Immune Checkpoint Inhibitors in Lung Cancer

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Conflict of Interest

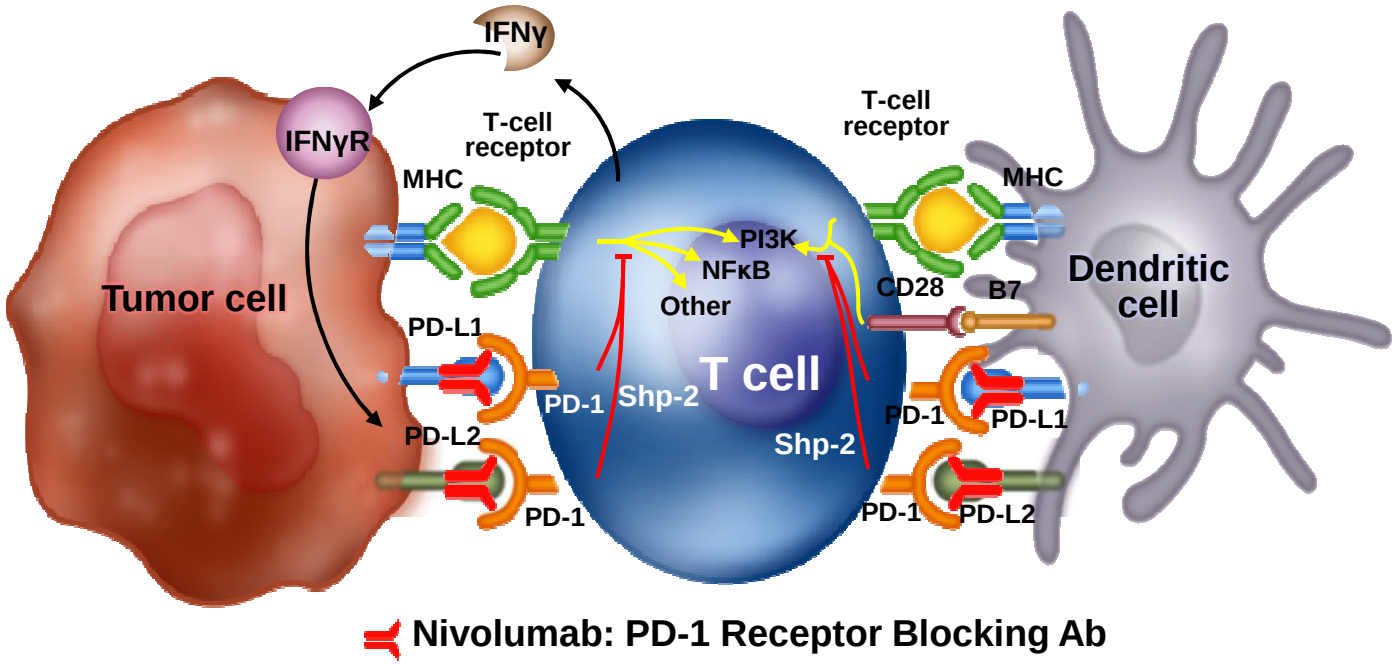
- **Research funding:** Astra Zeneca
- **Consulting:**
  - Compensated: Merck, Genentech
  - Uncompensated: BMS, Xcovery, Bayer
- **Speaker fee:** Biodesix
- There will not be discussion about the use of products for non-FDA approved indications in this presentation.

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

Drug	RR	PDL1+/PDL-
Nivolumab	17%	15%/14%
Pembrolizumab	22%%	17-37%/10%
Atezolizumab	23%	31%/14%
Durvalumab	16%	25%/10%

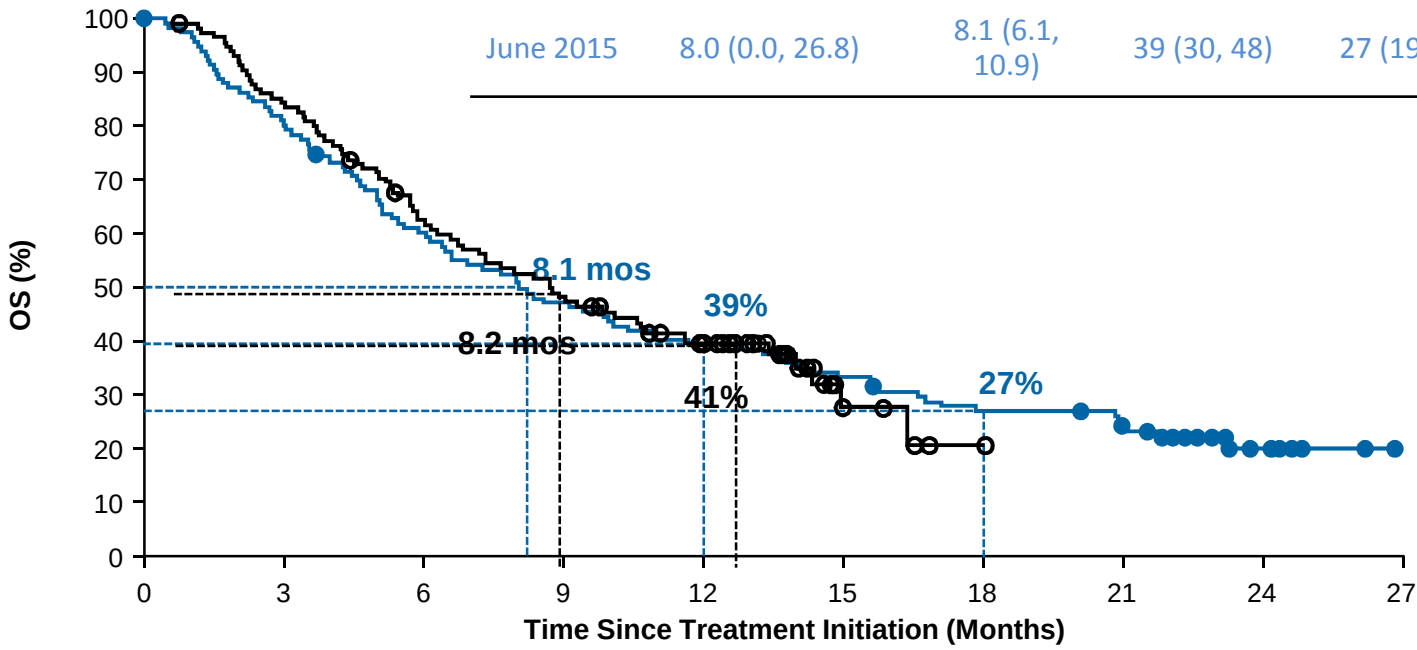
Nivolumab Mechanism of Action

- Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[11–13]



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



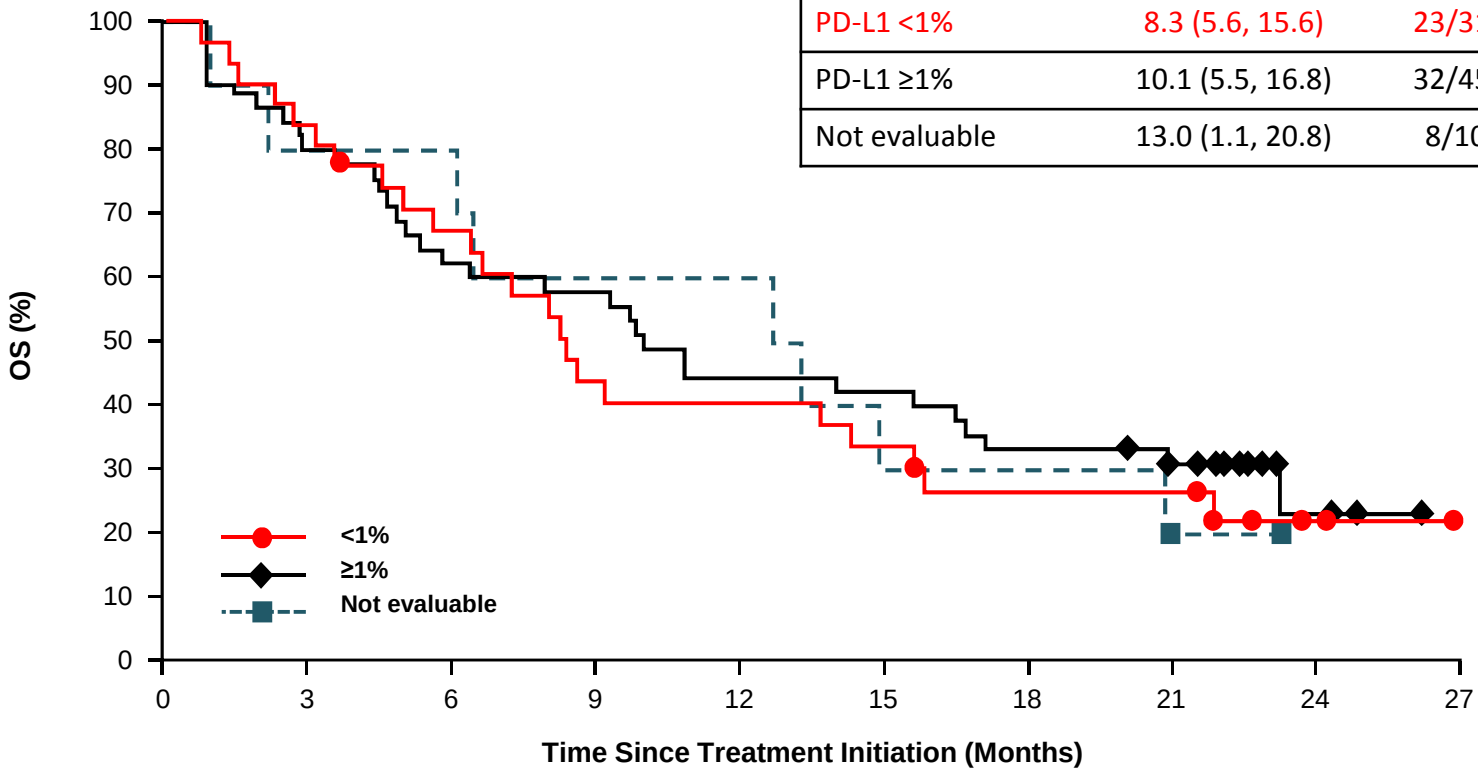
Number of patients at risk:

July 2014 DBL	117	93	68	51	28	5	0	0	0	0
June 2015 DBL	117	93	69	54	45	38	30	24	6	0

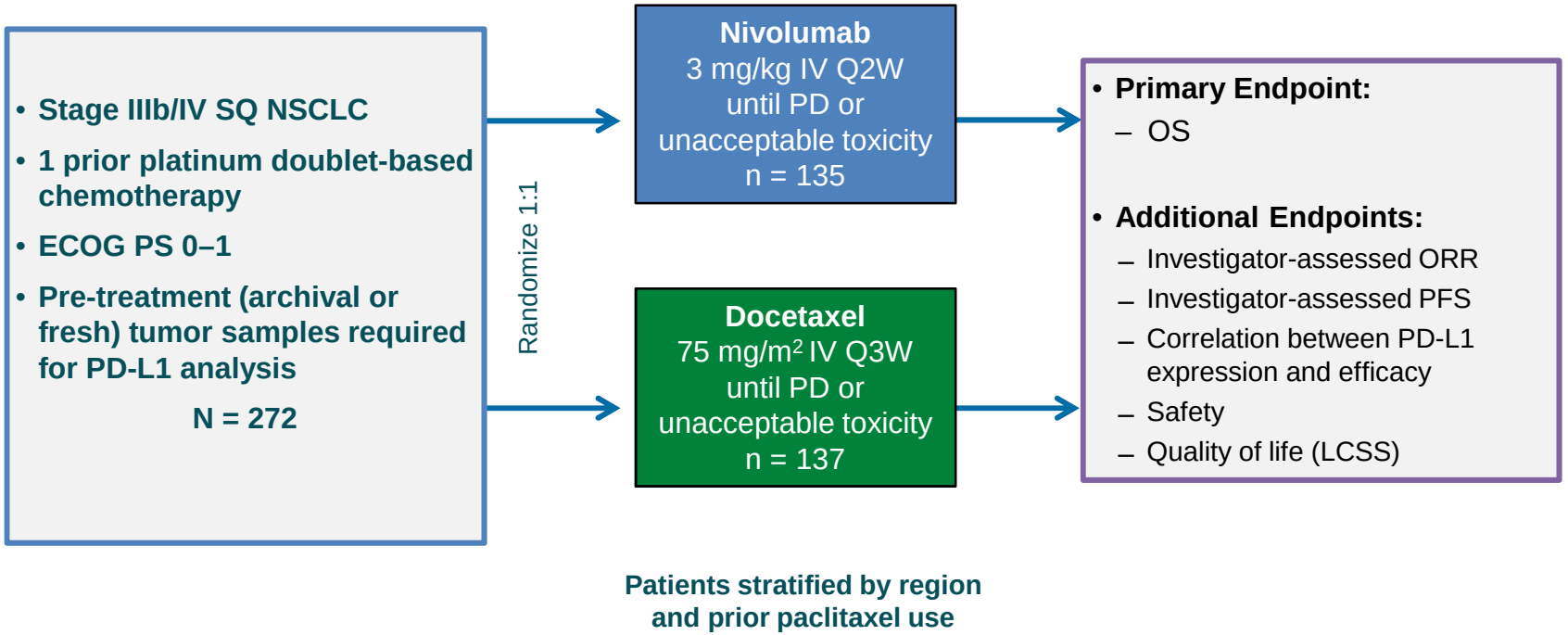
Horn et al., WCLC 2015

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



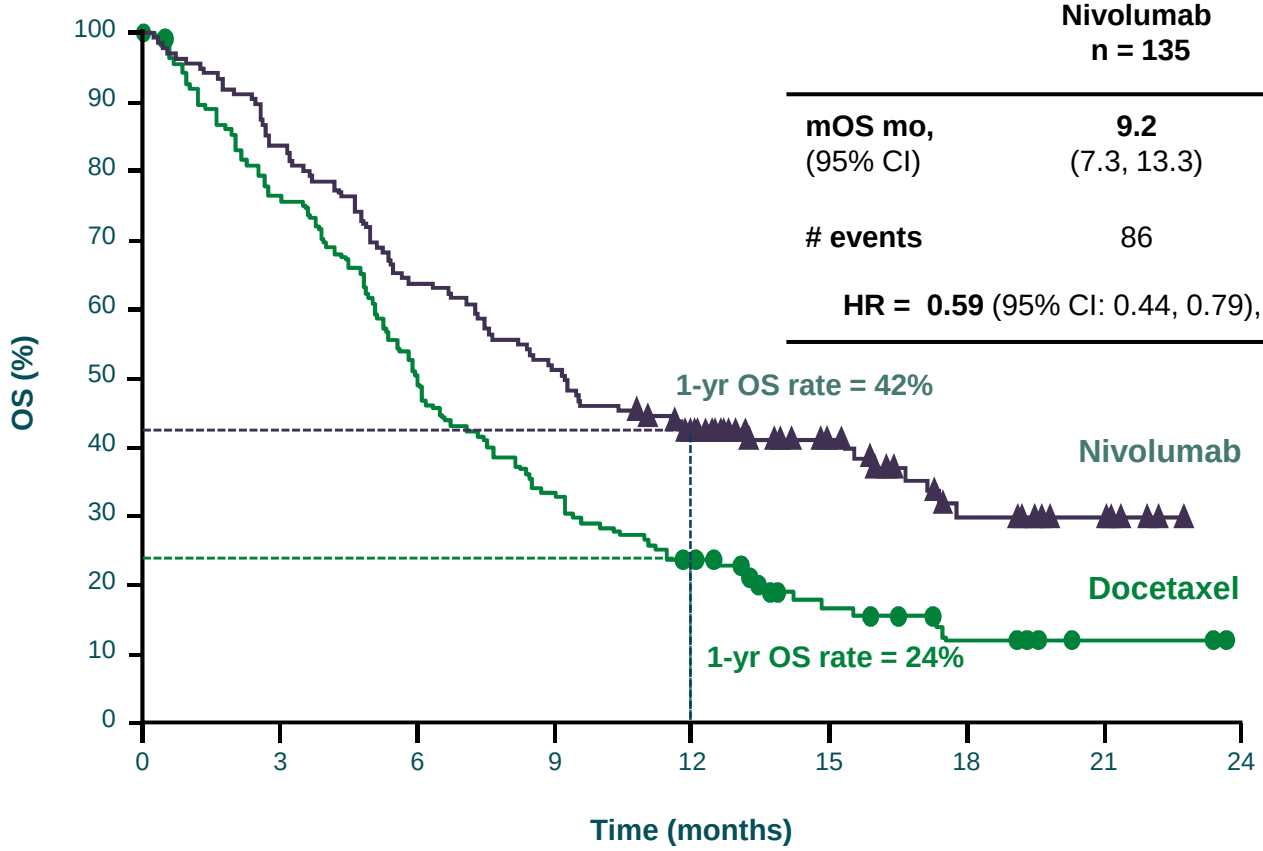
CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was *P* <0.03

LCSS = Lung cancer symptom scale

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

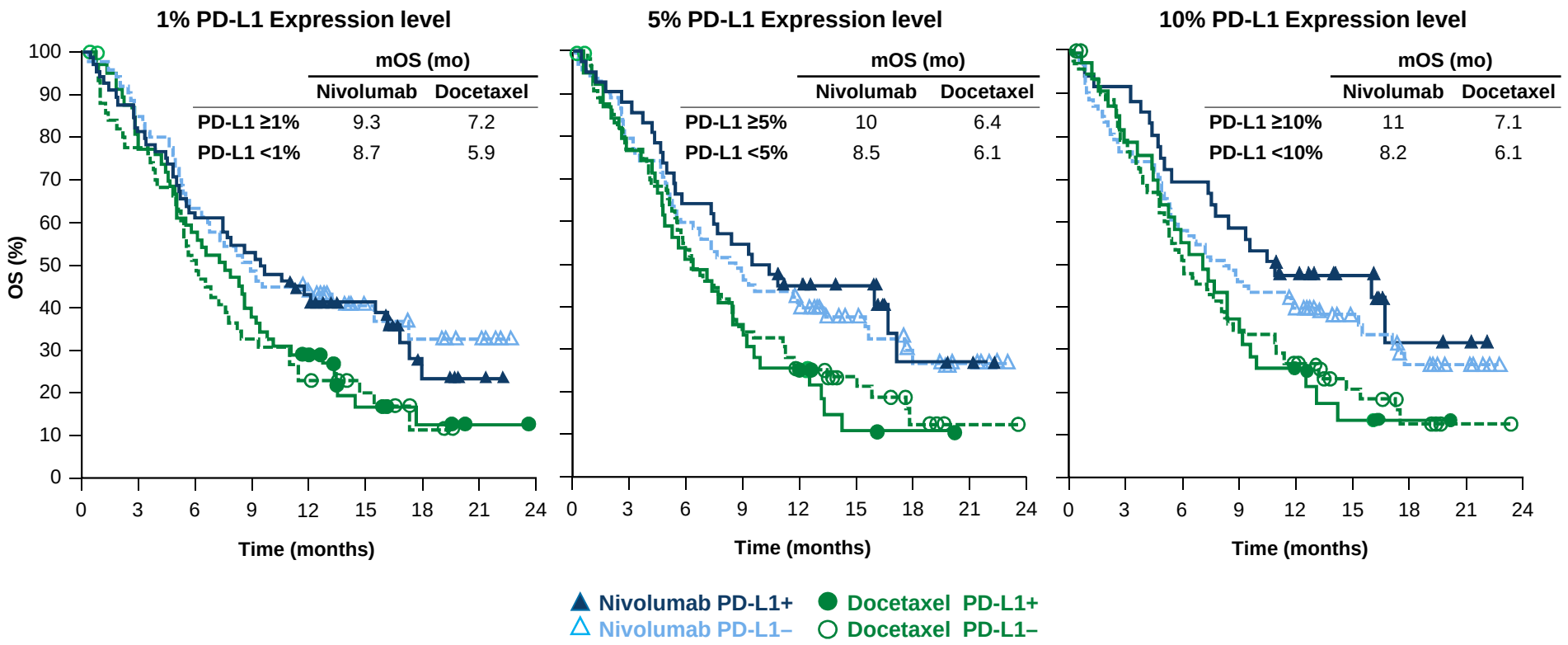
ORR by PD-L1 Expression

- ORR was independent of PD-L1 expression and consistently higher for nivolumab vs docetaxel

PD-L1 Expression Level							
	≥1%	<1%	≥5%	<5%	≥10%	<10%	Not quantifiable[a]
Nivolumab							
ORR,[b] % (n/N)	**18** (11/63)	**17** (9/54)	**21** (9/42)	**15** (11/75)	**19** (7/36)	**16** (13/81)	**39** (7/18)
Docetaxel							
ORR,[b] % (n/N)	**11** (6/56)	**10** (5/52)	**8** (3/39)	**12** (8/69)	**9** (3/33)	**11** (8/75)	**3** (1/29)
Interaction *P*-value	**0.94**		**0.29**		**0.64**		

[a] Percent of randomized pts with PD-L1 expression not quantifiable. [b] CR+PR per RECIST v1.1 criteria confirmation of response required (Investigator Assessment).

OS by PD-L1 Expression

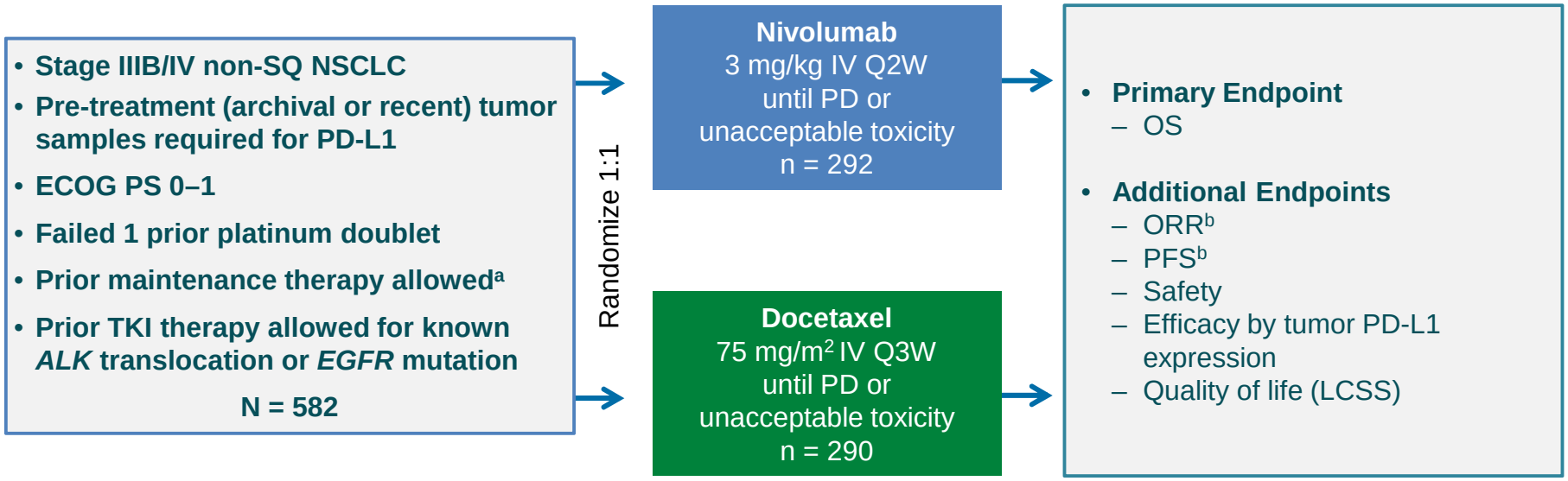


Treatment-related Select AEs

	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

[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.

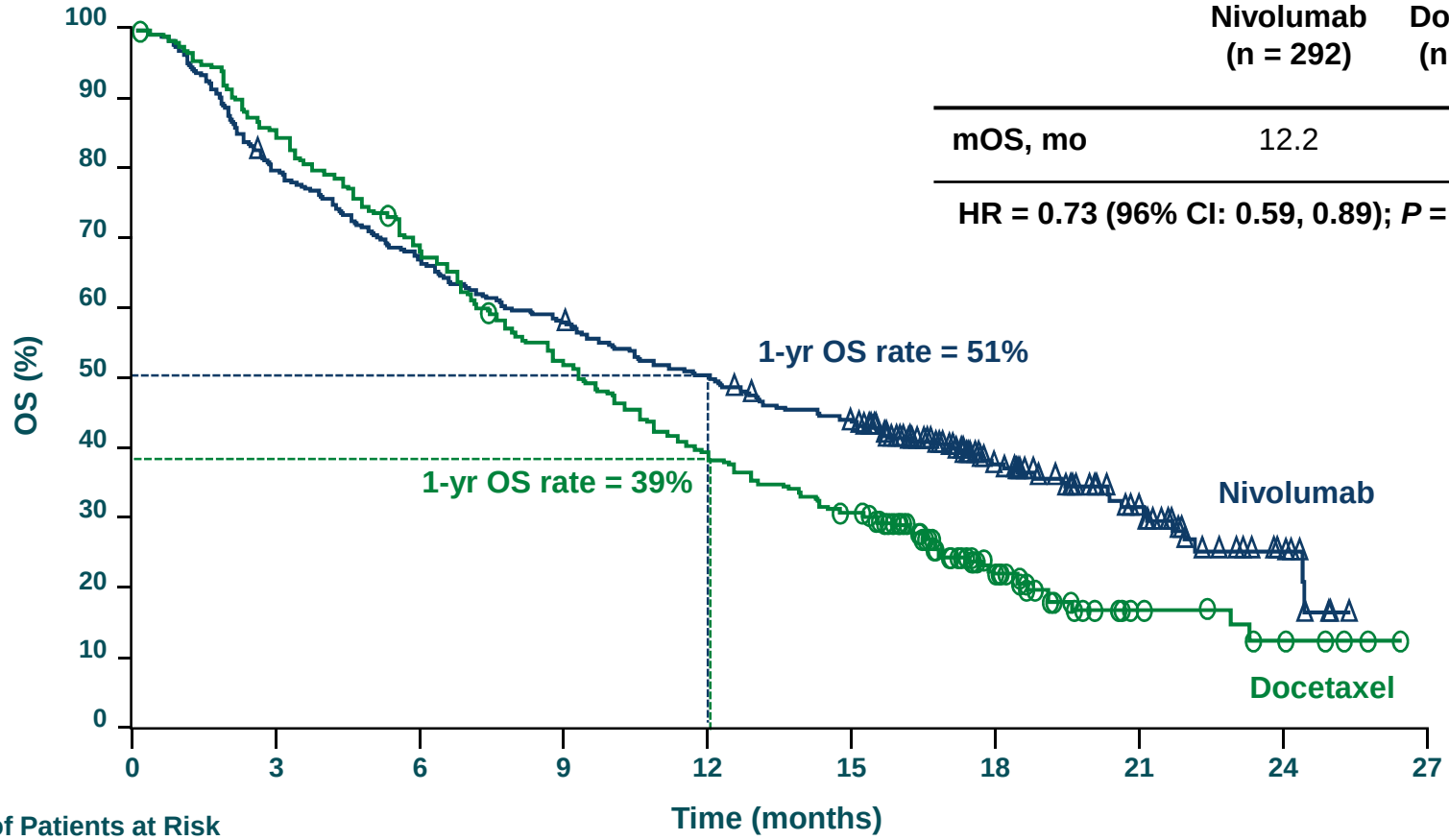
CheckMate 057 (NCT01673867) Study Design



- 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.

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk

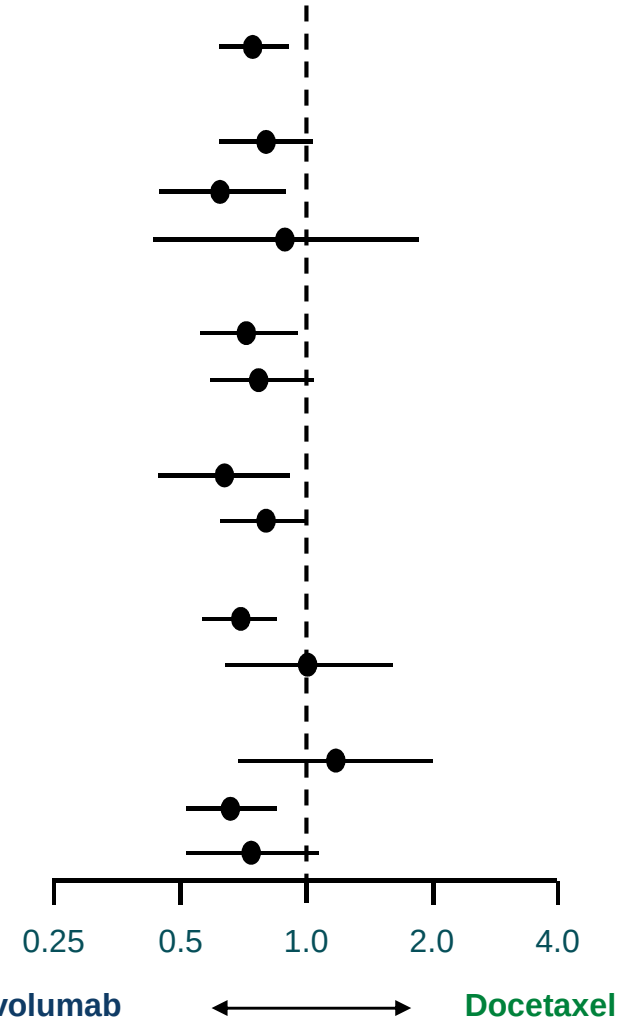
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Paz-Ares L et a., Oral presentation. Presented at ASCO 2015.

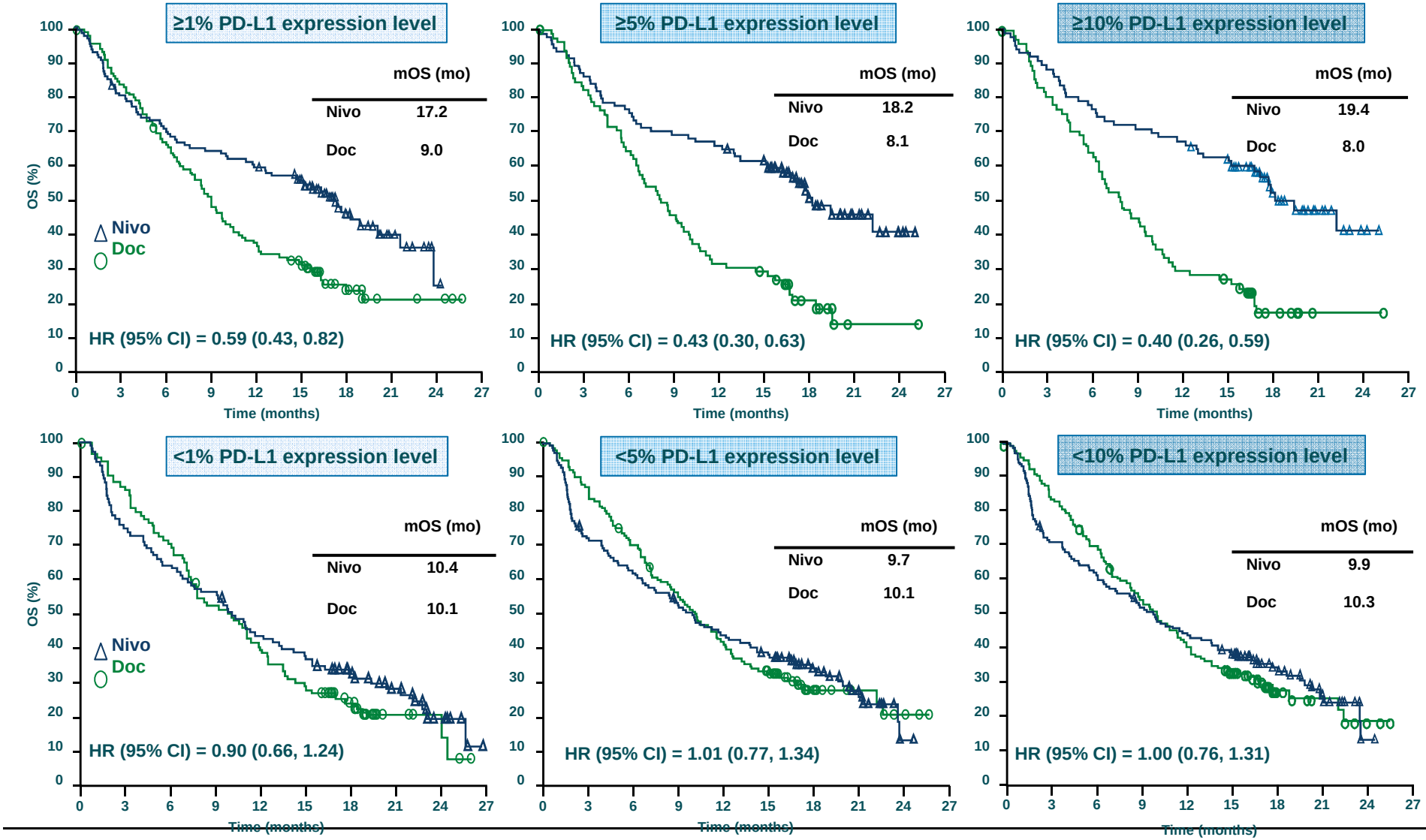
Treatment Effect on OS in Predefined Subgroups

	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).

OS by PD-L1 Expression



ORR by PD-L1 Expression

PD-L1 expression level	≥1%	<1%	≥5%	<5%	≥10%	<10%	Not quantifiable
Nivolumab							
ORR,[a] %	30.9	9.3	35.8	10.3	37.2	11.0	13.1
Median DOR, mos (95% CI) n	16.0 (8.4, NE) 38	18.3 (4.2, NE) 10	16.0 (8.4, NE) 34	18.3 (5.5, NE) 14	16.0 (6.9, NE) 32	18.3 (7.5, NE) 16	7.3 (2.2, NE) 8
Docetaxel							
ORR,[a] %	12.2	14.9	12.8	13.8	12.7	13.8	9.1
Median DOR, mos (95% CI) n	5.6 (3.0, 5.7) 15	5.6 (4.2, 9.9) 15	5.6 (3.0, 7.0) 11	5.6 (4.2, 7.1) 19	5.6 (1.6, 6.2) 10	5.6 (4.2, 7.1) 20	6.6 (2.8, 14.2) 6

[a]CR+PR as per RECIST v1.1 criteria confirmation of response required (Investigator Assessment).
CI = confidence interval; CR = complete response; DOR = duration of response; NE = not evaluable; ORR = objective response rate; PD-L1 = programmed cell death ligand 1; PR = partial response.

Paz-Arez L et a., Oral presentation. Presented at ASCO 2015.

Treatment-related Select AEs

	Nivolumab (n = 287)		Docetaxel (n = 268)	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Endocrine, %				
Hypothyroidism	7	0	0	0
Gastrointestinal, %				
Diarrhea	8	1	23	1
Hepatic, %				
ALT increased	3	0	1	<1
AST increased	3	<1	1	0
Pulmonary, %				
Pneumonitis	3	1	<1	<1
Skin, %				
Rash	9	<1	3	0
Pruritus	8	0	1	0
Erythema	1	0	4	0
Hypersensitivity/Infusion reaction, %				
Infusion-related reaction	3	0	3	<1

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

Includes events reported in ≥2.5% of patients.

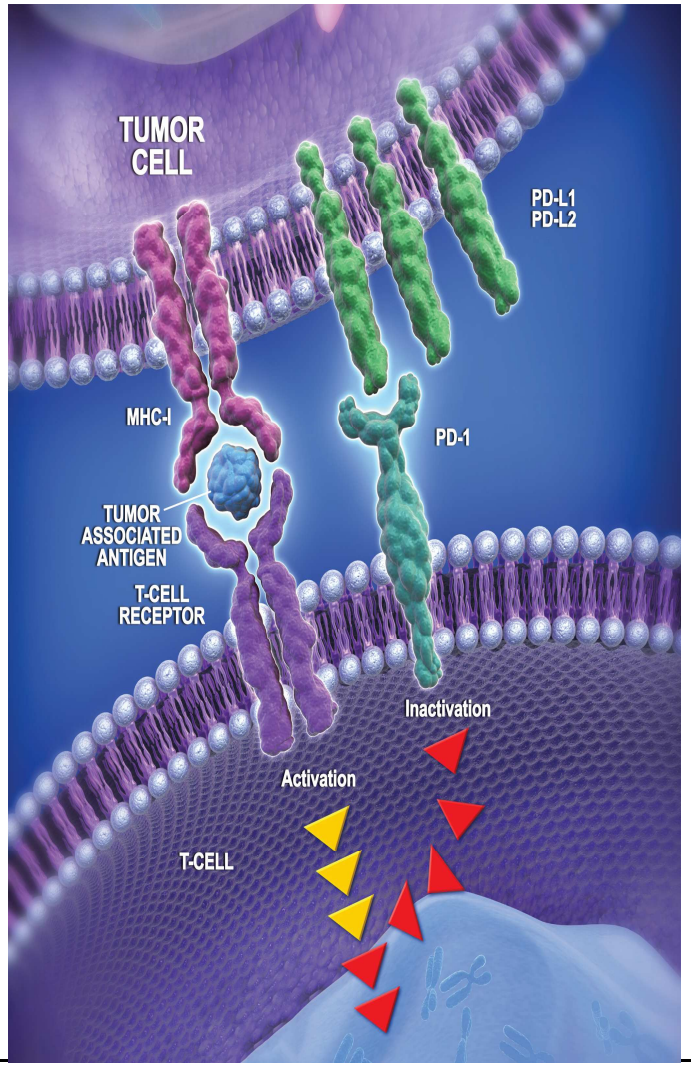
[a] No grade 5 events were reported at DBL;1 grade 5 event for nivolumab was reported post-DBL.

Paz-Arez L et a., Oral presentation. Presented at ASCO 2015.

Nivolumab is an investigational compound and is not approved yet in Canada. Its safety and efficacy have not yet been fully established

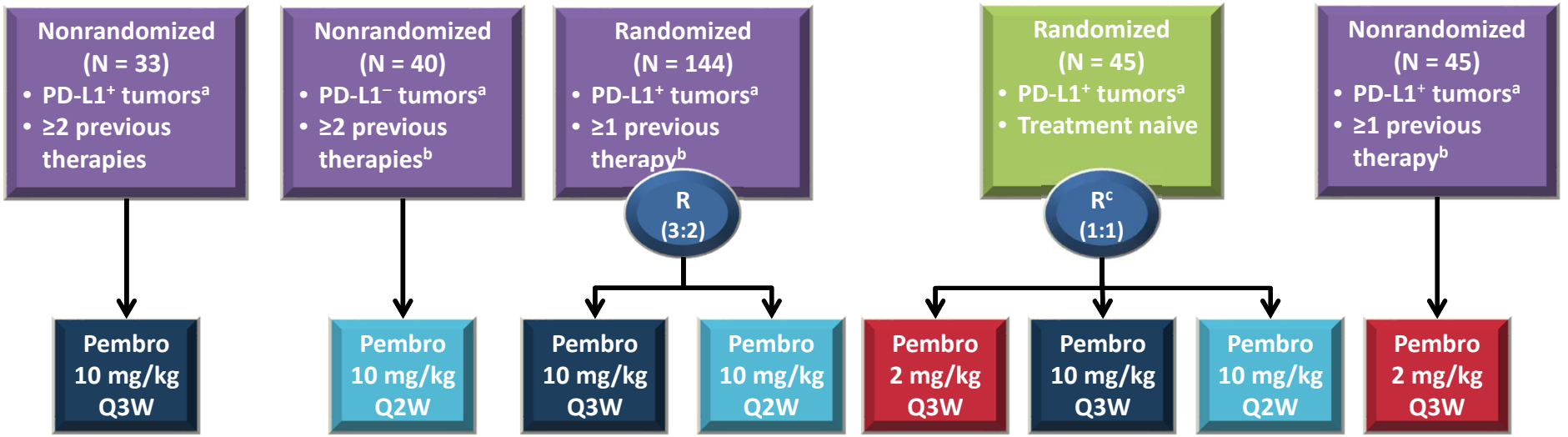
Programmed Death 1 (PD-1) and Pembrolizumab

- Binding of the inhibitory receptor PD-1 to its ligands, PD-L1 or PD-L2, inhibits tumor-specific T-cell responses
- Tumors can exploit this pathway to escape T-cell–induced antitumor activity
- Pembrolizumab is a high-affinity antibody against PD-1 that blocks its interaction with PD-L1 and PD-L2
  - Robust antitumor activity and manageable safety profile in multiple tumor types
  - Approved in several countries for the treatment of advanced melanoma
  - In development for ≥30 tumor types



Ott et al. Oral Presentation ASCO 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.

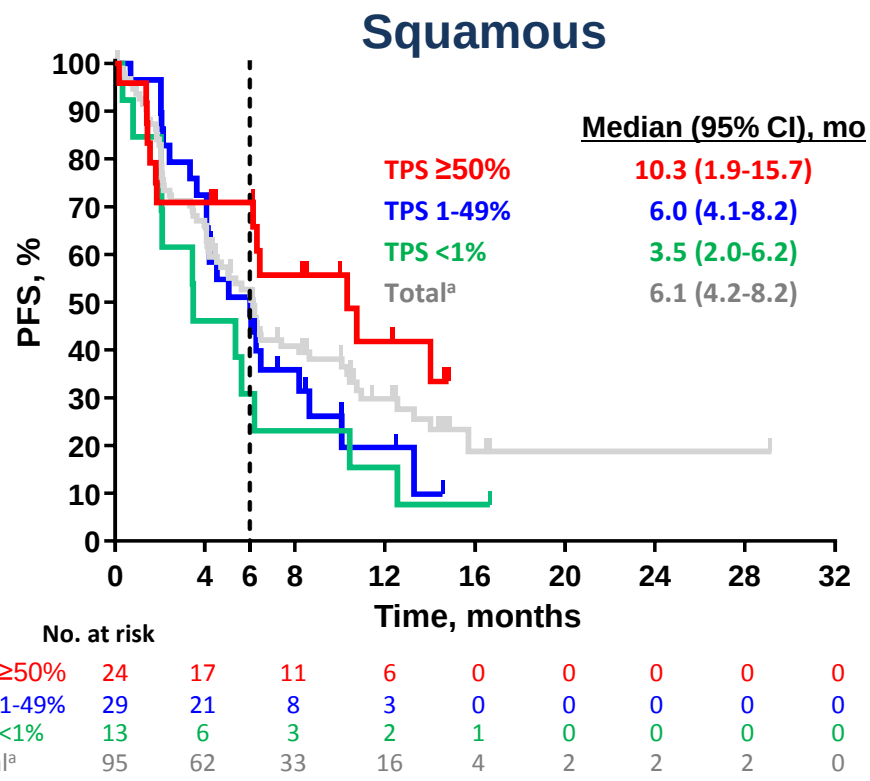
1. Eisenhauer EA et al. *Eur J Cancer*. 2009;45:228-247. 2. Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412-20.

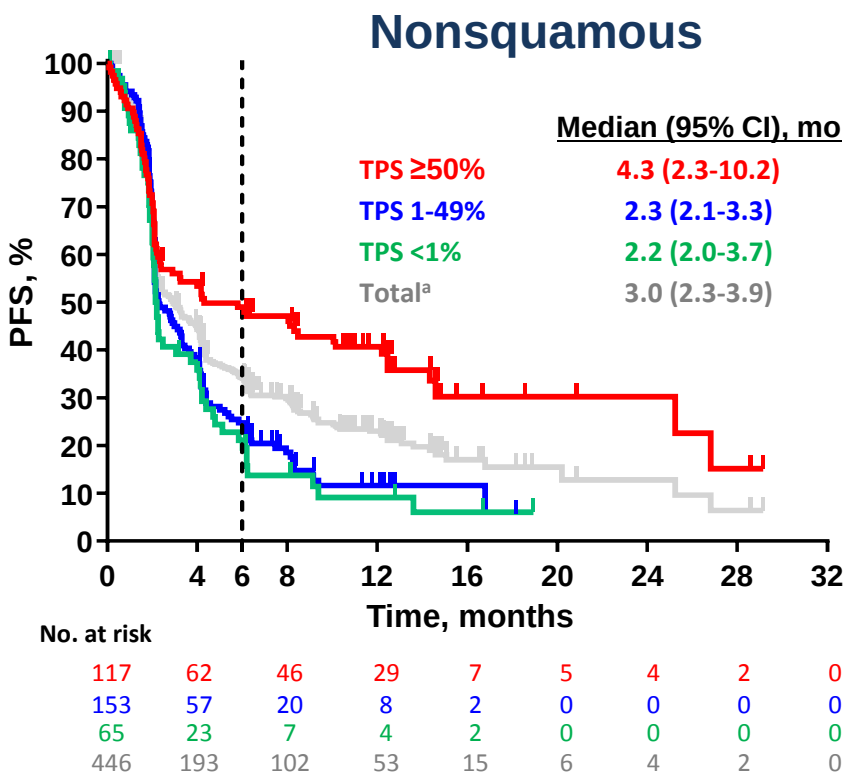
Antitumor Activity by Histology

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
Squamous	24	50.0 (29.1-70.9)	29	17.2 (5.8-35.8)	13	0.0 (0.0-24.7)	95	26.3 (17.8-36.4)
Nonsquamous	117	35.9 (27.2-45.3)	153	11.1 (6.6-17.2)	65	12.3 (5.5-22.8)	446	19.1 (15.5-23.0)

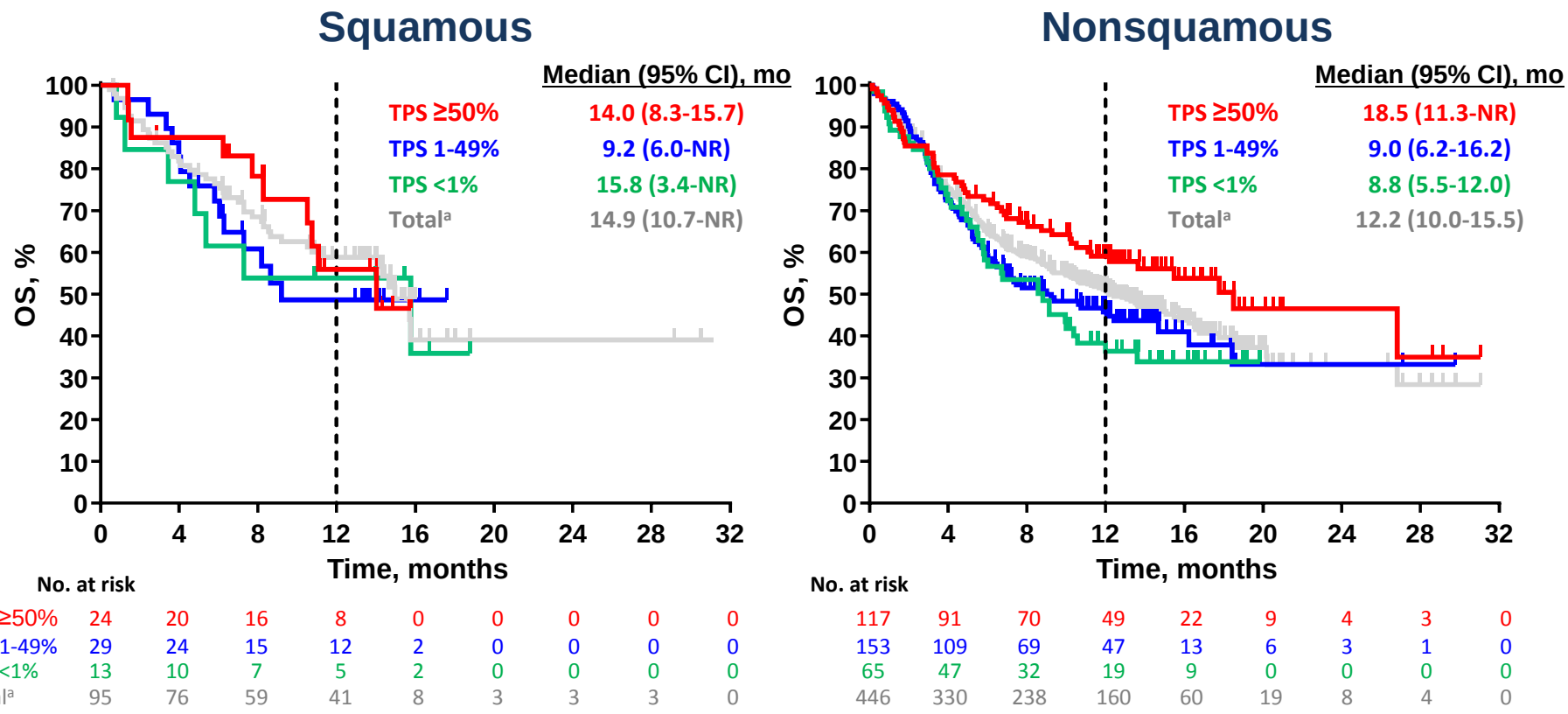
[a]Includes patients for whom a PD-L1 TPS could not be assigned (n = 141). For the histology breakdown, data are not shown for patients with adenosquamous (n = 7) or unknown (n = 2) histology.
Data cutoff date: January 23, 2015.

PFS by Histology





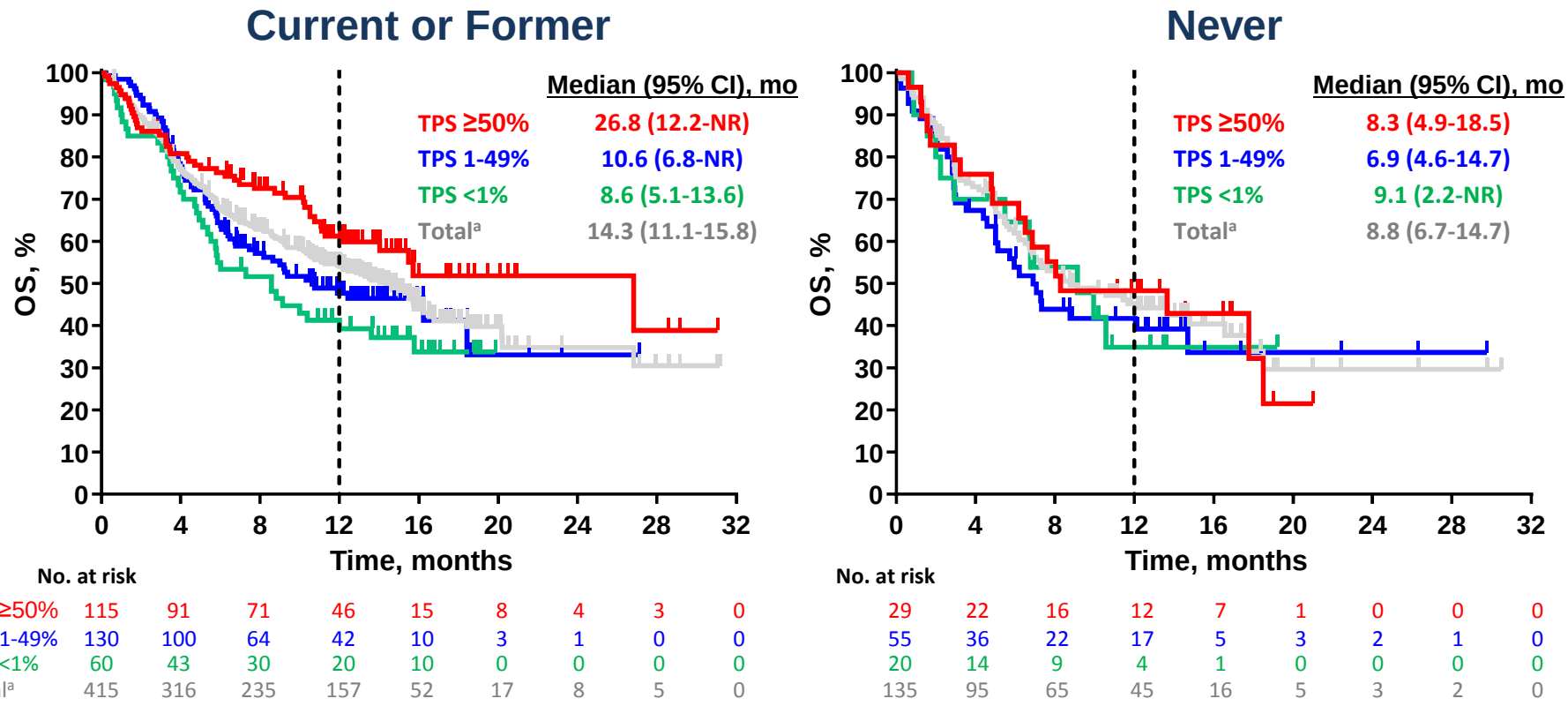
OS by Histology



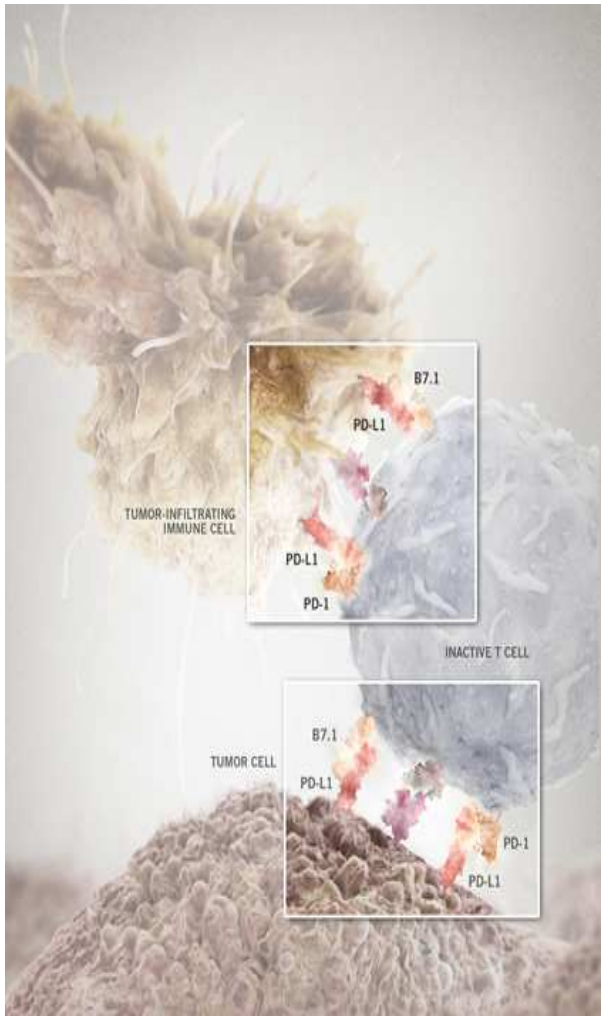
Antitumor Activity by Smoking History

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
Current or former	115	40.0 (31.0-49.6)	130	14.6 (9.0-21.9)	60	13.3 (5.9-24.6)	415	23.4 (19.4-27.7)
Never	29	31.0 (15.3-50.8)	55	5.5 (1.1-15.1)	20	0.0 (0.0-16.8)	135	10.4 (5.8-16.8)

OS by Smoking History

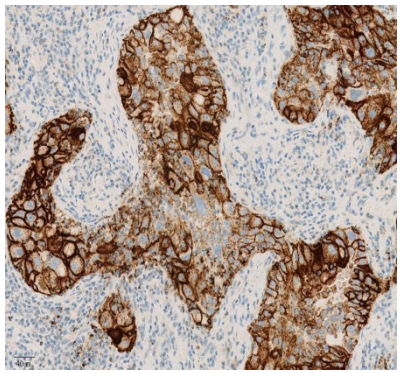


Atezolizumab is a Humanized Anti-PDL1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1

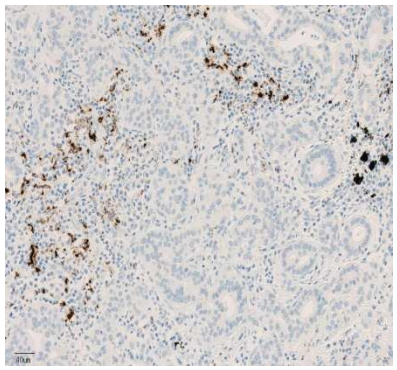


- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming
- Targeting PD-L1 leaves the PD-L2/PD-1 interaction intact, thereby potentially preserving peripheral immune homeostasis
- Atezolizumab (anti-PDL1; MPDL3280A) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor cells (TC) and/or tumor-infiltrating immune cells (IC); (Spigel et al., ASCO 2015; Horn et al., ASCO 2015; Liu et al., ASCO 2015)

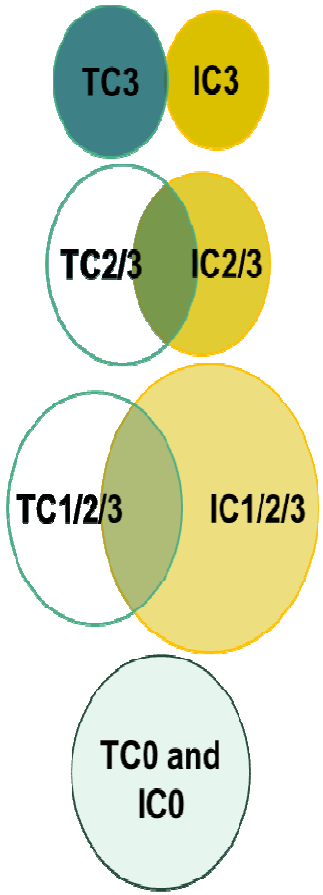
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC



Intrinsic PD-L1 expression in tumor cells (TC)



Adaptive PD-L1 expression in tumor-infiltrating immune cells (IC)



PD-L1 expression levels and TC/IC overlap in POPLAR

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] (Gettinger et al., ASCO 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al., ASCO 2015)

[a]TC scored as percentage of tumor cells and IC scored as percentage of tumor area. **TC3 or IC3** = TC ≥ 50% or IC ≥ 10% PD-L1+; **TC2/3 or IC2/3** = TC or IC ≥ 5% PD-L1+; **TC1/2/3 or IC1/2/3** = TC or IC ≥ 1% PD-L1+; **TC0 and IC0** = TC and IC < 1% PD-L1+, respectively.

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

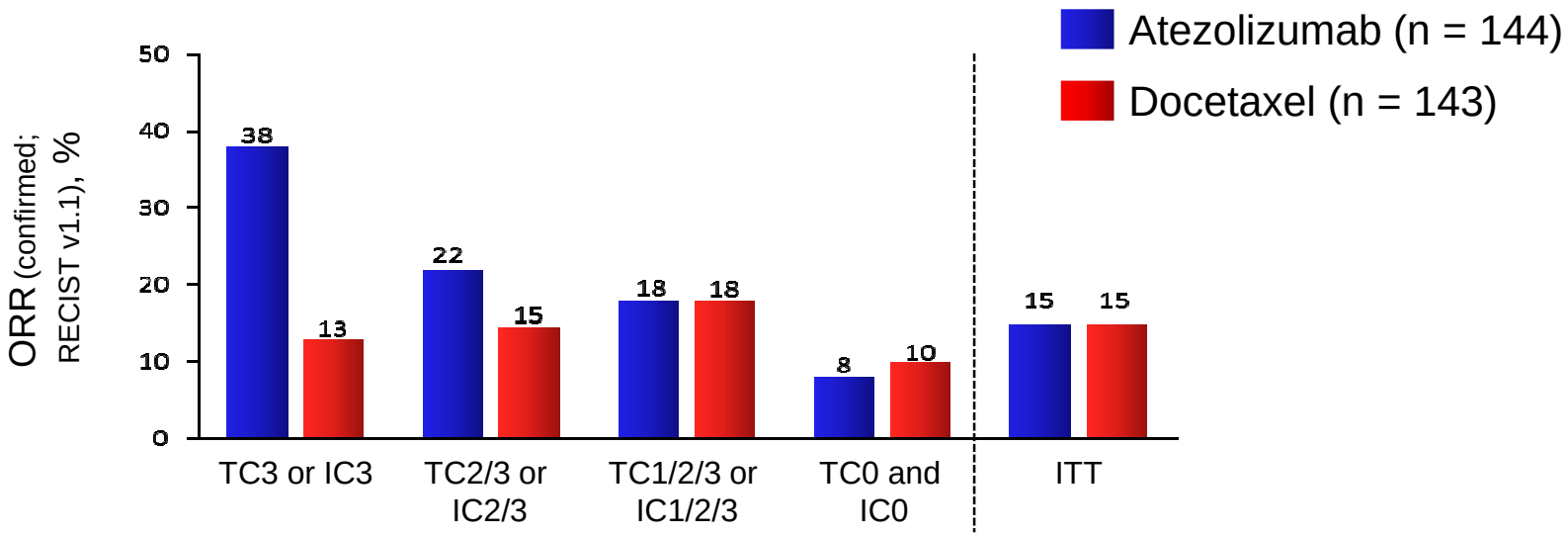
Interim analysis is based on 153 events with a minimum follow-up 10 months

POPLAR Baseline Characteristics, ITT Population

		Atezolizumab (n=144)	Docetaxel (n=143)
Median age, y		62	62
≥65 years, %		40%	39%
Male, %		65%	53%
Histology	Non-squamous	66%	66%
	Squamous	34%	34%
ECOG score 0/1		33% / 67%	32% / 68%
No. of prior chemotherapies, 1/2		65% / 35%	65% / 35%
History of tobacco use	Never	19%	20%
	Current	17%	15%
	Previous	64%	65%

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

Atezolizumab vs. Docetaxel in NSCLC (POPLAR Study): Overall Response Rates & Survival

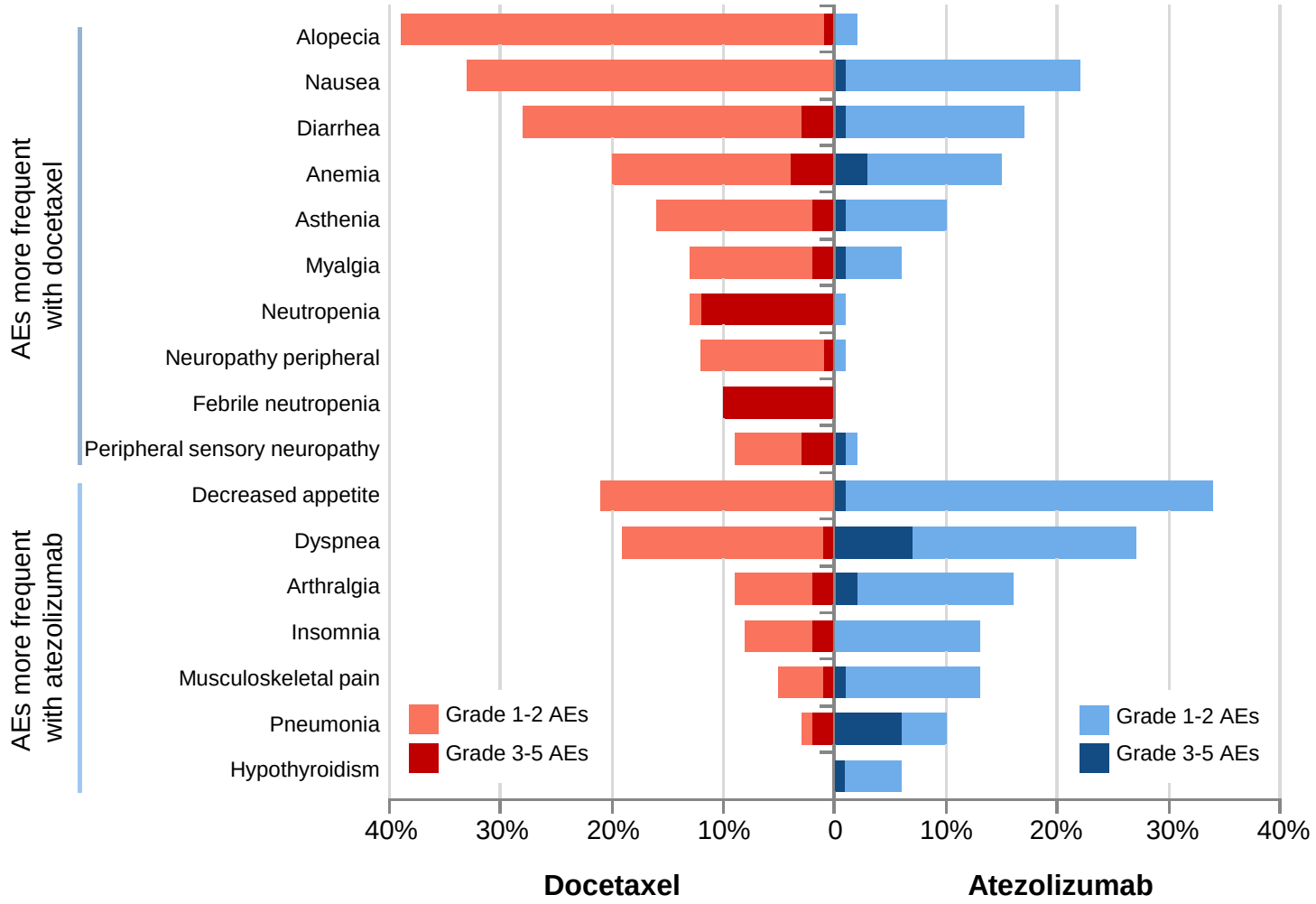


	Median OS months			
	TC3 or IC 3 (n=47)	TC2/3 or IC 2/3 (n=105)	TC or IC 1/2/3 (n = 195)	TC0 or IC0 (n = 92)
Atezolizumab	NR (9.8 – NE)	13.0 (8.4 – NE)	11.0 (11.0 – NE)	9.7 (8.6 – 12.0)
Docetaxel	11.0 (6.4 – 14)	7.4 (6.0 – 12.5)	9.1 (7.4 – 12.8)	9.7 (6.7 – 11.4)
	HR[a] = 0.46 (0.19, 1.09) P value = 0.070	HR[a] = 0.56 (0.33, 0.94) P value = 0.026	HR[a] = 0.63 (0.42, 0.94) P value = 0.024	HR[a] = 1.12 (0.64, 1.93) P value = 0.70

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

POPLAR: All-cause AEs

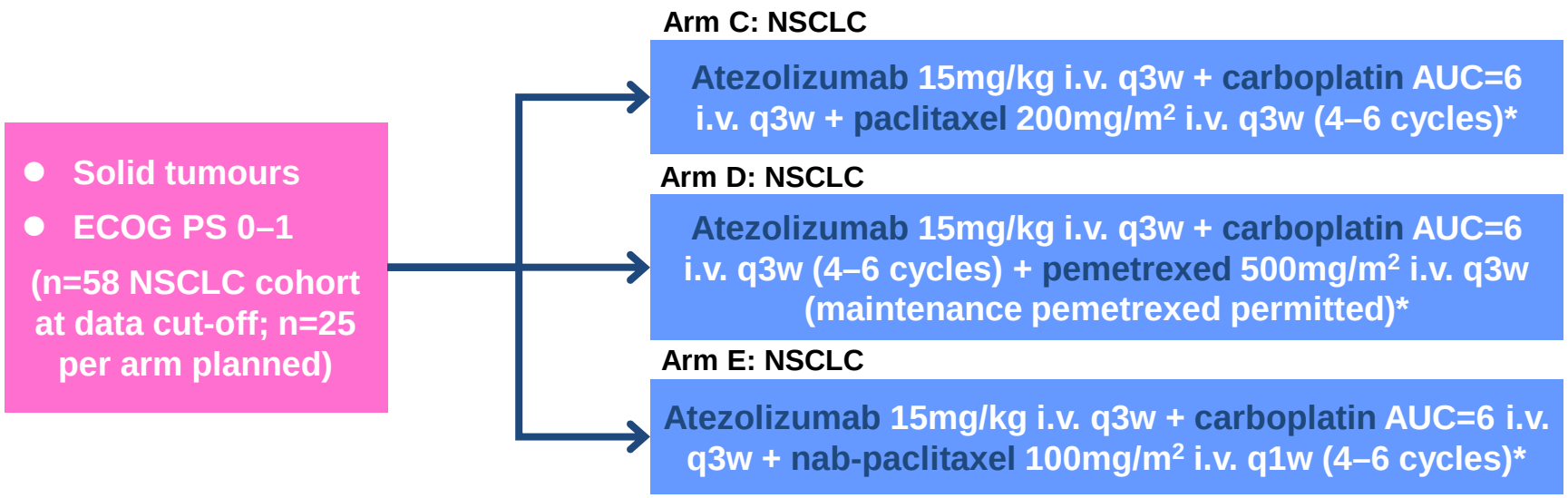
(≥ 5% difference between arms)



- 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.

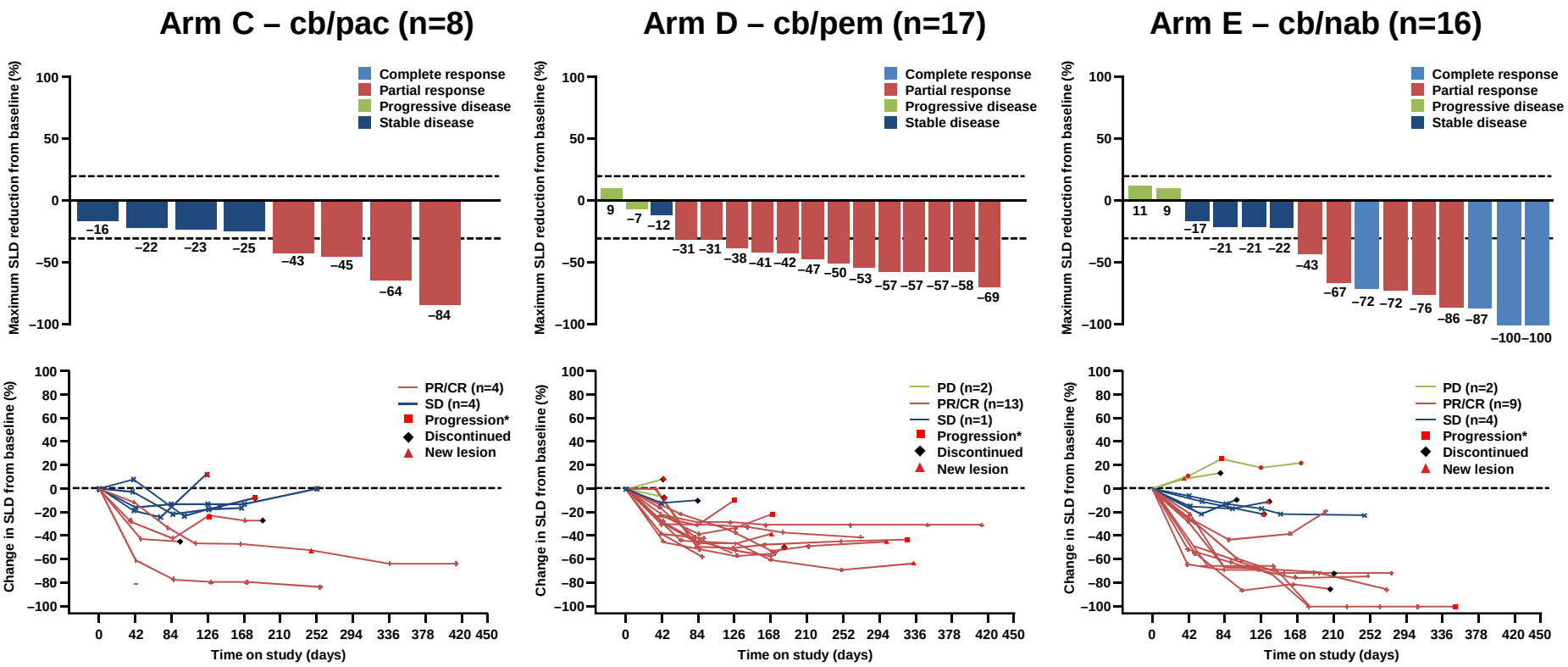
Phase Ib GP28328 study design and endpoints: NSCLC cohort



- Primary endpoint: safety (including dose-limiting toxicities)
- Secondary endpoints: pharmacokinetics; best overall response; objective response rate (ORR); duration of response (DOR); progression-free survival (PFS)
- Date of cut-off: 10 Feb 2015; median safety follow-up: 128.5 days (4.2 months)

***supportive care (including steroids if necessary) was permitted, at the investigators' discretion; atezolizumab was given until loss of clinical benefit**

Depth of response and changes in tumor burden by treatment arm



Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015; SLD, sum of longest diameters; *PD for reasons other than new lesions

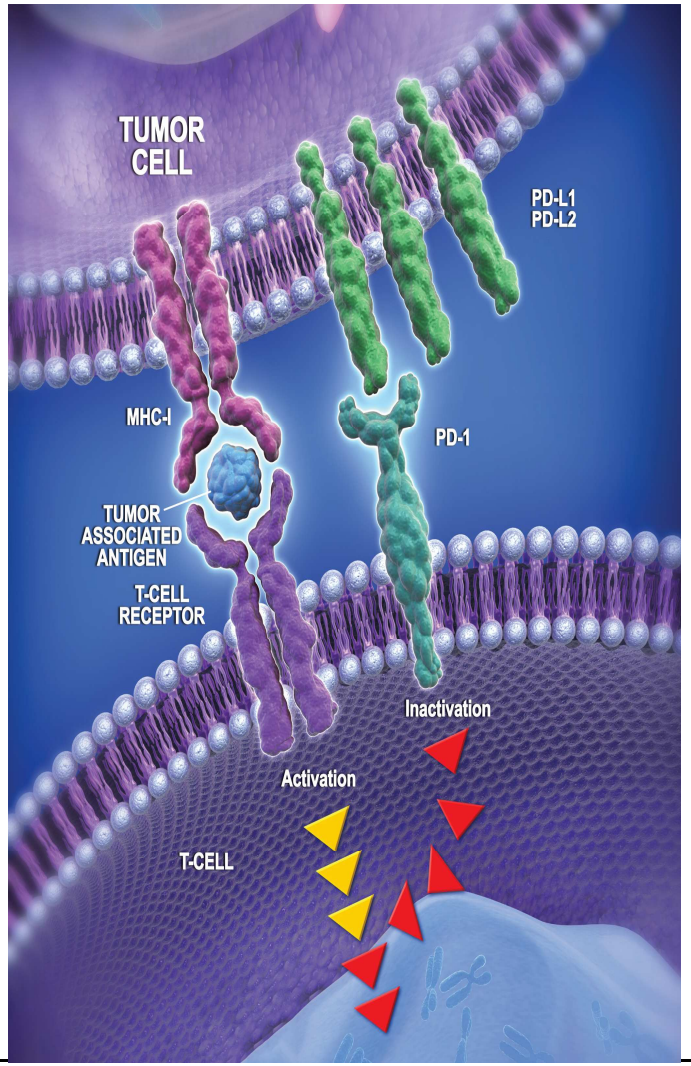
Grade 3/4 treatment-related AEs* in ≥3% of patients

AE, n (%)	Arm C – cb/pac (n=14)	Arm D – cb/pem (n=24)	Arm E – cb/nab (n=20)	All NSCLC patients (n=58)
Neutropenia	5 (35.7)	9 (37.5)	9 (45.0)	23 (39.7)
Anemia	2 (14.3)	2 (8.3)	4 (20.0)	8 (13.8)
Thrombocytopenia	0 (0)	5 (20.8)	2 (10.0)	7 (12.1)
Fatigue	1 (7.1)	2 (8.3)	2 (10.0)	5 (8.6)
Alanine aminotransferase increased	0 (0)	1 (4.2)	2 (10.0)	3 (5.2)
Aspartate aminotransferase increased	0 (0)	1 (4.2)	2 (10.0)	3 (5.2)
Dehydration	1 (7.1)	2 (8.3)	0 (0)	3 (5.2)
Hypokalemia	0 (0)	1 (4.2)	1 (5.0)	2 (3.4)
Leukopenia	0 (0)	2 (8.3)	0 (0)	2 (3.4)
Nausea	0 (0)	0(0)	2 (10.0)	2 (3.4)

***includes AEs attributed to chemotherapy and/or atezolizumab; data cut-off: 10 Feb 2015**

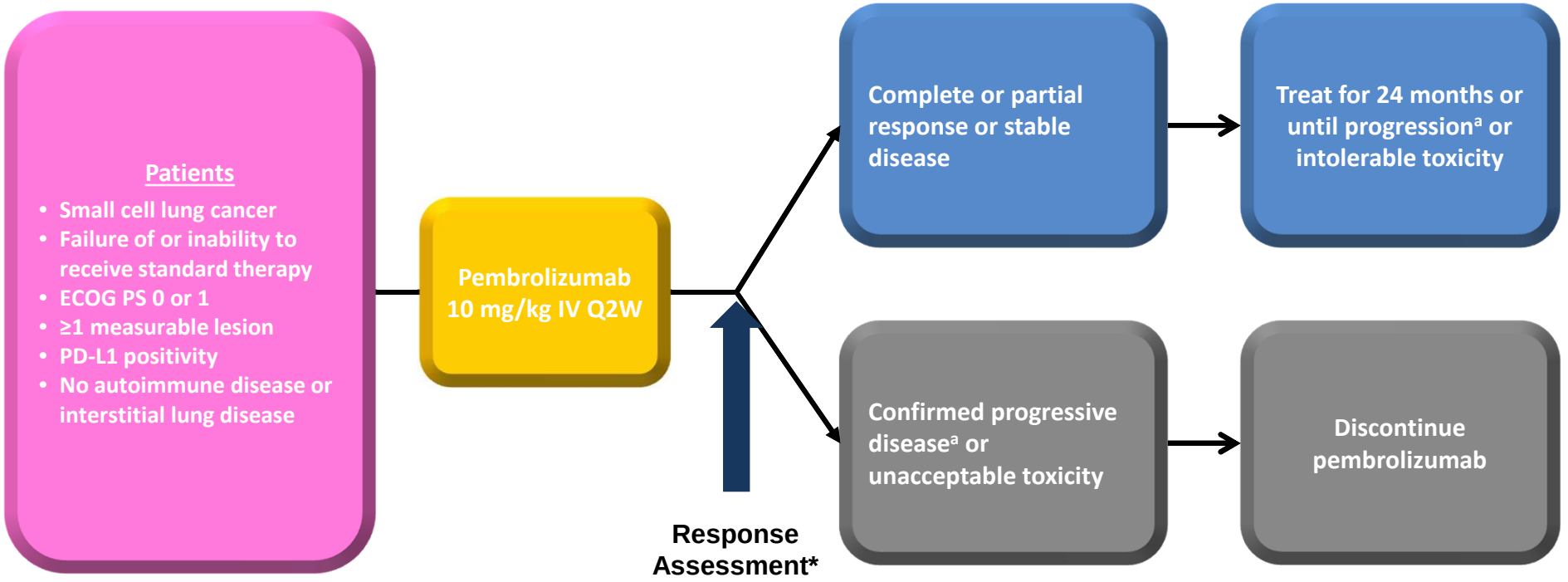
Programmed Death 1 (PD-1) and Pembrolizumab

- Binding of the inhibitory receptor PD-1 to its ligands, PD-L1 or PD-L2, inhibits tumor-specific T-cell responses
- Tumors can exploit this pathway to escape T-cell–induced antitumor activity
- Pembrolizumab is a high-affinity antibody against PD-1 that blocks its interaction with PD-L1 and PD-L2
  - Robust antitumor activity and manageable safety profile in multiple tumor types
  - Approved in several countries for the treatment of advanced melanoma
  - In development for ≥30 tumor types



Ott et al. Oral Presentation ASCO 2015

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1^{+} Advanced Solid Tumors



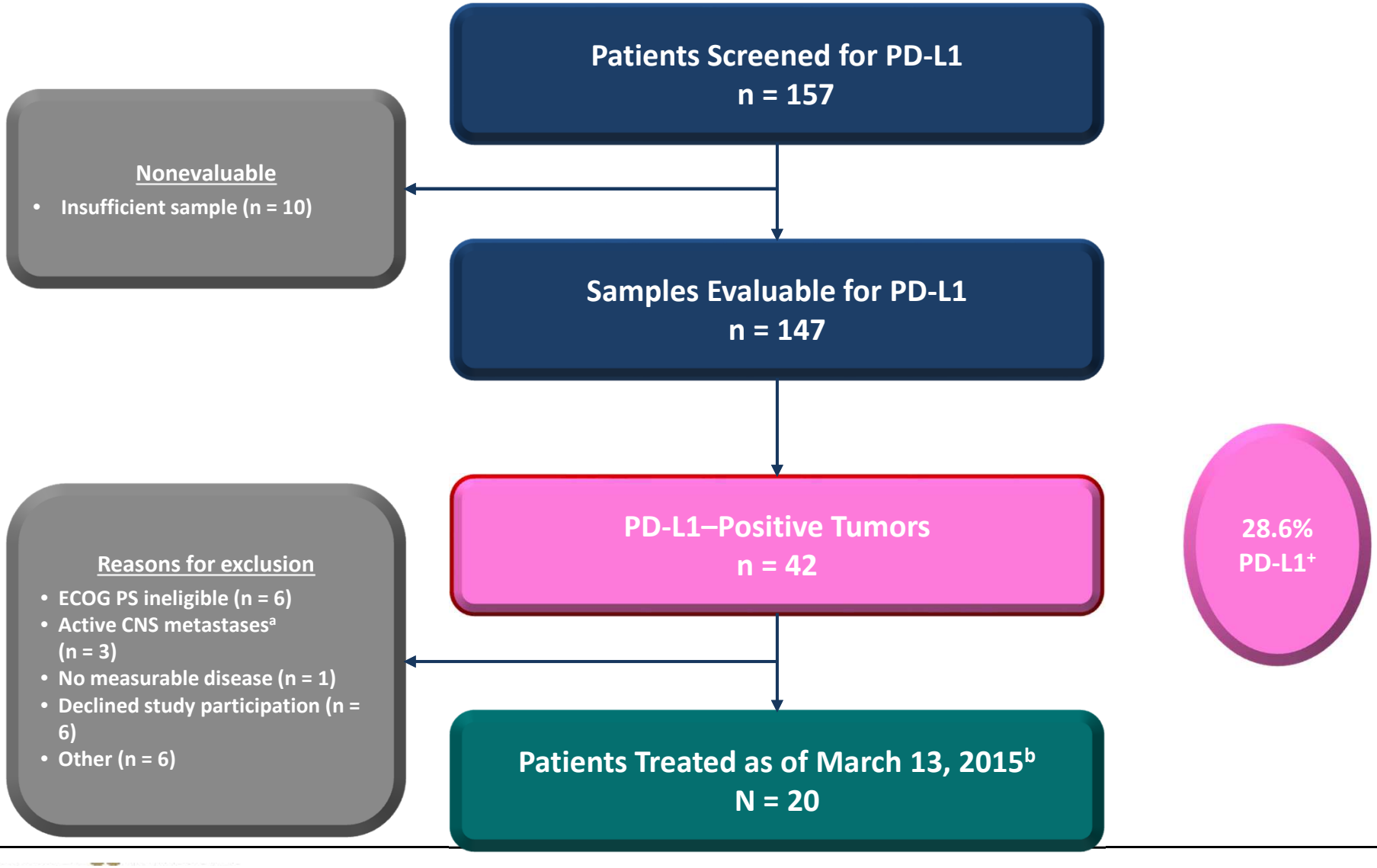
***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

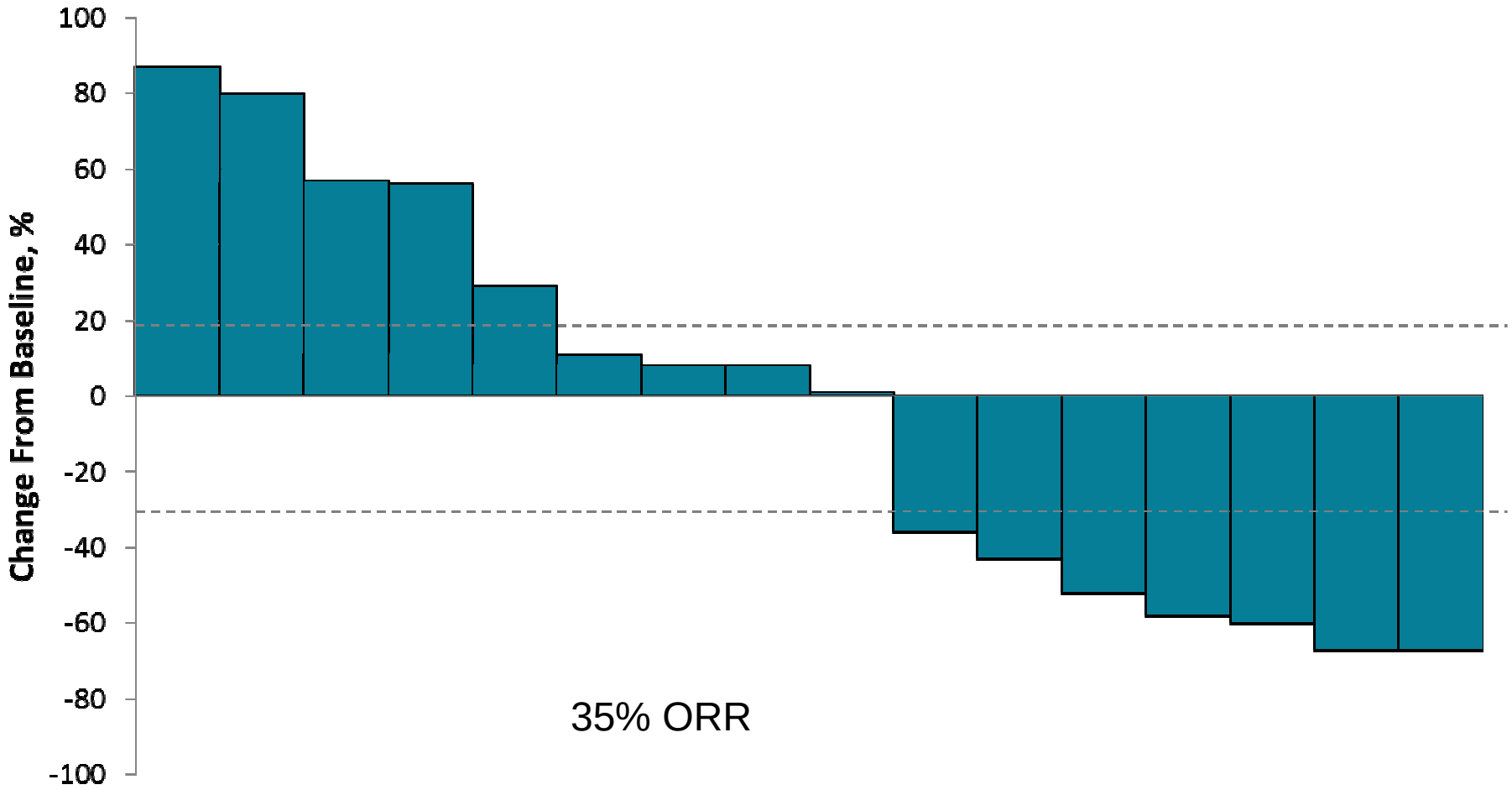
[a]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

PD-L1 Screening: SCLC Cohort



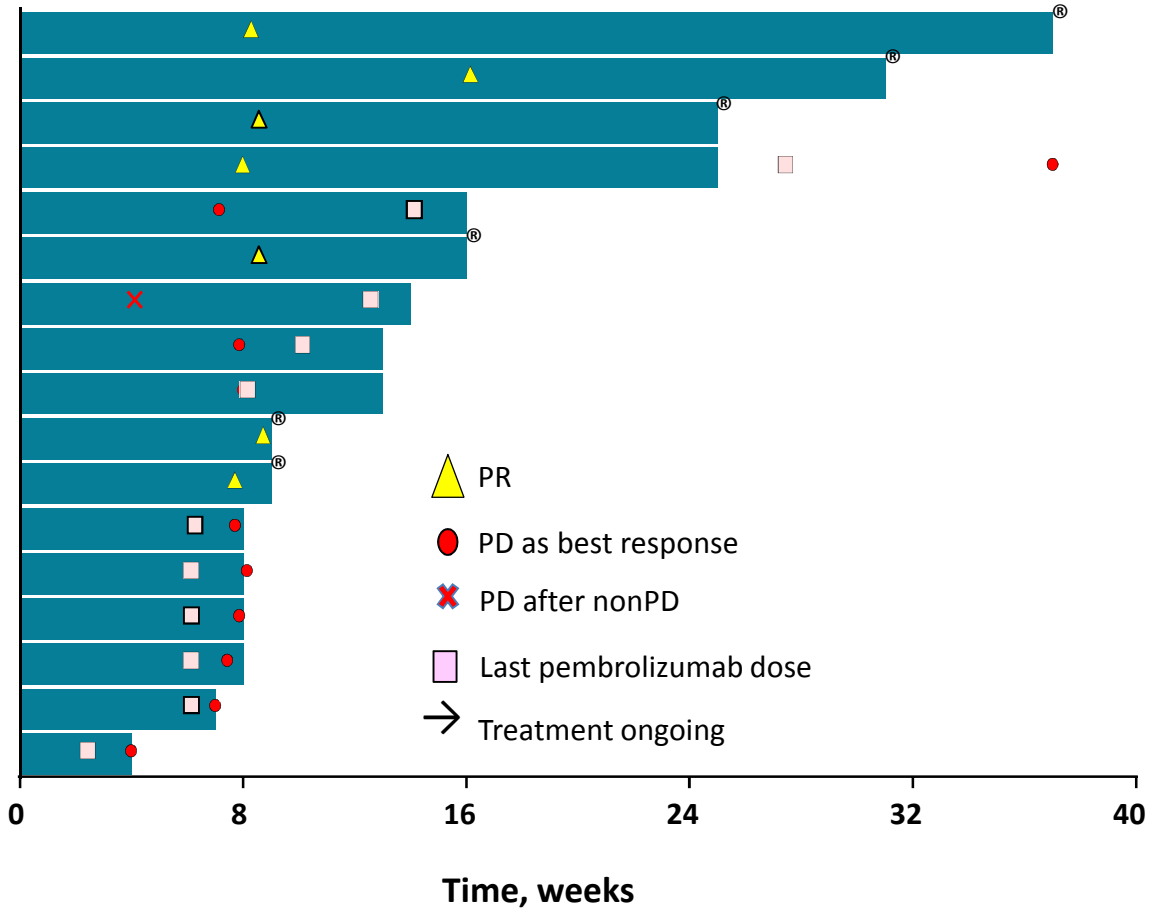
[a]Patients with CNS metastases that were stable for ≥4 weeks could enroll.
[b]1 additional patient was misenrolled and never treated. An additional 4 patients were enrolled and treated after the March 13, 2015, data cutoff date of this analysis.

Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



Only patients with ≥1 evaluable postbaseline tumor assessment are included (n = 16).
Data cutoff date: March 13, 2015.

Treatment Exposure and Response Duration (RECIST v1.1, Investigator Review)



- Time to response
  - Median: 8.6 weeks
  - Range: 7.7-16.1 weeks
- Duration of response
  - Median: 29.1 weeks
  - Range: 0.1+ to 29.1 weeks
- 6 of 7 responses ongoing at time of data cutoff

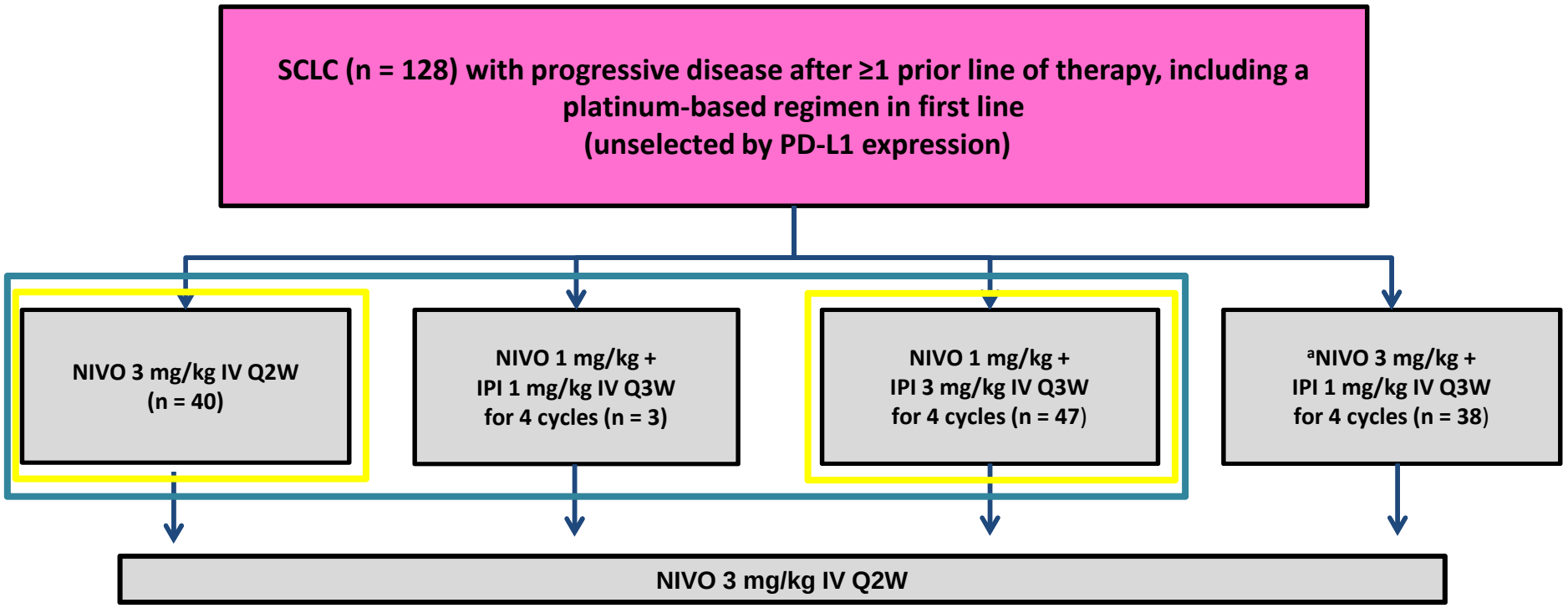
Bar length is equivalent to the time to the last imaging assessment. Includes patients with ≥1 postbaseline tumor assessment (n = 17).
Data cutoff date: March 13, 2015.

Adverse Events of Special Interest

Event	n (%)	Resulted in Treatment Interruption
Rash[a] (all grade 1)	2 (10)	No
ALT/AST increased (grade 1)	1 (5)	No
Infusion-related reaction (grade 1)	1 (5)	No
Autoimmune thyroiditis (grade 2)	1 (5)	Yes
Colitis (grade 5)	1 (5)	Yes

[a]Includes maculopapular rash.
Data cutoff date: March 13, 2015.

CheckMate 032 Study Design



Primary objective: ORR per RECIST v1.1
Secondary objective: Safety
Exploratory objectives: PFS, OS, Biomarker analysis

Efficacy analysis

Safety analysis

Database lock: February 16, 2015

Summary of Clinical Activity

	NIVO (n = 40)	NIVO + IPI (n = 46[a])
ORR, n (%)	7 (18)	8 (17.4)
CR, n (%)	0	1 (2.2)
PR, n (%)	7 (18)	7 (15.2)
SD, n (%)	8 (20)	17 (37)
DCR, n (%)	15 (38)	25 (54.3)
PD, n (%)	21 (53)[b]	17 (37)
Death prior to first response assessment, n (%)	4 (10)	3 (6.5)[c]
Not evaluable (no tumor assessment follow-up)	0	1 (2.2)[d]
Median time to objective response, months	1.6	2.1
Median DOR, months (95% CI)	NR	6.9 (1.5, NR)
Range	4.1-11+	1.5-11.1+

DBL, database lock; NR, not reached.
[a]Data combined for NIVO 1 + IPI 1 and NIVO 1 + IPI 3 cohorts. In the NIVO 1 + IPI 3 cohort, 4 pts had not reached first tumor assessment at DBL
[b]1 pt had PD in spine requiring surgery
[c]1 pt died due to unrelated AE, 1 pt died due to treatment-related myasthenia gravis, 1 pt died due to PD
[d]1 pt had unrelated AE leading to permanent discontinuation and had no post baseline tumor assessment

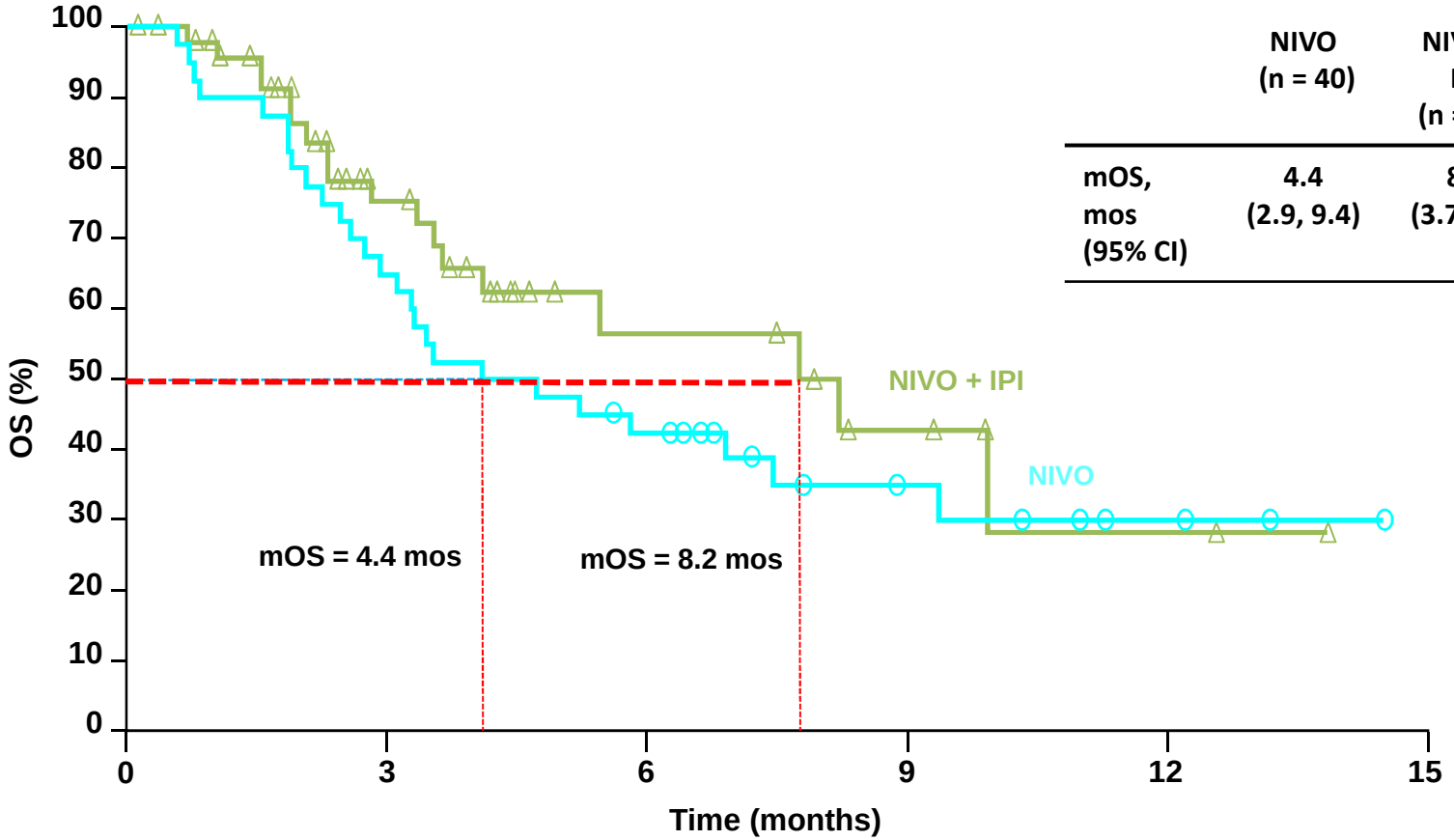
- **Of 17 pts with SD (NIVO + IPI), 7 pts had a PR confirmed after the database lock, resulting in an updated ORR of 32.6% for NIVO + IPI**
- **No additional responses occurred in the NIVO monotherapy arm after database lock**

Treatment-related AEs in ≥5% Patients

	NIVO (n = 40)		NIVO1 + IPI3 (n = 47)	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Total TRAEs	**53**	**15**	**77**	**34**
Fatigue	18	3	21	0
Diarrhea	13	0	23	9
Nausea	10	0	13	2
Vomiting	3	0	9	4
Decreased appetite	10	0	4	0
Pruritus	8	0	19	2
Rash	3	0	21	4
Rash maculopapular	0	0	13	4
Hypothyroidism	5	0	15	0
Hyperthyroidism	3	0	13	0
AST increased	5	0	4	0
Amylase increased	3	3	6	2
Lipase increased	0	0	11	6
Pneumonitis	5	0	2	2

Limbic encephalitis of grade 2 occurred in 2 pts (NIVO, n = 1; NIVO 1 + IPI 3, n = 1) and resolved under immunosuppressive treatment. One pt (NIVO, n = 1) had grade 4 limbic encephalitis with minor response to immunosuppressive treatment

Overall Survival



	NIVO (n = 40)	NIVO + IPI (n = 50)
mOS, mos (95% CI)	4.4 (2.9, 9.4)	8.2 (3.7, NR)

Number of Subjects at Risk

NIVO	40	26	16	7	3	0
NIVO + IPI	50	25	10	5	2	0

Summary

- Anti-PD1 and PD-L1 antibodies have demonstrated promising results as second line therapy in NSCLC patients
  - Nivolumab is FDA approved as second line therapy in squamous cell lung cancer
  - Nivolumab nonsquamous trial was also positive for OS
  - Atezolizumab phase II data shows similar results
- PD-L1 expression predicts for response
  - But responses are seen in PD-L1 negative patients and not all PD-L1 positive patients are responding
- PD-L1 inhibitors are safe in combination with chemotherapy
- Anti-PD1 antibodies look promising in small cell lung cancer patients
- Length of therapy with immune checkpoint inhibitors in lung cancer patients needs to be established