Winship Cancer Institute of Emory University

Immune Checkpoint Inhibitors and Other New Agents in NSCLC

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Disclosures

- Research Funding: Bristol-Myers Squibb and Genentech.

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Objectives

- Review immune checkpoints in cancer
- Discuss immune related response criteria (irRC)
- Assess PD-L1 expression as a biomarker
- Updates from ASCO 2014 on PD-1 targeted therapies in NSCLC

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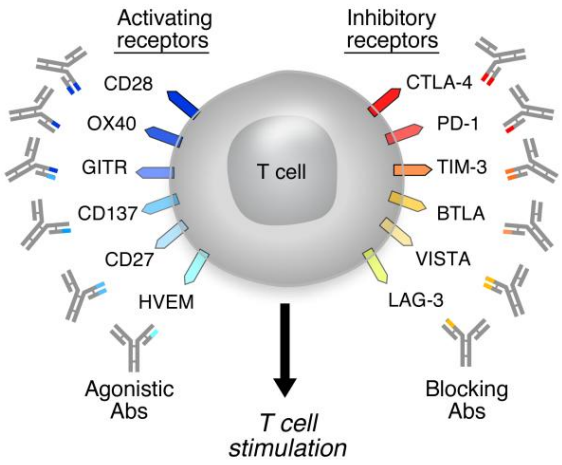
T-Cell Targets for Immunotherapy



Mellman I, et al. Nature 2011: 480.

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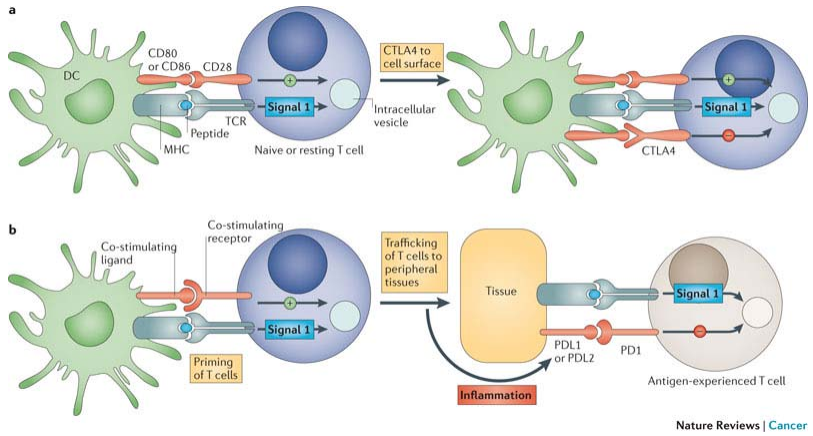
CTLA4 and PD-1 Function



Pardoll DM. Nat Rev Cancer 2012: 12.

Targeting PD-1 and PD-L1

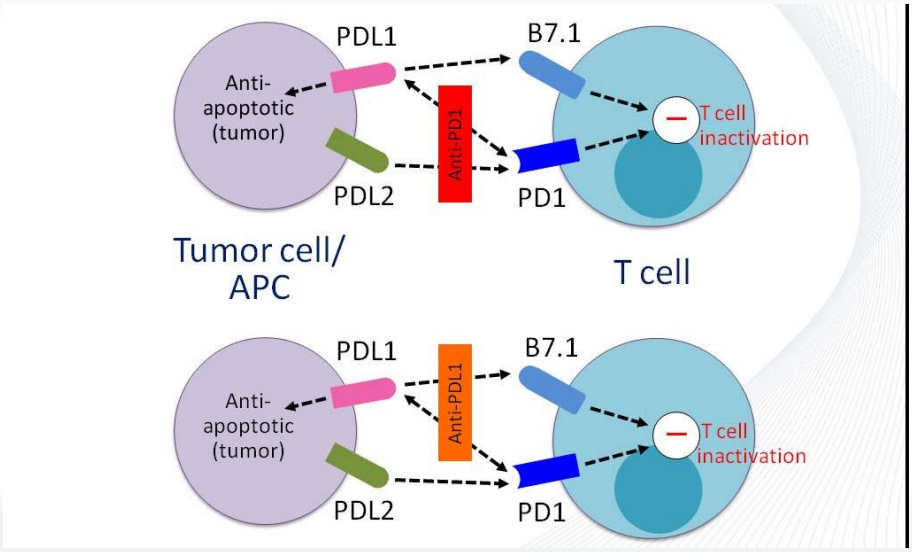
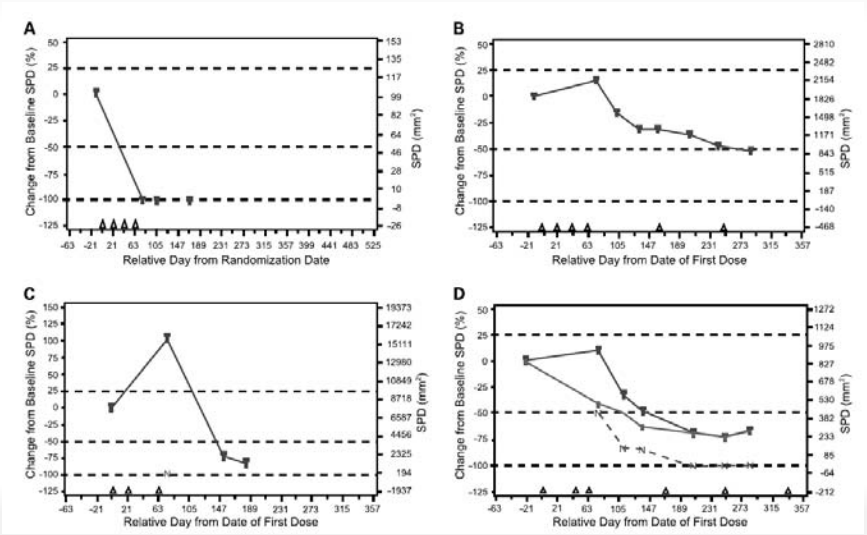


Figure from Scott Gettinger ASCO 2014.

Patterns of Response: Pseudoprogression



Wolchok JD et al. Clin Cancer Res 2009: 15(23).

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Immune-Related Response Criteria

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Wolchok JD et al. Clin Cancer Res 2009: 15(23).

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PD-1 Inhibitors in Development

Drug	Company	Target/Antibody type	Phase of Study
Nivolumab	Bristol-Myers Squibb	PD-1 IgG4	Phase 3
Pembrolizumab (MK-3475)	Merck	PD-1 IgG4 (humanized)	Phase 3
MPDL3280A	Genentech/ Roche	PD-L1 IgG1	Phase 3
MEDI-4736	Medimmune/ AstraZeneca	PD-L1 IgG1	Phase 2
Pidilizumab	CureTech	PD-1 IgG1 (humanized)	Phase 2
AMP-224	Medimmune/ AstraZeneca	PD-1/B7 Fc fusion protein	Phase 1
AMP-514	Medimmune/ AstraZeneca	PD-1 IgG1	Phase 1
MSB0010718C	EMD Serono	IgG	Phase 1
	Novartis	IgG	Phase 1

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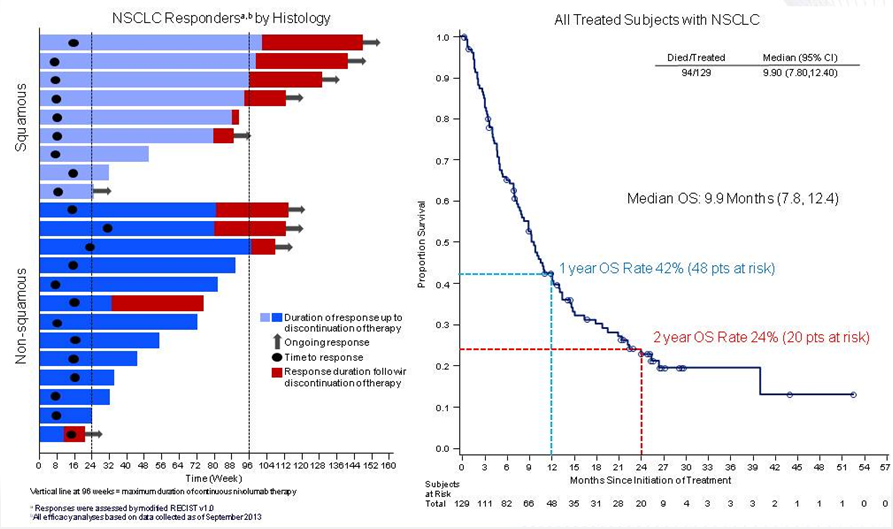
Nivolumab in Pre-Treated NSCLC



Brahmer JR. WCLC 2013

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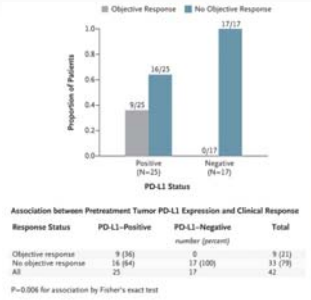
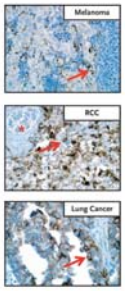
PD-L1 and Response with Nivolumab



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
	number (percent)		
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



Nivomulab studies: PD-L1 positive ≥ 5% membranous staining of tumor cells

Topalian SL, et al. NEJM 2012

		PD-L1 Positive		PD-L1 Negative	
	Total	Count (N)	ORR	Count (N)	ORR
NSCLC (all)	129	33	15% (5/33)	35	14% 5/35
Squamous	54	15	13% 2/15	14	21% 3/14
Non-squamous	74	18	17% 3/18	21	10% 2/21

Brahmer JR, et al. ASCO 2014

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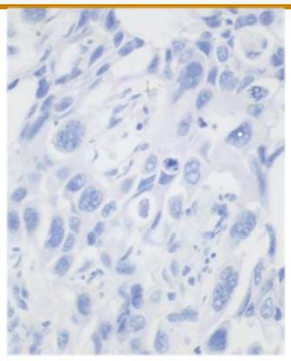
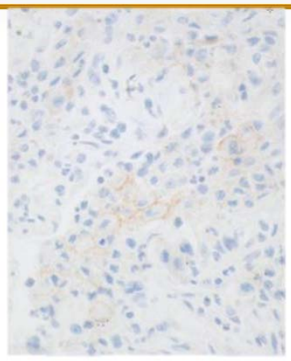
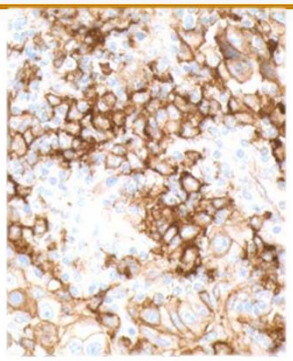
PD-L1 Expression in MK-3475 Studies



PD-L1 Negative



Weak Positive (1-49%)



Strong Positive (50-100%)

Gandhi L. AACR 2014 Abstract CT 105.

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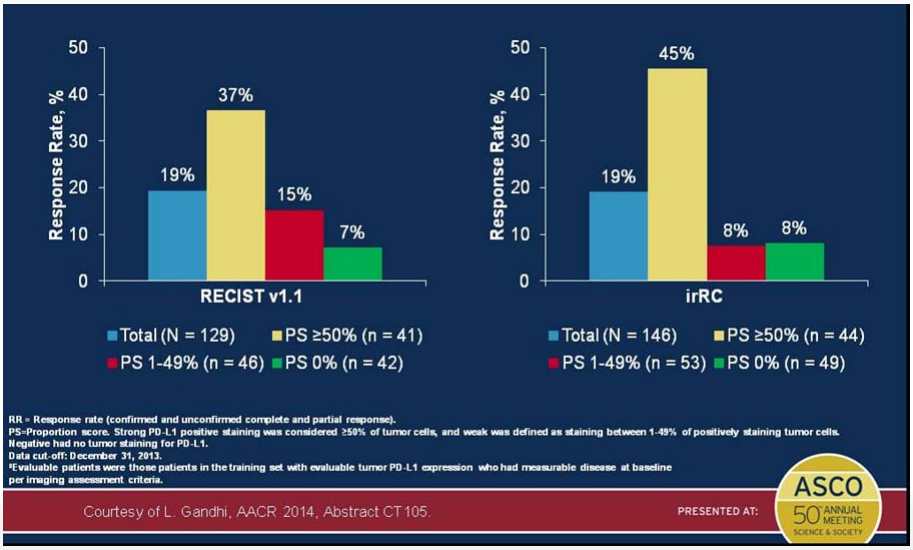
MK-3475 Response Rate by PD-L1 Expression



Rizvi NA, et al. Abstract 8007, ASCO 2014.

Limitations of PD-L1 as a Biomarker

- What is PD-L1 positive?
  - Variability of antibody used
  - Tumor surface staining or infiltrating lymphocytes
  - Threshold for PD-L1 positivity by IHC
- What specimen should be stained?
  - Archival tissue or fresh biopsy
- Why do some PD-L1 negative patients still benefit from PD-1 or PD-L1 antibodies?

Safety and Clinical Activity of Pembrolizumab (MK-3475) as Initial Therapy in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

NA Rizvi, et al. Abstract #8007

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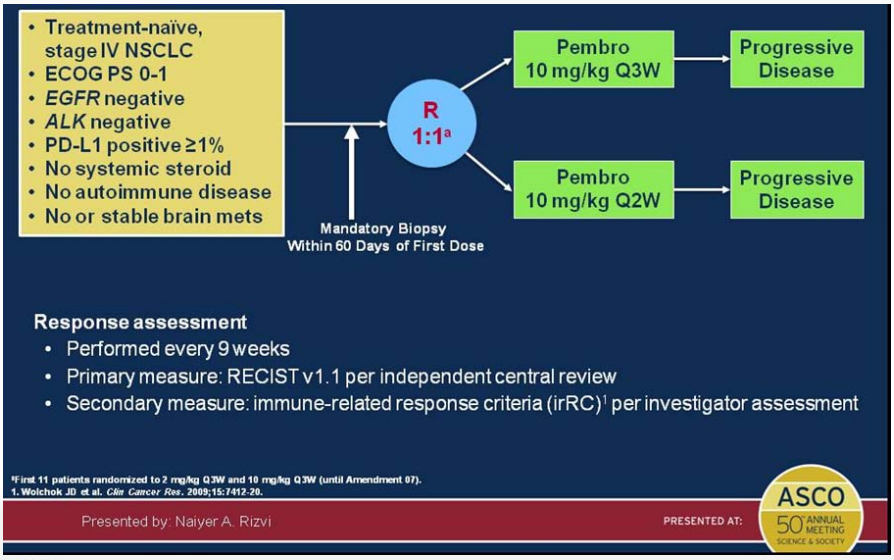
Study Design



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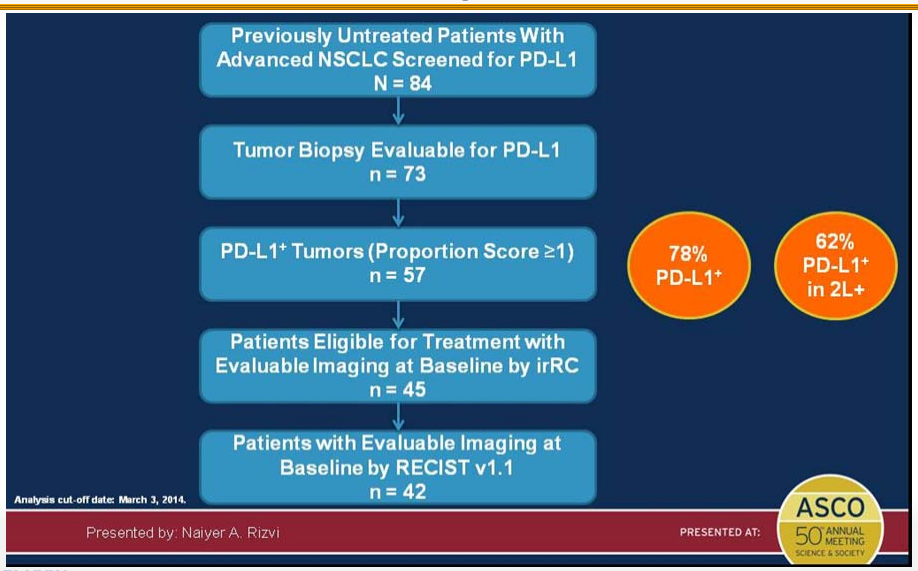
PD-L1 Expression



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Baseline Demographics

Characteristic	N = 45
Median age, year (range)	70 (48 – 86)
Sex	
Male	25 (56%)
Female	20 (44%)
Mutation	
EGFR	1/41 (2%)
KRAS	4/15 (27%)
ALK rearrangement	1/38 (3%)
Histology	
Non-Squamous	34 (76%)
Squamous	10 (22%)
Unknown	1 (2%)
ECOG performance status	
0	22 (49%)
1	23 (51%)

Characteristic	N = 45
Race	
Asian	1 (2%)
Black or African American	1 (2%)
White	42 (93%)
Native Hawaiian/ Pacific Islander	1 (2%)
Smoking status	
Current	8 (18%)
Former	31 (69%)
Never	5 (11%)
Unknown	1 (2%)

Analysis cut-off date: March 3, 2014.

Presented by: Naiyer A. Rizvi

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

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Treatment-Related Adverse Events

AEs of Any Grade, Incidence >5%

Treatment-Related Adverse Event, n (%)	Total N = 45
Any	36 (80%)
Fatigue	10 (22%)
Pruritus	6 (13%)
Hypothyroidism	4 (9%)
Dermatitis acneiform	3 (7%)
Diarrhea	3 (7%)
Dyspnea	3 (7%)
Rash	3 (7%)

Grade 3-4 AEs or AEs Leading to Discontinuation

Treatment-Related Adverse Event, n (%)	Total N = 45	Resulted in Discontinuation
Blood creatine phosphokinase increased (Gr 4)	1 (2%)	No
Pericardial effusion (Gr 3)	1 (2%)	No
Pneumonitis (Gr 3)	1 (2%)	Yes
Acute kidney injury (Gr 2)	1 (2%)	Yes

- Specific AE terms listed are grade 1-2 only

Analysis cut-off date: March 3, 2014.

Presented by: Naiyer A. Rizvi

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Efficacy

Pembro Dose	RECIST v1.1, Central Review[a] n	RECIST v1.1, Central Review[a] ORR[b] n (%) [95% CI]	RECIST v1.1, Central Review[a] DCR[b] n (%) [95% CI]	irRC, Investigator Review n	irRC, Investigator Review ORR[b] n (%) [95% CI]	irRC, Investigator Review DCR[b] n (%) [95% CI]
2 mg/kg Q3W	6	2 (33%) [4%-78%]	3 (50%) [12%-88%]	6	4 (67%) [22%-96%]	5 (83%) [36%-100%]
10 mg/kg Q3W	20	4 (20%) [6%-44%]	14 (70%) [46%-88%]	22	10 (46%) [24%-68%]	18 (82%) [60%-95%]
10 mg/kg Q2W	16	5 (31%) [11%-59%]	10 (63%) [35%-85%]	17	7 (41%) [18%-67%]	12 (71%) [44%-90%]
Total	42	11 (26%) [14%-42%]	27 (64%) [48%–78%]	45	21 (47%) [32%-62%]	35 (78%) [63%-89%]

- Interim median PFS[c]:
  - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
  - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

Analysis cut-off date: March 3, 2014. DCR = Disease control rate (complete response + partial response + stable disease)
[a]3 patients did not have measurable disease by RECIST v1.1 per independent central review at baseline and were not evaluated for response by RECIST v1.1.
[b]Includes confirmed and unconfirmed responses.
[c]From product-limit (Kaplan-Meier) method for censored data.

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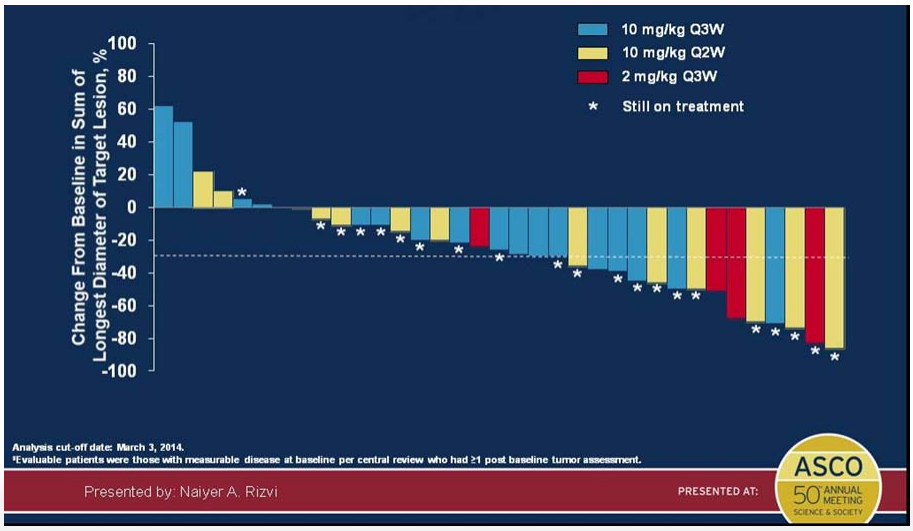
Response by RECIST 1.1



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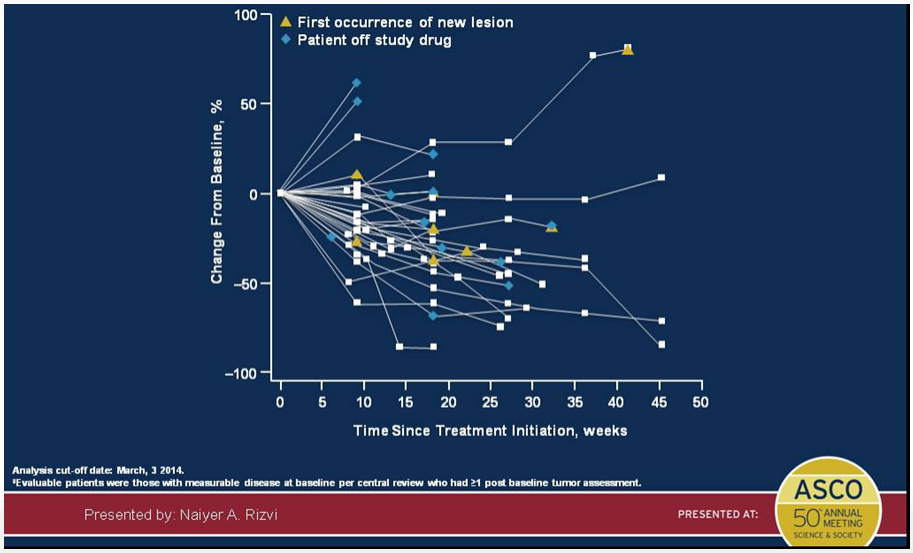
Change from Baseline in Tumor Size



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Conclusions from MK-3475 First-line Study

- Pembrolizumab has activity in PD-L1 positive treatment naïve NSCLC
  - ORR 26% by RECIST, 47% by irRC
  - Median PFS 27 weeks by RECIST, 37 weeks by irRC
- Tolerable toxicity profile
  - Grade 3/4 AEs in 9% patients
- Basis for phase 3 study: pembrolizumab versus platinum doublet chemotherapy

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Garon, et al. MK-3475 in Previously Treated NSCLC (Abstract #8020)

- Expansion cohort including 217 NSCLC patients
- Randomized to 10 mg/kg MK-3475 q2weeks or q3weeks
- ORR 20% by RECIST, 18% by irRC
- Grade 3-5 drug related AEs = 10% (any AE = 64%)

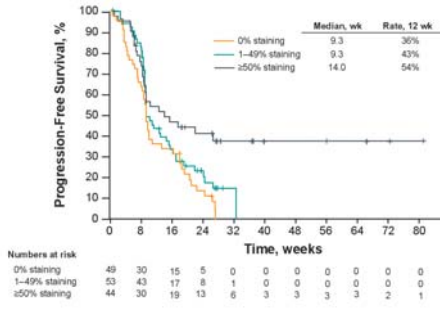

Table 2. Antitumor Activity by PD-L1 Expression as Assessed by a Prototype Assay

	RECIST v1.1, Independent Central Review		irRC, Investigator Review	
	PD-L1+	PD-L1-	PD-L1+	PD-L1-
Best overall response*	n = 159	n = 35	n = 177	n = 40
ORR, % (95% CI)	23 (16-30)	9 (2-23)	19 (14-26)	13 (4-27)
DCR, % (95% CI)	42 (34-50)	31 (17-49)	51 (44-59)	53 (36-69)
Time to response, wk, median (range)	9 (6-31)	14 (9-18)	9 (6-22)	13 (9-18)
Response duration, wk, median (range)	31 (0+ to 37+)	NR (9+ to 22+)	NR (0+ to 37+)	NR (0+ to 30+)
PFS	n = 177	n = 40	n = 177	n = 40
Median, wk (95% CI)	11 (9-16)	10 (9-16)	16 (10-18)	16 (9-28)

CI = confidence interval; DCR = disease control rate; NR = not reached; ORR = overall response rate.
*Includes confirmed and unconfirmed responses as assessed in patients with measurable disease at baseline.

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Brahmer, et al. MEDI4736 in NSCLC (Abstract # 8021)

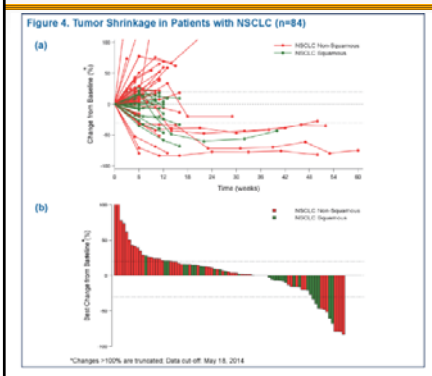
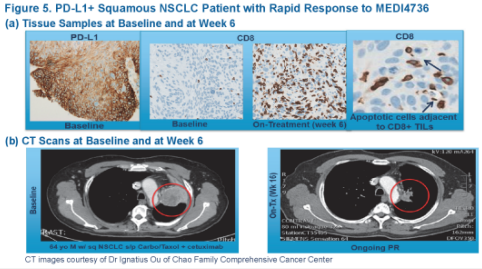


Table 5. Objective Response/Disease Control Rate in Patients with NSCLC[a]

	MEDI4736 10 mg/kg q2w	MEDI4736 All doses
RECIST Response[b]		
Response evaluable[c]	13% (6/47)	16% (9/58)
PD-L1+	39% (5/13)	25% (5/20)
PD-L1-	5% (1/19)	3% (1/29)
Disease Control Rate[d]		
Response evaluable[c]	30% (14/47)	35% (20/58)
PD-L1+	54% (7/13)	45% (9/20)
PD-L1-	32% (6/19)	24% (7/29)

Figure 5. PD-L1+ Squamous NSCLC Patient with Rapid Response to MEDI4736



CT images courtesy of Dr Ignatius Ou of Chao Family Comprehensive Cancer Center

ORR 16%
Drug-related AEs = 29%
Grade 3/4 related AEs = 3%

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Rizvi, et al. Erlotinib and Nivolumab in EGFR Mutated NSCLC (abstract # 8022)

- Included 21 EGFR mutated NSCLC patients
- ORR 19% (15% in erlotinib resistant patients)
- PFS at 24 weeks = 51%, 1 year OS 73%
- Responders included patients with T790M mutation
- No pneumonitis was seen, 24% grade 3/4 AEs

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Antonia, et al. Nivolumab and Ipilumumab in First-Line NSCLC (abstract #8023)

- Nivolumab + ipilumumab x 4 cycles followed by nivolumab x 1 year
- ORR 11-33%
- 24 week PFS rate 20-51%
- High treatment related AE rate: 49% grade 3/4
  - Most common diarrhea
- PD-L1 expression not predictive of efficacy

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Gettinger, et al. Nivolumab in First-Line NSCLC (abstract #8024)

- 20 patients with PD-L1 positive treatment naïve NSCLC
- ORR 30% with 2 complete responses
- PFS rate at 24 weeks = 60%
- 1 year OS = 75%
- Most common AE was fatigue, 20% grade 3/4 AE (no pneumonitis)

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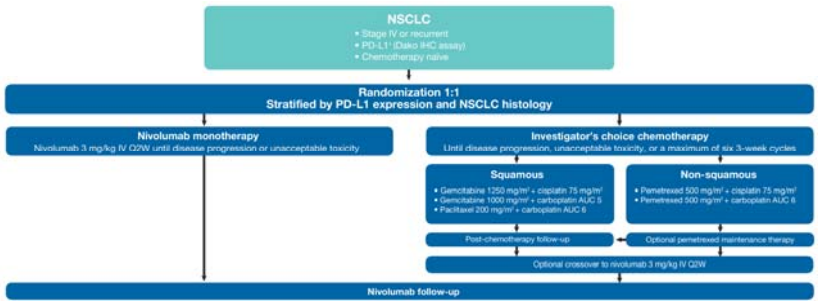
CA209-026: Phase III Nivolumab vs. Chemotherapy as First-line Therapy in PD-L1 Positive NSCLC



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Conclusions

- Immune checkpoint therapy has robust anti-tumor activity in NSCLC with a tolerable safety profile.
- Future directions:
  - Verifying results in larger randomized studies
  - Defining PD-L1 positivity and developing better biomarkers
  - Imaging studies to distinguish pseudoprogression from progression
  - Combination strategies with chemotherapy and targeted therapies

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