SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

PD1/PDL1 axis in solid tumors: evidences in advanced NSCLC

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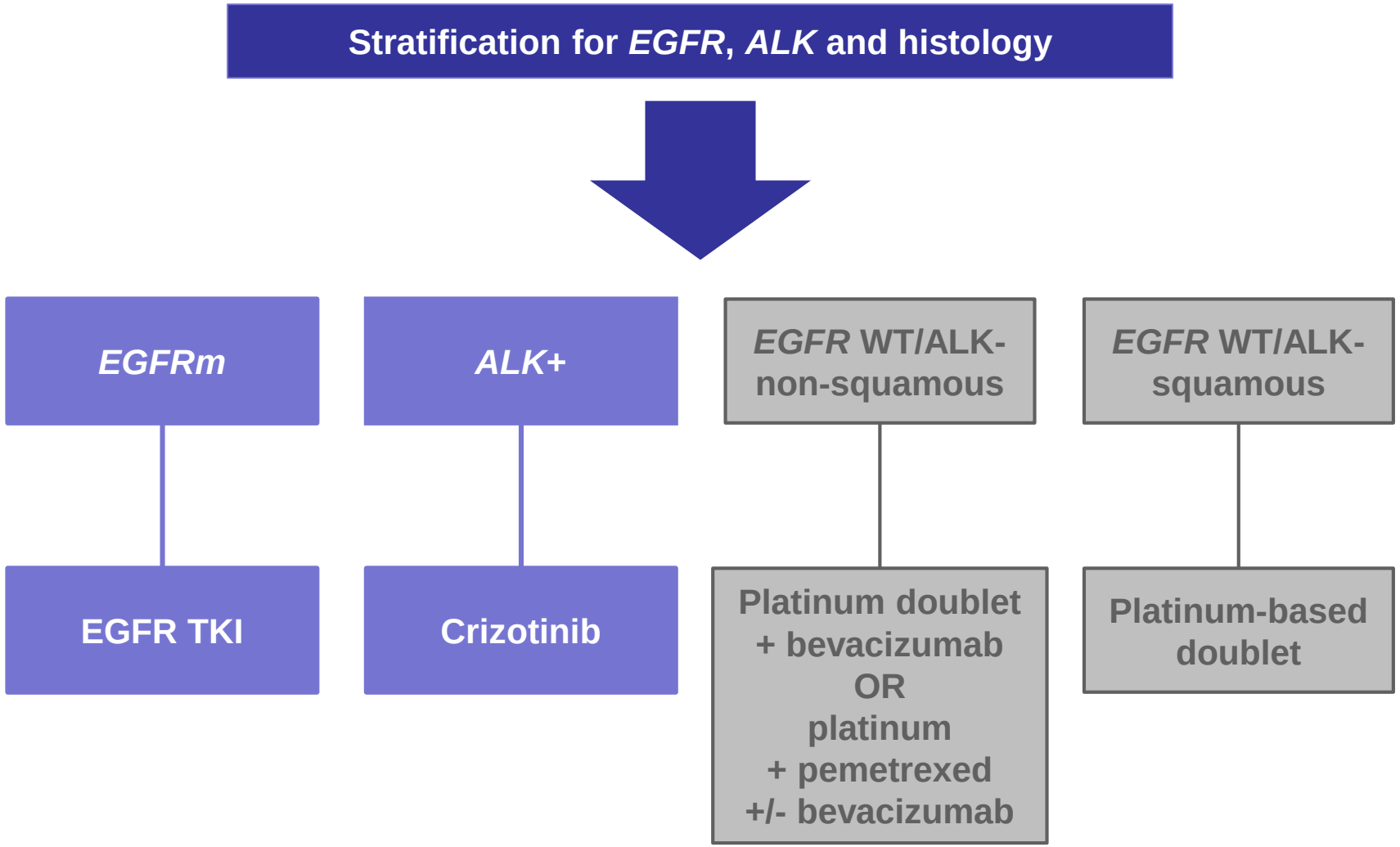
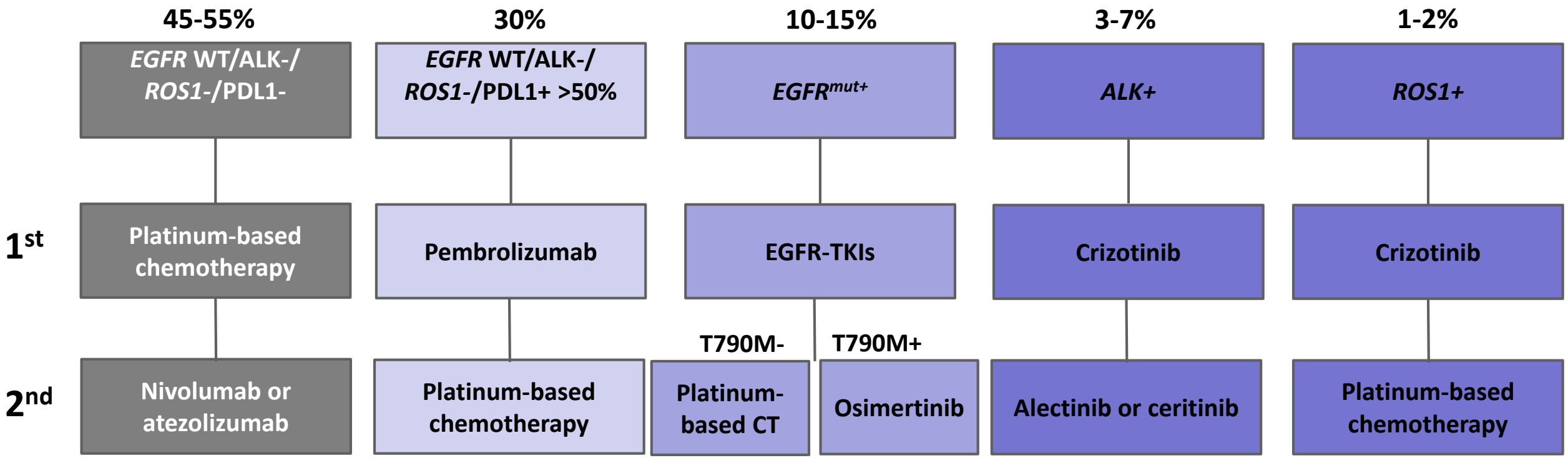
First-line therapy for metastatic NSCLC in 2016

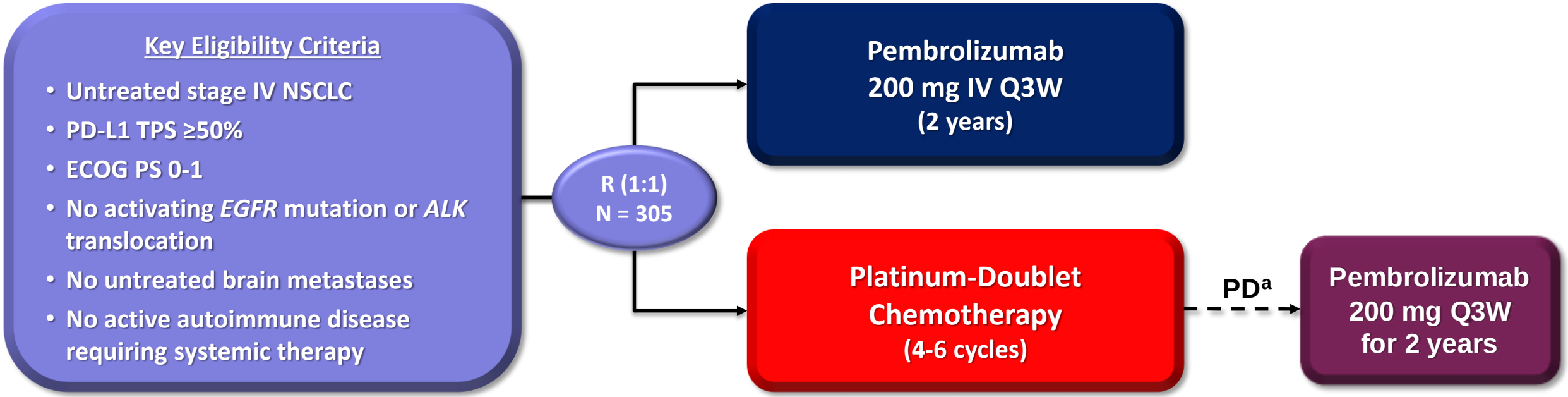


Novello S, et al. Ann Oncol 2016 ; NSCLC, NCCN guidelines 2016

Options for metastatic NSCLC in 2017



KEYNOTE 024 study design



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

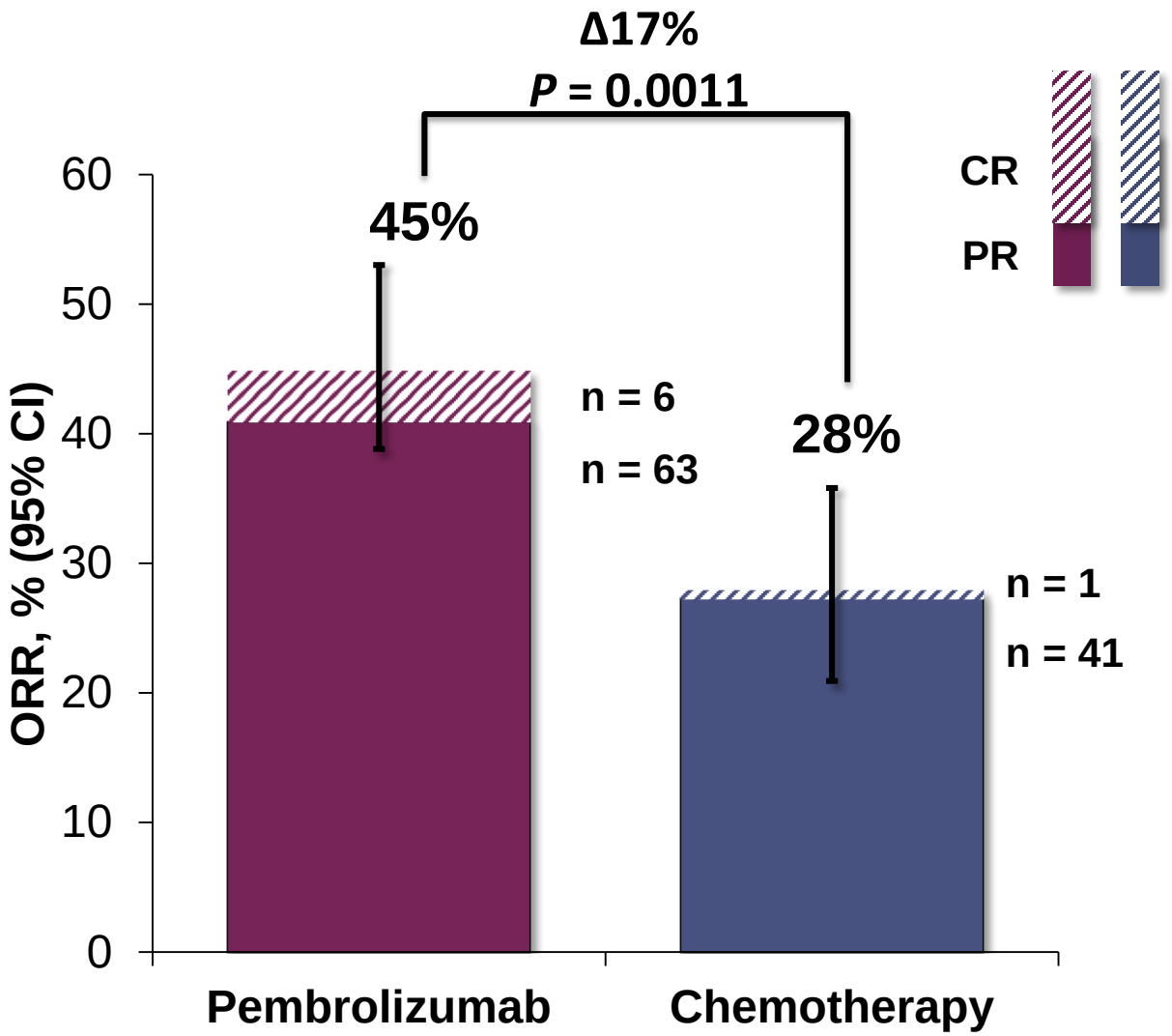
Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck M, et al. NEJM 2016

Response to the therapy

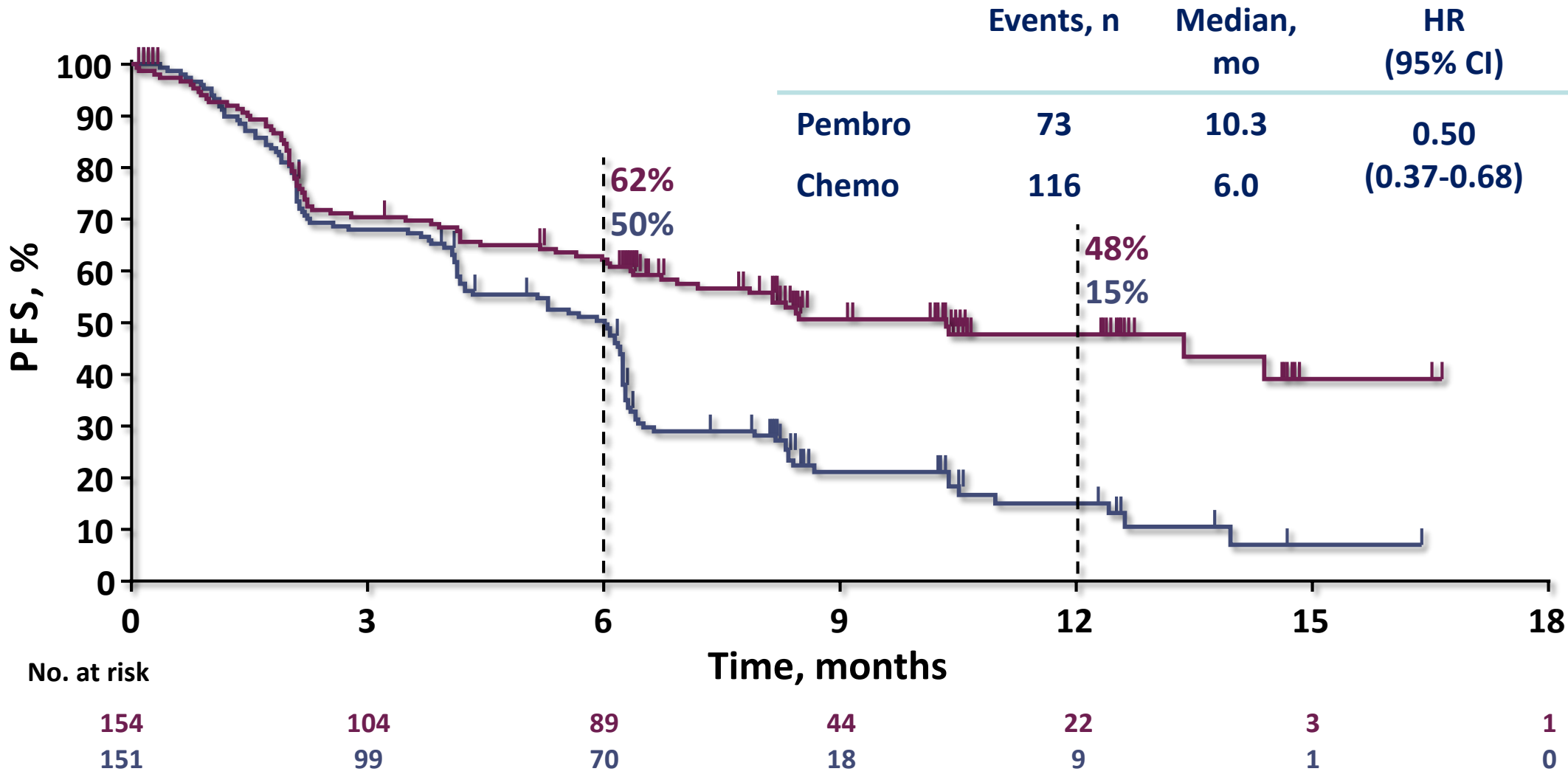


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck M et al. NEJM 2016

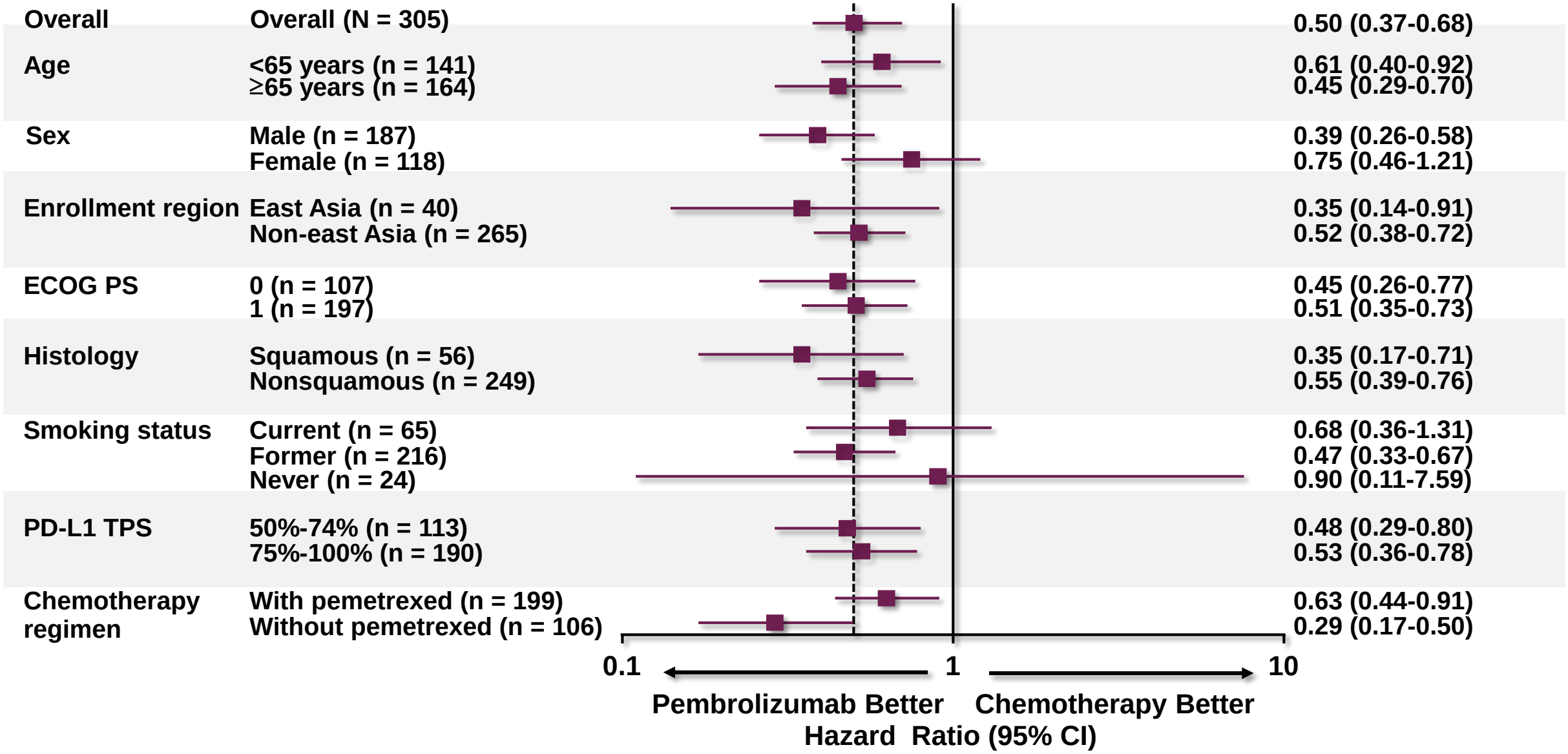
Progression-free survival



Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck M , et al. NEJM 2016

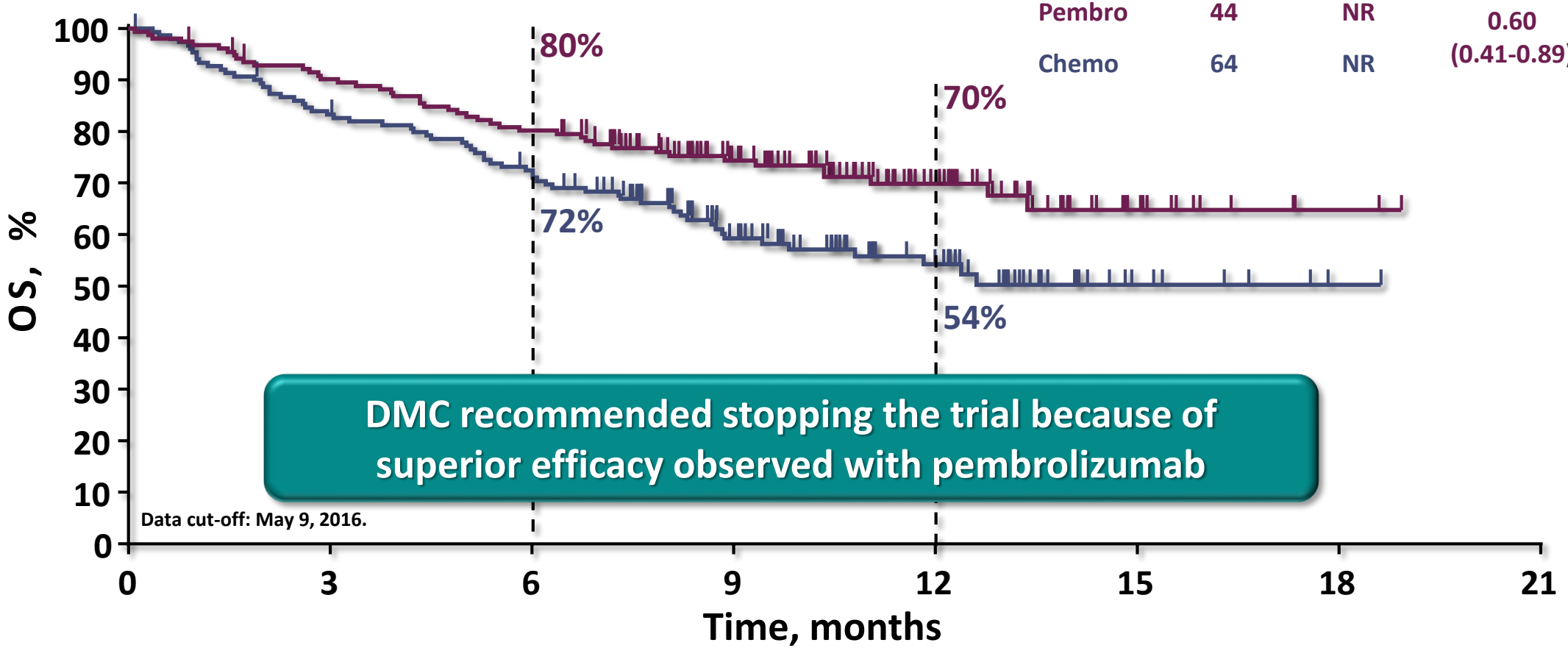
Progression-Free survival in subgroups



Reck M et al. NEJM 2016

Overall survival

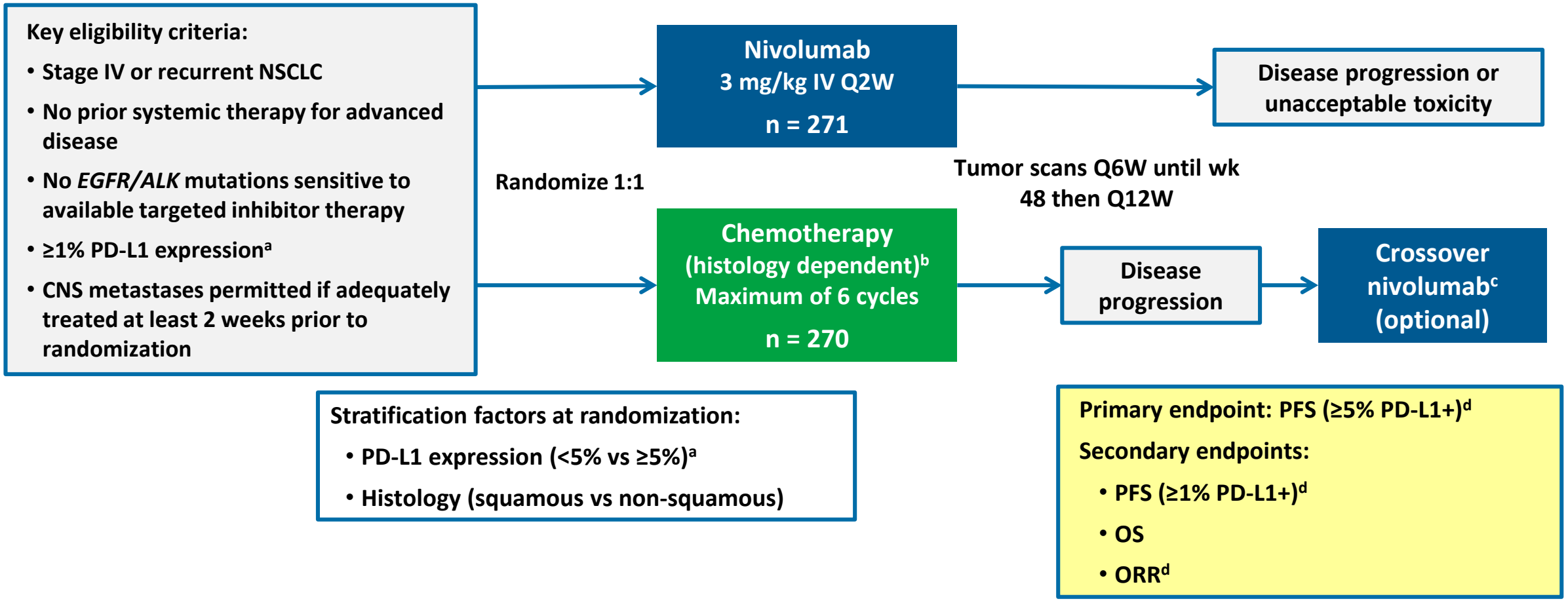
	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



No. at risk							
Pembro	154	136	121	82	39	11	2	0
Chemo	151	123	106	64	34	7	1	0

Reck M , et al. NEJM 2016

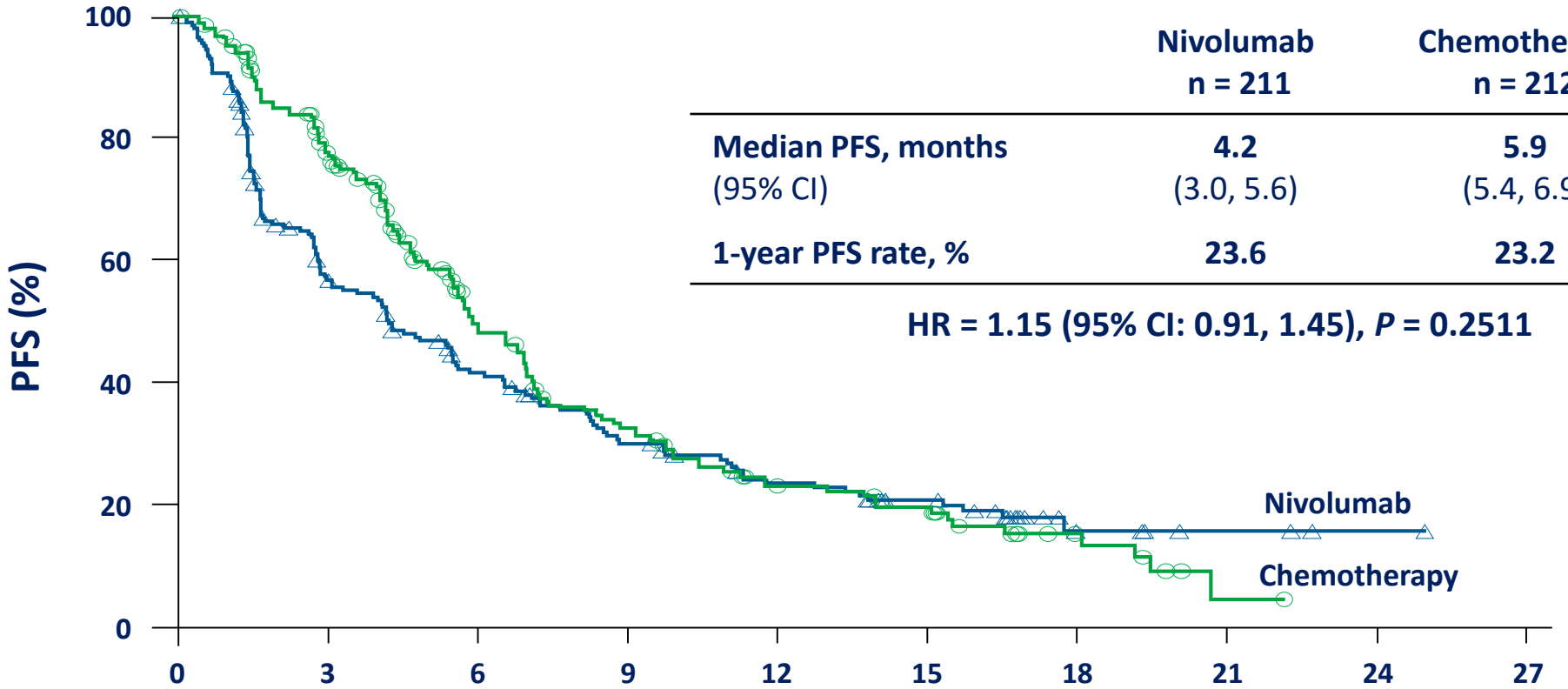
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



Socinski M et al. ESMO 2016

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

HR = 1.15 (95% CI: 0.91, 1.45), *P* = 0.2511

No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

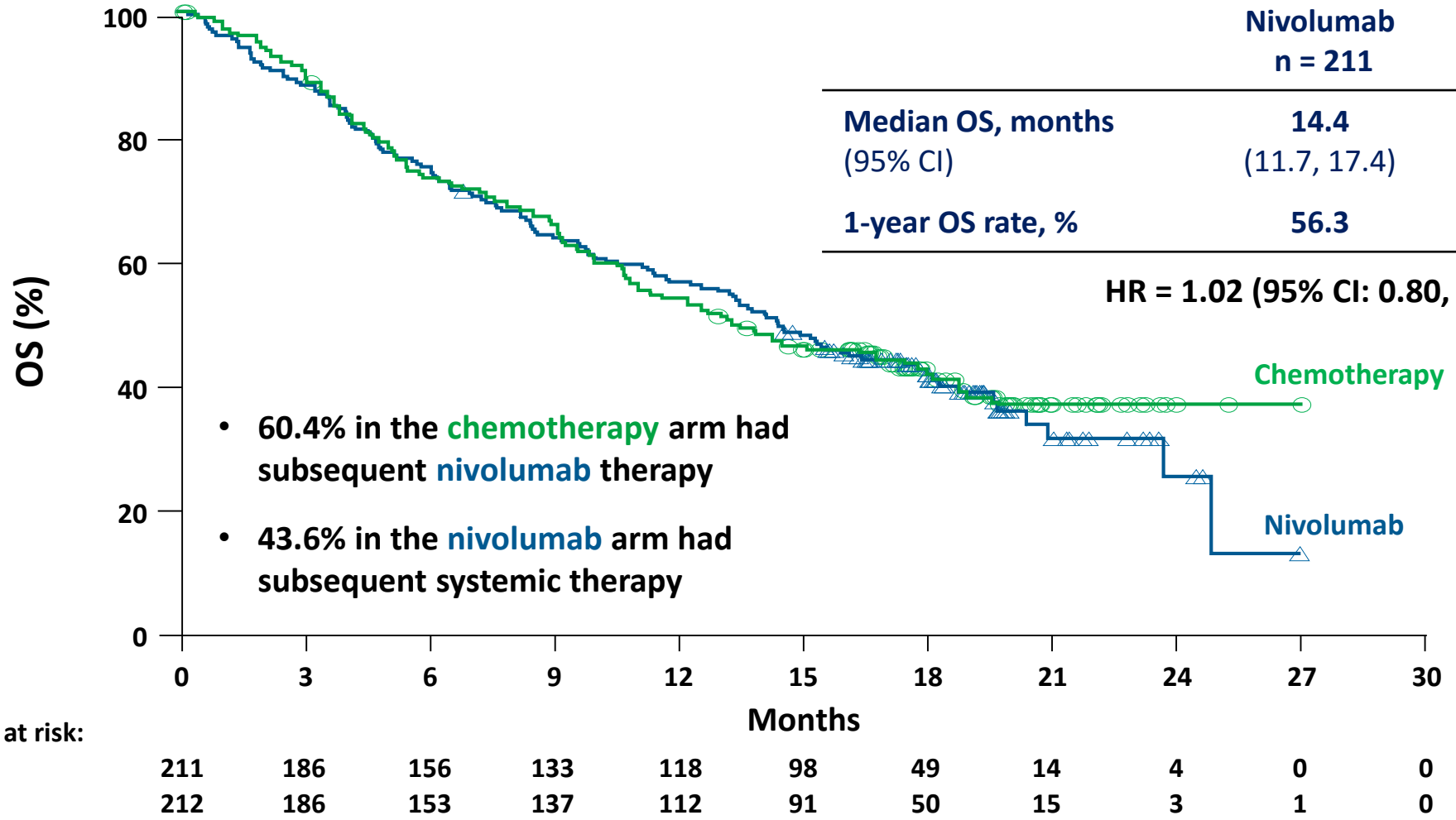
Socinski M et al. ESMO 2016

OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**

HR = 1.02 (95% CI: 0.80, 1.30)



- **60.4% in the chemotherapy arm had subsequent nivolumab therapy**
- **43.6% in the nivolumab arm had subsequent systemic therapy**

No. of patients at risk:											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

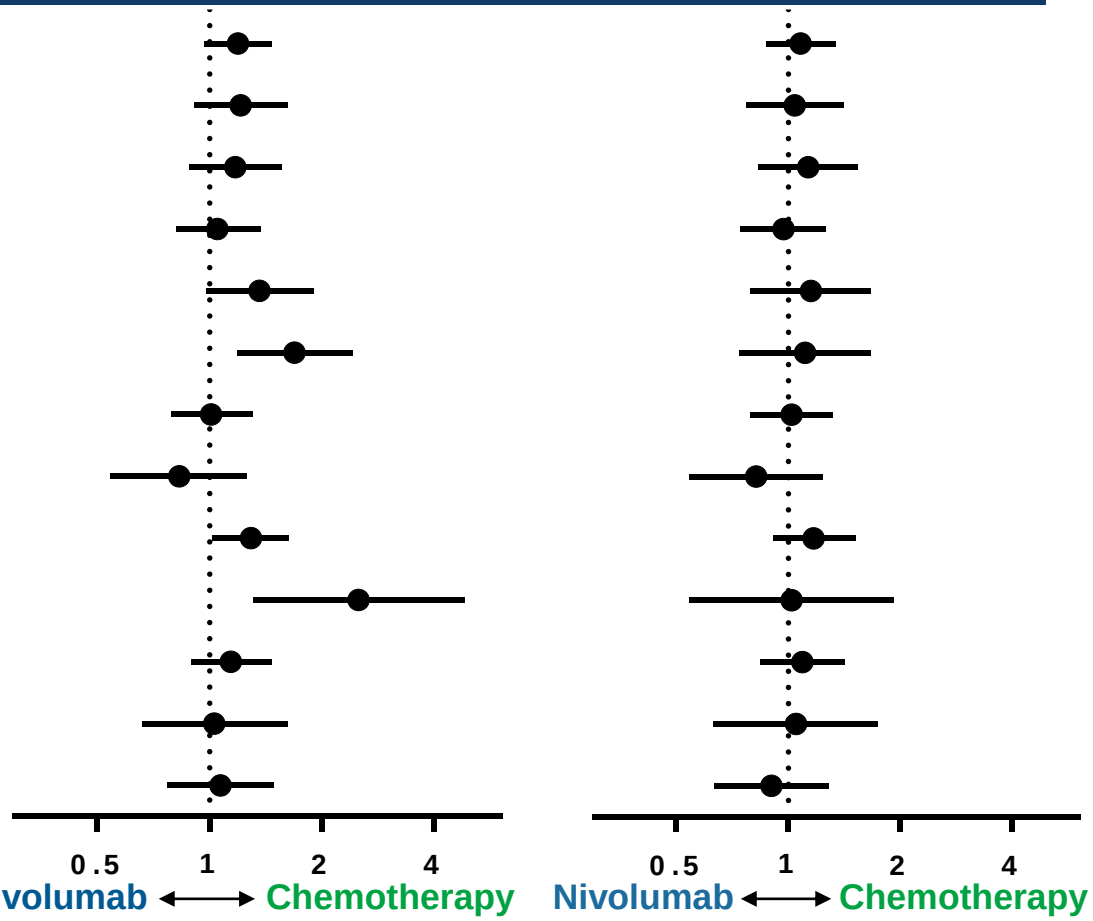
All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

Socinski M et al. ESMO 2016

PFS and OS Subgroup Analyses (All Randomized Patients)

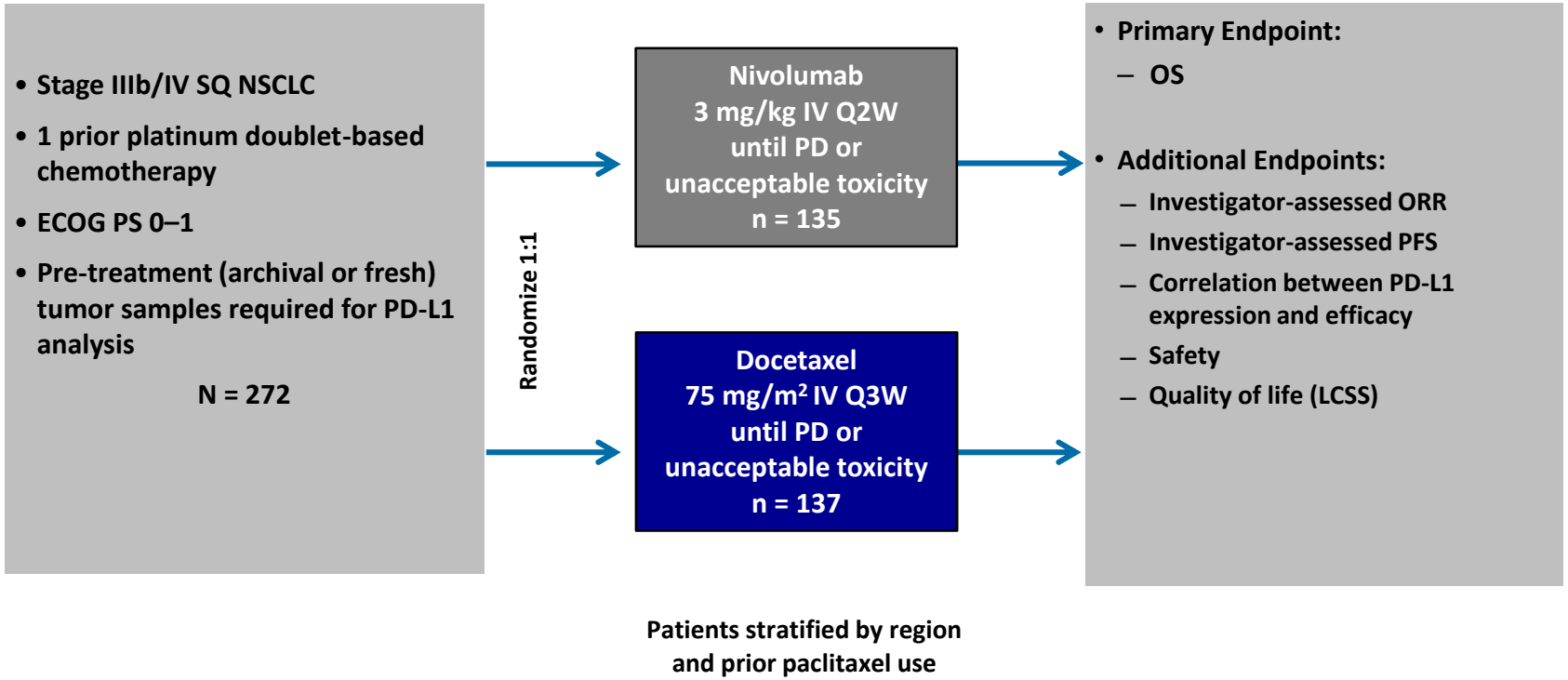
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

Subgroup	Patients, n		Unstratified HR	
	Nivolumab	Chemotherapy	PFS	OS
Overall	271	270	1.19	1.08
≥65 years	123	137	1.21	1.04
<65 years	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Non-squamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥50% PD-L1+	88	126	1.07	0.90



Socinski M et al. ESMO 2016

CheckMate 017 (NCT01642004) - Study Design

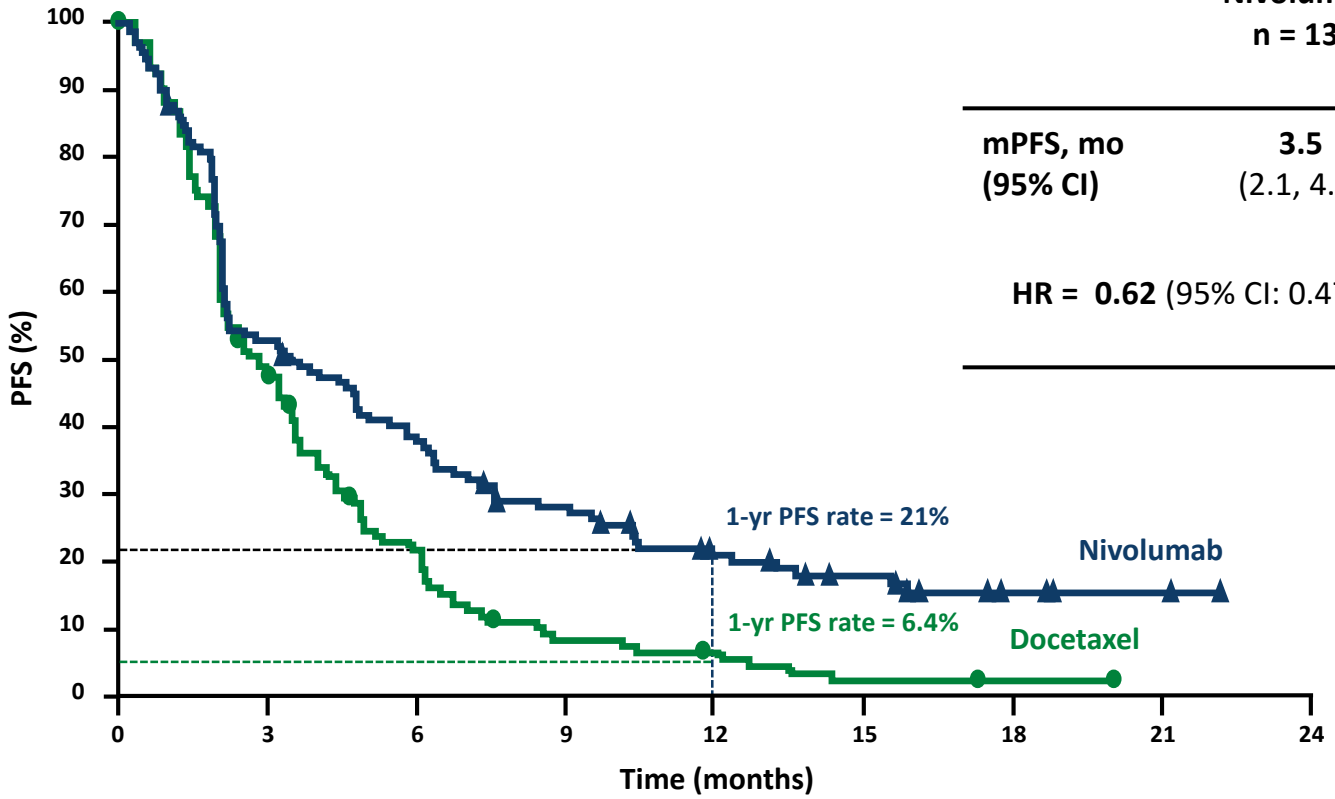


- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

Brahmer J, et al. NEJM 2015

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)

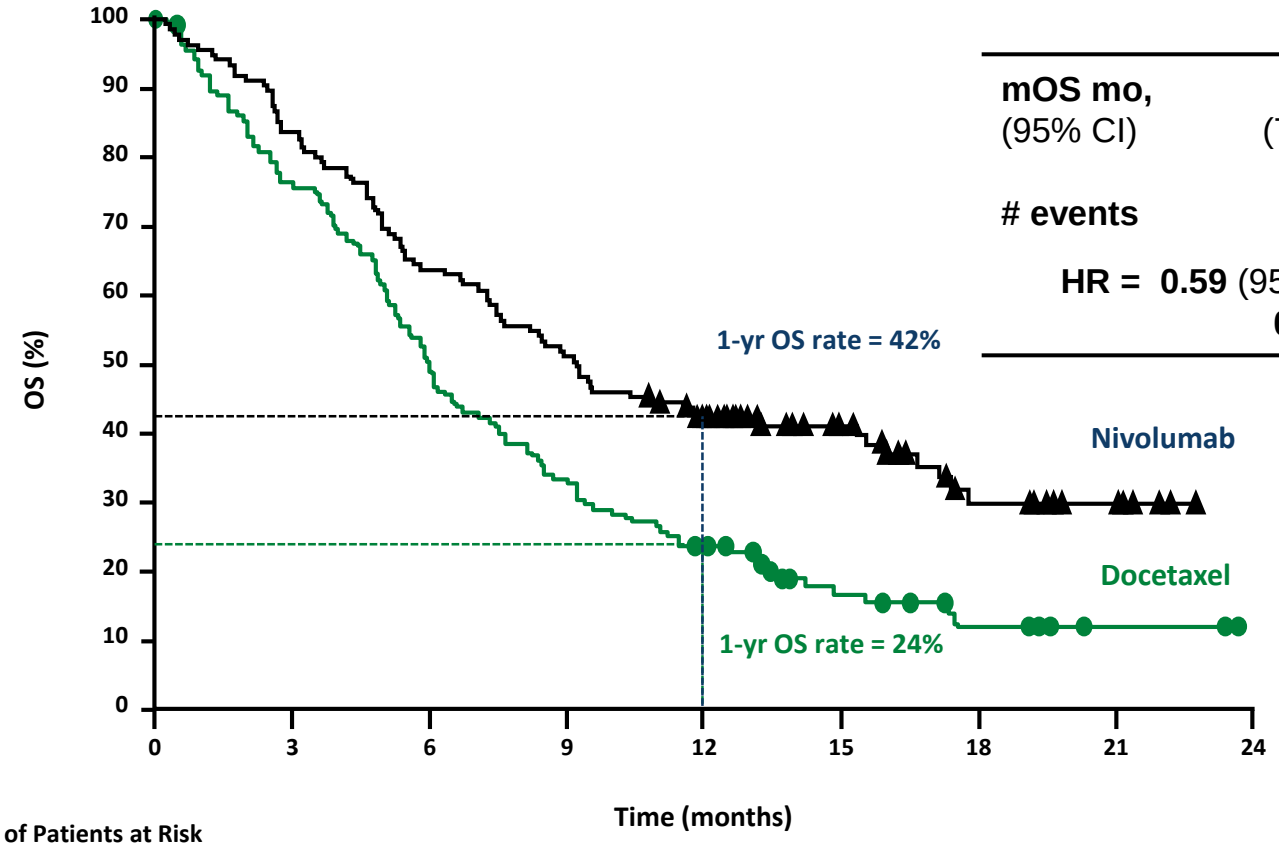
HR = 0.62 (95% CI: 0.47, 0.81); ***P*** **= 0.0004**

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.

Brahmer J, et al. NEJM 2015

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**

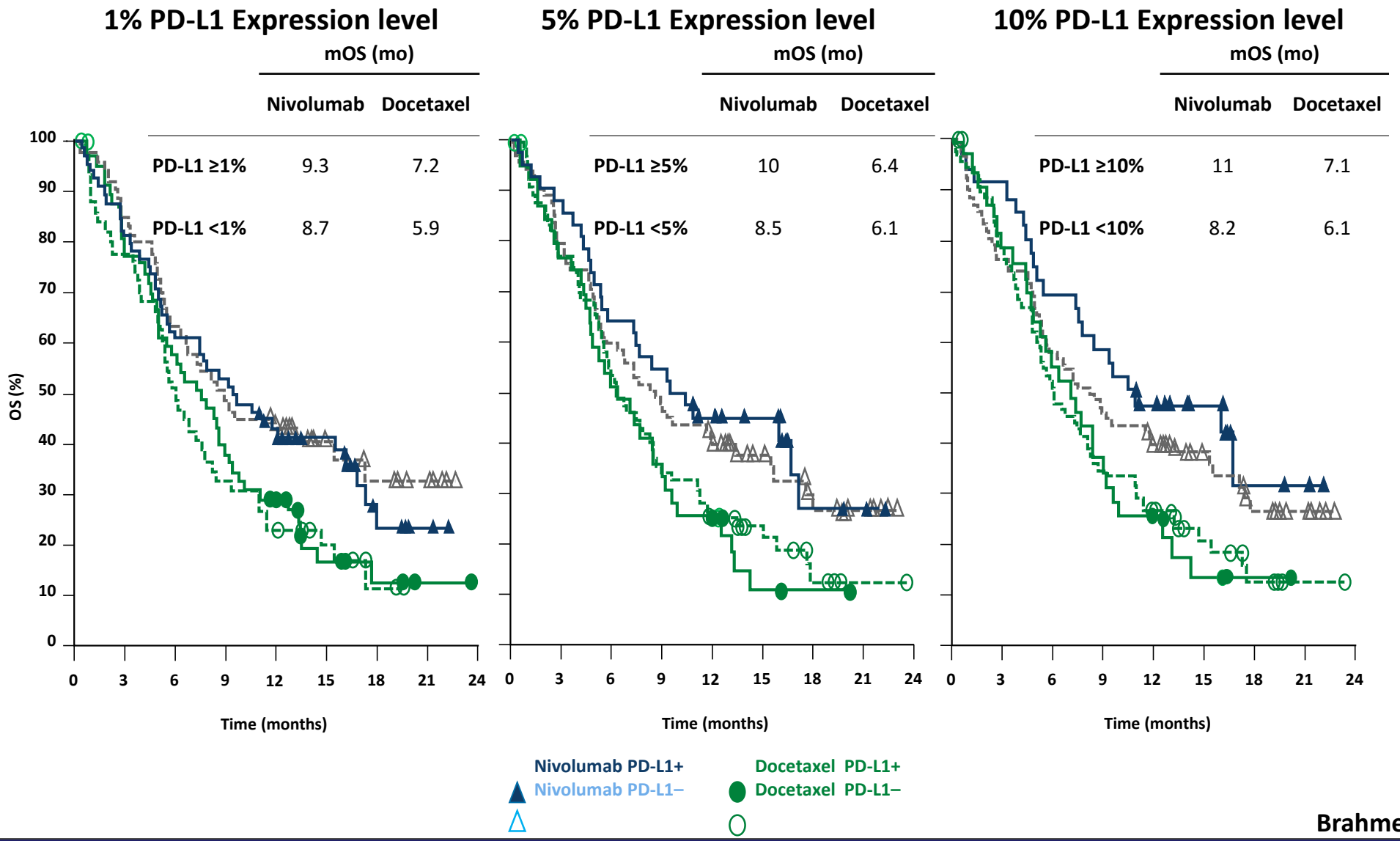
Number of Patients at Risk

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

Symbols represent censored observations

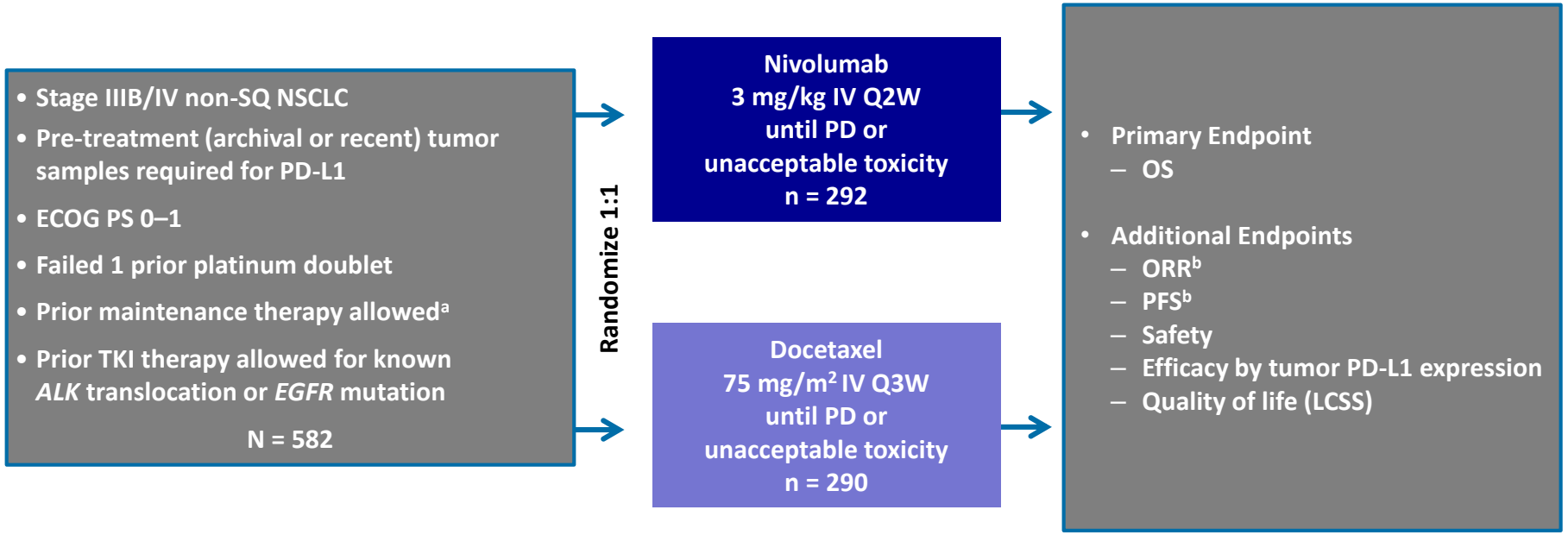
Brahmer J, et al. NEJM 2015

OS by PD-L1 Expression



Brahmer J, et al. NEJM 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**

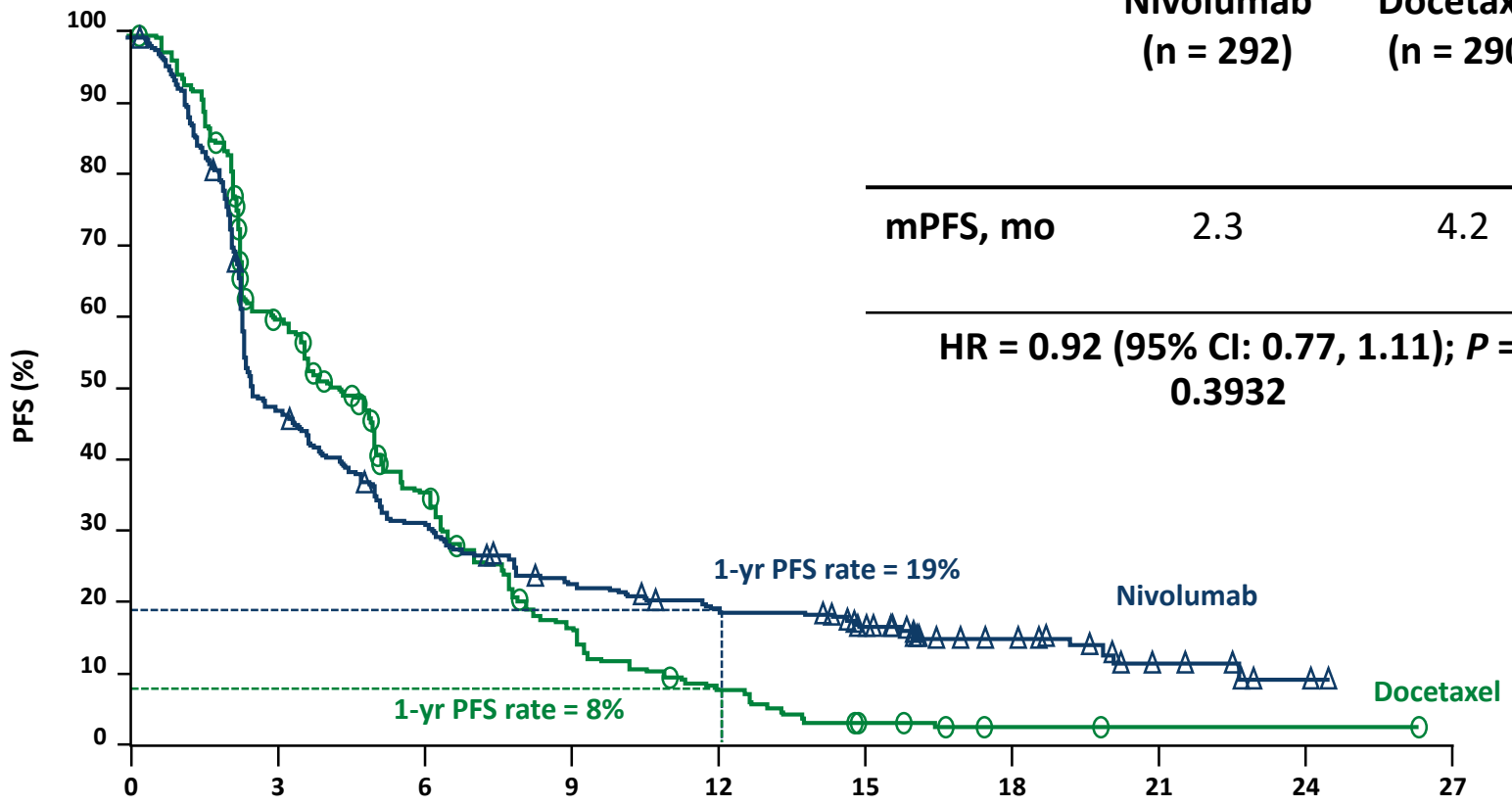
[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Borghaei H et al NEJM 2015

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

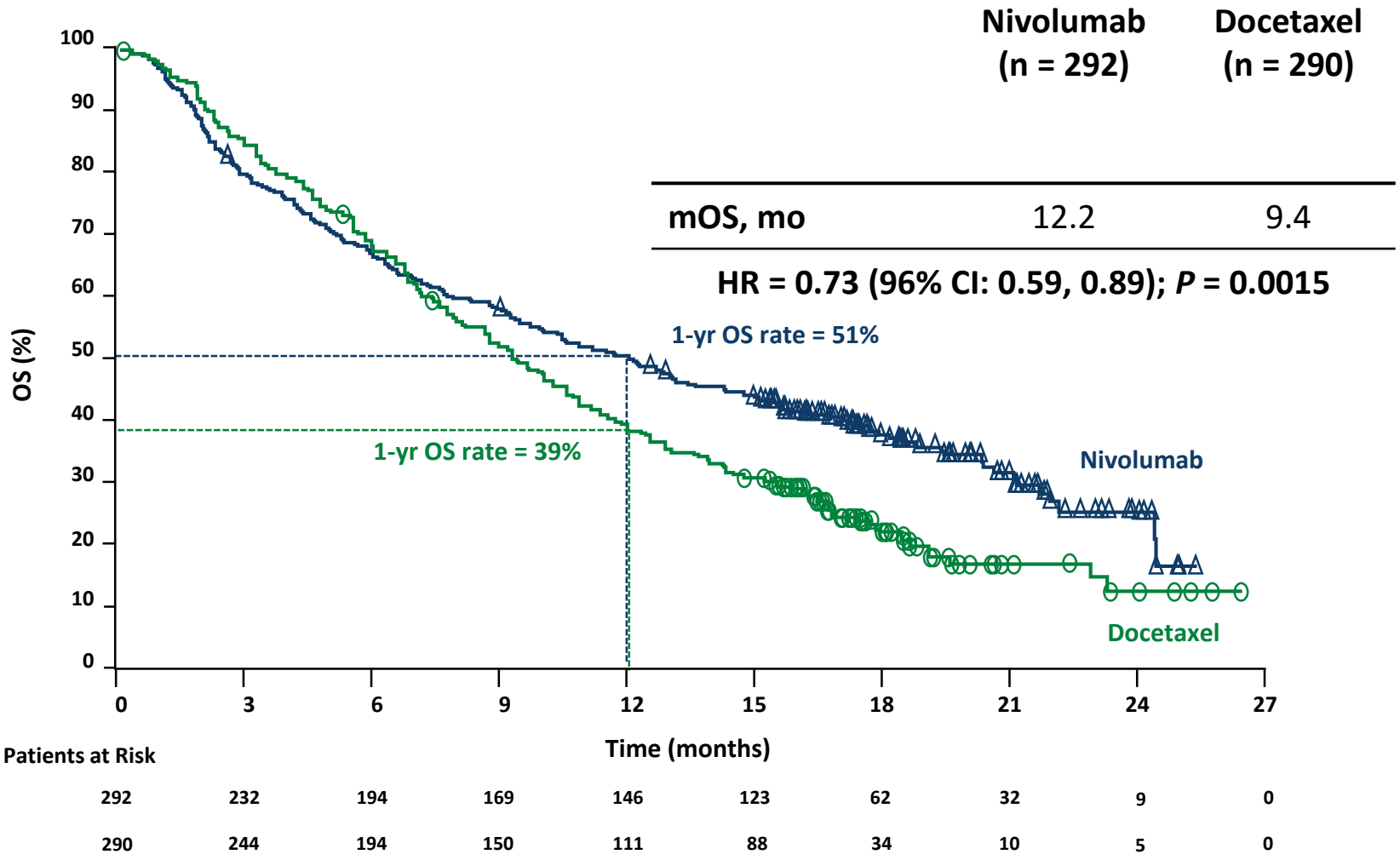


Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

Borghaei H et al NEJM 2015

Overall Survival

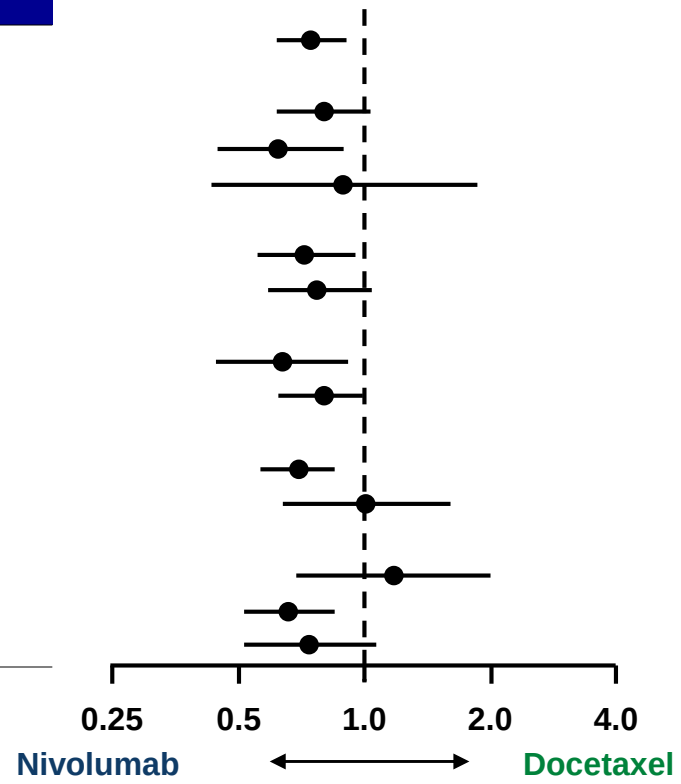


Symbols represent censored observations.

Borghaei H et al NEJM 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)



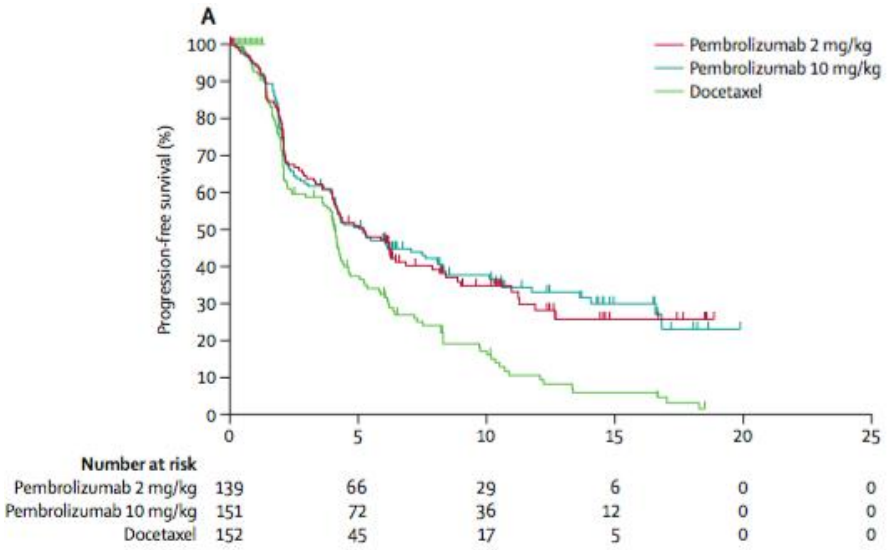
All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

Borghaei H et al NEJM 2015

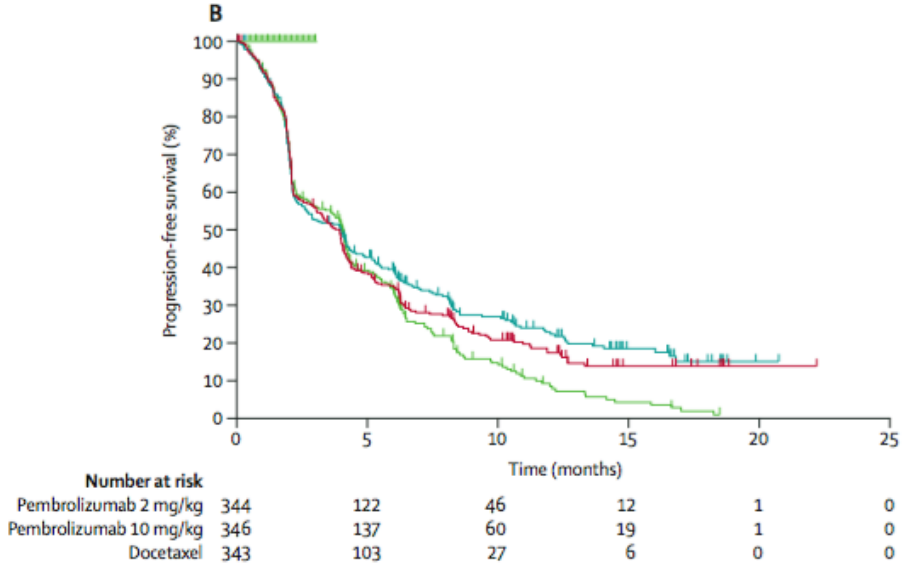
Pembrolizumab versus docetaxel in pretreated NSCLC with PD-L1 expression

PFS results of the KEYNOTE 010 trial

PD-L1 score 50% or greater



Study population

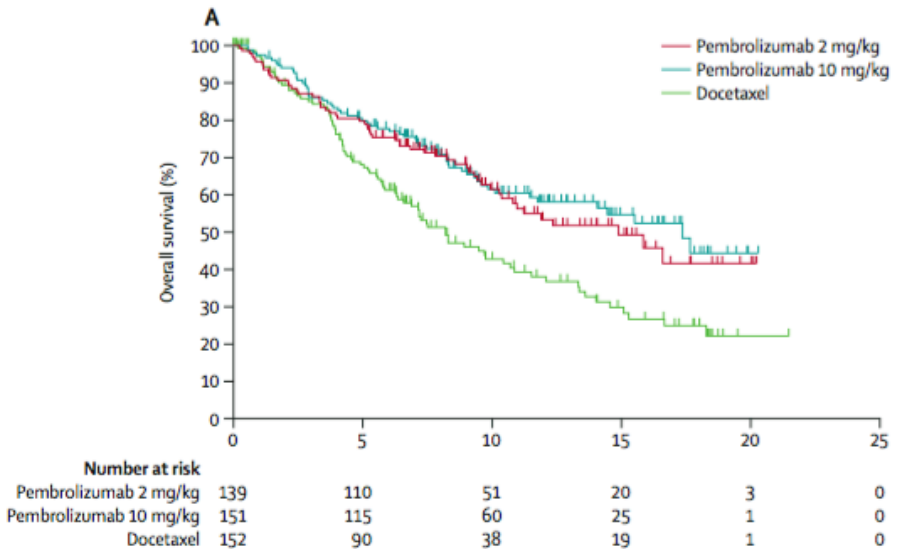


Herbst R et al, Lancet 2015

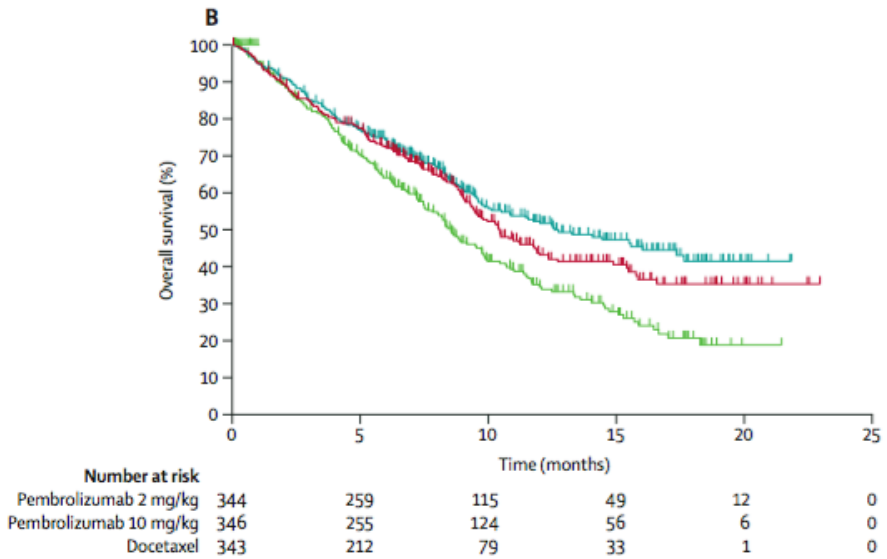
Pembrolizumab versus docetaxel in pretreated NSCLC with PD-L1 expression

Survival results of the KEYNOTE 010 trial

PD-L1 score 50% or greater

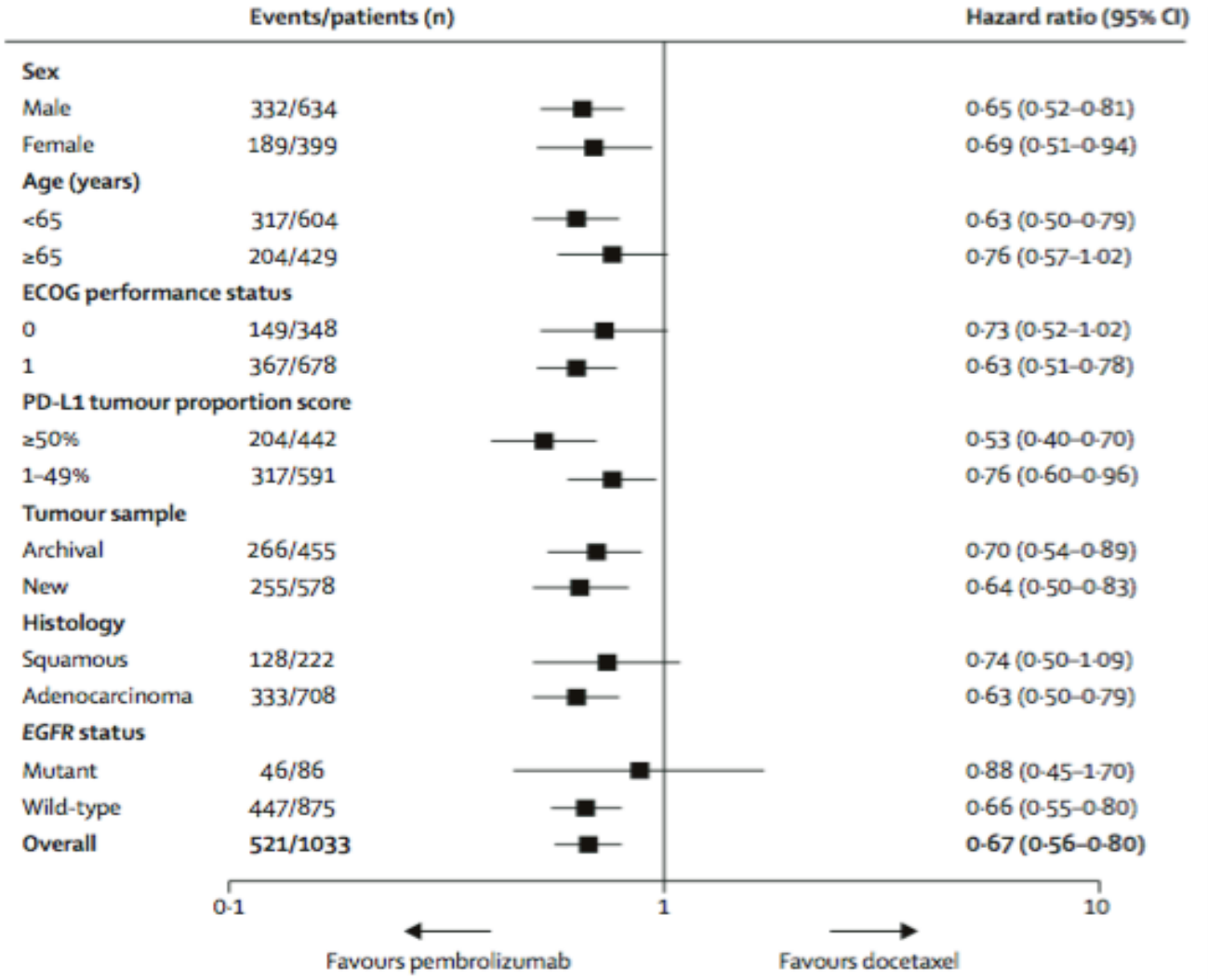


Study population



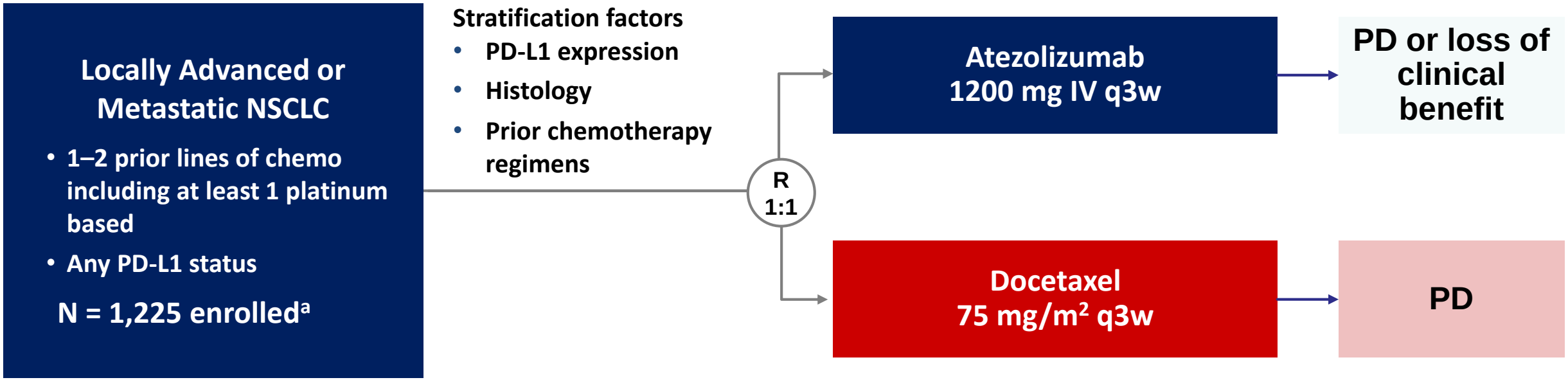
Herbst R et al, Lancet 2015

Survival superiority for pembrolizumab in all subgroups



Herbst R et al, Lancet 2015

OAK study design



Primary Endpoints (first 850 enrolled patients):

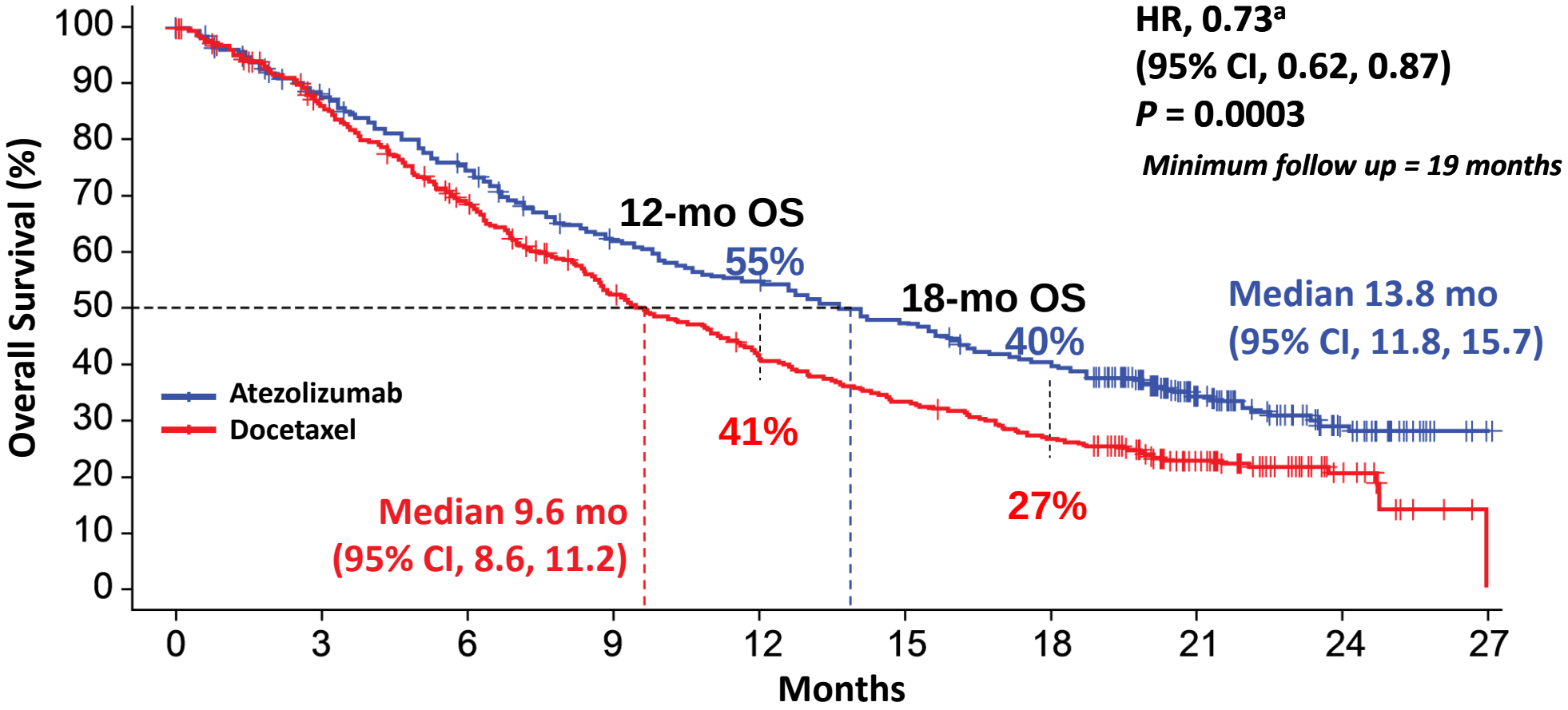
- **OS in the ITT population**
- **OS in patients with PD-L1 expression on ≥ 1% TC or IC**

Secondary Endpoints: ORR, PFS, DoR, Safety

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
TC, tumor cells; IC, tumor-infiltrating immune cells.

Barlesi et al. ESMO 2016

Overall survival, ITT (n = 850)



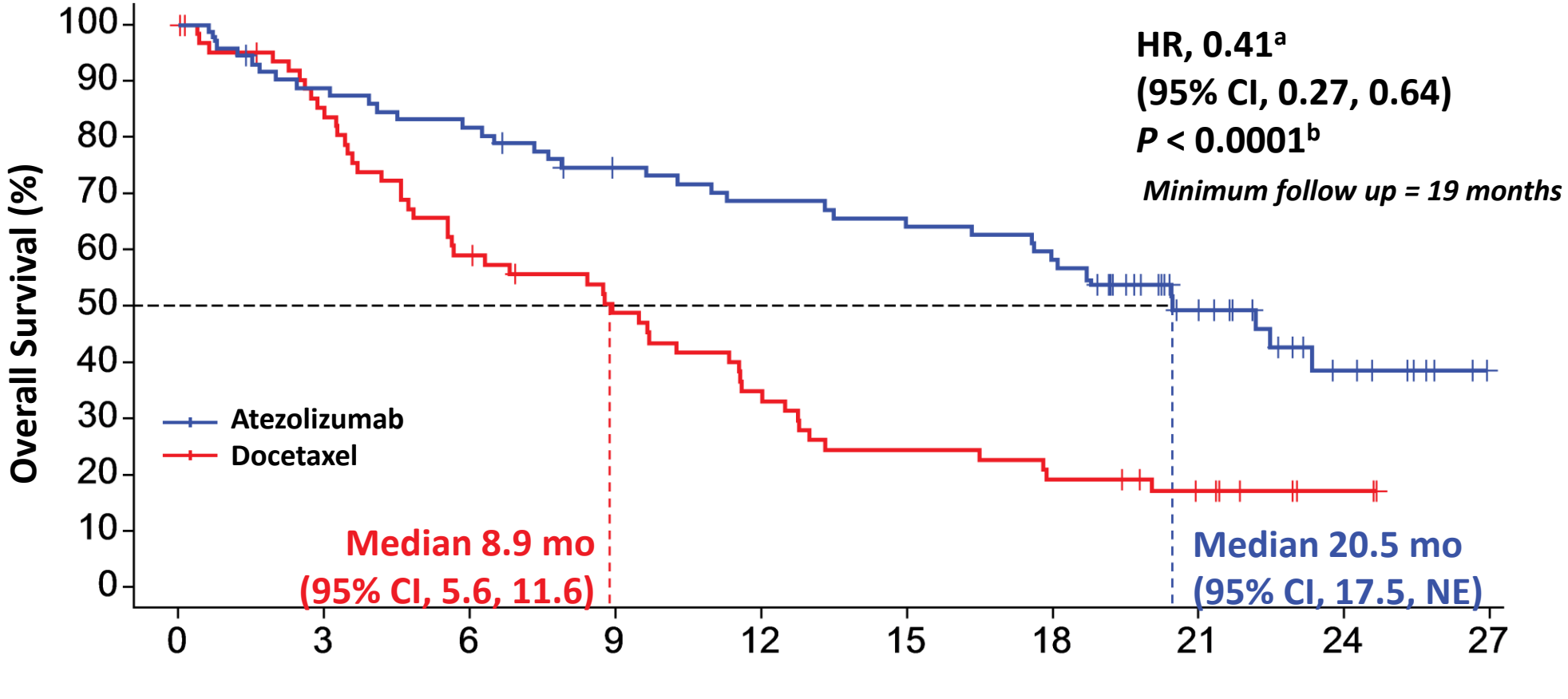
No. at Risk																										
Atezolizumab	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

[a]Stratified HR.

Barlesi et al. ESMO 2016

OS, PD-L1 expression on ≥ 50% TC or ≥ 10% IC

TC3 or IC3; 16% of patients



No. at Risk																									
Atezolizumab	72	69	65	63	61	59	58	55	51	50	49	47	46	46	44	43	43	42	39	34	28	19	16	11	8	6	2
Docetaxel	65	59	57	51	45	40	36	32	32	28	25	24	20	15	14	14	14	13	11	11	9	7	4	3	2		

[a]Unstratified HR.

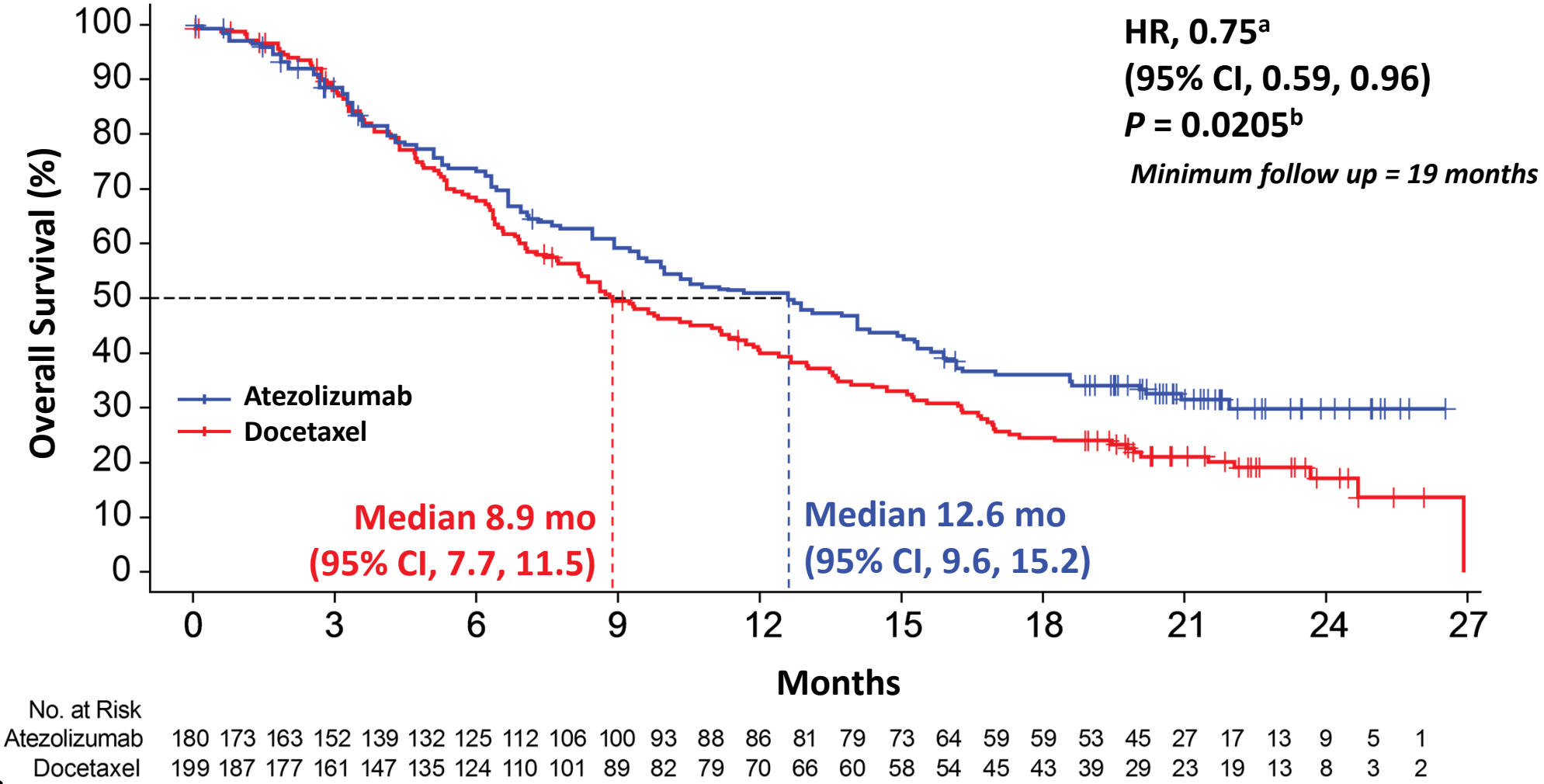
[b]*P* values for descriptive purpose only.

TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Barlesi et al. ESMO 2016

OS, PD-L1 expression on < 1% TC and IC

TC0 and IC0; 45% of patients



[a]Unstratified HR.

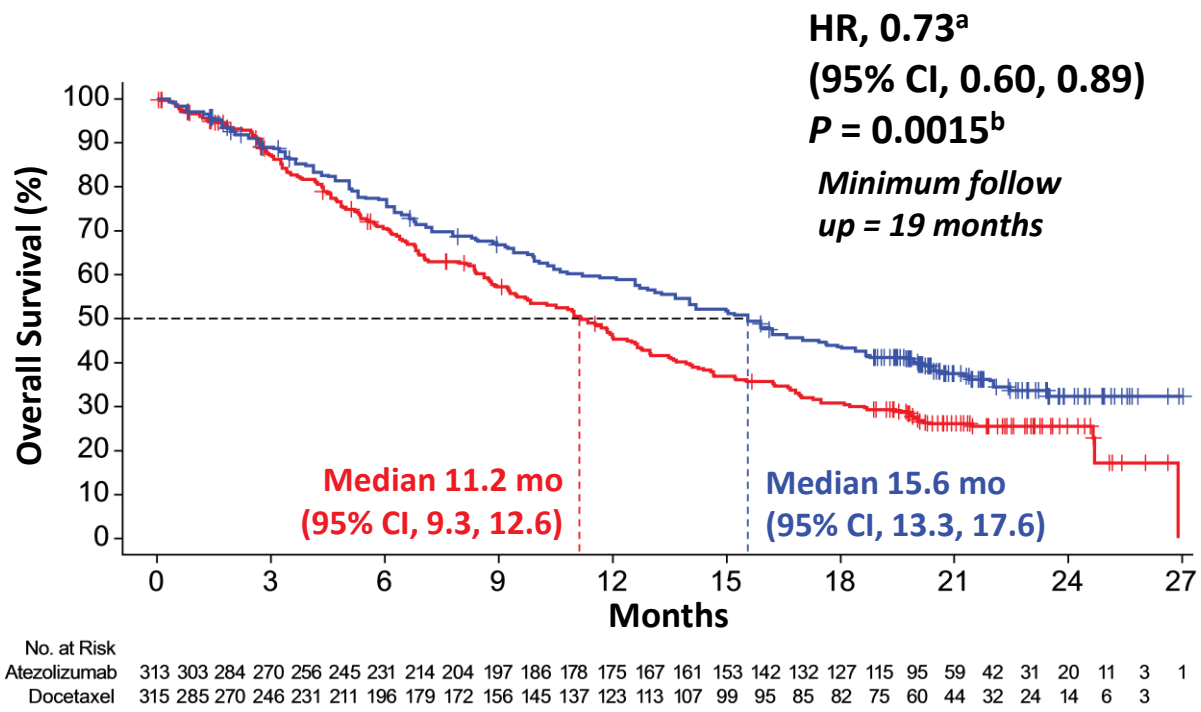
[b]*P* values for descriptive purpose only.

TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

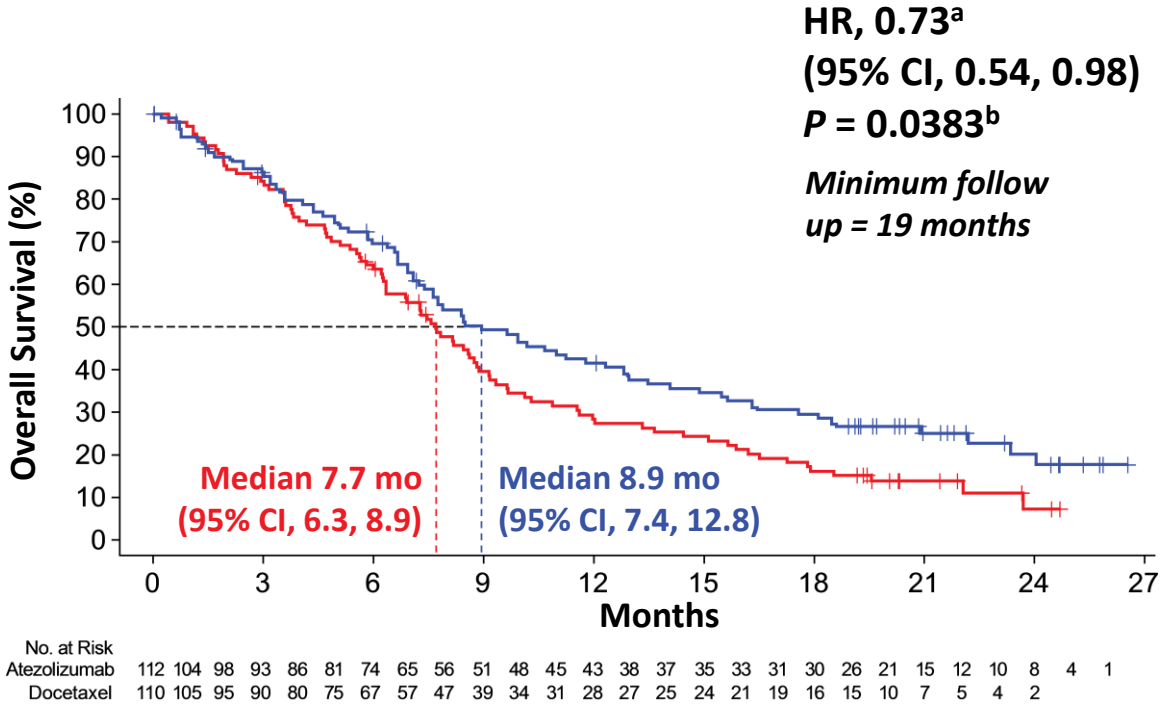
Barlesi et al. ESMO 2016

OS by histology

Non-squamous



Squamous



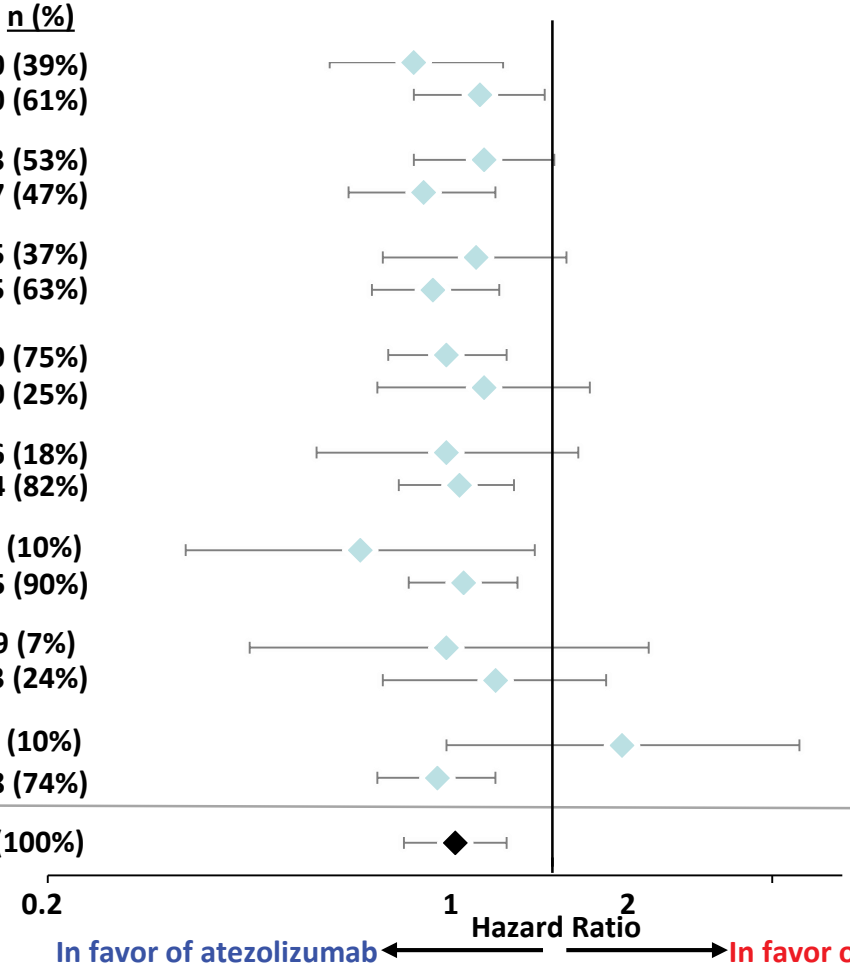
[a]Unstratified HRs.
[b]*P* values for descriptive purpose only.
Histology information from eCRF.
OS, overall survival.

Atezolizumab
Docetaxel

Barlesi et al. ESMO 2016

Overall survival in selected subgroups in OAK trial

Subgroup	n (%)	HR[a]	Median OS, mo Atezolizumab n = 425	Median OS, mo Docetaxel n = 425
Female	330 (39%)	0.64	16.2	11.2
Male	520 (61%)	0.79	12.6	9.2
< 65 years	453 (53%)	0.80	13.2	10.5
≥ 65 years	397 (47%)	0.66	14.1	9.2
ECOG PS 0	315 (37%)	0.78	17.6	15.2
ECOG PS 1	535 (63%)	0.68	10.6	7.6
1 prior therapy	640 (75%)	0.71	12.8	9.1
2 prior therapies	210 (25%)	0.80	15.2	12.0
Never smokers	156 (18%)	0.71	16.3	12.6
Current/previous smokers	694 (82%)	0.74	13.2	9.3
CNS mets	85 (10%)	0.54	20.1	11.9
No CNS mets	765 (90%)	0.75	13.0	9.4
KRAS mutant	59 (7%)	0.71	17.2	10.5
KRAS wildtype	203 (24%)	0.83	13.8	11.3
EGFR mutant	85 (10%)	1.24	10.5	16.2
EGFR wildtype	628 (74%)	0.69	15.3	9.5
ITT	850 (100%)	0.73	13.8	9.6



[a]Stratified HR for ITT. Unstratified HR for subgroups.

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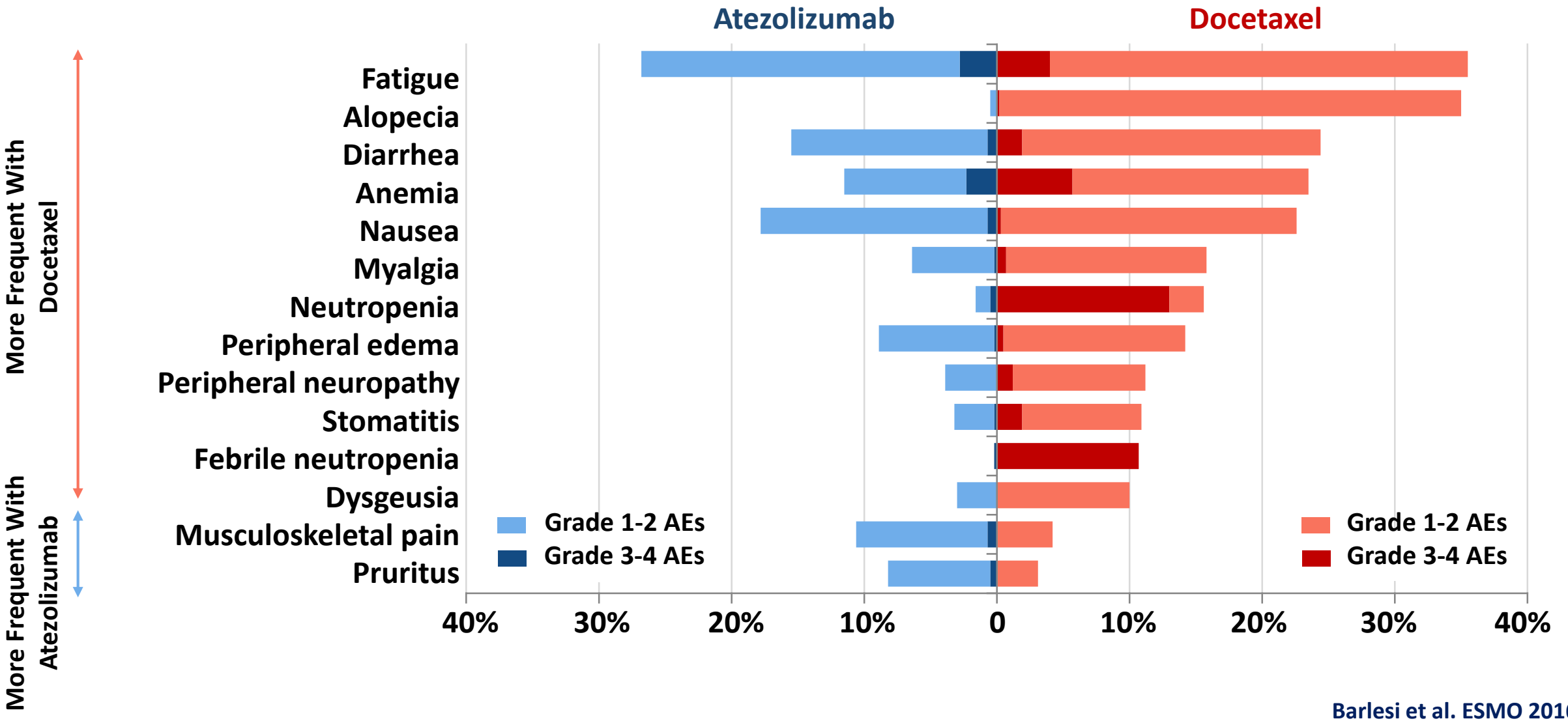
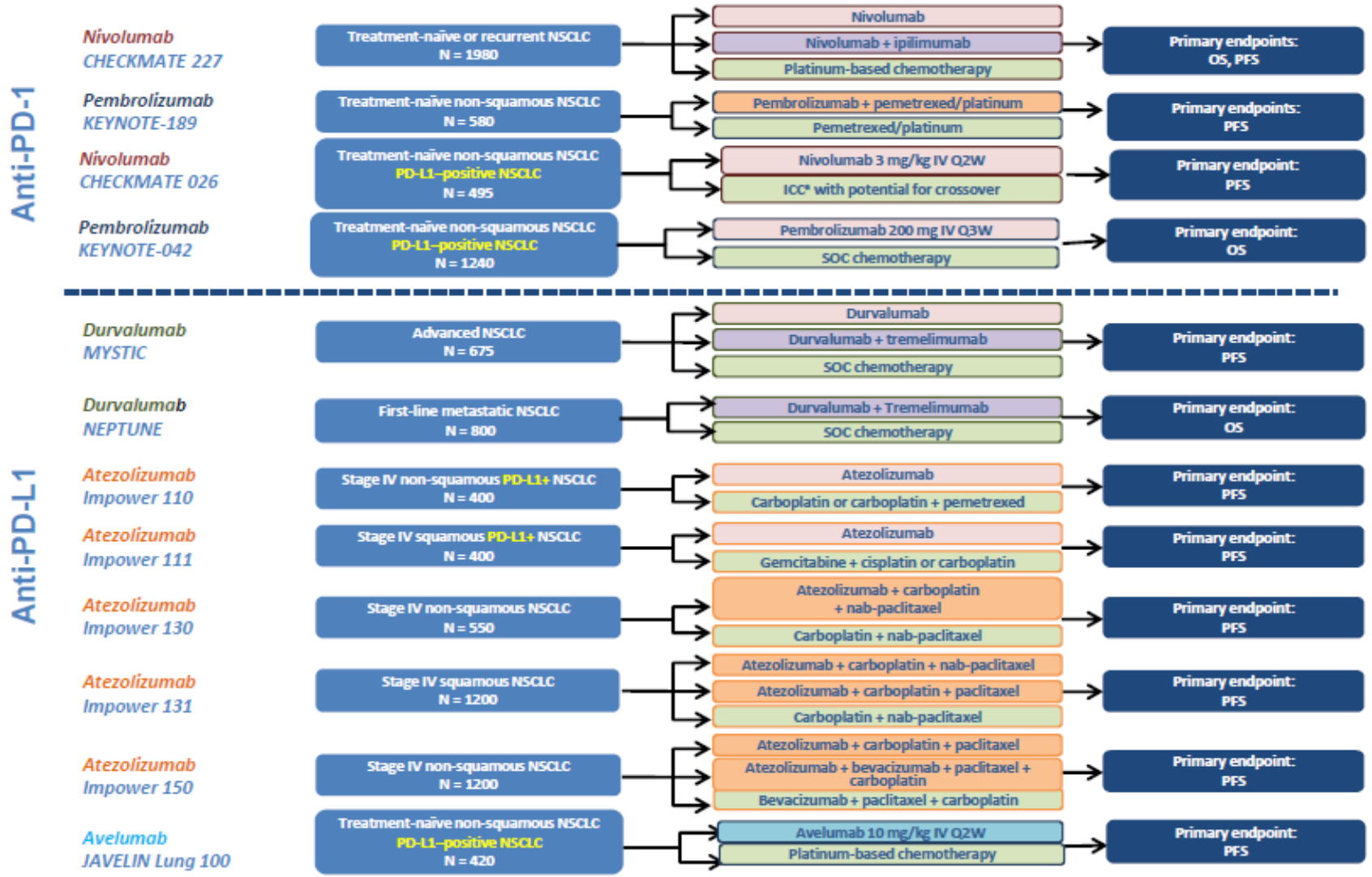
All cause Aes

>5% difference between arms



Barlesi et al. ESMO 2016

Ph. III Anti-PD1/PD-L1 combination trials in first line advanced NSCLC



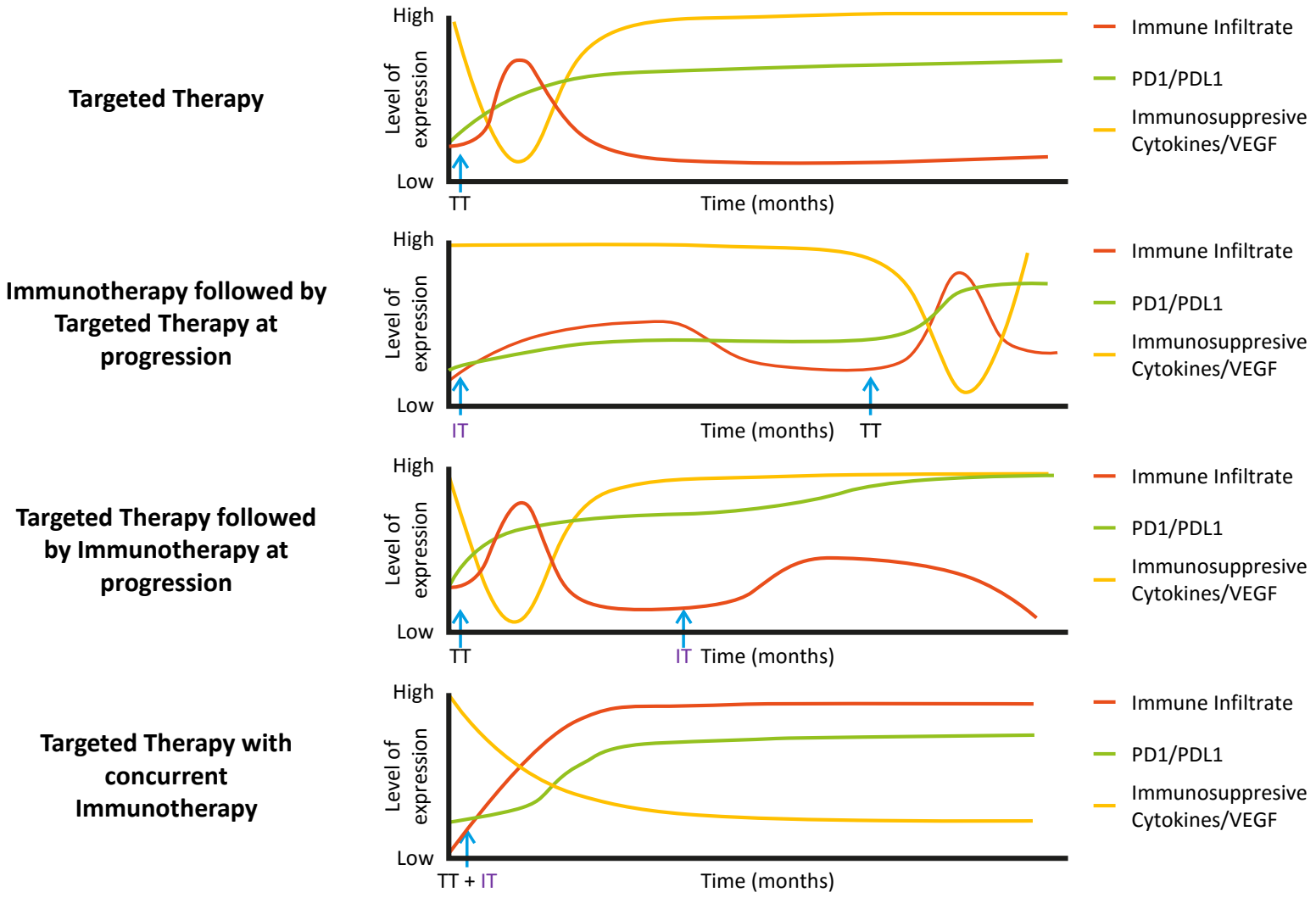
First-line combination studies with anti-PDL1/PD1 therapy

Combinations with chemotherapy | **Immune doublets**

	GP28328[1] PhIb solid tumours (incl. 1L NSCLC) Atezolizumab + chemotherapy (n=58)			KEYNOTE-021[2,3] PhI/II 1L NSCLC Cohort G: Chemotherapy ± pembrolizumab (n=123)		CheckMate 012[4] PhI 1L NSCLC Nivolumab (N) + chemotherapy (n=56)				CheckMate 012[5,6] PhI 1L NSCLC Nivolumab (N) + ipilimumab (I) (n=49)			
	Atezo + carbo + pac	*Atezo + carbo + pem*	*Atezo + carbo + nab-pac*	*Carbo + pem*	*Pembro + carbo + pem*	*N10 + cis + gem*	*N10 + cis + pem*	*N10 + carbo + pac*	*N5 + carbo + pac*	*N1 q3w + I1 q3w*	*N1 q2w + I1 q6w*	*N3 q2w + I1 q12w*	*N3 q2w + I1 q6w*
N	8*	17*	16*	63	60	12	15	15	14	31	40	38	39
ORR, %	50	77	56	29	55	33	47	47	43	13	25	47	39
Grade 3–4 treatment-related AEs	*69%*			*23%*	*37%*	*45%*				29%	35%	37%	33%
	71%	*54%*	*85%*			*25%*	*47%*	*73%*	*29%*				

1. Giaccone, et al. ECC 2015; 2. Langer, et al. ESMO 2016; 3. Langer, et al. Lancet 2016;
4. Rizvi, et al. J Clin Oncol 2016; 5. Rizvi, et al. WCLC 2015; 6. Hellmann, et al. ASCO 2016

Combining immunotherapy with targeted therapies



Wargo J, et al. Cancer Discov 2014

TATTON: Osimertinib + durvalumab arm

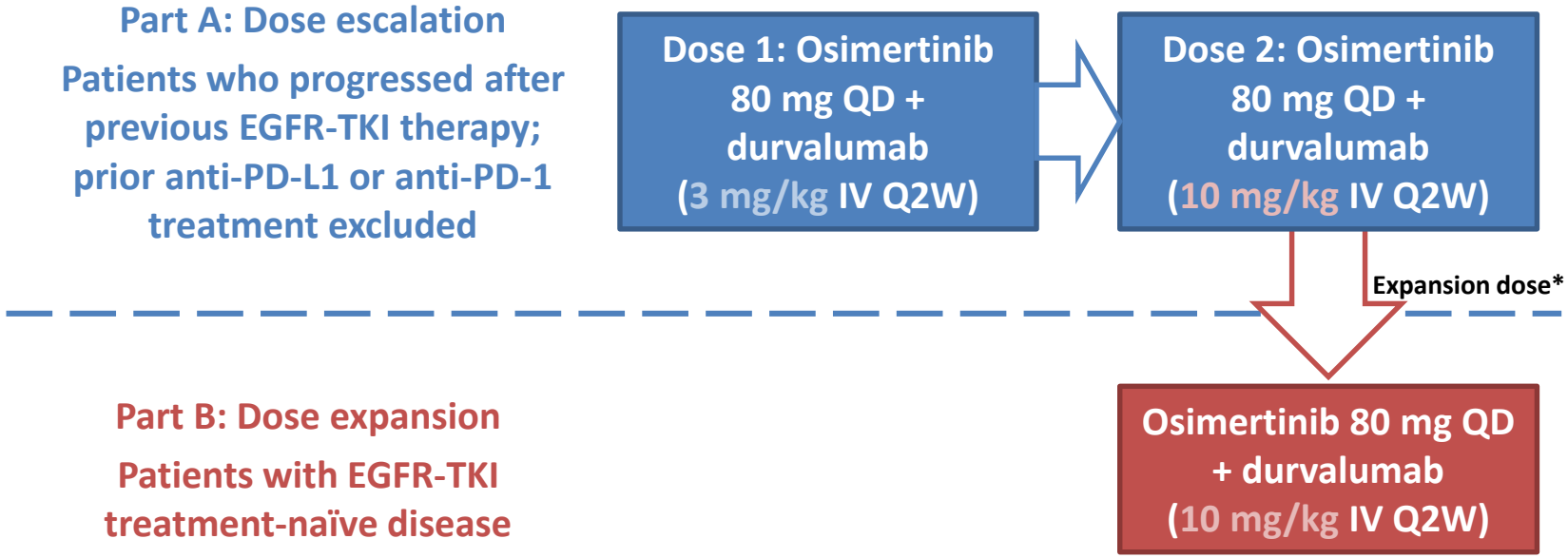
Primary objective: safety and tolerability

Treatment location: Asia and USA

Key inclusion criteria: EGFRm NSCLC; adequate performance status and organ function

Key exclusion criteria: History of ILD; live vaccine or immunosuppressants within 1 month

Data cut-off: 13 November 2015

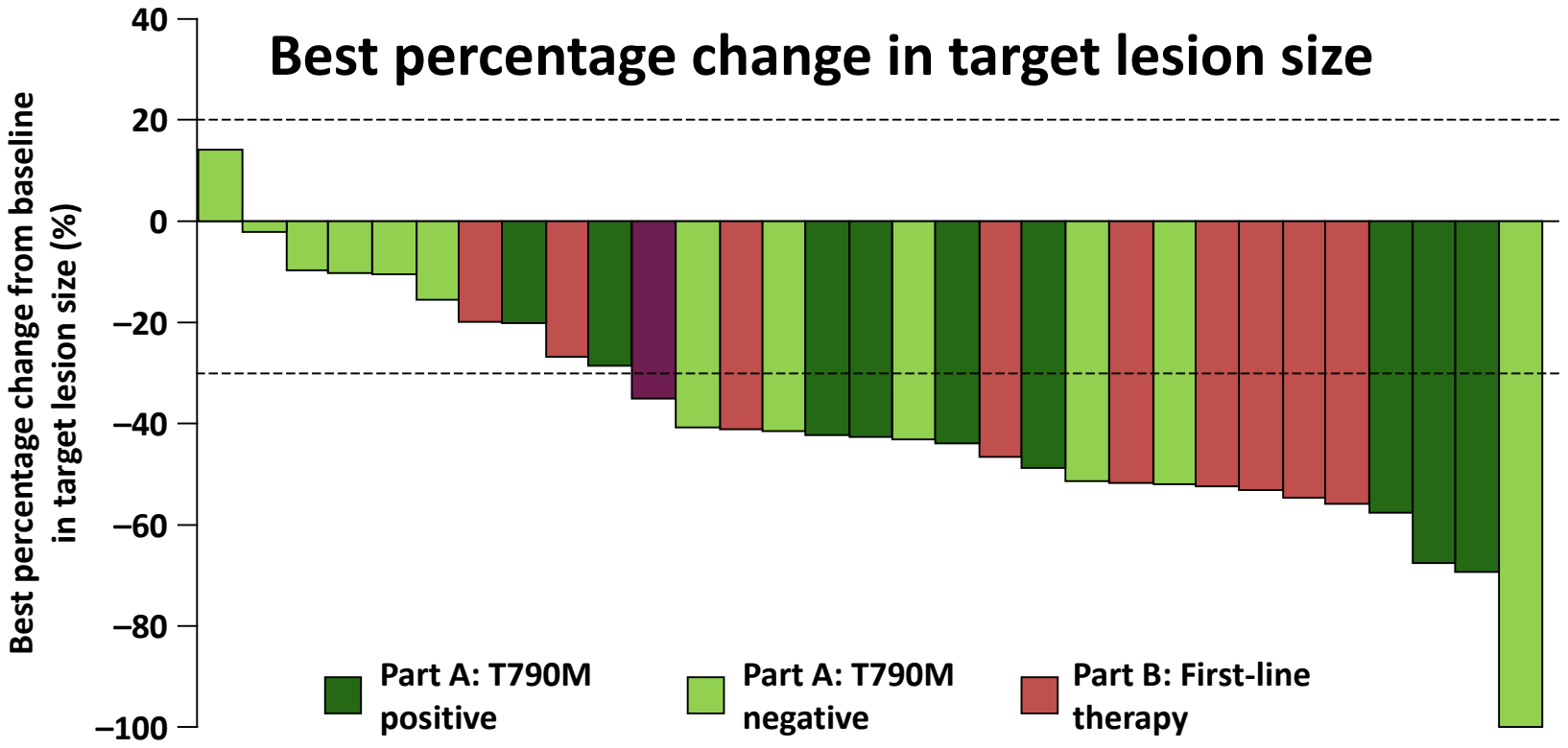


*Part B combination dose chosen based on preliminary signal of clinical efficacy and an acceptable safety and tolerability profile

ILD, interstitial lung disease; IV, intravenous; QD, once daily; Q2W, once every two weeks

Myung-Ju Ahn, et al. ELCC 2016

Tumour response to osimertinib + durvalumab



Population: evaluable for response set; data cut off: 13 Nov 2015

ORR, objective response rate

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All-causality adverse events

AE by preferred term, occurring in >3 patients at any dose, n	Part A				Part B	
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Rash (grouped terms)	5	1	6	0	7	0
ILD (grouped terms)	2	1	4	1	7*	3
Diarrhoea	3	0	3	0	5	0
Pyrexia	2	0	2	0	4	0
Stomatitis	1	0	1	0	4	0
Nausea	3	0	5	0	3	0
Anaemia	4	0	4	1	1	0
Vomiting	7	1	2	0	0	0
Decreased appetite	3	1	4	0	1	0

*One patient reported ILD following 13 Nov 2015 data cut off

ILD, interstitial lung disease; IV, intravenous; ORR, objective response rate;
QD, once daily; Q2W, once every two weeks

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Conclusions

- **Landscape of NSCLC therapy is rapidly evolving**
- **Immunotherapy is now the standard therapy for *EGFR*^{wt}, *ALK*^{wt} NSCLC in second line irrespective of clinical or biological characteristics.**
- **Immunotherapy is replacing chemotherapy in first-line setting in PD-L1 expressing NSCLC**
- **New combination strategies are under investigation**