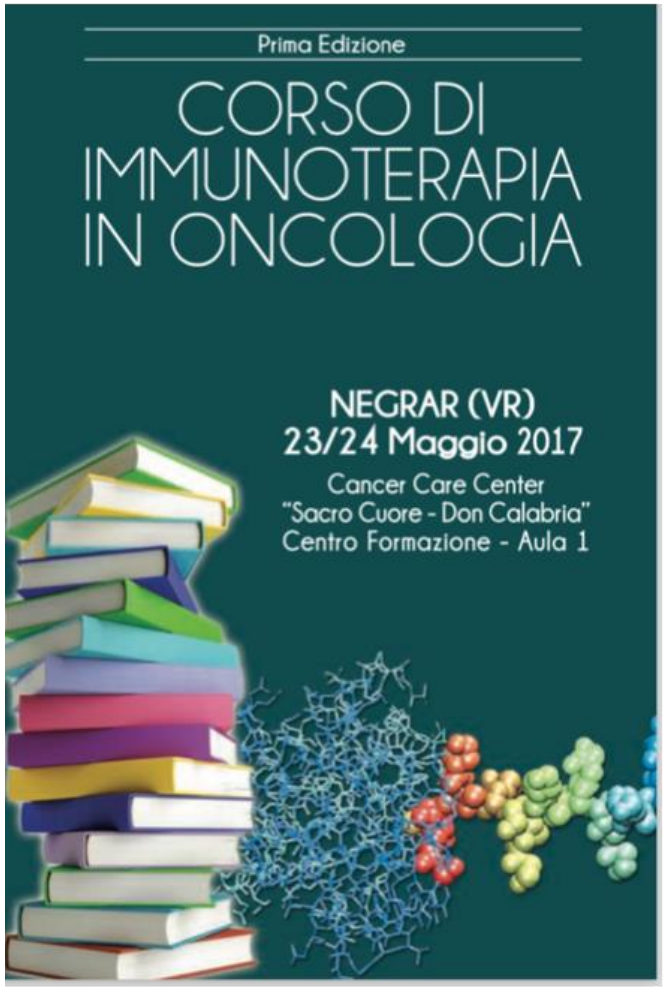
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

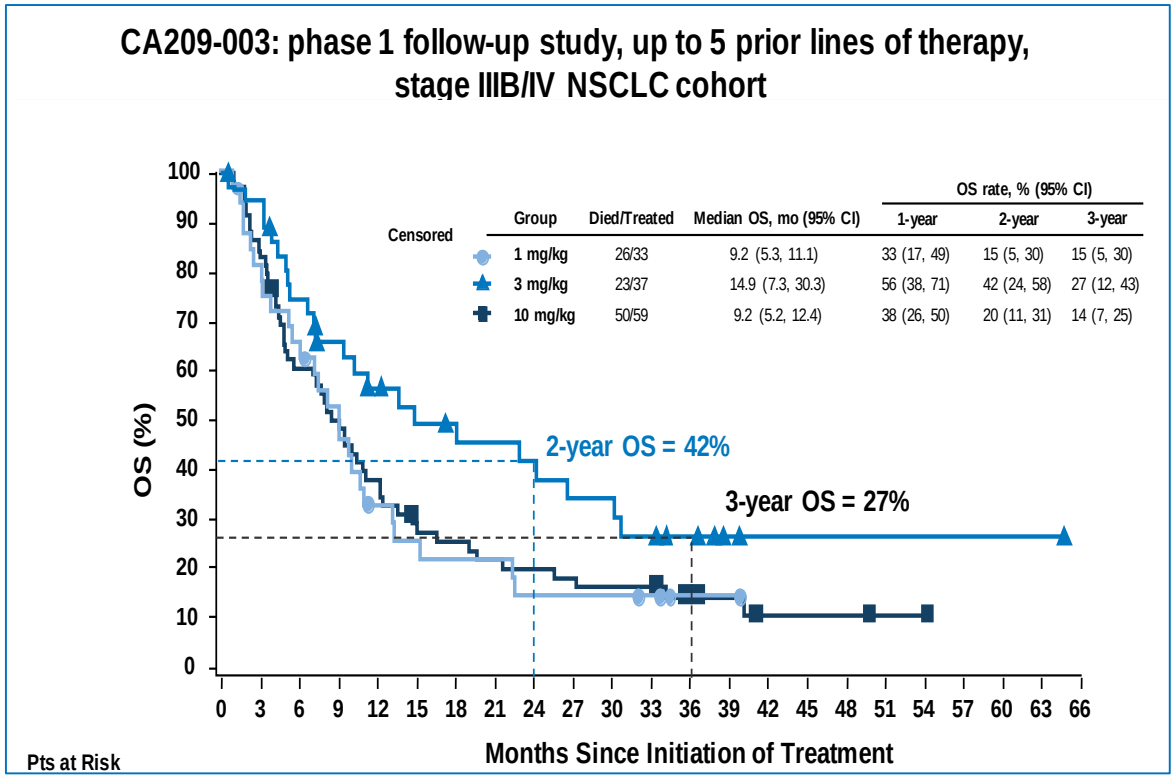


Checkpoint inhibitors as the new standard of care in the II line setting of NSCLC

Chiara Bennati
AUSL della Romagna
Ravenna, Italy

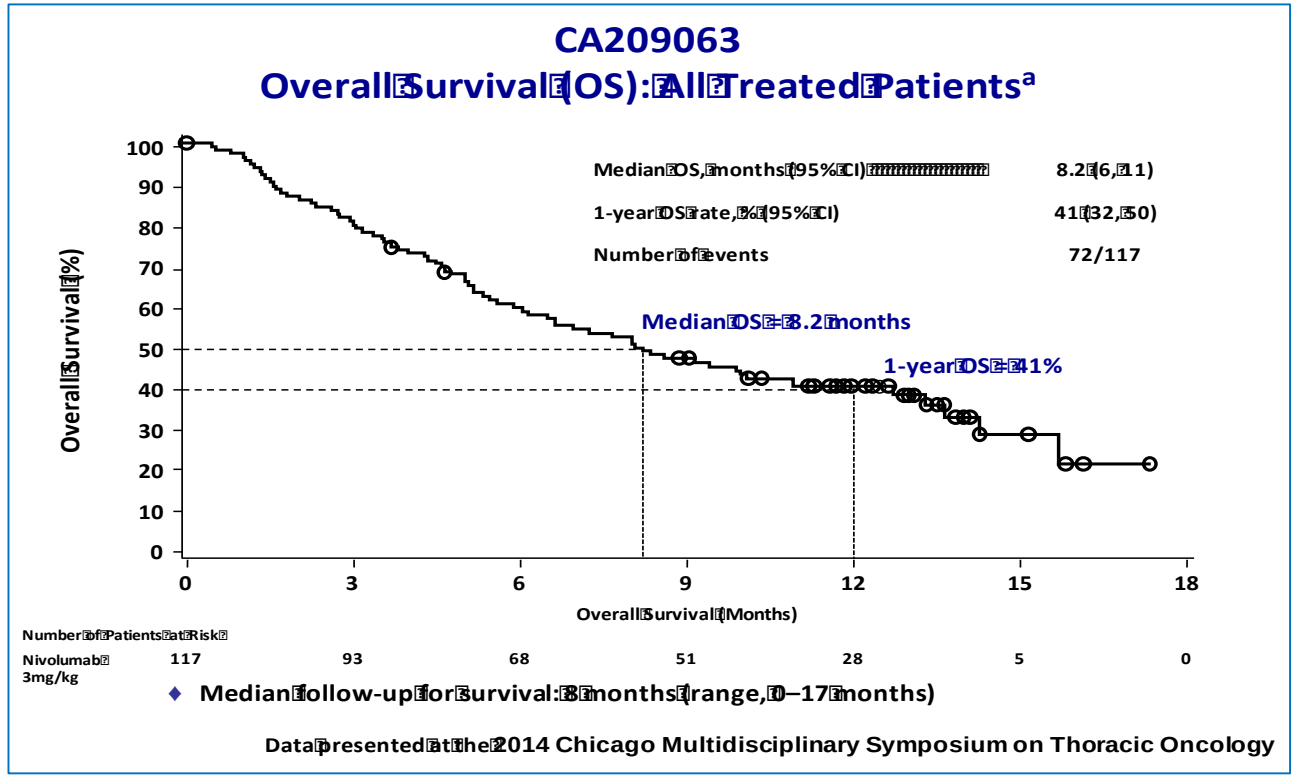
Early studies suggested superiority of immunotherapy versus standard of care in pretreated NSCLC

Nivolumab in all comers



- 54% receiving ≥3 prior therapies
- 57% non-squamous histology

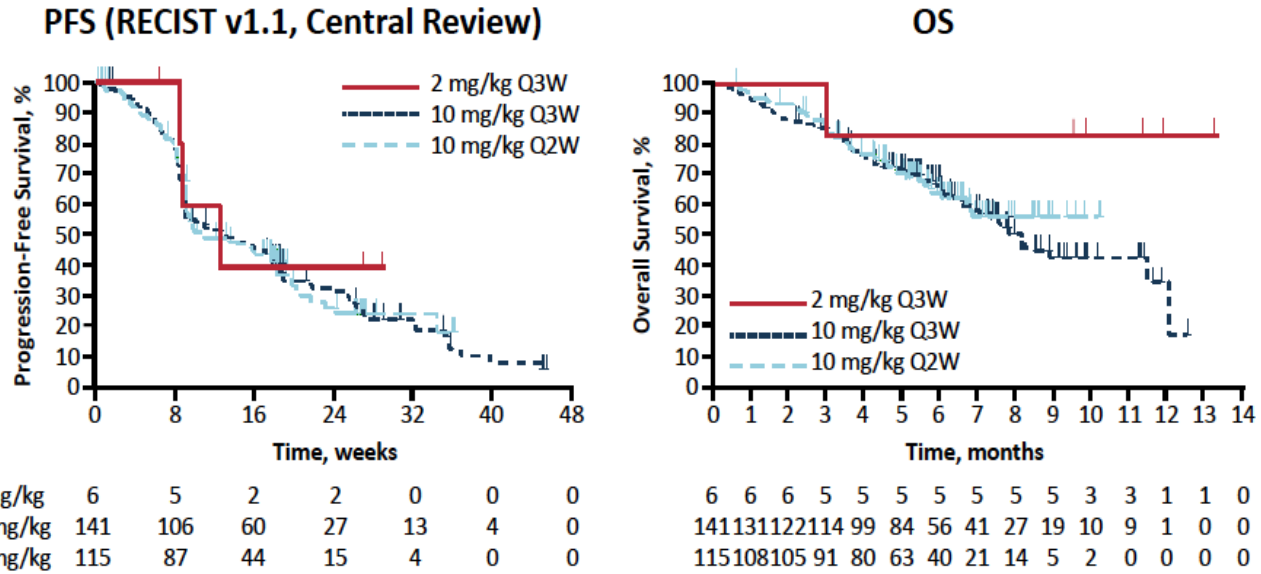
Nivolumab in squamous



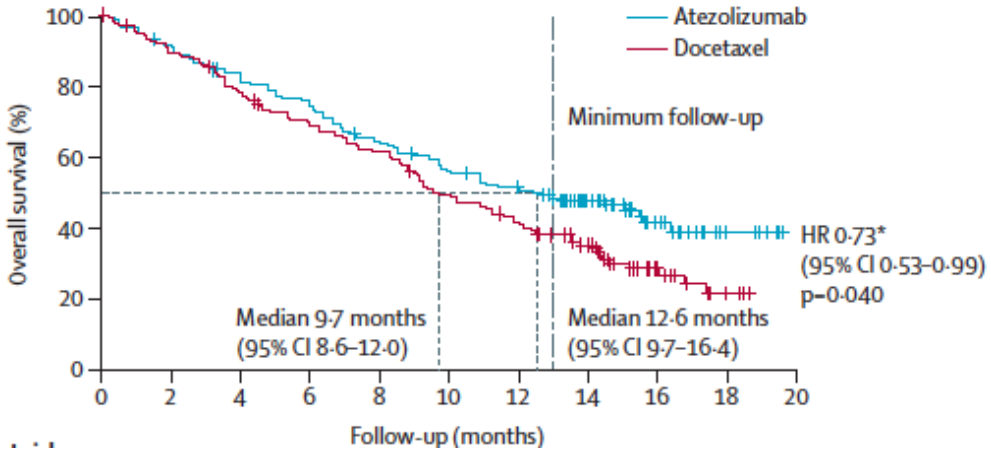
- ≥2 prior systemic therapies

Early studies suggested superiority of immunotherapy versus standard of care in pretreated NSCLC

Pembrolizumab



Atezolizumab



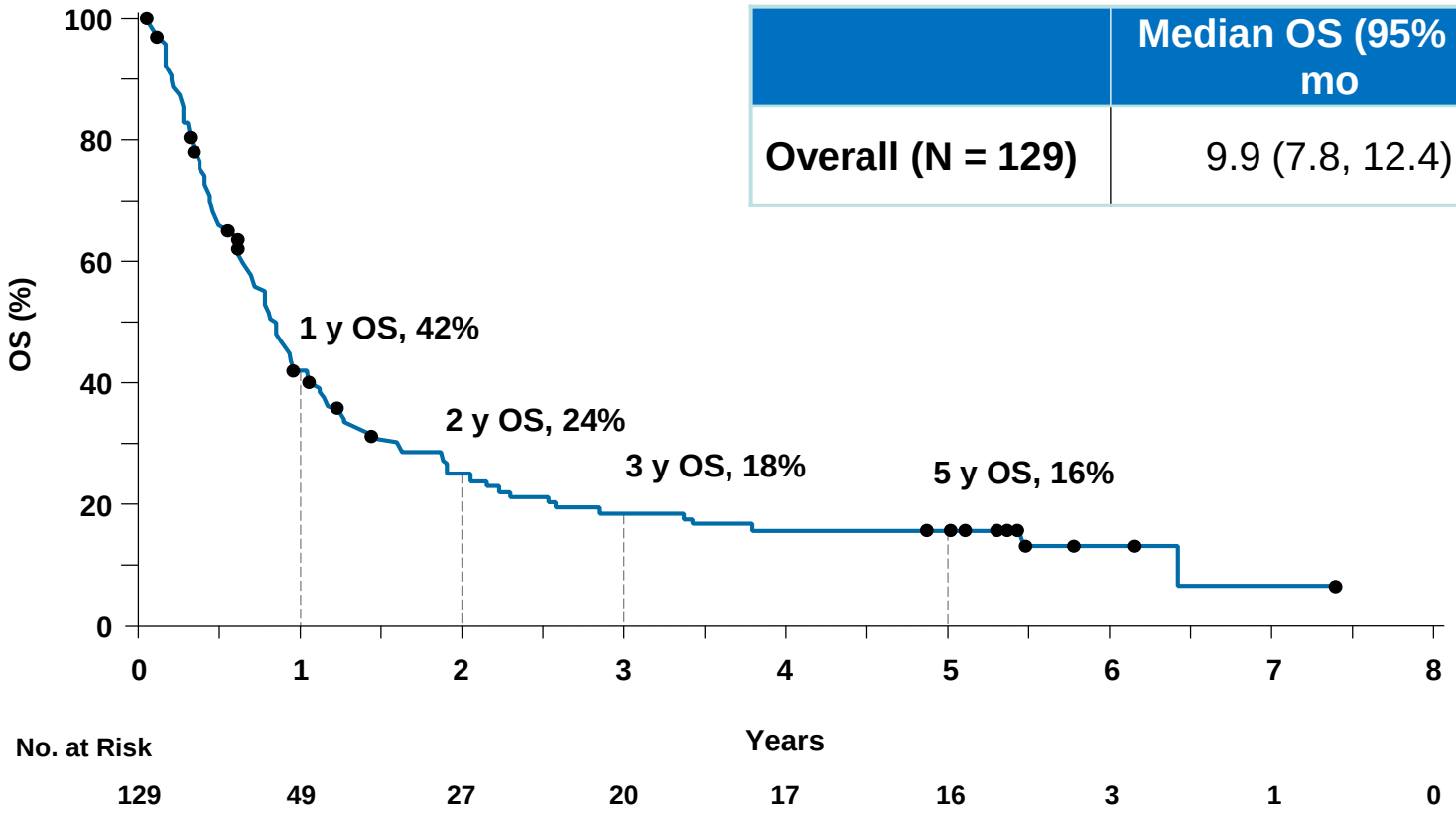
Activity of second line therapy was low in NSCLC

	Docetaxel	Pemetrexed	Erlotinib
Objective RR, %	5.0-12.0	7.1-11.8	7.9-9.0
Median PFS, months	2.0-3.1	2.6-2.9	2.2-3.6
Median OS, months	5.7-8.0	6.7-8.9	6.7-7.9
1-YS, %	28.7-37.0	29.7-38.5	31.0-35.7

Shepherd FA, JCO 2000; Fossella FV, JCO 2000; Ramlau R, JCO 2006; Paz-Ares L, BJC 2008; Kim ES, Lancet 2008; Krzakowski M, JCO 2010; Hanna N, JCO 2004; Cullen MH, Ann Oncol 2010; Shepherd FA, NEJM 2005; Ciuleanu T, Lancet Oncol 2012

5-Year Estimates of OS[a]

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

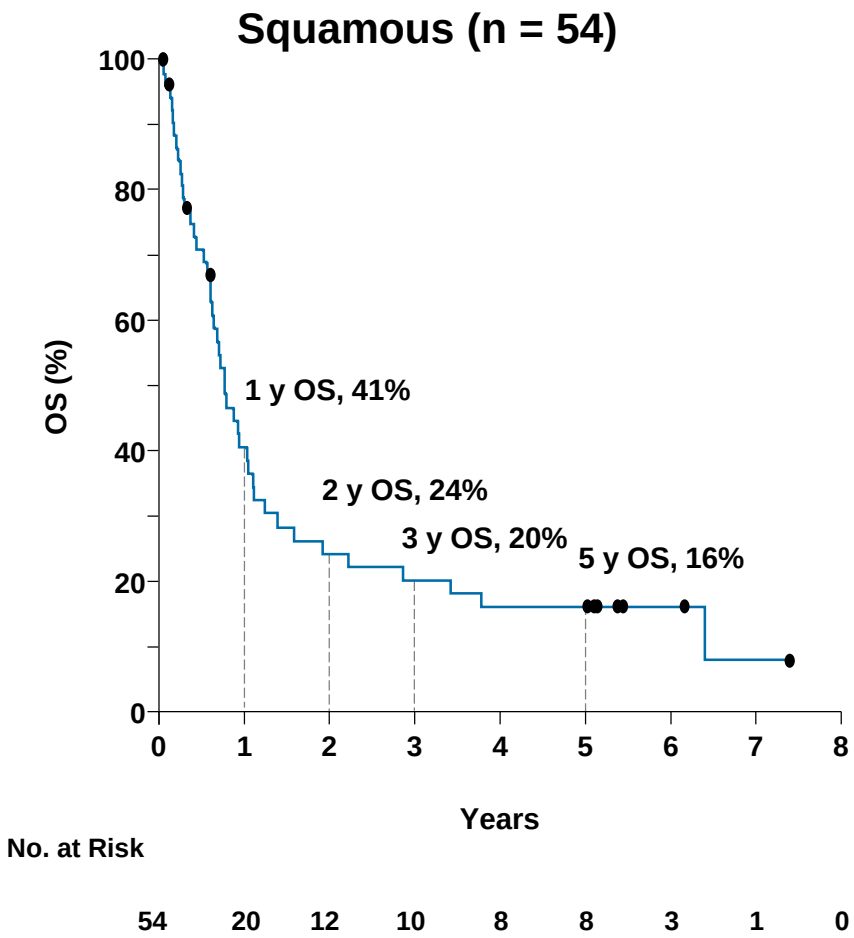


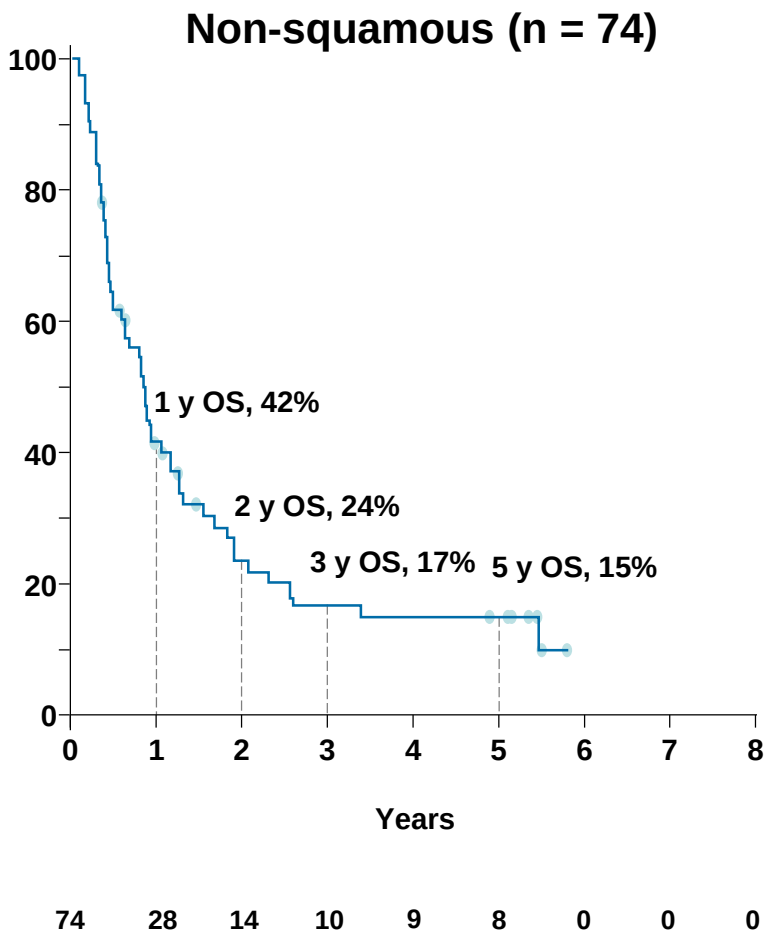
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

5-Year Estimates of OS by Histology

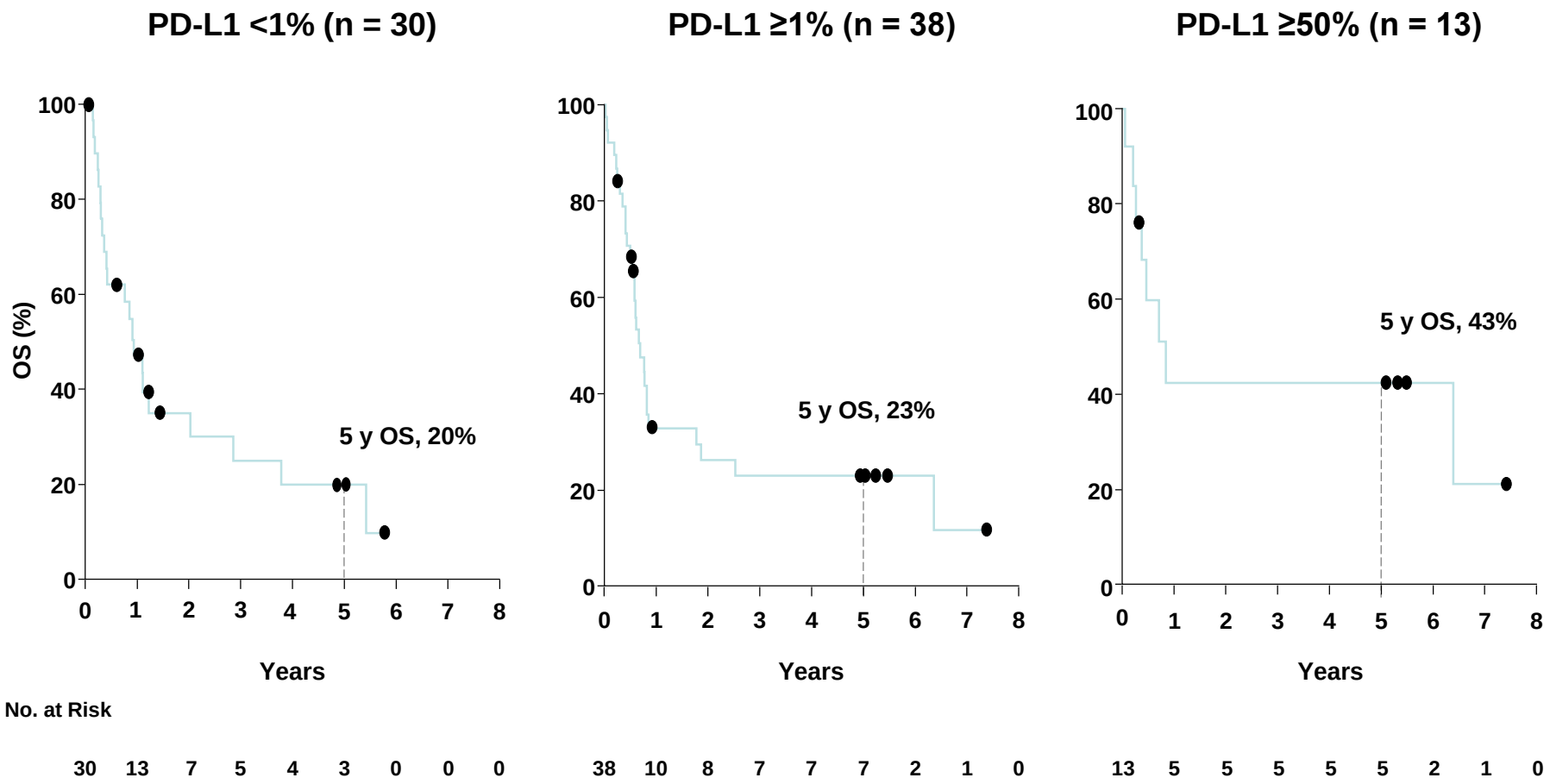
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC





5-Year Estimates of OS by PD-L1 Status[a]

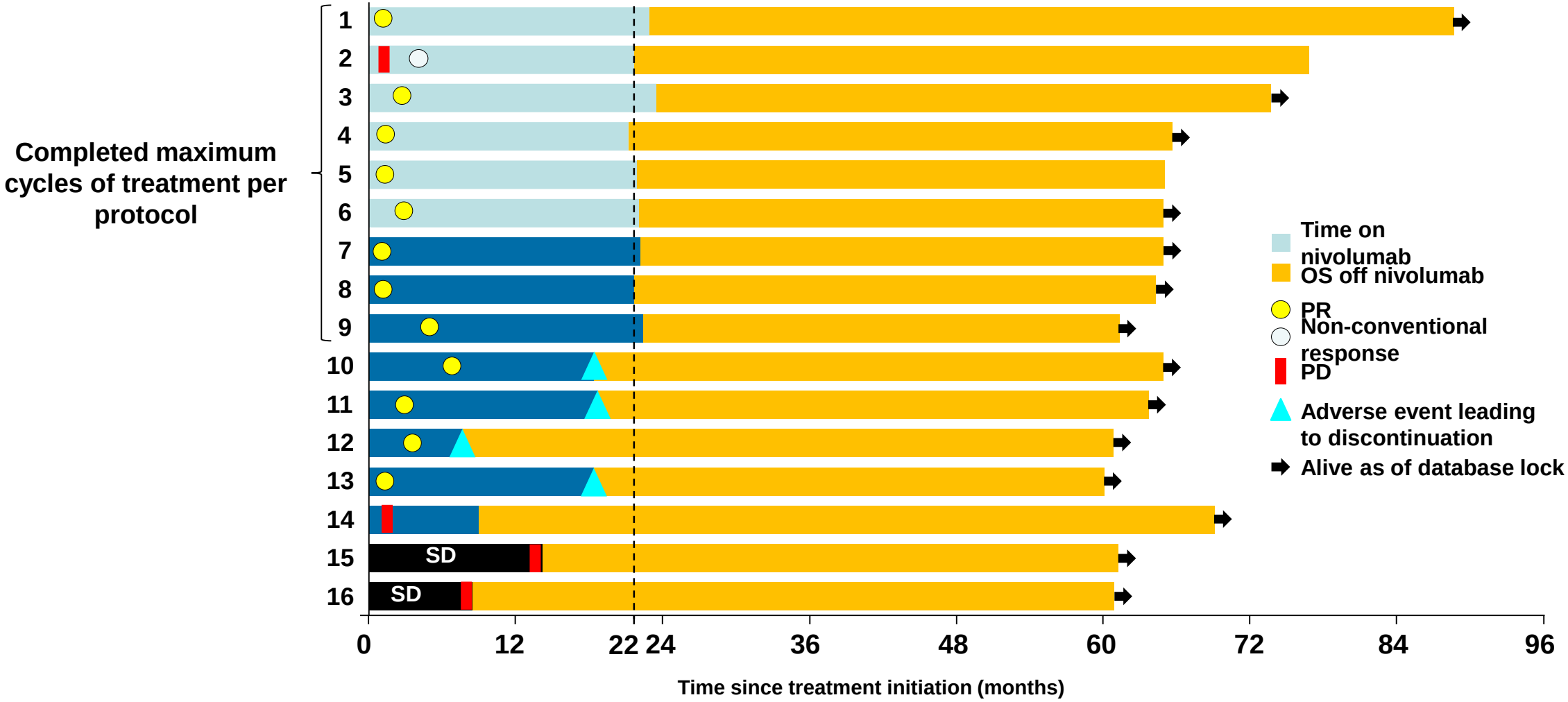
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



[a]PD-L1 status was not evaluable in 61 (47%) of 129 patients; the estimated 5-y OS rate in patients with unknown PD-L1 status was 10%

Outcomes of 5-Year Survivors (n = 16)

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



- 12 (75%) patients had a PR (including both early and late responses), 2 (12%) had SD, and 2 (12%) had PD as BOR
- One patient had a non-conventional response <2 months after initial progression

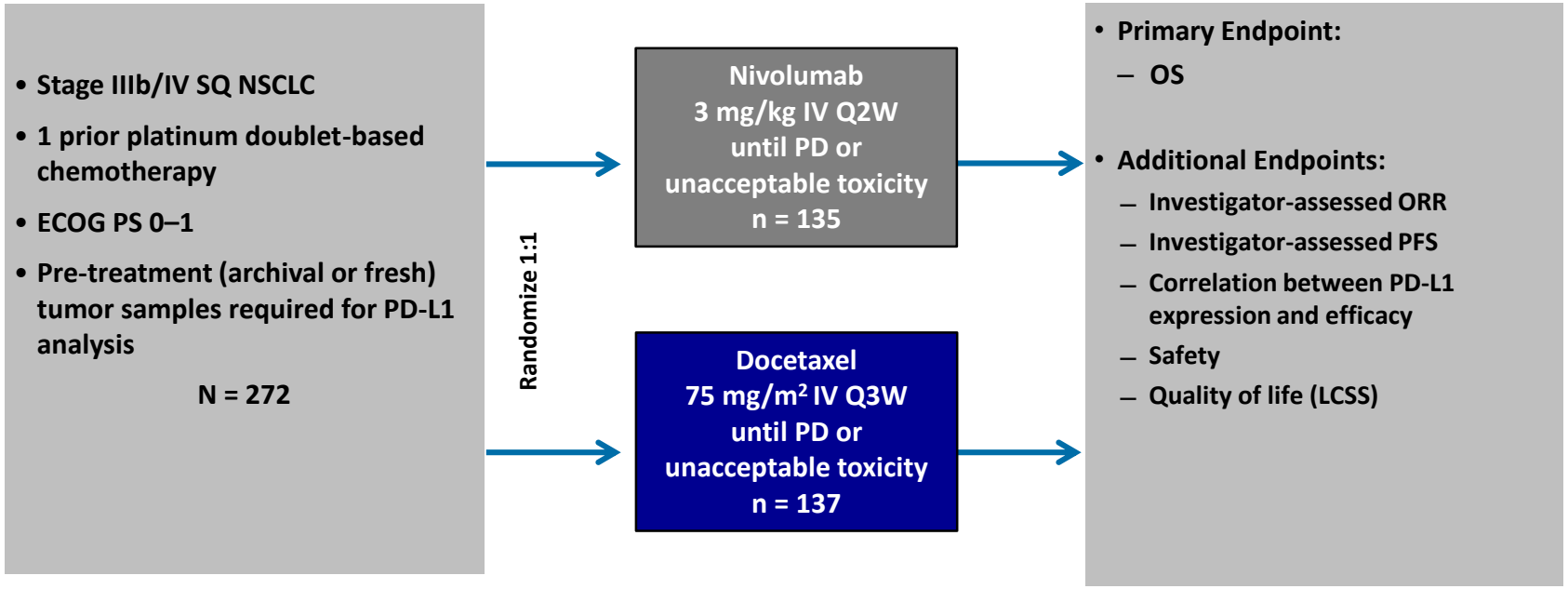
Summary of phase III studies of immunotherapy in previously treated patients

	CheckMate 017[1] Nivolumab vs docetaxel	CheckMate 057[1] Nivolumab vs docetaxel	KEYNOTE-010[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel	OAK[3] Atezolizumab vs docetaxel
Phase of study	**III**	**III**	**II/III**	**III**
PD-L1 selected	**No**	**No**	**Yes (TPS* ≥1%)**	**No**
Study size, n	**272 (135 vs 137)**	**582 (292 vs 290)**	**1,033 (344 vs 346 vs 343)**	**1,225 (425 vs 425)***
Histology	**Squamous**	**Non-squamous**	**All-comers**	**All-comers**
Line of therapy, %				
2L	**100**	**88**	**69**	**75**
3L	**0**	**11**	**20**	**25**
>3L	**0**	**<1**	**9**	**0**
Other/unknown	**0**	**0**	**<1**	**0**
Subsequent CIT (immunotherapy arm vs chemo arm), %	**<1 vs 2**	**1 vs 2**	**0.6 vs 1.7 vs 13.1**	**4.5 vs 17.2**
Crossover from chemo arm to study immunotherapy, %	**4**	**6**	**Not permitted**	**Not permitted**
Median OS, months	**9.2 vs 6.0**	**12.2 vs 9.5**	**10.4 vs 12.7 vs 8.5**	**13.8 vs 9.6**
HR vs docetaxel (p value)	**0.62 (p=0.0004)**	**0.75 (p<0.001)**	**2mg/kg: 0.71 (p=0.0008) 10mg/kg: 0.61 (p<0.0001)**	**0.73 (p=0.0003)**

*850 in primary population
NR = not reached

1. Borghaei, et al. ASCO 2016
2. Herbst, et al. Lancet 2015; 3. Barlesi, et al. ESMO 2016

CheckMate 017 (NCT01642004) - Study Design

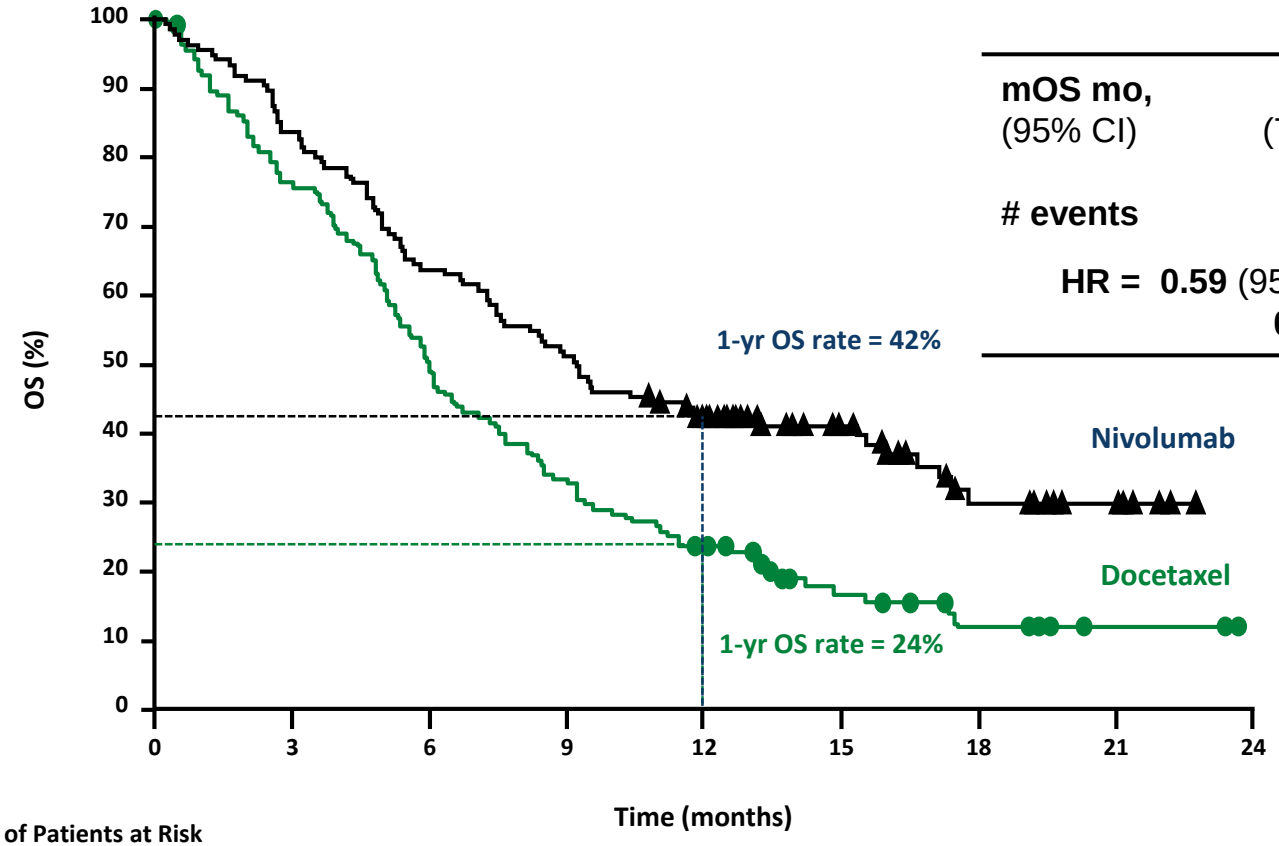


- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

Brahmer J, et al. NEJM 2015

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**

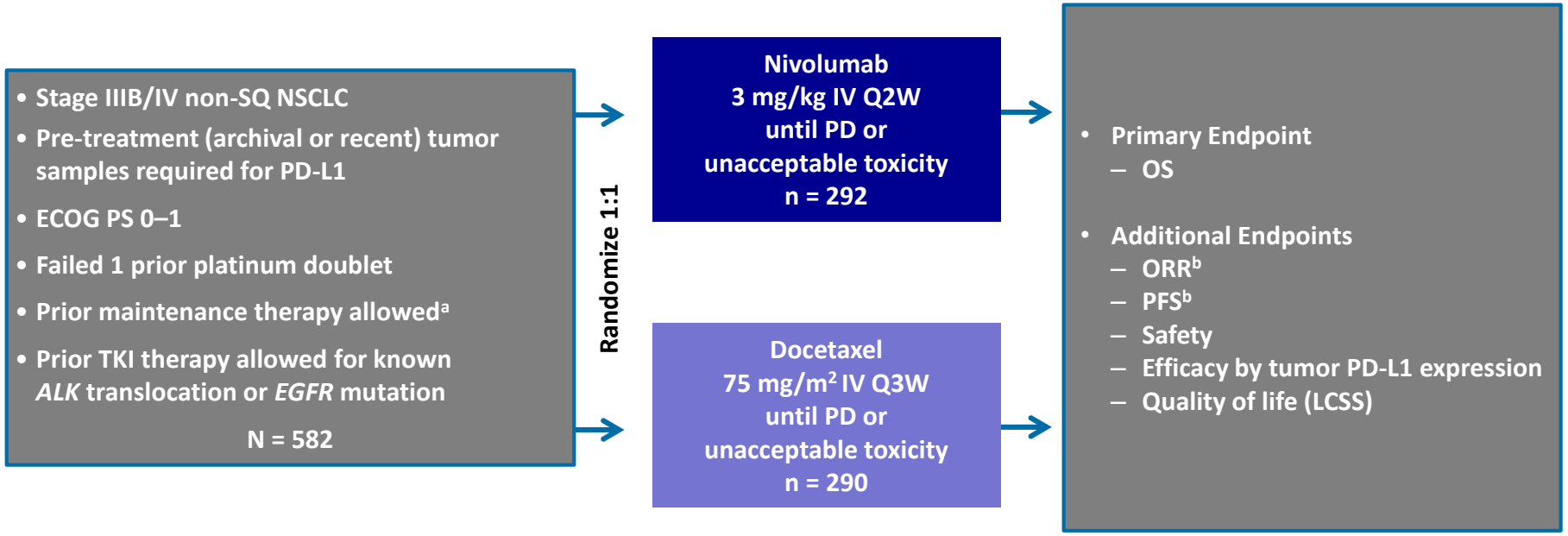
Number of Patients at Risk

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

CheckMate 057 (NCT01673867) Study Design



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

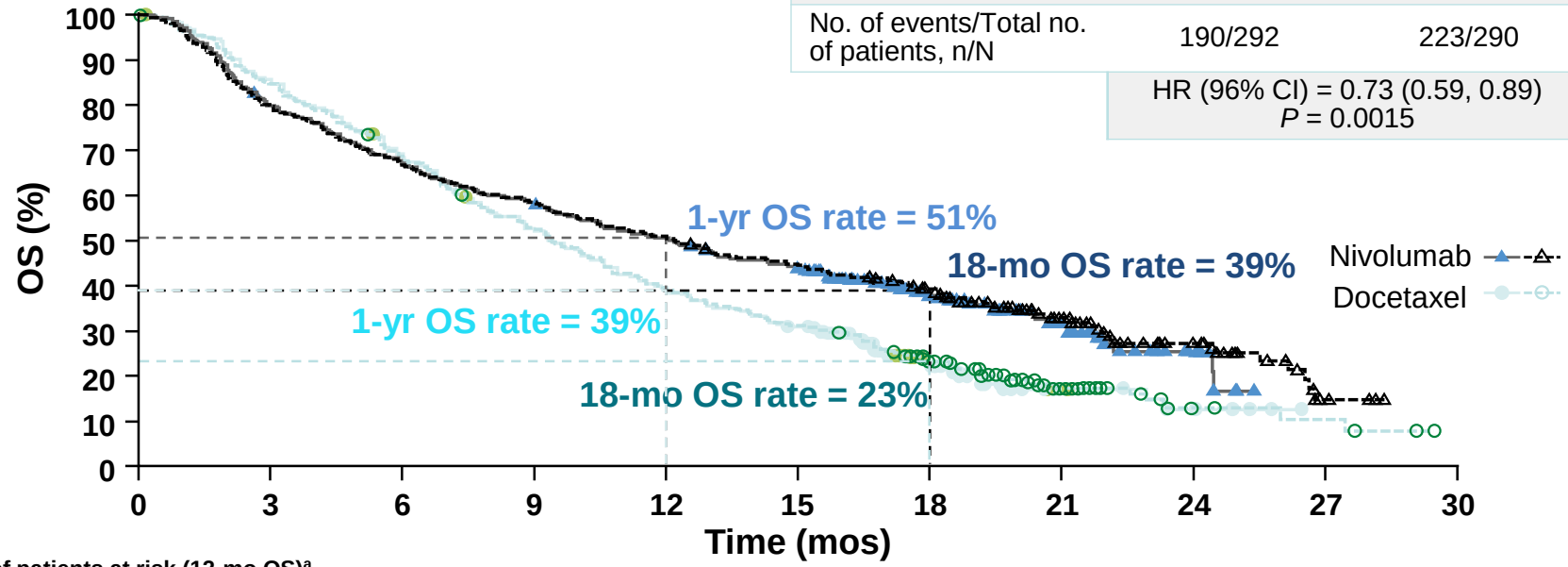
- **PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]**
  - **Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness**

[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

Overall Survival

	12-mo OS[a] (13.2 mo minimum follow-up)		18-mo OS[b] (17.1 mo minimum follow-up)	
	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
	HR (96% CI) = 0.73 (0.59, 0.89) *P* = 0.0015		HR (95% CI) = 0.72 (0.60, 0.88) Post-hoc *P* = 0.0009	

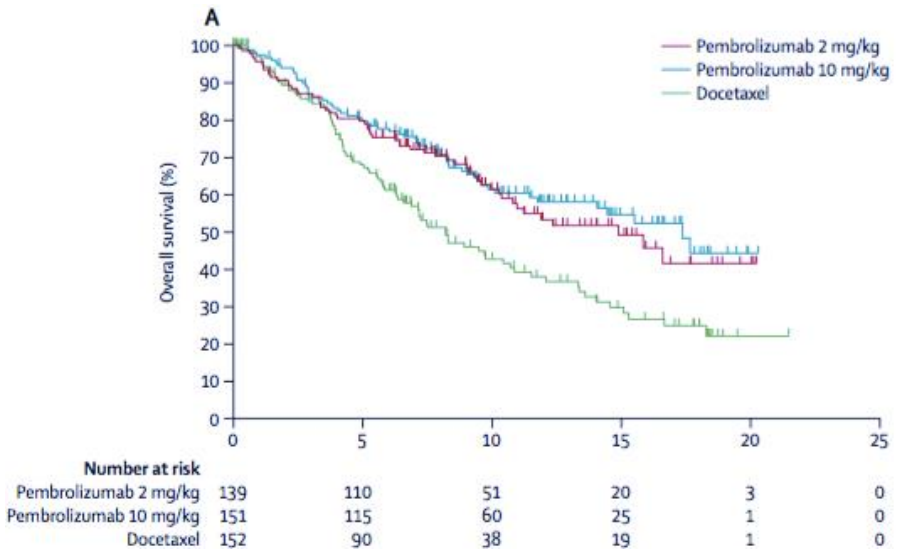


No. of patients at risk (12-mo OS)[a]											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. of patients at risk (18-mo OS)[b]											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

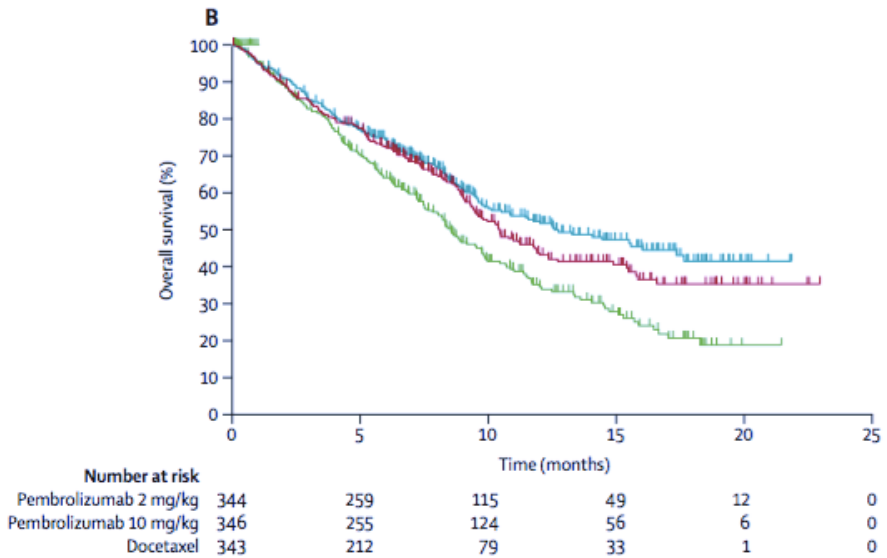
Borghaei H et al NEJM 2015

Pembrolizumab versus docetaxel in pretreated NSCLC with PD-L1 expression
Survival results of the KEYNOTE 010 trial

PD-L1 score 50% or greater

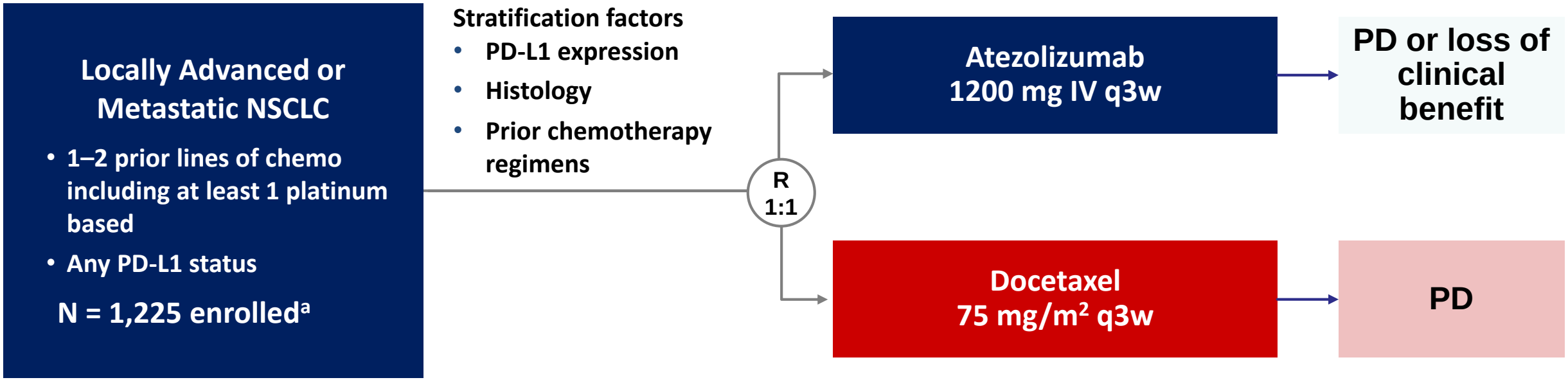


Study population



Herbst R et al, Lancet 2015

OAK study design



Primary Endpoints (first 850 enrolled patients):

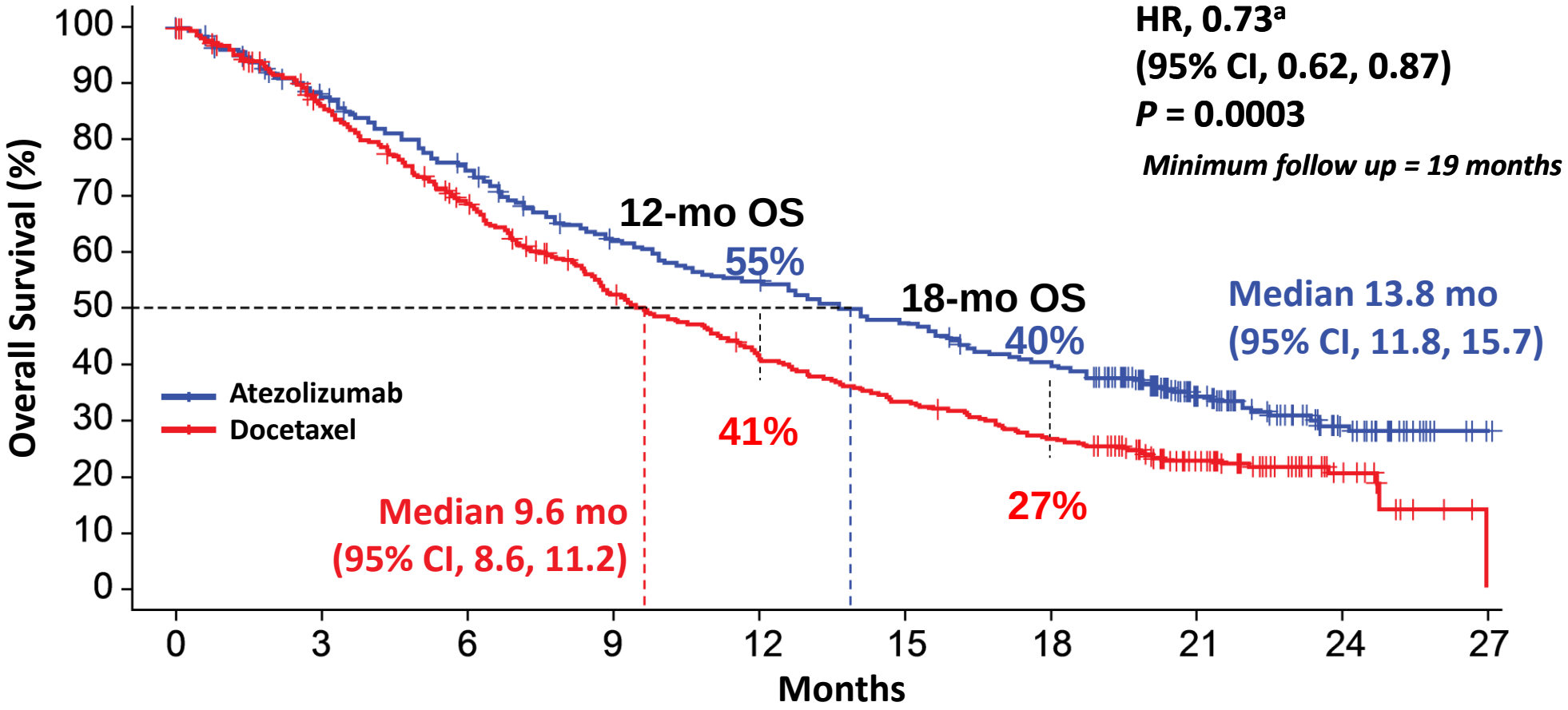
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

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

COMPLETED PHASE III TRIALS OF PD-1 / PDL-1 INHIBITORS IN PREVIOUSLY-TREATED NSCLC: ADVERSE EVENTS

		Nivolumab	Pembrolizumab	Atezolizumab	Docetaxel
TR AEs	Any grade	58-69%	63-66%	64%	81-88%
	Grade ≥3	7-10%	13-16%	37%	35-57%
	Discontinued	2-4%	4-5%	8%	7%
Pneumonitis	Any grade	5%	4-5%		0%
	Grade ≥3	1%	2%	1%	0%
Colitis	Any grade	1%	1%		0%
	Grade ≥3	1%	0.5%	0.3%	0%

Paul Mitchell, WCLC 2016

What do I really need to exclude pts from IO?

- Is PD-L1 expression a valuable predictor of efficacy of checkpoint-inhibitors?
- Which other biomarkers with predictive potential can be identified?
- Special populations (EGFR+, brain metastases, elderly)
- Are there clinical predictors?

What do I really need to exclude pts from IO?

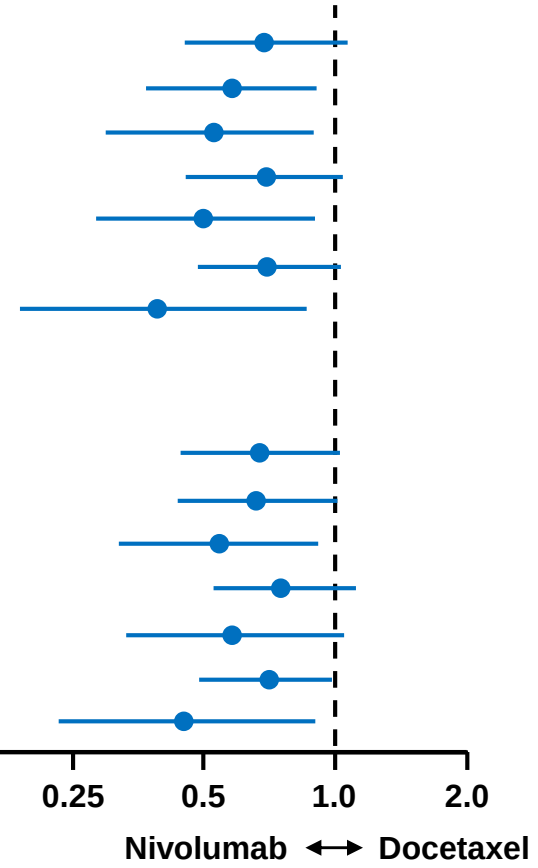
- Is PD-L1 expression a valuable predictor of efficacy of checkpoint-inhibitors?

CA209-017

Brahmer J, et al. NEJM 2015

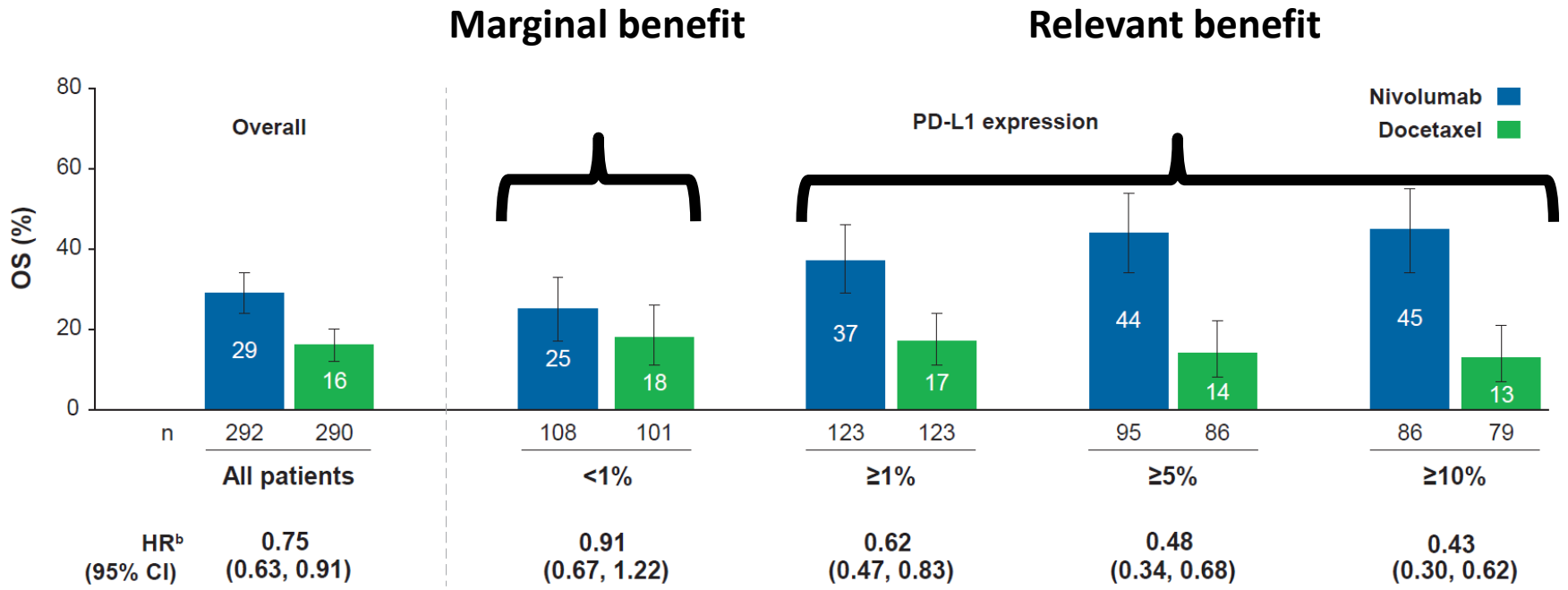
Plot of OS and PFS Hazard Ratios by PD-L1 Expression Level at Baseline

PD-L1 expression	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)	



Do we need PD-L1 testing for second-line immunotherapy?

Nivolumab versus docetaxel in non-squamous lung cancer



- In CheckMate 057, consistent with the primary analysis,[2] PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)

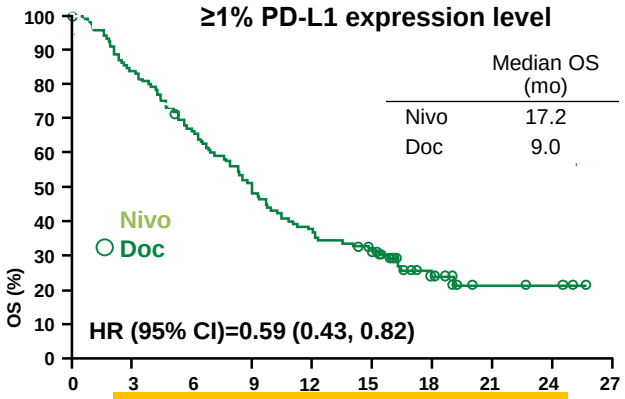
[a]Kaplan–Meier estimates, with error bars indicating 95% CIs
[b]For the comparison of the full Kaplan–Meier survival curves for each treatment group

Borghaei H et al ASCO 2016

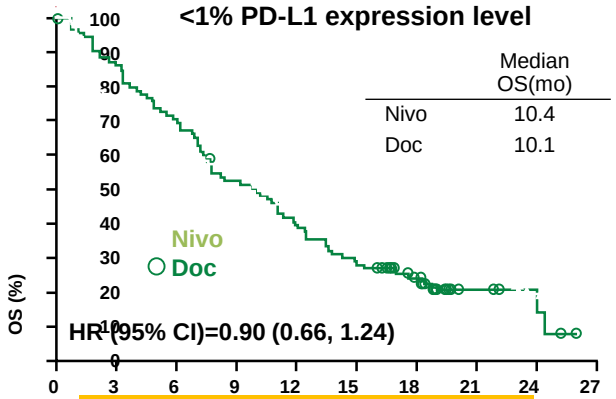
OS by PD-L1 expression:

Rizvi NA, et al. *Lancet Oncol* 2015
R Herbst et al. Lancet 2016
Barlesi, et al. ESMO 2016

- Chechmate 057 (Nivolumab)

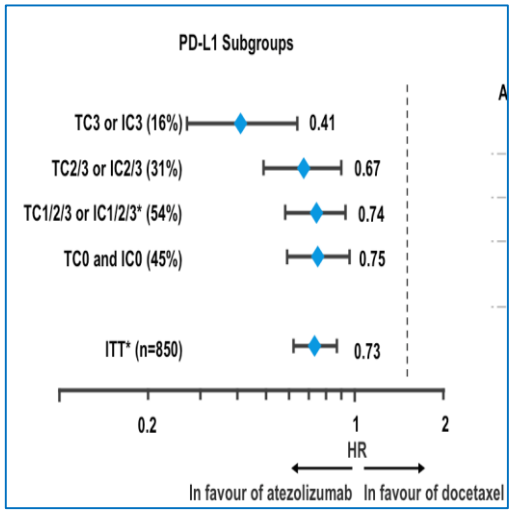


> % 1 PD-L1 HR 0.59



< % 1 PD-L1 HR 0.90

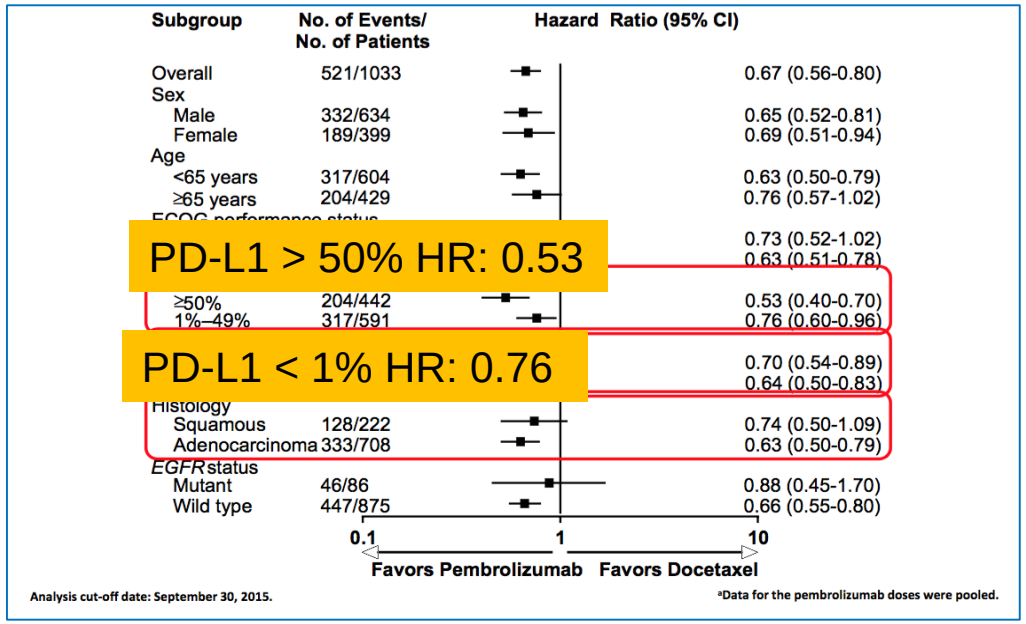
- OAK Trial (Atezolizumab)



TC3 or IC3 HR: 0.41

TC0 and IC0% HR: 0.75

- Keynote 10 (Pembrolizumab)



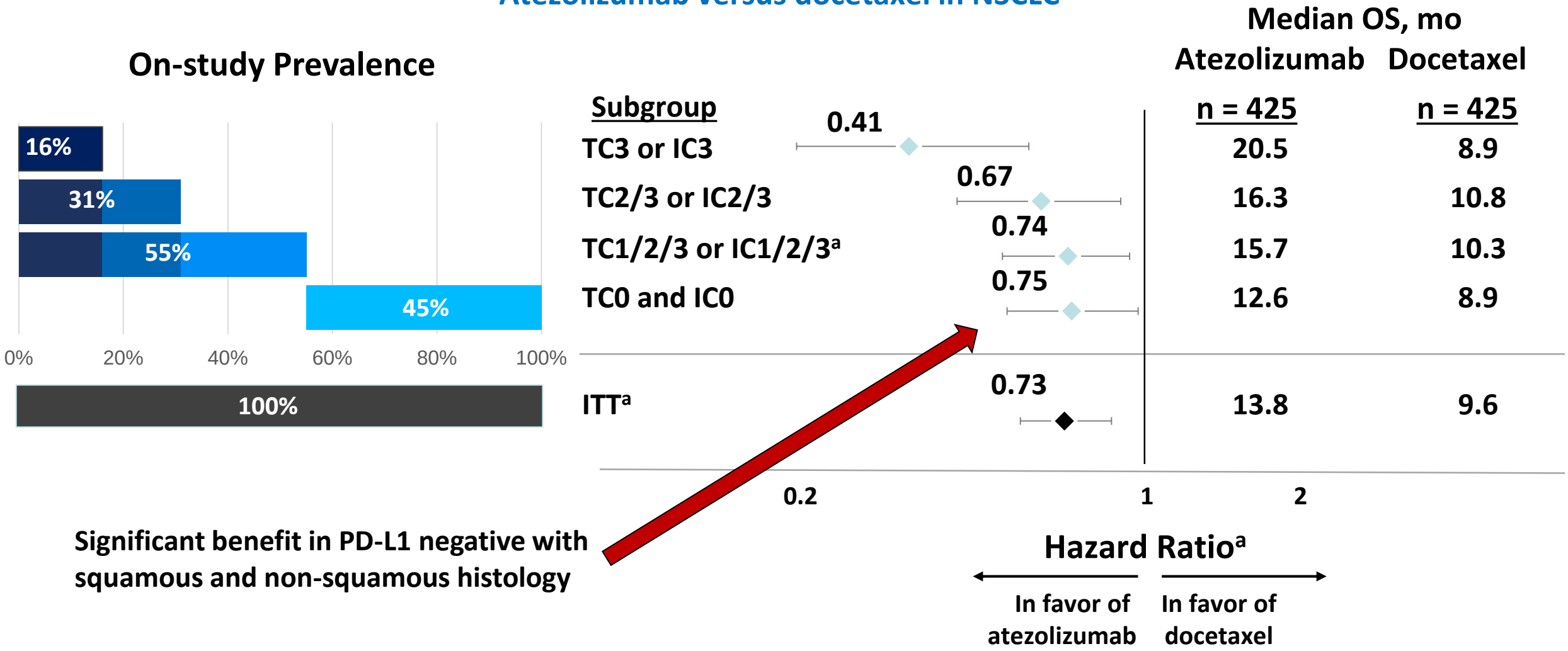
PD-L1 > 50% HR: 0.53

PD-L1 < 1% HR: 0.76

In the II line setting, do we really select patients according a more favorable HR?

Do we need PD-L1 testing for second-line immunotherapy?

Atezolizumab versus docetaxel in NSCLC



Significant benefit in PD-L1 negative with squamous and non-squamous histology

[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Barlesi et al. ESMO 2016

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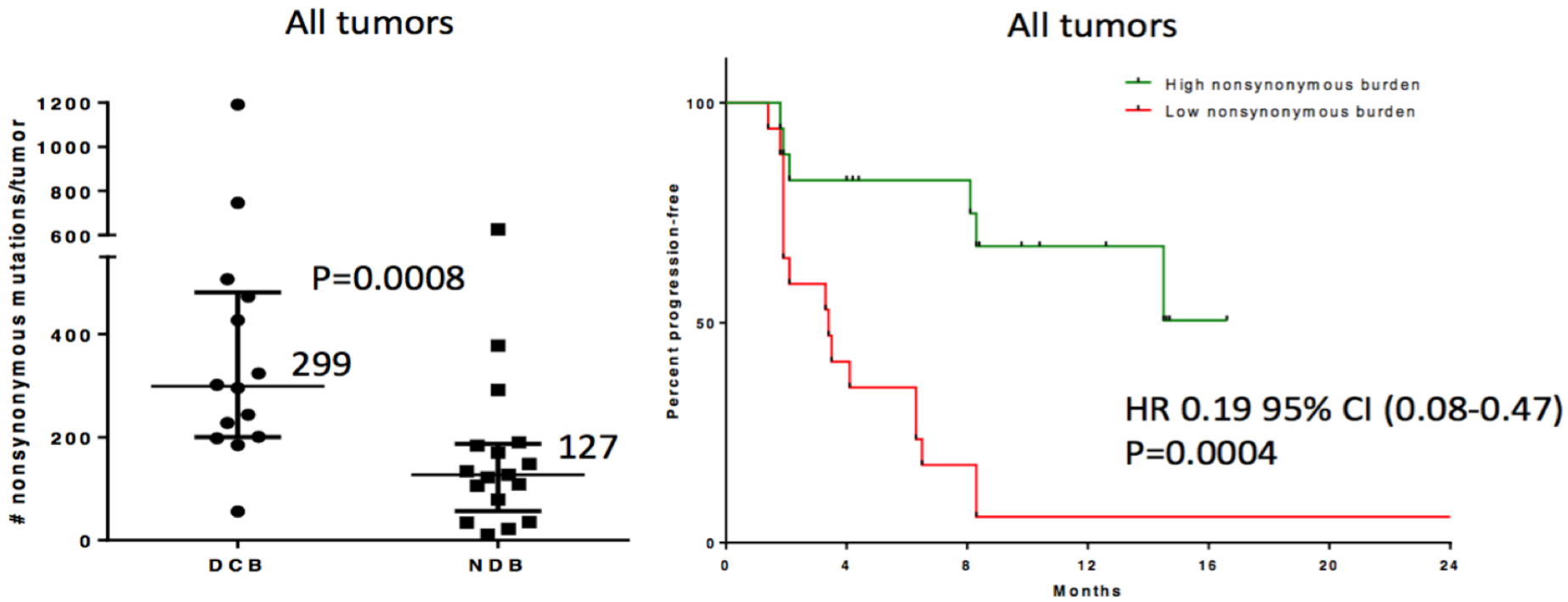
- Are there clinical predictors?

Mutation burden significantly correlates with clinical benefit in NSCLC treated with Pembrolizumab



Rizvi et al, Science 2015

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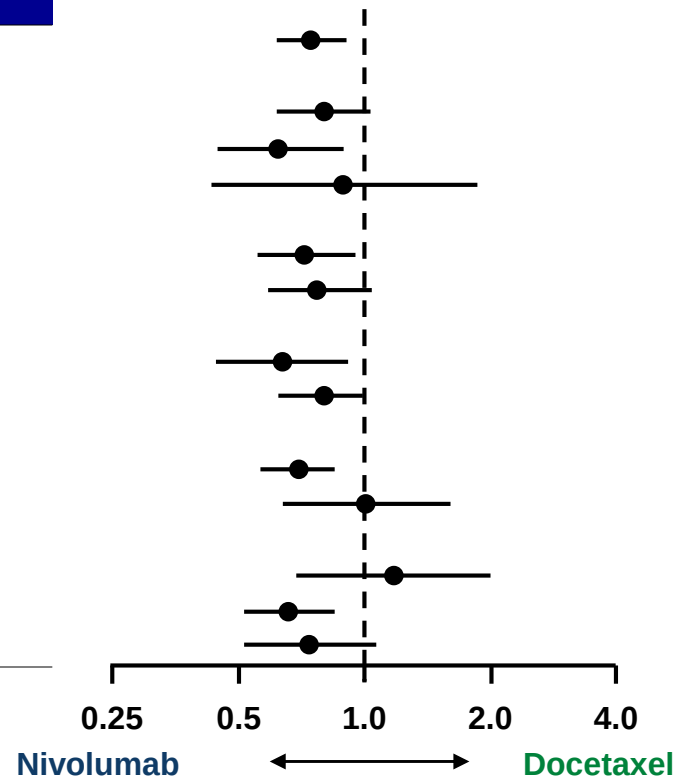
- Which other biomarkers with predictive potential can be identified?
- Special populations (EGFR+, brain metastases, elderly)
- Are there clinical predictors?

Which patients are not candidate for second-line immunotherapy?

Overall survival in EGFR mutant NSCLC in checkmate 057 trial

	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)

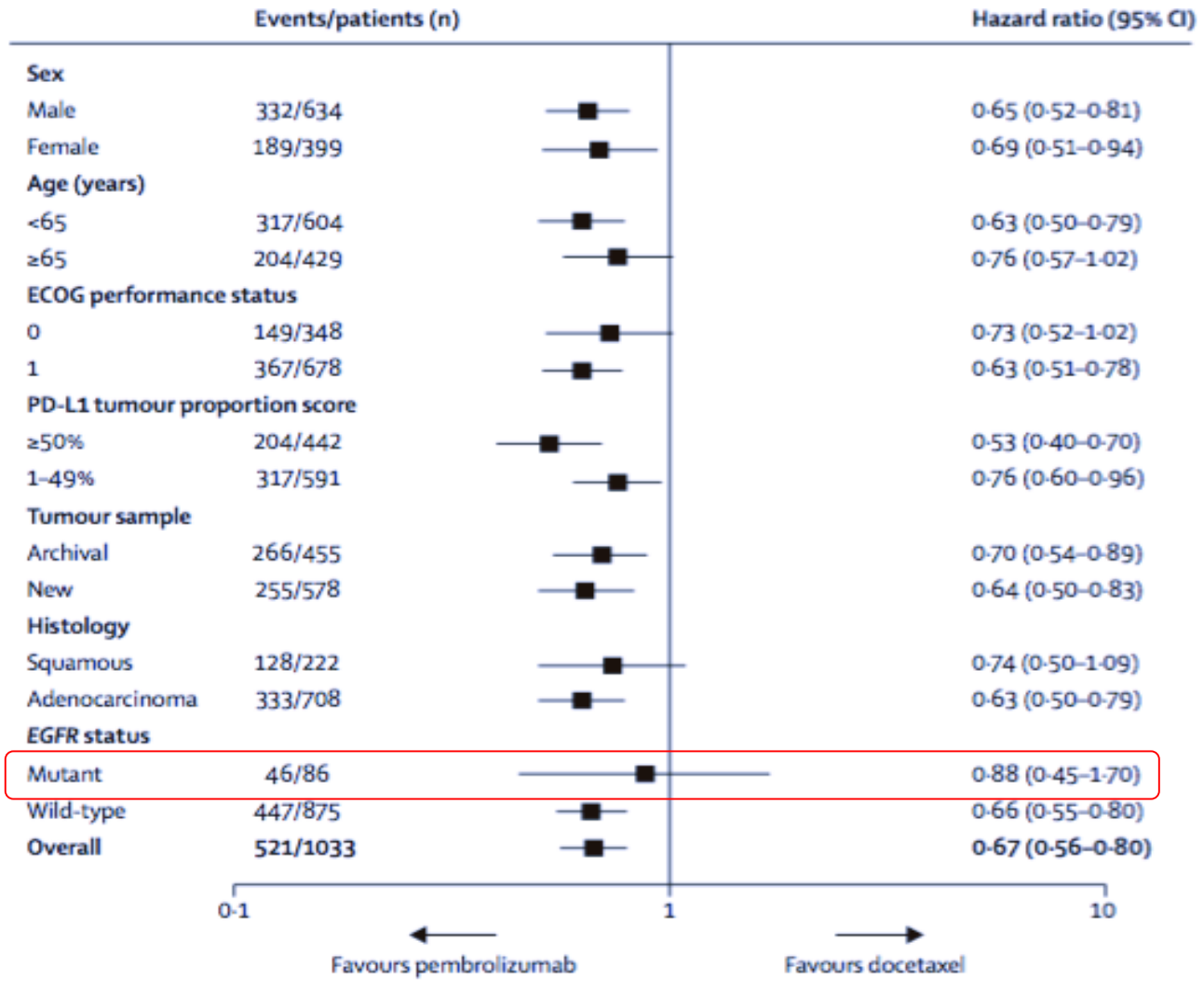


All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

Borghaei H et al NEJM 2015

Which patients are not candidate for second-line immunotherapy?

Overall survival in EGFR mutant NSCLC in the Keynote 010 trial

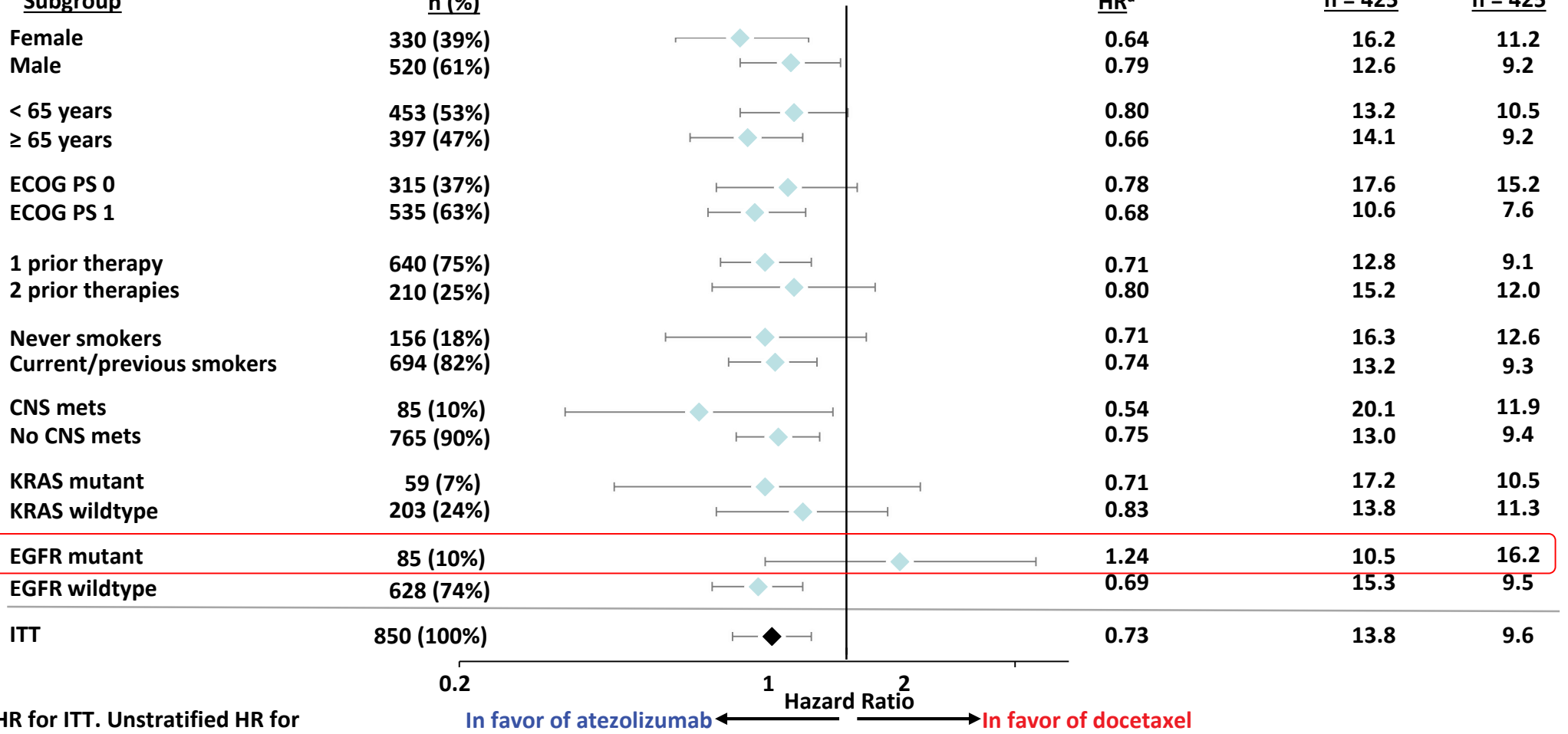


Herbst R et al, Lancet 2015

Which patients are not candidate for second-line immunotherapy?

Overall survival in EGFR mutant NSCLC in the OAK trial

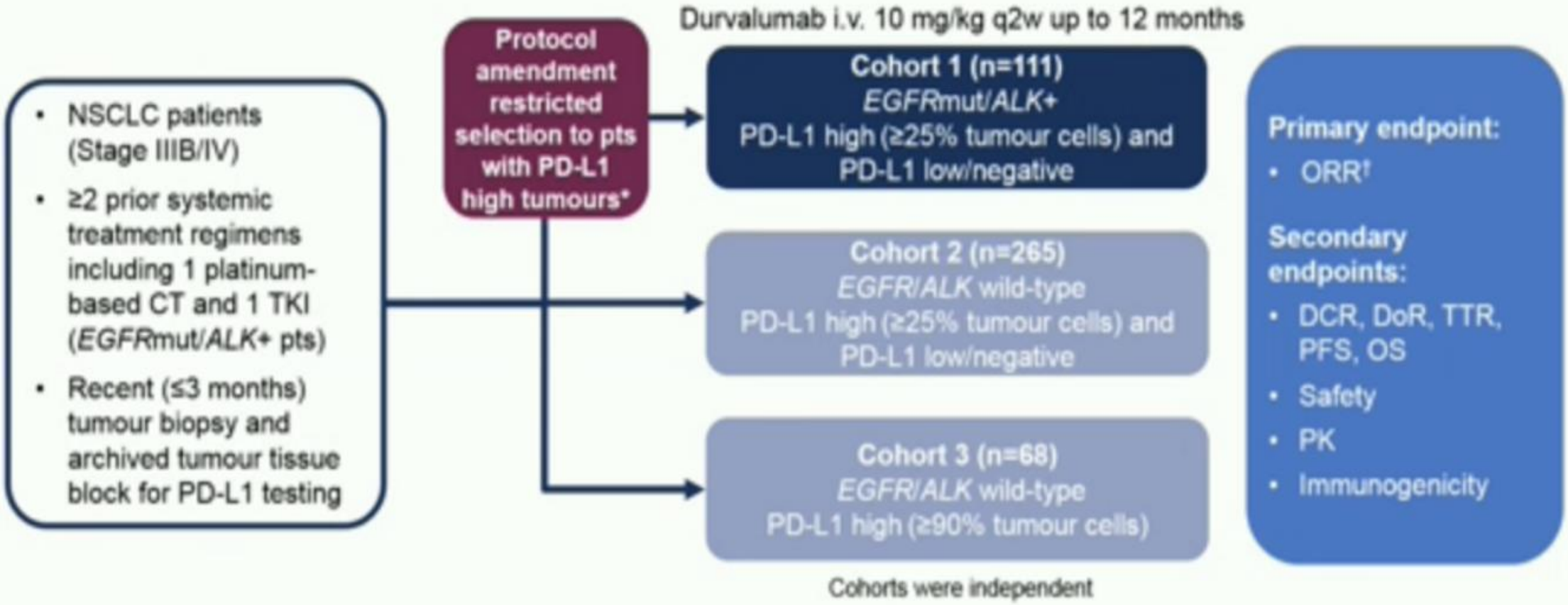
Subgroup	n (%)	HR[a]	Median OS, mo Atezolizumab n = 425	Median OS, mo Docetaxel n = 425
Female	330 (39%)	0.64	16.2	11.2
Male	520 (61%)	0.79	12.6	9.2
< 65 years	453 (53%)	0.80	13.2	10.5
≥ 65 years	397 (47%)	0.66	14.1	9.2
ECOG PS 0	315 (37%)	0.78	17.6	15.2
ECOG PS 1	535 (63%)	0.68	10.6	7.6
1 prior therapy	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.

Barlesi et al. ESMO 2016

ATLANTIC: phase 2, open-label, single-arm study



*PD-L1 expression levels assessed by immunohistochemistry (VENTANA PD-L1 [SP263] Assay); †ORR by independent central review (RECIST v1.1)
CT, chemotherapy; DCR, disease control rate; DoR, duration of response; TKI, tyrosine kinase inhibitor

ClinicalTrials.gov number: NCT02087423

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Anti-tumour activity (full analysis set*)

	PD-L1 high (≥25%)			PD-L1 low/neg (<25%)
	*EGFR*mut/*ALK*+ (n=74†)	*EGFR*mut (n=64†)	*ALK*+ (n=10)	*EGFR*mut/*ALK*+ (n=28)
Confirmed ORR‡, n (%) [95% CI]	9 (12.2) [5.7–21.8]	9 (14.1) [6.6–25.0]	0	1 (3.6) [0.1–18.3]
Stable disease ≥8 weeks, n (%)	23 (31.1)	21 (32.8)	2 (20.0)	5 (17.9)
Progressive disease, n (%)	40 (54.1)	32 (50.0)	8 (80.0)	22 (78.6)
Median DoR, months (95% CI)	7.4 (5.4, 9.2)	7.4 (5.4, 9.2)	NC	7.9 (NC)

*Patients evaluable for response per Independent Central Review; †2 patients were not evaluable due to incomplete post baseline assessments;
‡All responses were partial responses. NC, not calculated (due to zero or one responders)

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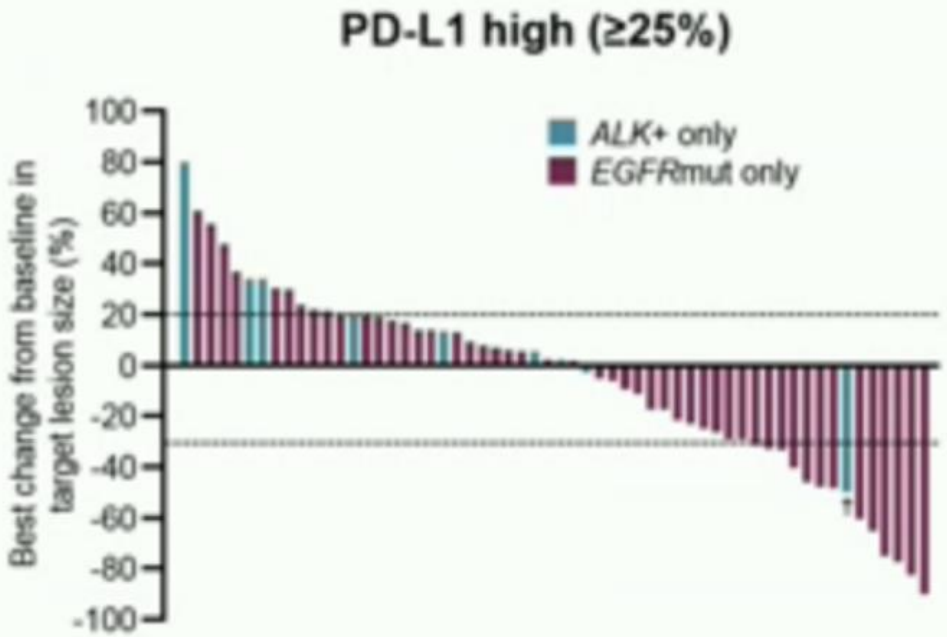
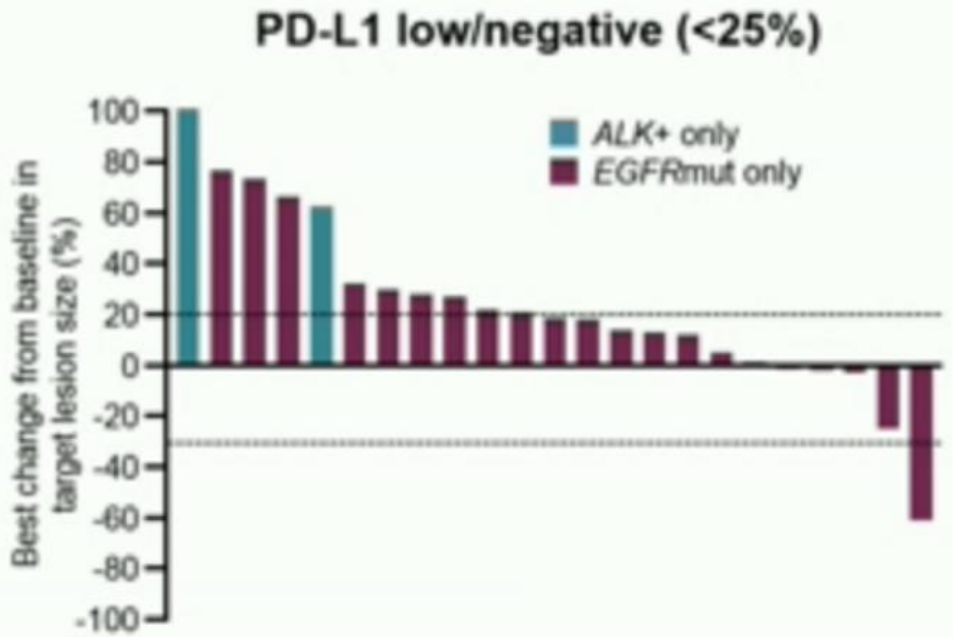
Best change in target lesion size (full analysis set*)





*Patients evaluable for response per Independent Central Review (only patients who had a post-baseline tumour assessment are shown on the graphs); †Best objective response is progression, due to disease progression in non-target lesions

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SAFETY AND EFFICACY ANALYSES OF ATEZOLIZUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH OR WITHOUT BASELINE BRAIN METASTASES

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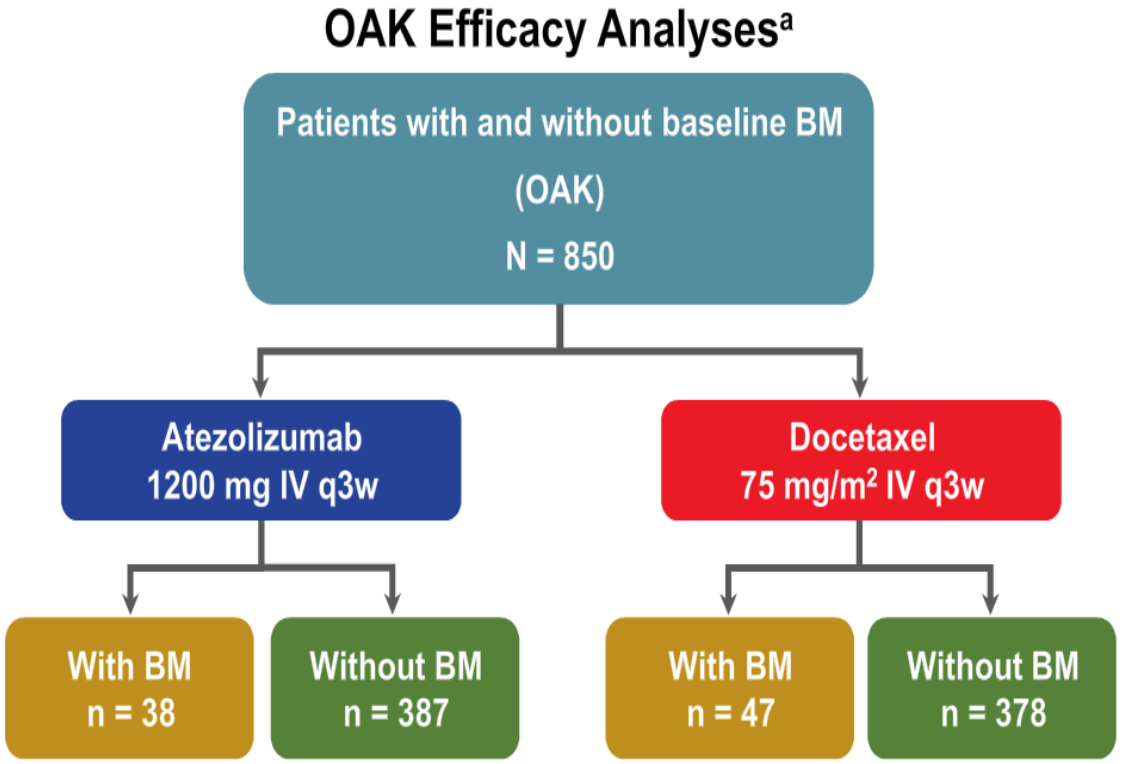
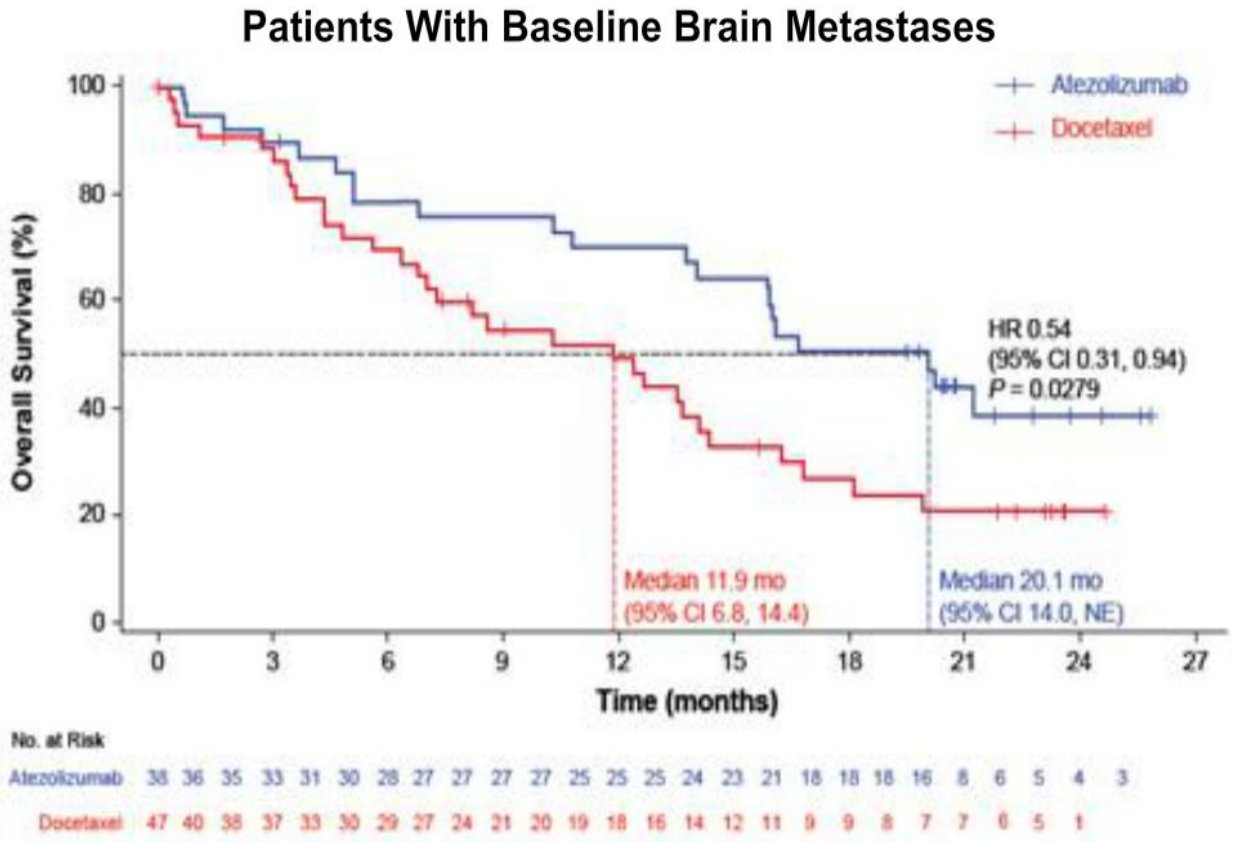


- OS
- Time to development of new brain lesions

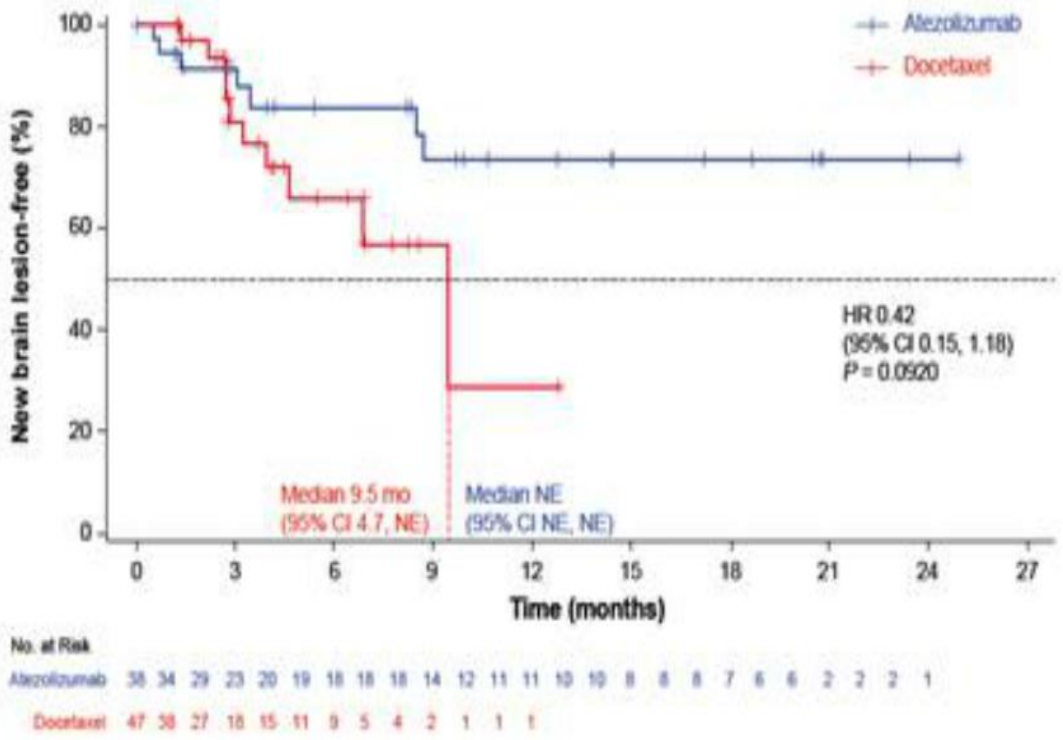
EFFICACY ANALYSIS FROM OAK – OVERALL SURVIVAL



- In patients with pre-treated brain metastases, mOS was longer in those treated with atezolizumab vs docetaxel

TIME TO DEVELOPMENT OF NEW BRAIN LESIONS

Patients With Baseline Brain Metastases



	Atezolizumab (n = 38)	Docetaxel (n = 47)
New brain lesion–free rate, %		
6 months	84%	66%
12 months	73%	28%
18 months	73%	NE (≤ 28%)
24 months	73%	NE (≤ 28%)

“Immunosenescence” may reduce the efficacy of the immune based therapies

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Journal of Geriatric Oncology

Review article

Immunotherapy comes of age: Immune aging & checkpoint inhibitors

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Summary of major age-associated changes in immune cell function that might impact ICIs.

Type of cells	Alterations with aging
Dendritic cells	• Decreased number of cells [35–41] • Impaired TLR signaling [42] • Decreased phagocytic and migratory function [43] • Down-regulation of CD80 and CD86 [37,45] • Decreased secretion of IFN-α [40,44–48]
CD4 + T cells	• Decreased TCR diversity [62] • Impaired function of naïve CD4 + T cells [63] • Decreased CD28 expression [64–66] • Decreased CD40 ligand expression [64,65]
CD8 + T cells	• Decreased lymphocyte production [51–55] • Decreased CD8 + naïve T cell pool [71] • Decreased TCR diversity [63] • Increased late stage cells with decreased CD28 expression [74–76] • Decreased clonal expansion [77] • Higher expression of CD57 [80,81] • Increased PD-1 expression [68–70] • Increased sensitivity to apoptotic signals [73] • Lower levels of perforin and granzyme [70]
T regulatory cells	• Increased number of CD4 + T regulatory cells [76,99–102] • Higher suppressive activity [76,99–102] • Increased number of CD8 + T regulatory cells [103]
MDSC	• Age-associated increase in numbers in both tumor stroma and circulation [117]
M2 Macrophages	• Controversial but suggestion of increased M2 polarization with age [121–123]

Efficacy and Safety of Nivolumab in Elderly Patients With Advanced Squamous NSCLC Participating in the Expanded Access Program in Italy

Francesco Grossi,[1] Lucio Crinò,[2] Andrea Misino,[3] Paolo Bidoli,[4] Angelo Delmonte,[5] Francesco Gelsomino,[6] Claudia Proto,[7] Maria Laura Mancini,[8] Lorenza Landi,[9] Daniele Turci,[10] Silvia Quadrini,[11] Paola Antonelli,[12] Paolo Marchetti,[13] Luca Toschi,[14] Sabrina Giusti,[15] Francesco Di Costanzo,[16] Francesca Rastelli,[17] Paolo Sandri,[18] Vieri Scotti,[16] Filippo de Marinis[19]

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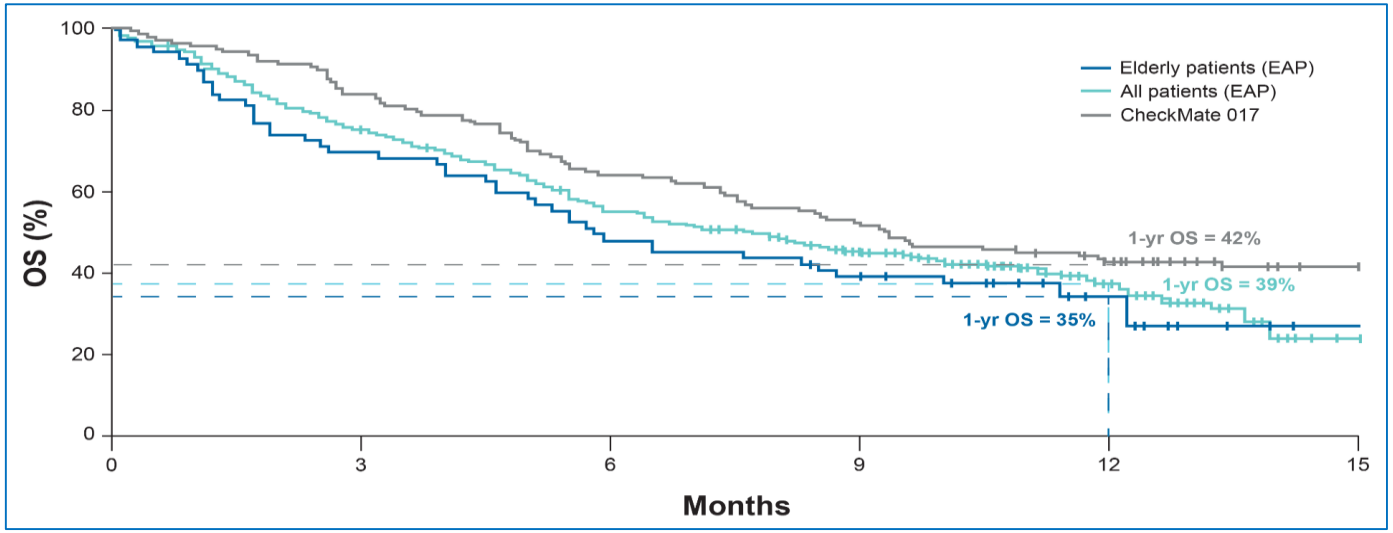
ESMO 2016

Response	Elderly patients[a] (n = 70)		All patients (N = 371)	
	First tumor assessment	Best response	First tumor assessment	Best response
ORR, n (%)	8 (11)	13 (19)	51 (14)	67 (18)
DCR, n (%)	25 (36)	30 (43)	151 (41)	175 (47)
Overall response, n (%)				
CR	0	0	1 (<1)	4 (1)
PR	8 (11)	13 (19)	50 (14)	63 (17)
SD	17 (25)	17 (24)	100 (27)	108 (29)
PD	43 (61)	38 (54)	212 (57)	189 (51)
Not determined	2 (3)	2 (3)	8 (2)	7 (2)

[a]Patients aged ≥75 years

Event	Elderly patients[a] (n = 70)		All patients (N = 371)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any treatment-related AE	20 (29)	2 (3)	109 (29)	21 (6)

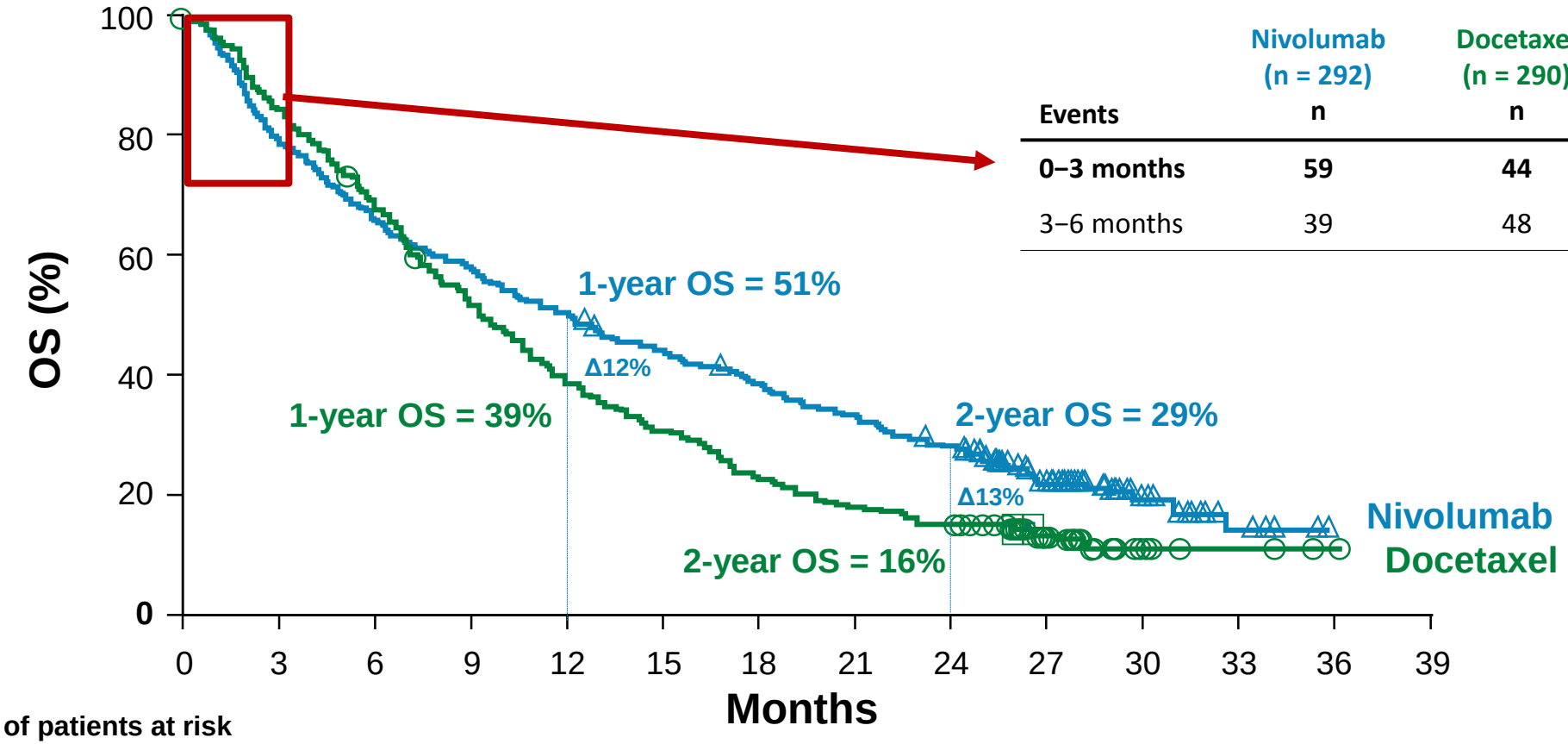


Discontinuations	Elderly patients[a] (n = 70)	All patients (N = 371)
Discontinued treatment, n (%)	56 (80)	281 (76)

What do I really need to exclude pts from IO?

- Is PD-L1 expression a valuable predictor of efficacy of checkpoint-inhibitors?
- Which other biomarkers with predictive potential can be identified?
- Special populations (EGFR+, brain metastases, elderly)
- Are there clinical predictors?

Post-hoc multivariate analysis on patient outcome during the first 3 months in the CHECKMATE 057



Events	Nivolumab (n = 292) n	Docetaxel (n = 290) n	Difference n
0–3 months	**59**	**44**	**15**
3–6 months	39	48	[9]

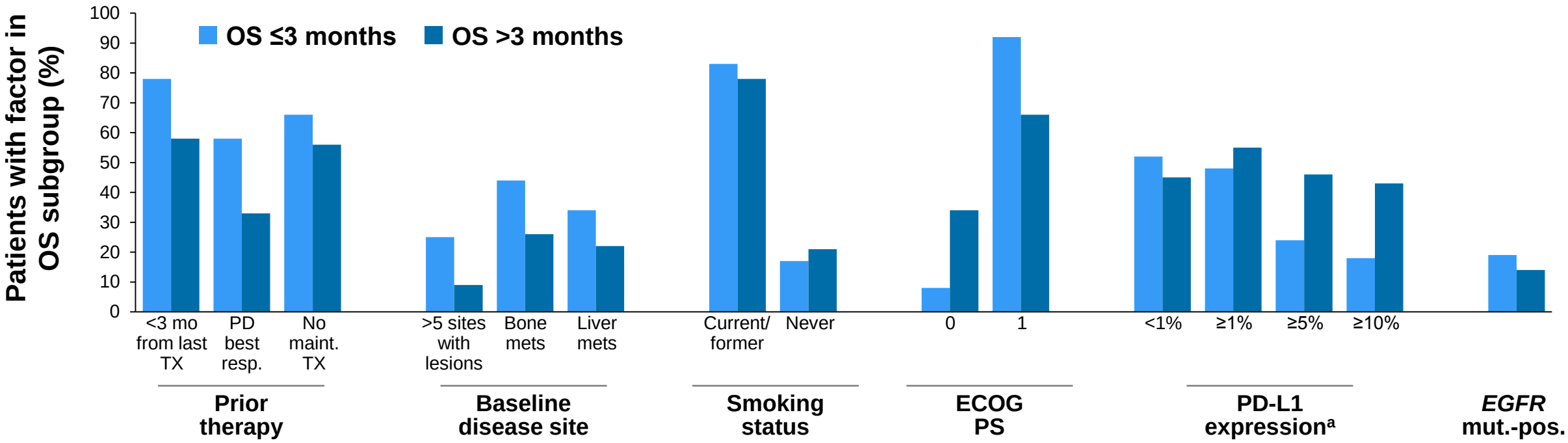
Number of patients at risk

Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

Peters S, et al WCLC 2016

Which patients are not candidate for second-line immunotherapy?

Combination of clinical factors and PD-L1 expression in Checkmate 057



- **Post-hoc, exploratory multivariate analysis suggested that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower or no tumor PD-L1 expression may be at higher risk of death within the first 3 months**
  - **These included the following known prognostic factors: <3 months since last treatment, PD as best response to prior treatment, and ECOG PS = 1**

Peters S, et al WCLC 2016

Conclusions

- **Immunotherapy is now the standard therapy for *EGFR*^{wt}, *ALK*^{wt} NSCLC in second line irrespective of clinical or biological characteristics.**
- **PD-L1 expression is not critical for second-line immunotherapy**
- **Landscape of NSCLC therapy is rapidly evolving (recent Pembrolizumab approval in first line setting)**