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

Immuno-Oncology for patients with metastatic non-small-cell lung cancer

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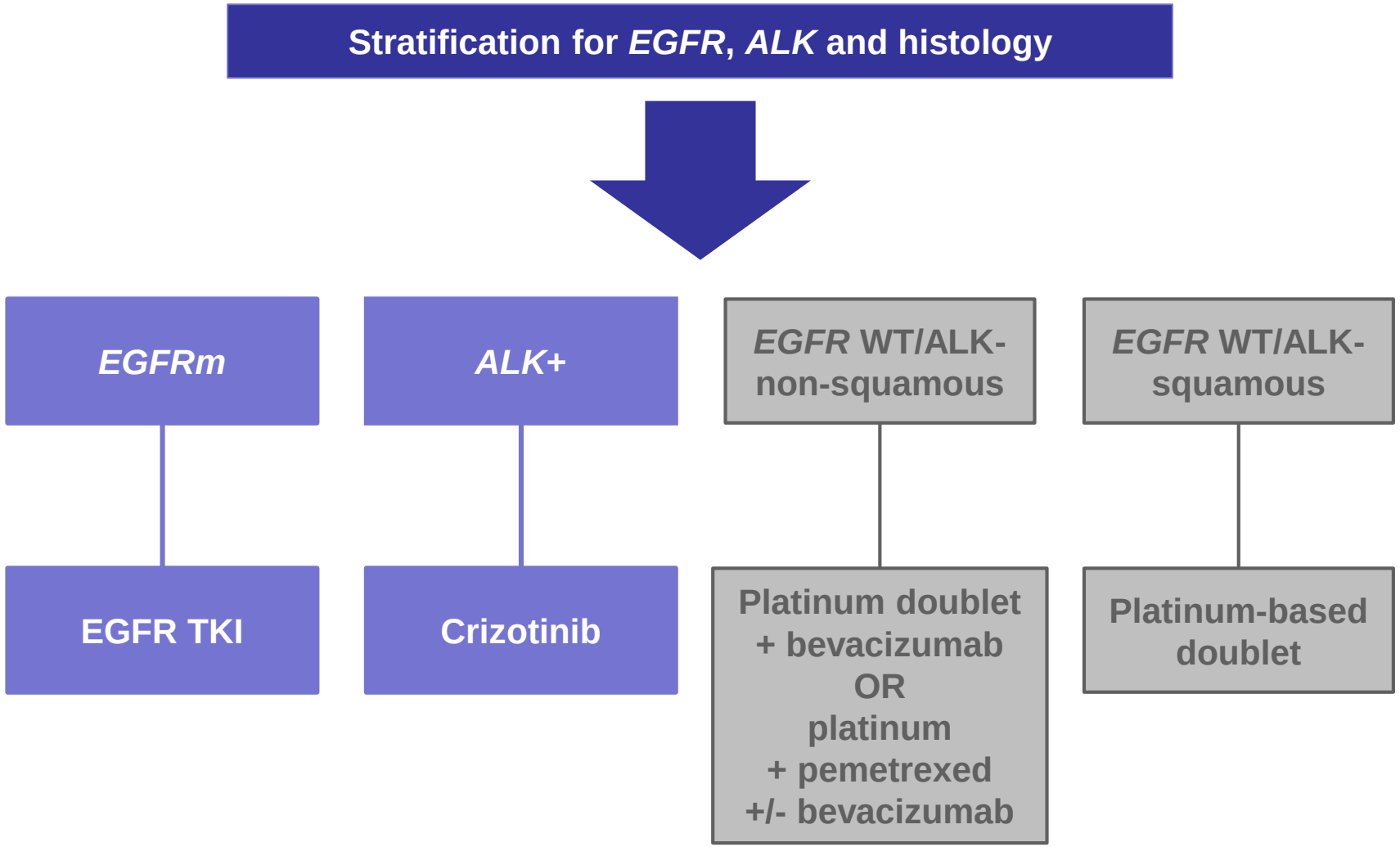
First-line therapy for metastatic NSCLC in 2016



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

Immunotherapy superior to platinum-based chemotherapy in patients with high levels of PD-L1 expression

KEYNOTE-024 Study design

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

- Pembrolizumab 200 mg IV Q3W (2 years)
- Platinum-Doublet Chemotherapy (4-6 cycles) → PD[a] → Pembrolizumab 200 mg Q3W for 2 years

Key End Points

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

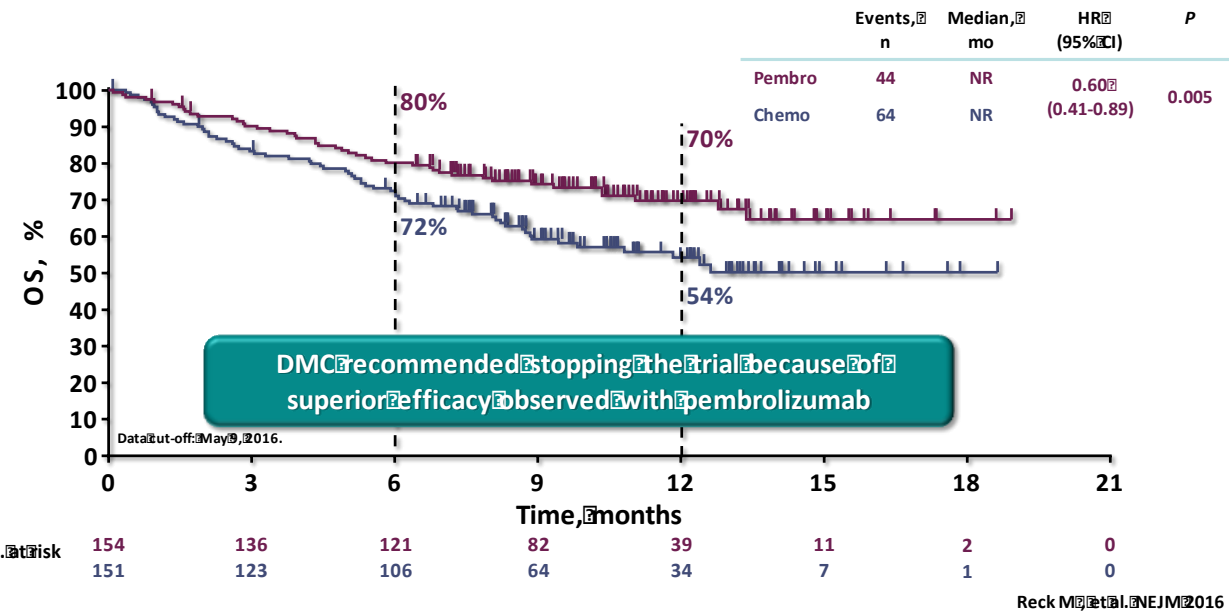
Secondary: OS, ORR, safety

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

Overall Survival



Reck M, et al. NEJM 2016

Immunotherapy not superior to platinum-based chemotherapy in patients with low levels of PD-L1 expression

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression[a]
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

Randomize 1:1

Nivolumab 3 mg/kg IV Q2W
n = 271

Chemotherapy (histology dependent)[b] Maximum of 6 cycles
n = 270

Tumor scans Q6W until wk 48 then Q12W

Disease progression or unacceptable toxicity

Disease progression

Crossover nivolumab[c] (optional)

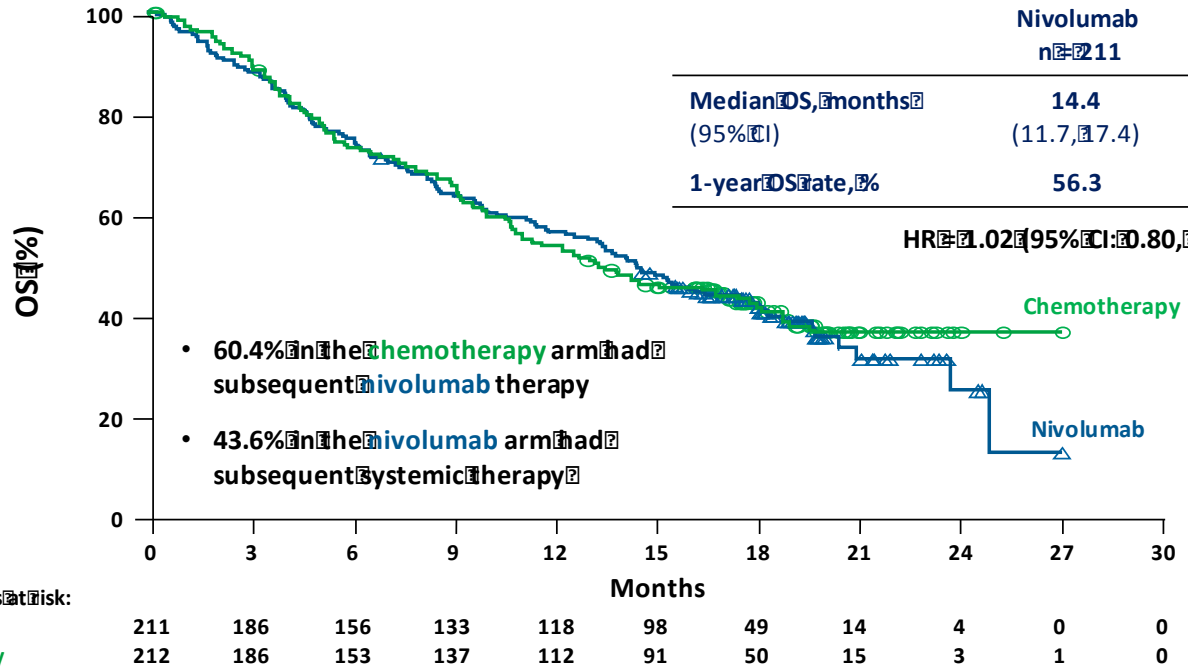
Stratification factors at randomization:
- PD-L1 expression (<5% vs ≥5%)[a]
- Histology (squamous vs non-squamous)

Primary endpoint: PFS (≥5% PD-L1+)[d]

Secondary endpoints:
- PFS (≥1% PD-L1+)[d]
- OS
- ORR[d]

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)

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

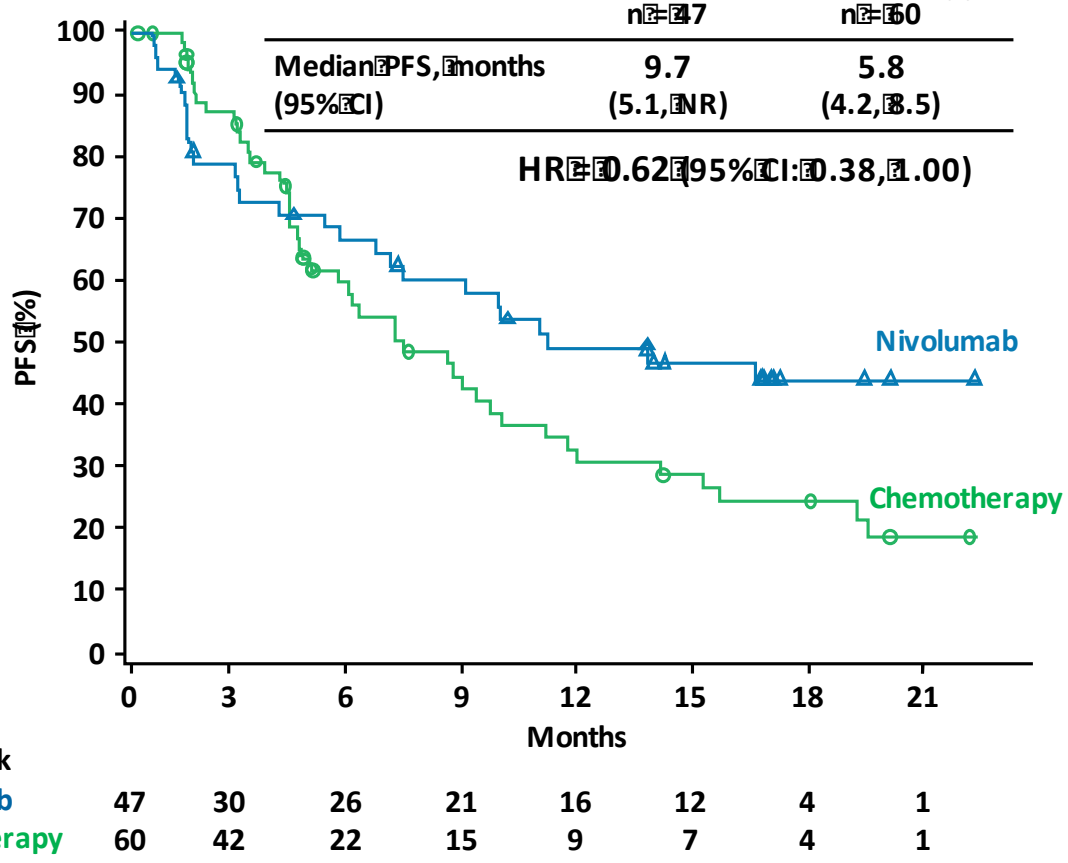
Do we need additional tests for first-line I-O selection?

Role of Tumor Mutation Burden in CheckMate 026 study

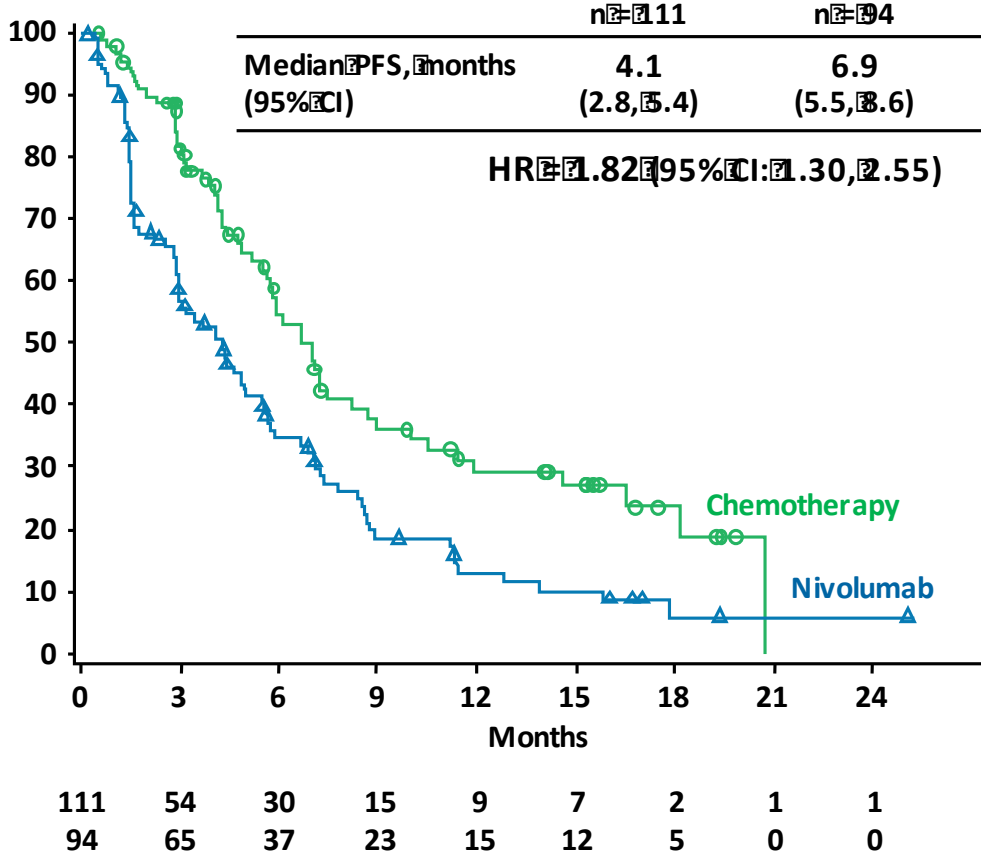
30% of tumors were High TMB
55% of high TMB were PD-L1 <50%

PFS

High TMB



Low/medium TMB



Peters S, et al. AACR 2017

OS by Tumor Mutation Burden Subgroup

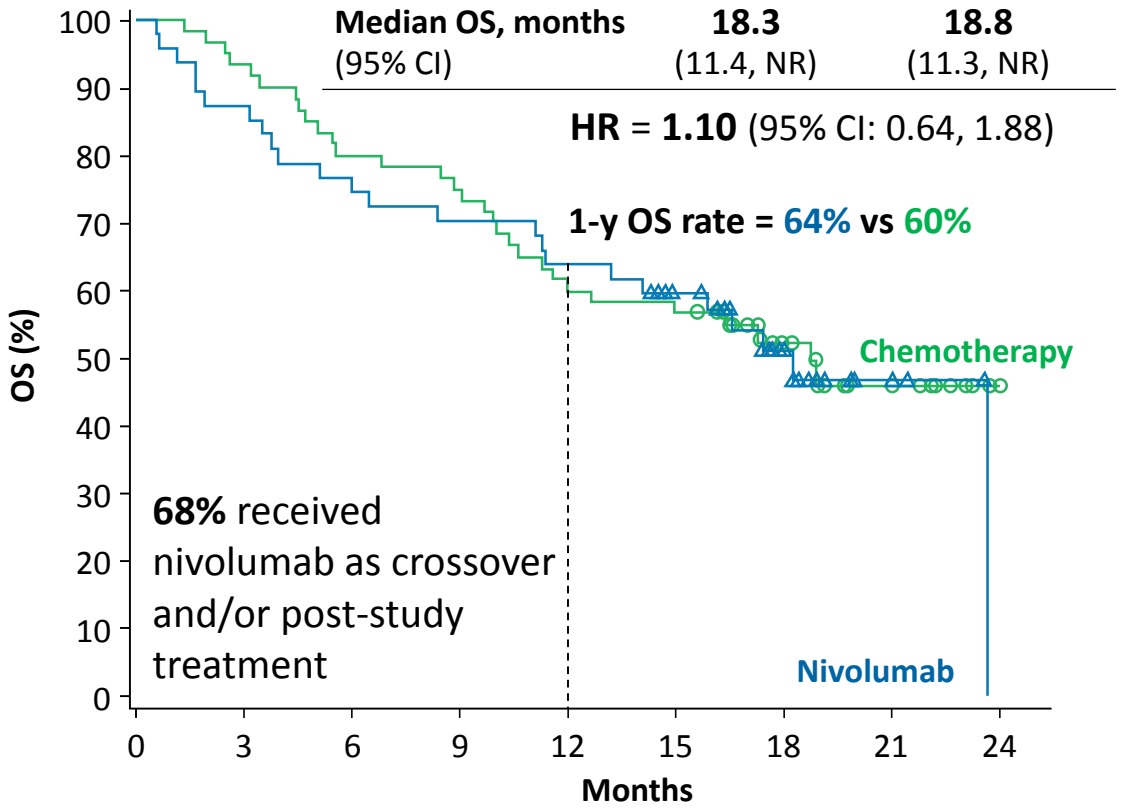
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median OS, months (95% CI)	**18.3** (11.4, NR)	**18.8** (11.3, NR)

HR = 1.10 (95% CI: 0.64, 1.88)

1-y OS rate = 64% vs 60%



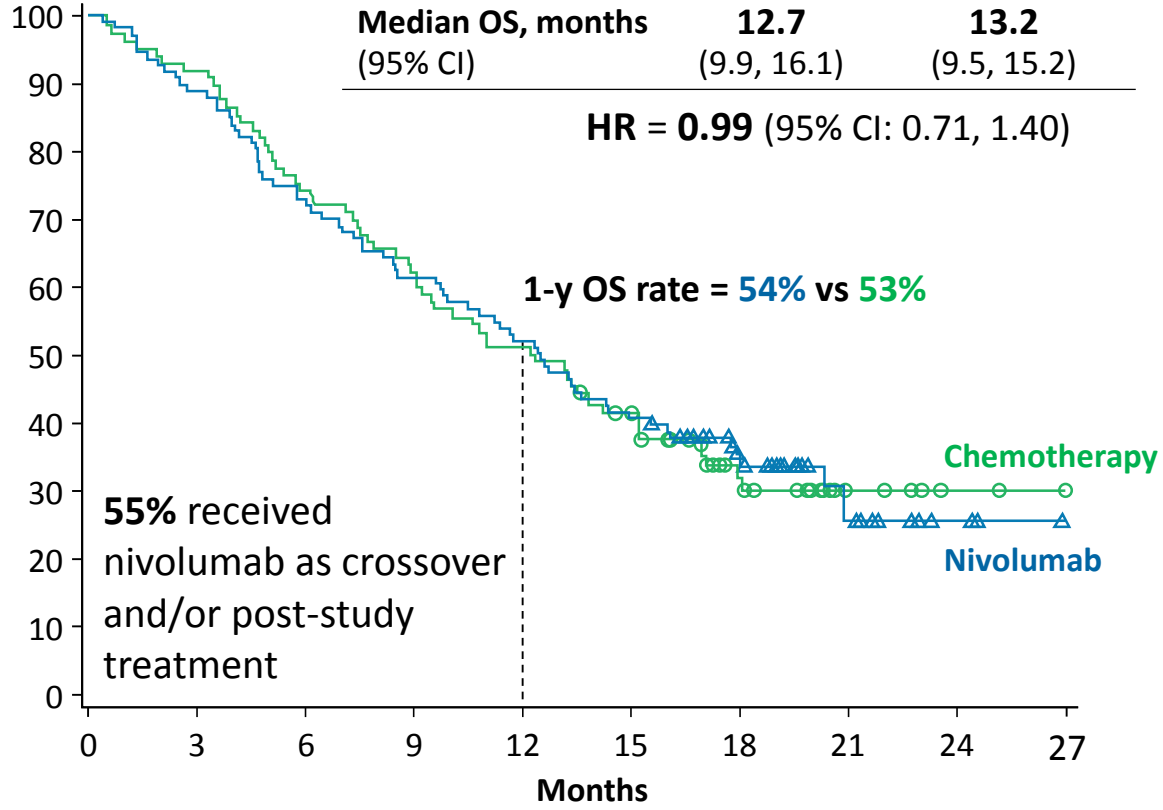
No. at Risk										
Nivolumab	47	41	35	33	30	24	13	4	0	
Chemotherapy	60	56	48	45	36	34	19	9	1	

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median OS, months (95% CI)	**12.7** (9.9, 16.1)	**13.2** (9.5, 15.2)

HR = 0.99 (95% CI: 0.71, 1.40)

1-y OS rate = 54% vs 53%

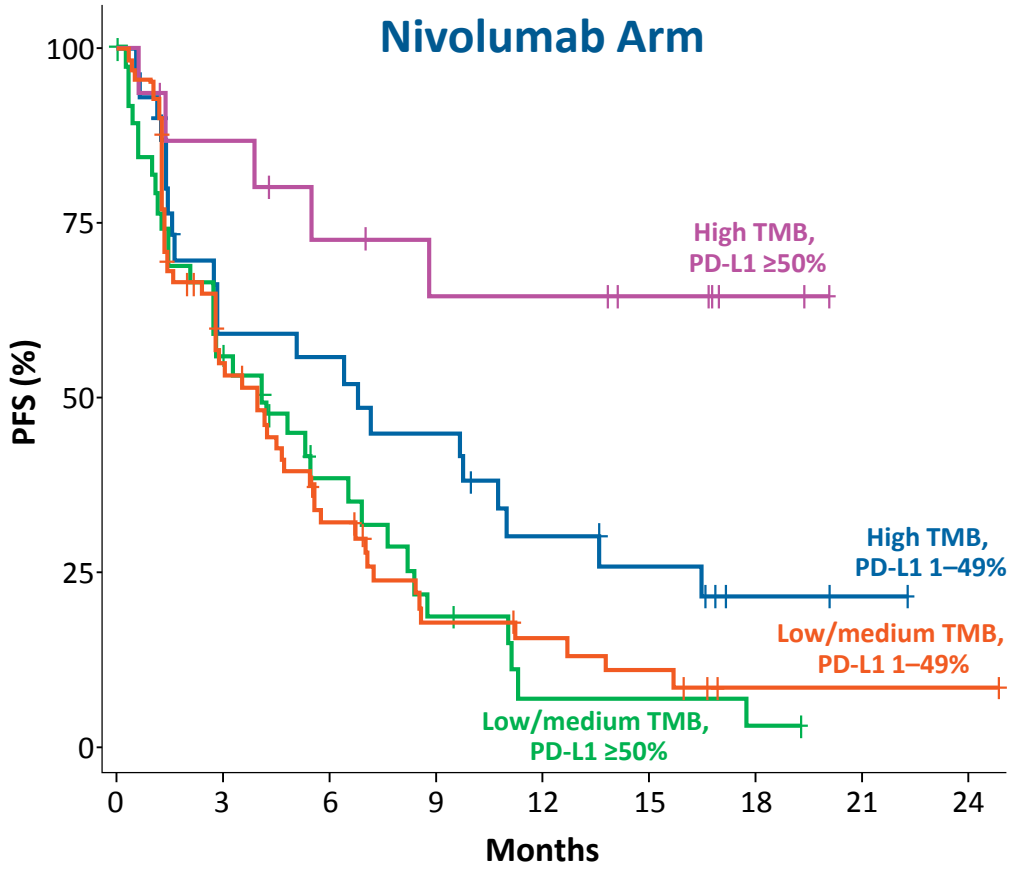


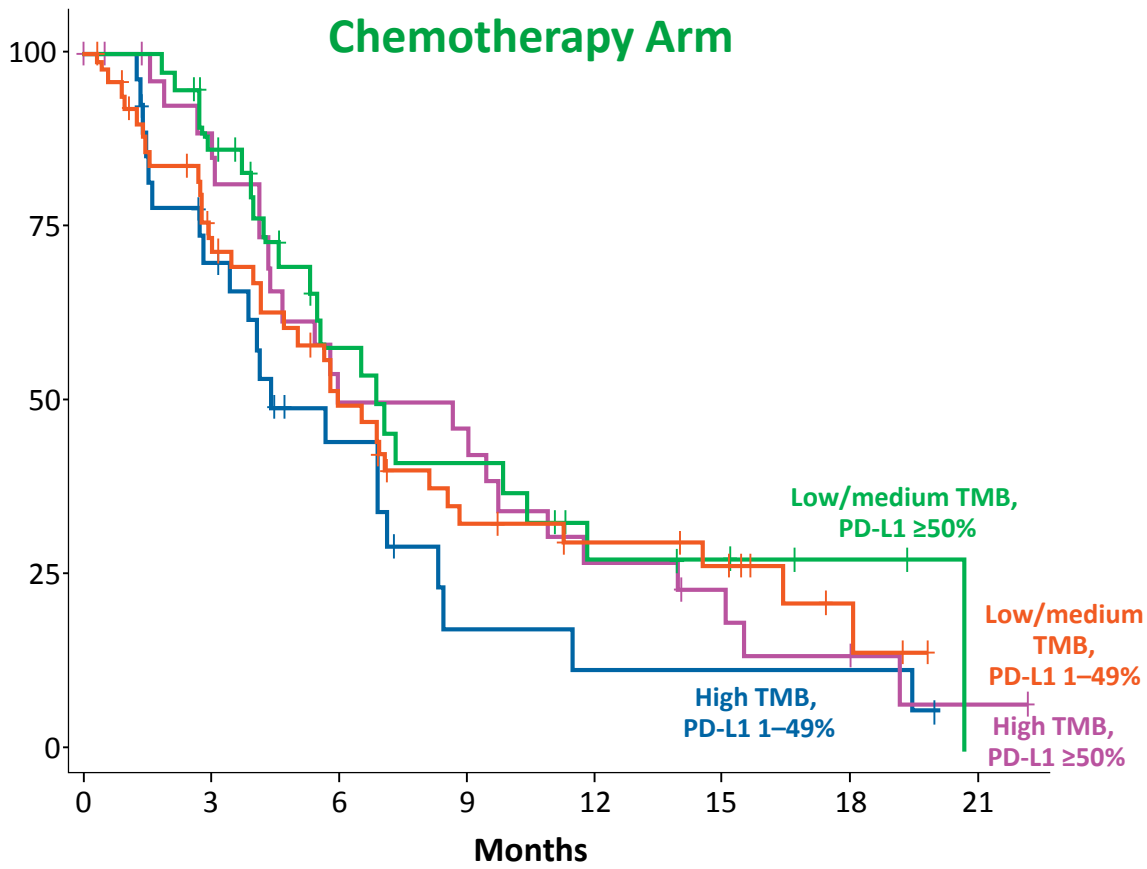
111	99	82	69	59	47	28	11	3	0	
94	87	71	60	50	38	21	6	2	1	

Peters S,et al AACR 2017

PFS by TMB Subgroup and PD-L1 Expression

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



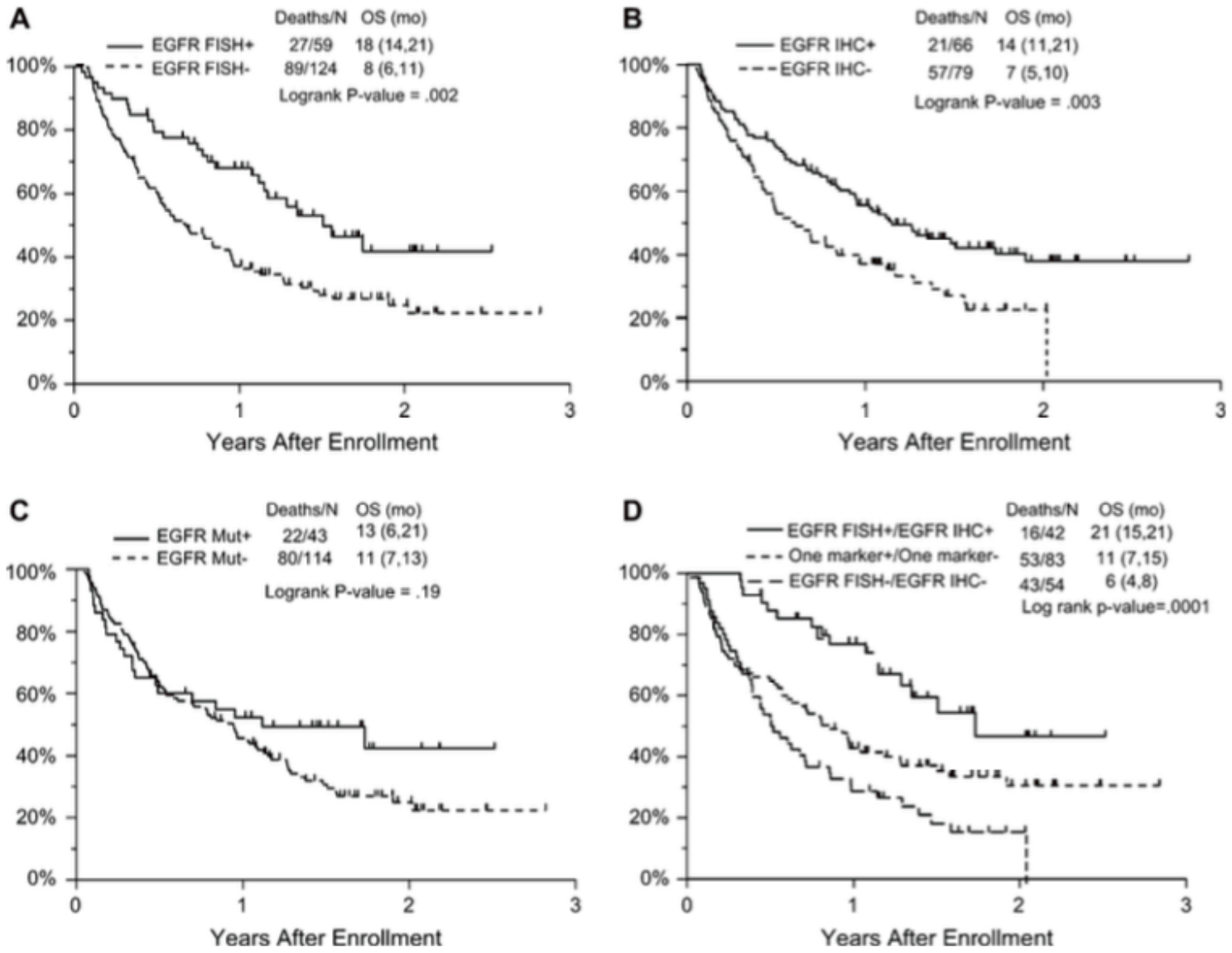


No. at Risk																
High TMB, PD-L1 ≥50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1–49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1–49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Peters S,et al AACR 2017

Two tests are better than one: Is it useful?

Data from a retrospective study of gefitinib



Hirsch FR, Ann Oncol 2007

Overview of phase III studies of anti-PD1/PDL1 therapy in previously treated NSCLC

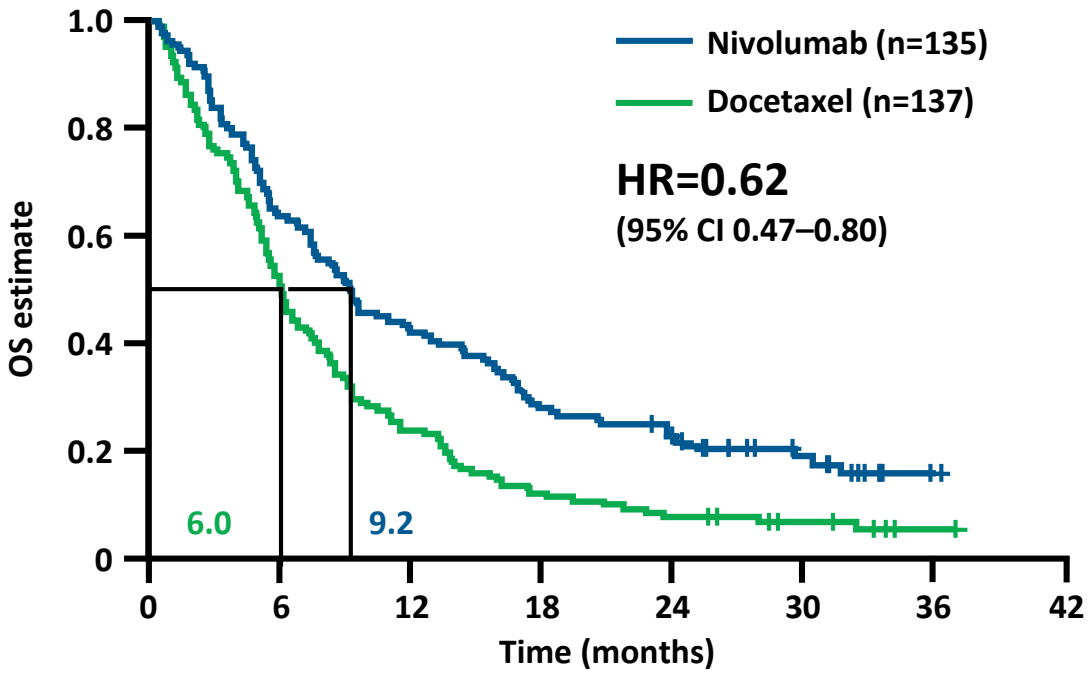
	CheckMate 017[1]	CheckMate 057[1]	KEYNOTE-010[2]	OAK[3]
Study arms	Nivolumab vs docetaxel	Nivolumab vs docetaxel	Pembrolizumab 2 or 10mg/kg vs docetaxel	Atezolizumab vs docetaxel
Phase of study	III	III	II/III	III
PD-L1 selected	No	No	Yes (TPS* ≥1%)	No
Study size, n	272 (135 vs 137)	582 (292 vs 290)	1033 (344 vs 346 vs 343)	850 in primary analysis§ (425 vs 425)
Histology, %				
Non-squamous	0	100	70	74
Squamous	100	0	21	26
Other/unknown	-	-	8	-
Line of therapy, %				
2L	100	88	69	75
3L	0	11	20	25
>3L	0	<1	9	0
Other/unknown	0	0	<1	0
Minimum follow-up of latest data	~24 months	~24 months	~19 months	~19 months

*Tumour proportion score (TPS) is the proportion of viable tumour cells showing partial or complete membrane PD-L1 expression; §1225 patients enrolled in total

1. Barlesi, et al. ESMO 2016; 2. Herbst, et al. ESMO 2016; 3. Barlesi, et al. ESMO 2016

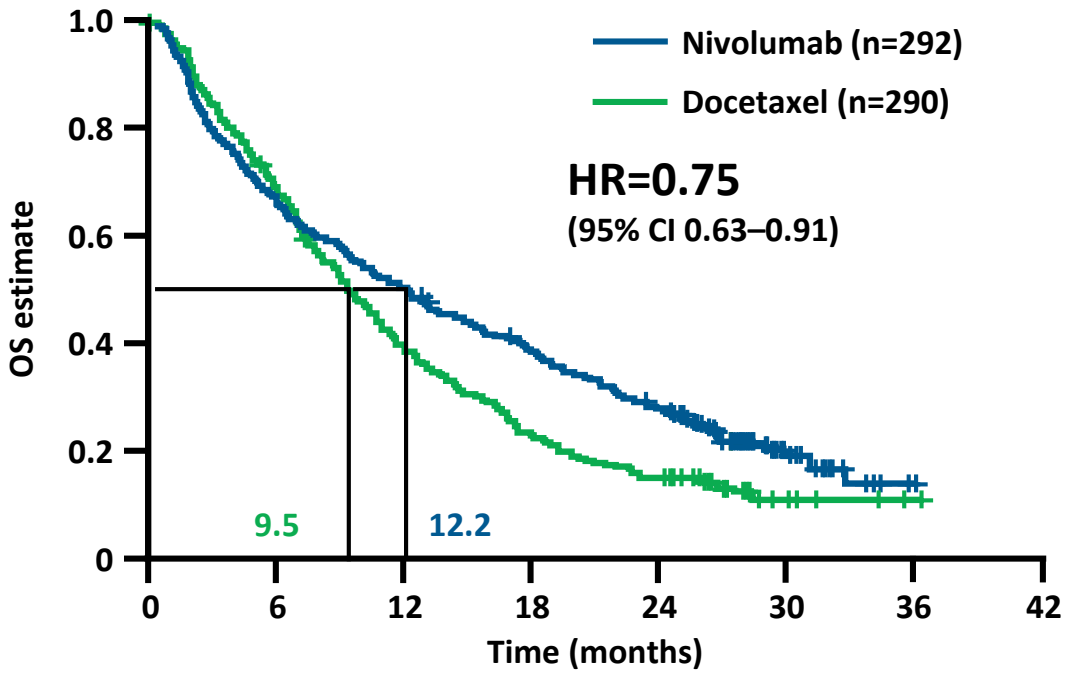
Phase III studies of nivolumab in previously treated NSCLC: OS 2 years minimum follow-up

CheckMate 017 (squamous NSCLC)



	Nivolumab (n=135)	Docetaxel (n=137)
12-month OS rate, %	42	24
24-month OS rate, %	23	8

CheckMate 057 (non-squamous NSCLC)

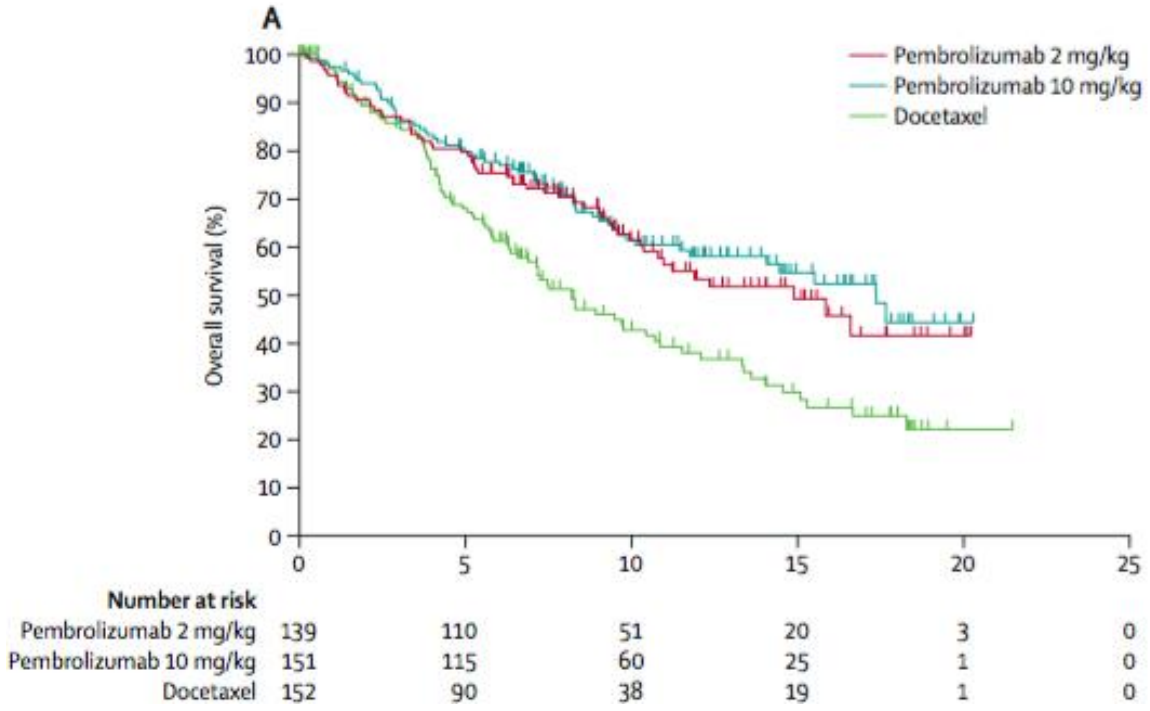


	Nivolumab (n=292)	Docetaxel (n=290)
12-month OS rate, %	51	39
24-month OS rate, %	29	16

Pembrolizumab versus docetaxel in pretreated NSCLC with PD-L1 expression

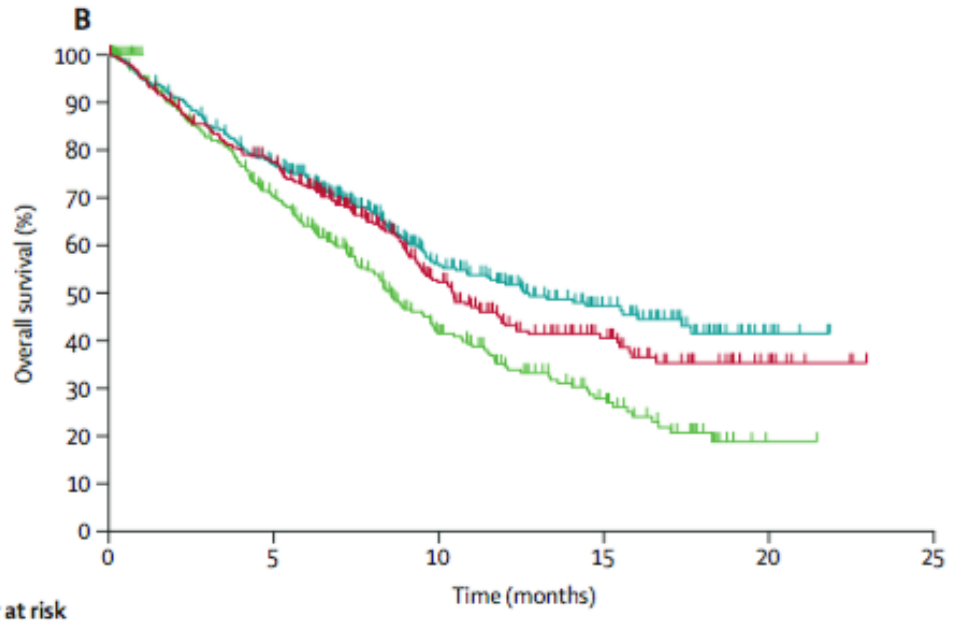
Survival results of the KEYNOTE 010 trial

PD-L1 score 50% or greater



Number at risk						
Pembrolizumab 2 mg/kg	139	110	51	20	3	0
Pembrolizumab 10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

Study population

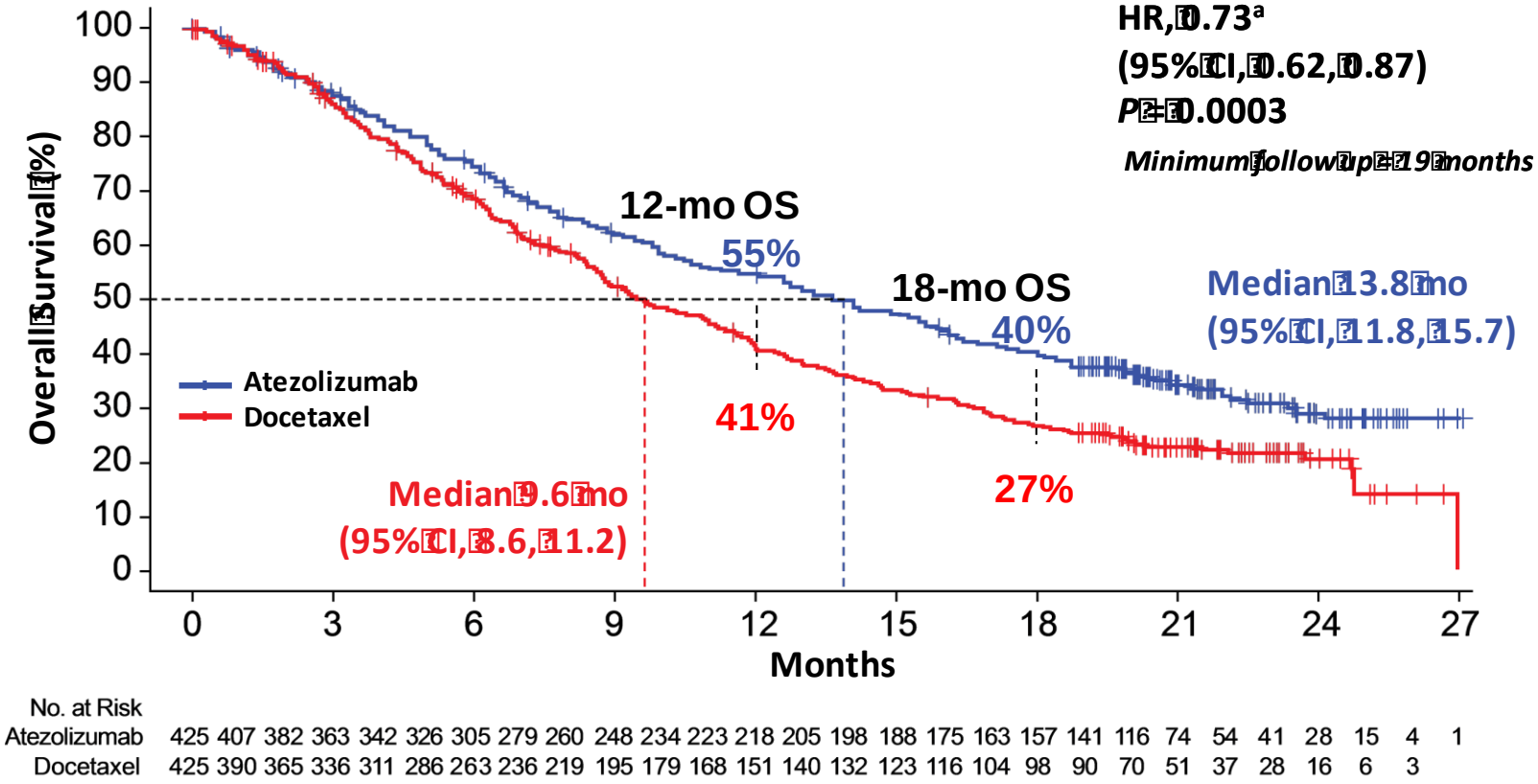


Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Herbst R et al, Lancet 2015

Atezolizumab versus docetaxel in NSCLC: OAK trial

Overall Survival, ITT (n = 850)

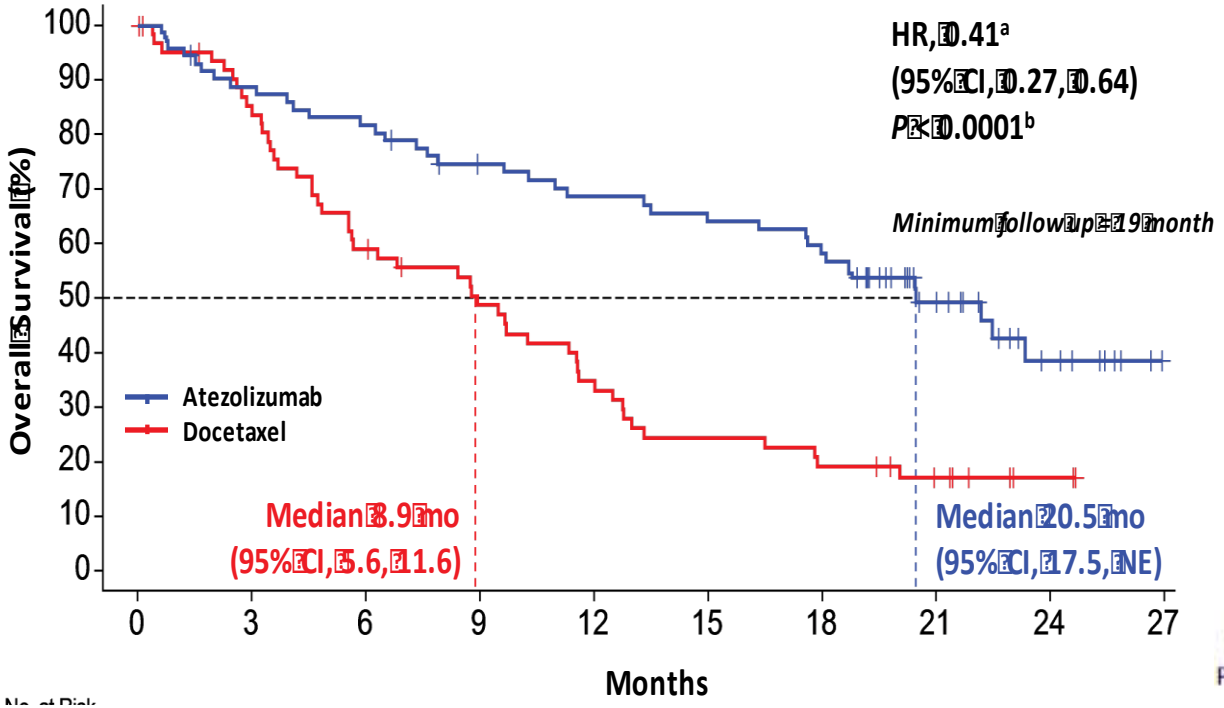


[a]Stratified HR.

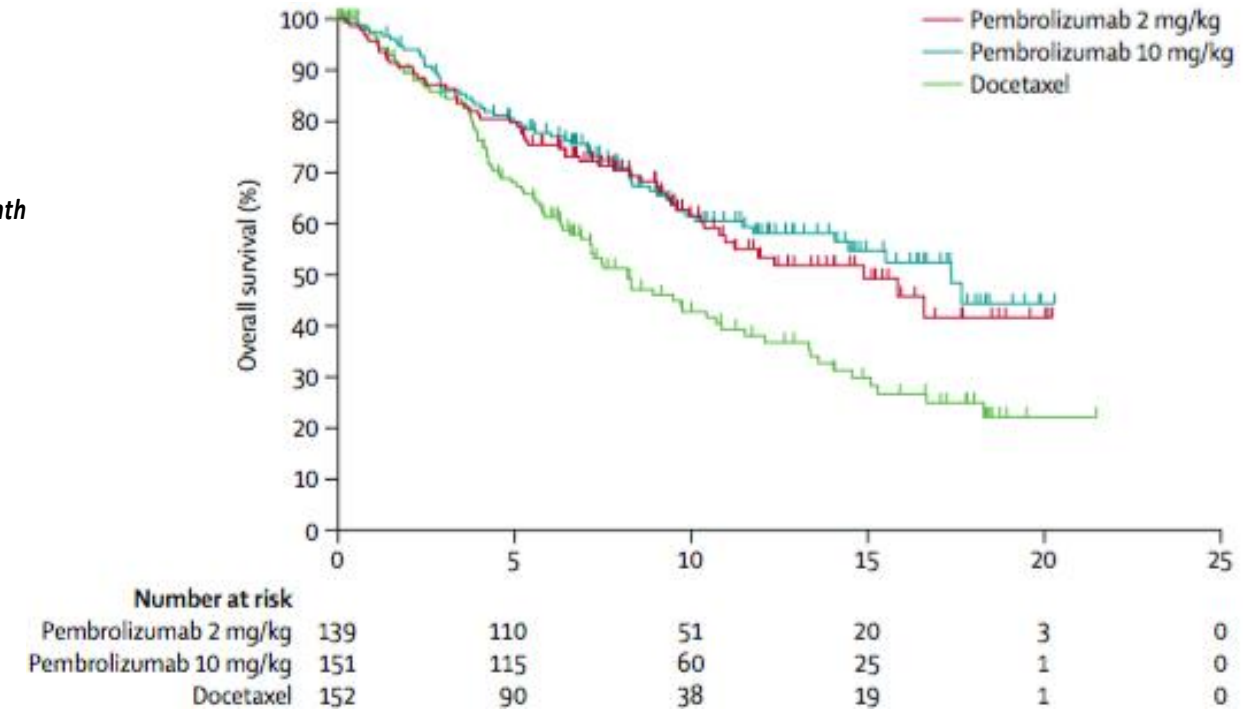
Barlesi F, et al. ESMO 2016

High levels of PD-L1 expression predicts higher OS benefit with immunotherapy

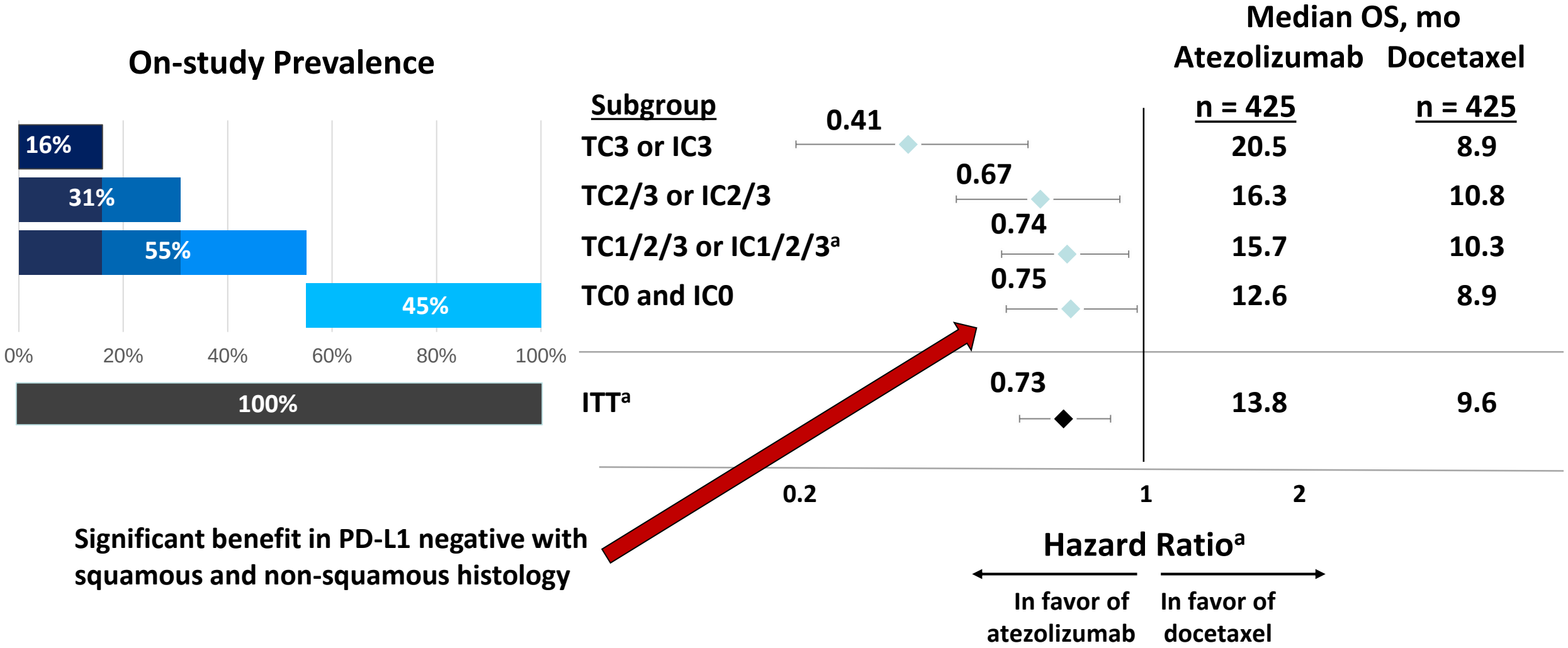
Atezolizumab in PD-L1+++



Pembrolizumab in PD-L1 score 50% or higher



Evidence of survival benefit in PD-L1 negative: OAK trial results

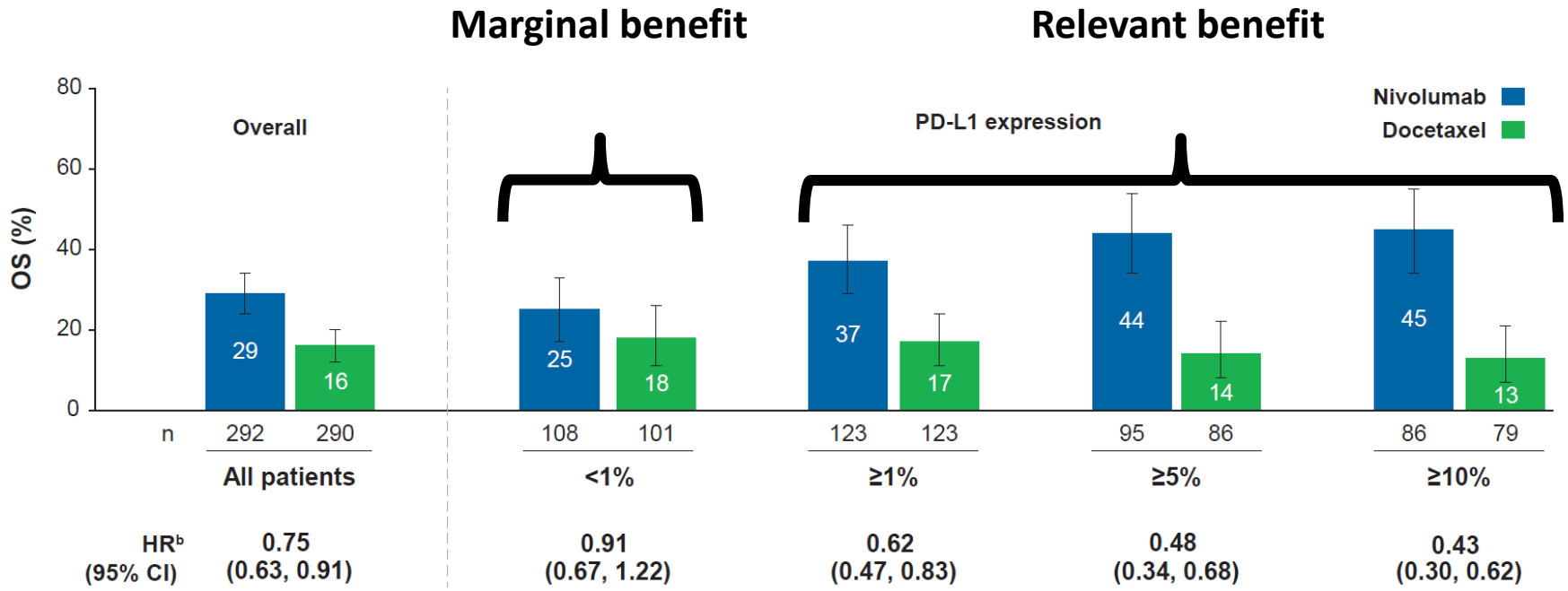


Significant benefit in PD-L1 negative with squamous and non-squamous histology

[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

2-year OS Rates Overall and by PD-L1 Expression Level in CheckMate 057 (non-SQ NSCLC)



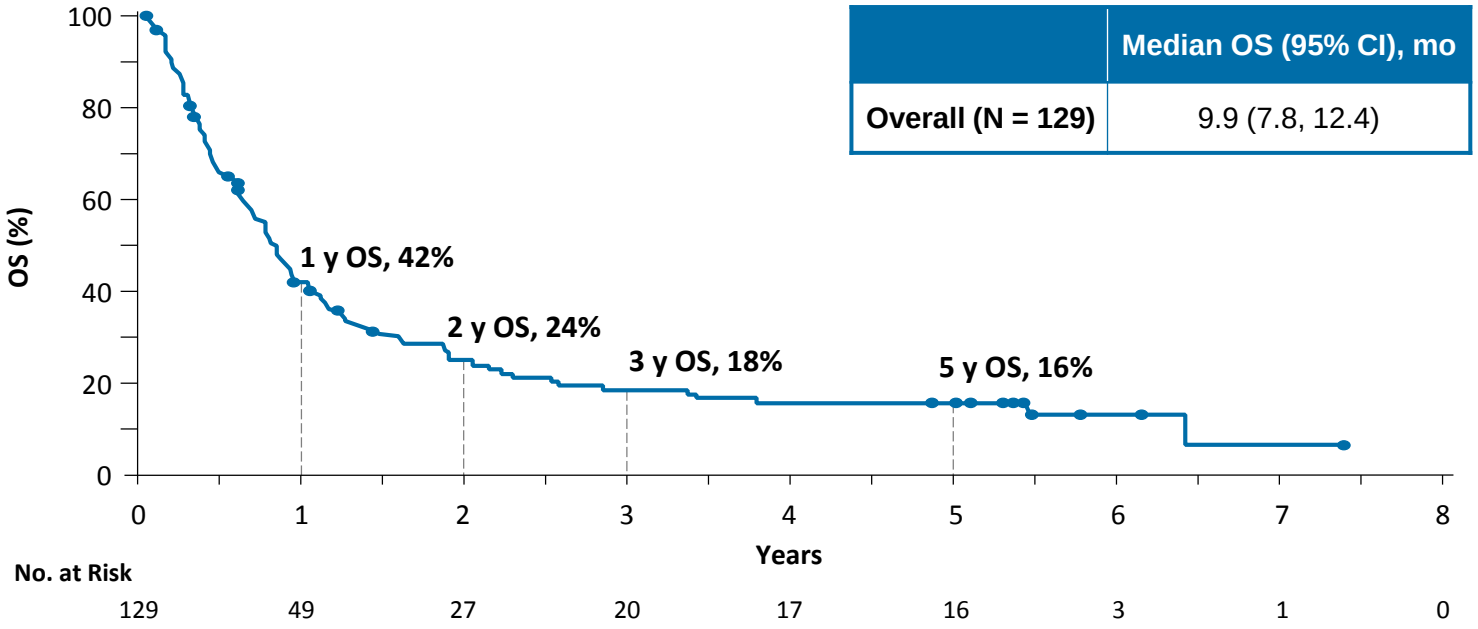
- In CheckMate 057, consistent with the primary analysis,[2] PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)

[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

Who are long-term survivors?

5-Year Estimates of OS in CA209-003: Phase 1 Nivolumab in Advanced NSCLC



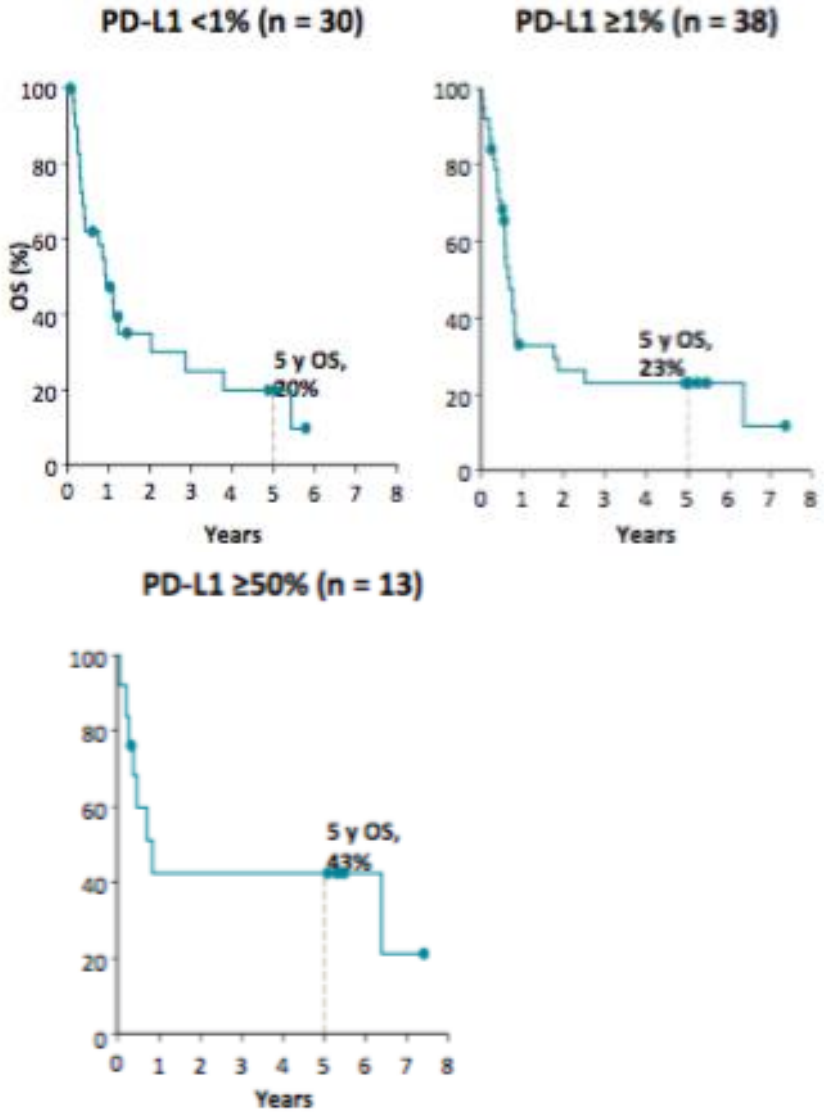
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

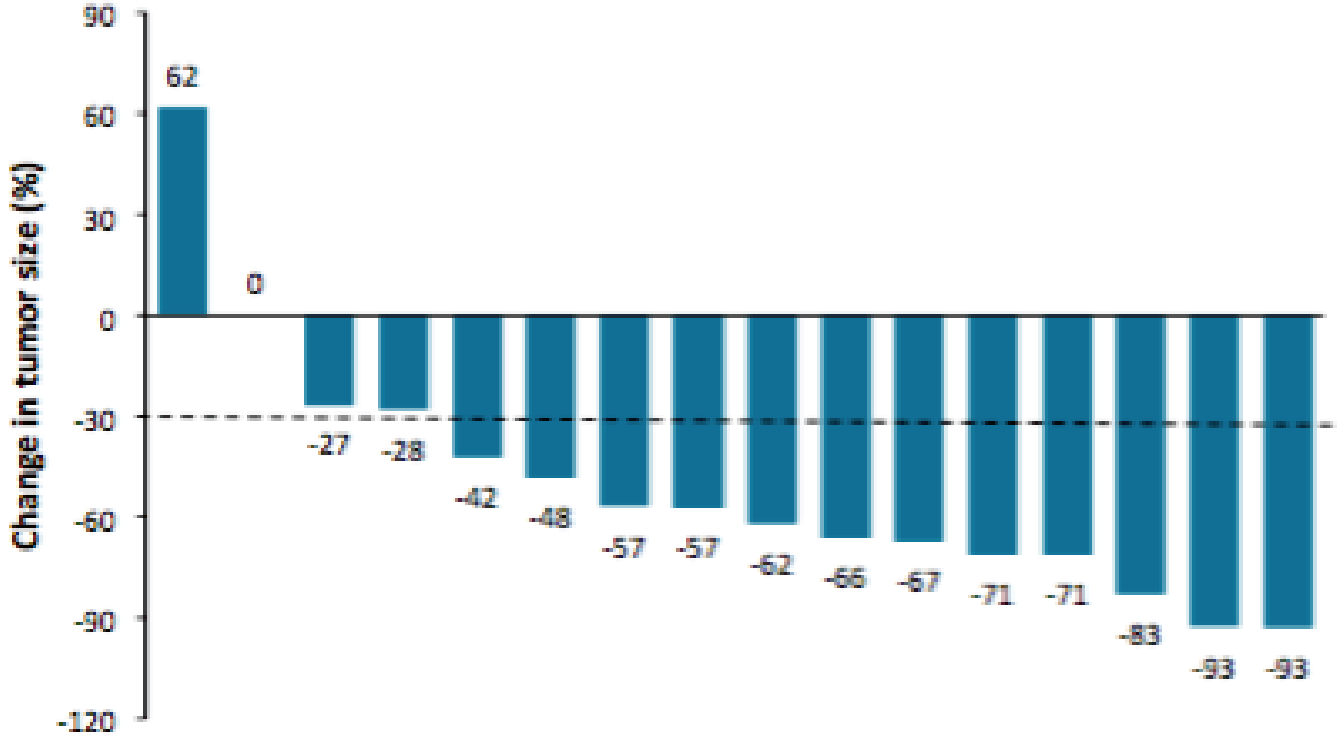
No difference in squamous and non-squamous histology (5 years survival 16% and 15%)

Brahamer J, AACR 2017

Who are long-term survivors?

5-Year Estimates of OS in CA209-003: Phase 1 Nivolumab in Advanced NSCLC



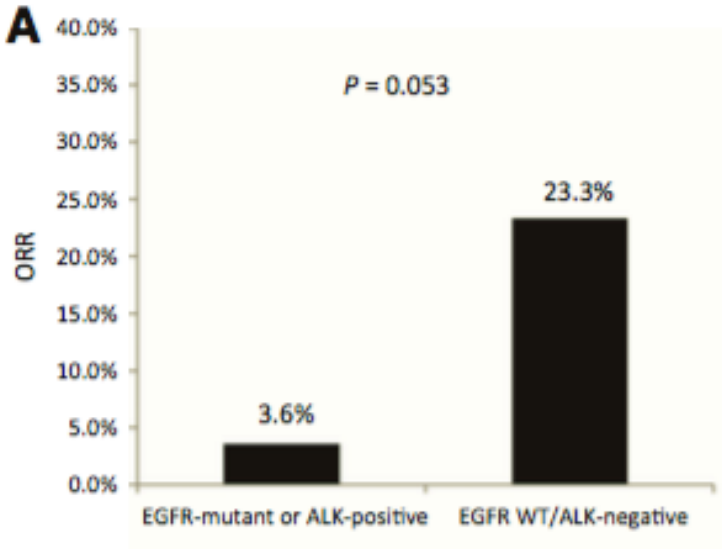


Brahamer J, AACR 2017

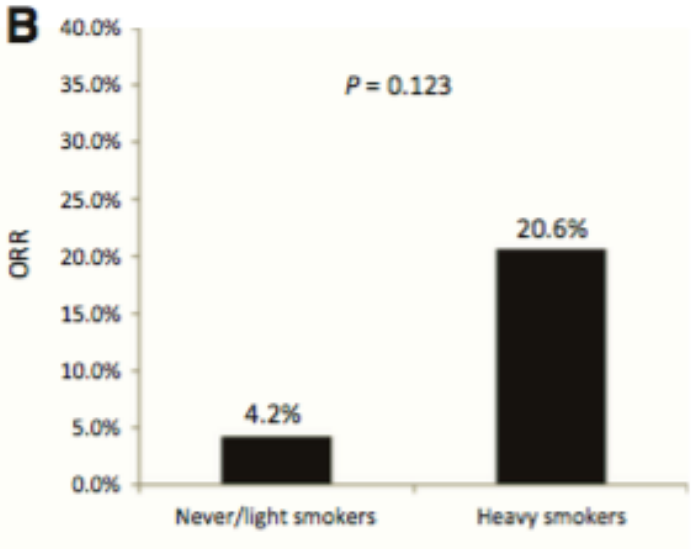
Which patients are not candidate for second-line immunotherapy?

Low efficacy of checkpoint inhibitors in *EGFR*$^{mut+}$ or *ALK*$^{+}$

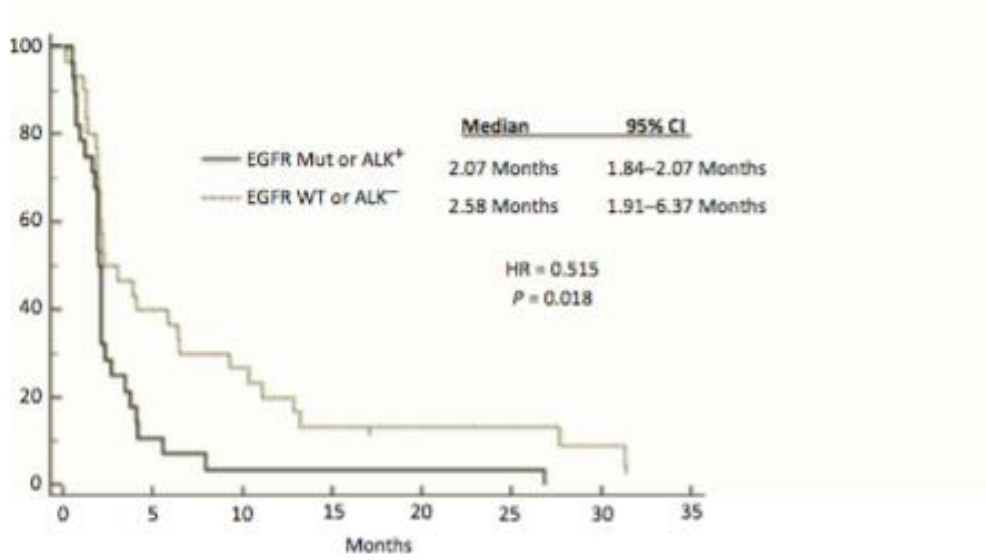
Response in *EGFR*$^{mut+}$ or *ALK*$^{+}$



Response according to smoke



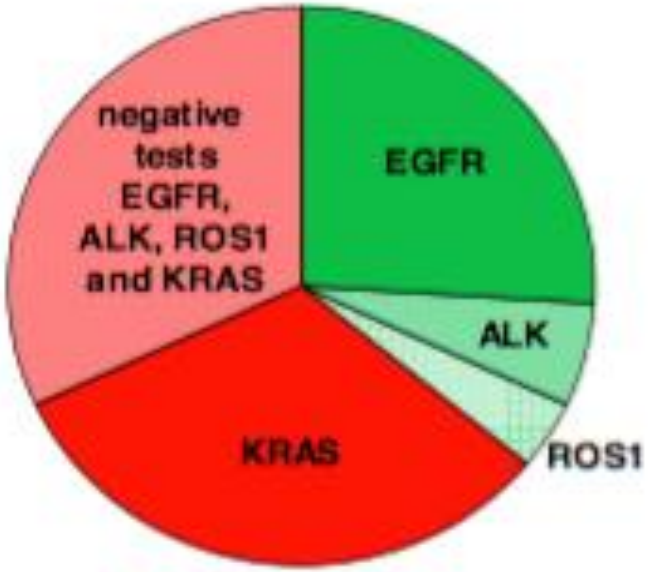
PFS in *EGFR*$^{mut+}$ or *ALK*$^{+}$



Gainor JF, et al. Clin Cancer Res 2016

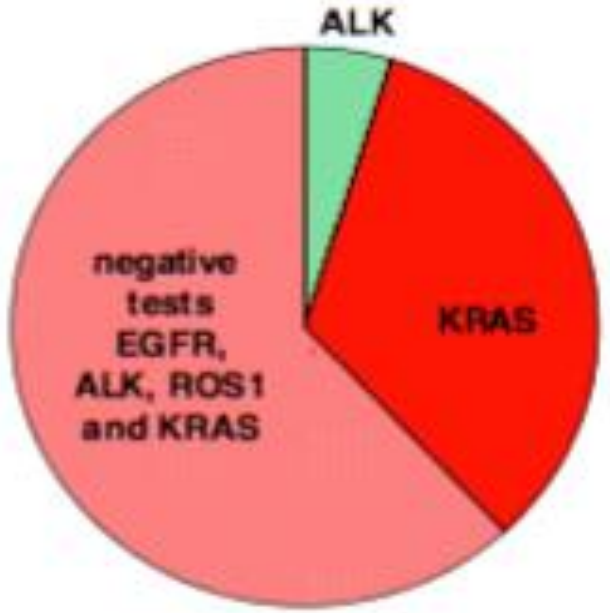
PD-L1 frequently not expressed in presence of driver mutations

PD-L1 <50%



driver oncogene with approved inhibitor (36.0%, 18/50)

PD-L1>50%

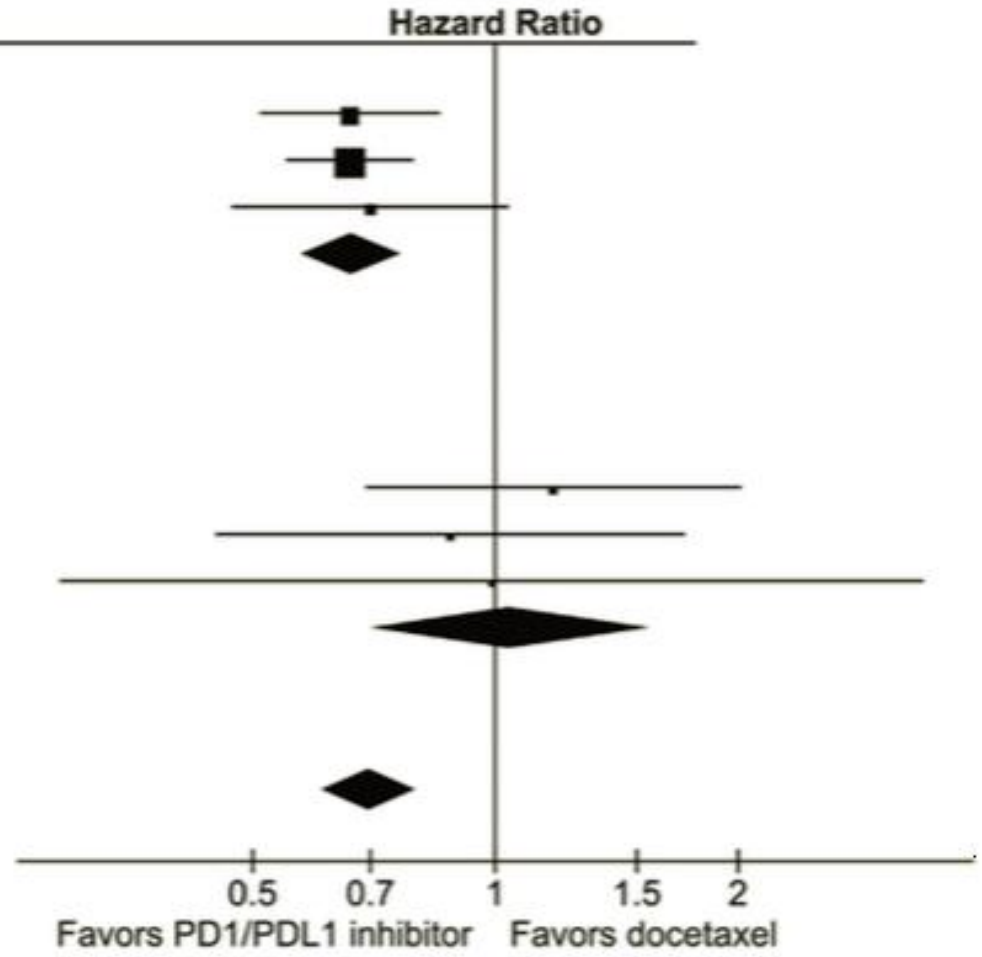


driver oncogene with approved inhibitor (4.8%, 1/21)

Rangachari D et al, JTO 2017

Meta-analysis of trials with checkpoint inhibitors in patients with *EGFR* mutations

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**

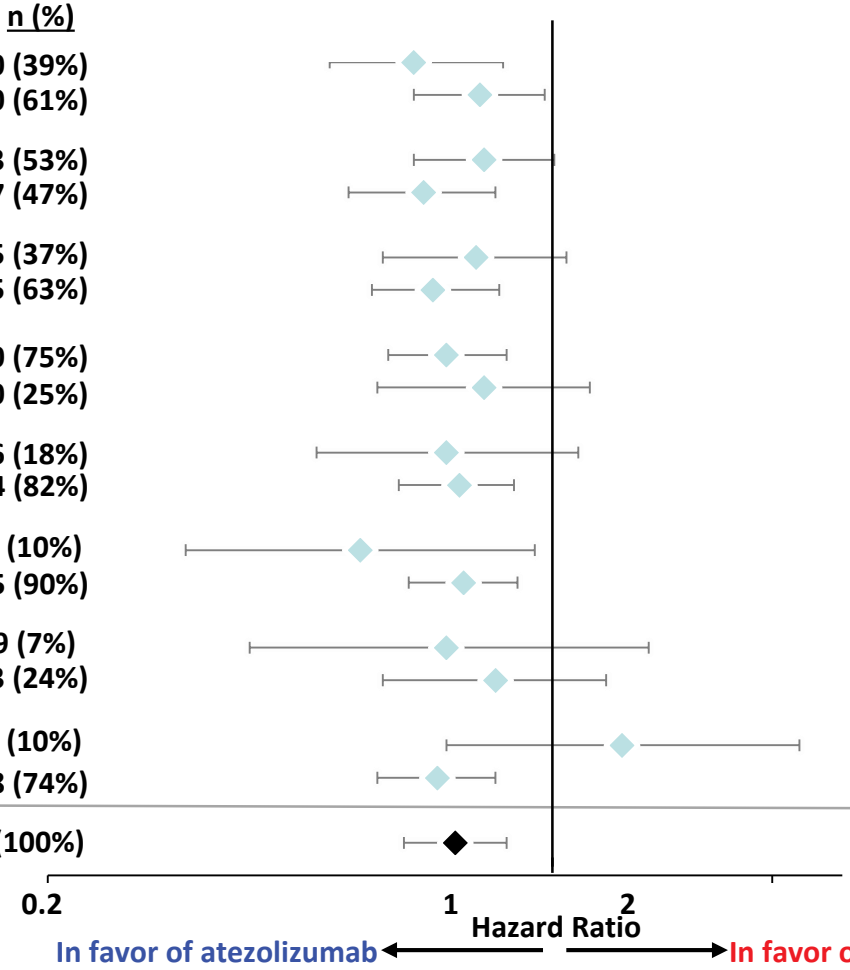


Lee CK et al, JTO 2017

Which patients are not candidate for second-line immunotherapy?

Overall survival in EGFR mutant NSCLC in the OAK trial

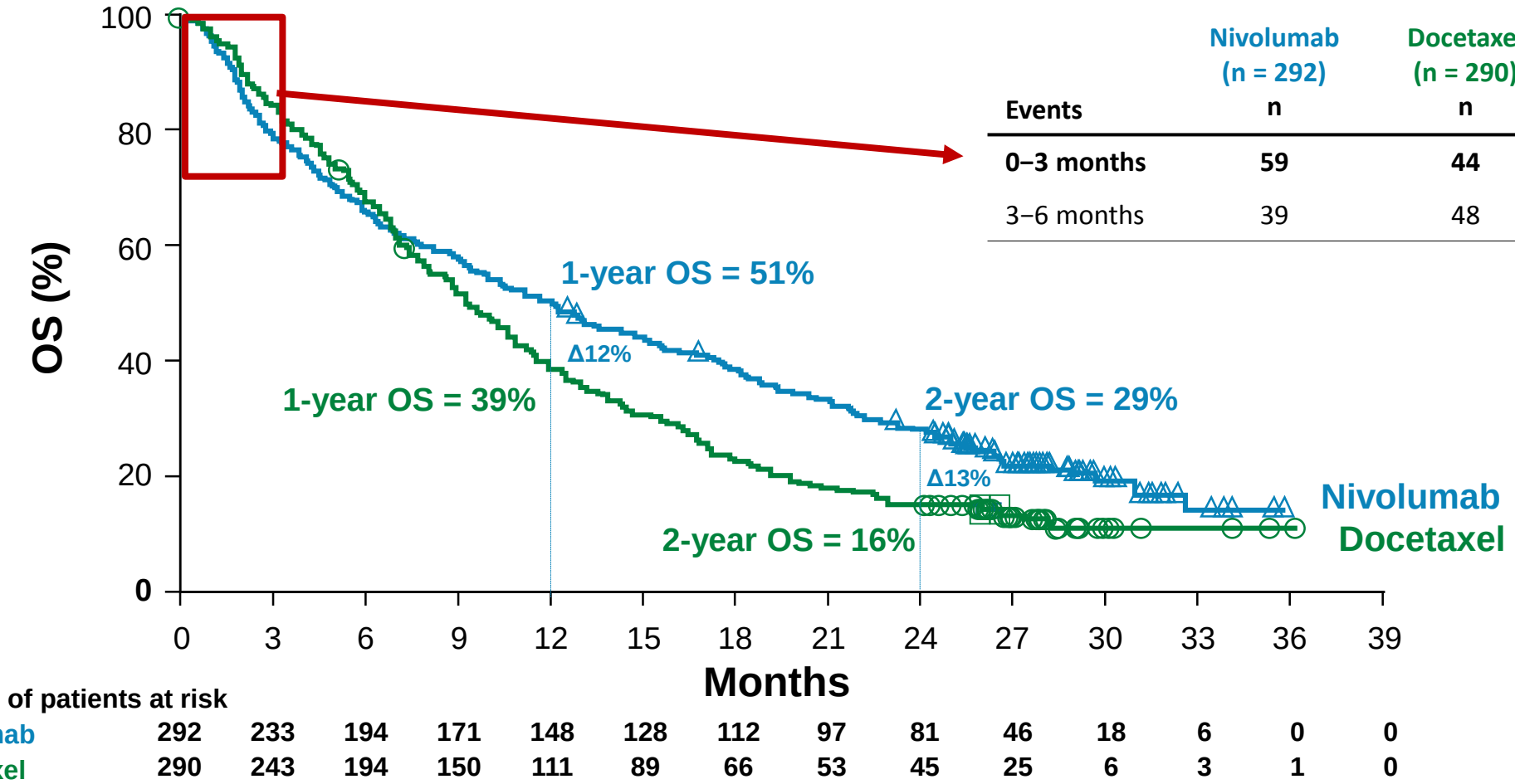
Subgroup	n (%)	HR[a]	Median OS, mo Atezolizumab n = 425	Median OS, mo Docetaxel n = 425
Female	330 (39%)	0.64	16.2	11.2
Male	520 (61%)	0.79	12.6	9.2
< 65 years	453 (53%)	0.80	13.2	10.5
≥ 65 years	397 (47%)	0.66	14.1	9.2
ECOG PS 0	315 (37%)	0.78	17.6	15.2
ECOG PS 1	535 (63%)	0.68	10.6	7.6
1 prior therapy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

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]

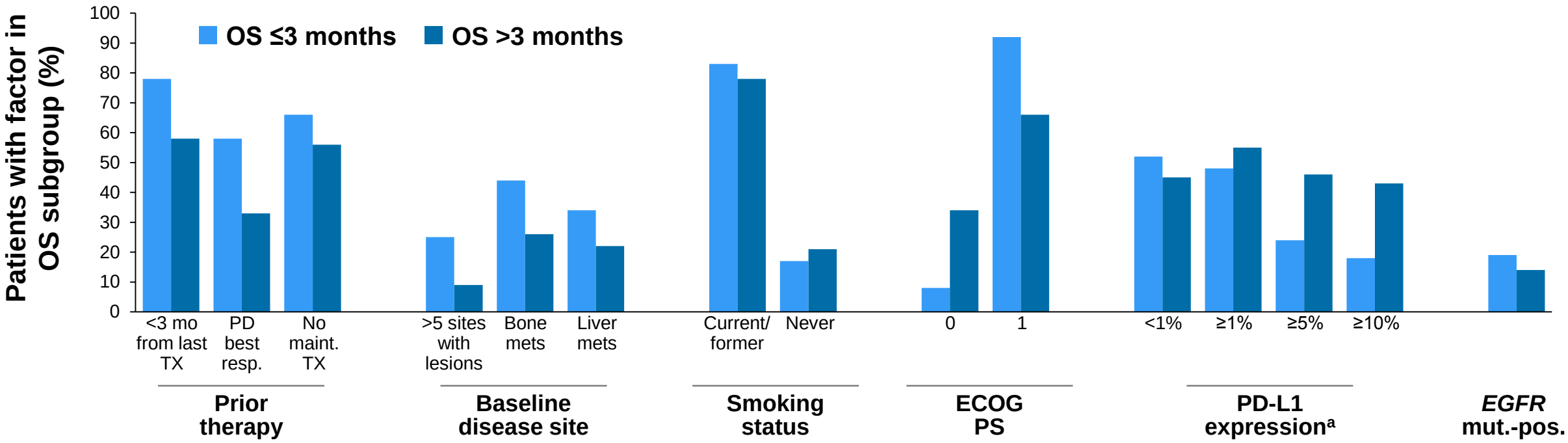
Number of patients at risk

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?

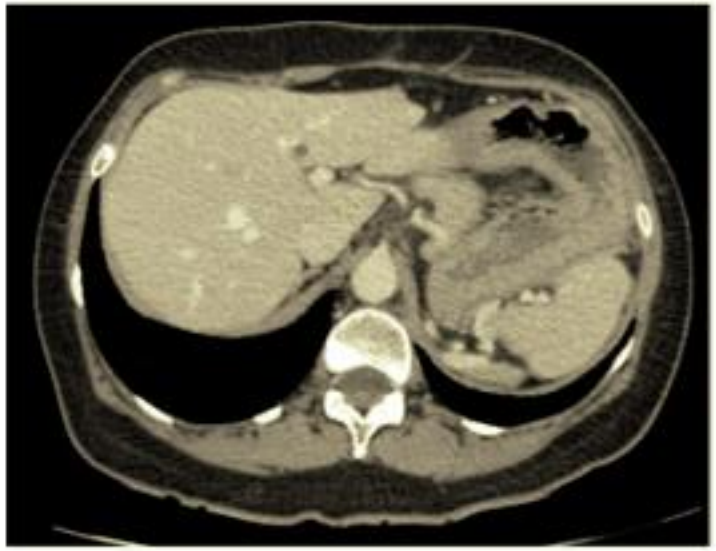
Combination of clinical factors and PD-L1 expression in Checkmate 057



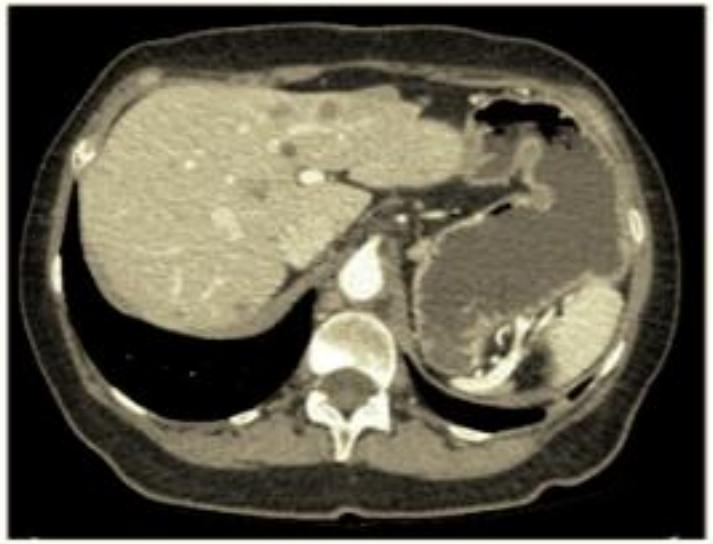
- **Post-hoc, exploratory multivariate analysis suggested that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower or no tumor PD-L1 expression may be at higher risk of death within the first 3 months**
  - **These included the following known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

Peters S, et al WCLC 2016

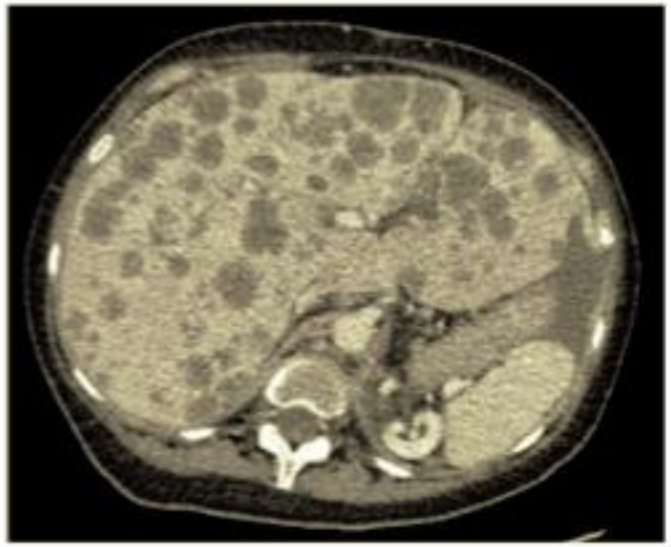
Hyperprogressive disease is a new pattern of progression in patients treated by anti-PD-1/PD-L1



Before



Baseline

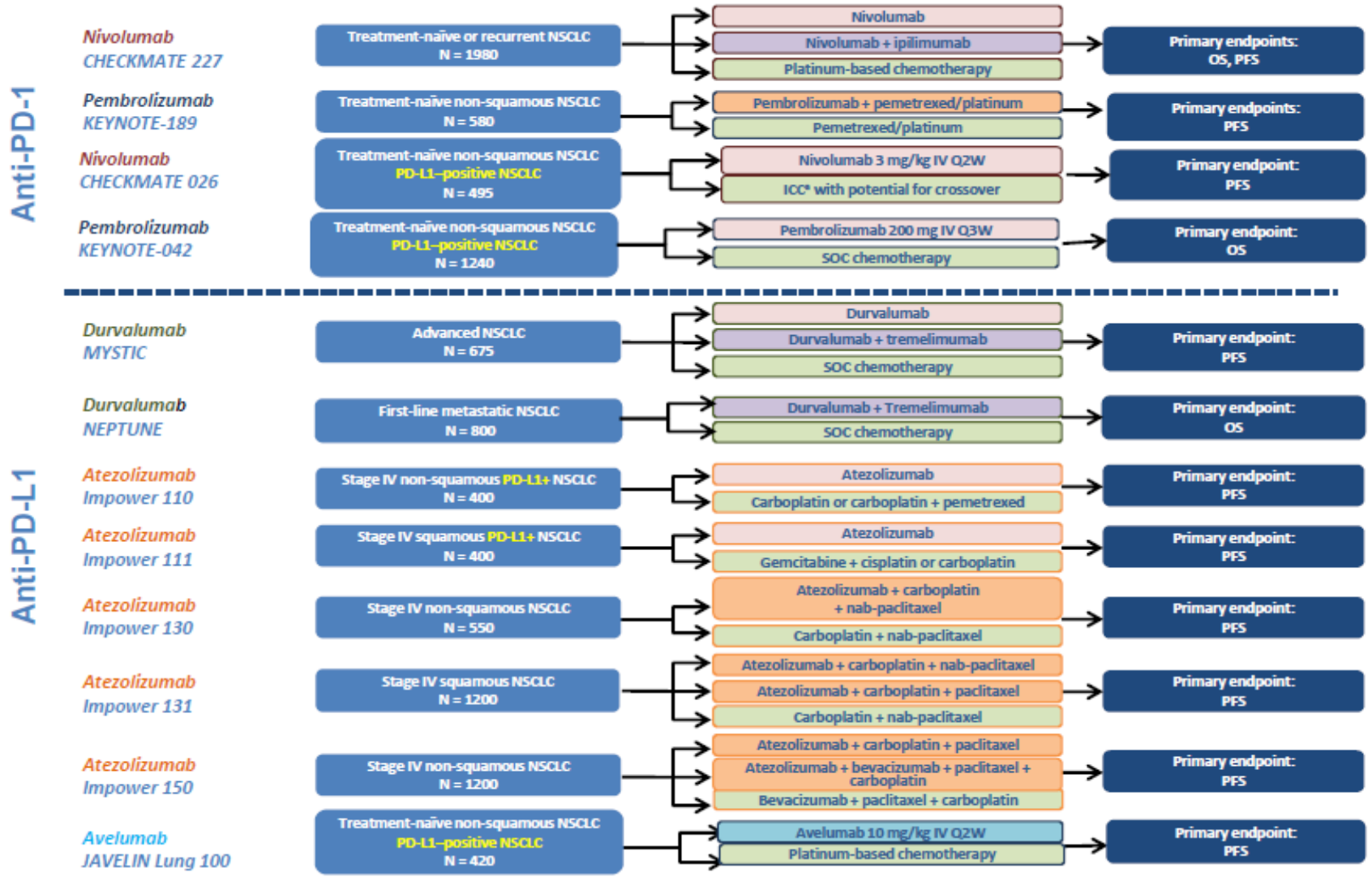


1st Evaluation

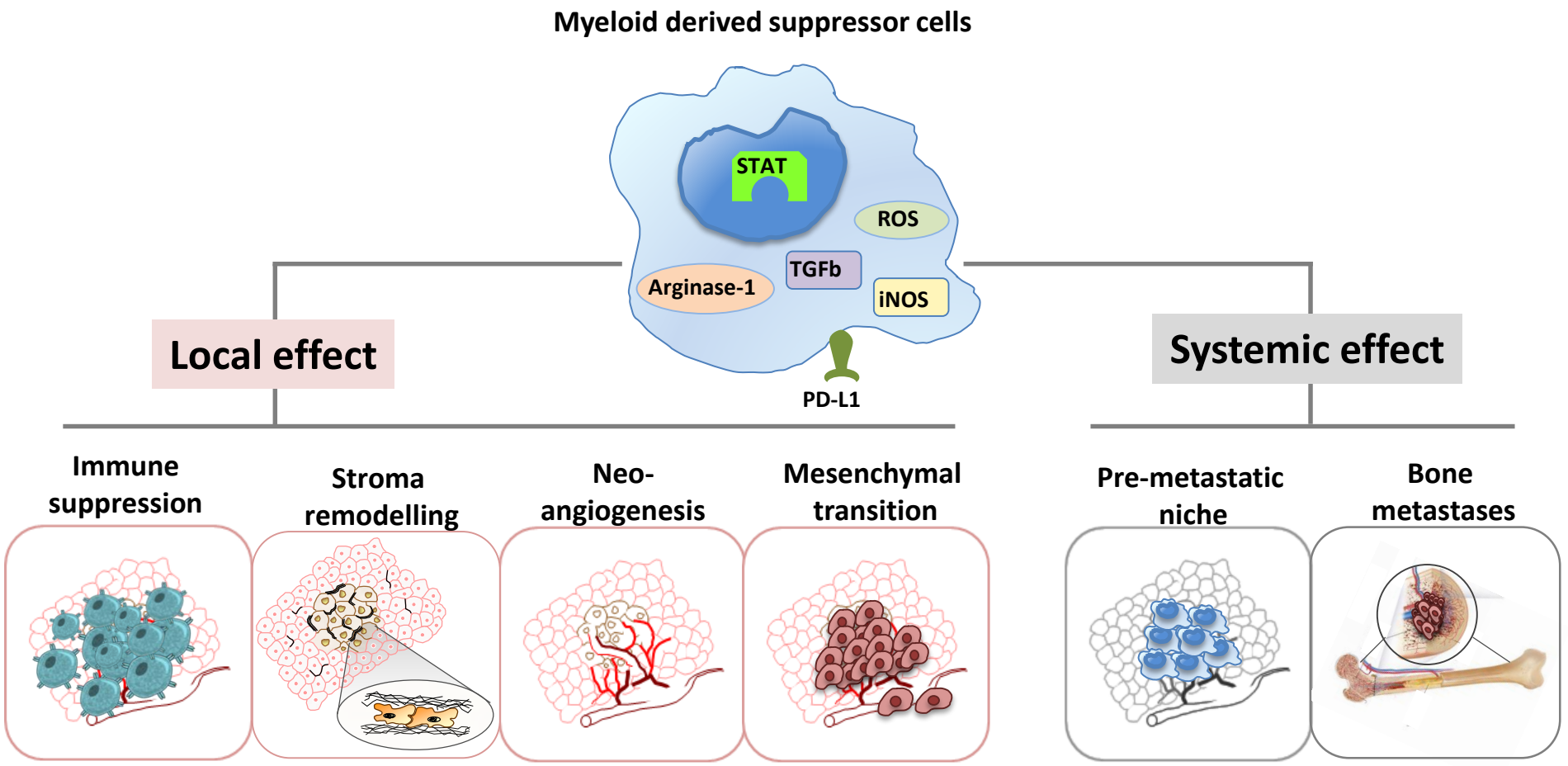
	All patients ($n = 131$)	Non-HPD ($n = 119$)	HPD ($n = 12$)	*P* value (Wilcoxon test)
Tumor burden (estimated by RECIST 1.1), mm	78 (12–364)	76 (12–364)	91.6 (12–167)	0.64
Age, y	55 (22–82)	55 (22–82)	65.5 (32–82)	0.007
Leukocytes (1.e+9/L)	7.1 (2.4–41.7)	7.1 (2.4–41.7)	7.95 (3.5–21.0)	0.45
Lymphocytes (1e+9/L)	1.2 (0.1–3.5)	1.2 (0.1–3.5)	0.95 (0.6–2.9)	0.64
Neutrophils (1e+9/L)	5.1 (1.4–37.9)	5.1 (1.4–37.9)	5.0 (2.0–18.7)	0.69
CRP (mg/L)	21.1 (0.5–317.7)	21.1 (0.5–317.7)	21.7 (5.2–68)	0.97
Fibrinogen (g/L)	4.8 (2.8–9.6)	4.9 (2.8–9.6)	4.7 (3.2–7.1)	0.43
LDH (UI/L)	204 (9–1195)	198 (9–1195)	248 (132–547)	0.097
Albumin (g/L)	36 (20–61)	36 (20–61)	34.5 (30–39)	0.23

Champiat et al. Clin Cancer Res 2016

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

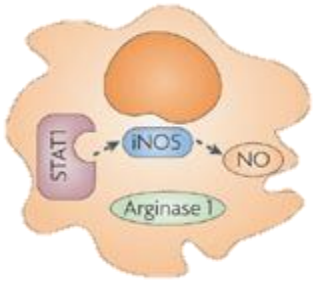


Myeloid-derived suppressor cells: the best tumor allies



Immunomodulating properties of non-immunological cancer therapies

Myeloid derived suppressor cells



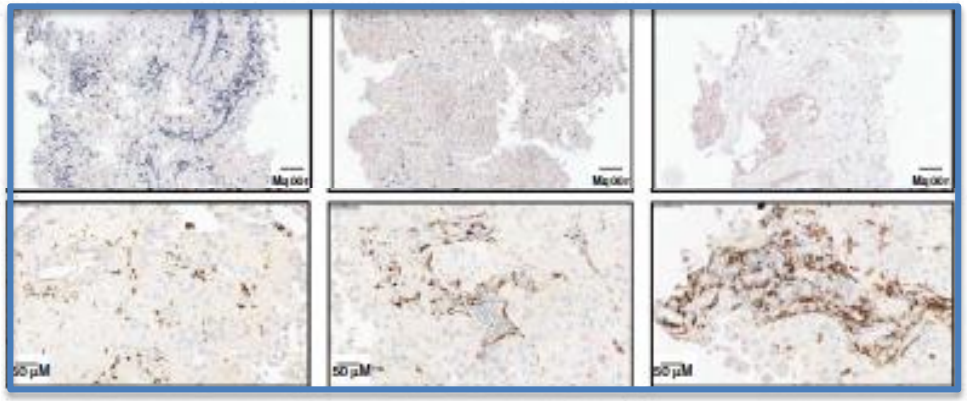
Anthracyclines
Gemcitabine
Fotemustine

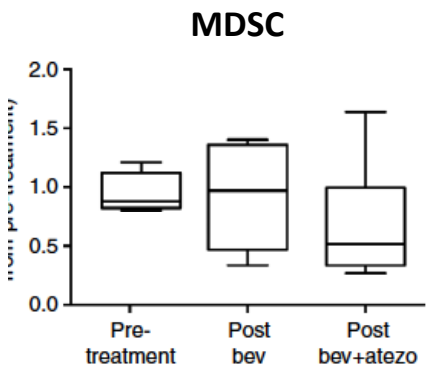
Dasatinib
Ibrutinib
Bevacizumab
Sunitinib
Pazopanib
Axitinib
PI3Ki

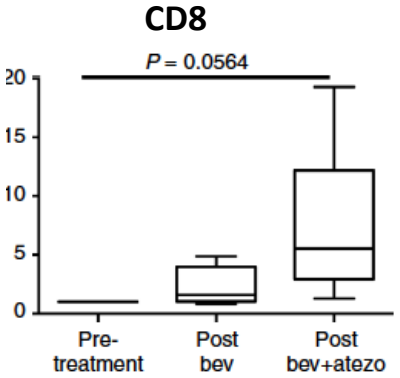
Radiotherapy

IDOi
Anti-TGFb
Anti-CSF1R

Strong rationale for combining bevacizumab with immunotherapy

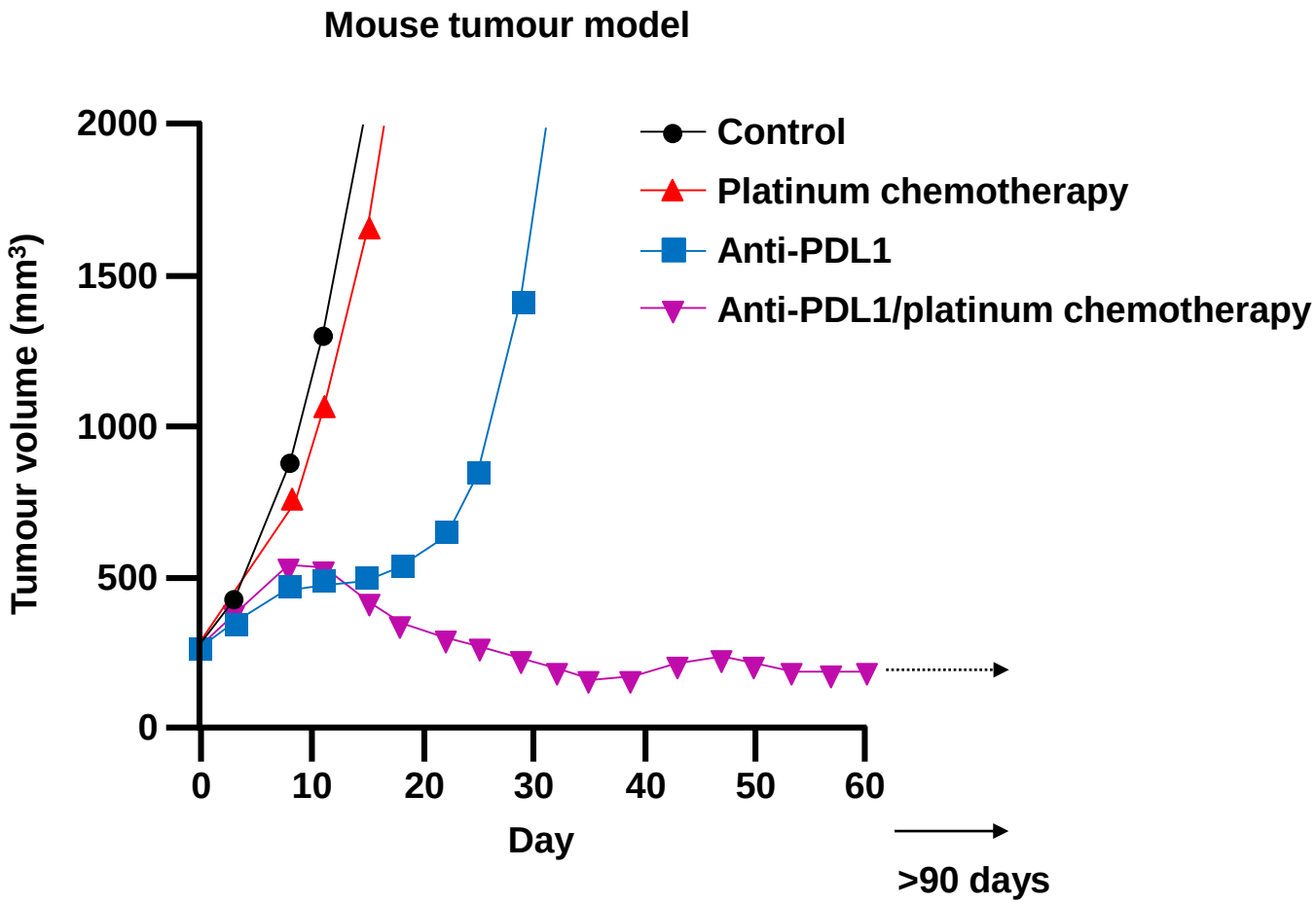






Wallin et al., Nature Communications 2016

Chemotherapy can promote an immune response and may combine synergistically with checkpoint inhibition

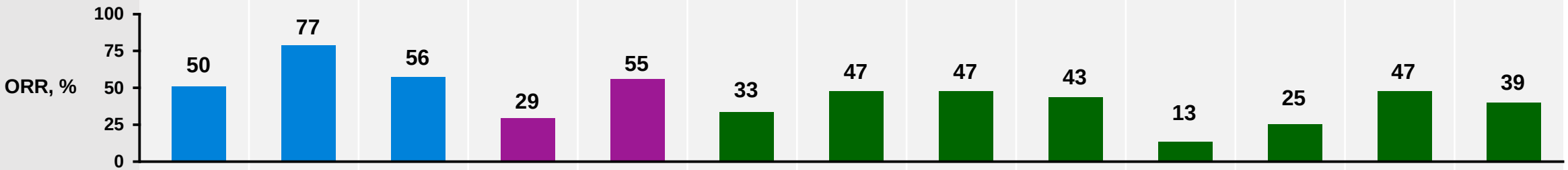


Camidge, et al. WCLC 2015 (Abs ORAL02.07)

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

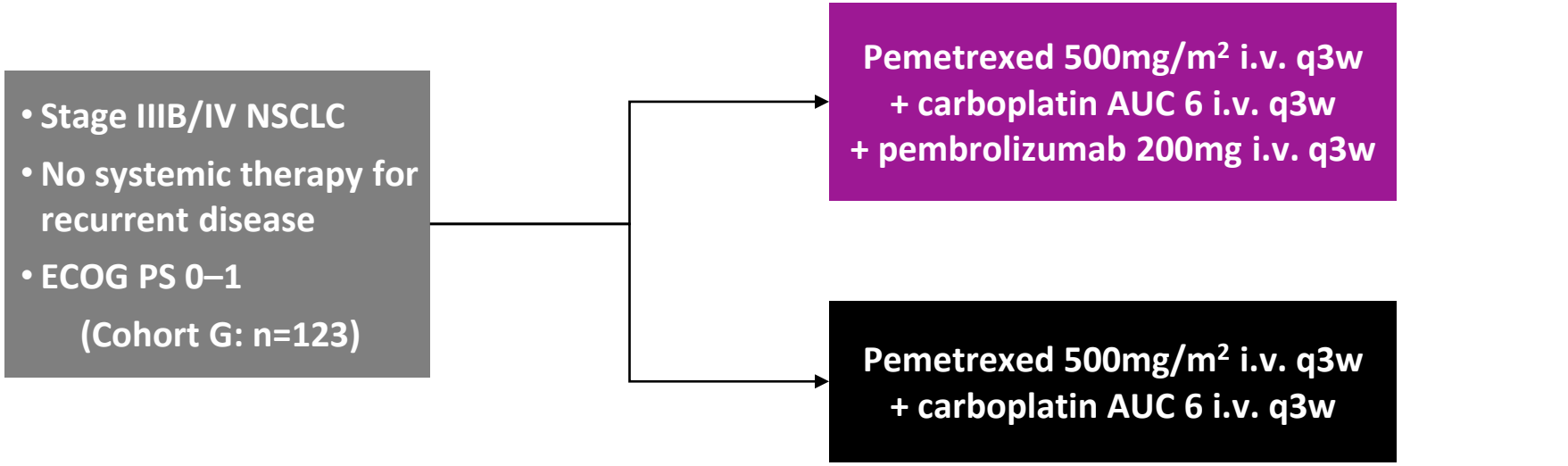
Combinations with chemotherapy | **Immune doublets**

	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

First-line immunotherapy plus chemo combination: pembrolizumab plus chemo (KEYNOTE-021, cohort G)



Endpoints

1 **ORR**

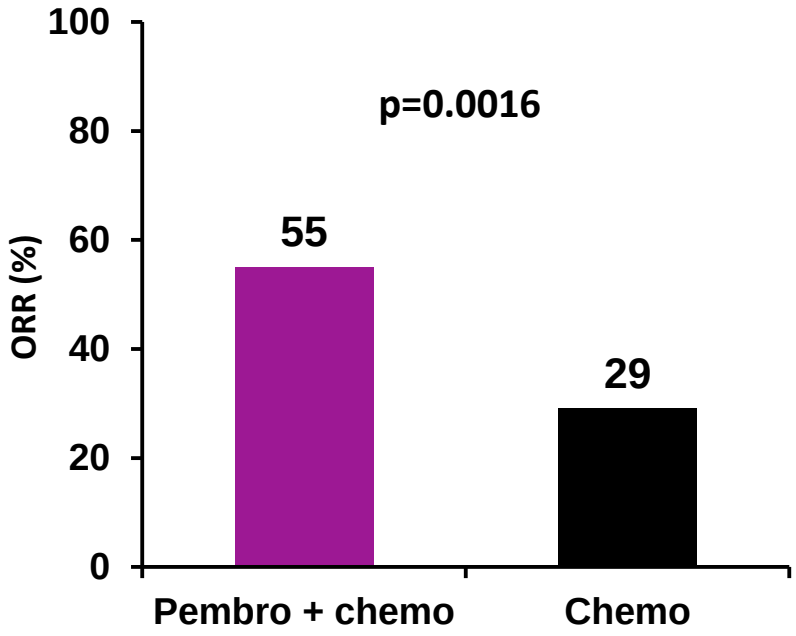
2 **OS, PFS and DoR**

Cohorts A–C are pembrolizumab + platinum doublet chemotherapy; Cohorts D and H are
pembrolizumab + ipilimumab; Cohorts E and F are pembrolizumab + EGFR TKI

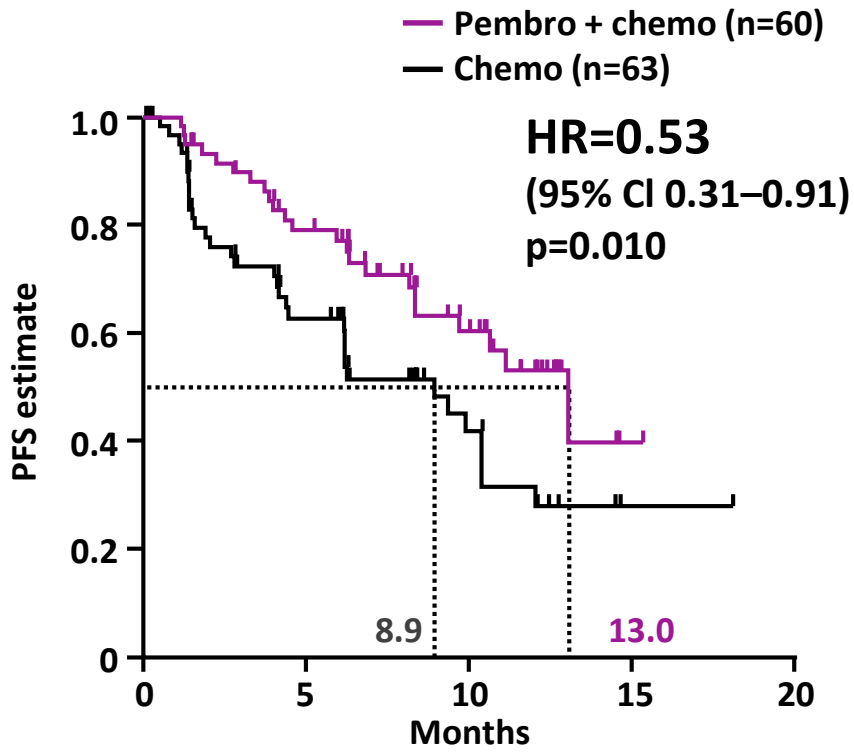
Langer, et al. Lancet Oncol 2016 17(11): 1497–508

First-line immunotherapy plus chemo combination: pembrolizumab plus chemo (KEYNOTE-021, cohort G)

ORR



PFS



Langer, et al. Lancet Oncol 2016 17(11): 1497–508

Options for metastatic NSCLC in 2017