2016 NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

LIVE WEBINARS

Immunotherapy in Patients with Non-Small Cell Lung Cancer

Presented by:

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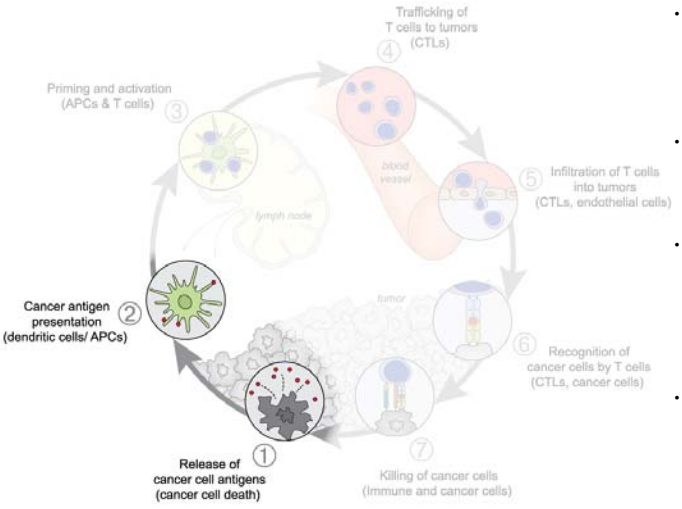
Vanderbilt-Ingram Cancer Center

July 14, 2016

Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

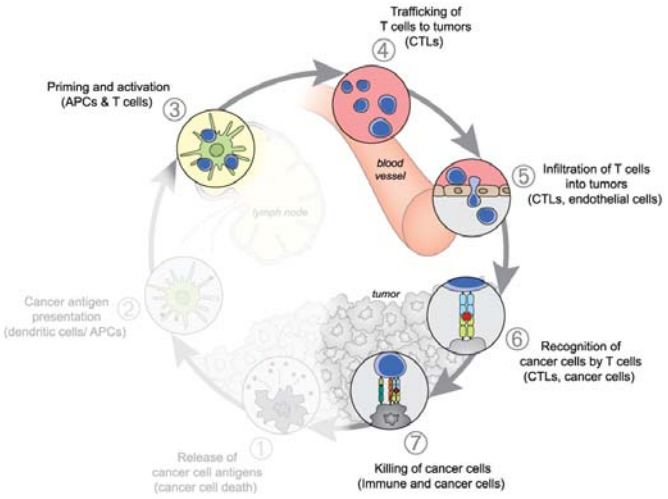
Cancer Immunotherapy



- Cancer cells may express tumor-specific antigens due to the presence of mutations
- These antigens may induce an immune response
- Up-regulation of PD-L1 in the tumor microenvironment enables cancers to evade T-cell–mediated killing
- Inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interaction may restore antitumor T-cell activity

Chen DS, Mellman Immunity 39(1): 1-10 (2013)

Cancer Immunotherapy



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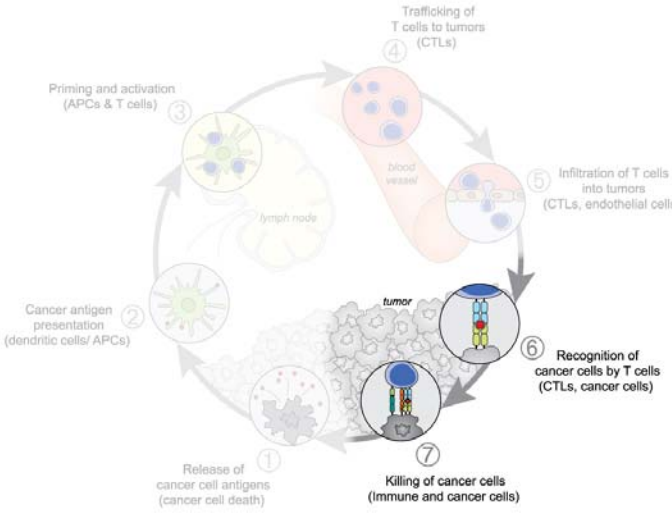

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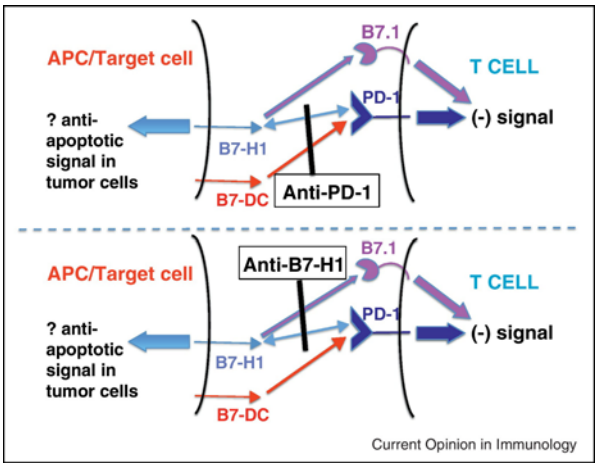
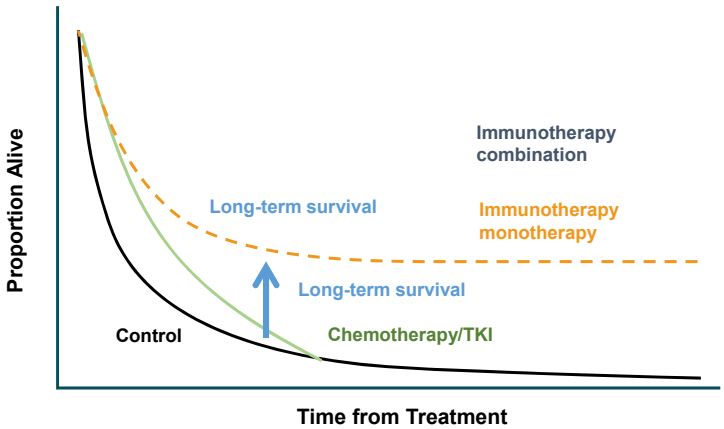
Chen DS, Mellman Immunity 39(1): 1-10 (2013)

Potential Differences in PD-1 vs. PD-L1 Blockade



Topalian SL, et al. Curr Opin Immunol.24:207-212 (2012)

Hypothetical Goals of Immunotherapies



Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

TKI = tyrosine kinase inhibitor.
Adapted from Sharma P, Allison JP. *Cell*. 2015;161(2):205-214.

Clinical Development of Immune Checkpoint Inhibitors

Target	Antibody	Molecule	Development stage
CTLA-4	Ipilimumab	Human IgG1	Approved in Melanoma
	Tremelimumab	Human IgG2	Phase 3
PD-1	Nivolumab	Human IgG4	MEL, NSCLC, RCC
	Pembrolizumab	Humanized IgG4	MEL, PD-L1 + NSCLC
	PDR001	Humanized IgG4	Phase 1
	REGN2810	Human IgG4	Phase I
PD-L1	Durvalumab	Engineered human IgG1	Phase 3
	Atezolizumab	Engineered human IgG1	Approved in Bladder Cancer
	Avelumab	Human IgG1	Phase 3

PD-L1 Testing Is Controversial

- Different assays have not been compared
- Each assay has different cut point that defines PD-L1 positive
- What is better: archival tissue or fresh tissue?
- Where do you biopsy: the primary tumor or metastatic site?
- Is tissue from a core the only way to evaluate for expression?

Comparison of Response by PD-L1 Status: Phase I Data

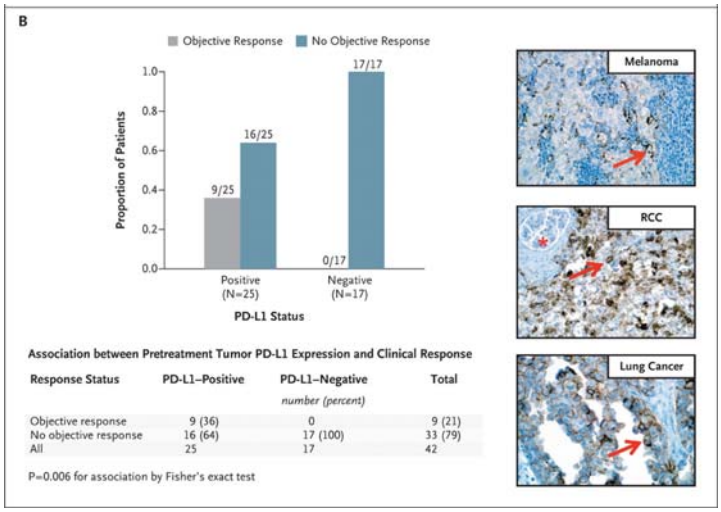
Drug	Target	RR	PDL1+/PDL-
Nivolumab	PD-1	17%	15%/14%
Pembrolizumab	PD-1	22%%	17-37%/10%
Atezolizumab	PD-L1	23%	31%/14%
Durvalumab	PD-L1	16%	25%/10%
Avelumab	PD-L1	12%	14%/10%

PD-L1 as a Prognostic Marker

- PD-L1 expression has been identified as a negative prognostic marker
  - Increased risk of metastases and death in renal cell cancer[1]
  - More aggressive phenotype in melanoma[2]
  - Increased risk of metastases and death in lung cancer[3]
  - Increased risk of metastatic disease in gastric cancer[4]

1. Thompson et al. Proc Natl Acad Sci USA. 2004; 101:17174-9
2. Mu et al. Med Oncol. 2011;28:682-8.
3. Massi et al. Ann Oncol. 2014; 25(12):2433-42
4. Chin J Cancer Res. 2014; 26(1): 104–111

PD-L1 as a Predictive Marker: Response Based on PD-L1 Expression



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

RCC = renal cell cancer

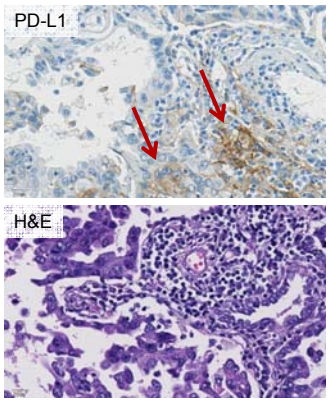
Topalian SL et al. N Engl J Med 2012;366:2443-2454.

PD-L1 Is Broadly Expressed in NSCLC

Positive PD-L1 staining in NSCLC

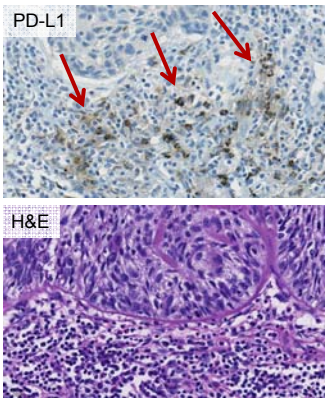
Adenocarcinoma

Prevalence of PD-L1 ≈ 45%



Squamous cell carcinoma

Prevalence of PD-L1 ≈ 50%



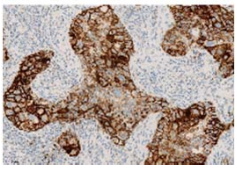
Koeppen H. and Kowanetz M., Proprietary assay PD-L1 IHC

High sensitivity and specificity in formalin-fixed, paraffin-embedded (FFPE) samples

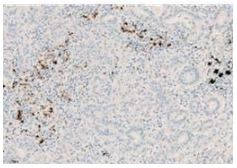
Soria et al. ESMO 2013

PD-L1 expression on TCs and ICs

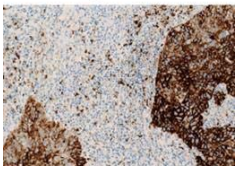
Staining in TCs



Staining in ICs



Staining in TCs and ICs



IC Score	PD-L1 IC staining	TC Score	PD-L1 TC staining
IC3	IC ≥ 10%	TC3	TC ≥ 50%
IC2	IC ≥ 5% and < 10%	TC2	TC ≥ 5% and < 50%
IC1	IC ≥ 1% and < 5%	TC1	TC ≥ 1% and < 5%
IC0	IC < 1%	TC0	TC < 1%

IC = tumor-infiltrating immune cell ; TC = tumor cell

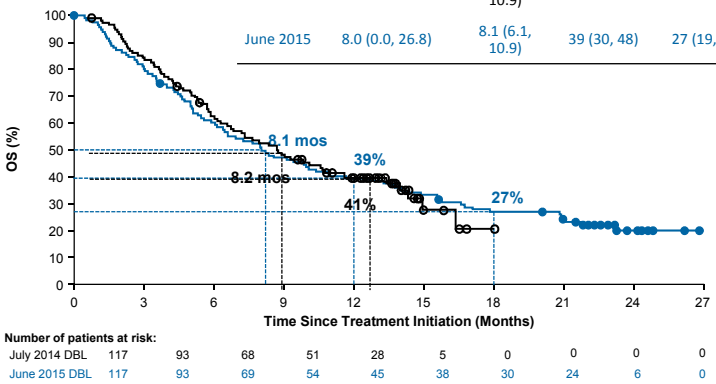
RS Herbst *et al. Nature* 515, 563-567 (2014)

What assay do we use ?
LDT or FDA approved assay ? Cut off ?

	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)	Durvalumab (anti-PD-L1)	Atezolizumab (anti-PD-L1)	Avelumab (anti-PD-L1)
Clones	22C3	28-8	SP263	SP142	?
Machines Utilized	Link 48	Link 48	BenchMark ULTRA	BenchMark ULTRA	?
Compartment	TM	TM	TM	TC/IC	?
Variables	% of cells	% of cells	% of cells	% of cells	?
Definition of positive	PD-L1(+): >1% Strong(+): >50%	PD-L1(+): >1% Strong(+): >5%	PD-L1(+): ≥25%	TC / IC 3(+) TC / IC 2(+) TC / IC 1(+) TC / IC 0(–)	?

Phase 2: CHECKMATE-063: Overall Survival (OS) : All Treated Patients

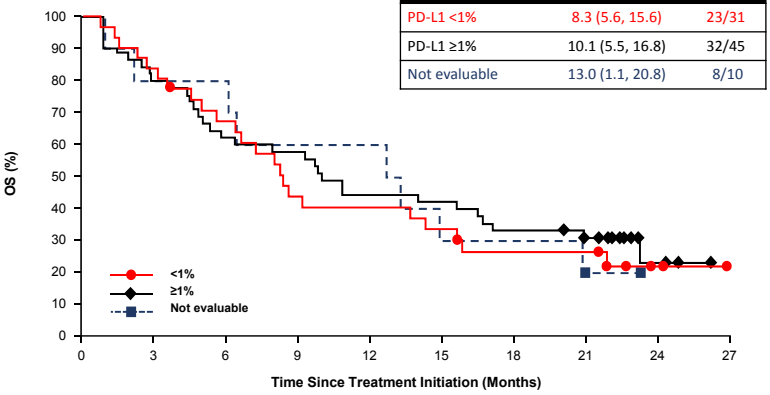
DBL	Median follow-up, mos (range)	Median OS, mos (95% CI)	1-yr OS rate, % (95% CI)	18-mo OS rate, % (95% CI)	Events, n/N
July 2014	8.0 (0.0, 17.3)	8.2 (6.1, 10.9)	41 (32, 50)	–	72/117
June 2015	8.0 (0.0, 26.8)	8.1 (6.1, 10.9)	39 (30, 48)	27 (19, 35)	90/117



Horn et al., WCLC 2015

Overall Survival by PD-L1 Expression

	Median OS, mos (95% CI)	Events, n/N
PD-L1 <1%	8.3 (5.6, 15.6)	23/31
PD-L1 ≥1%	10.1 (5.5, 16.8)	32/45
Not evaluable	13.0 (1.1, 20.8)	8/10



Horn et al., WCLC 2015

CheckMate 017 (NCT01642004)

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

N = 272

Randomize 1:1

Nivolumab
3 mg/kg IV Q2W
until PD or
unacceptable toxicity
n = 135

Docetaxel
75 mg/m² IV Q3W
until PD or
unacceptable toxicity
n = 137

- **Primary Endpoint:**
  - OS
- **Additional Endpoints:**
  - Investigator-assessed ORR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

CheckMate 057 (NCT01673867)

- Stage IIIB/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed[a]
- Prior TKI therapy allowed for known *ALK* translocation or *EGFR* mutation

N = 582

Randomize 1:1

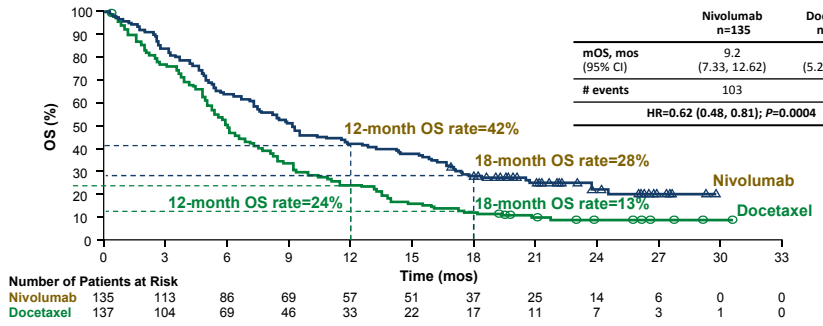
Nivolumab
3 mg/kg IV Q2W
until PD or
unacceptable toxicity
n = 292

Docetaxel
75 mg/m² IV Q3W
until PD or
unacceptable toxicity
n = 290

- **Primary Endpoint**
  - OS
- **Additional Endpoints**
  - ORR[b]
  - PFS[b]
  - Safety
  - Efficacy by tumor PD-L1 expression
  - Quality of life (LCSS)

Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

Checkmate 017: Overall Survival



	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122

HR=0.62 (0.48, 0.81); *P*=0.0004

Number of Patients at Risk

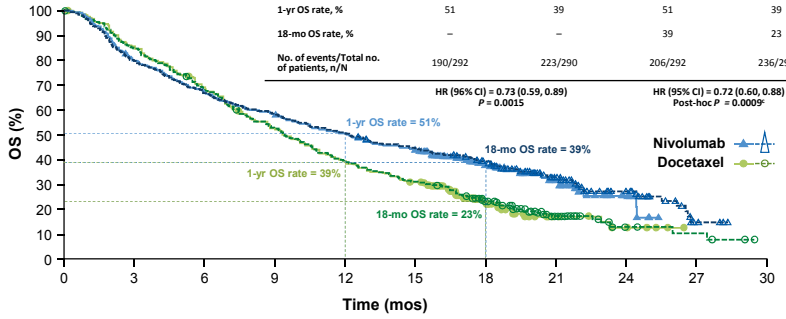
Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 months

Reckamp et al., WCLC 2015

Checkmate 057: Overall Survival

	12-mo OS[a]		18-mo OS[b]	
	Nivo (n = 292)	Doc (n = 290)	Nivo (n = 292)	Doc (n= 290)
mOS, mos	12.2	9.4	12.2	9.4
1-yr OS rate, %	51	39	51	39
18-mo OS rate, %	–	–	39	23
No. of events/Total no. of patients, n/N	190/292	223/290	206/292	236/290
	HR (96% CI) = 0.73 (0.59, 0.89) *P* = 0.0015		HR (95% CI) = 0.72 (0.60, 0.88) Post-hoc *P* = 0.0009[c]	



No. of patients at risk (12-mo OS)[a]											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. of patients at risk (18-mo OS)[b]											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

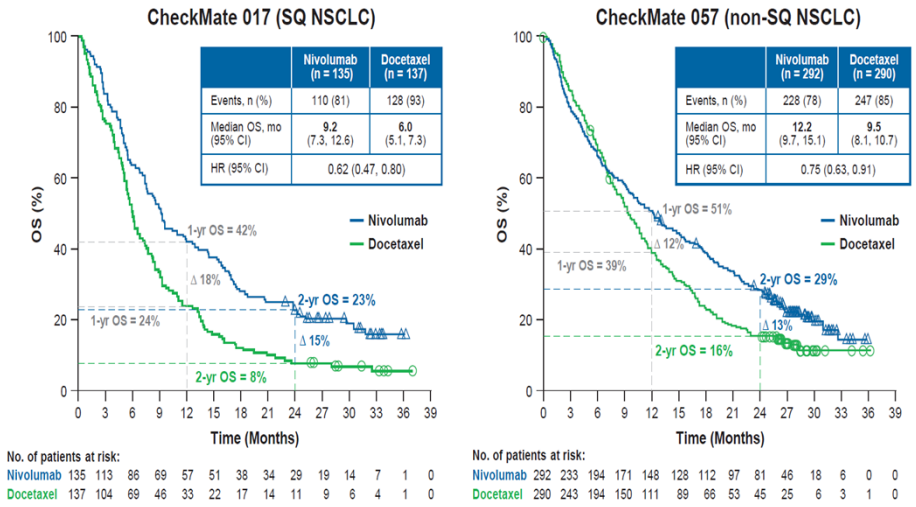
• Minimum follow-up for 12-mo OS rate, 13.2 mos; for 18-mo OS rate, 17.1 mos

[a]Based on a March 18, 2015, DBL. [b]Based on a July 2, 2015, DBL. [c]The formal primary end point testing was based on the interim analysis (March 18, 2015). For full description of the additional follow-up data, an updated p-value is provided based on the July 2, 2015, DBL.
Symbols represent censored observations.

Horn et al. ESMO

Nivolumab 2 year OS

Figure 4. Kaplan–Meier estimates of OS (2 years minimum follow-up)



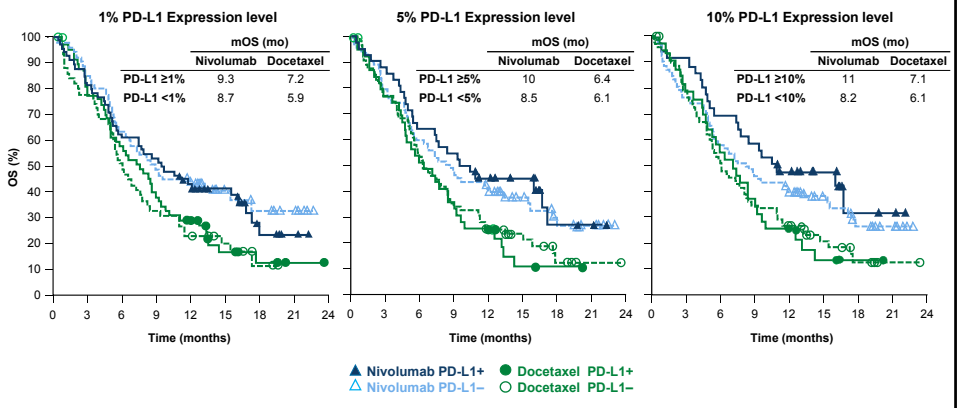
Borghaei H, et al ASCO 2016: Abstract 9025.

ORR to Nivolumab by PD-L1 Expression

	PD-L1 Expression Level						
	≥1%	<1%	≥5%	<5%	≥10%	<10%	Not quantifiable[a]
Squamous							
ORR,[b] % (n/N)	18	17	21	15	19	16	39
Nonsquamous							
ORR,[a] %	30.9	9.3	35.8	10.3	37.2	11.0	13.1

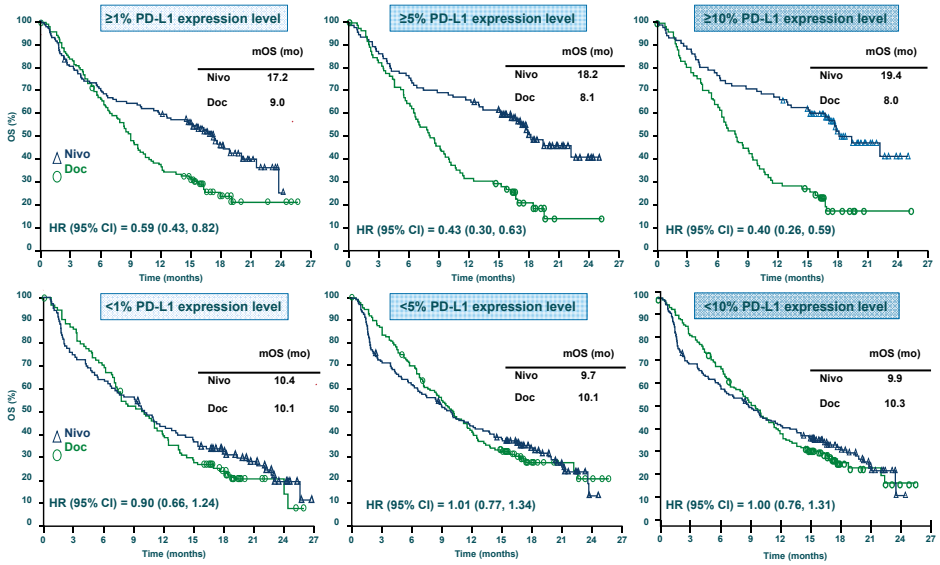
Reckamp et al., WCLC 2015; Horn et al., ESMO 2015

OS by PD-L1 Expression: Squamous



Spigel D et al., ASCO 2015.

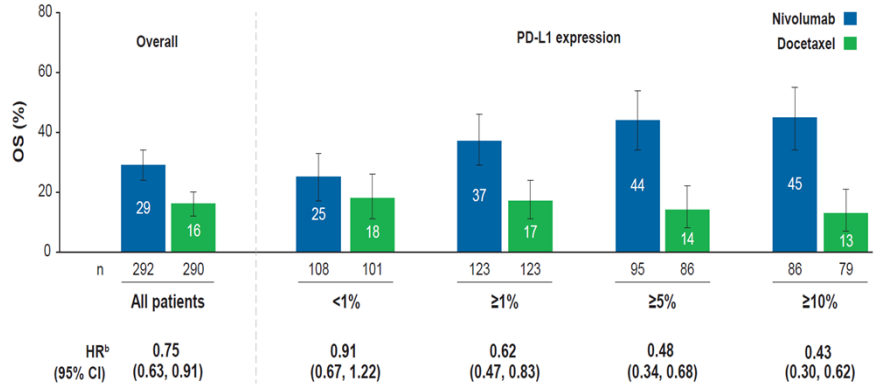
OS by PD-L1 Expression: Nonsquamous



Paz-Arez L et al., ASCO 2015.

Symbols represent censored observations.

2-Year OS Rates[a] Overall and by PD-L1 Expression Level in CheckMate 057 (Non-SQ NSCLC)



- In CheckMate 057, consistent with the primary analysis,[2] PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)

[a]Kaplan–Meier estimates, with error bars indicating 95% CIs
[b]For the comparison of the full Kaplan–Meier survival curves for each treatment group

Borghaei H, et al ASCO 2016: Abstract 9025.

Updated Treatment and Safety Summary: Squamous

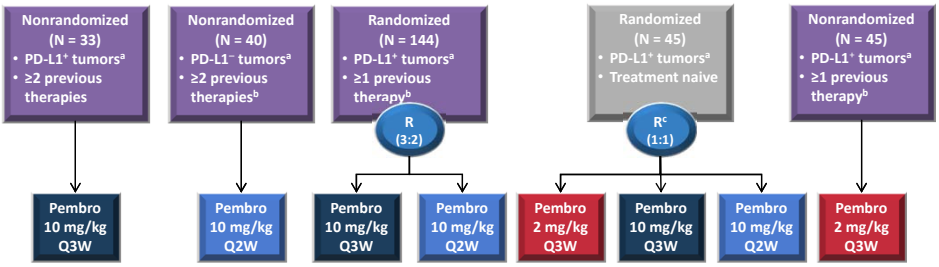
	Nivolumab n=131		Docetaxel n=129	
	Any grade	Grade 3–5[a]	Any grade	Grade 3–5
Treatment-related AEs, %	59	8	87	58
Treatment-related AEs leading to discontinuation, %	5[b]	3	10[c]	7
Treatment-related deaths, %	0		2[d]	

- Median number of doses was 8 (range, 1–56) for nivolumab and 3 (range, 1–29) for docetaxel

Based on June 2015 DBL. Includes events reported between first dose and 30 days after last dose of study therapy. [a]No grade 5 events were reported with nivolumab. [b]1% of pts had increased ALT, increased AST, increased lipase, myasthenic syndrome, colitis, or rash, and 2% of pts had pneumonitis. [c]Peripheral neuropathy (3%) and fatigue (2%) were the most frequently reported events (≥2% patients) leading to discontinuation. [d]Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 pt each)

Reckamp et al., WCLC 2015

KEYNOTE-001 Study: Pembrolizumab (MK3475) in NSCLC Expansion Cohorts (N = 550)

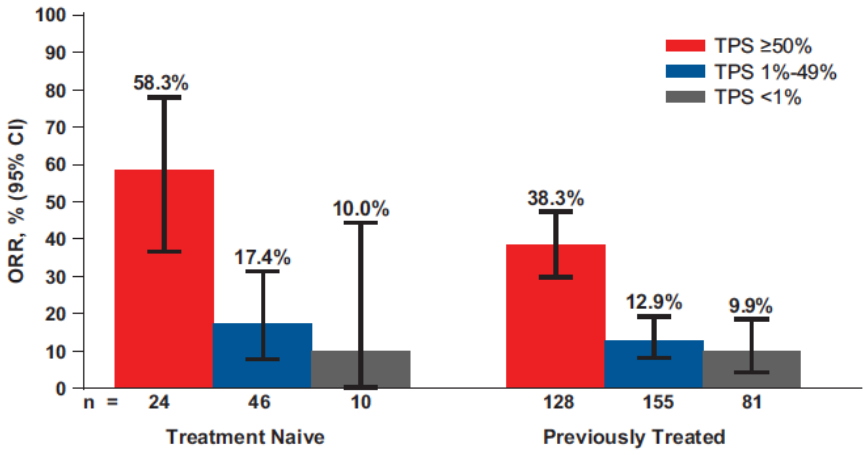


- Response assessment
  - Primary measure: ORR by RECIST v1.1[1] per independent central review
  - Secondary measure: immune-related response criteria (irRC)[2] per investigator assessment
- Pembrolizumab was given until disease progression, unacceptable toxicity, or death
  - Analysis cut-off date: March 3, 2014[d]

[a]Tumor PD-L1 expression was determined by a prototype assay to inform enrollment. Samples were independently reanalyzed using a clinical trial IHC assay. [b]Including ≥1 therapy platinum-containing doublet. [c]First 11 patients randomized to 2 mg/kg Q3W and 10 mg/kg Q3W. The remaining 34 patients were randomized to 10 mg/kg Q2W and 10 mg/kg Q3W. [d]Analysis cut-off date is September 11, 2014 for the nonrandomized cohort of 45 patients treated at 2 mg/kg Q3W.
1. Eisenhauer EA et al. *Eur J Cancer*. 2009;45:228-247. 2. Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412-20.

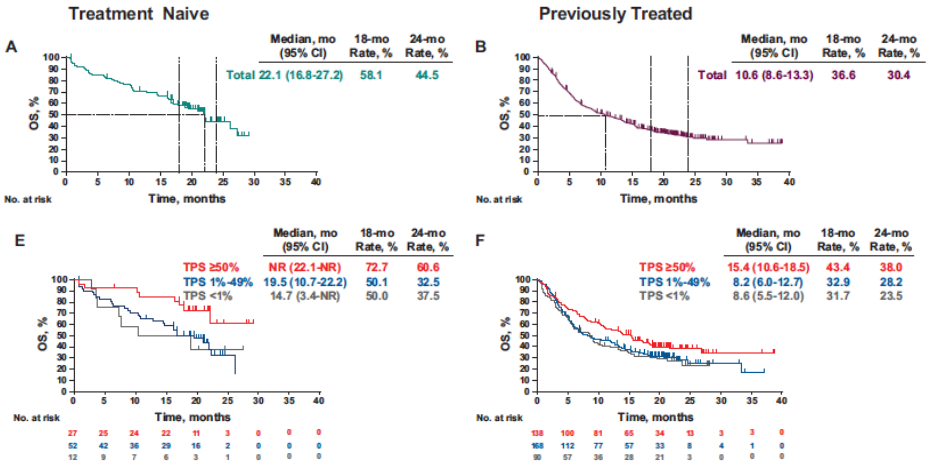
Hellman et al., WCLC 2015

Keynote-001 Pembrolizumab Response



Hui R, et al ASCO 2016: Abstract 9026.

Keynote-001 Pembrolizumab OS



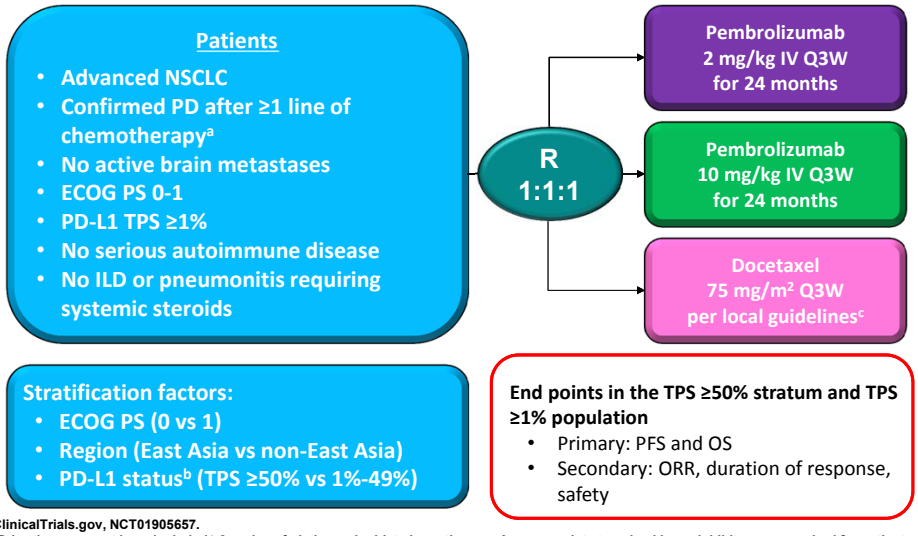
Hui R, et al ASCO 2016: Abstract 9026.

Keynote-001 Pembrolizumab OS in Key Subgroups

Subgroup	TPS ≥50%		TPS ≥1%		TPS <1%	
	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)	n/N[a]	Median, months (95% CI)
Histology						
Squamous	16/28	14.0 (8.0-NR)	33/54	14.0 (8.3-17.9)	12/15	14.7 (1.2-18.4)
Nonsquamous	65/108	15.4 (9.9-18.8)	164/248	10.5 (7.1-13.7)	50/73	8.6 (5.5-10.6)
Smoking history						
Current or former	59/108	15.7 (11.1-NR)	136/221	13.2 (9.4-15.6)	47/66	8.6 (4.9-13.3)
Never	23/30	8.2 (4.9-17.3)	63/85	7.3 (5.1-13.7)	17/24	9.1 (4.2-21.3)
EGFR mutation status						
Wild type	60/109	15.7 (11.1-NR)	152/245	13.2 (9.2-15.4)	51/71	9.1 (5.8-13.6)
Mutant	17/19	6.5 (2.0-13.7)	37/45	6.5 (4.4-12.6)	11/17	5.7 (2.2-NR)

Hui R, et al ASCO 2016: Abstract 9026.

KEYNOTE-010 Study Design



ClinicalTrials.gov, NCT01905657.
[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.
[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).
[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

ORR (RECIST v1.1, Central Review)

PD-L1 TPS ≥50%	Pembro 2 mg/kg n = 139	Pembro 10 mg/kg n = 151	Docetaxel n = 152
ORR, % (95% CI)	30 (23-39) P < 0.0001[a]	29 (22-37) P < 0.0001[a]	8 (4-13)

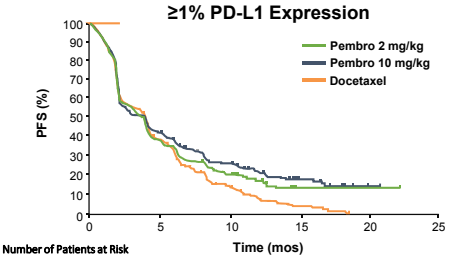
PD-L1 TPS ≥1%	Pembro 2 mg/kg n = 344	Pembro 10 mg/kg n = 346	Docetaxel n = 343
ORR, % (95% CI)	18 (14-22) P = 0.0005[a]	18 (14-23) P = 0.0002[a]	9 (6-13)

Analysis cut-off date: September 30, 2015.

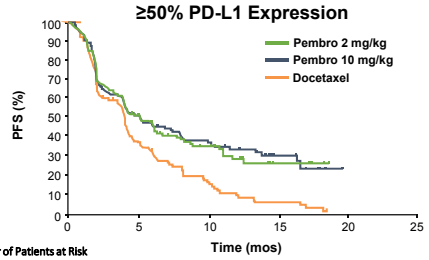
Herbst RS et al. Oral presentation at ESMO Asia 2015

[a]Comparison of pembrolizumab vs docetaxel.

Progression-Free Survival at TPS ≥1% and TPS ≥50%



Number of Patients at Risk						
2 mg/kg	344	122	46	12	1	0
10 mg/kg	346	137	60	19	1	0
Docetaxel	343	103	27	6	0	0



Number of Patients at Risk						
2 mg/kg	139	66	29	6	0	0
10 mg/kg	151	72	36	12	0	0
Docetaxel	152	45	17	5	0	0

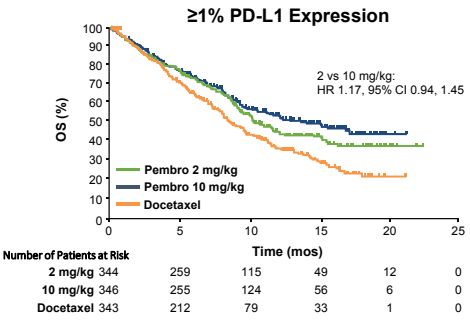
Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	3.9 (3.1, 4.1)	0.88 (0.74, 1.05)	0.07
Pembro 10 mg/kg	4.0 (2.7, 4.3)	0.79 (0.66, 0.94)	0.004
Docetaxel	4.0 (3.1, 4.2)	–	–

Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	5.0 (4.0, 6.5)	0.59 (0.44, 0.78)	0.0001
Pembro 10 mg/kg	5.2 (4.1, 8.1)	0.59 (0.45, 0.78)	<0.0001
Docetaxel	4.1 (3.6, 4.3)	–	–

[a]Comparison of pembrolizumab vs docetaxel. Analysis cut-off date: September 30, 2015.
HR = hazard ratio; mos = months; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; PFS = progression-free survival; TPS = tumor proportion score.

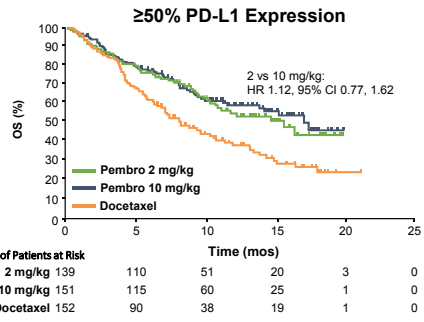
Herbst RS et al. Oral presentation at ESMO Asia 2015.

Overall Survival at TPS ≥1% and TPS ≥50%



Number of Patients at Risk						
2 mg/kg	344	259	115	49	12	0
10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Treatment Arm	Median (95% CI), mo	Rate at 1-yr	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	10.4 (9.4, 11.9)	43.2%	0.71 (0.58, 0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0, 17.3)	52.3%	0.61 (0.49, 0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	–	–



Number of Patients at Risk						
2 mg/kg	139	110	51	20	3	0
10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

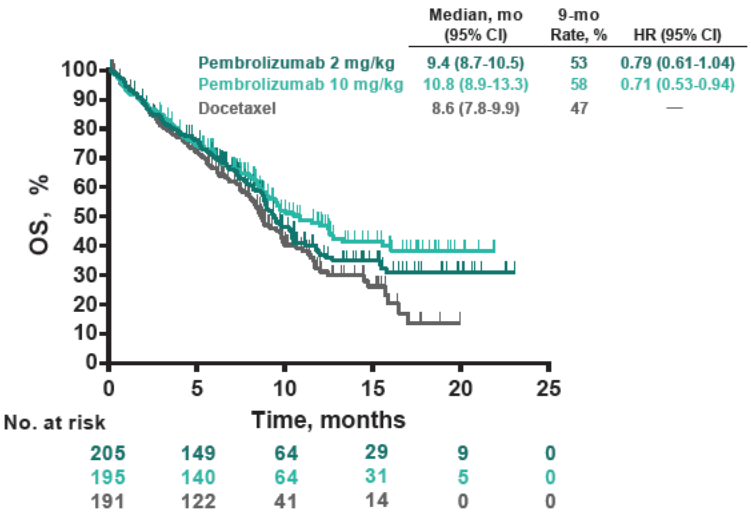
Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P* value
Pembro 2 mg/kg	14.9 (10.4, NR)	0.54 (0.38, 0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8, NR)	0.50 (0.36, 0.70)	<0.0001
Docetaxel	8.2 (6.4, 10.7)		–

[a]Comparison of pembrolizumab vs docetaxel. Analysis cut-off date: September 30, 2015.
HR = hazard ratio; mos = months; NR = not reached; OS = overall survival; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; TPS = tumor proportion score.

Herbst RS et al. Oral presentation at ESMO Asia 2015.

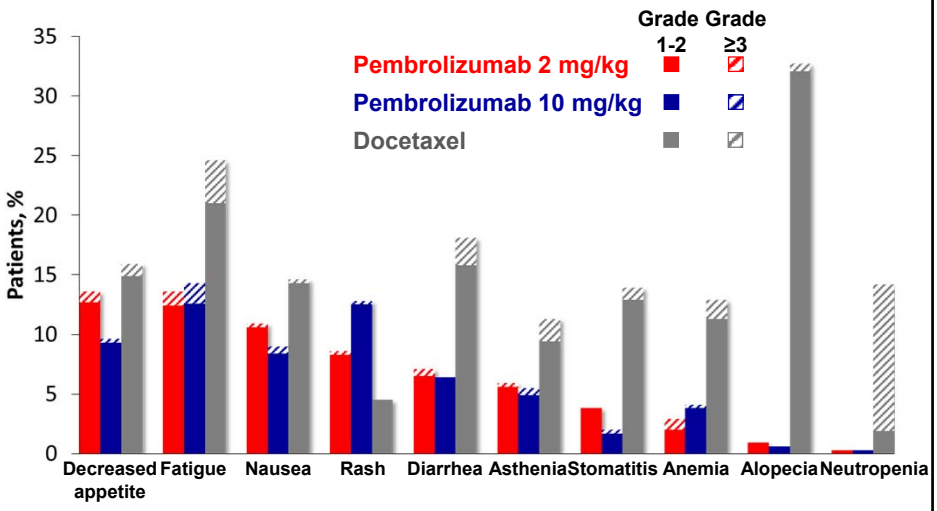
Keynote-010

Figure 2. Kaplan-Meier estimates of OS in the PD-L1 TPS 1%-49% stratum.



Garon et al, ASCO 2016

Treatment-Related AEs With Incidence ≥10% in Any Arm, TPS ≥1%



Analysis cut-off date: September 30, 2015.

Herbst RS et al. Oral presentation at ESMO Asia 2015

POPLAR: A Randomized All-comer Phase II Study

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on a prior platinum therapy
N = 287

Stratification Factors
- PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

R 1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m^2 IV q3w
until disease progression

Primary study objective:
- **Estimate OS by PD-L1 expression**

Secondary study objectives:
- Estimate PFS, ORR and DOR by PD-L1 expression
- Evaluate safety

Interim analysis is based on 153 events with a minimum follow-up 10 months.

Spira AI, et al: Presented at ASCO 2015; Oral Presentation #8010.

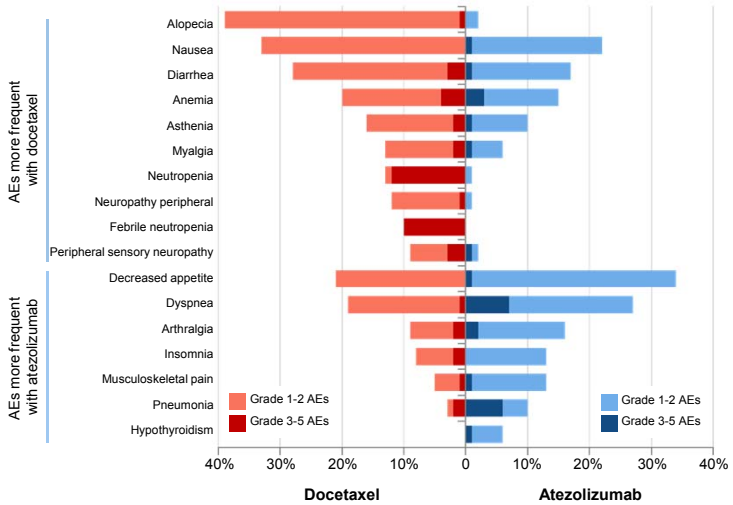
POPLAR: Atezolizumab vs Docetaxel in NSCLC Updated OS, Biomarker analyses

	Atezolizumab		Docetaxel		HR (95% CI)	P Value
	n	Median OS, Mos	n	Median OS, Mos		
ITT	144	12.6	143	9.7	0.69 (0.52-0.92)	.011
TC3 or IC3	24	Not reached	23	11.1	0.45 (0.22-0.95)	.033
TC2/3 or IC2/3	50	15.1	55	7.4	0.50 (0.31-0.80)	.003
TC1/2/3 or IC1/2/3	93	15.1	102	9.2	0.59 (0.41-0.83)	.003
TC0 and IC0	51	9.7	41	9.7	0.88 (0.55-1.42)	.601
Squamous	49	10.1	48	8.6	0.66 (0.41-1.05)	.075
Nonsquamous	95	14.8	95	10.9	0.69 (0.49-0.98)	.039

Smith DA, et al. ASCO 2016. Abstract 9028.

POPLAR: All-cause AEs

(≥ 5% difference between arms)



- AE profiles consistent with previous studies
- For atezolizumab, other immune-mediated AEs (any grade) included:
  - AST increased (4%)
  - ALT increased (4%)
  - Pneumonitis (2%)
  - Colitis (1%)
  - Hepatitis (1%)

Dry skin, stomatitis and nail disorder were additional AEs with ≥ 5% higher frequency in docetaxel.
Safety population includes patients who received any amount of either study treatment.
Data cut-off Jan 30, 2015.

Adapted from Spira AI, et al: Presented at ASCO 2015; Oral Presentation #8010.

First Line Therapy

JAVELIN: Phase Ib Trial of First-line Avelumab in NSCLC

- Open-label, dose-escalation phase Ib trial of avelumab (10 mg/kg Q2W) in advanced NSCLC not previously treated for metastatic disease

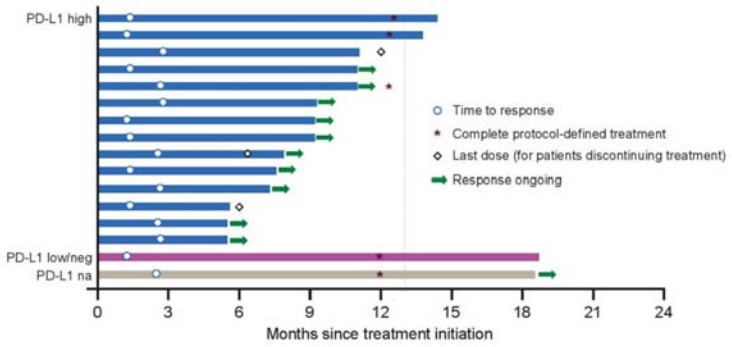
Outcome, %	N = 75
ORR	18.7
DCR	64.0
CR	1.3
PR	17.3
SD	45.3
Median PFS	11.6 wks

- Well tolerated, low rate of grade 3/4 AEs
- Tx-related AEs: 56.6% (9% grade 3/4)
- No tx-related deaths

Verschraegen CF, et al. ASCO 2016. Abstract 9036.

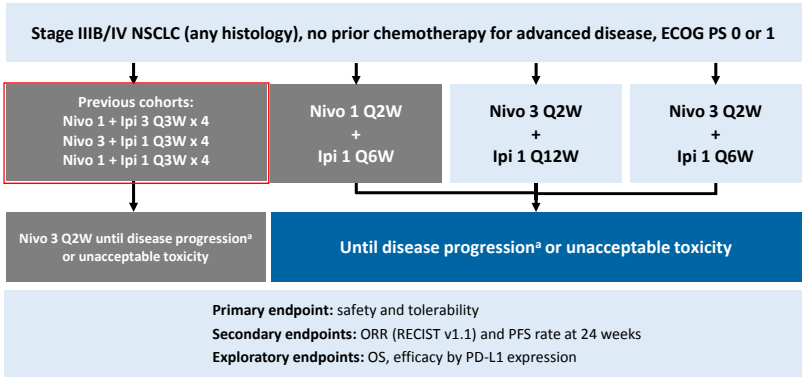
Phase I/II Trial of Durvalumab in Treatment-Naive Advanced NSCLC

- Dose-escalation/dose-expansion phase I/II trial of durvalumab (10 mg/kg Q2W) in pts with treatment-naive PD-L1+ NSCLC
- **ORR: 27%** (N = 59); 29% for PD-L1 high (n = 49); 11% for PD-L1 low or negative (n = 9)



Antonia SJ, et al. ASCO 2016. Abstract 9029.

Phase 1 CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC



- The safety and tolerability of the nivolumab–ipilimumab combination was improved with less frequent ipilimumab dosing[5]
- Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis[5]
- Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules[b]

[a]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
[b]February 2016 database lock
Ipilimumab and nivolumab dosing are shown in mg/kg IV (eg, nivo 1 = nivolumab 1 mg/kg IV)

Hellmann MD, et al. ASCO 2016: Abstract 3001.

Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

NC = not calculated (when >25% of patients are censored); NR = not reached
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

Hellmann MD, et al. ASCO 2016: Abstract 3001.

Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy by Tumor PD-L1 Expression

	Nivo 3 Q2W + Ipi 1 Q12W	Nivo 3 Q2W + Ipi 1 Q6W	Nivo 3 Q2W
ORR, % (n/N)			
<1% PD-L1	30 (3/10)	0 (0/7)	14 (2/14)
≥1% PD-L1	57 (12/21)	57 (13/23)	28 (9/32)
≥50% PD-L1	100 (6/6)	86 (6/7)	50 (6/12)
Median PFS (95% CI), mo			
<1% PD-L1	4.7 (0.9, NR)	2.4 (1.7, 2.9)	6.6 (2.0, 11.2)
≥1% PD-L1	8.1 (5.6, NR)	10.6 (3.6, NR)	3.5 (2.2, 6.6)
≥50% PD-L1	13.6 (6.4, NR)	NR (7.8, NR)	8.4 (2.2, NR)
1-year OS rate (95% CI), %			
<1% PD-L1	NC	NC	79 (47, 93)
≥1% PD-L1	90 (66, 97)	83 (60, 93)	69 (50, 82)
≥50% PD-L1	NC	100 (100, 100)	83 (48, 96)

NC = not calculated (when >25% of patients are censored); NR = not reached due to high percentage of ongoing response
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

Hellmann MD, et al. ASCO 2016: Abstract 3001.

Nivolumab Plus Ipilimumab in First-line NSCLC: Safety Summary

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W (n = 52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	82	37	72	33	71	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab[6]

Hellmann MD, et al. ASCO 2016: Abstract 3001.

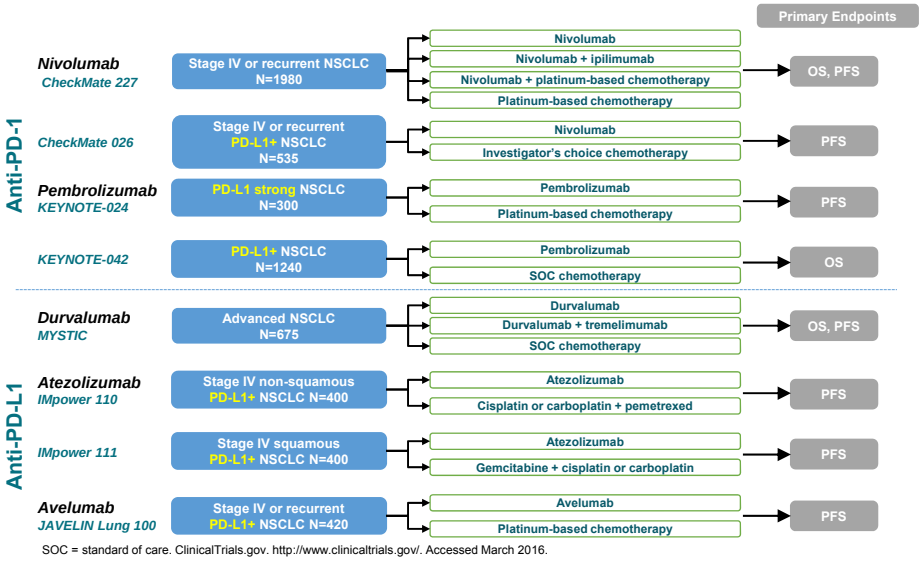
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

Combination Immune Checkpoint Blockade

	Nivolumab + Ipilimumab				MEDI4736 + TREME
	Melanoma	Renal	SCLC	NSCLC	
ORR, %	57.6%	29-39%	32%	31-39%	23%
PFS	11.5 months			8 months	
Cut Off	5%			1%	25%
ORR in PD-L1 +	72.1%			48%	22%
ORR in PD-L1 -	57.5%			0-22%	29%

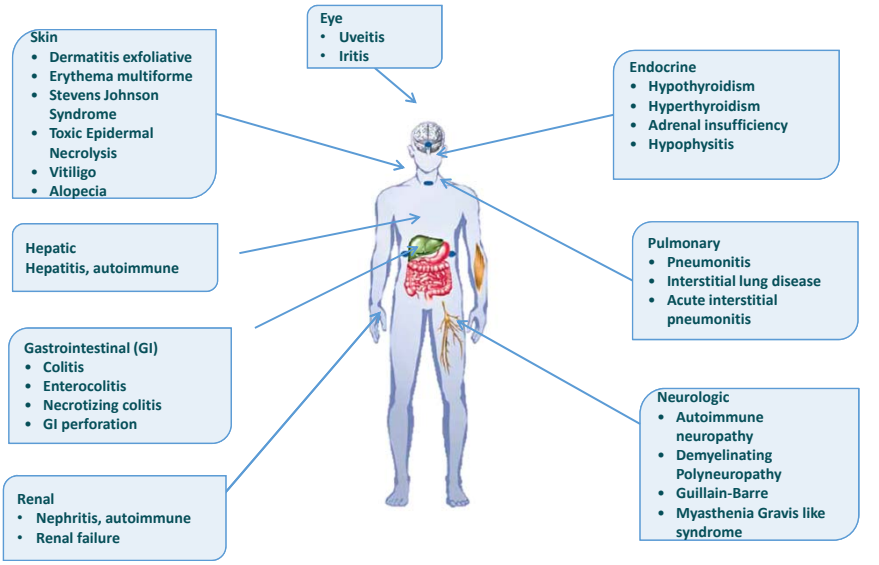
Larkin et al, NEJM 2015 Hammers et al, ASCO 2015 Antonia et al, ASCO 2015 Rizvi, et al. WCLC 2015 Antonia et al, Lancet Onc 2016

Select Ongoing Phase III Studies of PD-1/PD-L1 Inhibitors: I-O Monotherapy in 1L Advanced NSCLC



SOC = standard of care. ClinicalTrials.gov. http://www.clinicaltrials.gov/. Accessed March 2016.

irAEs with Immunotherapy



If not vigilant, may result in more serious immune-related adverse events.

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

Onset:

Average is 6-12 wks after initiation of therapy
Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy

Occasional (5% to 20%)

- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. Weber JS, et al. J Clin Oncol. 2015.

Toxicity Guidelines for Immune Checkpoint Inhibitors

- TFTs, CBCs, LFTs and metabolic panels should be obtained at each treatment and q6-12 wks for 6 mos posttreatment in all pts receiving checkpoint protein antibodies
- ACTH, cortisol should also be checked in pts with fatigue and nonspecific symptoms, plus testosterone in men
- Frequency of follow-up testing should be adjusted to individual response and AEs that occur
- Corticosteroids can reverse nearly all toxicities associated with these agents, but should be reserved for grade 3/4, or prolonged grade 2, infusion-related AEs (irAEs)

Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Summary

- Anti-PD1 and PD-L1 antibodies have demonstrated promising results as second line therapy in patients with NSCLC
  - Nivolumab is FDA approved as second line therapy in squamous and nonsquamous NSCLC
  - Pembrolizumab is FDA approved as second line therapy in patients with NSCLC with tumors that are PD-L1 positive ≥ 50%
  - Atezolizumab phase II data show similar results
- PD-L1 expression predicts for response
  - But responses are seen in patients with PD-L1 negative tumors and not all patients with PD-L1 positive tumors are responding
- PD-1 and PD-L1 inhibitors are currently being evaluated as first line therapy for NSCLC, in combination with immunotherapy or chemotherapy; PD-1 and PD-L1 inhibitors are also being evaluated in small cell lung cancer
- Toxicity profile is different than chemotherapy and requires close evaluation

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