Updates in Immunotherapy for Lung Cancer

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Outline

- Neoadjuvant setting
  - CheckMate 816
- Adjuvant settings
  - IMpower010
  - KEYNOTE-091
- Perioperative settings
  - KEYNOTE-671
  - NEOTORCH
  - AEGEAN
- Advanced/Metastatic settings
  - KEYNOTE-789 (post EGFR TKI)
  - STK11, KEAP1, KRAS and TMB
  - Dual vs single immune checkpoint blockade based

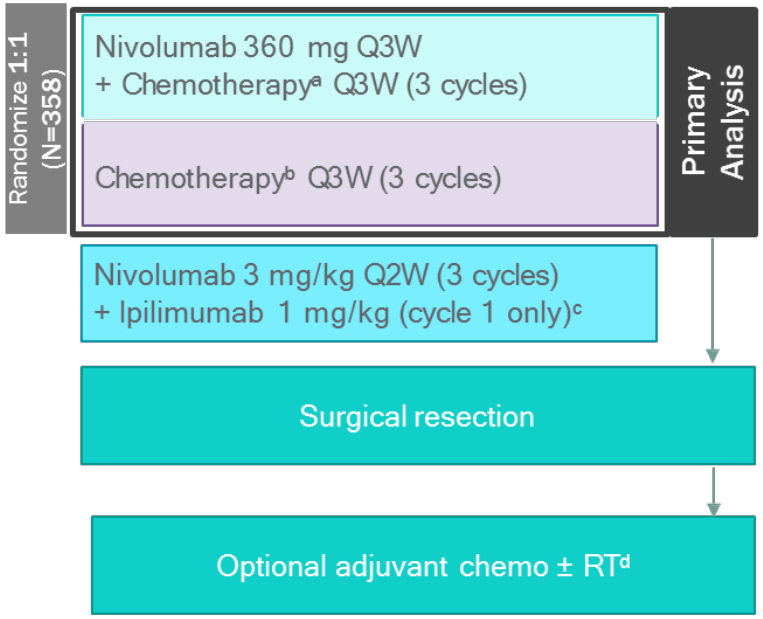
Outline

- Neoadjuvant settings
    - CheckMate 816

Neoadjuvant Nivolumab +CT in Resectable Stage IB-IIIA (CheckMate 816): Study Design and Patients

Key eligibility criteria

- Newly diagnosed, resectable, untreated, unselected, stage IB-IIIA, patients with NSCLC
- No known sensitizing *EGFR* mutations or *ALK* alterations



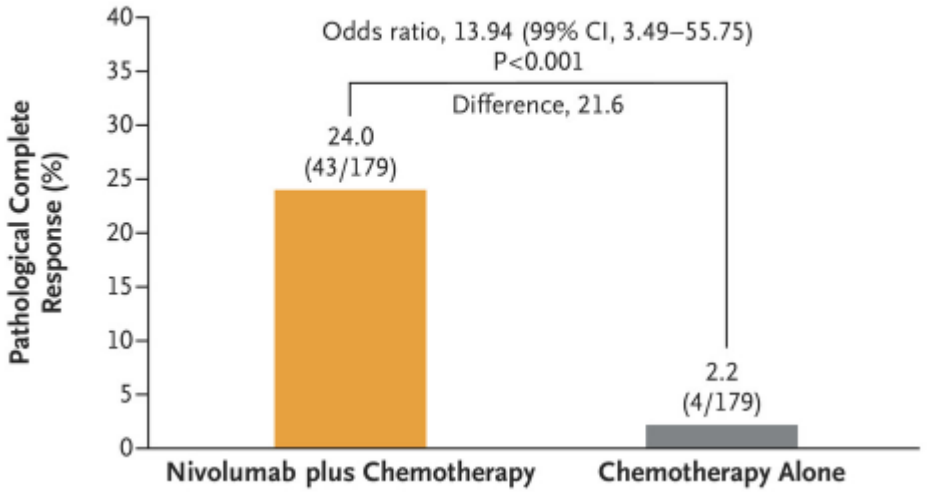
Patient Characteristics, %		Nivo + chemo (n=179)	Chemo (n=179)
Median age (range), years		64 (41-82)	65 (34-84)
Female, %		28	29
Region[e], n (%)	North America	23	28
	Europe	23	14
	Asia	48	51
Clinical stage[f], n (%)	IB-II[g]	36	35
	IIIA	63	64
Histology, %	Squamous	49	53
	Non-squamous	51	47
Smoking status[h], %	Current / former	89	88
	Never	11	11
Tumor PD-L1 expression, %[i]	Not evaluable	7	7
	<1%	44	43
	≥1%	50	50
	1-49%	28	16
	≥50%	21	24
TMB, %[j]	Not evaluable / not reported	51	50
	<12.3 mut/Mb	27	30
	≥12.3 mut/Mb	22	21

Primary endpoints: pCR by BIPR, EFS by BICR
Secondary endpoints: MPR by BIPR, OS, time to death or distant metastases
Exploratory endpoints: ORR by BICR, predictive biomarkers (PD-L1, TMB, ctDNA[k])

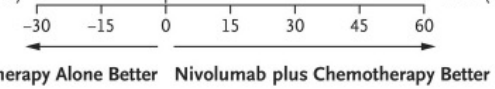
- **Baseline characteristics in the Nivolumab + Ipilimumab (exploratory) arm were generally similar to the NIVO + chemo and chemo arms**

BICR, Blinded Independent Central Review; BIPR, Blinded Independent Pathology Review; EFS, event-free survival, NSCLC, non small cell lung cancer; ORR, overall response rate; pCR, pathological complete response.
[a]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [b]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [c]Randomized exploratory arm (enrollment closed early); [d]Per healthcare professional choice; [e]Rest of the world: 7% of patients in each of the NIVO + chemo and chemo arms; [f]Disease stage by CRF, with TNM 7 th edition used for classification; 1 patient in each of the NIVO + chemo and chemo arms had stage IV disease; [g]Stage IB, IIA, IIB disease: 6%, 17%, and 14% of patients in the NIVO + chemo arm, and 4%, 18%, and 13% in the chemo arm, respectively; [h]Smoking status unknown: 1 patient in chemo arm; [i]Percentages are based on ITT; [j]TMB was not analyzed for patients in China, and these patients are included in the "not reported" category; [k]Performed using tumor guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).
1. NCT02998528. 2. Forde P, et al. American Association for Cancer Research Annual Meeting 2021. Presentation CT003.

CheckMate 816: pCR and subgroup analysis

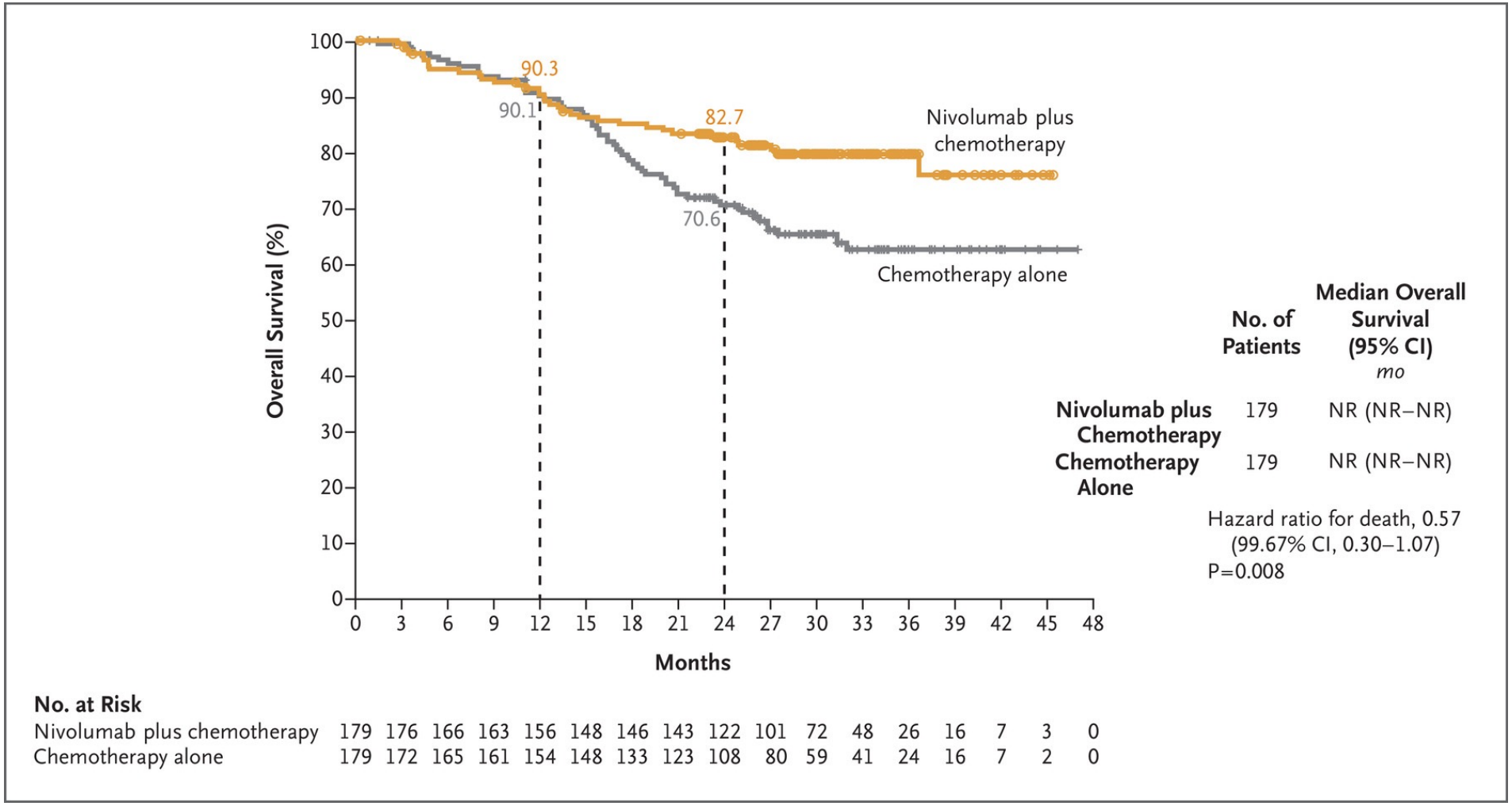


Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (–7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)



Forde, N Engl J Med 2022; 386:1973-1985

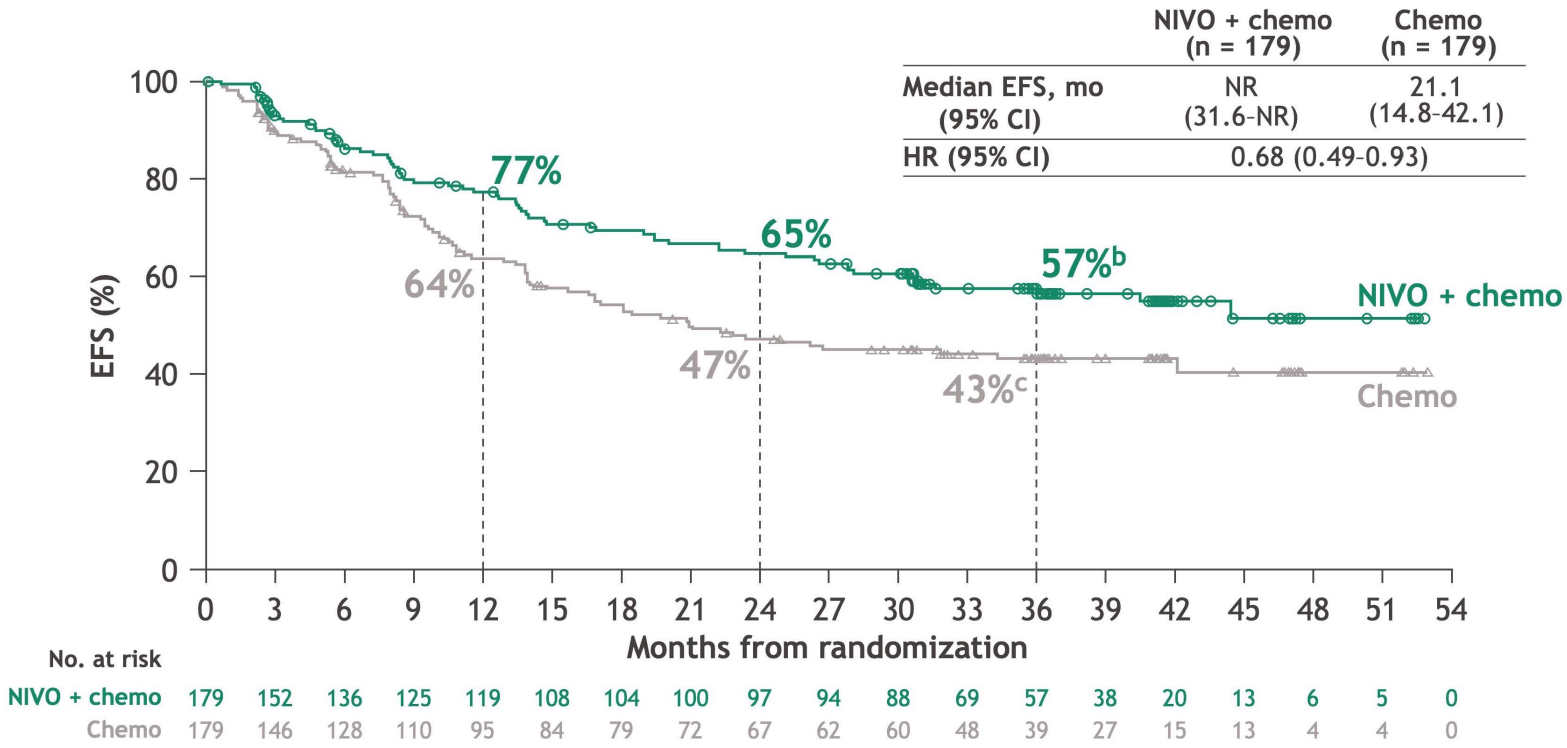
CheckMate-816: OS



Forde, N Engl J Med 2022; 386:1973-1985

CheckMate 816: EFS - 3 year follow up

CheckMate 816: 3-y efficacy/safety update and biomarker analyses



Minimum/median follow-up: 32.9/41.4 months.

[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

[b,c]95% CIs for 3-year EFS rates: [b]48–64; c35–51.

Girard N, European Lung Cancer Congress 2023

CheckMate-816: Key Points

- Three-year update to the randomized phase III CheckMate 816 study showed improved long-term event-free survival in patients with resectable NSCLC.
- Among patients who underwent surgery, fewer in the nivolumab-plus-chemotherapy arm had disease recurrence compared with patients who received chemotherapy alone (28% vs 42%). Fewer distant recurrences were observed with nivolumab plus chemotherapy (10% of patients) vs chemotherapy alone (22%), with a significant reduction in central nervous system recurrences (4% vs 15%).
- Results also demonstrated an improved overall survival trend and tolerable safety profile.
- Exploratory biomarker analysis (four-gene inflammatory signature, CD8A, STAT1, LAG3, and CD274, assessed by transcriptome) suggested potential for identifying patients who may derive the greatest clinical benefit.

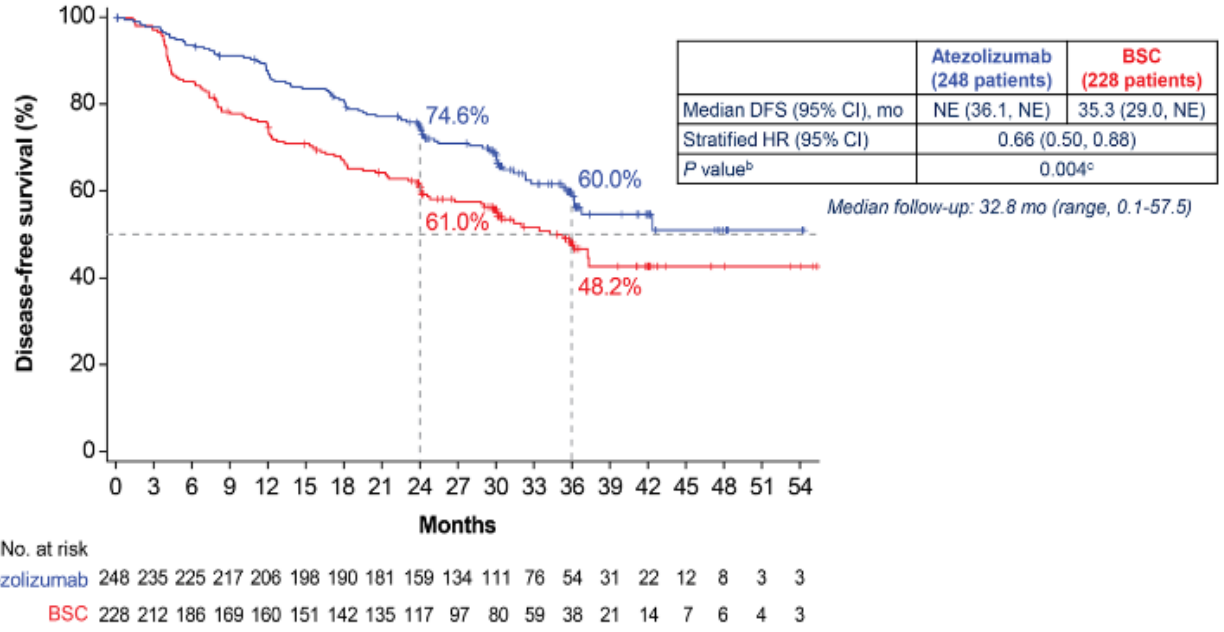
https://ascopost.com/issues/may-10-2023/checkmate-816

Outline

- Adjuvant setting
  - IMpower-010
  - KEYNOTE-091

IMpower-010

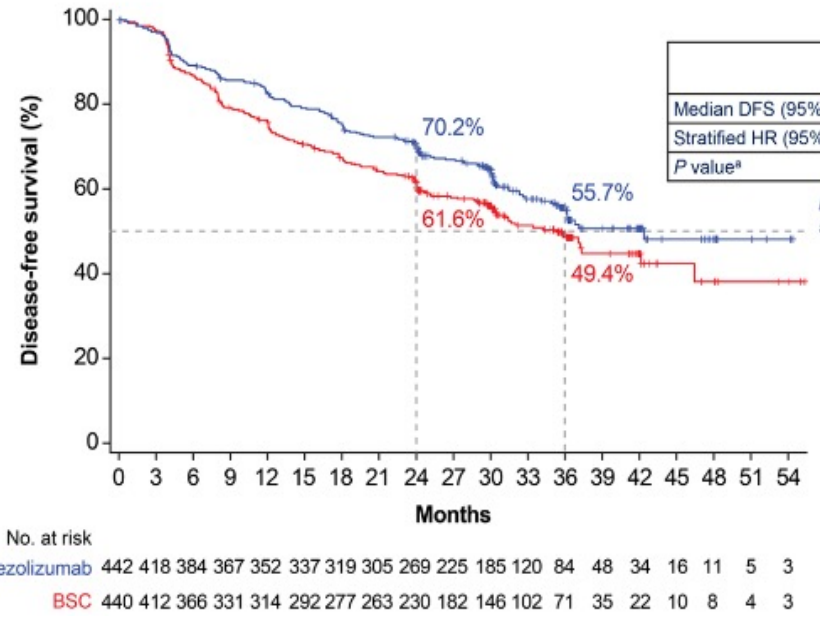
A. Patients With PD-L1 TC ≥ 1% Stage II-IIIA NSCLC



	Atezolizumab (248 patients)	BSC (228 patients)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

B. All Randomly Assigned Patients With Stage II-IIIA NSCLC



	Atezolizumab (442 patients)	BSC (440 patients)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

J Clin Oncol 39, 2021 (suppl 15; abstr 8500)

IMpower-010 – Role of KRAS mutation

	Atezolizumab median DFS, mo	BSC median DFS, mo	DFS HR (vs BSC) 95% CI
Stage II-IIIA WES-BEP	NR n=270	31.4 n=266	0.70 0.54, 0.91
KRAS WT stage II-IIIA WES-BEP	42.3 n=208	31.4 n=210	0.74 0.55, 1.00
mKRAS stage II-IIIA WES-BEP	NR n=62	25.2 n=56	0.56 0.32, 0.99
mKRAS SP263-evaluable stage II-IIIA WES-BEP	NR n=61	25.2 n=56	0.57 0.32, 1.02
mKRAS SP263-evaluable PD-L1 TC ≥1% stage II-IIIA WES-BEP	NR n=39	21.7 n=32	0.52 0.25, 1.08
mKRAS SP263-evaluablePD-L1 TC <1% stage II-IIIA WES-BEP	NR n=22	31.6 n=24	0.67 0.26, 1.73

NR, not reached; WT, wild type.

https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.8522

PEARLS/KEYNOTE-091: Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)

Placebo Q3W for ≤18 administrations (~1 yr)

Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

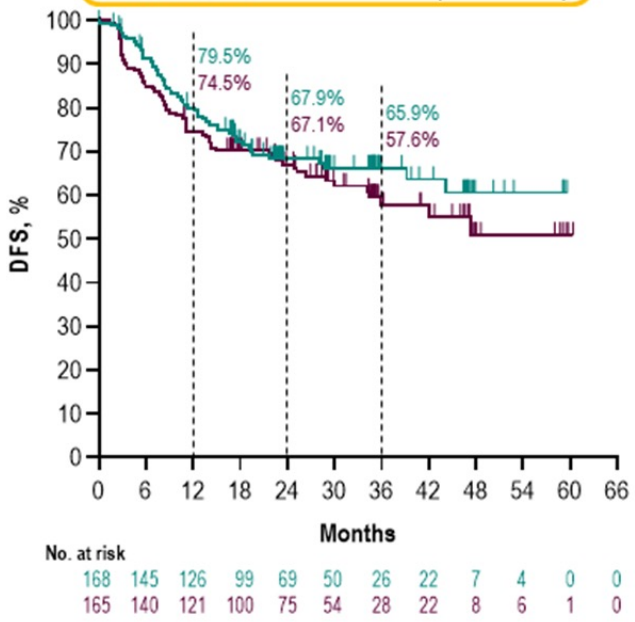
Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ClinicalTrials.gov identifier, NCT02504372.

DFS: Pembrolizumab vs Placebo by PD-L1 TPS

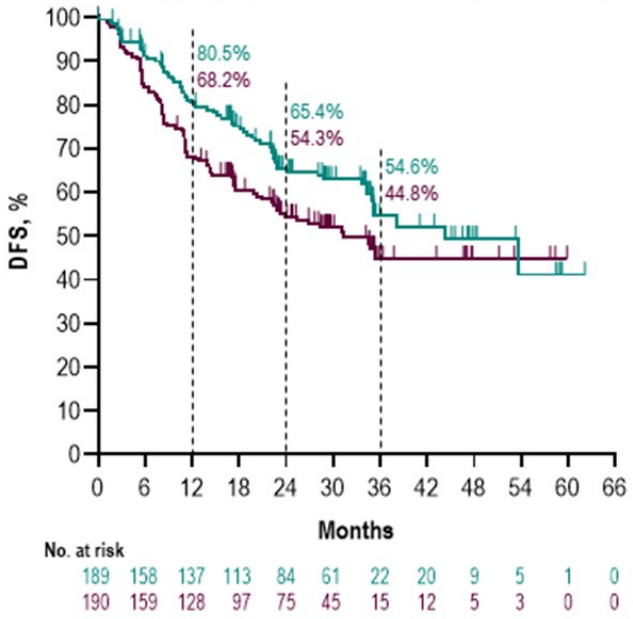
TPS ≥50%
HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

Median (95% CI), mo
Pembrolizumab: NR (44.3-NR)
Placebo: NR (35.8-NR)



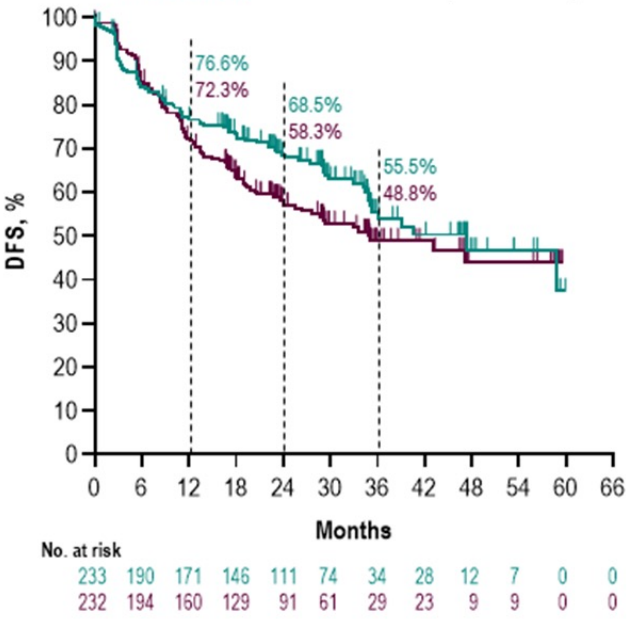
TPS 1-49%
HR 0.67 (95% CI, 0.48-0.92)

Median (95% CI), mo
Pembrolizumab: 44.2 (34.9-NR)
Placebo: 31.3 (22.5-NR)



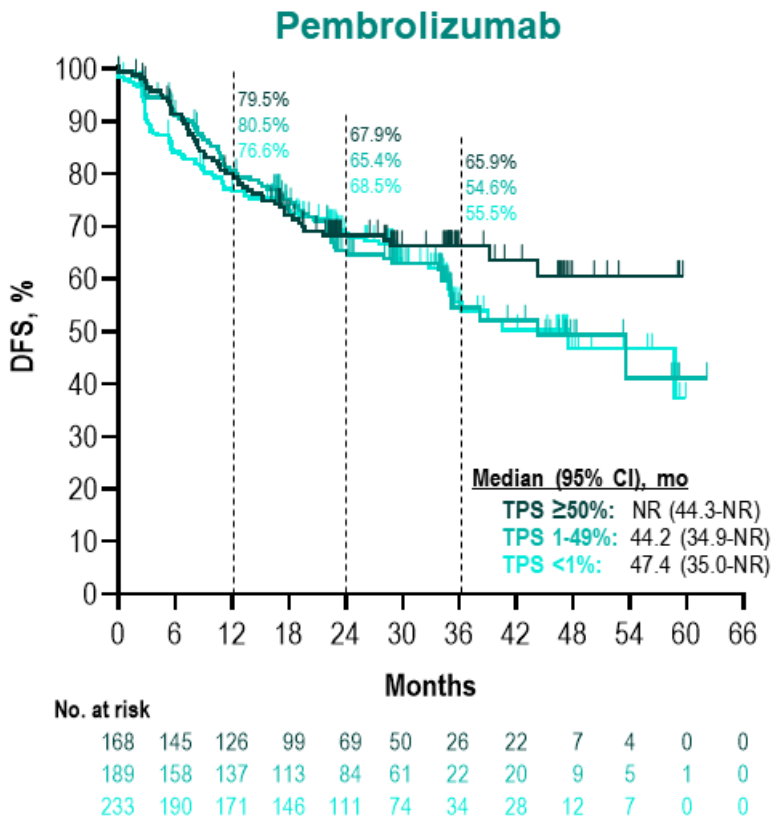
TPS <1%
HR 0.78 (95% CI, 0.58-1.03)

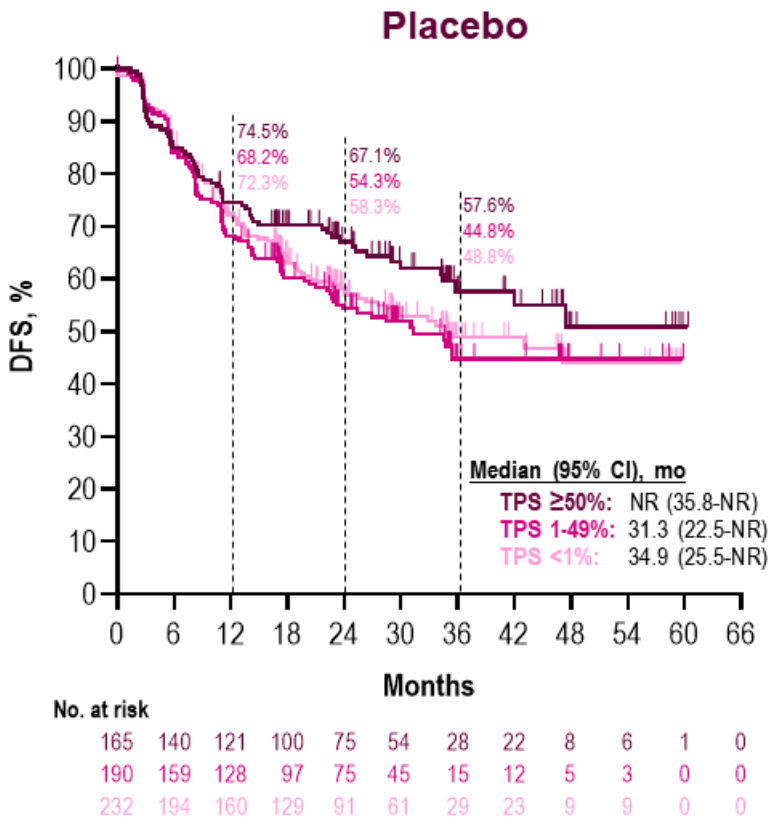
Median (95% CI), mo
Pembrolizumab: 47.4 (35.0-NR)
Placebo: 34.9 (25.5-NR)



Data cutoff date: September 20, 2021

DFS: Pembrolizumab and Placebo by PD-L1 TPS





Data cutoff date: September 20, 2021

Perioperative NSCLC Immune Checkpoints:

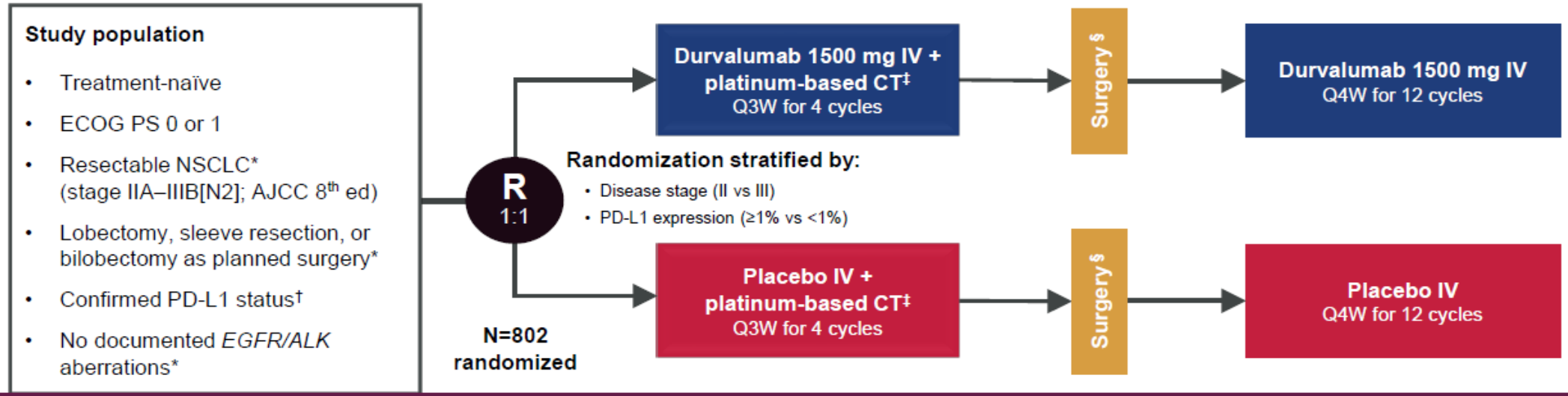
- Both studies are positive and agents approved by FDA; however, efficacy is rather modest and no OS data yet
- Surprising discrepancy of the PDL1 role as a predictive marker
- Similar expected rates of irAEs
- Will be more controversy now with neoadjuvant and perioperative data
- Controversy about use in EGFR mutated tumors (especially after ADAURA resulted)

https://ascopost.com/issues/may-10-2023/checkmate-816

Outline

- Perioperative setting
  - AEGEAN
  - KEYNOTE-671
  - NEOTORCH

AEGEAN: A Phase 3 Trial of Neoadjuvant Durvalumab + Chemotherapy



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

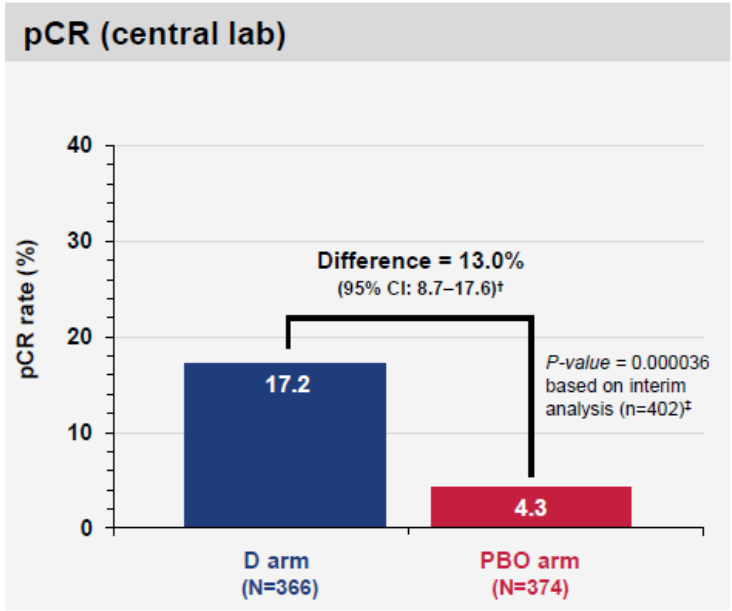
Key secondary:

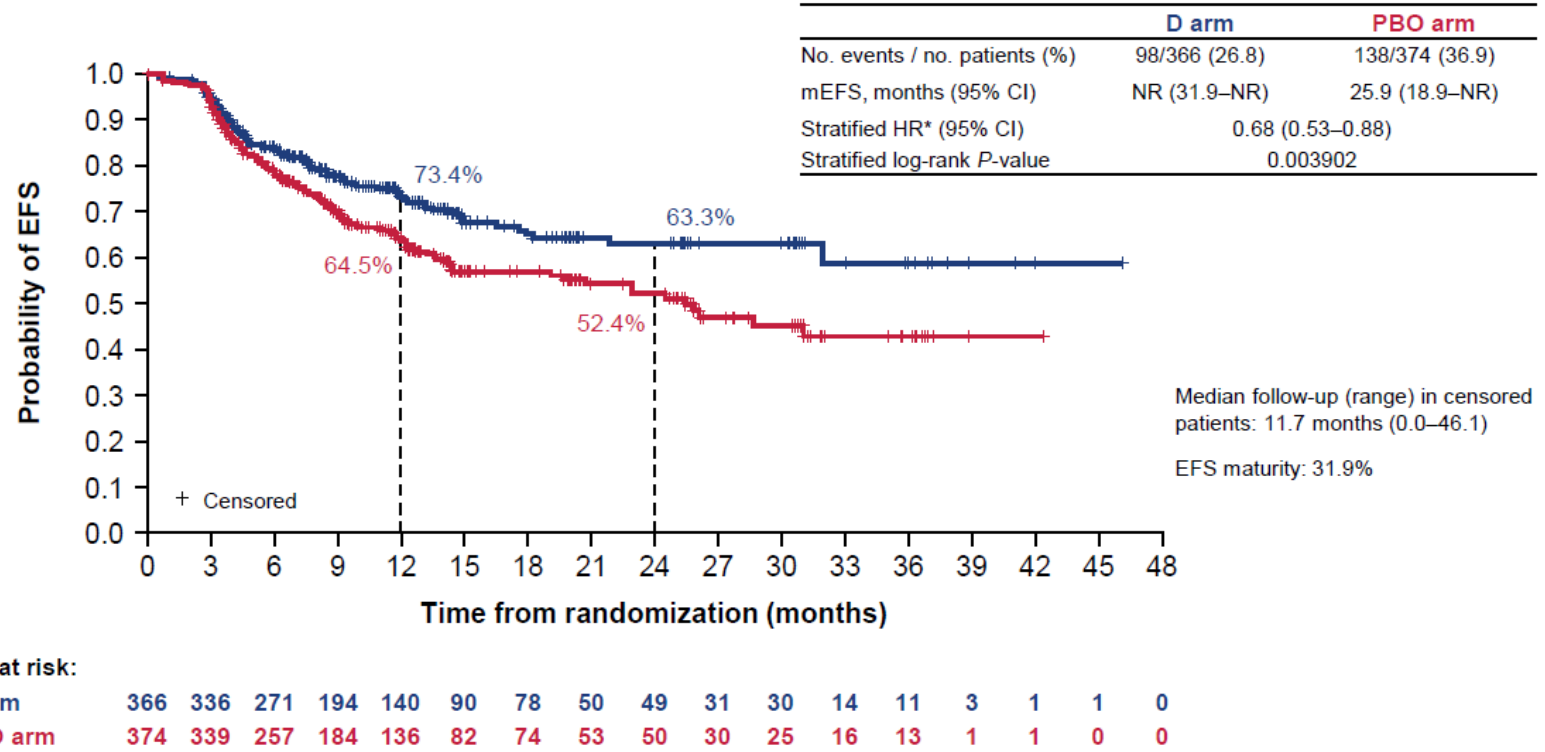
- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations.

Heymach AACR 2023

AEGEAN: pCR and EFS using RECIST v1.1 (BICR) (mITT)





	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	

Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

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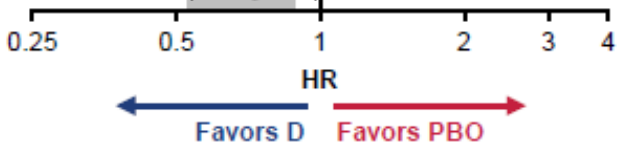
AEGEAN: EFS subgroup analysis

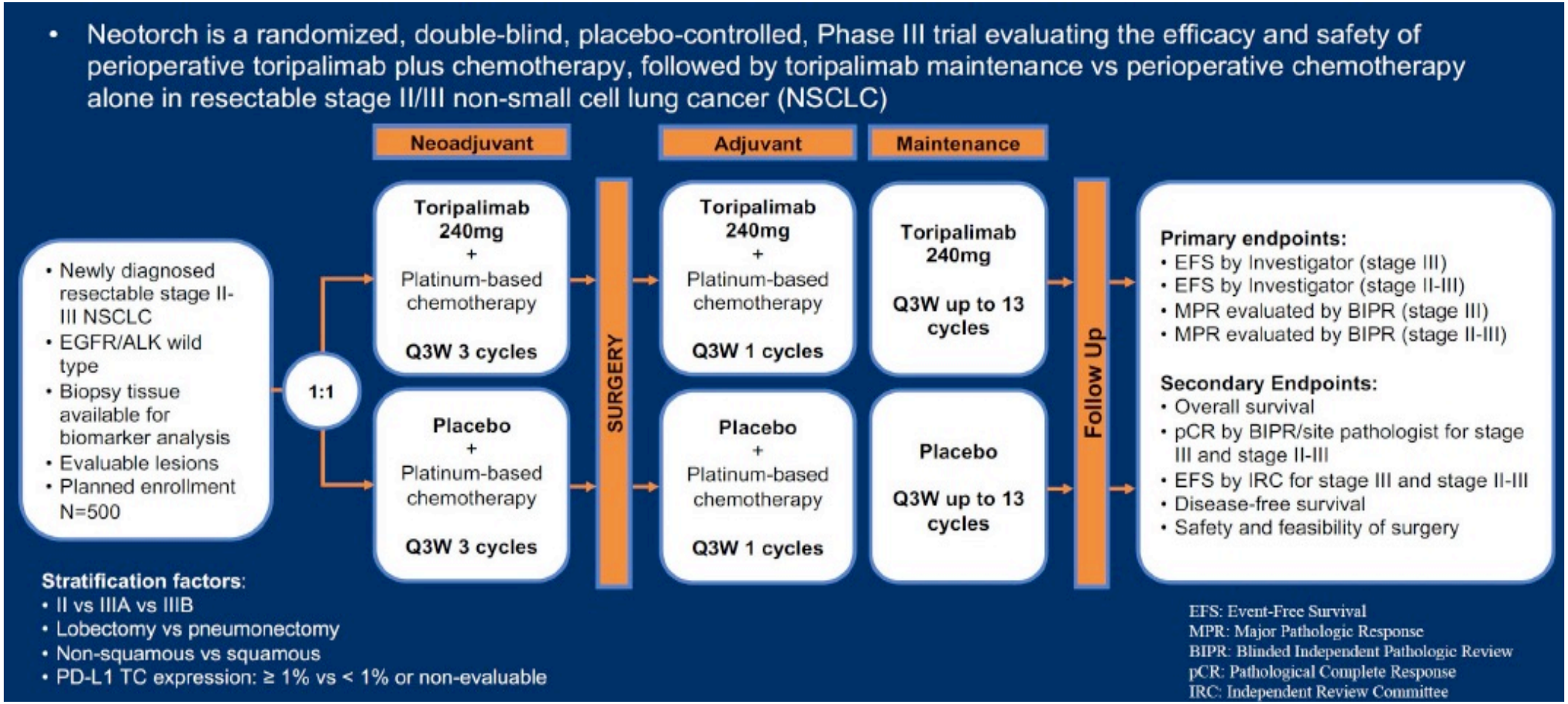
Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)



DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

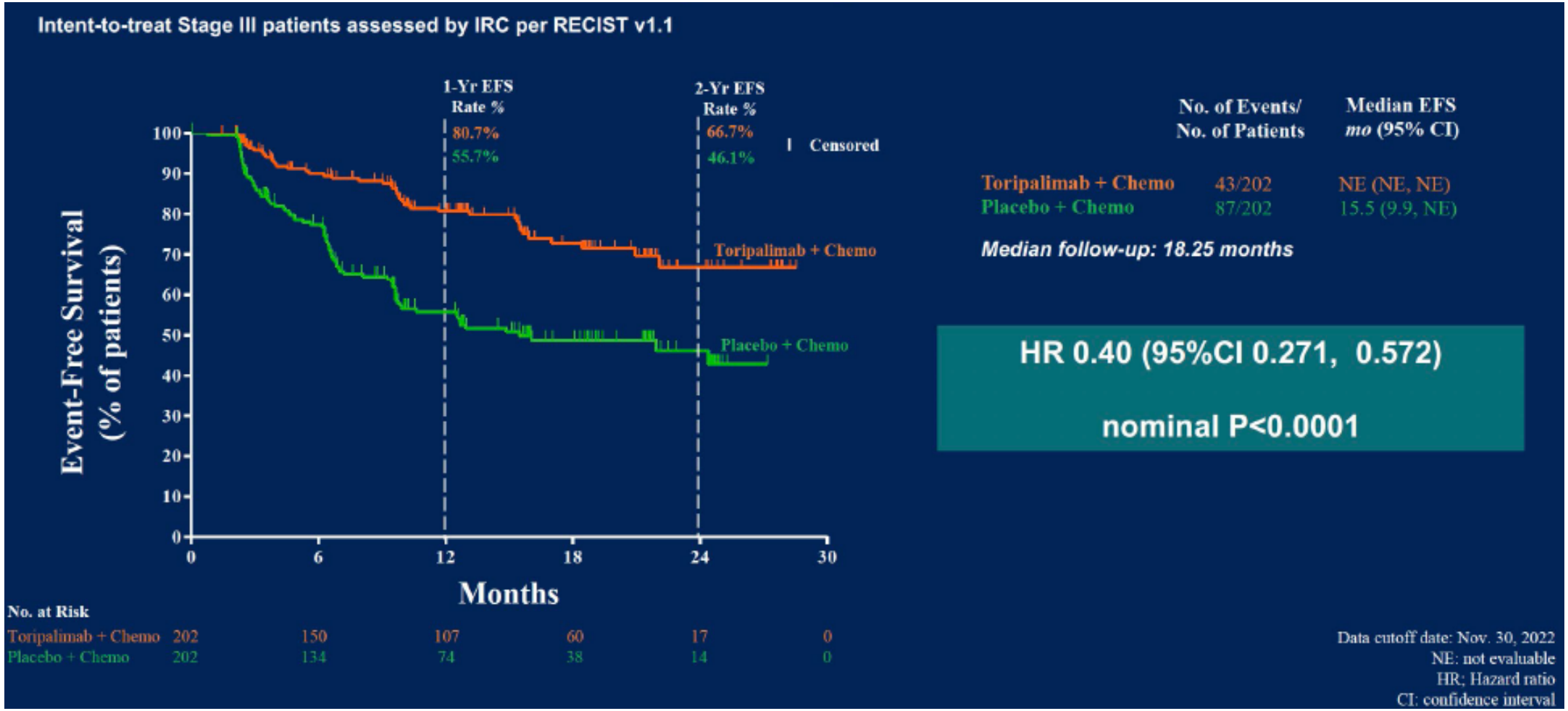
Heymach AACR 2023

NEOTORCH: Perioperative Toripalimab + Chemo vs Chemo in Resectable Stage II/III NSCLC



Lu, S, ASCO 2023

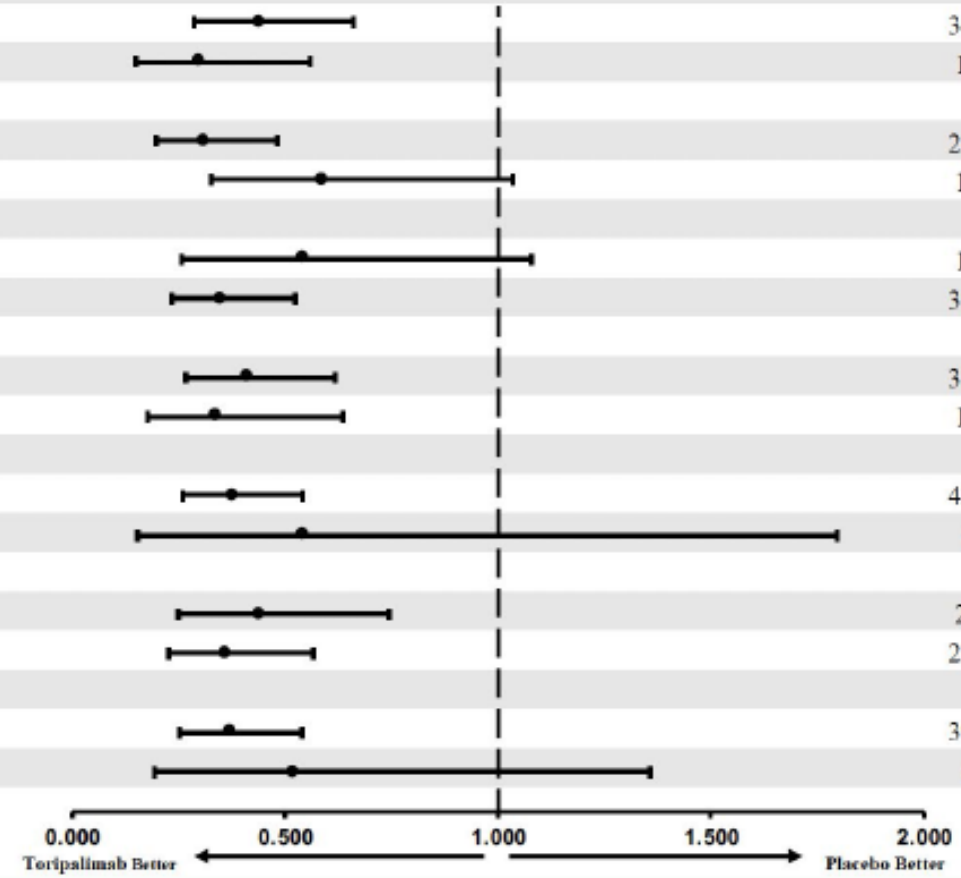
NEOTORCH: EFS



Lu, S, ASCO 2023

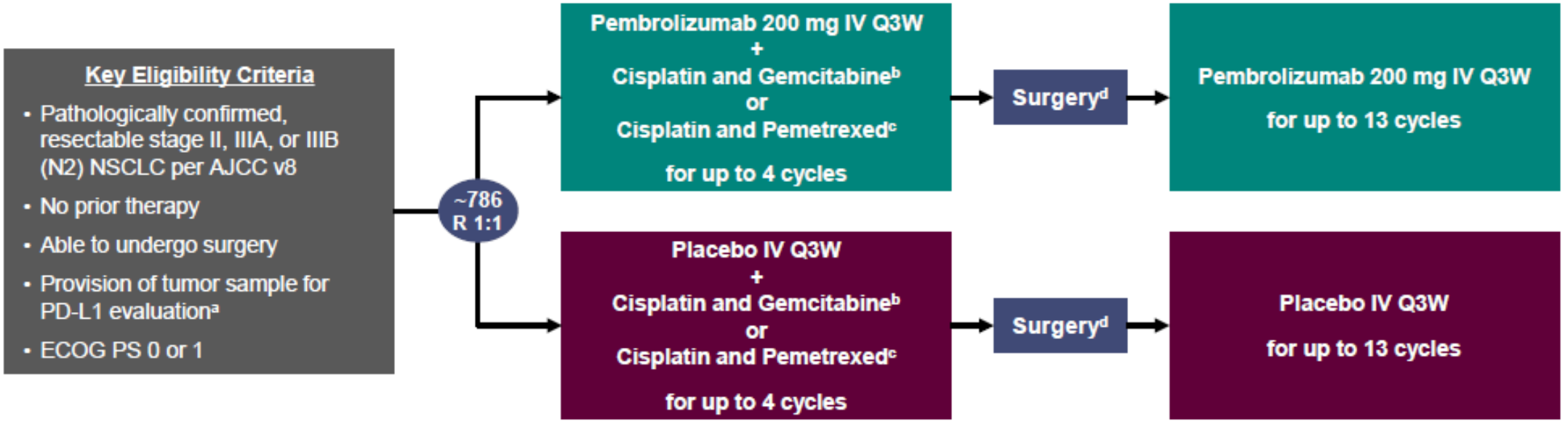
NEOTORCH: Subgroup Analysis

Subgroups	Toripalimab + Chemo Events/Total	Placebo + Chemo Events/Total	Hazard Ratio (95% CI)
Disease Stage			
IIIA	34/136	65/136	0.44 (0.287, 0.661)
IIIB	13/65	31/64	0.30 (0.149, 0.559)
PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)
Pathological Type			
Non-squamous Cell Carcinoma	12/45	21/45	0.54 (0.257, 1.079)
Squamous Cell Carcinoma	35/157	76/157	0.35 (0.234, 0.523)
Age			
<65	33/140	66/138	0.41 (0.267, 0.618)
>=65	14/62	31/64	0.34 (0.177, 0.635)
Sex			
Male	42/181	91/189	0.38 (0.259, 0.541)
Female	5/21	6/13	0.54 (0.154, 1.796)
ECOG			
0	20/70	38/73	0.44 (0.249, 0.743)
1	27/132	59/129	0.36 (0.226, 0.566)
Smoking			
Yes (Including Smoker or Former)	39/174	88/181	0.37 (0.252, 0.539)
No	8/28	9/21	0.52 (0.193, 1.358)



Lu, S, ASCO 2023

KEYNOTE-671 Randomized, Double-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

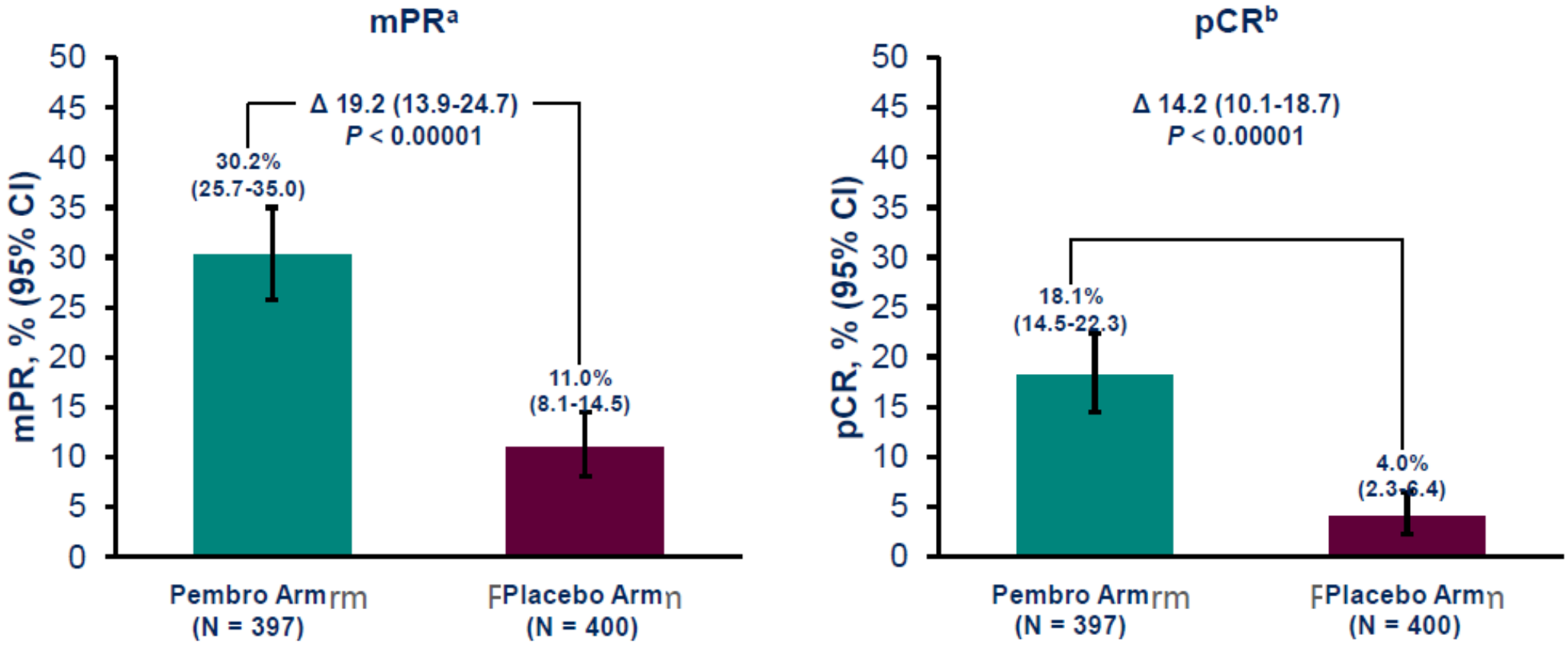
Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

Wakelee ASCO 2023

KEYNOTE-671: mPR and pCR



[a] Per IASLC criteria, defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. [b] Per IASLC criteria, defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). Data cutoff date for IA1: July 29, 2022.

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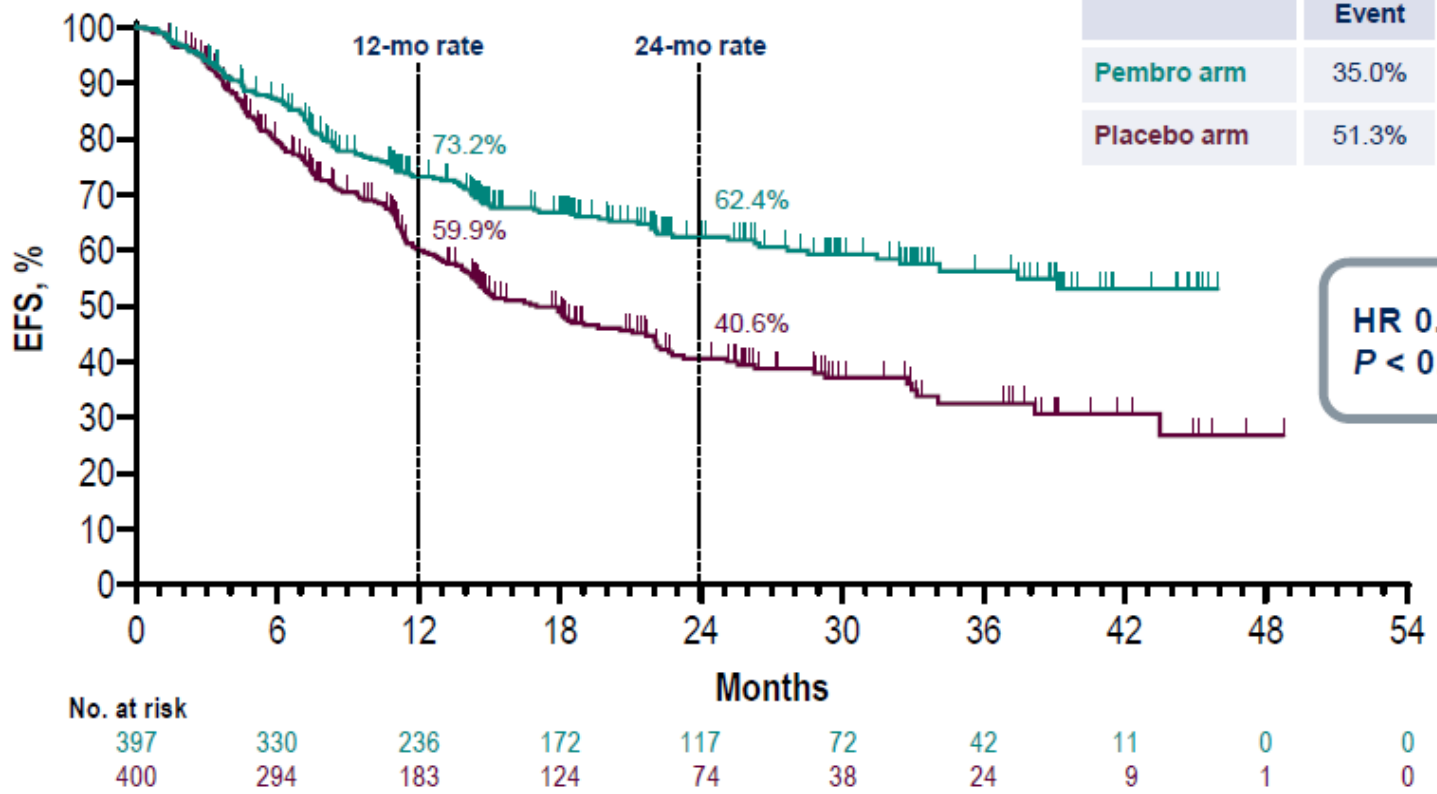
KEYNOTE-671: EFS



	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

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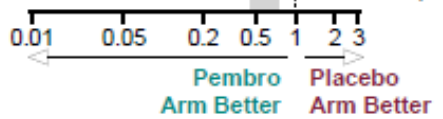
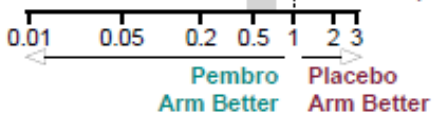
KEYNOTE-671: Subgroup Analysis

Subgroup	Events/participants: Pembro Arm	Events/participants: Placebo Arm	Hazard ratio (95% CI)
Overall	139/397	205/400	0.58 (0.46-0.72)
Age			
<65 y	74/221	113/214	0.53 (0.39-0.71)
≥65 y	65/176	92/186	0.64 (0.46-0.88)
Sex			
Female	31/118	55/116	0.44 (0.28-0.68)
Male	108/279	150/284	0.63 (0.49-0.80)
Race			
White	85/250	123/239	0.54 (0.41-0.72)
All others	46/134	70/145	0.62 (0.42-0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45-0.99)
Not east Asia	96/274	148/279	0.54 (0.41-0.69)
Smoking status			
Current	37/96	57/103	0.52 (0.34-0.78)
Former	84/247	128/250	0.57 (0.43-0.75)
Never	18/54	20/47	0.68 (0.36-1.30)
Histology			
Nonsquamous	73/226	107/227	0.58 (0.43-0.78)
Squamous	66/171	98/173	0.57 (0.41-0.77)

Subgroup	Events/participants: Pembro Arm	Events/participants: Placebo Arm	Hazard ratio (95% CI)
Overall	139/397	205/400	0.58 (0.46-0.72)
Pathologic stage			
II	34/118	48/121	0.65 (0.42-1.01)
IIIA	80/217	124/225	0.54 (0.41-0.72)
IIIB	25/62	33/54	0.52 (0.31-0.88)
pN status			
pN0	51/148	70/142	0.57 (0.40-0.82)
pN1	25/81	33/71	0.60 (0.36-1.01)
pN2	63/168	102/187	0.57 (0.42-0.78)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55-1.07)
1-49%	44/127	62/115	0.51 (0.34-0.75)
≥50%	32/132	63/134	0.42 (0.28-0.65)
***EGFR* mutation**			
No	31/111	64/127	0.48 (0.31-0.74)
Yes	1/14	10/19	0.09 (0.01-0.74)
Unknown	107/272	131/254	0.64 (0.49-0.83)
***ALK* translocation**			
No	29/104	76/133	0.41 (0.26-0.62)
Unknown	106/281	128/258	0.63 (0.49-0.82)





Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA1: July 29, 2022.

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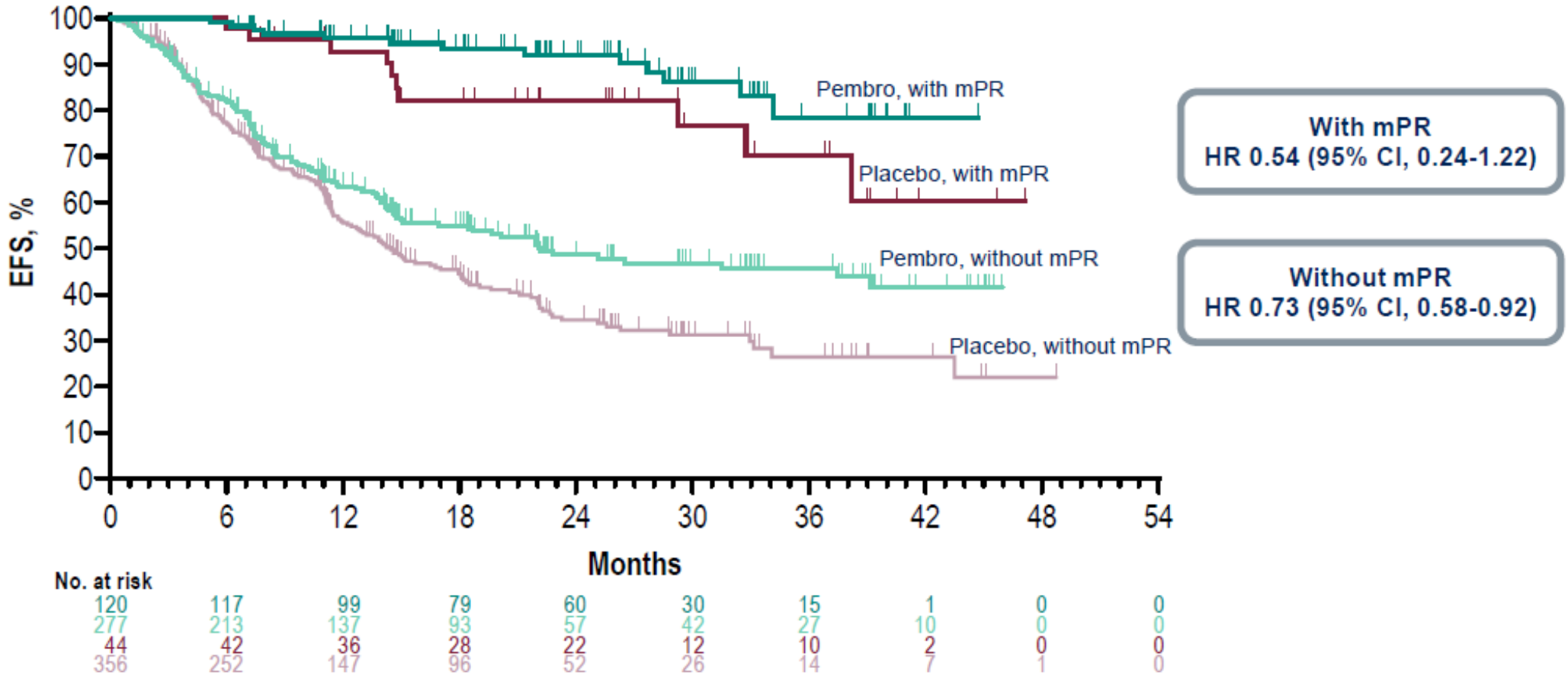
KEYNOTE-671: Exploratory EFS Analysis by mPR



mPR defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022.

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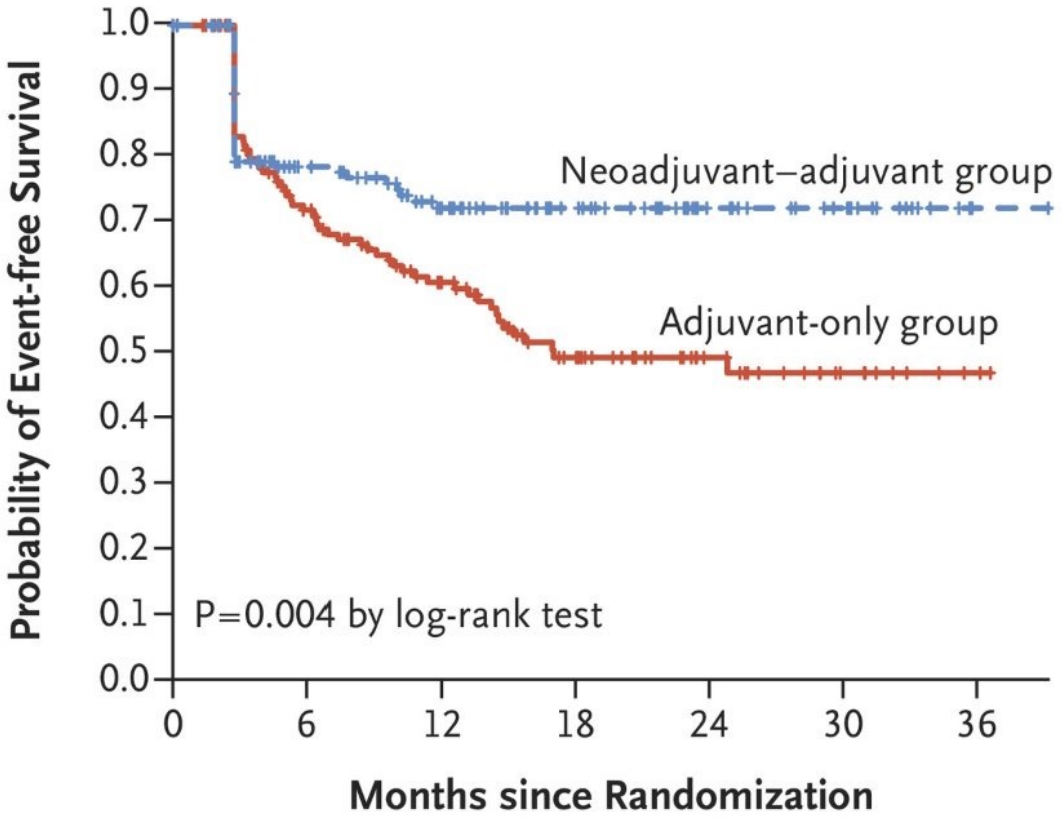
Perioperative NSCLC Immune Checkpoints:

- Impressive and similar EFS and pCR rate in all three trials. Similar study design.
- No obvious tumor or demographic characteristics to serve as predictor factors, except PDL-1
- Similar rates of irAEs in all three studies
- Awaiting approval. Will be more controversy when to use neoadjuvant, adjuvant and perioperative regimens
- Controversy about use in EGFR and ALK mutated tumors (KN-671 included these)
- Ongoing work to define more precise molecular predictors. Has to be easy, fast and adaptable in all healthcare settings

https://ascopost.com/issues/may-10-2023/checkmate-816

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma



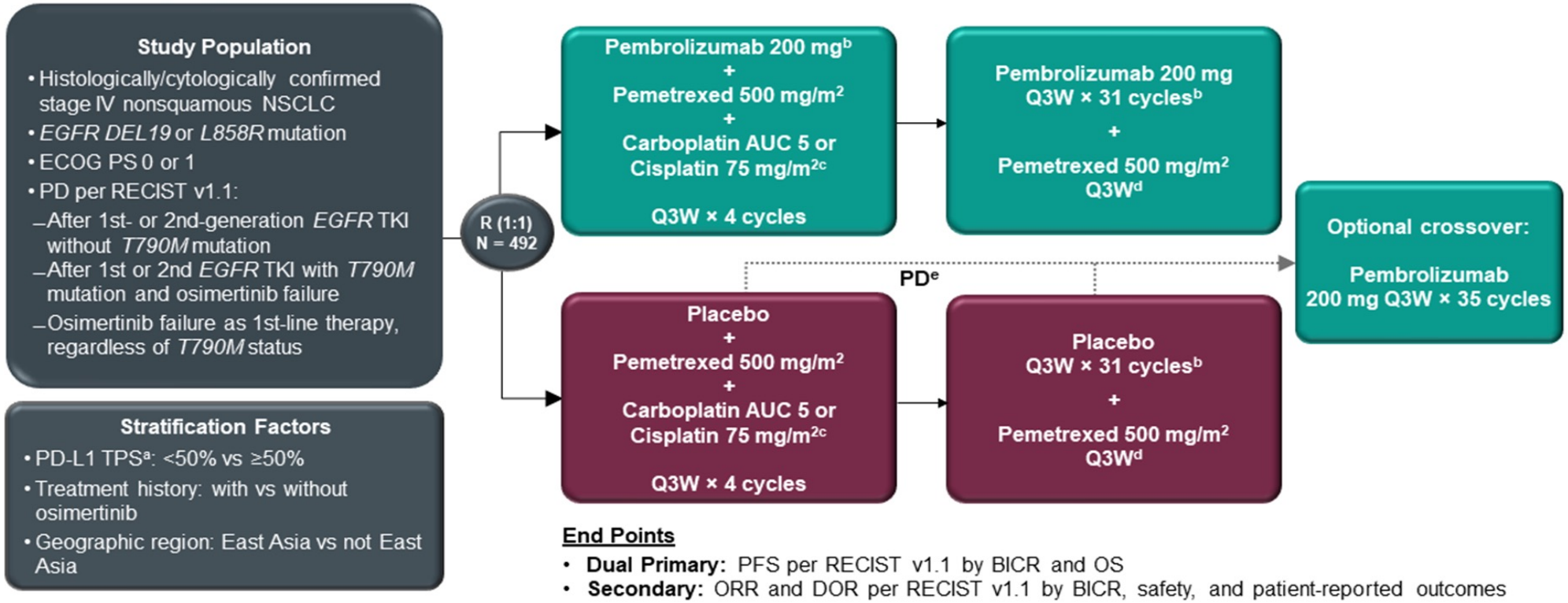
No. at Risk							
Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

Patel, Ribas, N Engl J Med 2023 Mar 2;388(9):813-823

Outline

- Advanced/Metastatic settings
  - KEYNOTE-789 (post EGFR TKI)
  - STK11, KEAP1, KRAS and TMB
  - Dual vs single immune checkpoint blockade based

KEYNOTE-789: Phase 3 Randomized Study (NCT03515837)



End Points

- **Dual Primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

[a]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). [b]If a patient has documented PD but is benefiting clinically, they may receive pembrolizumab monotherapy to complete a total of 35 pembrolizumab administrations. [c]Carboplatin or cisplatin therapy is at the investigator's choice. [d]Maintenance pemetrexed may continue past 35 cycles until reaching a discontinuation criterion if the patient is receiving benefit; however, pembrolizumab or saline placebo are limited to 35 cycles. [e]Patients could crossover at any time during the treatment. To be eligible for crossover, PD must have been verified by BICR.

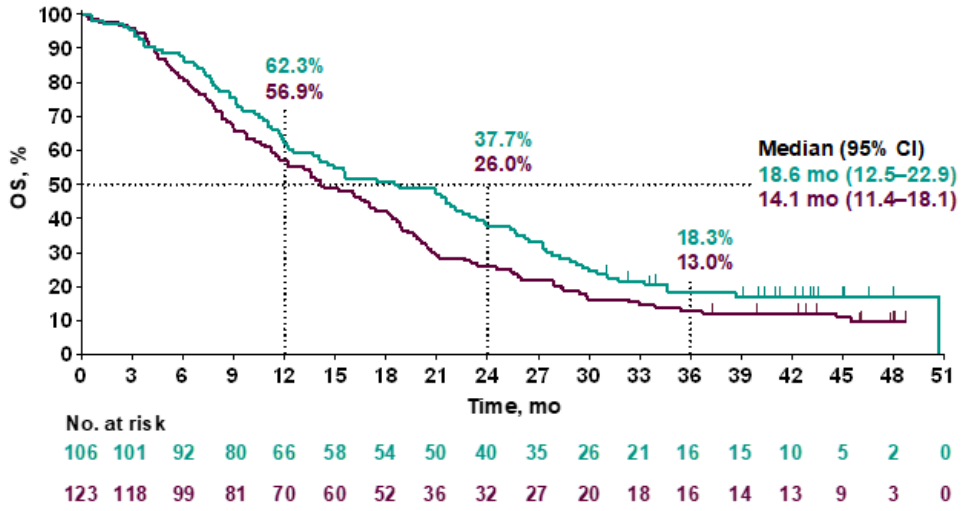
KEYNOTE-789: OS

J C-H Yang. ASCO 2023

Overall Survival in PD-L1 TPS ≥1% and <1% at FA

PD-L1 TPS ≥1%

	Events, n (%)	HR (95% CI)
Pembrolizumab + chemo	88 (83.0)	0.77 (0.58–1.02)
Placebo + chemo	110 (89.4)	

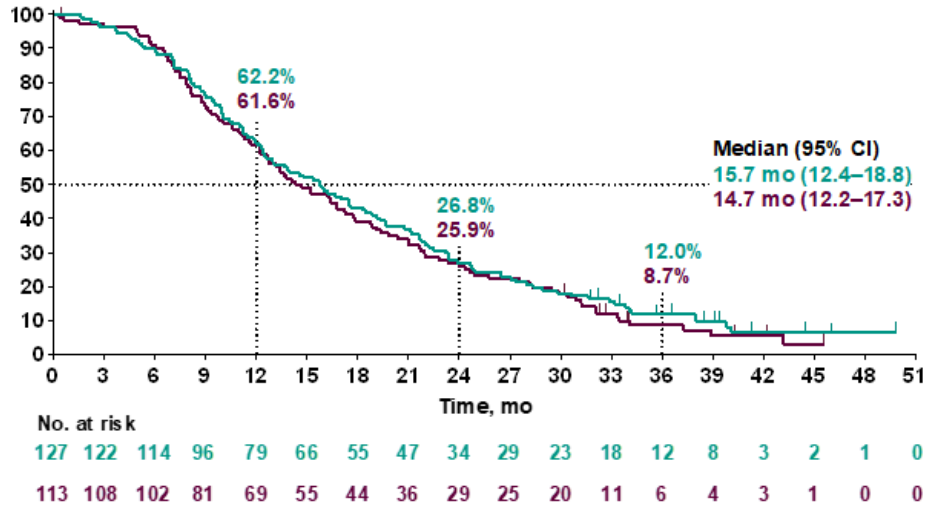


No. at risk

106	101	92	80	66	58	54	50	40	35	26	21	16	15	10	5	2	0
123	118	99	81	70	60	52	36	32	27	20	18	16	14	13	9	3	0

PD-L1 TPS <1%

	Events, n (%)	HR (95% CI)
Pembrolizumab + chemo	115 (90.6)	0.91 (0.70–1.19)
Placebo + chemo	104 (92.0)	



No. at risk

127	122	114	96	79	66	55	47	34	29	23	18	12	8	3	2	1	0
113	108	102	81	69	55	44	36	29	25	20	11	6	4	3	1	0	0

Data cutoff date: January 17, 2023.

STK11: Dual vs Single ICI

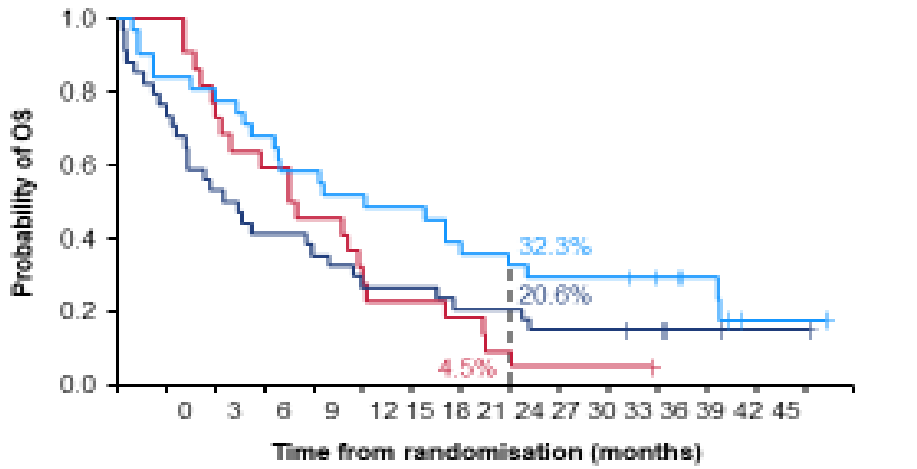
OS by *STK11* Mutation Status

Dr. Solange Peters, WCLC, 2022

OS benefit observed for T+D+CT vs CT in STK11m with HR 0.56 and estimated 32.3% alive at 2 yrs vs 4.5%

*STK11*m

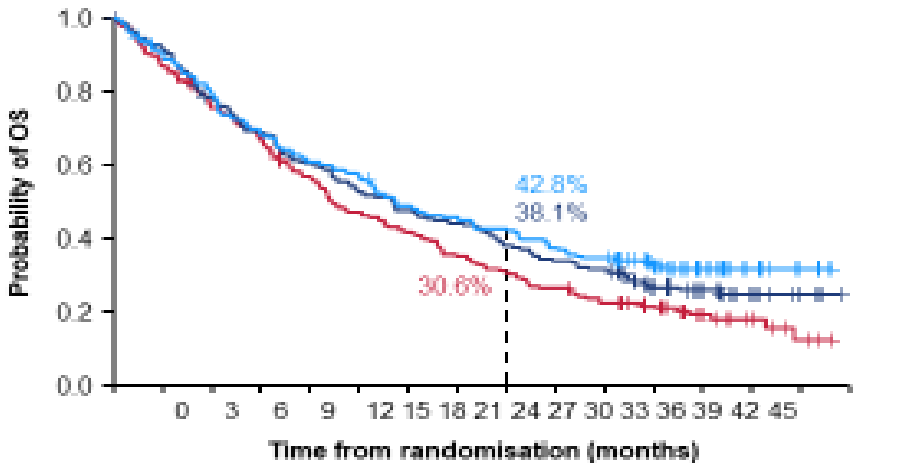
	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–



No. at risk																
T+D+CT	31	26	24	21	18	15	15	11	10	9	9	7	5	1	1	0
D+CT	34	26	18	14	12	9	9	7	7	5	5	4	2	1	0	0
CT	22	22	16	13	10	6	5	4	1	1	1	0	0	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events, n/N	118/177	123/169	141/179
mOS, mo (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.73** (0.57–0.93)	**0.81** (0.64–1.04)	–



No. at risk																
T+D+CT	177	159	140	120	107	100	86	79	74	65	60	40	25	11	5	0
D+CT	169	155	130	114	100	87	79	73	63	56	52	33	23	10	4	0
CT	179	154	131	116	97	80	71	60	52	45	37	29	15	8	4	0

DCO, data cut-off; mo, months; mOS, median OS

Dr. Solange Peters, WCLC, 2022

KEAP1: Dual vs Single ICI

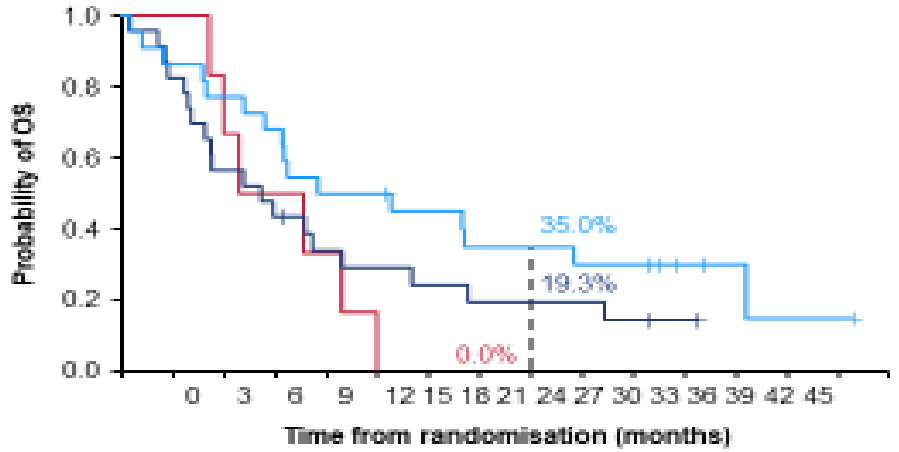
OS by *KEAP1* Mutation Status

Dr. Solange Peters, WCLC, 2022

OS benefit observed for T+D+CT vs CT in KEAP1m with HR 0.43 (small sample size)

*KEAP1*m

	T+D+CT	D+CT	CT
Events, n/N	16/22	19/23	6/6
mOS, mo (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–

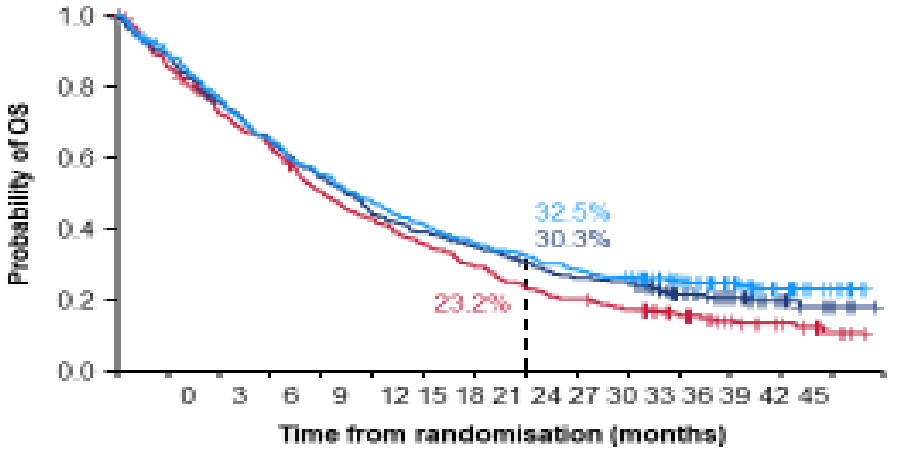


No. at risk

T+D+CT	22	19	17	15	11	11	9	7	7	6	6	3	2	1	1	0
D+CT	23	19	13	10	7	6	5	4	4	4	3	1	0	0	0	0
CT	6	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events, n/N	226/303	241/307	262/312
mOS, mo (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.79** (0.66–0.94)	**0.85** (0.71–1.01)	–



No. at risk

T+D+CT	303	268	230	194	165	142	123	108	97	85	78	57	38	19	8	0
D+CT	307	272	230	198	165	134	119	106	91	79	76	49	33	15	5	0
CT	312	264	221	192	153	129	108	88	70	61	51	38	21	13	6	0

HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

IASLC | Speaker: Hossein Borghaei, MS, DO, Fox Chase Cancer Center, USA | @TLCconference #TexasLung23

KRAS: Dual vs Single ICI

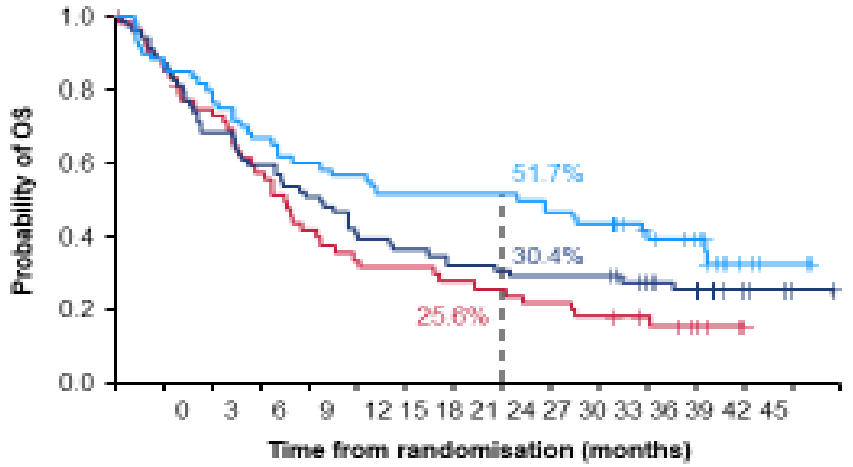
OS by *KRAS* Mutation Status

Dr. Solange Peters, WCLC, 2022

OS benefit observed for T+D+CT vs CT in KRASm with HR 0.56 and estimated 51.7% alive at 2 yrs vs 25.6%

*KRAS*m

	T+D+CT	D+CT	CT
Events, n/N	38/60	51/69	43/53
mOS, mo (95% CI)	**25.7** (9.9–36.5)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.56** (0.36–0.88)	**0.80** (0.53–1.21)	–

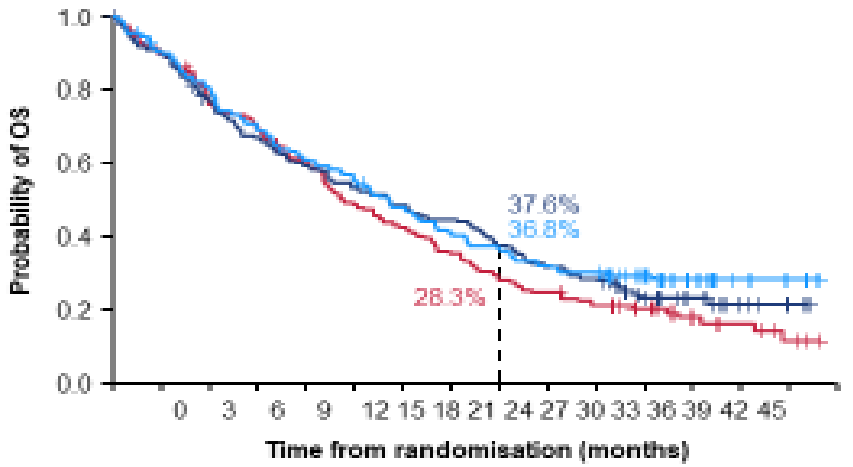


No. at risk

T+D+CT	60	53	46	40	36	34	31	31	31	28	26	17	14	4	2	0
D+CT	69	61	47	41	35	27	25	22	21	20	20	14	9	4	1	0
CT	53	44	37	29	21	17	16	14	13	11	9	7	3	0	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events, n/N	104/148	101/134	119/148
mOS, mo (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.80** (0.62–1.04)	**0.86** (0.66–1.12)	–

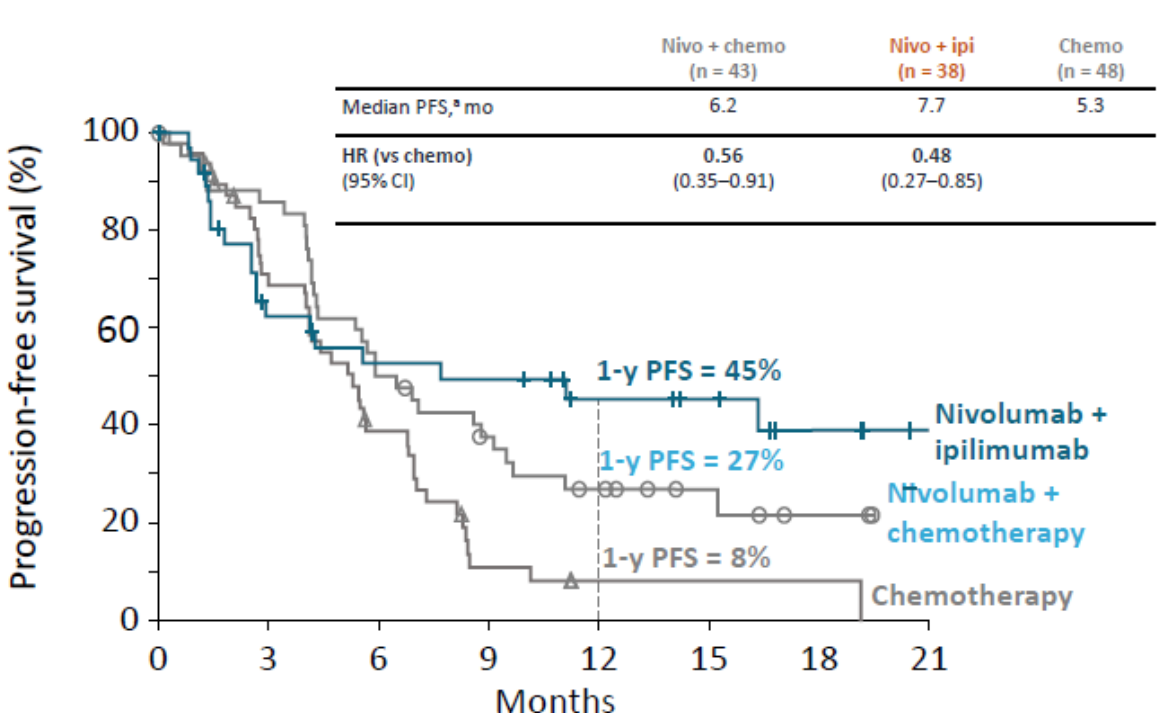


No. at risk

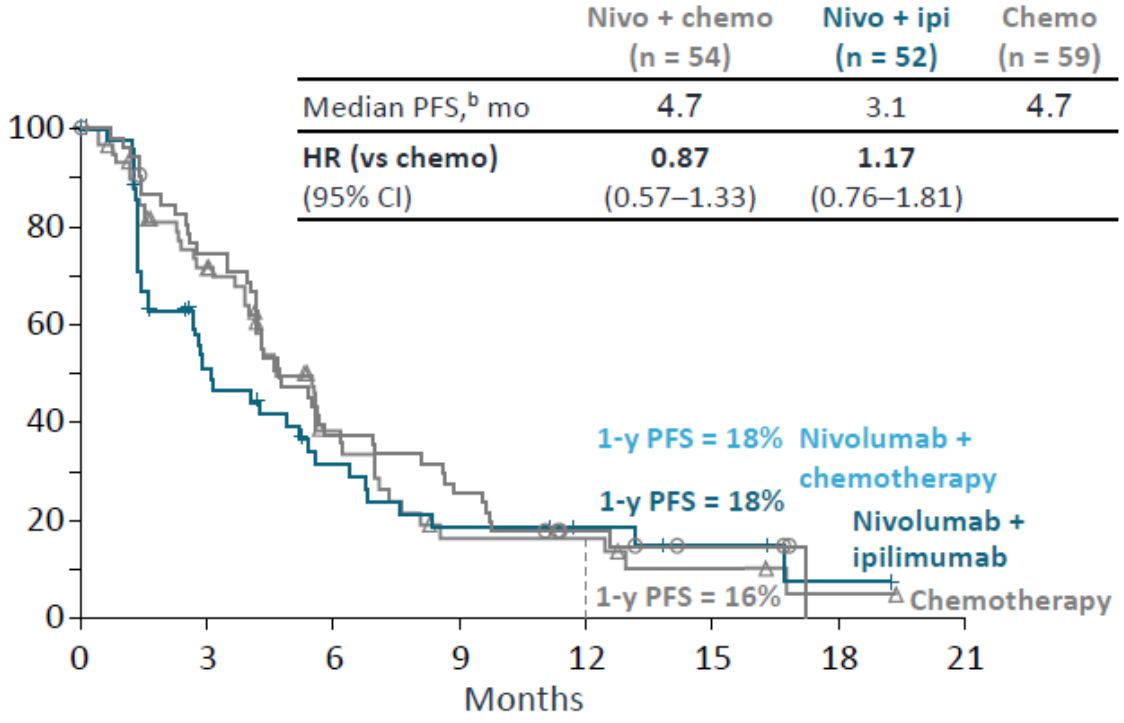
T+D+CT	148	132	118	101	89	81	69	59	53	46	43	30	16	8	4	0
D+CT	134	120	101	87	77	69	63	58	49	41	37	23	16	7	3	0
CT	148	132	110	100	86	69	60	50	40	35	29	22	12	8	4	0

IASLC | Speaker: [redacted] | @TLCconference #TexasLung23

CheckMate227: Nivolumab +/- Ipilimumab. TMB.



TMB ≥10 mut/Mb and <1% tumor PD-L1 expression



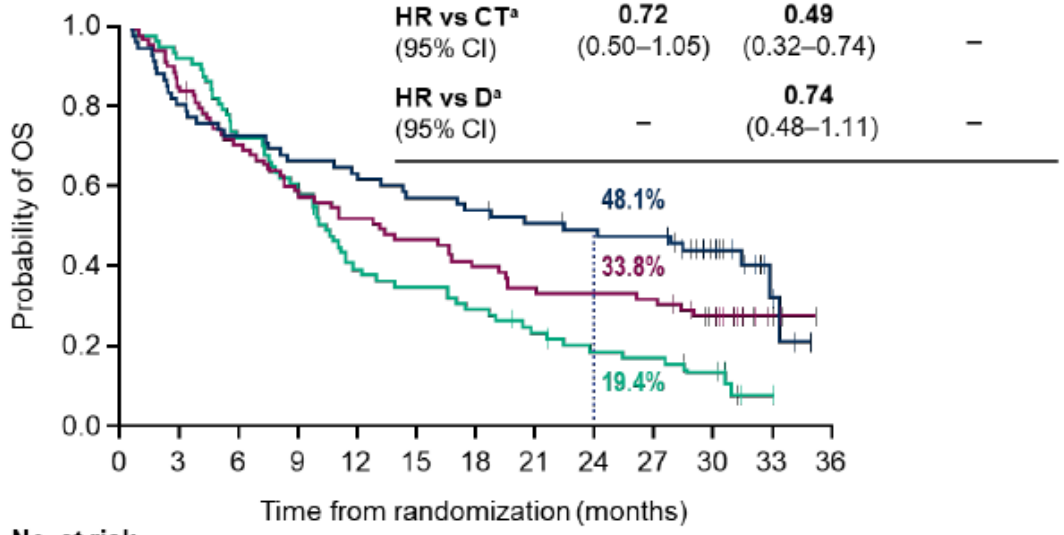
TMB <10 mut/Mb and <1% tumor PD-L1 expression

BorghaeiH, et al. ASCO 2018. Abstract 9001

MYSTIC: Durvalumab +/- Tremelimumab. bTMB.

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	**12.6** (7.8–18.6)	**21.9** (11.4–32.8)	**10.0** (8.1–11.7)
HR vs CT[a] (95% CI)	**0.72** (0.50–1.05)	**0.49** (0.32–0.74)	–
HR vs D[a] (95% CI)	–	**0.74** (0.48–1.11)	–

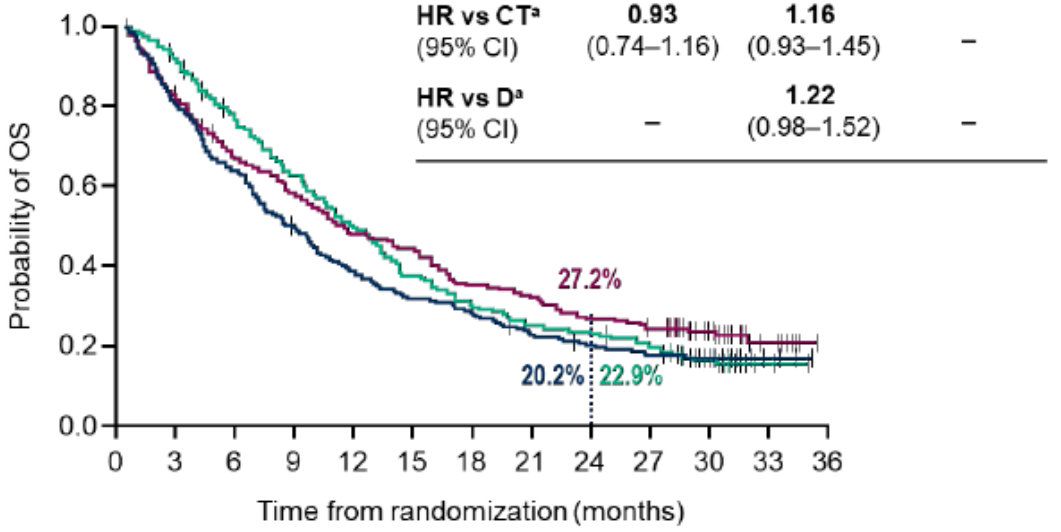


No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	**11.0** (8.9–14.9)	**8.5** (6.7–9.8)	**11.6** (9.6–13.1)
HR vs CT[a] (95% CI)	**0.93** (0.74–1.16)	**1.16** (0.93–1.45)	–
HR vs D[a] (95% CI)	–	**1.22** (0.98–1.52)	–



209	167	134	114	98	86	72	63	55	49	21	8	0
204	161	129	98	75	65	55	45	39	35	18	4	0
185	162	135	110	89	68	53	45	41	34	17	1	0

Rizvi NA, et al. ASCO 2019. ESMO 2019

Metastatic NSCLC Immune Checkpoints:

- Potential role for ICI in EGFR mutated tumors with high PDL1. However, clinical trial can be better solution
- Presence of KEAP1 or STK11 or KRAS mutations favors dual immune checkpoint blockade
- High TMB, in particular, with low PDL1 favors dual immune checkpoint blockade

https://ascopost.com/issues/may-10-2023/checkmate-816

Acknowledgment

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Department of Medical Oncology and Therapeutics Research