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Perioperative Immunotherapy in NSCLC

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10/28/2023

PIM Postgraduate Institute for Medicine

Bio Ascend™

Declaration of interests

Speaker fees/honoraria: AstraZeneca, Bristol Myers Squibb, Clinical Care Options, IDEOlogy Health, Mark Foundation for Cancer Research, Medscape, OncLive, PER®, PeerView, Roche and Society for Immunotherapy of Cancer

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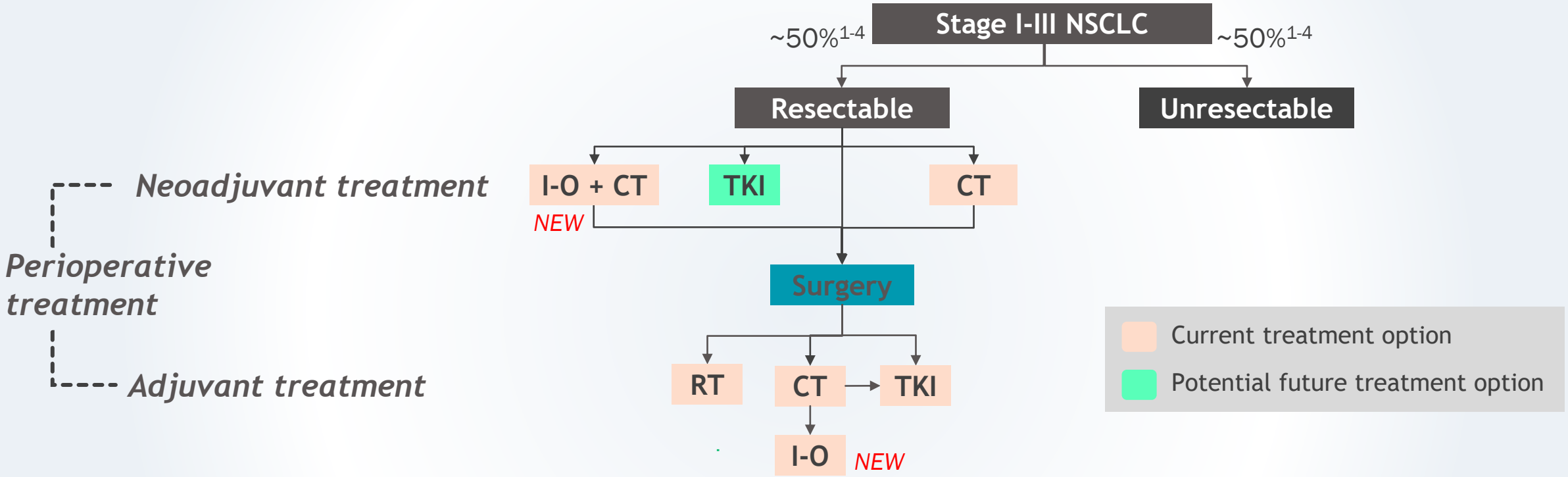
Travel and/or food/beverage: AstraZeneca, Bristol Myers Squibb, Dava Oncology, Genentech, IDEOlogy Health, International Association for the Study of Lung Cancer, OncLive, Parker Institute for Cancer Immunotherapy, PER® and Society for Immunotherapy of Cancer

Past 36 months

Current and potential future treatment options for resectable NSCLC



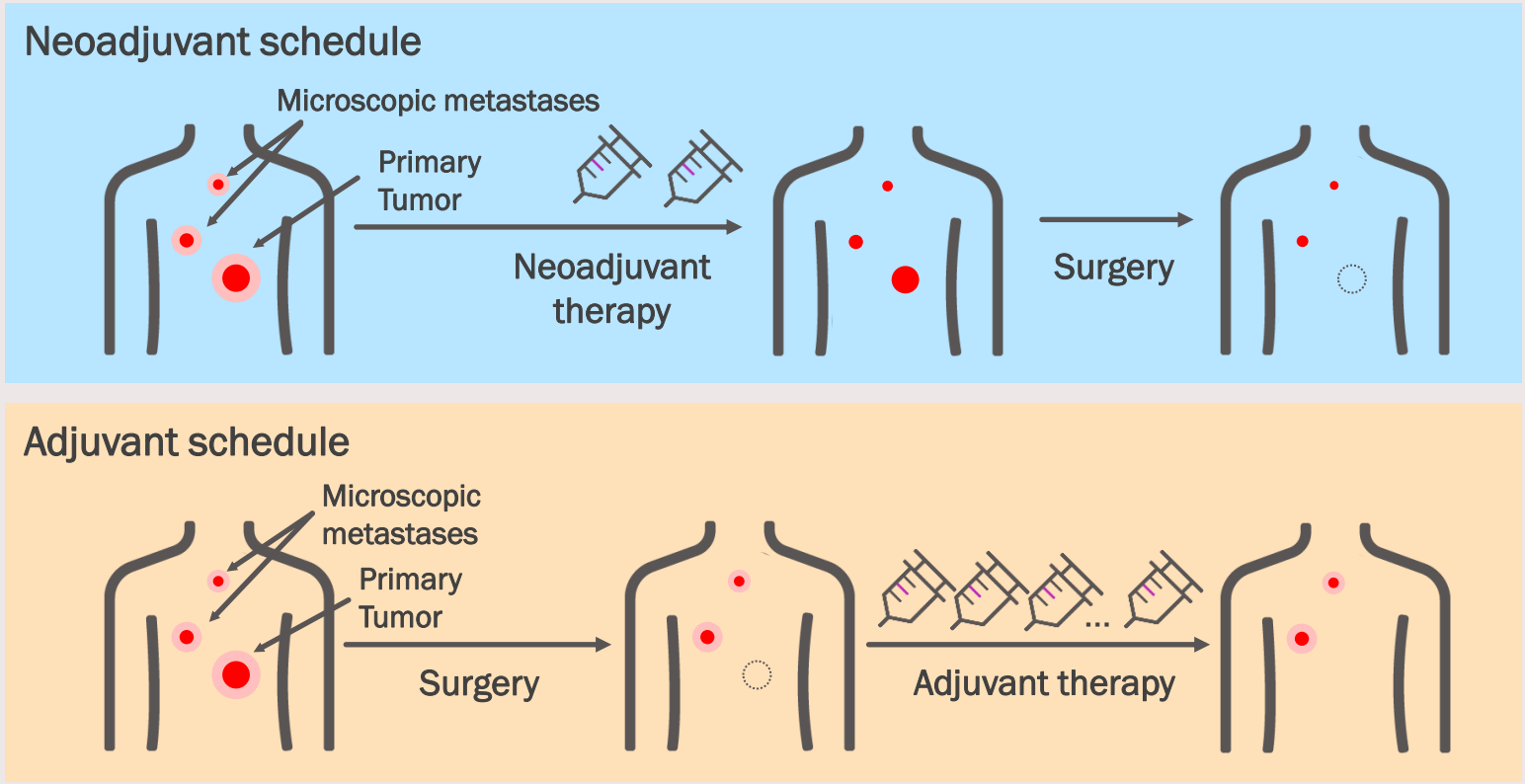
- Despite curative resection, ~30%-55% of patients with stage II-IIIB NSCLC develop recurrence and ultimately die of their disease[5,6]
- Neoadjuvant or adjuvant chemotherapy has been an option for patients with high risk of recurrence, but provides only a modest (~5%) improvement in 5-year overall survival[7,8]

CT=chemotherapy; RT=radiotherapy.

1. World Health Organization. Lung. Globocan 2020: Lung Fact Sheet. Published December 2020. Accessed September 27, 2023. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. 2. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Lung and Bronchus Cancer. Accessed September 27, 2023. https://seer.cancer.gov/statfacts/html/lungb.html. 3. Datamonitor Healthcare. Epidemiology: Non-small Cell Lung Cancer. Updated July 23, 2018. Accessed September 27, 2023. https://pharmastore.informa.com/product/disease-analysis-non-small-cell-lung-cancer-nsclc/. 4. Datta D et al. Chest. 2003 Jun;123(6):2096-103. 5. Uramoto H et al. *Transl Lung Cancer Res*. 2014;3(4):242-249. 6. Taylor MD et al. *Ann Thorac Surg*. 2012;93(6):1813-1820. 7. NSCLC Meta-analysis Collaborative Group. *Lancet*. 2010;375(9722):1267-1277. 8. NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383(9928):1561-1571.

Biological rationale for use of I-O in resectable NSCLC

In localized disease, the tumor is intact with potential high neoantigen burden and minimal clonal resistance, suggesting optimal timing for patient response to I-O[1-3]



- Neoadjuvant I-O may activate the immune system robustly prior to surgery, when tumor neoantigens are present and clonal resistance is minimal[3-6]
- Adjuvant I-O may help restore antitumor immunity that may have been impaired by surgery[6,7]

1. O'Donnell JS et al. *Clin Cancer Res*. 2019;25:5743-5751. 2. Gonzalez H et al. *Genes Dev*. 2018;32:1267-1284. 3. McGranahan N et al. *Science*. 2016;351(6280):1463-1469. 4. Tohme S et al. *Cancer Res*. 2017;77(7):1548–1552. 5. Topalian SL et al. *Science*. 2020;367(525):eaax0182. 6. Chaft JE et al. *Nat Rev Clin Oncol*. 2021;18(9):547-557. 7. Bakos O, et al. *J Immunother Cancer*. 2018; 6(1):86.

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC

Completed and Ongoing Select Phase 3 Trials

Resectable NSCLC

Neoadjuvant

Trial	Regimen
CheckMate 816[1]	Nivolumab + Chemotherapy
CheckMate 816[2]	Nivolumab + Ipilimumab

Adjuvant

Trial	Regimen
KEYNOTE-091/PEARLS[3]	Pembrolizumab
IMpower010[4]	Atezolizumab
CCTC BR31[5]	Durvalumab
ANVIL[6]	Nivolumab
NADIM-ADJUVANT[7]	Nivolumab + Chemotherapy

Perioperative

Trial	Regimen
CheckMate 77T[8]	Nivolumab + Chemotherapy → Nivolumab
IMpower030[9]	Atezolizumab + Chemotherapy → Atezolizumab
AEGEAN[10]	Durvalumab + Chemotherapy → Durvalumab
KEYNOTE-671[11]	Pembrolizumab + Chemotherapy → Pembrolizumab
Neotorch[12]	Toripalimab + Chemotherapy → Toripalimab + Chemotherapy → Toripalimab

1. Forde PM et al. *N Engl J Med*. 2022. 2022;386(21):1973-1985. 2. Awad M ESMO Congress 2023 Abstract 3. O'Brien M et al. *Lancet Oncol.* 2022 Oct;23(10):1274-1286. 4. Felip E et al. *Lancet*. 2021;398(10308):1344-1357. 5. Clinicaltrials.gov. NCT02273375. 6. Chaft JE et al. *Journal of Clinical Oncology* 36, no. 15_suppl 2018. Abstract TPS8581. 7. Calvo V et al. *Journal of Clinical Oncology* 39, no. 15_suppl 2021. Abstract TPS8581. 8. Cascone T, ESMO Congress 223 LBA1. 9. Peters S et al. *Annals of Oncology*. Volume 30, Supplement 2, 2019. Abstract 82TiP. 10. Heymach JV et al. *N Engl J Med 2023*. 11. Wakelee H e al. *N Engl J Med*. 2023 Jun 3. 12. Lu S et al. *Journal of Clinical Oncology* 41, no. 16_suppl 2023. 8501-8501.

Adapted and Updated from ESMC Congress 2023 Industry Satellite Symposium

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC

Completed and Ongoing Select Phase 3 Trials

Resectable NSCLC

Neoadjuvant

Trial	Regimen
CheckMate 816[1]	Nivolumab + Chemotherapy
CheckMate 816[2]	Nivolumab + Ipilimumab

1. Forde PM et al. *N Engl J Med*. 2022. 2022;386(21):1973-1985. 2. Awad M ESMO Congress 2023 Abstract

Adapted and Updated from ESMC Congress 2023 Industry Satellite Symposium

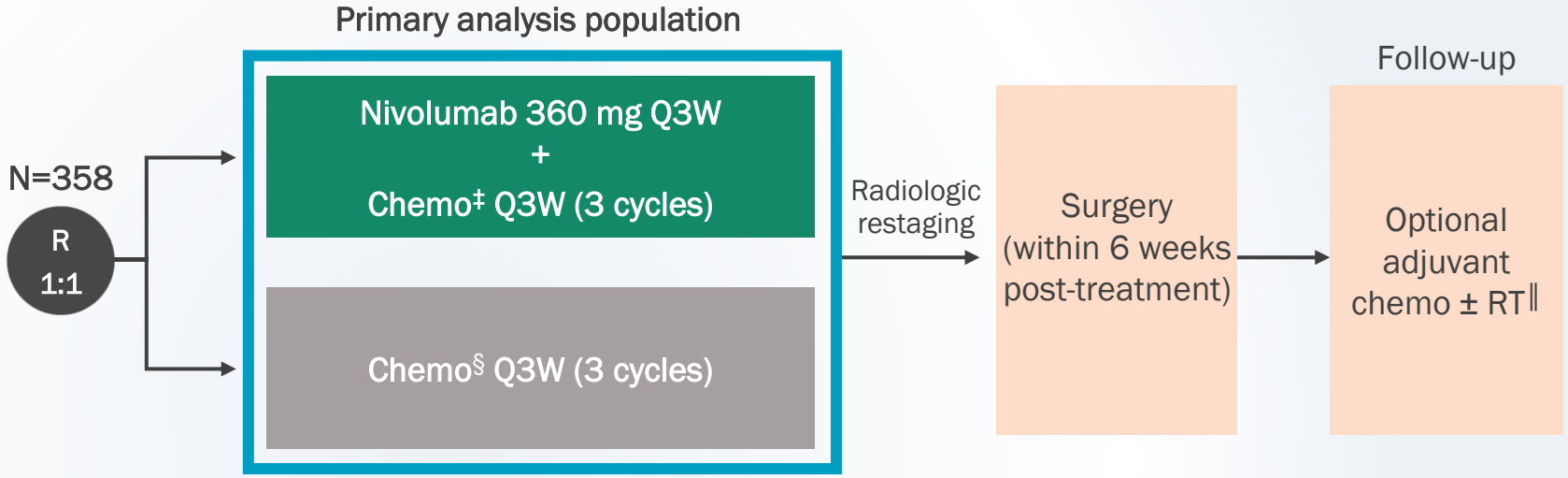
CheckMate 816: First phase 3 study evaluating neoadjuvant I-O + chemo in patients with resectable NSCLC[1]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥4 cm)–IIIA NSCLC (per AJCC 7th edition)
- ECOG performance status 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by

Stage (IB–II vs IIIA), PD-L1* (≥1% vs <1%†), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Neoadjuvant nivolumab + chemo is approved in the US for patients with resectable (tumors ≥4 cm or node positive) NSCLC[2]

Neoadjuvant nivolumab + chemo is approved in the EU for resectable NSCLC at high risk of recurrence and whose tumors have PD-L1 expression ≥1%[3]

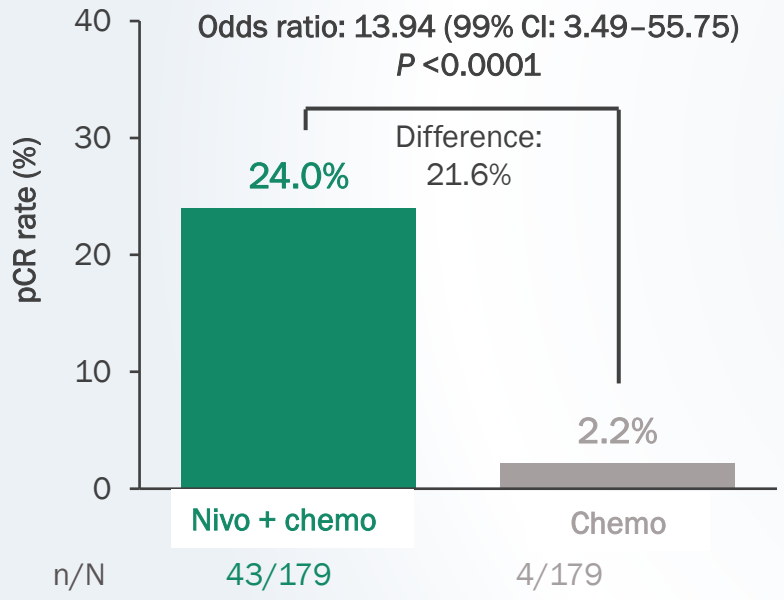
*Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). †Included patients with PD-L1 expression status not evaluable and indeterminate. ‡NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin. §Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin. ‖Per healthcare professional choice.
BICR=blinded independent central review; BIPR=blinded independent pathological review; ECOG=Eastern Cooperative Oncology Group; EFS=event-free survival; MPR=major pathologic response; pCR=pathologic complete response; Q3W=every 3 weeks; R=randomization.

1. Forde PM et al. *N Engl J Med*. 2022;386(21):1973-1985. 2. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 3. OPDIVO (SPC). Bristol-Myers Squibb Pharma EEIG; 2023.

CheckMate 816: Neoadjuvant Nivo + CT significantly improved pCR and EFS for resectable stage IB-IIIA NSCLC[1,2]

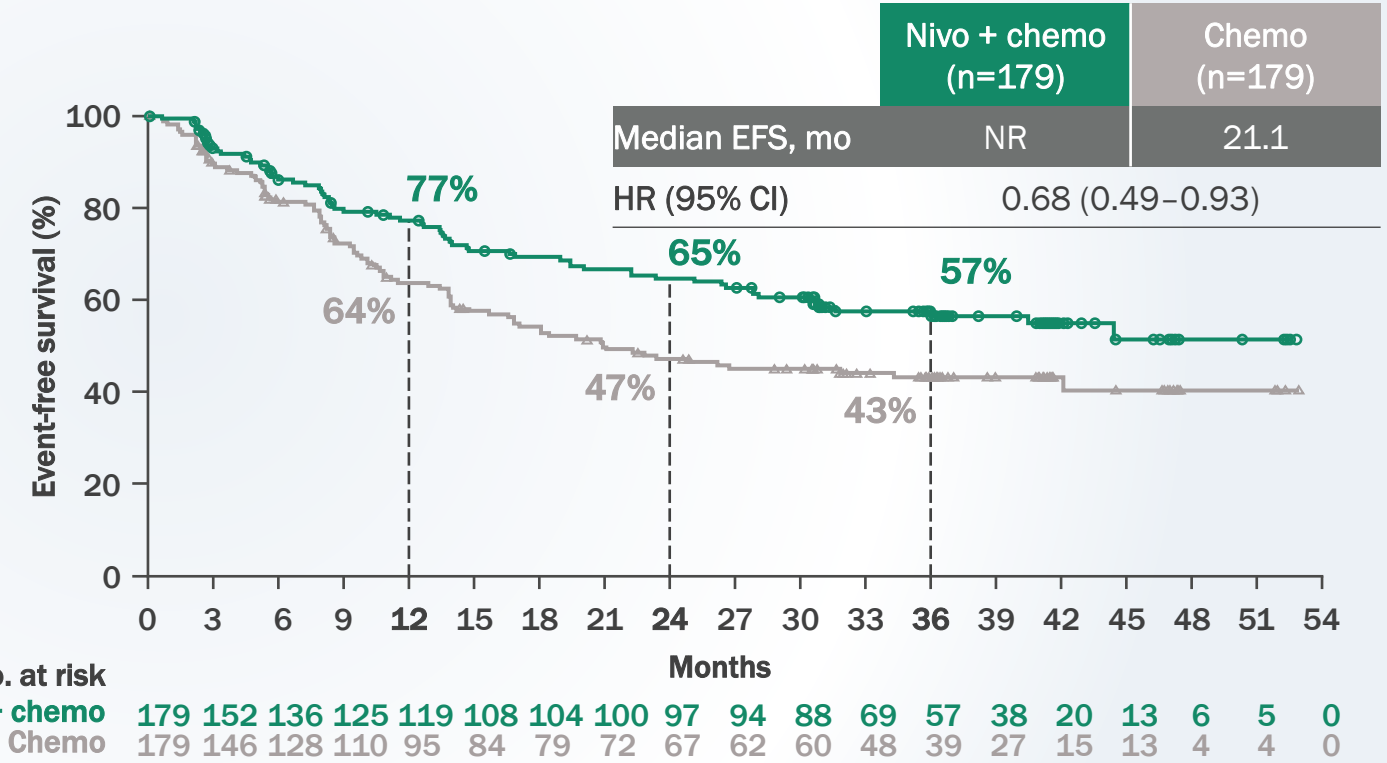
pCR rate (ypT0N0) per BIPR[1]

(Resected + non-resected population)



EFS per BICR[2]*

PD-L1 AC, stage IB-IIIA

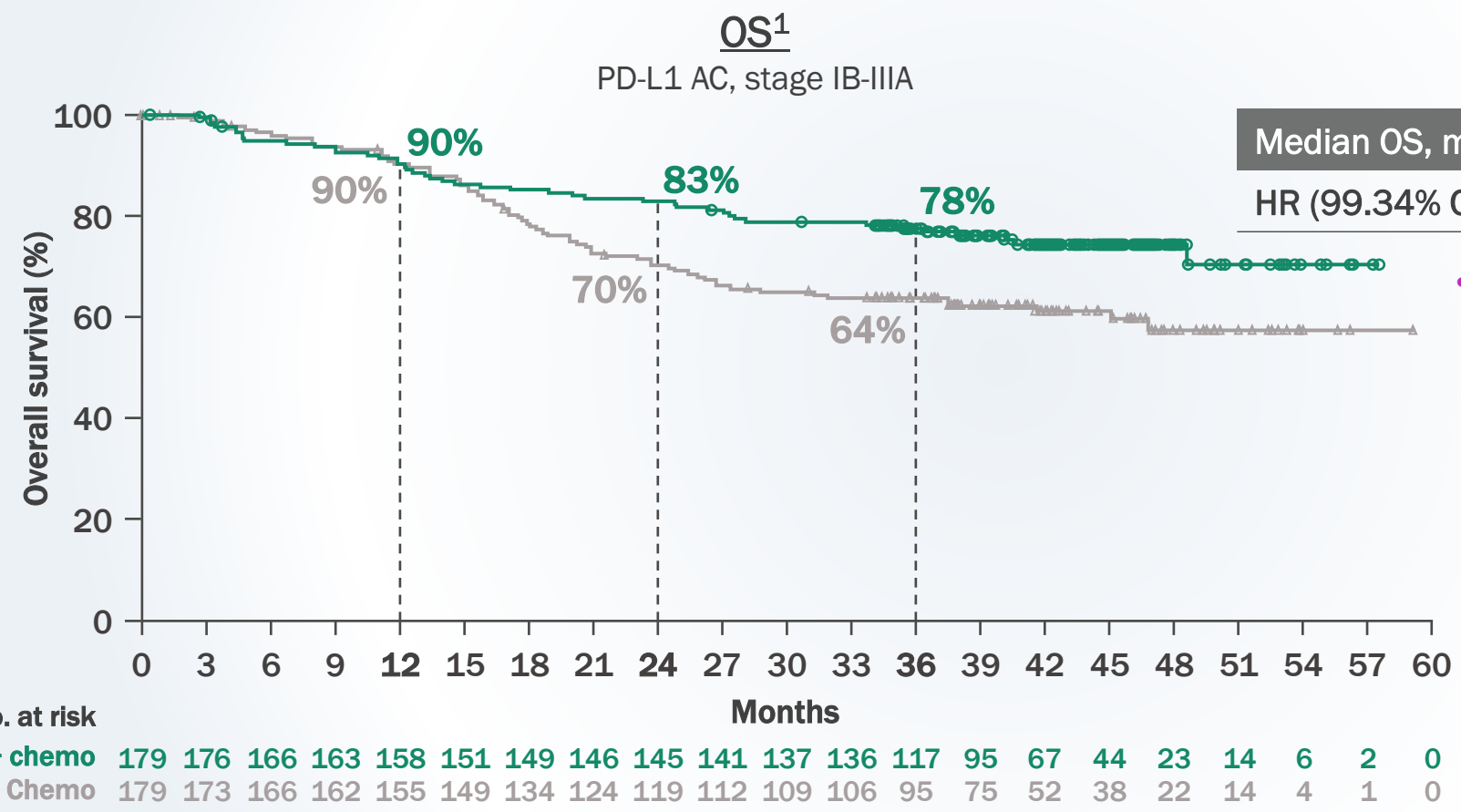


Database lock for pCR rate: September 16, 2020. Database lock for EFS: October 14, 2022; minimum/median follow-up: 32.9/41.4 months.
Neoadjuvant nivolumab + chemo is approved in the US for patients with resectable (tumors ≥4 cm or node positive) NSCLC,[3] and in the EU for patients with resectable NSCLC at high risk of recurrence and whose tumors have PD-L1 ≥1%.[4]

*EFS statistical significance was established at the primary database lock (minimum follow-up of 21 months); HR=0.63 (97.38% CI, 0.43-0.91); *P*=0.005.

1. Forde PM et al. *N Engl J Med*. 2022. 2. Forde PM et al. Oral presentation at ELCC 2023..

CheckMate 816: Neoadjuvant Nivo + CT showed a trend toward improved OS for patients with resectable NSCLC



	Nivo + chemo (n=179)	Chemo (n=179)
Median OS, mo	NR	NR
HR (99.34% CI)	0.62 (0.36–1.05); *P*=0.0124	

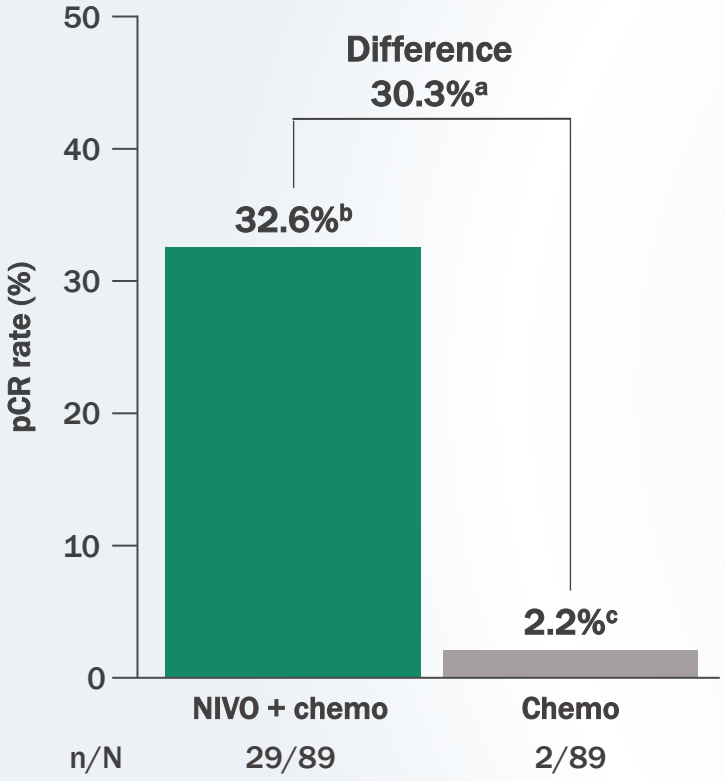
- Significance boundary for OS was not crossed at this interim analysis. Results should be interpreted with caution due to the immaturity of the data. OS will be monitored over time

Database lock: October 14, 2022; minimum/median follow-up: 32.9/41.4 months.

Forde PM et al. Oral presentation at ELCC 2023.

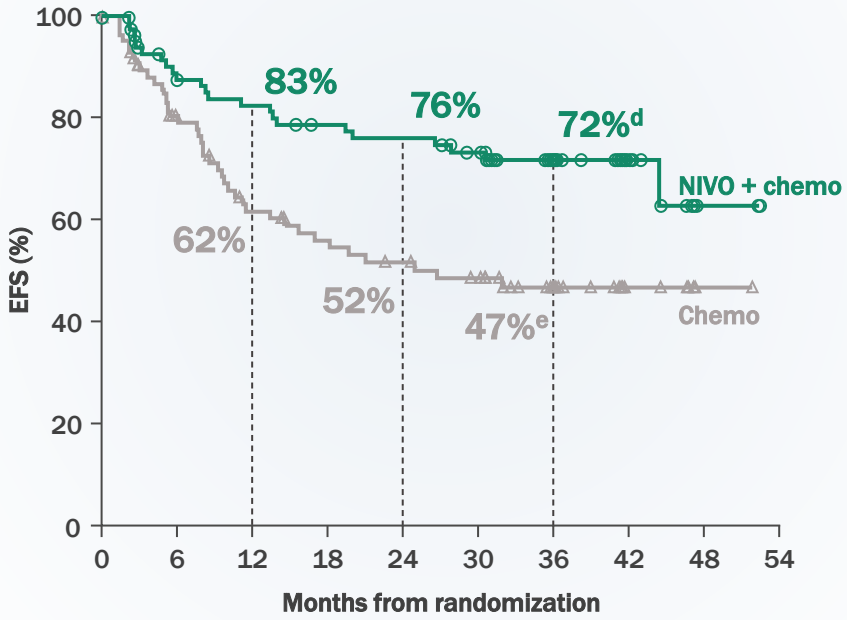
Efficacy outcomes in patients with tumor PD-L1 ≥ 1%

pCR



EFS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS, mo (95% CI)	NR (44.4–NR)	26.7 (13.4–NR)
HR (95% CI)	0.46 (0.28–0.77)	

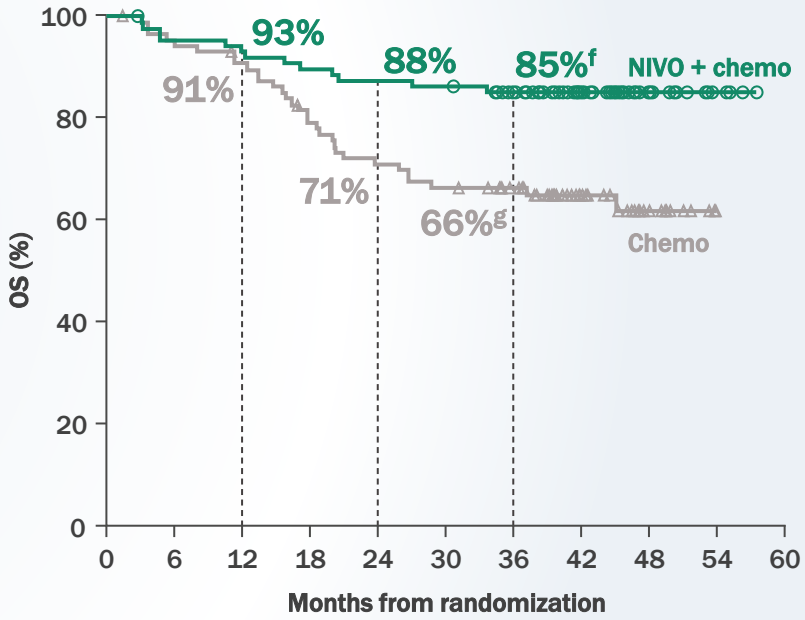


No. at risk

NIVO + chemo	89	69	65	60	58	53	37	11	2	0
Chemo	89	61	45	39	35	31	19	7	1	0

OS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median OS, mo (95% CI)	NR (NR–NR)	NR (45.1–NR)
HR (95% CI)	0.37 (0.20–0.71)	



NIVO + chemo	89	84	82	79	77	76	66	37	13	4	0
Chemo	89	83	79	68	61	57	51	27	10	0	0

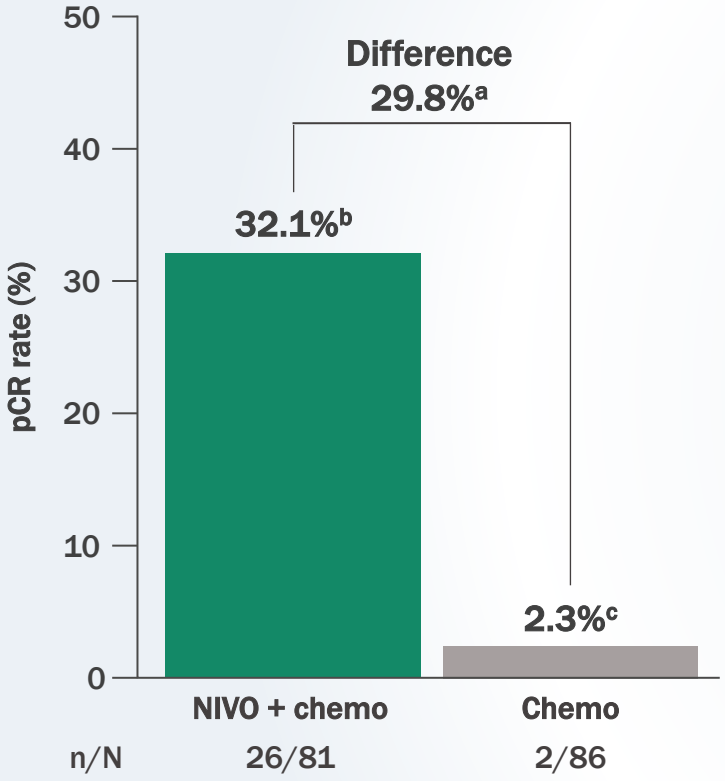
- Median TTDM (95% CI) in months was NR vs NR (18.8–NR) for NIVO + chemo vs chemo (HR, 0.35; 95% CI, 0.19–0.62); 3-year TTDM rates were 82%[h] vs 53%[i]

Minimum/median follow-up: 32.9/41.4 months.
MPR rates were 44.9% (95% CI, 34.4–55.9) with NIVO + chemo and 5.6% (95% CI, 1.8–12.6) with chemo (difference, 39.3%; 95% CI, 27.3–50.1). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a–g]95% CI: [a]19.9–40.7; [b]23.0–43.3; [c]0.3–7.9; [d]61–81; [e]35–58; [f]76–91; [g]56–75; [h]71–88; [i]41–63.

Provencio Pulla M, Oral presentation at ESMO Congress 2023

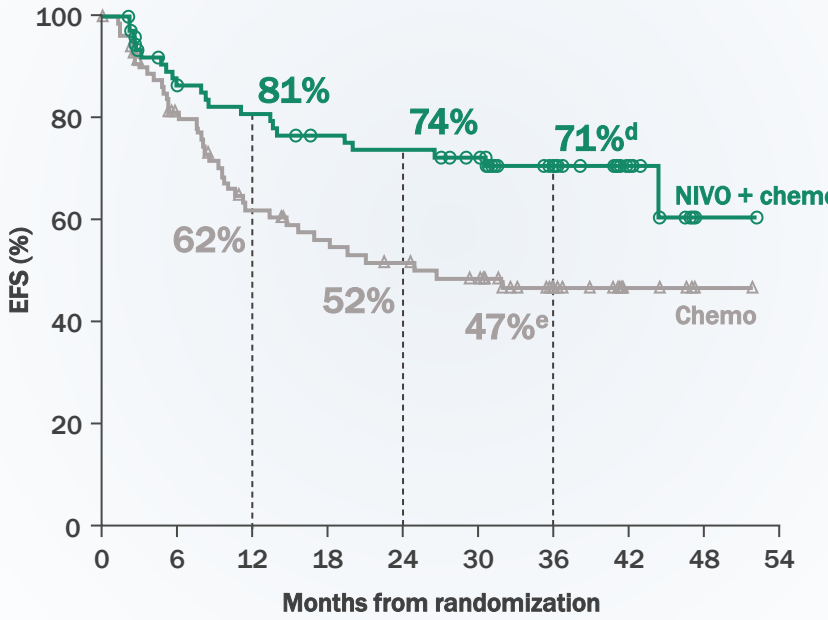
Efficacy outcomes in patients with tumor PD-L1 ≥ 1% and stage II–IIIA disease

pCR



EFS

	NIVO + chemo (n = 81)	Chemo (n = 86)
Median EFS, mo (95% CI)	NR (44.4–NR)	26.7 (13.4–NR)
HR (95% CI)	0.49 (0.29–0.83)	

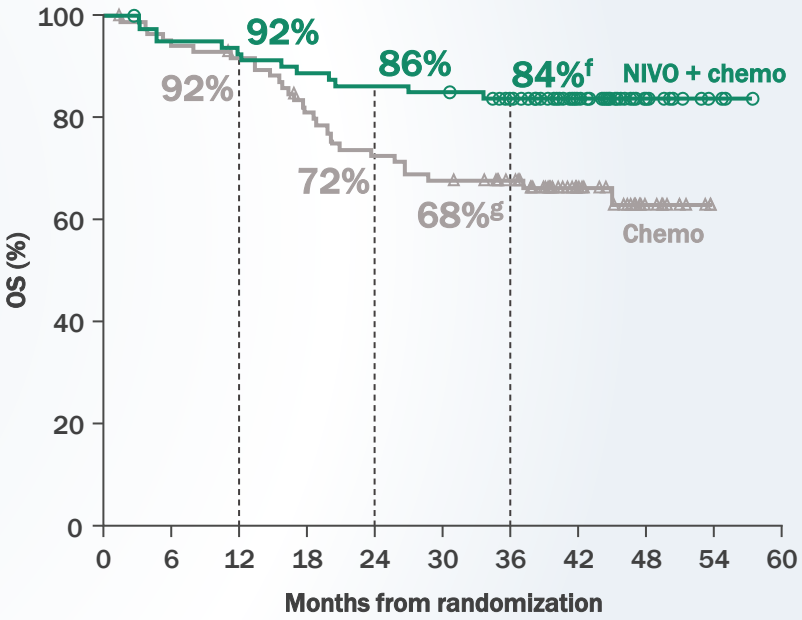


No. at risk

NIVO + chemo	81	62	58	53	51	47	32	10	1	0
Chemo	86	60	44	38	34	30	18	7	1	0

OS

	NIVO + chemo (n = 81)	Chemo (n = 86)
Median OS, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.43 (0.22–0.83)	



NIVO + chemo	81	76	74	71	69	68	59	33	11	3	0
Chemo	86	80	77	67	60	56	50	27	10	0	0

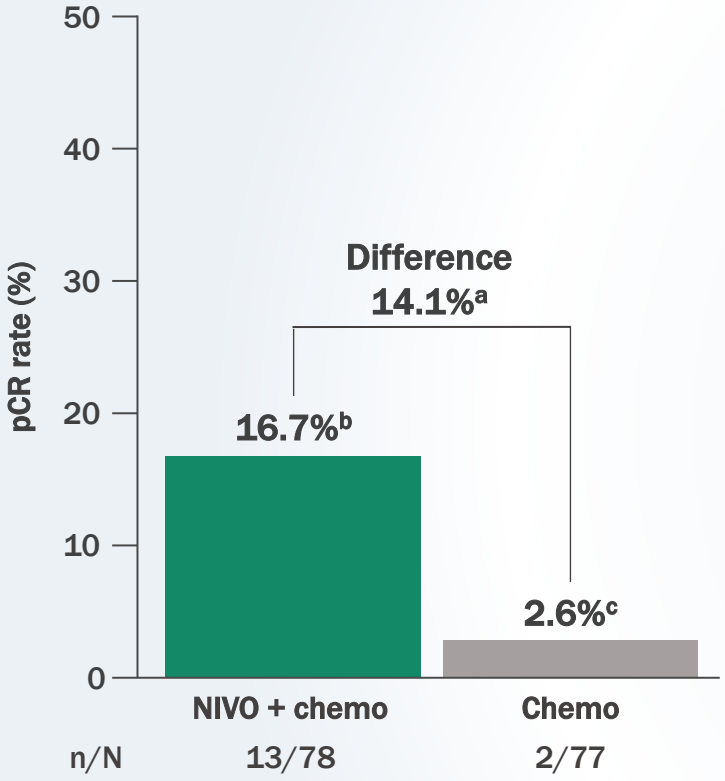
- Median TTDM (95% CI) in months was NR (44.4–NR) vs NR (18.8–NR) for NIVO + chemo vs chemo (HR, 0.40; 95% CI, 0.22–0.72)

Minimum/median follow-up: 32.9/41.4 months.
MPR rates were 45.7% (95% CI, 34.6–57.1) with NIVO + chemo and 5.8% (95% CI, 1.9–13.0) with chemo (difference, 39.9%; 95% CI, 27.3–51.2). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a–g]95% CI: [a]19.0–40.7; [b]22.2–43.4; [c]0.3–8.1; [d]59–80; [e]35–58; [f]74–90; [g]56–77.

Provenio Pulla M, Oral presentation at ESMO Congress 2023

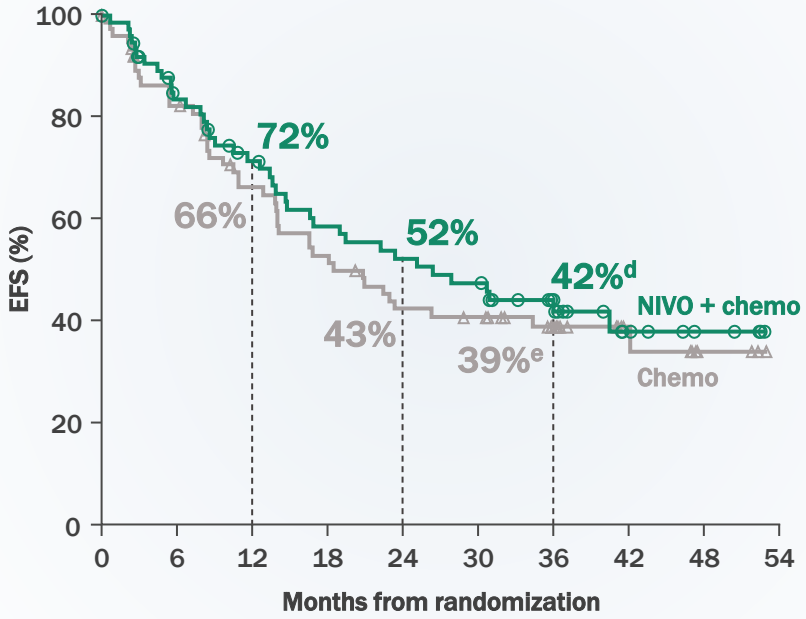
Efficacy outcomes in patients with tumor PD-L1 < 1%

pCR



EFS

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median EFS, mo (95% CI)	26.4 (14.8–NR)	20.8 (13.9–42.1)
HR (95% CI)	0.87 (0.57–1.35)	

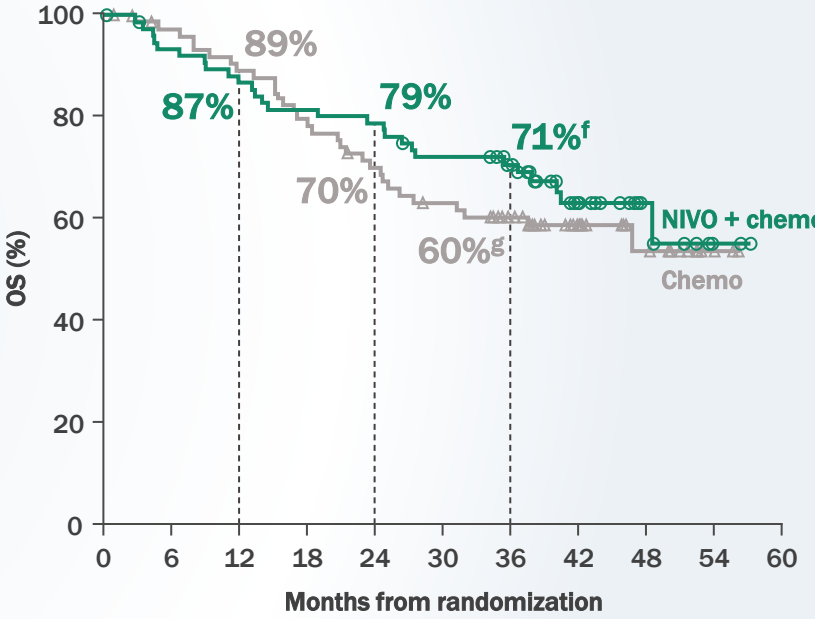


No. at risk

NIVO + chemo	78	57	46	37	33	30	18	8	4	0
Chemo	77	59	45	36	28	26	18	8	3	0

OS

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median OS, mo (95% CI)	NR (48.6–NR)	NR (31.2–NR)
HR (95% CI)	0.81 (0.48–1.36)	



NIVO + chemo	78	71	66	62	60	54	46	26	8	2	0
Chemo	77	72	66	59	51	45	37	22	11	3	0

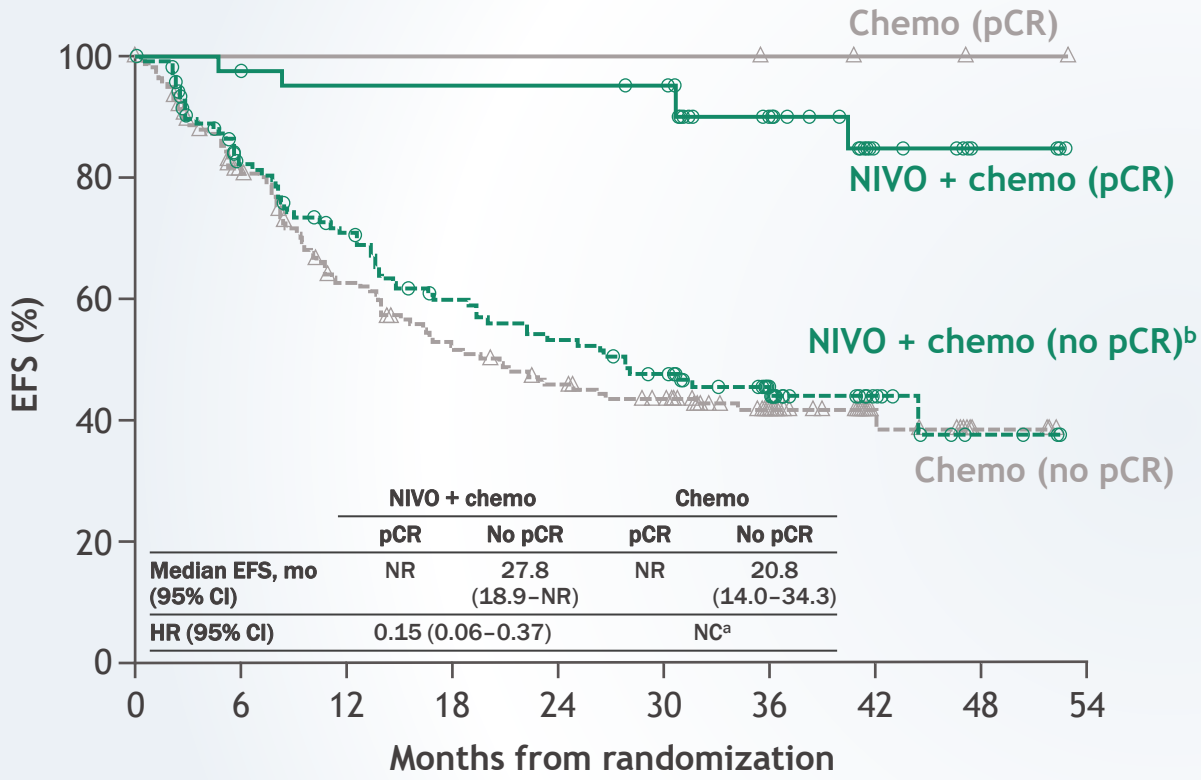
- Median TTDM (95% CI) was 48.6 mo (36.6–NR) vs 27.4 mo (21.4–NR) for NIVO + chemo vs chemo (HR, 0.72; 95% CI, 0.45–1.15); 3-year TTDM rates were 63%[h] vs 46%[i]
- Baseline characteristics were generally similar between tumor PD-L1 subgroups and treatment arms, although a higher proportion of patients with tumor PD L1 < 1% had ECOG PS 1 (both arms)

Minimum/median follow-up: 32.9/41.4 months.
MPR rates were 29.5% (95% CI, 19.7–40.9) with NIVO + chemo and 14.3% (95% CI, 7.4–24.1) with chemo (difference, 15.2%; 95% CI, 2.1–27.7). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a–g]95% CI: [a]4.8–24.0; [b]9.2–26.8; [c]0.3–9.1; [d]30–54; [e]28–51; [f]59–80; [g]48–71; [h]51–74; [i]34–57.

Provenio Pulla M, Oral presentation at ESMO Congress 2023

CheckMate 816: Efficacy outcomes by pCR status in randomized patients

EFS

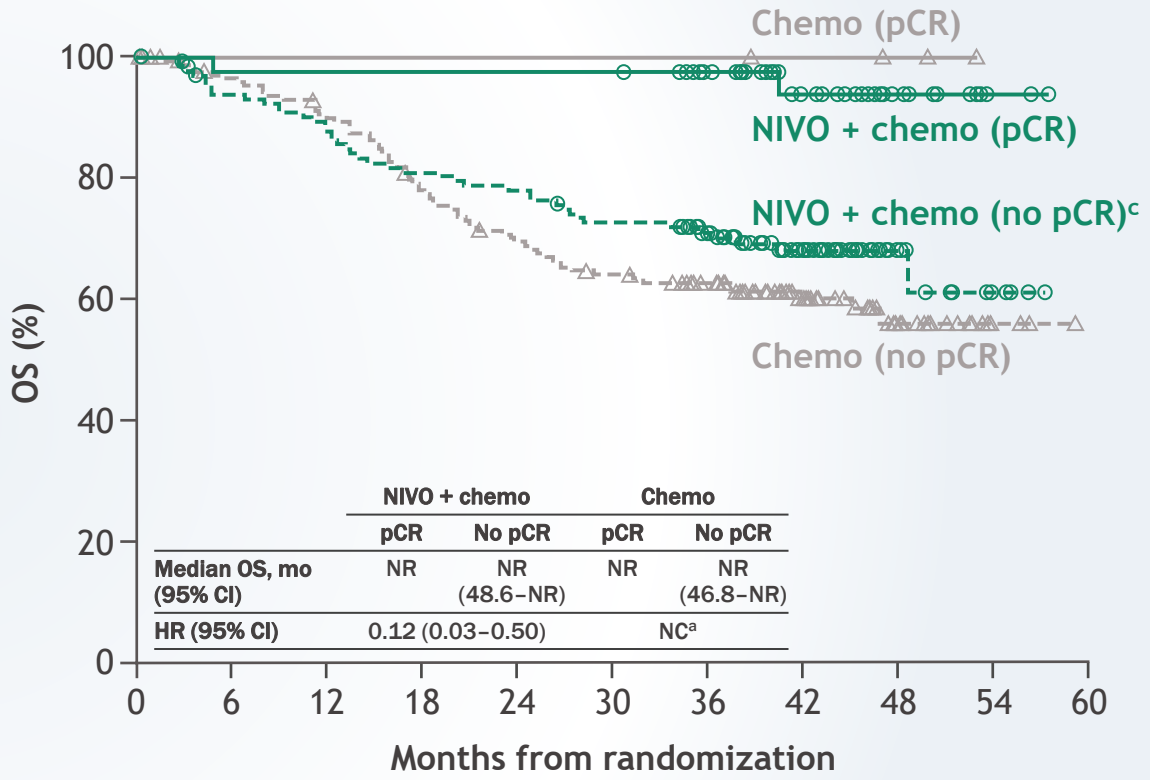


	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS, mo (95% CI)	NR	27.8 (18.9–NR)	NR	20.8 (14.0–34.3)
HR (95% CI)	0.15 (0.06–0.37)		NC[a]	

No. at risk

pCR	43	41	40	40	40	39	26	9	3	0
pCR	4	4	4	4	4	4	3	2	1	0
No pCR	136	95	79	64	57	49	31	11	3	0
No pCR	175	124	91	75	63	56	36	13	3	0

OS



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo (95% CI)	NR	NR (48.6–NR)	NR	NR (46.8–NR)
HR (95% CI)	0.12 (0.03–0.50)		NC[a]	

	43	42	42	42	42	42	36	22	10	2	0
	4	4	4	4	4	4	4	3	2	0	0
	136	124	116	107	103	95	81	45	13	4	0
	175	162	151	130	115	105	91	49	20	4	0

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

[a]HR was NC for the chemo arm due to few patients having a pCR (n = 4). [b]EFS HR was 0.89 (95% CI, 0.64-1.22) for patients with NIVO + chemo vs chemo without pCR. [c]OS HR was 0.77 (95% CI, 0.52-1.14) for patients with NIVO + chemo vs chemo without pCR.

Provenio Pulla M, Oral presentation at ESMO Congress 2023

CheckMate 816: Neoadjuvant Nivo+Ipi vs CT in NSCLC

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per AJCC TNM 7th edition)
- ECOG performance status 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), tumor PD-L1[b] (≥ 1% vs < 1%[c]), and sex

R

NIVO 360 mg Q3W (3 cycles) + chemo[d] Q3W (3 cycles)

Chemo[e] Q3W (3 cycles) (n = 108)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f] (n = 113)

Exploratory analysis population[g]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT → Follow-up

Primary analysis (NIVO + chemo vs chemo)

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory analysis (NIVO + IPI vs chemo)

- **EFS by BICR**
- **pCR and MPR by BIPR**
- **OS**
- **EFS, pCR, and MPR by 4-gene inflammatory signature score**

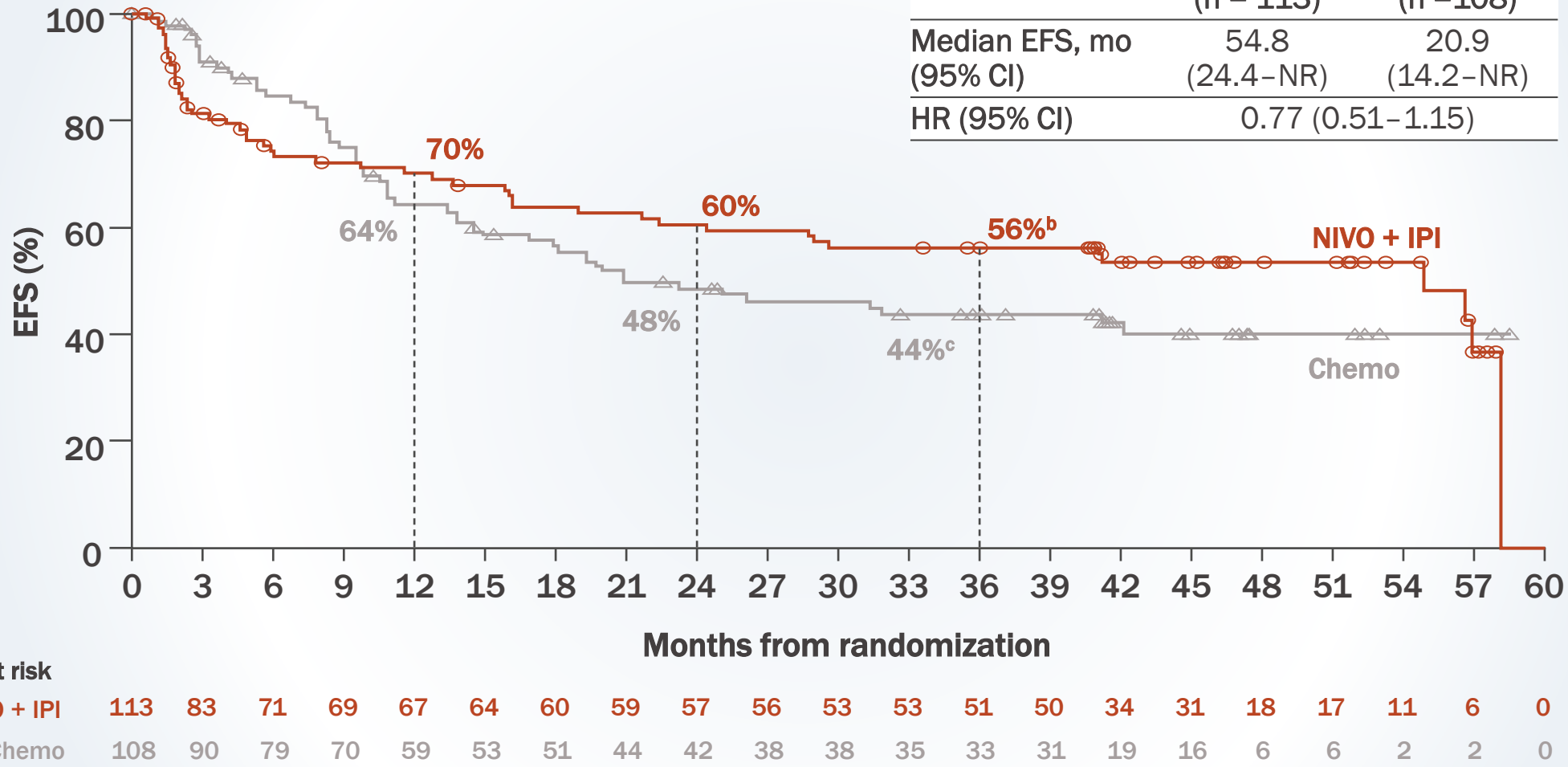
Database lock date: October 14, 2022. Minimum/median follow-up: 37.1/49.2 months.

[a]NCT02998528. [b]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Non-squamous: pemetrexed + cisplatin or paclitaxel + carboplatin. Squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (non-squamous only), or paclitaxel + carboplatin. [f]Enrollment to the NIVO + IPI arm closed early after the primary analysis population of the study was changed to patients concurrently randomized to NIVO + chemo vs chemo based on evolving external trial data.[1,2] [g]Only included patients concurrently randomized to the NIVO + IPI or chemo arms.

1. Cascone T, et al. *Nat Med* 2021;27:504–514. 2. Provencio M, et al. *Lancet Oncol* 2020;21:1413–1422.

EFS with neoadjuvant Nivo+Ipi vs CT

	NIVO + IPI (n = 113)	Chemo (n =108)
Median EFS, mo (95% CI)	54.8 (24.4–NR)	20.9 (14.2–NR)
HR (95% CI)	0.77 (0.51–1.15)	



No. at risk

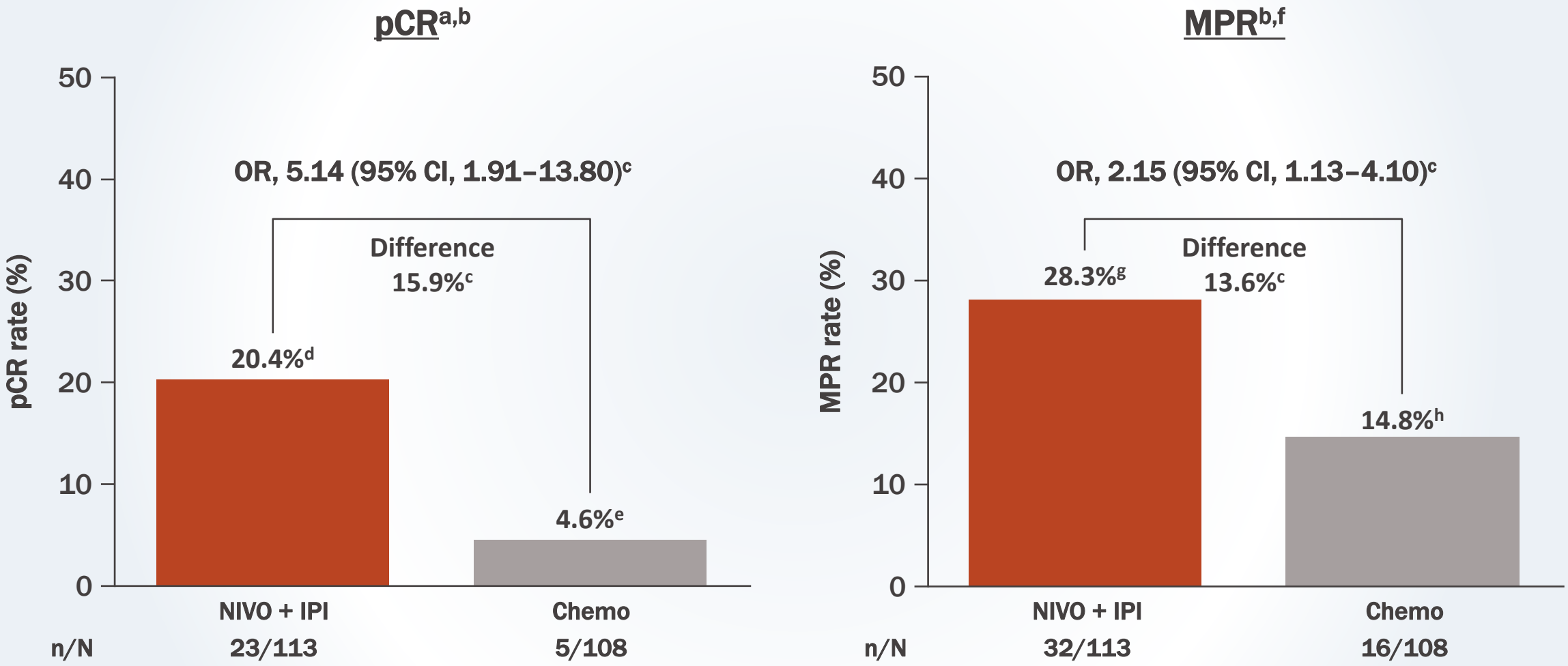
NIVO + IPI	113	83	71	69	67	64	60	59	57	56	53	53	51	50	34	31	18	17	11	6	0
Chemo	108	90	79	70	59	53	51	44	42	38	38	35	33	31	19	16	6	6	2	2	0

Minimum/median follow-up: 37.1/49.2 months.

[a]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% CI: [b]46-65; [c]33-54.

Awad M, ESMO Congress 2023 Oral Presentation

pCR and MPR with neoadjuvant Nivo+Ipi vs CT



Database lock date: September 16, 2020.

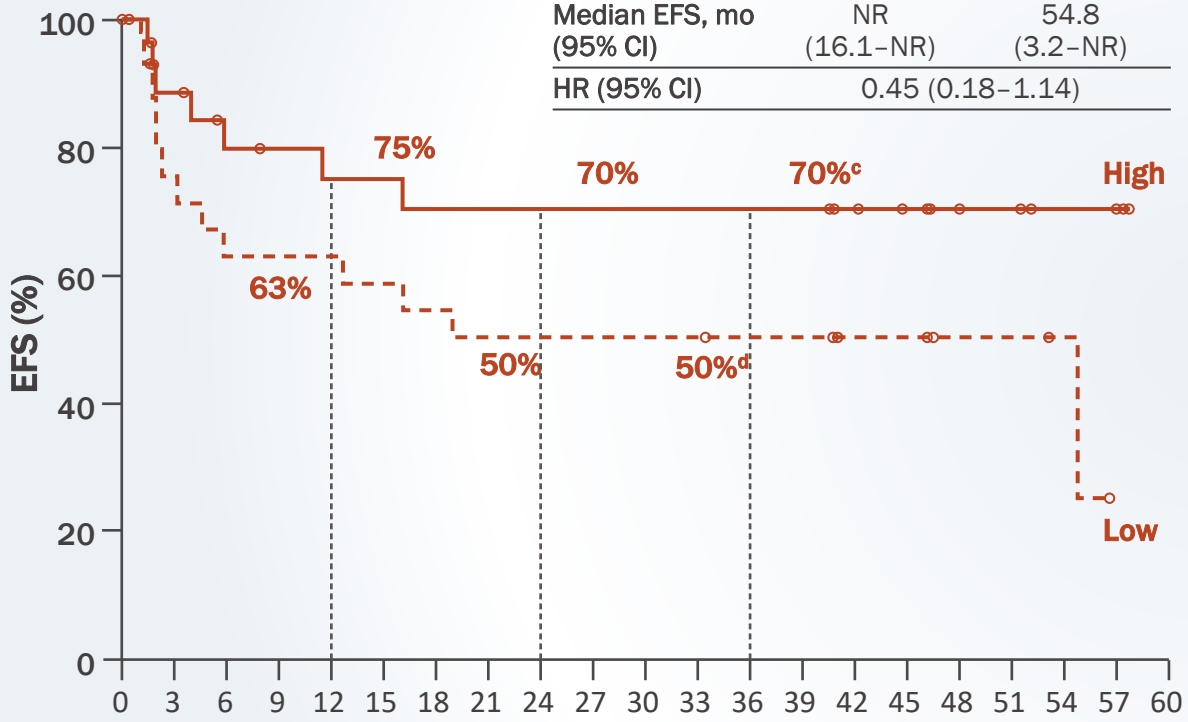
[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [b]Patients who did not undergo surgery were classified as nonresponders. [c]Calculated using stratified Cochran–Mantel–Haenszel method. [d,e]95% CI: [d]13.4–29.0; [e]1.5–10.5. [f]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [g,h]95% CI: [g]20.2–37.6; [h]8.7–22.9.

Awad M, ESMO Congress 2023 Oral Presentation

Baseline 4-gene inflammatory signature score and EFS

NIVO + IPI

	High 4-gene inflammatory score (n = 28)	Low 4-gene inflammatory score (n = 27)
Median EFS, mo (95% CI)	NR (16.1–NR)	54.8 (3.2–NR)
HR (95% CI)	0.45 (0.18–1.14)	

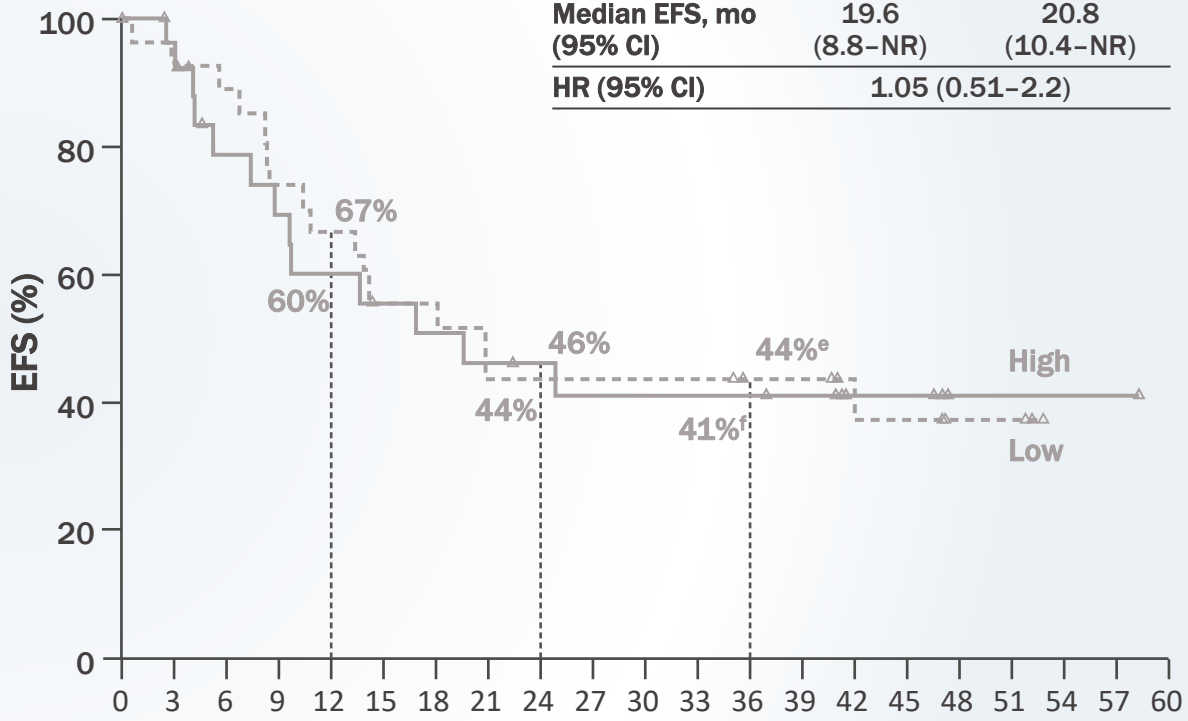


No. at risk

High	28	22	18	17	16	16	15	15	15	15	15	15	15	15	12	10	8	7	4	4	0
Low	27	18	15	15	15	14	13	12	12	12	12	12	11	11	7	7	3	3	2	0	0

Chemo

	High 4-gene inflammatory score (n = 27)	Low 4-gene inflammatory score (n = 27)
Median EFS, mo (95% CI)	19.6 (8.8–NR)	20.8 (10.4–NR)
HR (95% CI)	1.05 (0.51–2.2)	



No. at risk

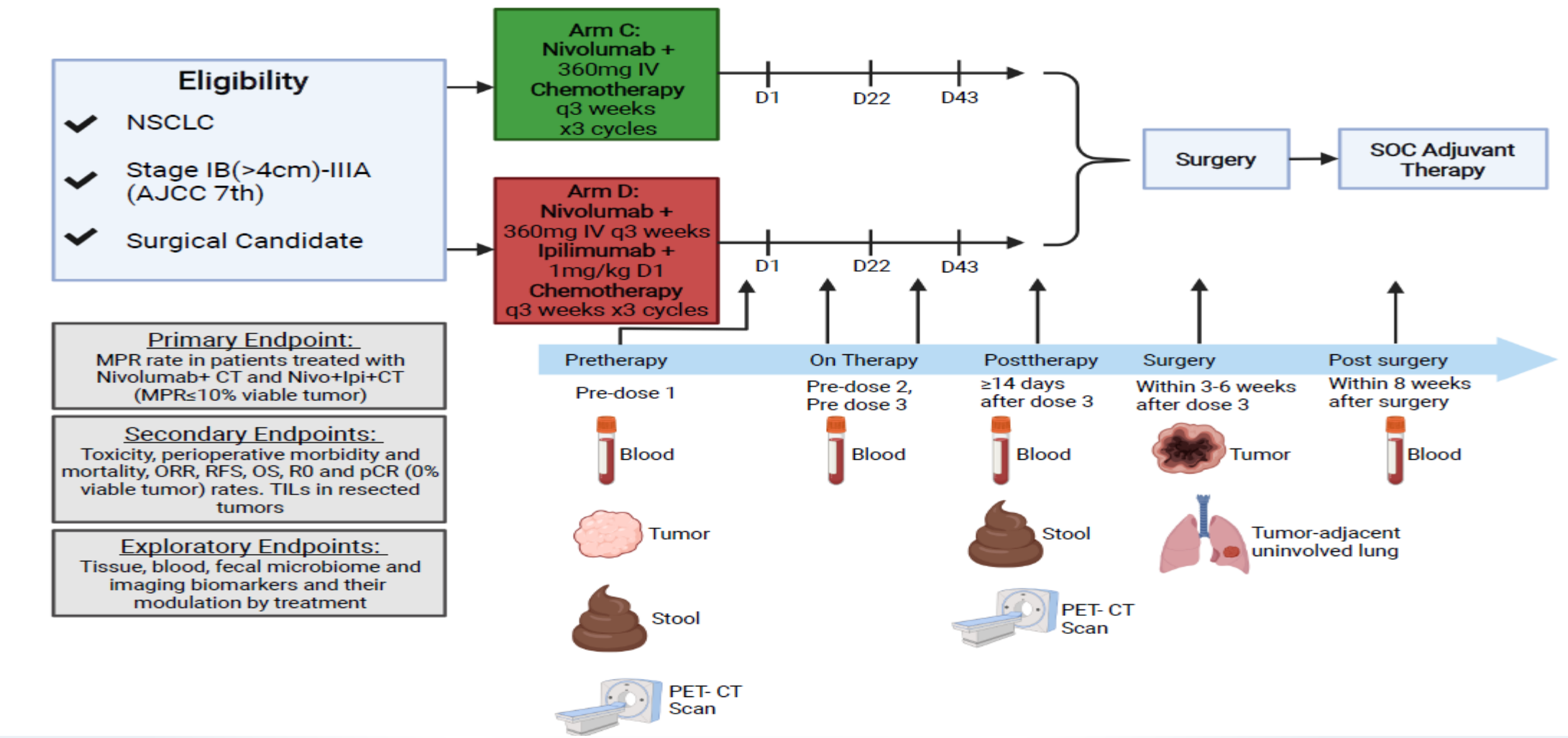
High	27	24	17	15	13	12	11	10	9	8	8	8	8	7	4	4	1	1	1	1	0
Low	27	25	24	20	18	14	14	11	11	11	11	11	9	9	7	6	3	3	0	0	0

Minimum/median follow-up: 37.1/49.2 months.

[a]4-gene inflammatory signature scores were grouped as high or low relative to the median z-score across the dataset. [b]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. [c-f]95% CI: [c]54–92; [d]34–75; [e]28–67; [f]25–68.

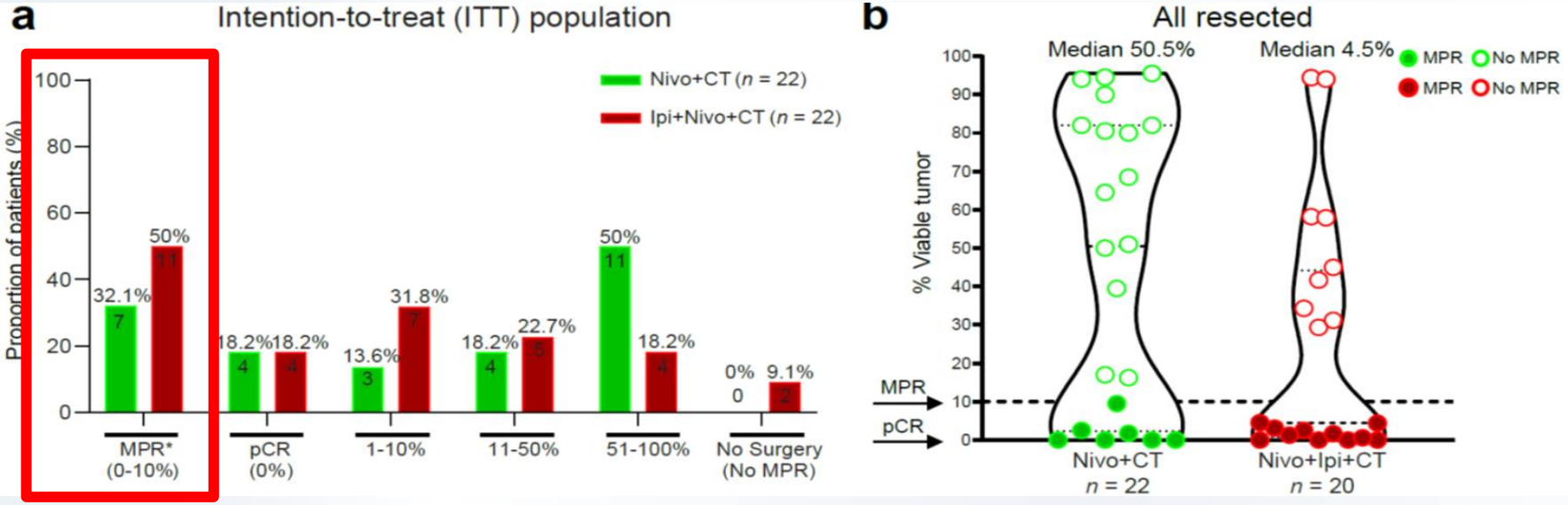
Awad M, ESMO Congress 2023 Oral Presentation

Modular platform design of NEOSTAR: Single-arm studies to test chemo-IO combos

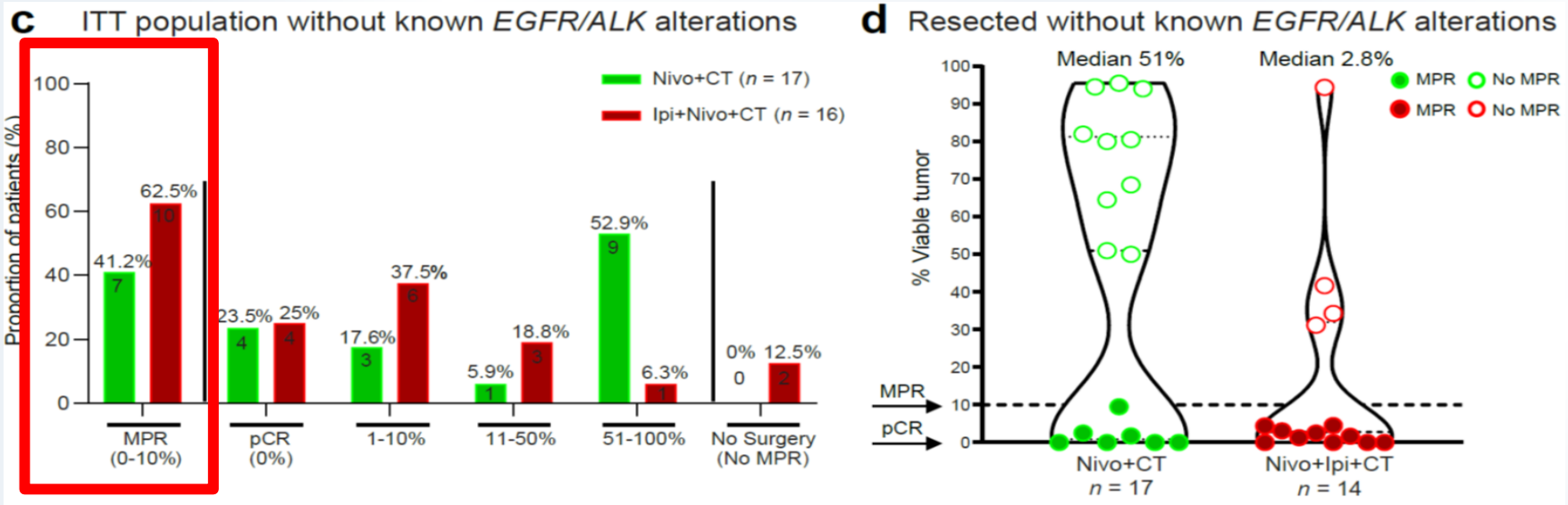


Cascone, T et al. *Nat Medicne,* 2023

NEOSTAR platform: MPR rates to neoadjuvant Nivo+CT and Ipi+Nivo+CT in NSCLC



ITT population:
Nivo+CT MPR rate: **32.1%**
Ipi+Nivo+CT MPR rate **50%**



Without known *EGFR/ALK* alterations:
Nivo+CT MPR rate: **41.2%**
Ipi+Nivo+CT MPR rate: **62.5%**

Cascone, T et al. *Nat Medicne,* 2023

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC

Completed and Ongoing Select Phase 3 Trials

Resectable NSCLC

Adjuvant

Trial	Regimen
KEYNOTE-091/PEARLS[3]	Pembrolizumab
IMpower010[4]	Atezolizumab
CCTC BR31[5]	Durvalumab
ANVIL[6]	Nivolumab
NADIM-ADJUVANT[7]	Nivolumab + Chemotherapy

3. O'Brien M et al. *Lancet Oncol.* 2022 Oct;23(10):1274-1286. 4. Felip E et al. *Lancet*. 2021;398(10308):1344-1357. 5. Clinicaltrials.gov. NCT02273375. 6. Chaft JE et al. *Journal of Clinical Oncology* 36, no. 15_suppl 2018. Abstract TPS8581. 7. Calvo V et al. *Journal of Clinical Oncology* 39, no. 15_suppl 2021. Abstract TPS8581.

Adapted and Updated from ESMO Congress 2023 Industry Satellite Symposium

IMpower010: Adjuvant atezolizumab after chemotherapy in patients with completely resected stage IB-IIIA NSCLC[1]

N=1280

Key eligibility criteria

- Completely resected stage IB (≥4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0–1
- PD-L1 all-comers

Stratified by

Sex, histology, stage of disease (IB vs II vs IIIA), PD-L1 expression*

Up to 4 cycles of:
Cisplatin 75 mg/m²
+
Vinorelbine 30 mg/m²
or
Docetaxel 75 mg/m²
or
Gemcitabine 1250 mg/m²
or
Pemetrexed 500 mg/m²

N=1005

R
1:1

No crossover permitted

Atezolizumab 1200 mg
Q3W, 16 cycles

Best supportive care

Primary endpoints

- **DFS tested hierarchically**
  - **PD-L1 TC ≥1%†, stage II–IIIA population**
  - **All-randomized stage II–IIIA population**
  - ITT population IB–IIIA

Secondary endpoints

- OS in ITT population
- DFS in patients with PD-L1 TC ≥50%† and stage II–IIIA disease
- 3- and 5-year DFS in all populations

Adjuvant atezolizumab after resection and chemotherapy is approved in the US for patients with stage II-IIIA NSCLC and PD-L1 TC ≥1%

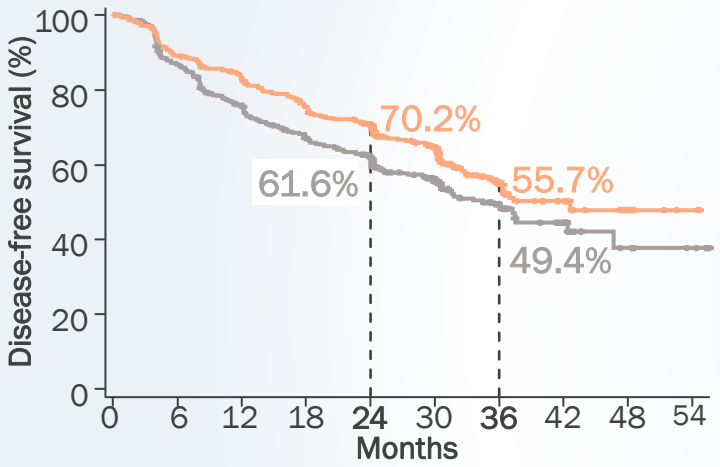
Adjuvant atezolizumab after resection and chemotherapy is approved in the EU for patients with NSCLC with high risk of recurrence whose tumors have PD-L1 TC ≥50%

*Per SP142 assay (Ventana). †Per SP263 assay (Ventana).
DFS=disease-free survival.

. Felip E et al. *Lancet*. 2021

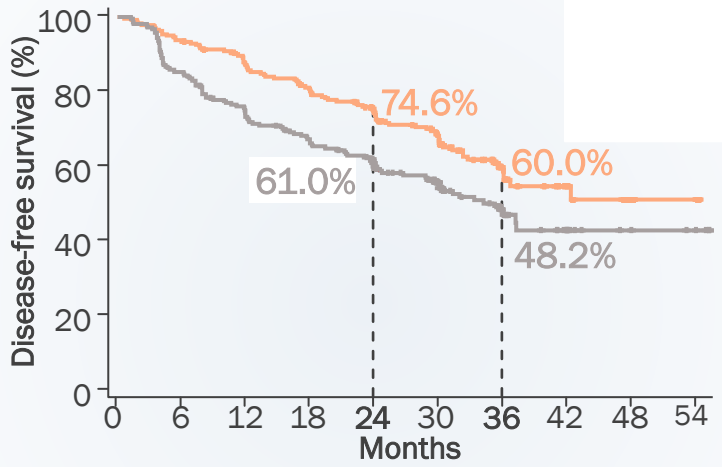
IMpower010: Adjuvant atezolizumab after chemotherapy showed highest DFS benefit in patients with PD-L1 TC ≥50%

Stage II-IIIA population, all-randomized[1]



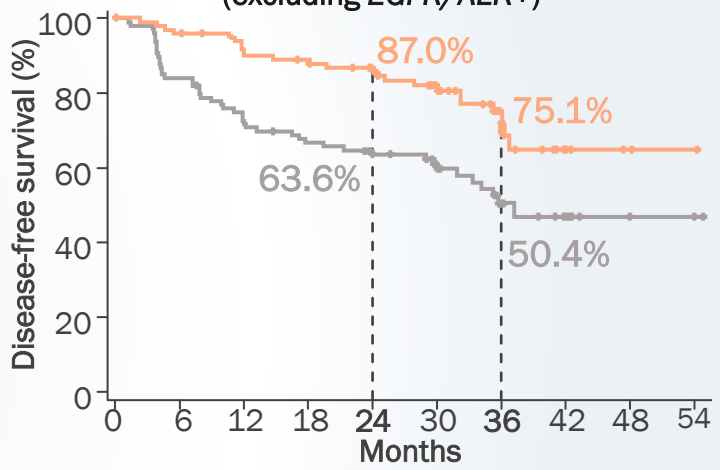
	Atezo (n=442)	BSC (n=440)
Median DFS, mo	42.3	35.3
HR (95% CI)	0.79 (0.64–0.96), *P*=0.02†	

Stage II-IIIA population, PD-L1 TC ≥1%[1]*



	Atezo (n=248)	BSC (n=228)
Median DFS, mo	NR	35.3
HR (95% CI)	0.66 (0.50–0.88), *P*=0.004†	

Stage II-IIIA population, PD-L1 TC ≥50%[2]† (excluding *EGFR/ALK*+)



	Atezo (n=106)	BSC (n=103)
Median DFS, mo	NR	37.3
HR (95% CI)	0.43 (0.26–0.71)	

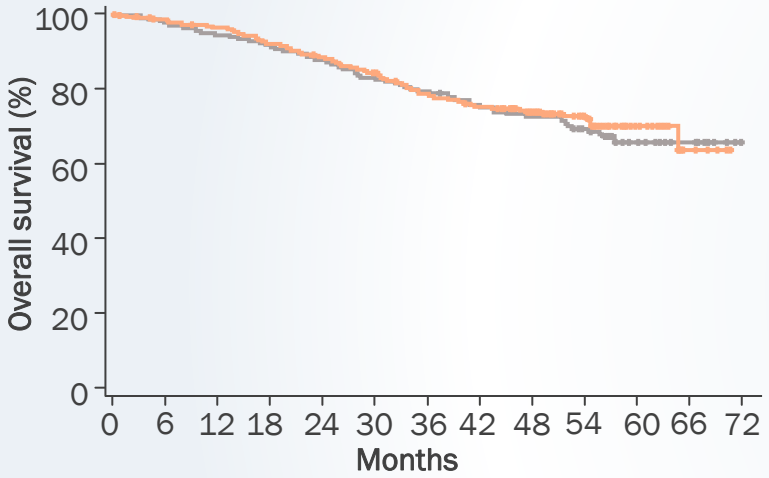
- Median DFS in the ITT population (IB-IIIA*) was not reached with atezolizumab and was 37.2 months with BSC (HR [95% CI]: 0.81 [0.67-0.99]) after median follow-up of 32.2 months; this endpoint did not cross the significance boundary at interim analysis[1]

Median follow-up: 32.2 months.
*Crossed the significance boundary for DFS. †Per SP263 assay (Ventana).

1. Felip E et al. *Lancet*. 2021. 2. Felip E et al. Oral presentation at ELCC 2022.

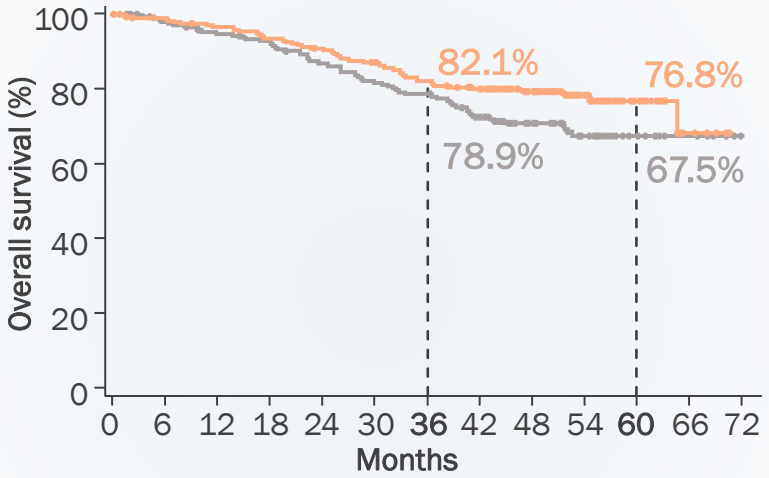
IMpower010: Adjuvant atezolizumab showed a trend towards improved OS in patients with PD-L1 TC ≥50%

Stage II-IIIA population, all-randomized[1]



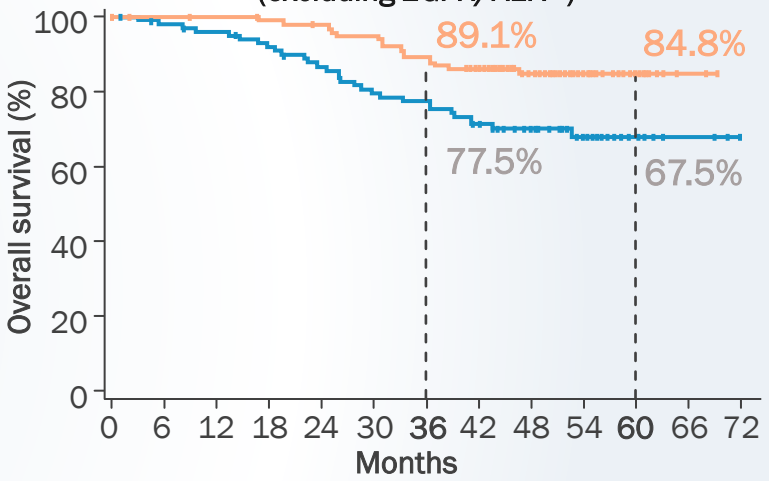
	Atezo (n=442)	BSC (n=440)
Median OS, mo	NR	NR
HR (95% CI)†	0.95 (0.74–1.24)	

Stage II-IIIA population, PD-L1 TC ≥1%[1]*



	Atezo (n=248)	BSC (n=228)
Median OS, mo	NR	NR
HR (95% CI)†	0.71 (0.49–1.03)	

Stage II-IIIA population, PD-L1 TC ≥50%[2]* (excluding *EGFR/ALK*+)



	Atezo (n=106)	BSC (n=103)
Median OS, mo	NR	NR
HR (95% CI)†	0.42 (0.23–0.78)	

- OS was not formally tested, and OS data were immature at this pre-specified OS interim analysis

Median follow-up: 45.3 months. *Per SP263 assay (Ventana). †Stratified.

Felip E et al. Oral presentation at WCLC 2022. 2. Rittmeyer A et al. Poster presentation at ESMO I-O 2022.

KEYNOTE-091: Adjuvant pembrolizumab after chemotherapy in patients with completely resected stage IB-IIIA NSCLC[1]

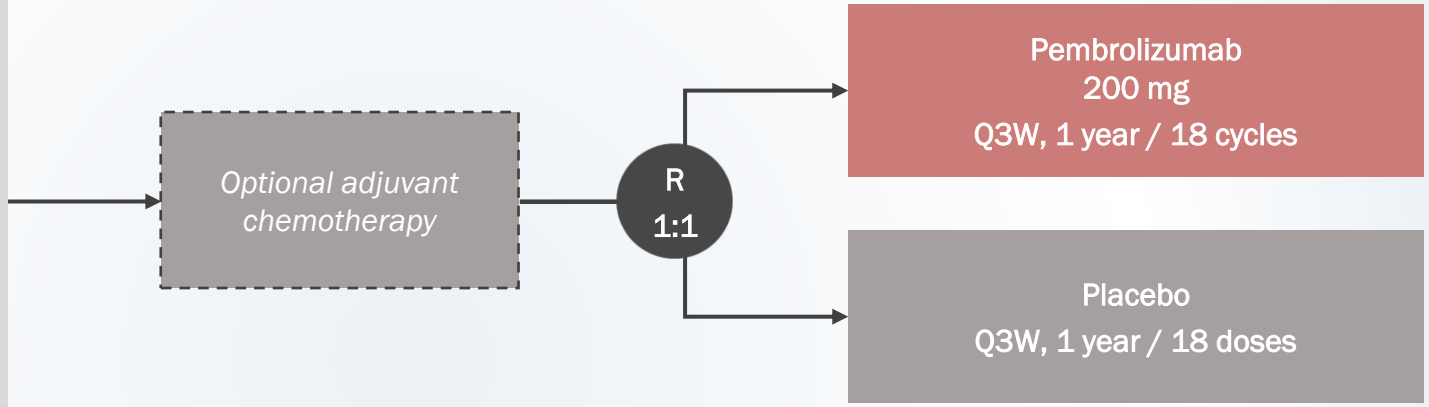
N=1177

Key Eligibility Criteria

- Completely resected stage IB (≥4 cm)–IIIA NSCLC (per AJCC 7th edition)
- ECOG performance status 0–1
- PD-L1 all-comers

Stratified by:

Stage of disease (IB vs II vs IIIA), adjuvant chemotherapy (yes vs no), PD-L1 status* (TPS 0% vs 1-49% vs ≥50%), region (Western vs Eastern Europe vs ROW)



Primary endpoints
- DFS† in ITT
- DFS† in patients with PD-L1 ≥50%

Secondary endpoints
- OS in ITT population
- LCSS

Adjuvant pembrolizumab after resection and chemotherapy is approved in the US for patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC

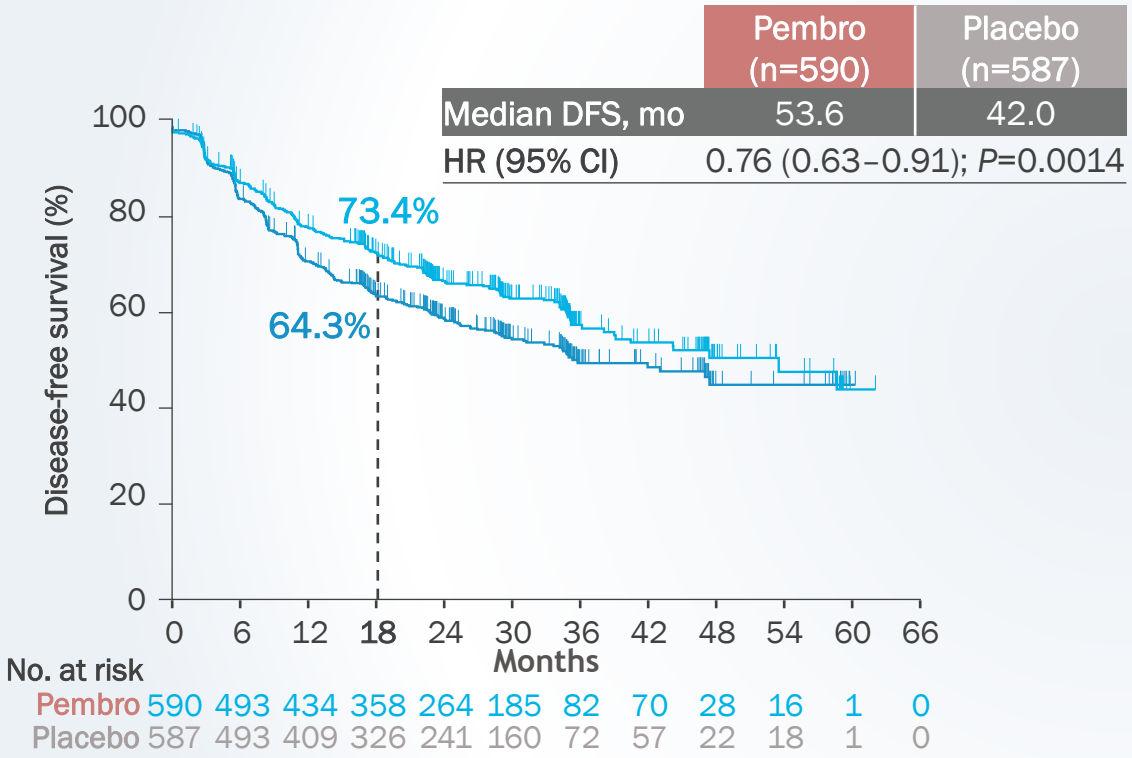
Adjuvant pembrolizumab is recommended by the CHMP to be approved for adult patients with NSCLC who are at high risk of recurrence following resection and chemotherapy

*Per 22C3 (Dako). †Assessed by RECIST v1.1 by investigator review.
LCSS=lung cancer-specific survival; RECIST=Response Evaluation Criteria In Solid Tumors; ROW=rest of the world; TPS=tumor proportion score; UICC=Union for International Cancer Control.

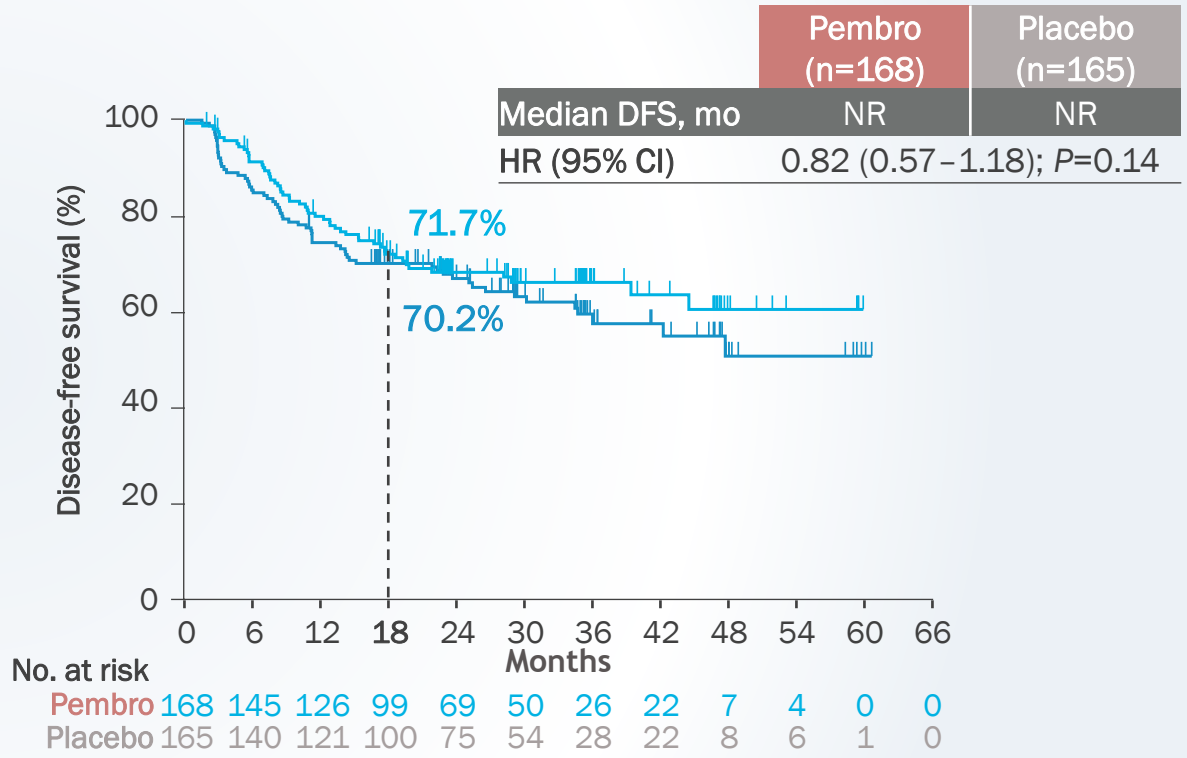
1. O'Brien M et al. *Lancet Oncol.* 2022

KEYNOTE-091: Adjuvant pembrolizumab showed DFS benefit among patients with stage IB-IIIA, but DFS was not statistically significant in PD-L1 ≥50% pts*

Stage IB-IIIA population, all-randomized[1]



Stage IB-IIIA population, PD-L1 ≥50%[1*†]



Median follow-up: 35.6 months. *Per 22C3 (Dako). †DFS in patients with PD-L1 ≥50% was not significant at the interim analysis.

1. O'Brien M et al. *Lancet Oncol.* 2022.

IMpower010 & KEYNOTE-091: Safety summary following one year of adjuvant I-O

	IMpower010[1]*		KEYNOTE-091[2†]	
	Atezo (n=495)	BSC (n=495)	Pembro (n=580)	Placebo (n=581)
All AEs (%)	93	71	96	91
Grade 3–5 AEs (%)	22	12	34	26
Serious AEs, (%)	18	8	24	15
AEs, leading to interruption (%)	29	-	38	25
AEs, leading to discontinuation (%)	18	-	20	6
AEs, leading to death (%)	2	1	2	1

Adjuvant atezolizumab after resection and chemotherapy is approved in the US for patients with stage II-IIIA NSCLC and PD-L1 TC ≥1%,[3] and in the EU for patients with NSCLC with high risk of recurrence whose tumors have PD-L1 TC ≥50%.[4]
Adjuvant pembrolizumab after resection and chemotherapy is approved in the US for patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC,[5] and is recommended by the CHMP to be approved for adult patients with NSCLC who are at high risk of recurrence.[6]
Slide intended for educational purposes only. Cross-study comparisons are not intended.
*Data are from the safety population (all randomized patients who received atezolizumab or BSC). †Data are from the safety population (all randomized patients who received ≥1 dose of assigned treatment).

1. Felip E et al. *Lancet*. 2021. 2. O'Brien M et al. *Lancet Oncol.* 2022

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC

Completed and Ongoing Select Phase 3 Trials

Resectable NSCLC

Perioperative

Trial	Regimen
CheckMate 77T[8]	Nivolumab + Chemotherapy → Nivolumab
IMpower030[9]	Atezolizumab + Chemotherapy → Atezolizumab
AEGEAN[10]	Durvalumab + Chemotherapy → Durvalumab
KEYNOTE-671[11]	Pembrolizumab + Chemotherapy → Pembrolizumab
Neotorch[12]	Toripalimab + Chemotherapy → Toripalimab + Chemotherapy → Toripalimab

8. Cascone T, ESMO Congress 223 LBA1. 9. Peters S et al. *Annals of Oncology*. Volume 30, Supplement 2, 2019. Abstract 82TiP. 10. Heymach JV et al. *N Engl J Med 2023*. 11. Wakelee H e al. *N Engl J Med*. 2023 Jun 3. 12. Lu S et al. *Journal of Clinical Oncology* 41, no. 16_suppl 2023. 8501-8501.

Adapted and Updated from ESMC Congress 2023 Industry Satellite Symposium

AEGEAN: Neoadjuvant Durva + CT followed by adjuvant Durva in patients with resectable stage IIA-IIIB NSCLC

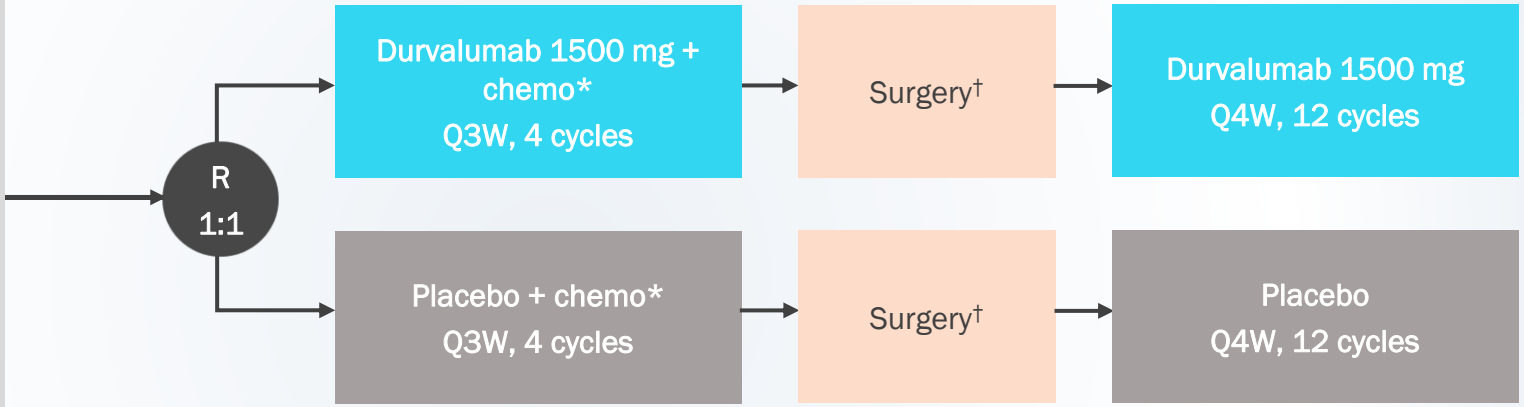
N=816

Key eligibility criteria

- Previously untreated resectable stage IIA-select IIIB (N2) NSCLC (per AJCC 8th edition)
- No *EGFR* mutations or *ALK* alterations
- ECOG performance status 0–1
- PD-L1 all-comers

Stratified by

Stage of disease (II vs III), PD-L1 TC expression (<1% vs ≥1%)



Primary endpoints

- pCR
- EFS

Secondary endpoints

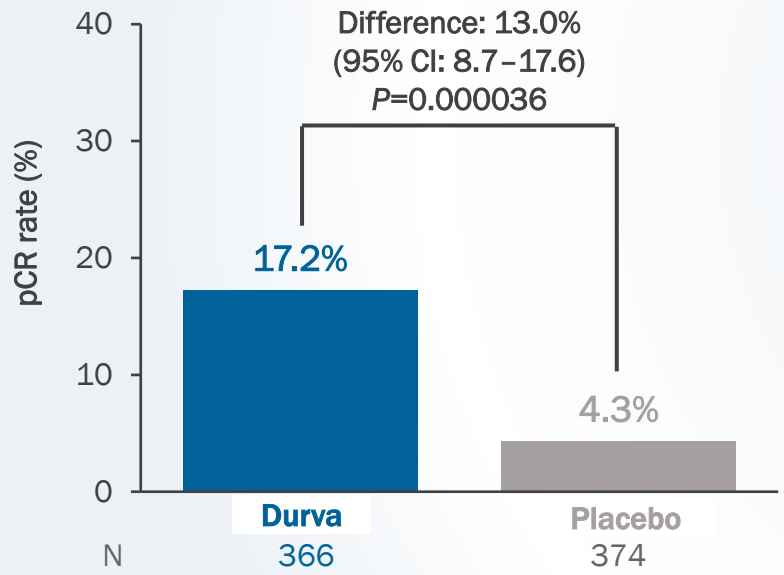
- MPR
- DFS
- OS
- pCR, MPR, EFS, DFS, OS in patients with PD-L1 ≥1%
- HRQoL/PROs

*Carboplatin + paclitaxel, cisplatin + gemcitabine, pemetrexed + cisplatin, or pemetrexed + carboplatin. †Lobectomy, bilobectomy, or sleeve resection as determined by the attending surgeon.
HRQoL=health-related quality of life; PRO=patient-reported outcome; Q4W=every 4 weeks.

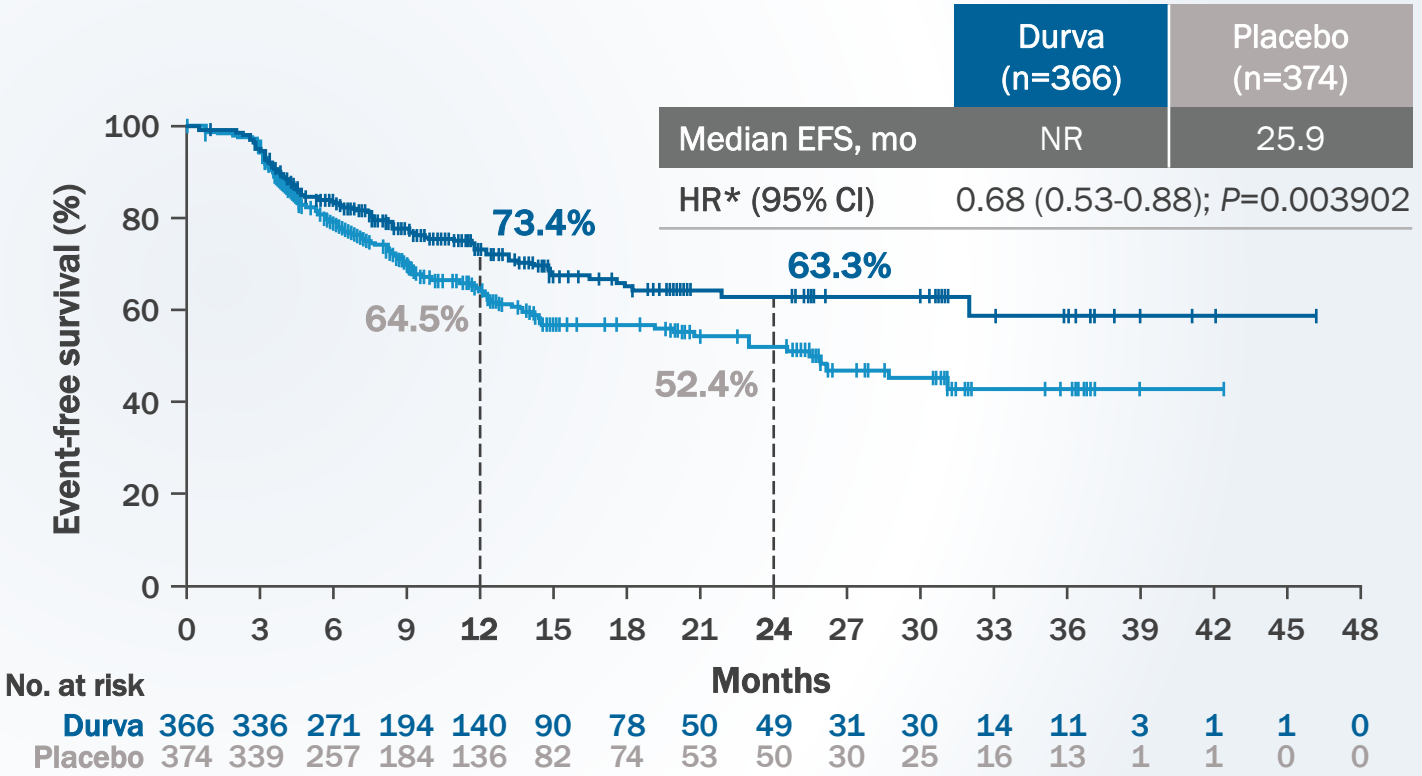
Heymach JV et al. *N Engl J Med* 2023

AEGEAN: Neoadjuvant durva + CT followed by adjuvant durva significantly improved pCR and EFS in patients with resectable stage IIA-IIIB (N2) NSCLC

pCR rate (central lab) per IASLC 2020 methodology



EFS per BICR

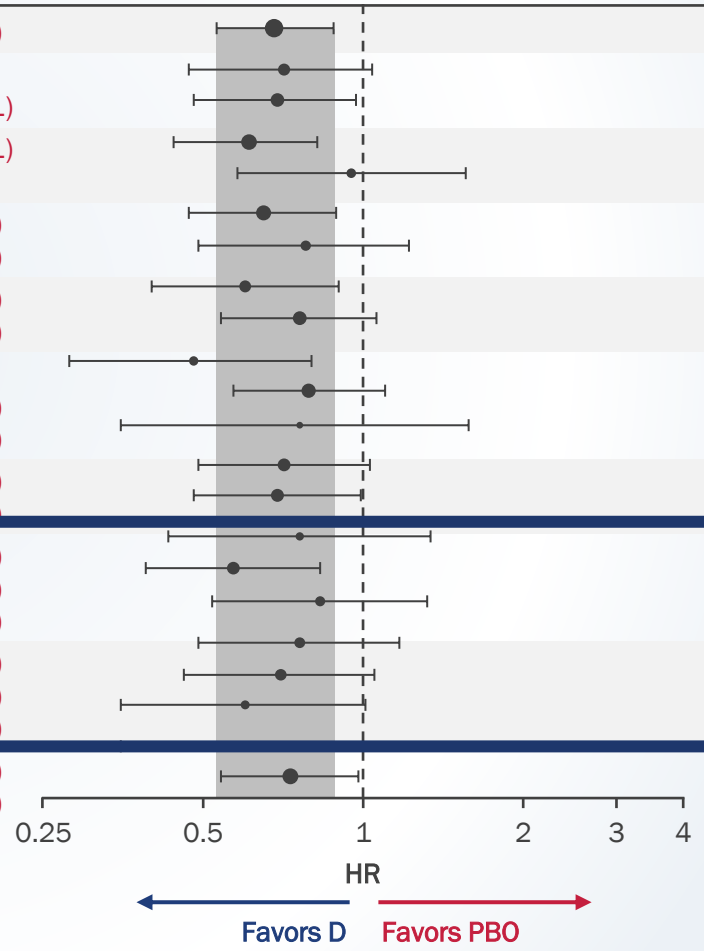


Database lock: November 10, 2022; median follow-up: 11.7 months.
*Stratified.
IASLC=International Association for the Study of Lung Cancer.

Heymach JV et al. *N Engl J Med* 2023

AEGEAN: EFS benefit from perioperative Durva + CT across subgroups

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 JV, *N Engl J Med* 2023

NEOTORCH: Neoadjuvant Tori + CT followed by adjuvant Tori + CT and Tori maintenance in resectable stage II-III NSCLC

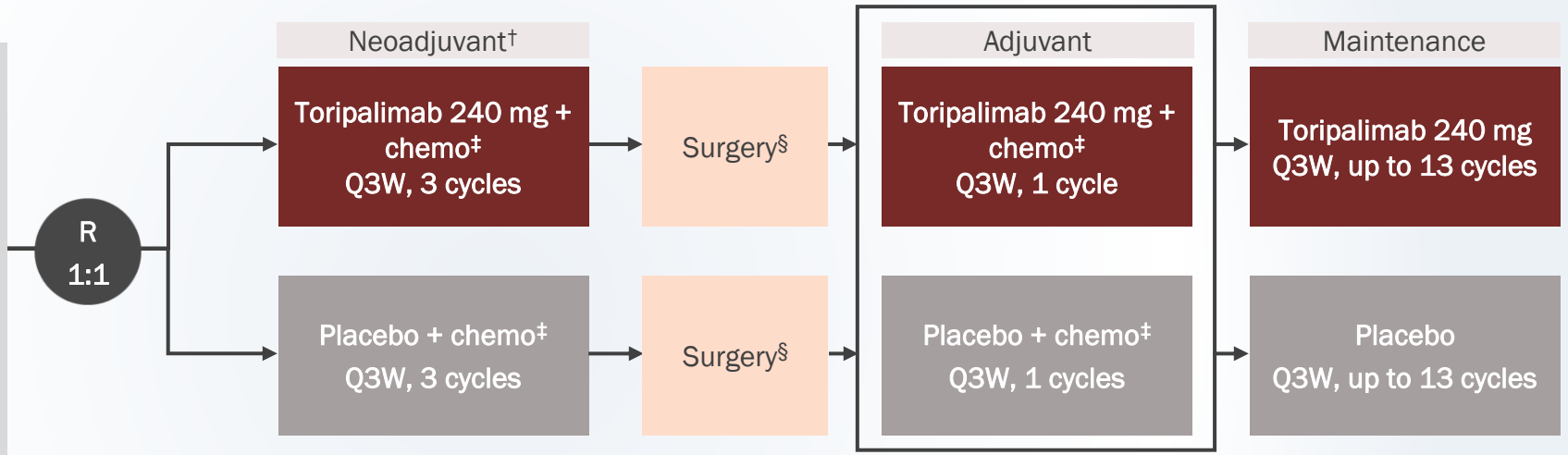
N=500*

Key eligibility criteria

- Newly diagnosed resectable stage II-III NSCLC
- No *EGFR* mutations or *ALK* alterations

Stratified by

Stage of disease (II vs IIIA vs IIIB), lobectomy vs pneumonectomy, non-squamous vs squamous, PD-L1 expression (≥1% vs <1% or non-evaluable)



Primary endpoints

- **EFS by investigator (stage III)**
- EFS by investigator (stage II-III)
- **MPR by BIPR (stage III)**
- MPR by BIPR (stage II-III)

Secondary endpoints

- **OS**
- **pCR by BIPR/site pathologist**
- EFS by IRC
- DFS
- Safety and feasibility of surgery

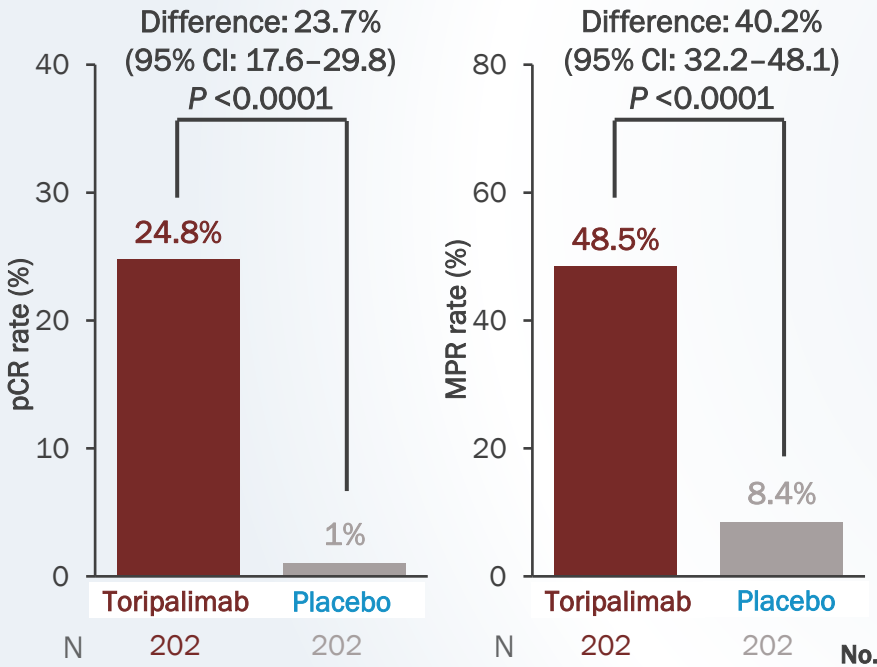
*About 400 patients with stage III NSCLC and about 100 patients with stage II NSCLC. †3 cycles of neoadjuvant chemo with 4 cycles of perioperative chemo in total were required in the study. ‡Platinum-based chemo. §Surgeons allowed to determine most appropriate timing for surgery based on the patient's condition.

Lu S et al. Oral presentation at ASCO 2023.

NEOTORCH: Perioperative Tori + CT significantly improved pCR and EFS in resectable stage III NSCLC; OS was immature

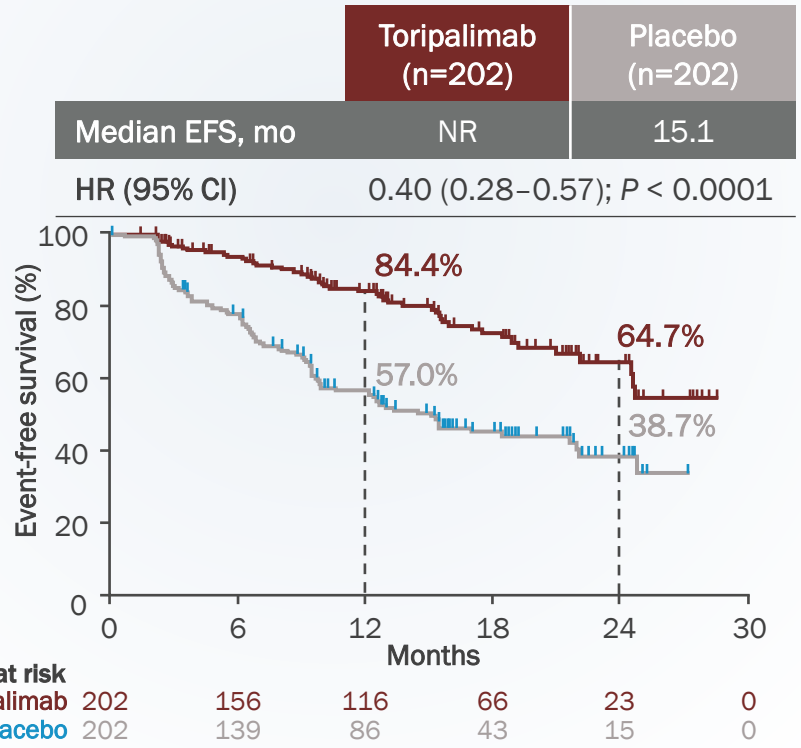
pCR and MPR rate per BIPR

Stage III population



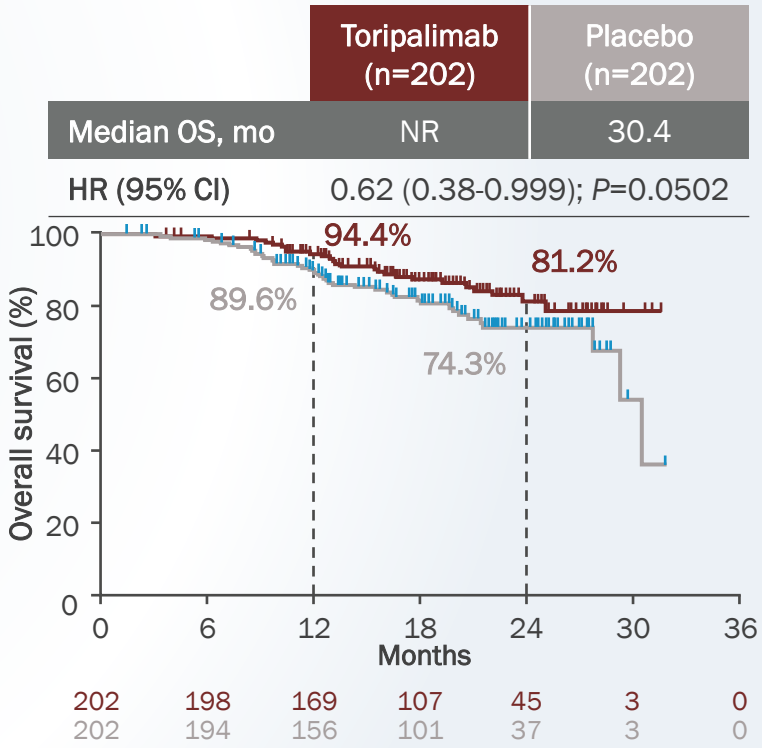
EFS per investigator

Stage III population



OS

Stage III population

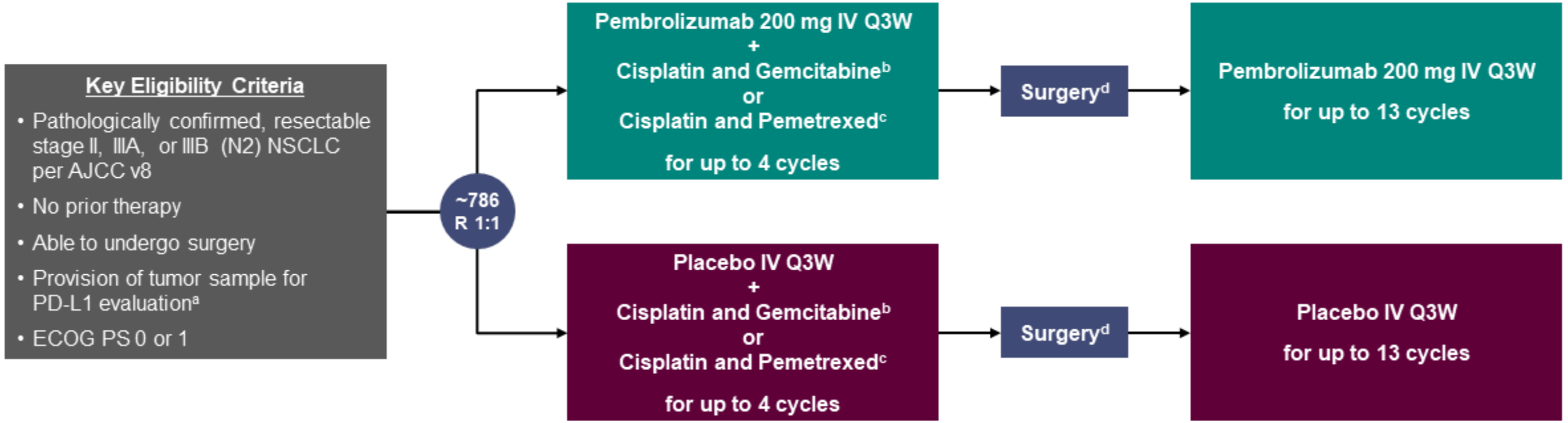


Database lock: November 30, 2022; median follow-up: 18.25 months.

Lu S et al. Oral presentation at ASCO 2023.

KEYNOTE-671 Study Design

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

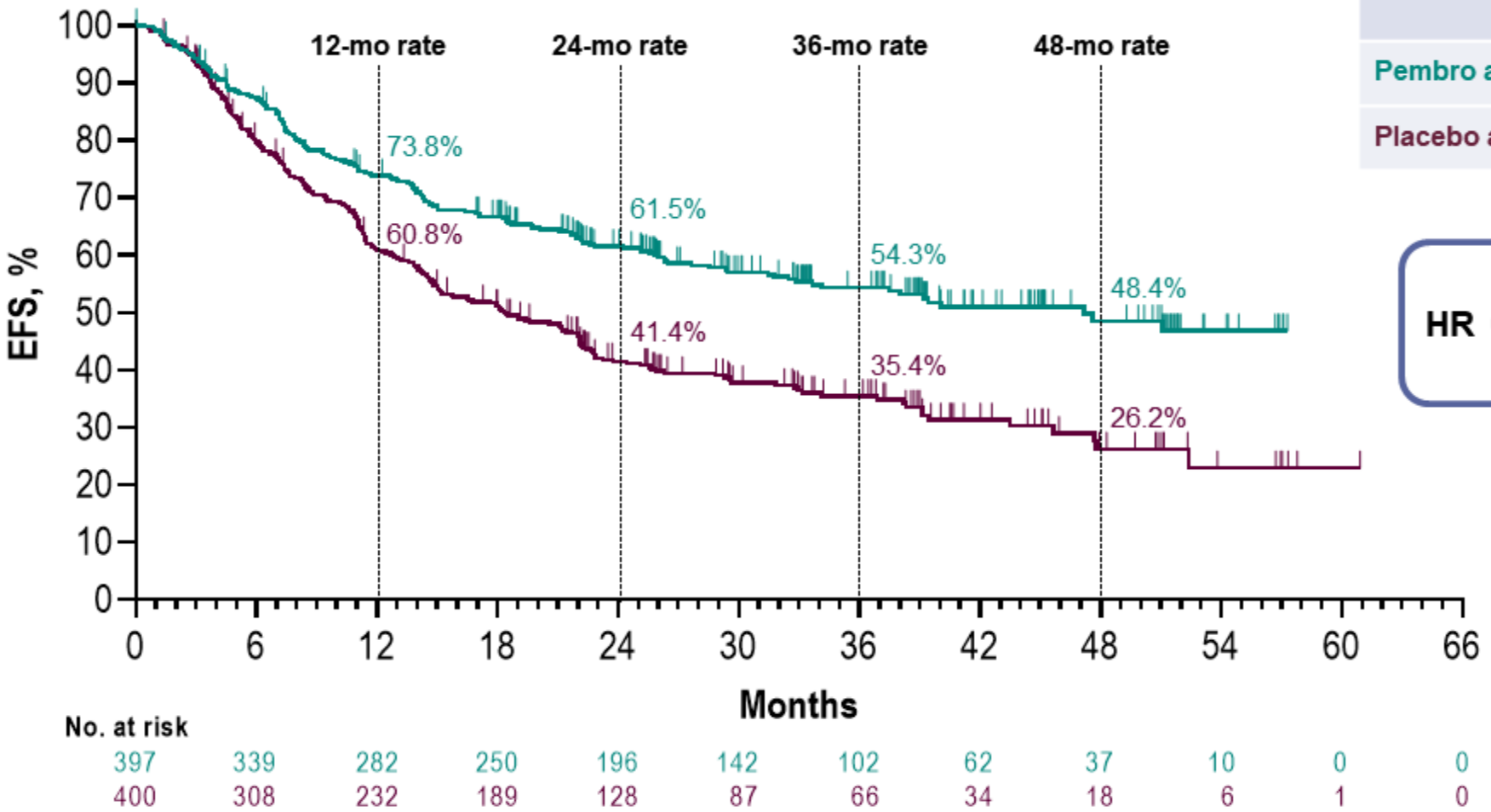
Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

Neoadjuvant pembrolizumab + chemo followed by adjuvant pembrolizumab is approved in the US for patients with stage II, IIIA, or IIIB (T3-4N2) NSCLC

[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.

Event-Free Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



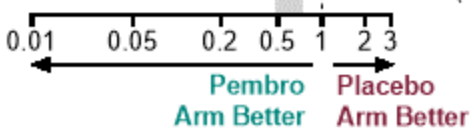
	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

HR 0.59 (95% CI, 0.48-0.72)

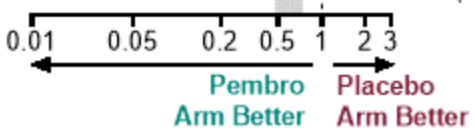
EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA2: July 10, 2023.

Event-Free Survival in Subgroups, IA2

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Age			
<65 y	88/221	136/214	0.51 (0.39-0.67)
≥65 y	86/176	112/186	0.70 (0.52-0.92)
Sex			
Female	47/118	70/116	0.52 (0.36-0.75)
Male	127/279	178/284	0.62 (0.49-0.78)
Race			
White	109/250	151/239	0.56 (0.44-0.72)
All others	57/134	85/145	0.63 (0.45-0.88)
Geographic region			
East Asia	51/123	70/121	0.63 (0.44-0.91)
Not east Asia	123/274	178/279	0.57 (0.45-0.72)
Smoking status			
Current	44/96	68/103	0.53 (0.36-0.77)
Former	105/247	155/250	0.59 (0.46-0.75)
Never	25/54	25/47	0.77 (0.44-1.35)
Histology			
Nonsquamous	102/226	131/227	0.66 (0.51-0.86)
Squamous	72/171	117/173	0.51 (0.38-0.69)



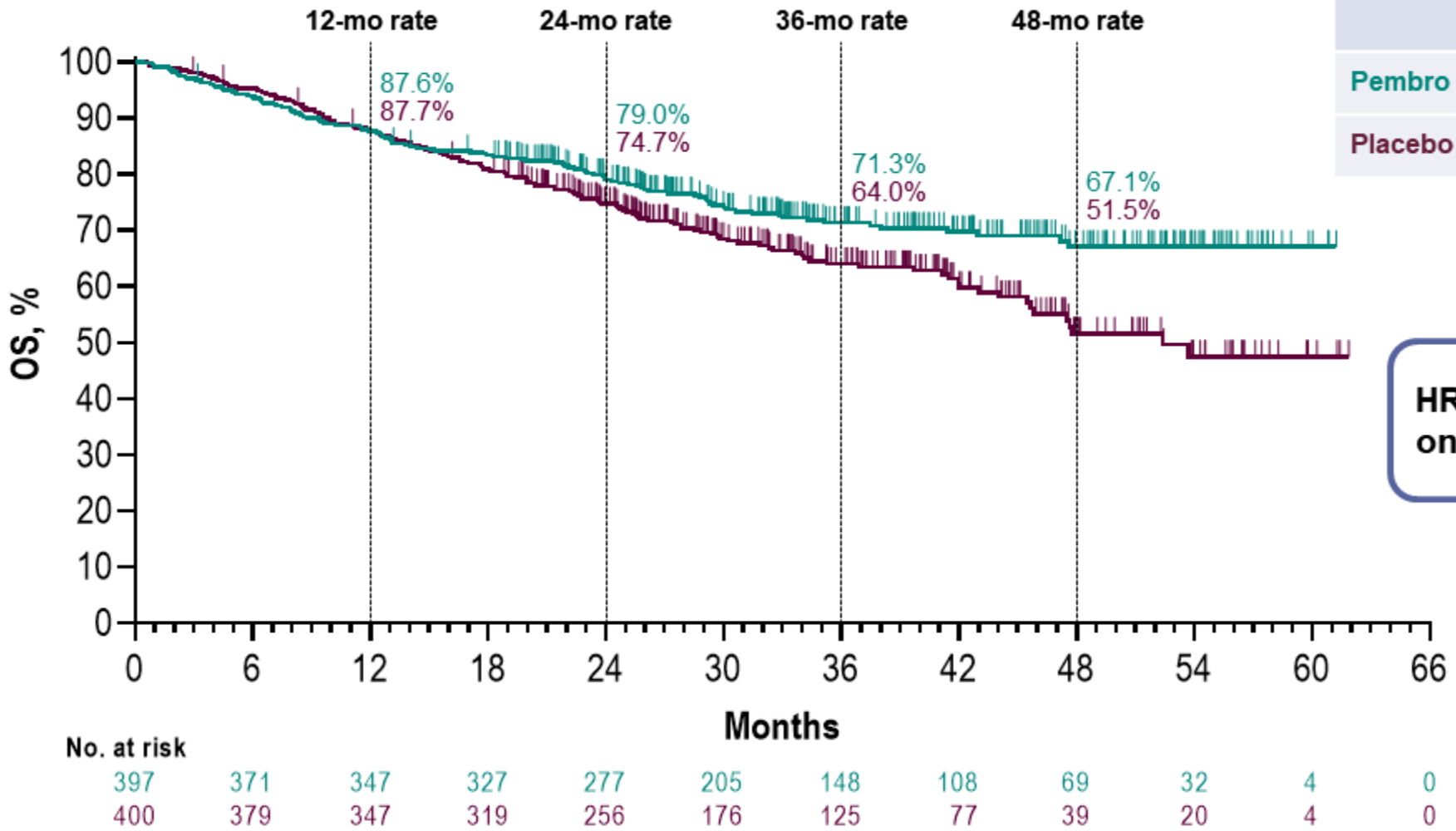
Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Clinical stage			
II	40/118	62/121	0.59 (0.40-0.88)
IIIA	100/217	145/224	0.57 (0.44-0.74)
IIIB	34/62	41/55	0.57 (0.36-0.90)
N status			
cN0	59/148	83/142	0.58 (0.41-0.81)
cN1	29/81	39/71	0.56 (0.35-0.91)
cN2	86/168	126/187	0.63 (0.48-0.82)
PD-L1 TPS			
≥50%	41/132	70/134	0.48 (0.33-0.71)
1-49%	55/127	76/115	0.52 (0.36-0.73)
<1%	78/138	102/151	0.75 (0.56-1.01)
***EGFR* mutation**			
No	42/111	72/124	0.55 (0.38-0.81)
Yes	5/14	13/19	0.32 (0.11-0.91)
Unknown	127/272	163/257	0.62 (0.49-0.79)
***ALK* translocation**			
No	42/104	85/132	0.50 (0.35-0.73)
Unknown	126/281	160/259	0.62 (0.49-0.78)



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 IA2: July 10, 2023.

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

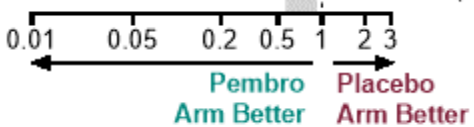
HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

Neoadjuvant pembrolizumab + chemo followed by adjuvant pembrolizumab is approved in the US for patients with stage II, IIIA, or IIIB (T3-4N2) NSCLC

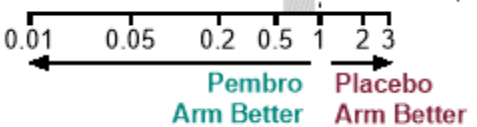
OS defined as time from randomization to death from any cause. [a] Significance boundary at IA2, one-sided *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in Subgroups, IA2

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Age			
<65 y	54/221	82/214	0.57 (0.40-0.80)
≥65 y	56/176	62/186	0.96 (0.67-1.38)
Sex			
Female	21/118	30/116	0.69 (0.39-1.20)
Male	89/279	114/284	0.73 (0.55-0.96)
Race			
White	73/250	97/239	0.66 (0.49-0.90)
All others	34/134	39/145	0.93 (0.59-1.48)
Geographic region			
East Asia	32/123	30/121	1.05 (0.64-1.73)
Not east Asia	78/274	114/279	0.63 (0.48-0.85)
Smoking status			
Current	31/96	48/103	0.59 (0.38-0.93)
Former	69/247	87/250	0.76 (0.56-1.05)
Never	10/54	9/47	1.00 (0.41-2.46)
Histology			
Nonsquamous	49/226	64/227	0.73 (0.50-1.06)
Squamous	61/171	80/173	0.71 (0.51-0.99)



Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Clinical stage			
II	26/118	39/121	0.67 (0.41-1.10)
IIIA	62/217	79/224	0.74 (0.53-1.03)
IIIB	22/62	26/55	0.69 (0.39-1.22)
N status			
cN0	40/148	52/142	0.70 (0.46-1.06)
cN1	21/81	24/71	0.74 (0.41-1.33)
cN2	49/168	68/187	0.74 (0.52-1.07)
PD-L1 TPS			
≥50%	23/132	39/134	0.55 (0.33-0.92)
1-49%	35/127	44/115	0.69 (0.44-1.07)
<1%	52/138	61/151	0.91 (0.63-1.32)
***EGFR* mutation**			
No	20/111	33/124	0.64 (0.37-1.11)
Yes	1/14	5/19	0.24 (0.03-2.03)
Unknown	89/272	106/257	0.75 (0.56-0.99)
***ALK* translocation**			
No	22/104	38/132	0.70 (0.41-1.18)
Unknown	87/281	105/259	0.72 (0.54-0.96)



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 IA2: July 10, 2023.

AEGEAN, KEYNOTE-671, & NEOTORCH: Safety summary following I-O-based perioperative treatment

	AEGEAN[1]*		KEYNOTE-671[2]‡		NEOTORCH[3]‖	
	Durva (n=400)	Placebo (n=399)	Pembro (n=396)	Placebo (n=399)	Tori + chemo (n=202)	Placebo + chemo (n=202)
All AEs (%)	96.5†	94.7†	96.7§	95.0§	99.5¶	98.5¶
Grade ≥3 AEs (%)	42.3†	43.4†	44.9§	37.3§	63.4¶	54.0¶
Serious AEs, (%)	37.5†	31.6†	17.7§	14.3§	40.6	28.2
AEs, leading to interruption (%)	-	-	-	-	28.2¶	14.4¶
AEs, leading to discontinuation (%)	12.0†	6.0†	12.6§	5.3§	9.4¶	7.4¶
AEs, leading to death (%)	5.8†	3.8†	1.0§	0.8§	3.0¶	2.0¶

Slide intended for educational purposes only. Cross-study comparisons are not intended.

*Data are from the safety population (all randomized patients who received ≥1 dose of assigned treatment), inclusive of the neoadjuvant, surgical, and adjuvant treatment phases. †All-causality AEs. ‡Across all treatment phases in patients who underwent randomization and received ≥1 dose of assigned treatment. §Treatment-related AEs. ‖In patients with resectable stage III NSCLC. ¶Treatment-emergent AEs.

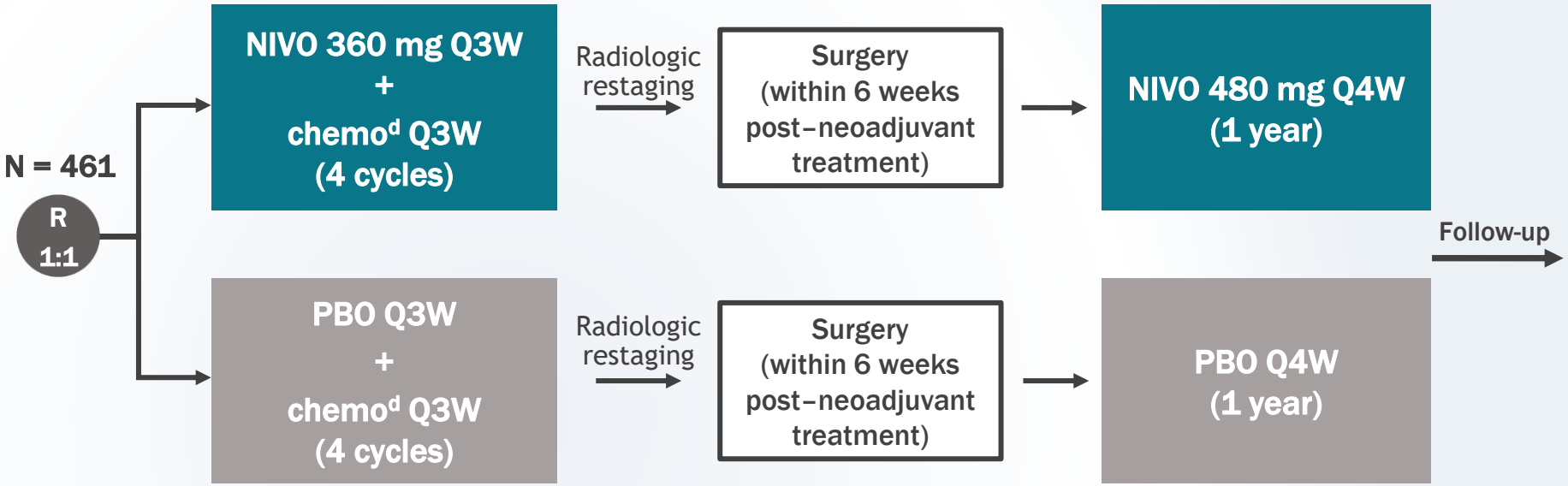
1. Heymach JV et al. *N Eng J Med* 2023. Abstract CT005. 2. Wakelee H et al. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2302983. 3. Lu S et al. Oral presentation at ASCO 2023. Abstract 8501.

CheckMate 77T[a] study design

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)–IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0–1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)



Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

Database lock date: September 6, 2023.

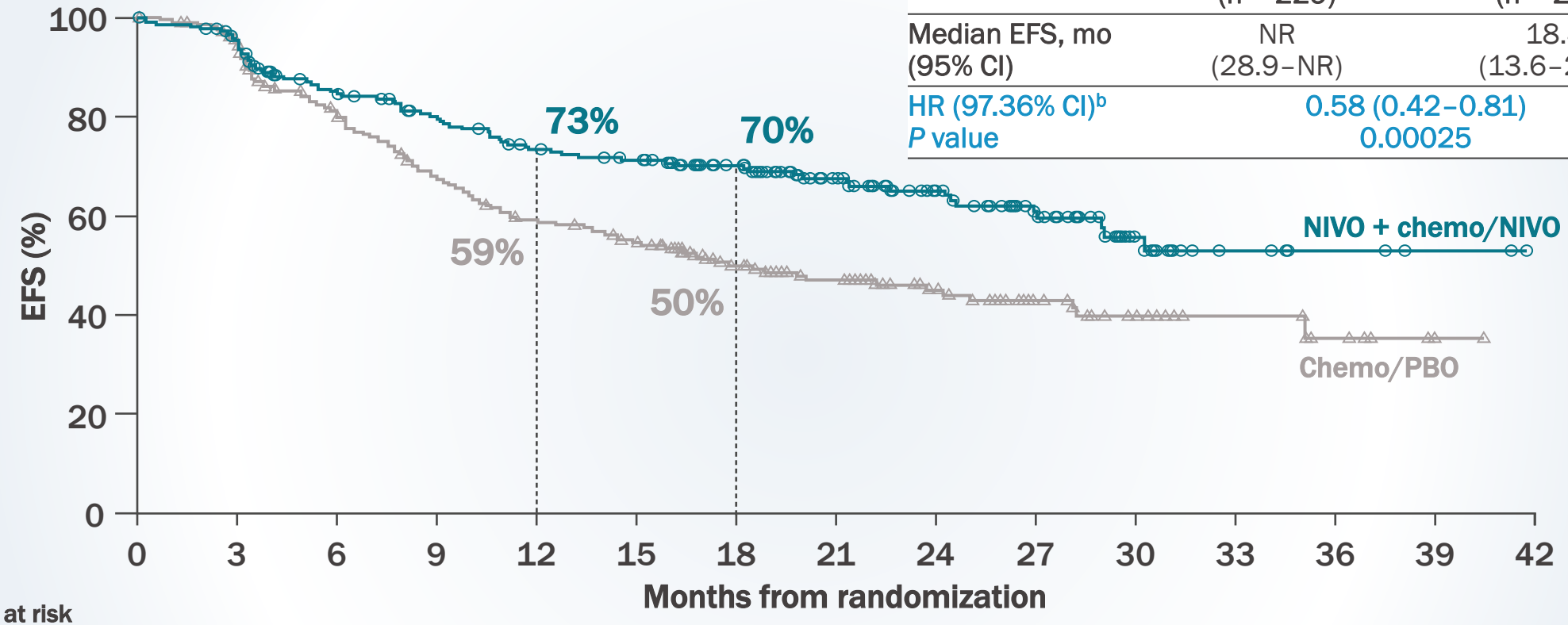
[a]NCT04025879. [b]*EGFR* testing was mandatory in all patients with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority–approved assays. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [e]Assessed per immune-related pathologic response criteria.[1] BICR, blinded independent central review; BIPR, blinded independent pathological review.

1. Cottrell TR, et al. *Ann Oncol* 2018:29:1853–1860.

Cascone T, ESMO Congress 2023, LBA1

Primary endpoint:
EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9–NR)	18.4 (13.6–28.1)
HR (97.36% CI)[b]	0.58 (0.42–0.81)	
P value	0.00025	



No. at risk															
NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

- **EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41–0.76**

Median follow-up (range): 25.4 months (15.7–44.2).

[a]Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b]Unstratified HR (95% CI), 0.59 (0.44–0.79).

Cascone T, ESMO Congress 2023, LBA1

EFS analysis by key subgroups

	Median EFS,[a] mo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
Overall (N = 461)	NR	18.4		0.59 (0.44–0.79)
< 65 years (n = 202)	NR	16.7		0.55 (0.36–0.85)
≥ 65 years (n = 259)	NR	20.1		0.61 (0.41–0.91)
Male (n = 327)	NR	16.7		0.53 (0.37–0.75)
Female (n = 134)	30.2	18.8		0.71 (0.41–1.20)
North America (n = 44)	30.2	9.4		0.59 (0.25–1.38)
Europe (n = 250)	NR	23.7		0.61 (0.40–0.92)
Asia (n = 115)	NR	13.9		0.47 (0.26–0.86)
ECOG PS 0 (n = 288)	NR	20.1		0.57 (0.39–0.83)
ECOG PS 1 (n = 173)	29.0	17.3		0.61 (0.39–0.97)
Stage II (n = 162)	NR	NR		0.81 (0.46–1.43)
Stage III (n = 297)	30.2	13.4		0.51 (0.36–0.72)
N0 (n = 167)[b]	NR	NR		0.80 (0.48–1.32)
N1 (n = 108)[b]	NR	28.1		0.58 (0.29–1.16)
N2 (n = 182)[b,c]	30.2	10.0		0.46 (0.30–0.70)
Single-station (n = 112)	30.2	10.0		0.49 (0.29–0.84)
Multi-station (n = 69)	NR	10.0		0.43 (0.21–0.88)
Squamous (n = 234)	NR	17.0		0.46 (0.30–0.72)
Non-squamous (n = 227)	28.9	18.4		0.72 (0.49–1.07)
Current/former smoker (n = 417)	NR	17.0		0.54 (0.40–0.74)
Never smoker (n = 44)	19.7	25.0		1.32 (0.54–3.20)
PD-L1 < 1% (n = 186)[d]	29.0	19.8		0.73 (0.47–1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8		0.52 (0.35–0.78)
PD-L1 1–49% (n = 159)[e]	30.2	28.1		0.76 (0.46–1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0		0.26 (0.12–0.55)
Cisplatin (n = 97)	27.0	15.8		0.61 (0.35–1.08)
Carboplatin (n = 347)	NR	17.3		0.53 (0.37–0.75)

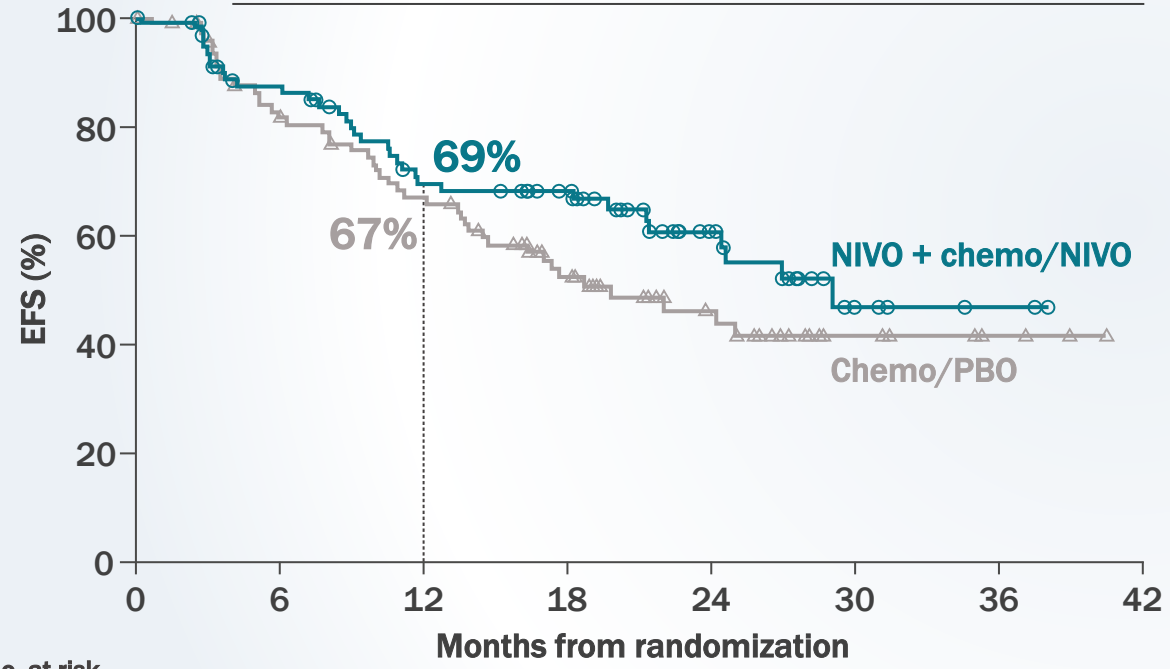
Median follow-up (range): 25.4 months (15.7–44.2).

Cascone T, ESMO Congress 2023, LBA1

EFS by tumor PD-L1 expression

Tumor PD-L1 < 1%

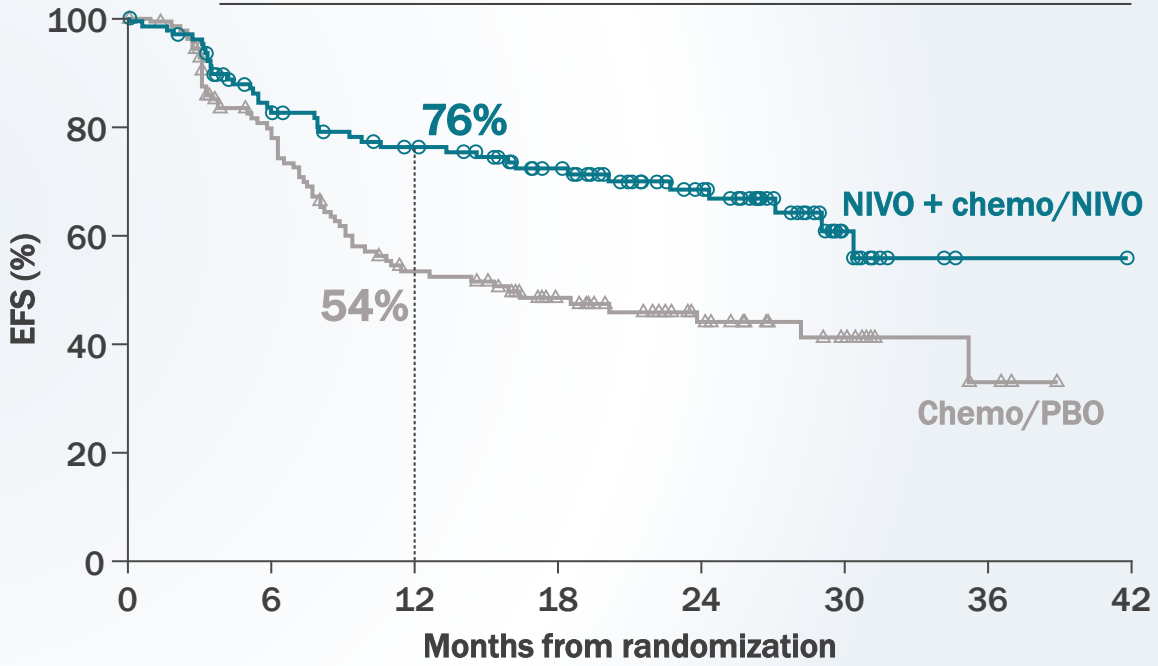
	NIVO + chemo/NIVO (n = 93)	Chemo/PBO (n = 93)
Median EFS, mo (95% CI)	29.0 (21.4–NR)	19.8 (13.9–NR)
HR (95% CI)	0.73 (0.47–1.15)	



No. at risk								
NIVO + chemo/NIVO	93	71	53	45	23	6	2	0
Chemo/PBO	93	69	55	34	19	7	3	0

Tumor PD-L1 ≥ 1%

	NIVO + chemo/NIVO (n = 128)	Chemo/PBO (n = 128)
Median EFS, mo (95% CI)	NR (28.9–NR)	15.8 (9.3–35.1)
HR (95% CI)	0.52 (0.35–0.78)	

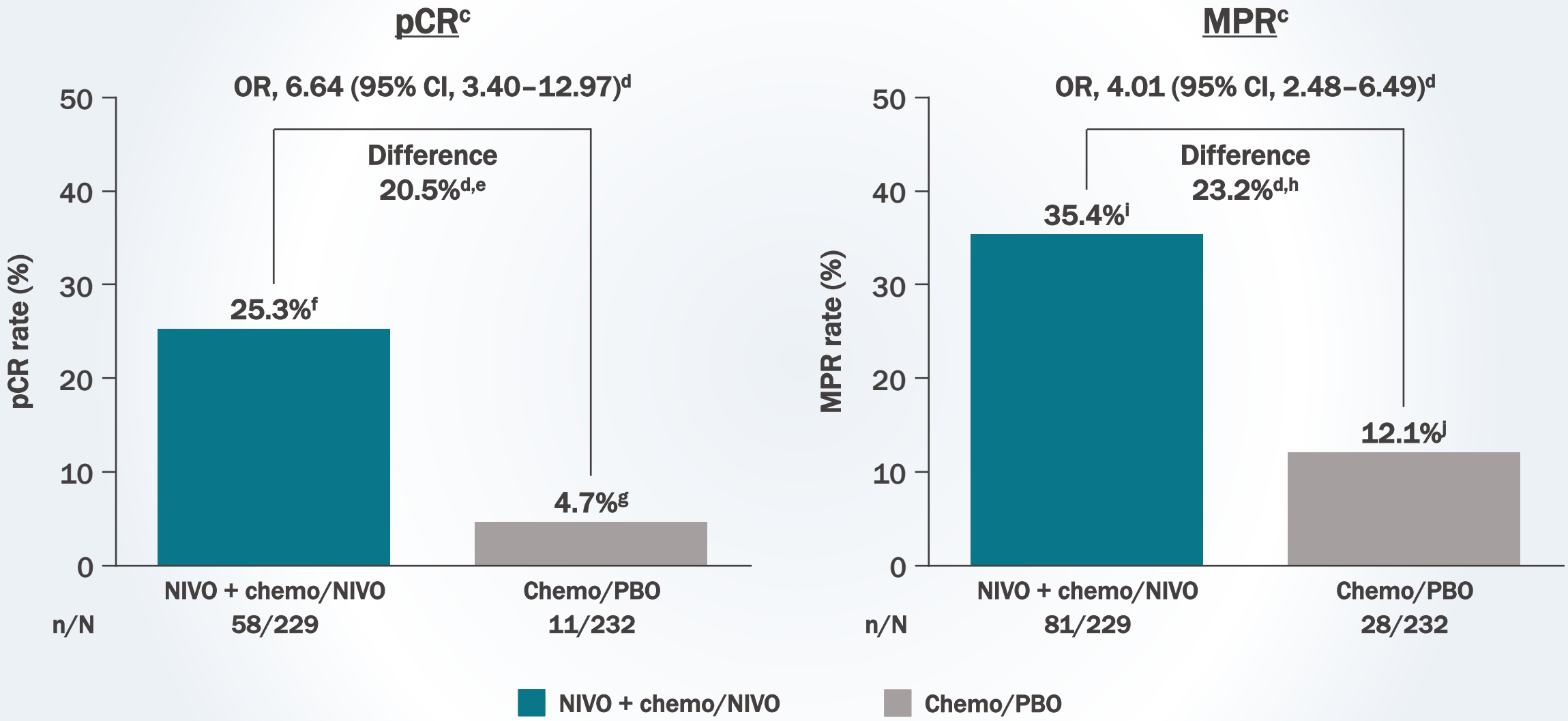


No. at risk								
NIVO + chemo/NIVO	128	95	82	66	43	12	1	0
Chemo/PBO	128	87	57	41	24	12	3	0

Median follow-up (range): 25.4 months (15.7–44.2).

Cascone T, ESMO Congress 2023, LBA1

pCR[a] and MPR[b] per BIPR



[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [b]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [c]Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-responders. [d]Calculated using the stratified Cochran–Mantel–Haenszel method. [e–j]95% CI: [e]14.3–26.6; [f]19.8–31.5; [g]2.4–8.3; [h]15.8–30.6; [i]29.2–41.9; [j]8.2–17.0. BIPR, blinded independent pathological review.

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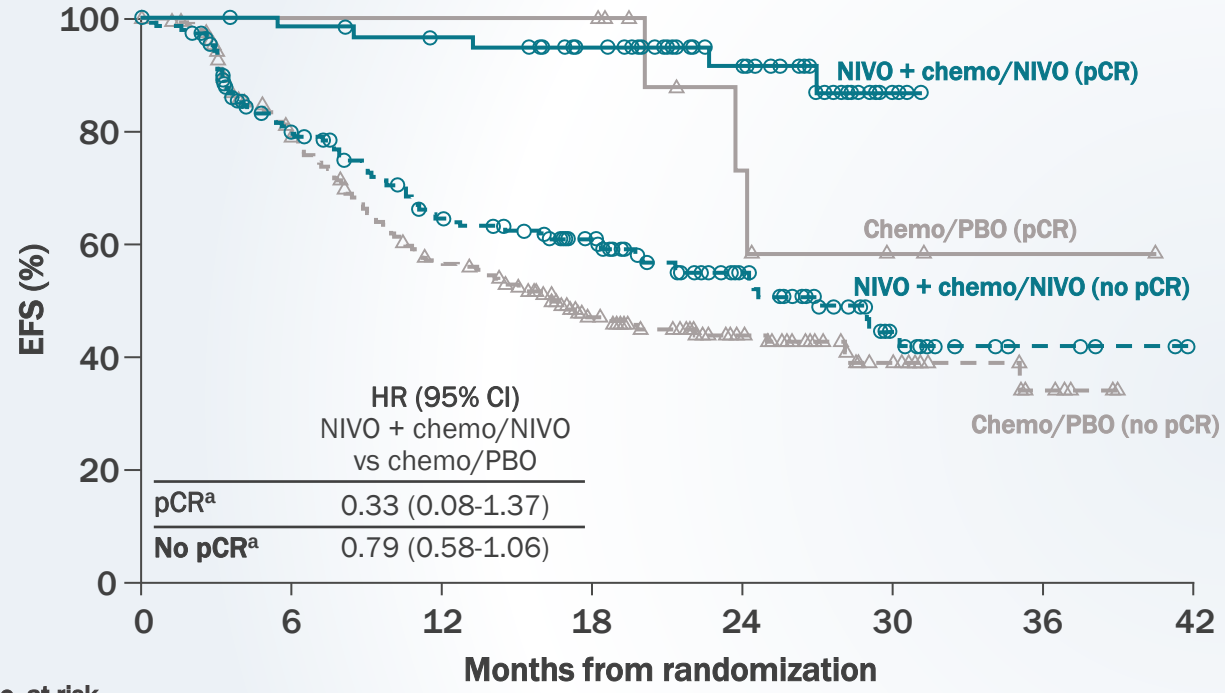
Exploratory analysis: EFS by pCR and MPR status

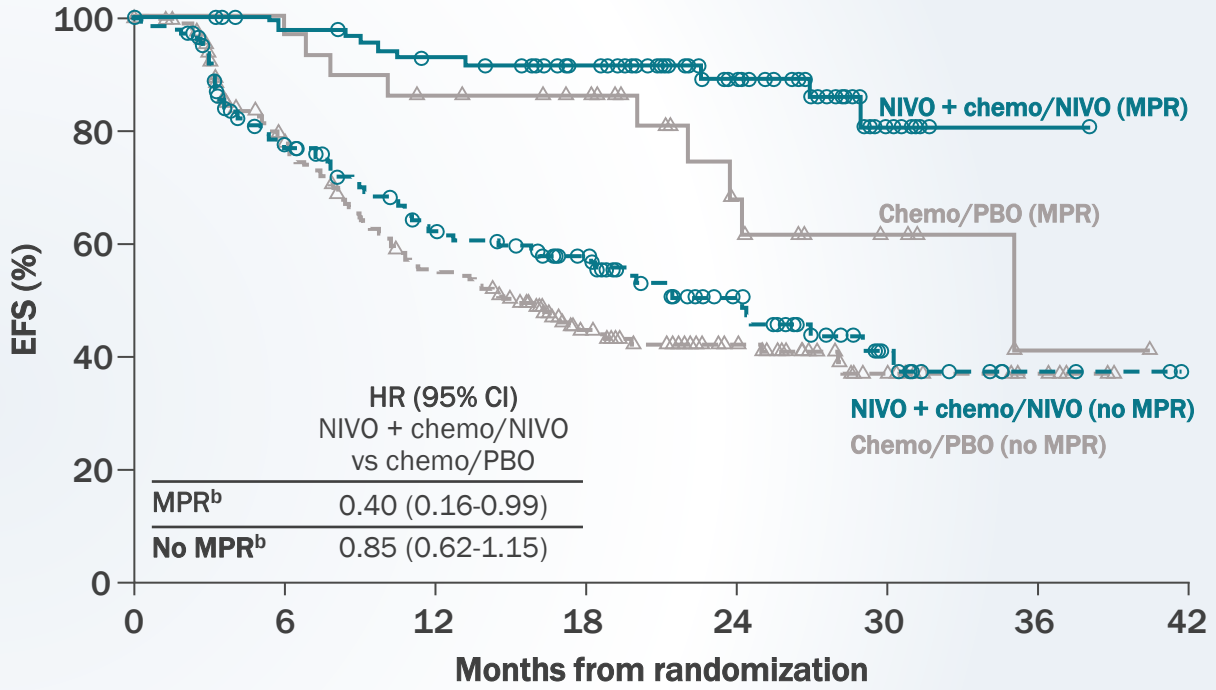
EFS by pCR



No. at risk

pCR	58	56	53	45	28	4	0	0
pCR	11	11	11	11	5	2	1	0
No pCR	171	117	88	70	41	16	4	0
No pCR	221	154	107	67	39	17	5	0

EFS by MPR



MPR	81	76	70	59	37	8	1	0
MPR	28	27	23	20	10	5	1	0
No MPR	148	97	71	56	32	12	3	0
No MPR	204	138	95	58	34	14	5	0

Median follow-up (range): 25.4 months (15.7–44.2).

[a]HR (95% CI), 0.14 (0.06–0.35) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.32 (0.10–1.00) in the chemo/PBO arm. [b]HR (95% CI), 0.18 (0.09–0.35) in patients with MPR vs those without in the NIVO + chemo/NIVO arm and 0.40 (0.20–0.78) in the chemo/PBO arm.

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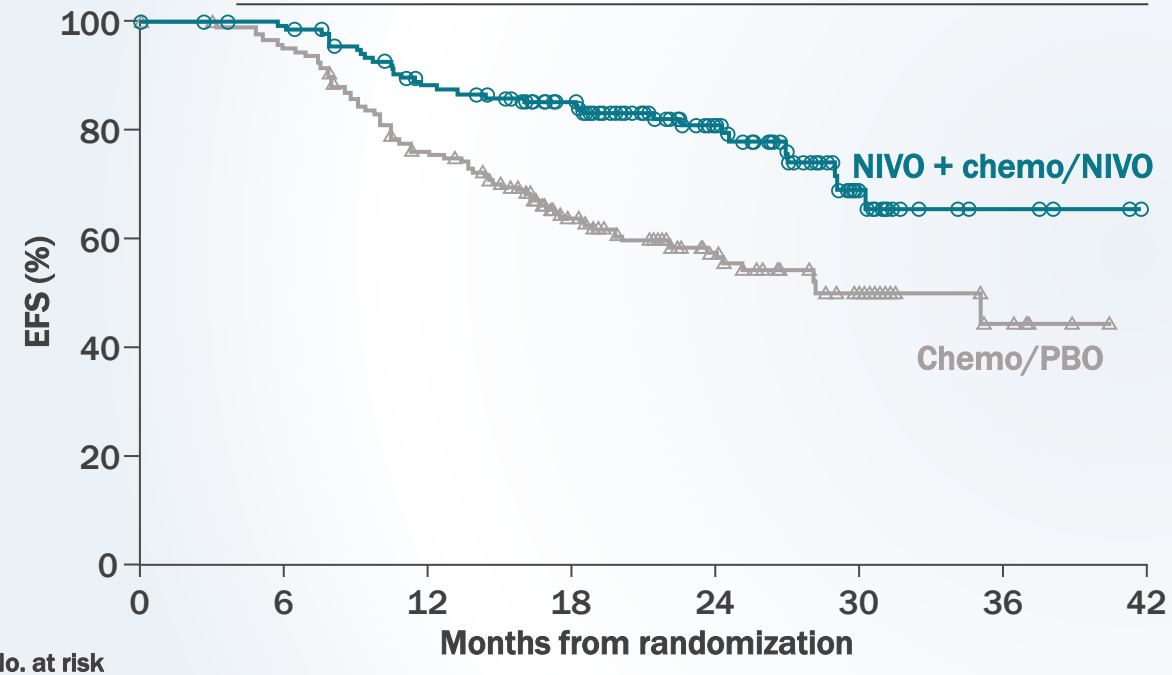
Exploratory analysis: EFS by adjuvant treatment status

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR–NR)	35.1 (22.0–NR)
HR (95% CI)	0.45 (0.29–0.69)	

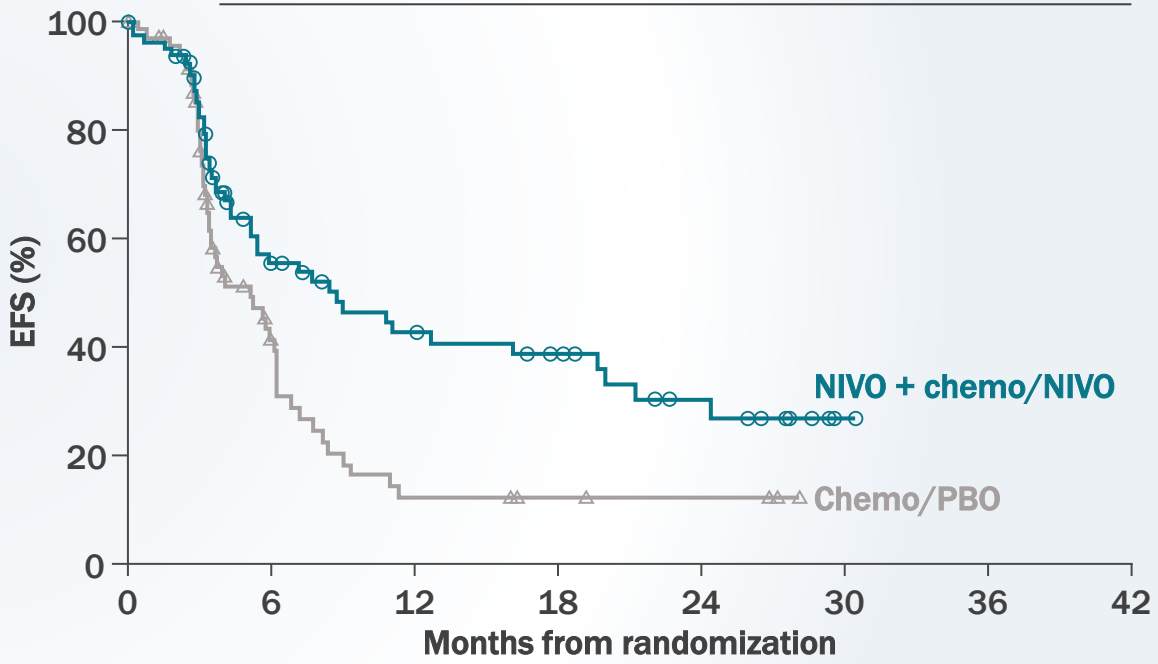


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

No adjuvant

	NIVO + chemo/NIVO (n = 87)	Chemo/PBO (n = 80)
Median EFS, mo (95% CI)	8.8 (5.2–19.7)	5.2 (3.4–6.2)
HR (95% CI)	0.55 (0.37–0.83)	



No. at risk

NIVO + chemo/NIVO	87	34	23	18	9	1	0	0
Chemo/PBO	80	21	6	4	3	0	0	0

- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29–0.69]) vs those who did not (HR [95% CI], 0.55 [0.37–0.83])[a]

Median follow-up (range): 25.4 months (15.7–44.2).

[a]HR (95% CI), 0.17 (0.11–0.27) in those who received adjuvant treatment vs those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10–0.22) in the chemo/PBO arm.

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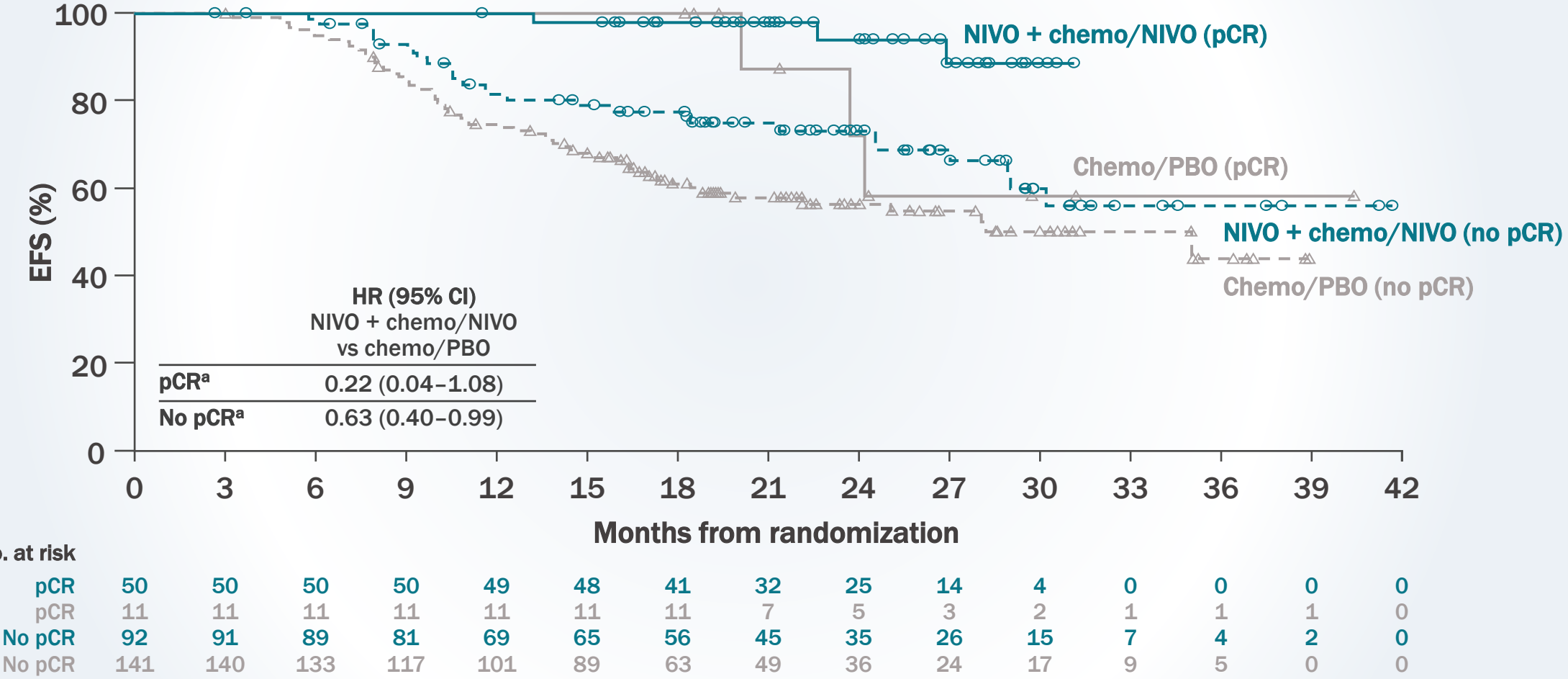
Exploratory analysis: EFS by pCR status in patients who received adjuvant treatment

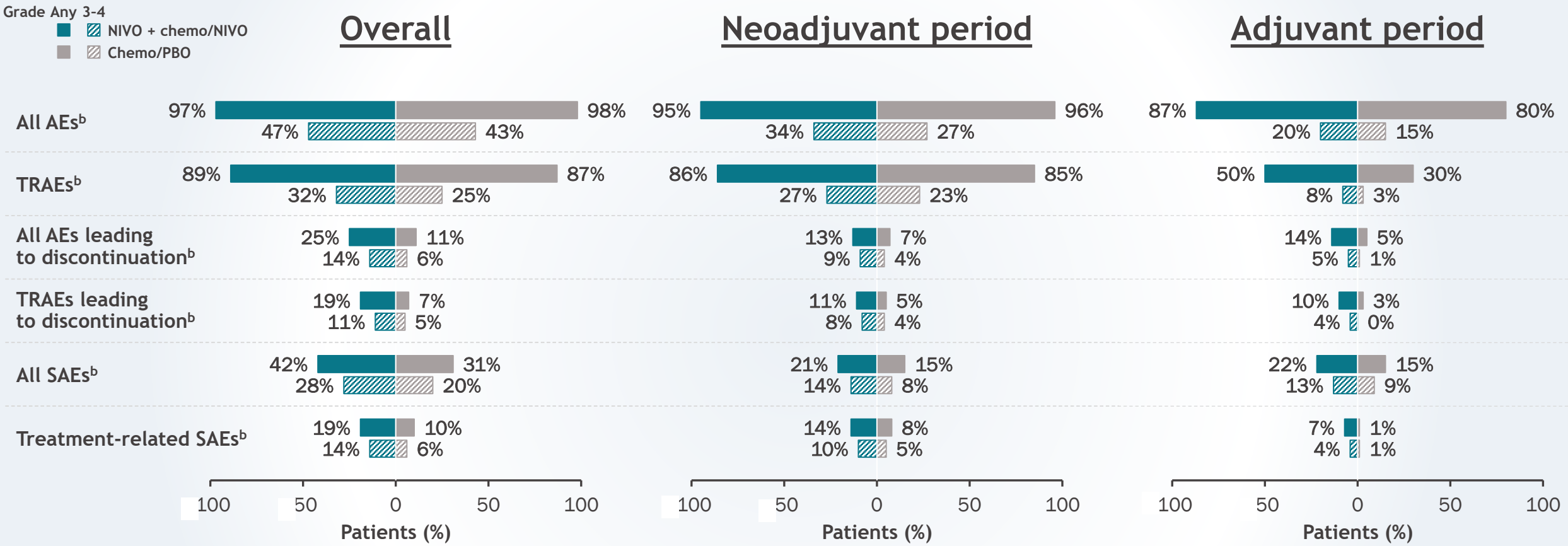


Median follow-up (range): 25.4 months (15.7–44.2).

[a]HR (95% CI), 0.17 (0.05–0.57) in patients with pCR vs those without in the NIVO + chemo/NIVO arm and 0.45 (0.14–1.45) in the chemo/PBO arm.

Cascone T, ESMO Congress 2023, LBA1

Safety summary[a] across study phases



- Any-grade surgery-related AEs occurred in 73 (41%) and 69 (39%) patients in the NIVO + chemo/NIVO and chemo/PBO arms, respectively; 21 (12%) patients in each arm experienced grade 3–4 events[c]
- Treatment-related deaths occurred in 2 (1%) patients in the NIVO + chemo/NIVO arm (1 due to grade 5[d] pneumonitis and 1 due to grade 4 pneumonitis, both occurring during the neoadjuvant period)

Median follow-up (range): 25.4 months (15.7-44.2).

[a]AEs per CTCAE v4.0 and MedDRA v26.0. [b]Includes events reported between the first dose and 30 days after the last dose of study treatment. [c]Includes events reported within 90 days after definitive surgery. Percentages calculated from treated patients who had definitive surgery (n = 178 in the NIVO + chemo/NIVO arm; n = 178 in the chemo/PBO arm). Grade 5 surgery-related AEs: NIVO + chemo/NIVO, 3 (2%) patients (1 each due to acute myocardial infarction, postprocedural hemorrhage, and septic shock); chemo/PBO, 1 (1%) patient (due to pneumonia); all were unrelated to study drug per investigator. dAEs that led to death within 24 hours of onset.

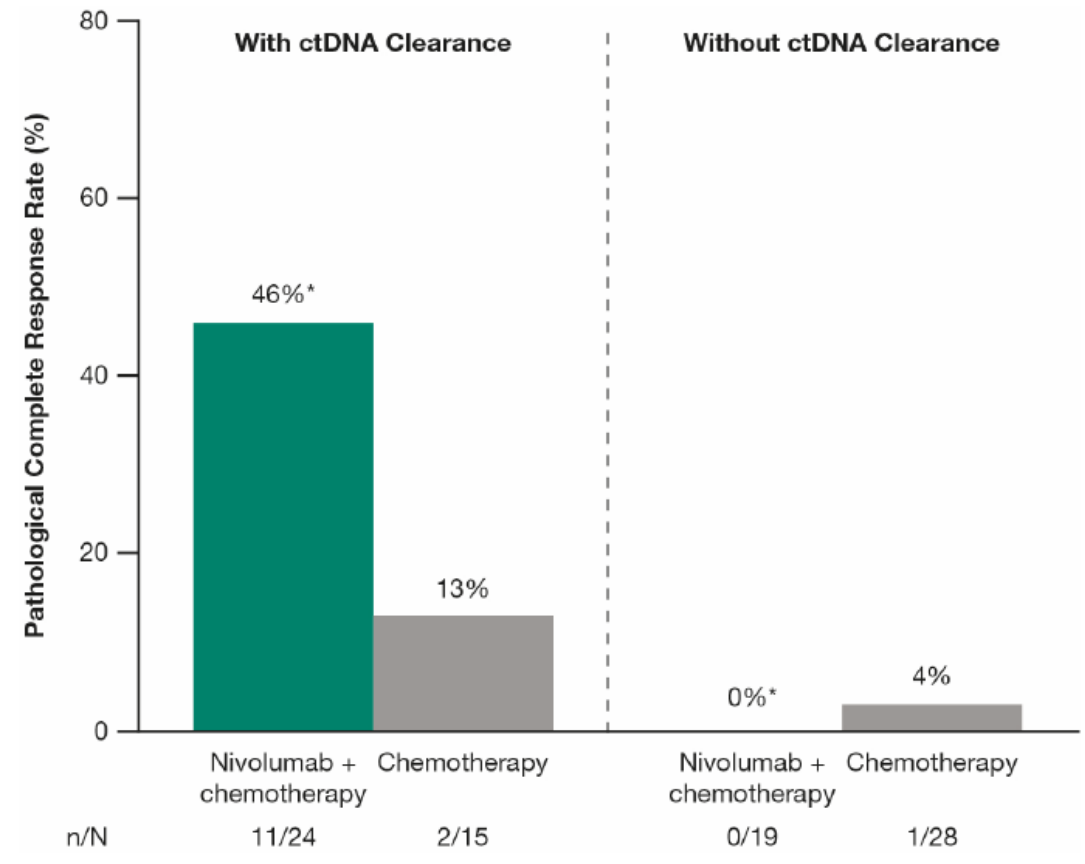
Advances of I-O-based treatments improved short-term and long-term outcomes for patients with resectable/resected NSCLC

- **Nivo + CT** is the first neoadjuvant I-O regimen to change the treatment paradigm by demonstrating pCR and long-term EFS benefits without impeding surgical feasibility (CheckMate 816)[1-3]
- **Atezo** (IMpower010) and **pembro** (KEYNOTE-091) are adjuvant I-O options after complete resection and adjuvant chemotherapy[4-5]
- Perioperative treatments (CheckMate 77T, KEYNOTE-671, AEGEAN, NEOTORCH) build on neoadjuvant I-O + CT by adding adjuvant I-O after surgery and have encouraging EFS/OS results[6-10]
- Which patients would benefit from neoadjuvant or adjuvant I-O treatments?
- In perioperative I-O era, which patients would benefit from the addition of adjuvant I-O after neoadjuvant I-O + CT?
- Which biomarker(s) can predict response or long-term benefit with I-O treatments in this setting?

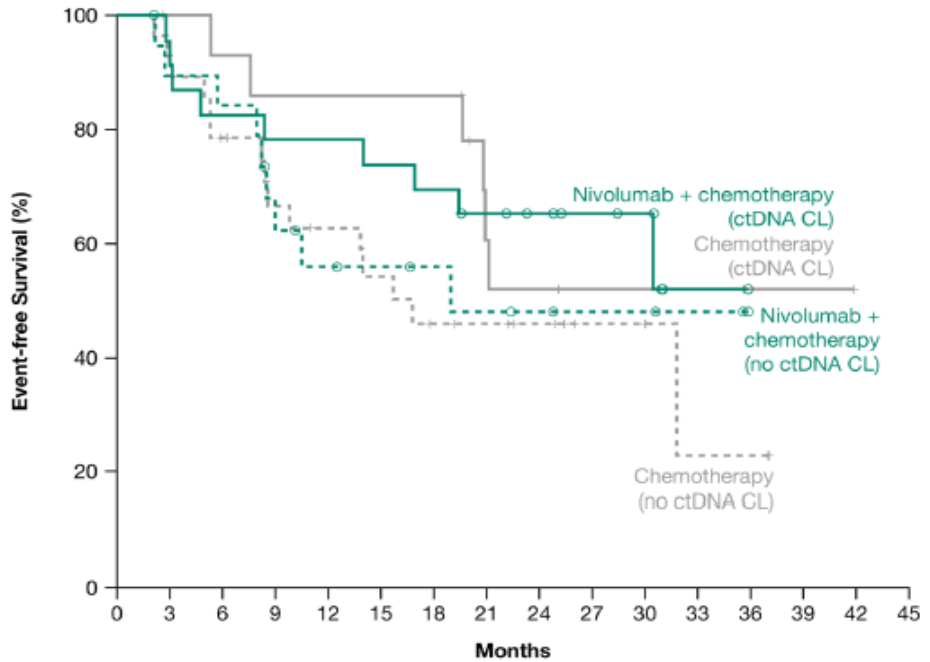
1. Forde PM et al. *N Engl J Med*. 2022;386(21):1973-1985. 2. Forde PM et al. Oral presentation at ELCC 2023. Abstract 840. 3. Spicer J et al. Poster presentation at ASCO 2023. Abstract 8521. 4. Felip E et al. *Lancet*. 2021;398(10308):1344-1357. 5. O'Brien M et al. *Lancet Oncol.* 2022;23(10):1274-1286. 6. Cascone T, Oral Presentation ESMO 2023. 7. Heymach JV et al. *N Engl J Med.* 2023. 8. Wakelee H et al. *N Engl J Med*. 2023. 9. Spicer J, Oral Presentation ESMO 2023. 10. Lu S et al. Oral presentation at ASCO 2023. Abstract 8501. 14.

Thank you!

CheckMate 816: pCR and EFS by ctDNA clearance



	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	



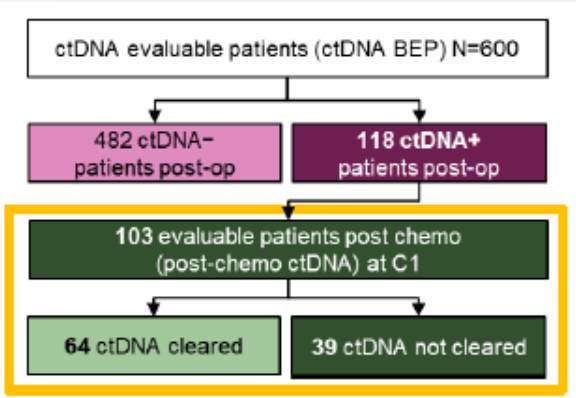
No. at Risk

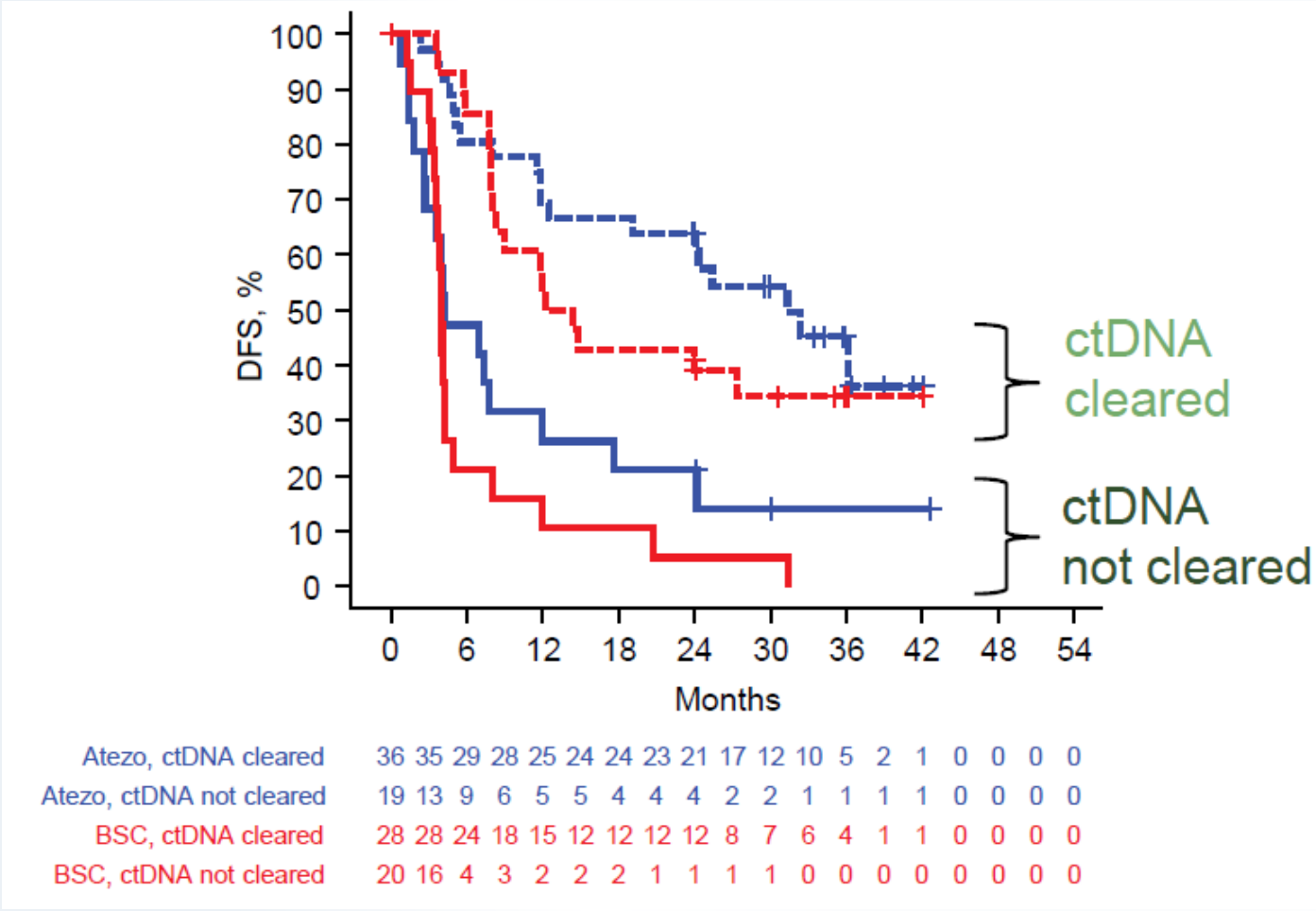
Nivolumab + chemotherapy (ctDNA CL)	24	21	19	18	18	17	16	13	11	8	7	1	0	0	0	0
Chemotherapy (ctDNA CL)	15	14	13	12	12	12	12	7	6	5	5	5	3	1	0	0
Nivolumab + chemotherapy (no ctDNA CL)	19	17	16	12	9	8	7	6	5	3	3	2	0	0	0	0
Chemotherapy (no ctDNA CL)	28	26	21	17	15	13	10	9	7	4	3	1	1	0	0	0

Database lock: October 20, 2021; minimum/median follow-up: 21/29.5 months.
ctDNA analyses were performed on plasma samples collected on day 1 before each of the three treatment cycles. * 95% CI for pCR rate with nivolumab plus chemotherapy: with ctDNA CL, 26–67; without ctDNA CL, 0–18.

Forde PM et al. *N Engl J Med*. 2022

IMpower010: DFS by post-chemo ctDNA clearance status





ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

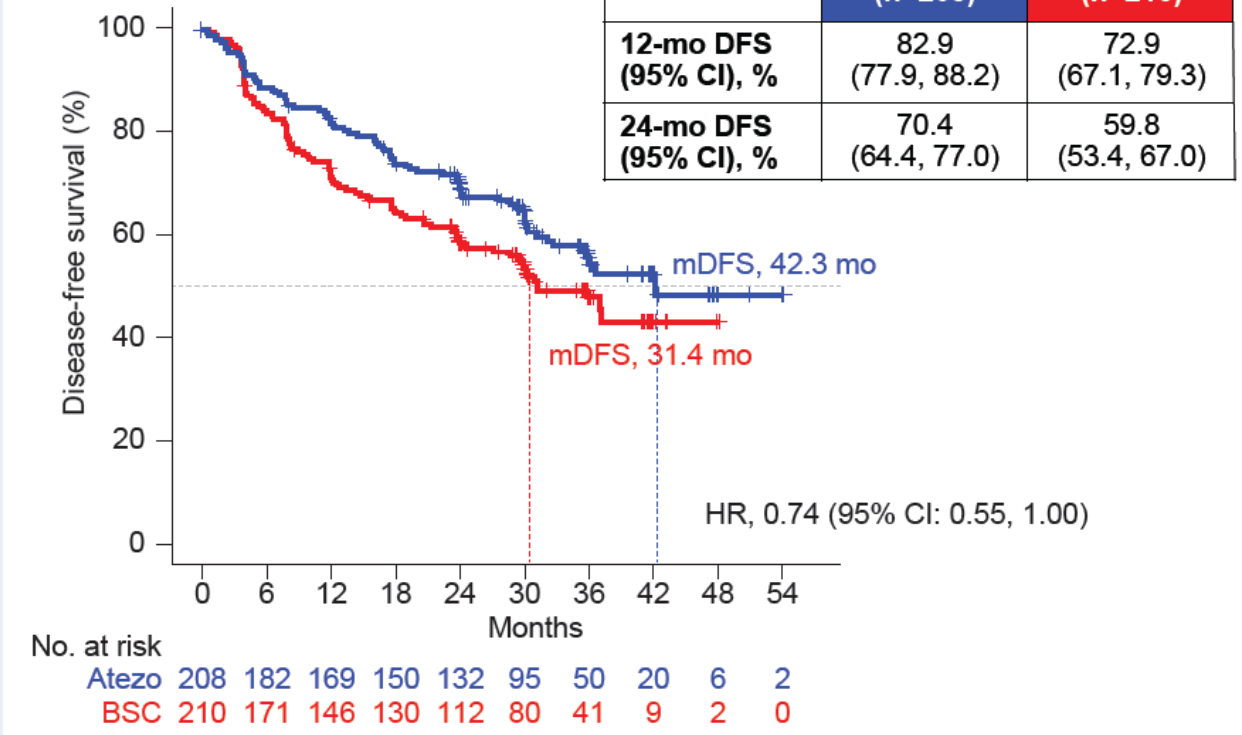
ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

Felip E, et al. Oral presentation at ESMO-IO 2022.

IMpower010: DFS by KRAS mutation status (stage II-IIIA*)

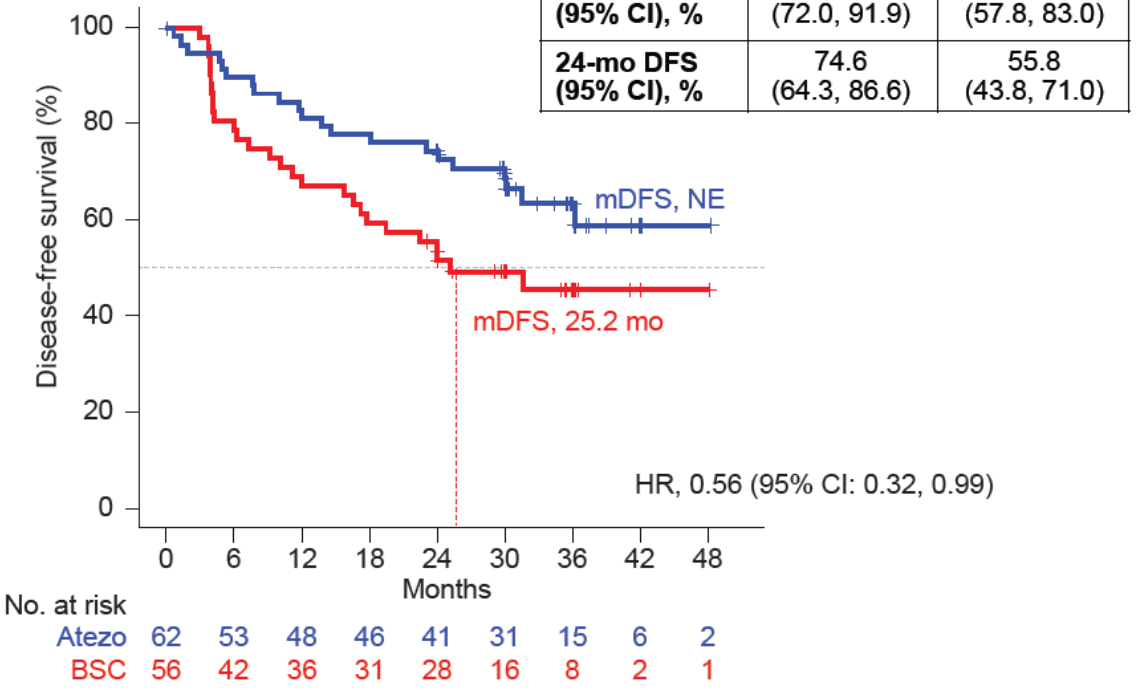
B ***KRAS* WT, stage II-IIIA**

	Atezo (n=208)	BSC (n=210)
12-mo DFS (95% CI), %	82.9 (77.9, 88.2)	72.9 (67.1, 79.3)
24-mo DFS (95% CI), %	70.4 (64.4, 77.0)	59.8 (53.4, 67.0)



C ***mKRAS*, stage II-IIIA**

	Atezo (n=62)	BSC (n=56)
12-mo DFS (95% CI), %	81.4 (72.0, 91.9)	69.2 (57.8, 83.0)
24-mo DFS (95% CI), %	74.6 (64.3, 86.6)	55.8 (43.8, 71.0)



*Per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria.

Reck M et al. Presentation at ASCO 2023.