NSCLC avanzato: quali novità nel 2018?
Negrar, 30 Ottobre 2018

Farmaci anti-PD1 e anti-PD-L1: quali differenze? Il punto di vista dell'oncologo

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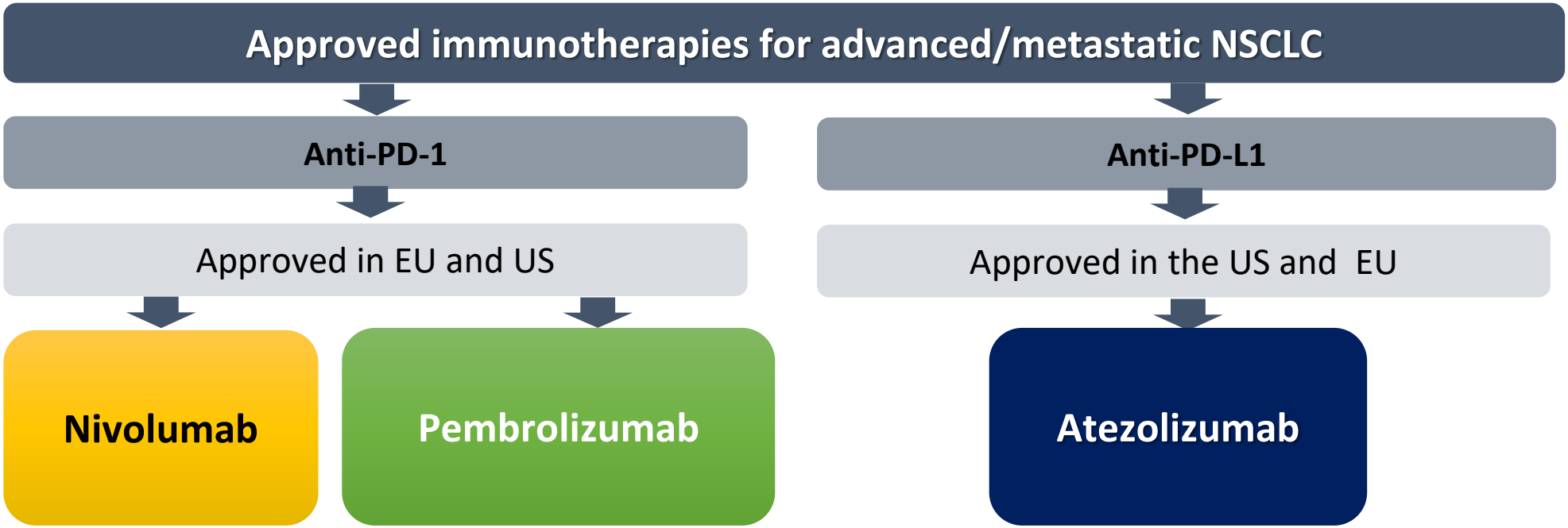
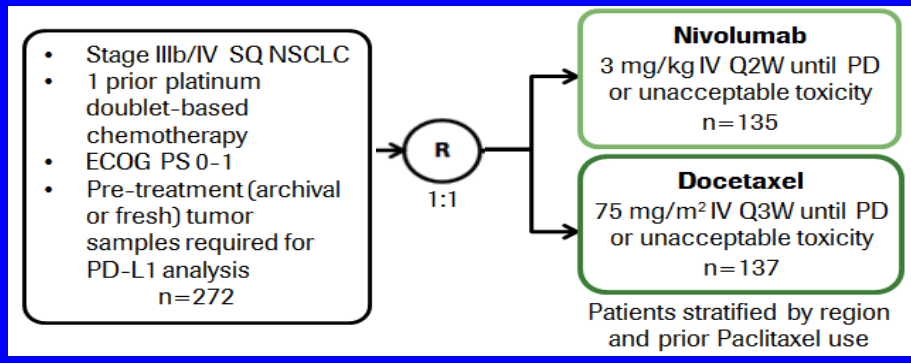
Anti PD1/PD-L1 approved in 2nd line NSCLC



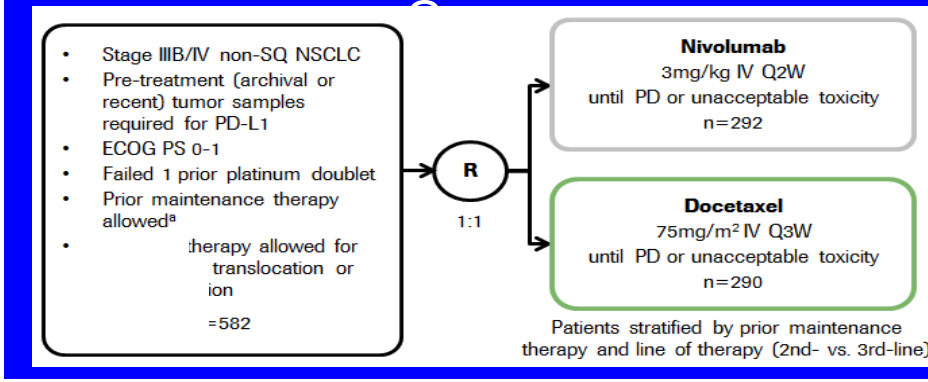
- **Evidence suggests, however, that the clinical activity of nivolumab and pembrolizumab is limited in patients with tumours expressing low level PD-L1.**

Immunotherapy in pretreated patients with advanced NSCLC

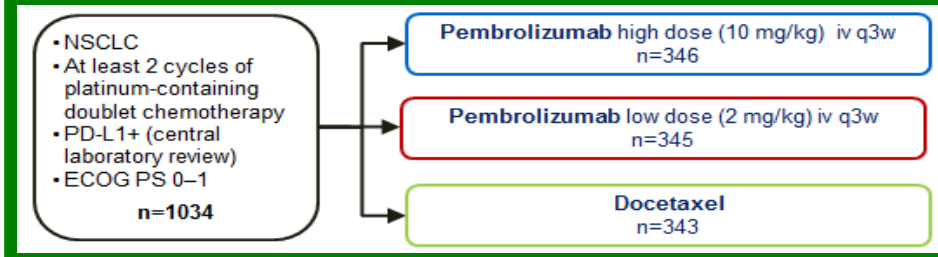
Nivolumab – CheckMate 017 (PIII)[1]
2nd Line, squamous, PD-L1 All-Comer



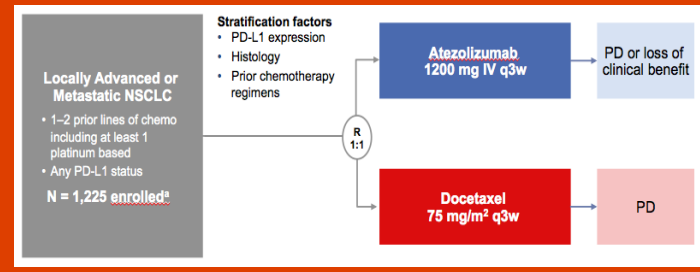
Nivolumab – CheckMate 057 (PIII)[2]
2nd Line, non-squamous, PD-L1 All-



Pembrolizumab - Keynote 010 (PII/III)[3]
2nd+ Line, PD-L1 TPS ≥1%

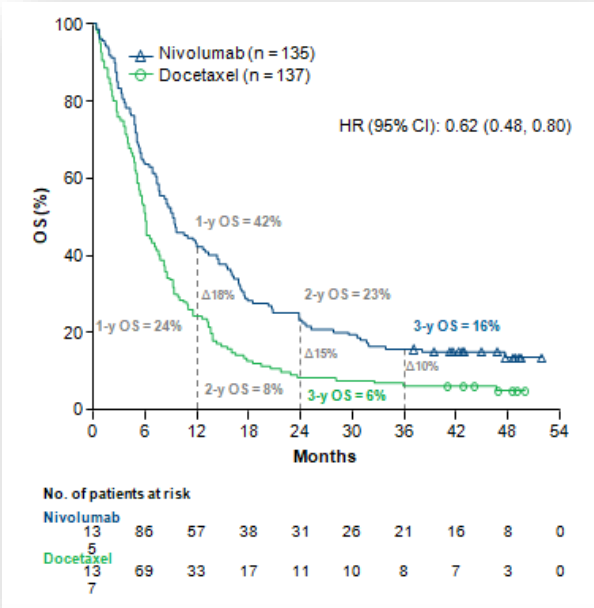


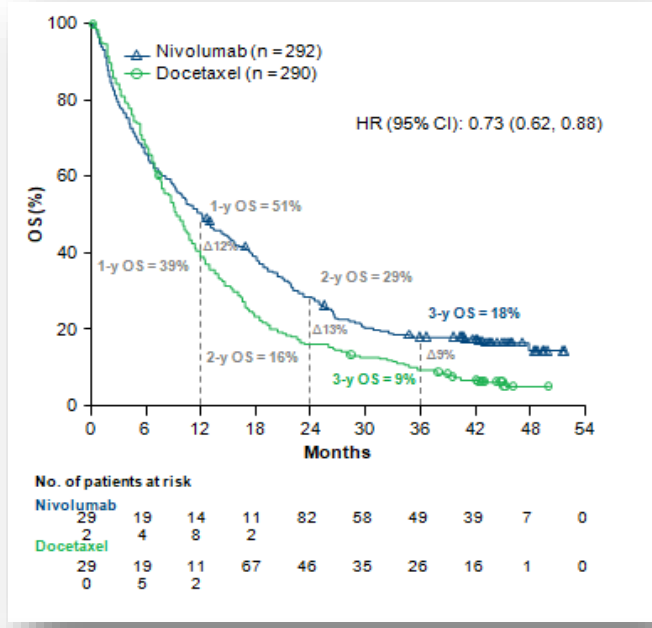
Atezolizumab – OAK (PIII)[4]
2nd+ Line, PD-L1 All-Comer

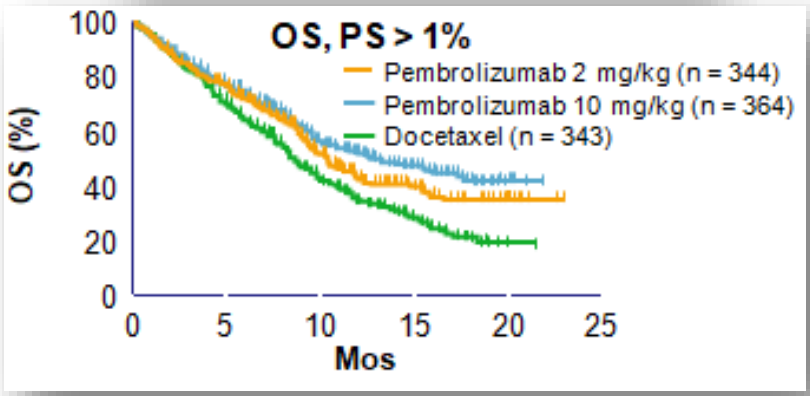


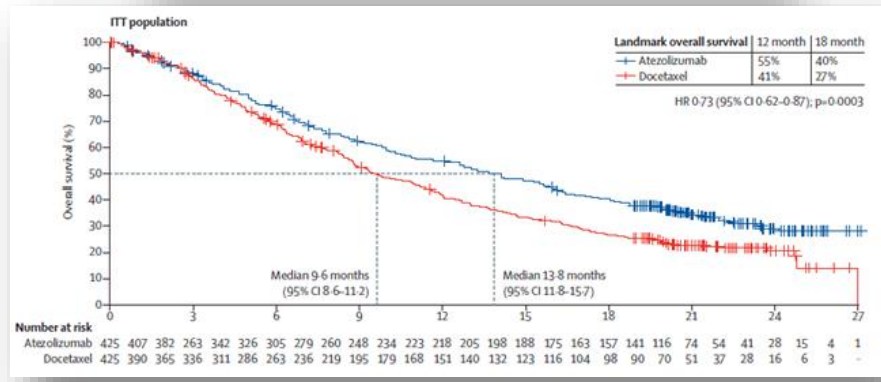
1. Borghaei H, ASCO 2016; 2. Brahmer JR, AACR 2017; 3. Herbst RS, ASCO 2017; 4. Rittmeyer A, Lancet 2017

Consistent benefit with anti-PD1-PD-L1 in second/third-line



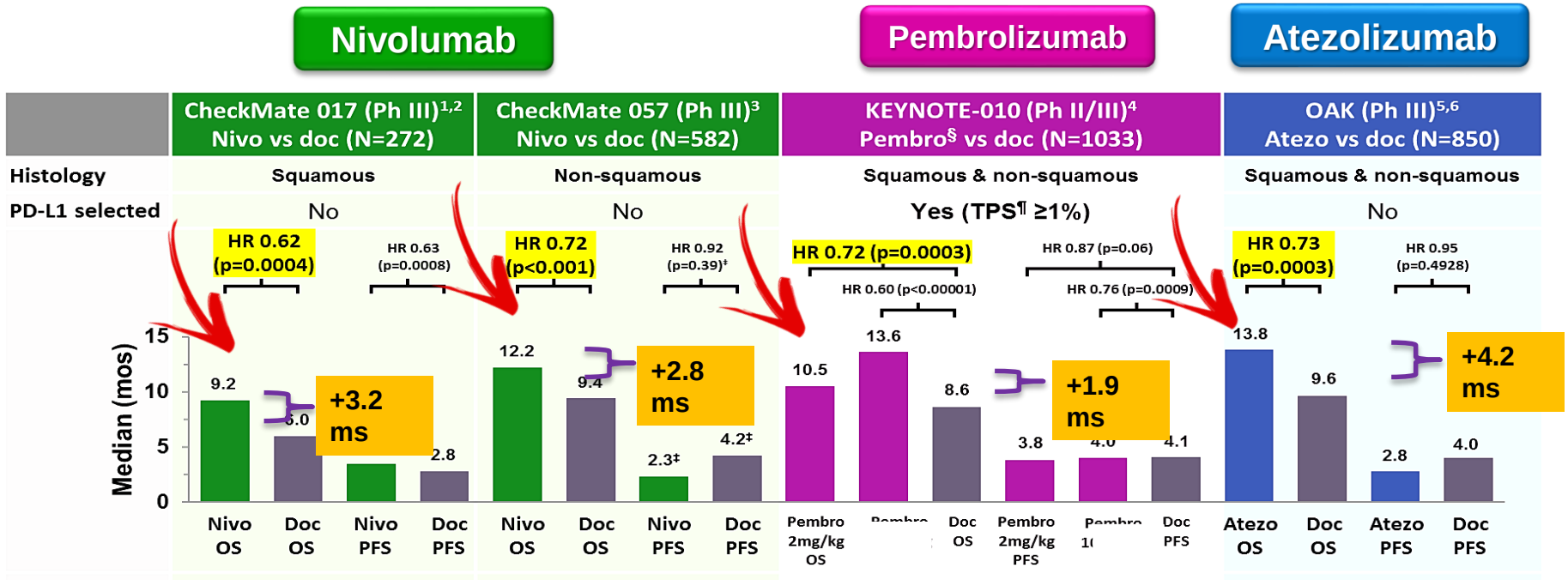






Felip E, ESMO 2017; Herbst RS, Lancet 2016; Rittmeyer A, Lancet 2017

Anti PD-1/PD-L1: efficacy in previous treated advanced NSCLC



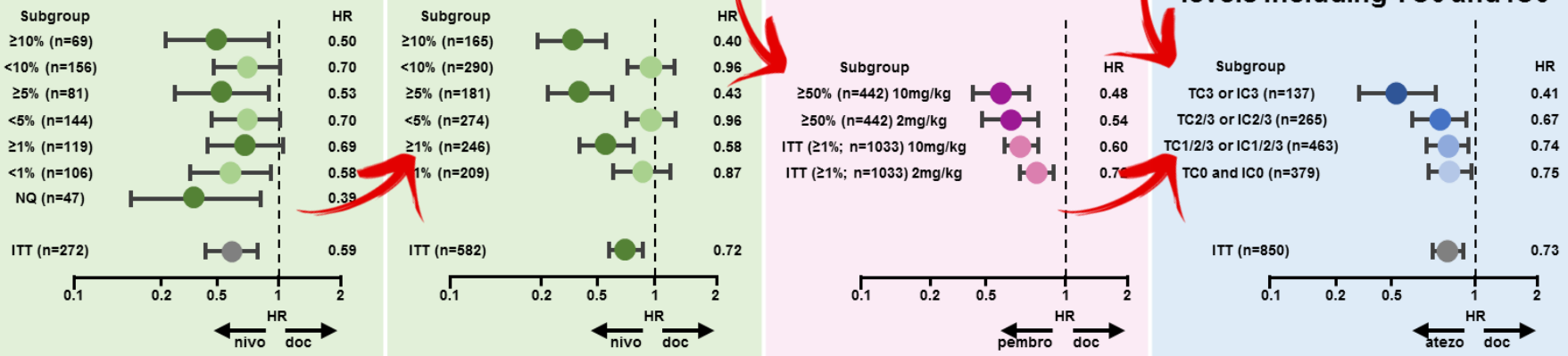
		Nivo 20% vs doc 9%*	Nivo 19% vs doc 12%‡	Pembro 19% vs doc 10%	Atezo 14% vs doc 13%
ORR, %					
LTS	1yS	42%	51%	43%	55%
	2ys	23%	29%	30%	31%
	3ys	16%	18%		

TPS: Tumour proportion score

1. Reckamp, et al. WCLC 2015 (ORAL02.01); 2. Brahmer, et al. N Engl J Med 2015
3. Borghaei, et al. N Engl J Med 2015; 4. Herbst, et al. ESMO 2016 (Abs LBA48)
5. Barlesi, et al. ESMO 2016 (Abs LBA44); 6. Rittmeyer, et al. Lancet 2017

Phase III trials of I/O in 2nd line NSCLC: efficacy by PD-L1 expression

	CheckMate 017 (PhIII)[1] Nivo vs doc (N=272)	CheckMate 057 (PhIII)[2] Nivo vs doc (N=582)	KEYNOTE-010 (PhII/III)[3] Pembro* vs doc (N=1033)	OAK (PhIII)[4,5] Atezo vs doc (N=850)
Histology	Squamous	Non-squamous	Squamous & non-squamous	Squamous & non-squamous
PD-L1 status	No	No	Yes (TPS‡ ≥1%)	No
HR for OS by PD-L1 status	**Benefit from nivo was independent from PD-L1 expression in Sq NSCLC**	**PD-L1 expression is predictive of nivo benefit in Non-Sq NSCLC**	**PD-L1 proportion score ≥50% showed greatest benefit from pembro**	**Improved survival with atezo seen across the whole range of PD-L1 expression levels including TC0 and IC0**
PD-L1 assay	**28-8 (Dako) on TCs**		**22C3 (Dako) on TCs**	**SP142 (Ventana) on ICs and TCs**



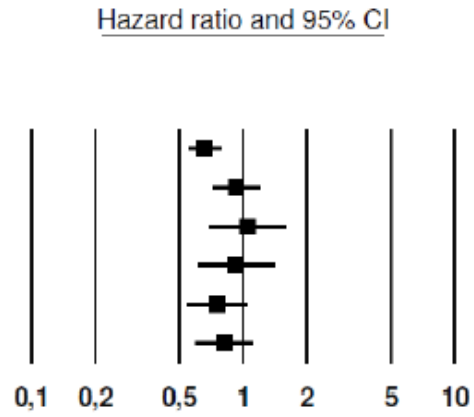
*Phase III dose: 2mg/kg q3w and 10mg/kg q3w
‡Tumour proportion score (TPS) is the proportion of viable tumour cells showing partial or complete membrane PD-L1 expression

1. Brahmer, et al. N Engl J Med 2015; 2. Borghaei, et al. N Engl J Med 2015
3. Herbst, et al. ESMO 2016 (Abs LBA48); 4. Barlesi, et al. ESMO 2016 (Abs LBA44)
5. Rittmeyer, et al. Lancet 2017

Nivo, Pembro, Atezo in non-squamous NSCLC data of a pooled analysis: efficacy

In PD-L1 ≥1% patients no significant differences were observed in the indirect comparisons of Atezolizumab vs Nivolumab (HR: 0.921, CI95%: 0.609-1.392, p=0.696), Atezolizumab vs Pembrolizumab (HR: 0.751, CI95%: 0.541-1.043, p=0.087), and Nivolumab vs Pembrolizumab (HR: 0.816, CI95%: 0.597-1.116, p=0.491).

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
I vs CHT (PD-L1>1%)	0,660	0,555	0,785	-4,681	0,000
I vs CHT (PD-L1<1%)	0,933	0,720	1,210	-0,524	0,601
I vs CHT (EGFR+)	1,052	0,695	1,593	0,239	0,811
A vs N (PD-L1>1)	0,921	0,609	1,392	-0,390	0,696
A vs P (PD-L1>1)	0,751	0,541	1,043	-1,710	0,087
N vs P (PD-L1>1)	0,816	0,597	1,116	-1,274	0,203



Tassinari D, WCLC 2018

Incidence of selected relevant irAEs observed with single-agent immune checkpoint inhibitors in NSCLC

ADVERSE EVENT	NIVOLUMAB		PEMBROLIZUMAB		ATEZOLIZUMAB	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
GENERAL						
Fatigue	16%	1%	10%-28%	1%	20%-26%	3%
Decreased appetite	10%-11%	0%	9%-14%	0%-1%	18%-24%	<1%
Myalgia/Arthralgia	2%	<1%	1%-2%	0%	6%-12%	<1%
ENDOCRINE						
Hypothyroidism	3%-7%	0%	7%-9%	0%	NR	NR
Hyperthyroidism	1%	0%	4%-8%	0%	NR	NR
Thyroiditis	1%-4%	0%	2%-3%	0%	NR	NR
Adrenal insufficiency	1%-2%	0%-1%	1%	0%	NR	NR
Hypophysitis	<1%	<1%	<1%	<1%	<1%	<1%
GASTROINTESTINAL						
Diarrhea	6%-10%	0%-3%	7%-14%	1%-4%	7%-15%	<1%
Colitis	1%	1%	1%-2%	1%	1%	<1%
HEPATIC						
Increased ALT	1%-3%	0%-2%	2%-5%	<1%	4%	2%
Increased AST	2%-3%	0%-2%	3%	<1%	4%	2%
PULMONARY						
Pneumonitis	3%-6%	1%-3%	4%-6%	2%-3%	3%	1%
RENAL						
Increased creatinine	2%-3%	0%	2%	0%	NR	NR
Nephritis	0%-1%	0%-1%	<1%	<1%	NR	NR
SKIN						
Rash	5%-19%	0%-2%	4%-10%	<1%-4%	NR	NR
Pruritus	2%-12%	0%-2%	7%-11%	0%	NR	NR

Genova C, Expert Opinion on Drug Safety 2017

Few Pts Treated with PD-L1/PD-1 Is Experience Severe irAEs

Selected irAEs in phase III trials of PD-L1/PD-1 inhibitors (immunotherapy arm)

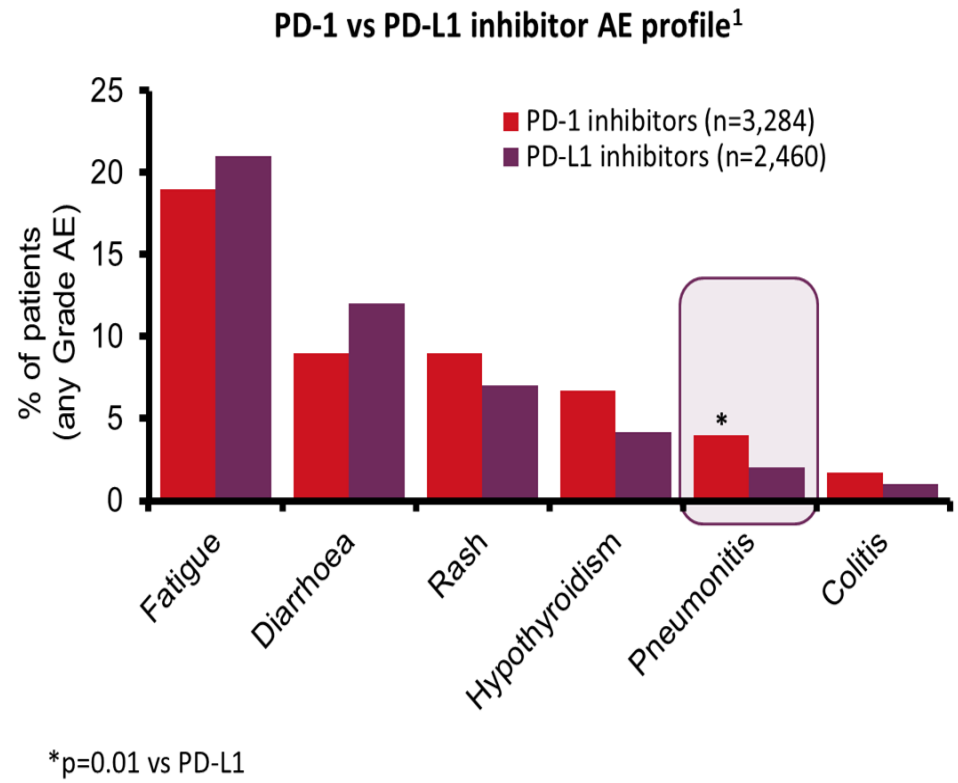
	CheckMate 017		CheckMate 057		KEYNOTE-010 (2mg/kg arm)		OAK	
	All Grade	Grade 3–4	All Grade	Grade 3–4	All Grade	Grade 3–4	All Grade	Grade 3–4
Pneumonitis	5%	1%	3%	1%	5%	2%	1%	0.7%
Hypothyroidism	4%	0%	7%	0%	8%	0%	NR	NR
Hyperthyroidism	NR	NR	1%	0%	4%	0%	NR	NR
Hepatitis	NR	NR	NR	NR	<1%	<1%	<1%	0.3%
Colitis	1%	1%	1%	<1%	1%	1%	<1%	0%

Incidence ≥5% Incidence 2–4% Incidence ≤1%

Brahmer, et al. N Engl J Med 2015; Borghaei, et al. N Engl J Med 2015; Herbst, et al. Lancet 2016; Rittmeyer, et al. Lancet 2017

Meta-analysis of safety profile of PD-1 vs PD-L1 inhibitors

	PD-1 Inhibitors N = 3284	PD-L1 Inhibitors N = 2460	*P*
Overall AEs, %	64	66	.8
Grade 3-5 AEs, %	13	21	.15
Fatigue of any grade, %	19	21	.4
Diarrhea of any grade, %	9	12	.4
Rash of any grade, %	9	7	.8
IRAEs, %	16	11	.07
Grade 3-5 IRAEs, %	3	5	.4
Hypothyroidism of any grade, %	6.7	4.2	.07
Pneumonitis of any grade, %	4	2	.01
Colitis of any grade, %	1.7	1	.4
Overall response rate, %	19	18.6	.17



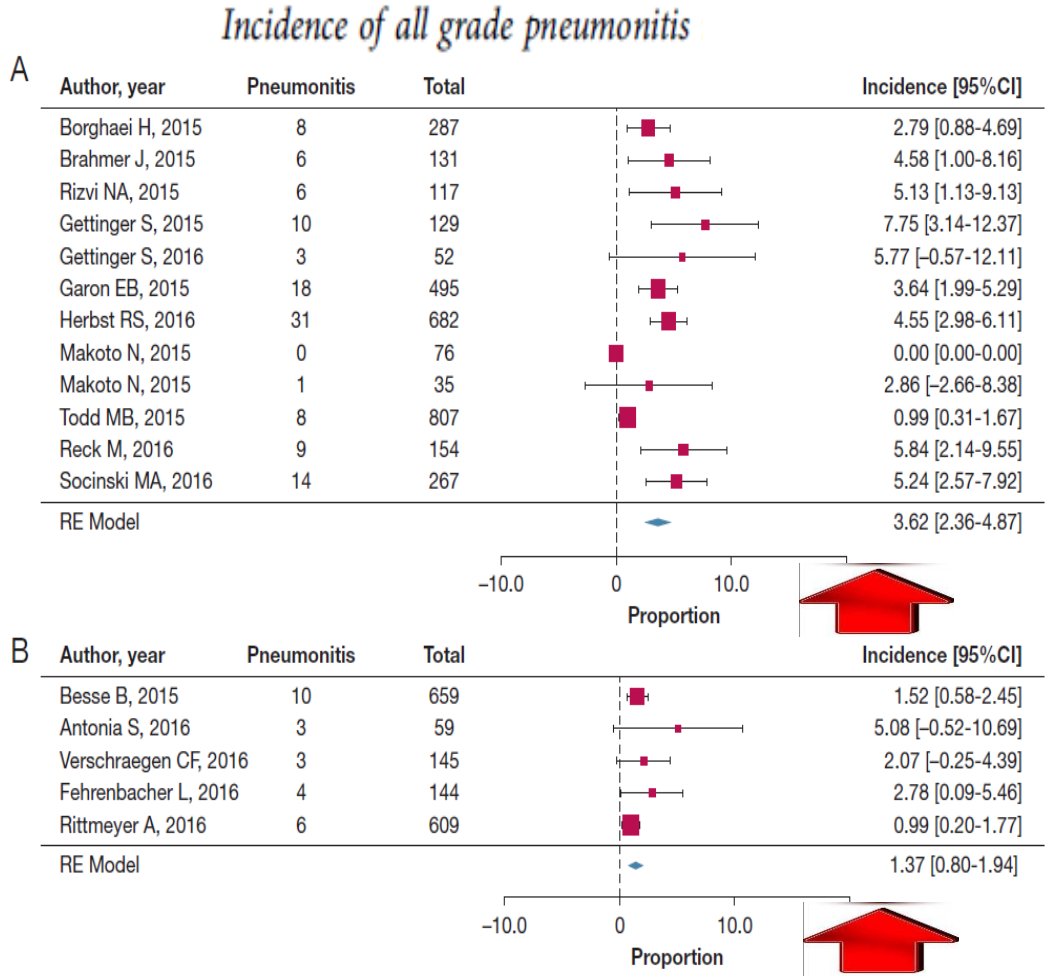
*p=0.01 vs PD-L1

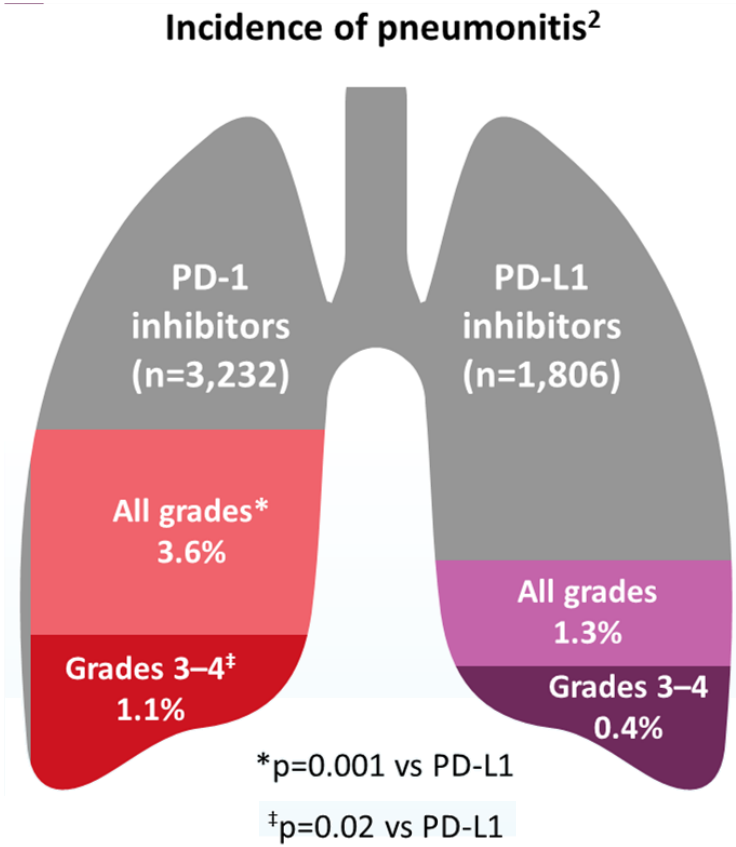
Pillai RN, Cancer 2018

Incidence of pneumonitis with PD-1/ PD-L1 in NSCLC: a Meta-analysis

PD-1

PD-L1

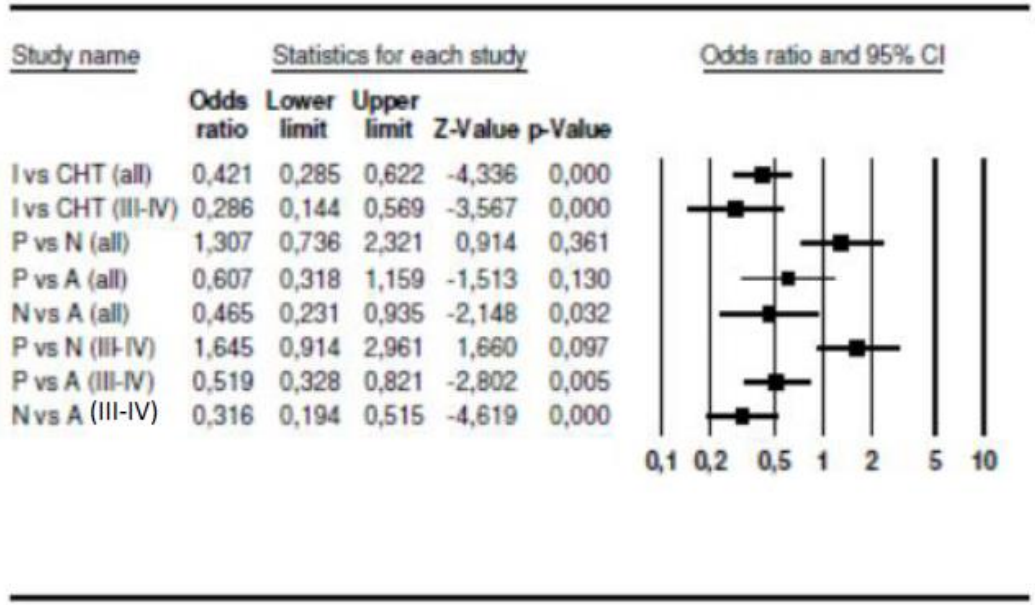




Kungher M, Chest 2017

Nivo, Pembro, Atezo in non-squamous NSCLC data of a pooled analysis: safety

•Considering all the side effects, no significant differences were observed indirect comparing Pembrolizumab vs Nivolumab (OR: 1.307, CI95%: 0.736-2.321, p=0.361) and Pembrolizumab vs Atezolizumab (OR: 0.607, CI95%: 0.318-1.159, p=0.13), while a significant difference was observed indirectly comparing Nivolumab vs Atezolizumab (OR: 0.465, CI95%: 0.231-0.934, p=0.032). Likewise, no significant differences were observed between Pembrolizumab and Nivolumab for any grade III-IV side effects, while a significant difference was observed for Pembrolizumab vs Atezolizumab (OR: 0.519, CI95%: 0.328-0.821, p=0.005) and Nivolumab vs Atezolizumab (OR: 0.316, CI95%: 0.193-0.516, p<0.001).

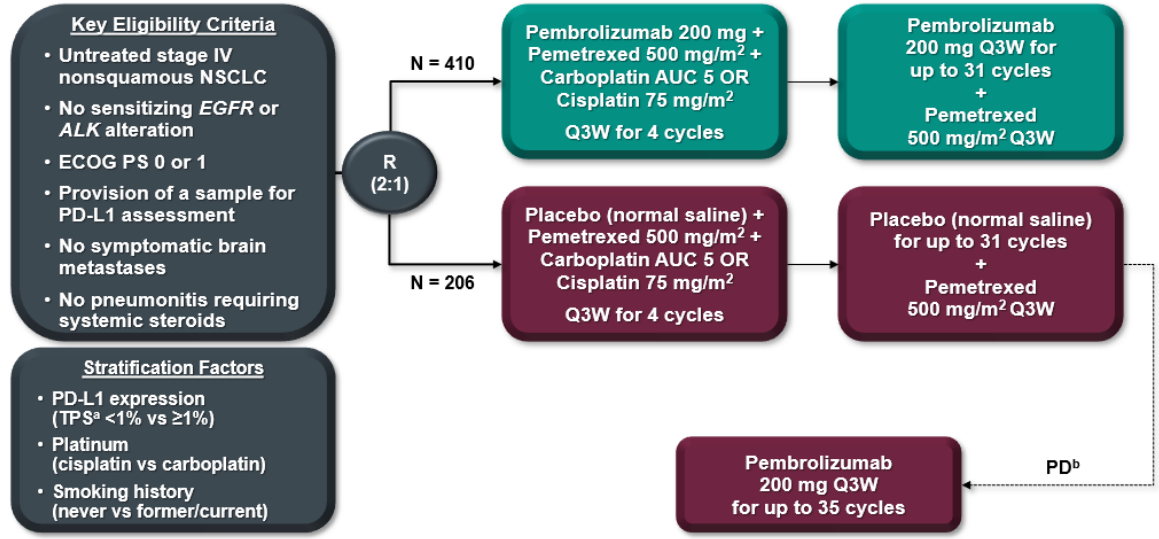


Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
I vs CHT (all)	0,421	0,285	0,622	-4,336	0,000
I vs CHT (III-IV)	0,286	0,144	0,569	-3,567	0,000
P vs N (all)	1,307	0,736	2,321	0,914	0,361
P vs A (all)	0,607	0,318	1,159	-1,513	0,130
N vs A (all)	0,465	0,231	0,935	-2,148	0,032
P vs N (III-IV)	1,645	0,914	2,961	1,660	0,097
P vs A (III-IV)	0,519	0,328	0,821	-2,802	0,005
N vs A (III-IV)	0,316	0,194	0,515	-4,619	0,000

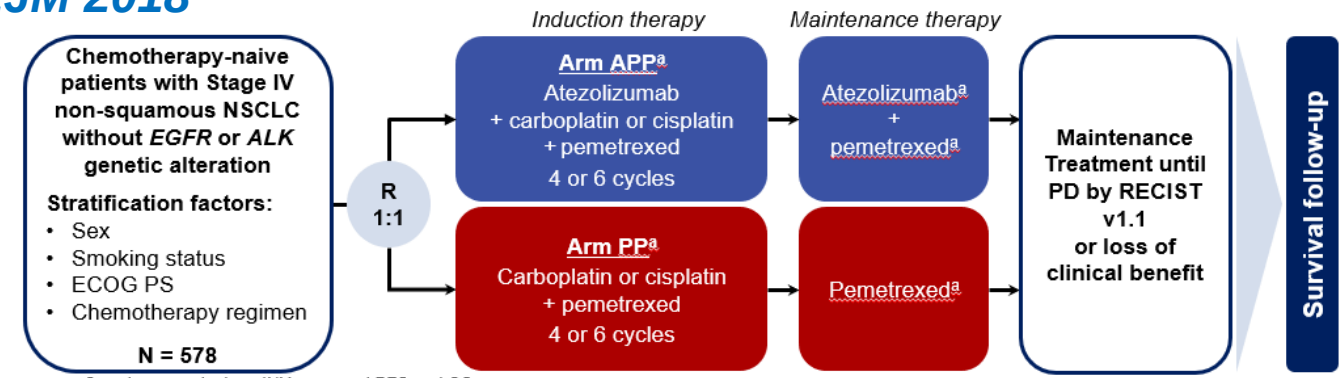
Tassinari D,

WCLC 2018

KEYNOTE-189 vs IMpower132: study design



Gandhi L, NEJM 2018



Papadimitrakopoulou VA, WCLC 2018

KEYNOTE-189 vs IMpower132: ORR

Best Response,[a] n (%)	Pembro/ Pem/Plat (N = 410)	Placebo/ Pem/Plat (N = 206)
CR	2 (0.5%)	1 (0.5%)
PR	193 (47.1%)	38 (18.4%)
SD	152 (37.1%)	106 (51.5%)
PD	36 (8.8%)	36 (17.5%)

Duration of response, mo	Pembro/ Pem/Plat (N = 195)	Placebo/ Pem/Plat (N = 39)
Median	11.2	7.8
Range	1.1+ to 18.0+	2.1+ to 16.4+

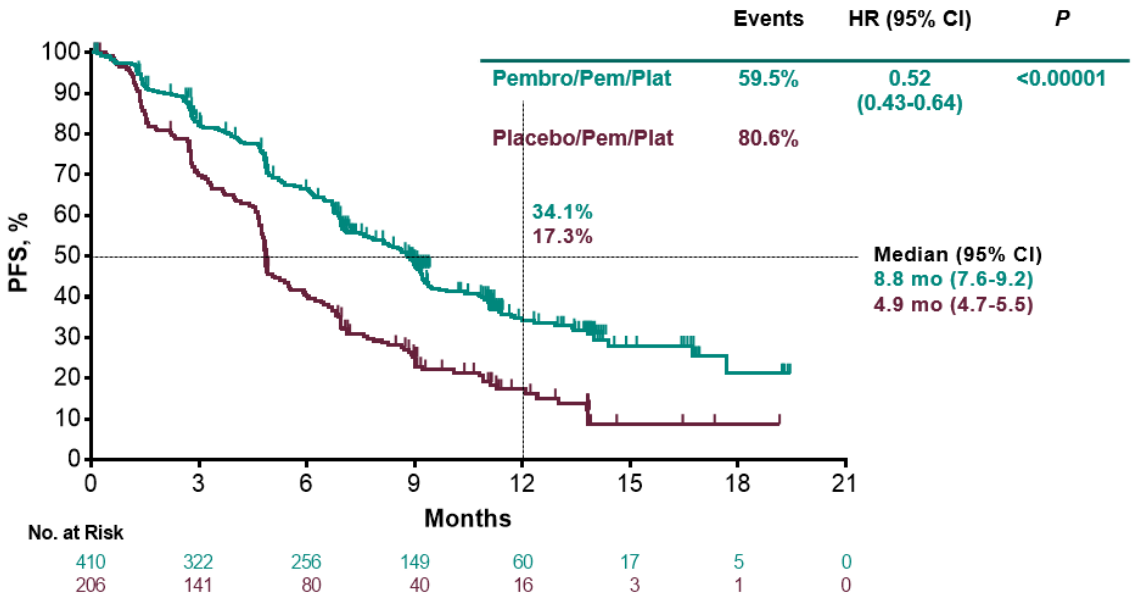
Gandhi L, NEJM 2018

	APP	PP
6-mo PFS	59.1%	40.9%
12-mo PFS	33.7%	17.0%

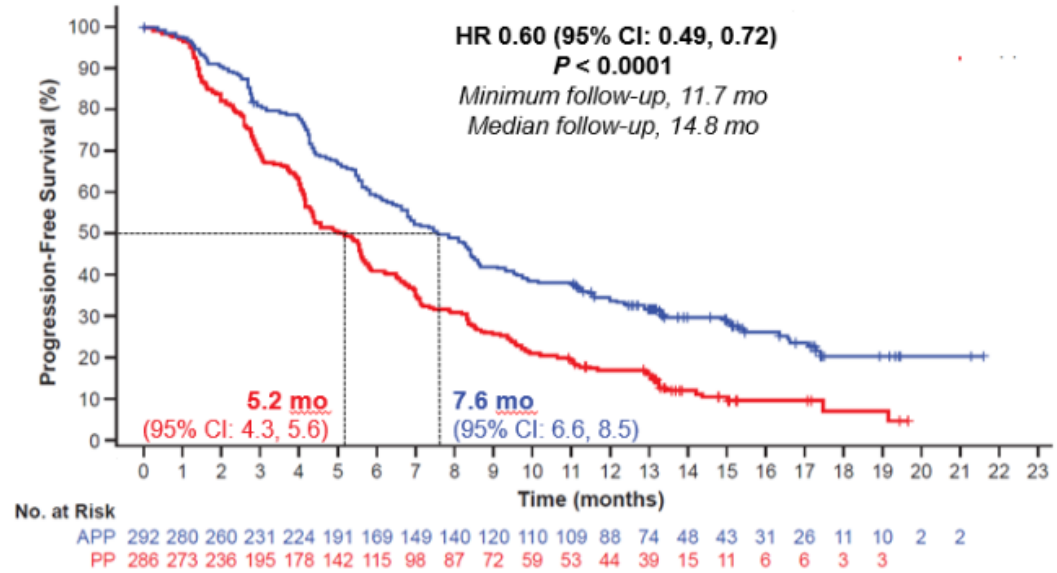
	APP	PP
ORR, %	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

Papadimitrakopoulou VA, WCLC 2018

KEYNOTE-189 vs IMpower132: PFS

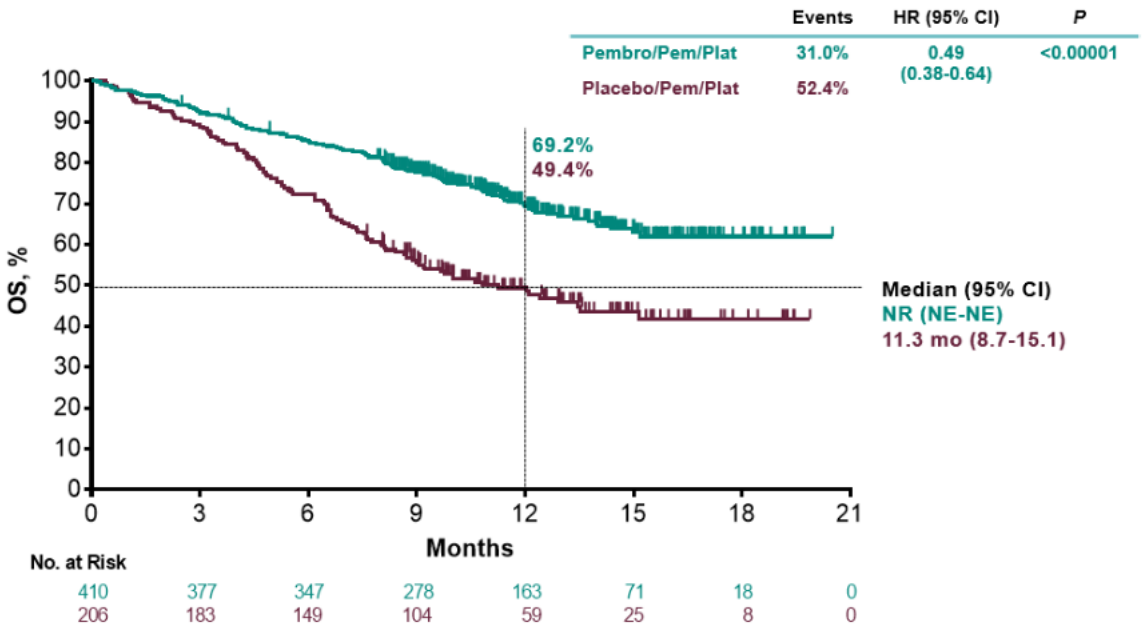


Gandhi L, NEJM 2018

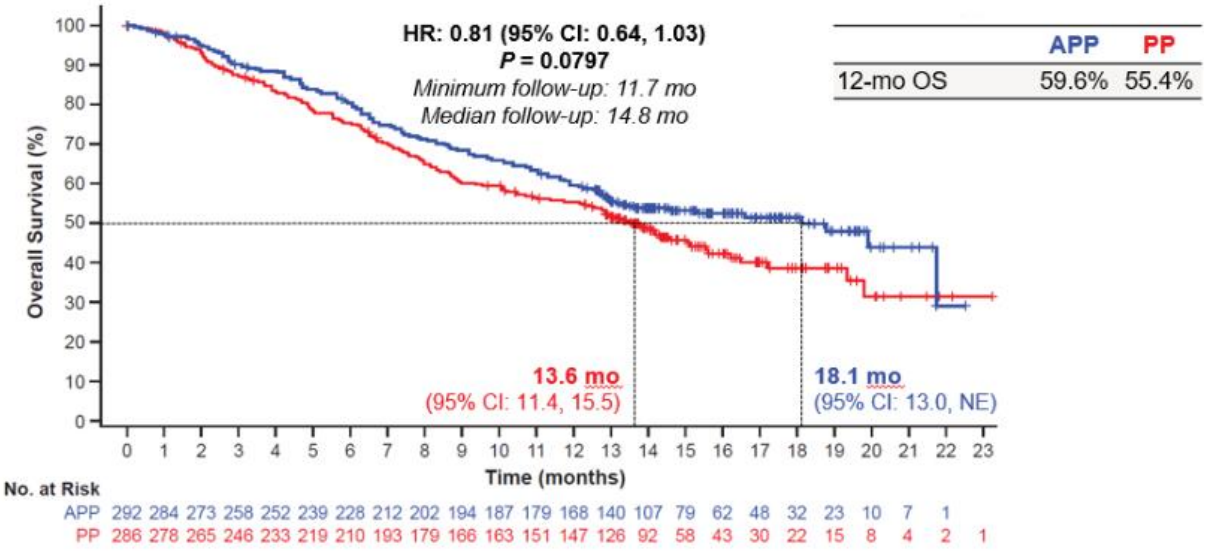


Papadimitrakopoulou VA, WCLC 2018

KEYNOTE-189 vs IMpower132: OS

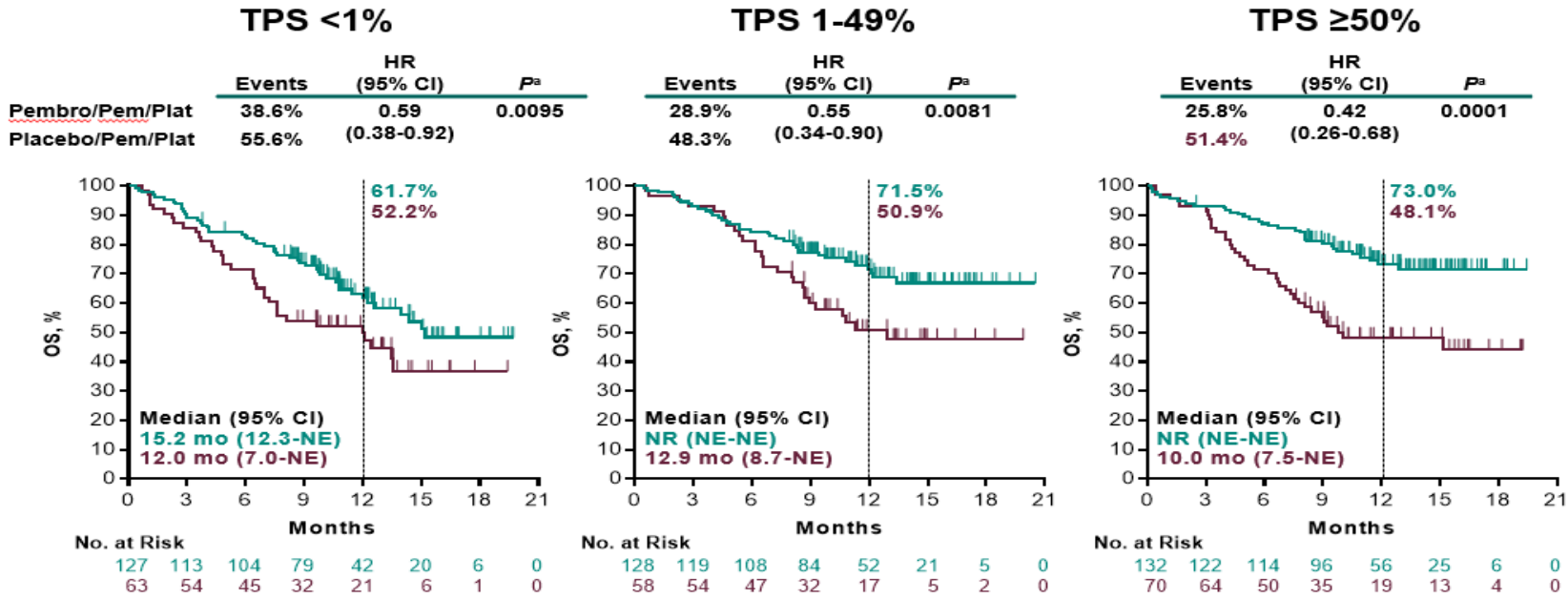


Gandhi L, NEJM 2018

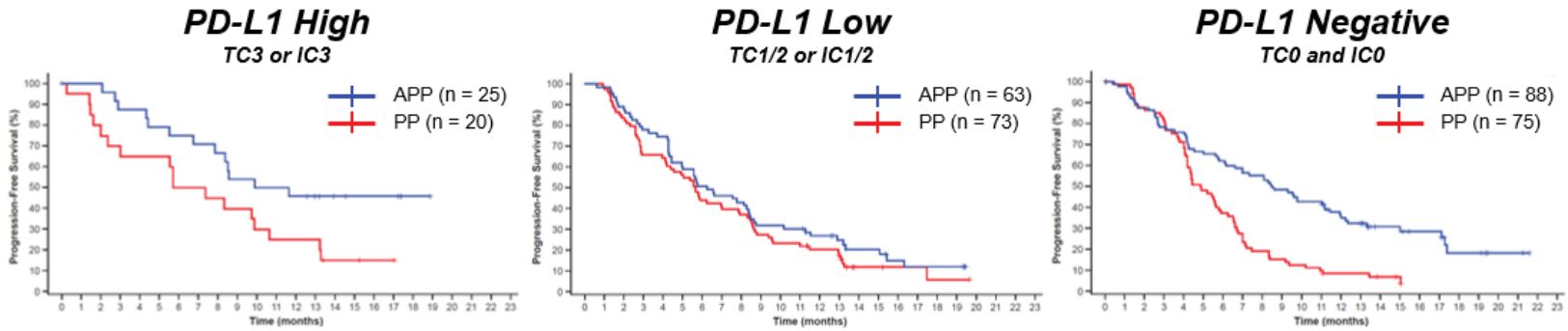


Papadimitrakopoulou VA, WCLC 2018

KEYNOTE-189 vs IMpower132: OS by PD-L1 TPS



Gandhi L, NEJM 2018



Papadimitrakopoulou VA, WCLC 2018

KEYNOTE-189 vs IMpower132: safety

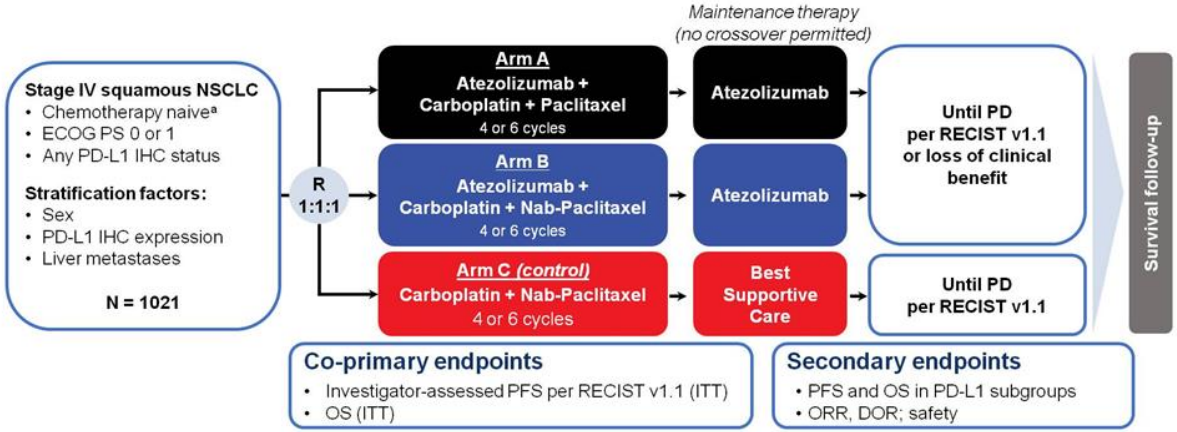
	Pembro/Pem/Platinum N = 405	Placebo/Pem/Platinum N = 202
All cause	404 (99.8%)	200 (99.0%)
Grade 3-5	272 (67.2%)	133 (65.8%)
Led to death	27 (6.7%)	12 (5.9%)
Led to discontinuation		
All treatment[a]	56 (13.8%)	16 (7.9%)
Any treatment	112 (27.7%)	30 (14.9%)
Immune mediated	92 (22.7%)	24 (11.9%)
Grade 3-5	36 (8.9%)	9 (4.5%)
Led to death	3 (0.7%)	0

Gandhi L, NEJM 2018

	APP (n = 291)	PP (n = 274)
All-cause AEs, n (%)	286 (98%)	266 (97%)
Grade 3-4	181 (62%)	147 (54%)
Grade 5	21 (7%)	14 (5%)
TRAEs, n (%)	267 (92%)	239 (87%)
Grade 3-4	156 (54%)	107 (39%)
Grade 5	11 (4%)	7 (3%)
SAEs, n (%)	134 (46%)	84 (31%)
Tx-related SAEs	96 (33%)	43 (16%)
AEs leading to withdrawal, n (%)		
Of any treatment	69 (24%)	48 (18%)
Of atezolizumab	44 (15%)	0
AESI, n (%)	141 (49%)	104 (38%)

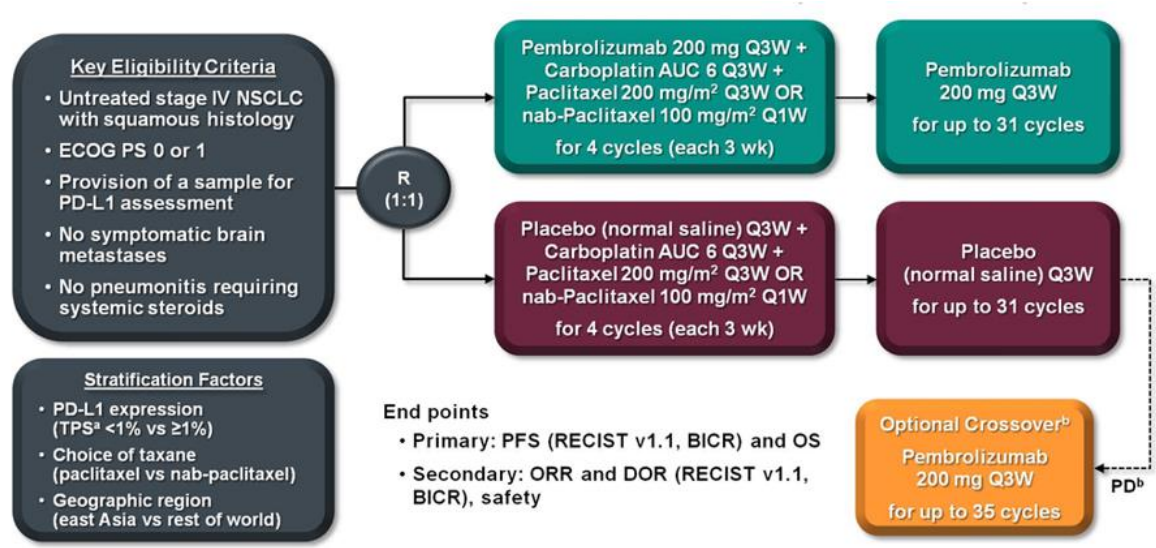
Papadimitrakopoulou VA, WCLC 2018

IMpower131 vs KEYNOTE-407: study design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

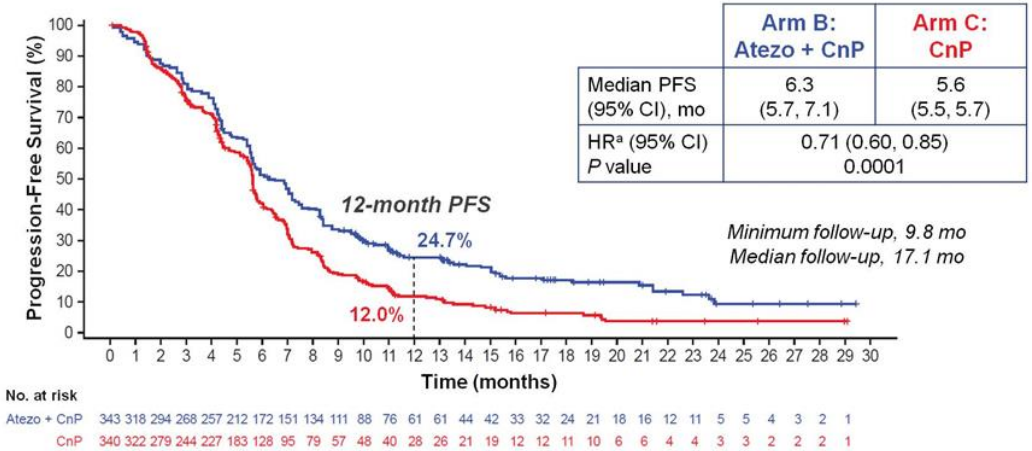
Jotte R, ASCO 2018



Paz-Ares L, ASCO 2018

IMpower131 vs KEYNOTE-407: PFS

INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



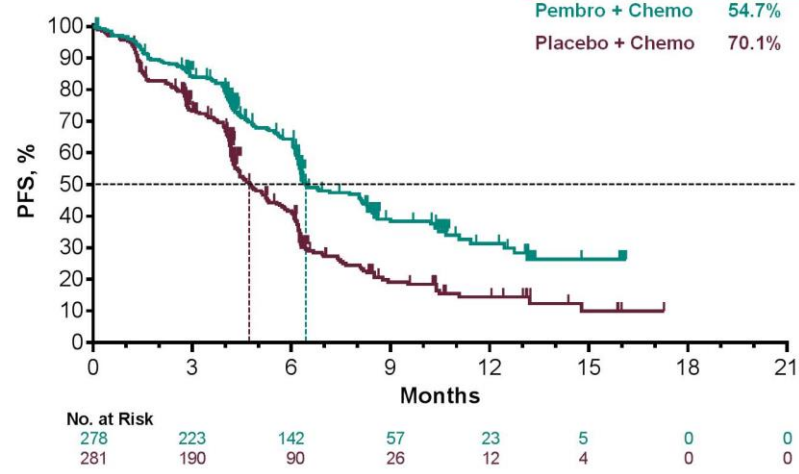
	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI)	0.71 (0.60, 0.85)	
P value	0.0001	

Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

Jotte R, ASCO 2018

Progression-Free Survival at IA2, ITT (RECIST v1.1, BICR)

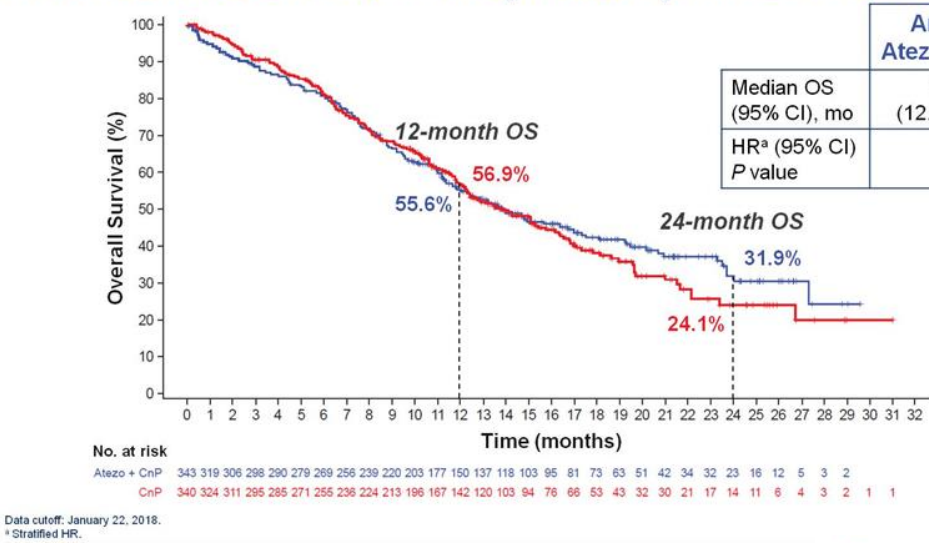


BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Paz-Ares L, ASCO 2018

IMpower131 vs KEYNOTE-407: OS

First Interim OS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI)	0.96 (0.78, 1.18)	
P value	0.6931	

Data cutoff: January 22, 2018.
[a] Stratified HR.

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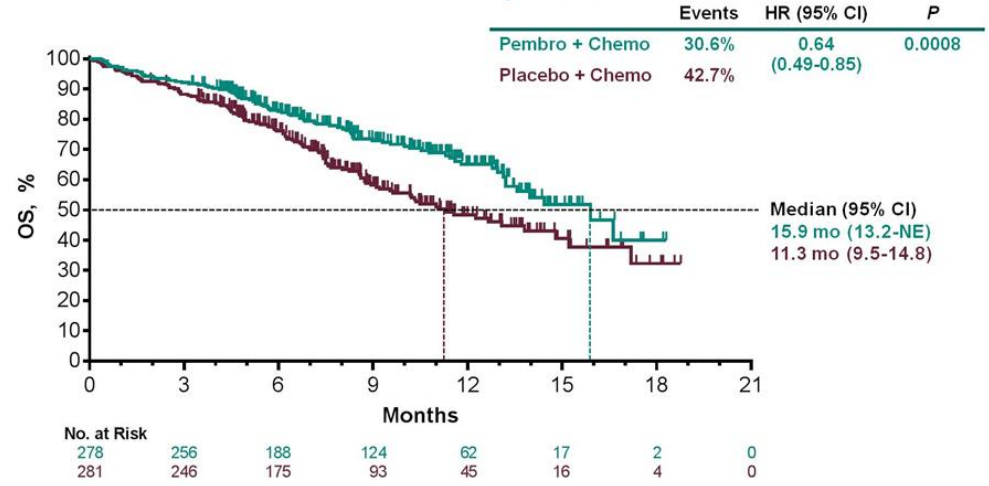
Overall Survival at IA2, ITT



Paz-Ares L, ASCO 2018

Grazie per l'attenzione!

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