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Congresso Nazionale sul carcinoma del polmone

CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2023?

9 OTTOBRE 2023
VERONA
Hotel Leon D'Oro

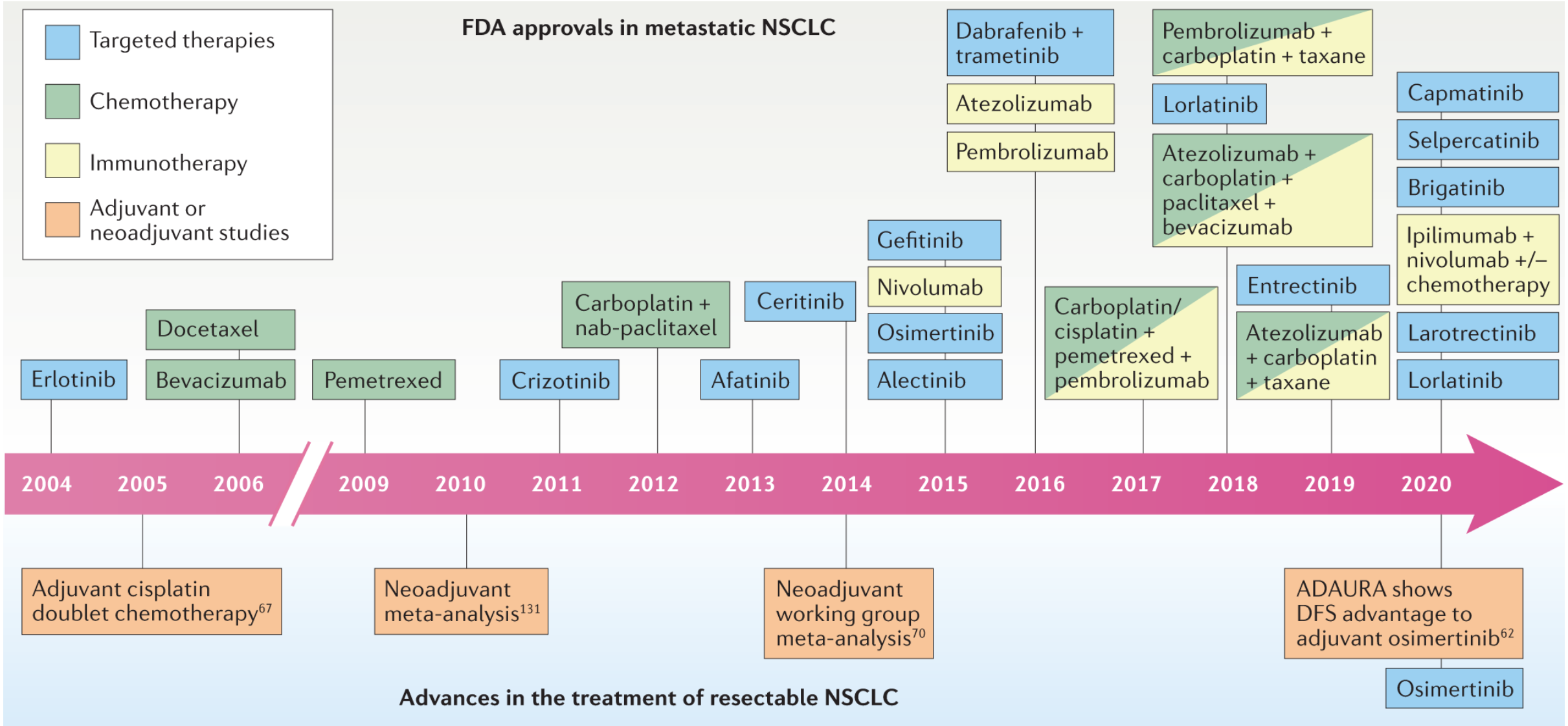
Responsabile scientifico
STEFANIA GORI

Immunoterapia neoadiuvante: evidenze disponibili e prospettive future

Ettore D'Argento
UOC Oncologia Medica

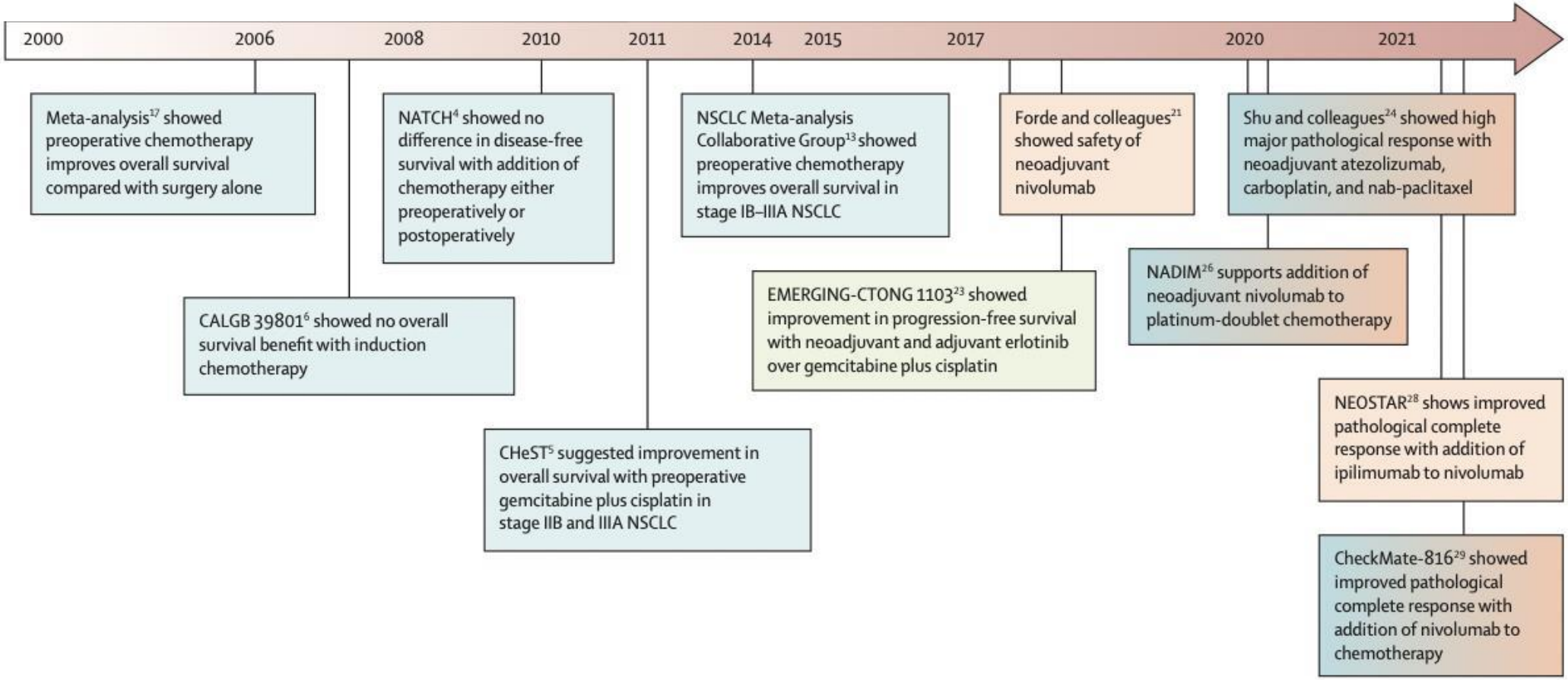
Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Comprehensive Cancer Center

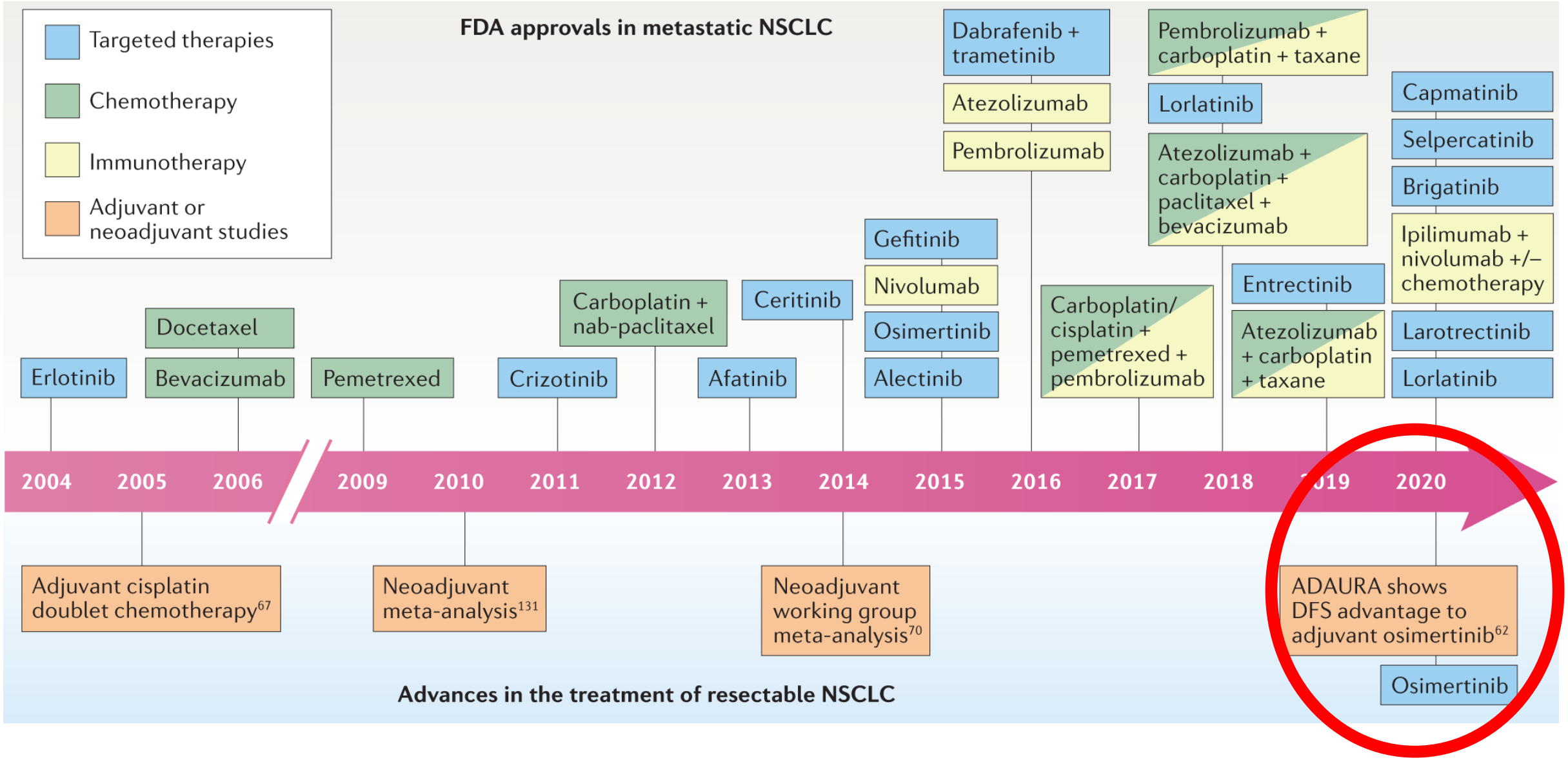


Chaft, J.E., et al. *Nat Rev Clin Oncol* (2021).

Timeline of main milestone in neoadjuvant systemic treatment of NSCLC



Saw et al, Lancet Oncology 2021

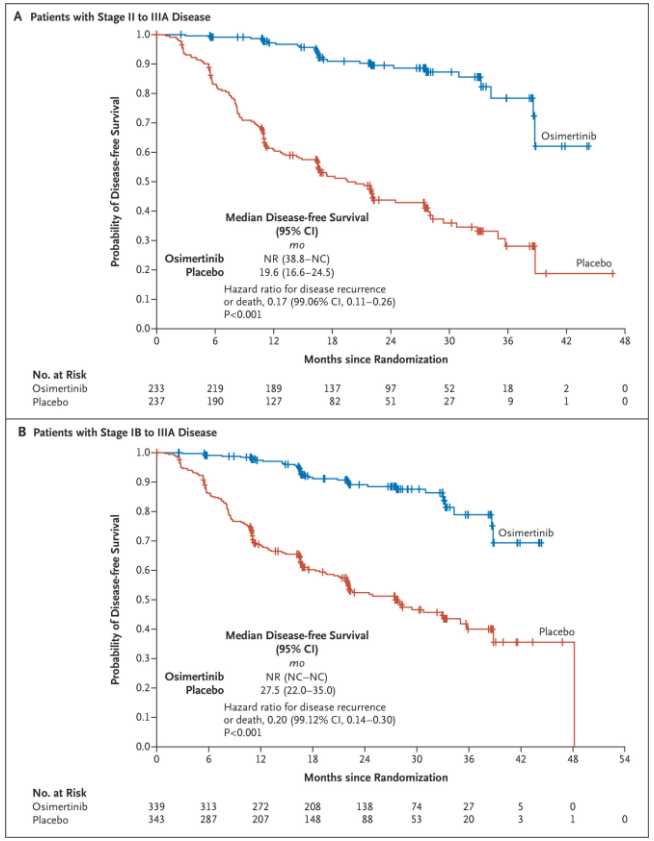


Chaft, J.E., et al. *Nat Rev Clin Oncol* (2021).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer



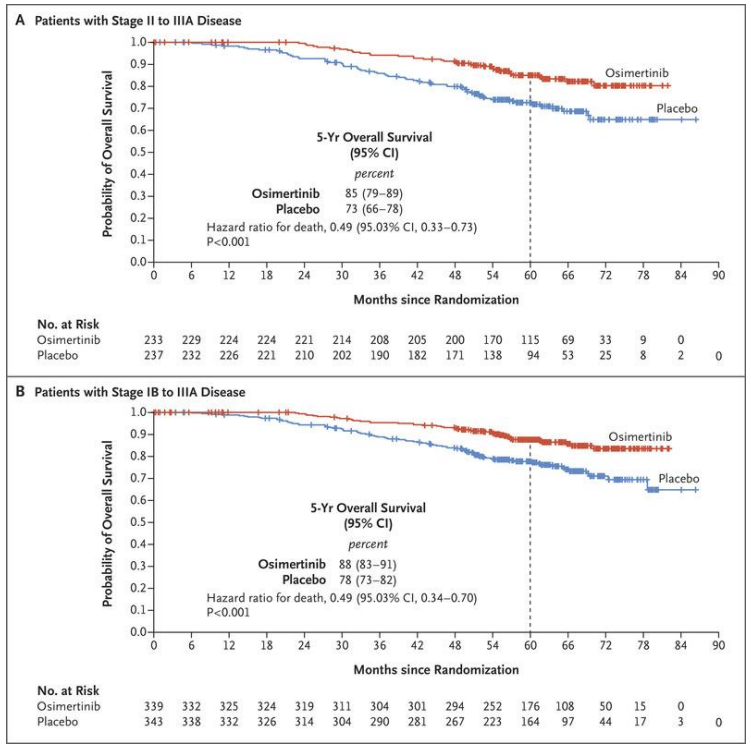
AGENZIA ITALIANA DEL FARMACO

Agenzia Italiana del Farmaco

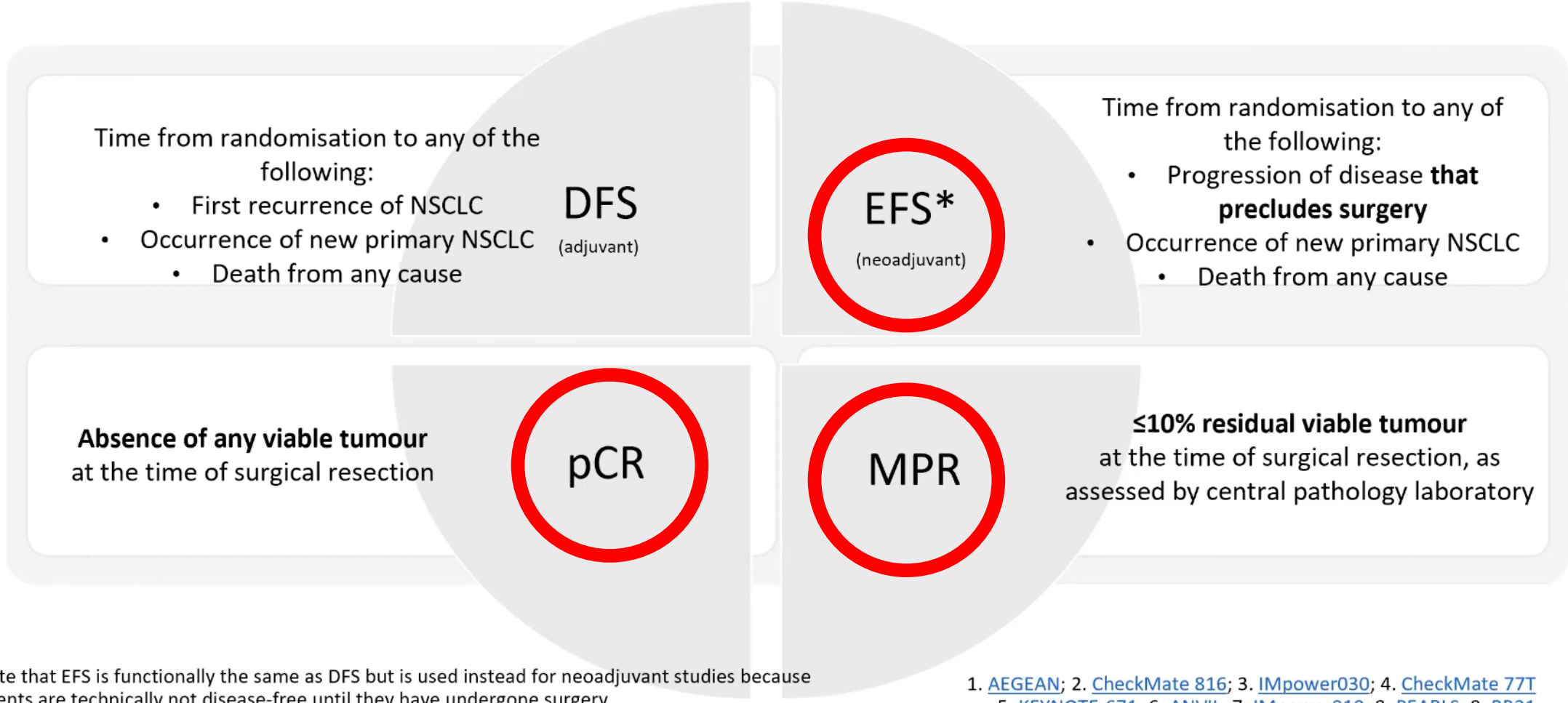
Attivazione web e pubblicazione schede di monitoraggio – Registro TAGRISSO_NSCLC adiuvante e Aggiornamento Registro TAGRISSO_ NSCLC avanzato - Attivazione web e pubblicazione schede di monitoraggio – Registro TAGRISSO_NSCLC adiuvante e Aggiornamento Registro TAGRISSO_ NSCLC avanzato

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC



2020 **2022** **2023**

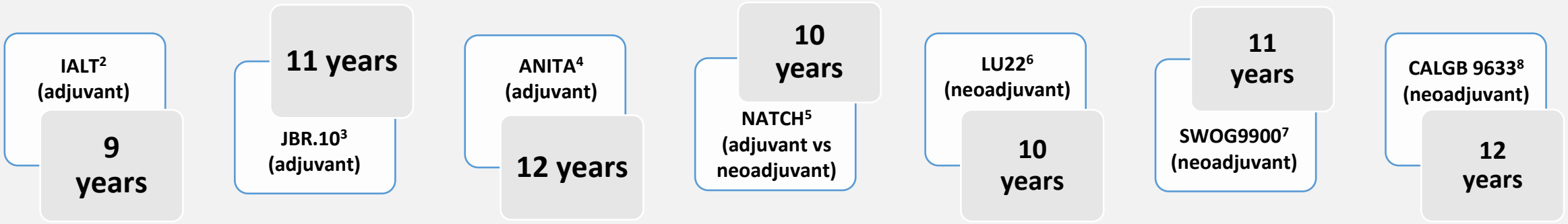


*Note that EFS is functionally the same as DFS but is used instead for neoadjuvant studies because patients are technically not disease-free until they have undergone surgery

1. AEGEAN; 2. CheckMate 816; 3. IMpower030; 4. CheckMate 77T
5. KEYNOTE-671; 6. ANVIL; 7. IMpower010; 8. PEARLS; 9. BR31

Extensive time to readout means surrogate endpoints are needed to bring effective treatments into the clinic rapidly

Time from first patient recruited until publication (NSCLC studies)[1]



This compares with ~2–4 years for a typical CIT study in advanced or metastatic NSCLC[9–13]

Adopting **meaningful surrogate endpoints for OS** may expedite the evaluation of new therapies and **bring new treatments to NSCLC patients sooner**

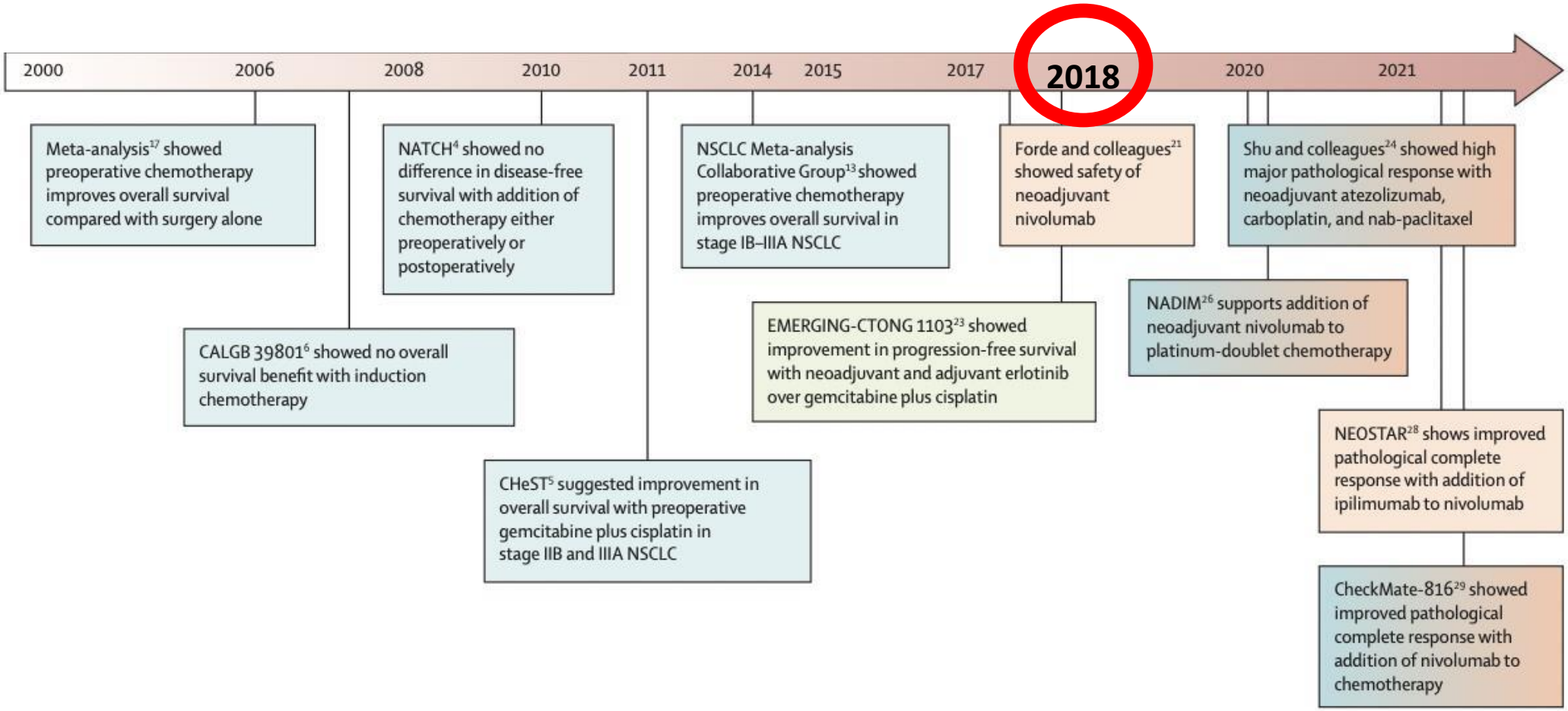
1. Hellmann, et al. Lancet Oncol 2014; 2. Arriagada, et al. N Engl J Med 2004; 3. Winton, et al. N Engl J Med 2005 4. Douillard, et al. Lancet Oncol 2006; 5. Felip, et al. J Clin Oncol 2010; 6. Gilligan, et al. Lancet 2007 7. Pisters, et al. J Clin Oncol 2010; 8. Strauss, et al. J Clin Oncol 2008; 9. Reck, et al. N Engl J Med 2016 10. Gandhi, et al. N Engl J Med 2018; 11. Socinski, et al. N Engl J Med 2018; 12. Paz-Ares, et al. N Engl J Med 2018; 13. West, et al. Lancet Oncol 2019

U.S. FOOD & DRUG ADMINISTRATION	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
DFS and EFS are listed as surrogate endpoints that were the basis of drug approvals or licensure by the FDA[1]	DFS and EFS are also accepted endpoints by the EMA[2]
DFS (adjuvant): Time from randomisation to any of the following: • First recurrence of NSCLC • Occurrence of new primary NSCLC • Death from any cause	**EFS*** (neoadjuvant): Time from randomisation to any of the following: • Progression of disease **that precludes surgery** • Occurrence of new primary NSCLC • Death from any cause
pCR: **Absence of any viable tumour** at the time of surgical resection	**MPR**: **≤10% residual viable tumour** at the time of surgical resection, as assessed by central pathology laboratory

*Note that EFS is functionally the same as DFS but is used instead for neoadjuvant studies because patients are technically not disease-free until they have undergone surgery

1. AEGEAN; 2. CheckMate 816; 3. IMpower030; 4. CheckMate 77T
5. KEYNOTE-671; 6. ANVIL; 7. IMpower010; 8. PEARLS; 9. BR31

Timeline of main milestone in neoadjuvant systemic treatment of NSCLC



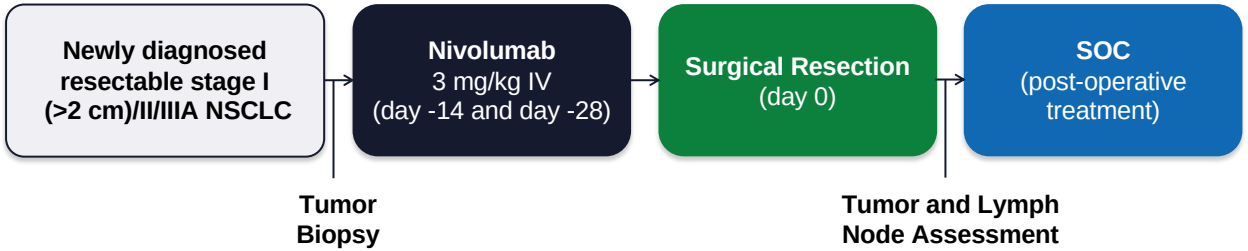
Saw et al, Lancet Oncology 2021

The NEW ENGLAND JOURNAL of MEDICINE

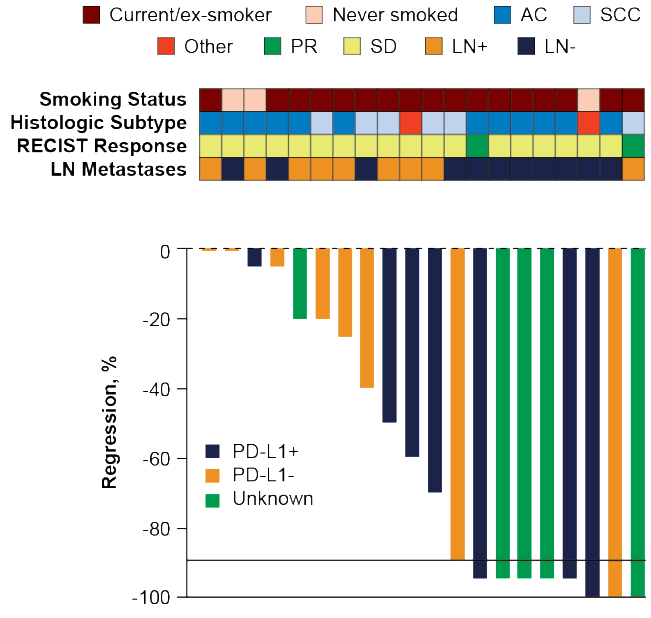
ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll



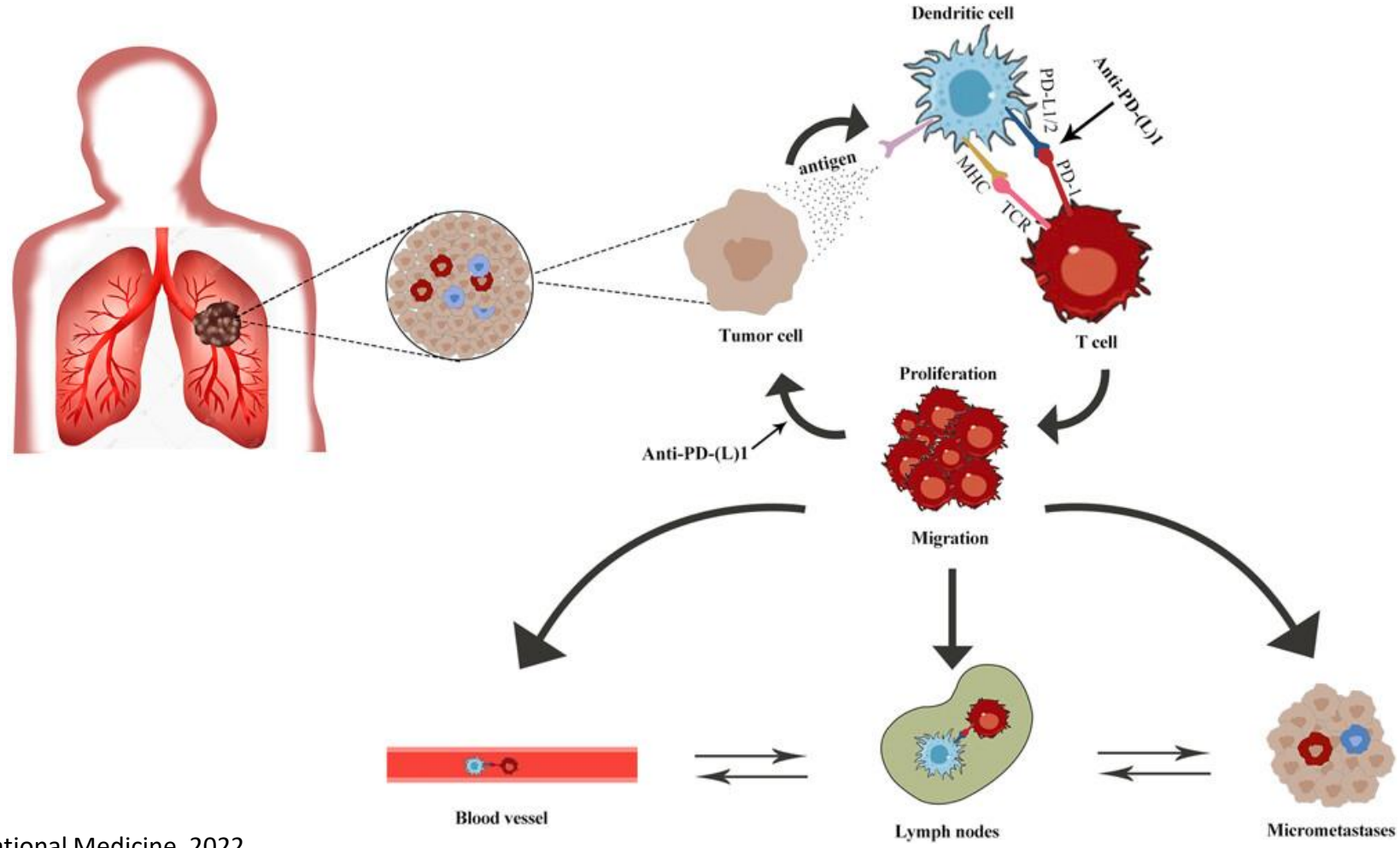
- **Primary endpoints:** Safety and feasibility
- **Also evaluated:** Tumor pathological response; expression of PD-L1; mutational burden; and mutation-associated, neoantigen-specific T-cell responses



- Major pathological response occurred in 9/20 resected tumors (45%; 95% CI, 23-68)

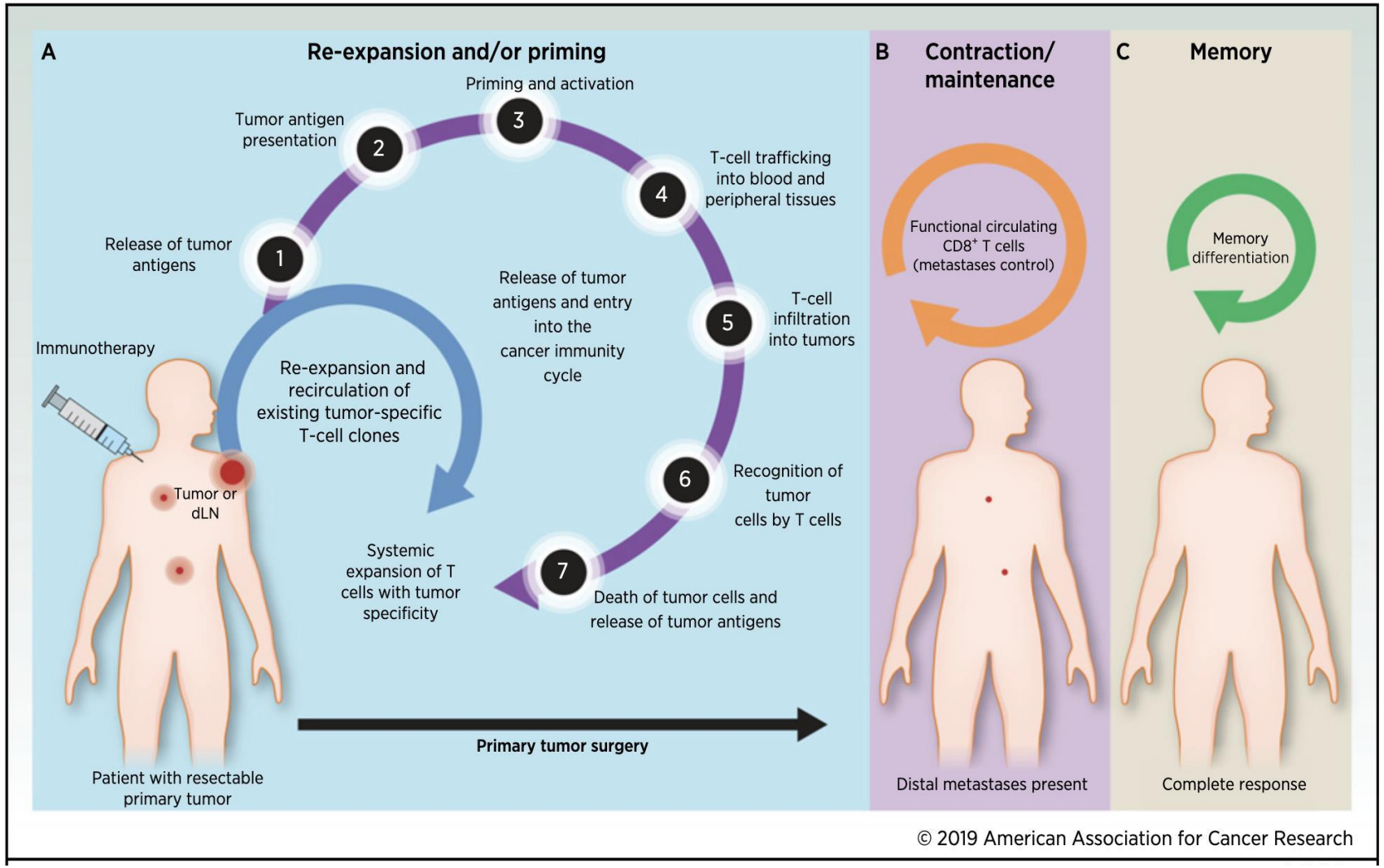
Treatment related adverse events in 23%
No treatment-related surgical delays

Enhancement of systemic antitumor T cell immunity after neoadjuvant PD-1 blockade



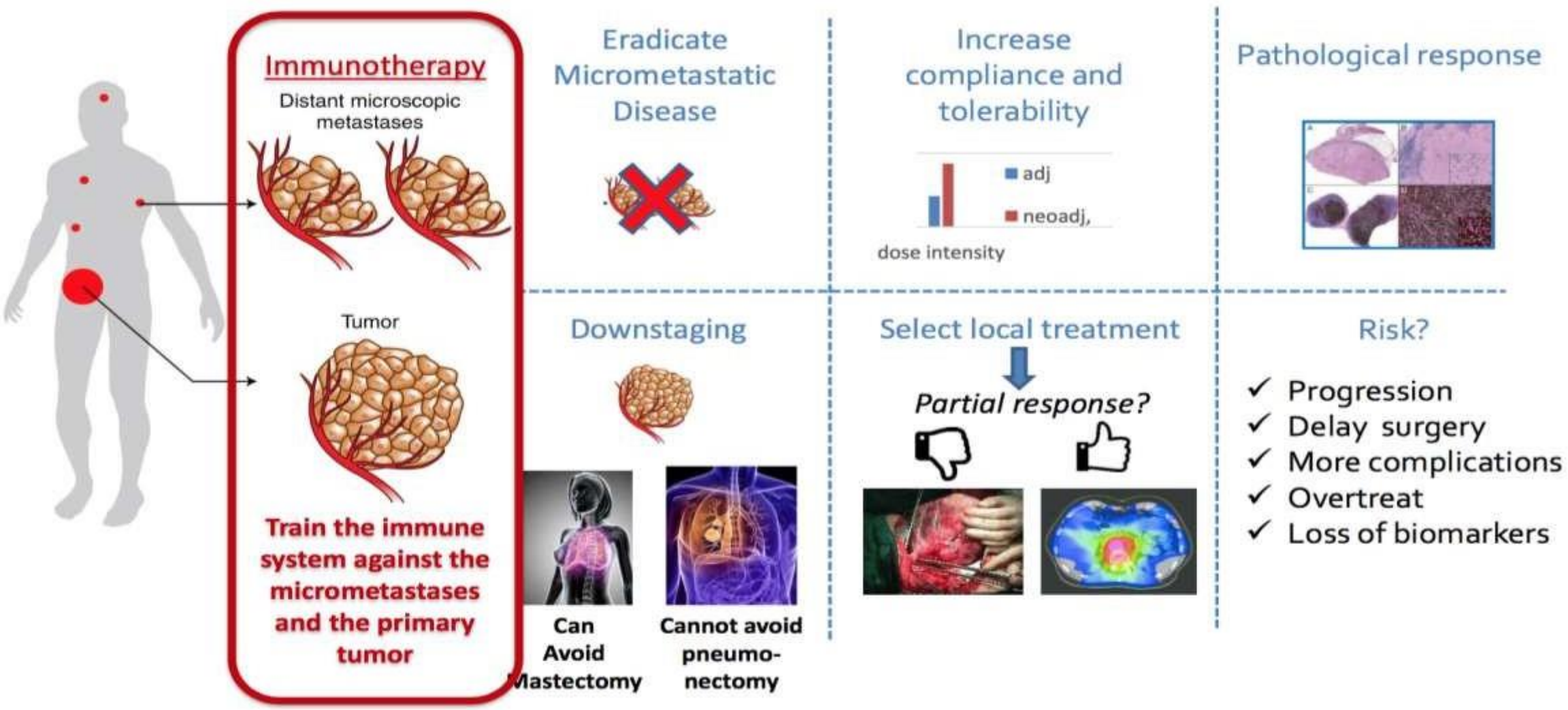
Chronic Diseases and Translational Medicine, 2022

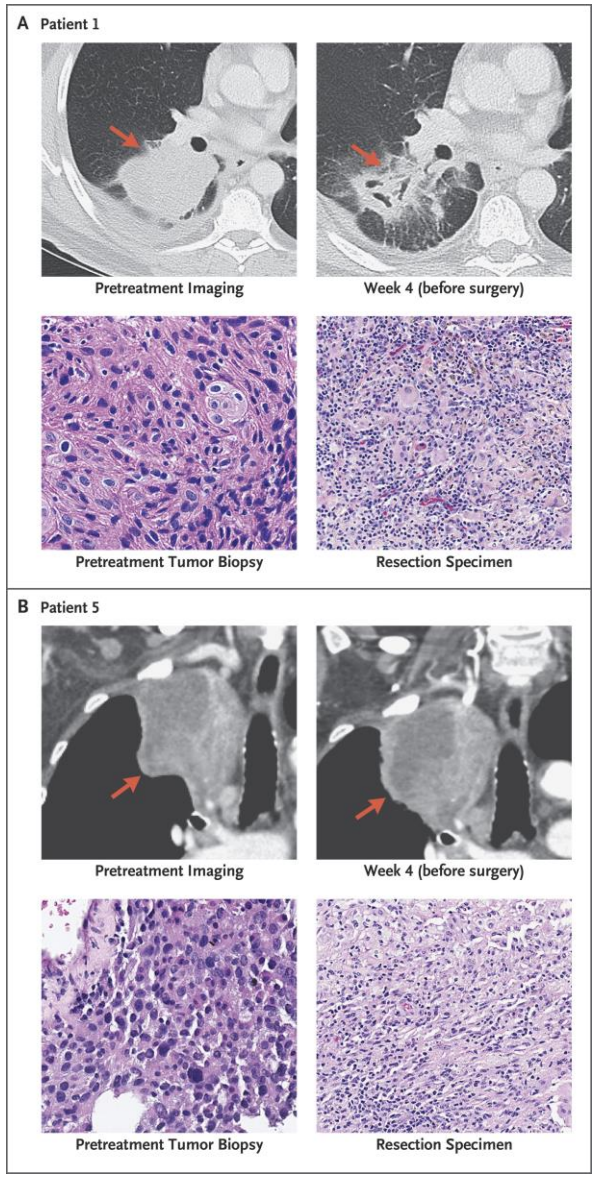
Neoadjuvant immunotherapy and the tumor-specific T-cell response.



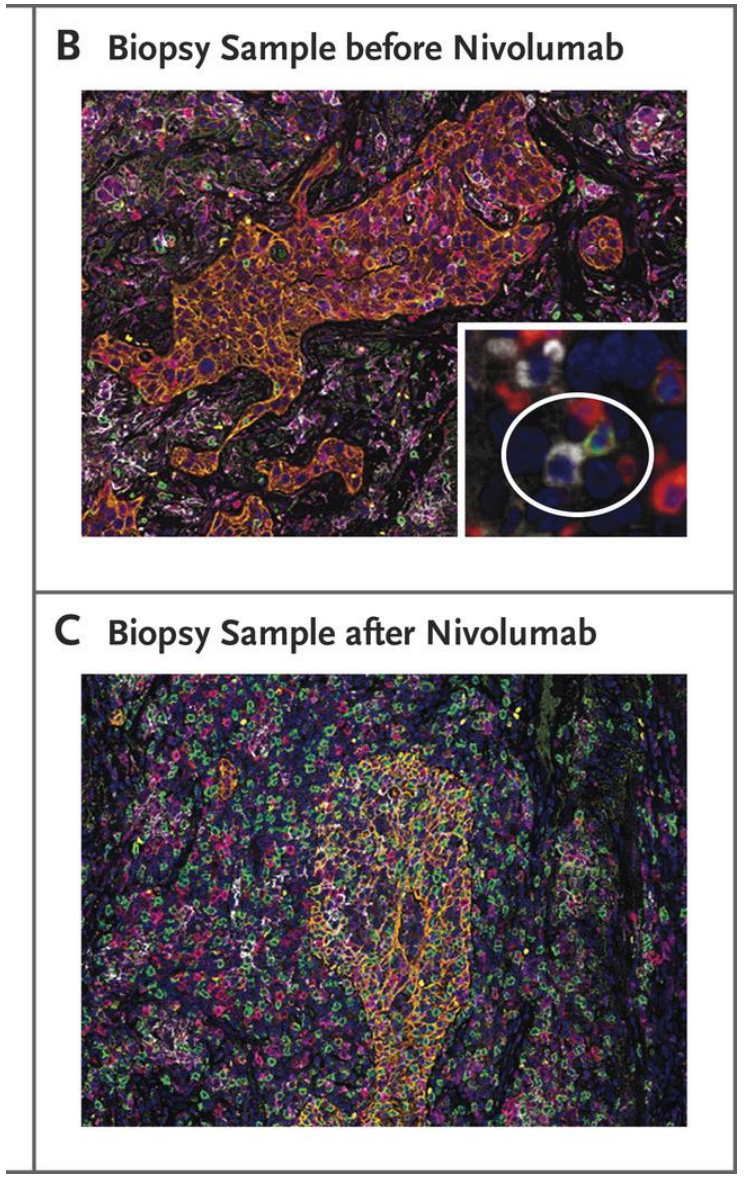
Liu et al, Cancer Discov 2016; O'Donnell CCR 2019

Theoretical benefit for induction treatment





Pathological Response to
Neoadjuvant Therapy with Nivolumab.



Forde P, et al. NEJM 2018

Neoadjuvant ICI or ICI Plus Chemotherapy in Patients With Resectable and Operable Stage I–III Lung Cancers Phase II Trials

Study	Registry No.	Stage	No. of Patients	Resected Patients	Experimental Arm	Control Arm	Primary Endpoint	MPR	pCR	1-Year OS
SKCCC-JHU Forde et al[58]	NCT02259621	IB, II, IIIA	22	20	Nivo, 2 cycles Q2W	None	Safety	9 (45%)	3 (13%)	—
LCMC3 Kwiatkowski et al[103]	NCT02927301	IB-IIIB (T3N2)	181	159	Atezolizumab, 2 cycles Q3W	None	MPR	30 (21%)	10 (7%)	
NEOSTAR Cascone et al[59]	NCT03158129	I-IIIA (single N2)	88: Nivo: 23 Nivo + Ipi: 21	39	Nivo, 3 cycles Q2W or Nivo 3 + Ipi 1	None	MPR	11: Nivo: 5 (22%) Nivo+ Ipi: 8 (38%)	8: 2 (9%) 6 (29%)	
IONESCO Wislez et al[104]	NCT03030131	IB, II, IIIA (non-N2)	50/81	46	Durva 3 cycles Q2W	None	Surgical resection R0	8 (18.6%)	3 (7%)	89.1%
COLUMBIA UNIVERSITY Shu et al[60]	NCT02716038	IB-IIIA	30	29	Atezolizumab + cCT, 4 cycles – SoC (adj)	None	MPR	17 (57%)	10 (33%)	—
NADIM Provencio et al[50]	NCT03081689	IIIA (N2)	46	41	Nivo + cCT, 3 cycles Q3W – Nivo (adj) 1 y	None	24 mo PFS	34 (83%)	26 (63%)	97.8%
SAKK 16/14 Rothschild et al[101]	NCT02572843	IIIA (N2)	67	55	Durva + cCT – Durva (adj)	None	EFS at 1 y	33 (60%)	10 (18%)	—
NADIM II Provencio et al[105]	NCT03838159	IIIA-IIIB	90	NA	Nivo + cCT - Nivo (adj) 6 mo	CT	pCR	NA	NA	—

THE LANCET

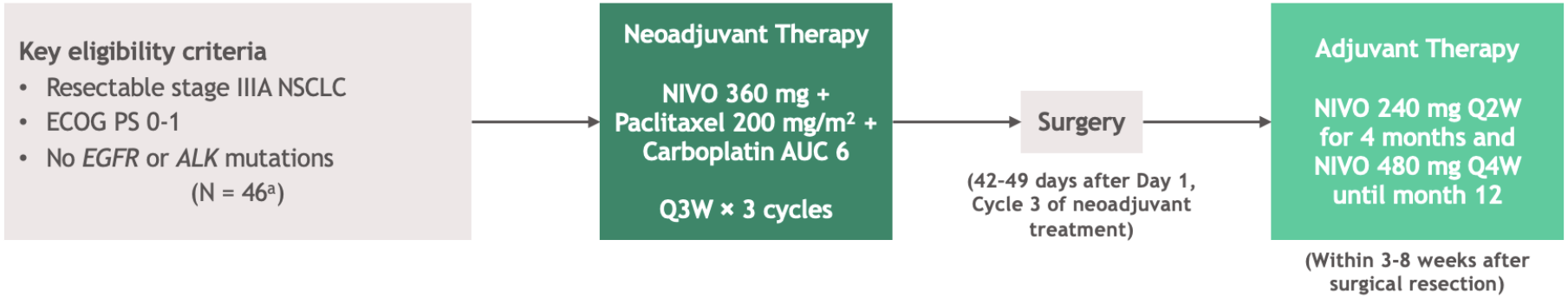
Articles

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Ana Royuela, Marta Casarrubios, Clara Salas Antón, Edwin R Parra, Ignacio Wistuba, Virginia Calvo, Raquel Laza-Briviesca, Atocha Romero, Bartomeu Massuti, Alberto Cruz-Bermúdez

NADIM trial: study design

- NADIM was a phase 2, open-label study that assessed neoadjuvant NIVO in combination with chemotherapy in resectable stage IIIA NSCLC
- Patients received the combination prior to surgical resection, followed by adjuvant NIVO therapy

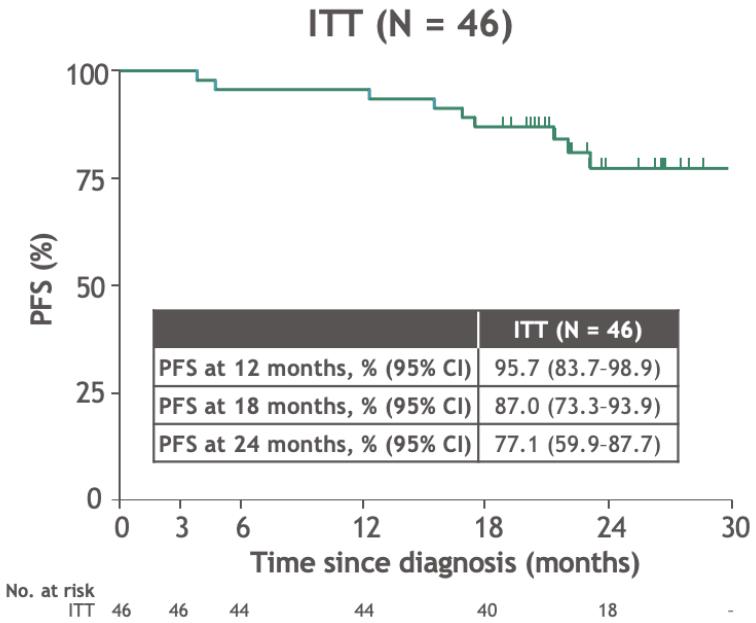


[a]Modified ITT population, which included all patients who received neoadjuvant treatment. Per-protocol population (n = 37) included all patients who had tumor resection and received ≥ 1 cycle of adjuvant treatment.

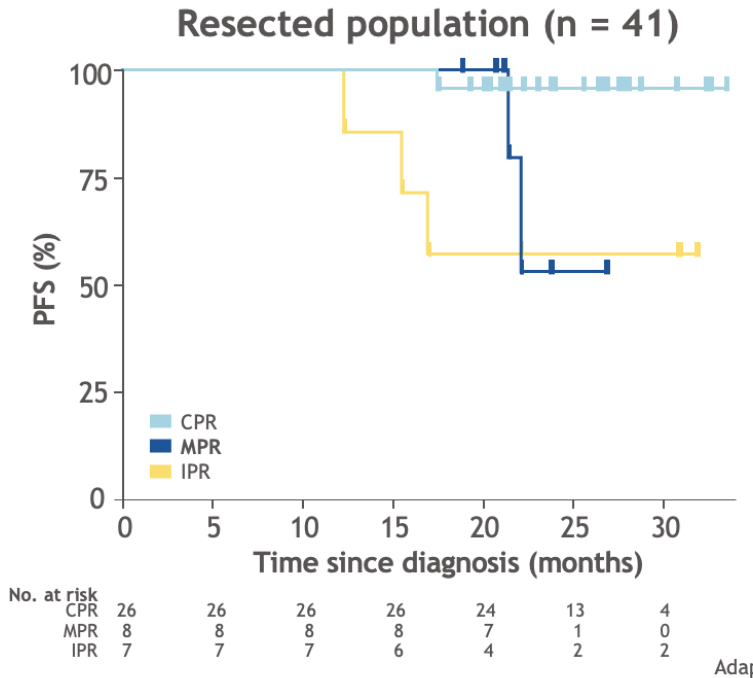
AUC, area under the curve; ctDNA, circulating tumor DNA; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status.

Provencio M et al. *Lancet Oncol.* 2020;21:1413-1422.

Progression-free survival at 24 months (primary endpoint)



	ITT (N = 46)
PFS at 12 months, % (95% CI)	95.7 (83.7-98.9)
PFS at 18 months, % (95% CI)	87.0 (73.3-93.9)
PFS at 24 months, % (95% CI)	77.1 (59.9-87.7)

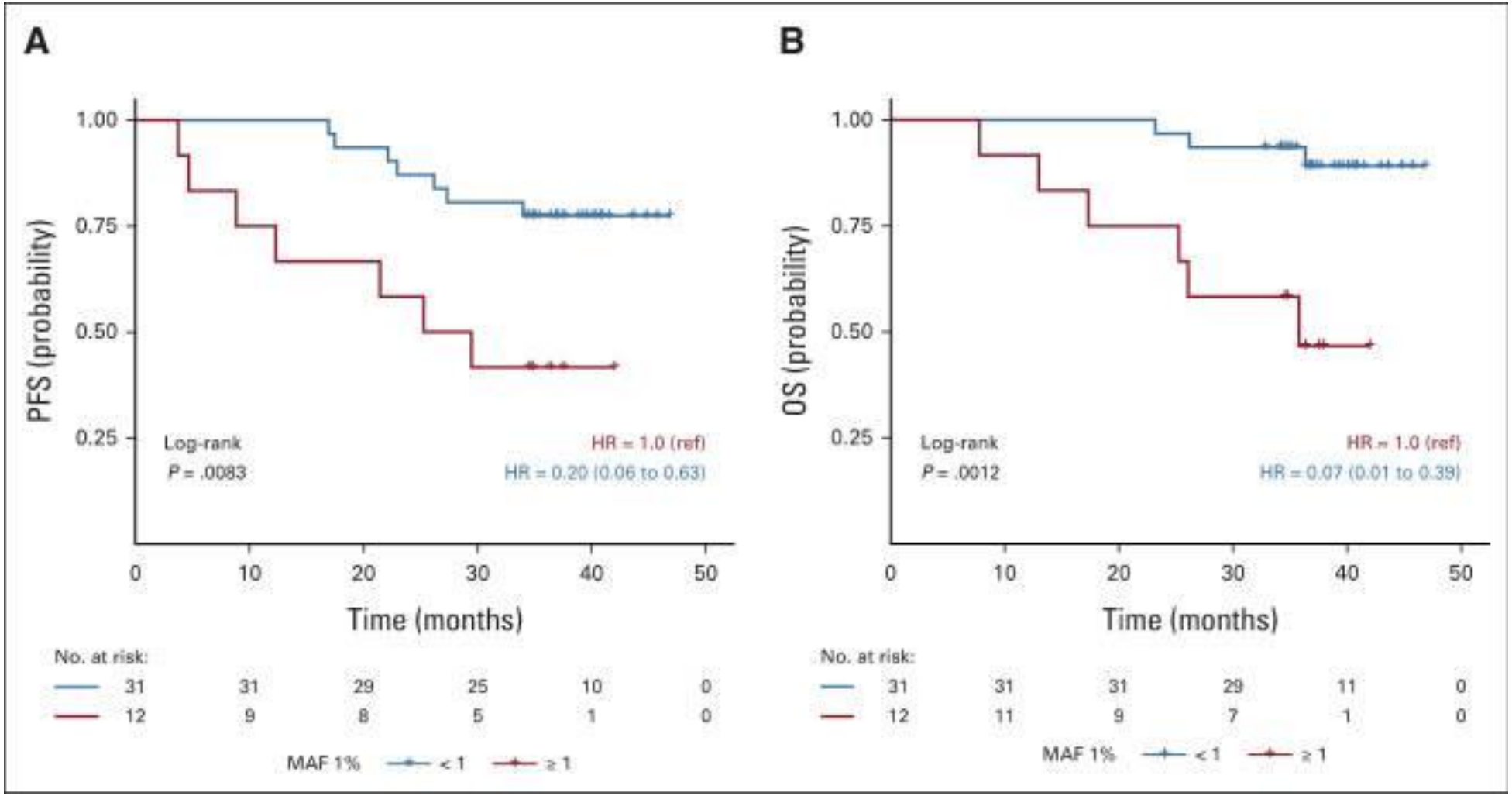


Adapted with permission.

- PFS in patients with CPR was 96% (95% CI: 76-99) at both 18 and 24 months, which was significantly higher than PFS in patients with IPR or MPR (*P* = 0.0023 and 0.041, respectively)
  - No differences were observed between IPR and MPR (*P* = 0.524)

Data analysis cutoff: January 31, 2020. Median follow-up: 24.0 months.
Log-rank *P* values.
CPR, complete pathologic response; IPR, incomplete pathologic response; MPR, major pathologic response; PFS, progression-free survival.
Provencio M et al. *Lancet Oncol*. 2020;21:1413-1422.

Survival by pretreatment ctDNA levels



The NEW ENGLAND JOURNAL of MEDICINE

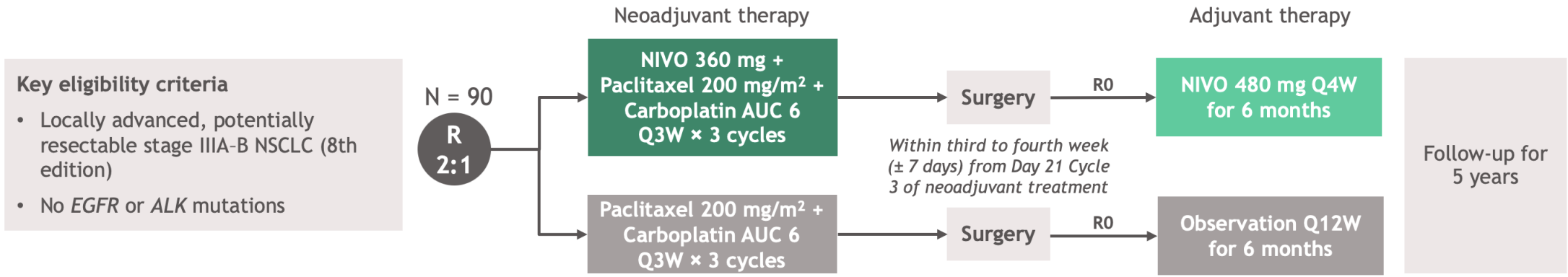
ORIGINAL ARTICLE

Perioperative Nivolumab and Chemotherapy in Stage III Non–Small-Cell Lung Cancer

M. Provencio, E. Nadal, J.L. González-Larriba, A. Martínez-Martí, R. Bernabé, J. Bosch-Barrera, J. Casal-Rubio, V. Calvo, A. Insa, S. Ponce, N. Reguart, J. de Castro, J. Mosquera, M. Cobo, A. Aguilar, G. López Vivanco, C. Camps, R. López-Castro, T. Morán, I. Barneto, D. Rodríguez-Abreu, R. Serna-Blasco, R. Benítez, C. Aguado de la Rosa, R. Palmero, F. Hernando-Trancho, J. Martín-López, A. Cruz-Bermúdez, B. Massuti, and A. Romero

NADIM II trial: study design

- NADIM II was a randomized, phase 2, open-label study that evaluated NIVO + chemo vs chemo in resectable stage IIIA–B NSCLC



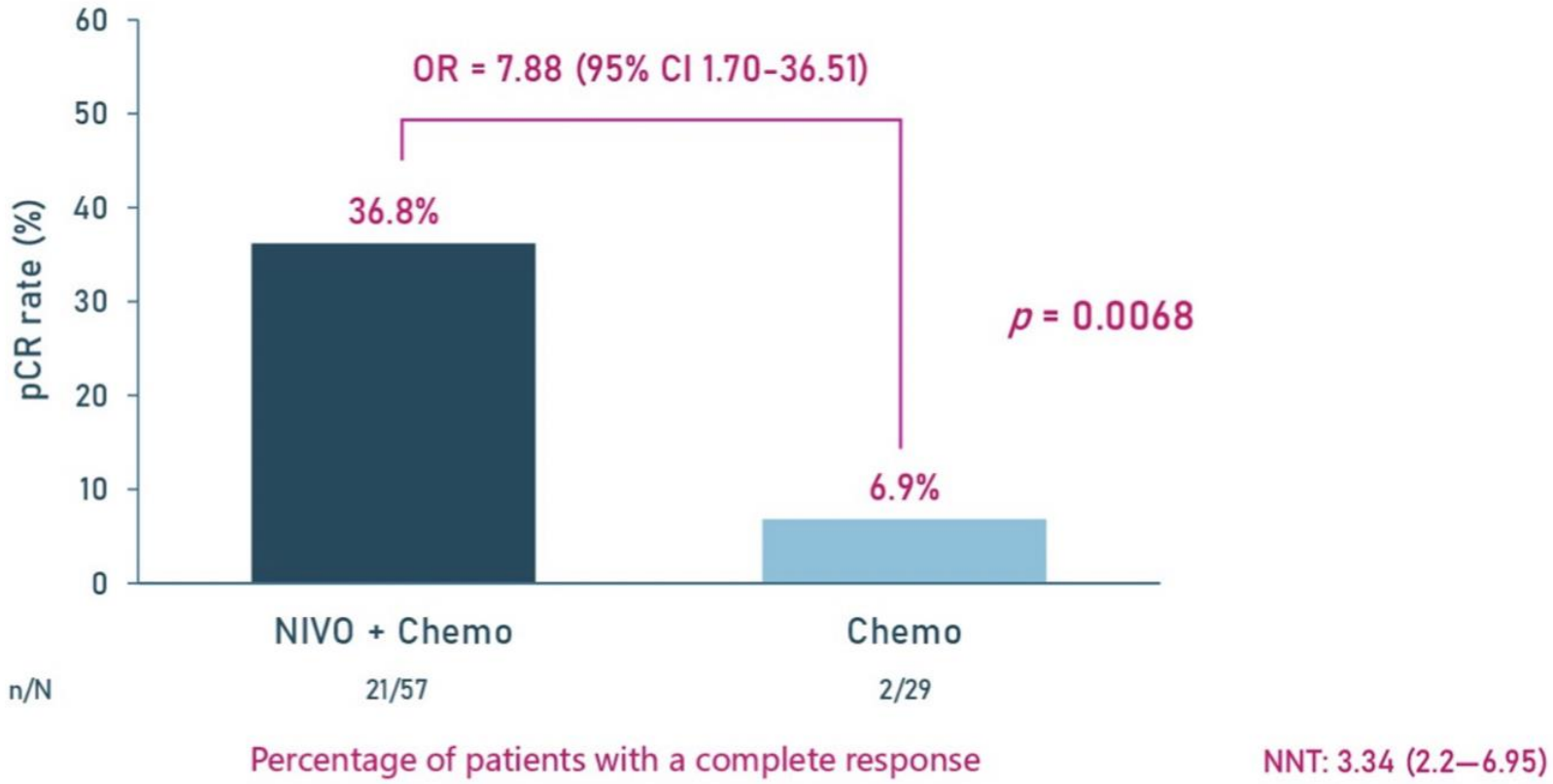
Primary endpoint
- pCR

Secondary endpoints
- MPR
- Surgical outcomes
- ORR
- Downstaging
- PFS, OS
- Predictive biomarkers (PD-L1, ctDNA)
  See also Pathologic Response Reactive Deck
- Safety

AUC, area under the curve; chemo, chemotherapy; ctDNA, circulating tumor DNA; MPR, major pathologic response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PFS, progression-free survival; R, randomized.

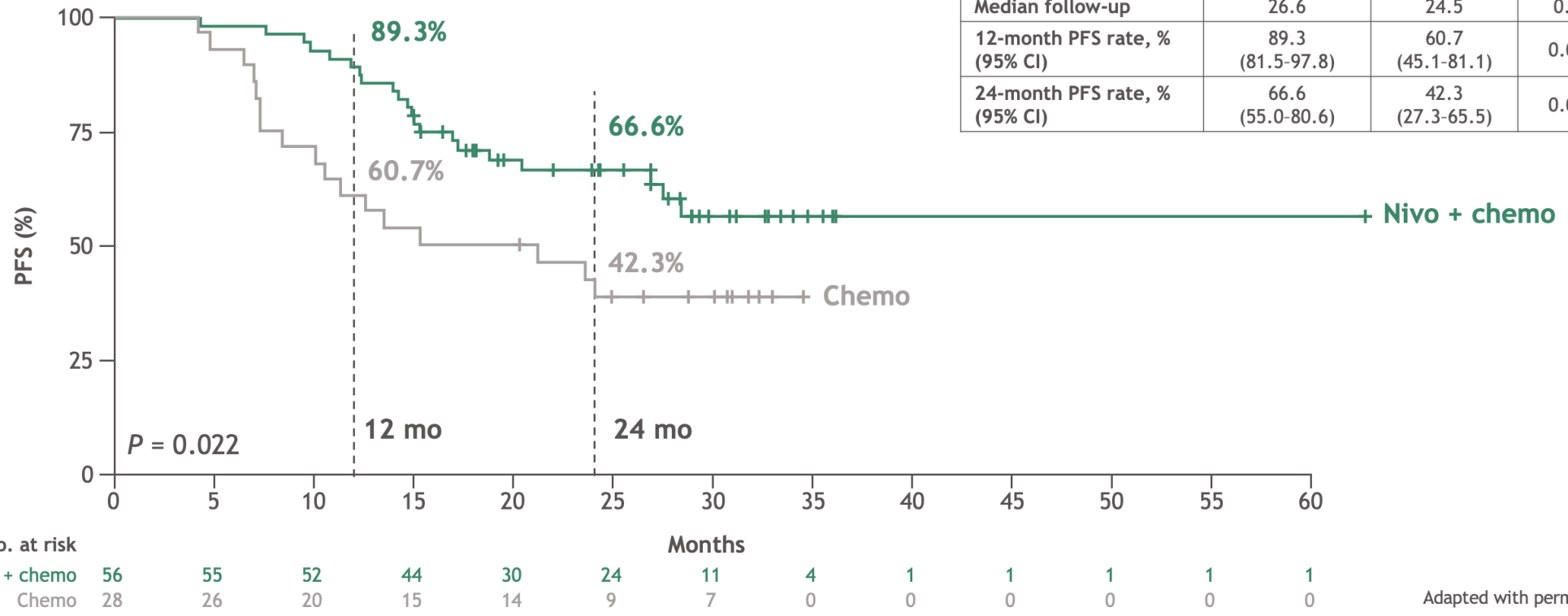
Provencio M et al. Oral presentation at World Conference on Lung Cancer (WCLC); August 6–9, 2022; Vienna, Austria. Presentation PL03.12.

NADIM II trial: pCR rate



NADIM II: progression-free survival

	NIVO + chemo (n = 57)	Chemo (n = 29)	*P* value
Median follow-up	26.6	24.5	0.19
12-month PFS rate, % (95% CI)	89.3 (81.5-97.8)	60.7 (45.1-81.1)	0.001
24-month PFS rate, % (95% CI)	66.6 (55.0-80.6)	42.3 (27.3-65.5)	0.012

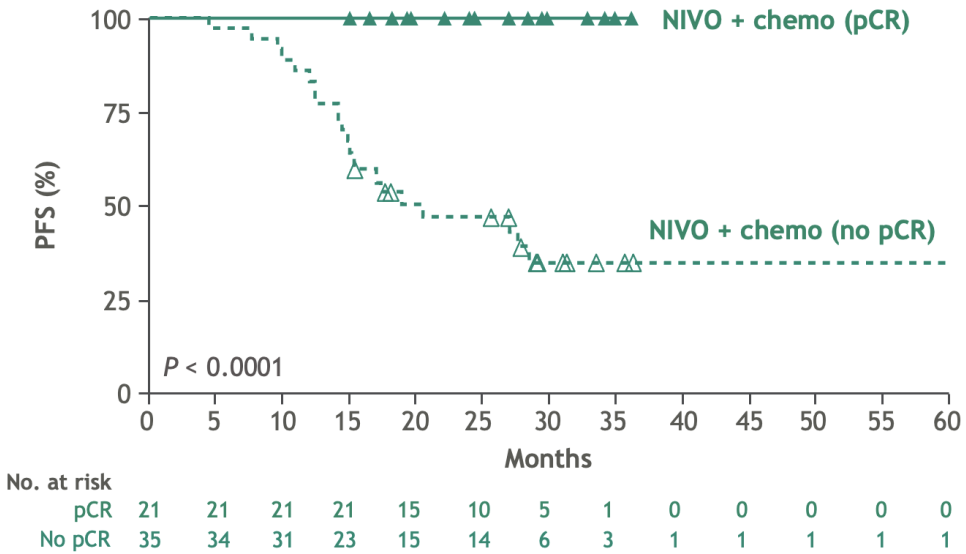


Adapted with permission.

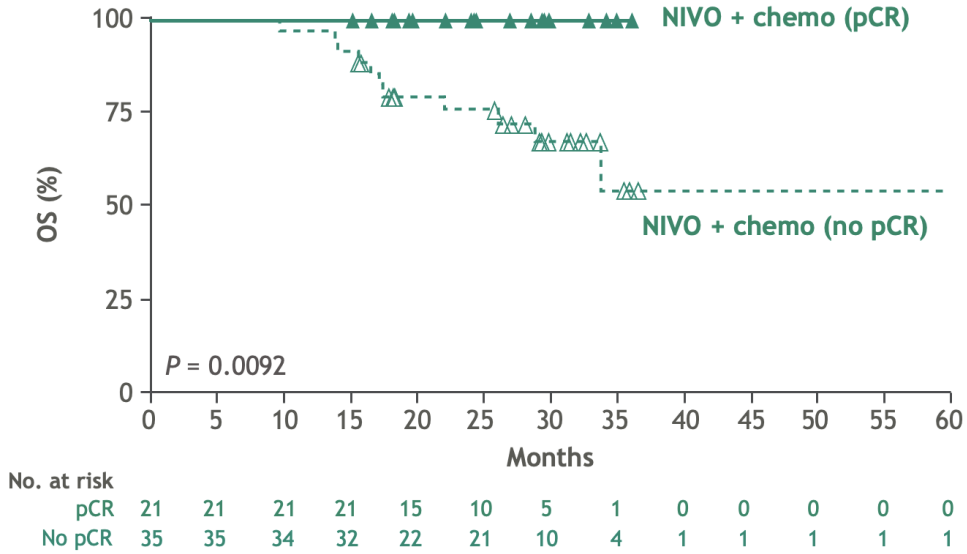
Median follow-up: 26.1 months. PFS was defined as the time from randomization to any of the following events: disease progression, disease recurrence, or death due to any cause. Progression/recurrence was determined according to RECIST 1.1.
chemo, chemotherapy; NIVO, nivolumab; PFS, progression-free survival.
Provencio M et al. Oral presentation at World Conference on Lung Cancer (WCLC); August 6-9, 2022; Vienna, Austria. Presentation PL03.12.

NADIM II: PS and OS by pCR status in Nivo plus Chemo arm

PFS



OS



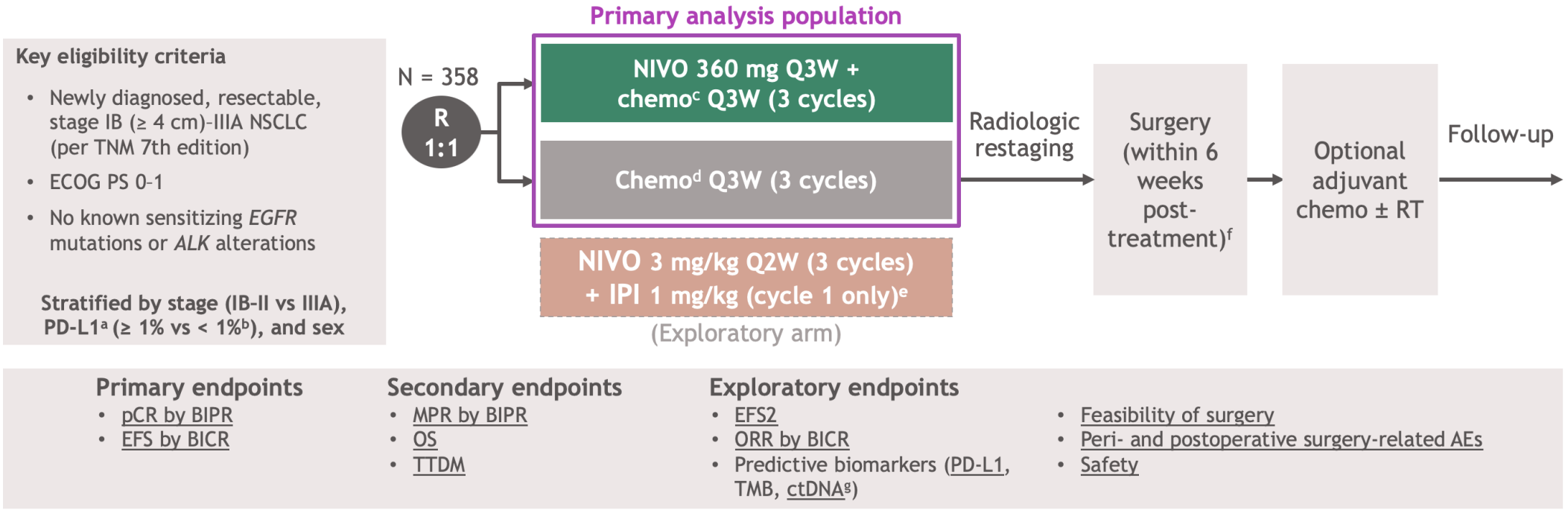
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

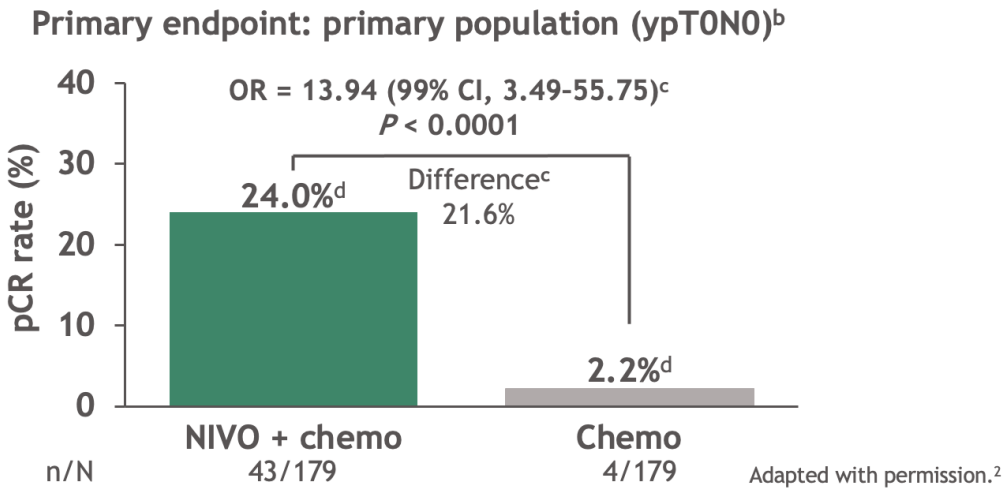
P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

Checkmate 816: study design

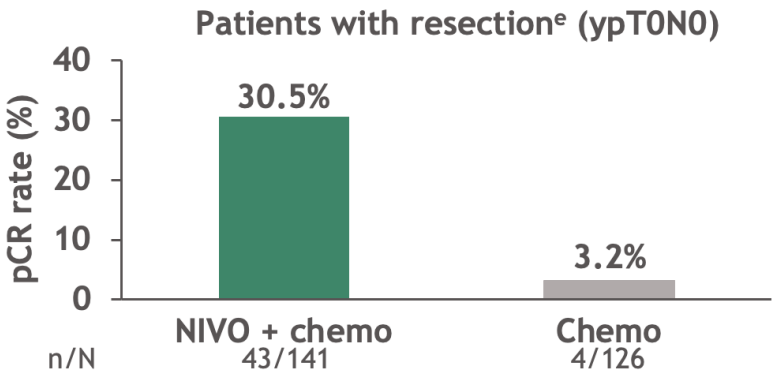


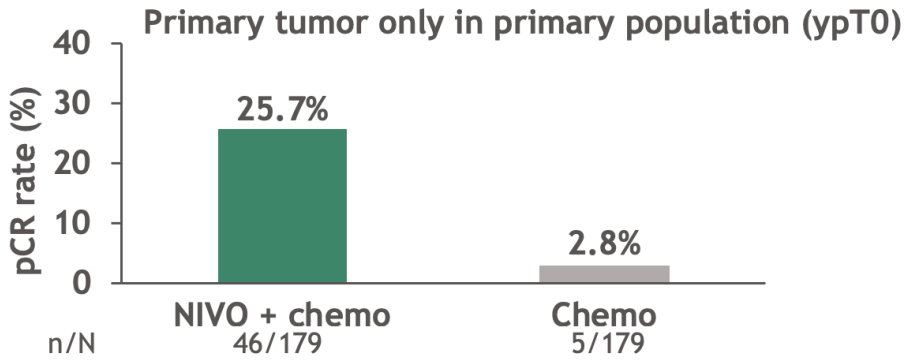
Forde PM et al. *N Engl J Med.* 2022

Checkmate 816: primary endpoint - pCR



Adapted with permission.[2]

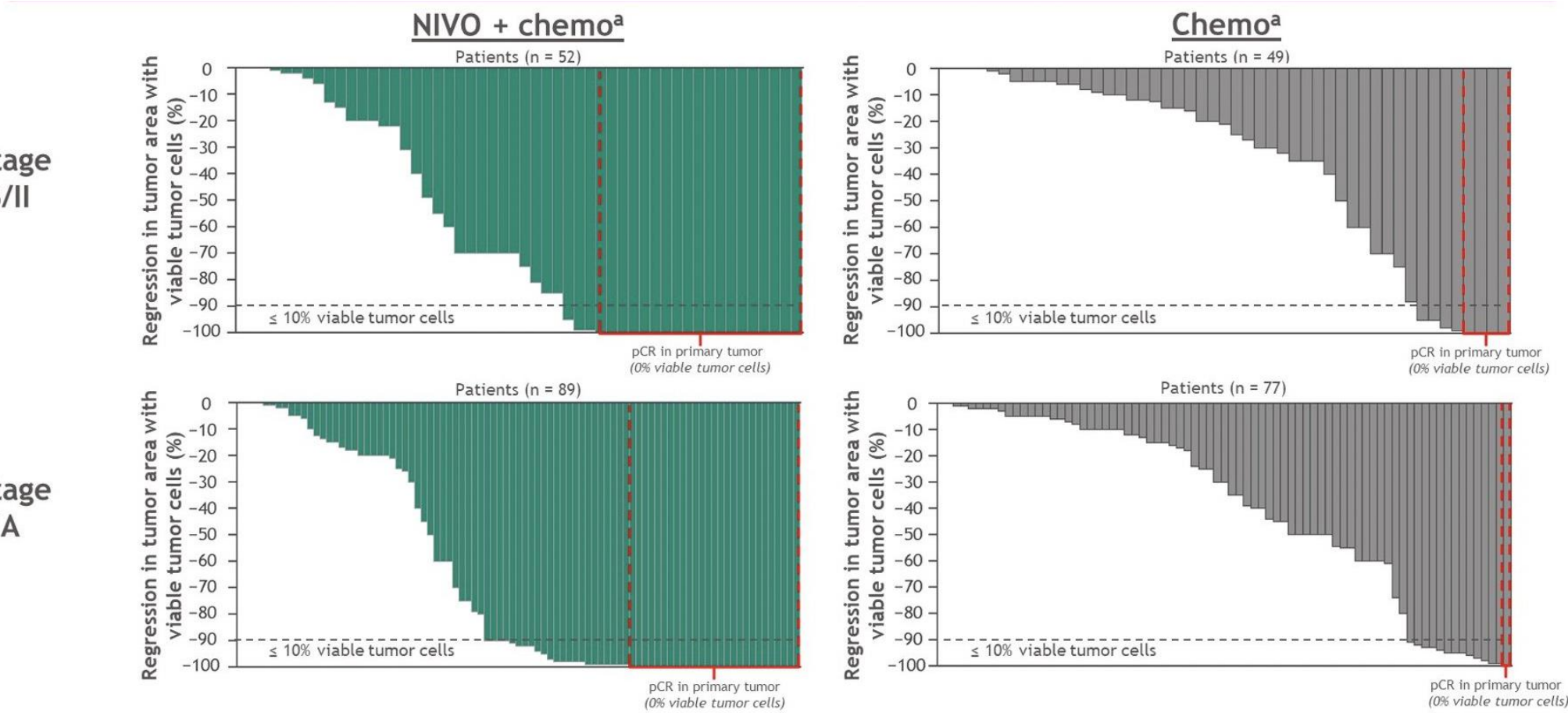




- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4–29.0)
- pCR rates in patients with lymph node involvement at baseline were
  - Any disease stage: 23.7% in the NIVO + chemo arm vs 1.0% in the chemo arm
  - Stage IIIA disease: 21.8% in the NIVO + chemo arm vs 0% in the chemo arm

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

Depth of patological regression in primary tumor by stage



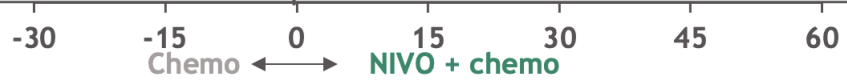
- The median residual viable tumor percentage in stage IB/II and IIIA was 28% and 8% with NIVO + chemo vs 79% and 70% with chemo, respectively

[a]Response-evaluable patients.

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

Checkmate 816: pCR subgroup analysis

	pCR[a] rate, % (95% CI)		Unweighted pCR difference, % (95% CI)	Unweighted pCR difference, % (95% CI)
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	24.0 (18.0-31.0)	2.2 (0.6-5.6)		21.8 (15.2-28.7)
< 65 years (n = 176)	26.9 (18.2-37.1)	0 (0-4.3)		26.9 (17.8-36.7)
≥ 65 years (n = 182)	20.9 (12.9-31.0)	4.2 (1.1-10.3)		17.8 (7.3-26.8)
Male (n = 255)	22.7 (15.7-30.9)	2.4 (0.5-6.7)		20.3 (12.6-28.4)
Female (n = 103)	27.5 (15.9-41.7)	1.9 (< 0.1-10.3)		25.5 (12.3-39.1)
North America (n = 91)	22.0 (10.6-37.6)	2.0 (< 0.1-10.6)		20.0 (6.9-34.8)
Europe (n = 66)	24.4 (12.4-40.3)	0 (0-13.7)		24.4 (7.4-39.3)
Asia (n = 177)	28.2 (19.0-39.0)	3.3 (0.7-9.2)		25.0 (14.7-35.5)
ECOG PS 0 (n = 241)	26.9 (19.1-35.3)	1.7 (0.2-6.0)		24.9 (16.7-33.4)
ECOG PS 1 (n = 117)	18.2 (9.1-30.9)	3.2 (0.4-11.2)		15.0 (3.8-27.3)
Stage IB-II (n = 128)	26.2 (16.0-38.5)	4.8 (1.0-13.3)		21.4 (9.0-33.6)
Stage IIIA (n = 228)	23.0 (15.6-31.9)	0.9 (< 0.1-4.7)		22.1 (14.3-30.7)
Squamous (n = 182)	25.3 (16.6-35.7)	4.2 (1.2-10.4)		21.1 (11.0-31.4)
Non-squamous (n = 176)	22.8 (14.7-32.8)	0 (0-4.3)		22.8 (14.2-32.4)
Current/former smoker (n = 318)	25.6 (19.1-33.1)	2.5 (0.7-6.4)		23.1 (15.9-30.5)
Never smoker (n = 39)	10.5 (1.3-33.1)	0 (0-16.8)		10.5 (-7.3-31.4)
PD-L1 < 1% (n = 155)	16.7 (9.2-26.8)	2.6 (0.3-9.1)		14.1 (4.8-24.0)
PD-L1 ≥ 1% (n = 178)	32.6 (23.0-43.3)	2.2 (0.3-7.9)		30.3 (19.9-40.7)
PD-L1 1-49% (n = 98)	23.5 (12.8-37.5)	0 (0-7.5)		23.5 (11.4-36.8)
PD-L1 ≥ 50% (n = 80)	44.7 (28.6-61.7)	4.8 (0.6-16.2)		40.0 (21.7-55.9)
TMB < 12.3 mut/Mb (n = 102)	22.4 (11.8-36.6)	1.9 (< 0.1-10.1)		20.6 (8.2-34.1)
TMB ≥ 12.3 mut/Mb (n = 76)	30.8 (17.0-47.6)	2.7 (< 0.1-14.2)		28.1 (11.6-43.9)
Cisplatin (n = 258)	21.8 (14.9-30.1)	2.2 (0.5-6.4)		19.5 (12.0-27.7)
Carboplatin (n = 72)	30.8 (17.0-47.6)	0 (0-10.6)		30.8 (14.7-46.4)



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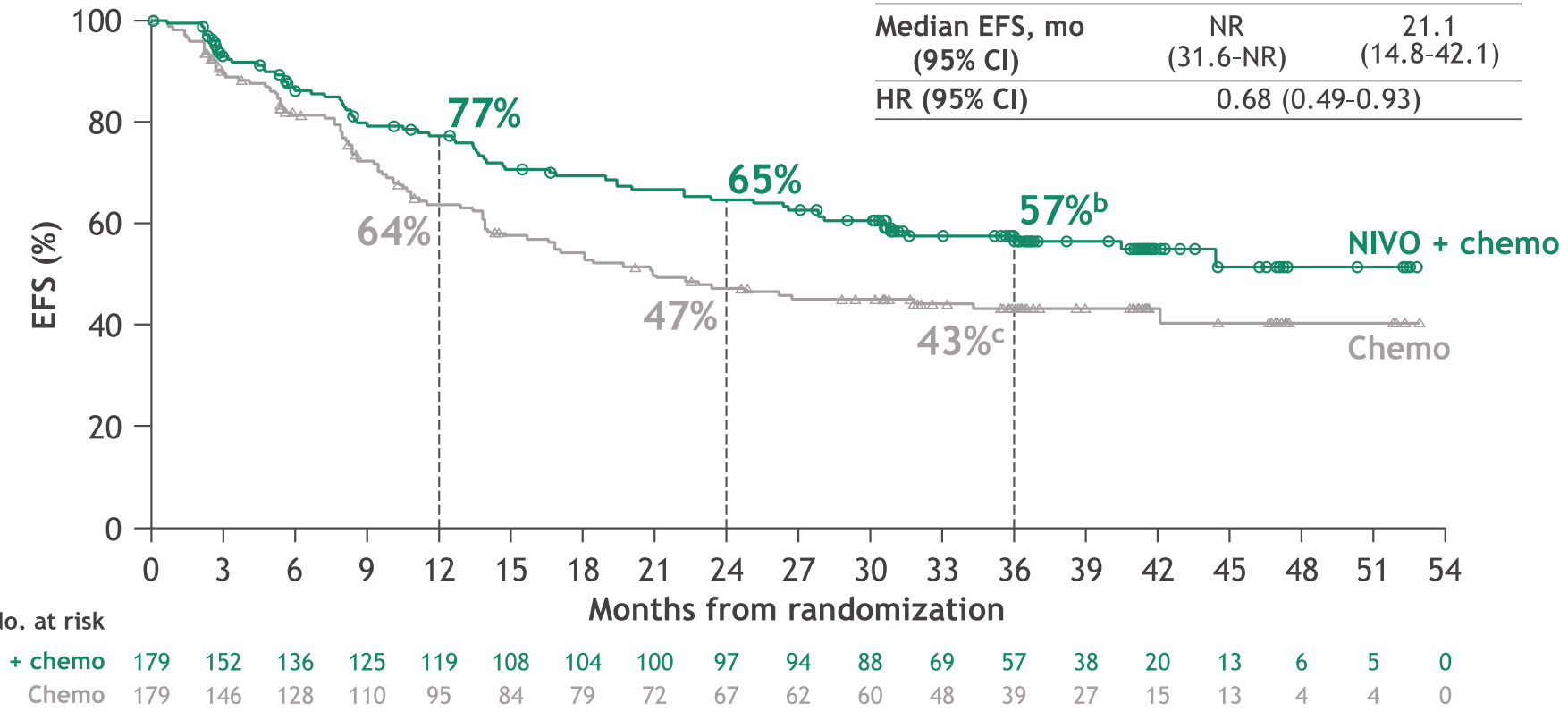
Checkmate 816: primary endpoint – EFS
3-year update

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



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; [c]35-51.

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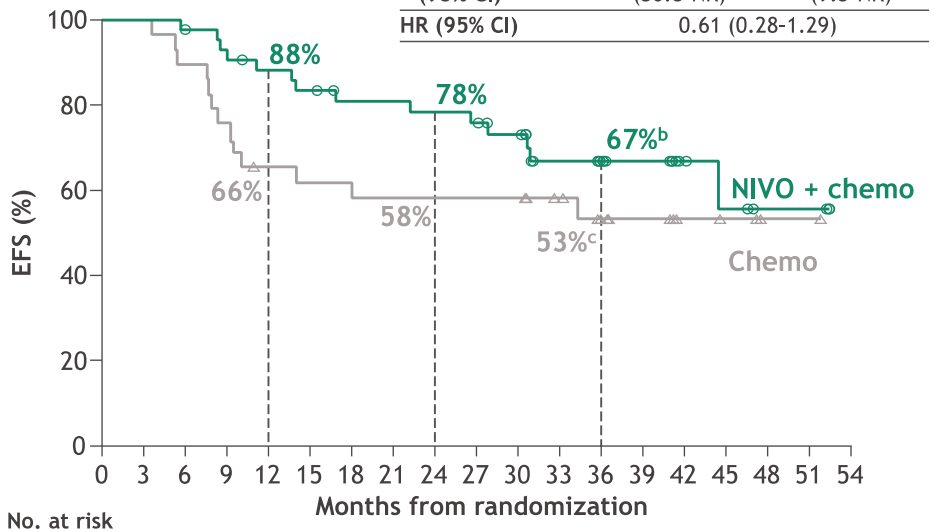
EFS by surgical approach
3-year update

Minimally invasive

	NIVO + chemo (n = 44)	Chemo (n = 29)
Median EFS, mo (95% CI)	NR (30.8-NR)	NR (9.5-NR)
HR (95% CI)	0.61 (0.28-1.29)	

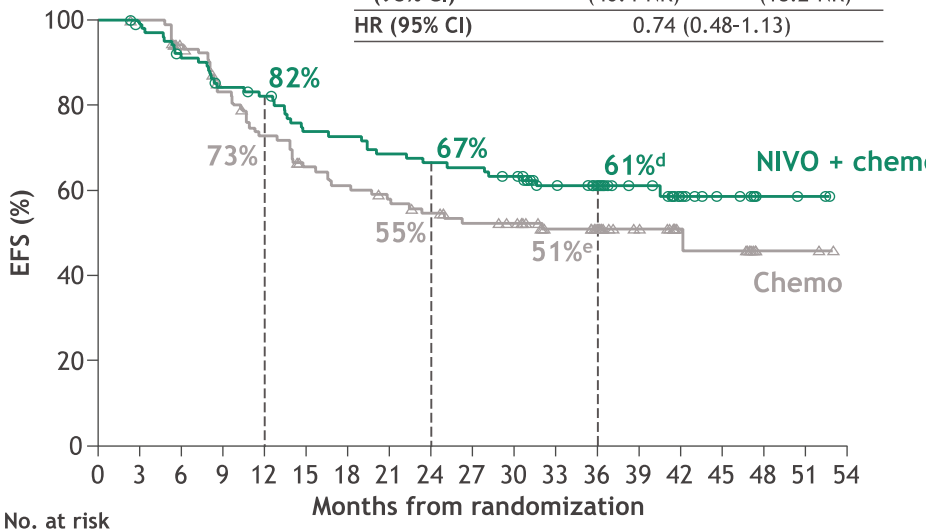


No. at risk

NIVO + chemo	44	44	42	40	37	35	32	32	31	30	27	19	16	12	7	5	3	3	0
Chemo	29	29	26	22	18	17	17	16	16	16	16	13	9	7	4	3	1	1	0

Thoracotomy or conversion

	NIVO + chemo (n = 105)	Chemo (n = 106)
Median EFS, mo (95% CI)	NR (40.4-NR)	42.1 (18.2-NR)
HR (95% CI)	0.74 (0.48-1.13)	



No. at risk

NIVO + chemo	105	102	91	83	80	71	70	66	64	63	60	49	41	26	13	8	3	2	0
Chemo	106	105	95	81	70	61	57	53	49	45	43	34	29	19	10	9	2	2	0

Minimum/median follow-up: 32.9/41.4 months.
[a]Among patients with definitive surgery in the NIVO + chemo and chemo arms, respectively, 30% and 21% had minimally invasive surgery; 70% and 79% had thoracotomy or conversion.
[b-e]95% CIs for 3-year EFS rates: [b]50-80; [c]33-70; [d]51-70; [e]40-61.

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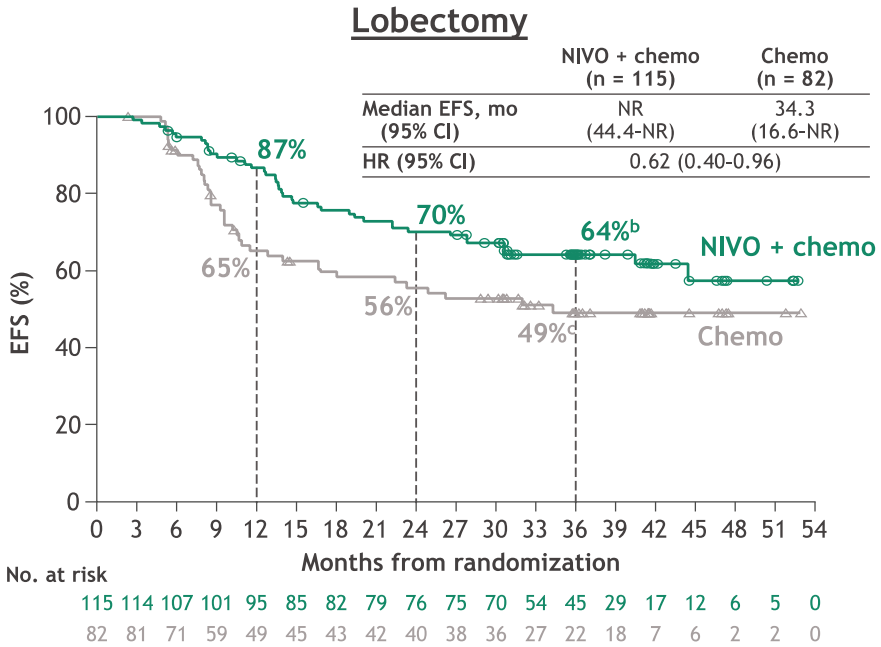
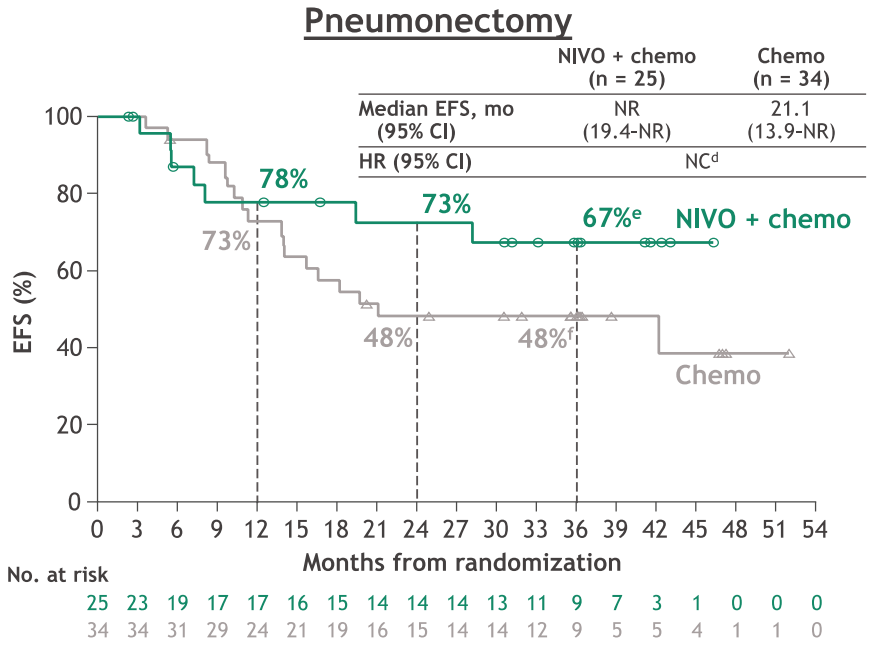
EFS by extent/completeness of resection
3-year update





- In patients with R0 resection,[a] 3-year EFS rates were 64%[g] vs 51%[h] for NIVO + chemo vs chemo, respectively (HR, 0.65; 95% CI, 0.43-0.98)

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

[a]Patients may have had ≥ 1 type of surgery. In the respective NIVO + chemo and chemo arms, surgery types included lobectomy (77% and 61%) and pneumonectomy (17% [11 right; 14 left] and 25% [12 right; 22 left]); patients with R0 resection: 83% and 78%. [b,c]95% CIs for 3-year EFS rates: [b]54-72; [c]37-60. [d]HR not calculated due to insufficient event numbers(< 10 per arm). [e-j]95% CIs for 3-year EFS rates: [e]43-83; [f]31-64; [g]55-72; [h]40-60. R0, no residual tumor.

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Checkmate 816: EFS subgroup analysis

	Median EFS,[a] mo (95% CI)		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	31.6 (30.2-NR)	20.8 (14.0-26.7)		0.63 (0.45-0.87)
< 65 years (n = 176)	NR (31.6-NR)	20.8 (14.0-NR)		0.57 (0.35-0.93)
≥ 65 years (n = 182)	30.2 (23.4-NR)	18.4 (10.6-31.8)		0.70 (0.45-1.08)
Male (n = 255)	30.6 (20.0-NR)	16.9 (13.8-24.9)		0.68 (0.47-0.98)
Female (n = 103)	NR (30.5-NR)	31.8 (13.9-NR)		0.46 (0.22-0.96)
North America (n = 91)	NR (25.1-NR)	NR (12.8-NR)		0.78 (0.38-1.62)
Europe (n = 66)	31.6 (13.4-NR)	21.1 (10.2-NR)		0.80 (0.36-1.77)
Asia (n = 177)	NR (30.2-NR)	16.5 (10.8-22.7)		0.45 (0.29-0.71)
ECOG PS 0 (n = 241)	NR (30.2-NR)	22.7 (16.6-NR)		0.61 (0.41-0.91)
ECOG PS 1 (n = 117)	30.5 (14.6-NR)	14.0 (9.8-26.2)		0.71 (0.41-1.21)
Stage IB-II (n = 127)	NR (27.8-NR)	NR (16.8-NR)		0.87 (0.48-1.56)
Stage IIIA (n = 228)	31.6 (26.6-NR)	15.7 (10.8-22.7)		0.54 (0.37-0.80)
Squamous (n = 182)	30.6 (20.0-NR)	22.7 (11.5-NR)		0.77 (0.49-1.22)
Non-squamous (n = 176)	NR (27.8-NR)	19.6 (13.8-26.2)		0.50 (0.32-0.79)
Current/former smoker (n = 318)	31.6 (30.2-NR)	22.4 (15.7-NR)		0.68 (0.48-0.96)
Never smoker (n = 39)	NR (5.6-NR)	10.4 (7.7-20.8)		0.33 (0.13-0.87)
PD-L1 < 1% (n = 155)	25.1 (14.6-NR)	18.4 (13.9-26.2)		0.85 (0.54-1.32)
PD-L1 ≥ 1% (n = 178)	NR (NR-NR)	21.1 (11.5-NR)		0.41 (0.24-0.70)
PD-L1 1-49% (n = 98)	NR (27.8-NR)	26.7 (11.5-NR)		0.58 (0.30-1.12)
PD-L1 ≥ 50% (n = 80)	NR (NR-NR)	19.6 (8.2-NR)		0.24 (0.10-0.61)
TMB < 12.3 mut/Mb (n = 102)	30.5 (19.4-NR)	26.7 (16.6-NR)		0.86 (0.47-1.57)
TMB ≥ 12.3 mut/Mb (n = 76)	NR (14.8-NR)	22.4 (13.4-NR)		0.69 (0.33-1.46)
Cisplatin (n = 258)	NR (25.1-NR)	20.9 (15.7-NR)		0.71 (0.49-1.03)
Carboplatin (n = 72)	NR (30.5-NR)	10.6 (7.6-26.7)		0.31 (0.14-0.67)

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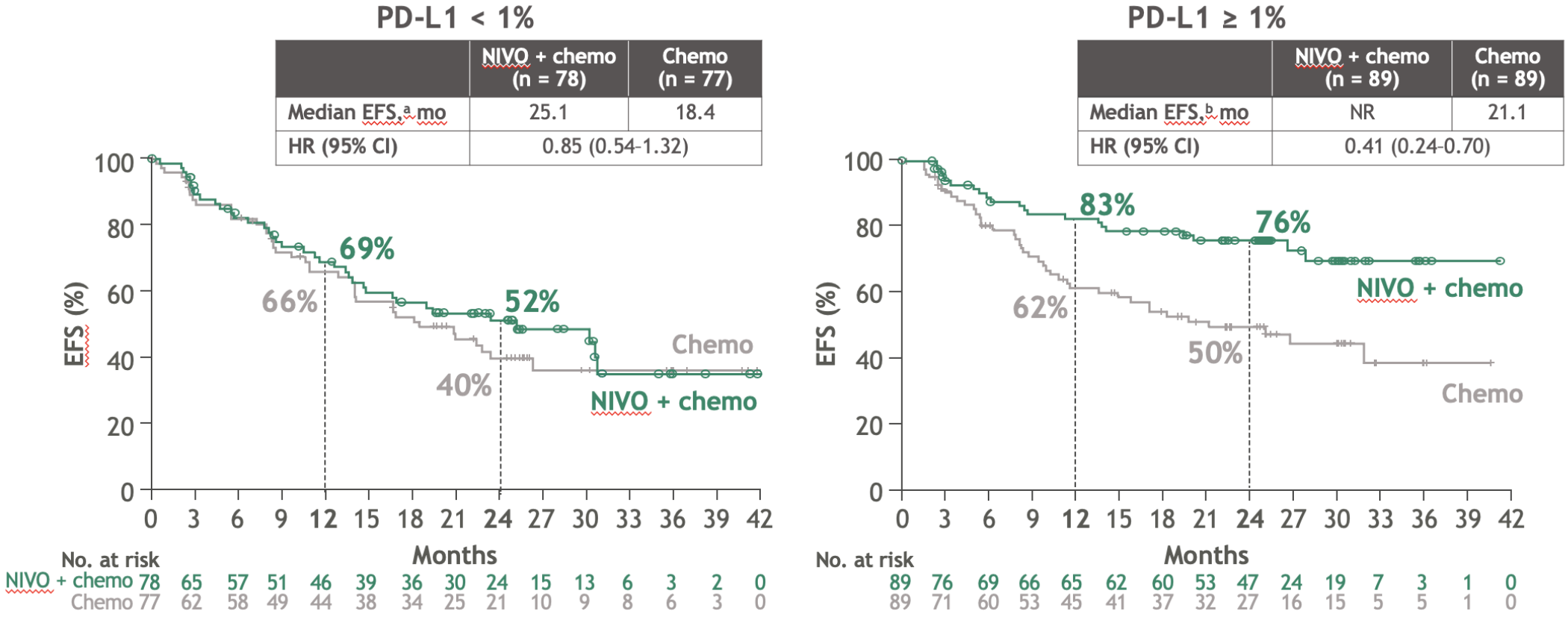
EFS by tumor PD-L1 expression < 1% or ≥ 1%



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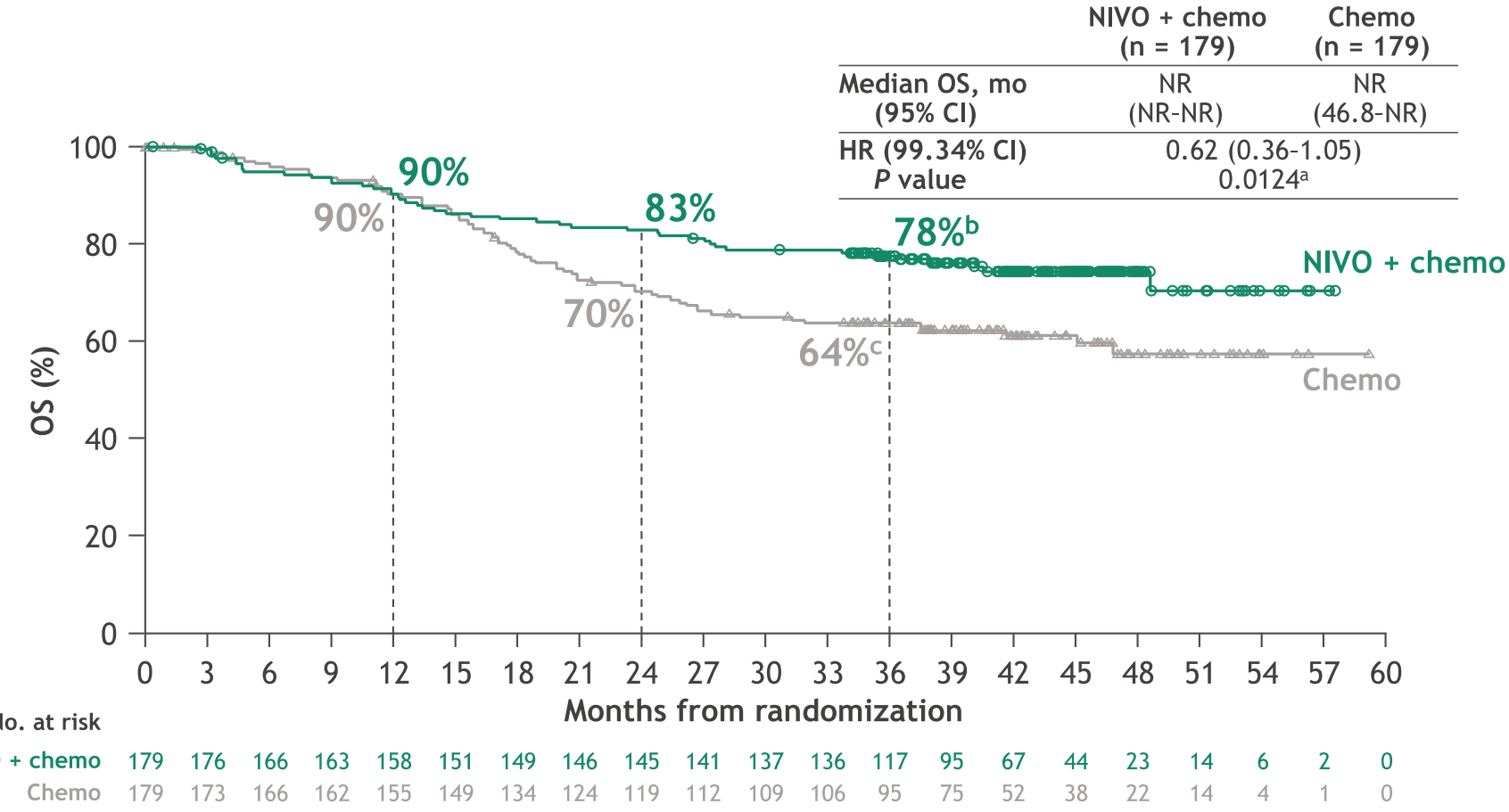
Checkmate 816: OS with neoadjuvant NIVO + chemo vs chemo 3-year update



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

[a]Significance boundary for OS was not crossed at this interim analysis. [b,c]95% CIs for 3-year OS rates: [b]71-83; [c]56-70.

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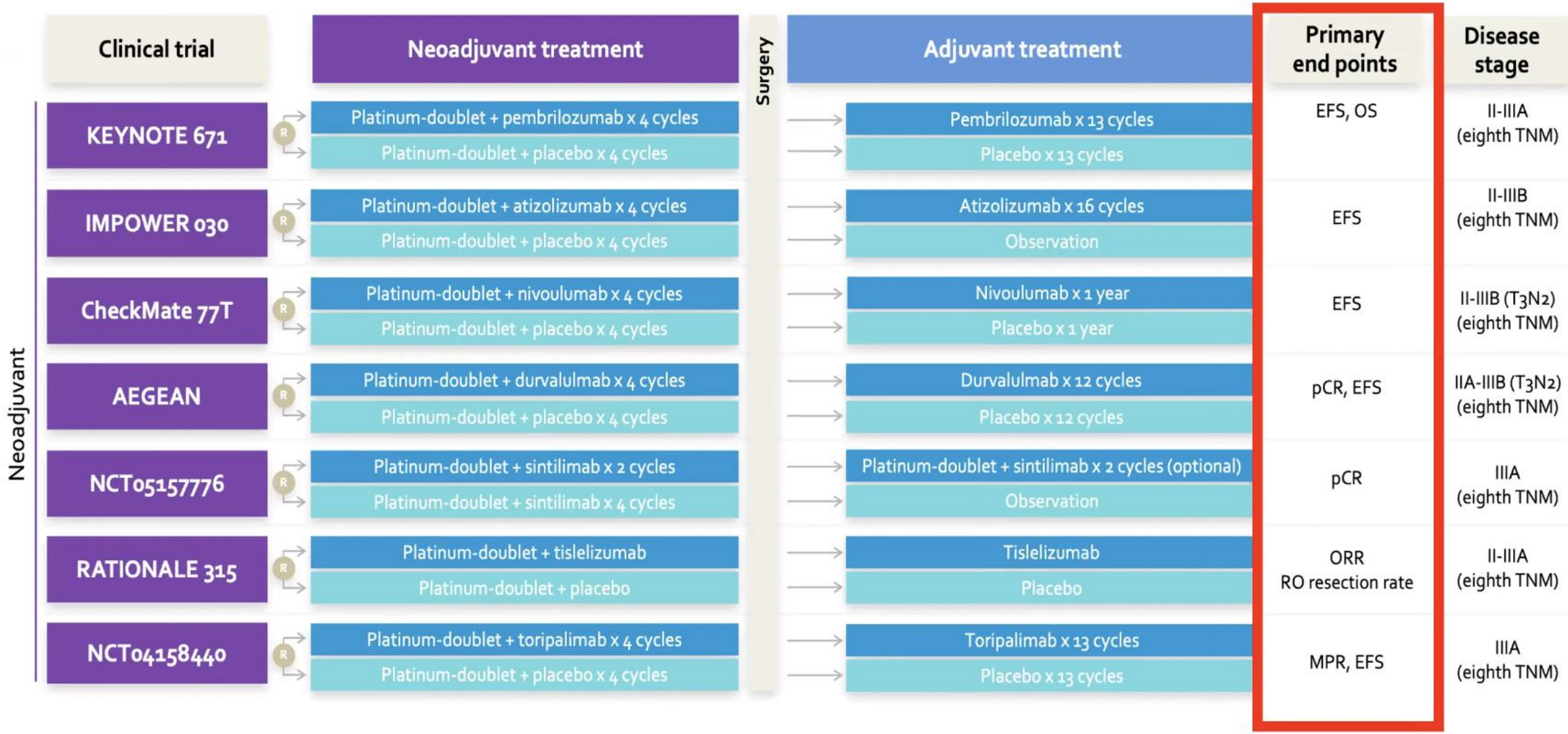
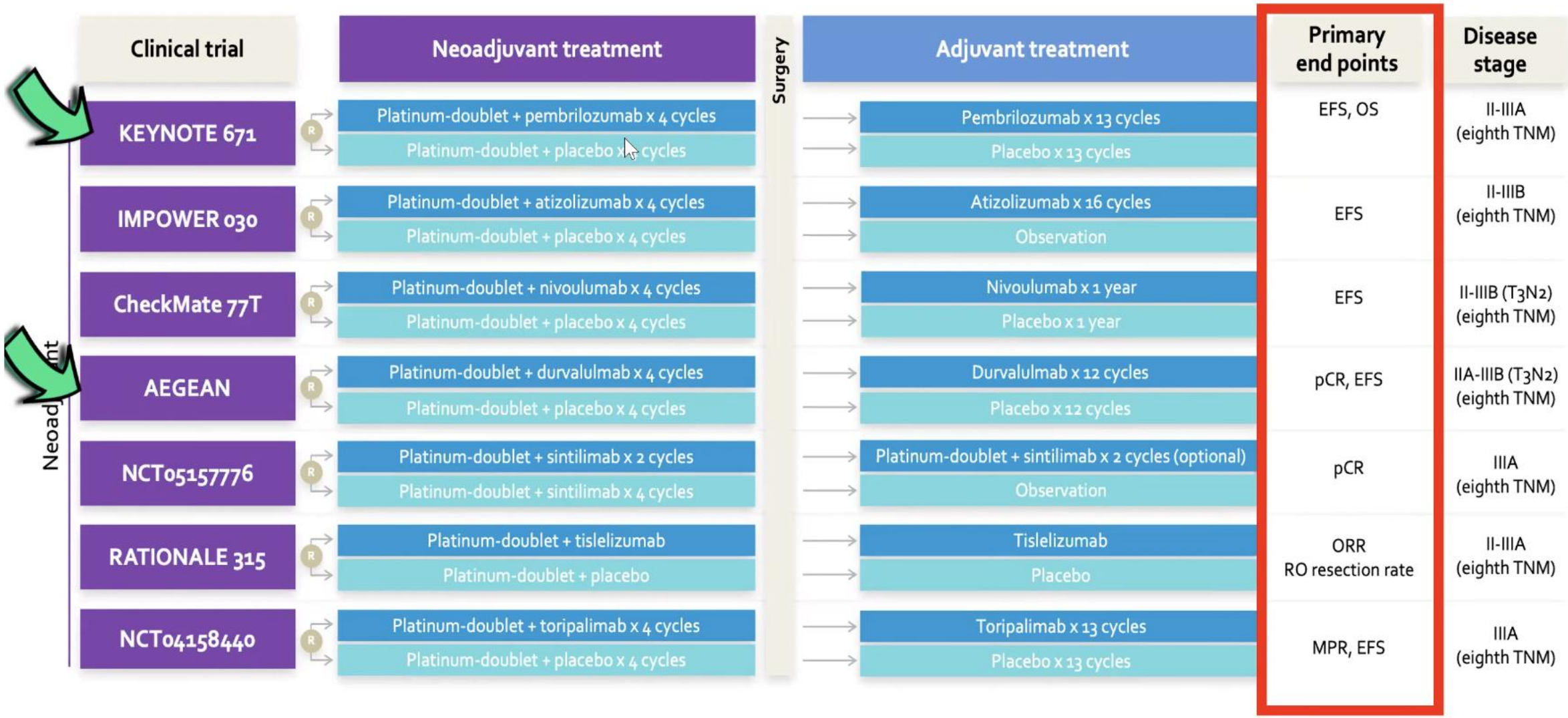
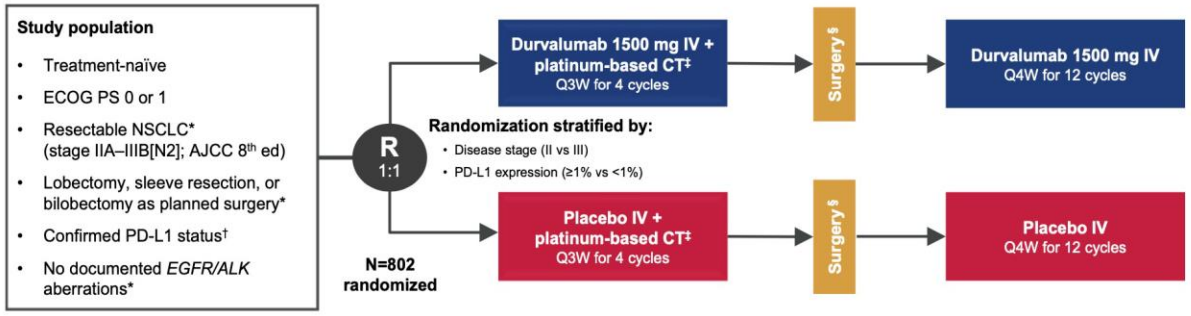
SCIENCE MEDICINES HEALTH

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.


Neoadjuvant
Clinical trial
Neoadjuvant treatment
Surgery
Adjuvant treatment
Primary end points
Disease stage
KEYNOTE 671
R
Platinum-doublet + pembrilozumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Pembrilozumab x 13 cycles
Placebo x 13 cycles
EFS, OS
II-IIIA (eighth TNM)
IMPOWER 030
R
Platinum-doublet + atizolizumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Atizolizumab x 16 cycles
Observation
EFS
II-IIIB (eighth TNM)
CheckMate 77T
R
Platinum-doublet + nivoulumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Nivoulumab x 1 year
Placebo x 1 year
EFS
II-IIIB (T3N2) (eighth TNM)
AEGEAN
R
Platinum-doublet + durvalulmab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Durvalulmab x 12 cycles
Placebo x 12 cycles
pCR, EFS
IIA-IIIB (T3N2) (eighth TNM)
NCT05157776
R
Platinum-doublet + sintilimab x 2 cycles
Platinum-doublet + sintilimab x 4 cycles
Platinum-doublet + sintilimab x 2 cycles (optional)
Observation
pCR
IIIA (eighth TNM)
RATIONALE 315
R
Platinum-doublet + tislelizumab
Platinum-doublet + placebo
Tislelizumab
Placebo
ORR
RO resection rate
II-IIIA (eighth TNM)
NCT04158440
R
Platinum-doublet + toripalimab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Toripalimab x 13 cycles
Placebo x 13 cycles
MPR, EFS
IIIA (eighth TNM)


Clinical trial
Neoadjuvant treatment
Surgery
Adjuvant treatment
Primary end points
Disease stage
KEYNOTE 671
Platinum-doublet + pembrilozumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Pembrilozumab x 13 cycles
Placebo x 13 cycles
EFS, OS
II-IIIA (eighth TNM)
IMPOWER 030
Platinum-doublet + atizolizumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Atizolizumab x 16 cycles
Observation
EFS
II-IIIB (eighth TNM)
CheckMate 77T
Platinum-doublet + nivoulumab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Nivoulumab x 1 year
Placebo x 1 year
EFS
II-IIIB (T3N2) (eighth TNM)
AEGEAN
Platinum-doublet + durvalulmab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Durvalulmab x 12 cycles
Placebo x 12 cycles
pCR, EFS
IIA-IIIB (T3N2) (eighth TNM)
NCT05157776
Platinum-doublet + sintilimab x 2 cycles
Platinum-doublet + sintilimab x 4 cycles
Platinum-doublet + sintilimab x 2 cycles (optional)
Observation
pCR
IIIA (eighth TNM)
RATIONALE 315
Platinum-doublet + tislelizumab
Platinum-doublet + placebo
Tislelizumab
Placebo
ORR
RO resection rate
II-IIIA (eighth TNM)
NCT04158440
Platinum-doublet + toripalimab x 4 cycles
Platinum-doublet + placebo x 4 cycles
Toripalimab x 13 cycles
Placebo x 13 cycles
MPR, EFS
IIIA (eighth TNM)
R

AEGEAN

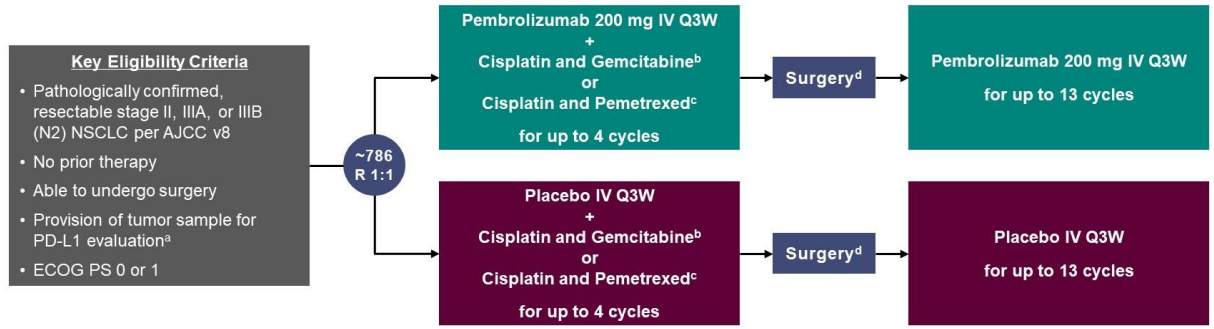


Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

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

KEYNOTE-671



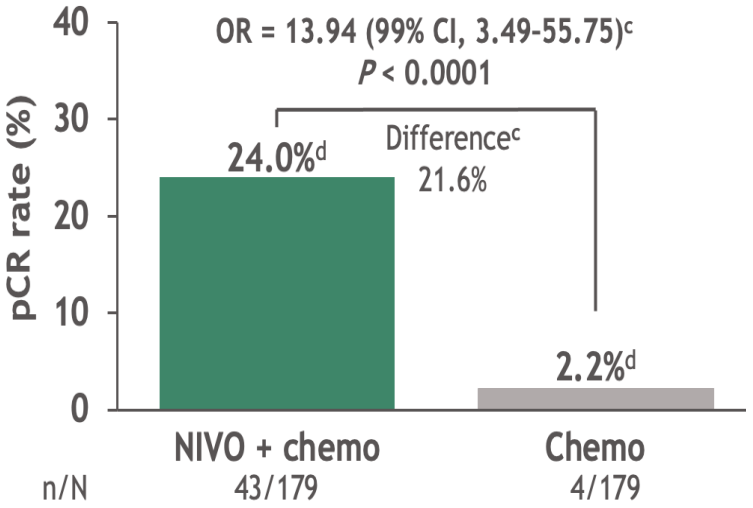
Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

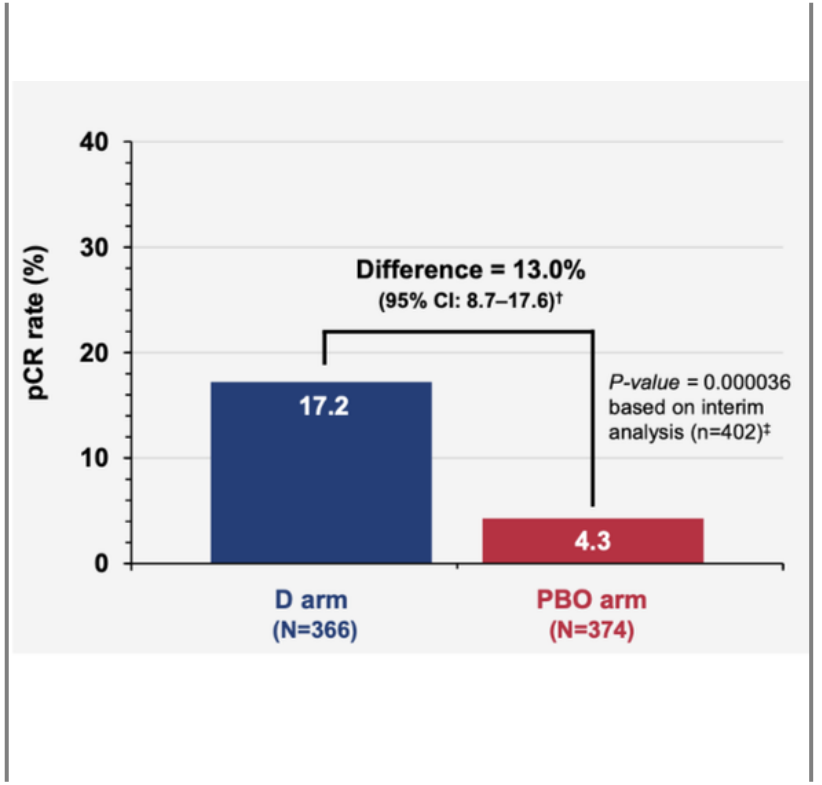
Dual primary end points: EFS per investigator review and OS

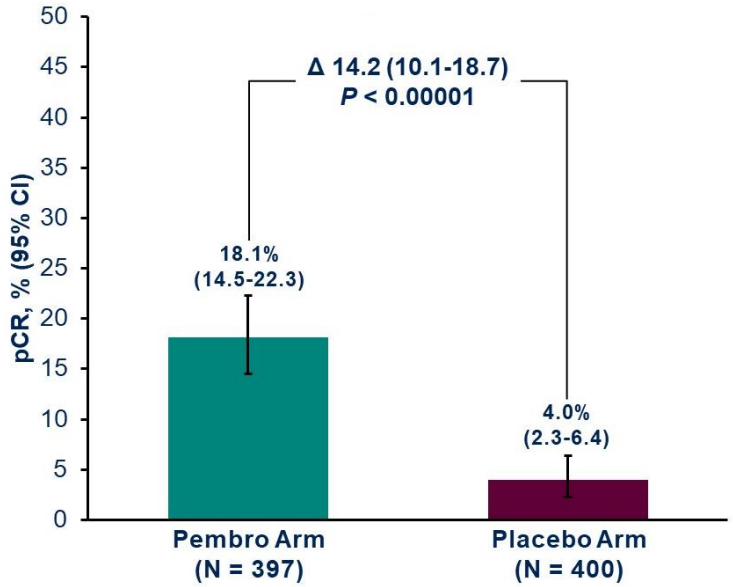
Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

AEGEAN NCT03800134	Resectable II - IIIB (N2) n=825	Durvalumab/placebo + chemo x 4 Surgery Consolidation durvalumab/placebo	pCR and EFS
KEYNOTE 671 NCT03425643	Resectable II-IIIB (N2) n=786	Pembrolizumab/placebo + chemo x 4 Surgery Consolidation pembrolizumab/placebo	EFS and OS

pCR



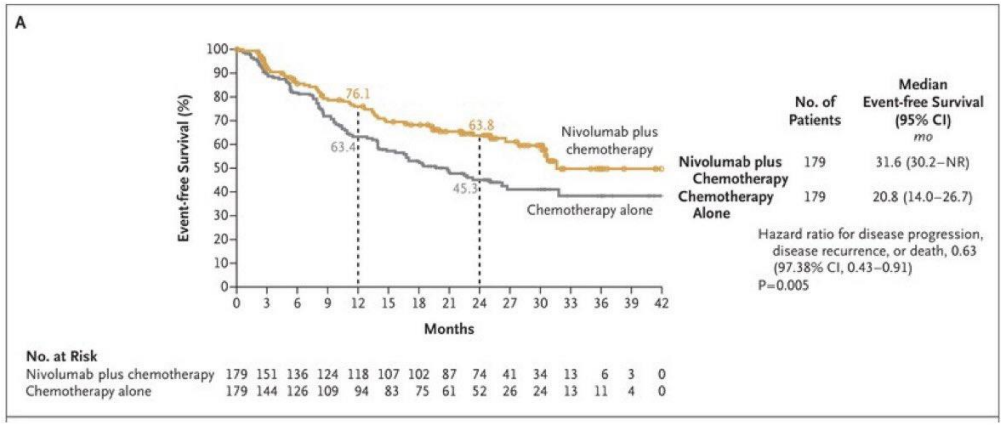




CHECKMATE 816 **AEGEAN** **KEYNOTE 671**

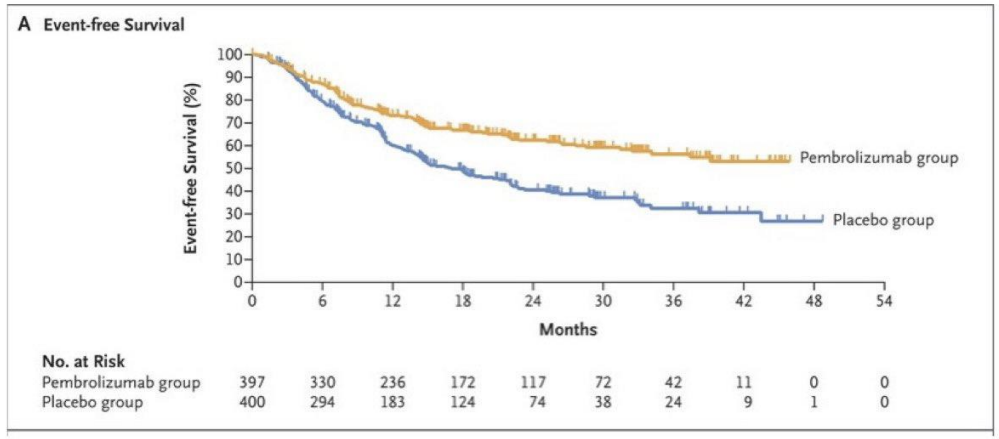
CHECKMATE 816: EFS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d] *P* value[e]	0.63 (0.43-0.91) 0.0052	



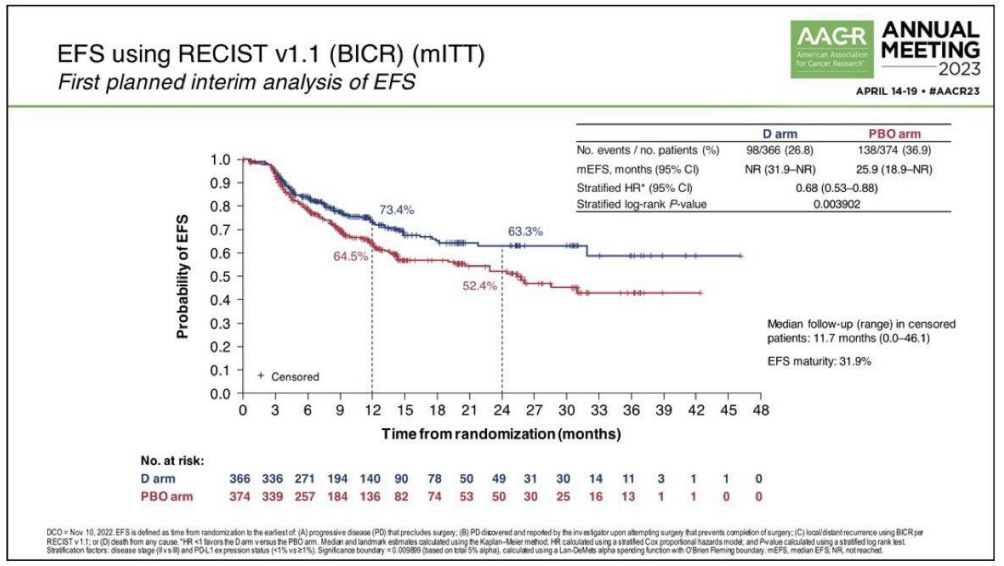
AEGEAN: EFS

	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	

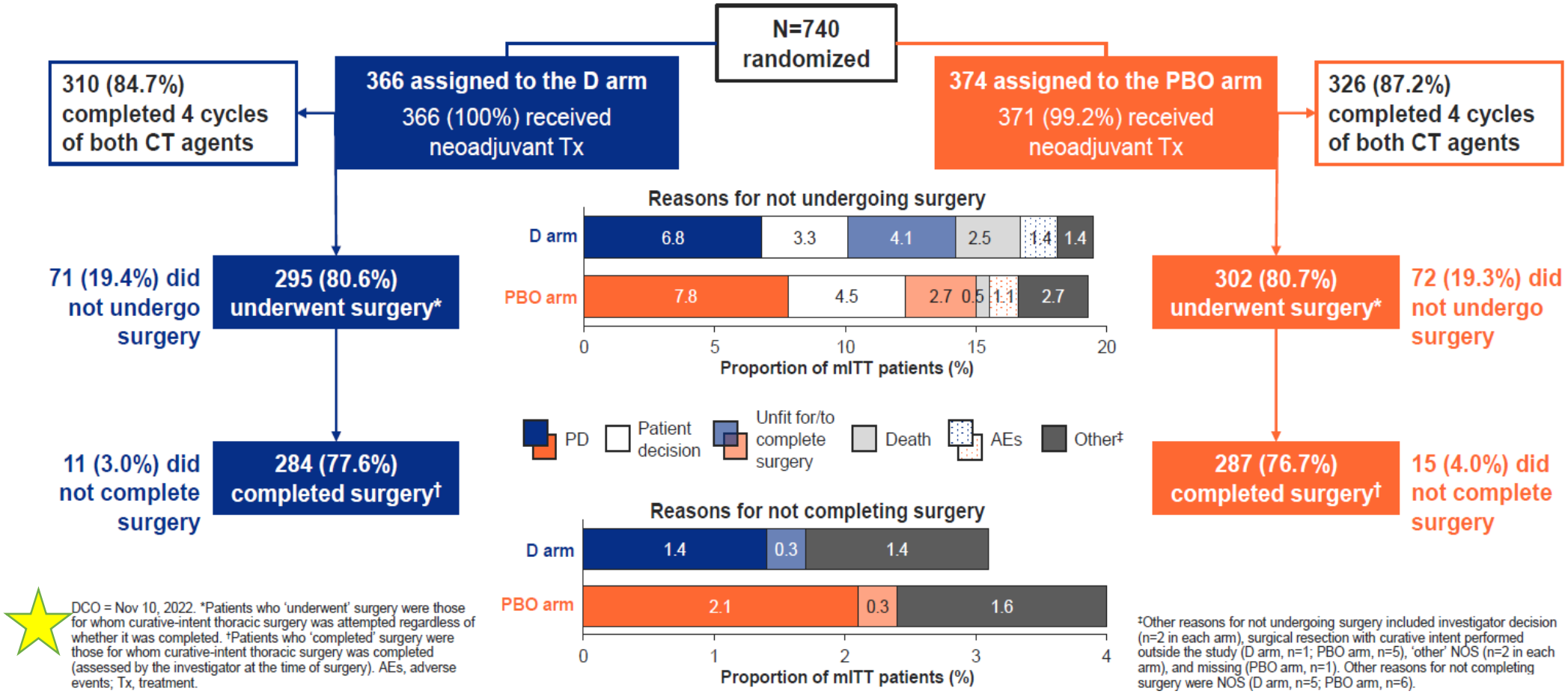


KEYNOTE-671: EFS

	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)



AEGEAN: Surgical Outcomes



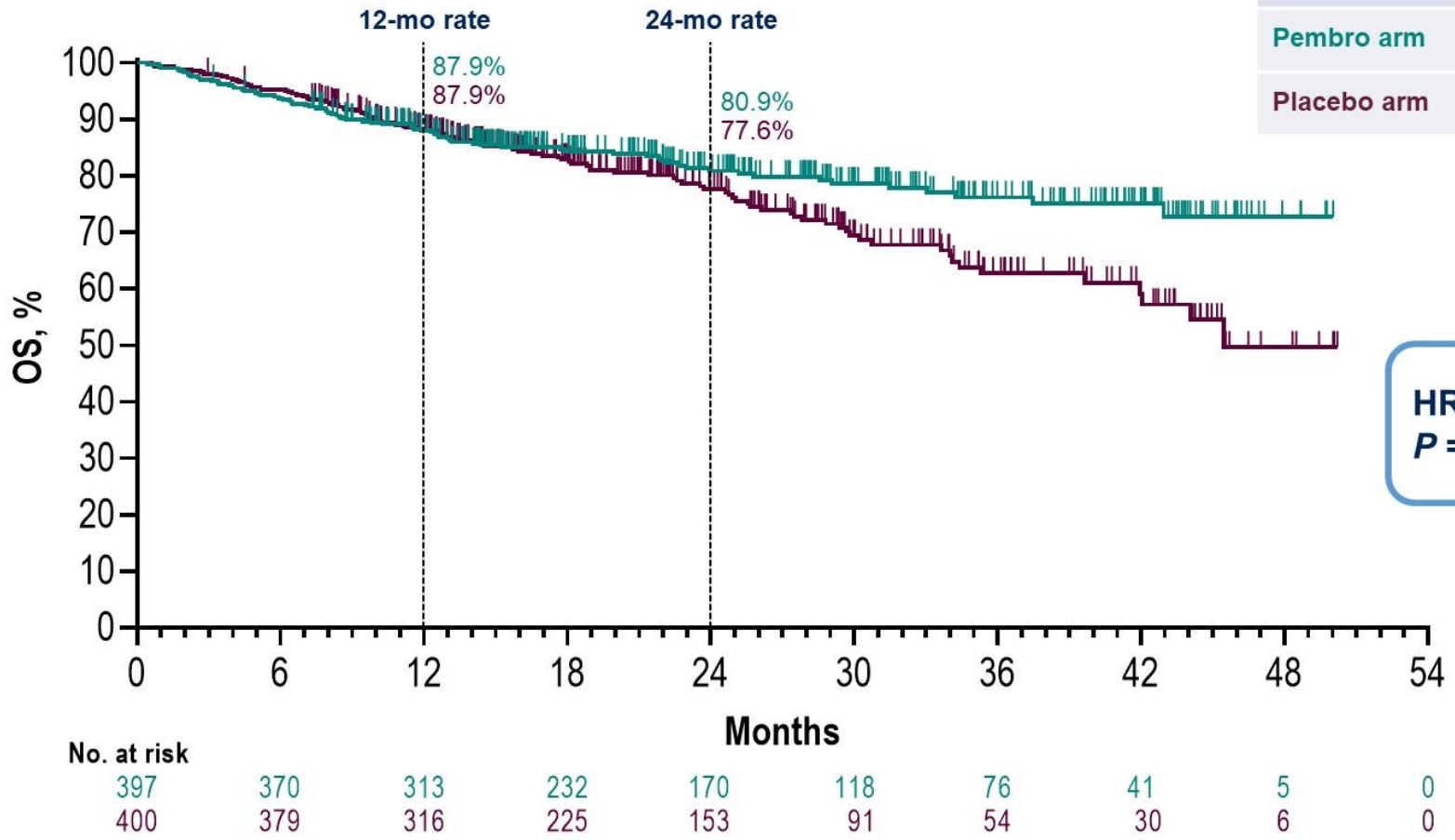
DCO = Nov 10, 2022. *Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. †Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed by the investigator at the time of surgery). AEs, adverse events; Tx, treatment.

‡Other reasons for not undergoing surgery included investigator decision (n=2 in each arm), surgical resection with curative intent performed outside the study (D arm, n=1; PBO arm, n=5), 'other' NOS (n=2 in each arm), and missing (PBO arm, n=1). Other reasons for not completing surgery were NOS (D arm, n=5; PBO arm, n=6).

Surgery miss is related to **PD** and **patient's selection** [rarely to AEs]

Mitsudomi T et al. WCLC 2023 [OA 12.05]

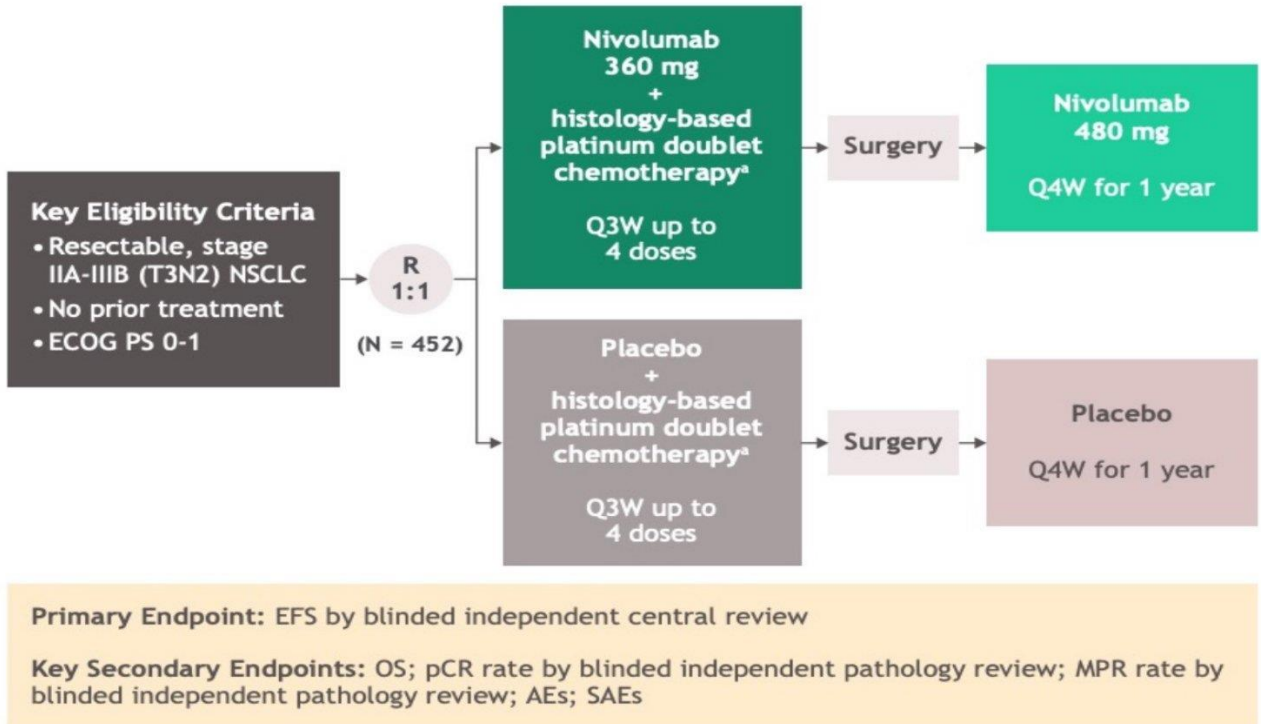
KEYNOTE-671: OVERALL SURVIVAL



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; OS will continue to be tested according to the analysis plan. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

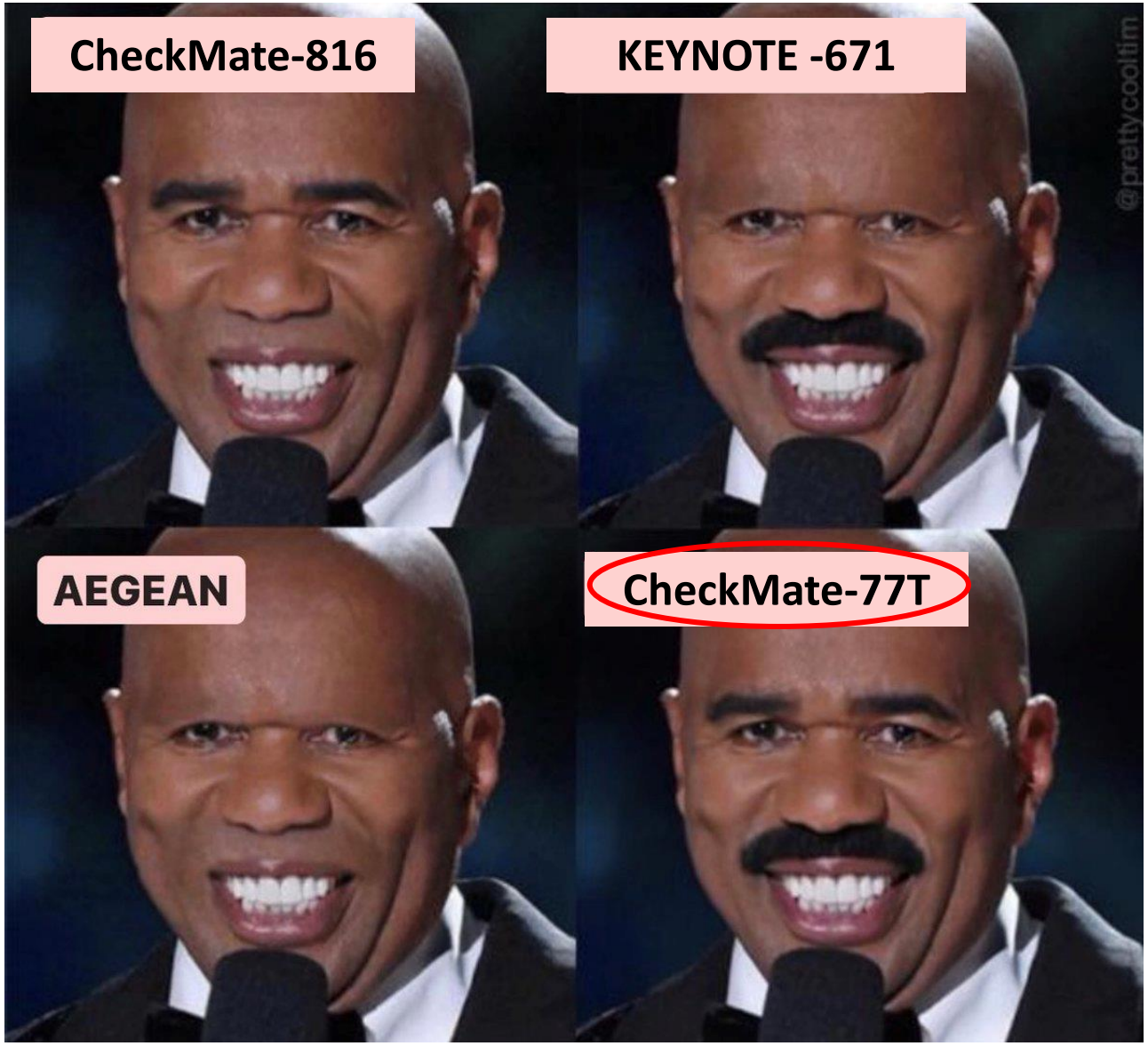


Bristol Myers Squibb Announces Perioperative Regimen of Neoadjuvant Opdivo (nivolumab) and Chemotherapy Followed by Adjuvant Opdivo Significantly Improves Event-Free Survival in Patients with Resectable Non-Small Cell Lung Cancer

09/22/2023

CATEGORY: Corporate/Financial News

CheckMate -77T represents the company's second positive Phase 3 trial with an immunotherapy-based combination for the treatment of non-metastatic non-small cell lung cancer


CheckMate-816
KEYNOTE -671
@prettycooltim
AEGEAN
CheckMate-77T

5 4 52 12,6K

Patrick Forde @FordePatrick · 1g

I tried to persuade a company to do a 3 arm trial of neoadjuvant & adjuvant (with a different PD-1 a in one arm and a novel drug + PD-1 combo in the third) vs. CM816. Market research (among thoracic oncs!) told them the control arm was suboptimal due to not including adjuvant! 🤷‍♂️

1 1 9 852

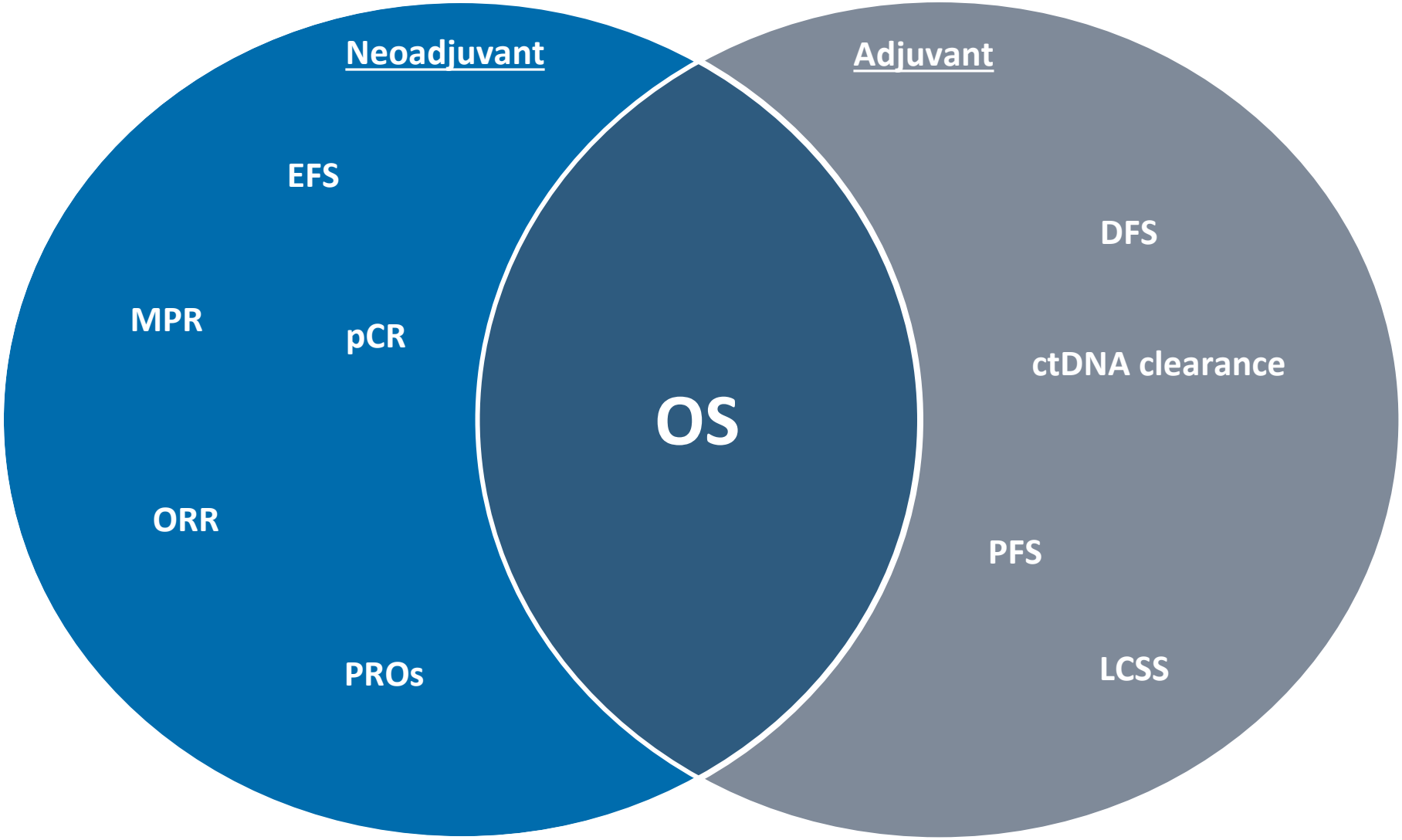
What we have:

Neoadjuvant Immunotherapy (Approved)		→ SURGERY
CheckMate 816	Nivolumab + Chemo x 3 cycles	

SURGERY →	Adjuvant Immunotherapy (Approved)	
	IMpower010	Chemo → Atezolizumab ~1 year (PD-L1 ≥1%)
	KEYNOTE-091	Chemo (optional) → Pembrolizumab ~1 year

PERIOPERATIVE IMMUNOTHERAPY Ph3 TRIALS

Study	Neoadjuvant Regimen →	SURGERY →	Adjuvant Regimen
KEYNOTE-671	Pembrolizumab + Chemo x 4 cycles		Pembrolizumab ~1 year
AEGEAN	Durvalumab + Chemo x 4 cycles		Durvalumab ~1 year
Neotorch	Toripalimab + Chemo x 3 cycles		Toripalimab + Chemo x 1 cycle → Toripalimab ~1 year
CheckMate 77T	Nivolumab + Chemo x 4 cycles		Nivolumab ~1 year
IMpower030	Atezolizumab + Chemo x 4 cycles		Atezolizumab ~1 year

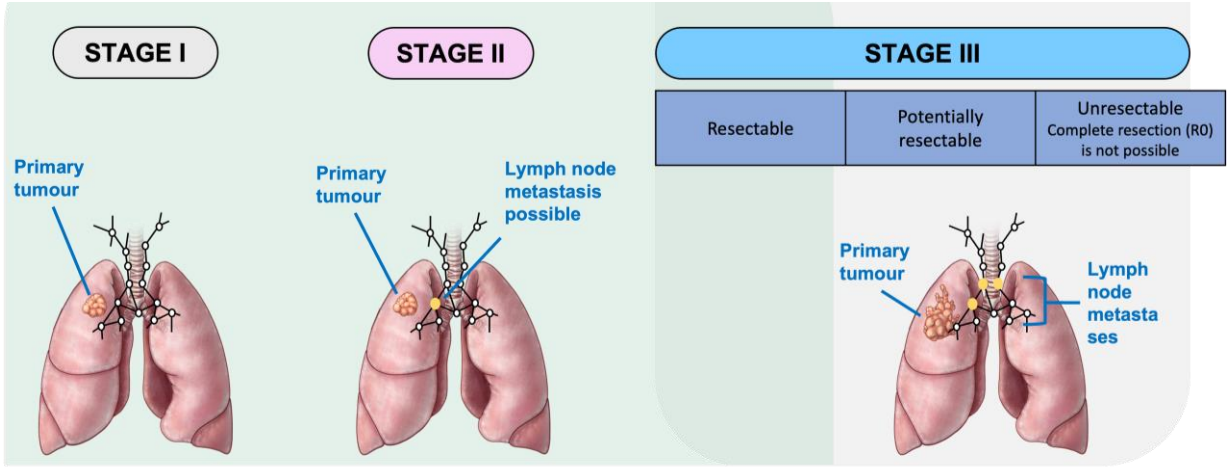

Neoadjuvant
EFS
MPR
pCR
ORR
PROs
OS
Adjuvant
DFS
ctDNA clearance
PFS
LCSS

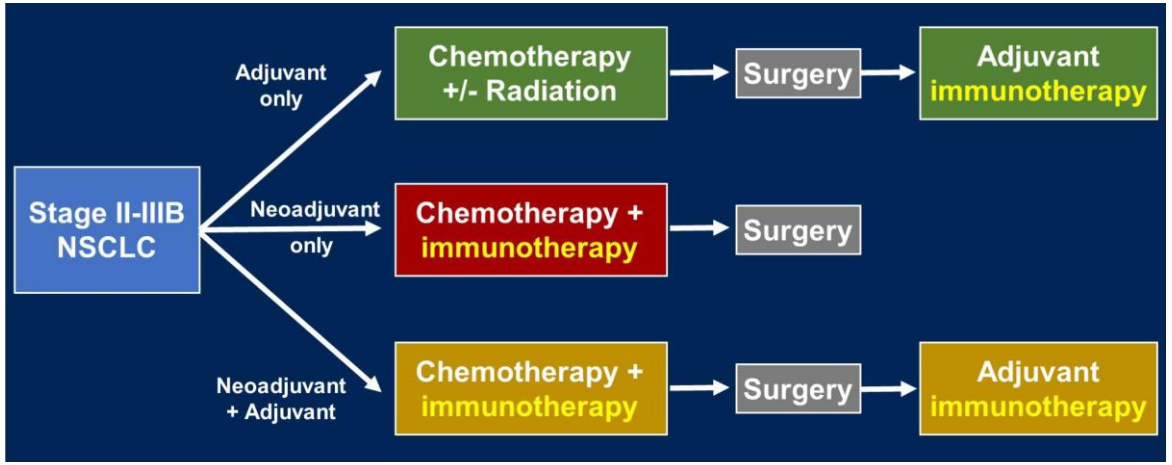
Overall Survival Result Summary (Interim Analyses)

Immunotherapy Setting	Trial	Median f/u	HR (95% CI)	P value
Neoadjuvant + Adjuvant	KEYNOTE-671	25.2 mo	0.73 (0.54, 0.99)	0.02124
	Neotorch	18.2 mo	0.62 (0.381, 0.999)	0.0502
Neoadjuvant	CheckMate 816	41.4 mo	0.62 (0.36, 1.05)	0.0124
Adjuvant	IMpower010	45-46 mo	ITT Stage IB-IIIA: 0.995 (0.78, 1.28) Stage II-IIIA: 0.95 (0.74, 1.24) Stage II-IIIA, PD-L1 TPS ≥1%: 0.71 (0.49, 1.03)	0.9661 N/A N/A
	KEYNOTE-091	35.6 mo	0.87 (0.67, 1.15)	0.17

Awad M. ASCO Annual Meeting 2023

WHAT WE WOULD NEED:





AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Grazie per l’attenzione!