

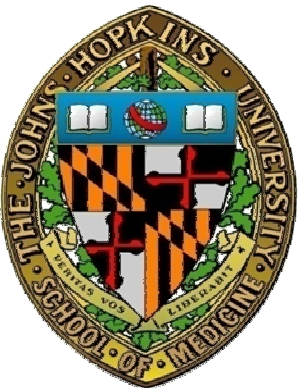
Immunotherapy in Non-Small Cell Lung Cancer: PD-1 Immune Checkpoint Blockade

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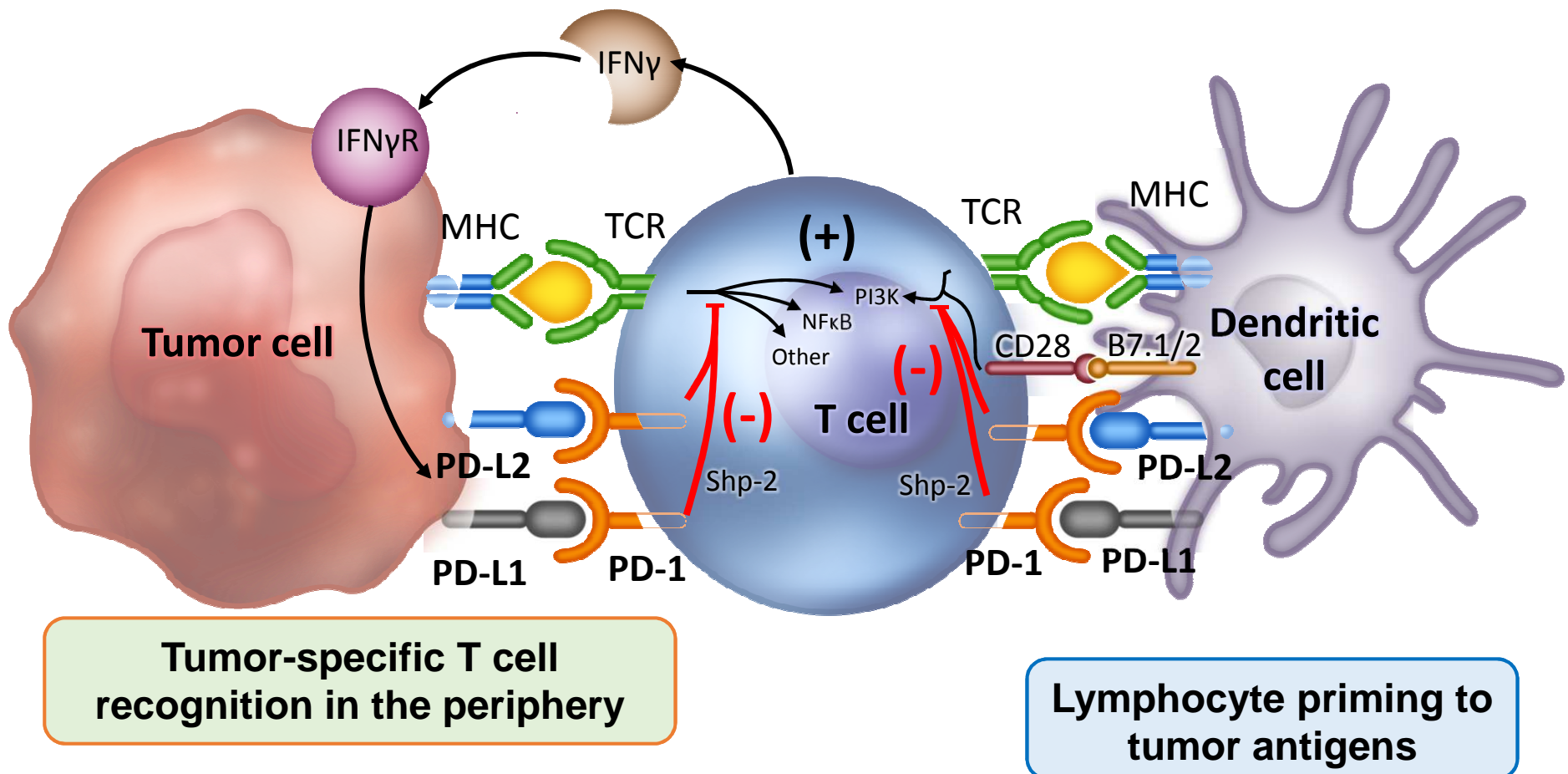
Disclosures

- Consultant/Advisory board member – BMS (Uncompensated), Merck (compensated)
- Institutional Research Support - BMS, Merck, MedImmune/Astra Zeneca, Celgene and Syndax

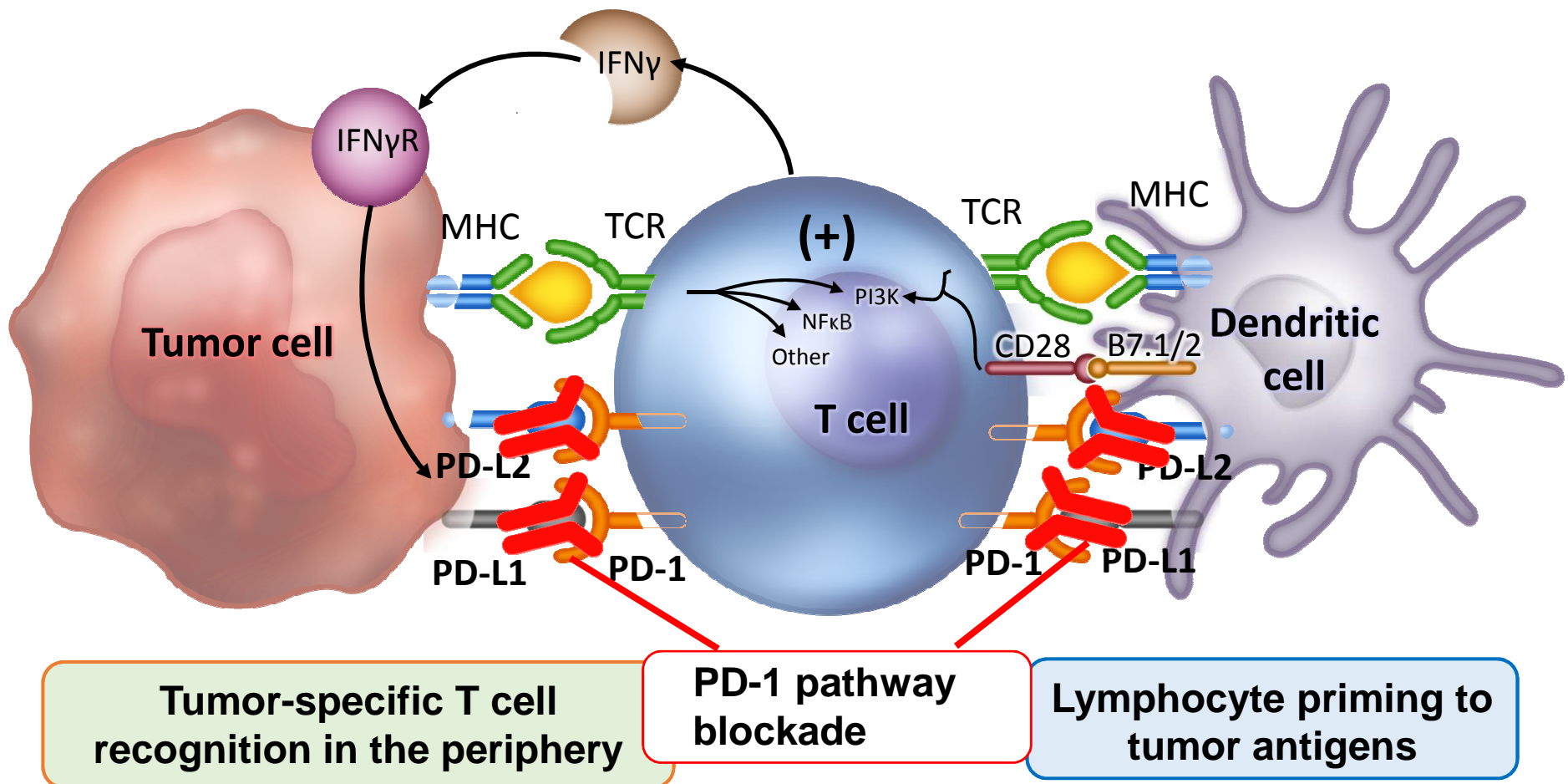
Potential Mechanisms for Immune Evasion in Lung Cancer

- Defective antigen presentation
- Immunosuppressive cell infiltrates - T reg and MDSCs
- Upregulation/secretion of immunosuppressive cytokines
- Checkpoint pathways

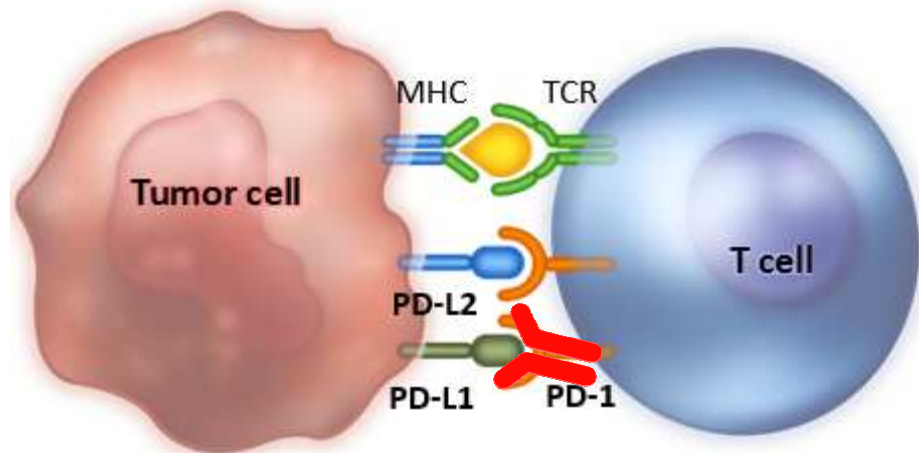
Role of the PD-1 Pathway in Suppressing Antitumor Immunity



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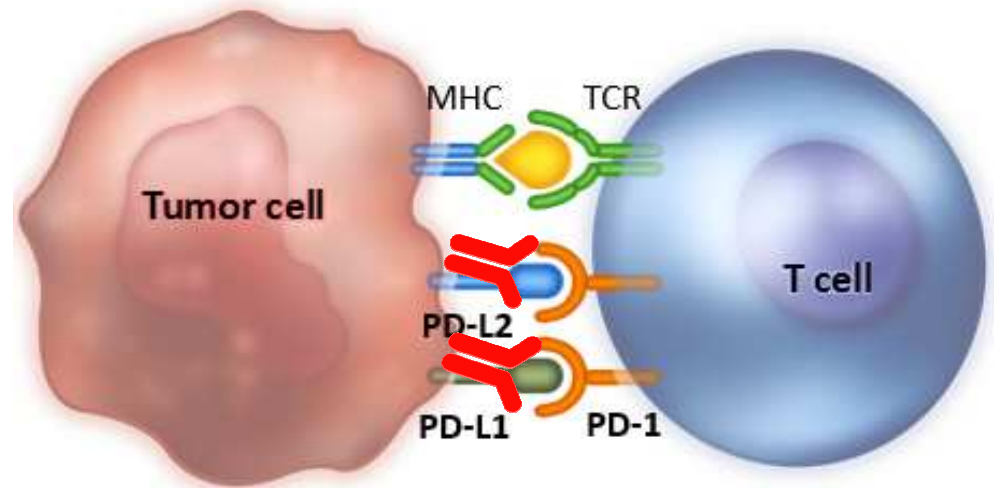


PD-1 Pathway Blockade



PD-L1 antibody blockade

PD-1 antibody blockade



Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab-BMS-936558	Fully human IgG4	Bristol-Myers Squibb	FDA approved
	Pembrolizumab MK-3475	Humanized IgG4	Merck	Phase III FDA fast track
PD-L1	Durvalumab Medl-4736	Engineered human IgG1	MedImmune/AstraZeneca	Phase III
	Atezolizumab MPDL-3280A	Engineered human IgG1	Genentech	Phase III FDA fast track
	MSB0010718C	Human IgG1	EMD Serono	Phase I-II

Multiple others PD-L1 and PD-1 antibodies are also in development.

Pretreated NSCLC –Phase I Trials

Regimens	Subgroup, n		ORR ⁺ , %	Median PFS (mo)	Median OS (mo)
Pembrolizumab ¹ (N=495)	10 mg/kg q 3wk	287	19	2.5	8.2
Nivolumab ² (N=129)	3 mg/kg q 2wk	37	24	1.9	14.9
Durvalumab (MEDI4736) ³ (N=155)	10 mg/kg q 2wk	150	15	NR	NR
Atezolizumab (MPDL-3280a) ⁴ (N=53)	Multiple doses	53	23	NR	NR

1. Garon et al; NEJM 2015.

2. Gettinger et al. JCO 2015

3. Antonio et al. ESMO, 2014; Abstract # 7629.

4. Soria et al; ECC, 2013; Abstract # 3408., Herbst R Nature 2014

CheckMate 017: Study Design

Key Inclusion Criteria

- Stage IIIB/IV NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0-1
- Pretreatment (archival or fresh) tumor samples required for PD-L1 analysis
- N=272

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- Open label
- Patients were stratified by region and prior paclitaxel use

Nivolumab
3 mg/kg IV Q2W
(n=135)

Docetaxel
75 mg/m² IV Q3W
(n=137)

Endpoints

Primary:

- OS

Secondary:

- Investigator-assessed ORR
- Investigator-assessed PFS
- Correlation between PD-L1 expression and efficacy
- Safety
- Quality of life (LCSS)

- One preplanned interim analysis for OS
- At time of database lock (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- Boundary for declaring superiority for OS at the preplanned interim analysis was $P < 0.03$

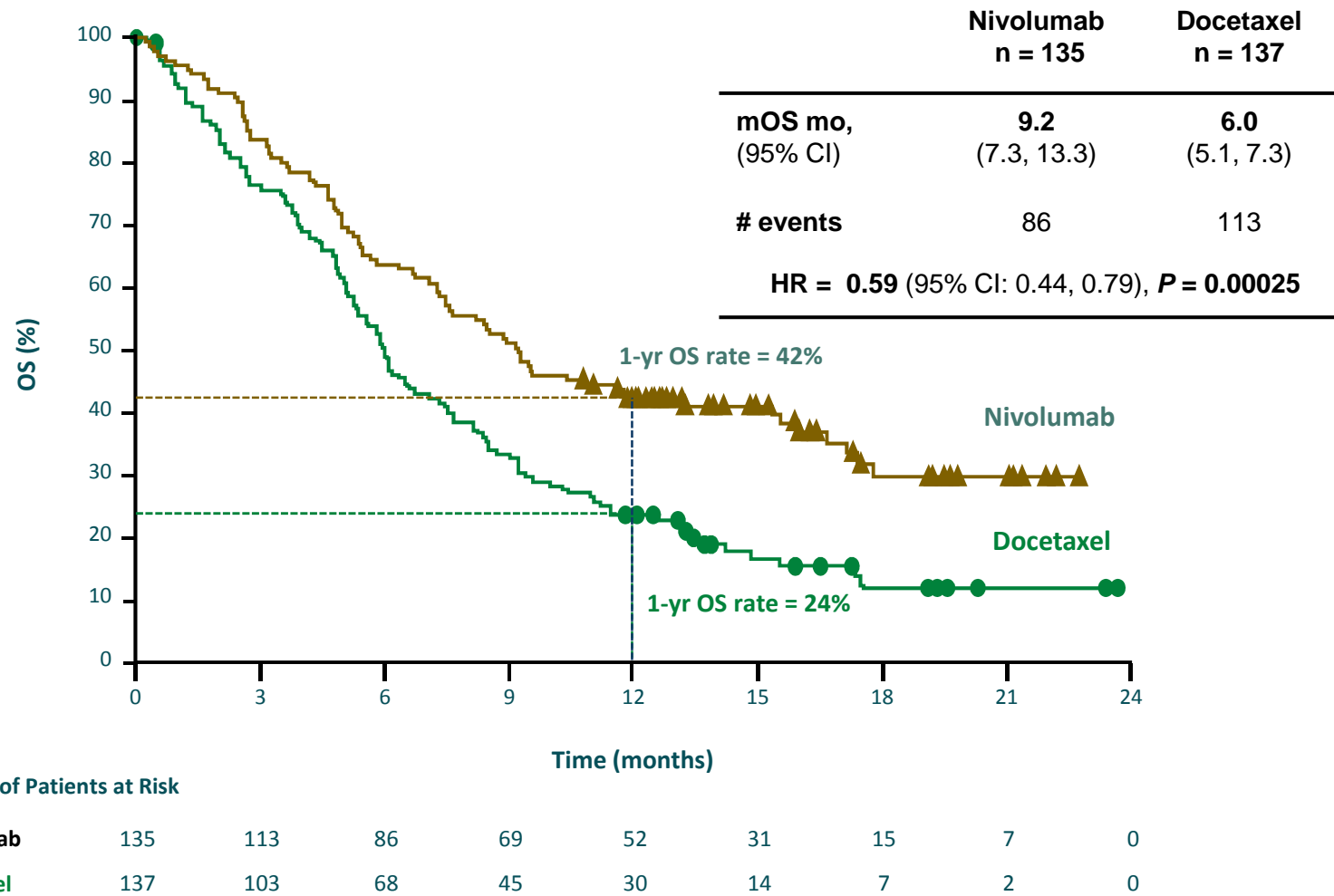
CheckMate 017: Baseline Characteristics

	Nivolumab n = 135	Docetaxel n = 137
Median age, years (range)	62 (39 – 85)	64 (42 – 84)
≥75, %	8	13
Male, %	82	71
Disease stage, ^a %		
Stage IIIb	21	18
Stage IV	78	82
Performance status, %		
0	20	27
1	79	73
CNS metastasis, %	7	6
Prior paclitaxel, %	34	34
Current/former smoker, %	90	94
PD-L1 expression, ^b %		
≥1%	47	41
≥5%	31	29
≥10%	27	24
Not quantifiable	13	21

^aNot reported in 1 pt each in the nivolumab and docetaxel arms. ^bPercentage of all randomized patients.

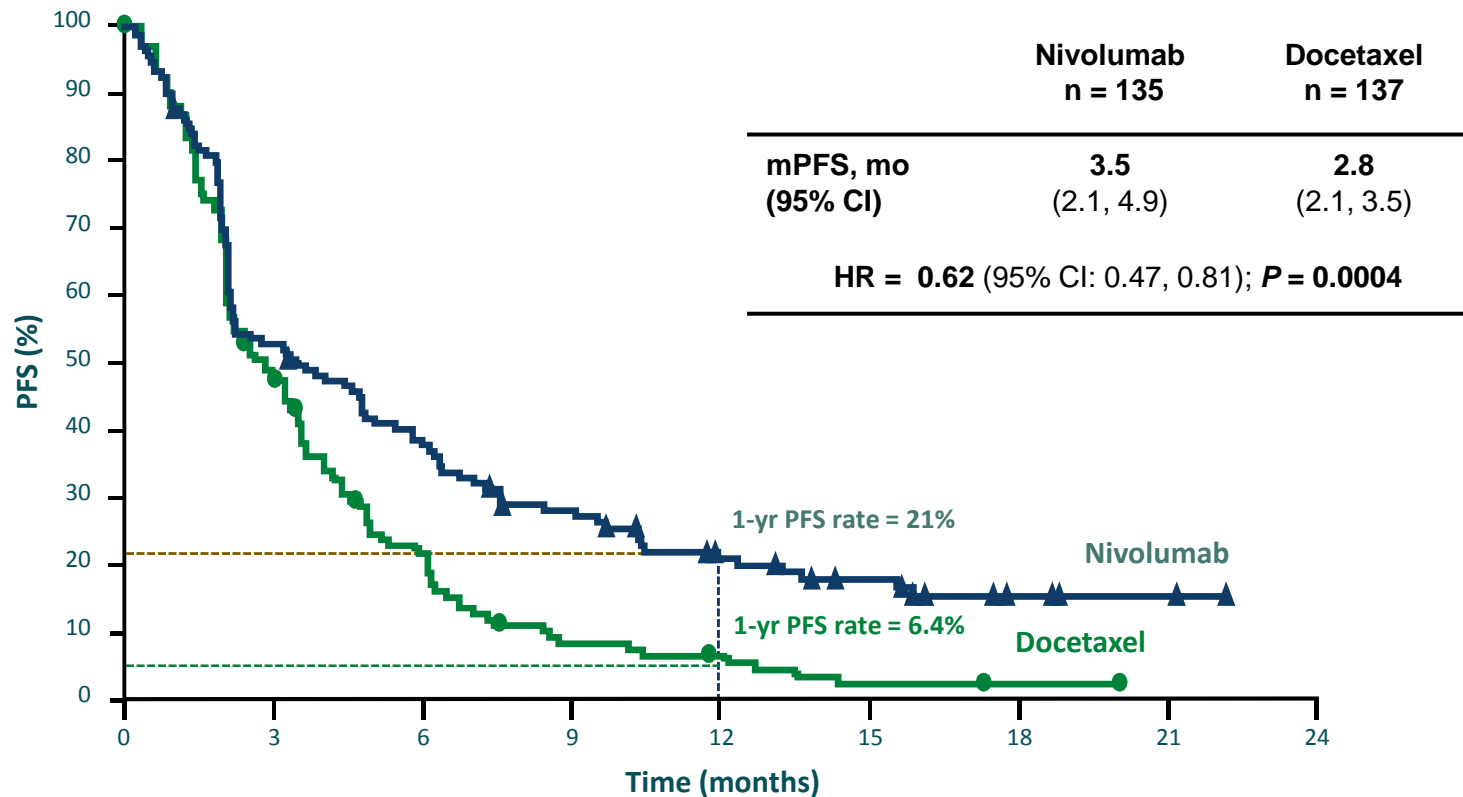
- **83% (225/272) of patients had quantifiable PD-L1 expression**

Checkmate 017: Overall Survival



Symbols represent censored observations

Checkmate 017: Progression-free Survival



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.

CheckMate 017: ORR

	Nivolumab (n=135)	Docetaxel n = 137
ORR, % (95% CI)	20 (14, 28)	9 (5, 15)
P value*	0.008	
Best overall response, %		
Complete response	1 [†]	0
Partial response	19	9
Stable disease	29	34
Progressive disease	41	35
Unable to determine	10	22
Median DOR, [‡] mo (range)	NR (2.9, 20.5+)	8.4 (1.4+, 15.2+)
Median time to response, [‡] mo (range)	2.2 (1.6, 11.8)	2.1 (1.8, 9.5)

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

*Based on two-sided stratified Cochran-Mantel-Haenszel test on estimated odds ratio of 2.6 (95% CI: 1.3, 5.5). [†]One pt experienced complete response. [‡]Values are all for confirmed responders per RECIST v1.1 (nivolumab, n=27; docetaxel, n=12). Symbol + indicates a censored value.

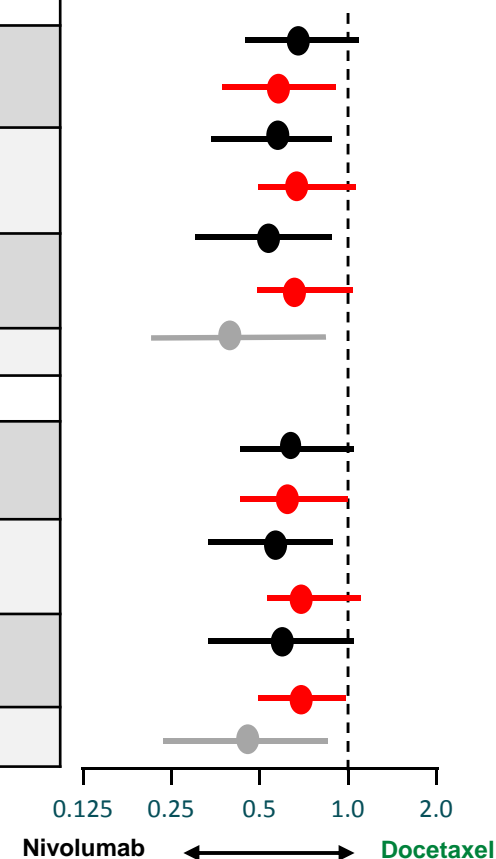
Brahmer J, et al. *N Engl J Med*. May 31, 2015 [Epub ahead of print].

Checkmate 017: 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 <i>P</i> -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 positive expression
- PD-L1 negative expression
- Not quantifiable



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

CheckMate 017: Treatment and Safety Summary

	Nivolumab (n=135)			Docetaxel (n=129)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Treatment-related AEs, %	58	7	0	86	55	2 [†]
Treatment-related AEs leading to discontinuation, %	3 [*]	2	0	10 [‡]	6.2	1 [§]
Treatment-related deaths, %	0			2		

- Median number of doses was 8 (range, 1-48) for nivolumab and 3 (range, 1-29) for docetaxel

*1% of pts had increased ALT/AST, increased lipase, myasthenic syndrome, or rash, and 2% of pts had pneumonitis. [†]1% of patients had interstitial lung disease, pulmonary hemorrhage, or sepsis. [‡]Peripheral neuropathy (3%) and fatigue (2%).

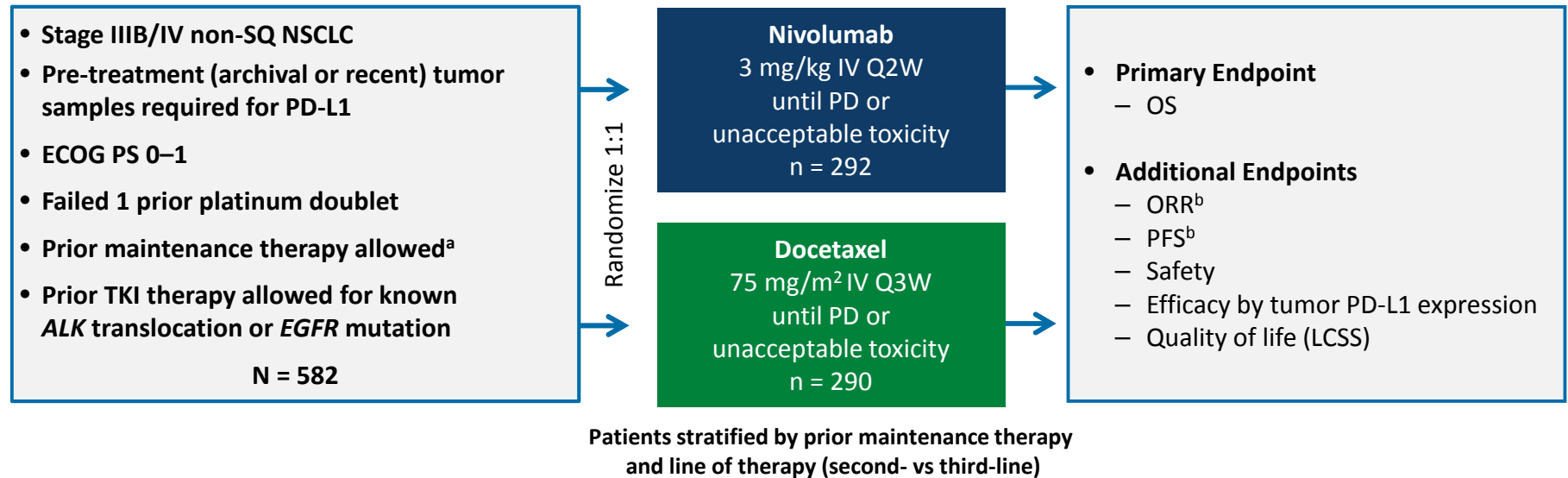
[§]Pulmonary hemorrhage. ^{||}Interstitial lung disease, pulmonary hemorrhage, sepsis (1 pt each).

Brahmer J, et al. *N Engl J Med*. May 31, 2015 [Epub ahead of print].

Checkmate 017: Treatment-Related AEs (≥5% of Patients)

	Nivolumab (n=135)		Docetaxel (n=129)	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Any 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
Arthralgia	5	0	7	0
Pyrexia	5	0	8	1
Pneumonitis	5	0	0	0
Rash	4	0	6	2
Mucosal inflammation	2	0	9	0
Myalgia	2	0	10	0
Anemia	2	0	22	3
Peripheral neuropathy	1	0	12	2
Leukopenia	1	1	6	4
Neutropenia	1	0	33	30
Febrile neutropenia	0	0	11	10
Alopecia	0	0	22	1

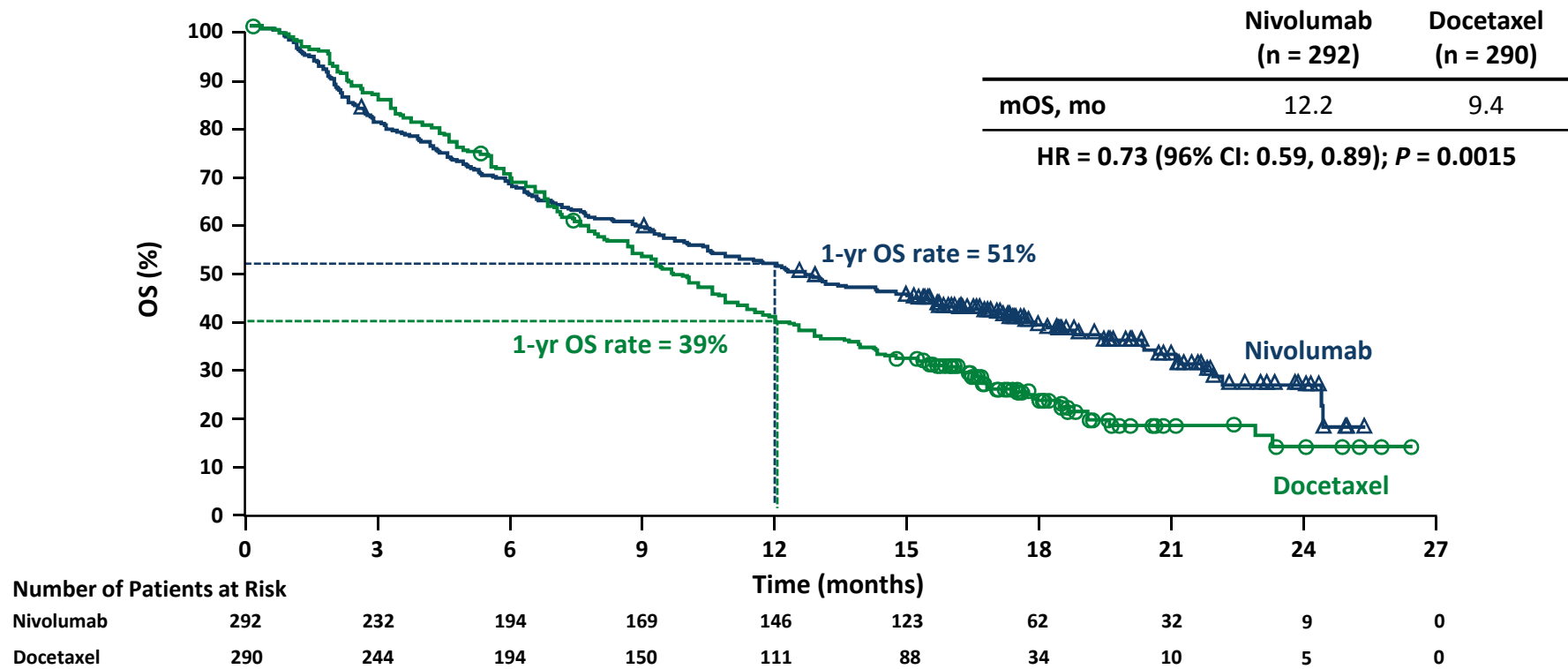
Checkmate 057 (NCT01673867) Study Design



- 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

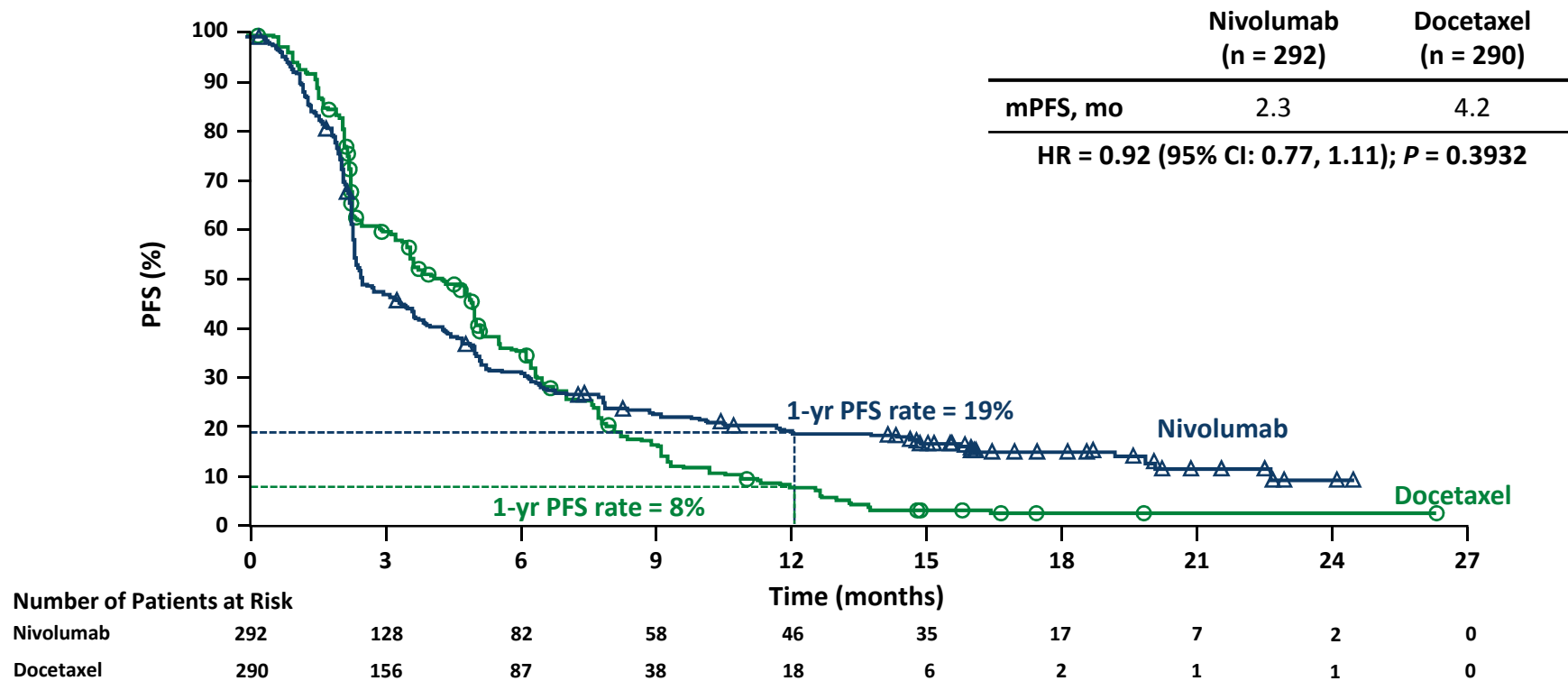
^a Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); ^b Per RECIST v1.1 criteria as determined by the investigator.

Checkmate 057: Overall Survival



Symbols represent censored observations.

Checkmate 057: Progression-free Survival



Symbols represent censored observations.

Checkmate 057: 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

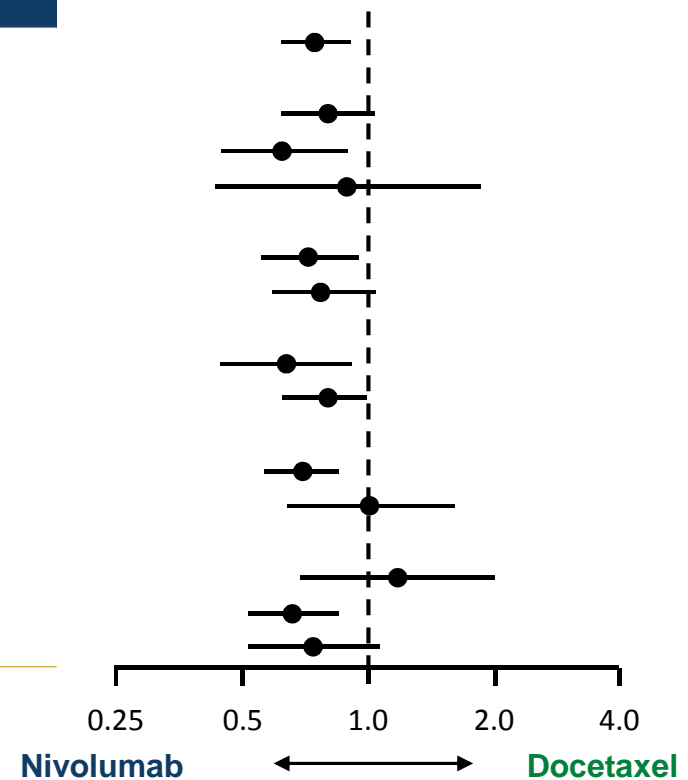
- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

^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.

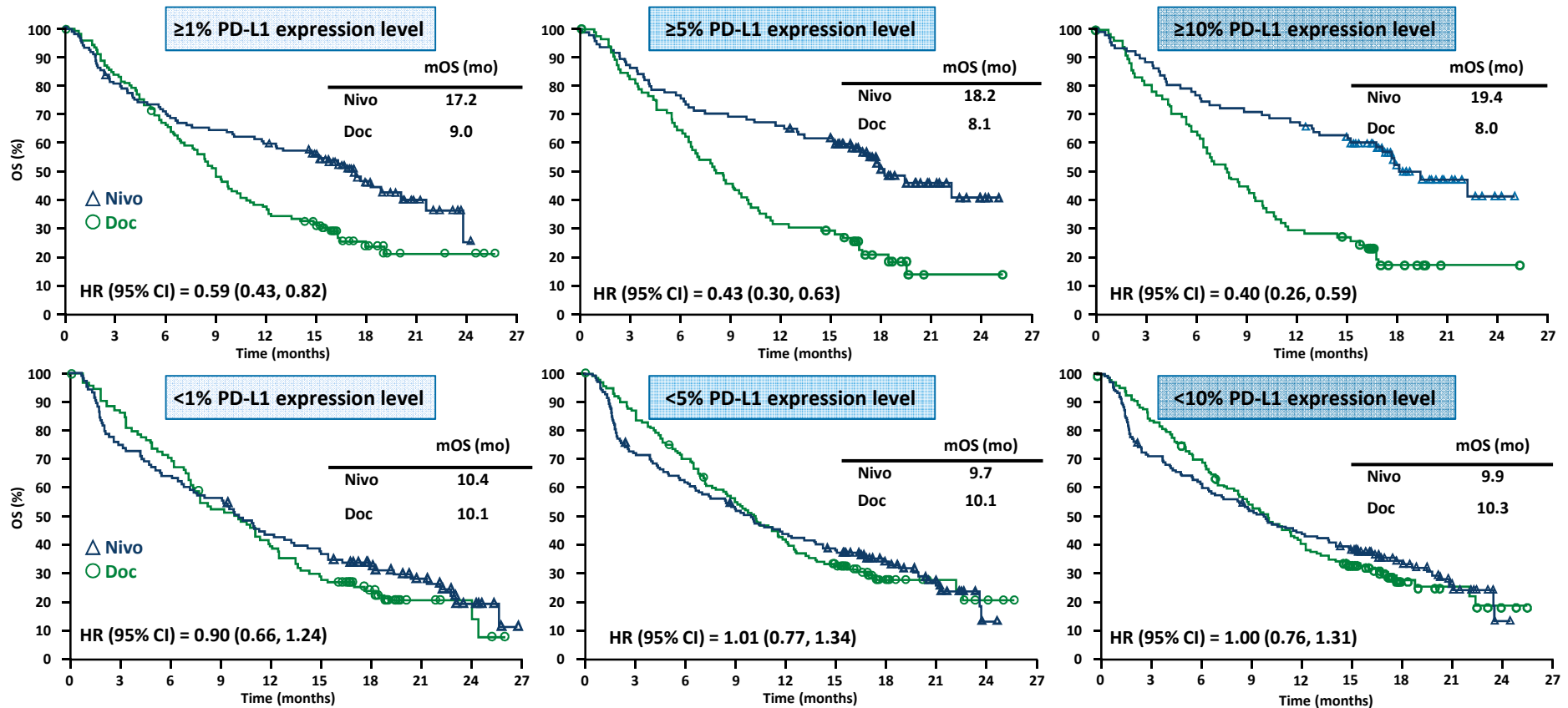
Checkmate 057: Treatment Effect on OS in Predefined Subgroups

	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).

Checkmate 057: OS by PD-L1 Expression



Symbols represent censored observations.

CheckMate 057: Treatment and Safety

	Nivolumab (n=287)		Docetaxel (n=268)	
Median number of doses received (range)	6 (1, 52)		4 (1, 23)	
Patients who received subsequent systemic therapy, %	42		50	
	Any Grade	Grade 3-4*	Any Grade	Grade 3-4*
Treatment-related AEs, %	69	10	88	54
Treatment-related SAEs, %	7	5	20	18
Treatment-related AEs leading to discontinuation, %	5	4	15	7
Treatment-related deaths, %	0 [†]		<1 [‡]	
Select AEs with potential immunologic etiology that require frequent monitoring/intervention				
Endocrine, % Hypothyroidism	7	0	0	0
Gastrointestinal, % Diarrhea	8	1	23	1
Hepatic, % ALT increased AST increased	3 3	0 <1	1 1	<1 0
Pulmonary, % Pneumonitis	3	1	<1	<1
Skin, % Rash Pruritus Erythema	9 8 1	<1 0 0	3 1 4	0 0 0
Hypersensitivity/ infusion reaction, % Infusion-related reaction	3	0	3	<1

*No grade 5 events were reported at DBL; 1 grade 5 event was reported for nivolumab post-DBL. [†]1 death attributed to nivolumab (encephalitis); association to nivolumab changed after DBL. [‡]1 death attributed to docetaxel-related drug toxicity (grade 4 febrile neutropenia).

DBL=database lock; SAE=serious adverse event.

Paz-Ares L, et al. Presented at: ASCO. 2015 (abstr LBA 109).

KEYNOTE-001: NSCLC Biomarker Cutoff Selection (Pooled Analysis)

Key Inclusion Criteria

- Treatment-naïve or previously treated
- Advanced NSCLC
- ECOG PS 0-1
- Known PD-L1 status
- (N=495, analyzed)

For biomarker cutoff selection, eligible patients were divided into 2 groups:

- Training group: n=182
- Validation group: n=313

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Pembrolizumab
2 mg/kg IV Q3W

Pembrolizumab
10 mg/kg IV Q3W

Pembrolizumab
10 mg/kg IV Q2W

Endpoints

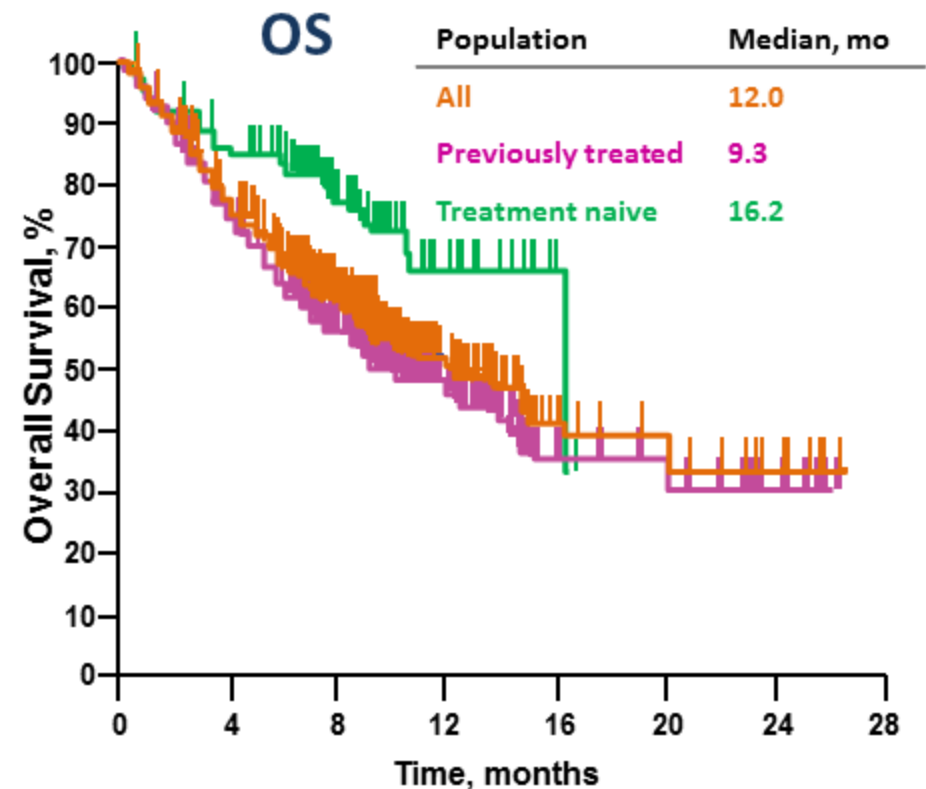
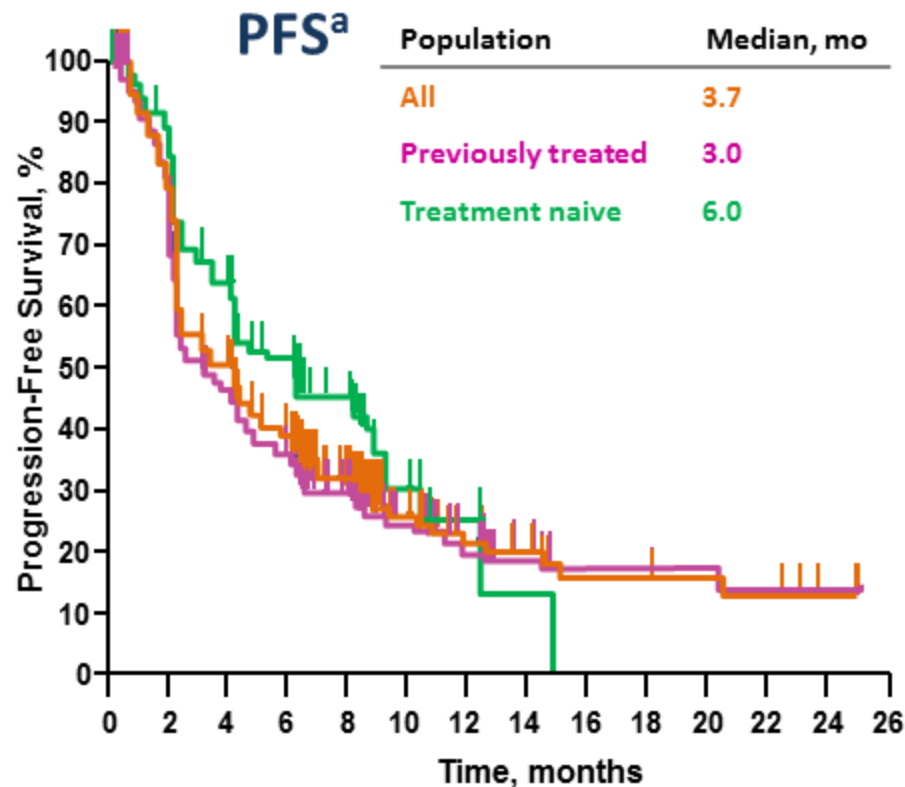
Primary:

- ORR by RECIST v1.1 central review

Secondary:

- ORR by irRC, investigator-assessed
- PFS
- OS
- DOR
- DCR

Pembrolizumab in NSCLC, Keynote 001: Outcomes



n at risk

495	361	230	167	97	47	26	12	7	6	6	5	2	0
394	275	173	125	75	40	23	11	7	6	6	5	2	0
101	86	57	42	22	7	3	1	0	0	0	0	0	0

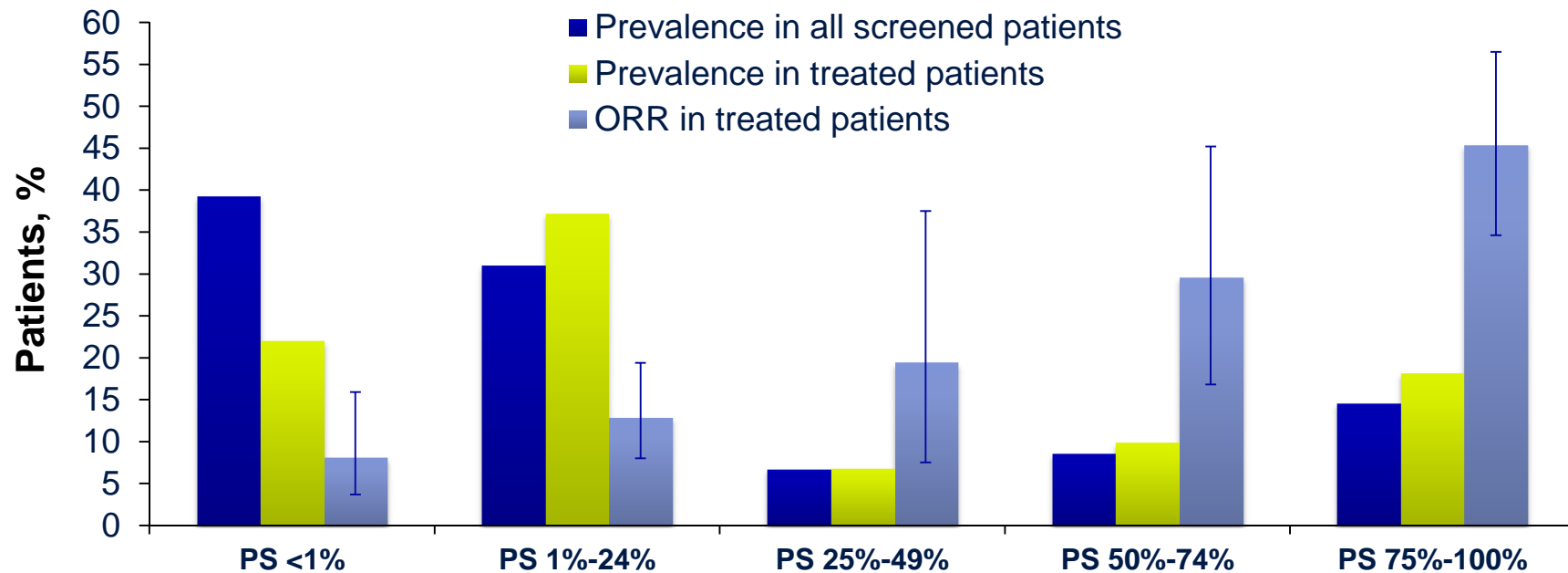
495	368	209	67	18	14	7	0
394	284	165	52	16	14	7	0
101	84	44	15	2	0	0	0

^aAssessed per RECIST v1.1 by central review.
Analysis cut-off date: August 29, 2014.

Garon_AACR 2015_19Apr15

KEYNOTE-001: ORR by Level of PD-L1 Expression

ORR 45.2% in PD-L1 PS $\geq 50\%$
(19.4% in all pts)



■ All screened patients, n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
■ All treated patients, n (%)	87 (22.0)	147 (37.2)	27 (6.8)	39 (9.9)	72 (18.2)
■ ORR in treated patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

KEYNOTE-001: Treatment-Related Adverse Events*

Adverse Event	Any Grade, n (%)	Grade 3-5, n (%)
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Asthenia	24 (4.8)	1 (0.2)
Anemia	21 (4.2)	5 (1.0)
Dyspnea	21 (4.2)	0
Pyrexia	21 (4.2)	19 (3.8)
Decrease weight	19 (3.8)	3 (0.6)
Dry skin	18 (3.6)	2 (0.4)
Pneumonitis	18 (3.6)	0
Elevation in aspartate aminotransferase	15 (3.0)	9 (1.8)
Infusion-related reaction	15 (3.0)	1 (0.2)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)

Listed are events that were considered to be related to treatment by the investigator and were reported in >2% of patients.
 Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.
 Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028.

Summary of Key Clinical Data

Agent	Nivolumab		Pembrolizumab		Atezolizumab	Durvalumab
Potential PD-L1+ definition	• TC ≥5%		• TC ≥50% (and 1% any stroma)		• Lung: IC ≥10% or • TC >50%	• TC ≥25%
Trial/ Analysis	CheckMate 057 ⁴	CheckMate 017 ⁵	KEYNOTE-001		POPLAR ^{1*}	All NSCLC*
			NSCLC ≥2L ²	All NSCLC ³		
N	292	272	217	495	287	200
ORR, % (95% CI)	19 (15-24)	20 (14-28)	20 (15-26) [†] 18 (31-24) [‡]	19 (16-23)	15	16 (11.2-21.8) [†]
TTR, median	2.1 mo	2.2 mo	9 wk	NA	NA	NA
DOR, median	17.2 mo (nivo, n=56) 5.6 mo (DTX, n=36)	NR (nivo) 8.4 mo (DTX)	31 wk	NA	NR (atez) 7.8 mo (DTX)	NA 0.1+-54.4+ (range in wks)
PFS, median	2.3 mo (nivo) 4.2 mo (DTX)	3.5 mo (nivo) 2.8 mo (DTX)	NA	3.7 mo	2.8 mo (atez) 3.4 mo (DTX)	NA
OS, median	12.2 mo (nivo) 9.4 mo (DTX)	9.2 mo (nivo) 6.0 mo (DTX)	NA	12.0 mo	9.5 mo (atez) 11.4 mo (DTX)	NR (PD-L1+) 8.9 mo (PD-L1-)
Any grade drug- related AEs	69%	58%	64%	71%	67%	50% (n=228)
Most frequent any grade drug- related AEs	Fatigue, nausea, decreased appetite	Fatigue, decrease appetite, asthenia, nausea	Fatigue, arthralgia, decreased appetite	Fatigue, pruritus, decreased appetite	Decreased appetite, dyspnea, nausea, anemia	Fatigue, decreased appetite, nausea

*Interim data. [†]Per RECIST v1.1. [‡]irRC.

2L=second line; DTX=docetaxel; NA=not available; TTR=time to response.

1. Spira AI, et al. Presented at: ASCO. 2015 (abstr 8010). 2. Garon EB, et al. Presented at: ASCO. 2014 (abstr 8020). 3.

4. Paz-Ares L, et al. Presented at: ASCO. 2015 (abstr LBA109). 5. Brahmer J, et al. *N Engl J Med*. May 31, 2015 [Epub ahead of print].

Moving Up to First Line—Can
Checkpoint Inhibitors Replace
Chemotherapy?
Hints from Phase I Trials

First-Line PD-1 Checkpoint Inhibitor Activity – Checkmate 003 and Keynote 001 Results

Treatment	RR (%) Recist 1.1	PFS (months)	1-Year Survival (%)	mOS (months)
Nivolumab unselected (n=52)	23	9	74	22.6
Nivo* PD-L1+ (N=26)	31%	15.4 wk	73	NR
Nivo PD-L1- (N=20)	15%	21.9 wk	74	NR
Pembro^ PD-L1+ (n=101)	25%	6	NR	16.2

*PD-L1 positivity defined as \geq 5% tumor cells with staining

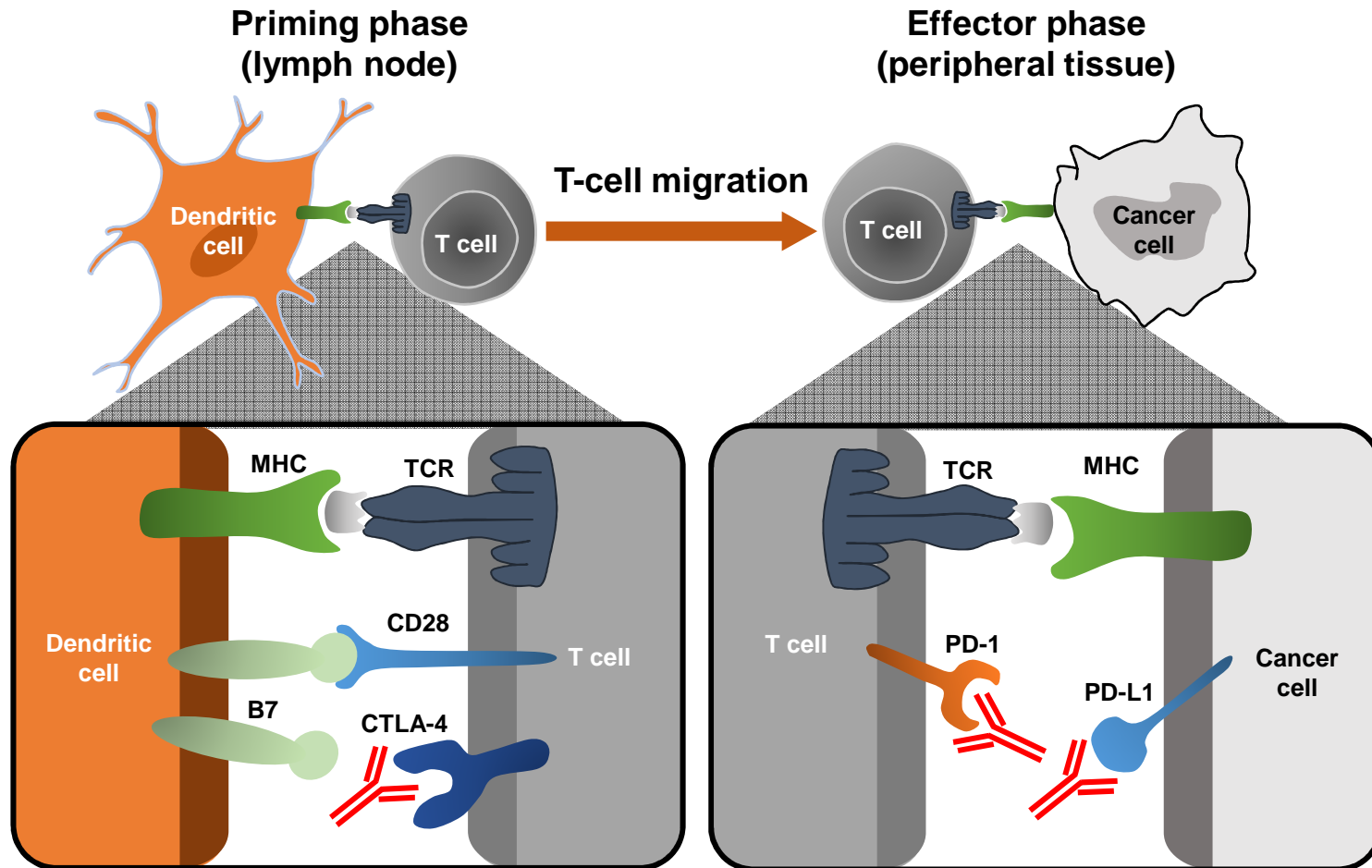
^PD-L1 positivity defined as \geq 1% tumor cells with staining

Efficacy and Safety in NSCLC Patients Treated With PD-1 Blockade Plus PT-DC

	NIVO 10 mg/kg			NIVO 5 mg/kg	Pembro 10/mg/kg
	Gem/Cis (n = 12)	Pem/Cis (n = 15)	Pac/Carb (n = 15)	Pac/Carb (n = 14)	Pem/Carbo (n=12)
ORR, % (95% CI)	33 (10, 65)	47 (21, 73)	47 (21, 73)	43 (18, 71)	42%
Median duration of response, weeks	45	25.4	23.9	NR	
1-year OS rate, % (95% CI)	50 (21, 74)	87 (56, 96)	60 (32, 80)	86 (54, 96)	Not reported
Median OS, weeks (range)	50.5 (19.7, 109.7)	83.4 (33.0, 128.9+)	64.9 (13.9, 129.0+)	NR (38.3, 108.0+)	Not reported
Median PFS, weeks (range)	24.7 (0.1+, 61.4)	29.7 (4.0+, 106.9+)	21.0 (3.0, 124.7+)	31.0 (0.1+, 108.0+)	Not reported
Grade 3-4 Rx related AEs	25%	47%	73%	29%	42%

+ = event (progression or death) not happened; CI = confidence interval; DCR = disease control rate; DOR = duration of response; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Combination Immune Checkpoint Blockade in NSCLC



CTLA-4 plus PD-1or PD-L1 Antibody Blockade in NSCLC – Phase I Preliminary Activity and Safety

	Nivolumab + Ipilimumab	Tremilimumab + MEDI4736	Pembrolizumab + Ipilimumab	
ORR, RECIST 1.1	16% (8/49)	28% (5/18)	33%	50%
SD	33% (16/49)	28% (5/18)	NR	
Treatment related AEs, n (%)	43 (88%)	18 (76%)	75%	100%
Grade 3/4 Treatment related AEs, n (%)	24 (49%)	6 (25%)		
Treatment related Deaths, n (%)	3 (6%)	1 (4%)		
Discontinuation due to toxicity, n	18 (37%)	3 (15%)		

Doses include Ipi 1 + Nivo 3 mg/kg or Ipi 3 + Nivo 1 q 3 wk x 4 then Nivo single agent

Doses include Tremi 1-10 mg/kg q 4 wk x6 then q 12 x3 + Medi 3-20 mg/kg q 4 wk

Doses include Pembro 2 and 10 mg/kg q 3 wks + Ipi 1 mg/kg q 3 wk x 4 then pembro single agent

Multiple Ongoing Current Trials of PD-1 or PD-L1 inhibitors in Stage 4 NSCLC

- **First Line Trials – PD-L1 + disease (ds)**
 - Chemo vs. PD-1 Ab (Pembro and Nivo trials ongoing)
 - Chemo plus PD-L1 Ab
- **Second Line Trials**
 - Pembrolizumab vs. docetaxel in PD-L1 positive ds
 - MPDL-3280a vs. docetaxel
- **Beyond 2nd Line**
 - Phase 1s of combination therapies or expansion cohorts ongoing with other PD-L1 Abs

Conclusions

- Nivolumab is the first PD-1 antibody to show a survival advantage over chemotherapy for 2nd-line treatment of squamous and nonsquamous NSCLC.
- Nivolumab is the first checkpoint inhibitor to be FDA approved for use in squamous lung cancer.
- Pembrolizumab shows promising activity in NSCLC particularly in PD-L1 positive disease.
- PD-L1 antibodies also show promising activity in NSCLC
- Other combinations with PD-1 checkpoint inhibitors show interesting preliminary activity.
- Development of combinations and moving these agents into the first line treatment setting is ongoing.