IMMUNOTHERAPY FOR NON SMALL CELL LUNG CANCER

Julie R. Brahmer, M.D., M.Sc.
Associate Professor of Oncology
Director of the Thoracic Oncology Program
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

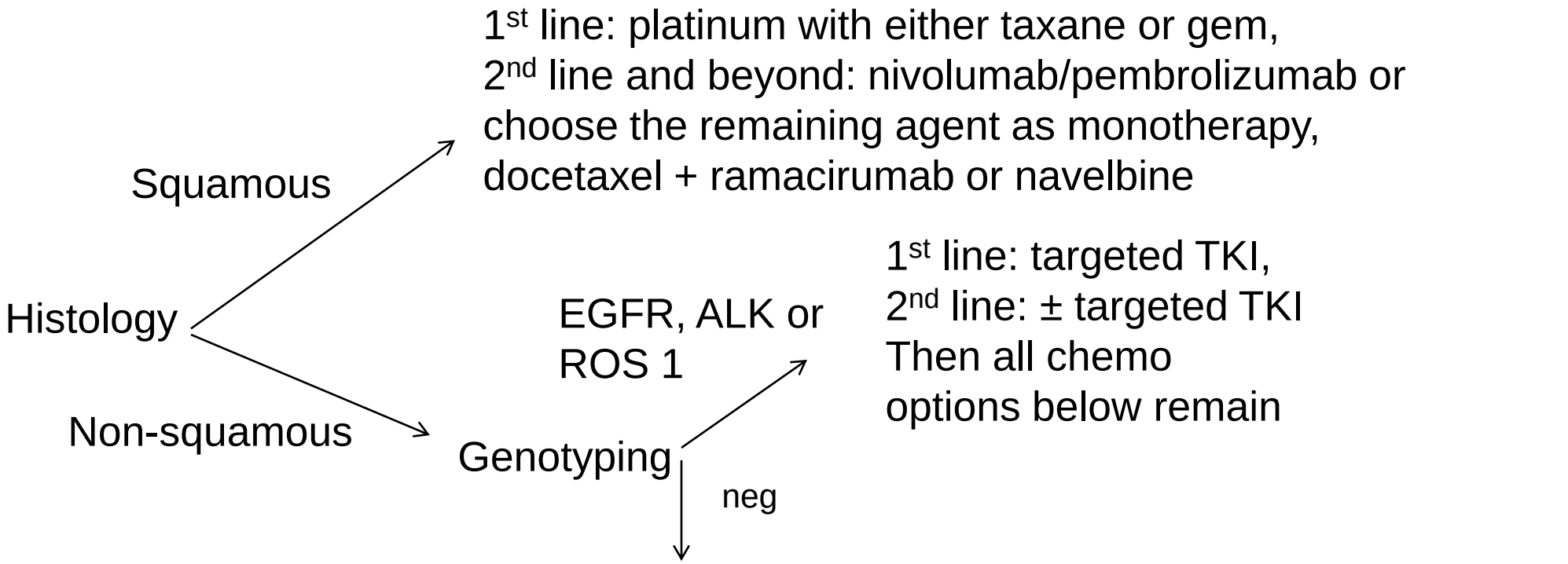
JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Disclosures

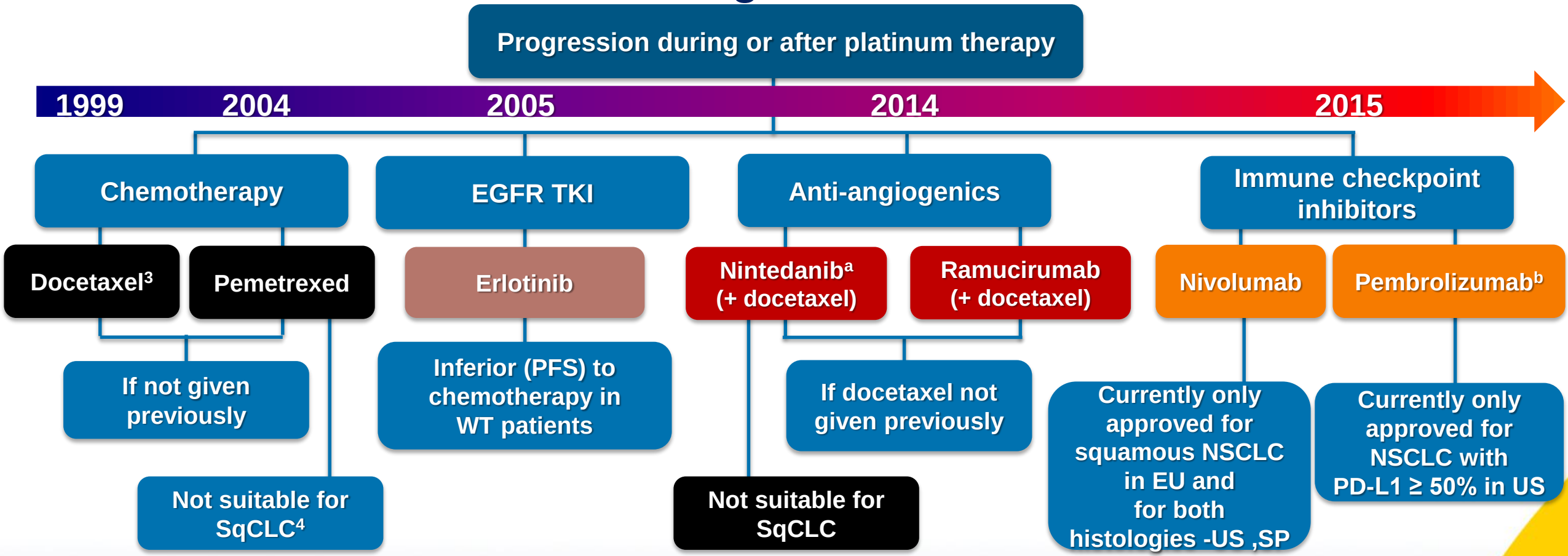
- Consultant/Advisor – BMS, Celgene, Lilly, and Merck

- Grant/Research Funding – BMS, Medimmune, AstraZeneca, and Merck
- I *will* be discussing non-FDA approved treatments during my presentation.

Common Algorithm for Approved Drugs in Advanced NSCLC – 2016



Approved Treatment Options in NSCLC for Post-Platinum Progression

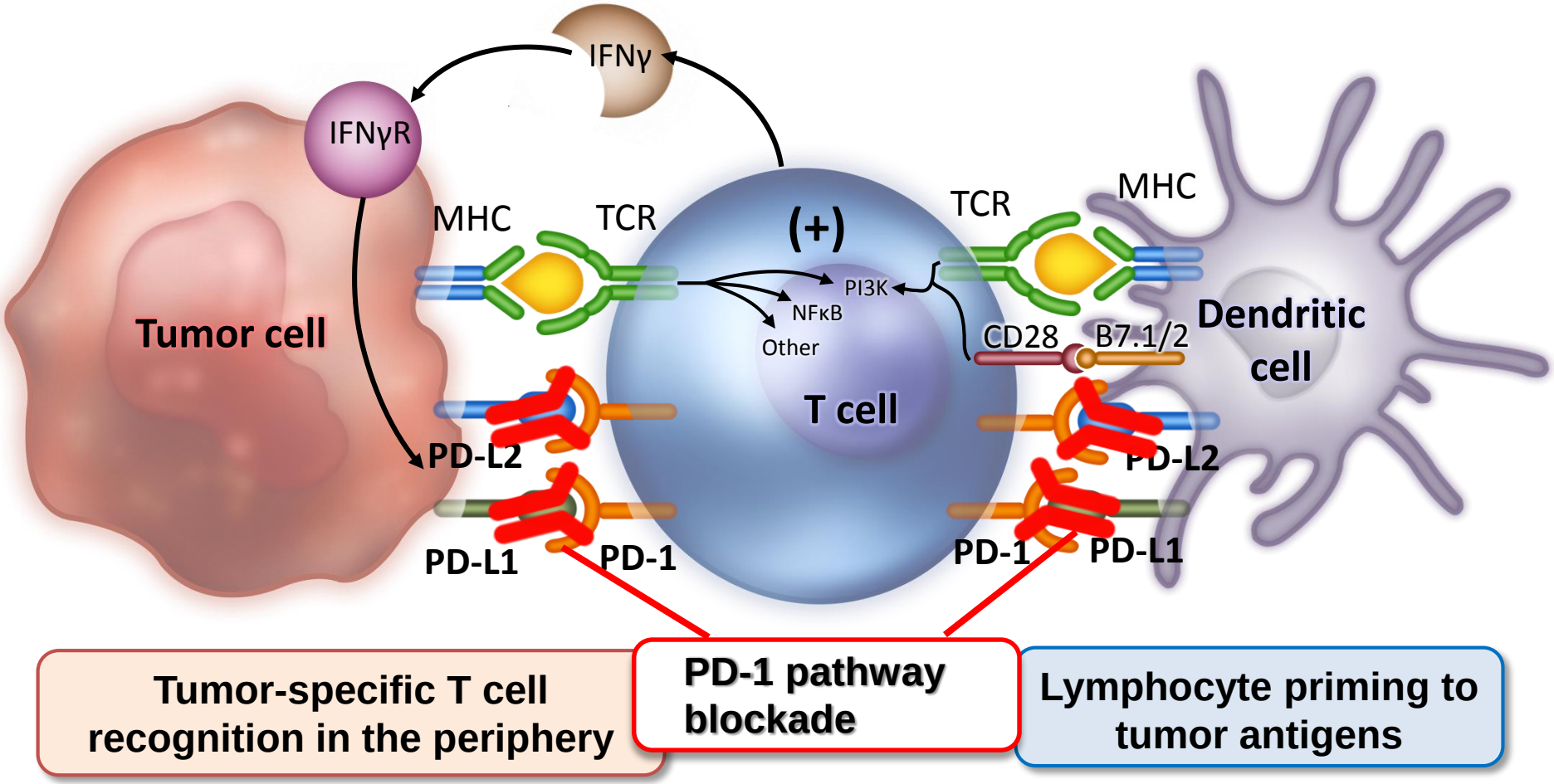


[a]Approved in EU only ; [b]Approved in US only

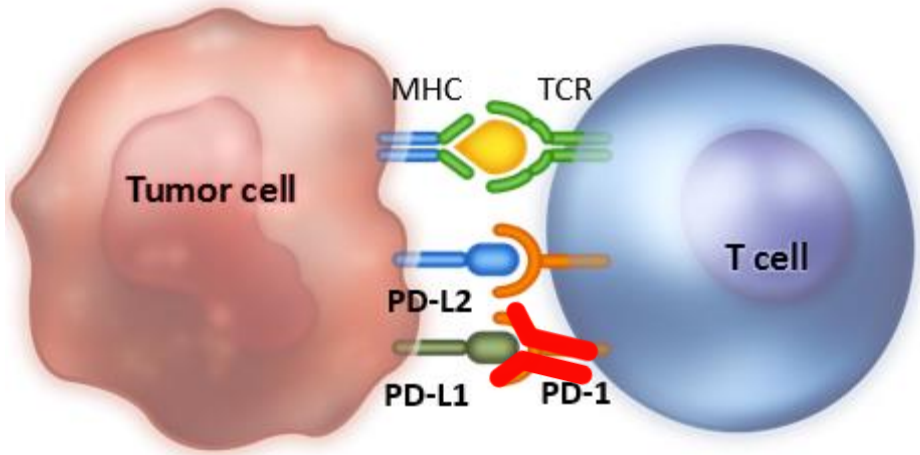
1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.6.2015; 2. Reck M et al. *Ann Oncol* 2014;25(suppl 3):27-39;
3. Sanofi Aventis. Taxotere (docetaxel) prescribing information. Nov 2014; 4. Eli Lilly and Company. Alimta (pemetrexed) prescribing information. Sep 2013;
5. Astellas Pharma and Genentech. Tarceva (erlotinib) prescribing information. Jun 2015; 6. Boehringer Ingleheim. Vargatef (nintedanib) summary of product characteristics. Mar 2015;
7. Eli Lilly and Company. Cyramza (ramucirumab) prescribing information. Apr 2015;
8. Bristol-Myers Squibb. Opdivo (nivolumab) prescribing information. Mar 2015

Courtesy M Perol

Role of the PD-1 Pathway in Suppressing Antitumor Immunity

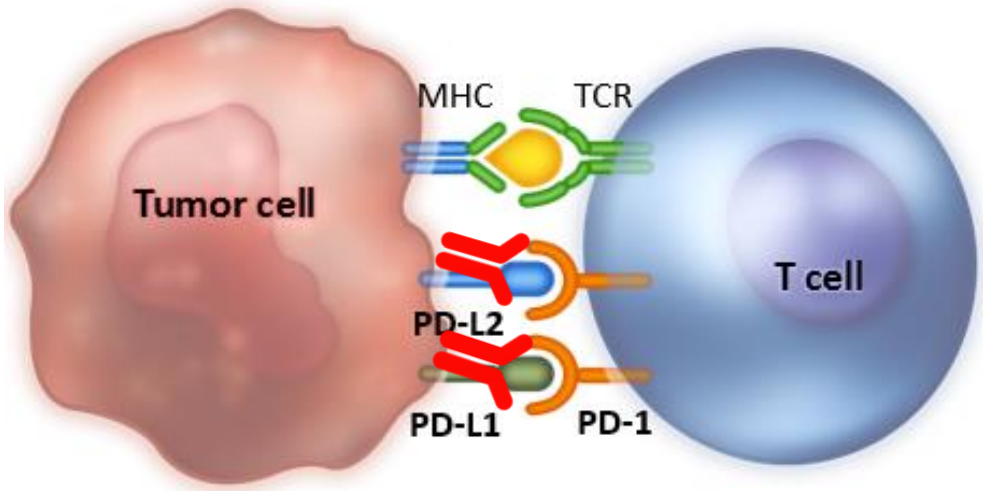


PD-1 Pathway Blockade



PD-L1 antibody blockade

PD-1 antibody blockade



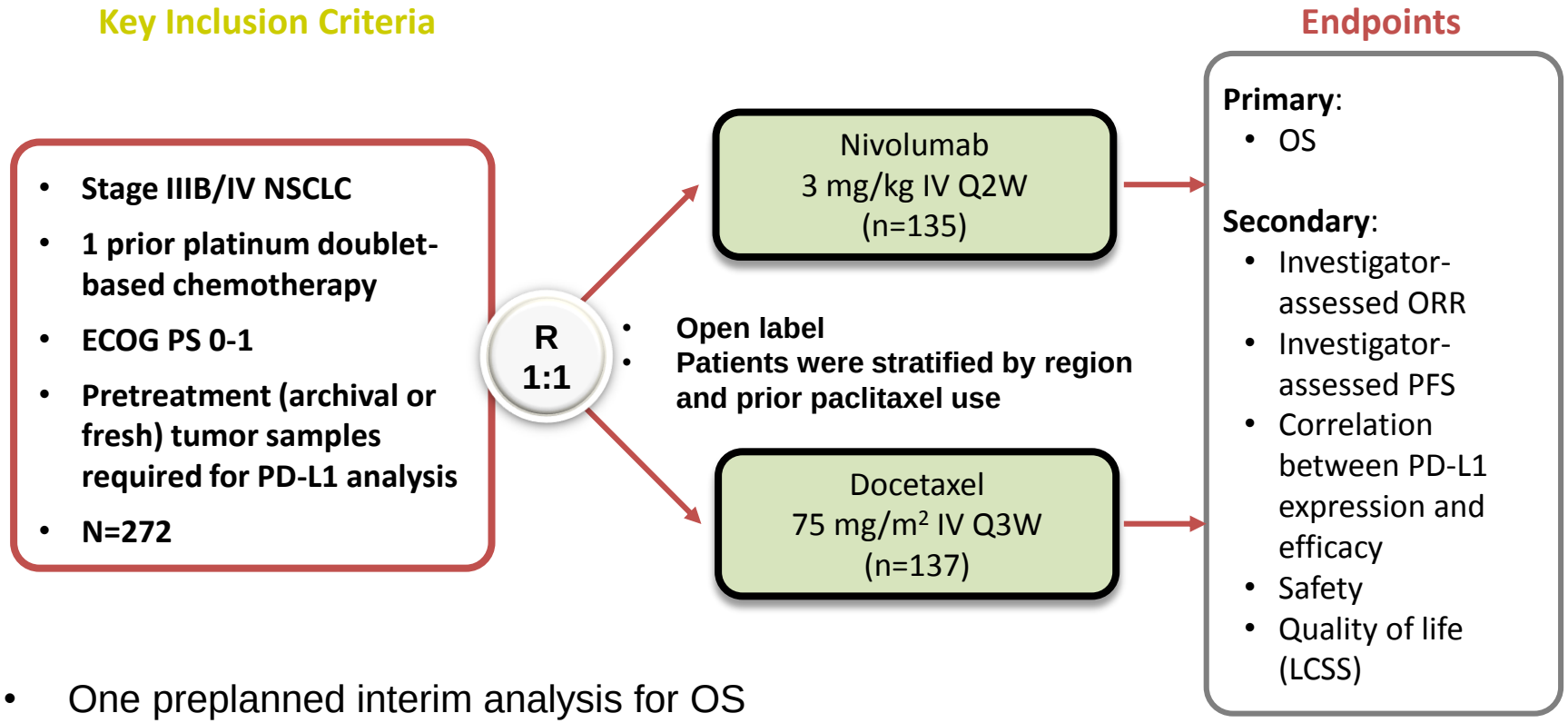
Clinical Development of Inhibitors of PD-1 Immune Checkpoint

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	FDA approved for PD-L1 positive
PD-L1	Durvalumab MedI-4736	Engineered human IgG1	MedImmune/ AstraZeneca	Phase III
	Atezolizumab MPDL-3280A	Engineered human IgG1	Genentech	Phase III FDA fast track
	Avelumab	Human IgG1	Pfizer	Phase III

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

Nivolumab

CheckMate 017: Study Design



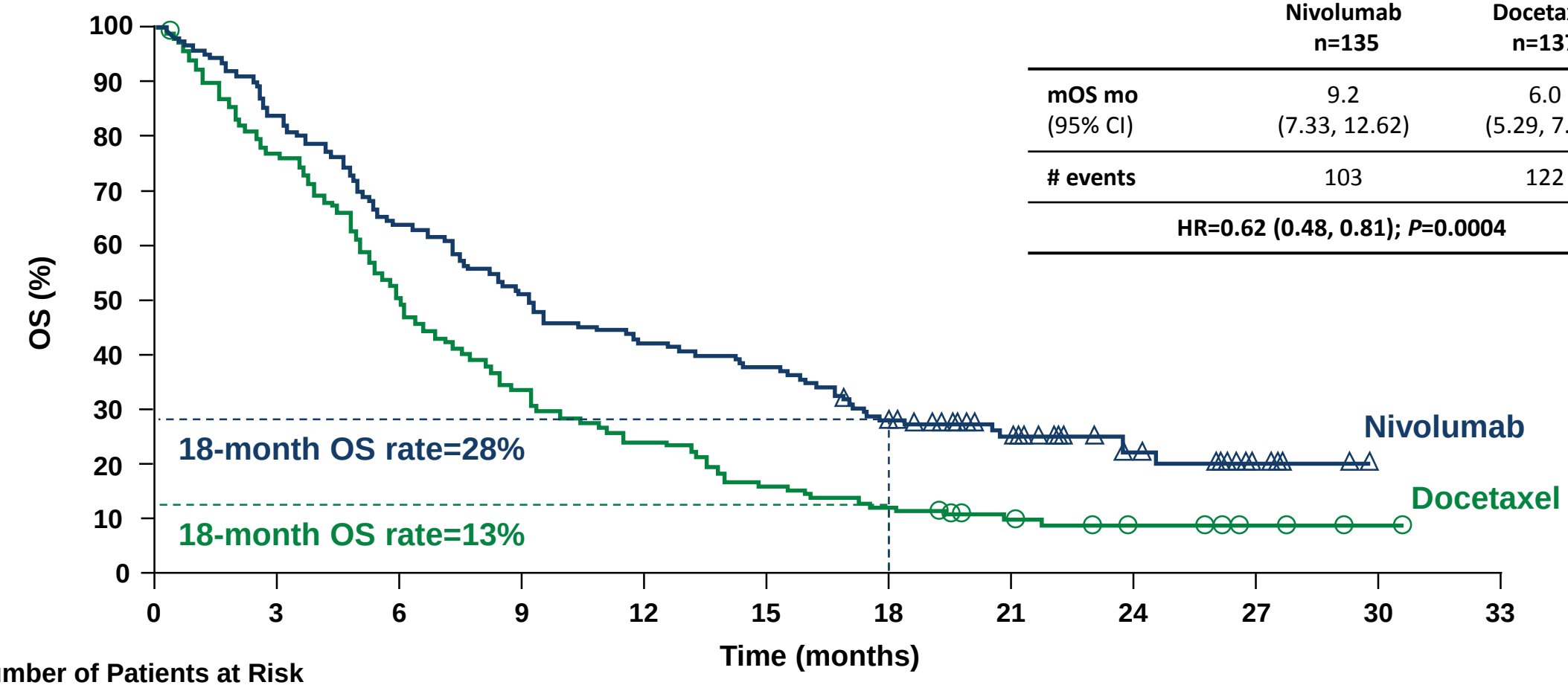
- One preplanned interim analysis for OS
- At time of database lock (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- Boundary for declaring superiority for OS at the preplanned interim analysis was $P<0.03$

LCSS=lung cancer symptom scale; PS=performance status.

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

Checkmate 017: Overall Survival

	Nivolumab n=135	Docetaxel n=137
mOS mo (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	4	1	0

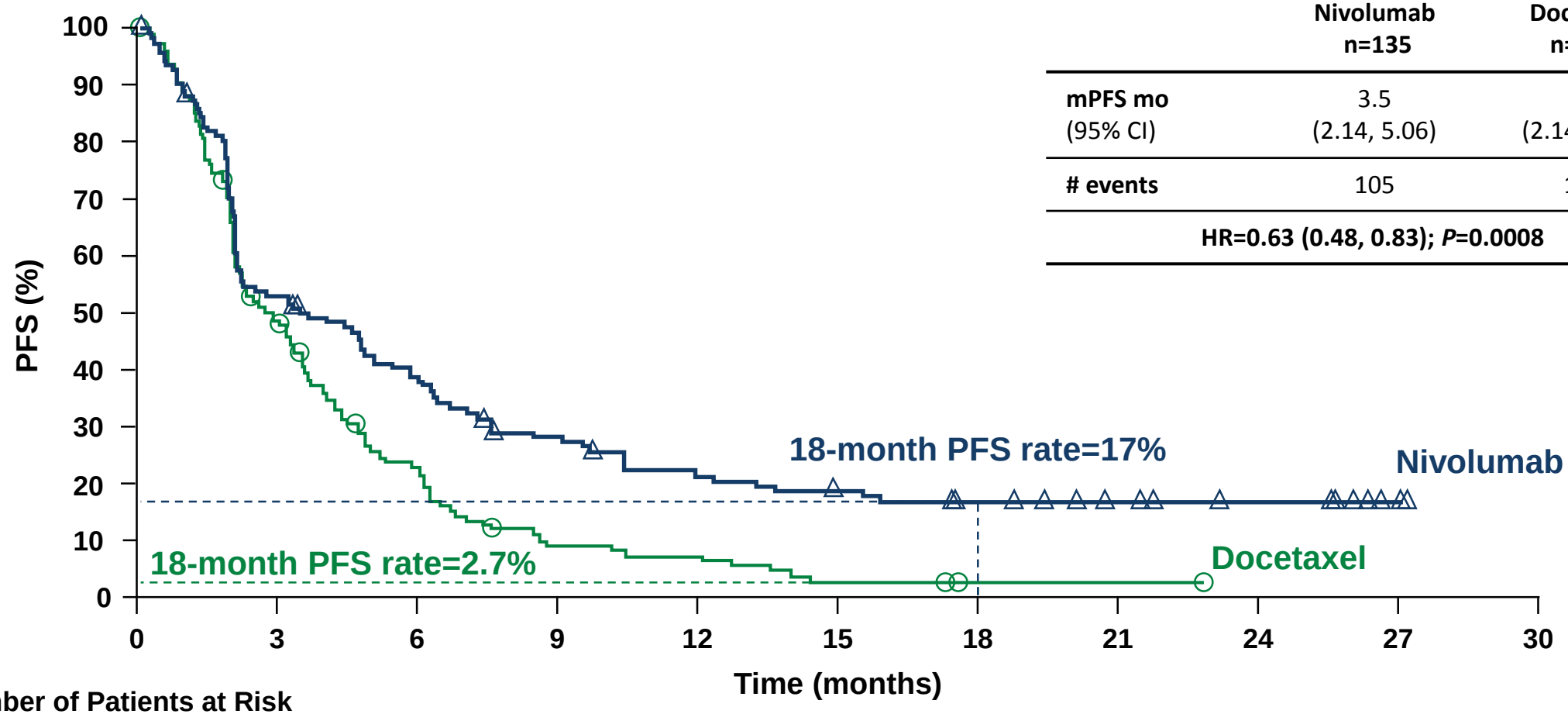
Minimum follow-up for survival: 18 months

- Survival was monitored until death or withdrawal of consent

Based on August 2015 DBL.
Symbols refer to censored observations.

Checkmate 017: Progression-Free Survival

	Nivolumab n=135	Docetaxel n=137
mPFS mo (95% CI)	3.5 (2.14, 5.06)	2.8 (2.14, 3.52)
# events	105	122
HR=0.63 (0.48, 0.83); *P*=0.0008		



Number of Patients at Risk

Nivolumab	135	68	48	33	24	20	16	12	8	2	0
Docetaxel	137	62	27	10	8	3	1	1	0	0	0

Minimum follow-up for survival: 18 months

Based on August 2015 DBL.
Symbols refer to censored observations.

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 Partial response Stable disease Progressive disease Unable to determine	 1† 19 29 41 10	 0 9 34 35 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)

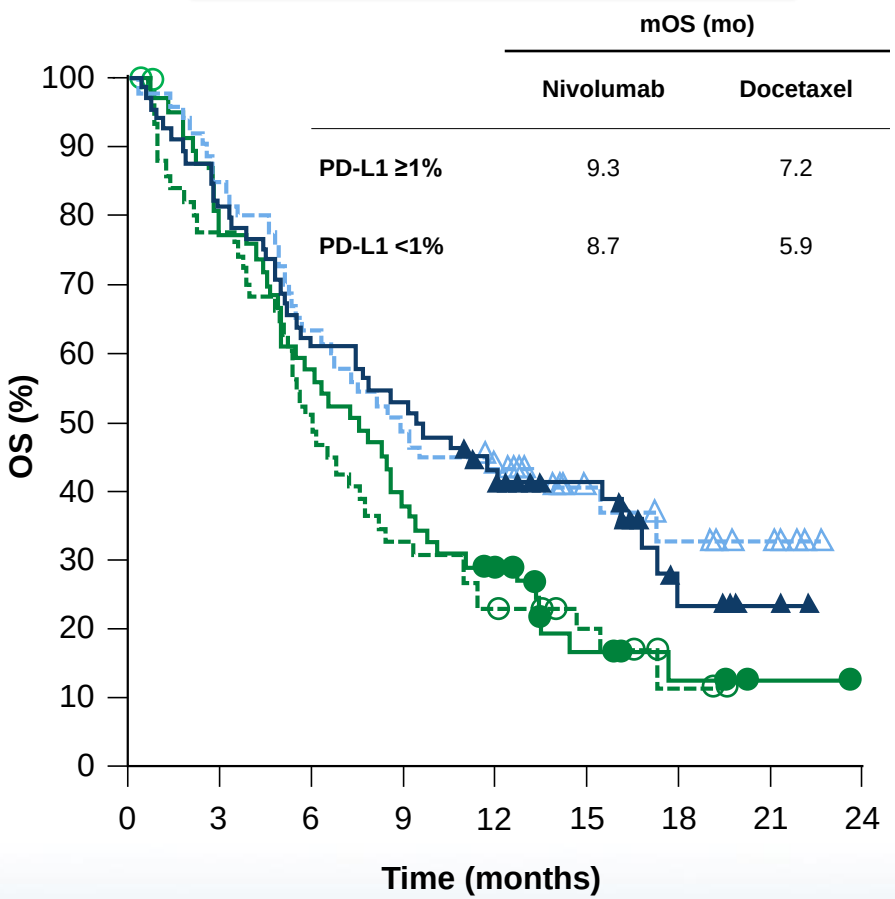
- 28 patients in the nivolumab arm were treated beyond RECIST v1.1-defined progression
- Nonconventional benefit was observed in 9 patients (not included in ORR)

*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.

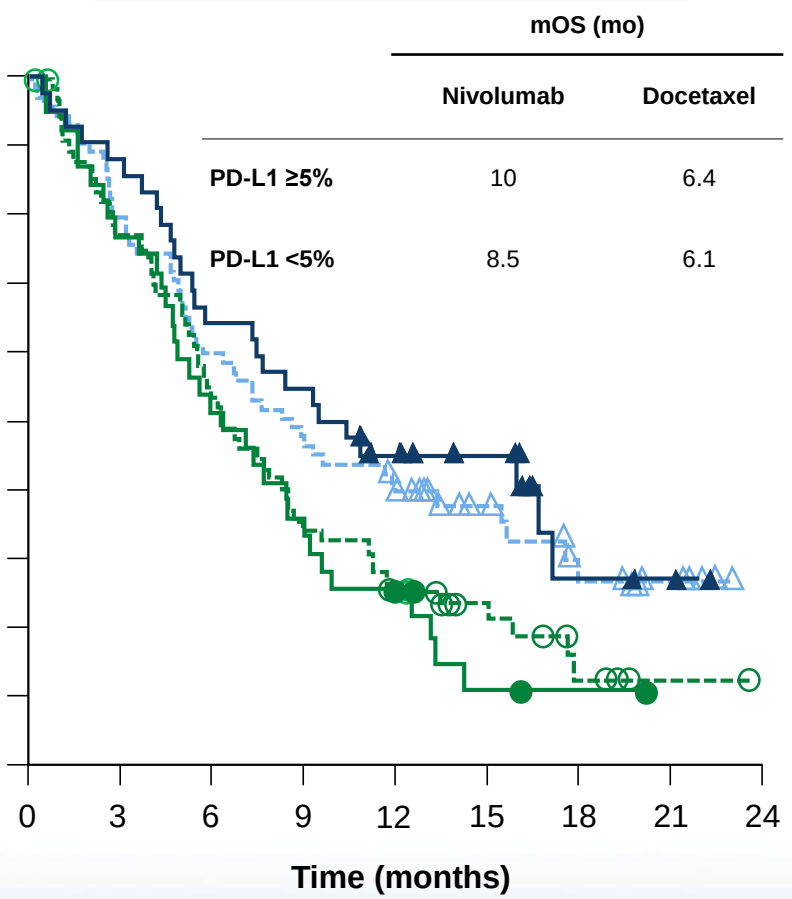
Brahmer J, et al. *N Engl J Med*. May 31, 2015 [Epub ahead of print].

Nivolumab OS by PD-L1 Expression (squamous)

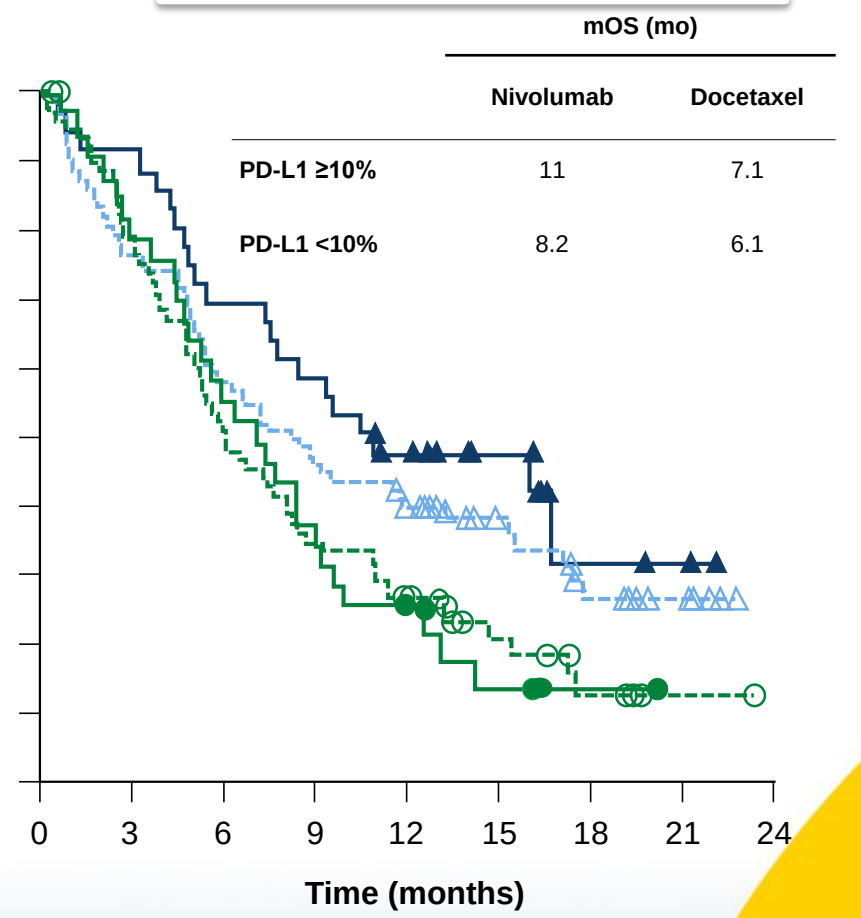
1% PD-L1 Expression level



5% PD-L1 Expression level



10% PD-L1 Expression level



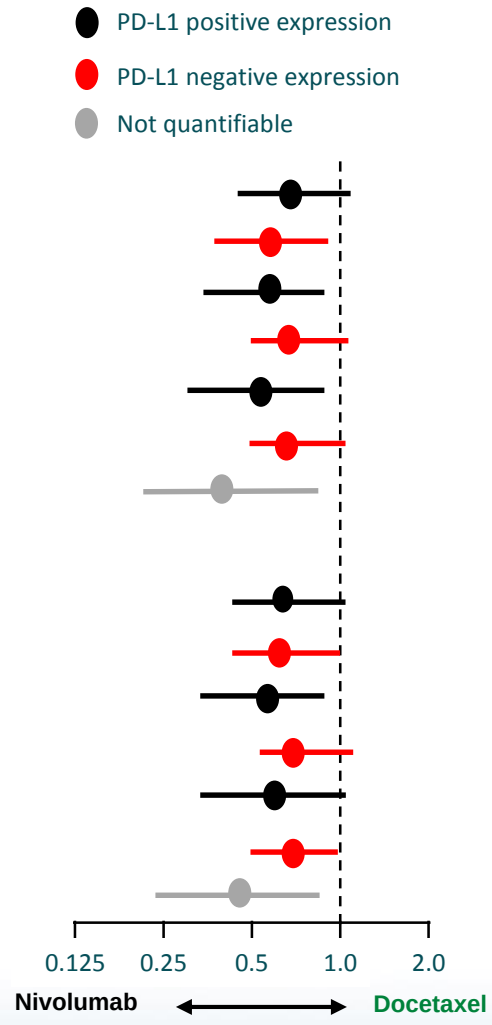
Nivolumab PD-L1+
Nivolumab PD-L1–
Docetaxel PD-L1+
Docetaxel PD-L1–

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

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 *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]

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

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

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].

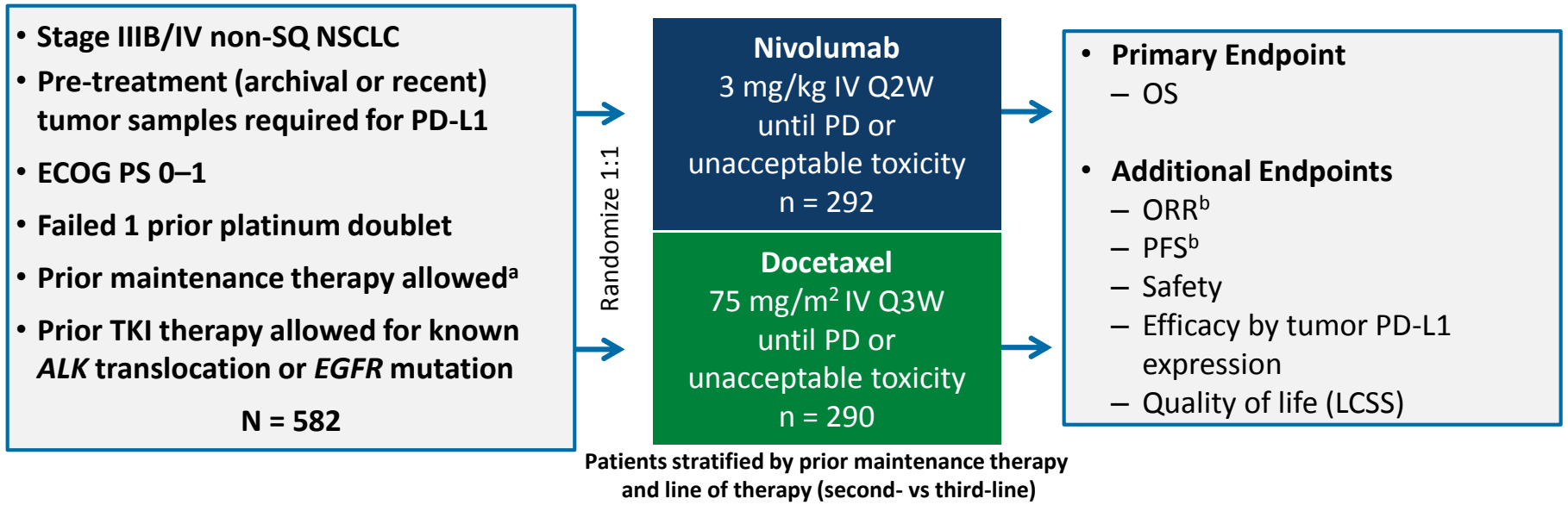
Checkmate 017: Treatment-Related AEs (≥5% of Patients)

	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

JOHN
MEDICINE

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

Checkmate 057 (NCT01673867) Study Design



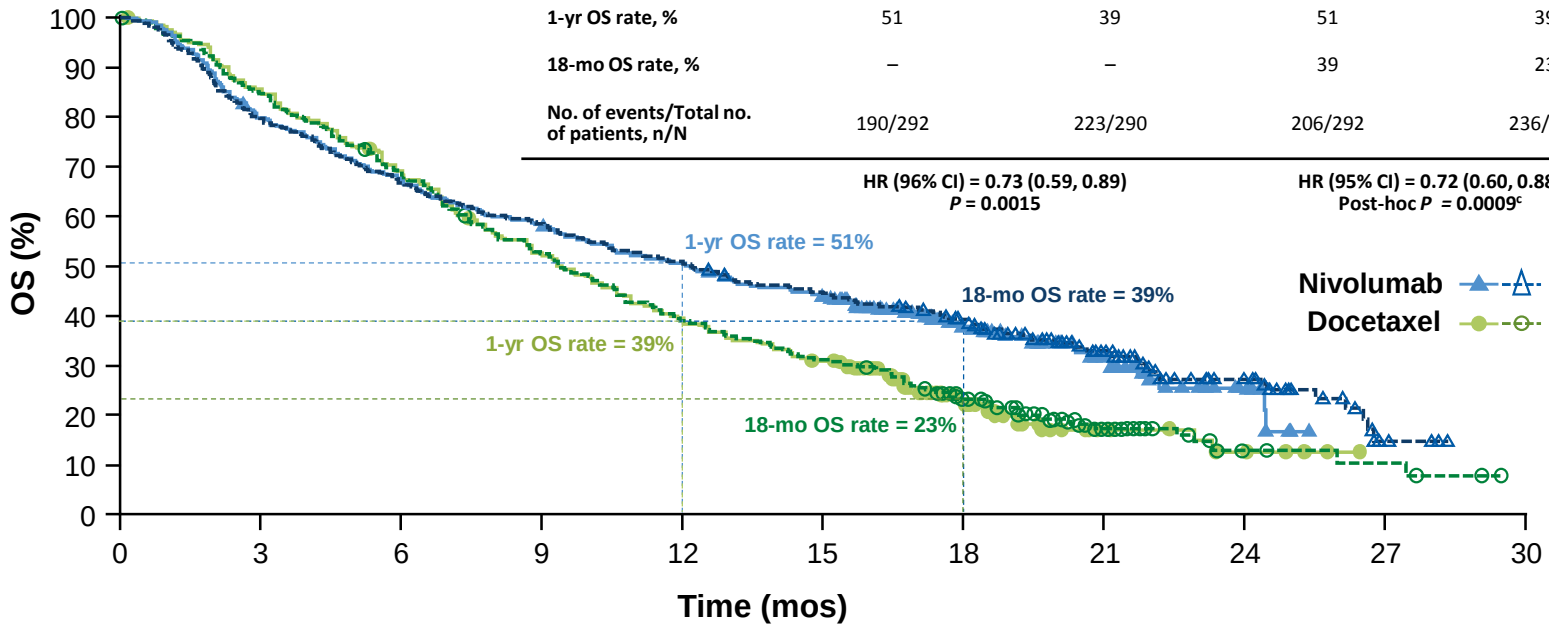
- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[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.

Borghaei H et al NEJM 2015

Nivolumab in Nonsquamous NSCLC
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



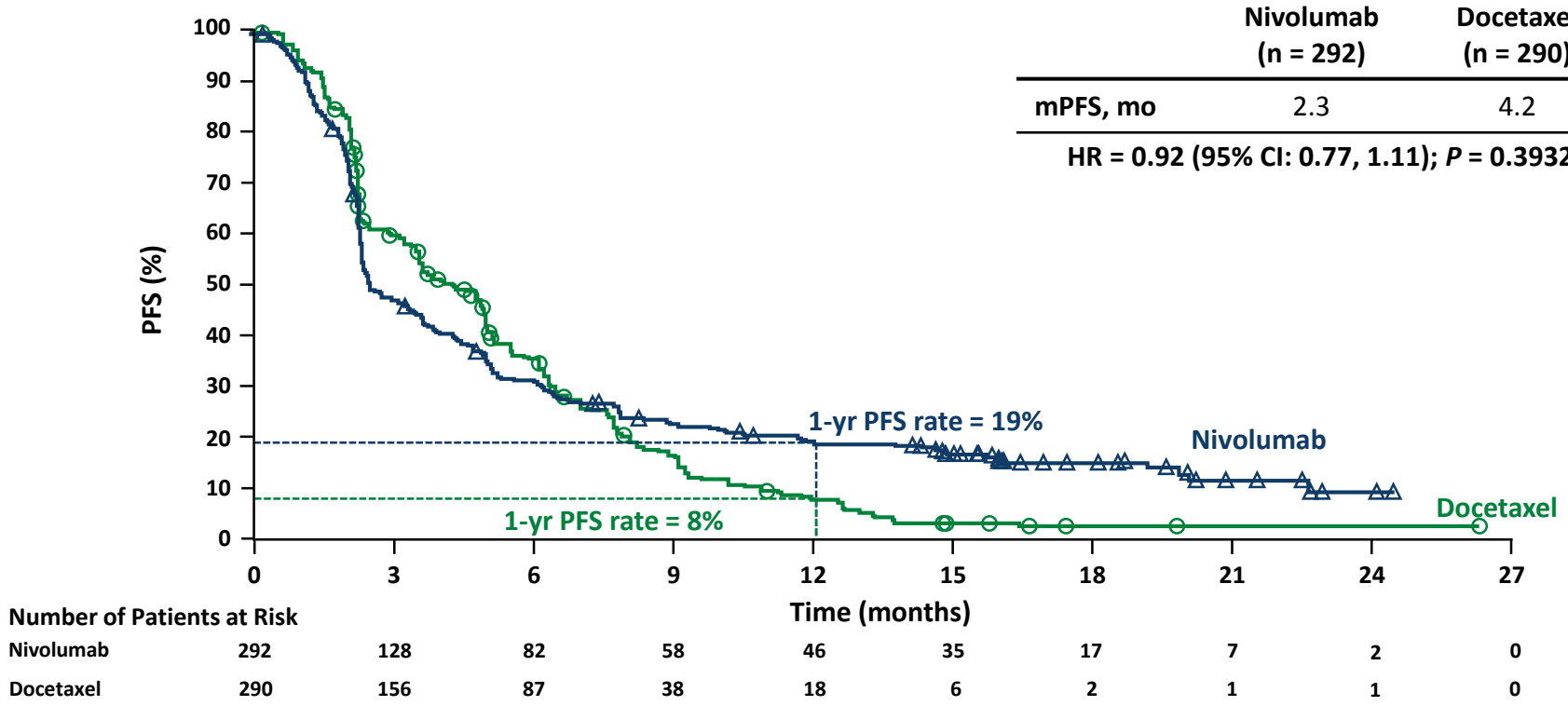
No. of patients at risk (12-mo OS)[a]											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. of patients at risk (18-mo OS)[b]											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

- 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.

Borghaei H et al NEJM 2015

Checkmate 057: Progression-free Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

Symbols represent censored observations.

Borghaei H et al NEJM 2015

CheckMate 057: ORR and PFS

	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR, % (95% CI)	**19** (15, 24)	**12** (9, 17)
Odds ratio (95% CI) *P*-value[a]	1.7 (1.1, 2.6) 0.0246	
Median time to response,[b] mos (range)	2.1 (1.2–8.6)	2.6 (1.4–6.3)
Median DOR,[b] mos (range)	**17.2** (1.8–22.6+)	**5.6** (1.2+–15.2+)
Ongoing response,[c] %	52	14
Median PFS, mos (95% CI)	2.3 (2.2, 3.3)	4.2 (3.5, 4.9)
1-yr PFS rate, % (95% CI)	19 (14, 23)	8 (5, 12)
HR (95% CI) *P*-value	0.92 (0.77, 1.11) 0.3932	

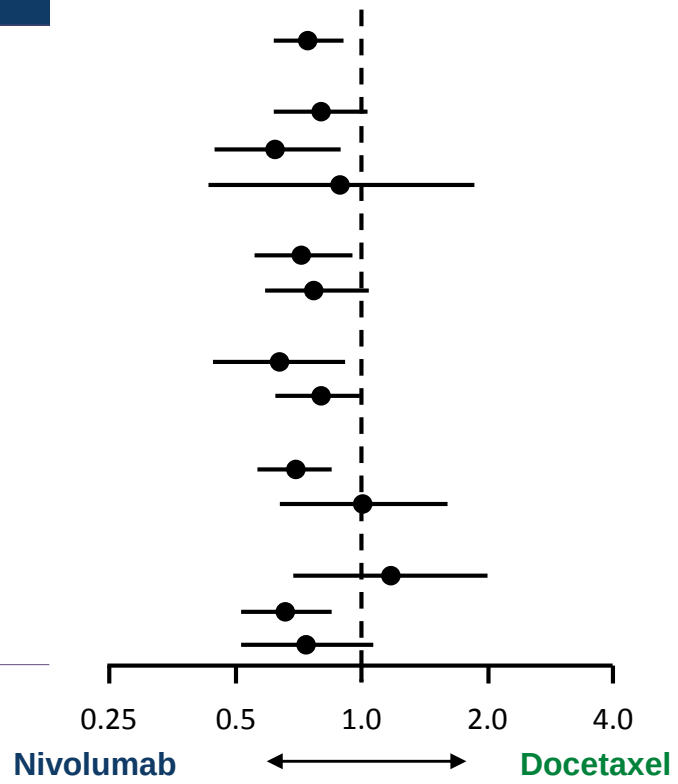
- 71 (24%) patients on nivolumab therapy were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16/71 (23%) patients (not included in best overall response)

[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.
Based on a March 18, 2015, DBL.

Borghaei H et al NEJM 2015

CheckMate 057: Treatment Effect on OS in Predefined Subgroups

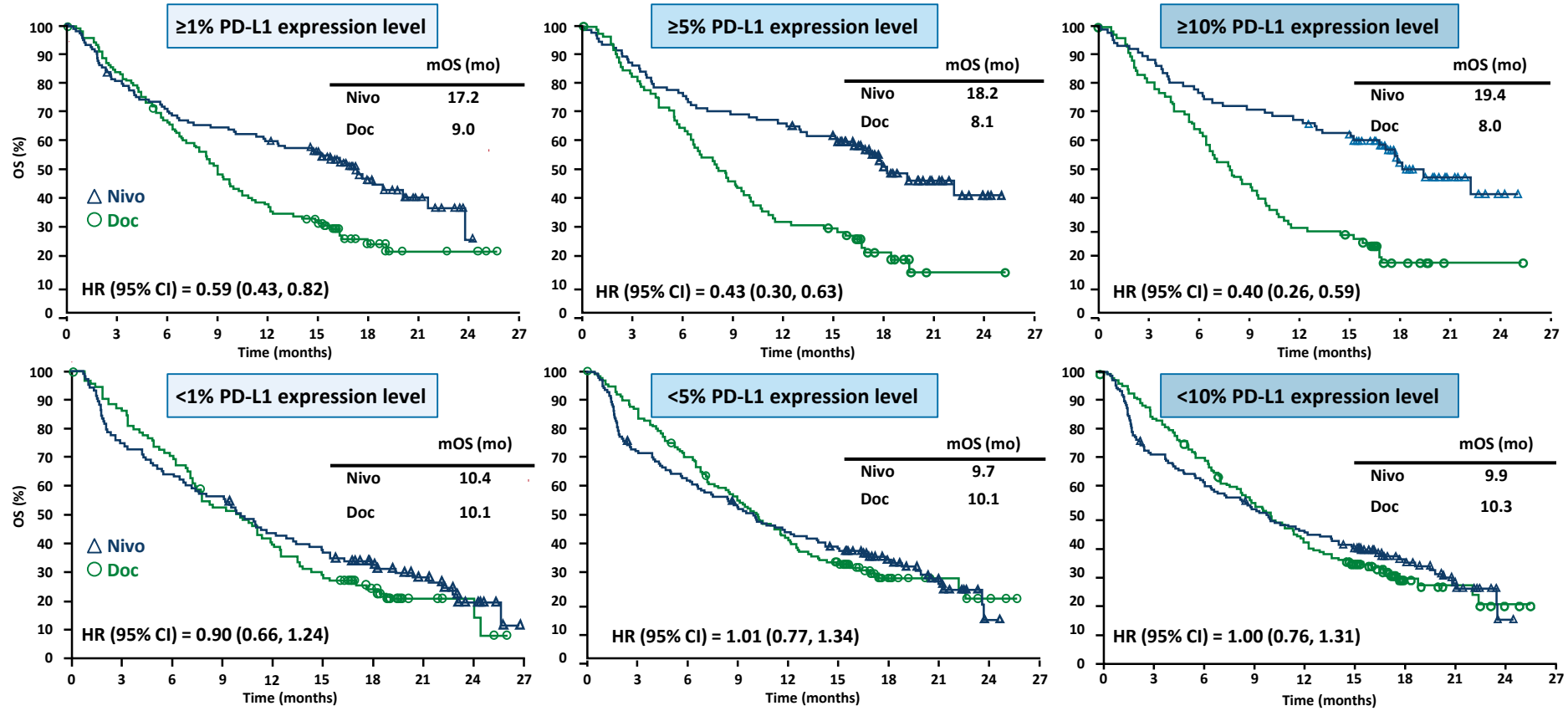
	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
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).

Borghaei H et al NEJM 2015

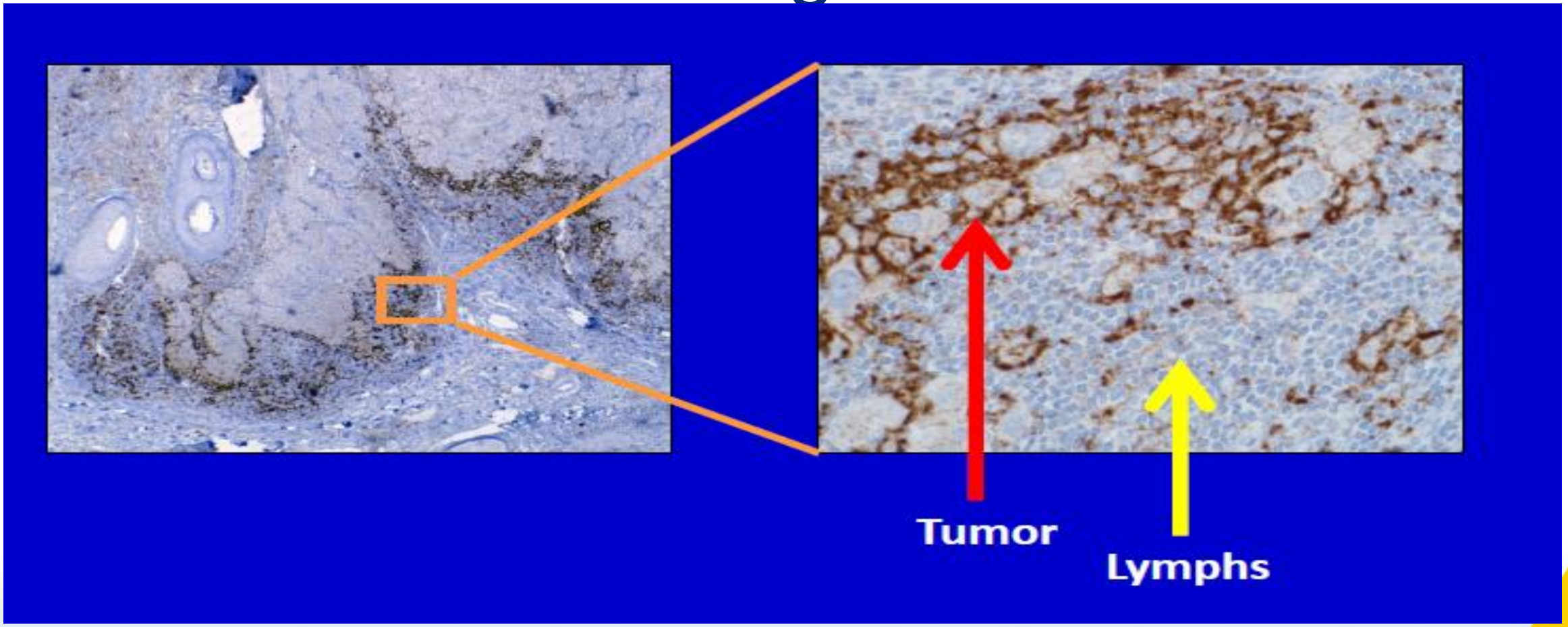
CheckMate 057: OS by PD-L1 Expression



Symbols represent censored observations.

Borghaei H et al NEJM 2015

PD-L1 Tumor Expression is Heterogeneous



PD-L1 testing

Characteristic	Assay			
	Pembrolizumab (Keytruda, MK-3475)	Nivolumab (Opdivo, BMS-936558)	Durvalumab (MEDI-4736)	Atezolizumab (MPDL3280A, RG7446)
Manufacturer	Merck Sharp & Dohme	Bristol-Myers Squibb	MedImmune/AstraZeneca	Genentech/Roche
mAb	Humanized IgG4	Human IgG4	Human Fc-modified IgG1	Human Fc-modified IgG1
Target	PD-1	PD-1	PD-L1	PD-L1
FDA approved	Melanoma	Melanoma, NSCLC	NA	Bladder, NSCLC[a]
coDx assay PD-L1 positive				
IHC assay developer	Dako	Dako	Ventana	Ventana
Antibody clone	22C3 mouse	28-8 rabbit	SP263 rabbit	SP142
Expression location	TCs and stroma	TCs	TCs	TICs and TCs
Cut-off	Melanoma, bladder, NSCLC: ≥1% TC (or any tumor stroma cell)	NSCLC: ≥1% to 5% TC Renal: ≥5% TC	NSCLC, SCCHN: ≥25% TC	Bladder, NSCLC, breast: IHC2$^+$ ≥5% to <10% TC or TIC or IHC3$^+$ ≥10% TC or TIC

Hansen et al. (2015). *JAMA Oncology*

PD-L1 Testing in Cancer: Challenges in Companion Diagnostic Development.

Pembrolizumab

KEYNOTE-010: Pembrolizumab Phase 2/3 Study

Patients

- Advanced NSCLC
- Confirmed PD after ≥2 cycles of platinum-doublet chemotherapy[a]
- PD-L1 TPS ≥1%
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease
- No ILD or pneumonitis requiring

R
1:1:1

- Pembrolizumab 2 mg/kg IV Q3W for 24 months
- Pembrolizumab 10 mg/kg IV Q3W for 24 months
- Docetaxel 75 mg/m^2 Q3W per local guidelines[c]

Stratification factors:
- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%-49%)

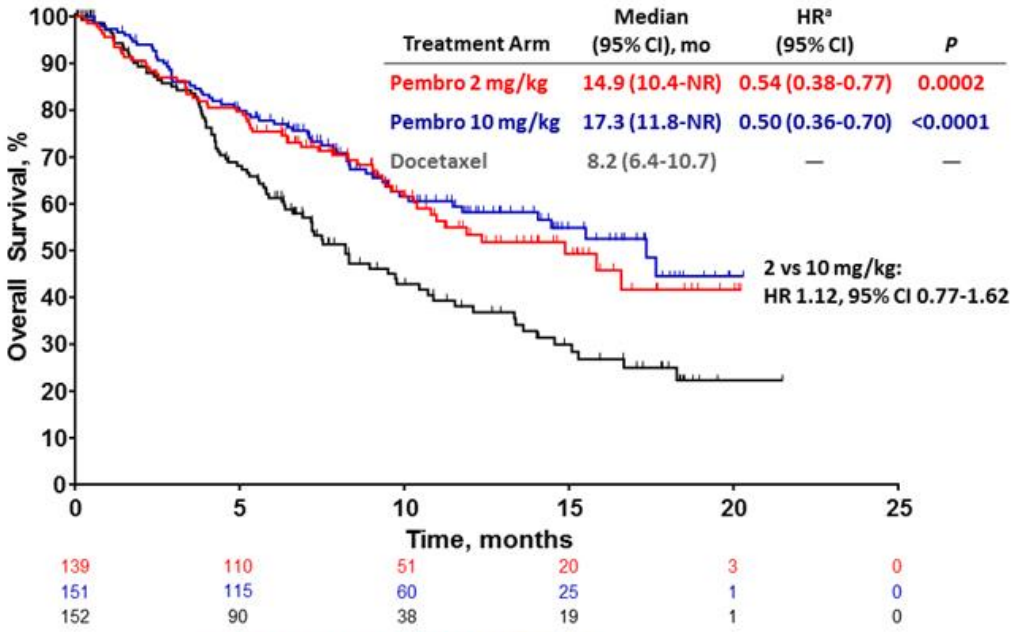
End points in the total population and TPS ≥50% stratum
- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

[a]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.

Keynote 010: PD-L1 Status and Survival

RS Herbst. Presented December 20, 2015

OS, PD-L1 TPS ≥50% Stratum



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
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)	—	—

2 vs 10 mg/kg:
HR 1.12, 95% CI 0.77-1.62

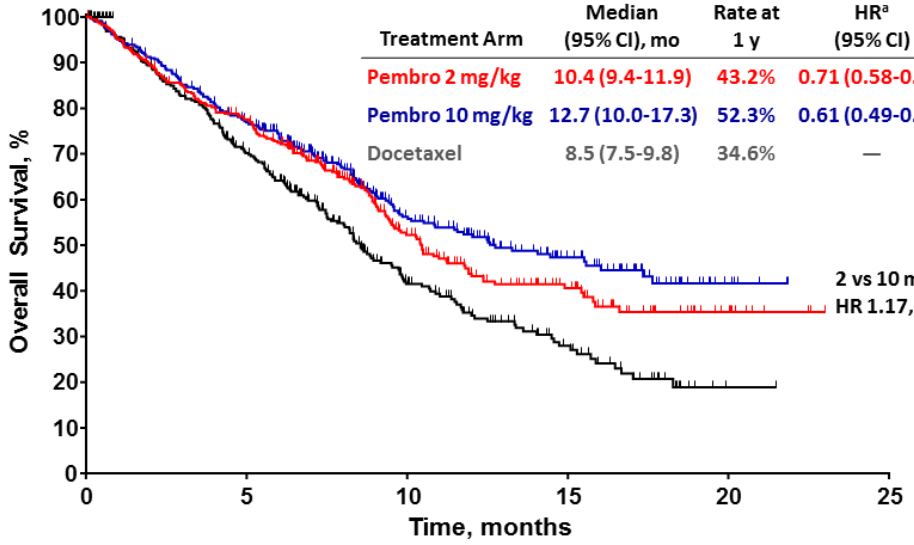
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Analysis cut-off date: September 30, 2015.

*Comparison of pembrolizumab vs docetaxel.

RS Herbst. Presented December 20, 2015

OS, PD-L1 TPS ≥1% (Total Population)



Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
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%	—	—

2 vs 10 mg/kg:
HR 1.17, 95% CI 0.94-1.45

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Analysis cut-off date: September 30, 2015.

*Comparison of pembrolizumab vs docetaxel.

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)

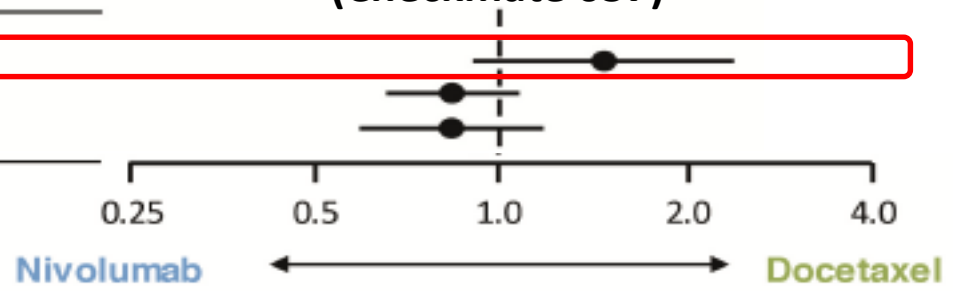
Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

Lack of Benefit of PD-1 Blockade vs Docetaxel in EGFR-mutant NSCLC (PFS)

PFS
(Checkmate 057)

	N	Unstratified HR (95% CI)
EGFR Mutation Status		
Positive	82	1.46 (0.90, 2.37)
Not Detected	340	0.83 (0.65, 1.06)
Not Reported	160	0.83 (0.59, 1.17)



PFS
PD-L1>1%
Keynote 010

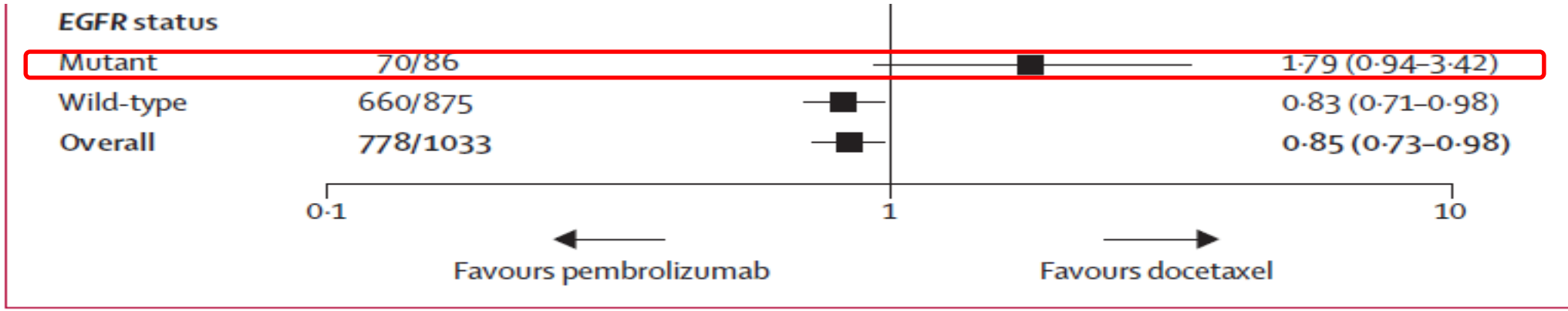


Figure 5: Subgroup analysis of progression-free survival

Borghaei, NEJM 2015, Herbst, Lancet 2016

Toxicities Associated with Immune Checkpoint Inhibitors

Hypophysitis

Thyroiditis

Adrenal insufficiency

Colitis

Dermatitis

Pneumonitis

Hepatitis

Pancreatitis

Motor & sensory neuropathies

Arthritis

- Less common: hematologic; cardiovascular; ocular, renal

PD-1 Checkpoint Inhibition Phase III Trials -Toxicities

Trial	Agent	Rx-Related AEs– All & Grade 3/4	Most Common Rx-Related AEs	Pneumonitis Rate
Checkmate 017	Nivolumab	58% 7%	Fatigue – 16% ↓appetite – 11% Asthenia – 10%	All – 5% Gr 3/4 – 0%
	Docetaxel	86% 55%	Neutropenia – 33% Fatigue – 33% Nausea 23%	0%
Checkmate 057	Nivolumab	69% 10%	Fatigue – 16% Nausea – 12% ↓appetite – 10%	All – 3% Gr 3/4 – 1%
	Docetaxel	88% 54%	Neutropenia – 31% Fatigue – 29% Nausea – 26%	0%
Keynote 010	Pembrolizumab 2 mg/kg dose	63% 13%	Fatigue – 20% Pruritis – 11% ↓appetite – 11%	All – 5% Grade 3-5 – 2% 2 deaths
	Docetaxel	81% 35%	Fatigue – 25% Diarrhea 18% ↓ appetite – 16%	0%

Brahmer J et al NEJM 2015; Borgahi H et al NEJM 2015; Herbst R et al Lancet 2015

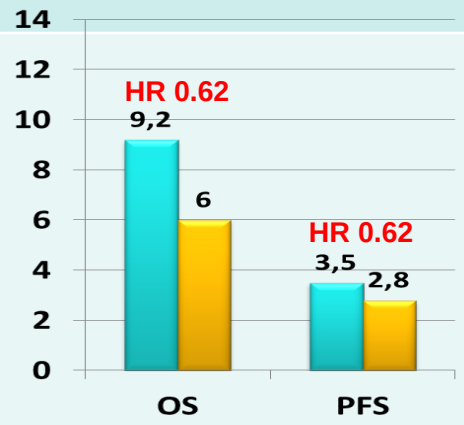
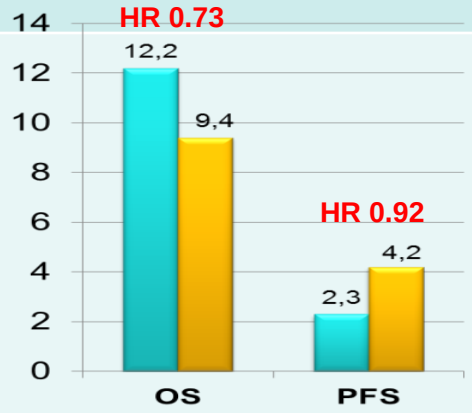
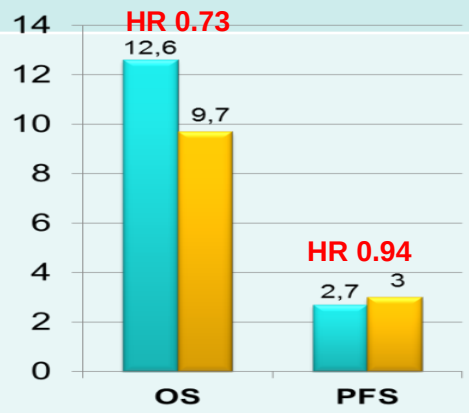
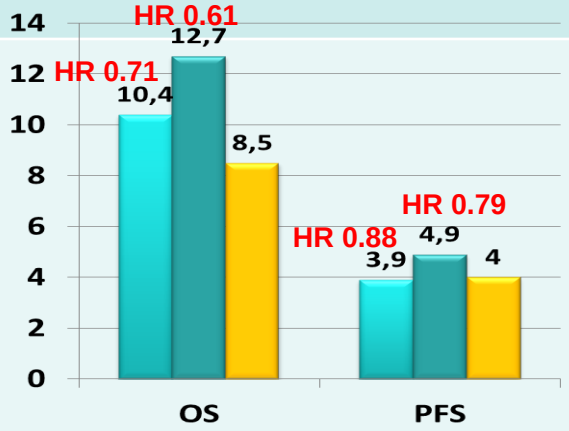
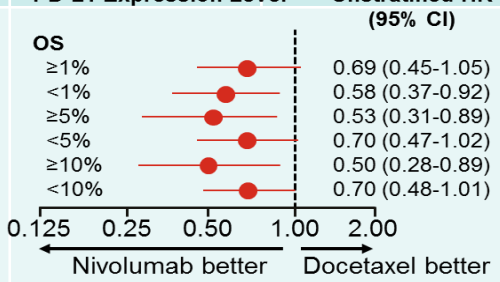
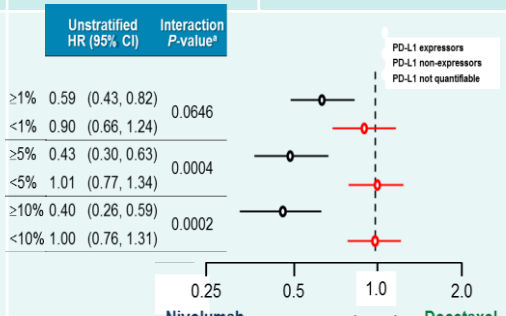
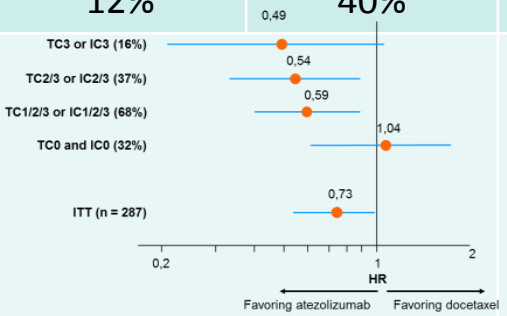
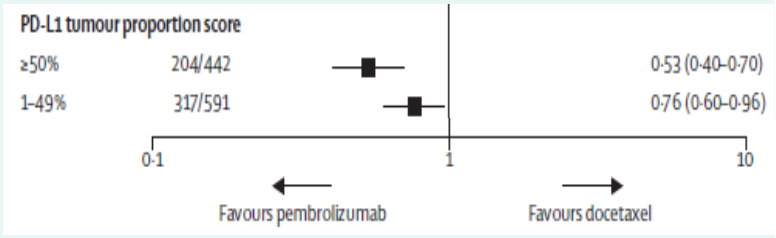
Where to find Treatment Management Guidelines – The Web or phone

(Nivolumab)

Opdivo App for HCP safety

KEYTRUDA® (pembrolizumab) Injection 100 mg

www.keytruda.com

	Nivolumab (PD1)		Atezolizumab (PDL1)	Pembrolizumab (PD1)
	Checkmate 017	**CheckMate 057**	**Poplar**	**Keynote 010**
Histology	**Nivolumab *vs* docetaxel N=272 Squamous 100%**	**Nivolumab *vs* docetaxel N=582 Non-Squamous 100%**	**Atezolizumab *vs* docetaxel N=287 Squamous: 34% Non-Squamous: 66%**	**Pembrolizumab *vs* docetaxel N=1034 Squamous 21%, Non-SCC 70%; PDL1≥1%**
Line of TT	2nd line 100%	2nd line 100%	2nd ~70%, 3rd 20%, > 3rd 10%	2nd line 65%, 3rd line 35%
OS and PFS (HR *vs* docetaxel)				
	Nivolumab	**Docetaxel**	**Nivolumab**	**Docetaxel**	**Atezolizum.**	**Docetaxel**	**Pembro 2**	**Pembro 10**	**Docetaxel**
ORR	**20%**	9%	**20%**	9%	**19%**	12%	**18%**	**18%**	9%
G3-≥4 AEs	8%	56%	10%	54%	12%	40%	13%	16%	35%
OS by PDL1 status				

2016: Proposal for Treatment Algorithm

Modified from Maurice Perol

Disease progression after platinum-based doublet

Decision-making factors

	Non-squamous Carcinoma	Squamous Carcinoma
	Consider rebiopsy: EGFR and ALK status if unknown, PDL1 expression	
	Wild-type EGFR and no *ALK rearrangement*	
	Co-morbidities, CI to immunotherapy, Eligibility to anti-angiogenic agents	
	CI to immunotherapy	No CI to immunotherapy Pembrolizumab (PD-L1 +) (cut-off?)
2nd line	Docetaxel + nintedanib Docetaxel + ramucirumab Docetaxel or pemetrexed if CI to anti-angiogenic agent	Nivolumab or pembrolizumab Nivolumab if no CI to immunotherapy
3rd line	Erlotinib Nivolumab if no CI to immunotherapy Docetaxel + nintedanib Docetaxel + ramucirumab Docetaxel or pemetrexed if CI to anti-angiogenic agent	Docetaxel ± ramucirumab Erlotinib or afatinib

NOW WHAT?

- Will it replace chemotherapy?
- What about combination immune therapy?
- Who will benefit from it?
- Mechanisms of resistance?
- Can immune therapy move into early stage treatment?

Conclusions

- Nivolumab is the first PD-1 antibody to show a survival advantage over chemotherapy for 2nd-line treatment of squamous and nonsquamous NSCLC.
- Pembrolizumab is a PD-1 antibody with a survival advantage in PD-L1 positive NSCLC.
- Immune related toxicities are associated with the mechanism of action.
- We have only cracked open the door for immunotherapy in lung cancer.