



## Best of WCLC 2023 San Francisco

# Immunotherapy for Advanced Stage Non-Small Cell Lung Cancer: Update from WCLC23 -Singapore

David R. Gandara, MD  
University of California Davis  
Comprehensive Cancer Center



# Immunotherapy therapeutic decision-making in advanced NSCLC is Complex: Phase III Trials in 1<sup>st</sup> Line Therapy

Study	Drug (vs CT)	PD-L1 selection	Control	Primary endpoint	HR primary endpoint	Result	Publication
KN-024	Pembro	≥50%	Platinum CT	PFS	0.50	Positive	Reck et al. <i>NEJM</i> 2016
CM026	Nivo	≥5%	Platinum CT	PFS	1.15	Negative	Carbone et al. <i>NEJM</i> 2017
KN-042	Pembro	≥1%	Platinum CT	OS	0.81 0.69 (50%)	Positive	Mok et al. <i>Lancet</i> 2019
IMpower110	Atezo	≥1%	Platinum CT	OS in TC3/IC3	0.59	Positive	Herbst et al. <i>NEJM</i> 2020
EMPOWER-Lung 1	Cemi	≥50%	Platinum CT	PFS, OS	0.54 (PFS) 0.57 (OS)	Positive	Sezer et al. <i>Lancet</i> 2021
MYSTIC	Durva or Durva/Tremi	≥25%	Platinum CT	PFS, OS	0.87 (PFS) durva 0.76 (OS) durva	Negative	Rizvi et al. <i>JAMA Oncol</i> 2020
CM227	Nivo or Nivo-Ipi	<1%/≥1% & TMB ≥10	Platinum CT	PFS, OS	0.58 (PFS) in TMB-H 0.62 (OS) in <1% 0.79 (OS) in ≥1%	Positive	Hellmann et al. <i>NEJM</i> 2018 Hellman et al. <i>NEJM</i> 2019
CM9LA	Nivo-Ipi-CT	≥1%	Platinum CT	OS	0.66	Positive	Paz Ares et al. <i>Lancet Oncol</i> 2021
KN-189 (NSQ)	Pembro-CT	≥1%	Platinum CT	PFS	0.52	Positive	Ghandi et al. <i>NEJM</i> 2018
KN-407 (SQ)	Pembro-CT	None	Platinum-Nab Pac	PFS, OS	0.56 (PFS) 0.64 (OS)	Positive	Paz Ares et al. <i>NEJM</i> 2018
IMpower150 (NSQ)	Atezo + Bev/Pac/Carbo	None	Bev/Pac/Carbo	PFS, OS	ACBP 0.71 (PFS) ACBP 0.78 (OS)	Positive	Socinski et al. <i>NEJM</i> . 2018
IMpower131 (SQ)	Atezo + nab Pac/Carbo	None	Pac/Carbo	PFS, OS	0.71 (PFS) 0.88 (OS)	Positive (PFS)	Jotte et al. <i>J Thorac Oncol</i> 2020
EMPOWER-Lung 3	Cemi-CT	None	Platinum CT	PFS, OS	0.56 (PFS) 0.71 (OS)	Positive	Gogishvili et al. <i>Nat Med</i> 2022
POSEIDON	Durva+Tremi-CT	None	Platinum CT	PFS, OS	0.77 (OS)	Positive	Johnson et al. <i>JCO</i> 2022

<b>Parameters</b>
<b>Test Regimen</b> ICI Monotherapy ICI+CT ICI+CT+Bev ICI + CTLA-4
<b>Biomarker</b> None PD-L1 TMB
<b>Histology</b> All SQ NSQ
<b>Primary Endpoint</b> PFS OS Both

# Advanced stage NSCLC: Checkpoint Immunotherapy (CPI)

## Themes:

- Long term survival on CPI-based therapy
- CPI-based therapy in EGFR-mutated NSCLC
- Patient reported outcomes (PROs) on CPI therapy

**KN-189/KN-407:** 5-Year Survival of pembrolizumab plus chemotherapy for metastatic NSCLC with **PD-L1 <1%** (**OA14.05**)  
-S Gadgeel

Survival of patients with metastatic NSCLC and **PD-L1 90%** receiving CPI monotherapy (either Cemiplimab or Pembrolizumab) or chemotherapy (**OA14.04**) -B Ricciuti

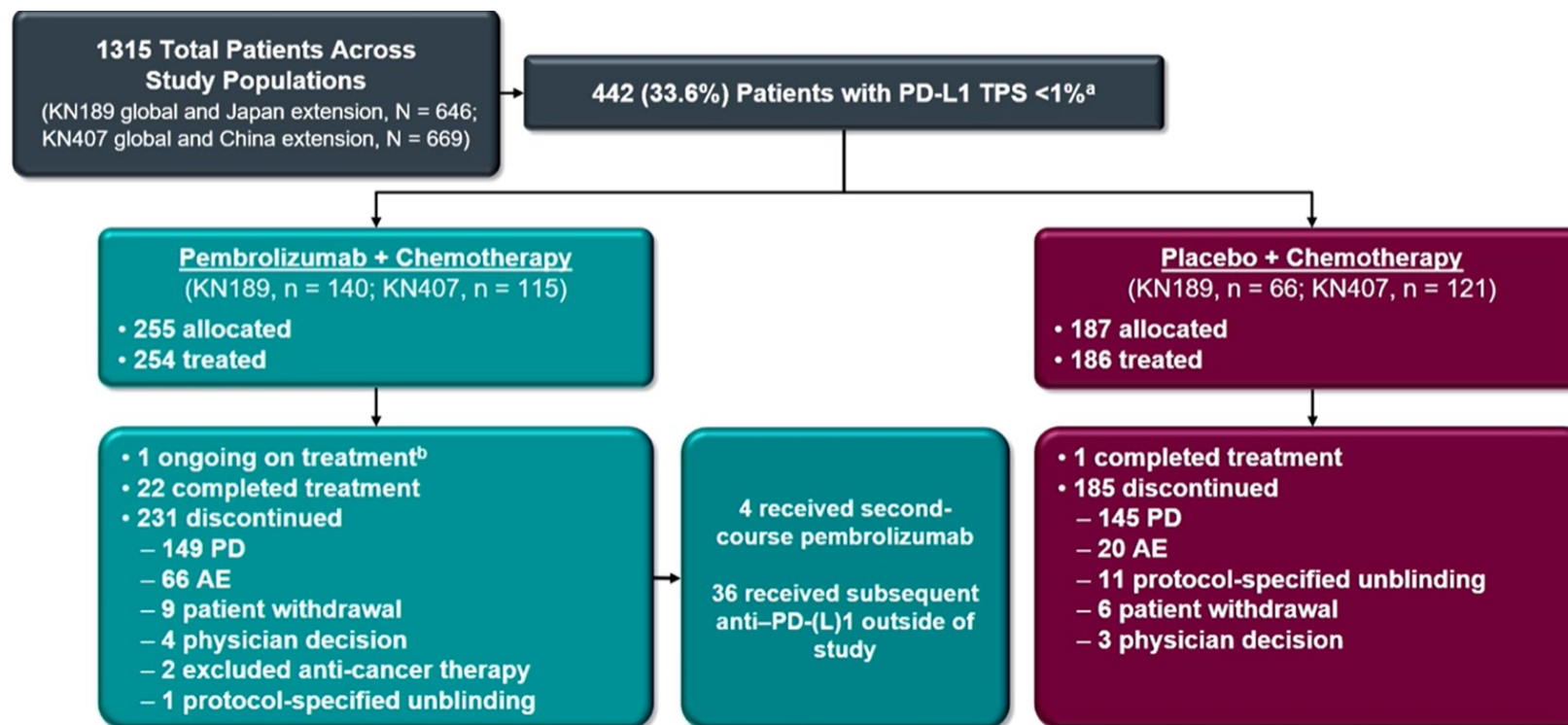
**IMpower151:** Phase III study of atezolizumab + bevacizumab + chemotherapy in 1L metastatic nonsquamous NSCLC (**OA09.06**)  
-C Zhou

**ILLUMINATE:** Efficacy and safety of durvalumab-tremelimumab and chemotherapy in *EGFR* mutant NSCLC following progression on EGFR inhibitors (**OA09.04**) -C Lee

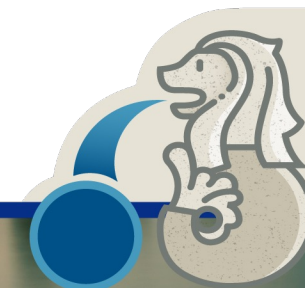
**EMPOWER-Lung 1 and 3:** Predictive utility of patient-reported outcomes (PROs) for survival in 1st-line treated patients with aNSCLC (**MA05.11**) -D Gandara



## KN-189/KN-407: Pembrolizumab + Chemo vs Chemo alone in metastatic NSCLC with PD-L1 <1%: 5-Year survival

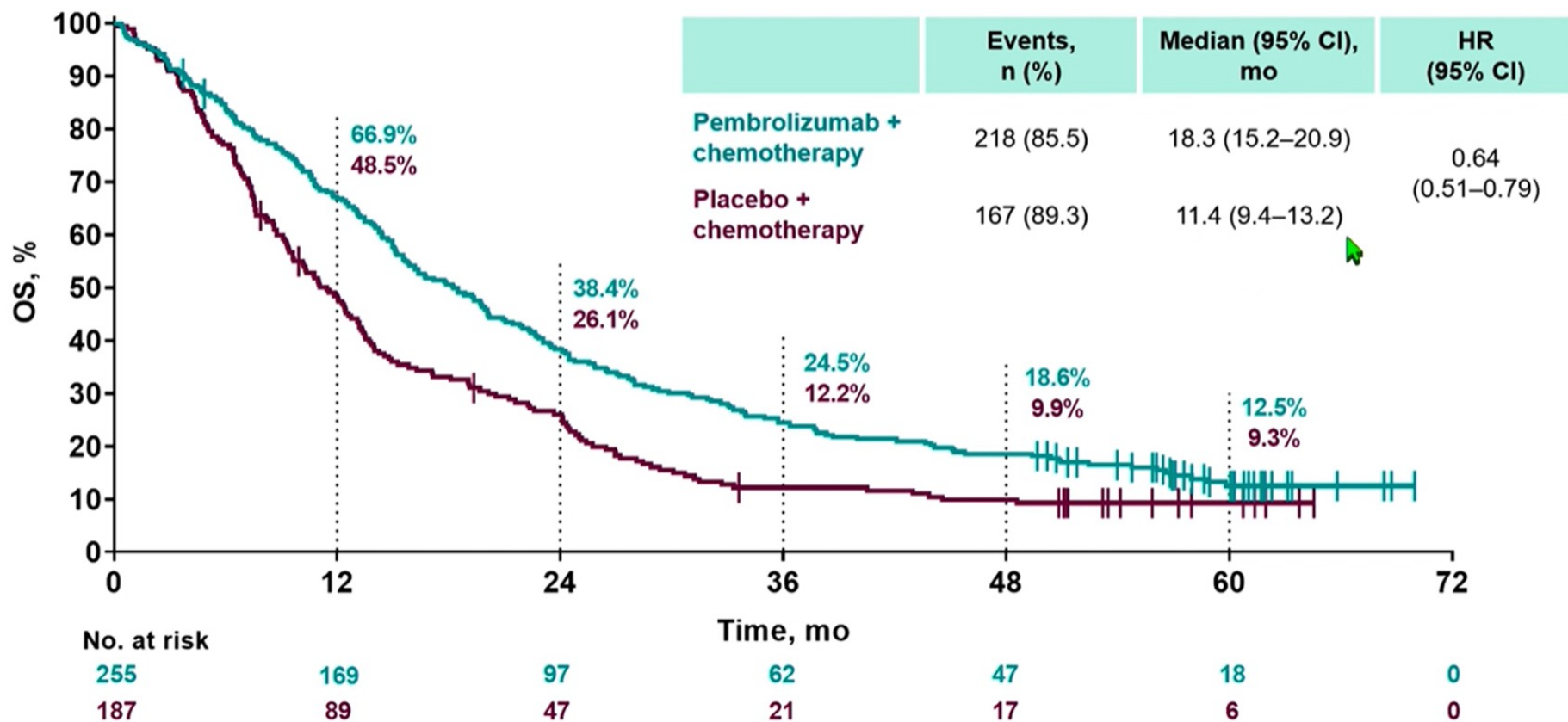


Gadgeel S, et al. WCLC 2023. Abstract OA14.05.





## KN-189/KN-407: 5-year survival in the PDL1<1% population

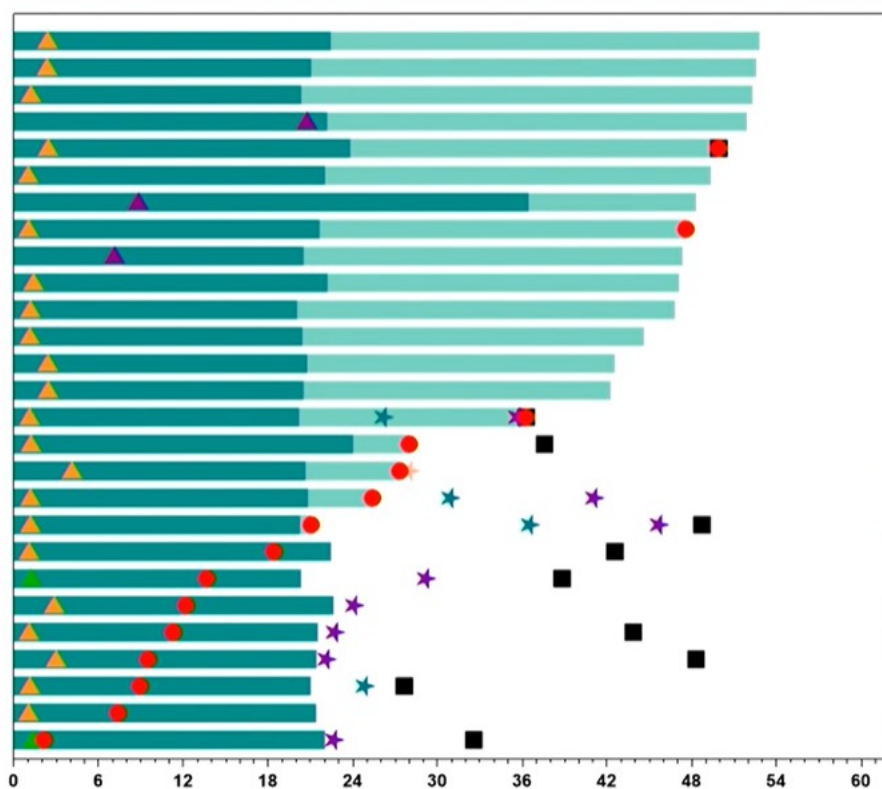


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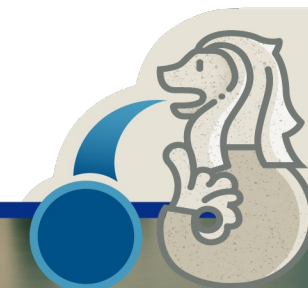




## KN-189: 5-Year Survival in patients completing the full 2 years of Pembrolizumab therapy



Outcome	Patients who completed 35 cycles <sup>a</sup> n = 27
ORR <sup>b</sup> (95% CI), %	92.6 (75.7–99.1)
Best overall response, n (%)	
Complete response	3 (11.1)
Partial response	22 (81.5)
Stable disease <sup>c</sup>	2 (7.4)
Median DOR (range), mo	55.1 (7.4 to 59.3+)
3-year OS rate after completing 35 cycles, %	56.7
Alive without subsequent therapy or PD, n (%)	12 (44.4)

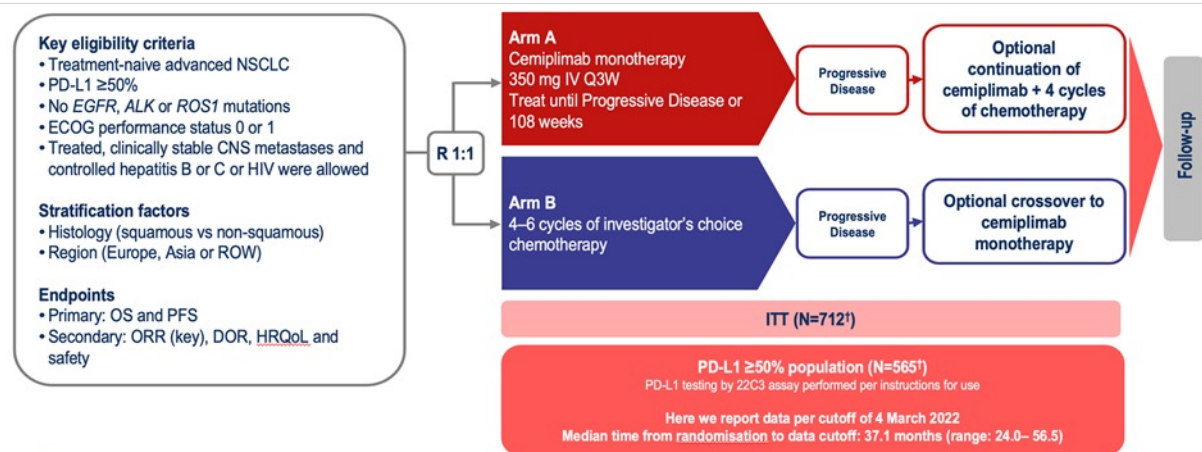




## OA14.04: Survival of patients with metastatic NSCLC and PD-L1 $\geq 90\%$ receiving CPI monotherapy (either Cemiplimab or Pembrolizumab) or chemotherapy

- Goal: To **examine 2 independent cohorts of patients** with advanced NSCLC and a PD-L1 TPS  $\geq 50\%$  who received PD-1 inhibition (comparing the groups 50-89% vs  $\geq 90\%$ ):
  - Cohort #1: EMPOWER-Lung-1
  - Cohort #2: retrospective academic cohort (DFCI, MSKCC, MDACC, MGH)

### EMPOWER-Lung-1



Biagio Ricciuti, et al. WCLC 2023 OA.14.04

### Academic Cohort

- Adv NSCLC receiving Pembro monotherapy
- Similar eligibility to EMPOWER-LUNG-1 (PD-L1 50-89% or  $\geq 90\%$ )



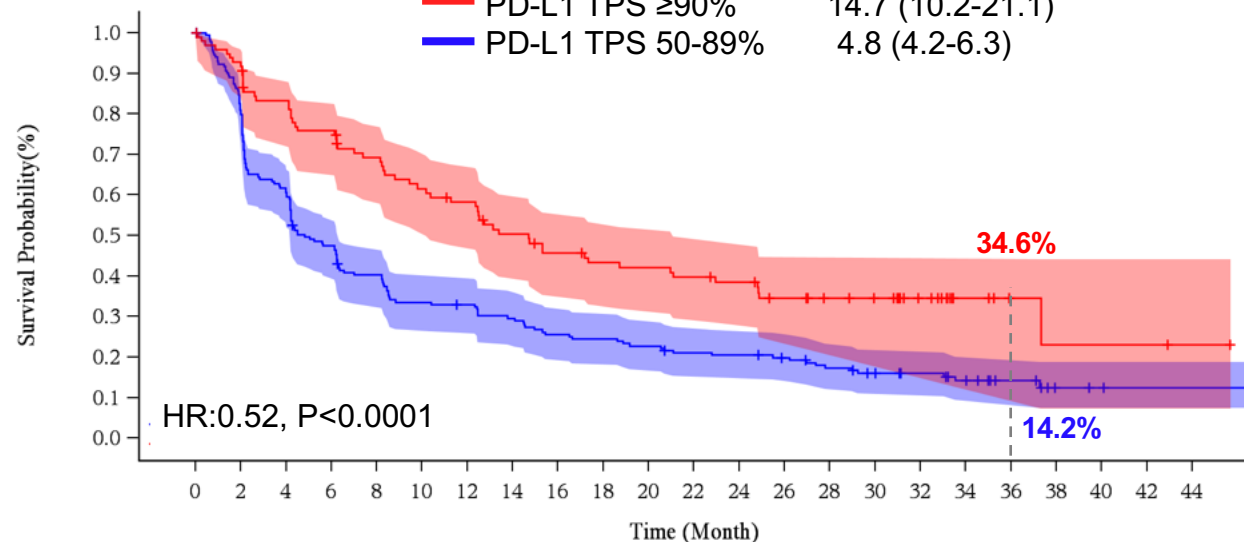


# EMPOWER-Lung-1: Three-years PFS and OS to first-line Cemiplimab by PD-L1 expression levels (50-89% vs ≥90%)

**Progression-free survival**

Median PFS, months (95%CI)

- PD-L1 TPS ≥90% 14.7 (10.2-21.1)
- PD-L1 TPS 50-89% 4.8 (4.2-6.3)

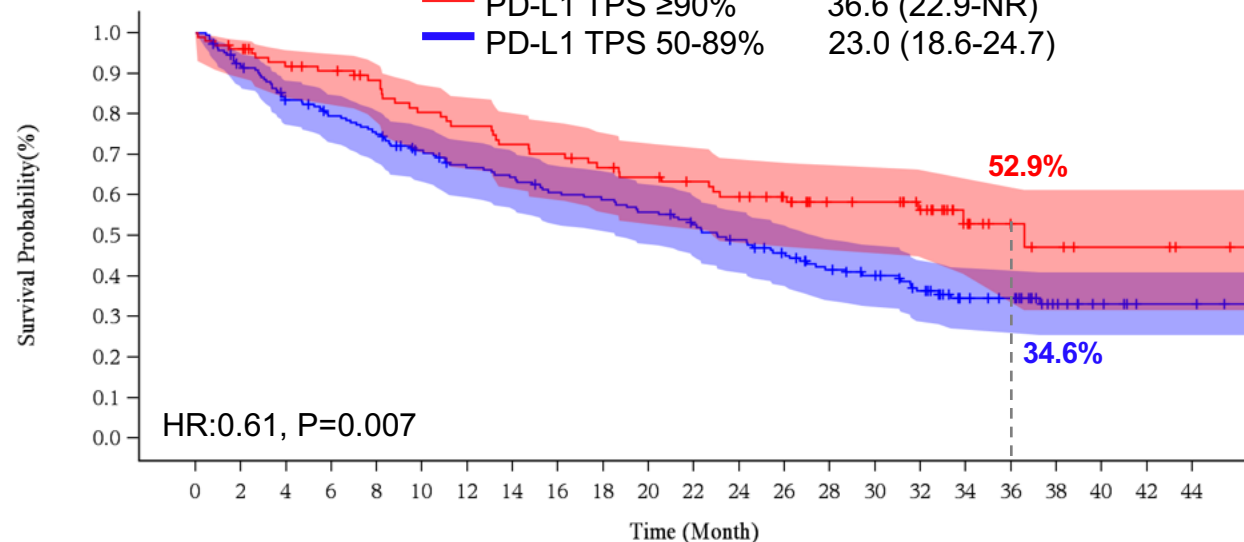


Number at risk

**Overall survival**

Median OS, months (95%CI)

- PD-L1 TPS ≥90% 36.6 (22.9-NR)
- PD-L1 TPS 50-89% 23.0 (18.6-24.7)



Number at risk

PD-L1: 50-89%	185	148	111	86	72	60	58	52	45	43	40	36	35	32	27	22	19	15	10	3	2	1	1
PD-L1: >=90%	99	90	78	71	63	56	52	44	39	36	35	33	31	26	23	21	15	6	3	2	2	2	1

PD-L1: 50-89%	185	167	149	140	132	119	110	106	99	96	91	84	77	69	60	54	46	34	31	17	12	8	8
PD-L1: >=90%	99	94	86	83	78	71	68	64	62	58	55	52	49	44	35	34	28	15	9	7	5	5	3



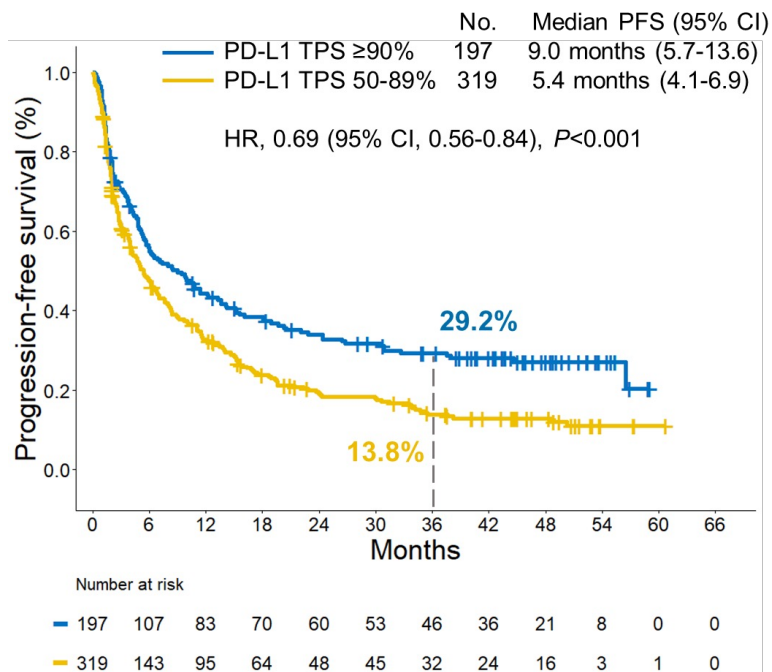




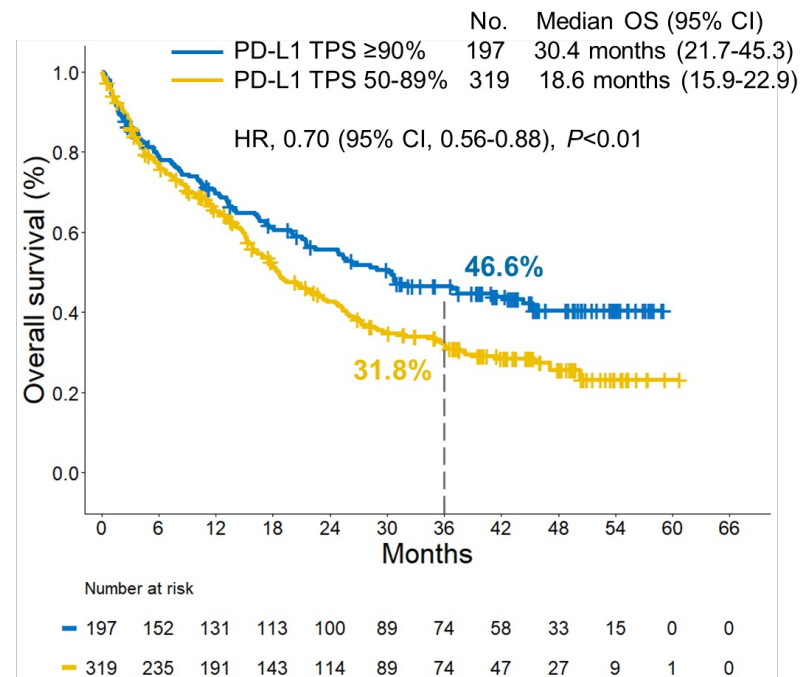


# Academic Cohort: Three-year PFS and OS to first-line Pembrolizumab by PD-L1 expression levels

Progression-free survival

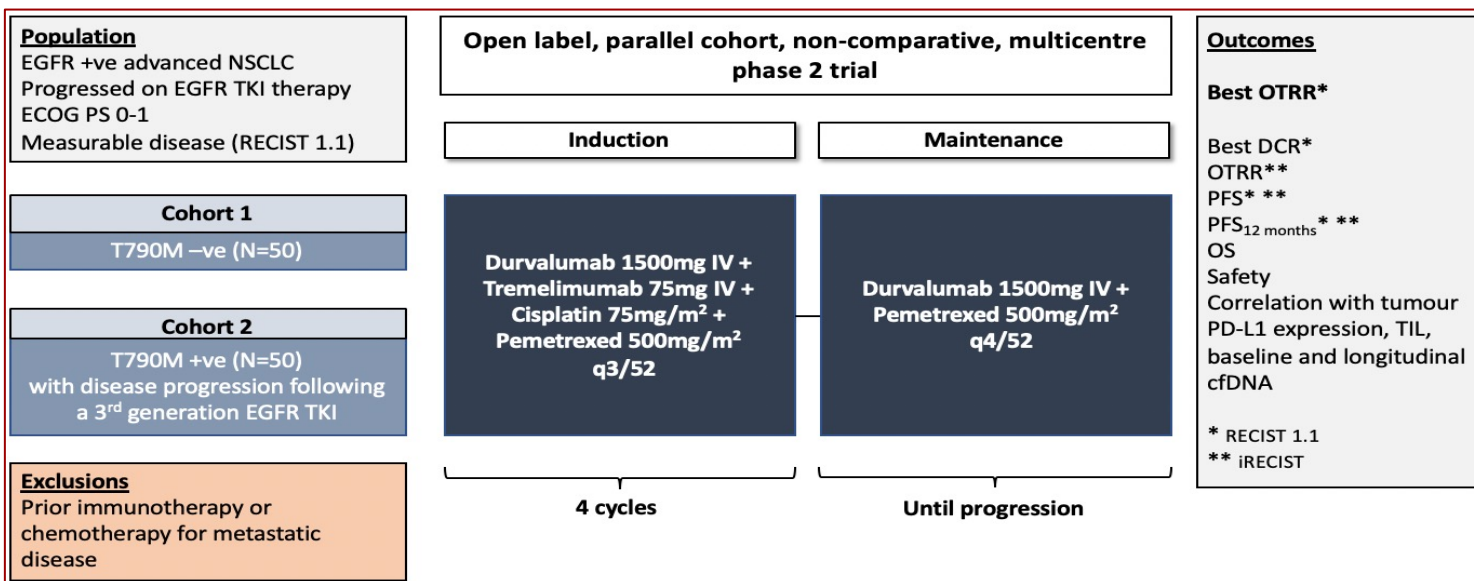


Overall survival

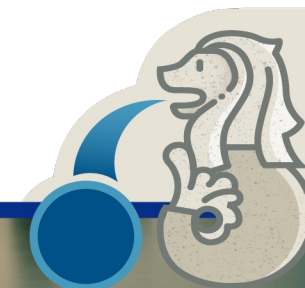




## ILLUMINATE: Durvalumab-Tremelimumab + Chemo for *EGFR*-mutated NSCLC following progression on EGFR inhibitors



Baseline characteristics (N=100)		n (%)
Age		Median 60 years (range 32–77)
Female		64 (64)
Performance status 0		49 (49)
Asian		77 (77)
EGFR mutation	Exon 19 deletion	57 (57)
	Exon 21 L858R	42 (42)
Current or former smoker		27 (27)
PD-L1 status	0–49%	47 (47)
	≥50%	12 (12)
No of prior TKI	1 line	43 (43)
	>1 line	50 (50)

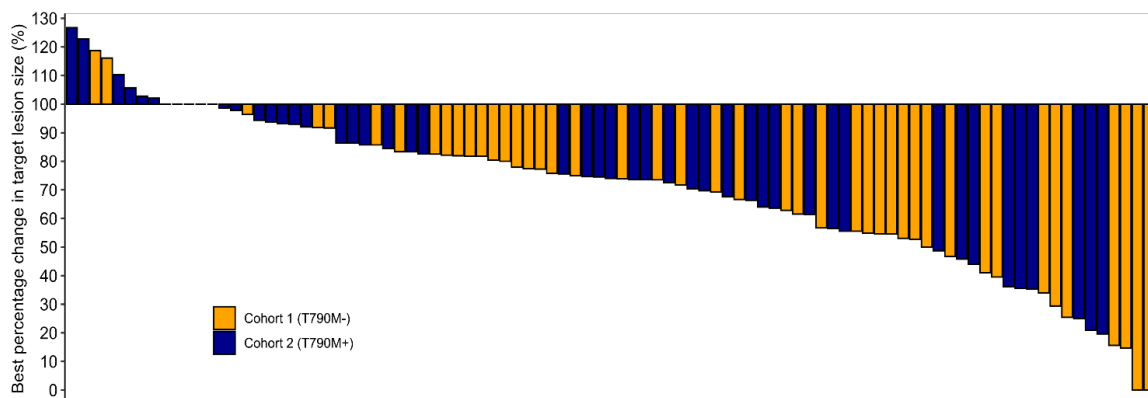




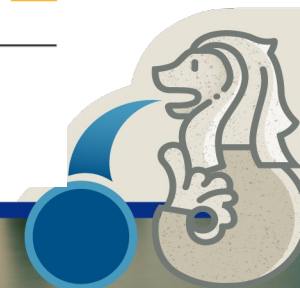
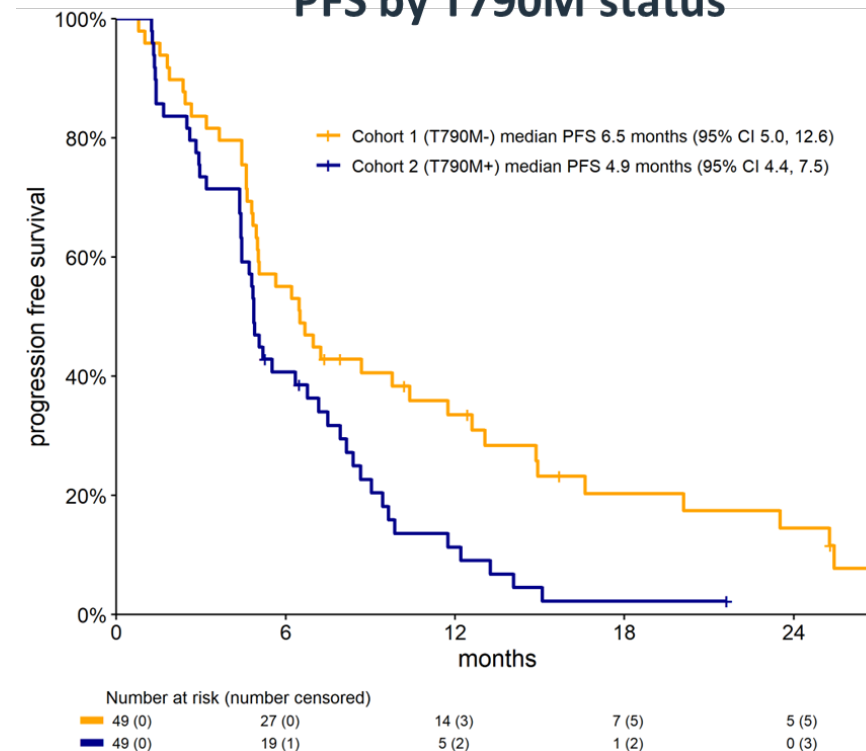
# ILLUMINATE: Efficacy of durvalumab-tremelimumab + Chemo for EGFR-mutated NSCLC following progression on EGFR inhibitors

Primary endpoint: ORR

	Cohort 1 (T790M-)	Cohort 2 (T790M+)
Confirmed ORR, n/N (%) [95% CI]	15/48 (31) [20, 45]	10/48 (21) [12, 34]
Unconfirmed ORR, n/N (%) [95% CI]	20/48 (42) [29, 56]	17/48 (35) [23, 50]

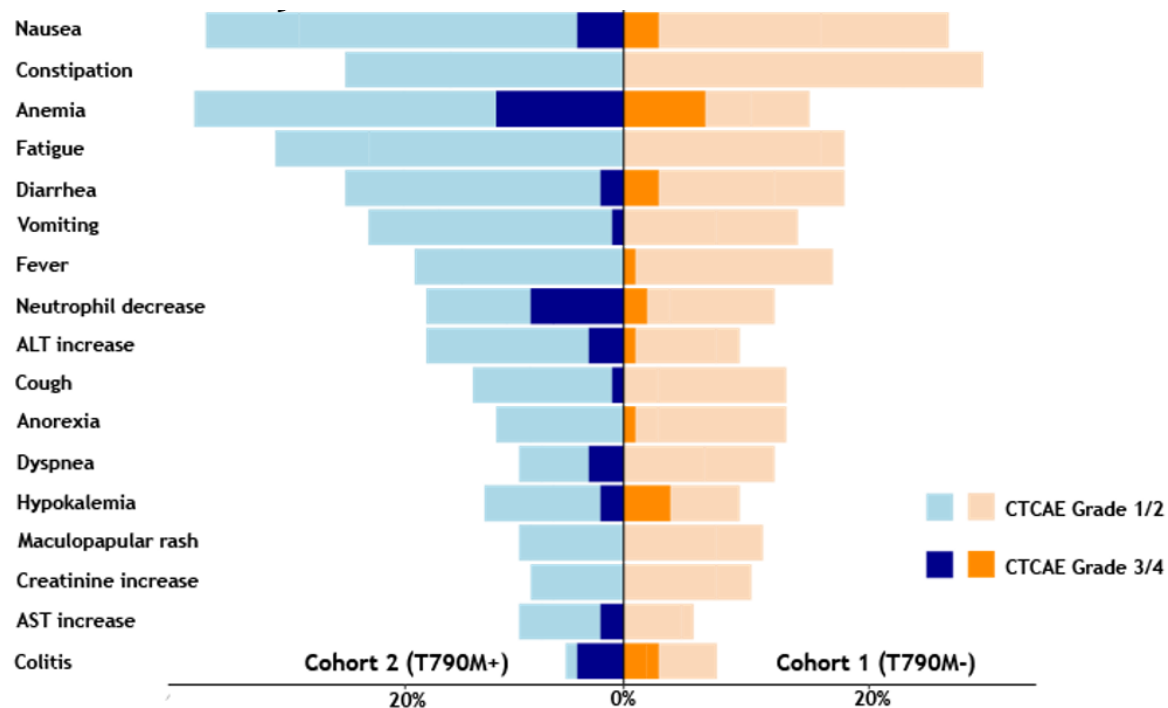


PFS by T790M status





# ILLUMINATE: Safety of Durvalumab-Tremelimumab + Platinum Chemo for EGFR-mutated NSCLC following progression on EGFR inhibitors

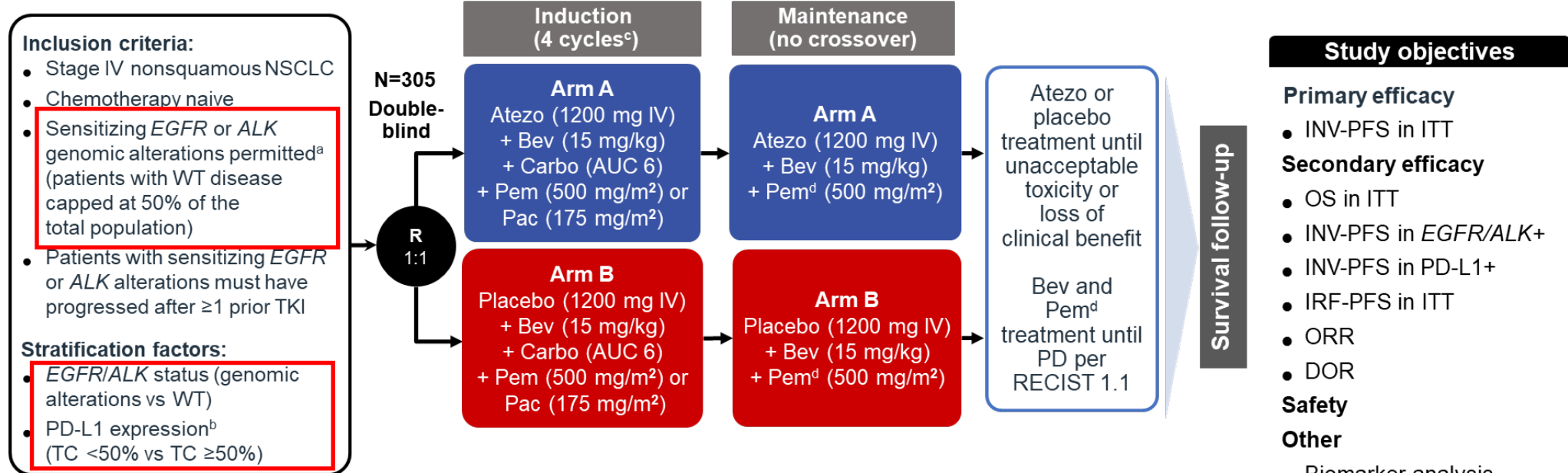


Grade 3–4 immune-related AEs	n (%)
Colitis	8 (8)
Hepatitis	4 (4)
Adrenal insufficiency	2 (2)
Pneumonitis	1 (1)





## IMpower151 (Phase 3): 1<sup>st</sup> Line Atezolizumab + Bevacizumab + Platinum Chemotherapy for metastatic NSQ-NSCLC

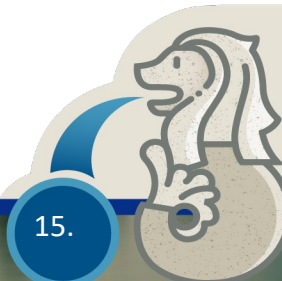
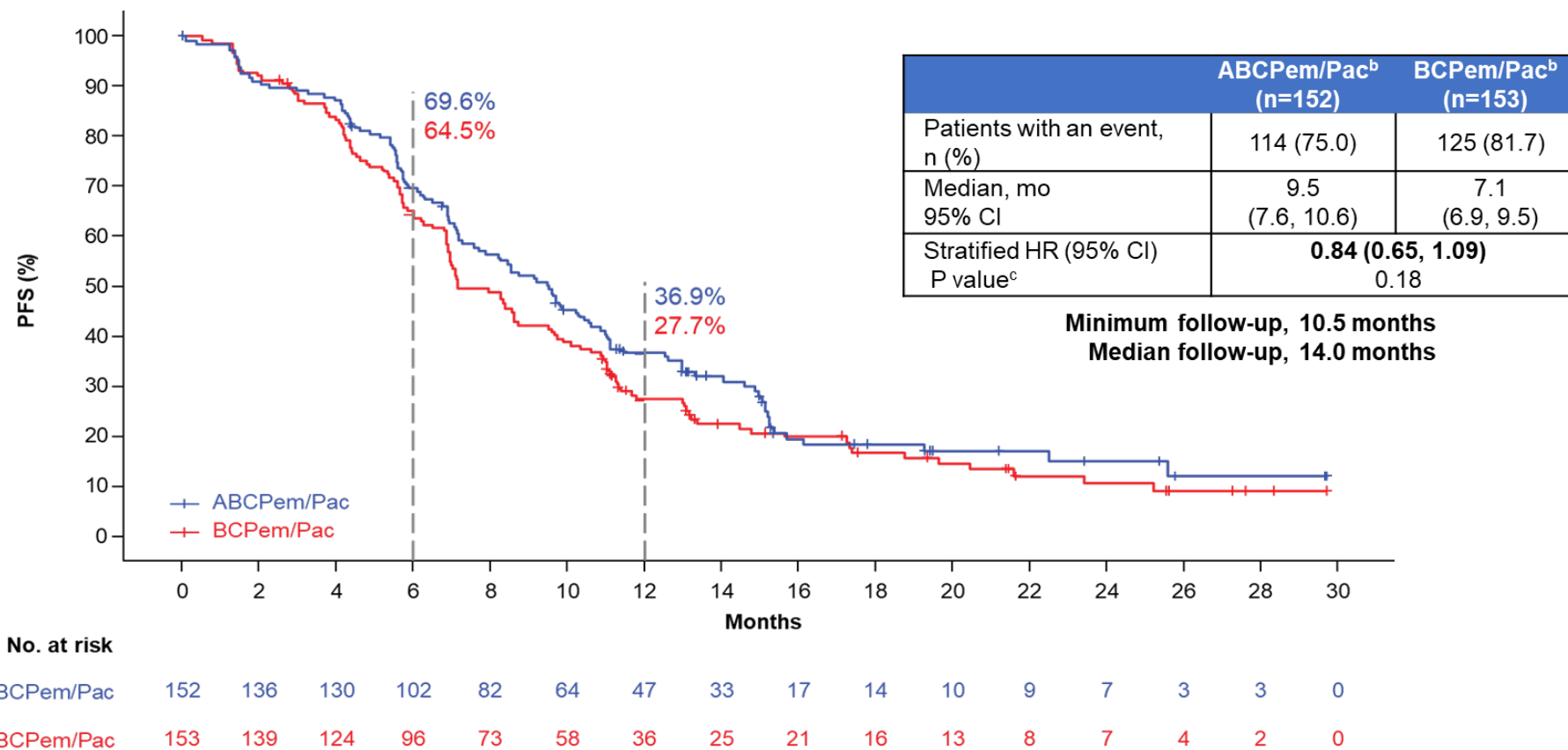


**Goal: Re-explore the role of CPI (Atezolizumab & anti-angiogenic (Bevacizumab)  
In a patient population enriched for EGFR-mutated NSCLC (reprising Impower 150)**



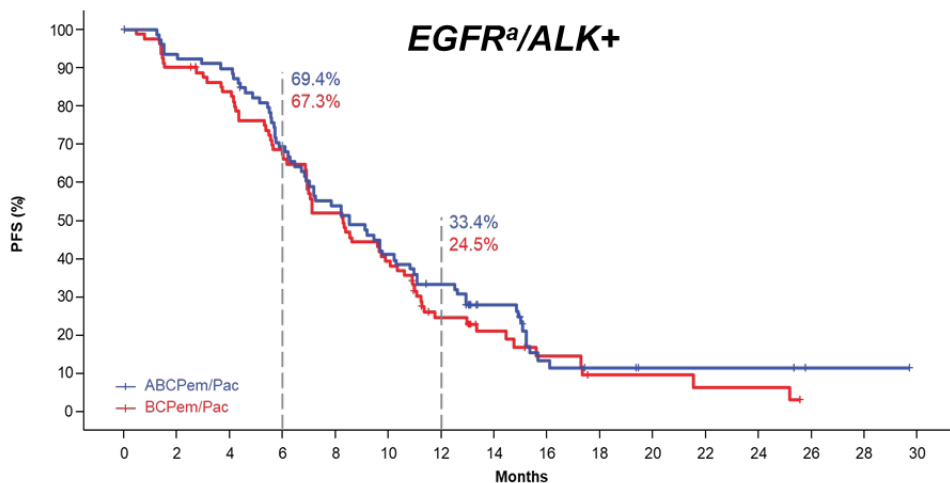


# Primary Endpoint: PFS in the ITT population



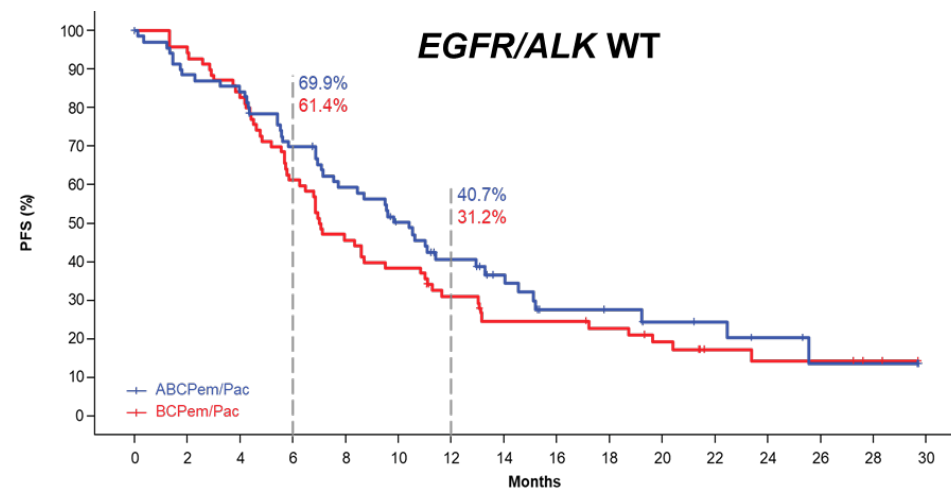


## Impower 151: PFS by *EGFR/ALK* Genotype



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
ABCPem/Pac	81	74	71	54	42	32	25	17	7	5	3	3	3	1	1	0
BCPem/Pac	82	73	66	53	41	31	16	10	8	3	3	2	2	0	0	0

	ABCPem/Pac (n=81)	BCPem/Pac (n=82)
Patients with an event, n (%)	65 (80.2)	68 (82.9)
Median, mo (95% CI)	8.5 (6.9, 10.3)	8.3 (6.9, 10.1)
Unstratified HR (95% CI)	<b>0.86</b> (0.61, 1.21)	



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
ABCPem/Pac	71	62	59	48	40	32	22	16	10	9	7	6	4	2	2	0
BCPem/Pac	71	66	58	43	32	27	20	15	15	13	10	6	5	4	2	0

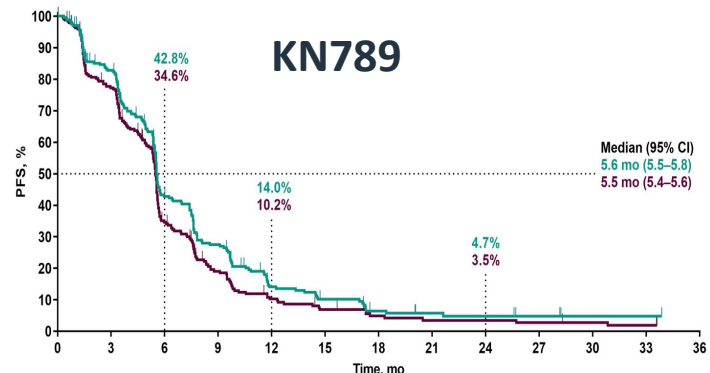
	ABCPem/Pac (n=71)	BCPem/Pac (n=71)
Patients with an event, n (%)	49 (69.0)	57 (80.3)
Median, mo (95% CI)	10.4 (7.6, 13.3)	7.0 (6.2, 9.5)
Unstratified HR (95% CI)	<b>0.81</b> (0.55, 1.19)	



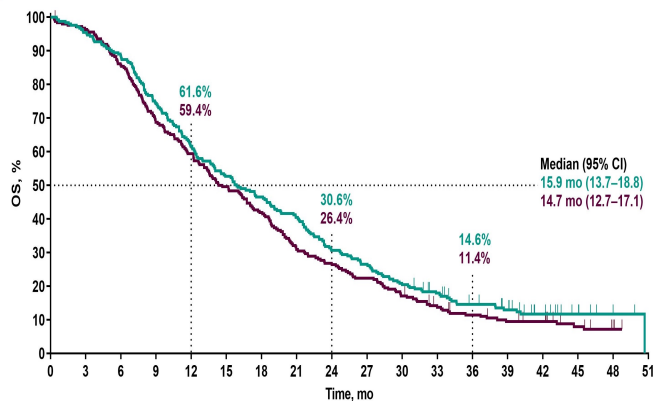




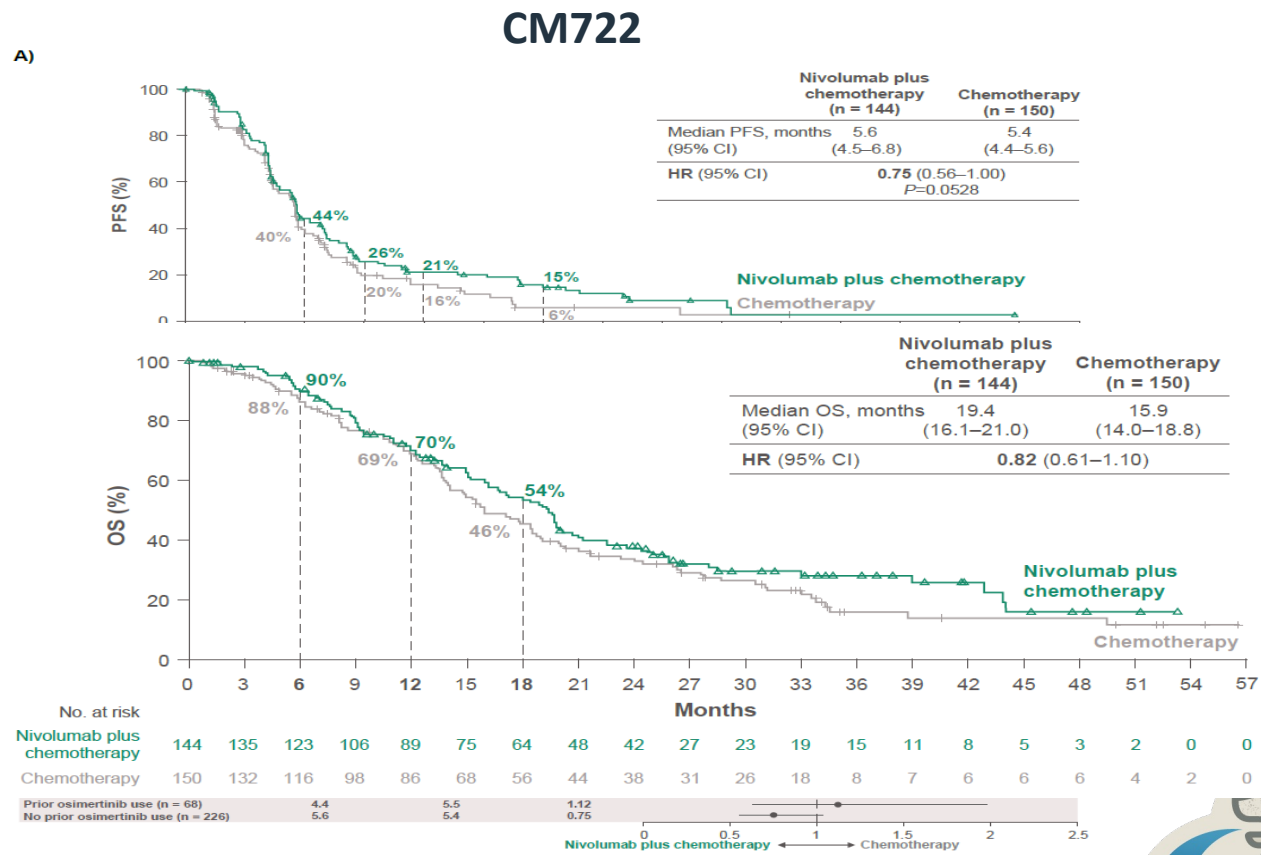
# Other recent trials show minimal impact of ICI in combination with Platinum Chemotherapy in patients with EGFR-mutated NSCLC and TKI failure



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Pembrolizumab + chemo	245	181	90	57	25	17	9	6	5	3	1	1	0
Placebo + chemo	247	184	75	37	19	12	7	5	5	4	3	2	0

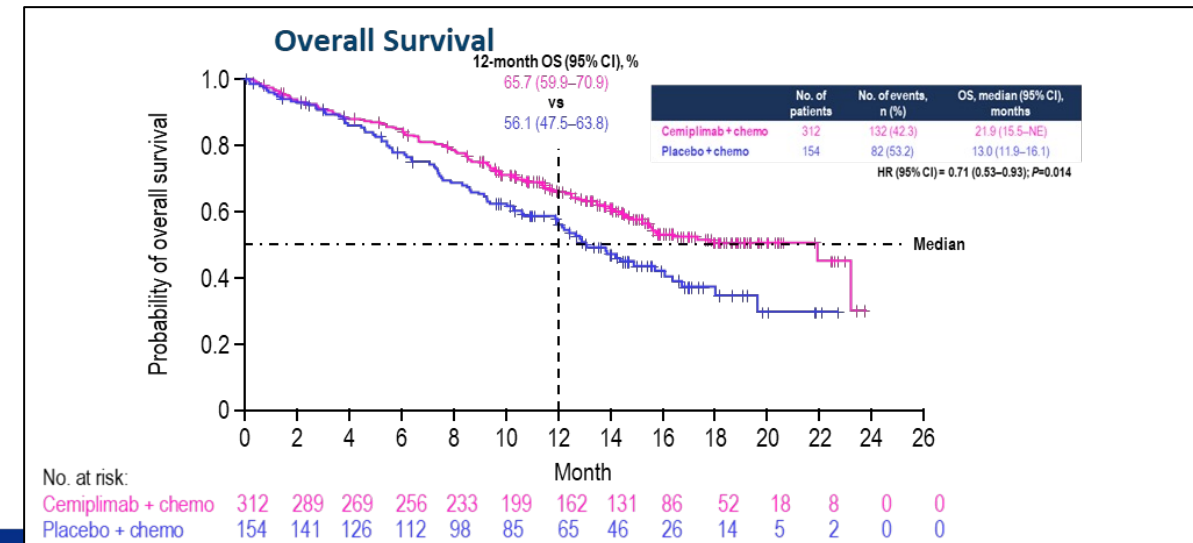
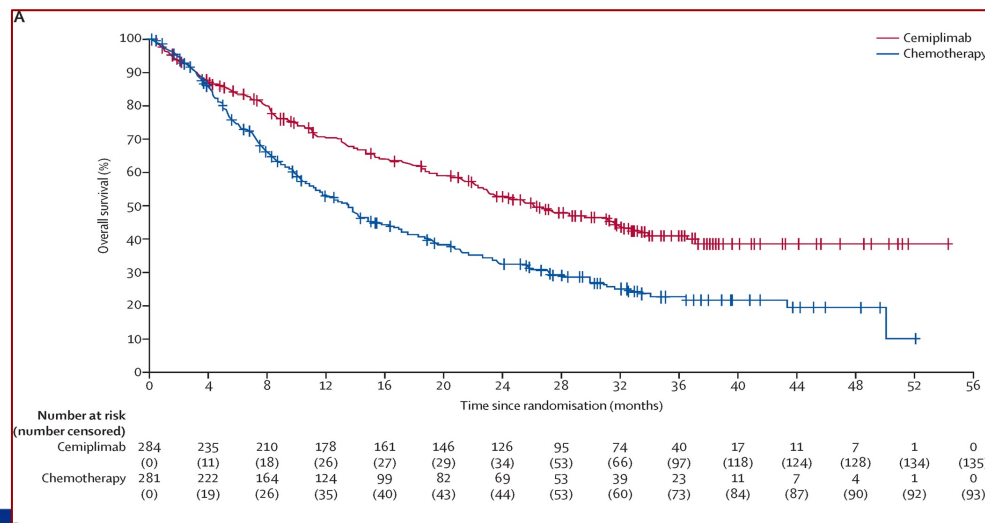
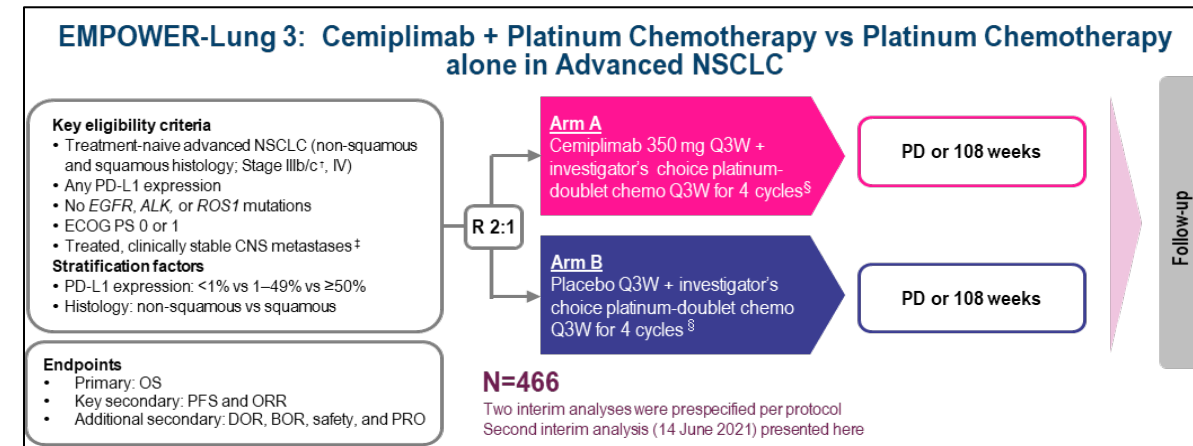
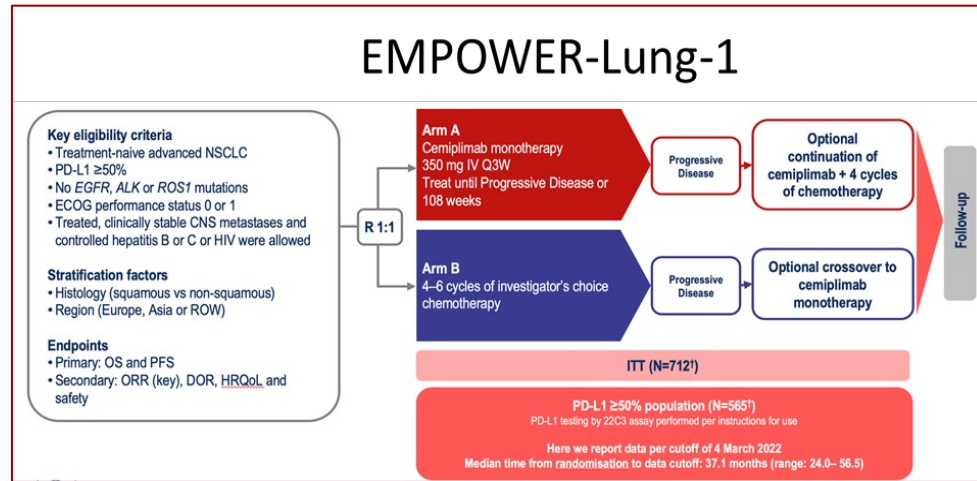


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Pembrolizumab + chemo	245	234	217	182	151	129	114	99	75	65	50	40	29	23	13	7	3	0
Placebo + chemo	247	237	211	169	146	122	103	76	65	55	42	31	24	19	17	10	3	0





## Predictive Utility of Patient-Reported Outcomes for Survival in 1st-Line Treated Patients with Advanced NSCLC in EMPOWER-Lung 1 and 3





## Predictive Utility of Patient-Reported Outcomes for Survival in 1st-Line Treated Patients with Advanced NSCLC in EMPOWER-Lung 1 and 3

**Table: Rank summary of predictive utility of PROs for OS**

EORTC QLQ-C30 and QLQ-LC13 scales	n	HR† (95% CIs)	P-value	C-stat
<b>Continuous variables</b>				
LC-dyspnea	591	1.19 (1.12, 1.26)	<0.001	0.635
Physical functioning	592	0.84 (0.78, 0.90)	<0.001	0.619
Fatigue	592	1.15 (1.08, 1.23)	<0.001	0.601
Role functioning	592	0.90 (0.85, 0.94)	<0.001	0.600
Dyspnea	592	1.11 (1.05, 1.16)	<0.001	0.598
Social functioning	593	0.88 (0.83, 0.93)	<0.001	0.597
Financial problems	591	1.08 (1.03, 1.13)	0.001	0.587
Pain	593	1.11 (1.05, 1.17)	<0.001	0.586
LC-pain in other parts	590	1.08 (1.03, 1.14)	0.003	0.572
Insomnia	592	1.07 (1.02, 1.12)	0.004	0.568
Global health status/QoL	593	0.91 (0.85, 0.98)	0.012	0.565
Constipation	593	1.08 (1.02, 1.14)	0.006	0.550
Appetite loss	592	1.08 (1.02, 1.13)	0.006	0.548
Emotional functioning	593	0.93 (0.87, 1.00)	0.048	0.545
<b>Categorical variables</b>				
Physical functioning	590			0.572
Intermediate vs low		0.72 (0.47, 1.10)	0.126	
High vs low		0.41 (0.24, 0.72)	0.002	
ECOG PS	595	1.38 (0.94, 2.05)	0.104	0.534

**14 out of 24 PROs** were significantly associated with overall survival and had greater predictive utility than physician-reported ECOG PS

**Dyspnea** (per EORTC QLQ-LC-13) and **physical functioning** (per EORTC QLQ-C30) had the highest predictability for OS.

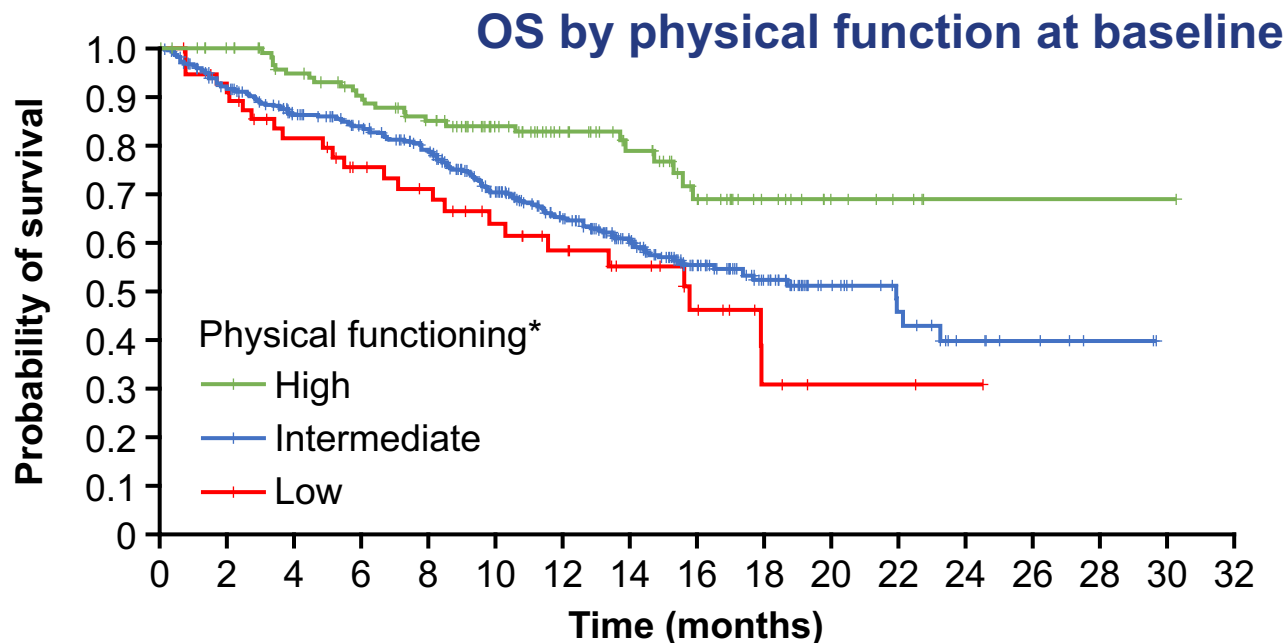
Only PRO scales with  $P < 0.05$  are shown in the table above. †HR is based on 10-point increase in the EORTC QLQ C30/LC13 scales.

ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LC, lung cancer; OS, overall survival; PRO, patient-reported outcome; QoL, quality of life.





## Predictive Utility of Patient-Reported Outcomes for Survival in 1st-Line Treated Patients with Advanced NSCLC in EMPOWER-Lung 1 and 3



Patients with higher baseline physical functioning\* had more favorable OS (high vs low, HR [95% CI]: 0.41 [0.24–0.72];  $P=0.002$ ). This represents a predicted 59% reduction in the risk of death

### Number of subjects at risk:

High	129	122	111	102	92	69	53	39	26	14	7	4	1	1	1	1	0
Intermediate	404	356	316	293	261	210	171	131	92	58	27	17	8	5	2	0	0
Low	57	51	42	35	31	25	20	15	10	4	2	2	1	0	0	0	0

\*Physical functioning baseline scores per EORTC QLQ-C30 Lung Cancer Module – Stage III/IV interquartile categories: Low, <46.7; intermediate, ≥46.7–≤86.7; high, >86.7. EORTC, European Organisation for Research and Treatment of Cancer; OS, overall survival.

