Keynote Lecture: Immunotherapy: A Step Forward in Treatment of Advanced Non-Small Cell Lung Cancer

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Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

Immunotherapy: A Step Forward in Treatment of NSCLC

Outline

- Rationale for immune-based antitumor therapies
- Immune-related response criteria
- Immunotherapy-associated adverse events
- Latest advances with immune-based antitumor therapies
- Biomarkers

Rationale for Immune-Based Antitumor Therapies in NSCLC

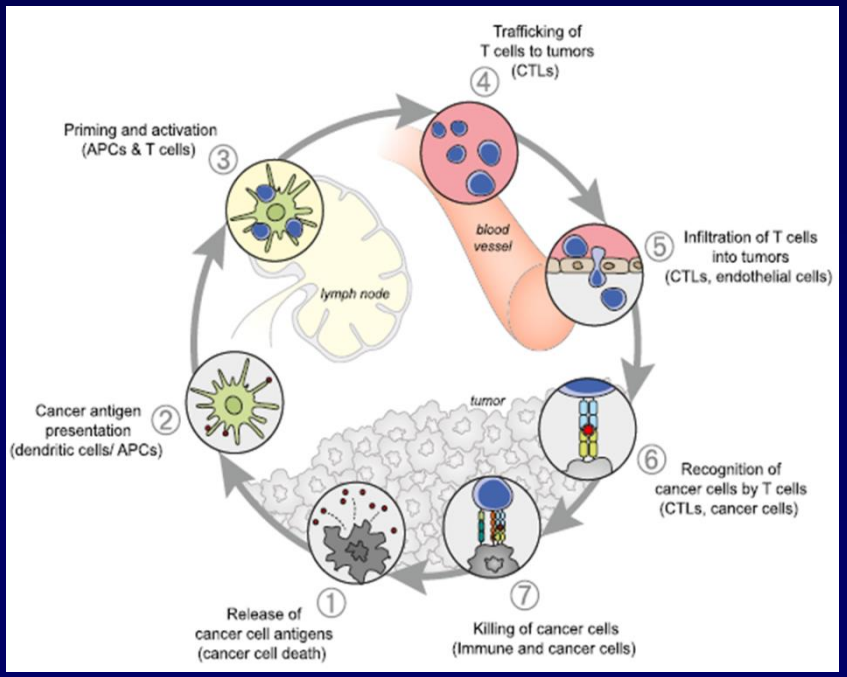
Immune System and Cancer

- Immune system recognizes and eliminates cancer cells from the body
- Evading immune control, a hallmark of cancer[1]
- T cells, crucial in anti-tumor immune response

1. Hanahan D, et al. *Cell.* 2011;144(5):646-674.

Immune System and Cancer: Optimal Activity

1. Antigens are released from tumor cells and captured by antigen-presenting cells (APCs)
2. APCs then present the tumor antigens to T cells
3. T cells require a costimulatory signal to become fully activated and proliferate to initiate an antitumor immune response
4. Activated T cells recognize tumor antigens
5. T cells kill tumor cells



Chen DS, et al. *Immunity*. 2013;39(1):1-10.

Immune System and Cancer: How Cancer Cells Evade Immune Destruction

Mechanisms used to evade immune destruction:

- **Ineffective presentation of cancer cell antigens**
- **Recruitment of immunosuppressive cell types**
- **Inhibition of attack by immune cells, eg, disruption of T cell-activating and checkpoint pathways**

Cancer Immunotherapy Approaches

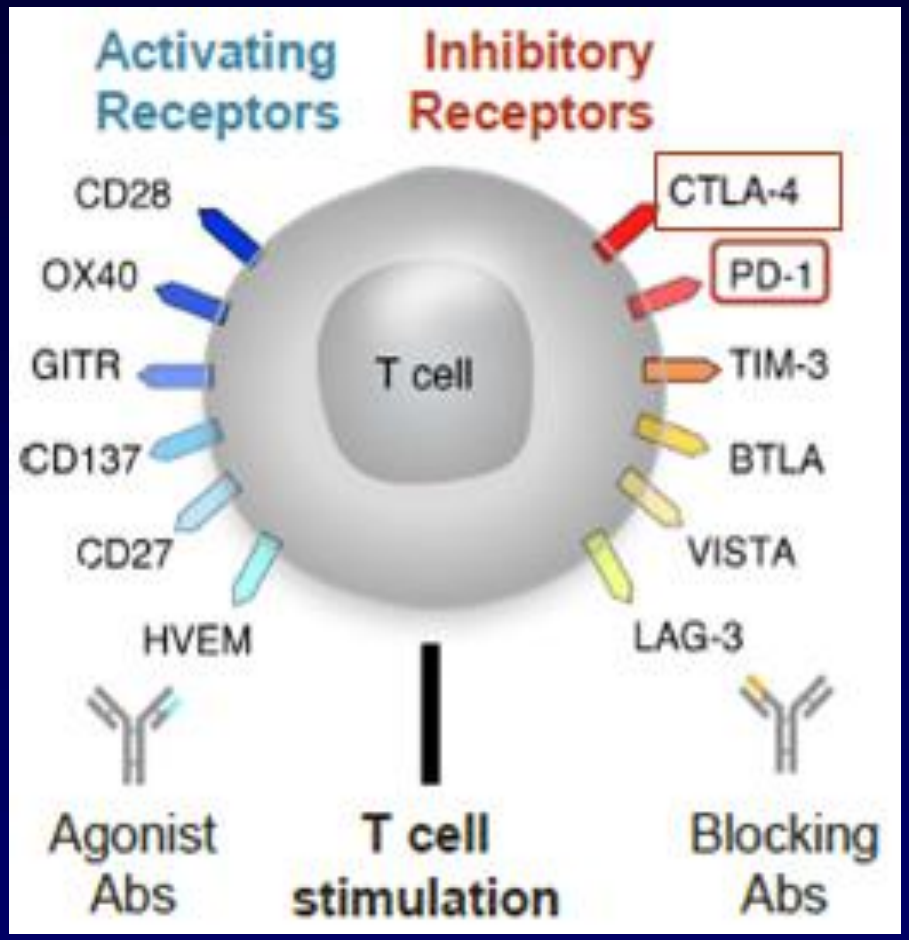
Cancer immunotherapy: Any interaction with the immune system to treat cancer

Active: Priming of the immune system

Passive: Delivery of compounds that may use immune system

Antigen-specific	Non-antigen-specific	Monoclonal antibodies	Adoptive cell transfer
→ AG-specific antibodies & cytotoxic T cells	→ Enhancement of immune system • Cytokines • Checkpoint inhibitors	• Cetuximab • Trastuzumab	• T cells engineering • CARs • Dendritic cells
Cancer vaccination therapy	**Cancer immunomodulation therapy**	**Targeted antibodies immunotherapy**	**Cellular immunotherapy**

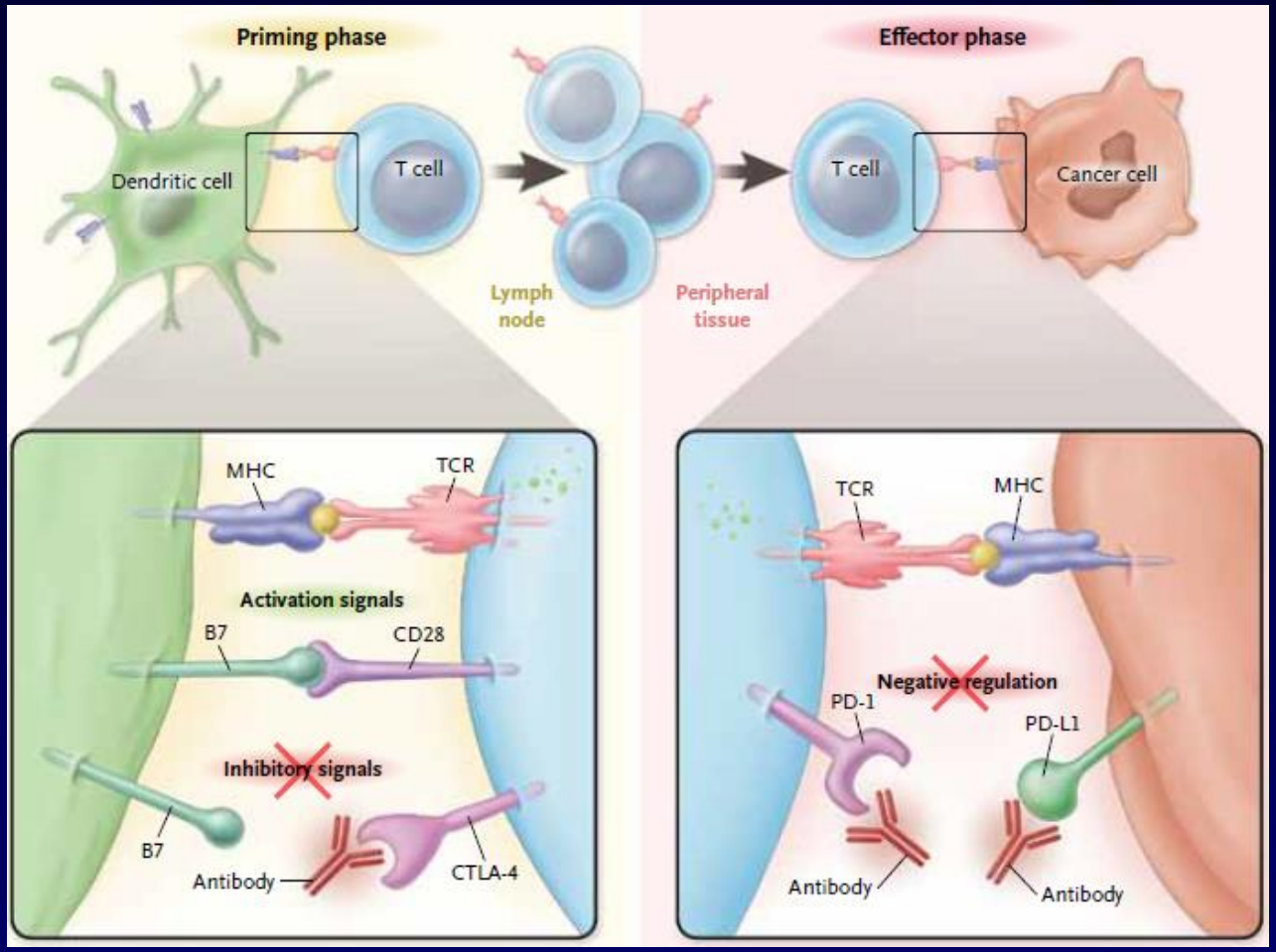
Targeting Checkpoint Pathways



- Tumors can deregulate checkpoint and activating pathways, and consequently alter the immune response
- Targeting checkpoint pathways may restore optimal immune response

Mellman I, et al. *Nature.* 2011;480(7378):480-489.

Blockade of CTLA-4 and PD-1 Signaling



- CTLA-4 blocks CD-28 related T-cell activation
- Antibody against CTLA-4 restores CD-28 related T-cell activation

- Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions
- Antibodies to PD-1 or PD-L1 inhibit the PD-1 pathway, allowing for T-cell mediated rejection of tumor

Ribas A. *N Engl J Med.* 2012;366 (26):2517-2519.

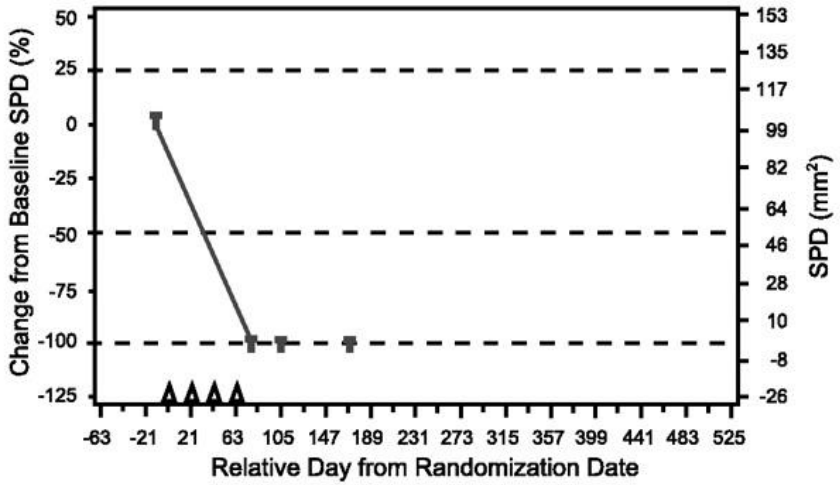
Rationale for PD1 and PDL1 Blockade in NSCLC

- Target immune system rather than tumor
- Activity in different tumor types including NSCLC, melanoma, renal cancer, bladder carcinoma, and head & neck
- May have greater activity in tumors with a large number of mutations
- Manageable toxicity profile
- Suspected impact on long-term survival

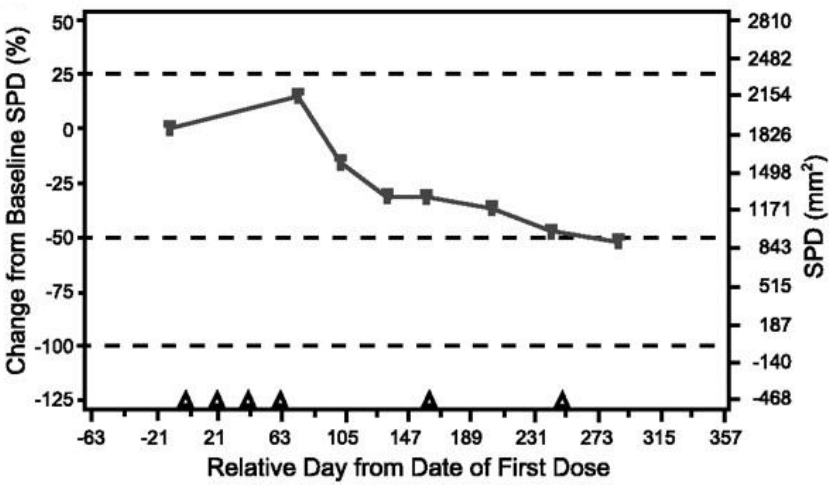
Immune-Related Response Criteria

Patterns of Response to Immunotherapy

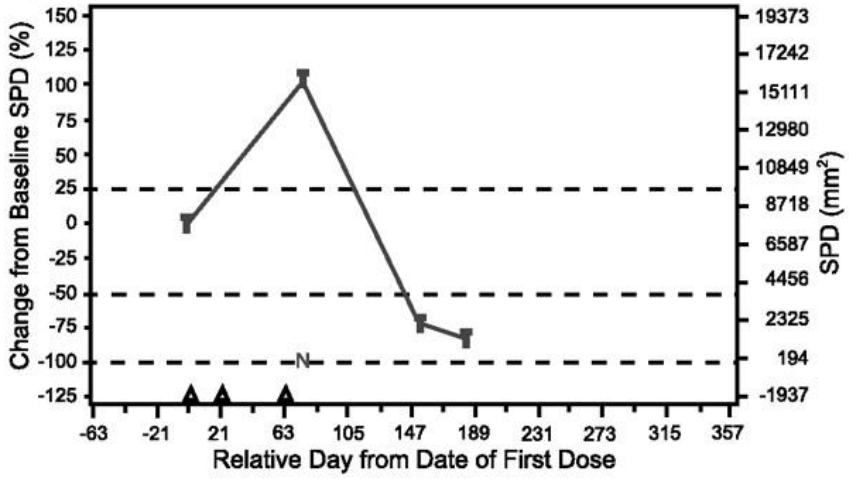
Initial response



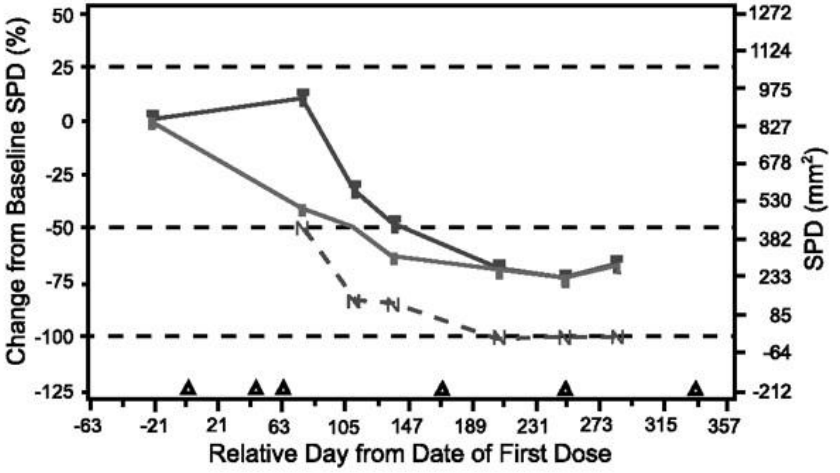
Stable disease



Initial ↑ of T volume then response



New lesions then response



Wolchok JD, et al. *Clin Cancer Res*. 2009;15(23):7412-7420.

Response Criteria for Immunotherapy

RECIST 1.1[1]			
CR	**PR**	**SD**	**PD**
Disappearance of all target lesions, reduction in short-axis diameter of pathology LN to <10 mm	≥30% decrease in sum of longest diameters of target lesions	Neither PR nor PD	≥20% increase (≥5 mm absolute increase) in sum of longest diameters, in comparison with smallest sum of longest diameters recorded during treatment
Immune-Related Response Criteria[2]			
irCR	**irPR**	**irSD**	**irPD**
Disappearance of all lesions on 2 consecutive observations ≥4 weeks apart	≥50% decrease in tumor burden compared with baseline in 2 observations ≥4 weeks apart	50% decrease in tumor burden compared with baseline not established, nor 25% increase vs nadir	≥25% increase in tumor burden compared with nadir (at any single timepoint) in 2 consecutive observations at least 4 weeks apart

1. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45(2):228-247. 2. Wolchok JD, et al. *Clin Cancer Res*. 2009;15(23):7412-7420.

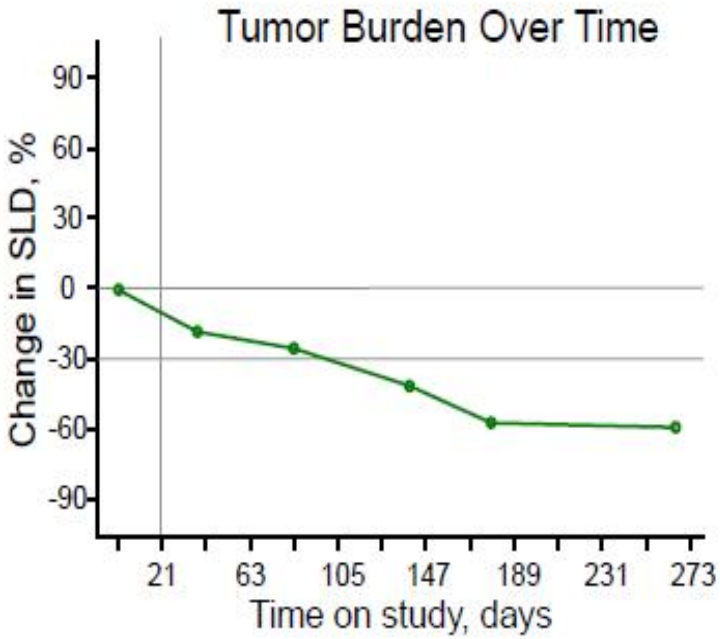
Pseudo-Progression

- **After 1 year of therapy with anti-PDL1 MPDL3280A**

Baseline (5-21-12)

Post-Tx (8-05-13)

Pseudo-Progression (6-28-13)



- Sustained response of target lesions with new/growing solitary FDG-avid nTL
- Excision of FDG-avid nTL revealed reactive lymph node without evidence of malignant involvement

Gettinger SN, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney, Australia. Abstract MO19.09.

Immunotherapy-Associated Adverse Events

Select Adverse Events Reported With Immune Checkpoint Inhibitors

Category	Adverse Events
Dermatologic	Pruritus, rash, vitiligo, urticaria, alopecia, pruritic rash, macular rash, hypopigmentation, erythema, erythematous rash
Gastrointestinal	Diarrhea, colitis, nausea, abdominal pain
Endocrine	Hypothyroidism, hyperthyroidism, hypopituitarism, hypophysitis, adrenal insufficiency, altered hormone levels
Hepatic	Hepatitis, increased liver function enzymes
Pulmonary	Pneumonitis, pulmonary edema
Ocular	Uveitis, episcleritis, eye pruritus
Pancreatic	Elevated lipase levels, hyperglycemia
Infusion-related	Infusion-related reaction or hypersensitivity
General	Fatigue, headache, decreased appetite, arthralgia

Davies M. *Cancer Manag Res.* 2014;6:63-75.

Immune-Related Toxicity Management: General Principles

Generally based on severity of symptoms:

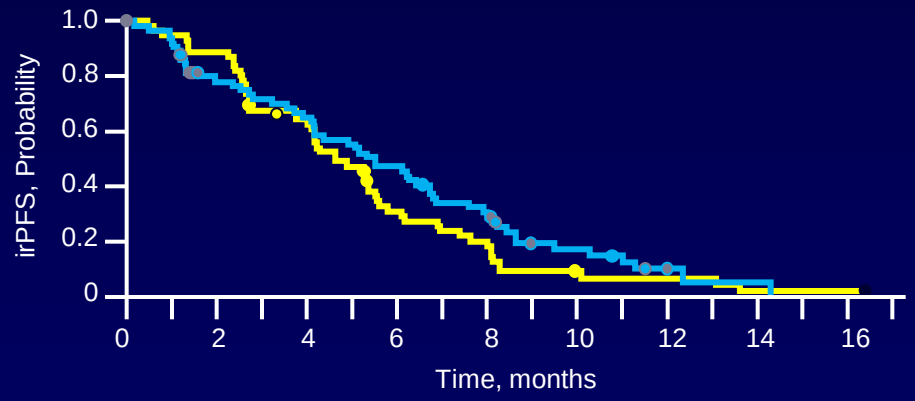
- **Grade 1:** Supportive care; +/- withhold drug
- **Grade 2:** Withhold drug, consider re-dose if toxicity resolves to ≤ grade 1. Low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) if symptoms do not resolve within a week
- **Grade 3-4:** Discontinue drug; high-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent) tapered over ≥1 month once toxicity resolves to ≤ grade 1
- Presence of irAEs may be a biomarker for response

Latest Advances With Immune-Based Antitumor Therapies in NSCLC

Ipilimumab Plus Carbo/Paclitaxel as First-Line Treatment in NSCLC

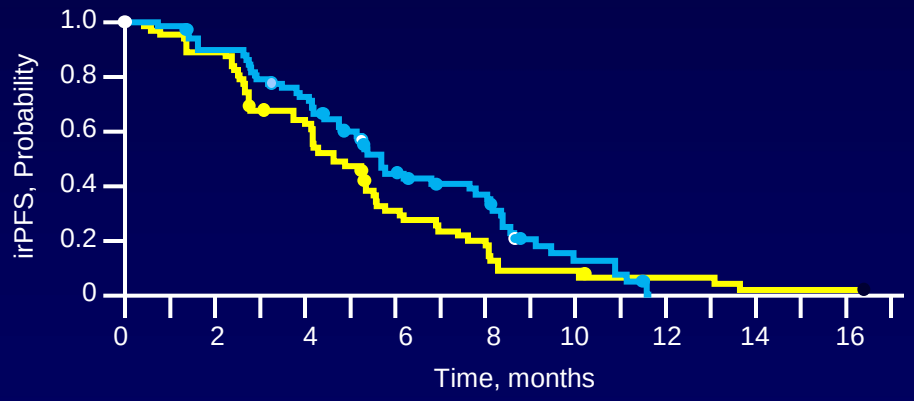
CA184-041: Phase II study results, no prior therapy for lung cancer, stage IIIB/IV NSCLC, ECOG PS ≤1, all histologies

Chemotherapy + concurrent ipilimumab



	Events/ patients	Median irPFS, months	95% CI	HR	*P* value
Placebo	56/66	4.63	4.14, 5.52		
Ipilimumab	55/70	5.52	4.17, 6.74	0.81	.13

Chemotherapy + phased ipilimumab



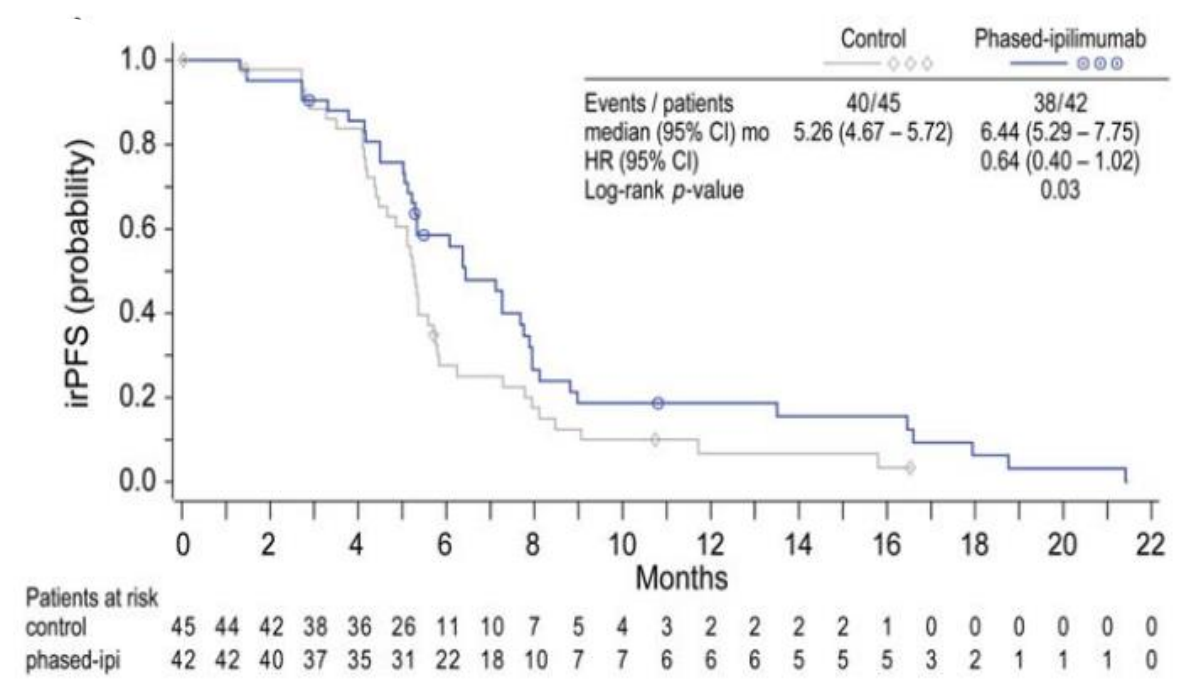
	Events/ patients	Median irPFS, months	95% CI	HR	*P* value
Placebo	56/66	4.63	4.14, 5.52		
Ipilimumab	54/68	5.68	4.76, 7.79	0.72	.05

irPFS, immune-related progression-free survival

Lynch TJ, et al. *J Clin Oncol.* 2012;30(17):2046-2054.

Ipilimumab Plus Carbo/Paclitaxel as First-Line Treatment in Extensive Disease SCLC

A Randomized Double Blind Multicenter Phase II Trial



Phased ipilimumab (I) improved irPFS *vs* control [HR 0.64, *P* = .03][1]

- **No improvement in PFS [HR 0.93, *P* = .37] or OS [HR 0.75, *P* = .13]**
- **Median irPFS: 6.4 months for phased I, 5.7 months for concurrent I, 5.3 months for control arm**
- **Median OS: 12.9 months for phased I, 9.1 months for concurrent I, 9.9 months for control arm**

Randomized phase III study in ED SCLC platin/etoposide +/- ipilimumab (accrual completed)[2]

1. Reck M, et al. *Ann Oncol.* 2013;24(1):75-83. 2. National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT01450761. Accessed 11 March 2015.

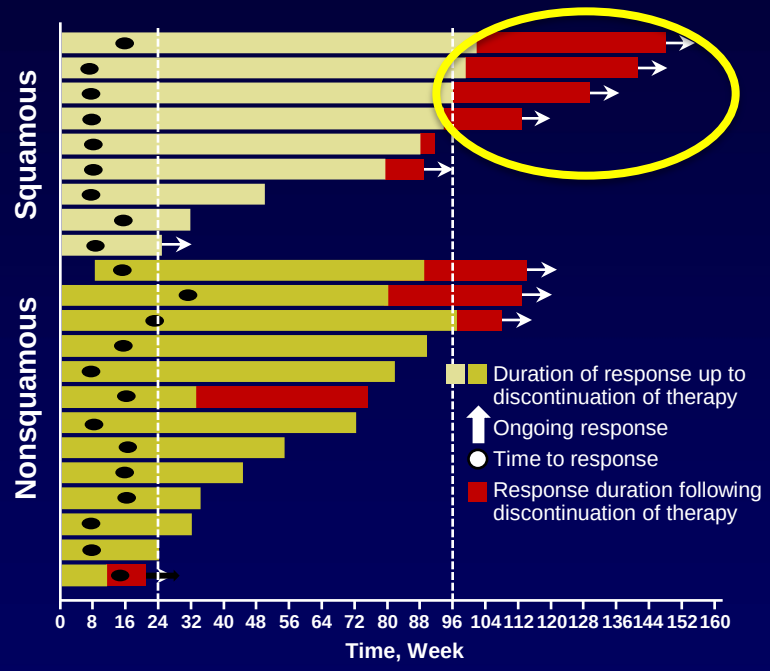
PD-1 and PD-L1 Immune Checkpoint Inhibitors in Clinical Trials

PD-1	Nivolumab-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase III
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II
	Pembrolizumab MK-3475	Humanized IgG4 mAb	Merck	Phase III
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase I
	MEDI4736	Engineered human IgG1 mAb	MedImmune	Phase III
	MPDL3280A	Engineered human IgG1 mAb	Roche/ Genentech	Phase III
	MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase II

Nivolumab (BMS-936558) in Advanced NSCLC: OS and Clinical Activity by Subgroup Analysis (n = 129)

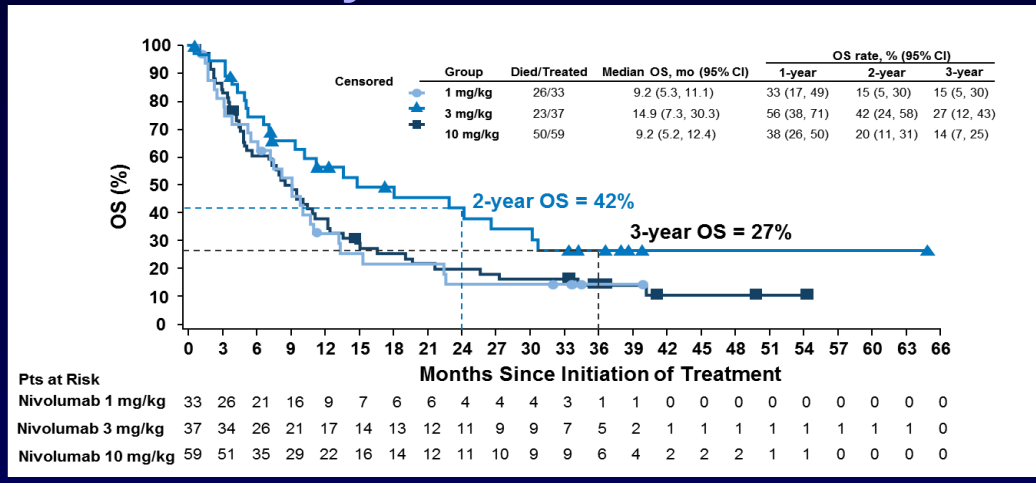
NSCLC Responders by Histology

- ORR 17% (24% in 3 mg/kg)

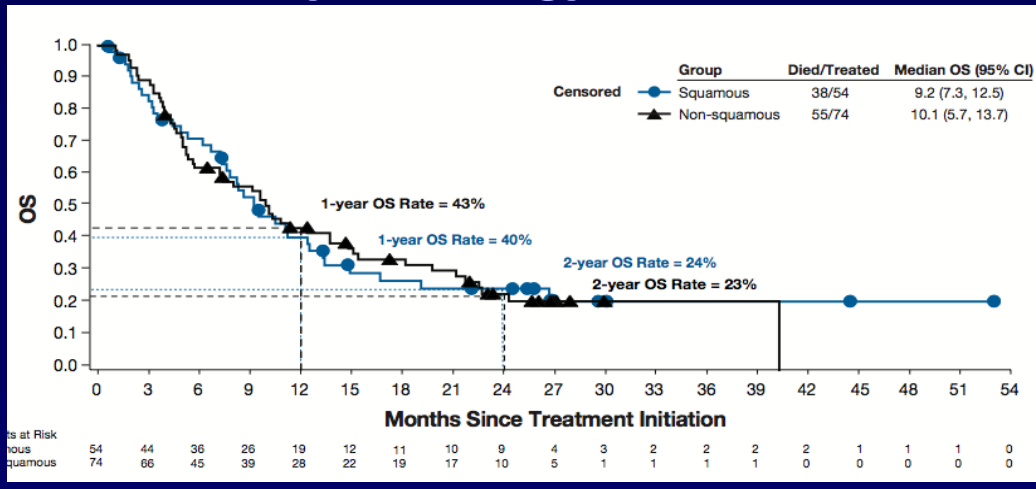


- Similar RR in SCC vs non-SCC (16.7% vs 17.6%)
- Responses in PD-L1-

OS by Dose in NSCLC[2]



OS by Histology in NSCLC



1. Brahmer JR, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8112. 2. Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 170.

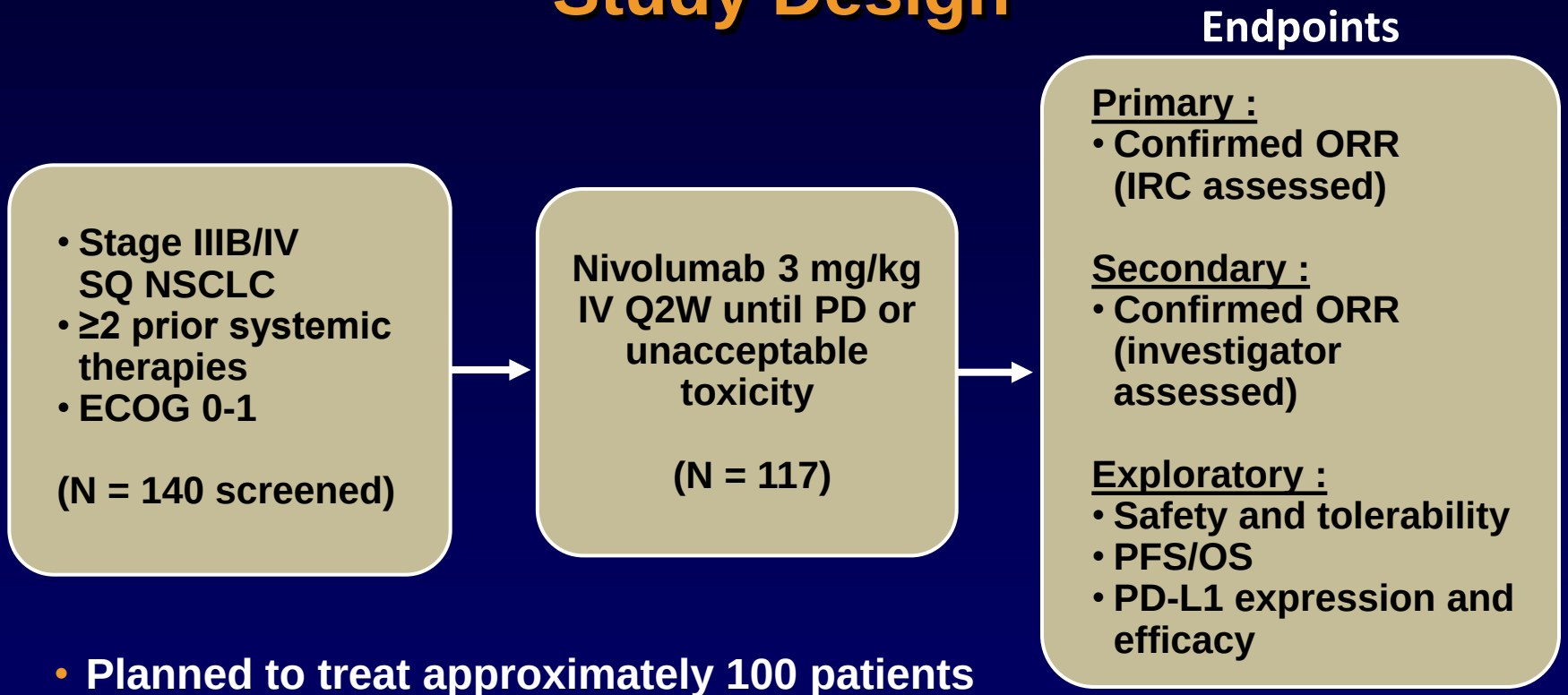
Adverse Events (≥1%) in NSCLC Patients Treated With Nivolumab

- No new safety signals emerging; all patients >1 year of follow-up

	Patients, n (%) [N = 129]	
	Any Grade	Grade 3-4
Any treatment-related select adverse event	41 (53)	5 (6)
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pneumonitis	8 (6)	3 (2)
Pulmonary	7 (9)	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

Brahmer JR, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8112.

Phase II Study of Nivolumab in Advanced, Refractory Squamous NSCLC (CheckMate 063): Study Design



- Planned to treat approximately 100 patients
  - Expected ORR of 10% to 50%, with 20% maximum width of exact 2-sided 95% confidence interval
- Assessments (RECIST v1.1) performed at week 8 and Q6W

Rizvi NA, et al. *Lancet Oncol.* 2015;16(3):257-265.

Phase II Study of Nivolumab in Advanced, Refractory Squamous NSCLC (N = 117)

	IRC Assessed (per RECIST v1.1)[a]
ORR, % (n) [95% CI]	14.5 (17) [8.7, 22.2]
Disease control rate, % (n)	40 (47)
Median DOR, months (range)	NR (2+, 12+)
Ongoing responders, % (n)	77 (13)
Median time to response, months (range)	3.3 (2.2, 4.8)
PFS rate at 1-year, % (95% CI)	20 (12.7, 28.5)
OS rate at 1-year, % (95% CI)	40.8 (31.6, 49.7)

IRC, independent review committee; ORR, overall response rate, DOR, duration of response

Rizvi NA, et al. *Lancet Oncol.* 2015;16(3):257-265.

4 March, 2015

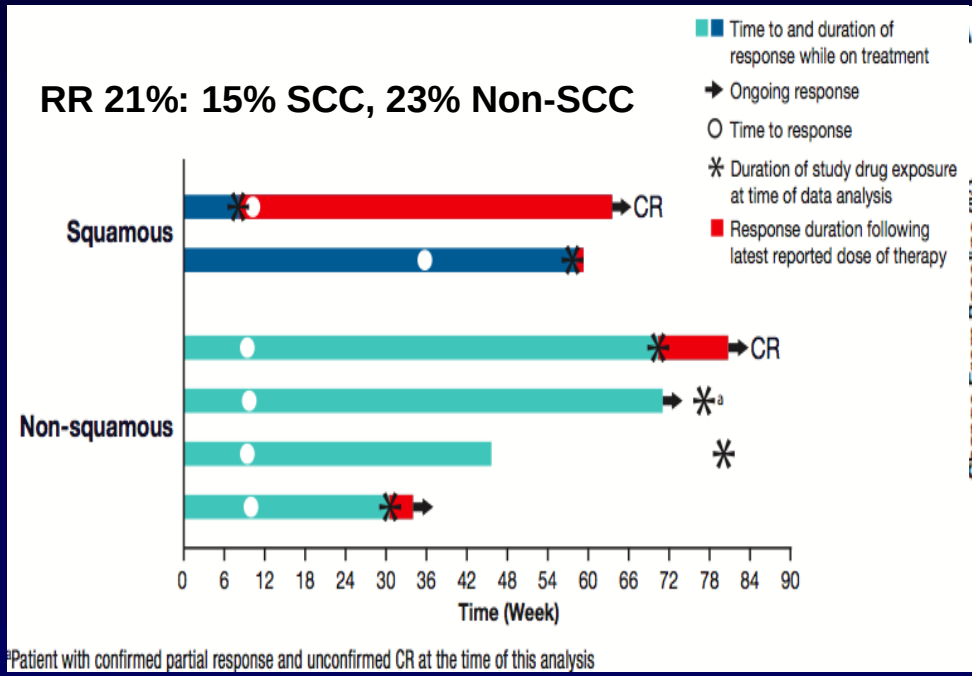
The US FDA Approved the PD-1 Inhibitor Nivolumab for the Treatment of Patients With Metastatic Squamous NSCLC Who Have Progressed on or After Platinum-Based CT

The approval was based on the results of an open-label, multicenter, multinational randomized trial of 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum-based chemotherapy regimen. Patients received nivolumab (n = 135) 3 mg/kg IV every 2 weeks or docetaxel (n = 137) 75 mg/m^2 IV every 3 weeks.

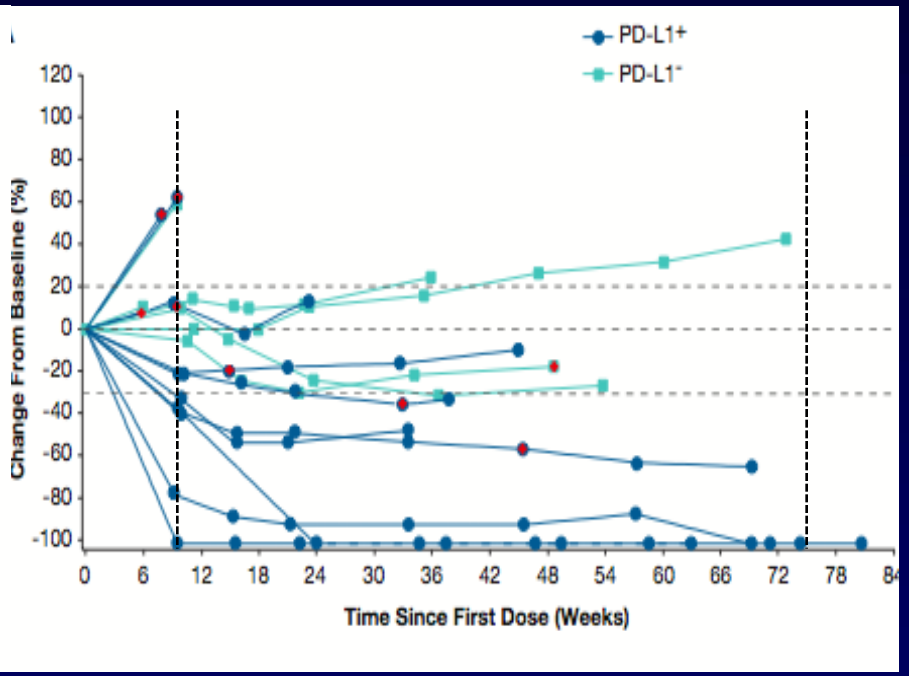
Nivolumab demonstrated a statistically significant improvement in overall survival as compared with docetaxel at the protocol-prespecified interim analysis. Median overall survival was 9.2 months (95% confidence interval [CI] = 7.3-13.3) for patients receiving nivolumab and 6 months (95% CI = 5.1-7.3) for those receiving docetaxel (hazard ratio = 0.59, 95% CI = 0.44-0.79, *P* = .00025).

First-line Nivolumab Monotherapy (3 mg/kg q 2 weeks): Safety, Efficacy, and Correlation With PDL1 Status (n = 52)

Responders by Histology



Responders by PDL1

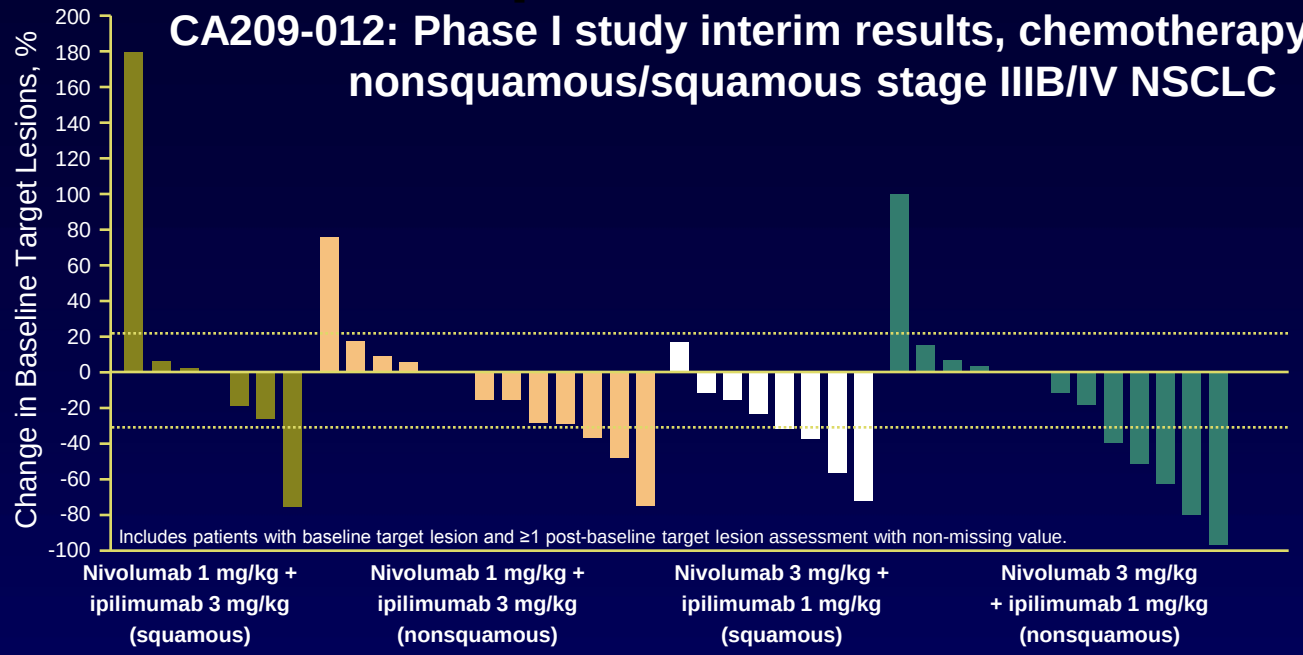


- **Key results:**
  - **PDL1 expression status correlate with RR (31% in PDL1+; 10% PDL1-)**
  - **Grade 3–4 treatment-related AEs 20%**

Rizvi NA, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 165.

First-Line Nivolumab / Ipilimumab in Advanced NSCLC

CA209-012: Phase I study interim results, chemotherapy-naïve, nonsquamous/squamous stage IIIB/IV NSCLC



	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg		Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	
	Squamous (n = 9)	Nonsquamous (n = 15)	Squamous (n = 9)	Nonsquamous (n = 16)
PFS rate at 24 weeks, % (95% CI)	25 (4, 56)	51 (21, 74)	44 (14, 72)	20 (5, 43)
	41 (20, 61)		29 (13, 48)	
Median PFS, weeks (range)	8.9 (0.1+, 44.7)	32.9 (0.1+, 54.1+)	20.6 (9.7, 33.3+)	9.9 (4.1+, 58.1+)
	16.1 (0.1+, 54.1+)		14.4 (4.1+, 58.1+)	
Median OS, weeks (range)	44.3 (1.4, 53.1+)	NR (4.9+, 54.1+)	NR (9.7, 50.1+)	NR (8.1, 58.1+)
	NR (1.4, 54.1+)		NR (8.1, 58.1+)	

Antonia SJ, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8023.

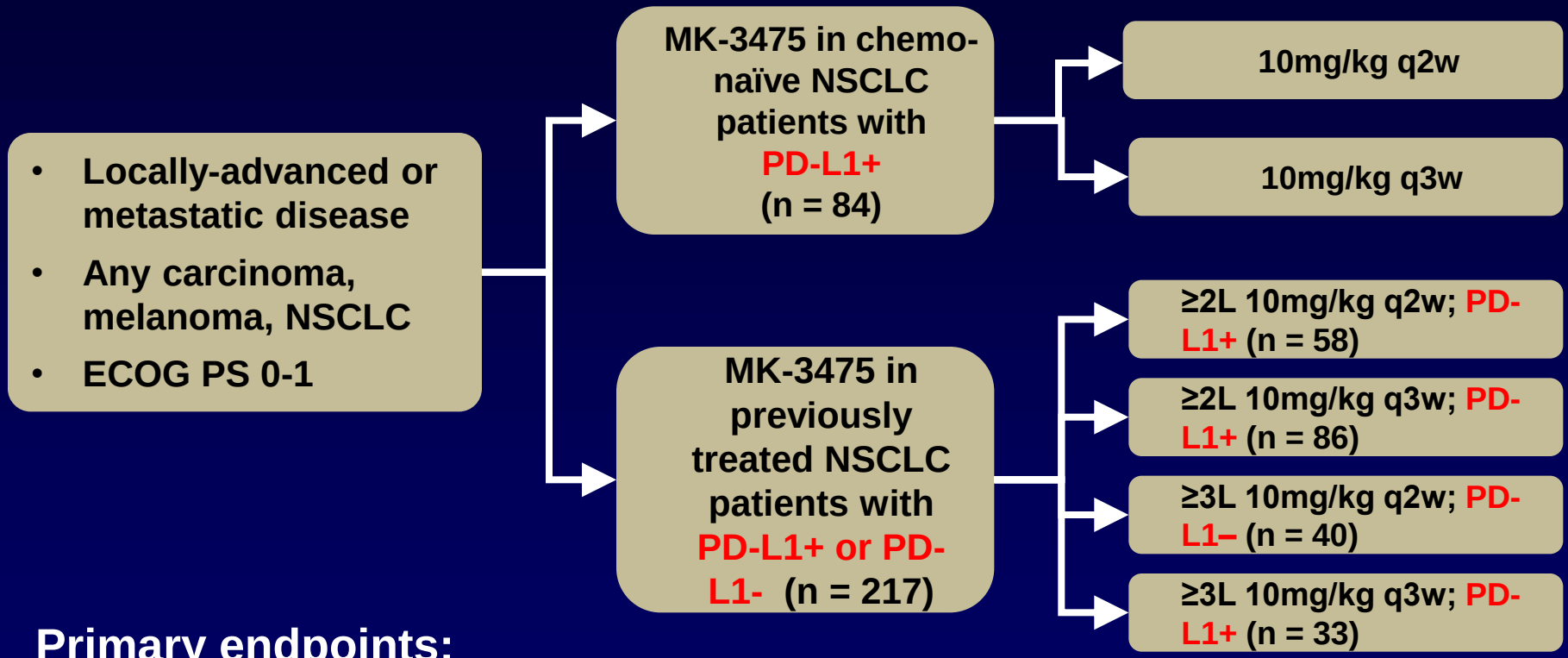
Nivolumab / Erlotinib in EGFR TKI-Resistant NSCLC

CA209-012: Phase I study, *EGFR* mutation–positive NSCLC

	Nivolumab + Erlotinib (N = 21)
ORR, n (%) [95% CI]	4 (19) [5.4, 41.9]
Estimated median DOR, weeks (95% CI)	NR (60.1,)
PFS rate at 24 weeks, % (95% CI)	51 (28, 70)
Median PFS, weeks (range)	29.4 (4.6, 81.7+)
1-year OS rate, % (95% CI)	71 (46, 88)
Median OS, weeks (range)	NR (10.7+, 86.9+)

Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8022.

Pembrolizumab (MK-3475) in Treated/Untreated NSCLC: Phase I



Primary endpoints:

- DLTs
- AEs
- Response rate (primary RECIST, secondary irRC)
- Biomarker expression

Garon EB, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8020. Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8007.

Phase I Study of Pembrolizumab in Pretreated NSCLC: Results

	RECIST v1.1		Immune-Related Response Criteria	
	PDL1+ n = 159	PDL1- n= 35	PDL1+ n = 177	PDL1- n = 40
ORR, %	23	9	19	12
Disease control rate, %	42	31	51	53
Response duration, weeks, median	31	NR	NR	NR

Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8007.

Pembrolizumab as Initial Therapy in Advanced NSCLC and PDL1 Expressing Tumors

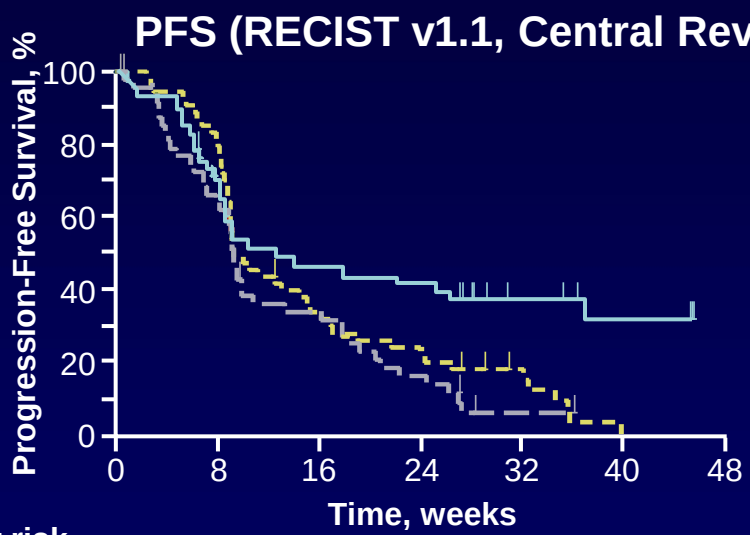
	RECIST v1.1 per Independent Central Review	Immune-Related Response Criteria per Investigator Assessment
ORR, %	26	47
Interim median PFS (95% CI), weeks	27.0 (13.6, 45.0)	37.0 (27.0, NR)
Responses ongoing, n/N (%)	11/11 (100)	19/21 (90)
Responders remaining on treatment, n/N (%)	7/11 (64)	18/21 (86)

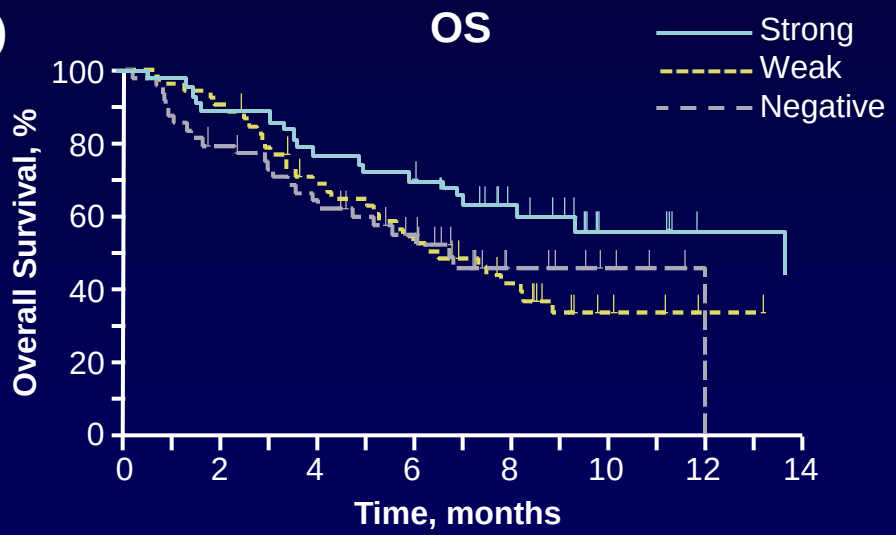
- Treatment-related AEs (any grade) occurring in >5% of patients: fatigue (22%), pruritus (13%), hypothyroidism (9%), dermatitis acneiform (7%), diarrhea (7%), dyspnea (7%) and rash (7%)

Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8007.

Activity of Pembrolizumab and Correlation with PDL1 Expression in a Pooled Analysis of Advanced NSCLC

Strong PDL1 positivity defined as staining in ≥50% of tumor cells, and weak PDL1 positivity as staining in 1% to 49% of tumor cells. Negative staining is no PDL1 staining in tumor cells





n at risk							
Strong	44	28	18	17	9	6	3
Weak	53	43	17	12	6	0	0
Negative	49	30	15	7	1	0	0

44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

- **MK-3475 effective, in particular in patients with strong PDL1 tumor expression**

Garon , et al. *Ann Oncol.* 2014;25(suppl 4):Abstract LBA43

MPDL3280A in Pretreated NSCLC

Phase Ia expansion study ongoing, ≥1 prior lines of therapy, stage IIIB/IV NSCLC cohort

	RECIST 1.1 ORR, %	SD ≥24 Weeks, %	24-Week PFS Rate, %
Overall (N = 175)	21	19	42
NSCLC (n = 53)	23	17	45
Nonsquamous (n = 42)	21	17	44
Squamous (n = 11)	27	18	46

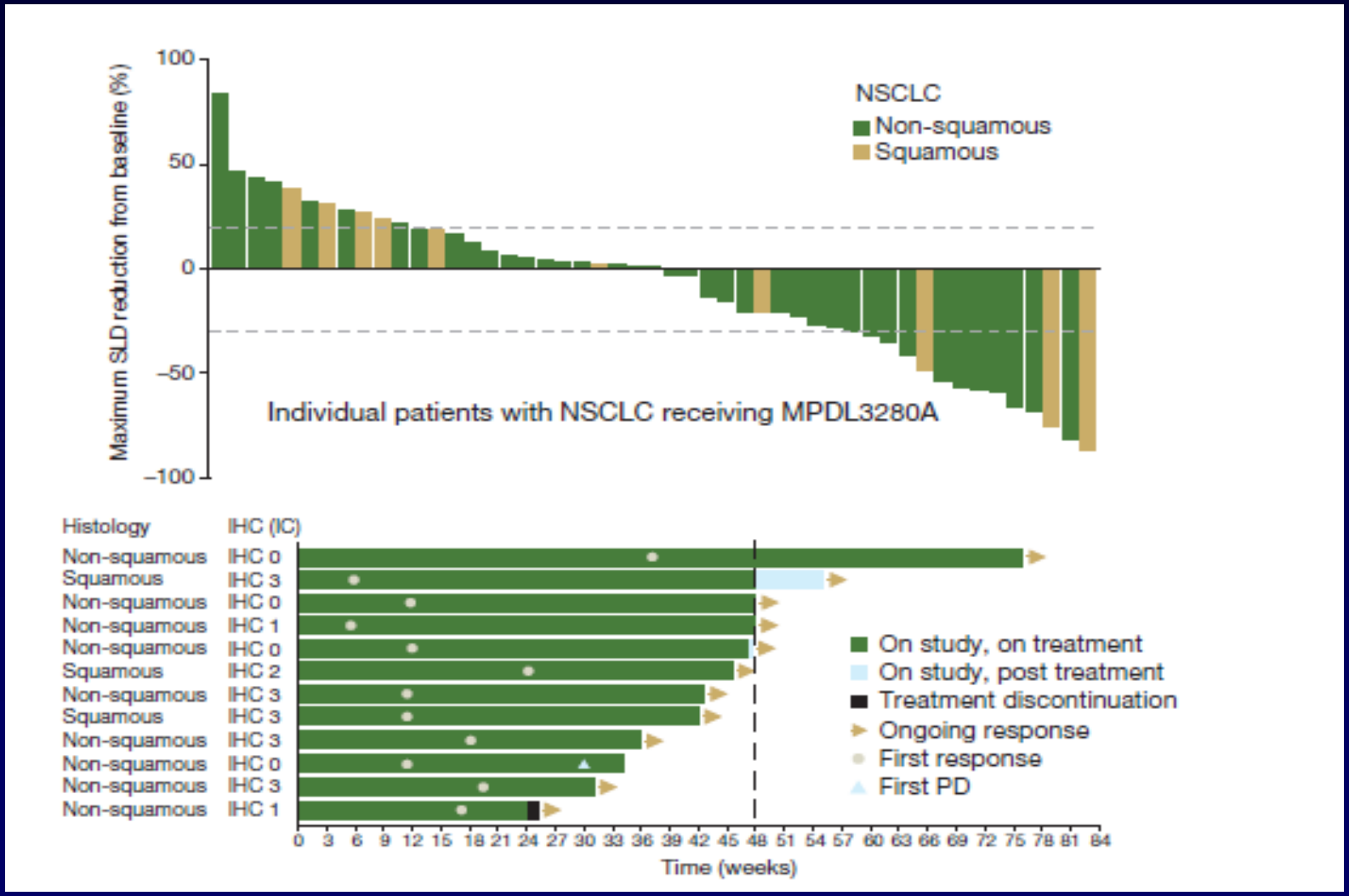
Herbst RS, et al. *Nature.* 2014;515(7528):563-567.

MPDL3280A Phase I: RR by PDL1 IHC Status

Diagnostic Population (n = 53)	ORR % (n/n)	PD Rate % (n/n)
IHC 3	83% (5/6)	17% (1/6)
IHC 2 and 3	46% (6/13)	23% (3/13)
IHC 1/2/3	31% (8/26)	38% (10/26)
All patients	23% (12/53)	40% (21/53)

Herbst RS, et al. *Nature.* 2014;515(7528):563-567.

MPDL3280A in Pretreated NSCLC



Herbst RS, et al. *Nature.* 2014;515(7528):563-567.

MPDL3280A Activity Across NSCLC Patient Subpopulations

Subgroup	ORR, % (n/N)
EGFR status	
Mutant	17 (1/6)
Wildtype	23 (9/40)
KRAS status	
Mutant	10 (1/10)
Wildtype	30 (8/27)
Smoking	
Current/former smokers	26 (11/43)
Never smokers	10 (1/10)

Herbst RS, et al. *Nature.* 2014;515(7528):563-567.

MPDL3280A in Pretreated NSCLC

Treatment-related AEs ($n = 277$)		
Events (≥4% of patients)	Any grade (n (%))	Grade 3–4 (n (%))
Any AE	194 (70.0)	35 (12.6)
Fatigue	67 (24.2)	5 (1.8)
Decreased appetite	33 (11.9)	–
Nausea	32 (11.6)	1 (0.4)
Pyrexia	32 (11.6)	–
Diarrhoea	29 (10.5)	–
Rash	29 (10.5)	–
Pruritus	23 (8.3)	–
Arthralgia	22 (7.9)	–
Headache	21 (7.6)	1 (0.4)
Chills	19 (6.9)	–
Influenza-like illness	16 (5.8)	1 (0.4)
Asthenia	15 (5.4)	2 (0.7)
Dyspnea	15 (5.4)	2 (0.7)
Pain	15 (5.4)	1 (0.4)
Myalgia	13 (4.7)	–
Anaemia	12 (4.3)	2 (0.7)
Dry skin	12 (4.3)	–
Night sweats	12 (4.3)	–
Vomiting	11 (4.0)	1 (0.4)
Other grade 3–4 AEs, ≥2 patients		
ALT increased	6 (2.2)	3 (1.1)
AST increased	4 (1.4)	3 (1.1)
Hypoxia	4 (1.4)	3 (1.1)
Hyperglycaemia	4 (1.4)	2 (0.7)
Hyponatraemia	4 (1.4)	2 (0.7)
Cardiac tamponade	2 (0.7)	2 (0.7)
Hypophosphataemia	2 (0.7)	2 (0.7)
Tumour lysis syndrome	2 (0.7)	2 (0.7)

- **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**

Herbst RS, et al. *Nature.* 2014;515(7528):563-567.

MEDI-4736 Activity and Safety in Pretreated NSCLC

Phase I dose expansion study, ≥1 prior lines of therapy, stage IIIB/IV squamous and non-squamous NSCLC cohort

	ORR RECIST v1.1, n/N (%)
	MEDI-4736 All Evaluated Doses
Total evaluable	9/58 (16)
PD-L1 positive	5/20 (25)
PD-L1 negative	1/29 (3)

- Low rates of treatment-related grade 3-4 AEs
  - 10 mg/kg Q2W, 4%; all doses: 3%
- Most common related grade ≥3 AE was arthralgia (1%)
- No drug-related colitis; no grade 3-4 pneumonitis or dyspnea

Brahmer JR, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8021.

Biomarkers in NSCLC

Which of the following statements regarding efficacy and safety of single agent therapy with an anti-programmed death-1 (PD-1) or anti-programmed death-1 ligand (PD-L1) antibody in pretreated NSCLC is FALSE?

1. Early-phase clinical trials of heavily-pretreated patients with advanced NSCLC receiving single-agent anti-PD-1 or anti PD-L1 therapy have shown response rates of approximately 20% (using RECIST criteria)
2. In some of the responding NSCLC patients treated with anti-PD-1 and anti-PD-L1 antibodies duration of response have been observed in the range of 1 to 2 years
3. Patients with squamous and non-squamous NSCLC respond similarly to these agents
4. Tumor responses to these agents may include initial increase in tumor size and appearance of new lesions
5. Only patients with PD-L1 expression respond
6. No grade 3/4 pneumonitis was reported with anti-PD-L1 antibodies

N Engl J Med. 2012;366(26):2443-2454.
The NEW ENGLAND JOURNAL of MEDICINE

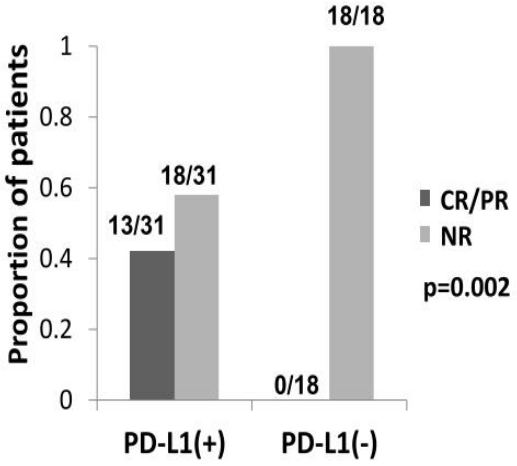
ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

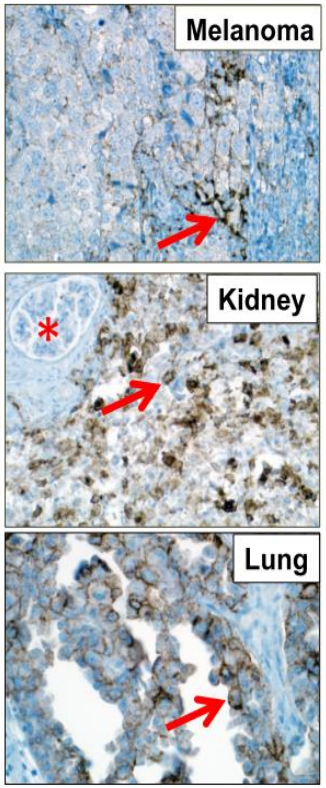
Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

Preliminary molecular marker studies: Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical response to anti-PD-1

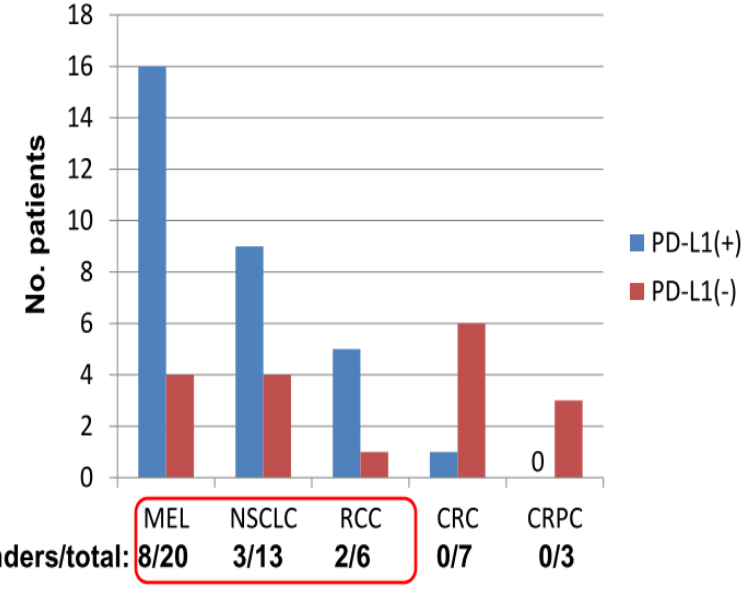


49 patients include 20 with melanoma,13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.



* Normal renal glomerulus

Correlation of PD-L1 expression with tumor type in 49 patients treated with anti-PD-1



Patients were "PD-L1+" if ≥5% of tumor cells in *any* tumor biopsy expressed cell surface PD-L1, using mAb 5H1 (L. Chen) and manual staining technique.

PDL1 Analysis: Differences in Evaluation and Interpretation

Agent	Assay	Analysis	Definition of positivity
BMS-936558 (Nivolumab)	Dako automated IHC assay (28-8 rabbit Ab) Analytically validated	Archival FFPE	1% and 5% cut-off among >100 evaluable tumour cells
MK-3475 (Pembrolizumab)	Dako automated IHC assay (22C3 mouse Ab)	New tumor biopsy within 60 days prior to first dose of pembrolizumab	Tumor dependent: Melanoma >1% NSCLC; PD-L1 (+): Strong (≥50%) and weak staining (1% to 49%) PD-L1 (–): no staining
MPDL3280A	Ventana automated clinical research IHC assay	Archival FFPE	PD-L1 (+): IHC 3 (≥10%), IHC 2,3 (≥5%), IHC 1,2,3 (≥1%) PD-L1 (–): IHC 0 (<1%)
MEDI-4736	First-generation or Ventana IHC Automated Assay (in development)	Archival FFPE	Not reported

Gettinger SN, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8024. Topalian SL, et al. *N Engl J Med*. 2012;366(26):2443-2454. Garon E, et al. 2014;32(5s): Abstract 8020. Gandhi L, et al. *AACR Meeting Abstracts.* 2013;Abstract CT105. Soria JC, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract 3408. 8. Rizvi N, et al. *J Clin Oncol.* 2014;32(5s): Abstract TPS 8123. Brahmer J, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8021.

Challenges With PDL1 Assessment

- Tumor heterogeneity
- Small tumor sample
- Fresh tumor vs archival samples
- PD-L1 expression may change over time
- Different IHC mAB, different cut-off for PDL1 positivity

PD1 and PDL1 Inhibitors: Questions to Answer

- Best predictive marker for response: PD-L1, smoking history, mutations?
- Optimal cut-off for PDL1 positivity and the best IHC mAb?
- Optimal dose and treatment sequence?
- Best surrogate of efficacy (RECIST vs irRC)?
- Activity in CNS?
- Any role in the adjuvant setting?

Immune-Based Antitumor Therapies in Advanced NSCLC: Conclusions

- Responses in all histologic types
- Toxicity profiles differ from that of CT; generally much better tolerated
- Identification of biomarkers is complex; PDL1 the most analyzed but some PDL1 negative patients also benefit
- PD1 and PDL1 inhibitors, promising results in NSCLC, suspected impact on long-term survival
- Treatment algorithm, first-line? Second-line?
- Targeting PD1/PDL1 means new hope for patients with NSCLC

Thanks!!

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