

# Updates in Immunotherapy for Lung Cancer (What's new in 2022?)

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# Themes of 2022

- FDA approvals and deferrals
- Long term follow-up of older clinical trial in metastatic disease
- Improving on PD-1/PD-L1 blockade

# FDA Approvals

Adjuvant Atezolizumab

Neoadjuvant Nivolumab

1<sup>st</sup> line Cemiplimab in  
patients with PD-L1 > 50%

# Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomized multicentre, open-label, phase 3 trial

Population	PD-L1 >1% n=476		II-IIIa n=882		IB-IIIa (intent to treat) n=1005	
	3 year PFS	48.2%	60%	55.7%	49.4%	57.9%
P-value	.0039		.020		.040	

	Atezolizumab group (n=495)	Best supportive care group (n=495)
<b>Adverse event</b>		
Any grade	459 (93%)	350 (71%)
Grade 3-4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
<b>Immune-mediated adverse events</b>		
Any grade	256 (52%)	47 (9%)
Grade 3-4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

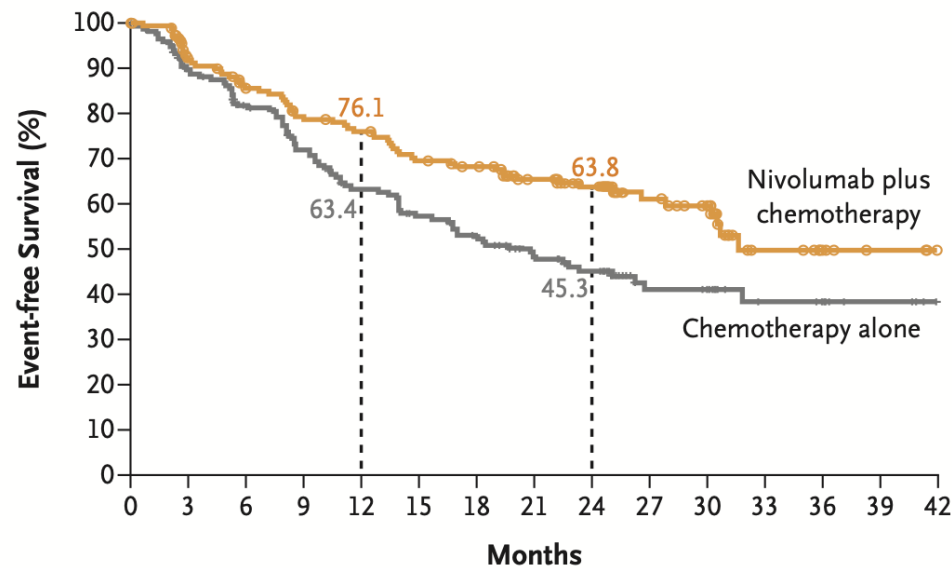
Data are n (%). \*Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

**Table 2: Safety summary in the safety evaluable population**



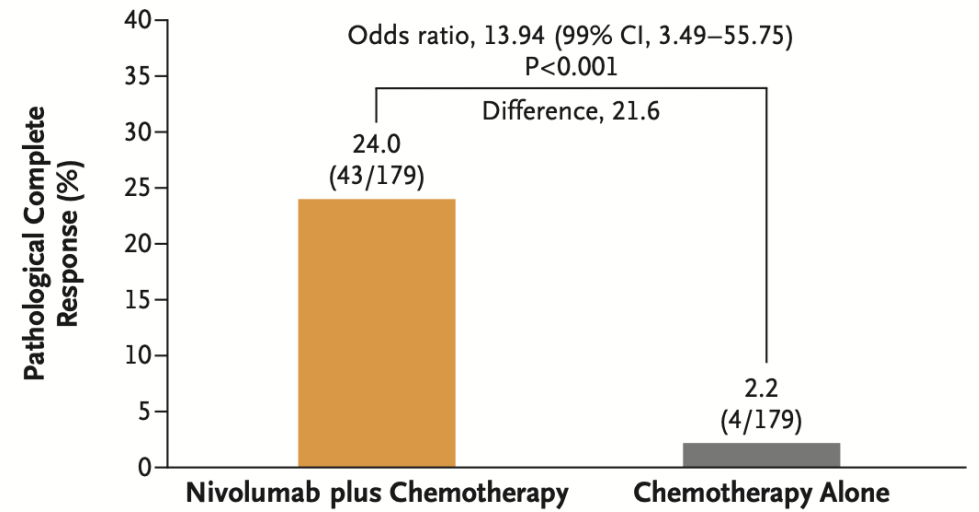
# Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

A



	No. of Patients	Median Event-free Survival (95% CI) mo
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)  
P=0.005

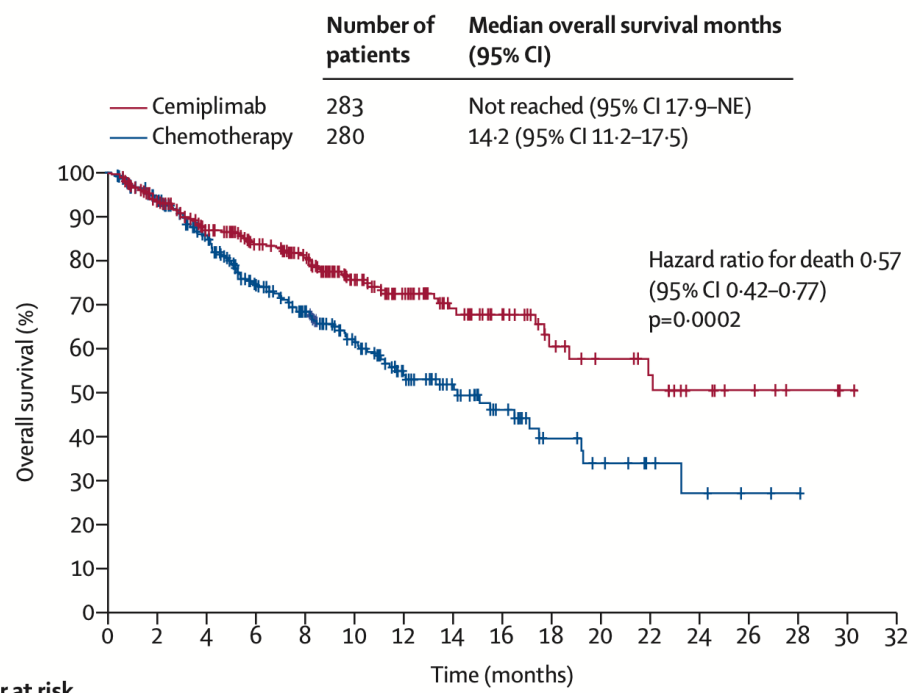


**No. at Risk**

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

# Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial.

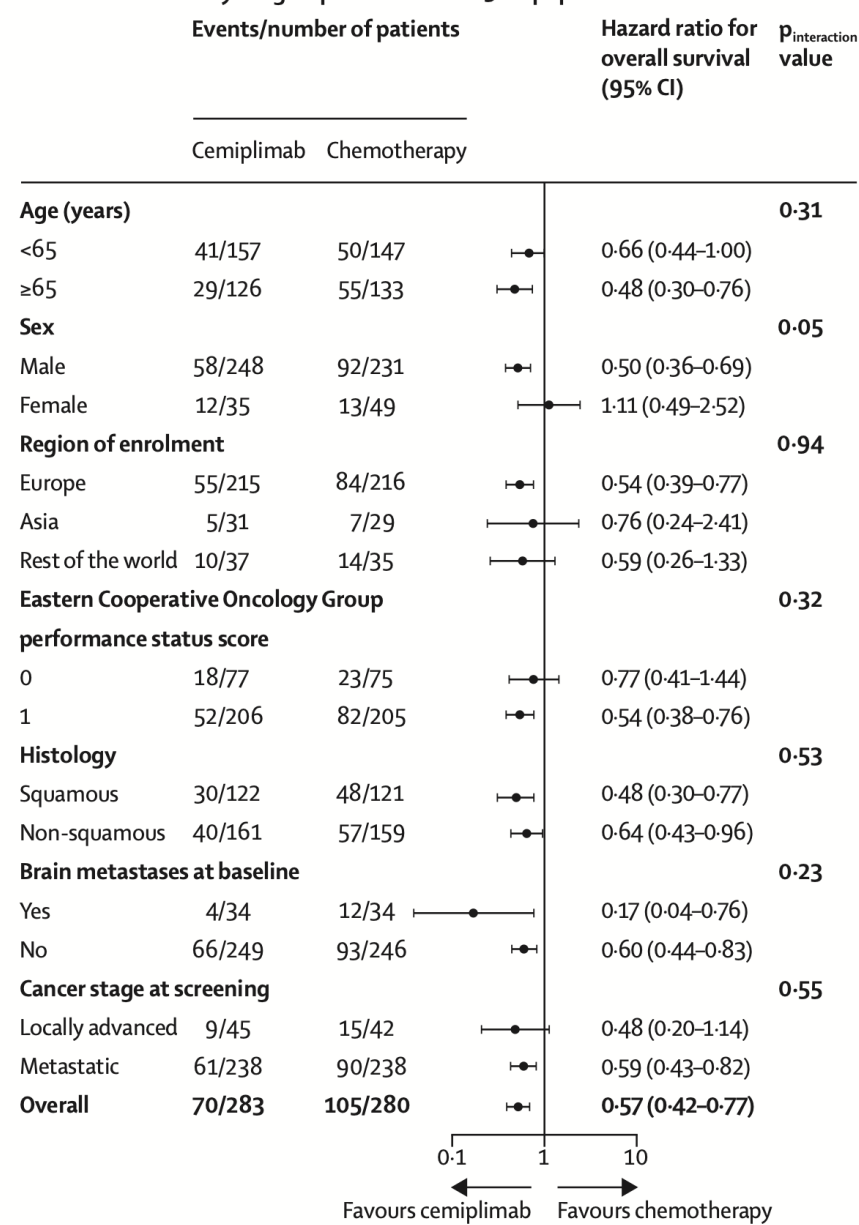
**A Overall survival in the PD-L1 ≥50% population**



	Number of patients	Median overall survival months (95% CI)
Cemiplimab	283	Not reached (95% CI 17.9-NE)
Chemotherapy	280	14.2 (95% CI 11.2-17.5)

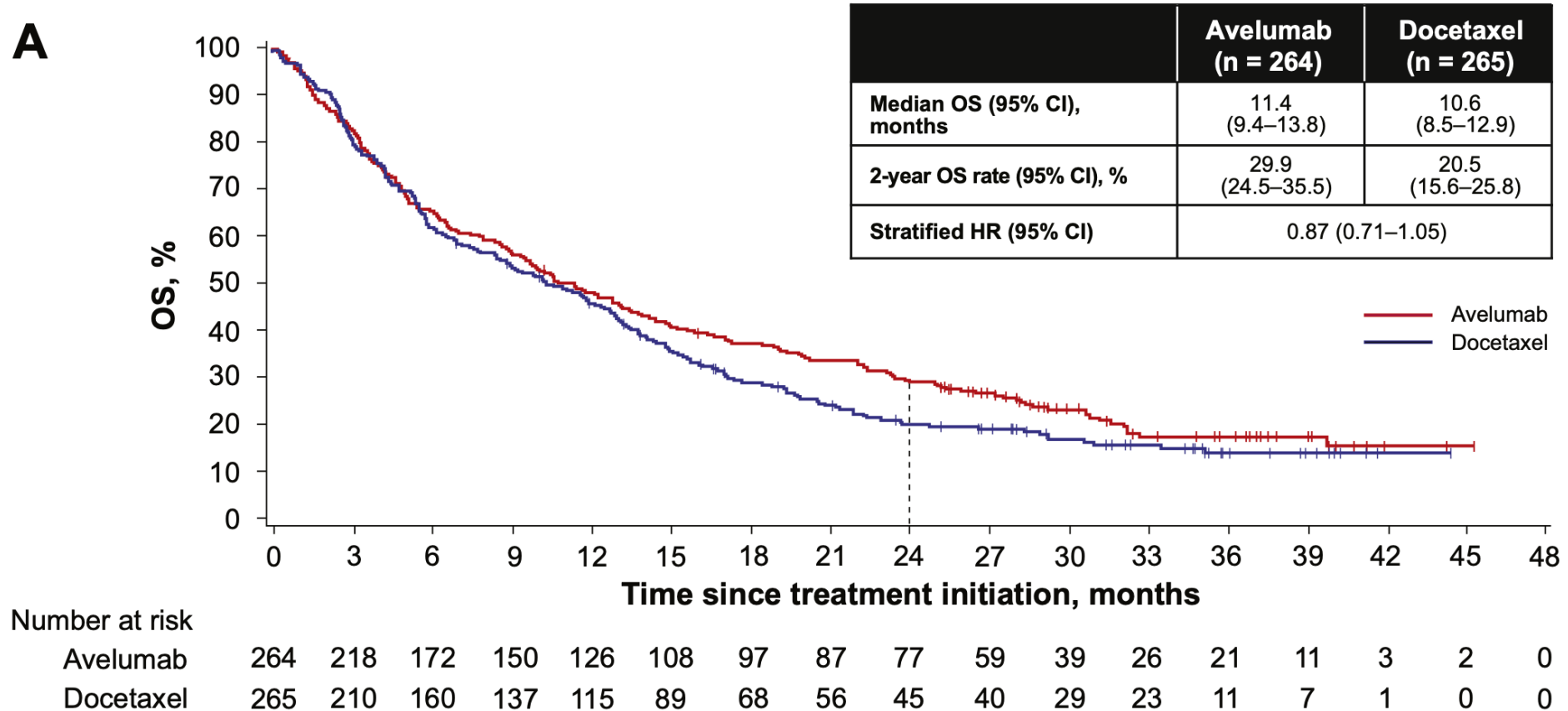
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	
<b>Number at risk (number censored)</b>	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0	
Cemiplimab	283	(0)	(21)	(46)	(65)	(82)	(119)	(140)	(165)	(177)	(192)	(197)	(199)	(203)	(207)	(210)	(212)	(213)
Chemotherapy	280	(0)	(24)	(45)	(66)	(82)	(110)	(130)	(144)	(156)	(163)	(165)	(170)	(171)	(173)	(174)	(175)	(175)

**C Overall survival by subgroups in the PD-L1 ≥50% population**



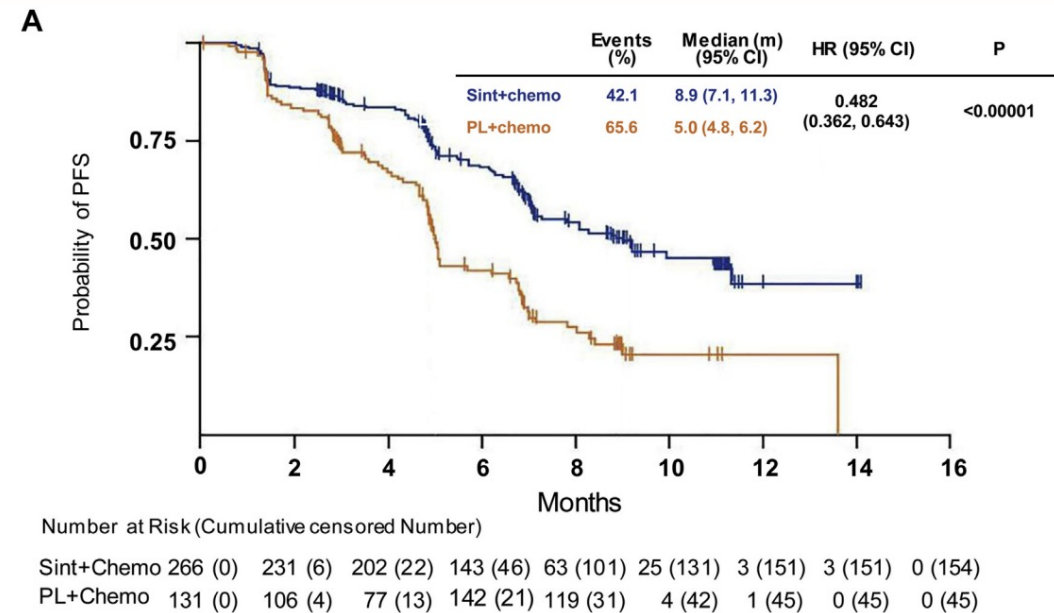
Not FDA approved

# Avelumab Versus Docetaxel in Patients With Platinum-Treated Advanced NSCLC: 2-Year Follow-Up From the JAVELIN Lung 200 Phase 3 Trial.

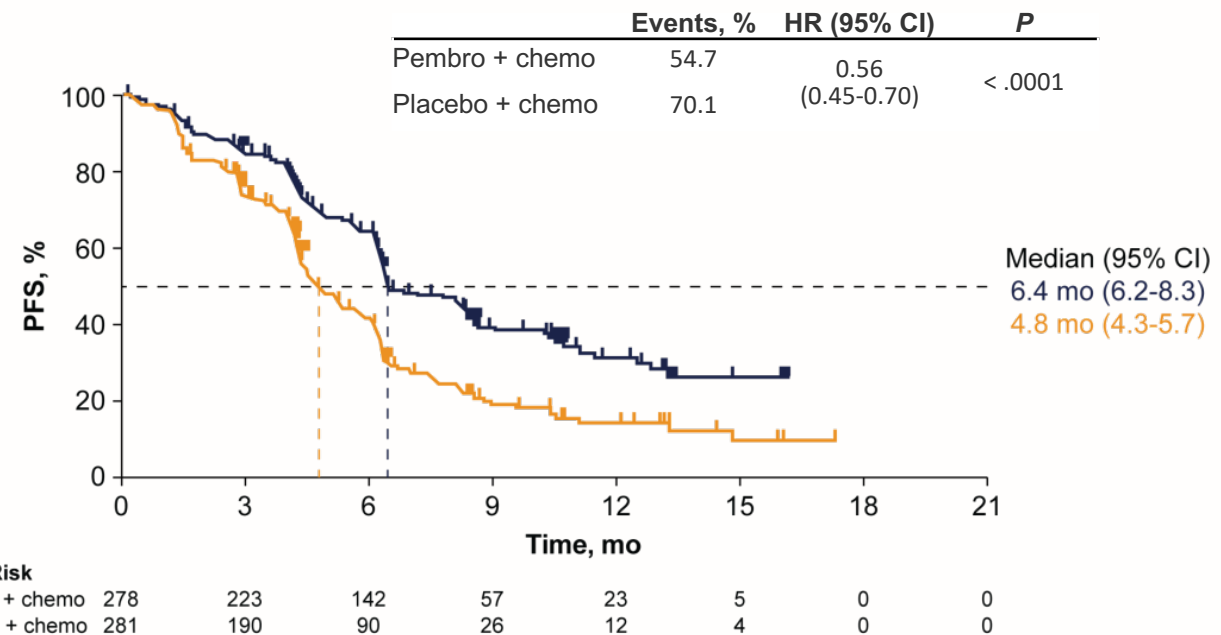


# No approval for Sintilimab

- Sintilimab Orient 11

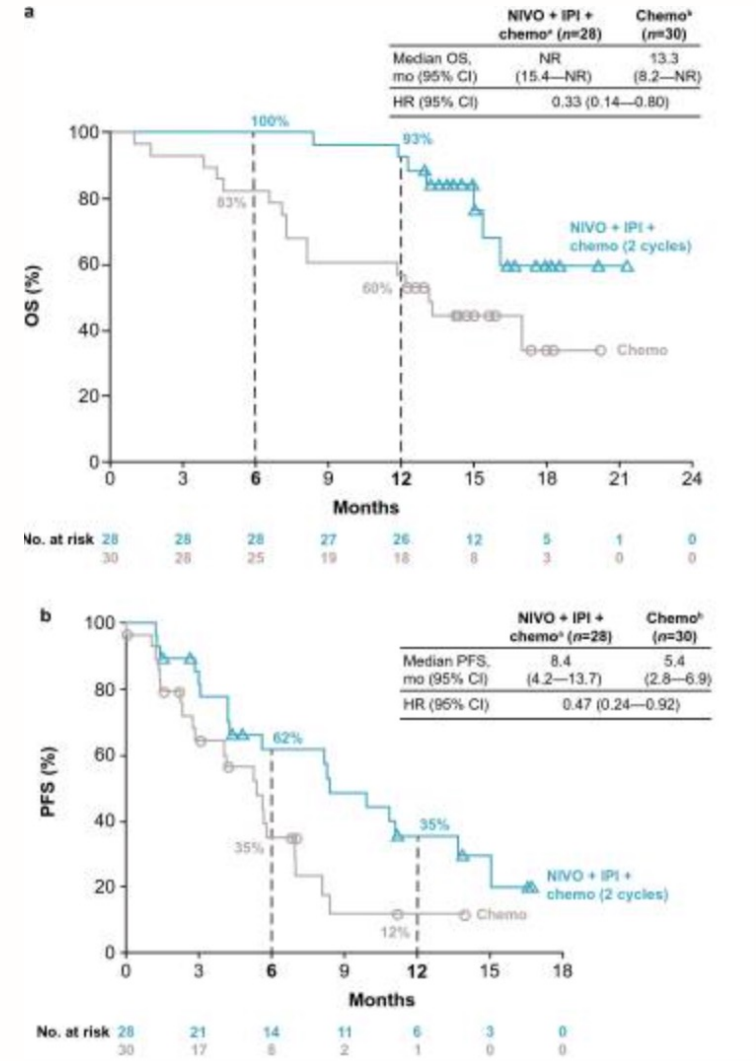


- Pembrolizumab Keynote 407



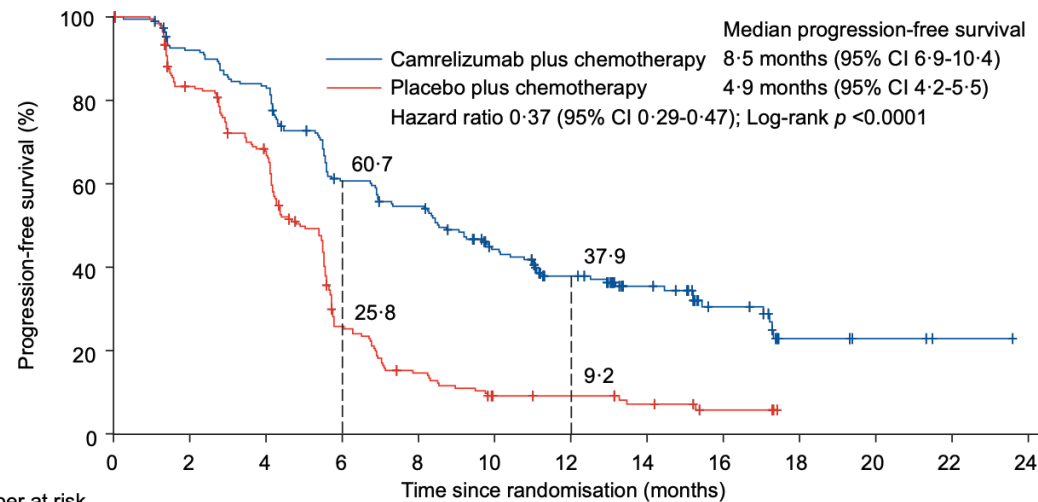
# Subset analysis of Asian patients in CheckMate 9LA

	NIVO + IPI + chemo <sup>a</sup> (n = 28)		Chemo <sup>b</sup> (n = 30)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Total patients with an event, <sup>c</sup> n (%)	28 (100)	16 (57)	29 (97)	18 (60)
TRAEs occurring in ≥ 15% of patients in either treatment arm, n (%)				
Decreased appetite	13 (46)	2 (7)	12 (40)	3 (10)
Constipation	12 (43)	0	17 (57)	0
Nausea	11 (39)	0	18 (60)	0
Neutrophil count decreased	10 (36)	5 (18)	8 (27)	5 (17)
Fatigue	8 (29)	1 (4)	7 (23)	0
Malaise	8 (29)	0	8 (27)	0
Maculopapular rash	8 (29)	3 (11)	2 (7)	0
Anemia	8 (29)	1 (4)	15 (50)	7 (23)
Rash	7 (25)	2 (7)	0	0
Alopecia	6 (21)	0	8 (27)	0
White blood cell count decreased	6 (21)	3 (11)	6 (20)	2 (7)
Diarrhea	5 (18)	0	3 (10)	1 (3)
Pyrexia	5 (18)	0	2 (7)	0
Platelet count decreased	4 (14)	1 (4)	7 (23)	1 (3)
Peripheral sensory neuropathy	3 (11)	0	9 (30)	0
Hiccups	3 (11)	0	8 (27)	0
TRAEs leading to treatment discontinuation <sup>d</sup> , n (%)	6 (21)	3 (11)	5 (17)	2 (7)



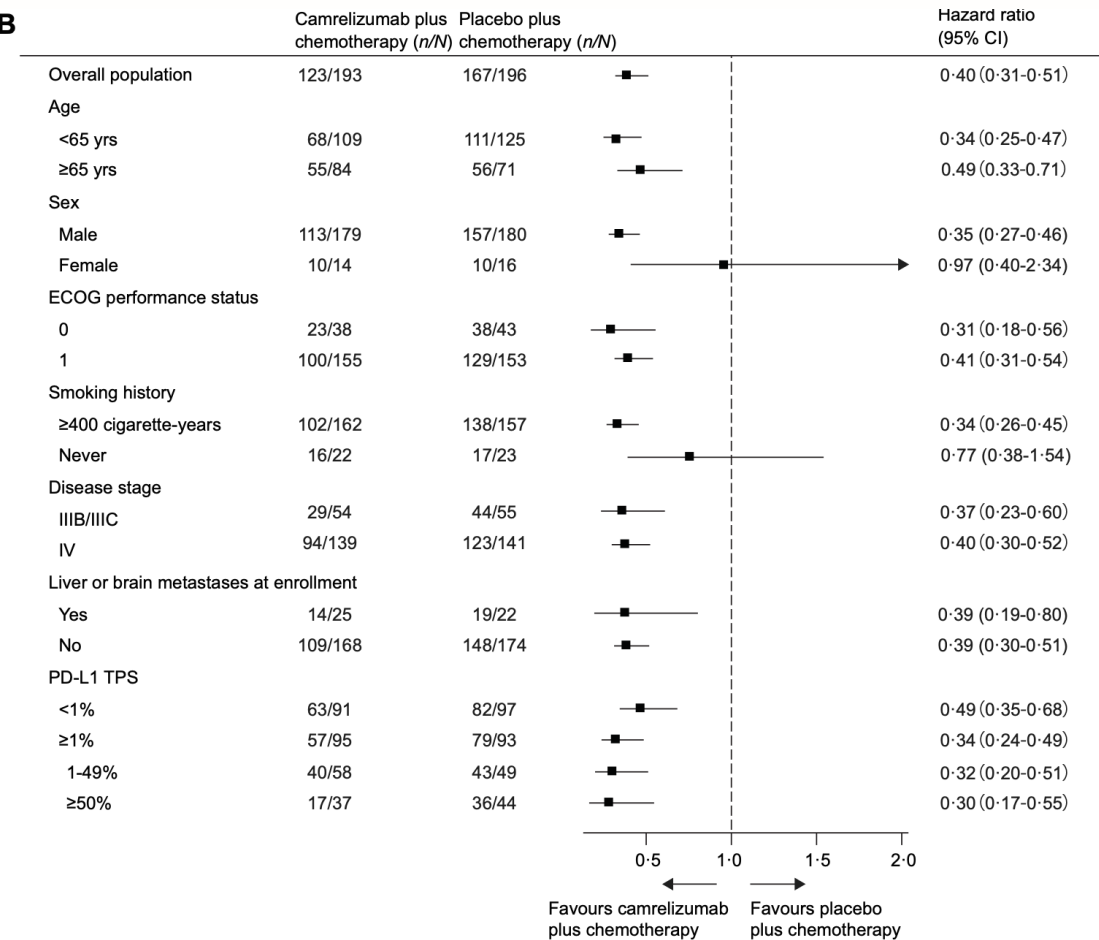
# Camrelizumab Plus Carboplatin and Paclitaxel as First-Line Treatment for Advanced Squamous NSCLC (CameL-Sq): A Phase 3 Trial.

**A**



	0	2	4	6	8	10	12	14	16	18	20	22	24
Camrelizumab plus chemotherapy	193	172	156	110	98	72	51	35	19	6	3	1	0
Placebo plus chemotherapy	196	157	125	44	24	12	11	7	3	0			

**B**

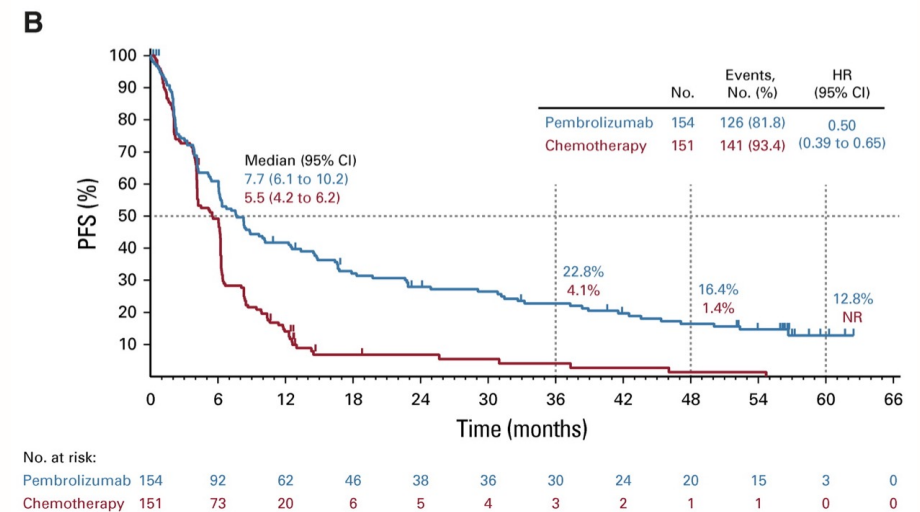
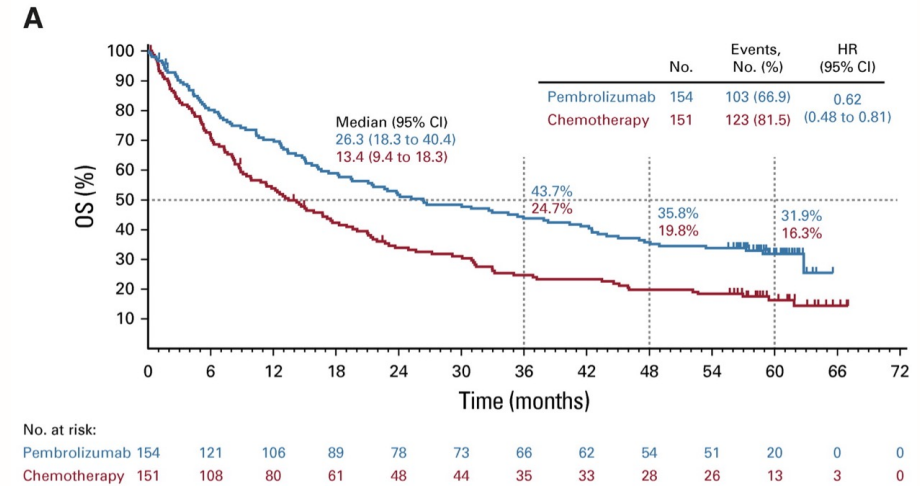
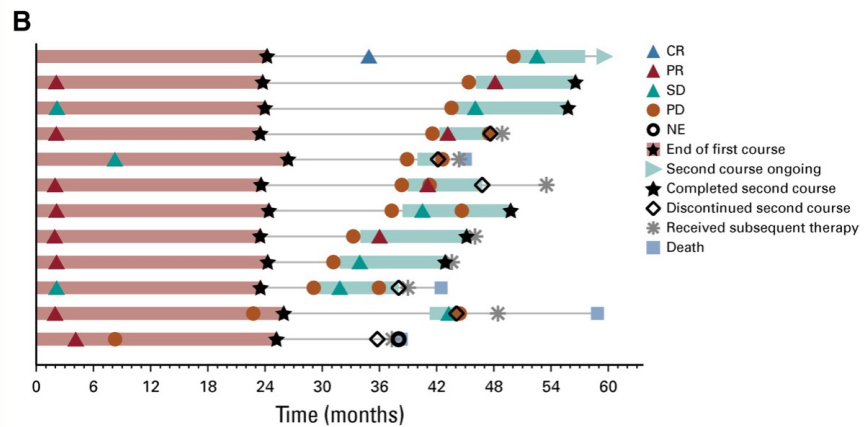
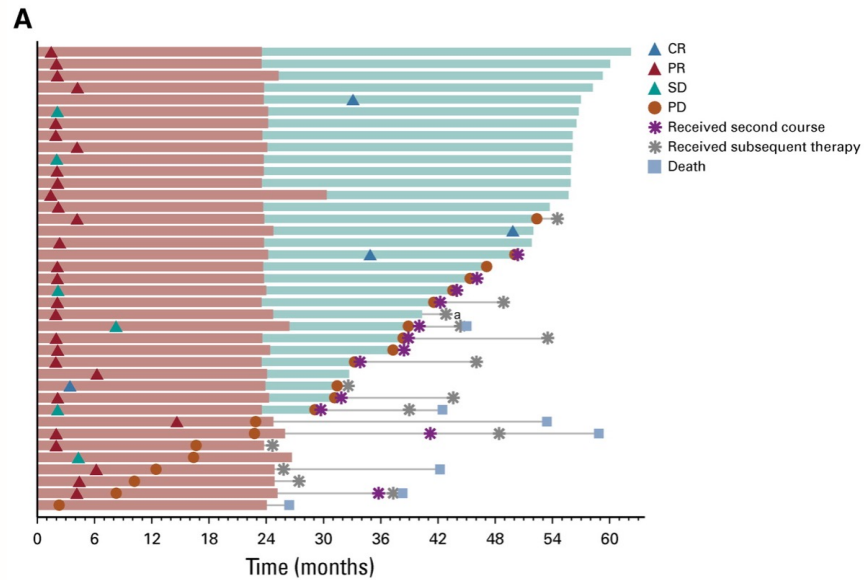


# Long Term Follow-up

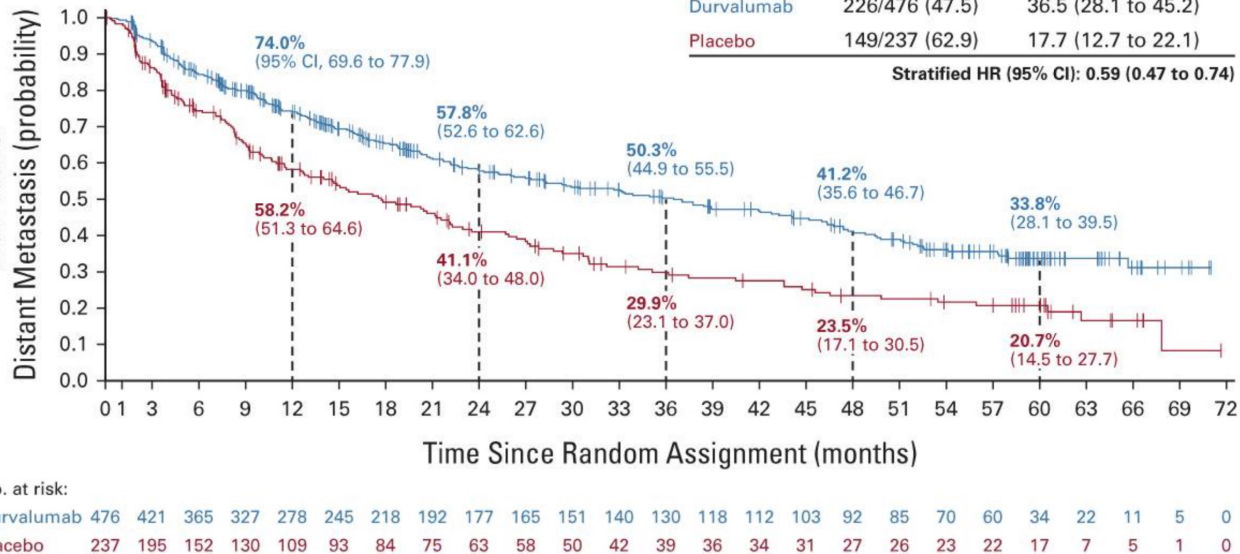


# Five-Year Outcomes from Keynote 024 With Pembrolizumab Versus Chemotherapy for Metastatic NSCLC With PD-L1 TP ≥ 50

After 35 cycles given

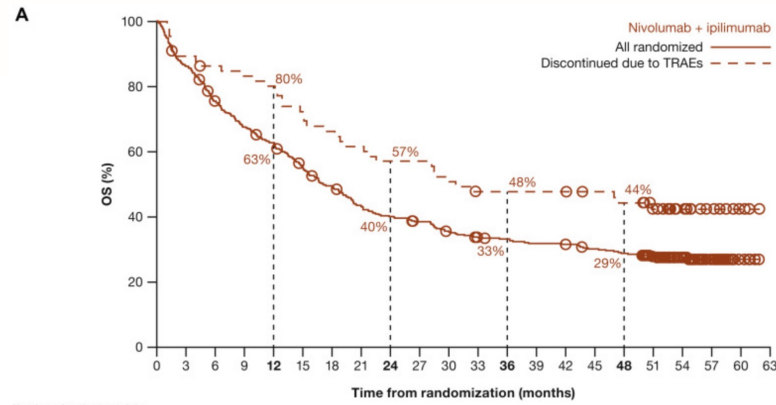


# Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer



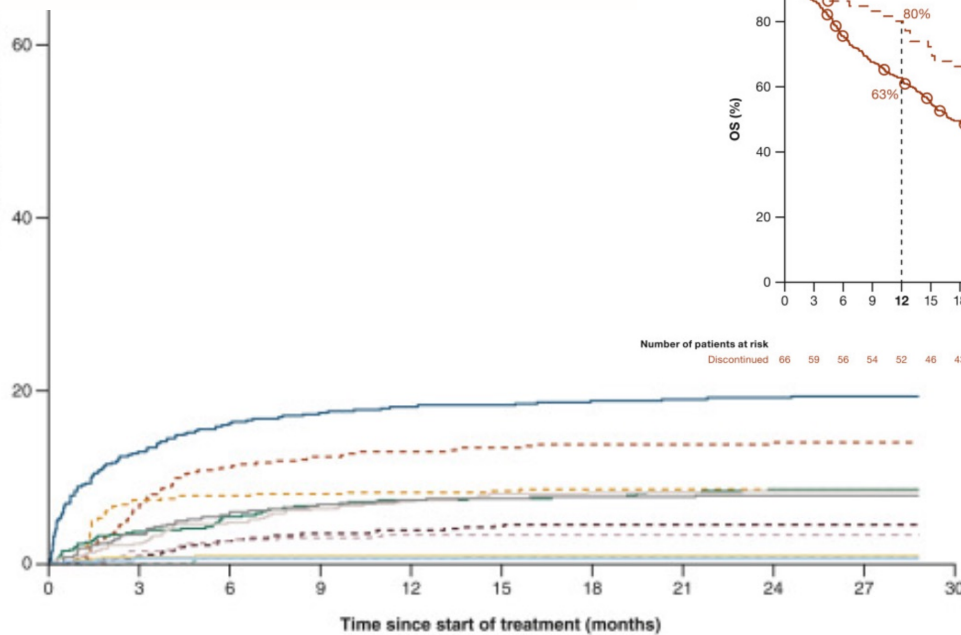
Group	No. of Events / No. of Patients (%)		Unstratified HR (95% CI)
	Durvalumab	Placebo	
<b>All patients</b>	268/476 (56.3)	175/237 (73.8)	0.58 (0.48 to 0.70)
<b>Sex</b>			
Male	192/334 (57.5)	122/166 (73.5)	0.61 (0.48 to 0.76)
Female	76/142 (53.5)	53/71 (74.6)	0.52 (0.36 to 0.74)
<b>Age at random assignment</b>			
< 65 years	140/261 (53.6)	100/130 (76.9)	0.46 (0.36 to 0.60)
≥ 65 years	128/215 (59.5)	75/107 (70.1)	0.76 (0.57 to 1.01)
<b>Smoking status</b>			
Smoker	246/433 (56.8)	158/216 (73.1)	0.61 (0.50 to 0.75)
Nonsmoker	22/43 (51.2)	17/21 (81.0)	0.33 (0.17 to 0.63)
<b>NSCLC disease stage</b>			
IIIA	132/252 (52.4)	95/125 (76.0)	0.53 (0.40 to 0.69)
IIIB	130/212 (61.3)	77/107 (72.0)	0.64 (0.48 to 0.85)
<b>Tumor histologic type</b>			
Squamous	138/224 (61.6)	74/102 (72.5)	0.71 (0.54 to 0.94)
All other	130/252 (51.6)	101/135 (74.8)	0.48 (0.37 to 0.63)
<b>Best response to prior treatment</b>			
Complete response	5/9 (55.6)	4/7 (57.1)	Not calculated <sup>a</sup>
Partial response	126/237 (53.2)	85/112 (75.9)	0.56 (0.43 to 0.74)
Stable disease	133/223 (59.6)	84/115 (73.0)	0.57 (0.44 to 0.76)
<b>Prior chemotherapy type</b>			
Gemcitabine-based	4/9 (44.4)	3/5 (60.0)	Not calculated <sup>a</sup>
Non-gemcitabine-based	264/467 (56.5)	172/232 (74.1)	0.58 (0.48 to 0.70)
Cisplatin	(54.9) 94/129	94/129 (72.9)	0.55 (0.42 to 0.71)
Carboplatin	114/199 (57.3)	76/102 (74.5)	0.62 (0.47 to 0.83)
Cisplatin and carboplatin	5/8 (62.5)	4/5 (80.0)	Not calculated <sup>a</sup>
<b>Last radiation to random assignment</b>			
< 14 days	62/120 (51.7)	49/62 (79.0)	0.45 (0.31 to 0.66)
≥ 14 days	206/356 (57.9)	126/175 (72.0)	0.64 (0.51 to 0.80)
<b>WHO PS</b>			
0 – Normal	127/234 (54.3)	82/114 (71.9)	0.62 (0.47 to 0.82)
1 – Restricted <sup>b</sup>	141/242 (58.3)	93/123 (75.6)	0.54 (0.41 to 0.70)
<b>Region</b>			
Asia	58/109 (53.2)	48/68 (70.6)	0.60 (0.41 to 0.88)
Europe	131/217 (60.4)	76/102 (74.5)	0.61 (0.46 to 0.82)
North and South America	79/150 (52.7)	51/67 (76.1)	0.47 (0.33 to 0.67)
<b>Race</b>			
White	195/337 (57.9)	117/157 (74.5)	0.58 (0.46 to 0.73)
Black or African American	7/12 (58.3)	2/2 (100.0)	Not calculated <sup>a</sup>
Asian	62/120 (51.7)	51/72 (70.8)	0.57 (0.39 to 0.83)
Other <sup>c</sup>	3/6 (50.0)	5/6 (83.3)	Not calculated <sup>a</sup>
<b>EGFR or ALK aberration status</b>			
Positive <sup>d</sup>	21/29 (72.4)	11/14 (78.6)	0.82 (0.39 to 1.71)
Negative	169/317 (53.3)	124/165 (75.2)	0.52 (0.41 to 0.65)
Unknown	78/130 (60.0)	40/58 (69.0)	0.74 (0.51 to 1.09)
<b>PD-L1 expression level</b>			
≥ 25%	61/115 (53.0)	33/44 (75.0)	0.44 (0.29 to 0.67)
< 25%	105/187 (56.1)	77/105 (73.3)	0.64 (0.48 to 0.86)
Unknown	102/174 (58.6)	65/88 (73.9)	0.60 (0.44 to 0.82)
1%–24% (post hoc analysis)	50/97 (51.5)	36/47 (76.6)	0.51 (0.33 to 0.78)
≥ 1% (post hoc analysis)	111/212 (52.4)	69/91 (75.8)	0.47 (0.35 to 0.64)
< 1% (post hoc analysis)	55/90 (61.1)	41/58 (70.7)	0.80 (0.53 to 1.20)

# First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227



Number of patients at risk

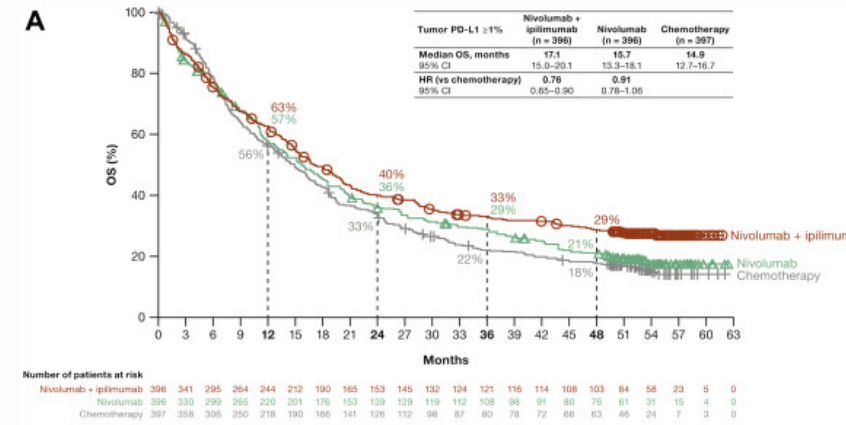
Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Discontinued	66	59	56	54	52	46	43	40	37	37	33	30	30	30	29	28	26	20	14	8	3	0



- Endocrine events**
  - Hypothyroidism/thyroiditis
  - Hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis
  - Diabetes mellitus
- Non-endocrine events**
  - Rash
  - Pneumonitis
  - Diarrhea/colitis
  - Hepatitis
  - Nephritis/renal dysfunction
  - Hypersensitivity

J Thorac Oncol. 2022 Feb;17(2):289-308.

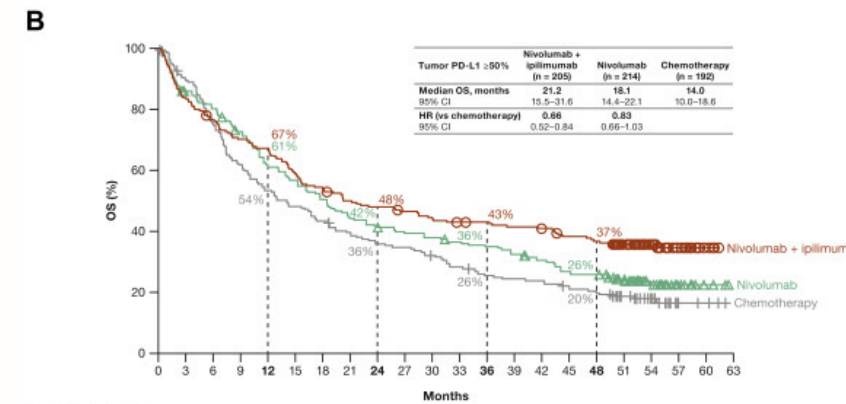
J Thorac Oncol. 2022 Feb;17(2):289-308.



Tumor PD-L1 ≥ 1%	Nivolumab + ipilimumab (n = 396)	Nivolumab (n = 396)	Chemotherapy (n = 397)
Median OS, months	17.1	15.7	14.9
95% CI	15.0-20.1	13.3-18.1	12.7-16.7
HR (vs chemotherapy)	0.76	0.81	
95% CI	0.65-0.90	0.78-1.05	

Number of patients at risk

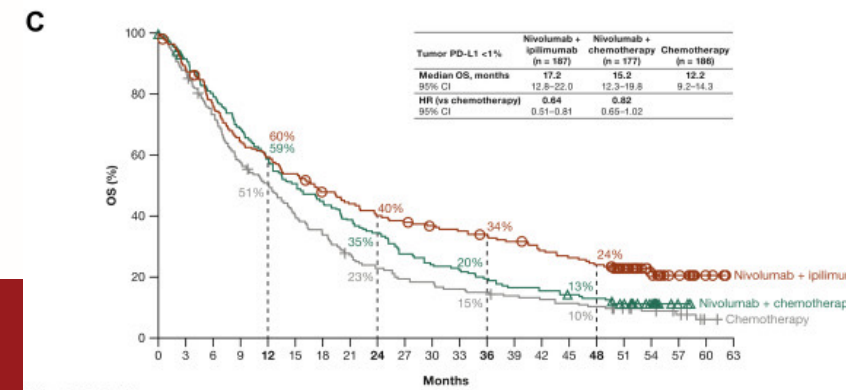
Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	132	124	121	116	114	108	103	84	58	23	5	0
Nivolumab	396	330	299	265	220	201	176	153	139	129	119	112	106	98	91	80	76	61	31	15	4	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	46	21	7	3	0



Tumor PD-L1 ≥ 50%	Nivolumab + ipilimumab (n = 205)	Nivolumab (n = 214)	Chemotherapy (n = 192)
Median OS, months	21.2	18.1	14.0
95% CI	15.5-31.5	14.4-22.1	10.0-18.6
HR (vs chemotherapy)	0.66	0.83	
95% CI	0.62-0.84	0.66-1.03	

Number of patients at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Nivolumab + ipilimumab	205	172	156	143	137	120	111	101	87	83	86	85	84	81	79	73	70	55	38	15	4	0
Nivolumab	214	181	169	151	137	118	104	92	82	81	78	74	72	68	65	62	51	41	25	9	3	0
Chemotherapy	192	169	142	116	101	91	82	74	67	65	59	52	45	44	43	38	35	25	16	4	3	0



Tumor PD-L1 < 1%	Nivolumab + ipilimumab (n = 187)	Nivolumab + chemotherapy (n = 177)	Chemotherapy (n = 186)
Median OS, months	17.2	15.2	12.2
95% CI	12.8-22.0	12.3-19.5	9.2-14.3
HR (vs chemotherapy)	0.64	0.82	
95% CI	0.51-0.81	0.65-1.02	

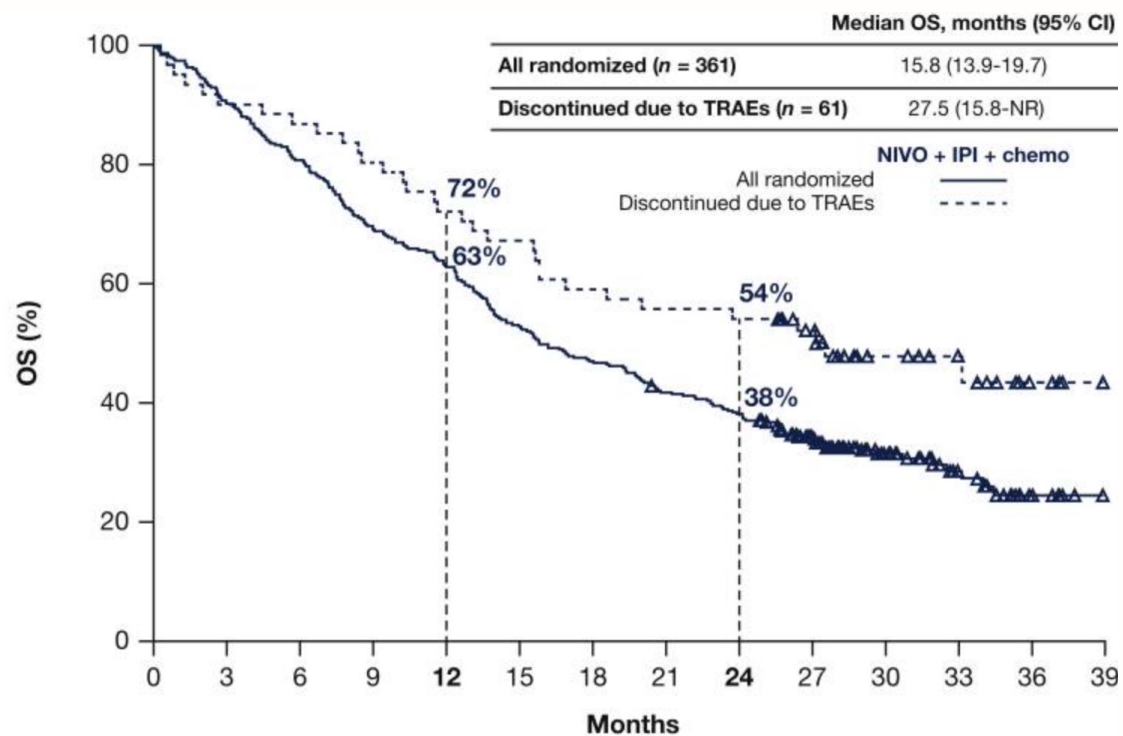
Number of patients at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Nivolumab + ipilimumab	187	165	142	120	110	100	87	80	73	69	65	62	59	55	48	45	41	31	19	12	4	0
Nivolumab + chemotherapy	177	159	139	119	102	88	78	67	60	48	42	39	34	29	24	22	17	10	7	2	0	0
Chemotherapy	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	15	13	10	7	1	0

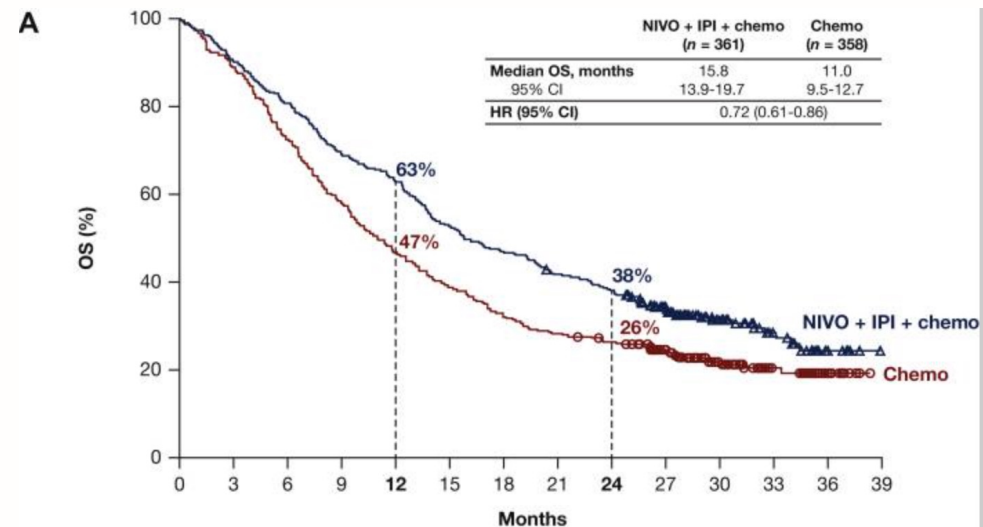


# First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update

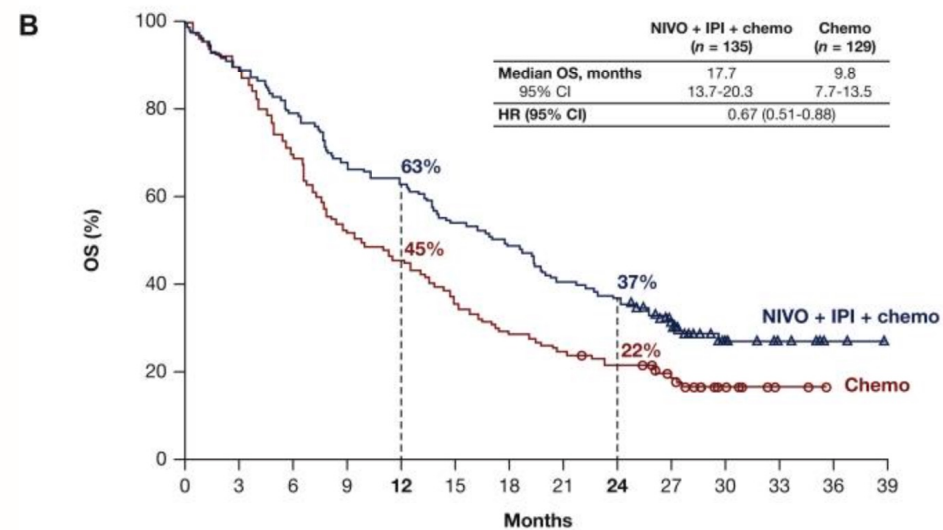
AE's may be good!



Number at risk (all randomized patients)														
NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Number at risk (patients who discontinued due to TRAEs)														
NIVO + IPI + chemo	61	55	53	49	44	41	36	34	33	26	15	11	4	0

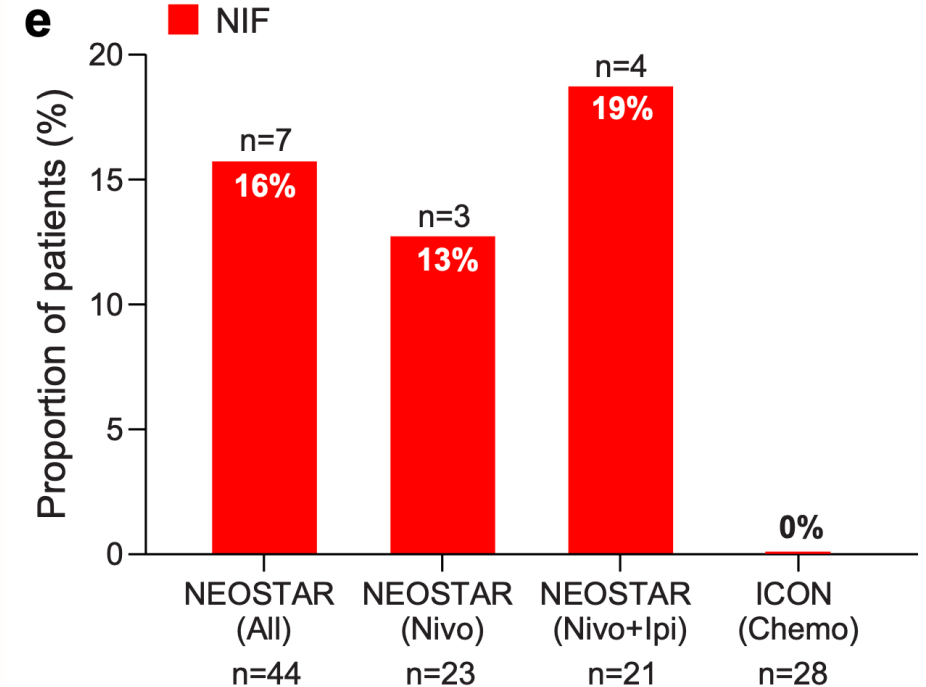
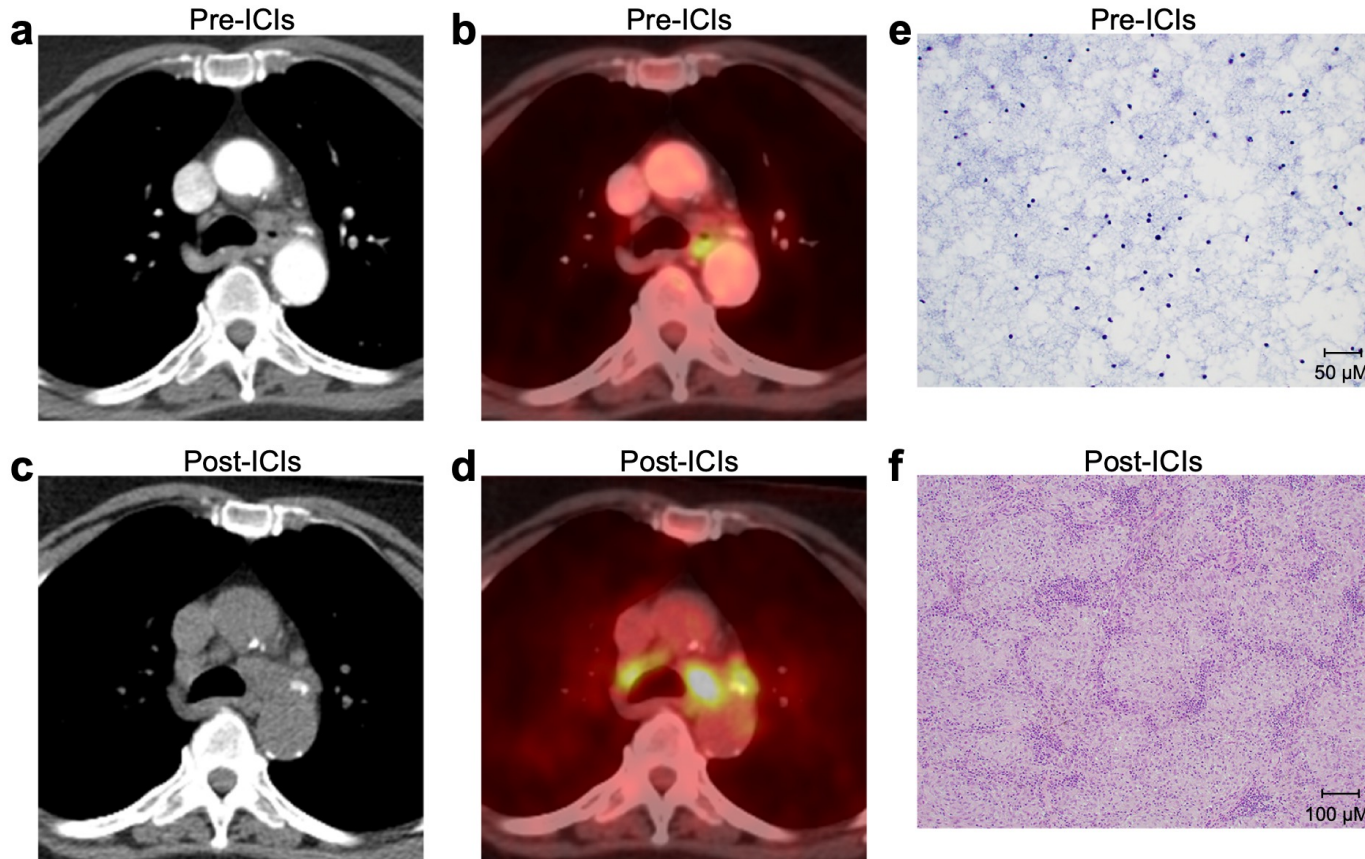


Number at risk	
NIVO + IPI + chemo	361 326 292 250 227 191 170 150 137 95 50 23 7 0
Chemo	358 319 260 208 168 139 115 102 93 69 40 18 8 0



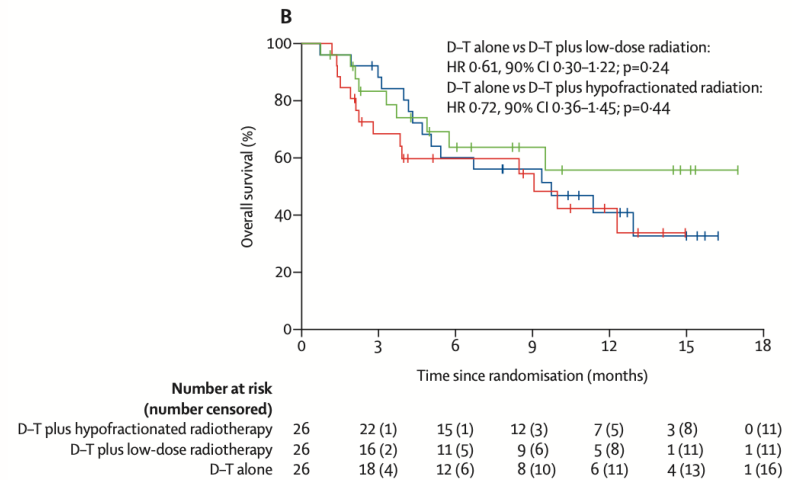
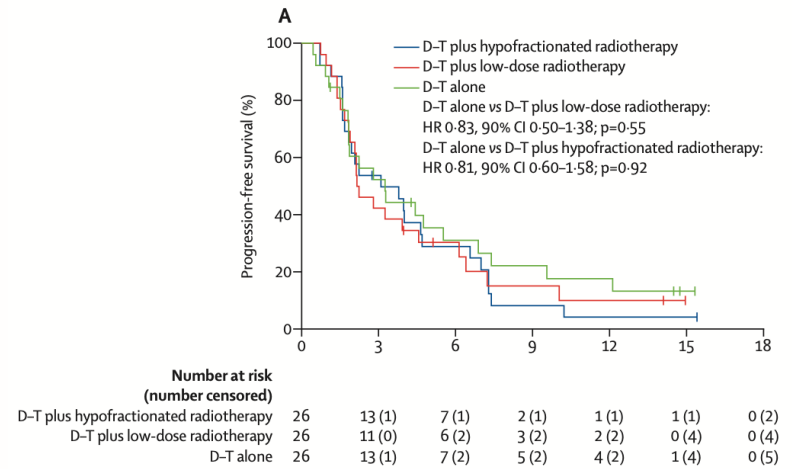
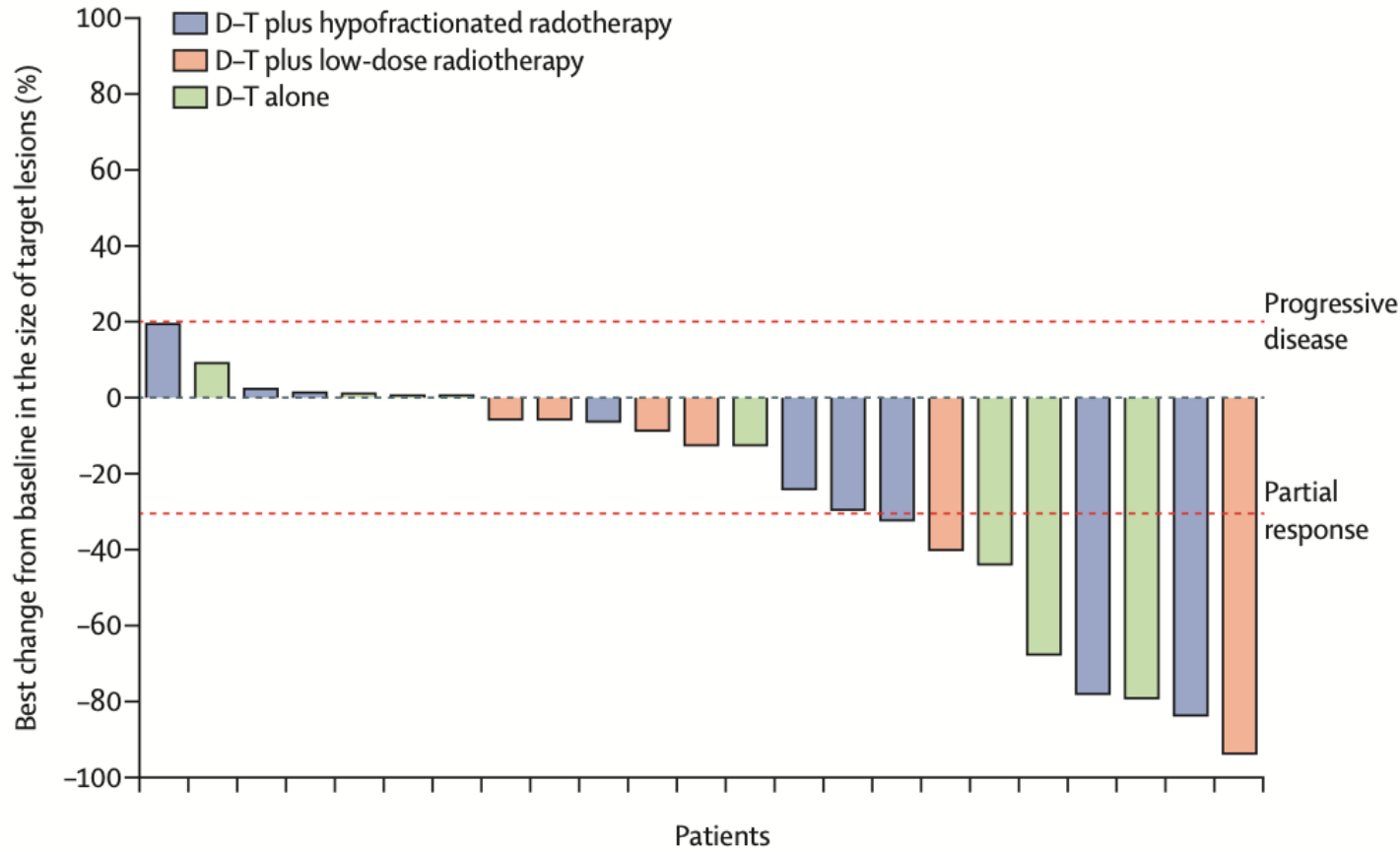
# Nodal immune flare mimics nodal disease progression following neoadjuvant immune checkpoint inhibitors in non-small cell lung cancer

## Nodal Immune Flare (NIF)



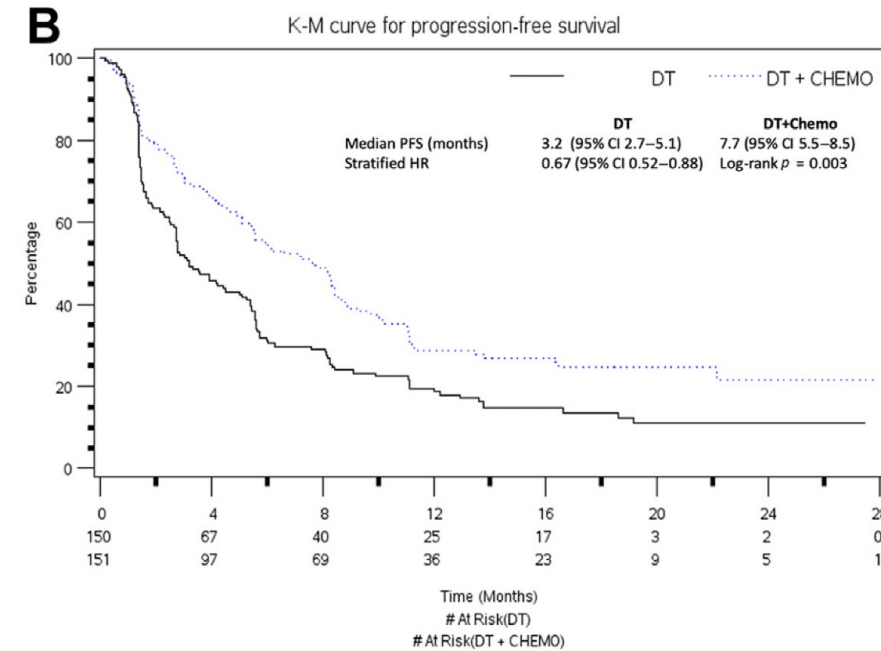
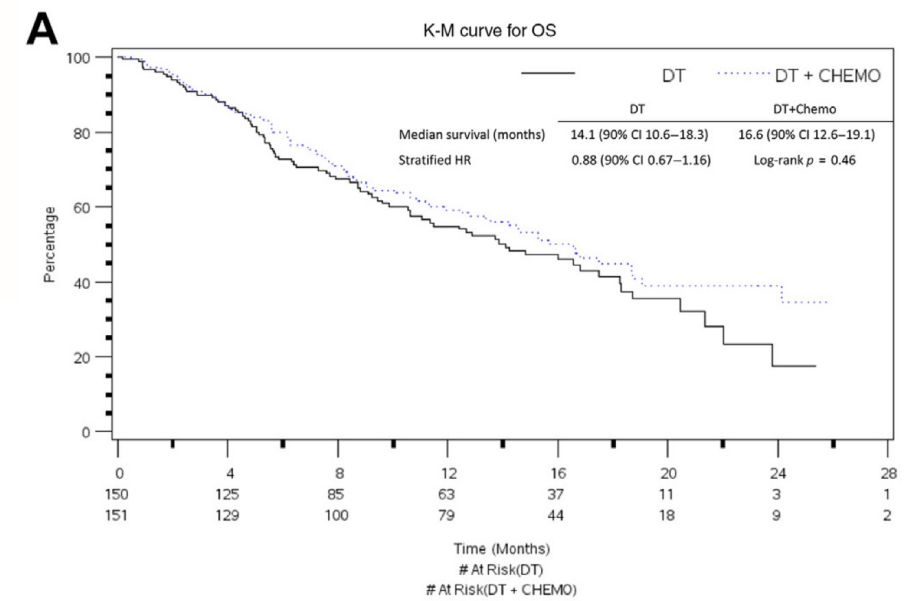
NIF is associated with an inflamed nodal immune microenvironment and with fecal abundance of genera belonging to the family Coriobacteriaceae of phylum Actinobacteria

# Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial.



# Improving on PD-L1 blockade

# CCTG BR34: A Randomized Phase 2 Trial of Durvalumab and Tremelimumab With or Without



**C**

Subgroup	No. of Patients	Median OS (months)		Hazard Ratio for Death (90% CI)	
		Durvalumab + Tremelimumab + Chemotherapy (n = 151)	Durvalumab + Tremelimumab (n = 150)		
<b>OS – Overall</b>	<b>301</b>	<b>16.6</b>	<b>14.1</b>	<b>0.88 (0.67–1.16)</b>	
<b>Age</b>					
<65	155	16.7	14.8	0.73 (0.49–1.06)	
≥65	146	15.3	10.6	0.85 (0.58–1.23)	
<b>Sex</b>					
Female	139	18.7	12.9	0.67 (0.45–1.02)	
Male	162	12.0	14.0	1.01 (0.72–1.42)	
<b>CNS Metastases</b>					
No	252	15.3	12.9	0.87 (0.66–1.16)	
Yes	49	NR	18.3	0.58 (0.28–1.17)	
<b>Liver Metastases</b>					
No	241	18.7	16.8	0.81 (0.60–1.11)	
Yes	60	7.9	8.7	0.81 (0.48–1.35)	
<b>Histology</b>					
Squamous	55	8.4	10.5	1.11 (0.65–1.88)	
Nonsquamous	246	18.7	16.0	0.76 (0.56–1.03)	
<b>Smoking Status</b>					
Never	30	16.7	14.8	0.72 (0.31–1.65)	
Former	201	15.3	12.9	0.91 (0.66–1.25)	
Current	70	NR	14.2	0.67 (0.38–1.17)	
<b>Disease Stage</b>					
IVA	103	18.7	17.5	0.99 (0.60–1.62)	
IVB	198	14.6	11.5	0.79 (0.58–1.07)	

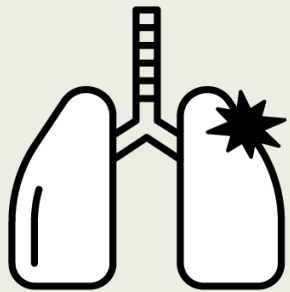
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## RCT: Nivolumab Plus Ipilimumab vs Nivolumab for Previously Treated Patients With Stage IV Squamous Cell Lung Cancer

### POPULATION

169 Men, 83 Women



Pretreated, immunotherapy-naive stage IV or recurrent squamous cell non-small cell lung cancer

Median age, 67.5 y (range, 41.8-90.3 y)

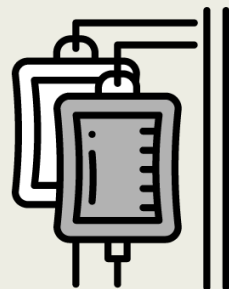
### SETTINGS / LOCATIONS



58 Institutions in the US through the National Clinical Trials Network

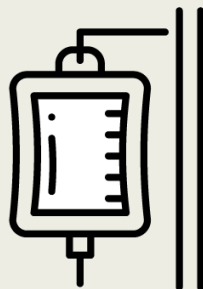
### INTERVENTION

252 Patients randomized and analyzed



#### 125 Nivolumab plus ipilimumab

Nivolumab, 3 mg/kg, intravenously every 2 wk with ipilimumab, 1 mg/kg, intravenously every 6 wk



#### 127 Nivolumab

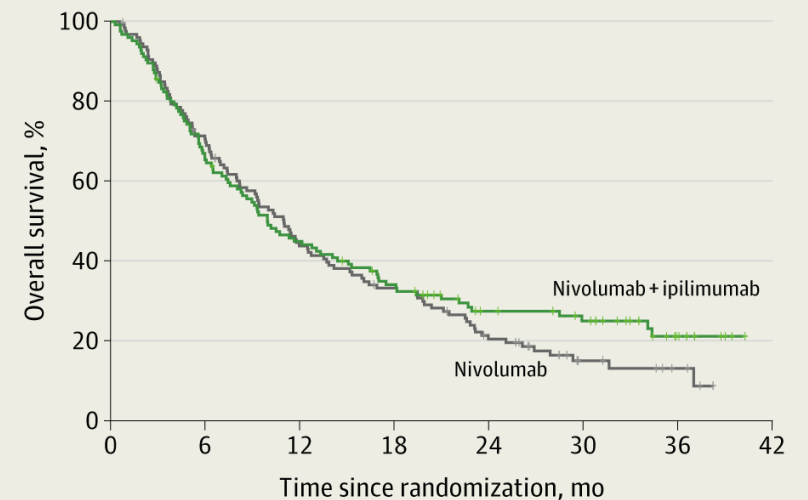
Nivolumab, 3 mg/kg, intravenously every 2 wk until disease progression or intolerable toxic effects

### PRIMARY OUTCOME

Overall survival, defined as time from randomization to death due to any cause

### FINDINGS

Ipilimumab added to nivolumab did not improve outcomes in patients with pretreated immunotherapy-naive squamous cell non-small cell lung cancer (HR, 0.87 [95% CI, 0.66-1.16];  $P = .34$ )

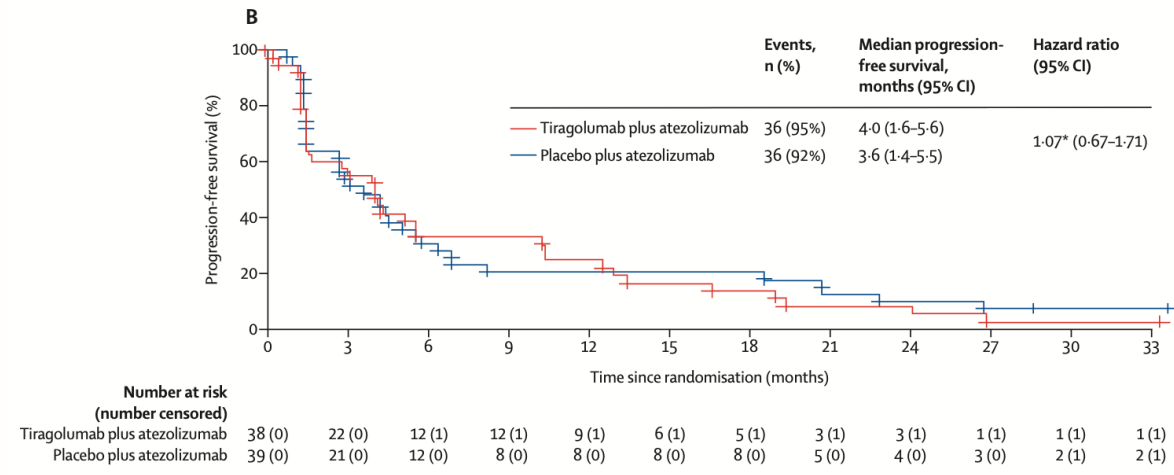
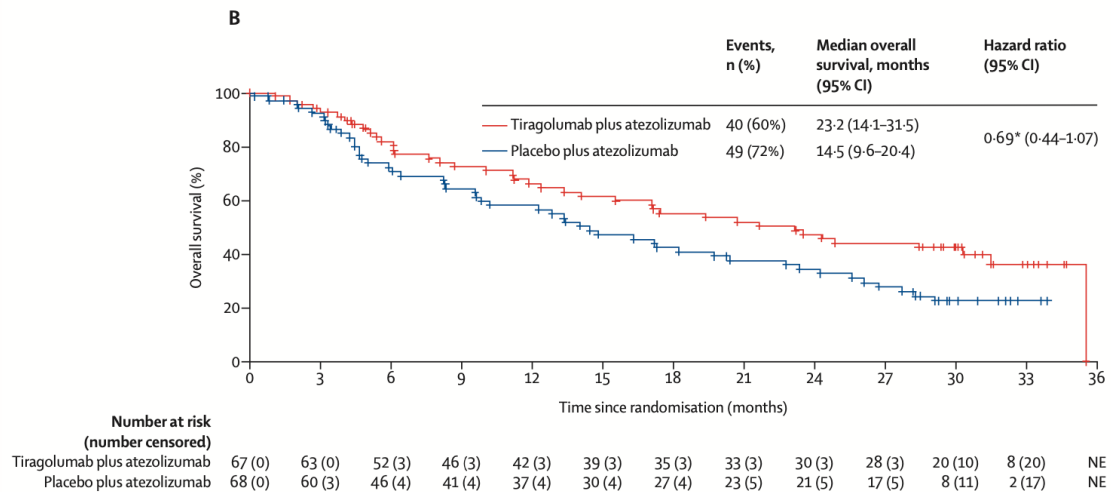
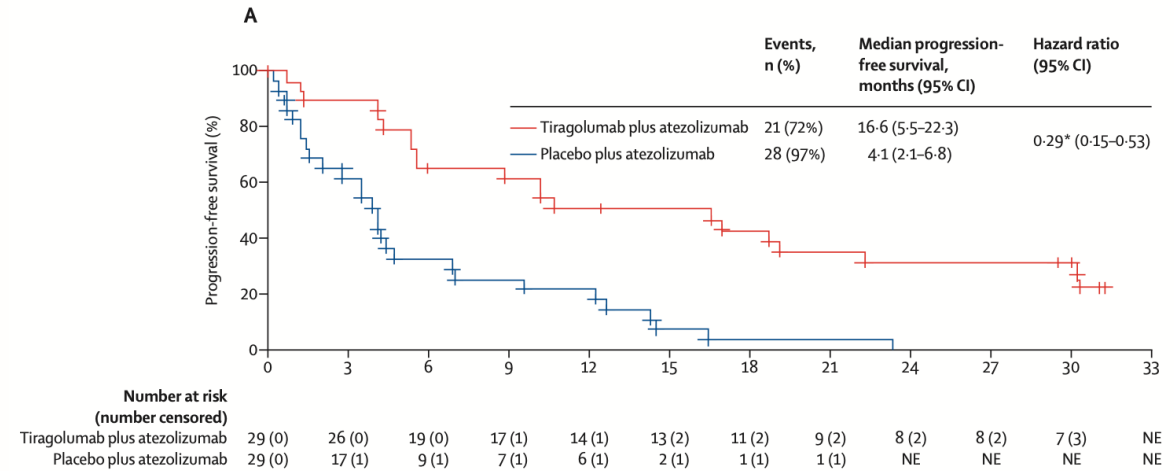
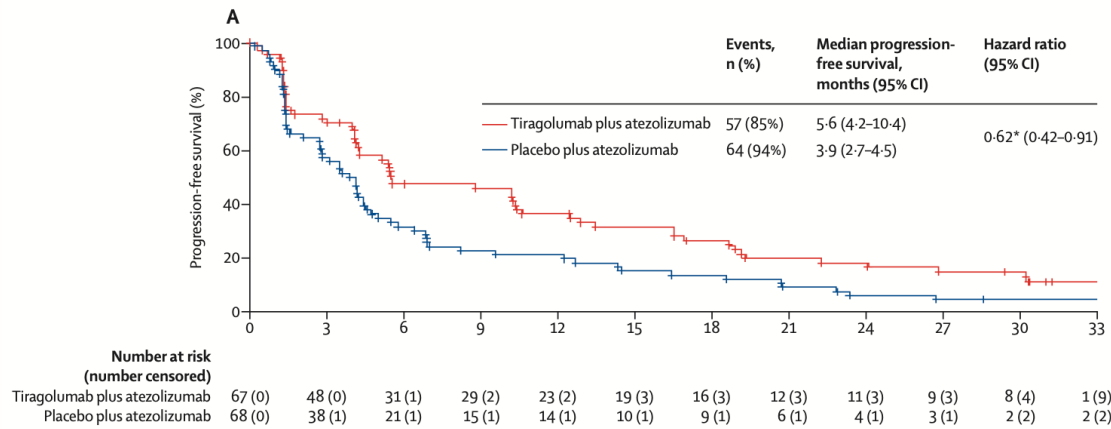


#### Median overall survival, mo:

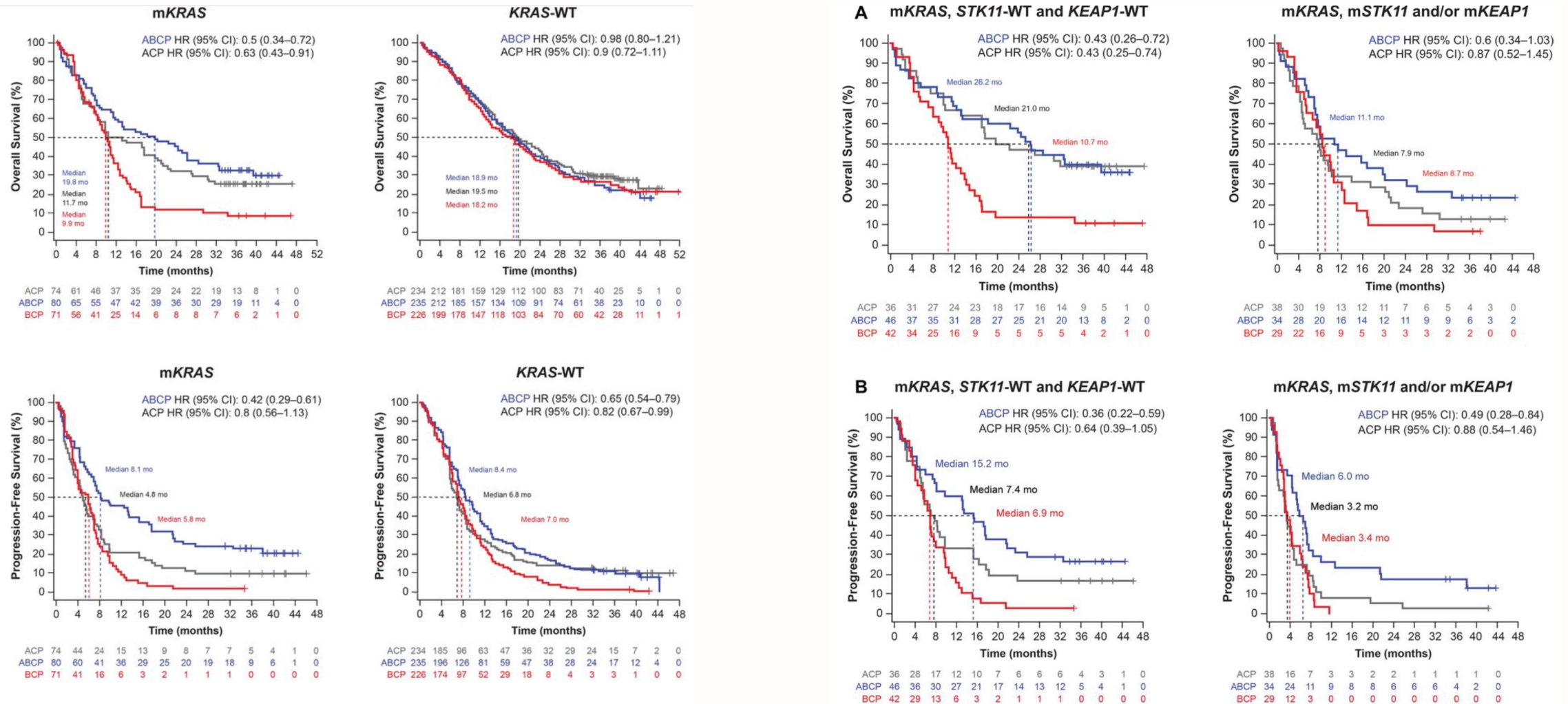
**Nivolumab plus ipilimumab:** 10 (95% CI, 8.0-14.4)

**Nivolumab:** 11 (95% CI, 8.6-13.7)

# Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow-up analyses of a randomised, double-blind, phase 2 study.

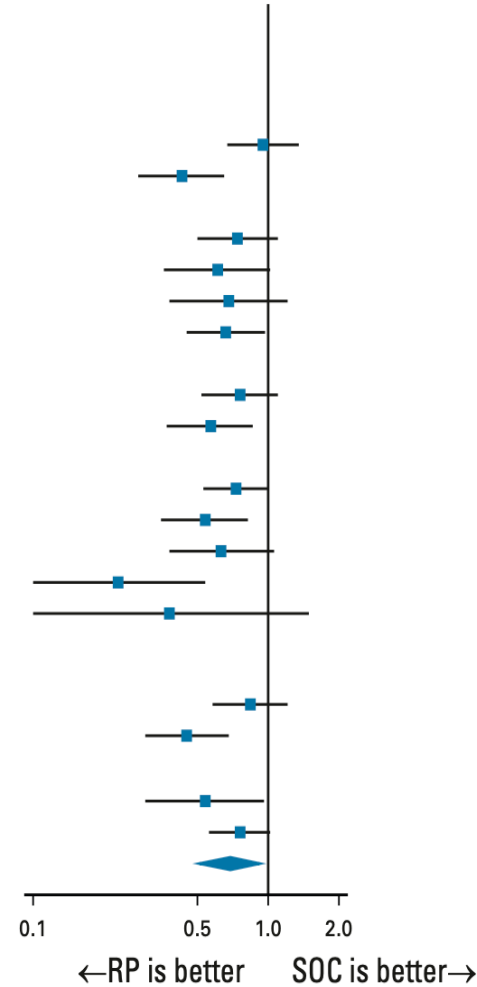


# Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in *KRAS*-mutated non-small cell lung cancer with *STK11*, *KEAP1*, or *TP53* comutations: subgroup results from the phase III IMpower150 trial.

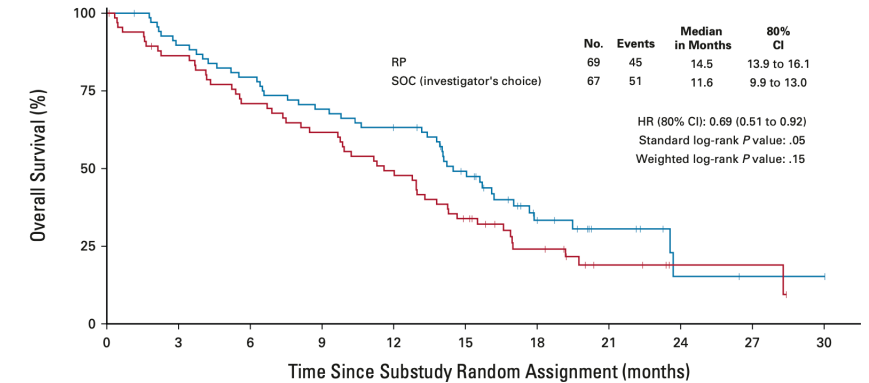


# Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non-Small-Cell Lung Cancer Previously Treated With Immunotherapy-Lung-MAP S1800A

	RP Events/n	SOC Events/n	HR (80% CI)	P
<b>Histology</b>				
Nonsquamous	27/40	27/39	0.95 (0.67 to 1.35)	.43
Squamous/mixed	18/29	24/28	0.43 (0.28 to 0.65)	.005
<b>PD-L1</b>				
0	21/29	21/26	0.74 (0.50 to 1.10)	.16
1-49	11/21	15/22	0.61 (0.36 to 1.02)	.11
≥ 50	8/12	12/16	0.68 (0.38 to 1.21)	.20
≥ 1	19/33	27/38	0.66 (0.45 to 0.97)	.08
<b>TMB</b>				
< 10	23/32	28/38	0.76 (0.52 to 1.10)	.17
≥ 10	18/33	20/25	0.57 (0.37 to 0.86)	.04
<b>Biomarker</b>				
TP53	31/48	35/48	0.73 (0.53 to 1.00)	.10
CDKN2A	18/27	21/24	0.54 (0.35 to 0.82)	.03
KRAS	12/21	13/16	0.63 (0.38 to 1.06)	.13
STK11	4/7	10/10	0.23 (0.10 to 0.54)	.01
KEAP1	1/3	7/10	0.38 (0.10 to 1.49)	.18
<b>Prior Treatment</b>				
IO + Chemotherapy combination	20/32	32/42	0.84 (0.58 to 1.21)	.27
Chemotherapy→IO	25/36	18/23	0.45 (0.30 to 0.68)	.006
<b>PS</b>				
0	15/23	8/9	0.54 (0.30 to 0.96)	.08
1	30/46	43/58	0.76 (0.56 to 1.02)	.12
<b>Overall</b>	45/69	51/67	0.69 (0.51 to 0.92)	.05

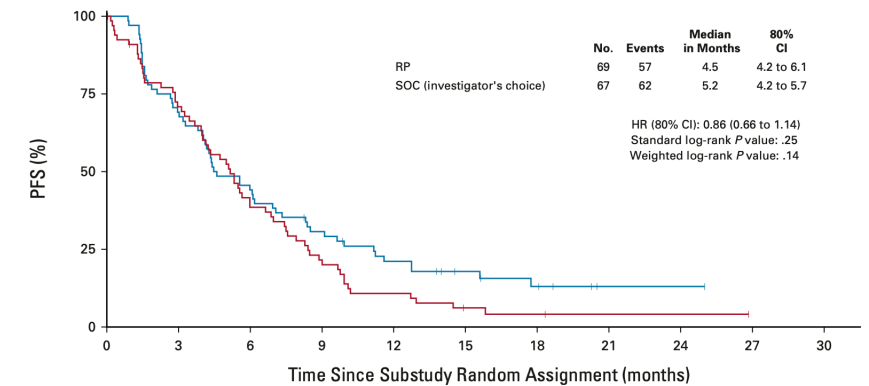


**A**



No. at risk (No. of events):  
RP  
SOC (investigator's choice)

**B**



No. at risk (No. of events):  
RP  
SOC (investigator's choice)





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Cancer Center  
Keck Medicine of USC