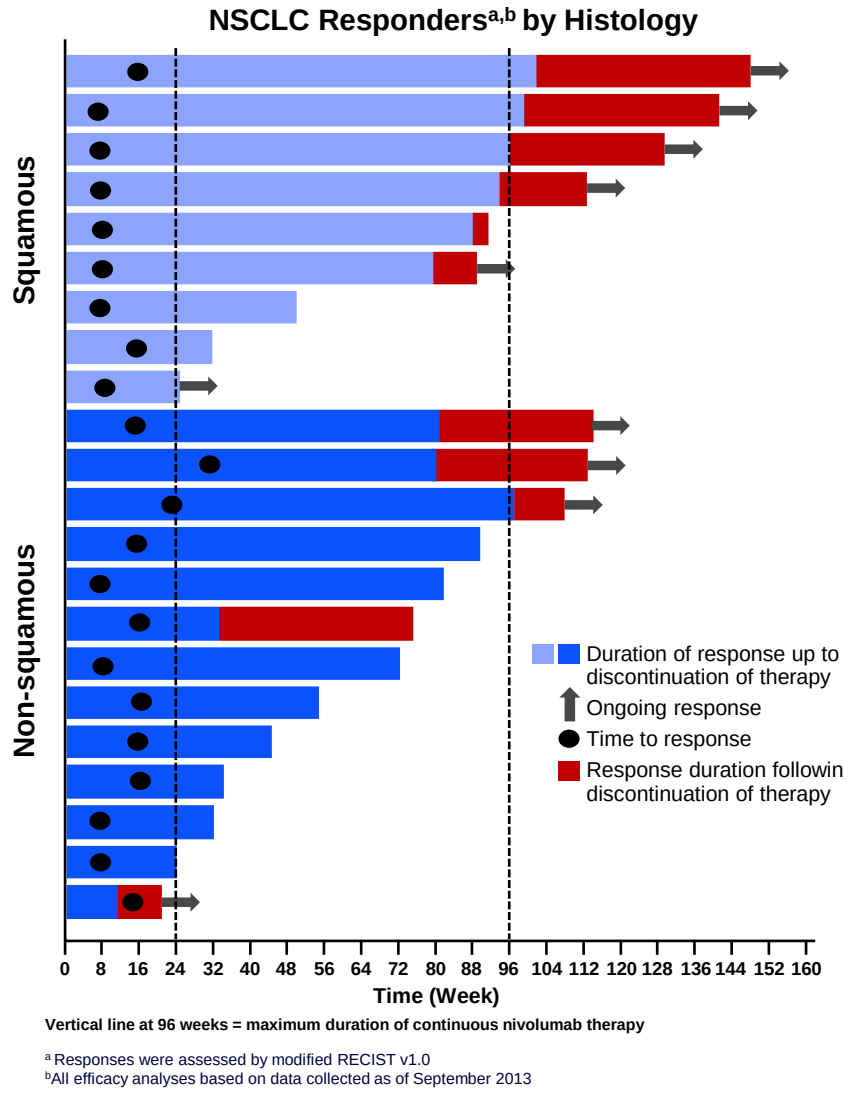
Pre/Post MDX 1106 (Dec / Feb ’10)

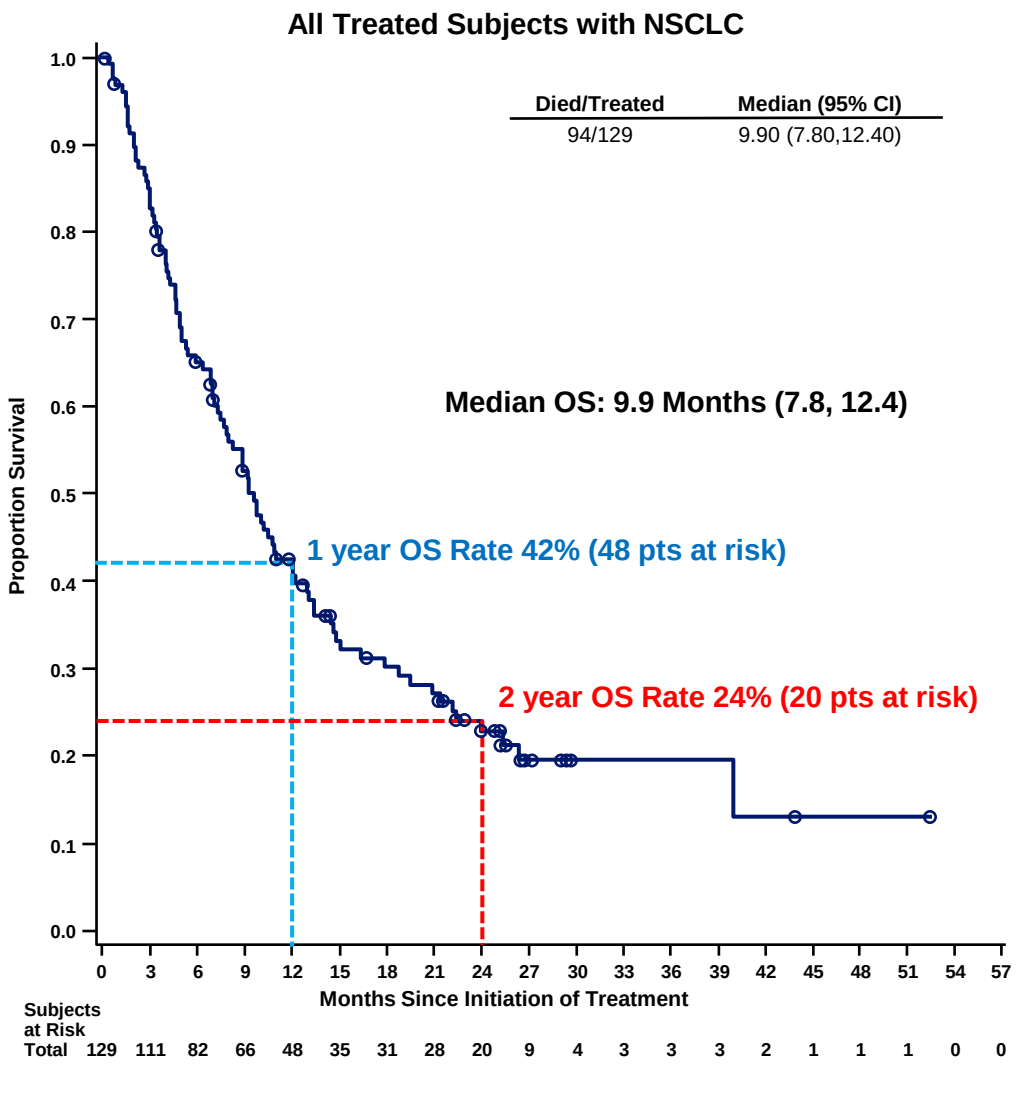




- 66 y/o ex smoker with KRAS mutant adenocarcinoma of the lung
- 5 prior treatments for Stage IV disease
- RUQ abdominal pain, anorexia and fatigue resolved within 2 months
- Duration of response: 10 months

Duration of Response and Overall Survival





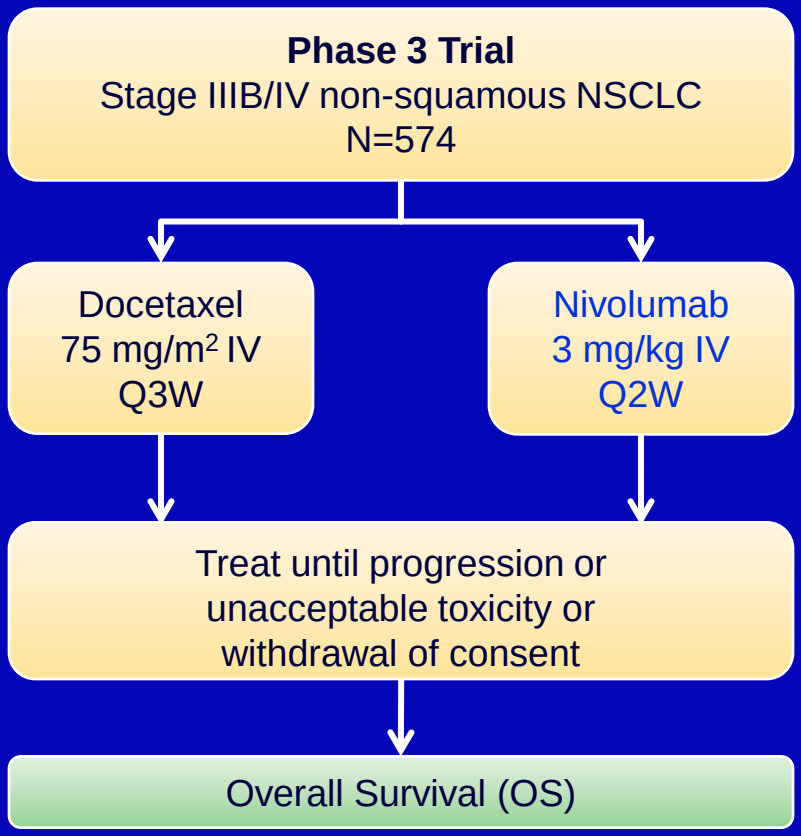
Drug-Related Select Adverse Events (≥1%) Occurring in NSCLC Patients (N=129) Treated with Nivolumab[a]

- No new safety signals emerging, with all patients now having ≥1 year of follow-up
- Select AE definition: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) with NSCLC had grade 3-4 pneumonitis of which 2 cases were fatal

Category	Treatment-related Select AE, % (n)	
	Any Grade % (n)	Grade 3-4 % (n)
Any treatment-related select AE	41 (53)	5 (6)
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pulmonary	7 (9)	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

[a]Safety data based on a March 2013 analysis

Phase 3 Study of Nivolumab Compared to Docetaxel in 2nd/3rd-Line Advanced/Metastatic Non-Squamous Cell NSCLC (CA209-057/NCT01673867)



Start Date: November 2012
Estimated Study Completion Date: November 2014
Estimated Primary Completion Date: November 2014
Status: Recruiting
Study Director: BMS

Primary Endpoints

- OS

Secondary Endpoints

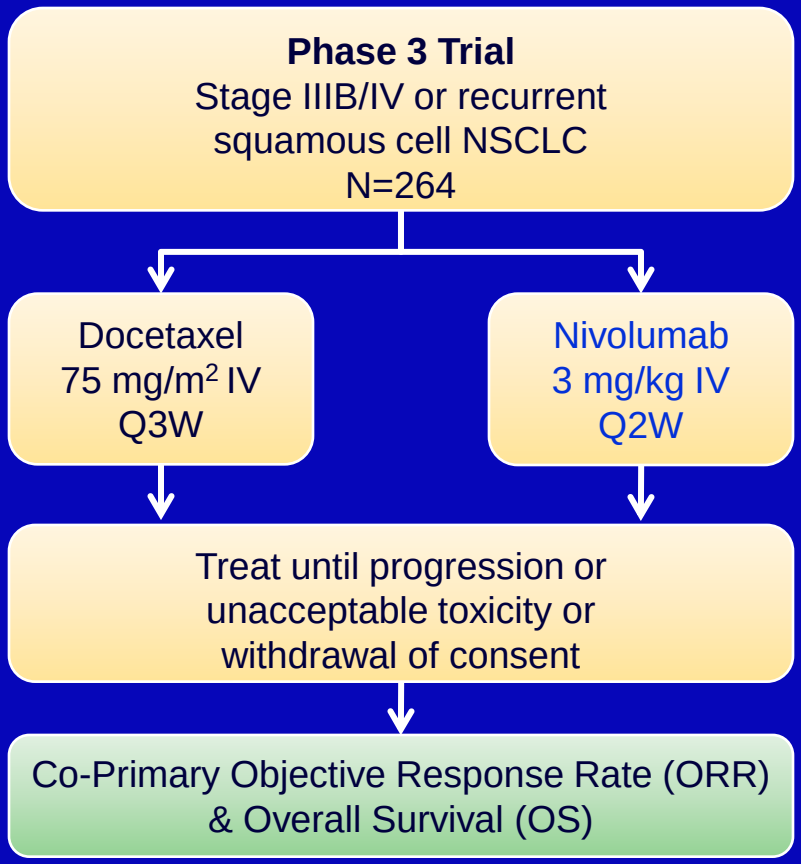
- PFS
- ORR
- QoL

Key Eligibility Criteria

- ≥ 18 years of age
- Stage IIIB/IV non-squamous NSCLC
- Prior Pt-containing chemotherapy (2nd-line) required: additional TKI therapy allowed (3rd-line)
- Patient may have received continuous or switch maintenance with pemetrexed, erlotinib or bevacizumab post Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation
- No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 or other antibody targeting T-cell co-stimulation or checkpoint pathways

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; Pt, Platinum; QoL, Quality of life; TKI, Tyrosine kinase inhibitor

Phase 3 Study of Nivolumab Compared to Docetaxel in 2nd-Line Advanced/Metastatic Squamous Cell NSCLC (CA209-017/NCT01642004)



Start Date: September 2012
Estimated Study Completion Date: August 2014
Estimated Primary Completion Date: August 2014
Status: Recruiting
Study Director: BMS

Primary Endpoints

- ORR
- OS

Secondary Endpoints

- PFS
- ORR and OS in PD-L1^{+} vs PD-L1^{-} subgroups
- Duration of OR
- Time to OR
- Proportion of patients exhibiting disease-related symptom progression per Lung Cancer Symptom Scale

Key Eligibility Criteria

- ≥ 18 years of age
- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

ECOG PS, Eastern Cooperative Oncology Group Performance Status; OR, objective response; PFS, progression-free survival; Pt, platinum; RT, radiotherapy

International Association for the Study of Lung Cancer

IASLC

IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

2416: PRELIMINARY CLINICAL SAFETY AND ACTIVITY OF MK-3475 MONOTHERAPY FOR THE TREATMENT OF PREVIOUSLY TREATED PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

Edward B. Garon,[1] Ani Balmanoukian,[2] Omid Hamid,[2] Rina Hui,[3] Leena Gandhi,[4] Natasha Leighl,[5] Matthew Gubens,[6] Jonathan W. Goldman,[1] Gregory M. Lubiniecki,[7] Kenneth Emancipator,[7] Marisa Dolled-Filhart,[7] Jared Lunceford,[7] Kevin Gergich,[7] Naiyer Rizvi[8]

[1]David Geffen School of Medicine at UCLA, Los Angeles, USA; [2]The Angeles Clinic, Los Angeles, USA; [3]Crown Princess Mary Cancer Centre, Westmead, Australia; [4]Dana Farber Cancer Institute, Boston, USA; [5]Princess Margaret Hospital, Toronto, Canada; [6]University of California San Francisco, San Francisco, USA; [7]Merck and Co, Inc, Whitehouse Station, USA; [8]Memorial Sloan-Kettering Cancer Center, New York, USA

MK-3475 (anti PD-1)

Drug-Related Adverse Events With Incidence ≥5% (N = 38)

Adverse event	All Grades, n (%)	Grades 3-5, n (%)
Rash	8 (21)	0 (0)
Pruritis	7 (18)	0 (0)
Fatigue	6 (16)	0 (0)
Diarrhoea	5 (13)	0 (0)
Arthralgia	4 (11)	0 (0)
Back pain	2 (5)	0 (0)
Cough	2 (5)	0 (0)
Decreased appetite	2 (5)	0 (0)

- 20 patients (53%) experienced ≥1 drug-related AE of any grade
- 1 instance of each of the following drug-related AEs of interest was observed: hyperthyroidism (grade 2), hypothyroidism (grade 2), pneumonitis (grade 2), and pulmonary oedema (grade 3)
- No patient experienced treatment-related death

MK-3475 (anti PD-1)

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—

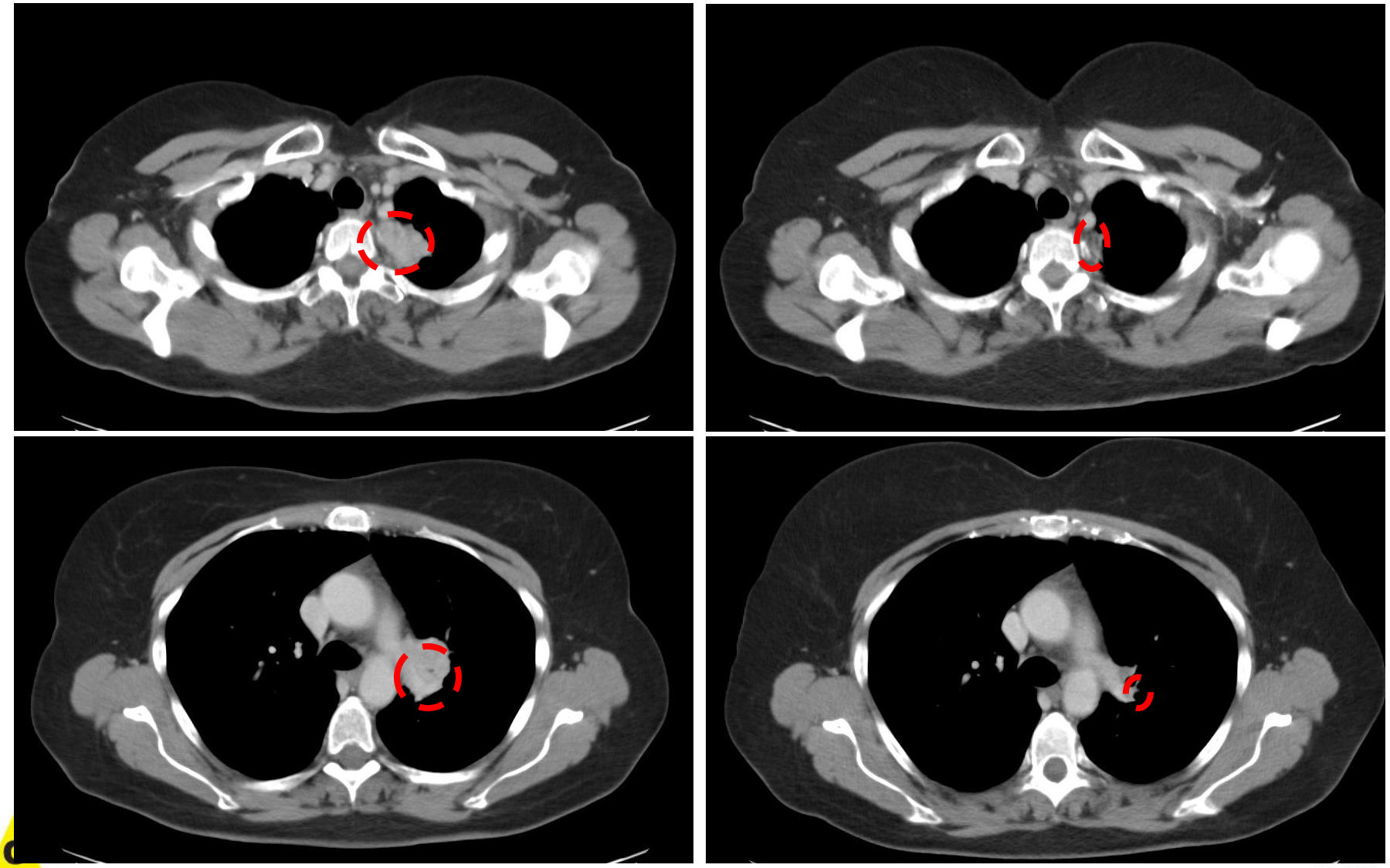
*Response rate per RECIST v1.1 is based on those patients who had ≥1 measurable lesion at baseline per central review. All responses were confirmed except for 2. One patient withdrew consent for treatment, unrelated to toxicity, after the first imaging assessment, and 1 patient had a confirmatory scan of PR at day 27.

Illustration of Response

56 year old female with large cell carcinoma who began responding by Week 12.

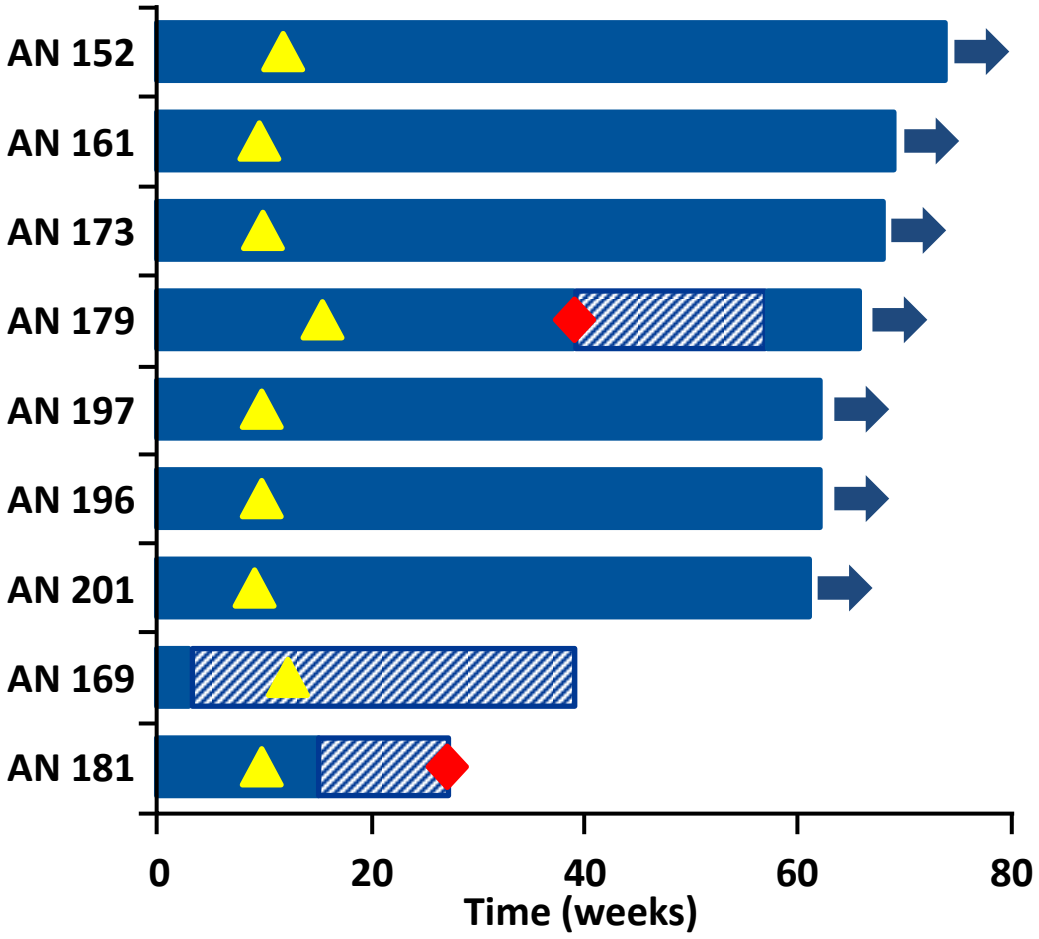
Baseline

After 9 months of therapy



MK-3475 (anti PD-1)

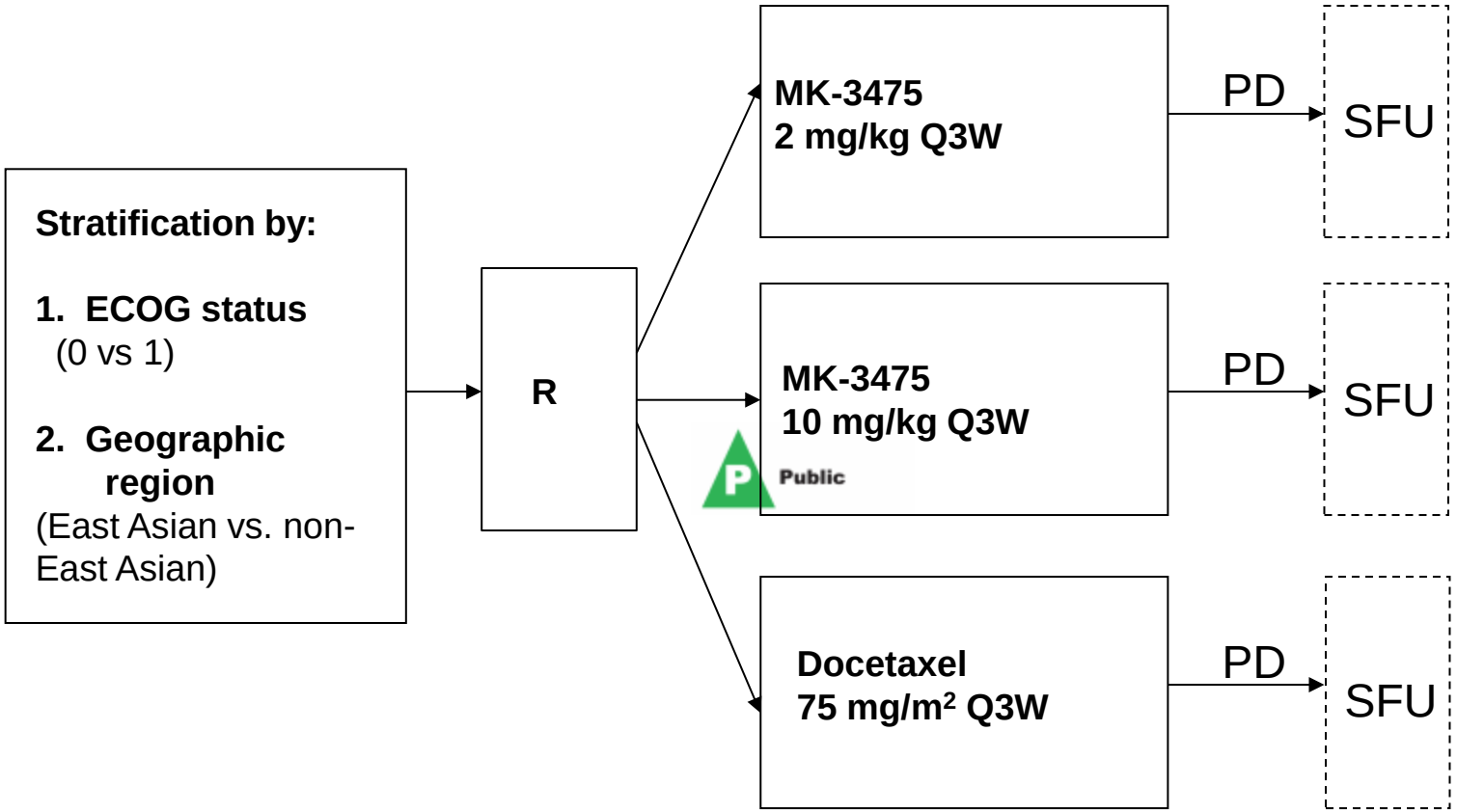
MK-3475 Responders Have Prolonged Duration of Response



- 7/9 responders on treatment at time of analysis
- Median PFS of responders not reached at 62 weeks
- AN 179: stopped MK for local therapy to brain metastasis; MK resumed based on continued systemic response
- AN 169: after 1 dose, MK stopped for unrelated grade 4 hypercalcemia; response maintained without further treatment; per protocol, follow-up ceased at 39 weeks

On therapy
Confirmed response
Off therapy
Progression
Therapy continuing

MK-3475 PN010-06: Previously-Treated NSCLC



R = Randomization PD = Progressive Disease SFU = Survival Follow-up

International Association for the Study of Lung Cancer

IASLC

IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

MO19.09: Molecular Correlates of PD-L1 Status and Predictive Biomarkers in Patients With Non-Small Cell Lung Cancer (NSCLC) Treated With the Anti-PDL1 Antibody MPDL3280A

Scott N. Gettinger[1], Marcin Kowanetz[2], Jean-Charles Soria[3], Leena Gandhi[4], Leora Horn[5], Michael S. Gordon[6], David R. Spigel[7], Cristina Cruz[8], Paul Conkling[9], Scott Antonia[10], Hartmut Koeppen[2], Yuanyuan Xiao[2], Ahmad Mokatrin[2], Xiaodong Shen[2], Gregg Fine[2], Roy S. Herbst[1]

[1]Yale School of Medicine, New Haven, USA; [2]Genentech Inc., South San Francisco, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Vanderbilt University Medical Center, Nashville, USA; [6]Pinnacle Oncology Hematology, Scottsdale, USA; [7]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, USA; [8]Vall d'Hebron University Hospital, Barcelona; [9]Virginia Oncology Associates, US Oncology, Norfolk, USA; [10]Moffitt Cancer Center, Tampa, USA

Treatment-Related Adverse Events – NSCLC

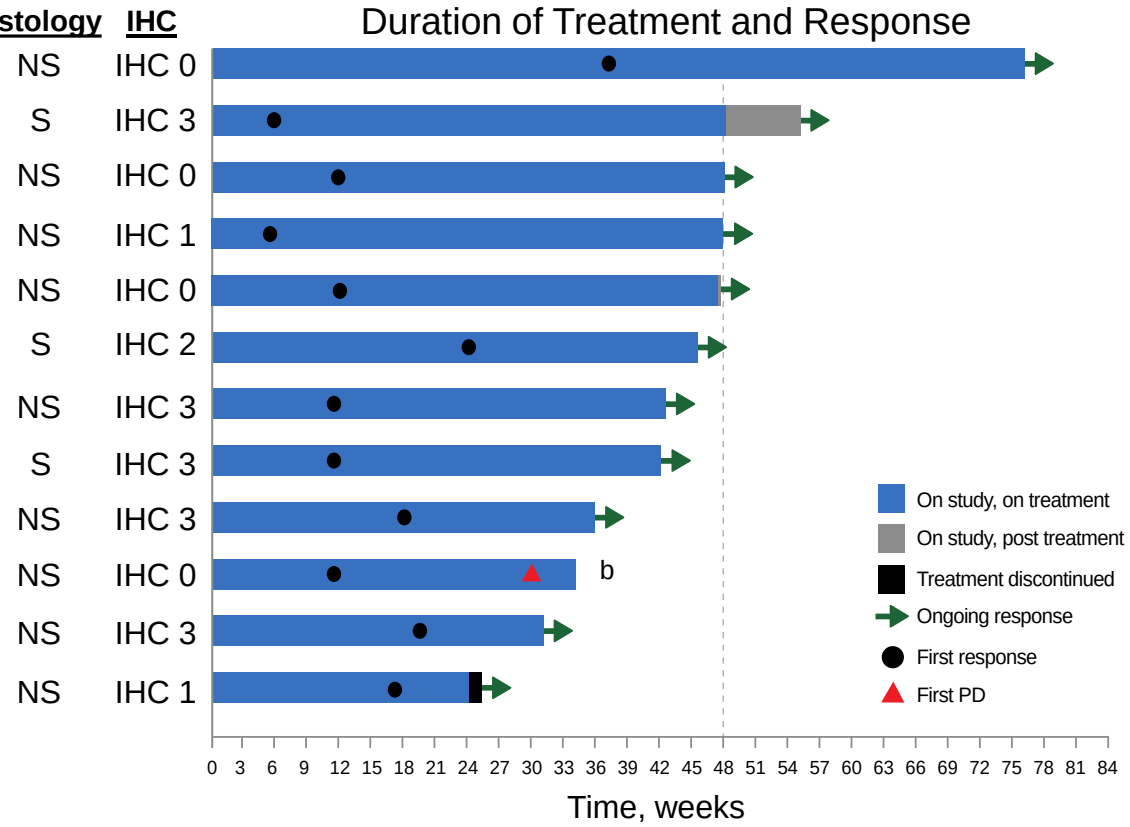
Adverse Event	Treatment-Related, n (%) n = 85	
	Any Grade[a]	**Grade 3-4[b]**
Any AE	56 (66%)	9 (11%)
Fatigue	17 (20%)	2 (2%)
Nausea	12 (14%)	1 (1%)
Decreased appetite	10 (12%)	0
Dyspnea	8 (9%)	1 (1%)
Diarrhea	7 (8%)	0
Asthenia	6 (7%)	0
Headache	6 (7%)	0
Rash	6 (7%)	0
Pyrexia	5 (6%)	0
Vomiting	5 (6%)	1 (1%)
Upper respiratory tract infection	4 (5%)	0

- The majority of AEs were Grade 1-2 and did not require intervention
- No maximum tolerated dose or dose-limiting toxicities
- No Grade 3-5 pneumonitis observed
- One treatment-related death (cardio-respiratory arrest) in a patient with sinus thrombosis and large tumor mass invading the heart at baseline
- Immune-related Grade 3-4 AE observed in 1 patient with large cell neuroendocrine NSCLC (diabetes mellitus, 1%)

[a] AEs occurring in ≥ 5% of patients.
[b] Grade 3-4 treatment-related AEs listed include treatment-related AEs for which the any grade occurrence was ≥ 5% of patients.
Data cutoff Apr 30, 2013.

MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status, Histology and Duration of Treatment and Response – NSCLC

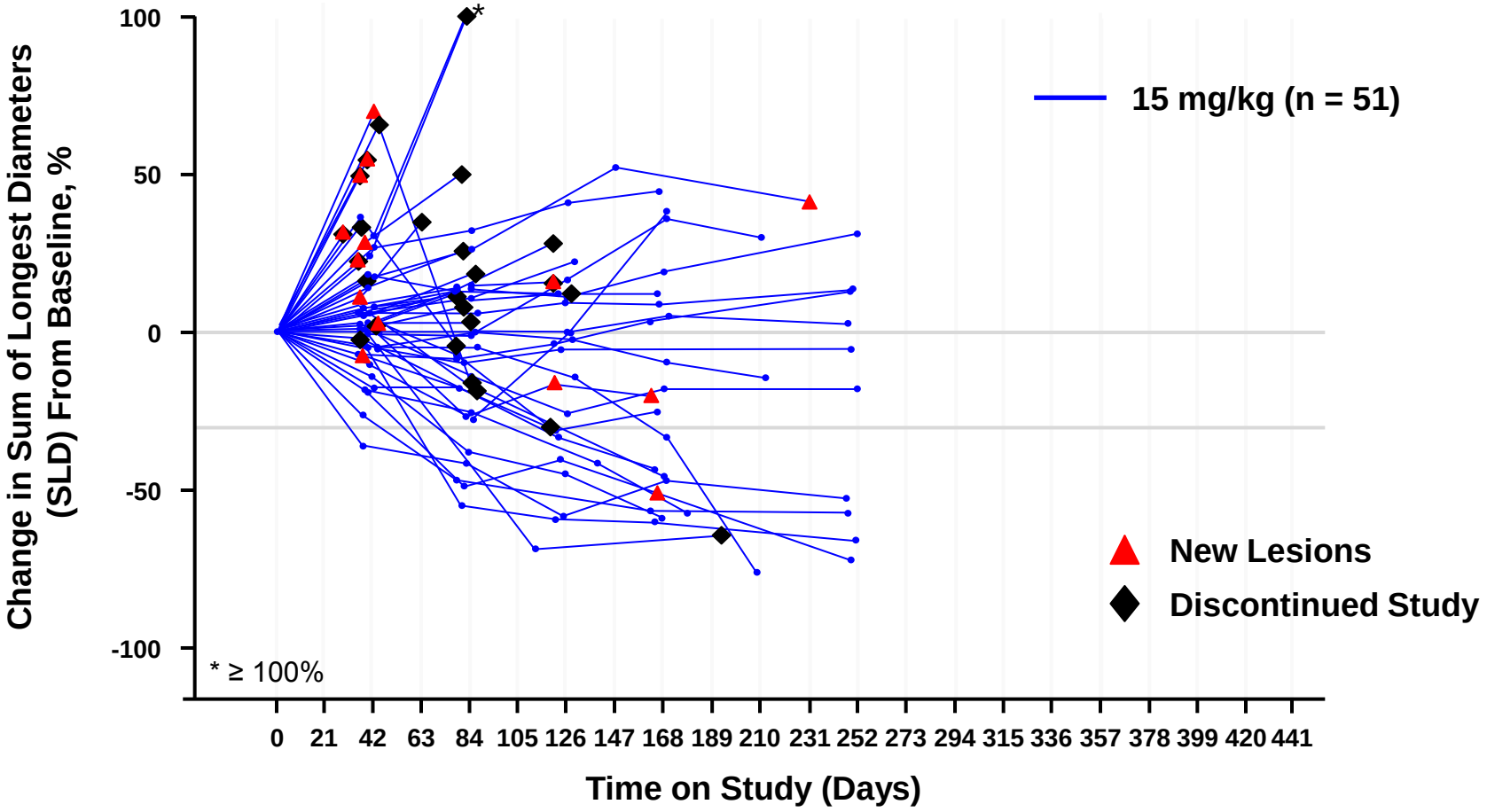
PD-L1 Status (n = 53)	ORR[a]	PD Rate
IHC 3 (n = 6)	**83%** (5/6)	**17%** (1/6)
IHC 2 and 3 (n = 13)	**46%** (6/13)	**23%** (3/13)
IHC 1/2/3 (n = 26)	**31%** (8/26)	**38%** (10/26)
All patients (IHC 0/1/2/3 and 7 patients with diagnostic unknown; n = 53)	**23%** (12/53)	**40%** (21/53)



[a] ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.
[b] Patient experiencing ongoing benefit per investigator.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff Apr 30, 2013.

NS, nonsquamous.
S, squamous.

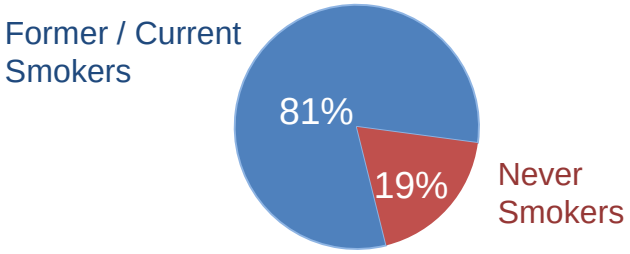
MPDL3280A Phase Ia: Tumor Burden Over Time (All)



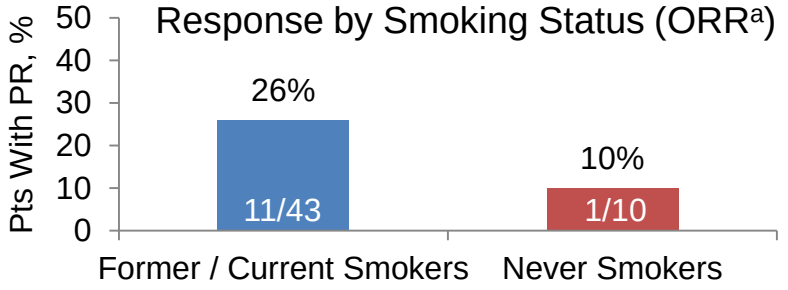
Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

MPDL3280A Phase Ia: Response by Smoking and Mutational Status

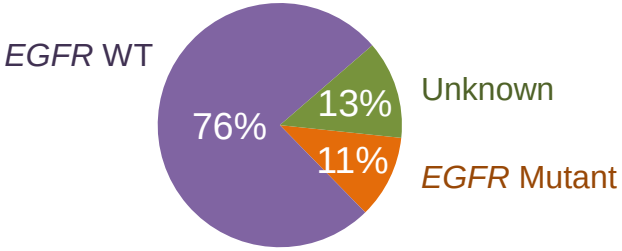
Smoking Status (NSCLC; n = 53)



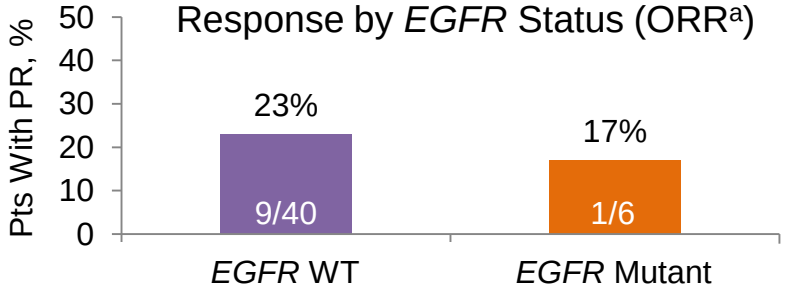
Response by Smoking Status (ORR[a])



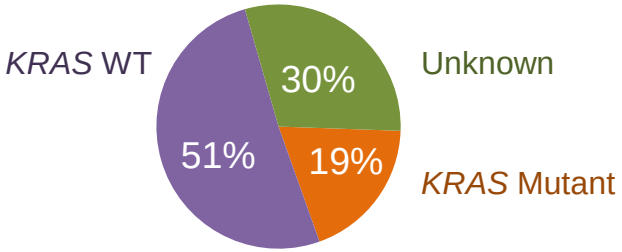
EGFR Status (NSCLC; n = 53)



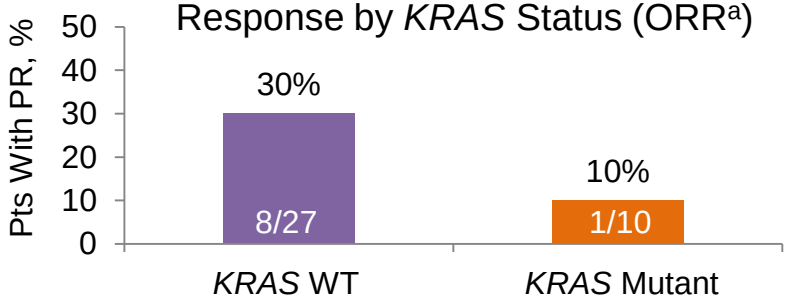
Response by *EGFR* Status (ORR[a])



KRAS Status (NSCLC; n = 53)



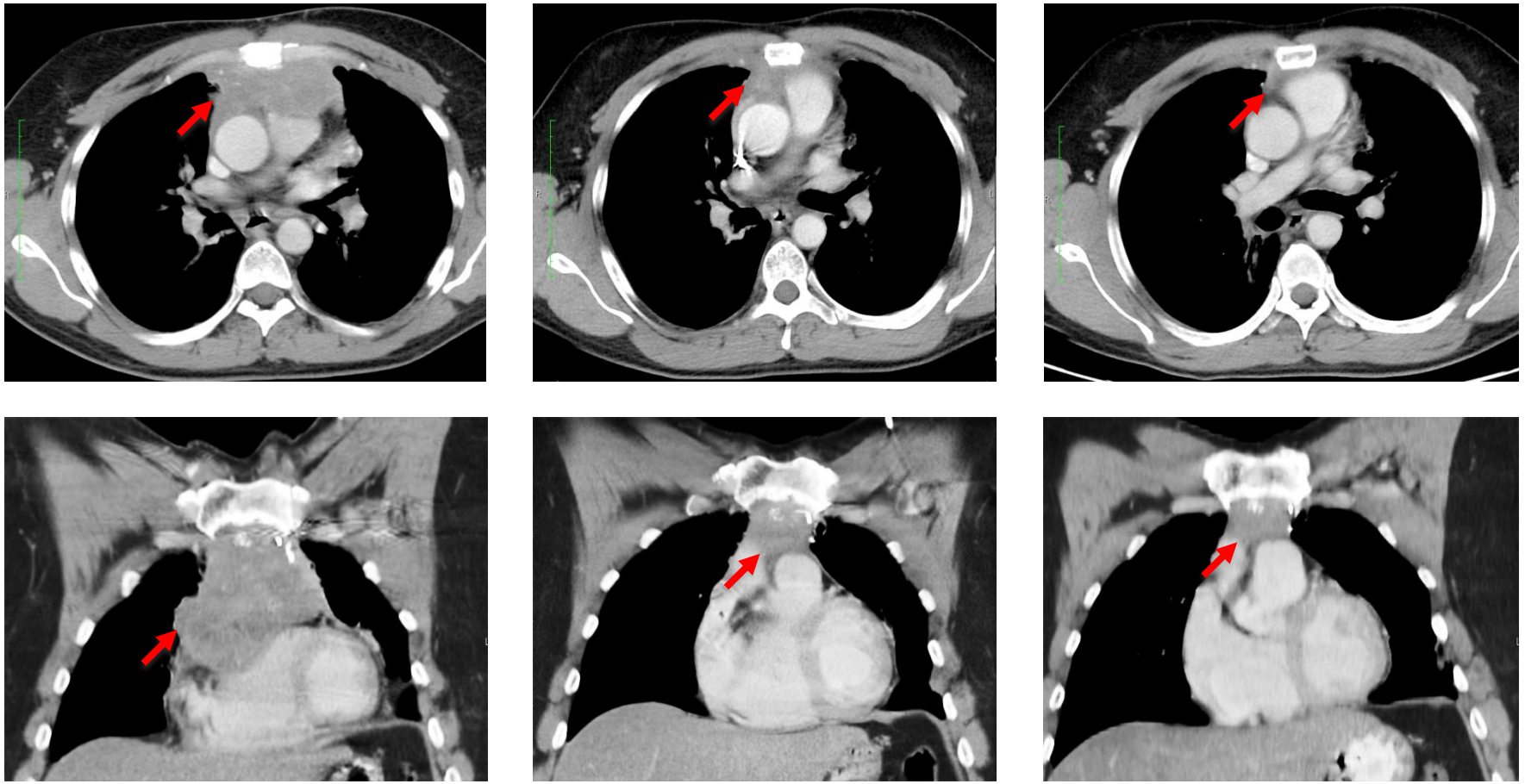
Response by *KRAS* Status (ORR[a])



[a] ORR includes investigator-assessed u/c PR by RECIST 1.1. Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff: Apr 30, 2013.

Clinical Activity of MPDL3280A in an NSCLC Patient

Baseline | **Post C6 (Week 18)** | **Post C12 (Week 36)**



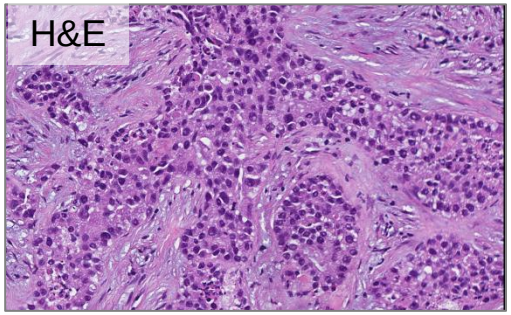
44-year-old male with adenocarcinoma NSCLC, s/p radiotherapy, gemcitabine + cisplatin, temozolomide + docetaxel, pemetrexed, bevacizumab, CDX-1401, PD-L1 negative

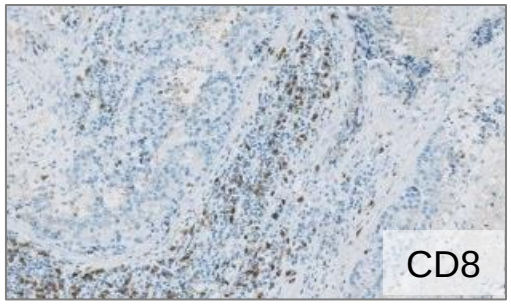
Images include data from after Feb 1, 2013.
Yale University (Gettinger/Herbst).

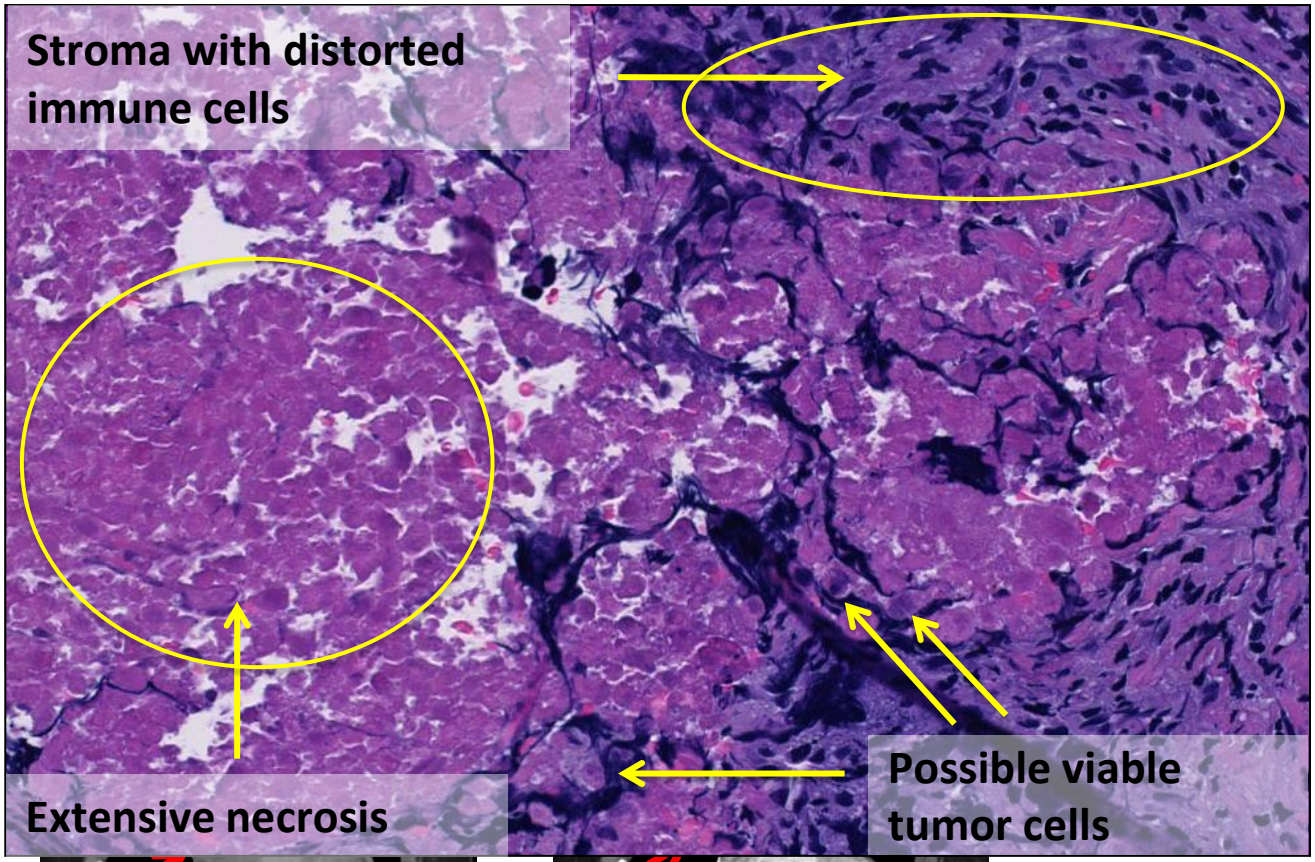
PRESENTED AT: ASCO Annual '13 Meeting

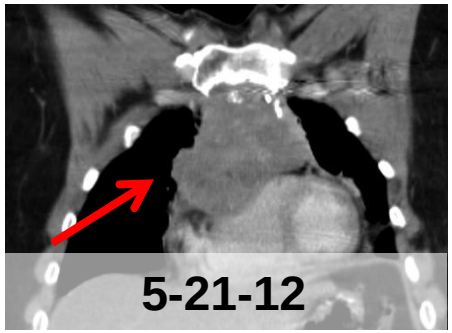
Correlation of Radiographic and Pathologic Response to MPDL3280A

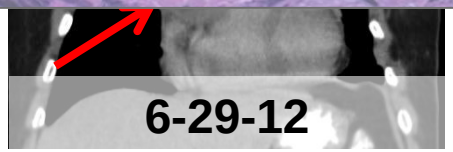
Baseline

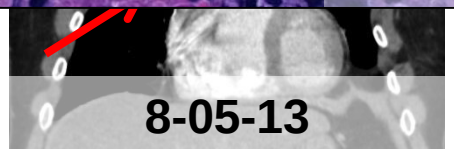












46 y.o. male, former smoker (20 PYH); *EGFR*–, *ALK*– and *RAS*–negative; PD-L1 IHC 1; 6 prior regimens

MEDI4736, an anti-PD-L1 antibody with engineered Fc domain: preclinical evaluation and early clinical results from a phase I study in patients with advanced solid tumors

Samir N. Khleif,[1] Jose Lutzky,[2] Neil H. Segal,[3] Scott Antonia,[4] Andy Blake-Haskins,[5] Ross Stewart,[6] Paul Robbins,[5] Xia Li,[5] Aiman Shalabi,[5] Ramy Ibrahim,[5] Jedd D. Wolchok[3]

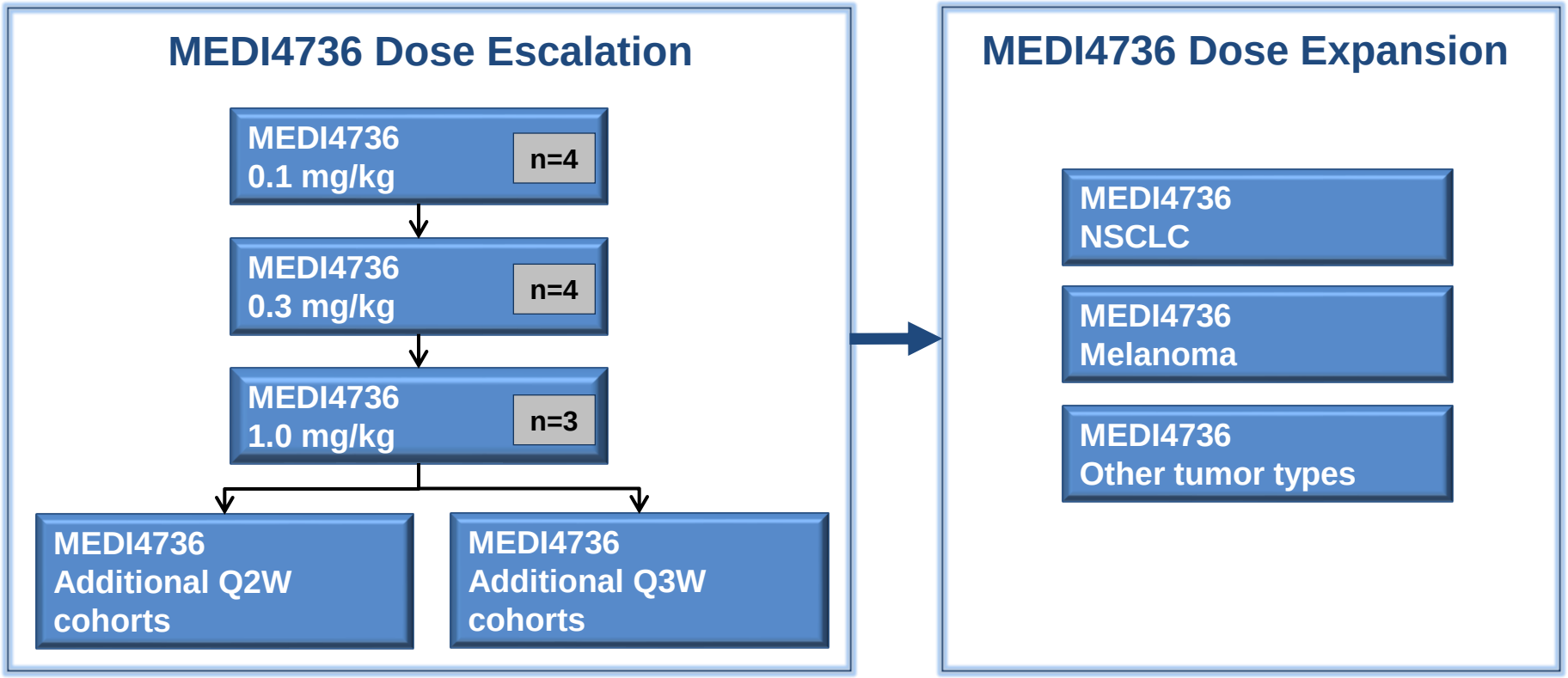
[1]Georgia Regents University Cancer Center, Augusta, GA; [2]Mount Sinai Medical Center, Miami Beach, FL; [3]Memorial Sloan-Kettering Cancer Center, New York, NY; [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [5]MedImmune, Gaithersburg, MD; [6]MedImmune, Cambridge, UK

ESMO • Amsterdam • 27 Sep–1 Oct 2013

WWW.ECCO-ORG.EU

Study Design

- Dose escalation and expansion study is ongoing
  - Standard 3+3 design
  - Evaluating 2 dosing schedules (Q2W and Q3W)



NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; Q3W, every 3 weeks.

Treatment-Related AEs

Adverse Event Term	By Dose Level, n			Total, n (%)	
	0.1 mg/kg (n=4)	0.3 mg/kg (n=4)	1.0 mg/kg (n=3)	Any Grade (N=11)	Grade 3/4 (N=11)
Diarrhea	1	1	0	2 (18.2)	0
Vomiting	1	1	0	2 (18.2)	0
Dizziness	0	1	1	2 (18.2)	0
Nausea	0	1	0	1 (9.1)	0
Fatigue	1	0	0	1 (9.1)	0
Infusion reaction	1	0	0	1 (9.1)	0
Pruritus	0	0	1	1 (9.1)	0
Rash	1	0	0	1 (9.1)	0

- No treatment-related grade 3/4 AEs or deaths

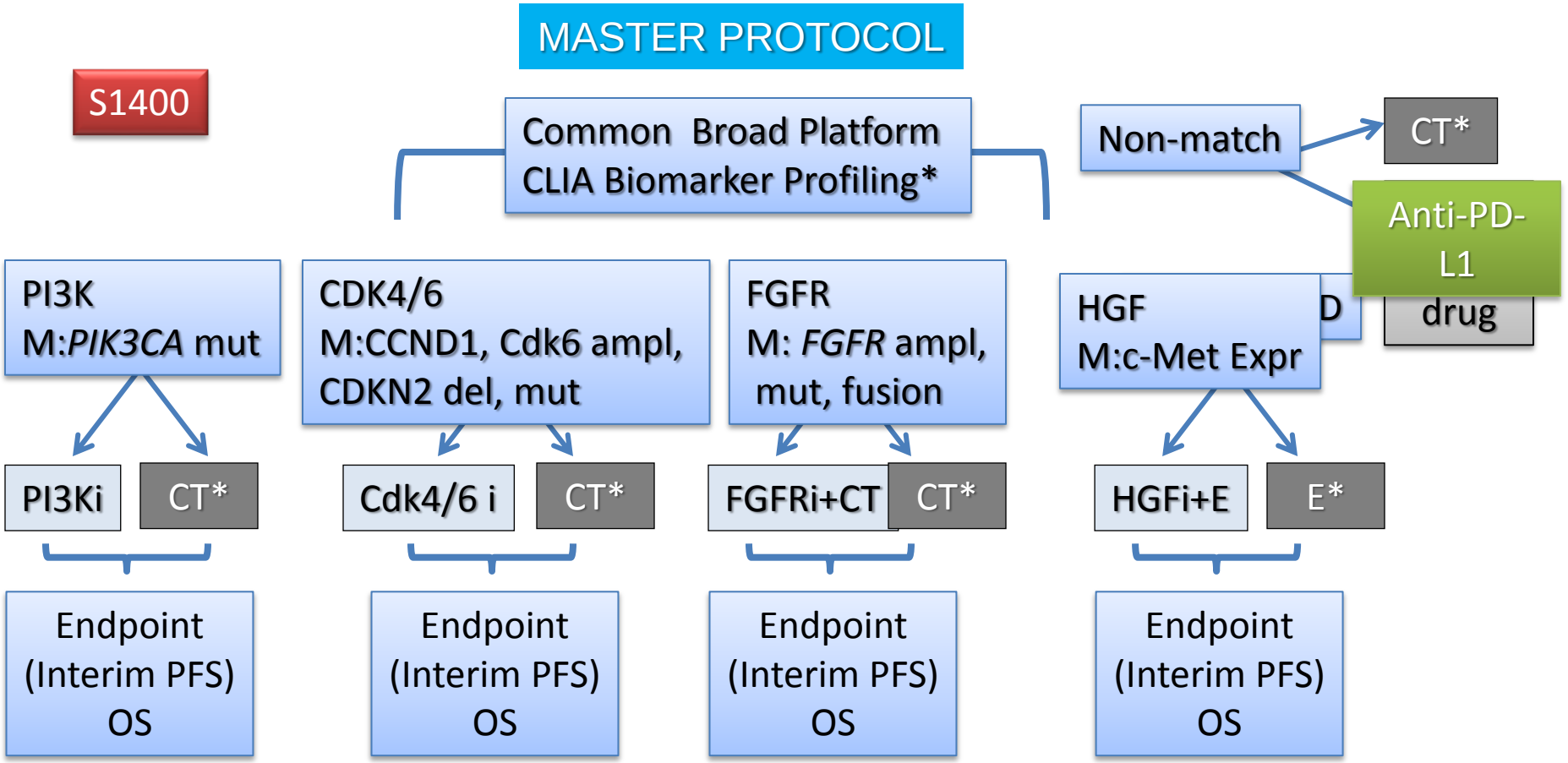
AE, adverse event.
Data as of 18 August 2013.

Clinical Activity

MEDI4736 Dose Level	Patient	Tumor Type	Number of Doses Received	Best Response (irRC)	% Change in Tumor Burden
0.1 mg/kg Q2W	1056201004*	NSCLC	22+	SD	-47.6%
0.1 mg/kg Q2W	1056201006	NSCLC	11	PD	+50.3%
0.1 mg/kg Q2W	1245501002	NSCLC	3	NE	NE
0.1 mg/kg Q2W	1245501003	Melanoma	8	PD	+55.8%
0.3 mg/kg Q2W	1094301002	CRC	5	PD	+>100%
0.3 mg/kg Q2W	1245501006	NSCLC	15+	uPR	-60.1%
0.3 mg/kg Q2W	1351901002	NSCLC	1	NE	NE
0.3 mg/kg Q2W	1351901004	NSCLC	14+	PR	-71.2%
1.0 mg/kg Q2W	1056201009	NSCLC	11+	SD	-42.2%
1.0 mg/kg Q2W	1094301003	NSCLC	10+	PR	-83.1%
1.0 mg/kg Q2W	1351901007	Melanoma	10+	PR	-69.1%

*Patient received prophylactic steroids prior to dosing.

CRC, colorectal cancer; irRC, immune-related response criteria; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response NE, not evaluable; Q2W, every 2 weeks; SD, stable disease; uPR, unconfirmed partial response.
Data as of 18 August 2013.



TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

*Archival FFPE tumor, fresh CNB if needed

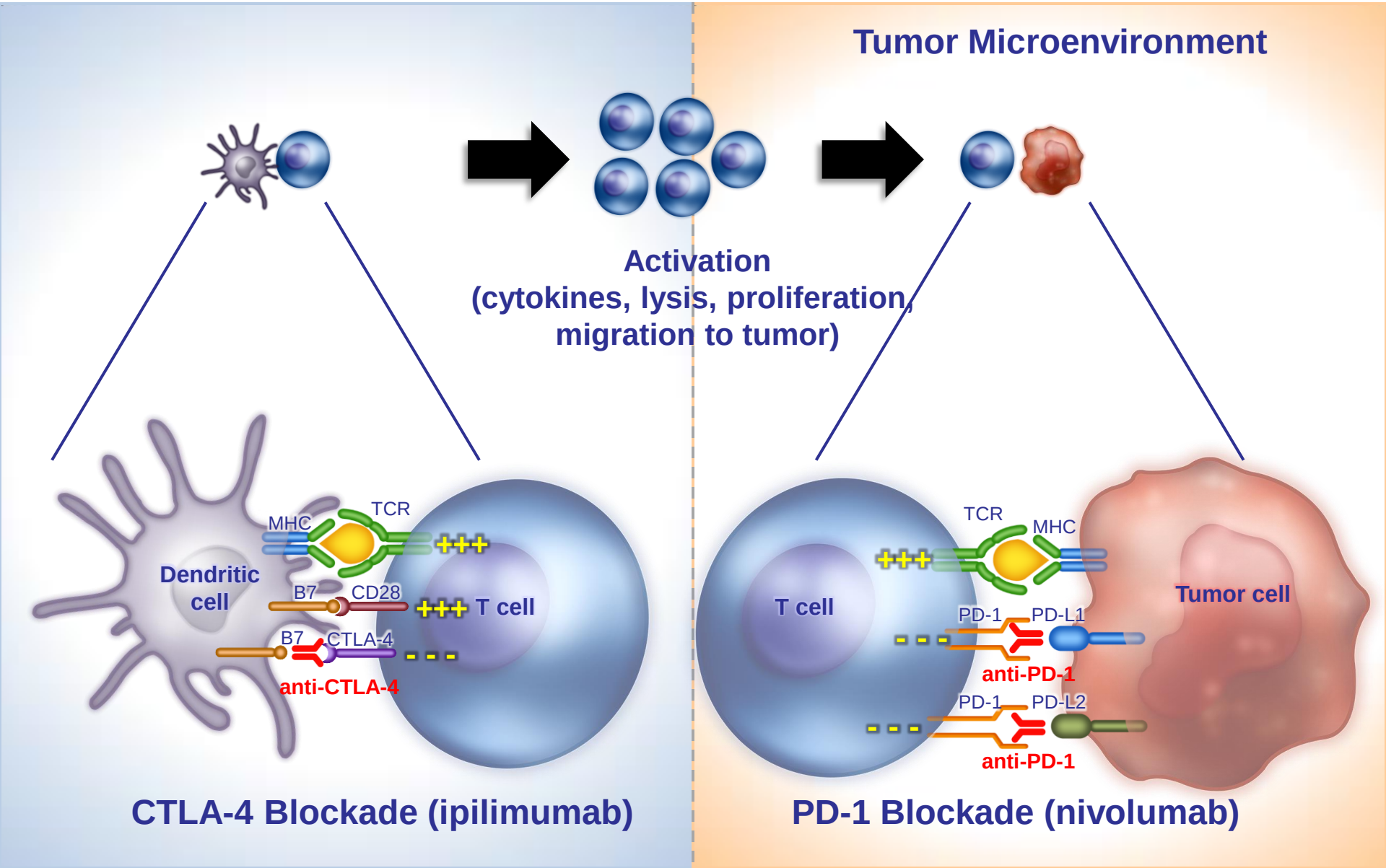
S1400 Master Protocol
Unique Private-Public Partnerships with the NCTN

PD1 Axis Blockade in the Clinic

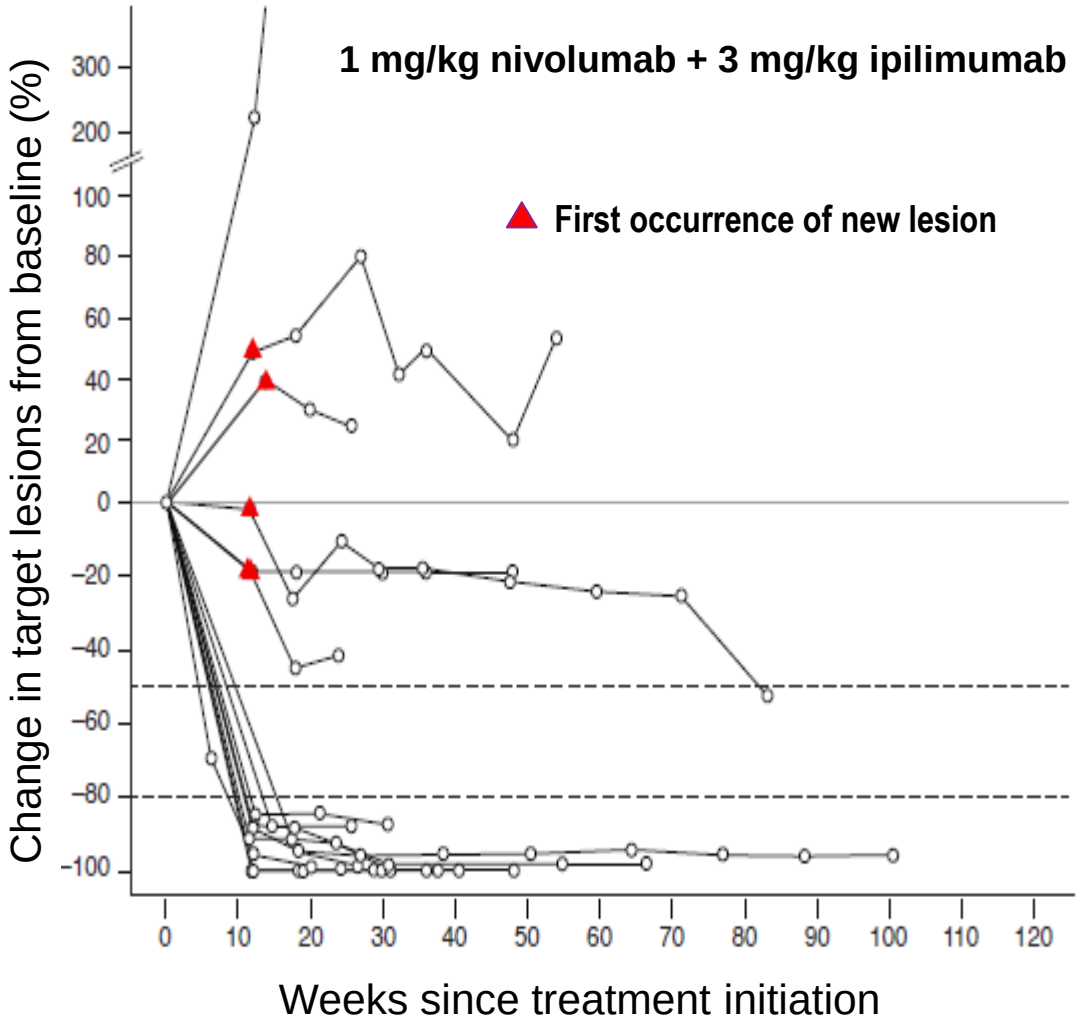
Agent	N	RR (%)	DOR (wk)	MS (mos)	1 yr (%)	2 yr (%)
PD1 Antibodies						
Nivolumab	129	17	74 wk	9.6 m	42	24
MK-3475	38 (MS) 33 (OR)	21 (n=33)		51 wk		
PDL1 Antibodies						
MPDL3280a	53	23				
BMS-936558	49	10				
MEDI-4736	6	3/6				
	270	18				

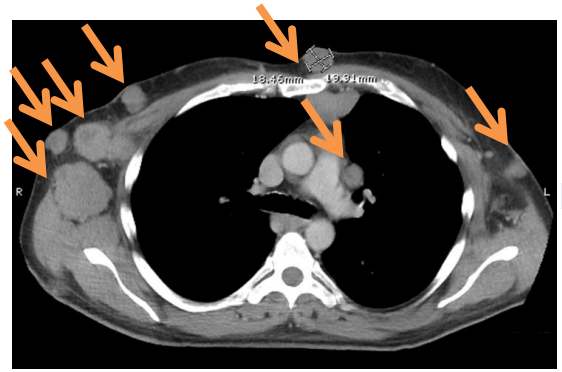
- Chemo-refractory population
- Similar response in squamous versus non-squamous
- RR does not take into account atypical immune-related responses
- Generally better tolerated than standard systemic therapies for NSCLC

Blocking CTLA-4 and PD-1

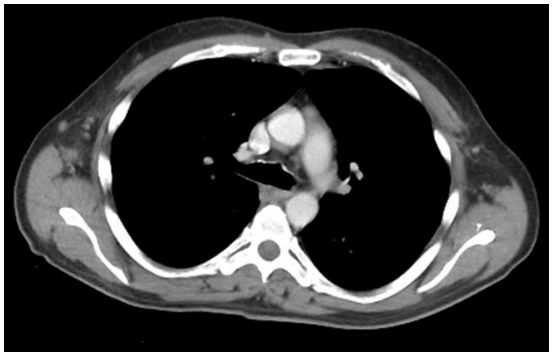


Rapid and Durable Changes in Target Lesions



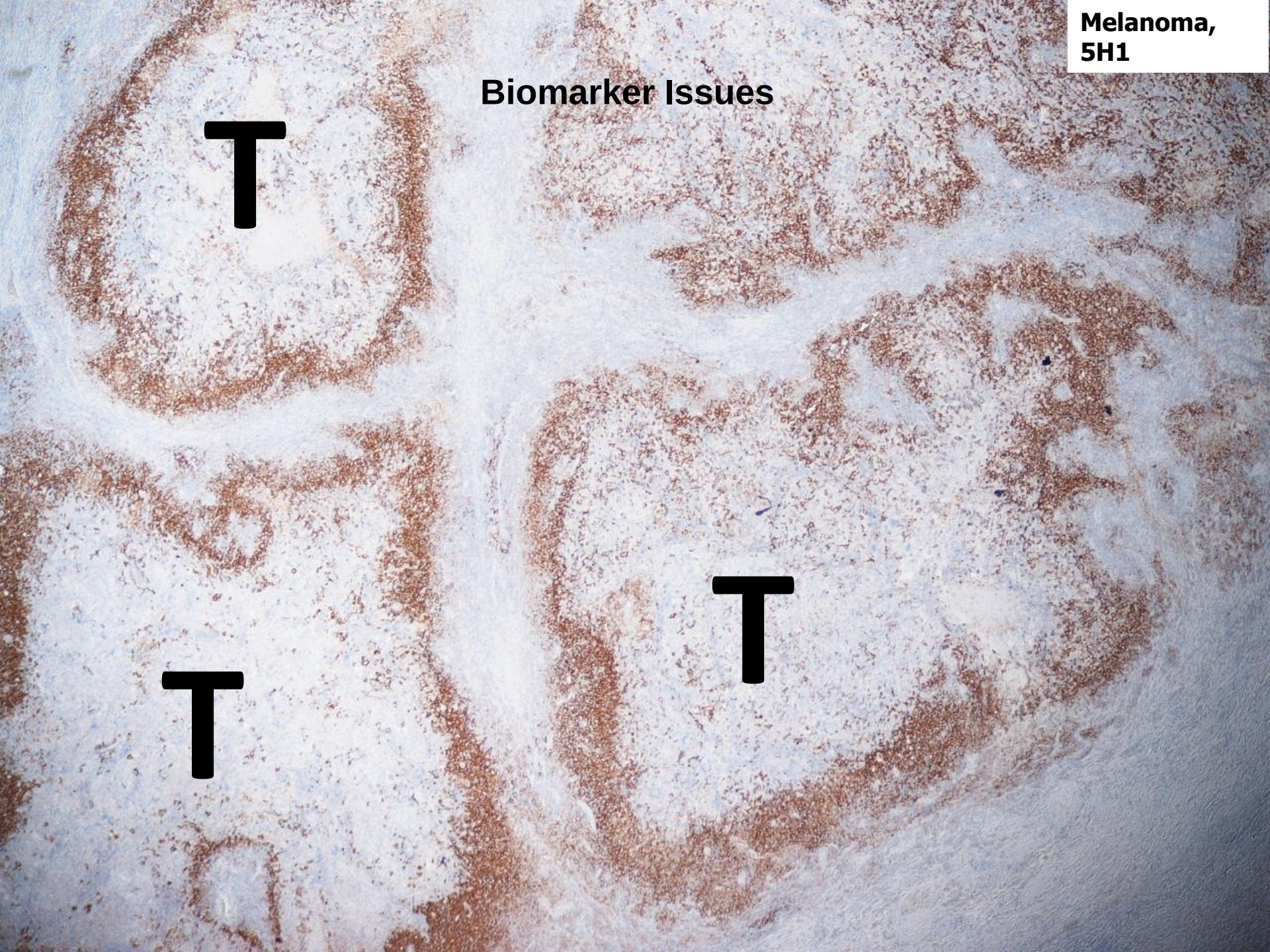


Pre-treatment

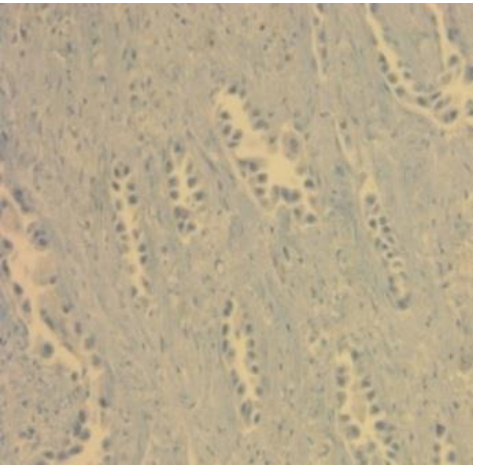
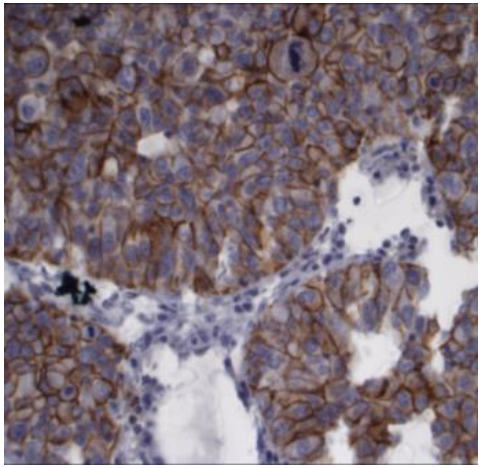
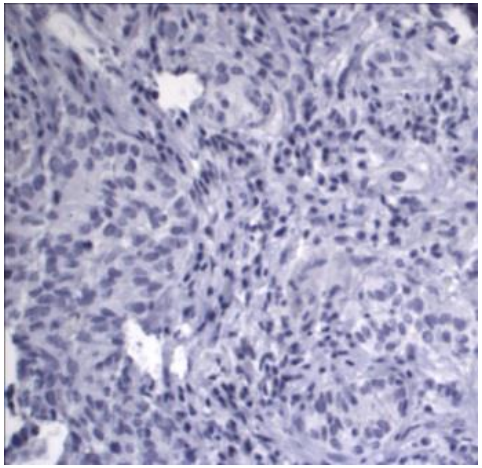
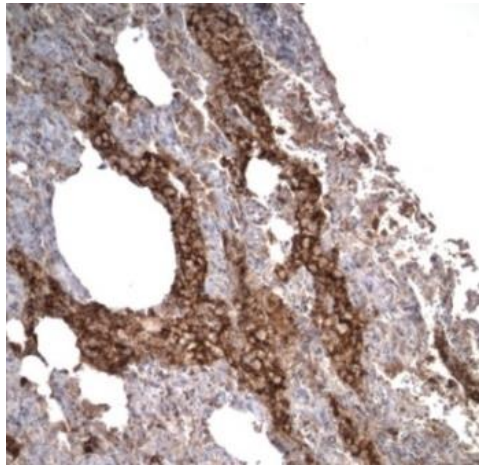


12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

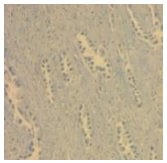

Melanoma,
5H1
Biomarker Issues
T
T
T

PD-L1 expression pattern in 457 lung cancer

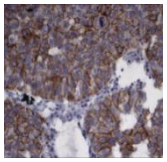
B7-H1-TIL-	B7-H1+TIL+	B7-H1-TIL+	B7-H1+TIL-
			
45%	17%	26%	12%

Velcheti et al, Lab. Invest. 2013

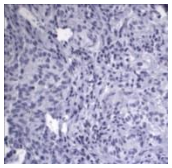
Implications of immune heterogeneity in TME for future combination therapy



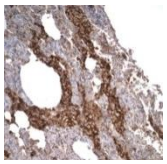
TIL-/PD-L1- (lack of inflammation): local radiation, anti-CTLA-4, chemoattraction, cancer vaccine, adoptive T cell therapy



TIL+/PD-L1+ (adaptive resistance): α-PD-1, α-PD-L1, both



TIL+/PD-L1- (immune tolerance): blockade of other inhibitors: LAG-3, BTLA, TIM-3, PD-1H etc.



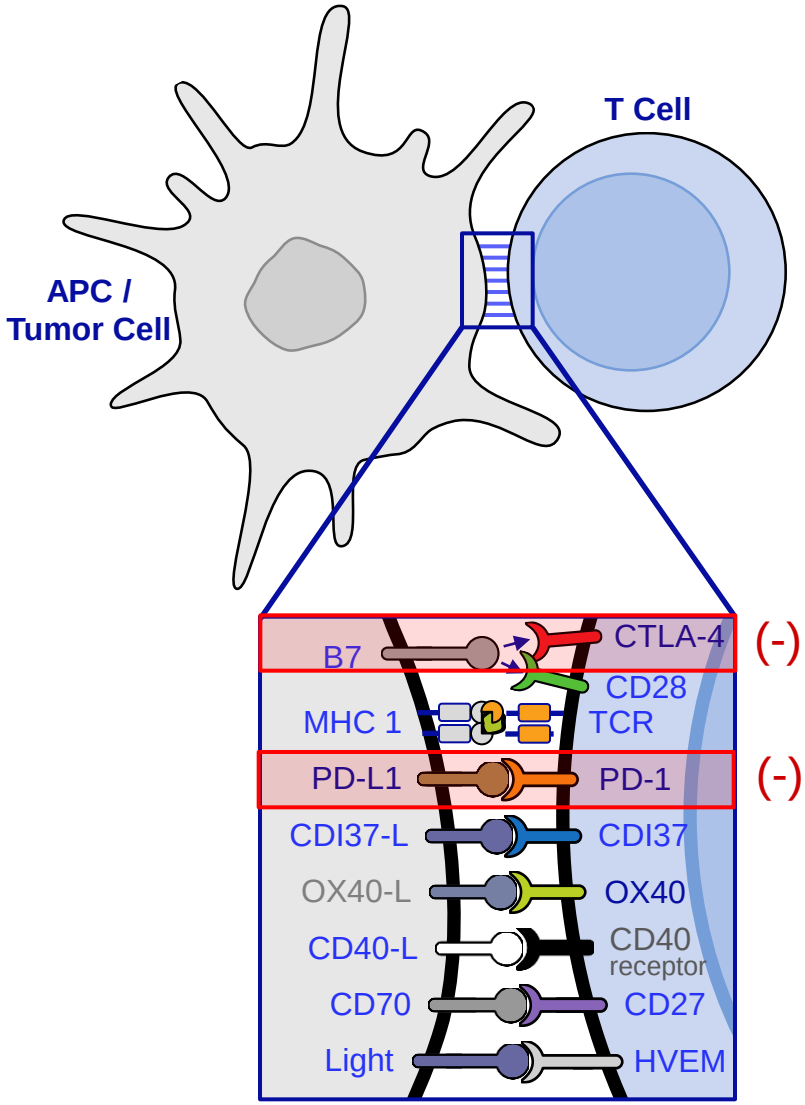
TIL-/PD-L1+ (innate resistance): EGFR inhibitor, PI3K inhibitors

Yale Rebiopsy Program

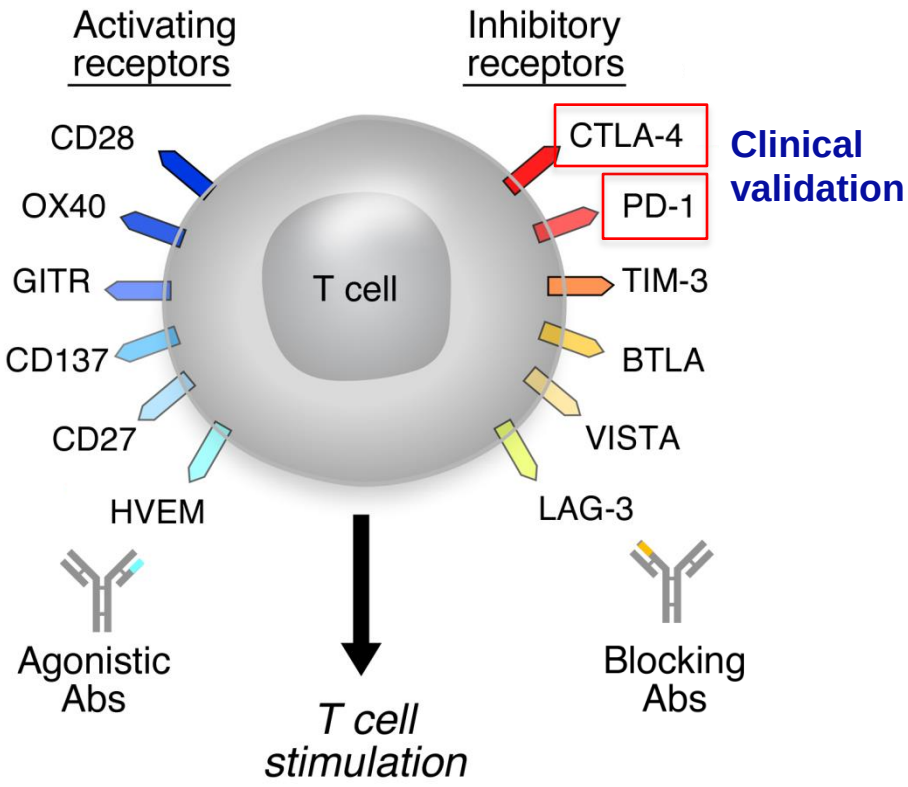
NCT number	Trial short name	Phase	Patients with Pathology Screening (n)	Patients Enrolled (n)	1st Patient Enrolled Date	Closed to Accrual Date
NCT00730639	BMS CA209-003[a]	I	n/a	38	11/11/08	1/12/12
NCT01375842	PCD4989g[b]	I	79	20	5/7/12	n/a
NCT01846416	Genentech FIR[c]	II	38	5	10/18/13	n/a
NCT01295827	Merck 001[d]	I	47	17	8/1/13	n/a
NCT01905657	Merck 010[e]	II/III	6	1	1/15/14	n/a
NCT01454102	BMS CA209-012[f]	I	n/a	45	6/22/12	n/a
NCT01642004	BMS CA209-017[g]	III	n/a	3	3/1/13	11/8/13
NCT01642004	BMS CA209-057[h]	III	n/a	8	4/26/13	11/8/13
NCT02000947	MedID4190C00006[i]	Ib	n/a	1	1/9/14	n/a
NCT01772004	EMD Serrono[j*]					
Not yet listed	Genentech BIRCH[k*]					
NCT01577745	MedI CD-ON-MEDI0639-1078[l*]					
Not yet listed	MedI4736-1161[m*]					

T cell activity is highly controlled – Need to respond against pathogens & cancer but not to our normal cells

Balance between inhibitory and stimulatory receptors determines T cell response



T cell targets for modulating activity



Mellman et. Al. Nature 2011

Challenges

- **Continue to investigate the biologic significance of all potential ligand receptor interactions in the tumor microenvironment**
- **Develop more accurate predictive markers of response**
- **Determine breath of activity in human malignancy**
- **Develop Potential Combinations of therapy that address key mechanisms in positive/negative regulation of the immune system (priming)**
- **Combinations with other therapies, move to earlier disease**