Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Non-Small Cell Lung Carcinoma

Liza C. Villaruz
University of Pittsburgh Cancer Institute

Cancer Immunology 101
July 31, 2015

sitc
Society for Immunotherapy of Cancer

Outline

- NSCLC Background
- Mechanism of Immune Checkpoint Inhibition in NSCLC
- Clinical Experience
- Potential Biomarkers to Improve Patient Selection
- Take Home Points

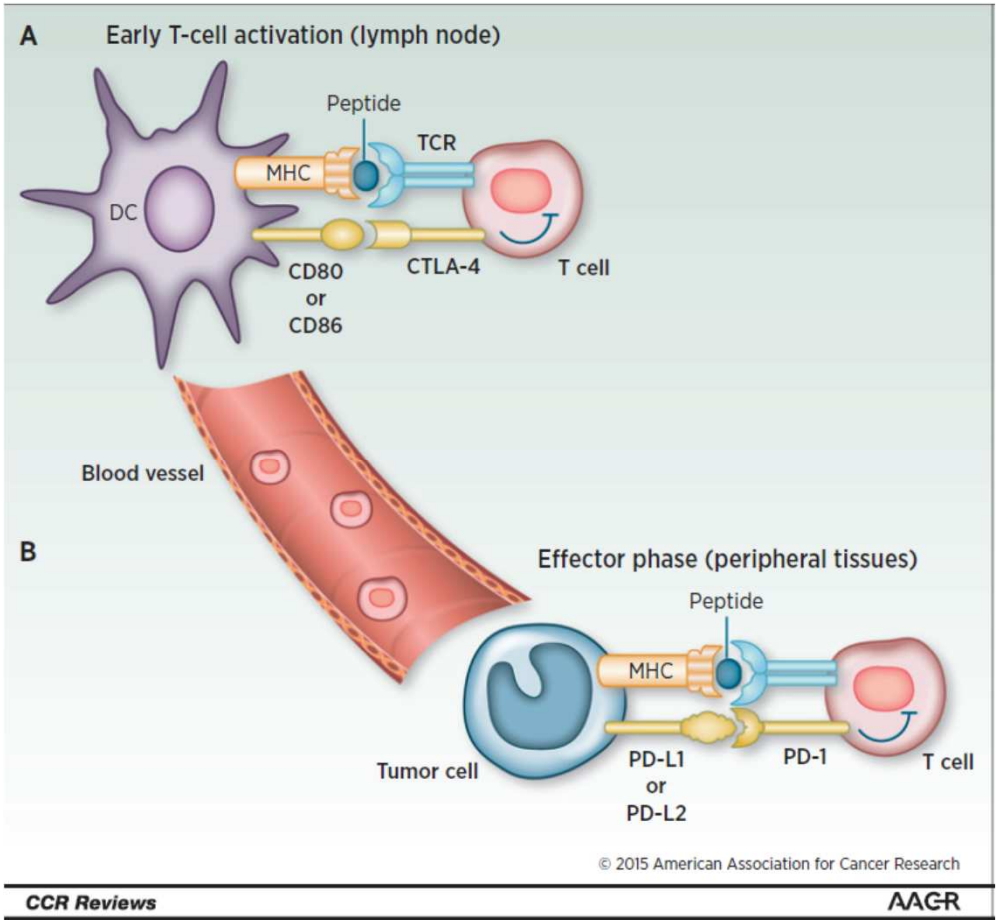
Background

- Significant therapeutic advances have been made in advanced NSCLC with the advent of genomic profiling and targeted therapies, e.g. EGFR mutant or ALK rearranged NSCLC.
- Patient with currently actionable oncogenic drivers comprise about 15-20% lung adenocarcinomas.
- In patients without actionable oncogenic drivers, chemotherapy has remained the mainstay of treatment.
- In particular, there are no validated genomic targets in Sq-NSCLC.

Background

- Immunotherapy in lung cancer has *until recently* been met with disappointing results.
- Lung cancer immune dysfunction is characterized by evasion of immunosurveillance.
  - Production of immunosuppressive chemokines by the tumor cells
  - Loss of MHC antigen expression
  - Higher proportion of T-regulatory (T_{reg}) cells in the tumor microenvironment

Immune Checkpoints



- CTLA-4 is expressed on T cells and regulates the early stages of T-cell activation
  - counteracts T-cell costimulatory receptor CD28 by competing for its ligands
- PD-1 mediates immune resistance in the tumor microenvironment by downregulating the activity of effector T cells in peripheral tissues

Clin Cancer Res 2015;21:976-984.

Immune Checkpoints

- Crucial for self-tolerance
- Co-opted by tumors
  - PD-1 ligands are frequently upregulated in human cancers, including NSCLC
  - PD-1 expressed on TILs, B cells, NK cells, monocytes and dendritic cells.
- Immune checkpoint blockade “releases the breaks”.

Clin Cancer Res 2015;21:976-984.

Phase 1 multi-cohort CA209-003 study: NSCLC cohort

- N = 129; most patients ≥ 3 lines of therapy
  - ORR similar across histologies (16.7% squamous and 17.6% non-squamous)
  - Durable responses (45% ongoing responses), occurred early (50% at first assessment; 8 wks); could continue following treatment discontinuation
    - 6/16 (38%) responders who discontinued therapy for reasons other than disease progression responded for ≥30 weeks following end of therapy; 5/6 (83%) were ongoing at time of reporting

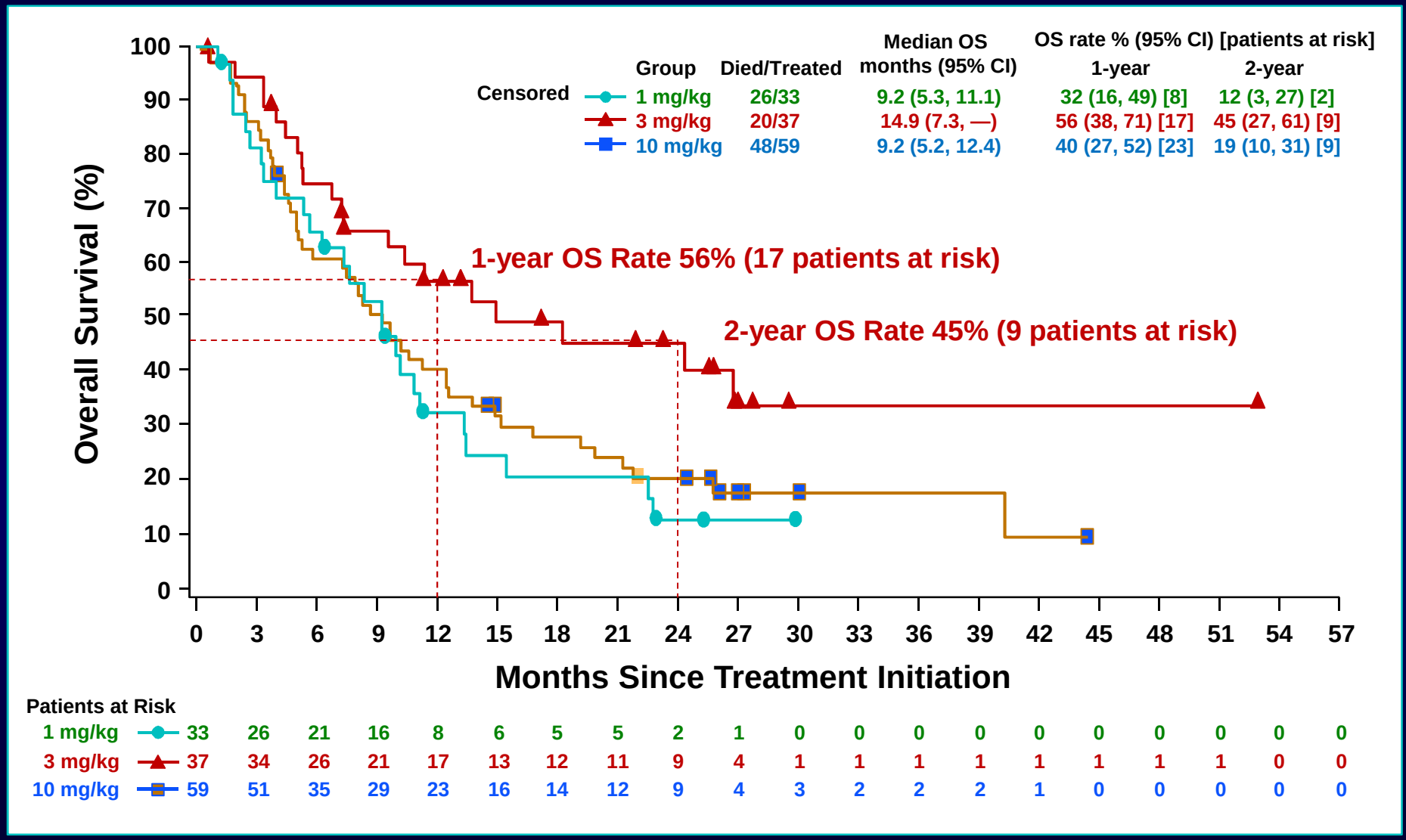
Efficacy of nivolumab monotherapy by dose in patients with NSCLC

Dose mg/kg	ORR %[a,b] (n/N)	Estimated Median DOR[c] wks (range)	SD Rate[a] ≥24 wks % (n/N)	Median PFS[d,e] months (95% CI)	Median OS[d,e] months (95% CI)
All patients	17 (22/129)	74 (6.1+, 133.9+)	10.1 (13/129)	2.3 (1.8, 3.7)	9.9 (7.8, 12.4)
1	3.0 (1/33)	63.9 (63.9, 63.9)	15.2 (5/33)	1.8 (1.7, 3.3)	9.2 (5.3, 11.1)
3	24.3 (9/37)	74 (16.1+, 133.9+)	8.1 (3/37)	1.9 (1.7, 7.3)	14.9 (7.3, NE)
10	20.3 (12/59)	83.1 (6.1+, 132.7+)	8.5 (5/59)	3.7 (1.9, 3.8)	9.2 (5.2, 12.4)

[a]Modified Response Evaluation Criteria In Solid Tumors (RECIST) v1.0. CIs for ORRs and SD rates were calculated using the Clopper-Pearson method; [b]Six patients with unconventional "immune-related" responses were not included as responders; [c]Time from first response to documented progression, death, or last tumor assessment (+ = censored); estimated median DORs were determined from Kaplan-Meier curves; [d]Median values for time-to-event endpoints (PFS, OS, DOR) were estimated using the Kaplan-Meier method; [e]Survival data were collected retrospectively

Brahmer, ASCO 2014

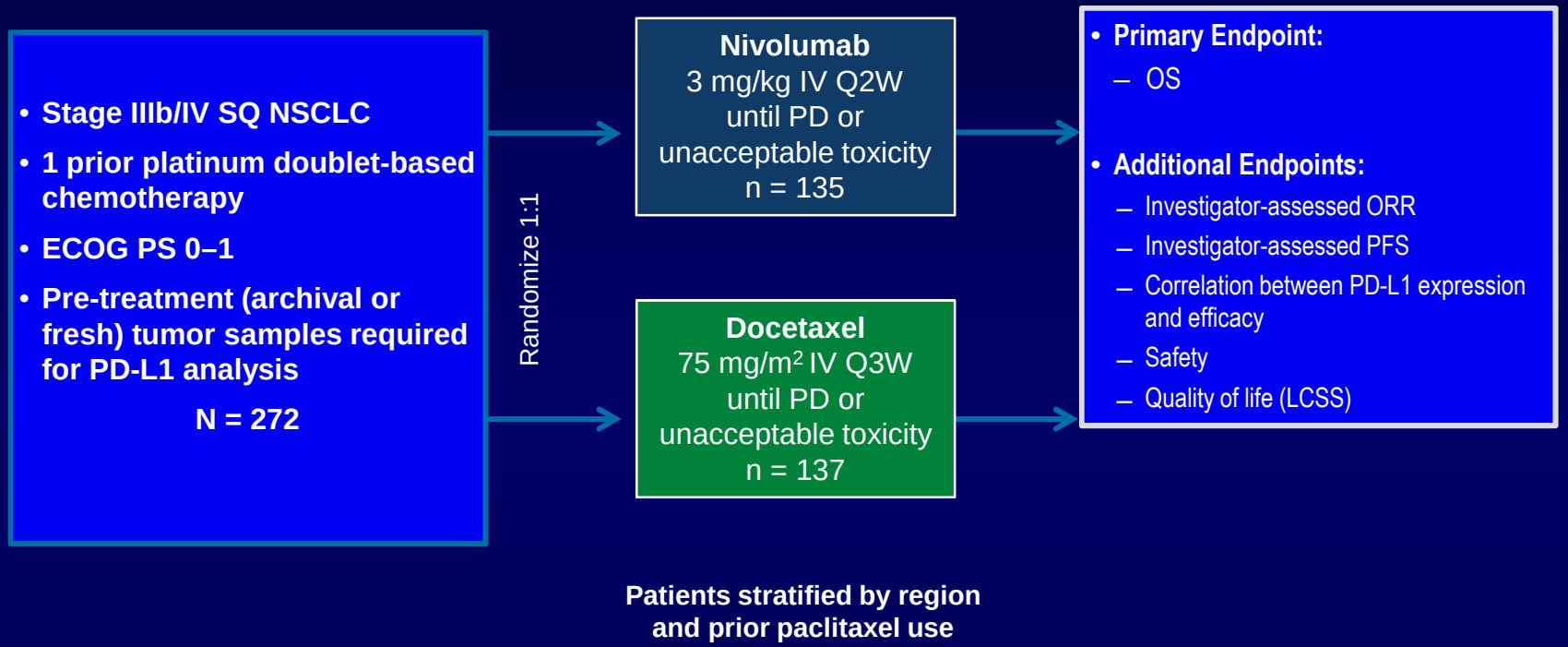
CA209-003 NSCLC Survival KM by Dose



Brahmer, ASCO 2014

OS = overall survival

CheckMate 017 (NCT01642004) - Study Design



- **83% (225/272) of patients had quantifiable PD-L1 expression**

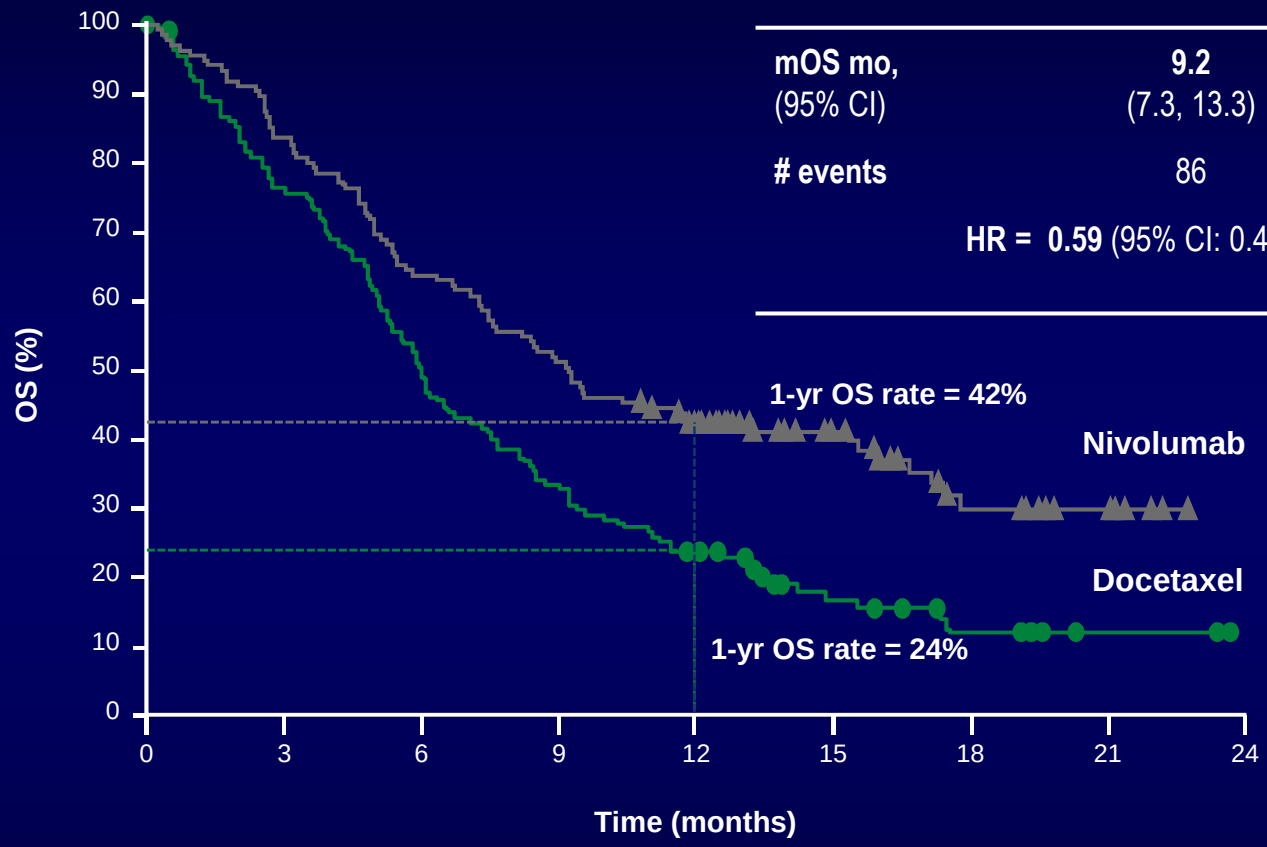
LCSS = Lung cancer symptom scale

Spigel, ASCO 2015

CheckMate 017 (NCT01642004): Overall Survival

	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

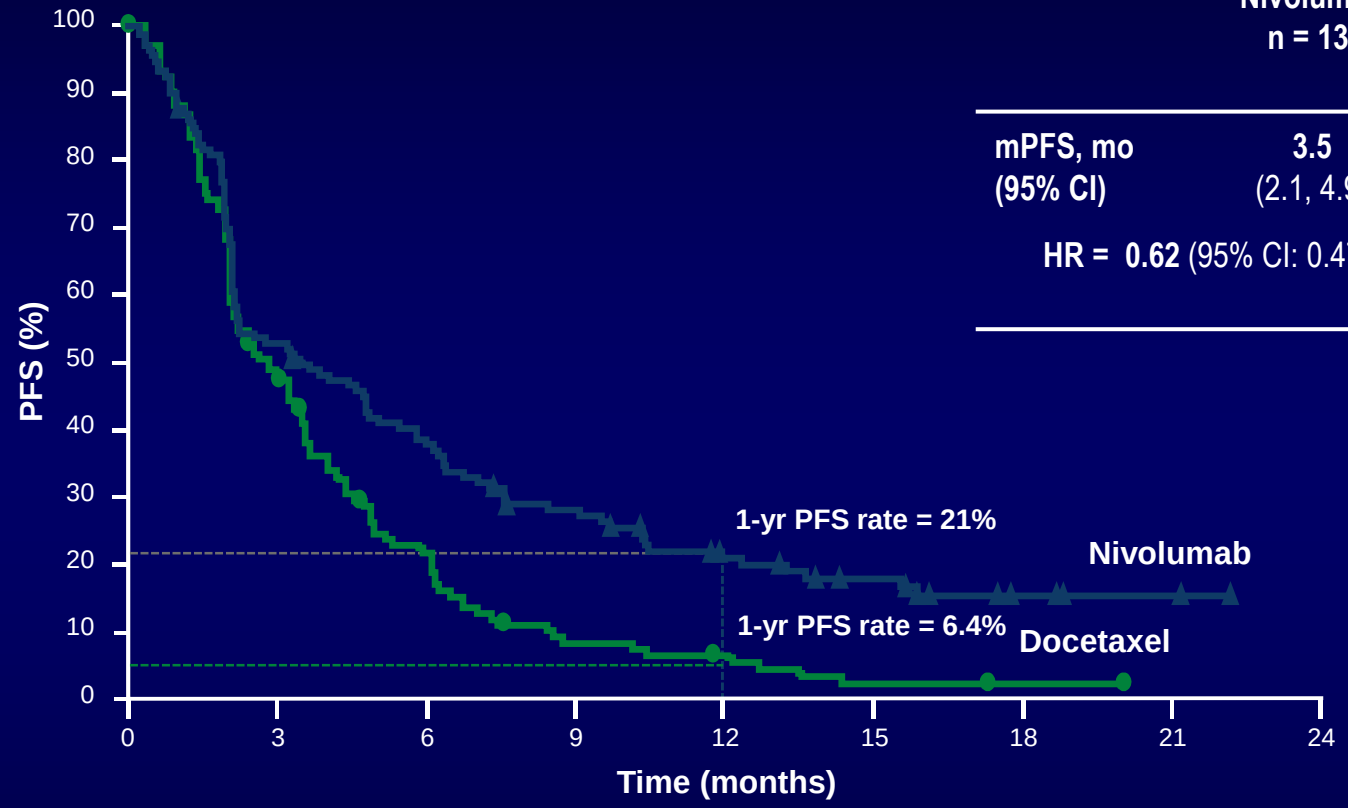


Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Spigel, ASCO 2015

CheckMate 017 (NCT01642004): Progression-Free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	**3.5** (2.1, 4.9)	**2.8** (2.1, 3.5)

HR = 0.62 (95% CI: 0.47, 0.81); ***P* = 0.0004**

Number of Patients at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

Spigel, ASCO 2015

Objective Response Rate

	Nivolumab n = 135	Docetaxel n = 137
ORR, % (95% CI)	**20** (14, 28)	**9** (5, 15)
***P*-value[a]**	**0.0083**	
Best overall response, %		
Complete response	1[b]	0
Partial response	19	9
Stable disease	29	34
Progressive disease	41	35
Unable to determine	10	22
Median DOR,[c] mo (range)	NR (2.9, 21+)	8.4 (1.4+, 15+)
Median time to response,[c] mo (range)	2.2 (1.6, 12)	2.1 (1.8, 9.5)

- 28 patients in the nivolumab arm were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 9 patients (not included in ORR)

[a]Based on two-sided stratified Cochran–Mantel–Haenszel test on estimated odds ratio of 2.6 (95% CI: 1.3, 5.5). [b]One pt experienced complete response.
[c]Values are for all confirmed responders per RECIST v1.1 (nivolumab, n = 27; docetaxel, n = 12). Symbol + indicates a censored value.
NR = not reached

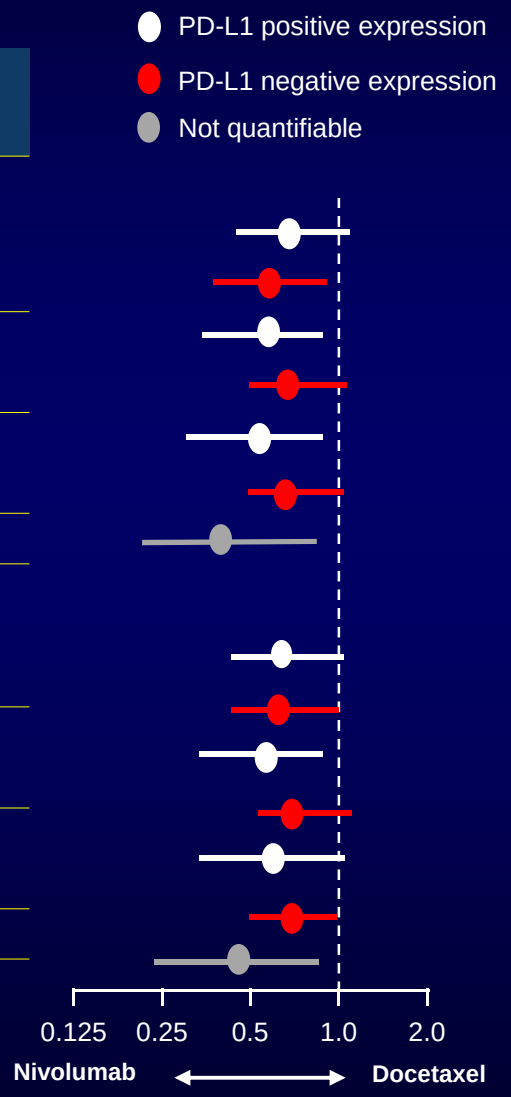
Spigel, ASCO 2015

OS and PFS by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	**0.70**
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	**0.16**
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	**0.35**
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

- PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]



Spigel, ASCO 2015

Treatment-related AEs (≥10% of patients)

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Total patients with an event, %	**58**	**7**	**86**	**55**
Fatigue	16	1	33	8
Decreased appetite	11	1	19	1
Asthenia	10	0	14	4
Nausea	9	0	23	2
Diarrhea	8	0	20	2
Vomiting	3	0	11	1
Myalgia	2	0	10	0
Anemia	2	0	22	3
Peripheral neuropathy	1	0	12	2
Neutropenia	1	0	33	30
Febrile neutropenia	0	0	11	10
Alopecia	0	0	22	1

Spigel, ASCO 2015

Treatment-related Select AEs

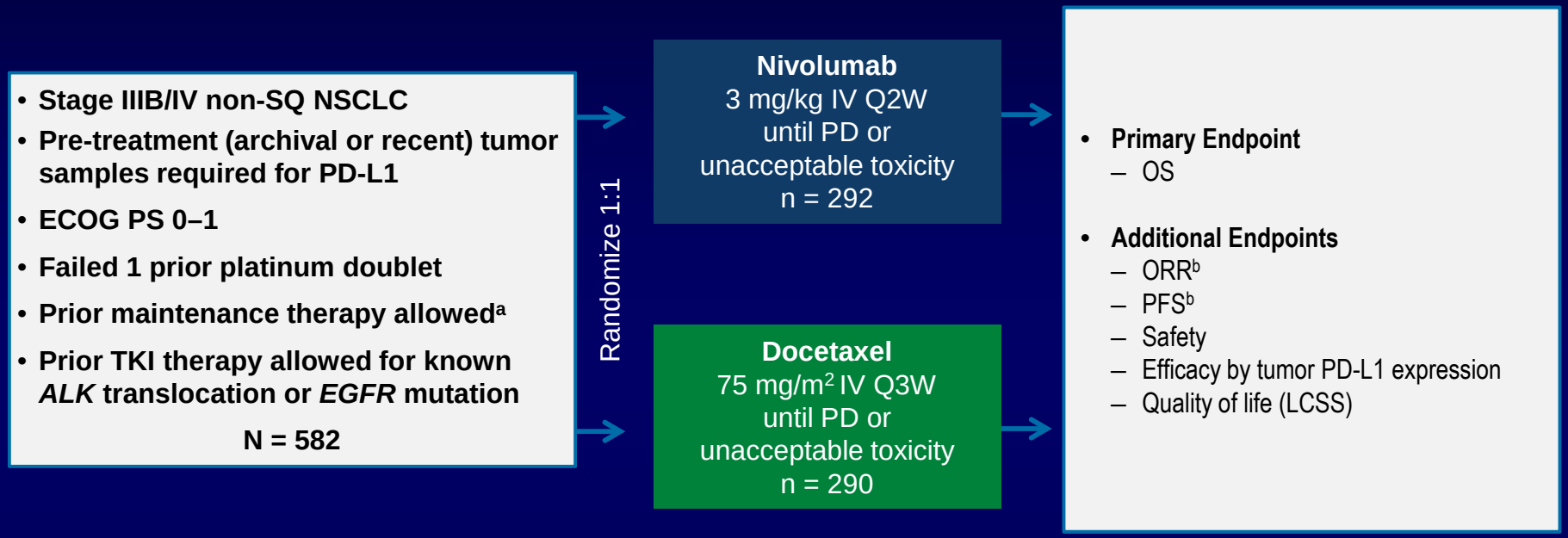
	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Endocrine, %	4	0	0	0
Hypothyroidism	4	0	0	0
Gastrointestinal, %	8	1	20	2
Diarrhea	8	0	20	2
Colitis	1	1	0	0
Hepatic,[a] %	2	0	2	1
ALT increased	2	0	1	1
AST increased	2	0	1	1
Pulmonary, %	5	1	1[b]	0
Pneumonitis	5	1	0	0
Lung infiltration	1	0	0	0
Interstitial lung disease	0	0	1[b]	0
Renal,[c] %	3	1	2	0
Blood creatinine increased	3	0	2	0
Tubulointerstitial nephritis	1	1	0	0
Skin,[d] %	9	0	9	2
Hypersensitivity/Infusion reaction, %	1	0	2	1
Hypersensitivity	0	0	2	1
Infusion-related reaction	1	0	1	0

- Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention

[a] No cases of increased bilirubin occurred in the nivolumab arm. [b] Grade 5 event. [c] No cases of renal failure were reported in the nivolumab arm. [d] Includes rash, pruritus, erythema, maculopapular rash, skin exfoliation, urticaria and palmar plantar erythrodysasthesia syndrome.

Spigel, ASCO 2015

CheckMate 057 (NCT01673867) - Study Design



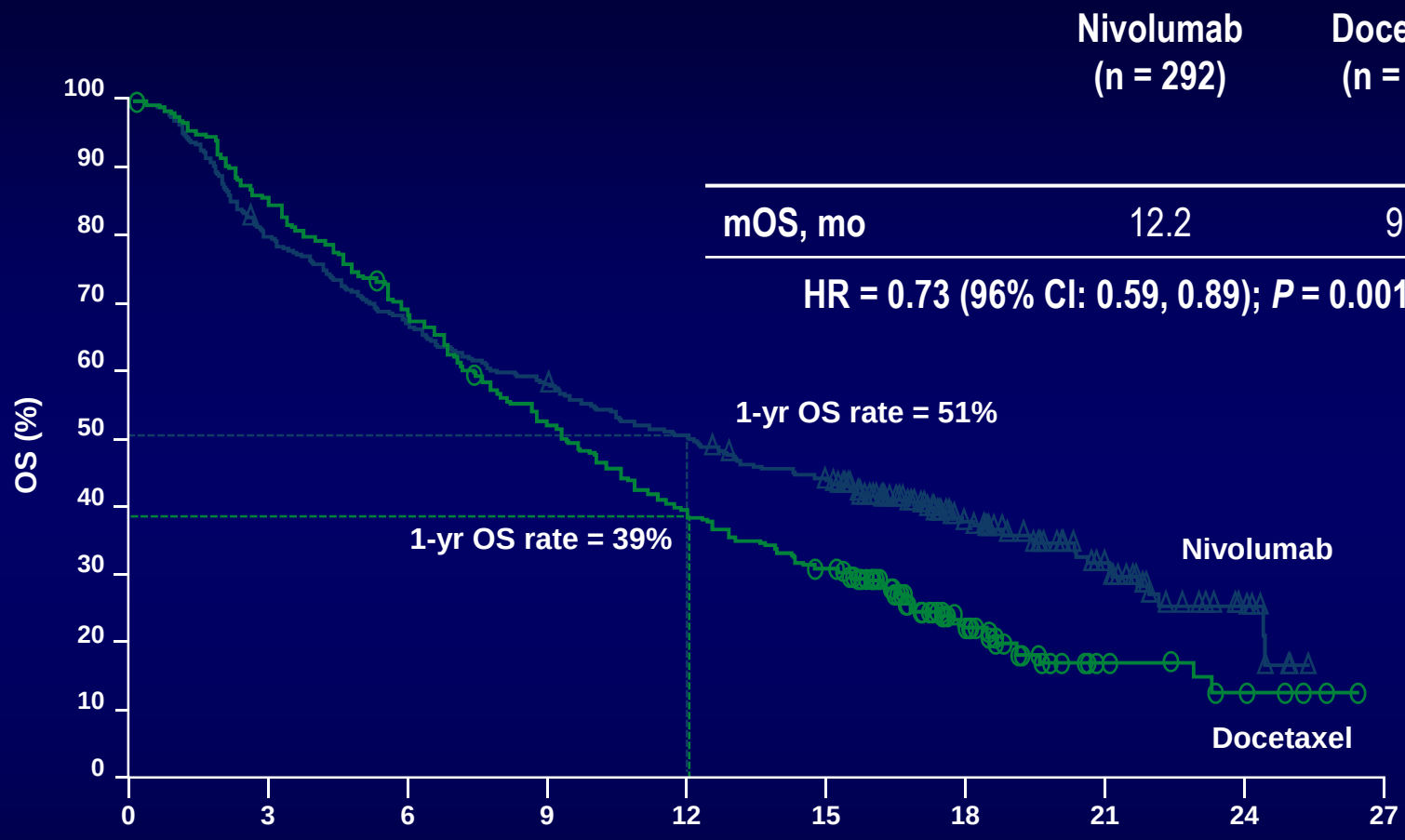
Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Paz-Ares, ASCO 2015

CheckMate 057 (NCT01673867): Overall Survival



Number of Patients at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Paz-Ares, ASCO 2015

Objective Response Rate

	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR (95% CI)	**19%** (15, 24)	**12%** (9, 17)
***Odds Ratio* (95% CI)** ***P*-value[a]**	1.72 (1.1, 2.6) 0.0246	
Best overall response, %		
Complete response	1	<1
Partial response	18	12
Stable disease	25	42
Progressive disease	44	29
Unable to determine	11	16
Median time to response,[b] mo (range)	2.1 (1.2, 8.6)	2.6 (1.4, 6.3)
Median DOR,[b] mo, (range)	**17.2** (1.8, 22.6+)	**5.6** (1.2+, 15.2+)
Ongoing response,[c] %	52	14

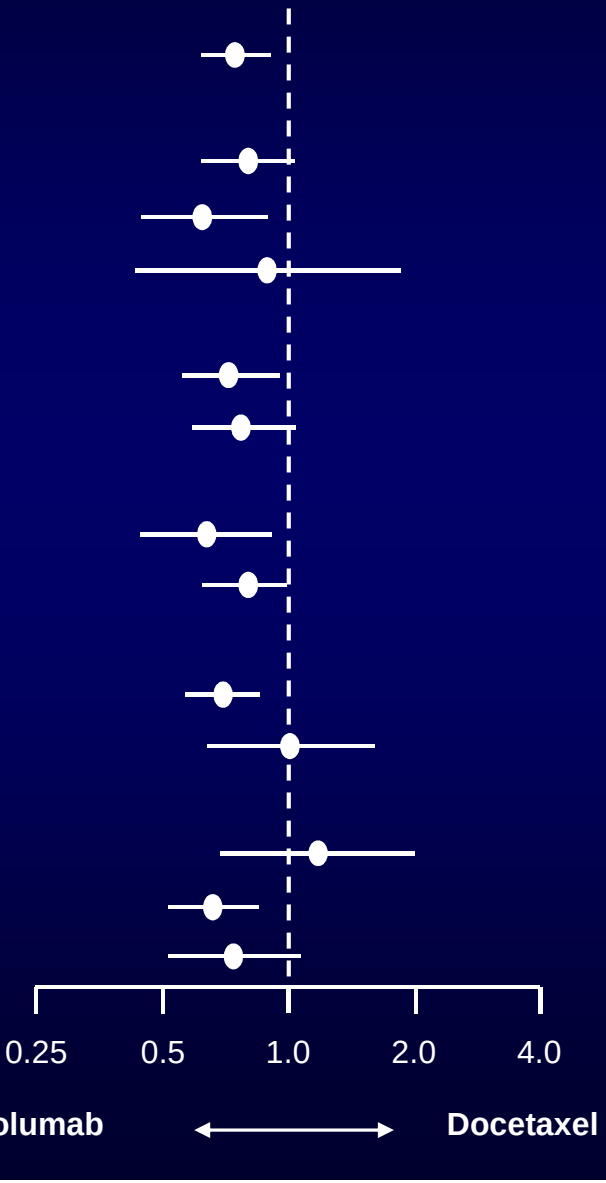
- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

[a] Based on two-sided stratified Cochran Mantel Haenszel test; [b] Values are for all responders (nivolumab, n = 56; docetaxel, n = 36);
[c] Ongoing response at last tumor assessment before censoring. Symbol + indicates a censored value.

Paz-Ares, ASCO 2015

Treatment Effect on OS in Predefined Subgroups

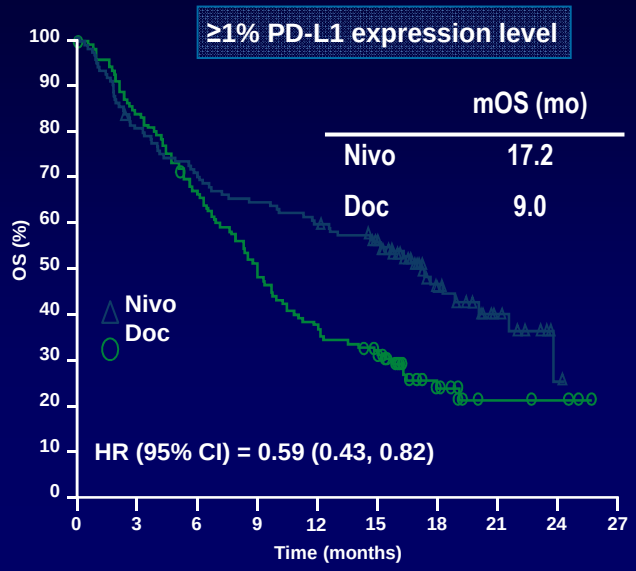
	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)

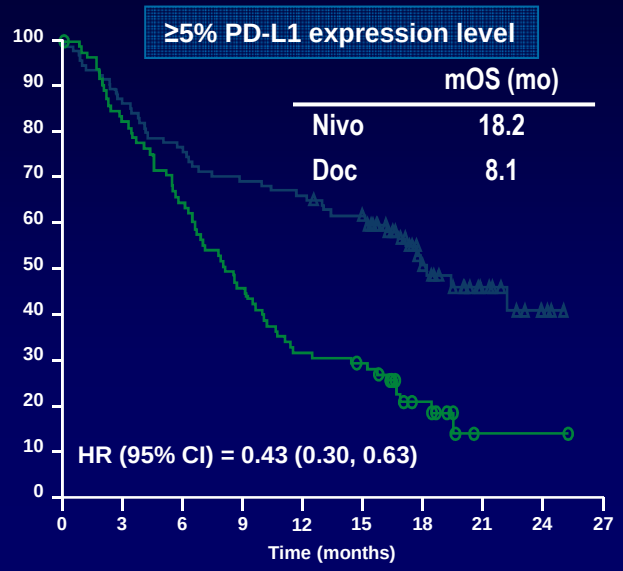


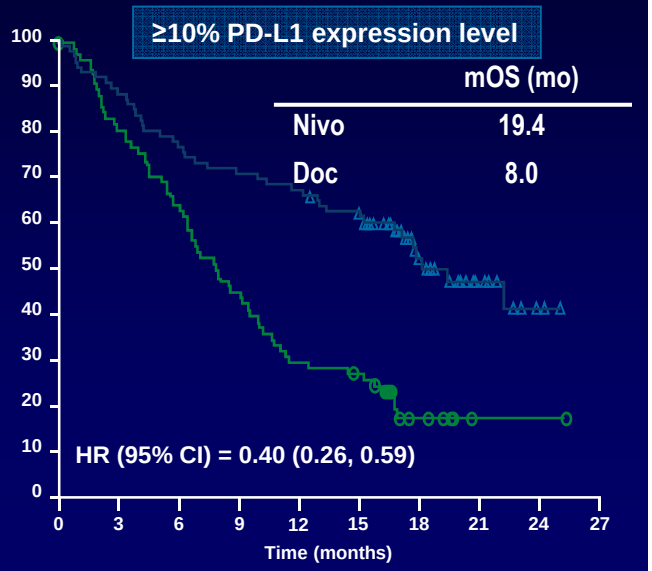
All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

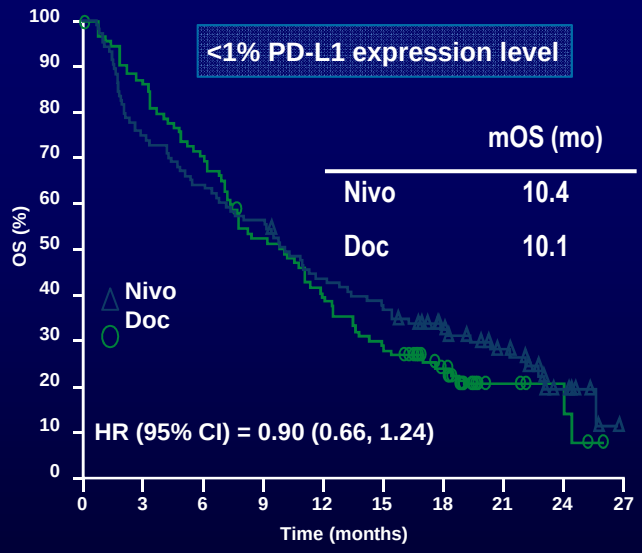
Paz-Ares, ASCO 2015

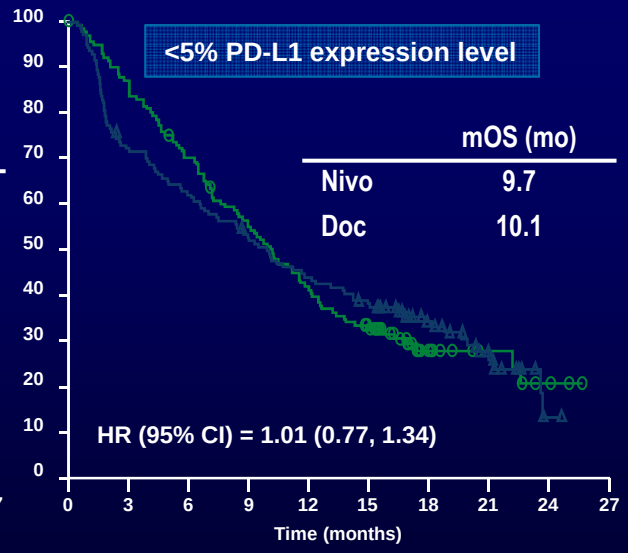
OS by PD-L1 Expression

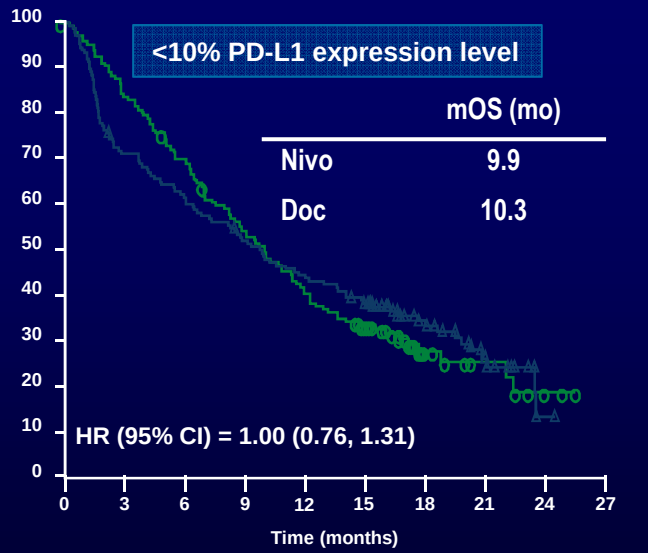








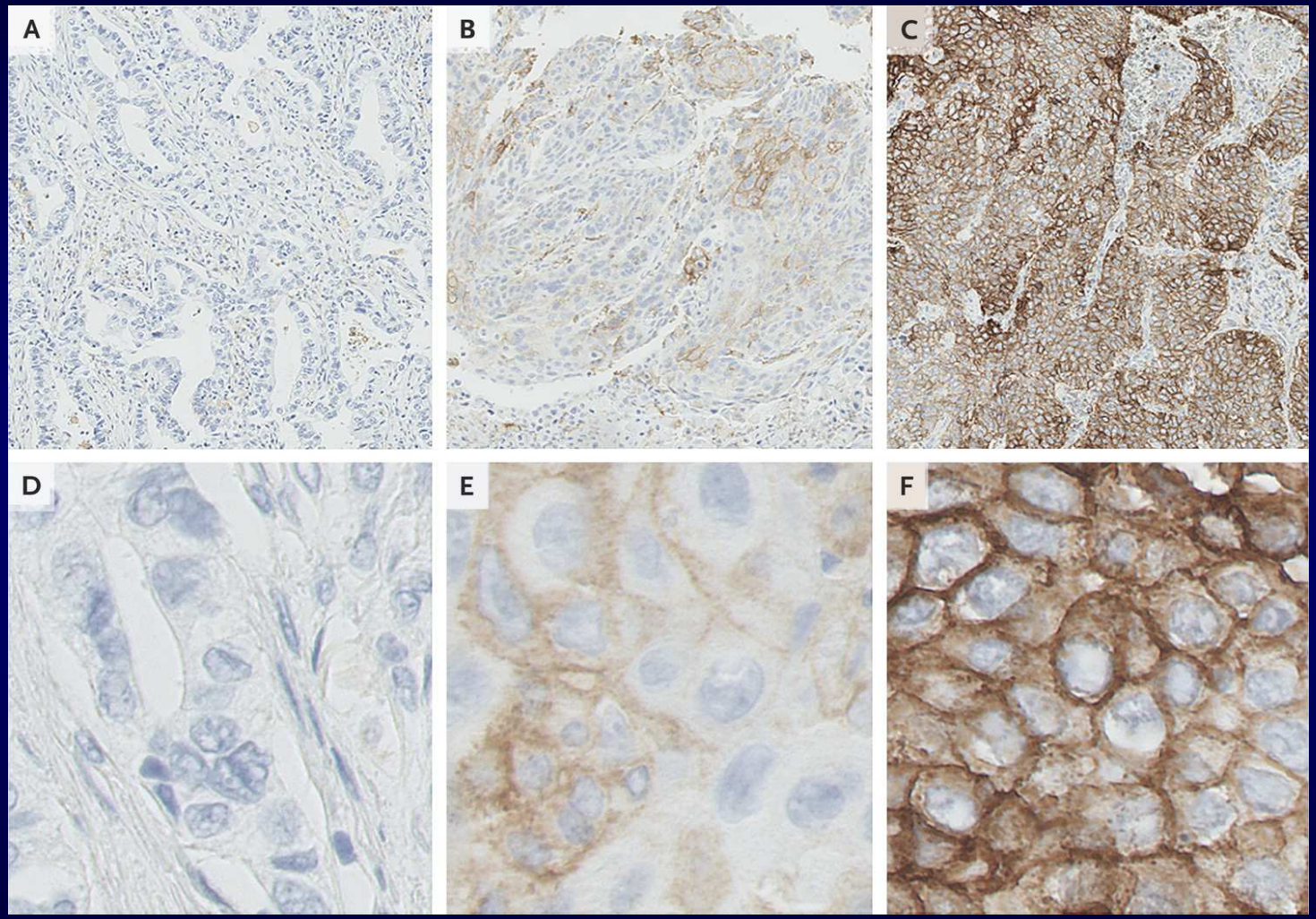




Symbols represent censored observations.

Paz-Ares, ASCO 2015

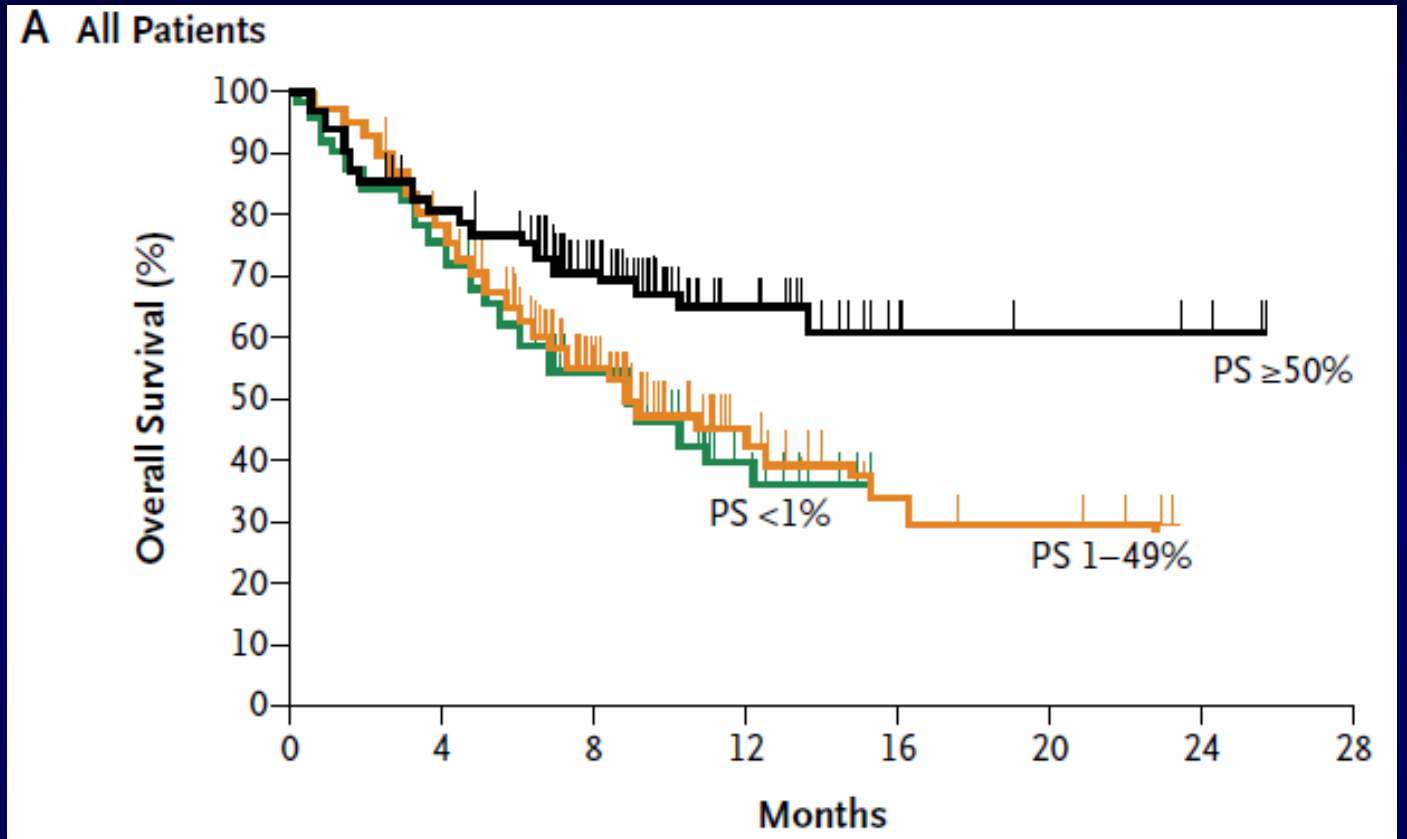
PD-L1 Expression in Non–Small-Cell Lung Cancers.



Garon EB et al. N Engl J Med 2015;372:2018-2028.

The NEW ENGLAND JOURNAL of MEDICINE

OS by PD-L1 Expression

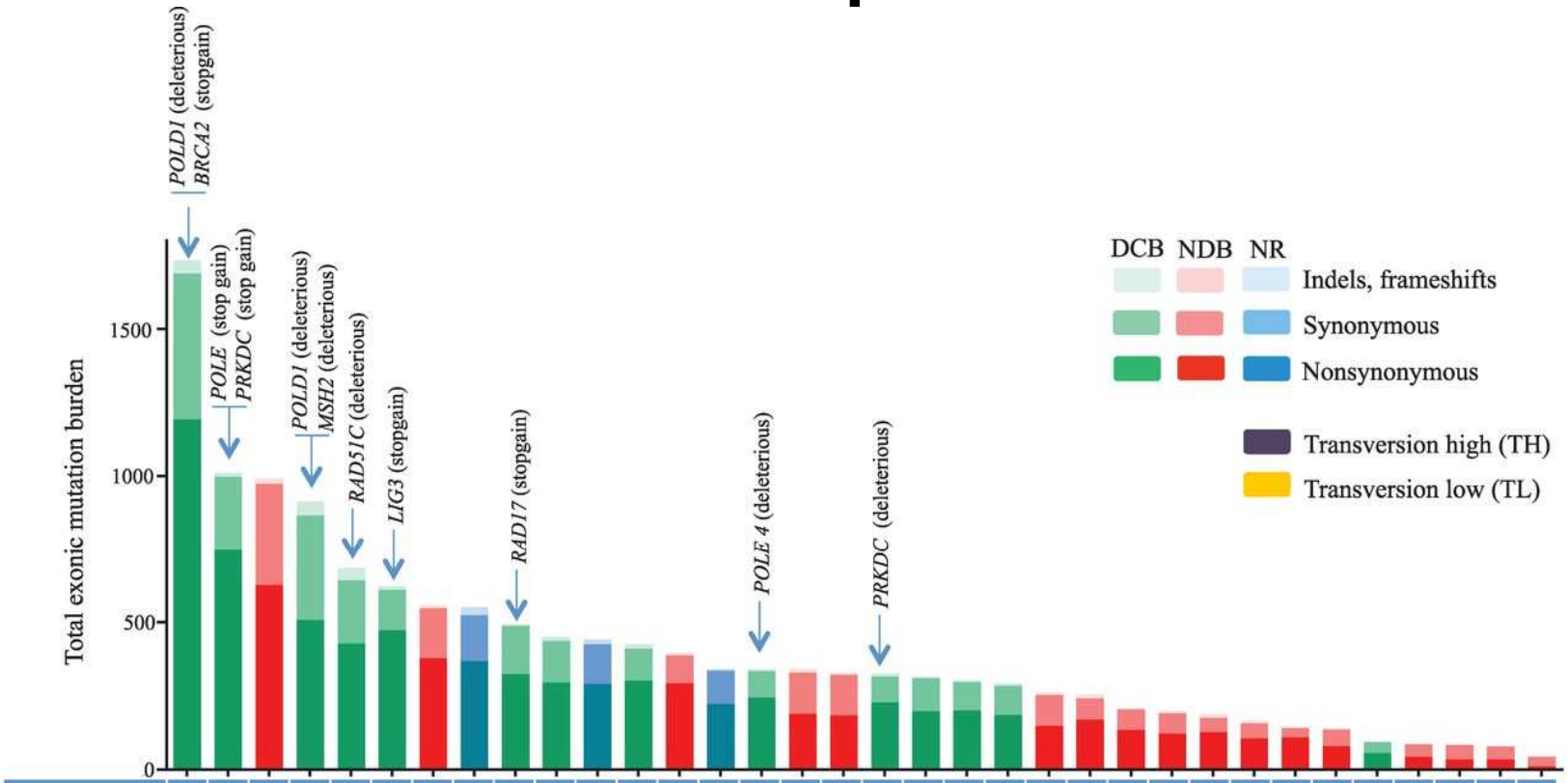


No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB et al. N Engl J Med 2015;372:2018-2028.

The NEW ENGLAND JOURNAL of MEDICINE

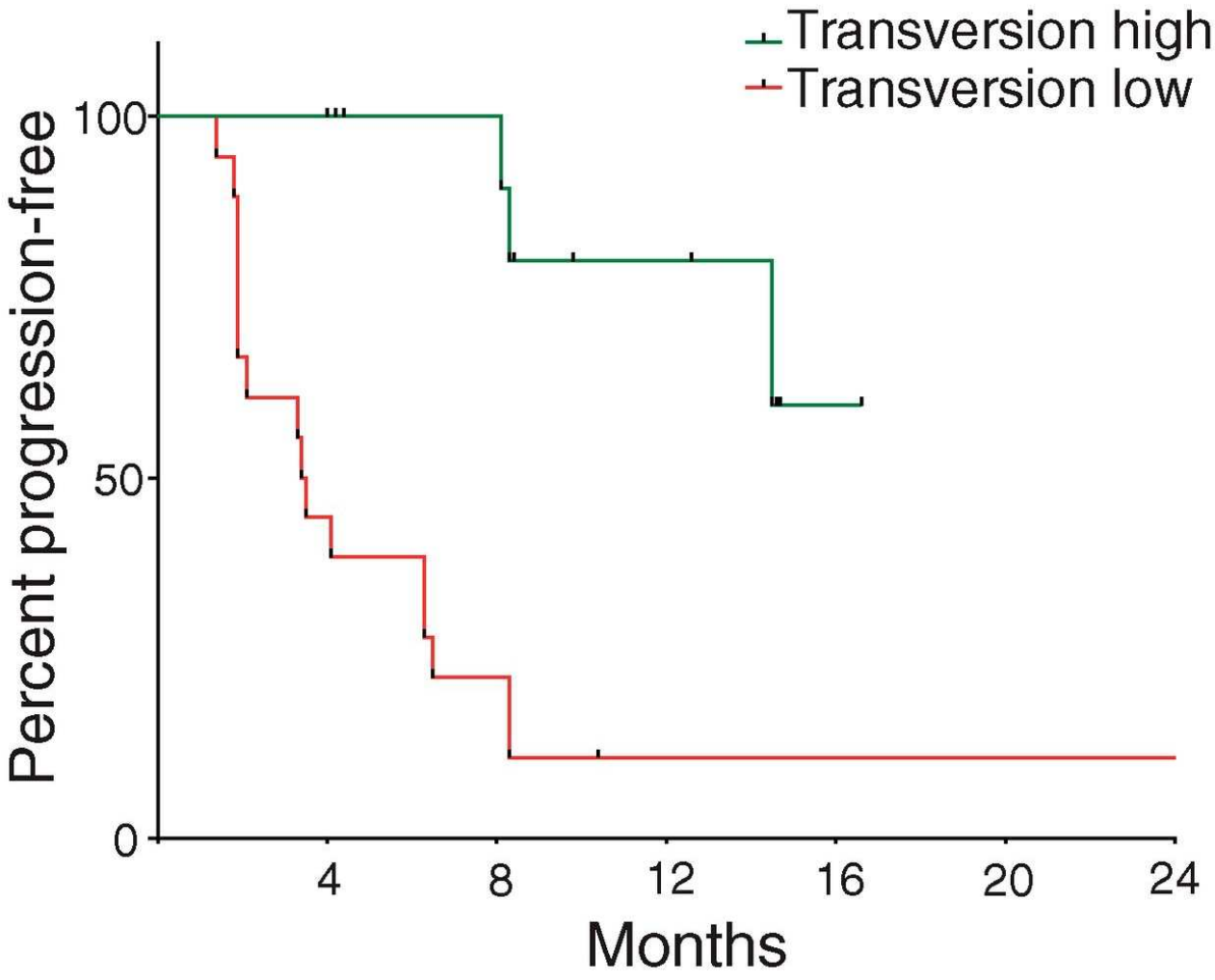
Mutational Burden and Response to PD1 blockade



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

Naiyer A. Rizvi et al. Science 2015;348:124-128

Molecular smoking signature and PD1 blockade



Naiyer A. Rizvi et al. Science 2015;348:124-128

Published by AAAS

Checkpoint inhibitors in NSCLC

Agent	Selected Trials
CTLA	
Ipilumumab	Ongoing Ph III with CP in Sq NSCLC
Tremelimumab	Ongoing Ph Ib with MEDI4736
PD-1	
Nivolumab	Ph III vs. docetaxel previously treated Sq & Non-Sq NSCLC Ph III 1st line vs. chemotherapy, PD-L1+
Pembrolizumab	Ph II/III vs. docetaxel previously treated NSCLC Ongoing Ph III 1st line vs. chemotherapy, PD-L1 + Ongoing Ph II in brain metastases
PD-L1	
MPDL-3280A	Ongoing Ph III vs. docetaxel previously treated NSCLC
MEDI4736	Ongoing Ph III following concurrent chemorads Ongoing Ph II after > 2 lines of therapy

Take Home Points

- Lung cancer evades the immune system by co-opting the PD1/PD-L1 immune checkpoint.
- The immune checkpoint inhibitors are associated with a high level of activity in advanced NSCLC
  - Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with advanced SQ and non-SQ NSCLC
  - Nivolumab benefit was independent of PD-L1 expression in SQ; in non-SQ it was predictive of benefit.
  - Responses are durable.
  - The safety profile of nivolumab was favorable versus docetaxel.
- Biomarkers such as mutational burden may serve to identify patients likely to respond to checkpoint inhibition.

sitc

Society for Immunotherapy of Cancer