SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Policlinico S. Orsola-Malpighi

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Immunotherapy in NSCLC: how to predict efficacy

Andrea Ardizzoni
UOC Oncologia Medica

Immunotherapy ICPIs) in A-NSCLC: Current standard of care

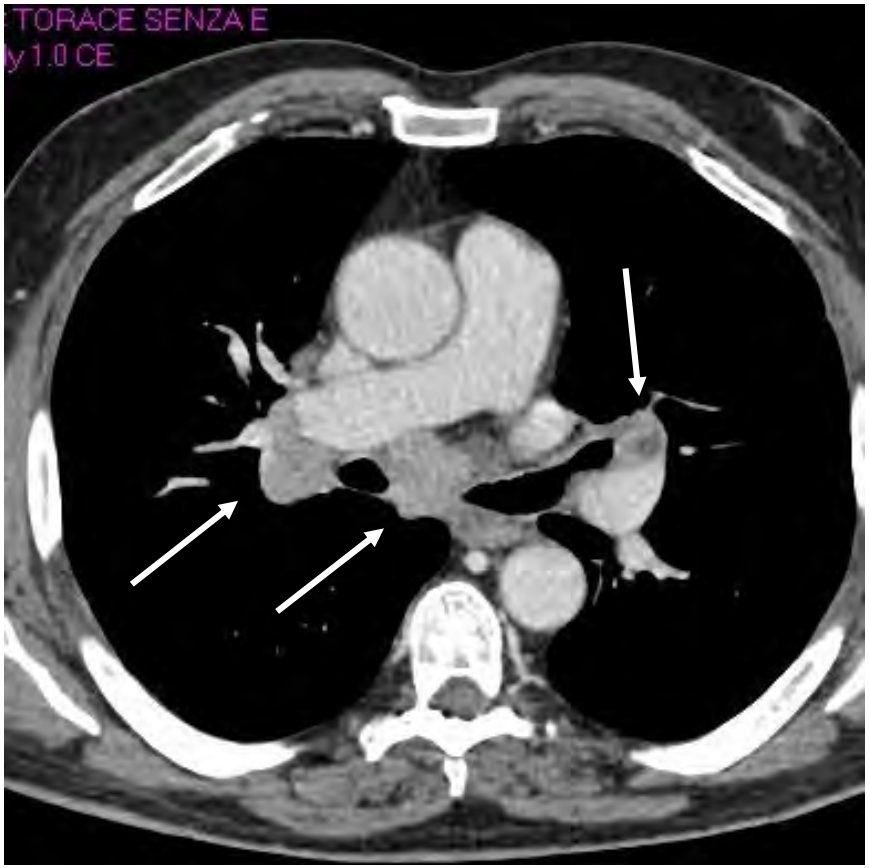
- **Single agent ICPIs in second/third line: nivolumab, atezolizumab & pembrolizumab (only PDL1+ ≥1%)**
- **Single agent durvalumab post-CT-RT in stage III (only PDL1+ ≥1%)**
- **Single agent pembrolizumab in first-line (only PDL1+ ≥50%)**
- **ICPCs (pembrolizumab/atezolizumab) combo with CT in first-line (regardless of PDL1 expression)**

Immunotherapy (ICPIs) in A-NSCLC: Outcomes in unselected patients

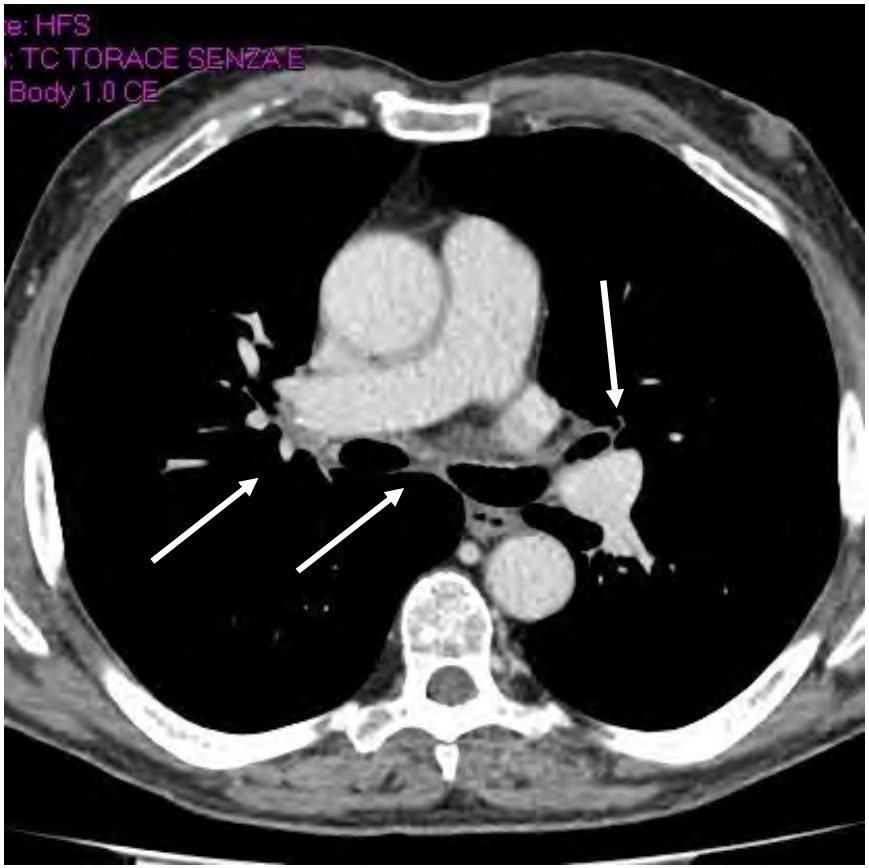
- **10-20% response rate**
- **10-15% iperprogressors**
- **9-12 months median OS (2° line)**
- **15-20% long-term survivors**

Long-lasting complete remission

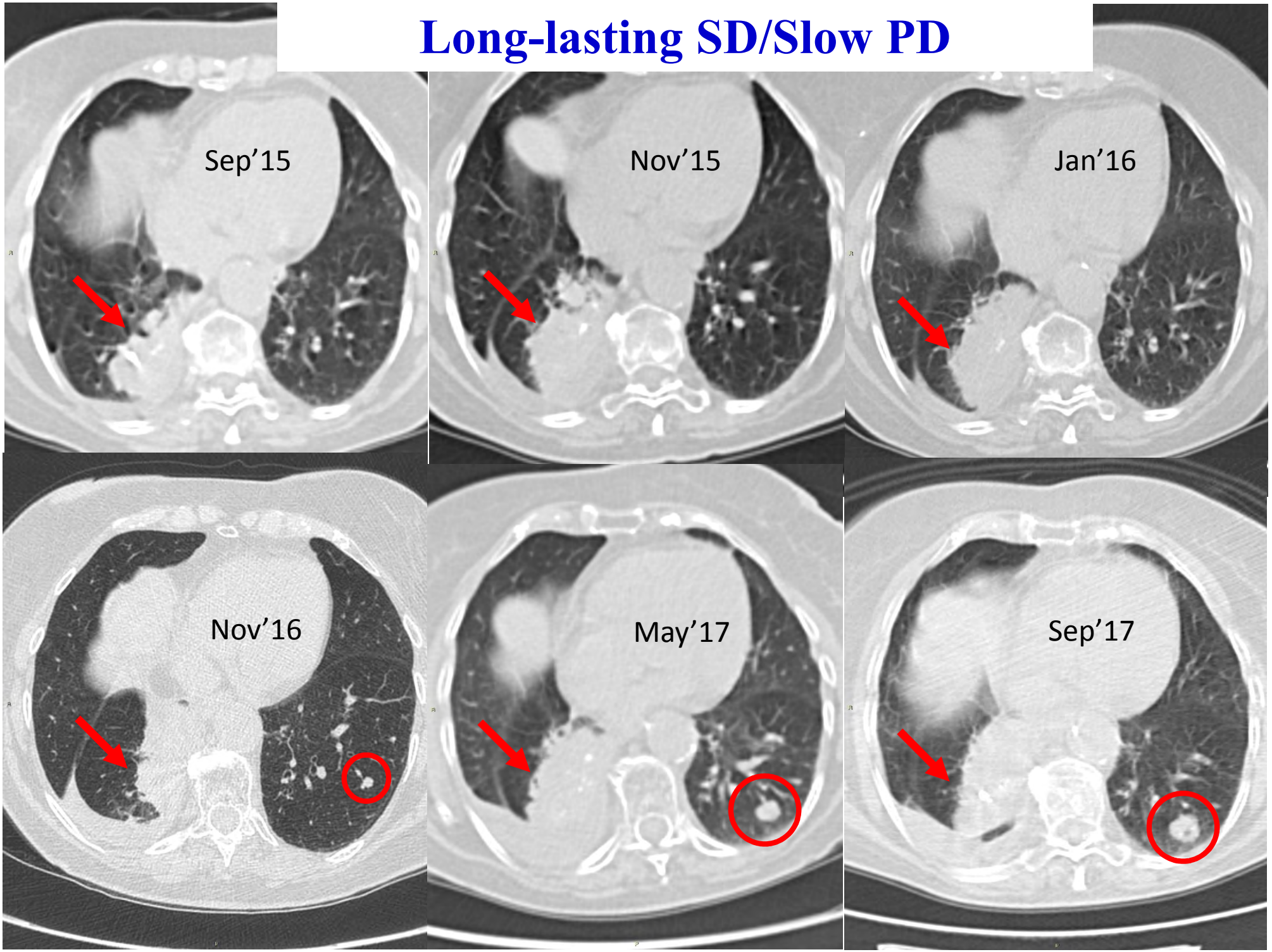
Baseline



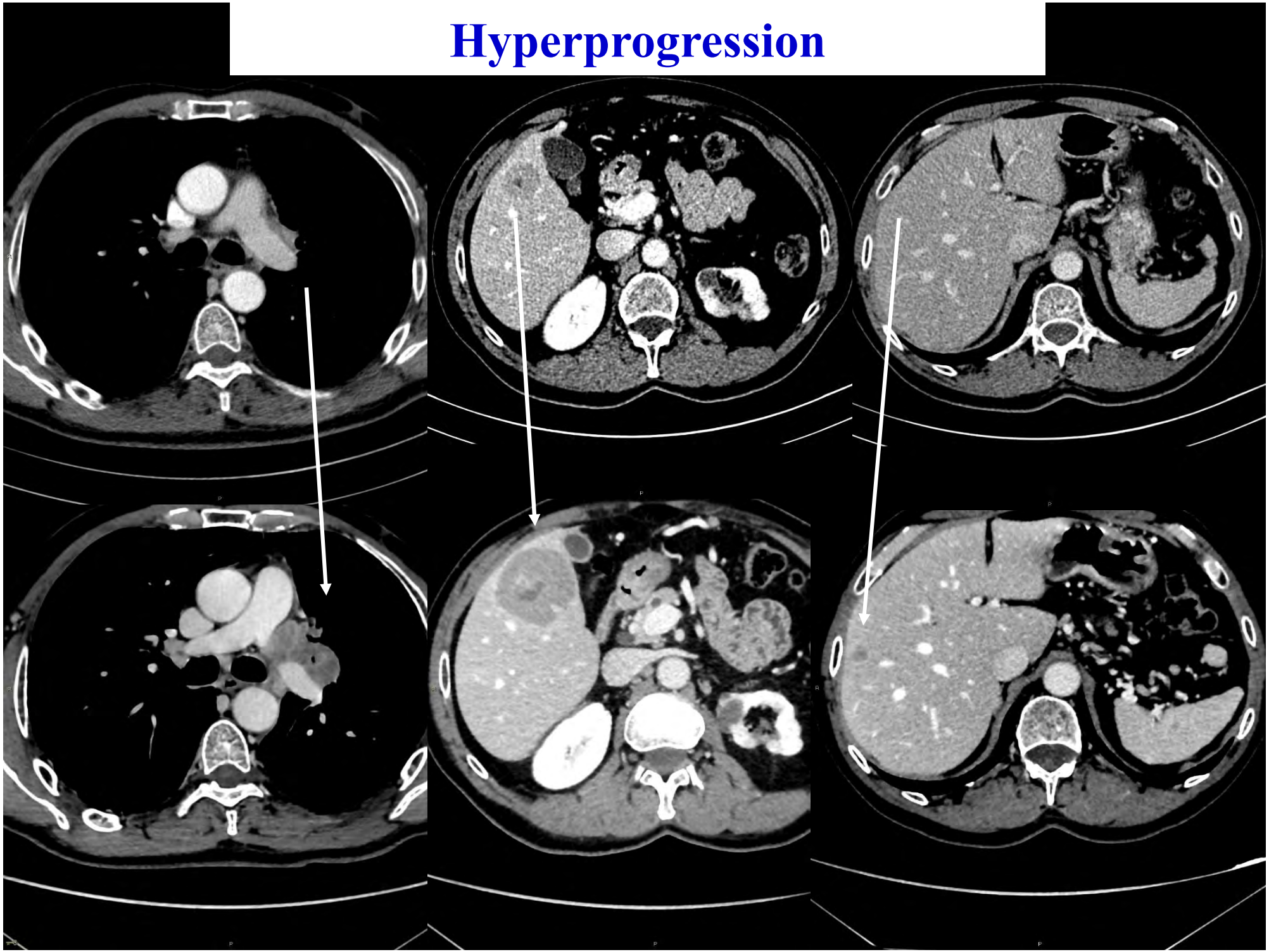
After 2 years of anti-PD1



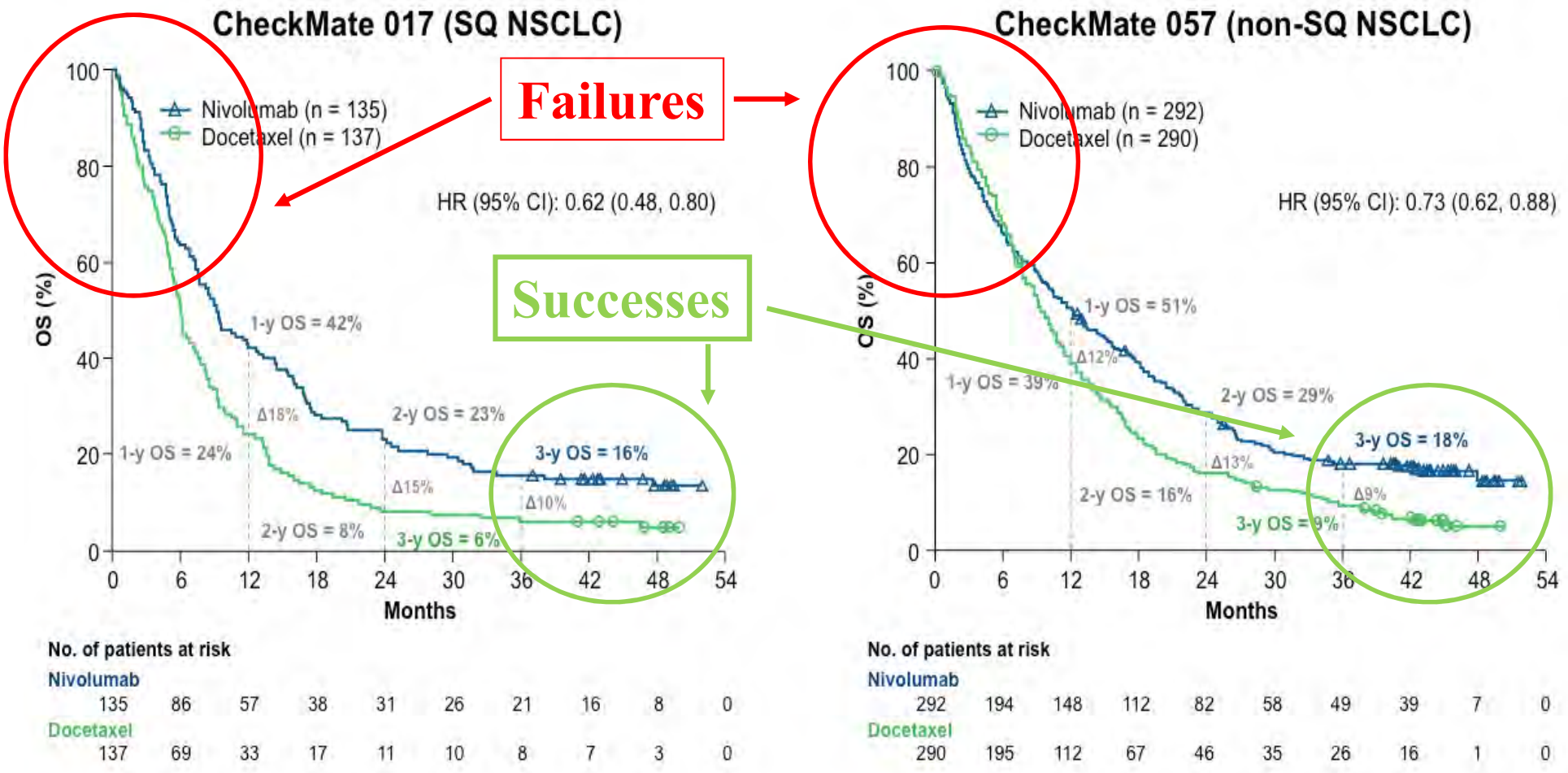
Long-lasting SD/Slow PD



Hyperprogression



Nivolumab: Kaplan-Meier Estimates of OS (3 Years Minimum Follow-up)



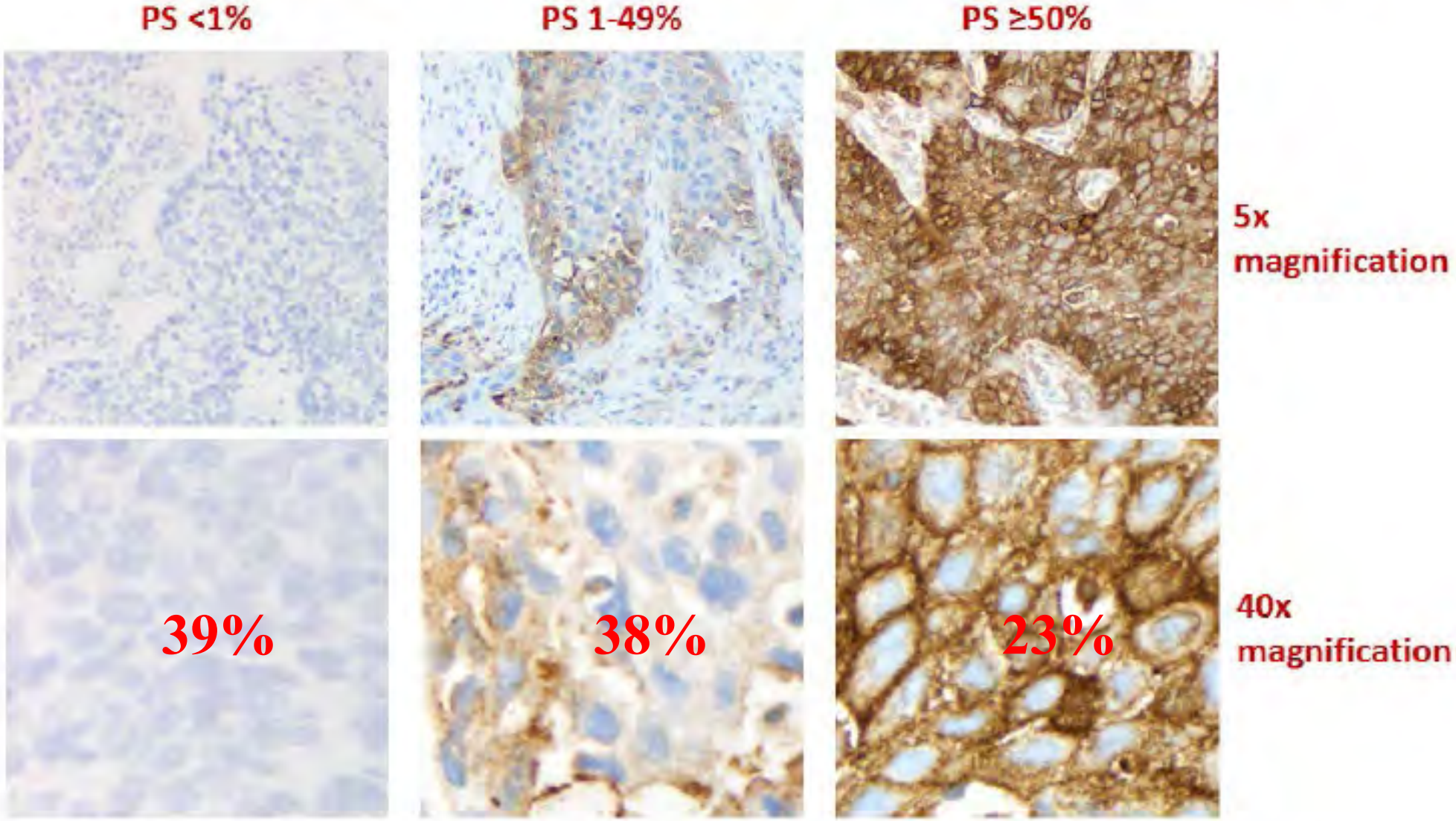
Felip et al, ESMO 2017

Can we predict so different treatment outcomes of I-O therapy?

Immunotherapy (ICPIs) in A-NSCLC: Possible predictors of efficacy

- **PDL1 expression**
- **TMB**
- **Miscellaneous (steroids, antibiotics, PPIs, irAEs....)**

Examples of PD-L1 IHC Staining of NSCLC Samples Using the Clinical Trial Assay

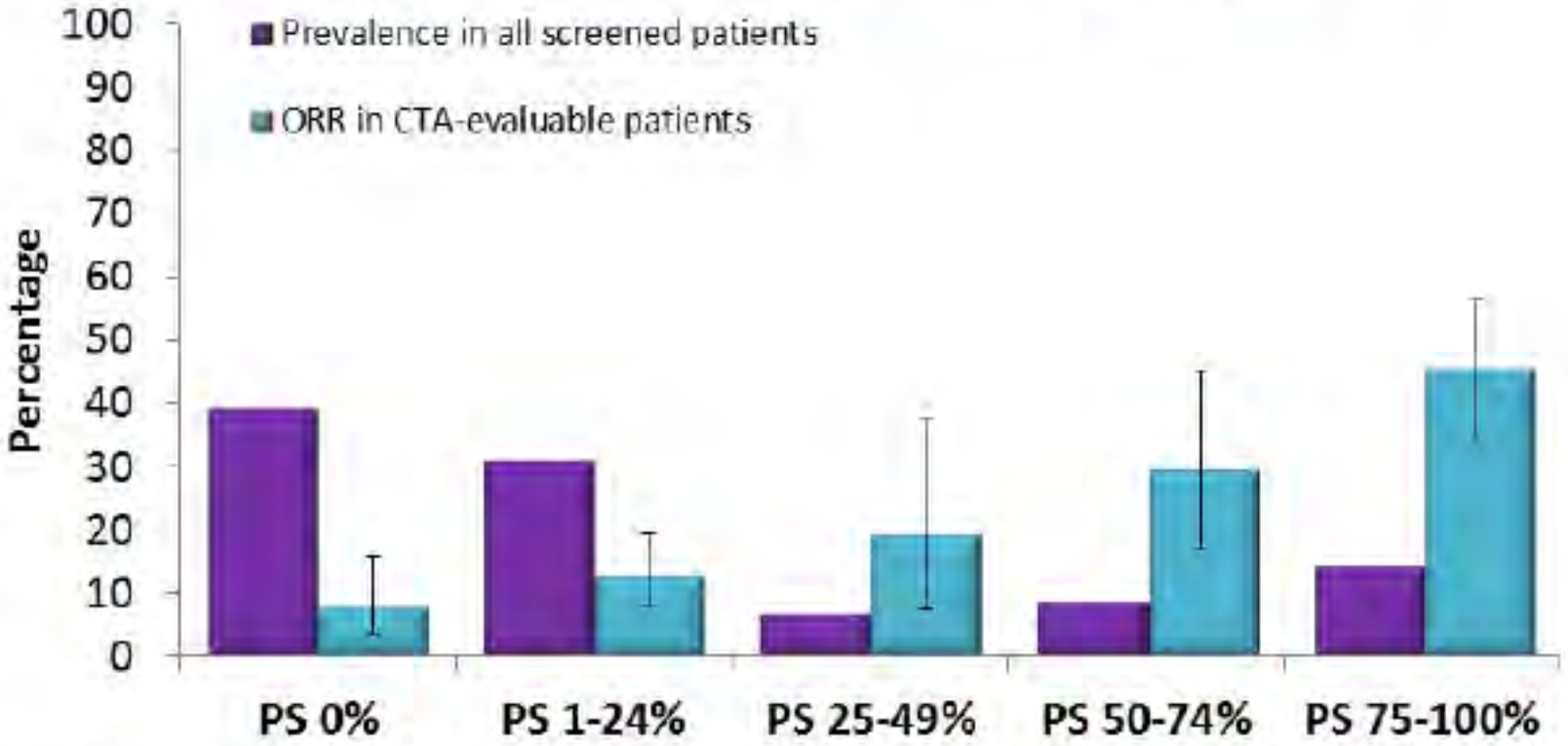


Brown chromogen: PD-L1 staining.
Blue color: hematoxylin counterstain.

Role of PDL1 expression (IHC) in predicting anti-PD1/PDL1efficacy in A-NSCLC

- **Single agent in second-line (metastatic disease)**
- **Single agent in first-line (metatsatic disease)**
- **Single agent adjuvant therapy after CT/RT (stage III)**
- **Combo with CT in first-line (metastatic disease)**

Prevalence of PD-L1 Positivity and ORR by Quartiles of PD-L1 Proportion Score



	PS 0%	PS 1-24%	PS 25-49%	PS 50-74%	PS 75-100%
Prevalence, all screened patients,[a] n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
ORR in CTA-evaluable patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

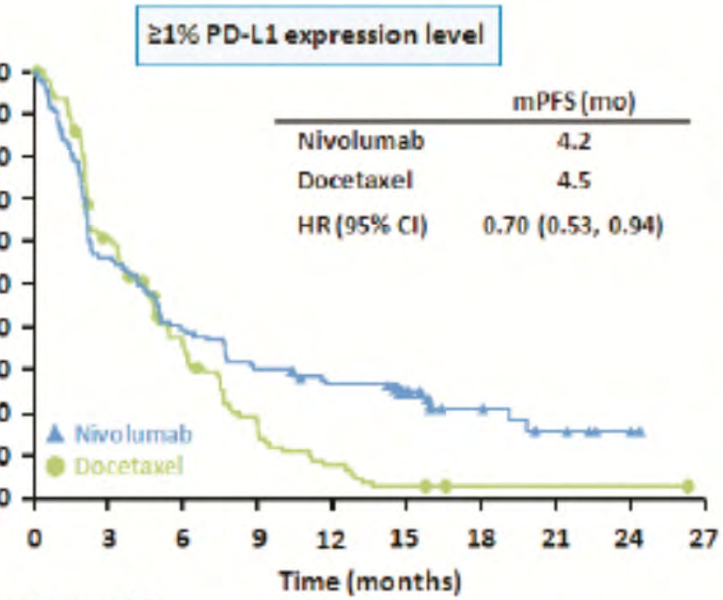
[a]Prevalence and ORR (RECIST v1.1 by central review) assessed in patients whose samples were evaluable by the CTA, regardless of the interval between cutting and staining.

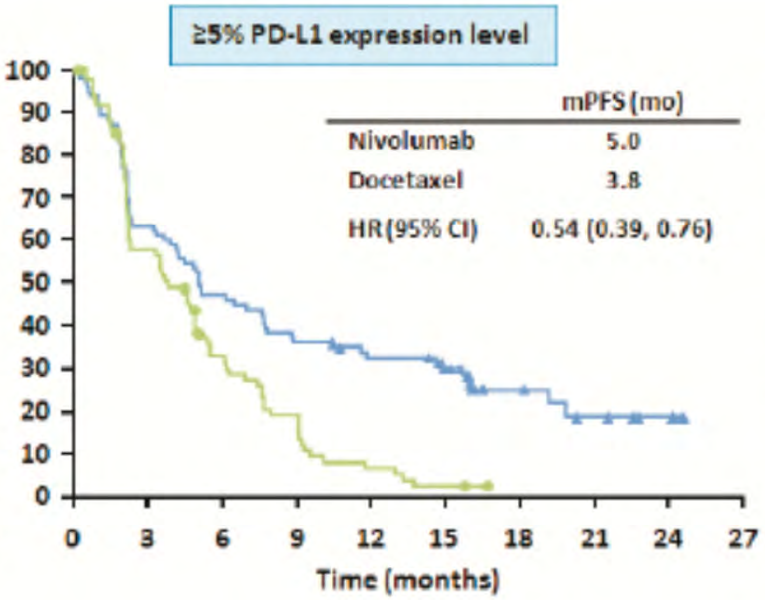
Analysis cut-off date: August 29, 2014.

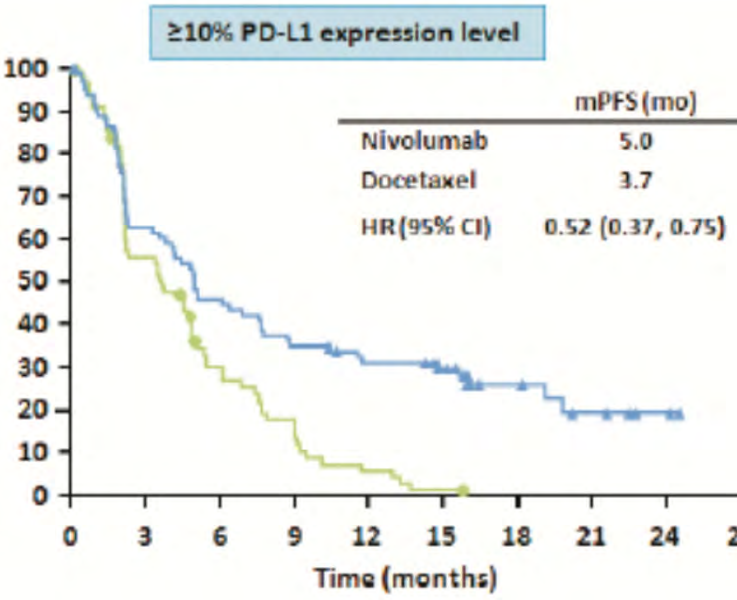
Phase III Studies of Docetaxel vs ICPIs in 2nd-line treatment of NSCLC

Study	ICPI	Population	mOS TXT (months)	mOS ICPI (months)	HR
[1]CM-017	Nivolumab (3 mg/kg q 2 wks)	Unselected Squamous	6.0	9.2	0.59
[2]CM-057	Nivolumab (3 mg/kg q 2 wks)	Unselected Non-Sq	9.4	12.2	0.73
[3]OAK	Atezolizumab (1200 mg q 3 wks)	Unselected NSCLC	9.6	13.8	0.73
[4]KN-010	Pembrolizumab (2 mg/kg q 3 wks)	PDL1 ≥1% NSCLC	8.5	10.4	0.71

1. Brahmer, NEJM'15; 2. Borghaei, NEJM'16; 3. Rittmeyer, Lancet'17; 4. Herbst, Lancet'16





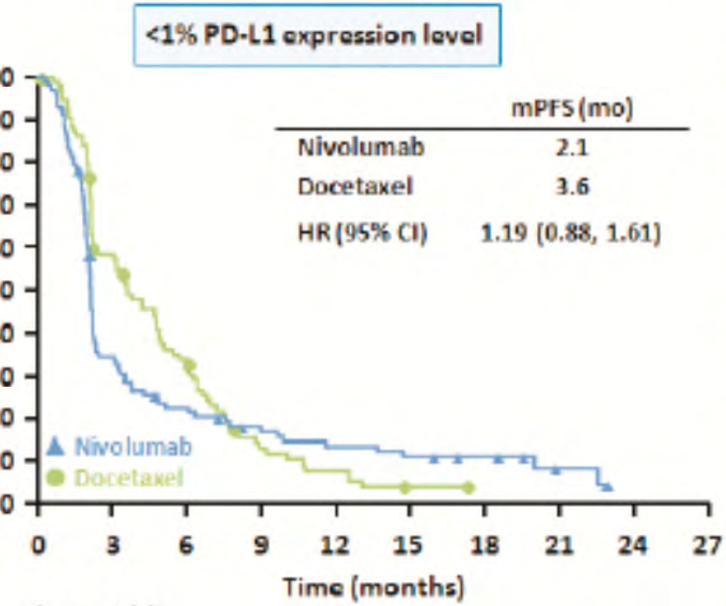


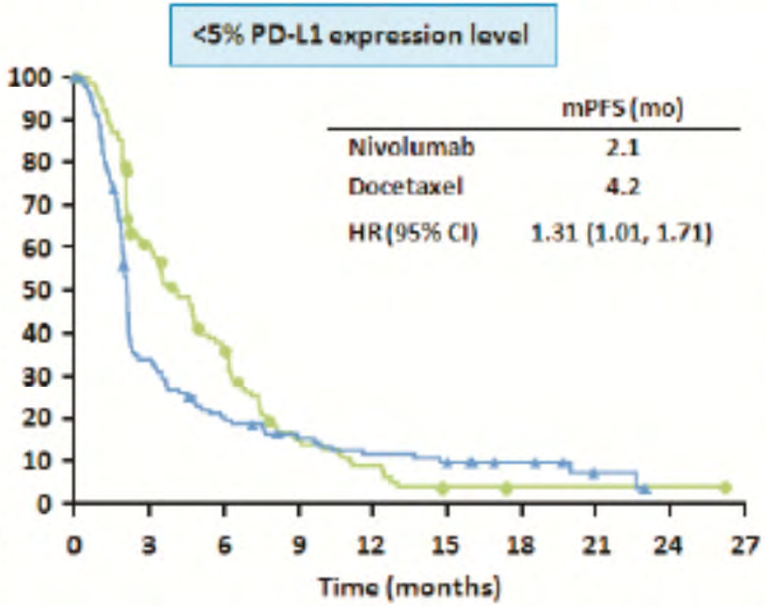
patients at risk

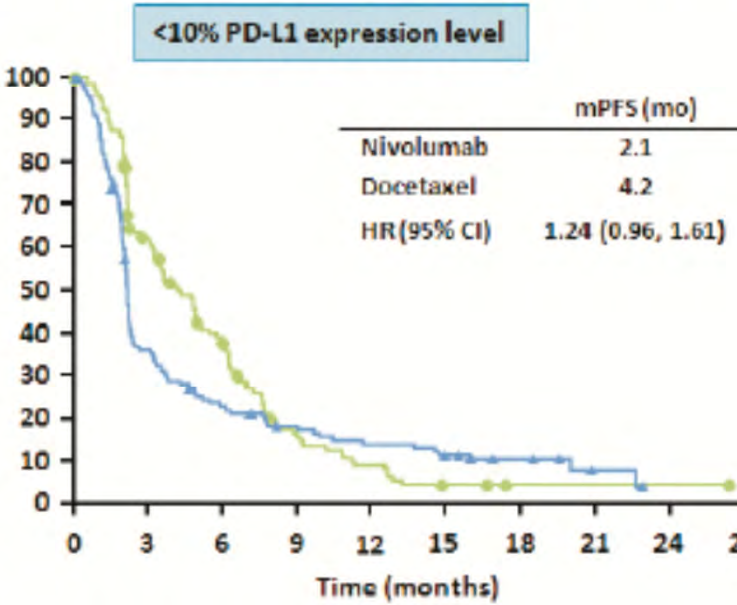
123	67	47	36	30	23	9	5	2	0	
123	68	38	19	8	3	1	1	1	0	

95	58	43	33	28	22	9	5	2	0	
86	46	24	14	5	2	0	0	0	0	

86	52	38	29	24	19	9	5	2		
79	41	20	12	4	1	0	0	0		







patients at risk

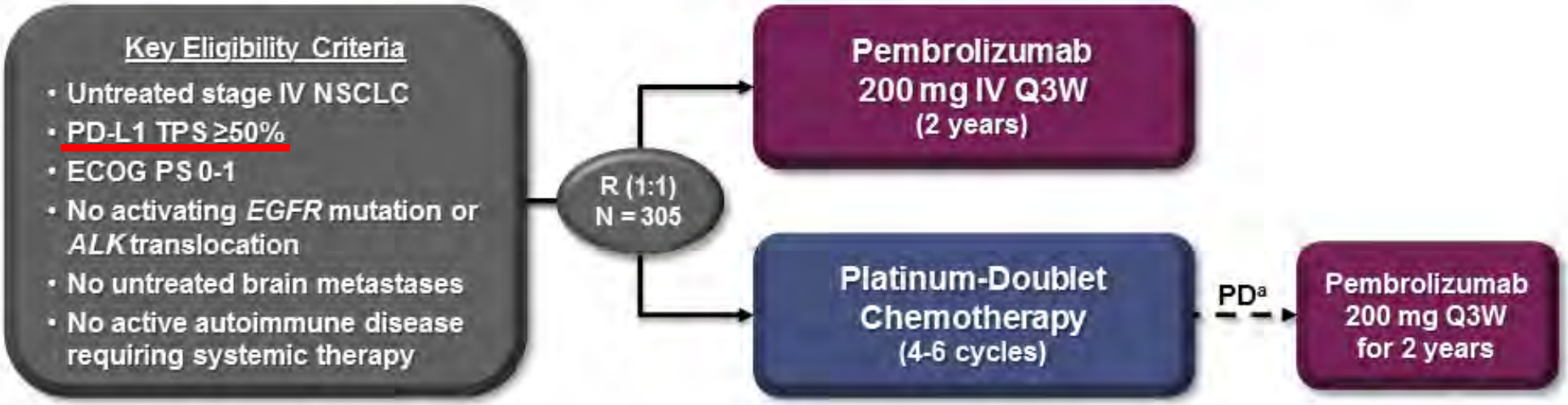
108	34	21	15	11	9	6	2	0	0

136	43	25	18	13	10	6	2	0	0

145	49	30	22	17	13	6	2	0	

M Reck. ESMO 2016.

KEYNOTE-024 Study Design (NCT02142738)



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.

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

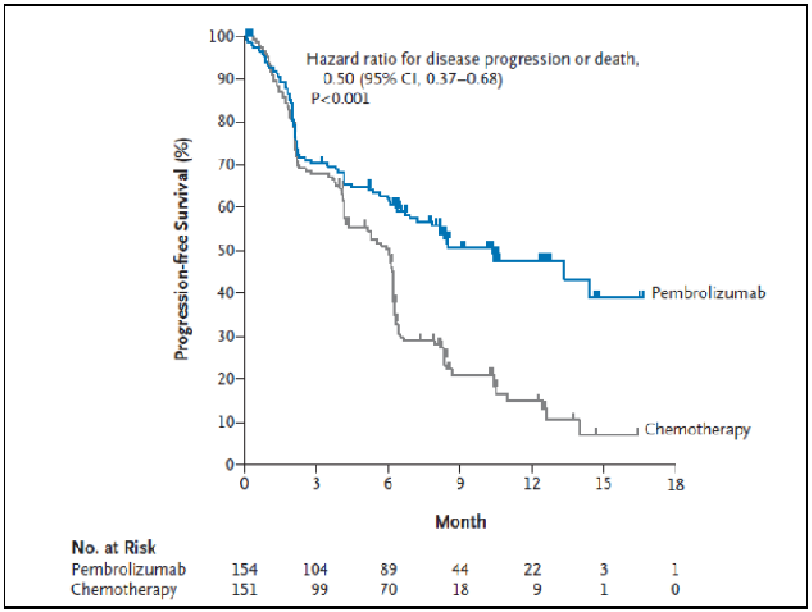
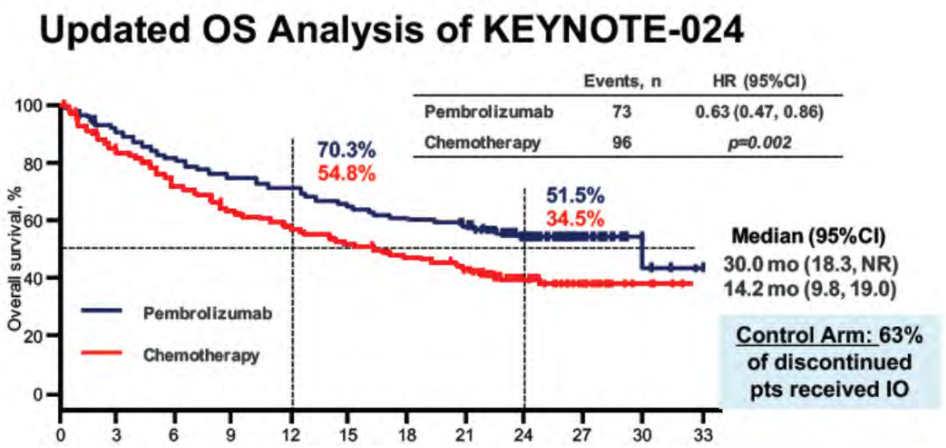


Table 2. Summary of Response in the Intention-to-Treat Population.*

Variable	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+



Reck, NEJM'16
Brahmer, WCLC'17

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

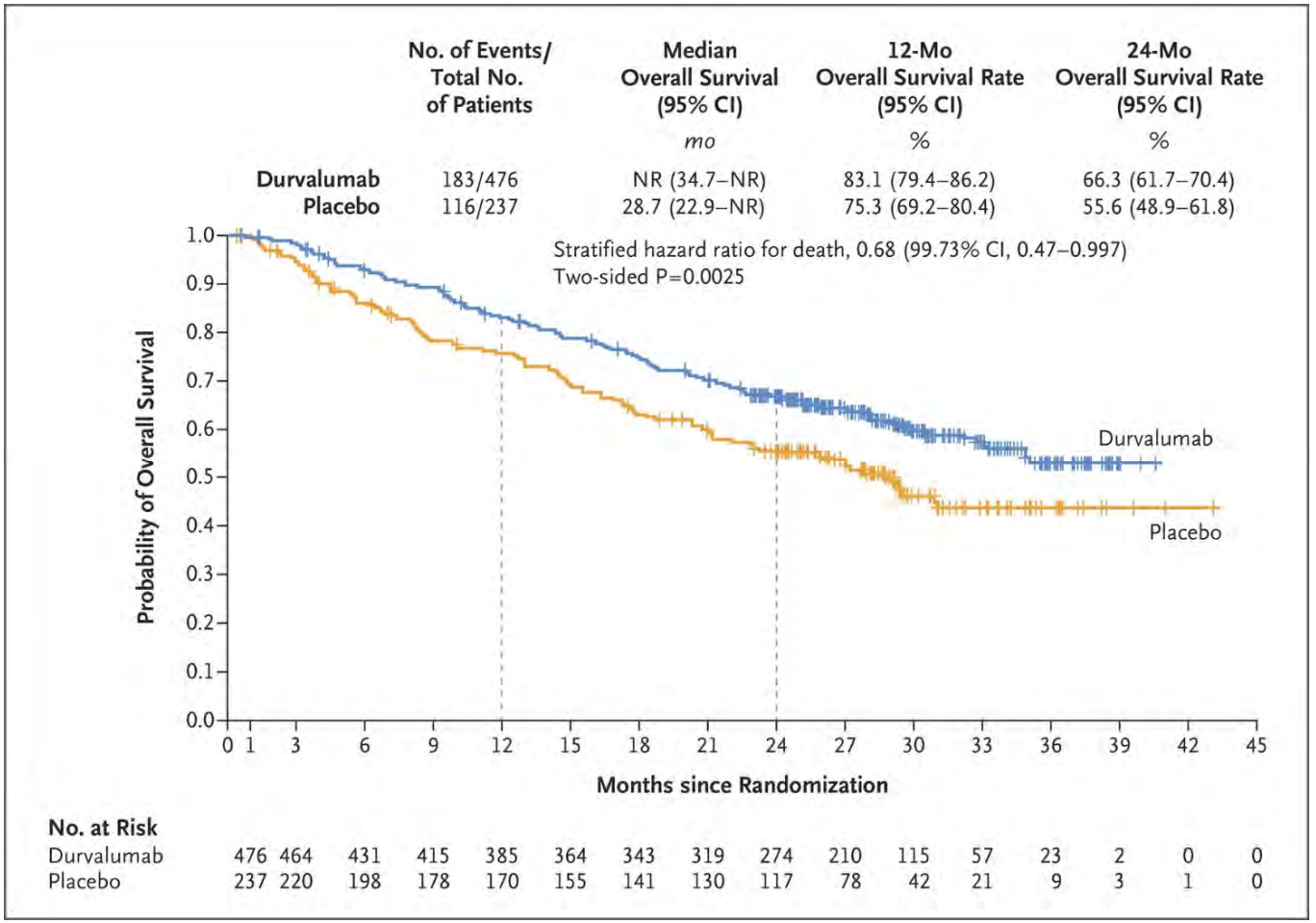
*Using the Ventana SP263 immunohistochemistry assay

†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29.

ORIGINAL ARTICLE

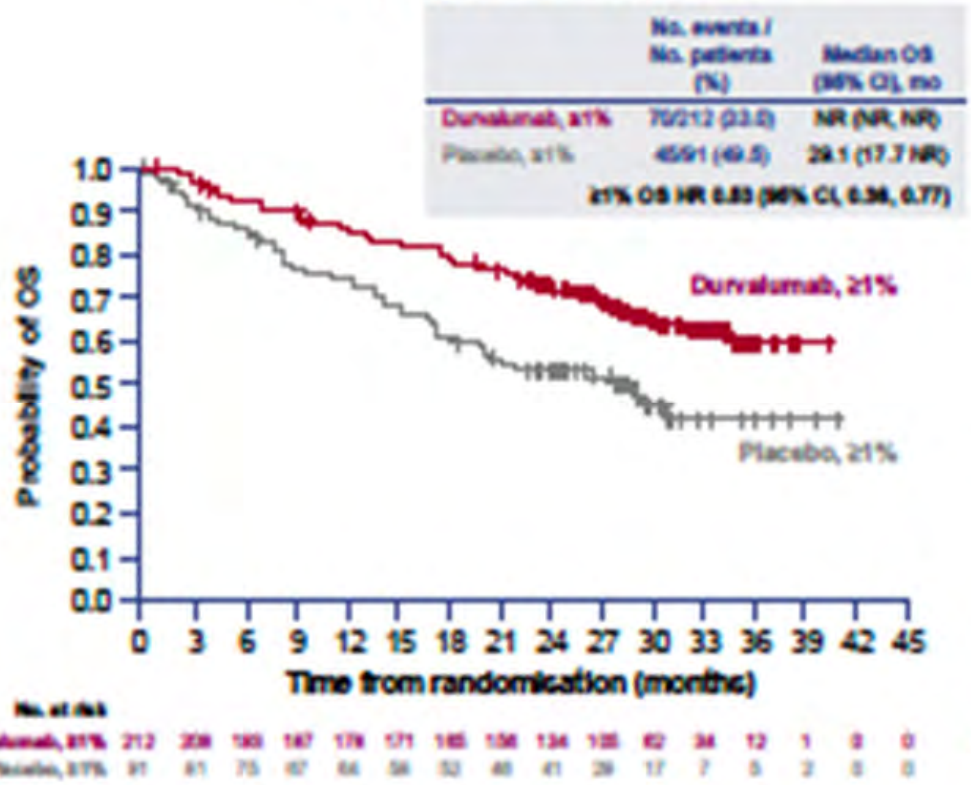
Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC



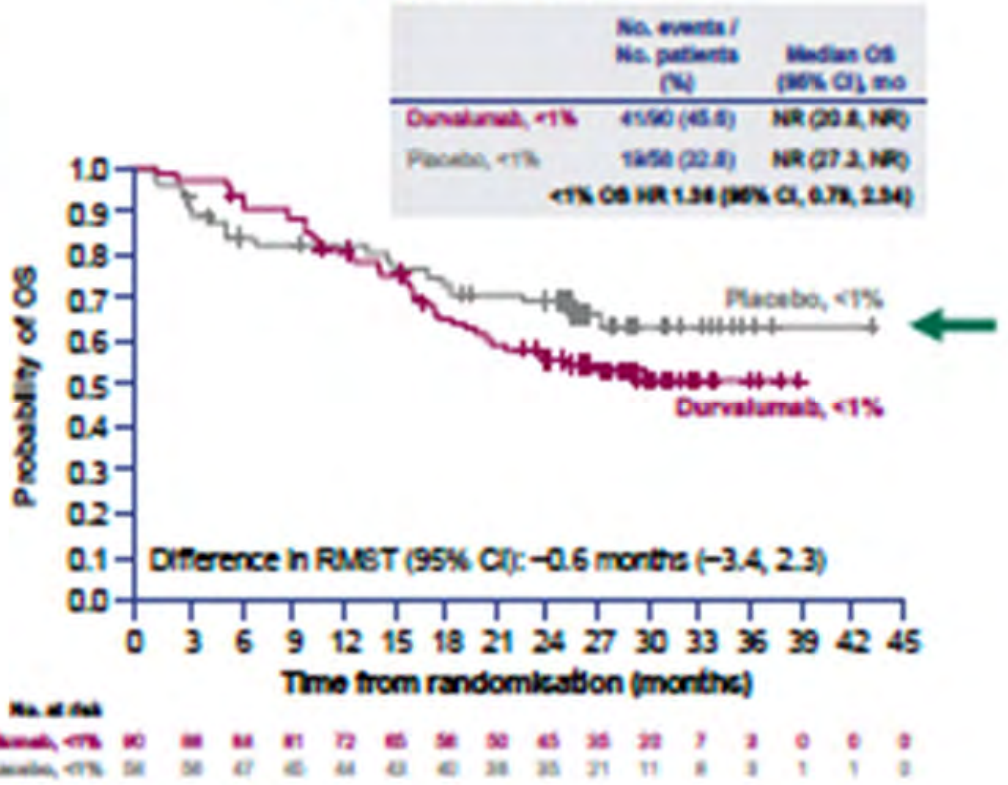
Antonia et al, NEJM'18

OS by PD-L1 TC ≥1% and <1%

OS by PD-L1 TC ≥1%



OS by PD-L1 TC <1%



- In the PD-L1 TC <1% subgroup, the number of events are low and overall the subgroup is small
- Imbalances in baseline characteristics

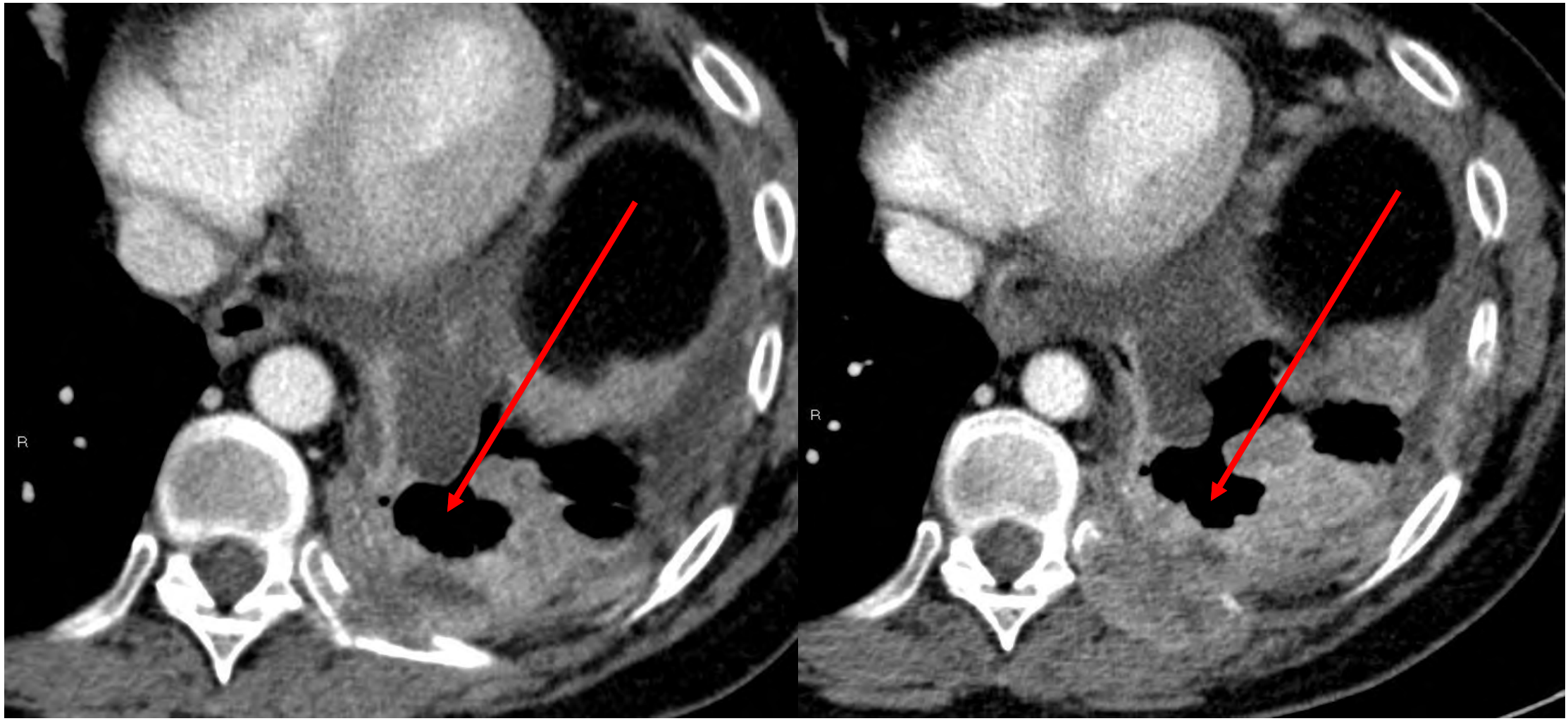
RMST, restricted mean survival time

Favre-Finn et al, ESMO 2018

PFS DCO: 13 February 2017; OS DCO: 22 March 2018

PD on Pembrolizumab at first assessment despite High PDL1 (+70%)

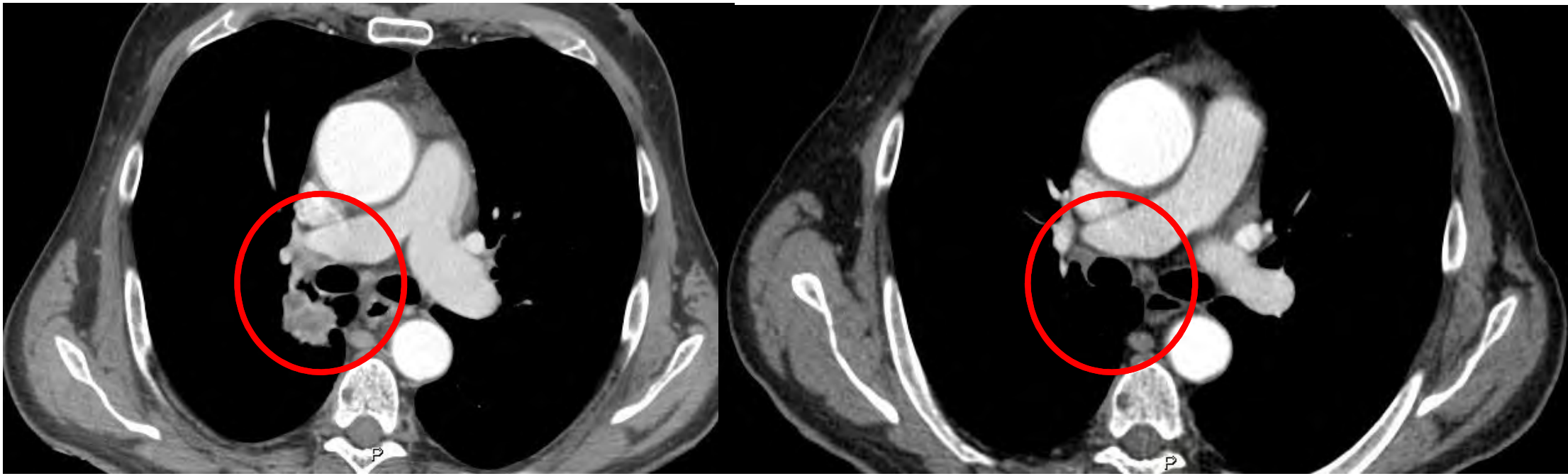
Baseline **After 2 months of therapy**



Durable CR on Nivolumab despite despite low PDL1 (+20%)

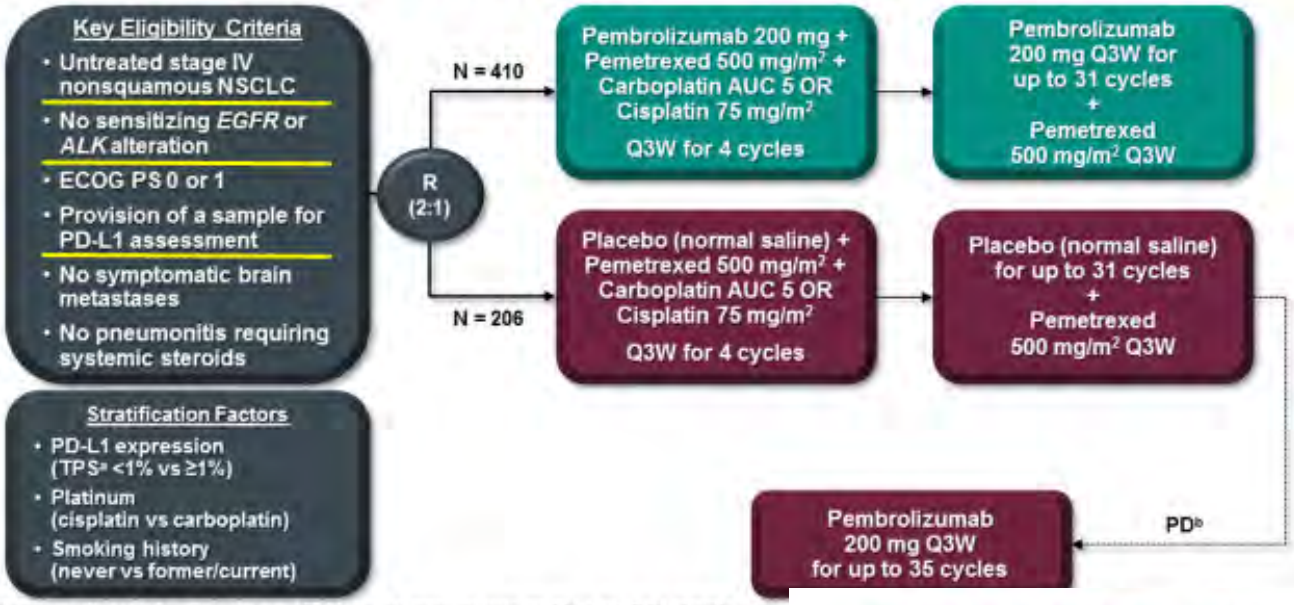
Baseline

After 2 years of therapy



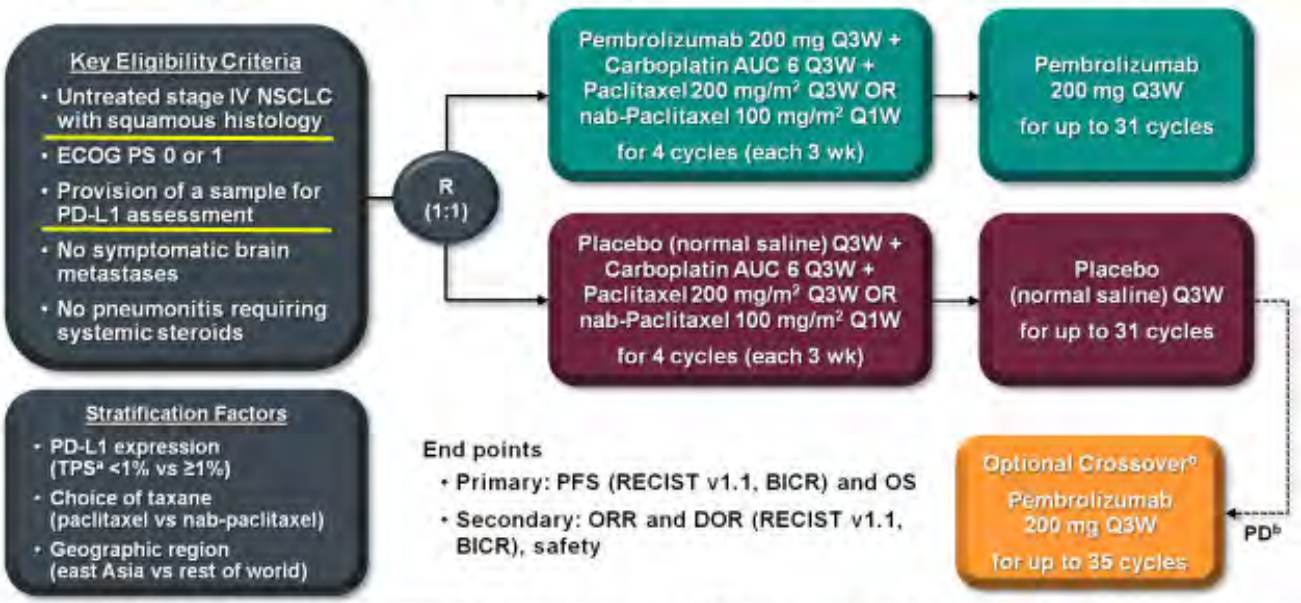
Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)



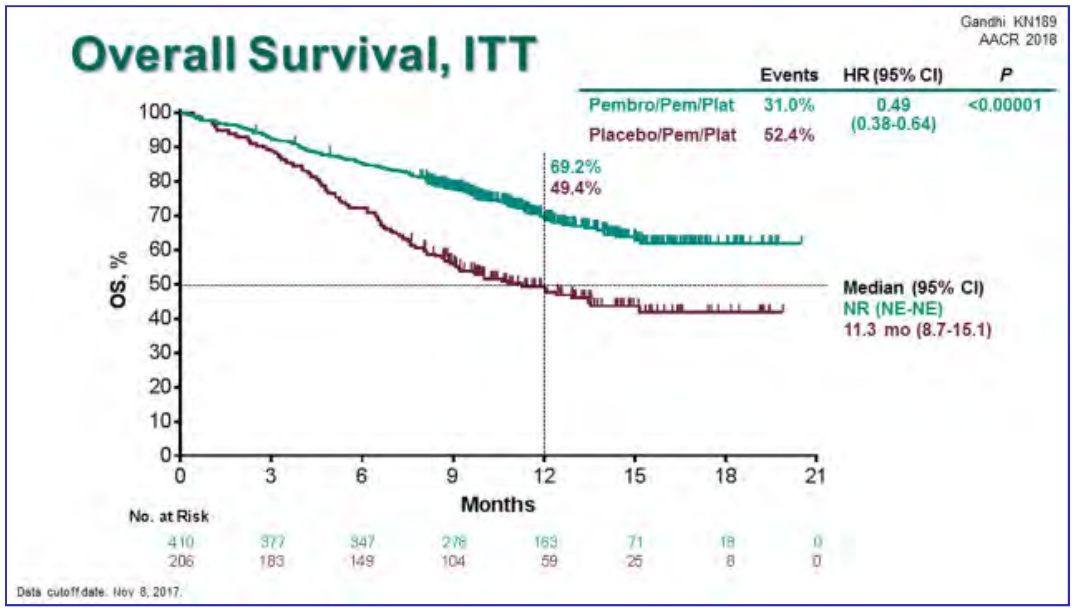
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all s

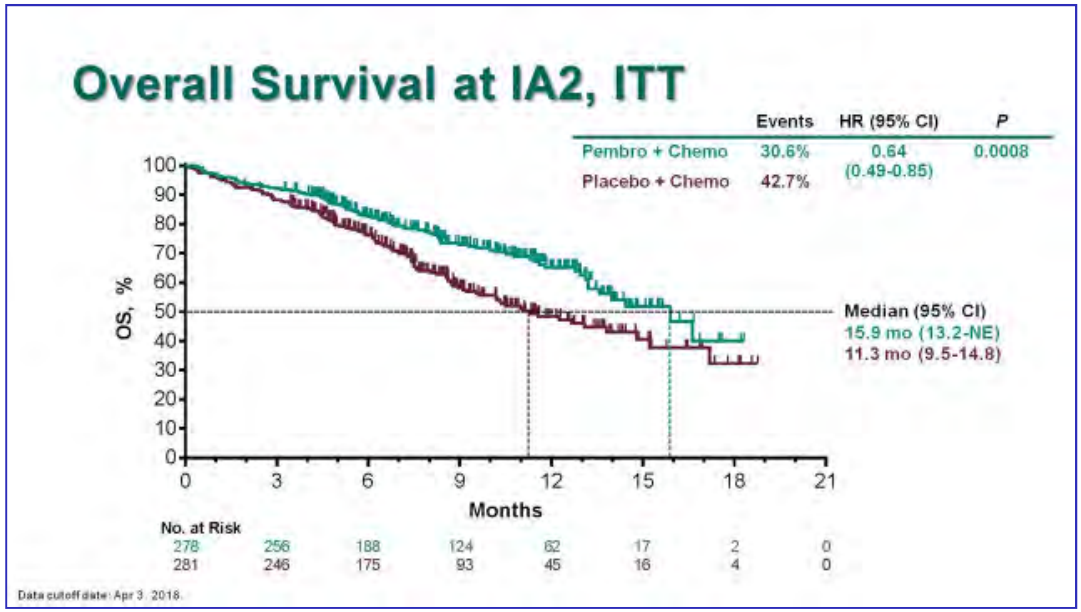
KEYNOTE-407 Study Design (NCT02775435)



BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Chemotherapy +/- Pembrolizumab in unselected A-NSCLC





Non-Squamous

Squamous

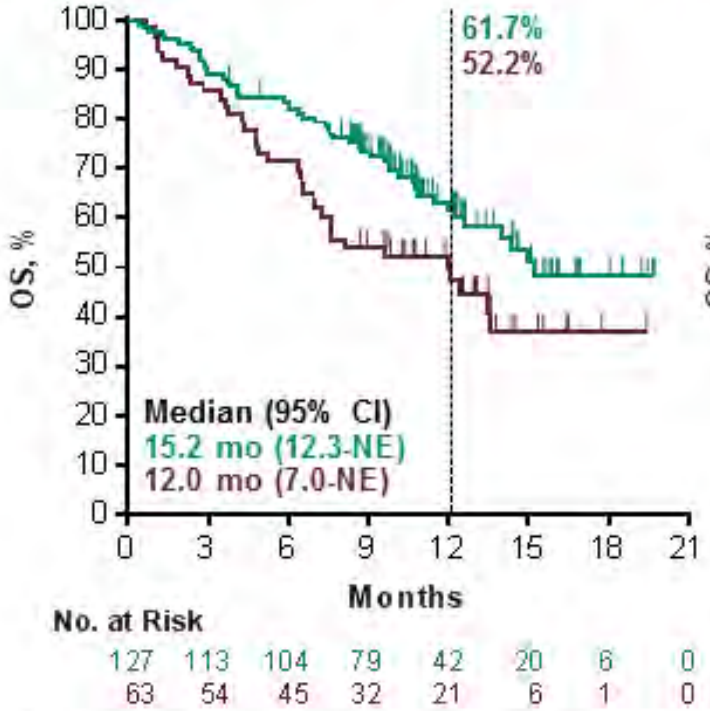
Gandhi, Paz-Ares, ASCO'18

Gandhi KN189
AACR 2018

Overall Survival by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	38.6%	0.59 (0.38-0.92)	0.0095
Placebo/Pem/Plat	55.6%		

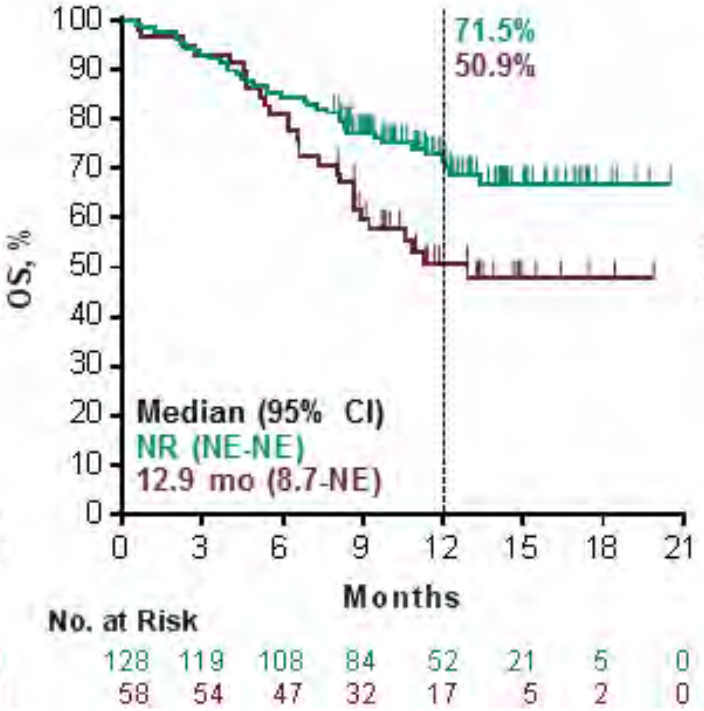


No. at Risk

127	113	104	79	42	20	6	0
63	54	45	32	21	6	1	0

TPS 1-49%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	28.9%	0.55 (0.34-0.90)	0.0081
Placebo/Pem/Plat	48.3%		

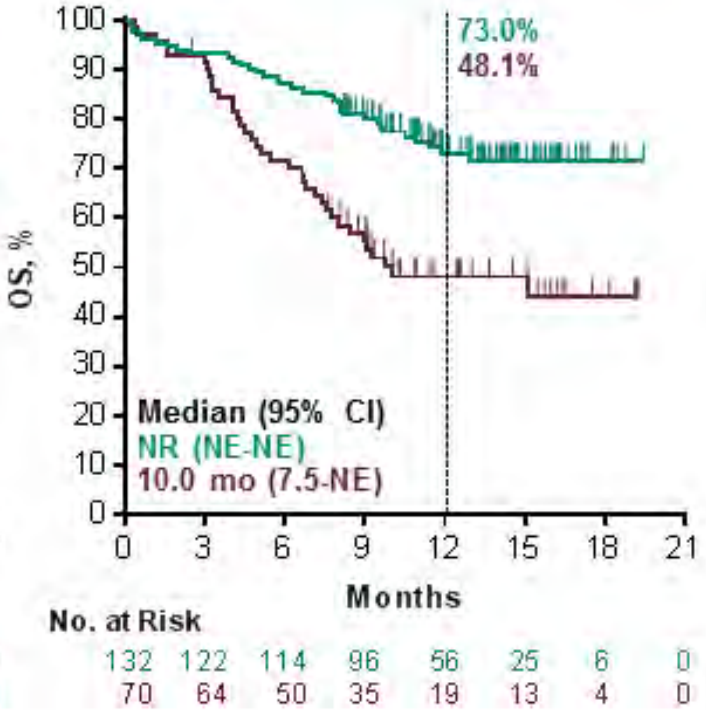


No. at Risk

128	119	108	84	52	21	5	0
58	54	47	32	17	5	2	0

TPS ≥50%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	25.8%	0.42 (0.26-0.68)	0.0001
Placebo/Pem/Plat	51.4%		



No. at Risk

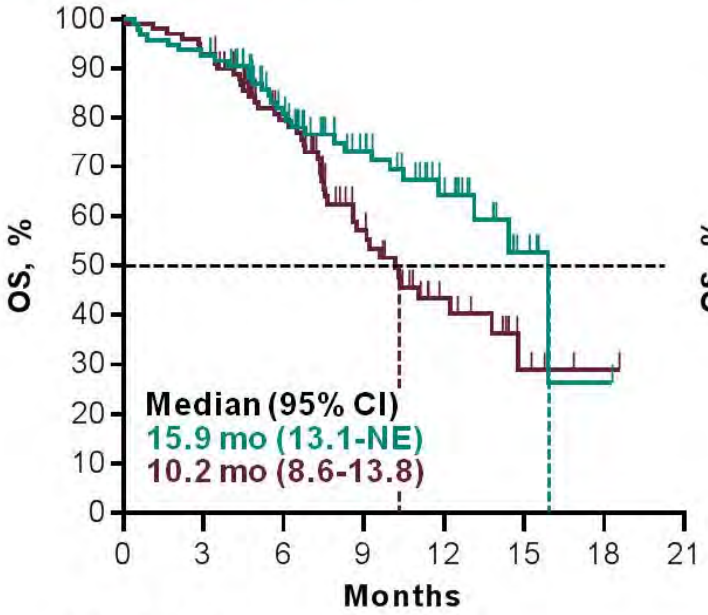
132	122	114	96	56	25	6	0
70	64	50	35	19	13	4	0

[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Overall Survival at IA2 by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	

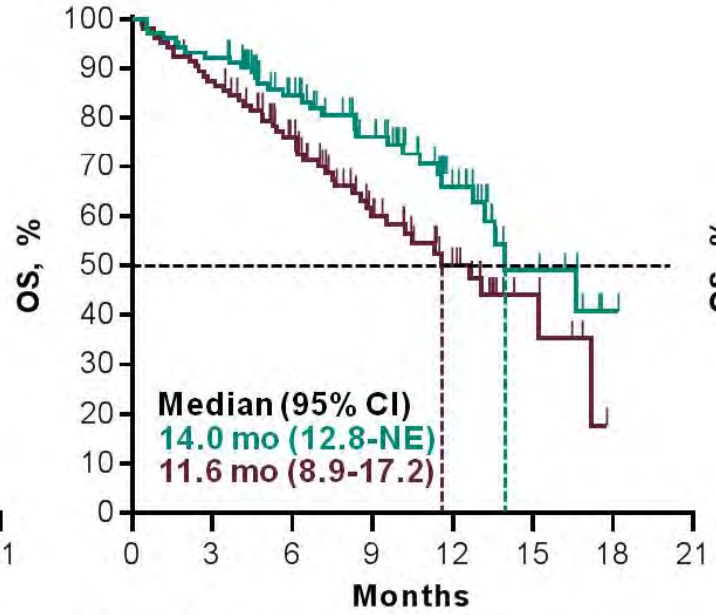


No. at Risk

95	88	62	41	20	5	1	0
99	92	63	32	14	4	1	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	30.1%	0.57 (0.36-0.90)
Placebo + Chemo	43.3%	

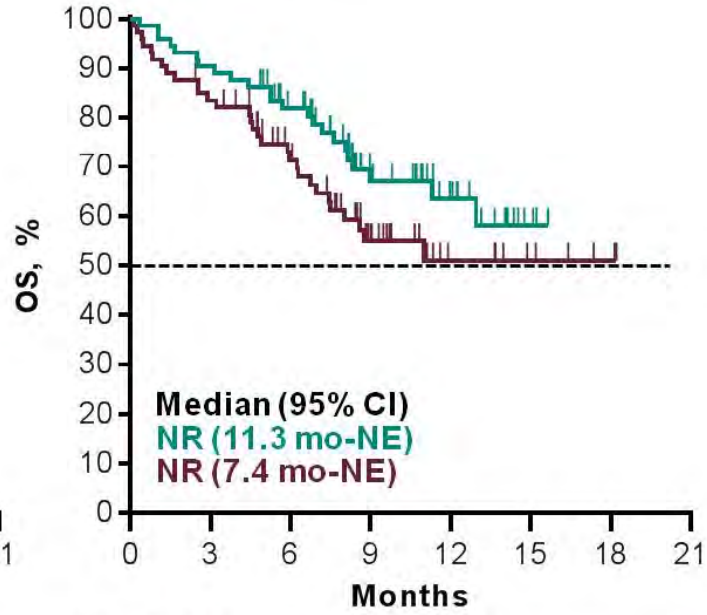


No. at Risk

103	95	68	50	25	9	1	0
104	90	66	37	21	6	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	31.5%	0.64 (0.37-1.10)
Placebo + Chemo	41.1%	

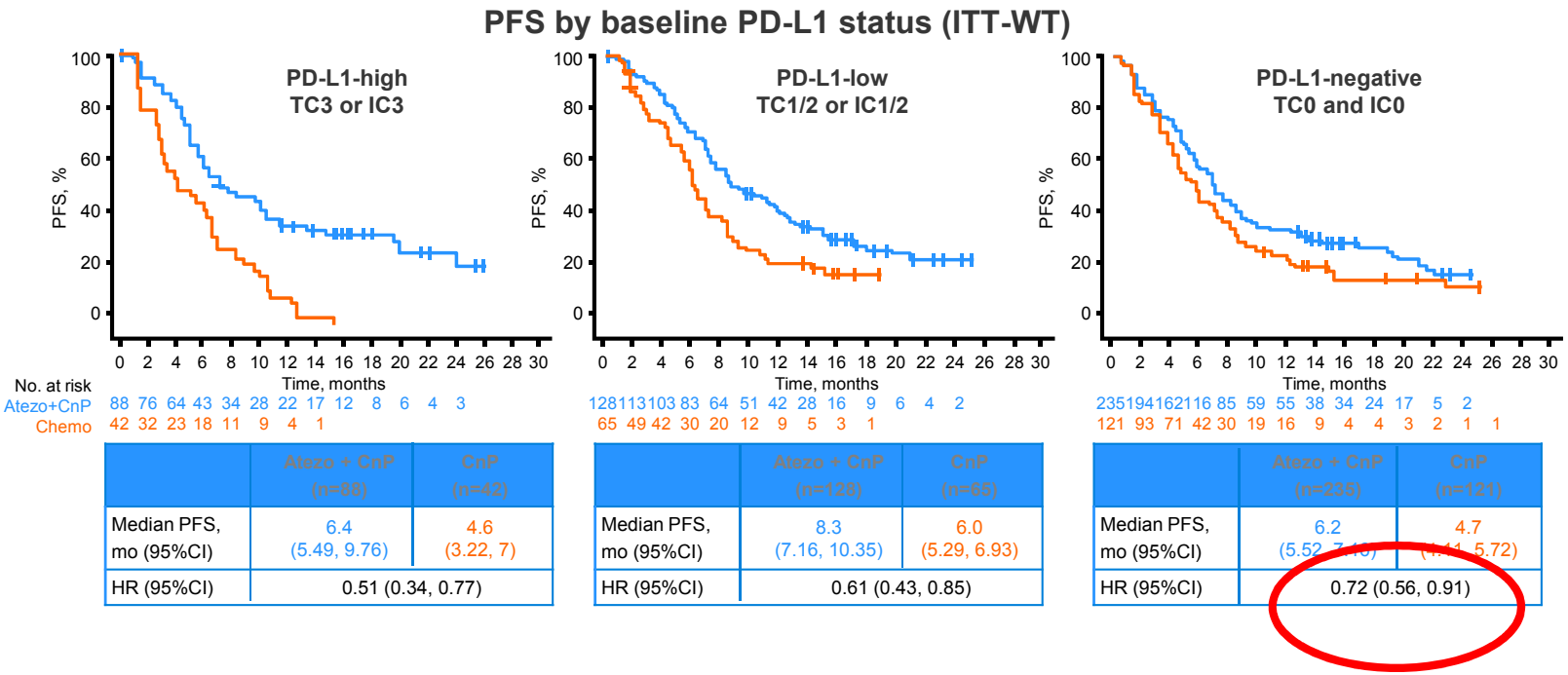


No. at Risk

73	66	53	28	15	3	0	0
73	60	42	21	9	5	2	0

Data cutoff date: Apr 3, 2018.

Nab-Paclitaxel/Carbo± Atezo in Non-Sq NSCLC Impower 130 Trial



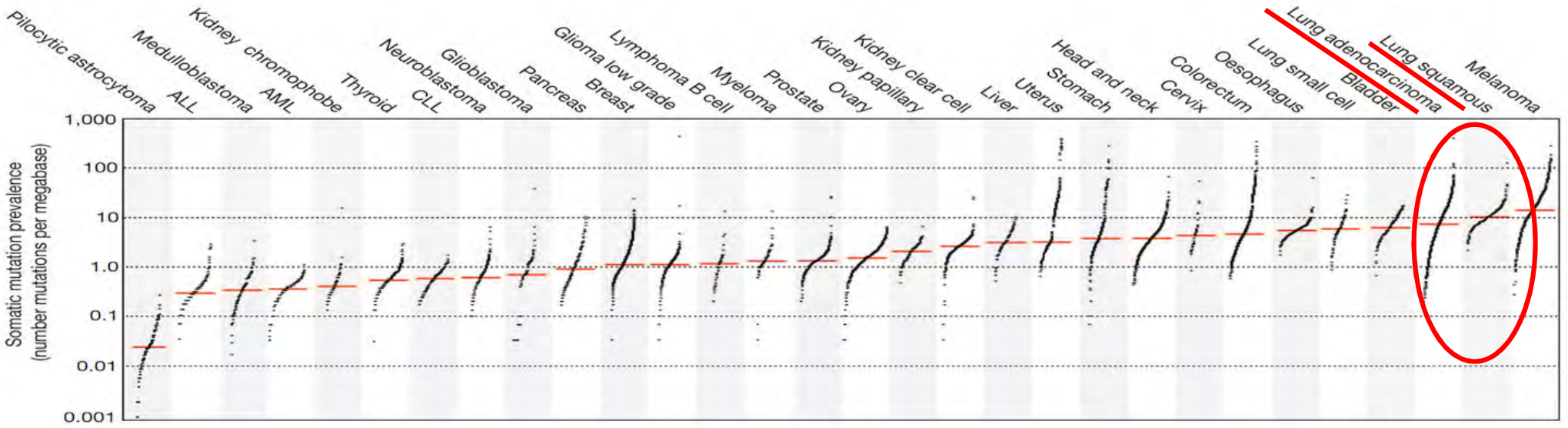
	Atezo + CnP (n=88)	CnP (n=42)
Median PFS, mo (95%CI)	6.4 (5.49, 9.76)	4.6 (3.22, 7)
HR (95%CI)	0.51 (0.34, 0.77)	

	Atezo + CnP (n=128)	CnP (n=65)
Median PFS, mo (95%CI)	8.3 (7.16, 10.35)	6.0 (5.29, 6.93)
HR (95%CI)	0.61 (0.43, 0.85)	

	Atezo + CnP (n=235)	CnP (n=121)
Median PFS, mo (95%CI)	6.2 (5.52, 7.1[illegible])	4.7 ([illegible], 5.72)
HR (95%CI)	0.72 (0.56, 0.91)	

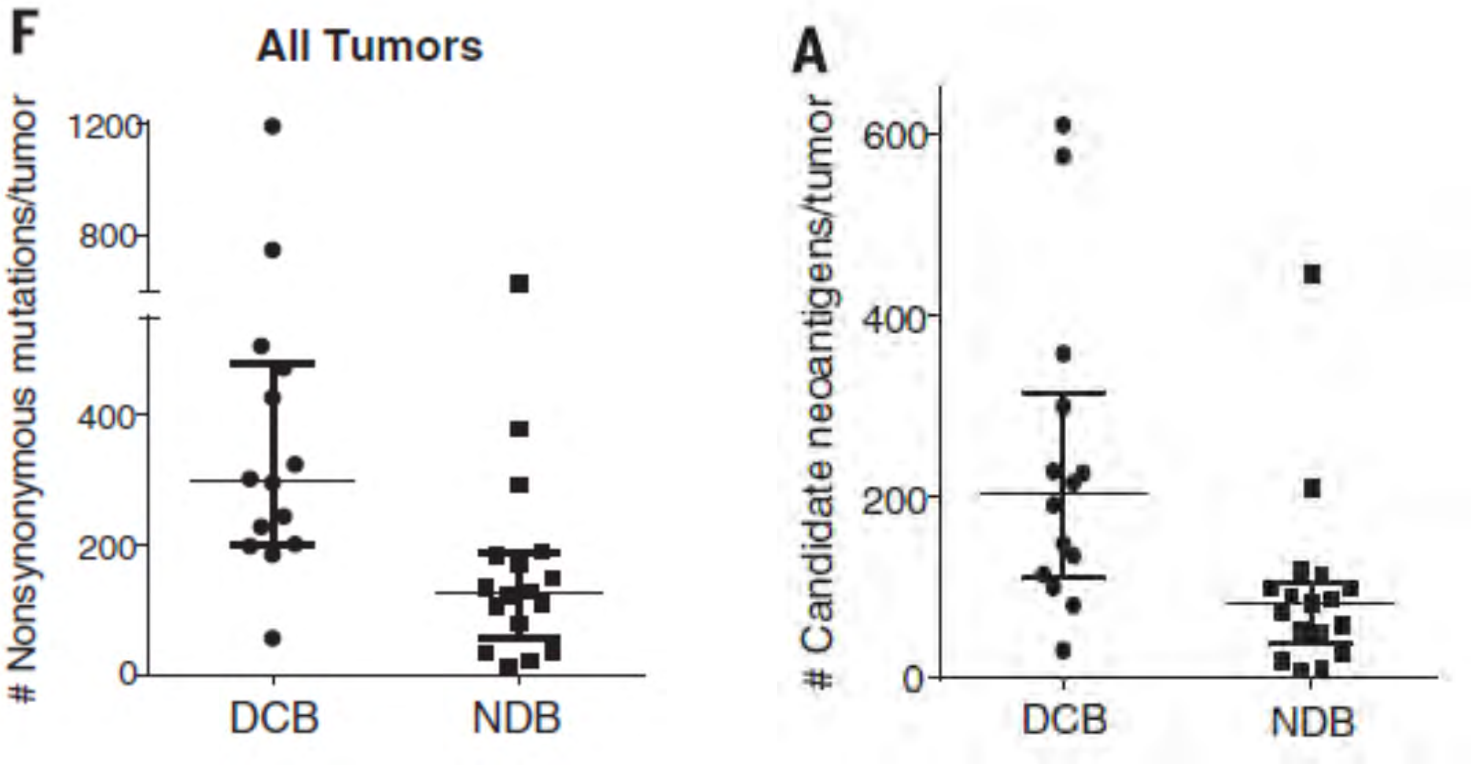
Cappuzzo F, et al. Ann Oncol 2018;29(suppl 5):Abstr LBA53

Somatic mutation prevalence in various tumors



Alexandrov *et al.*, Science 2013

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

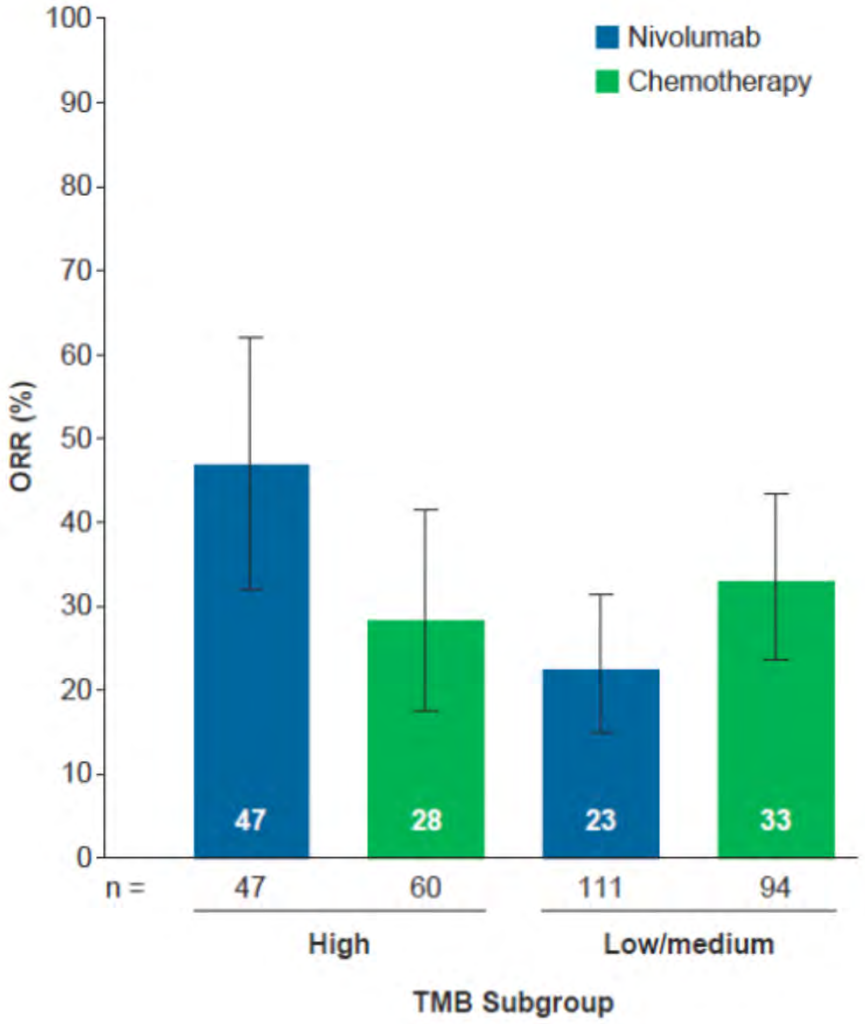


DCB= Durable Clinical Benefit; NDB= No Durable Benefit

Rizvi, Science'15

Studio CheckMate 026: CT vs Nivolumab in A-NSCLC with PDL1> 1%

Figure S12. Overall Response by Tumor Mutation Burden.

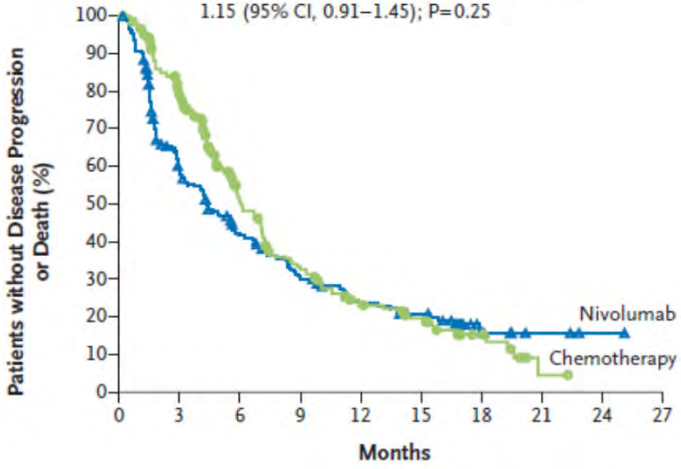


Carbone DP, NEJM'17

A Progression-free Survival

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25

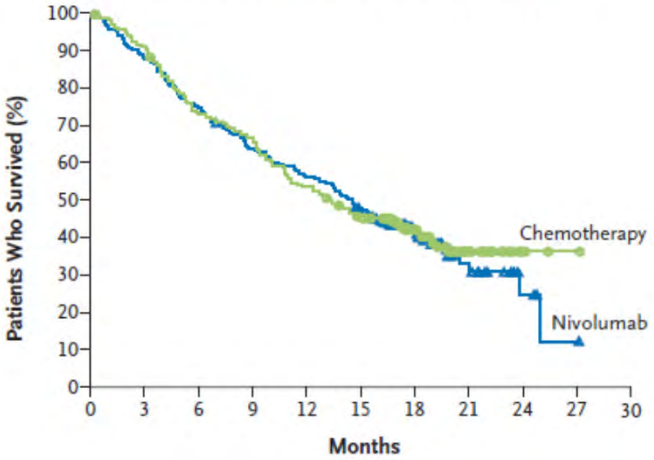


No. at Risk										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

B Overall Survival

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)

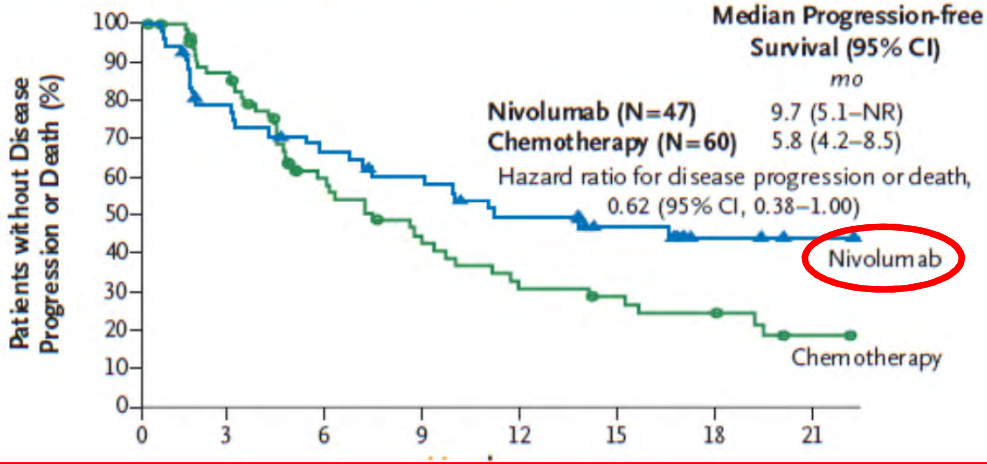


No. at Risk											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

C Progression-free Survival among Patients with High Tumor-Mutation Burden

	Median Progression-free Survival (95% CI)
	mo
Nivolumab (N=47)	9.7 (5.1–NR)
Chemotherapy (N=60)	5.8 (4.2–8.5)

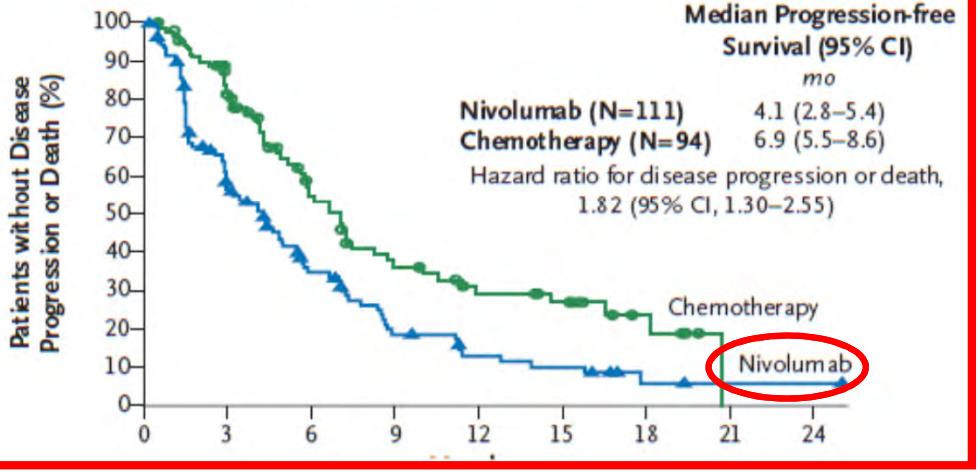
Hazard ratio for disease progression or death, 0.62 (95% CI, 0.38–1.00)



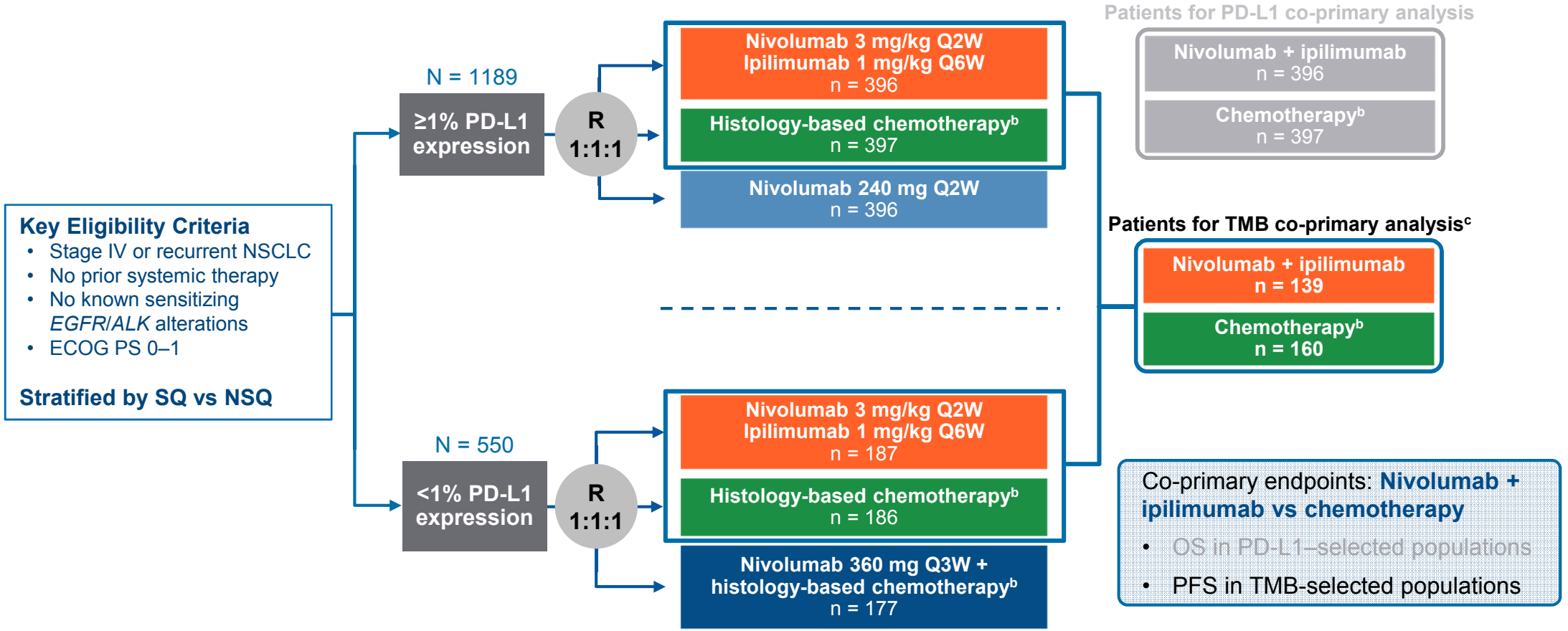
D Progression-free Survival among Patients with Low or Medium Tumor-Mutation Burden

	Median Progression-free Survival (95% CI)
	mo
Nivolumab (N=111)	4.1 (2.8–5.4)
Chemotherapy (N=94)	6.9 (5.5–8.6)

Hazard ratio for disease progression or death, 1.82 (95% CI, 1.30–2.55)



CheckMate 227 Part 1 Study Design[a]

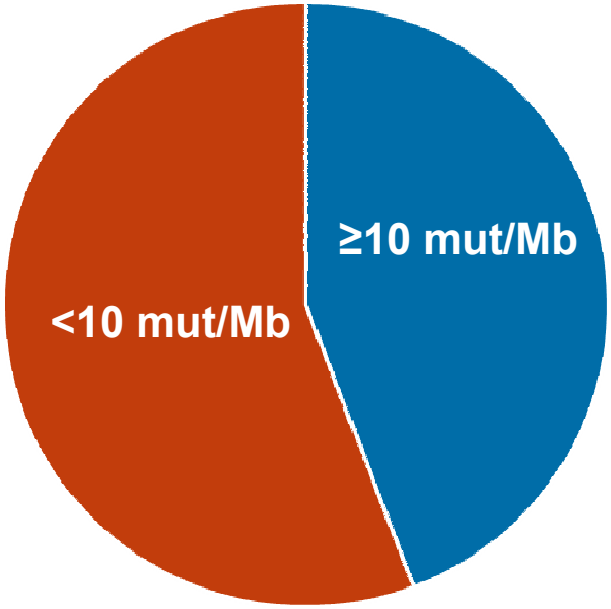


Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

TMB Analysis Using FoundationOne CDx™

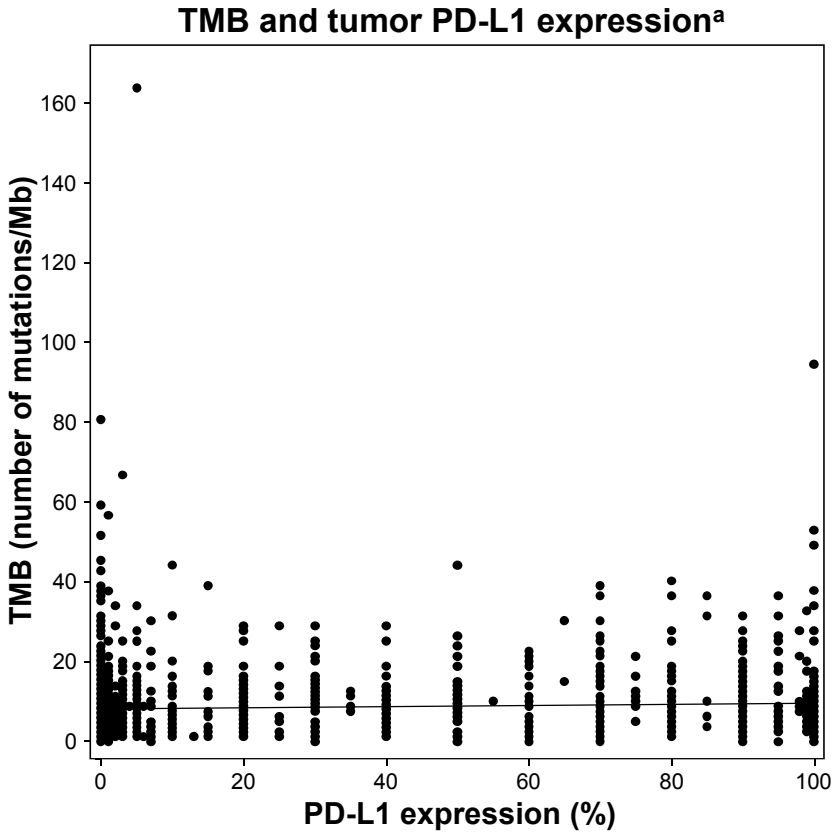
- 58% of all randomized patients had TMB-evaluable samples[a]

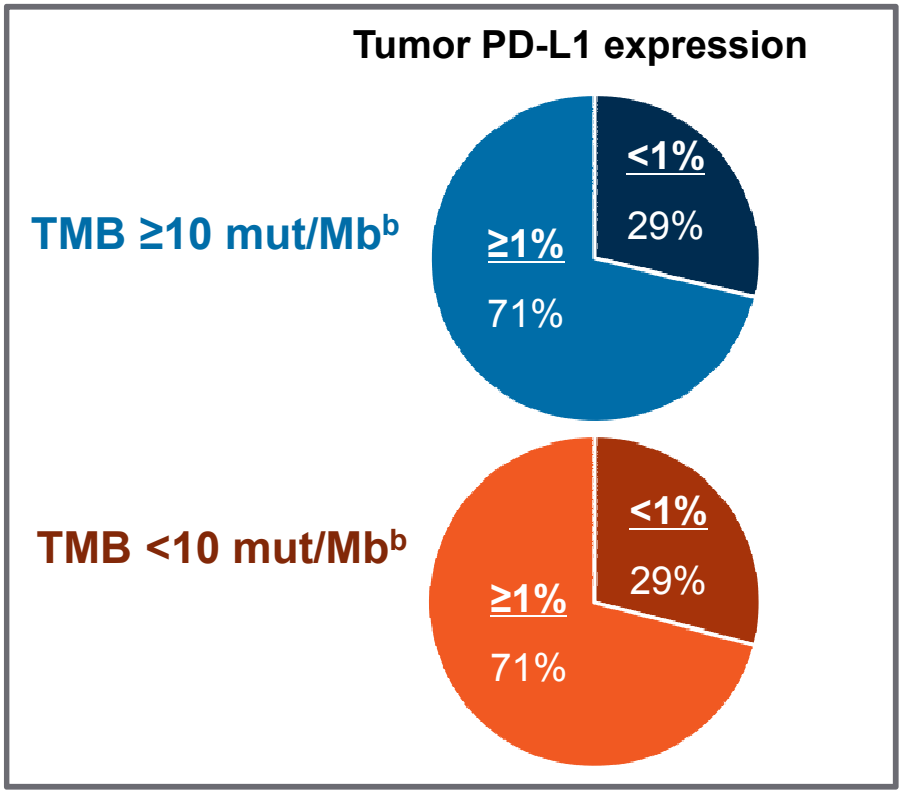


TMB-evaluable patients (n = 1004)

[a]Randomized patients include those from all treatment arms in part 1 (nivolumab + ipilimumab, nivolumab, chemotherapy, and nivolumab + chemotherapy arms). The FoundationOne CDx™ assay employs comprehensive QC criteria, including the following critical characteristics: tumor purity, DNA sample size, tissue sample size, library construction size, and hybrid capture yields

TMB and Tumor PD-L1 Expression Identify Distinct and Independent Populations of NSCLC



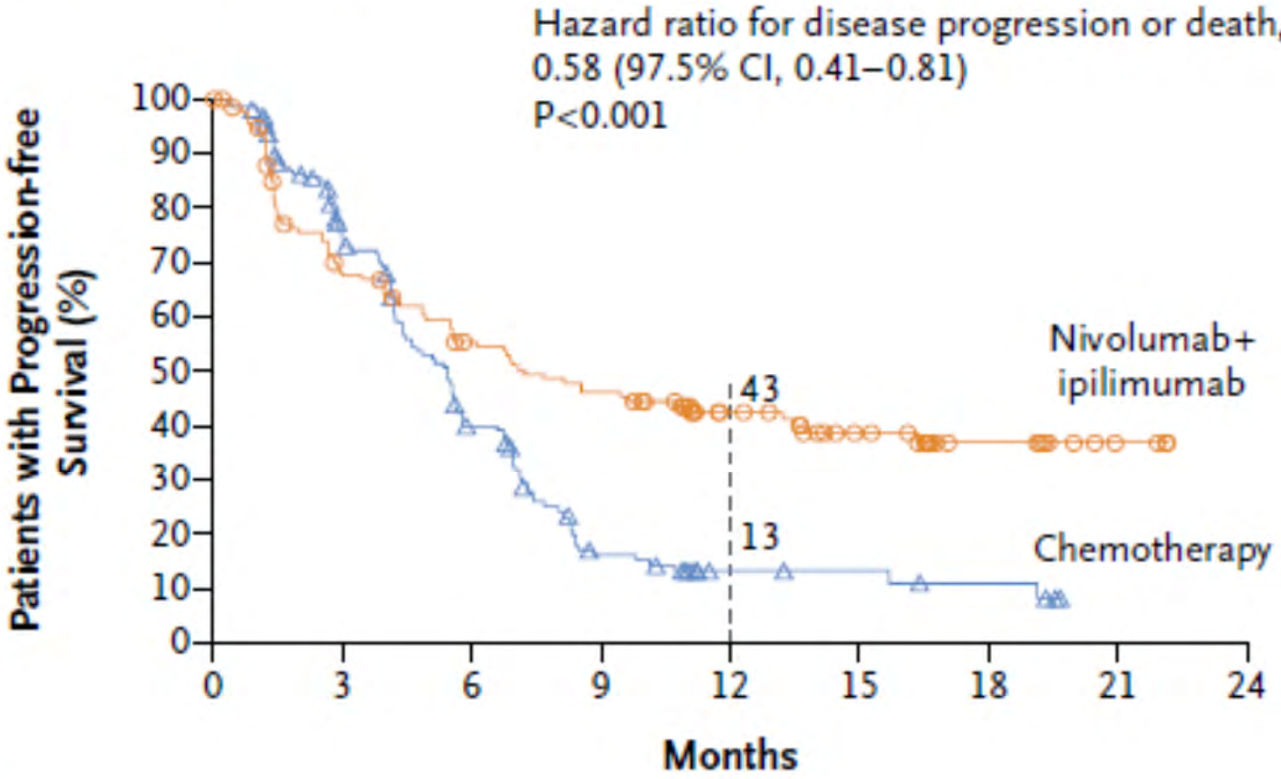


[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression as described by a linear regression model; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

Hellmann et al., NEJM 2018

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

A Progression-free Survival



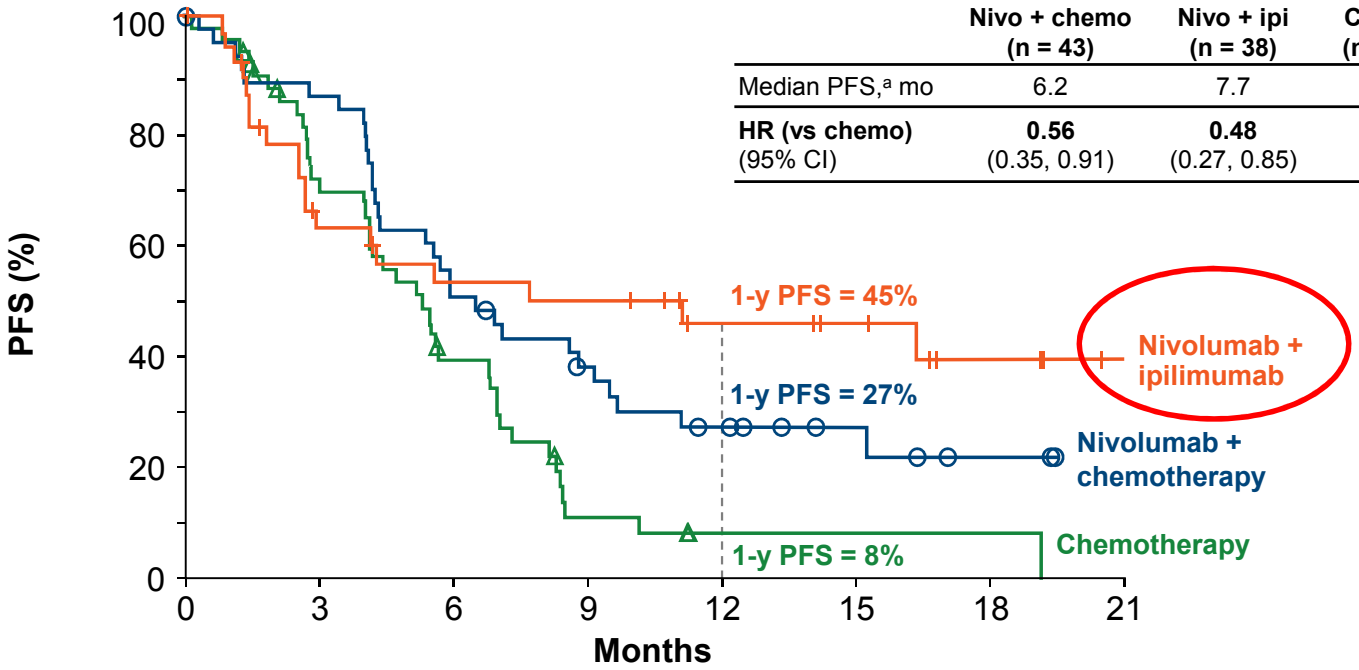
No. at Risk

Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

Hellmann, NEJM'18

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	



No. at risk								
Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

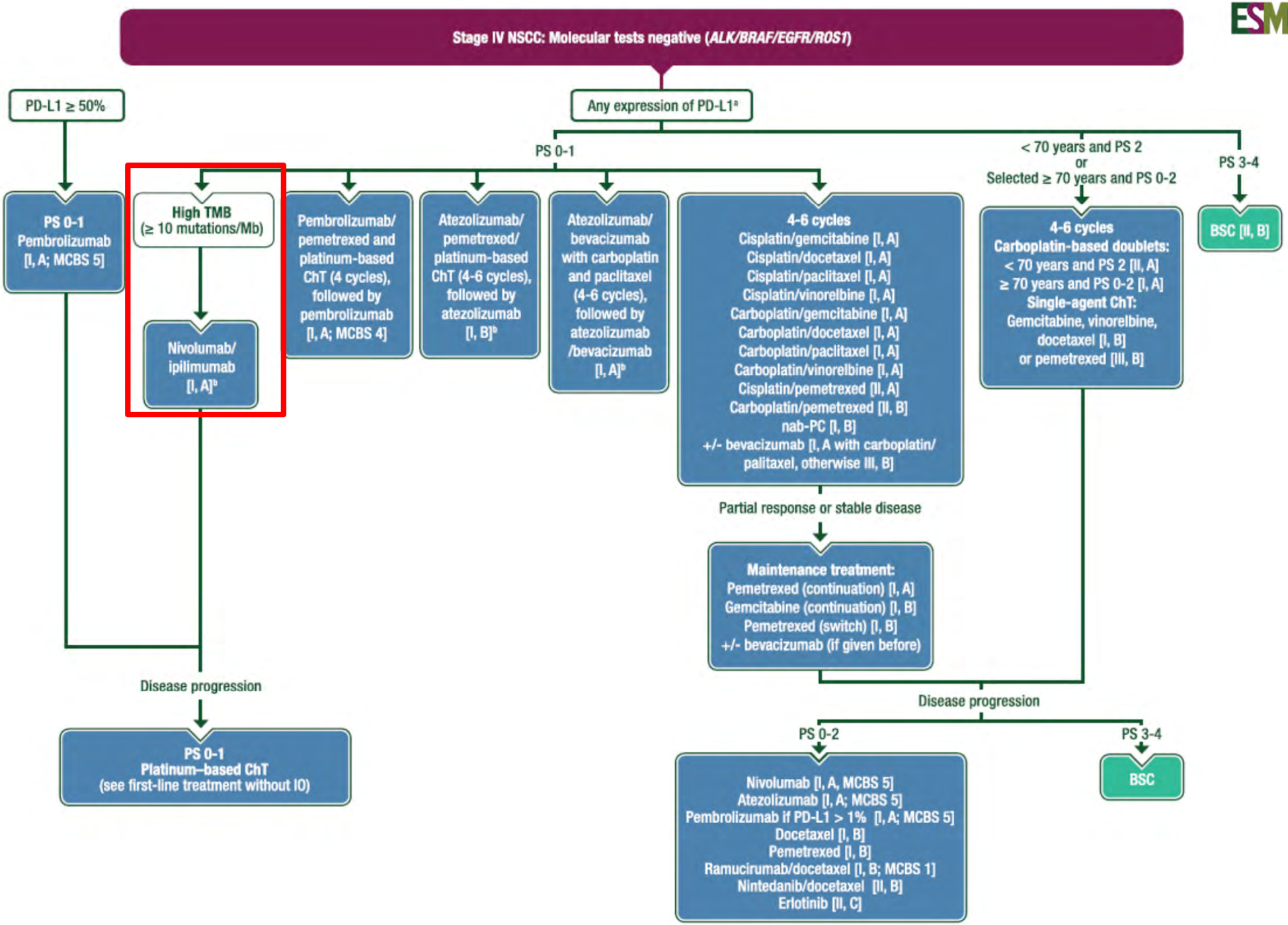
Exploratory analysis

[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo)

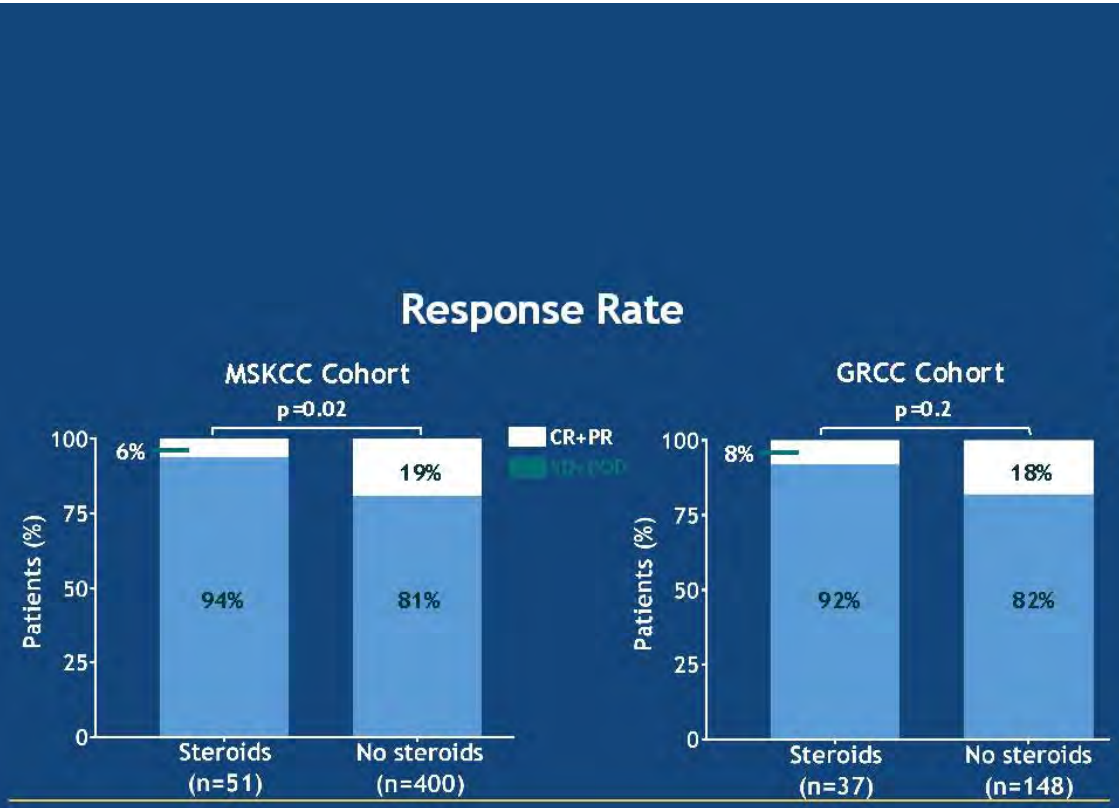
Press Release 19-10-2018

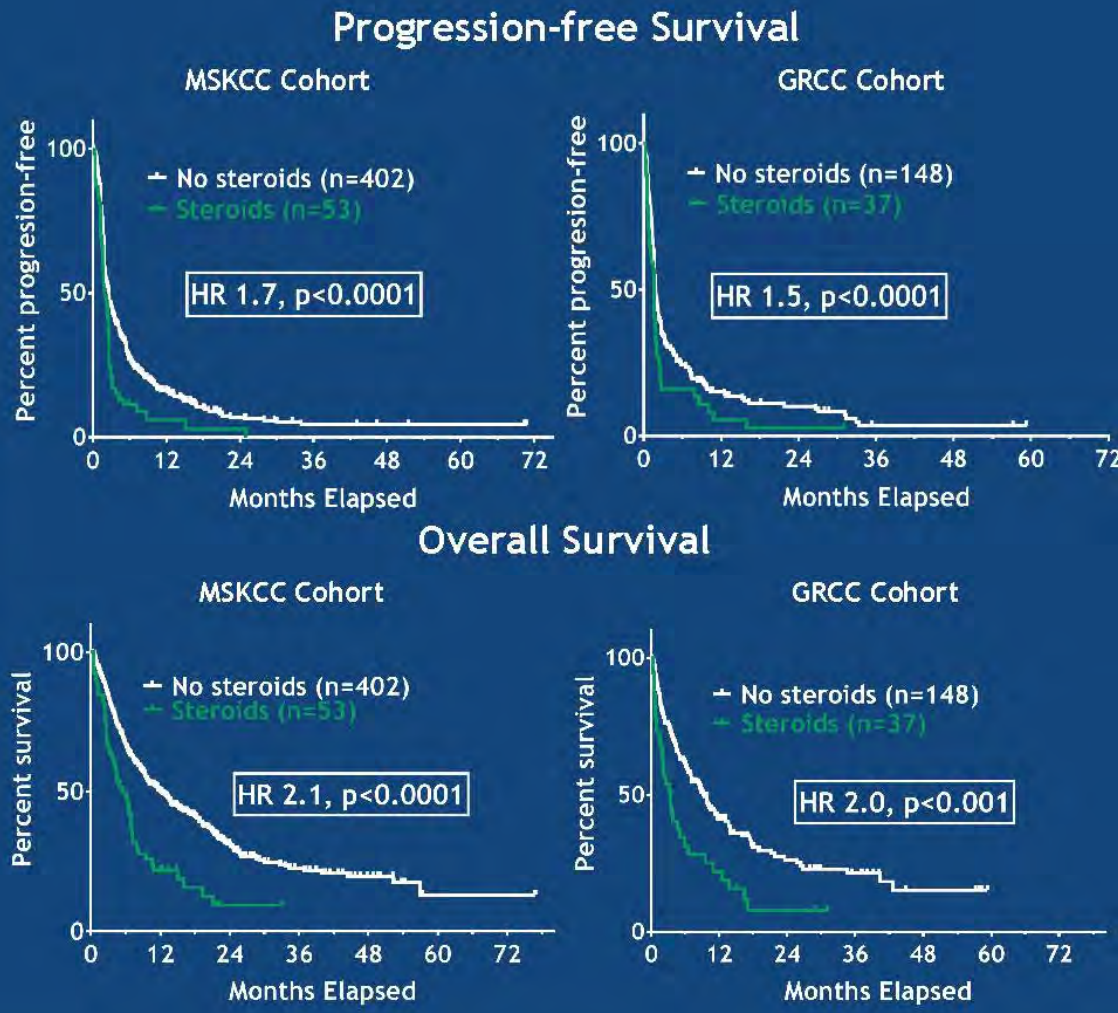
"Bristol-Myers Squibb Provides Update on the Ongoing Regulatory Review of Opdivo Plus Low-Dose Yervoy in First-Line Lung Cancer Patients with Tumor Mutational Burden ≥10 mut/Mb
New analysis submitted to U.S. Food and Drug Administration (FDA) constitutes a major amendment to the Company's supplemental Biologics License Application

	CT	NIVO-IPI	HR
OS (TMB < 10)	**12.42 (months)**	**16.20 (months)**	**0.78 (0.61-1.00)**
OS (TMB ≥ 10)	**16.72 (months)**	**23.03 (months)**	**0.77 (0.56-1.06)**


Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)
PD-L1 ≥ 50%
Any expression of PD-L1[a]
PS 0-1
< 70 years and PS 2
or
Selected ≥ 70 years and PS 0-2
PS 3-4
PS 0-1
Pembrolizumab
[I, A; MCBS 5]
High TMB
(≥ 10 mutations/Mb)
Nivolumab/
ipilimumab
[I, A][b]
Pembrolizumab/
pemetrexed and
platinum-based
ChT (4 cycles),
followed by
pembrolizumab
[I, A; MCBS 4]
Atezolizumab/
pemetrexed/
platinum-based
ChT (4-6 cycles),
followed by
atezolizumab
[I, B][b]
Atezolizumab/
bevacizumab
with carboplatin
and paclitaxel
(4-6 cycles),
followed by
atezolizumab
/bevacizumab
[I, A][b]
4-6 cycles
Cisplatin/gemcitabine [I, A]
Cisplatin/docetaxel [I, A]
Cisplatin/paclitaxel [I, A]
Cisplatin/vinorelbine [I, A]
Carboplatin/gemcitabine [I, A]
Carboplatin/docetaxel [I, A]
Carboplatin/paclitaxel [I, A]
Carboplatin/vinorelbine [I, A]
Cisplatin/pemetrexed [II, A]
Carboplatin/pemetrexed [II, B]
nab-PC [I, B]
+/- bevacizumab [I, A with carboplatin/
palitaxel, otherwise III, B]
4-6 cycles
Carboplatin-based doublets:
< 70 years and PS 2 [II, A]
≥ 70 years and PS 0-2 [I, A]
Single-agent ChT:
Gemcitabine, vinorelbine,
docetaxel [I, B]
or pemetrexed [III, B]
BSC [II, B]
Partial response or stable disease
Maintenance treatment:
Pemetrexed (continuation) [I, A]
Gemcitabine (continuation) [I, B]
Pemetrexed (switch) [I, B]
+/- bevacizumab (if given before)
Disease progression
Disease progression
PS 0-2
PS 3-4
PS 0-1
Platinum–based ChT
(see first-line treatment without IO)
Nivolumab [I, A, MCBS 5]
Atezolizumab [I, A; MCBS 5]
Pembrolizumab if PD-L1 > 1% [I, A; MCBS 5]
Docetaxel [I, B]
Pemetrexed [I, B]
Ramucirumab/docetaxel [I, B; MCBS 1]
Nintedanib/docetaxel [II, B]
Erlotinib [II, C]
BSC

Predictive role of steroids use

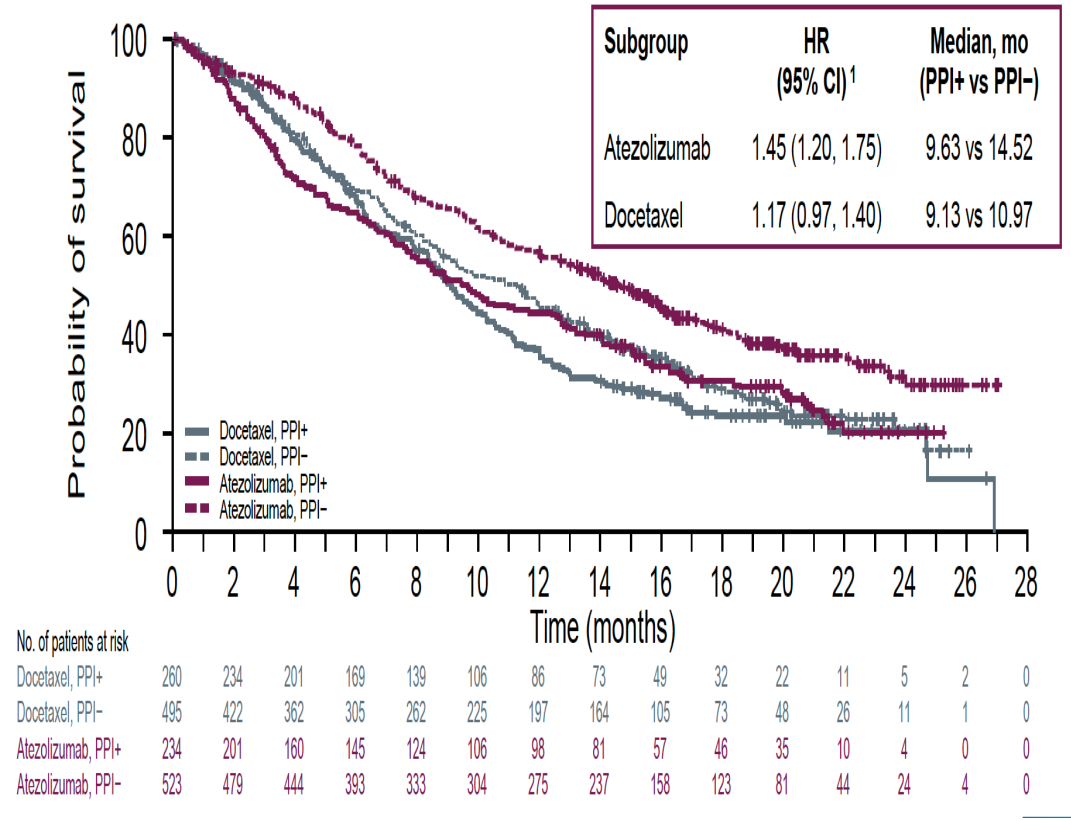




Arbour KC et Al, ASCO 2018 abs #9003

Slides are the property of the author, permission required for reuse.

Shorter OS observed in the atezolizumab PPI+ group

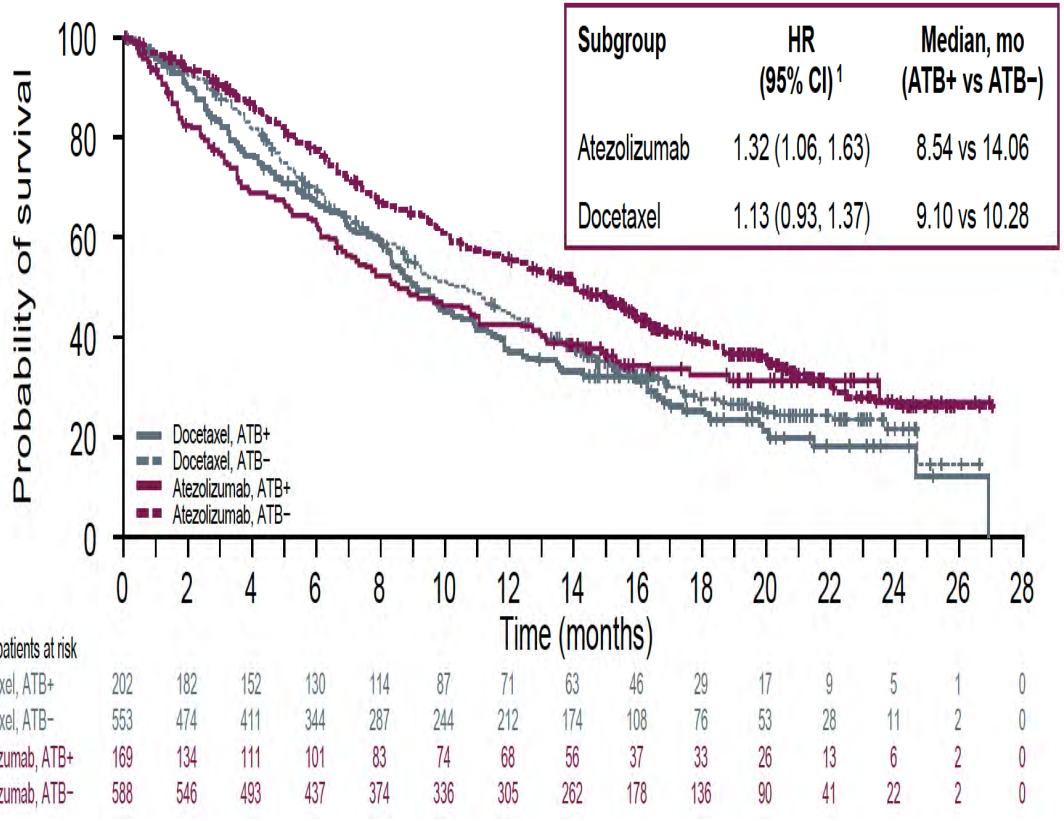


Subgroup	HR (95% CI)[1]	Median, mo (PPI+ vs PPI−)
Atezolizumab	1.45 (1.20, 1.75)	9.63 vs 14.52
Docetaxel	1.17 (0.97, 1.40)	9.13 vs 10.97

No. of patients at risk

Docetaxel, PPI+	260	234	201	169	139	106	86	73	49	32	22	11	5	2	0
Docetaxel, PPI−	495	422	362	305	262	225	197	164	105	73	48	26	11	1	0
Atezolizumab, PPI+	234	201	160	145	124	106	98	81	57	46	35	10	4	0	0
Atezolizumab, PPI−	523	479	444	393	333	304	275	237	158	123	81	44	24	4	0

Shorter OS observed in the atezolizumab ATB+ group



Subgroup	HR (95% CI)[1]	Median, mo (ATB+ vs ATB−)
Atezolizumab	1.32 (1.06, 1.63)	8.54 vs 14.06
Docetaxel	1.13 (0.93, 1.37)	9.10 vs 10.28

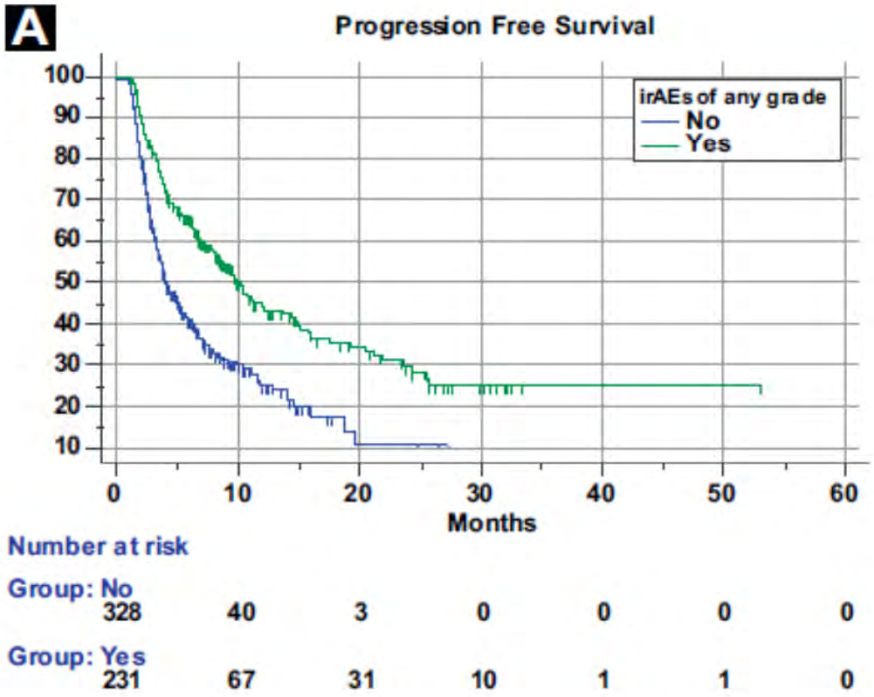
No. of patients at risk

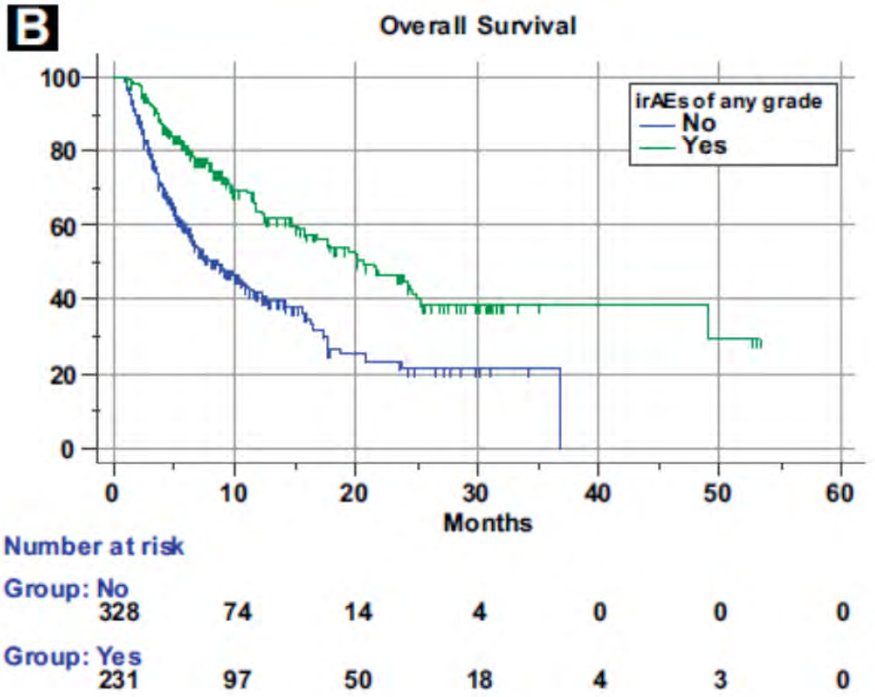
Docetaxel, ATB+	202	182	152	130	114	87	71	63	46	29	17	9	5	1	0
Docetaxel, ATB−	553	474	411	344	287	244	212	174	108	76	53	28	11	2	0
Atezolizumab, ATB+	169	134	111	101	83	74	68	56	37	33	26	13	6	2	0
Atezolizumab, ATB−	588	546	493	437	374	336	305	262	178	136	90	41	22	2	0

M Chalabi et al., ESMO-IO 2018; :Abstr LBA

Correlations Between the Immune-related Adverse Events Spectrum and Efficacy of Anti-PD1 Immunotherapy in NSCLC Patients

Figure 1 Kaplan-Meier Survival Curves According to irAEs of any Grade. (A) Progression-free Survival; (B) Overall Survival





Cortellini, CLC'19

Predictors of PD1/PDL1 inhibitors efficacy: Conclusions

- **PDL1 IHC the only validated biomarker for single agent therapy in first and second-line A-NSCLC and post-CT/RT in inoperable stage III NSCLC**
- **However PDL1 IHC far from being the ideal biomarker (large heterogeneity, inter-observer variability, outcome often unrelated with biomarker expression)**
- **TMB possible alternative to PDL1 IHC especially for combo I-O, but technically problematic and still not ready for prime time**
- **Preliminary evidence of negative predictive role of antibiotic, steroids and PPI use vs positive predictive role of irAEs**