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CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2024?

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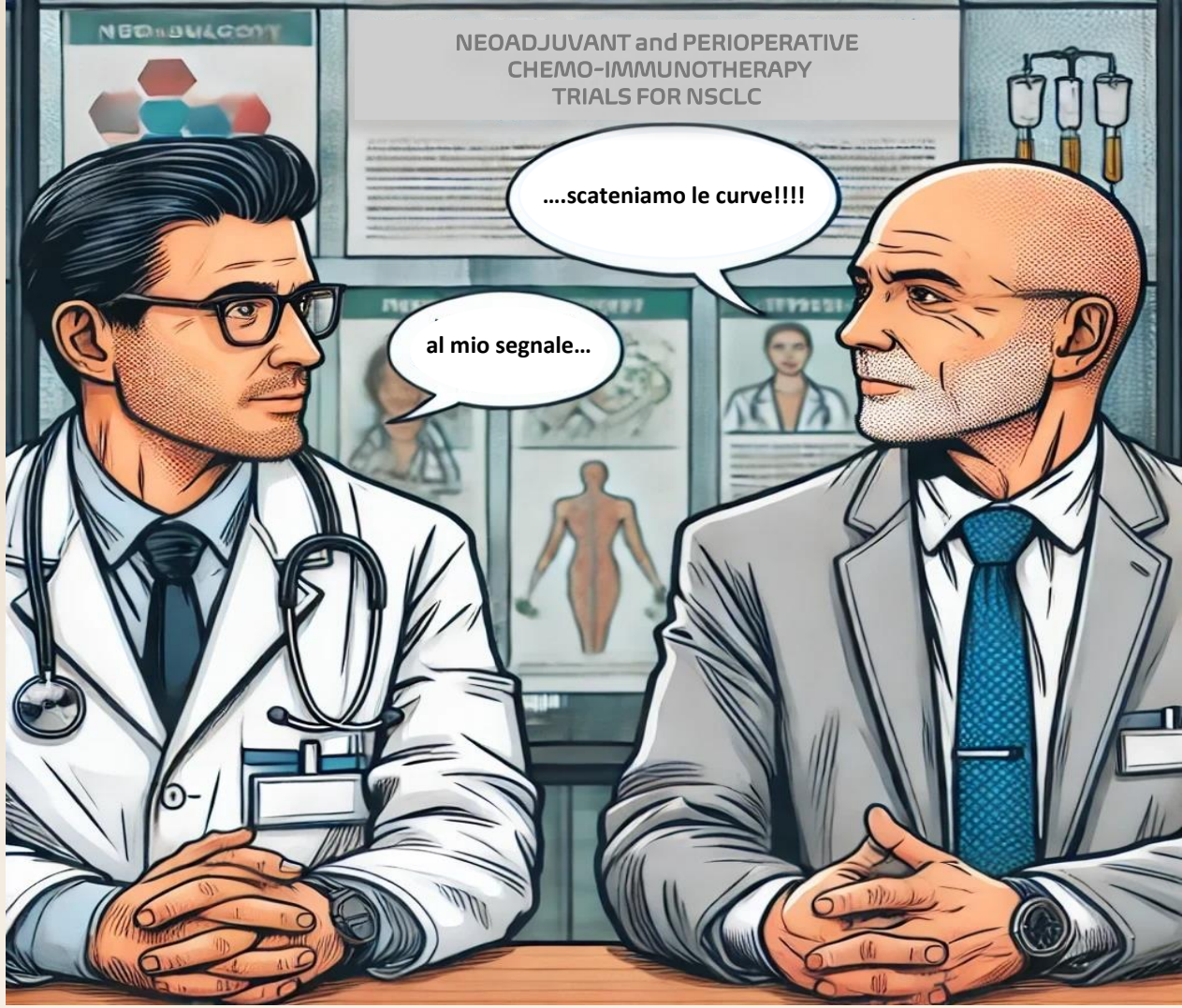


Immunoterapia neoadiuvante delle forme operabili: dialogo tra clinico e metodologo

Ettore D'ARGENTO
Giovanni L. PAPPAGALLO

CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?

20 Maggio 2022

IRCCS "Sacro Cuore - Don Calabria"
Negrar di Valpolicella
Sala Perez

Coordinatore Scientifico: **Dr.ssa Stefania Gori**

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

Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB-IIIB NSCLC: LCMC3 Trial Primary Analysis

Jay M. Lee,[1] Jamie Chaft,[2] Alan Nicholas,[3] G. Alexander Patterson,[4] Saiama N. Waqar,[4] Eric M. Toloza,[5] Eric Haura,[5] Dan J. Raz,[6] Karen L. Reckamp,[7] Robert E. Merritt,[8] Dwight Owen,[8] David J. Finley,[9] Ciaran J. McNamee,[10] Justin D. Blasberg,[11] Edward B. Garon,[1] John D. Mitchell,[12] Robert C. Doebele,[12] Frank Baciewicz,[13] Misako Nagasaka,[14] Harvey I. Pass,[15] Katja Schulze,[3] See Phan,[3] Ann Johnson,[3] Paul A. Bunn,[12] Bruce E. Johnson,[16] Mark G. Kris,[2] David J. Kwiatkowski,[10] Ignacio I. Wistuba,[17] David P. Carbone,[8] Valerie W. Rusch[2]

ARTICLES
https://doi.org/10.1038/s41591-020-01224-2
nature medicine

Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial

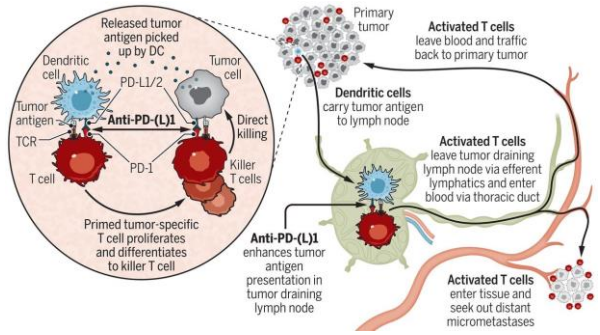
Tina Cascone[1,22], William N. William Jr[4,15], Annikka Weissferdt[2,3], Cheuk H. Leung[4], Heather Y. Lin[4], Apar Pataer[3], Myrna C. B. Godoy[5], Brett W. Carter[5], Lorenzo Federico[6], Alexandre Reuben[1], Md Abdul Wadud Khan[7], Hitoshi Dejima[8,16], Alejandro Francisco-Cruz[8], Edwin R. Parra[8], Luisa M. Solis[8], Junya Fujimoto[9], Hai T. Tran[1], Neda Kalhor[2], Frank V. Fossella[1], Frank E. Mott[1], Anne S. Tsao[1], George Blumenschein Jr[1], Xiuning Le[1], Jianjun Zhang[1], Ferdinandos Skoulidis[1], Jonathan M. Kurie[1], Mehmet Altan[1], Charles Lu[1], Bonnie S. Glisson[1], Lauren Averett Byers[1], Yasir Y. Elamin[1], Reza J. Mehran[3], David C. Rice[3], Garrett L. Walsh[3], Wayne L. Hofstetter[3], Jack A. Roth[3], Mara B. Antonoff[3], Humam Kadara[8], Cara Haymaker[8], Chantale Bernatchez[4,8], Nadim J. Ajami[9], Robert R. Jenq[9,10,21], Padmanee Sharma[12,13], James P. Allison[13], Andrew Futreal[8], Jennifer A. Wargo[7], Ignacio I. Wistuba[1,8], Stephen G. Swisher[3], J. Jack Lee[4], Don L. Gibbons[1], Ara A. Vaporciyan[3], John V. Heymach[1,14,17] and Boris Sepesi[3,17]

Ipilimumab improves clinical outcomes when combined with nivolumab in metastatic non-small cell lung cancer (NSCLC), but

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 Massutí, Alberto Cruz-Bermúdez

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



Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer: event-free survival results from the phase 3 CheckMate 816 trial

Nicolas Girard,[1] Jonathan Spicer,[2] Mariano Provencio,[3] Shun Lu,[4] Stephen Broderick,[5] Mark M. Awad,[6] Tetsuya Mitsudomi,[7] Keith Kerr,[8] Julie Brahmer,[5] Scott J. Swanson,[6] Enriqueta Felip,[9] Changli Wang,[10] Gene B. Saylors,[11] Ke-Neng Chen,[12] Fumihiro Tanaka,[13] Moishe Liberman,[14] Cecile Dorange,[15] Javed Mahmood,[15] Junliang Cai,[15] Patrick M. Forde[5]

[1]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [2]McGill University Health Center, Montreal, Québec, Canada; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [5]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [8]Aberdeen Royal Infirmary, Aberdeen, UK; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [11]Charleston Oncology, Charleston, SC, USA; [12]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [13]University of Occupational and Environmental Health, Kitakyushu, Japan; [14]University of Montreal, Centre de Recherche du CHUM, Montreal, Quebec, Canada; [15]Bristol Myers Squibb, Princeton, NJ, USA

Presentation Number CT012

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Congresso Nazionale sul carcinoma del polmone

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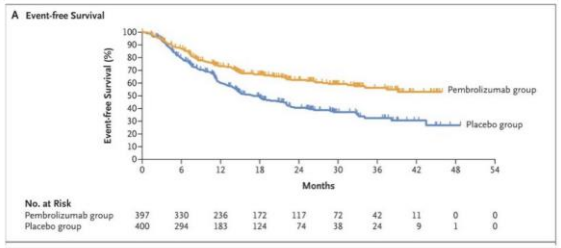
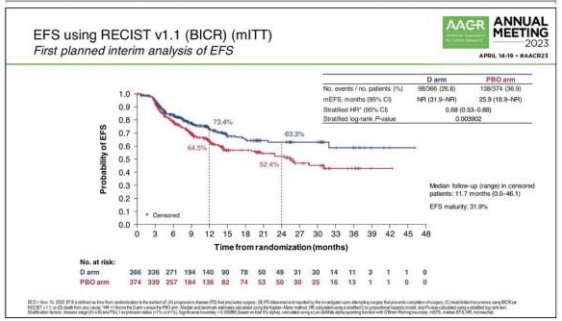
AEGEAN: EFS

	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	



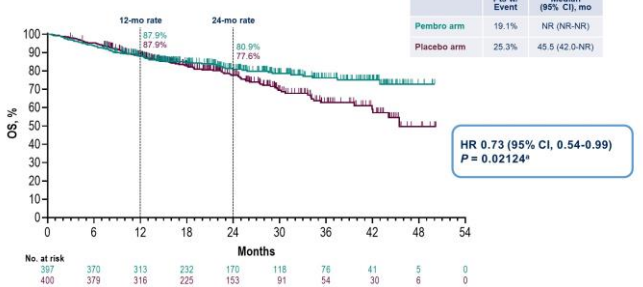
KEYNOTE-671: EFS

	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)



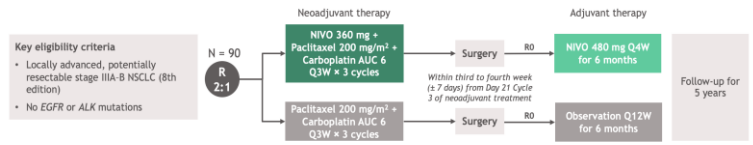
Overall Survival

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



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.

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

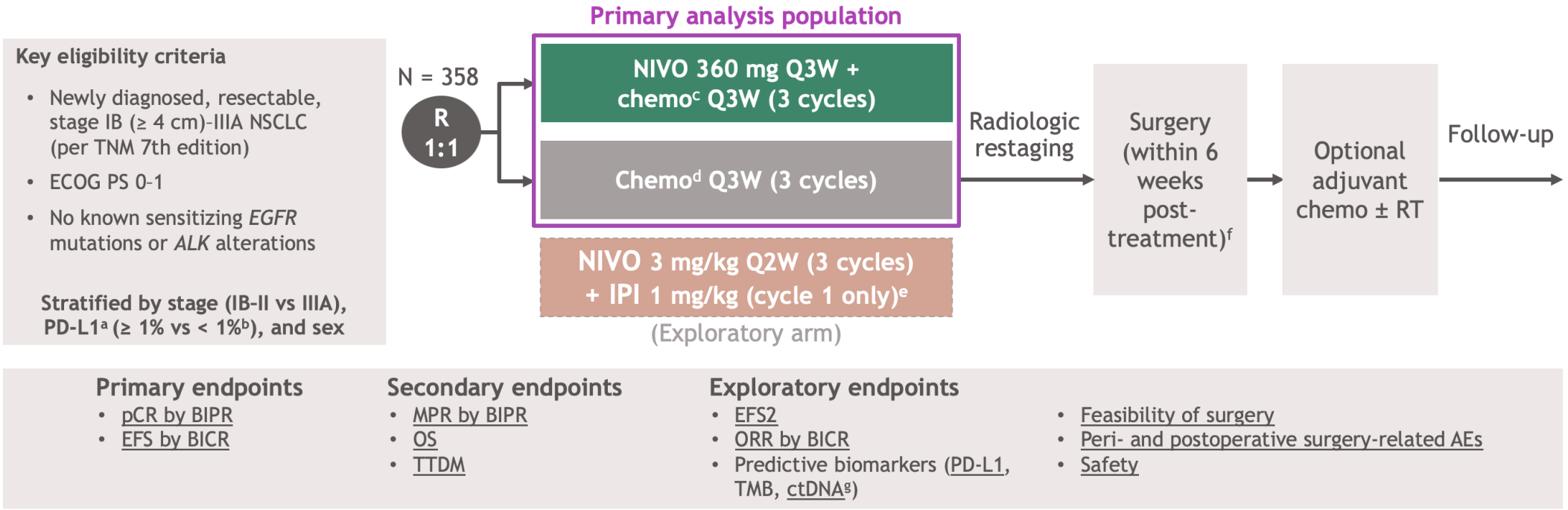
SPECIAL ARTICLE

Neoadjuvant and Adjuvant Treatments for Early Stage Resectable NSCLC: Consensus Recommendations From the International Association for the Study of Lung Cancer

Jonathan D. Spicer, MD, PhD,[a] Tina Cascone, MD, PhD,[b] Murry W. Wynes, PhD,[c] Myung-Ju Ahn, MD, PhD,[d] Sanja Dacic, MD, PhD,[e] Enriqueta Felip, MD, PhD,[f] Patrick M. Forde, MD, PhD,[g] Kristin A. Higgins, MD,[h] Mark G. Kris, MD,[i] Tetsuya Mitsudomi, MD, PhD,[j,k] Mariano Provencio, MD, PhD,[l] Suresh Senan, MD, PhD,[m] Benjamin J. Solomon, M.B.B.S., PhD,[n] Ming Sound Tsao, MD,[o] Masahiro Tsuboi, MD,[p] Heather A. Wakelee, MD,[q] Yi-Long Wu, MD,[r] James Chih-Hsin Yang, MD, PhD,[s] Caicun Zhou, MD, PhD,[t] David H. Harpole, MD,[u] Karen L. Kelly, MD[c,*]

J Thorac Oncol. 2024.

Checkmate 816: study design



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

Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-year update from CheckMate 816

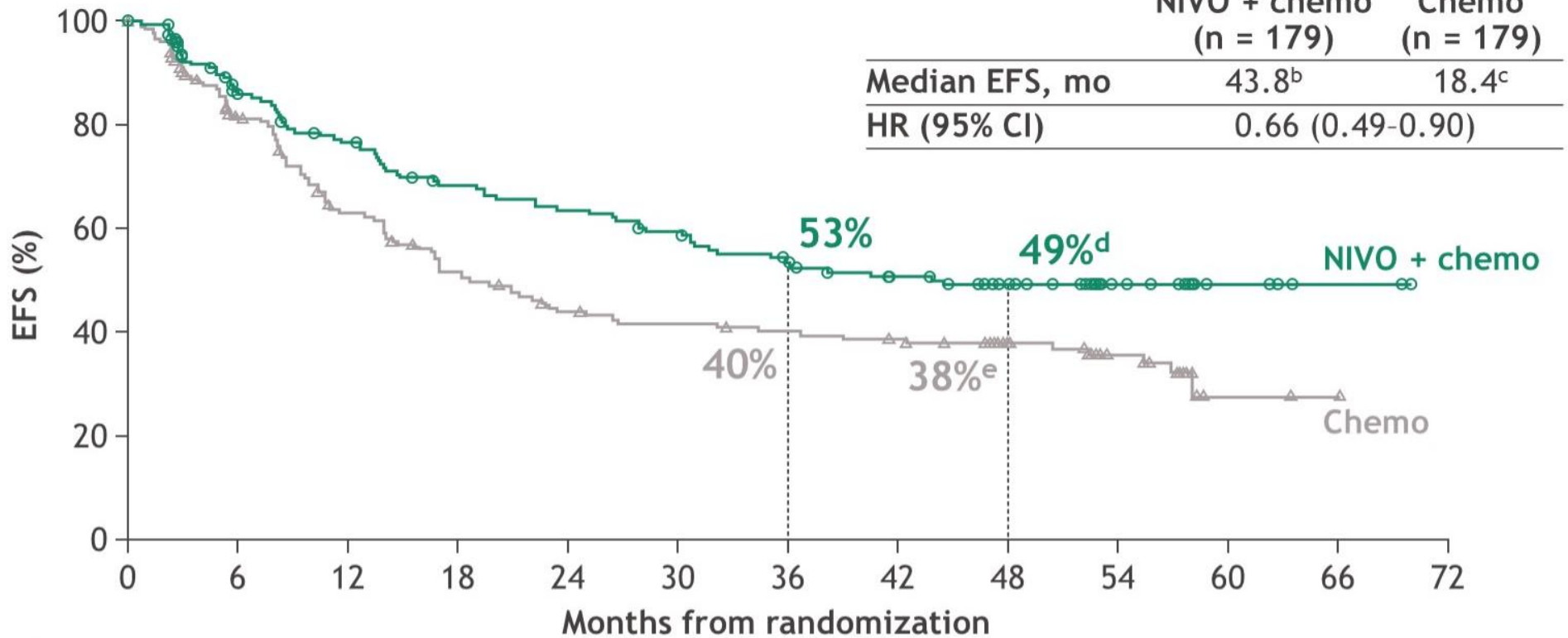
Jonathan D. Spicer,[1] Nicolas Girard,[2] Mariano Provencio Pulla,[3] Changli Wang,[4] Tetsuya Mitsudomi,[5] Mark M. Awad,[6] Everett E. Vokes,[7] Janis M. Taube,[8] Lorena Lupinacci,[9] Gene B. Saylors,[10] Fumihiro Tanaka,[11] Moishe Liberman,[12] Sung Yong Lee,[13] Aurelia Alexandru,[14] Manolo D'Arcangelo,[15] Phuong Tran,[16] Javed Mahmood,[16] Vishwanath Gharpure,[16] Apurva Bhingare,[16] Patrick M. Forde[8]

[1]McGill University Health Centre, Montreal, Quebec, Canada; [2]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [5]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [6]Dana-Farber Cancer Institute, Boston, MA; [7]University of Chicago Medicine, Chicago, IL; [8]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [10]Charleston Oncology, Charleston, SC; [11]University of Occupational and Environmental Health, Kitakyushu, Japan; [12]Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada; [13]Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [14]Institutul Oncologic București Prof. Dr. Alexandru Trestioreanu, Bucharest, Romania; [15]Azienda Unita Sanitaria Locale della Romagna, Ravenna, Italy; [16]Bristol Myers Squibb, Princeton, NJ

EFS: 4-year update[a]

- In CheckMate 816, neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo and demonstrated a favorable OS trend in patients with resectable NSCLC[1,2]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	



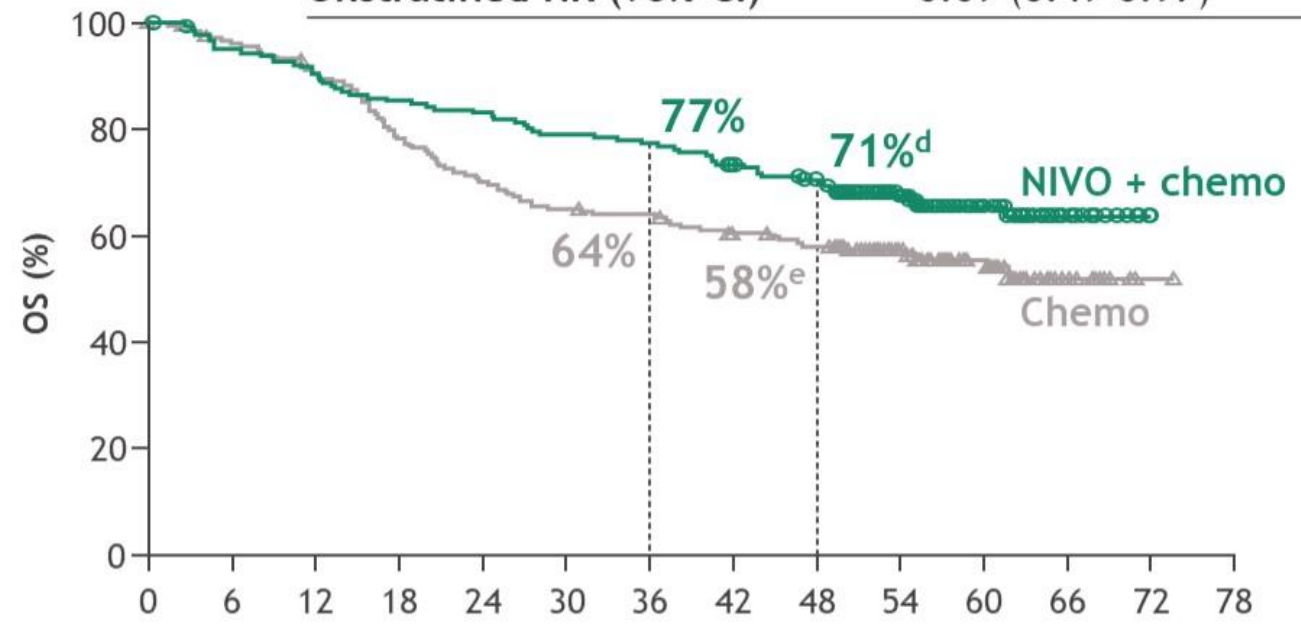
No. at risk													
NIVO + chemo	179	130	114	99	92	85	74	64	49	24	5	2	0
Chemo	179	124	92	73	60	56	53	50	37	22	2	1	0

Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.

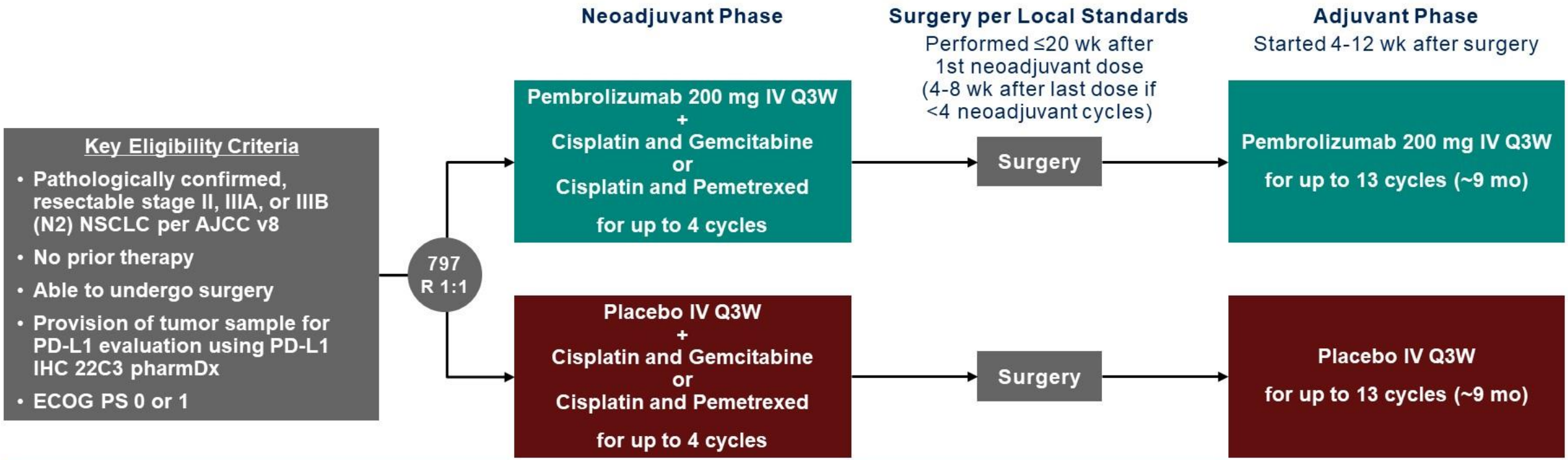
[a]Exploratory analysis. [b-e]95% CI: [b]30.6-NR; [c]14.0-26.7; [d]41-57; [e]30-46. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress (ELCC); March 29-April 1, 2023; Copenhagen, Denmark. Presentation 840.

Checkmate 816: OS 4y FU

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)	0.69 (0.49-0.97)	



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)

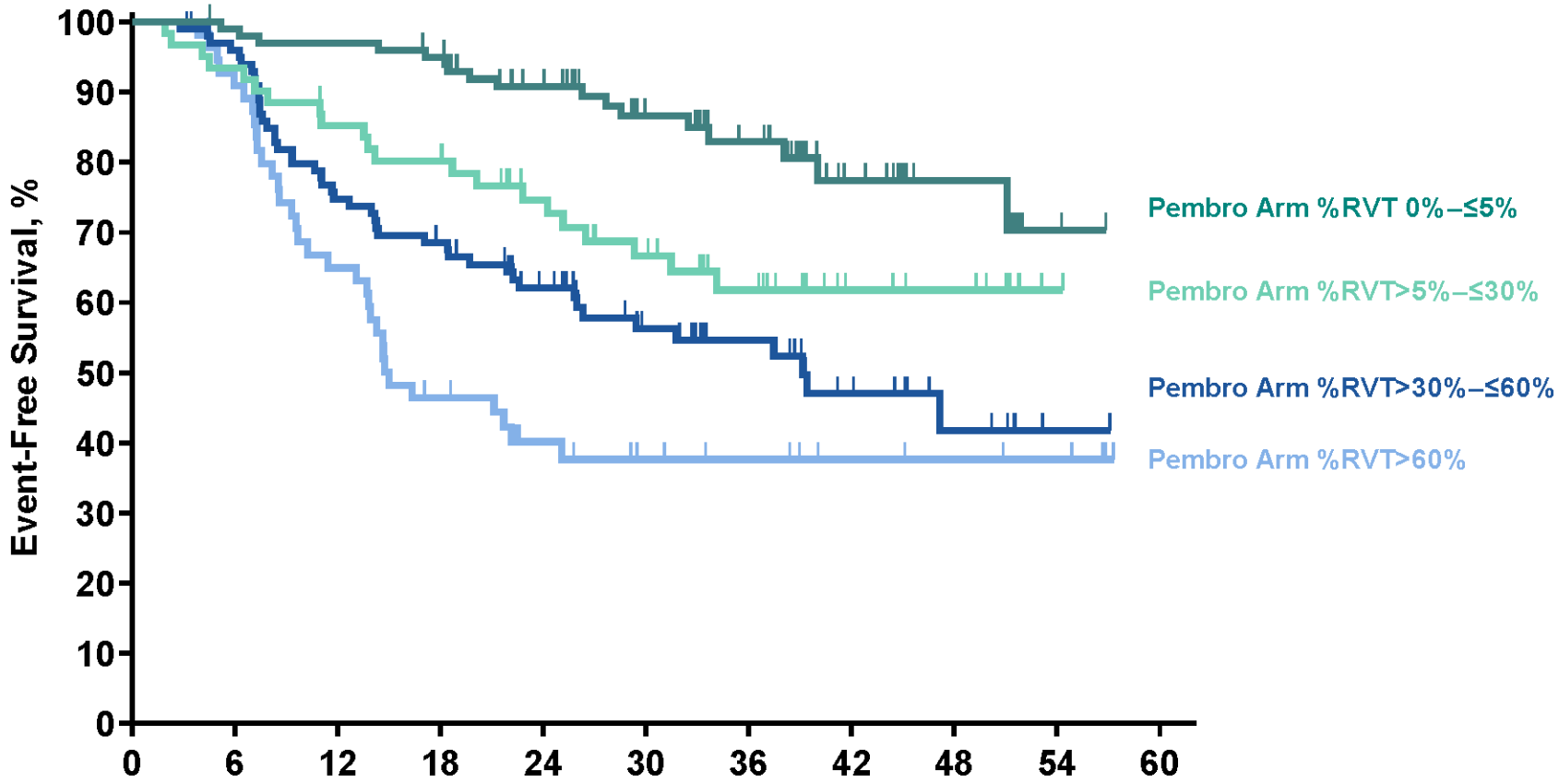
Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, change from baseline in HRQoL in the neoadjuvant and adjuvant phases, and safety

Wakelee H et al. *N Engl J Med* 2023;389:491-503. ClinicalTrials.gov identifier: NCT03425643.

Event-Free Survival

According to %RVT Categorization in the Pembrolizumab Arm



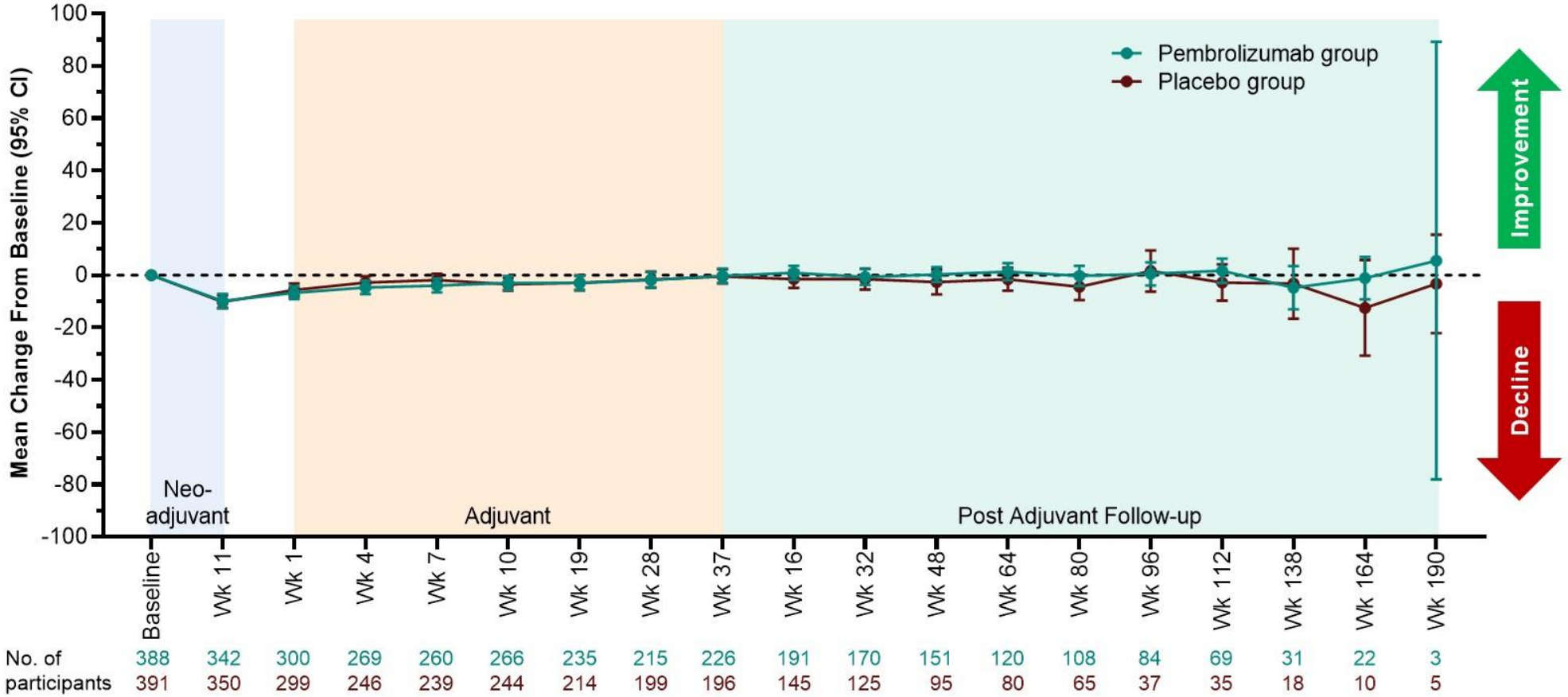
No. at risk											
%RVT 0%–≤5%	102	100	98	94	77	54	39	21	11	2	0
%RVT >5%–≤30%	61	57	51	48	38	32	23	13	11	1	0
%RVT >30%–≤60%	101	95	73	66	52	34	24	16	8	2	0
%RVT >60%	56	50	35	24	16	12	10	7	6	5	0

Health-Related Quality of Life Outcomes From the Randomized, Double-Blind Phase 3 KEYNOTE-671 Study of Perioperative Pembrolizumab for Early-Stage NSCLC

Marina C Garassino, Heather Wakelee, Jonathan D Spicer, Moishe Liberman, Terufumi Kato, Masahiro Tsuboi, Se-Hoon Lee, Ke-Neng Chen, Christophe Dooms, Margarita Majem, Ekkehard Eigendorff, Gastón L Martinengo, Olivier Bylicki, Delvys Rodríguez-Abreu, Jamie Chaft, Jing Yang, Ashwini Arunachalam, Josephine M Norquist, Steven M Keller, Shugeng Gao

Presented by Marina C Garassino of the University of Chicago School of Medicine and Biological Sciences, Chicago, IL, USA

Empirical Mean Change From Baseline Over Time
EORTC QLQ-C30 GHS/QoL



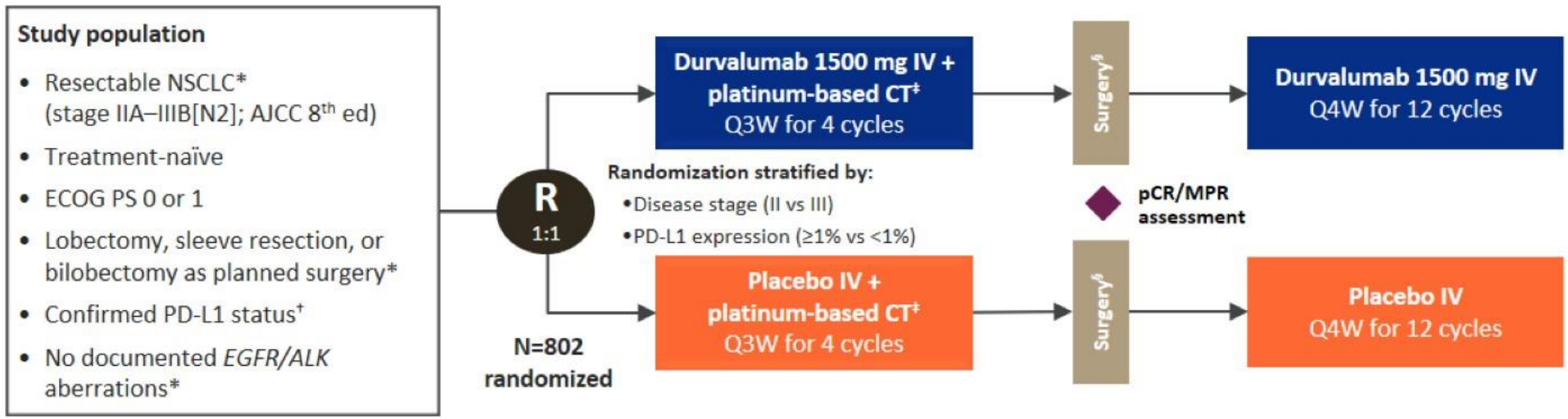
Completion of the QLQ-C30 at baseline and adjuvant week 10 was ≥68.6% in the pembrolizumab group and ≥62.1% in the placebo group; compliance was ≥92.2% and ≥92.9%, respectively. A ≥10-point difference in EORTC QLQ-C30 scales is generally considered clinically relevant. Data cutoff date for IA2: July 10, 2023.

Perioperative Durvalumab for Resectable NSCLC

Updated Outcomes from the Phase 3 AEGEAN Trial

John V. Heymach,[1] David Harpole,[2] Tetsuya Mitsudomi,[3] Janis M. Taube,[4] Shugeng Gao,[5] Laszlo Urban,[6] Jin Hyoung Kang,[7] Francisco J. Orlandi,[8] Jeronimo Rodriguez-Cid,[9] Bartomeu Massuti,[10] Luis Leon Mateos,[11] Giulia Pasello,[12] Quincy Chu,[13] Jaroslaw Kolb-Sielecki,[14] Masao Nakata,[15] Mike Aperghis,[16] Helen Mann,[16] Tamer M. Fouad,[17] Gary J. Doherty,[16] Martin Reck[18]

AEGEAN study design



Efficacy analyses were performed in the mITT population (or its resected subpopulation), which excluded patients with documented EGFR/ALK *aberrations*¶

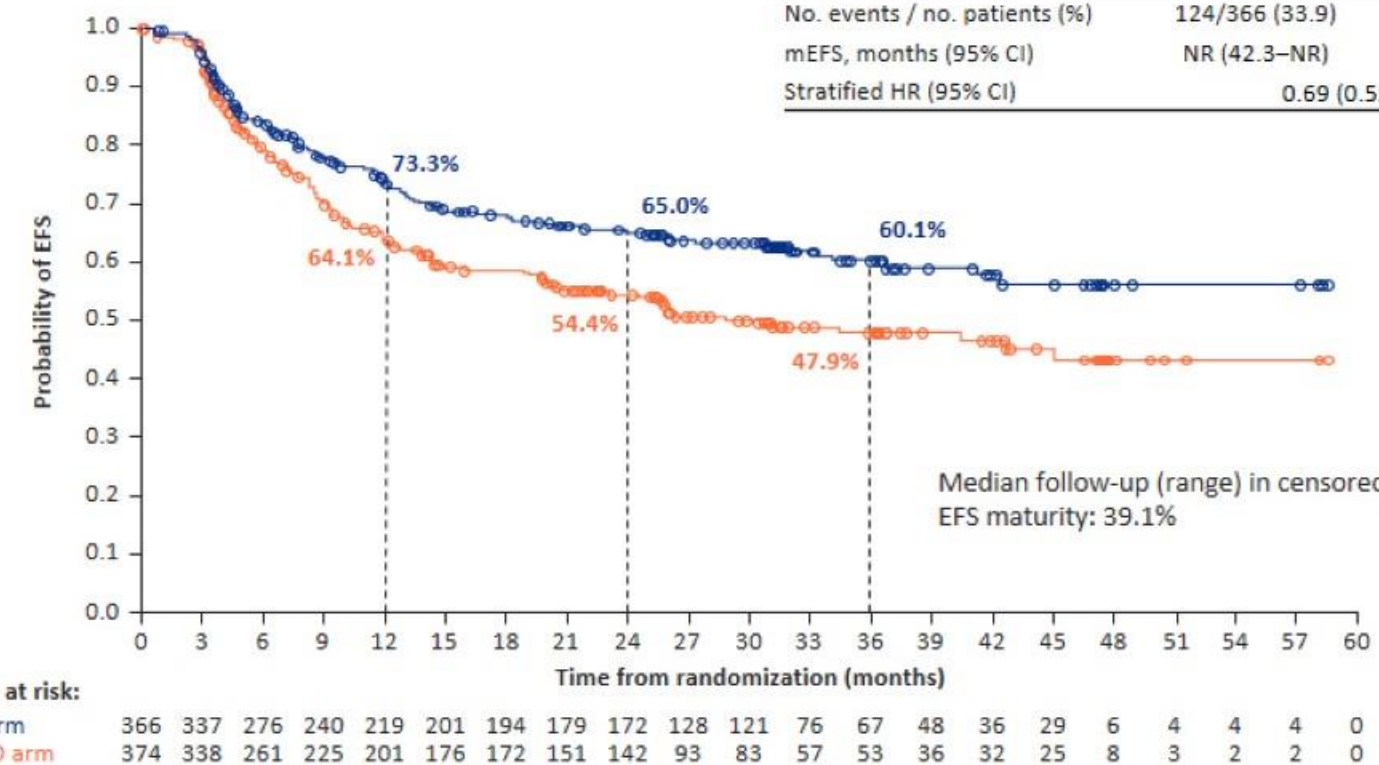
Primary endpoints: pCR, evaluated centrally (IASLC 2020[1]), and EFS per BICR (RECIST v1.1)

Key secondary endpoints: MPR, evaluated centrally (IASLC 2020[1]), DFS per BICR (RECIST v1.1) in the resected subpopulation, and OS

Updated EFS (second planned interim analysis; mITT)

- EFS benefit favoring the durvalumab arm was maintained and consistent with that reported previously[1]

	D arm	PBO arm
No. events / no. patients (%)	124/366 (33.9)	165/374 (44.1)
mEFS, months (95% CI)	NR (42.3–NR)	30.0 (20.6–NR)
Stratified HR (95% CI)	0.69 (0.55–0.88)	



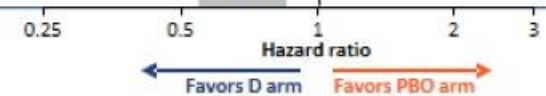
Median follow-up (range) in censored patients: 25.9 (0.0–58.6) months
EFS maturity: 39.1%

No. at risk:																					
D arm	366	337	276	240	219	201	194	179	172	128	121	76	67	48	36	29	6	4	4	4	0
PBO arm	374	338	261	225	201	176	172	151	142	93	83	57	53	36	32	25	8	3	2	2	0

Updated EFS by subgroup (mITT)

- EFS benefit was maintained across predefined subgroups

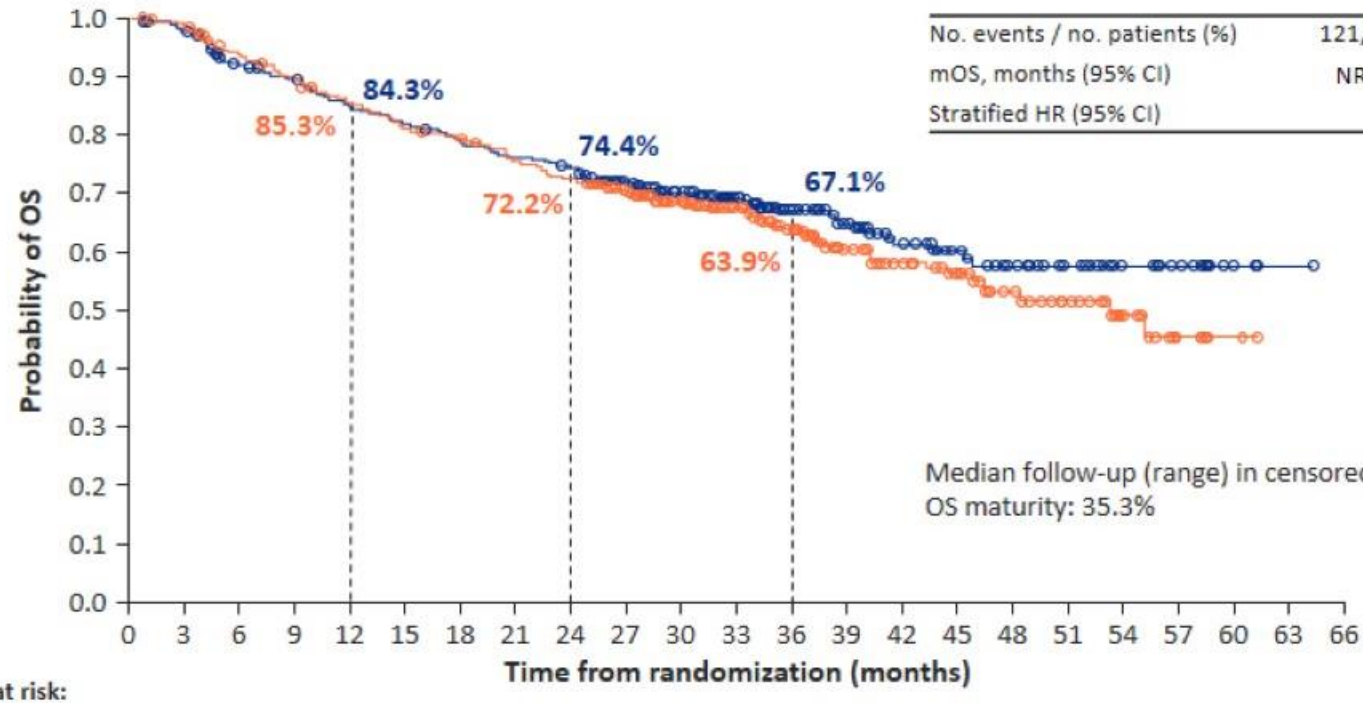
Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (42.3–NR)	30.0 (20.6–NR)	0.69 (0.55–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	34.4 (19.8–NR)	0.69 (0.48–0.97)
	≥65 years	382	NR (31.9–NR)	25.9 (15.1–NR)	0.71 (0.52–0.97)
Sex	Male	530	NR (41.2–NR)	25.9 (19.8–NR)	0.66 (0.50–0.88)
	Female	210	NR (33.2–NR)	40.4 (15.1–NR)	0.80 (0.52–1.23)
ECOG PS	0	506	NR (42.3–NR)	31.1 (19.5–NR)	0.66 (0.50–0.88)
	1	234	NR (21.8–NR)	28.6 (18.9–NR)	0.79 (0.52–1.20)
Race*	Asian	307	NR (42.3–NR)	25.9 (19.5–NR)	0.66 (0.45–0.95)
	Non-Asian	433	NR (33.2–NR)	31.1 (15.7–NR)	0.73 (0.54–0.99)
Smoking	Current	190	NR (33.2–NR)	20.4 (8.1–NR)	0.52 (0.32–0.82)
	Former	443	NR (41.2–NR)	30.0 (20.7–NR)	0.75 (0.56–1.02)
	Never	107	NR (13.0–NR)	34.4 (14.7–NR)	0.88 (0.47–1.61)
Histology	Squamous	360	NR (41.2–NR)	40.4 (15.1–NR)	0.70 (0.49–0.98)
	Non-squamous	375	NR (36.6–NR)	28.6 (19.8–NR)	0.73 (0.53–1.00)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (41.2–NR)	NR (34.4–NR)	0.82 (0.49–1.34)
	Stage IIIA	338	NR (42.3–NR)	25.8 (11.7–45.0)	0.60 (0.42–0.84)
	Stage IIIB	186	36.6 (12.7–NR)	19.8 (11.7–42.6)	0.81 (0.53–1.23)
Lymph node station	N2 single	273	NR (NR–NR)	22.8 (13.9–42.6)	0.58 (0.39–0.85)
	N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.78 (0.40–1.49)
PD-L1 expression at baseline†	TC <1%	247	NR (24.7–NR)	20.6 (14.3–NR)	0.69 (0.46–1.02)
	TC 1–49%	277	NR (31.9–NR)	25.9 (12.3–NR)	0.73 (0.50–1.05)
	TC ≥50%	216	NR (41.2–NR)	NR (24.5–NR)	0.71 (0.44–1.12)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	45.0 (13.9–NR)	0.58 (0.35–0.93)
	Carboplatin	544	NR (36.6–NR)	26.2 (20.6–NR)	0.75 (0.57–0.97)



DCO = May 10, 2024; median EFS follow-up in censored patients: 25.9 months; EFS maturity: 39.1%. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

OS (mITT)

- Based on 35% maturity, an OS trend favoring the durvalumab arm was observed



	D arm	PBO arm
No. events / no. patients (%)	121/366 (33.1)	140/374 (37.4)
mOS, months (95% CI)	NR (NR–NR)	53.2 (44.3–NR)
Stratified HR (95% CI)	0.89 (0.70–1.14)	

Median follow-up (range) in censored patients: 33.6 (0.7–64.3) months
OS maturity: 35.3%

No. at risk:

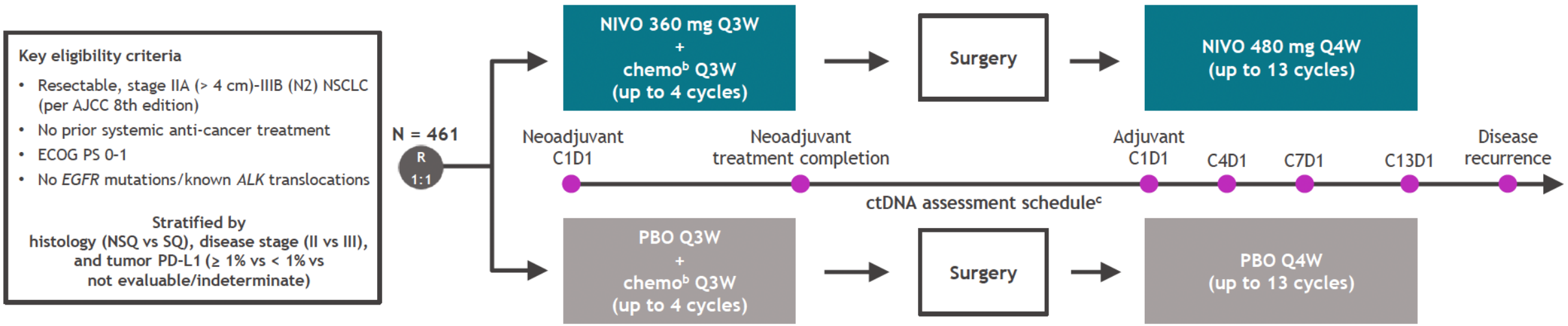
D arm	366	356	327	316	297	288	277	267	260	227	182	141	104	80	62	50	39	29	16	12	3	1	0
PBO arm	374	367	342	327	309	292	287	270	259	230	183	149	116	87	68	58	41	28	16	7	2	0	0

- Preplanned analysis censoring patients with cause of death due to COVID-19: OS HR = 0.84 (95% CI: 0.66–1.08)

DCO = May 10, 2024. mOS, median OS.

Background and study design

- In the phase 3 CheckMate 77T[a] study, perioperative NIVO demonstrated statistically significant and clinically meaningful EFS benefit vs PBO in patients with resectable NSCLC (HR, 0.58; 97.36% CI, 0.42-0.81; *P* < 0.001); pCR was also improved[1]
- **Here we report updated clinical outcomes from CheckMate 77T with a median follow-up of 33.3 months, exploratory outcomes by pCR status, and ctDNA analyses**



Primary endpoint
- EFS[d] by BICR

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

Exploratory analyses
- Outcomes by pCR status
- ctDNA clearance[f] and recurrence[g]

Database lock date: April 26, 2024; median follow-up (range): 33.3 months (23.6-52.1).

[a]NCT04025879. [b]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [c]ctDNA was measured using the Invitae Personalized Cancer Monitoring (tumor-informed) assay. [d]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. [e]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes. [f]Change from detectable ctDNA at neoadjuvant treatment initiation (C1D1) to no detectable ctDNA at neoadjuvant treatment completion (end of neoadjuvant treatment or prior to definitive surgery). [g]Change from no detectable ctDNA at adjuvant treatment initiation (C1D1) to detectable ctDNA during the post-operative period (adjuvant C4D1, C7D1, or C13D1; disease recurrence). 1. Cascone T, et al. *N Engl J Med* 2024;390:1756-1769.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Nivolumab in Resectable Lung Cancer

T. Cascone, M.M. Awad, J.D. Spicer, J. He, S. Lu, B. Sepesi, F. Tanaka, J.M. Taube, R. Cornelissen, L. Havel,* N. Karaseva, J. Kuzdzal, L.B. Petruzelka, L. Wu, J.-L. Pujol, H. Ito, T.-E. Ciuleanu, L. de Oliveira Muniz Koch, A. Janssens, A. Alexandru, S. Bohnet, F.V. Moiseyenko, Y. Gao, Y. Watanabe, C. Coronado Erdmann, P. Sathyanarayana, S. Meadows-Shropshire, S.I. Blum, and M. Provencio Pulla, for the CheckMate 77T Investigators†

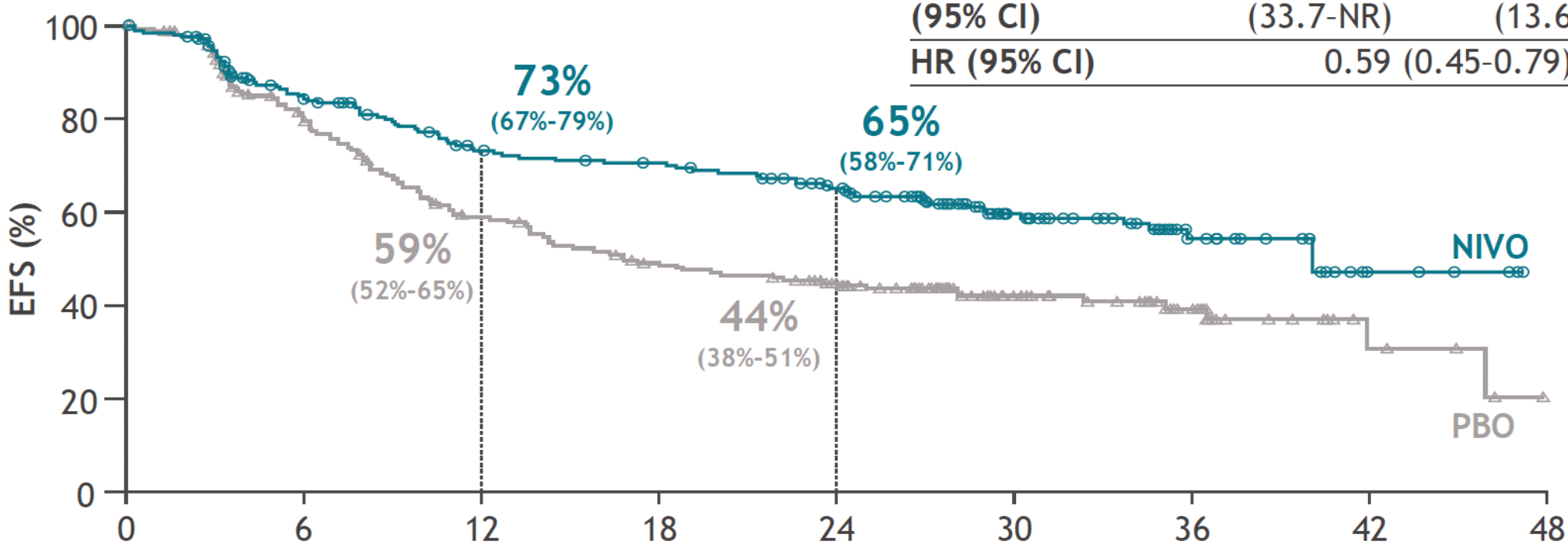
Perioperative nivolumab vs placebo in patients with resectable NSCLC: clinical update from the phase 3 CheckMate 77T study

Mariano Provencio Pulla,[1] Mark M. Awad,[2] Tina Cascone,[3] **Jonathan D. Spicer**,[4] Jie He,[5] Shun Lu,[6] Aurelia Alexandru,[7] Yasutaka Watanabe,[8] Robin Cornelissen,[9] Ludmila de Oliveira Muniz Koch,[10] Jaroslaw Kuzdzal,[11] Jean-Louis Pujol,[12] Petra Hoffknecht,[13] Jhanelle E. Gray,[14] Cinthya Coronado Erdmann,[15] Jaclyn Neely,[15] Vipul Devas,[15] Sumeena Bhatia,[15] Fumihiro Tanaka[16]

[1]Hospital Universitario Puerta de Hierro, Madrid, Spain; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]McGill University Health Centre, Montreal, Quebec, Canada; [5]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [6]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [7]Institutul Oncologic Bucuresti Prof. Dr. Alexandru Trestioreanu, Bucharest, Romania; [8]Saitama Cancer Center, Saitama, Japan; [9]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [10]Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [11]John Paul II Hospital, Krakow, Poland; [12]Montpellier Regional University Hospital, Montpellier, France; [13]Franziskus-Hospital Harderberg, Niels-Stensen-Kliniken, Georgsmarienhutte, Germany; [14]Moffitt Cancer Center, Tampa, FL, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]University of Occupational and Environmental Health, Kitakyushu, Japan

EFS per BICR

	NIVO (n = 229)	PBO (n = 232)
Median EFS, mo (95% CI)	40.1 (33.7-NR)	17.0 (13.6-28.1)
HR (95% CI)	0.59 (0.45-0.79)	



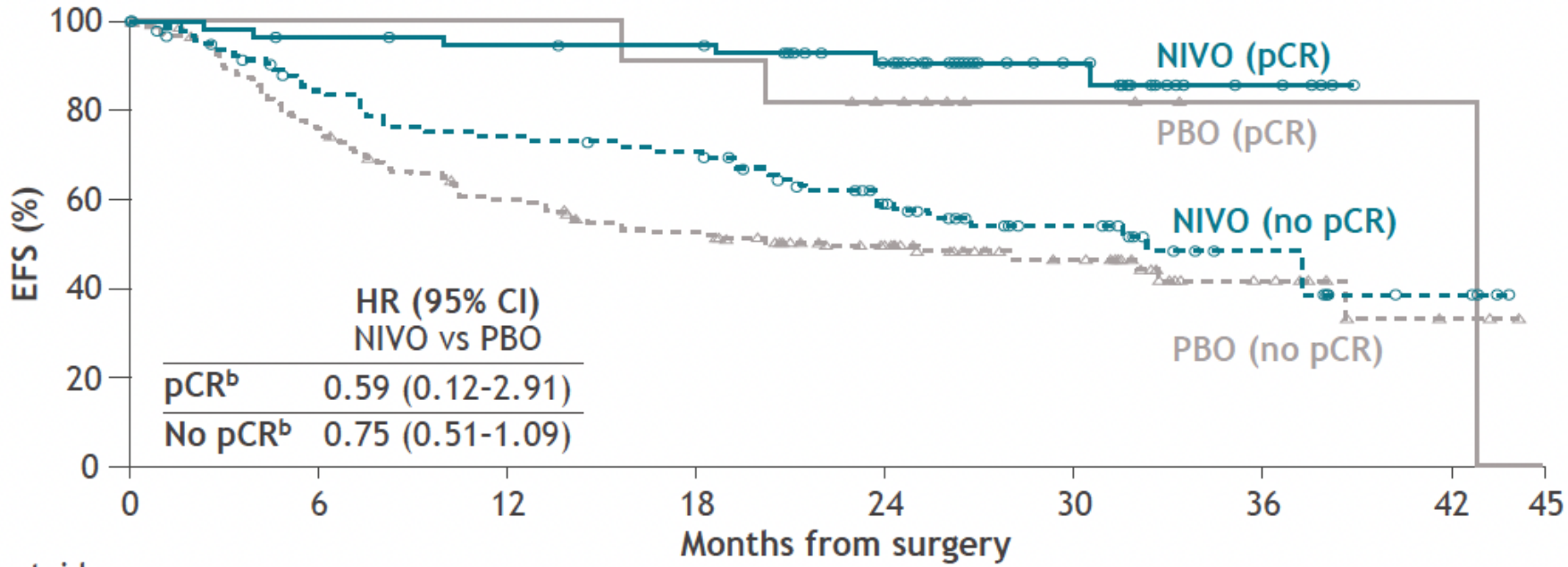
No. at risk

NIVO	229	172	140	132	114	63	26	5	0
PBO	232	164	117	92	78	39	22	5	0

- Landmark EFS from definitive surgery among patients who had definitive surgery for NIVO (n = 178) vs PBO (n = 178): HR = 0.52 (95% CI, 0.37-0.73)

Median follow-up (range): 33.3 months (23.6-52.1).
95% CIs for EFS rates are designated in the parentheses.

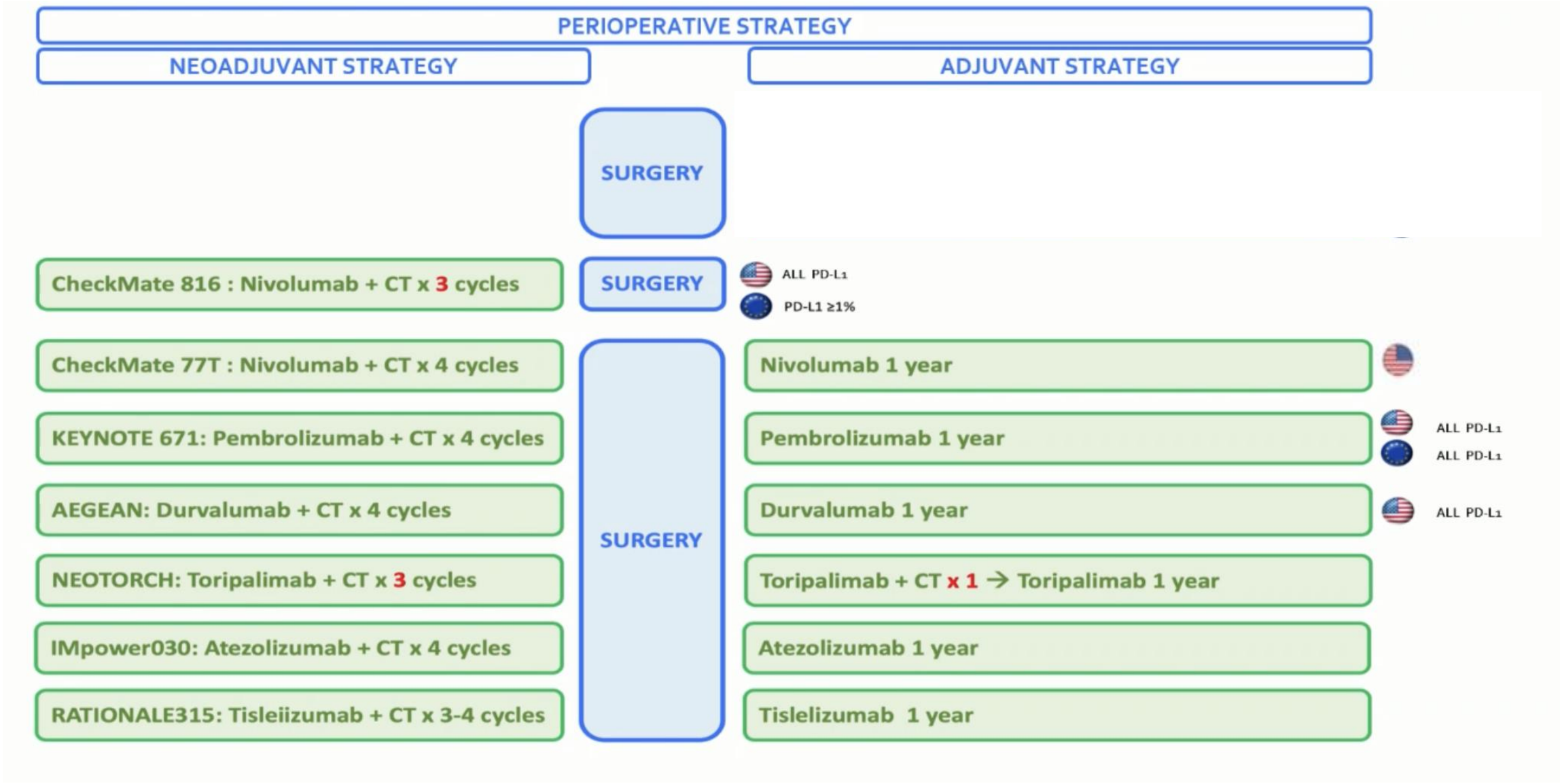
Landmark EFS from definitive surgery[a] by pCR status



No. at risk									
pCR	58	54	52	51	40	19	5	0	0
pCR	11	11	11	10	7	3	1	1	0
No pCR	98	74	65	61	40	26	10	4	0
No pCR	148	109	84	71	50	27	9	2	0

- Baseline characteristics were generally similar between patients with or without pCR and between treatment arms, except a higher proportion of patients with pCR had tumor PD-L1 ≥ 1% vs patients without pCR in the NIVO arm

FDA and EMA approvals ICB and TKIs early-stage NSCLC



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Congresso Nazionale

CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2024?

V EDIZIONE

28 OTTOBRE 2024

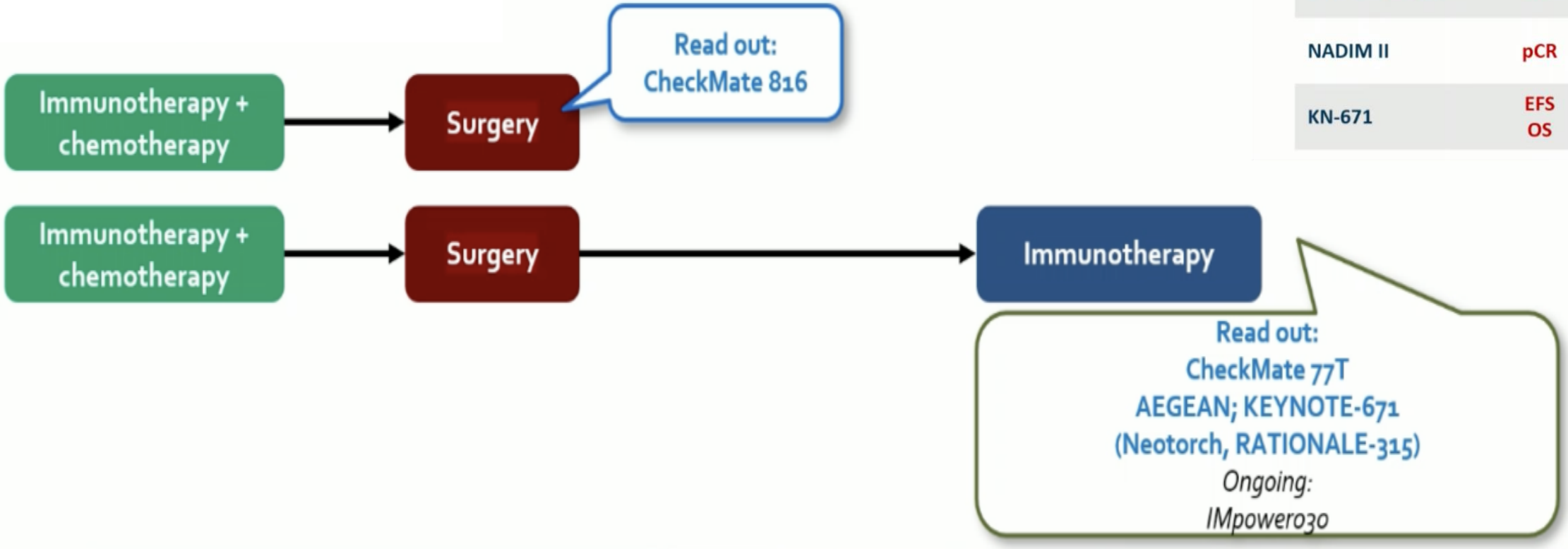
VERONA

Hotel Leon D'Oro

Responsabile Scientifico
STEFANIA GORI

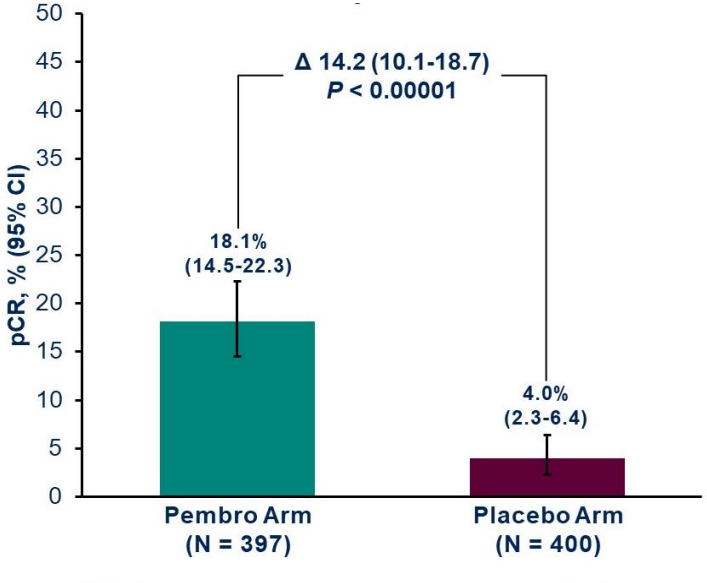
Neoadjuvant & Perioperative approaches

Trial	Primary endpoint
CheckMate 816	pCR EFS
AEGEAN	pCR EFS
CheckMate 77T	EFS
NADIM II	pCR
KN-671	EFS OS

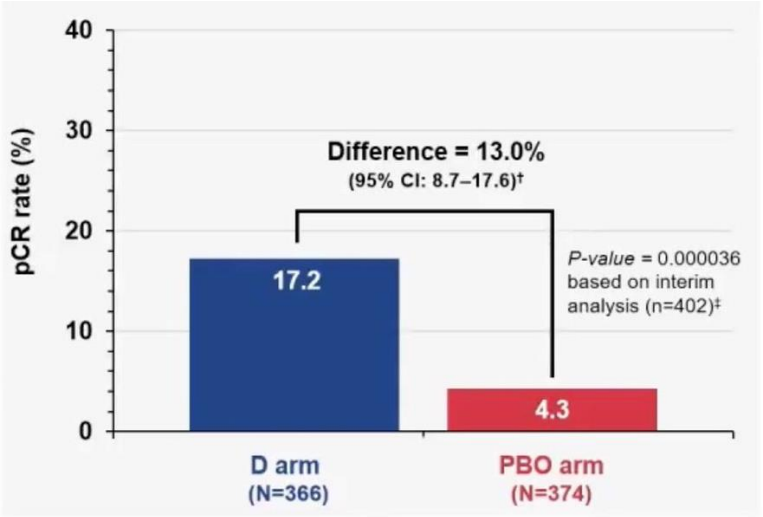


Perioperative Immunotherapy in early stage NSCLC

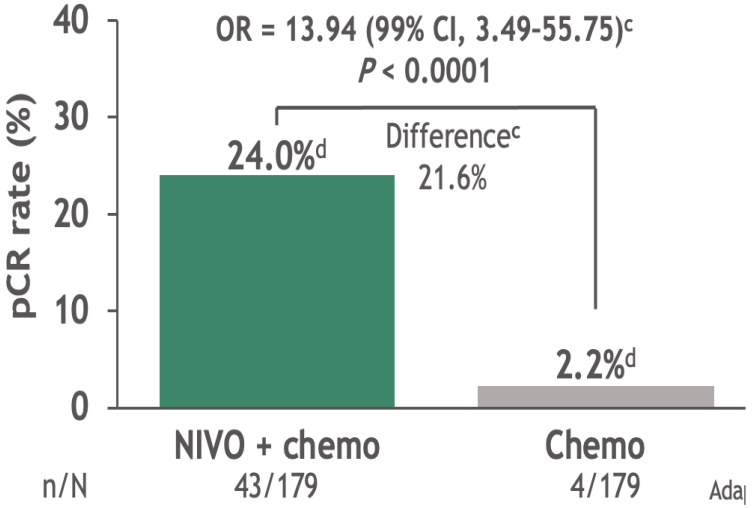
pCR



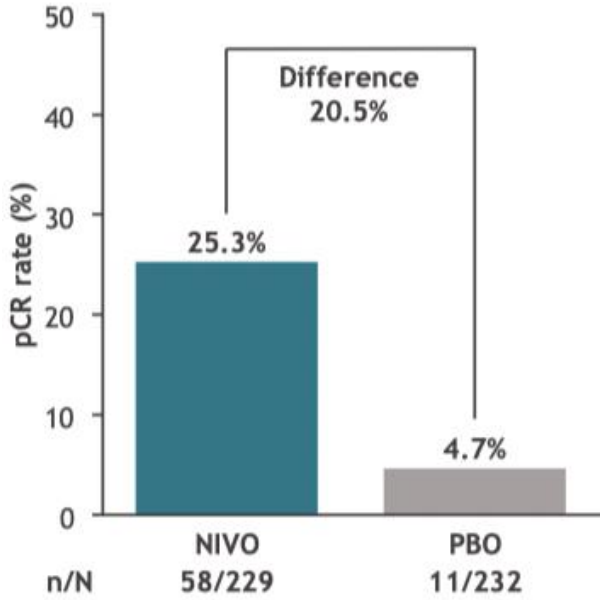
KEYNOTE 671



AEGEAN



CHECKMATE 816

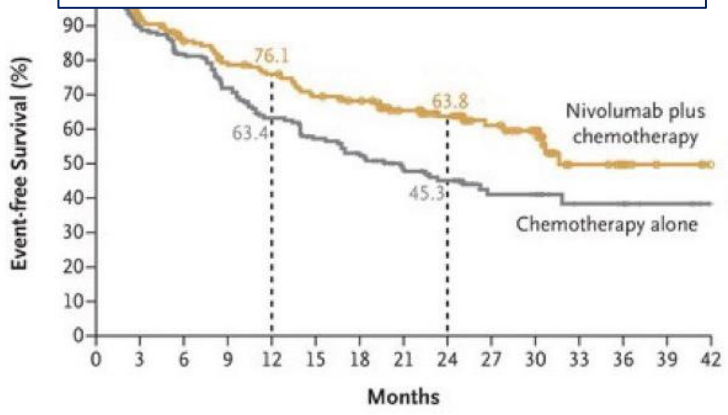


CHECKMATE - 77T

Perioperative Immunotherapy in early stage NSCLC

Consistent EFS Benefit

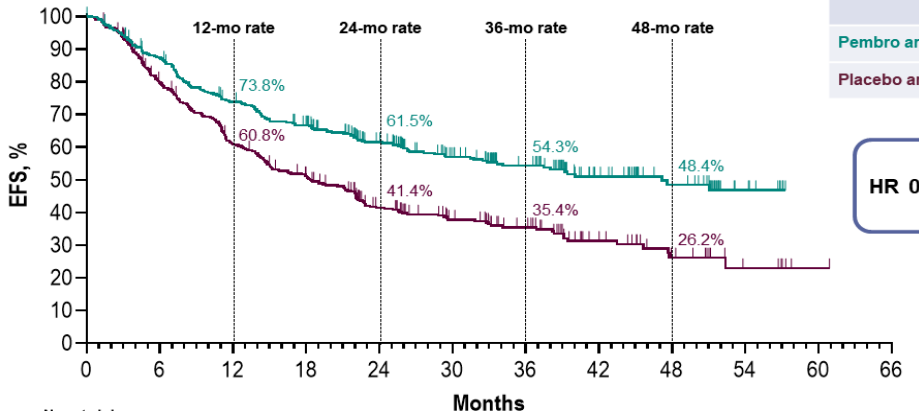
CHECKMATE-816



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

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

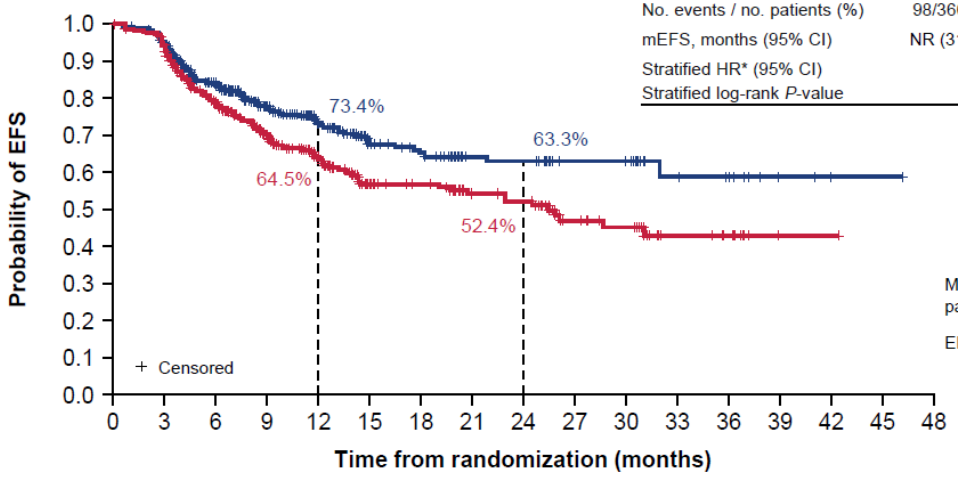
KEYNOTE-671: Pembro+CT



	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)

AEGEAN: Durva+CT

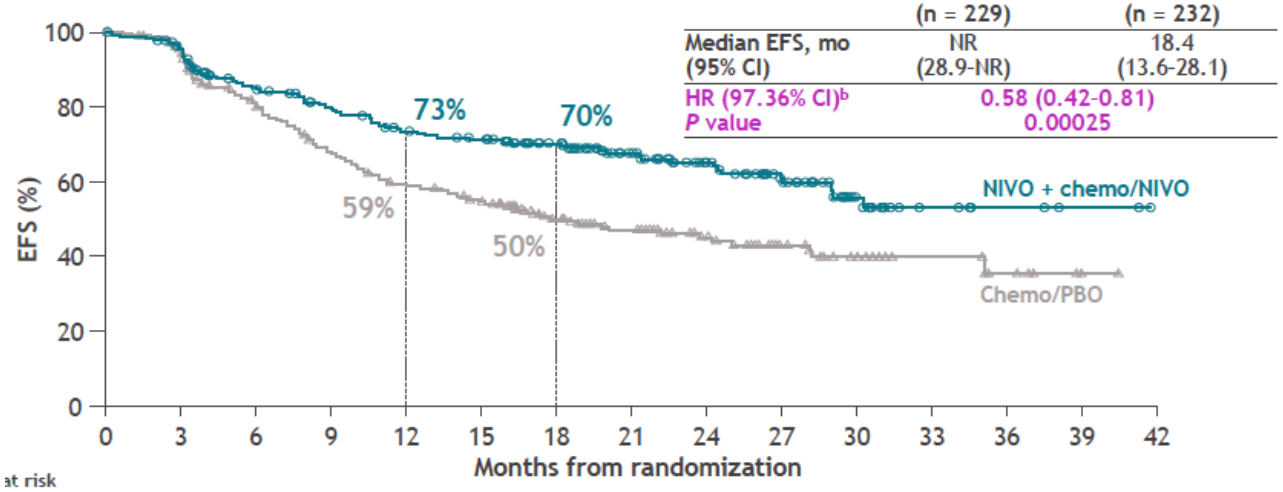


	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	

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

EFS maturity: 31.9%

CHECKMATE-77T: Nivo+CT

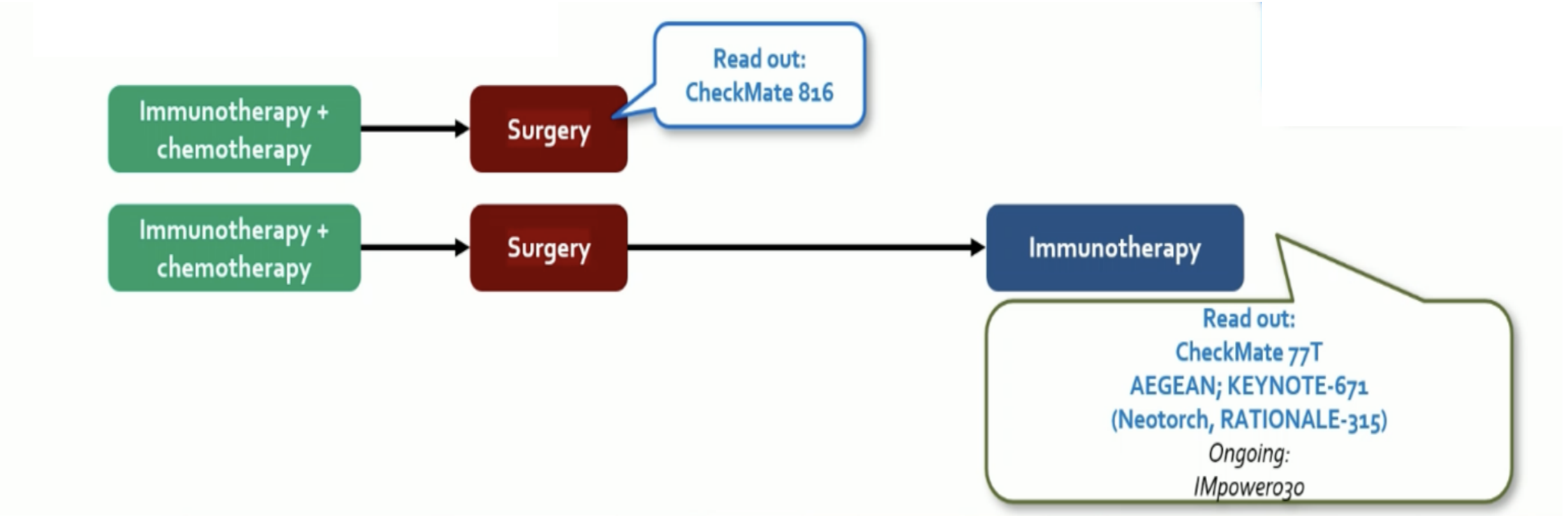


	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	

at risk

Spicer, ESMO 2023; Heymach, NEJM 2023; Cascone, ESMO 2023

Neoadjuvant & Perioperative approaches

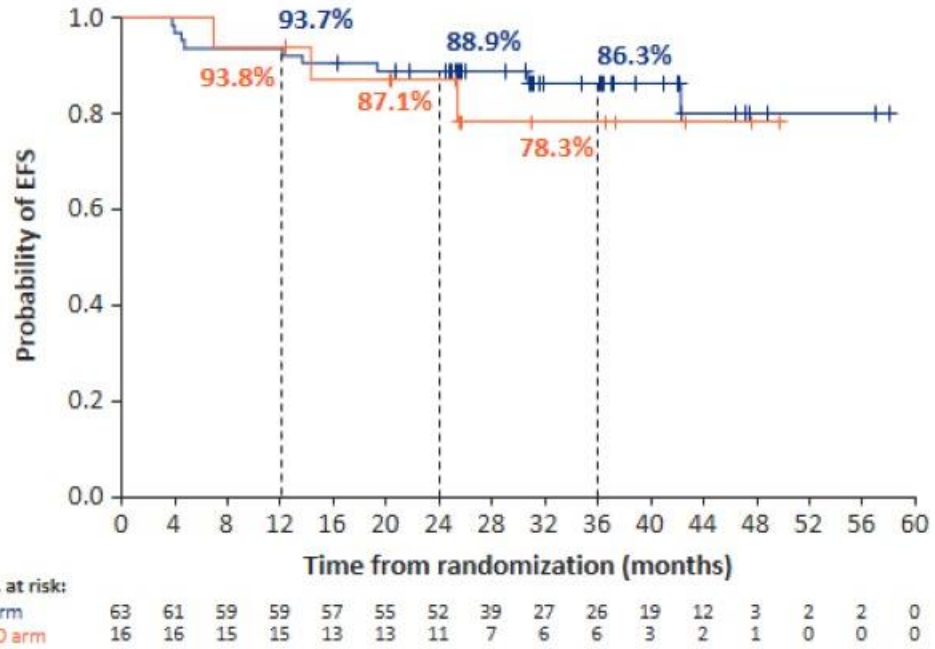


EFS by pCR status (exploratory analysis; mITT)

- EFS benefit favored the durvalumab arm regardless of whether patients demonstrated pCR

Patients with pCR

	D arm	PBO arm
No. events / no. patients (%)	9/63 (14.3)	3/16 (18.8)
mEFS, months (95% CI)	NR (NR–NR)	NR (25.4–NR)
Unstratified HR (95% CI)	0.73 (0.22–3.28)	

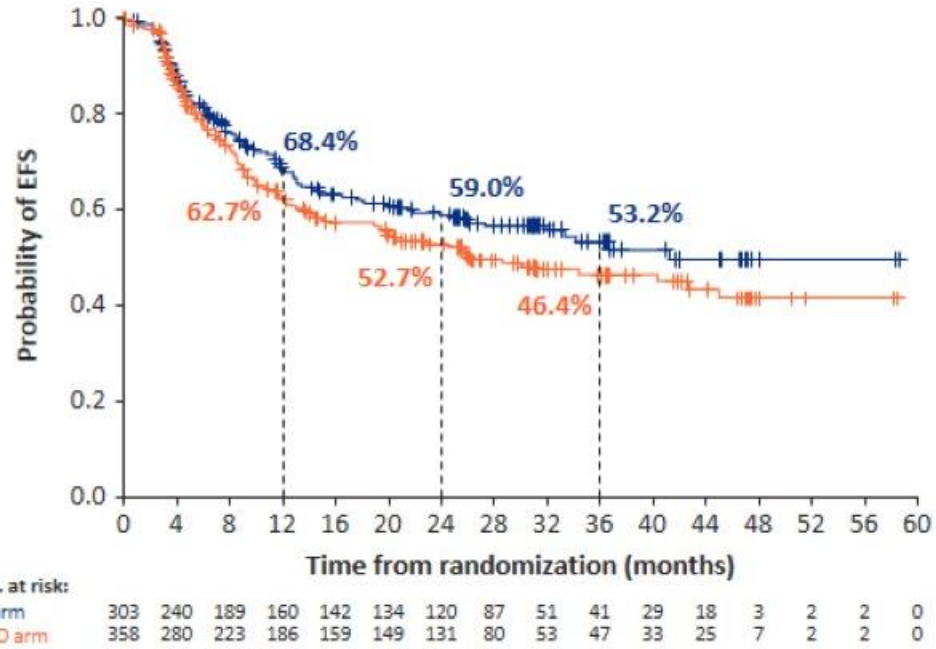


No. at risk:

D arm	63	61	59	59	57	55	52	39	27	26	19	12	3	2	2	0
PBO arm	16	16	15	15	13	13	11	7	6	6	3	2	1	0	0	0

Patients without pCR

	D arm	PBO arm
No. events / no. patients (%)	115/303 (38.0)	162/358 (45.3)
mEFS, months (95% CI)	41.2 (31.9–NR)	25.9 (19.8–45.0)
Unstratified HR (95% CI)	0.81 (0.64–1.03)	



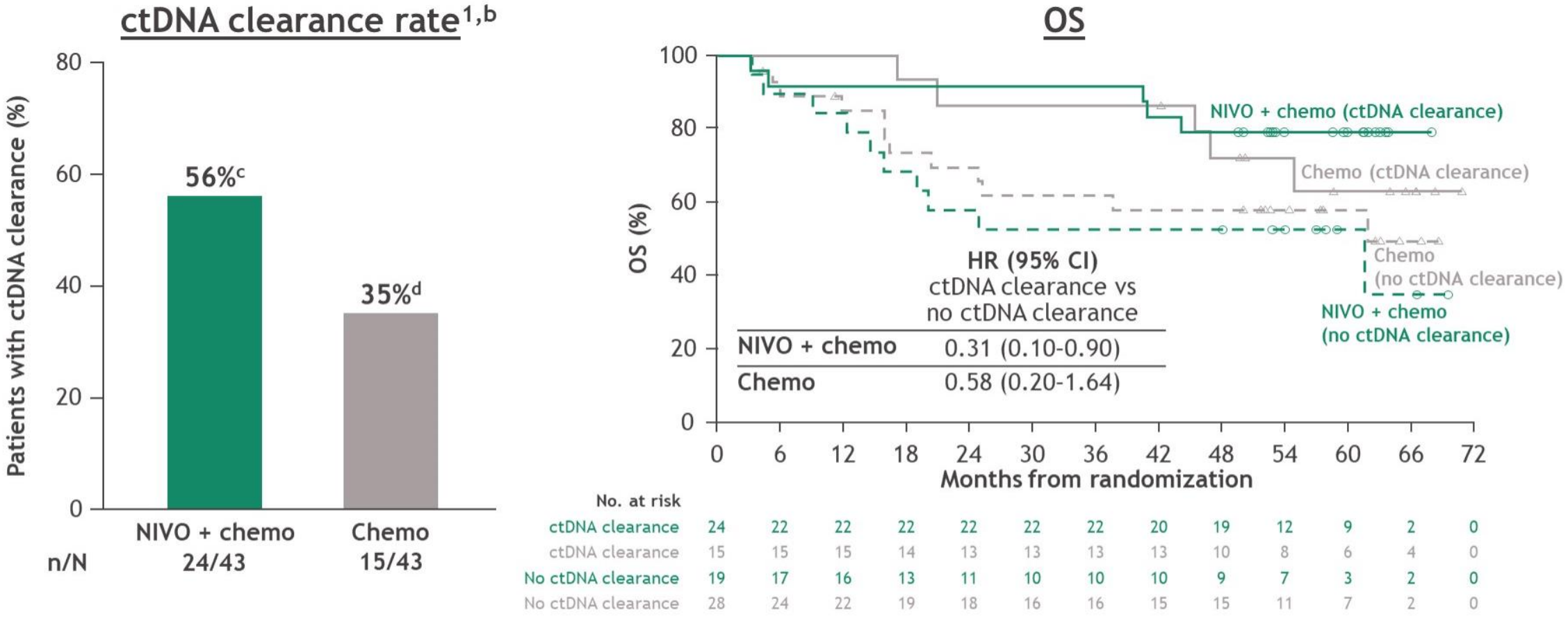
No. at risk:

D arm	303	240	189	160	142	134	120	87	51	41	29	18	3	2	2	0
PBO arm	358	280	223	186	159	149	131	80	53	47	33	25	7	2	2	0

DCO = May 10, 2024. The small number of patients and events in the pCR subgroup results in greater uncertainty in the point estimate and confidence intervals.

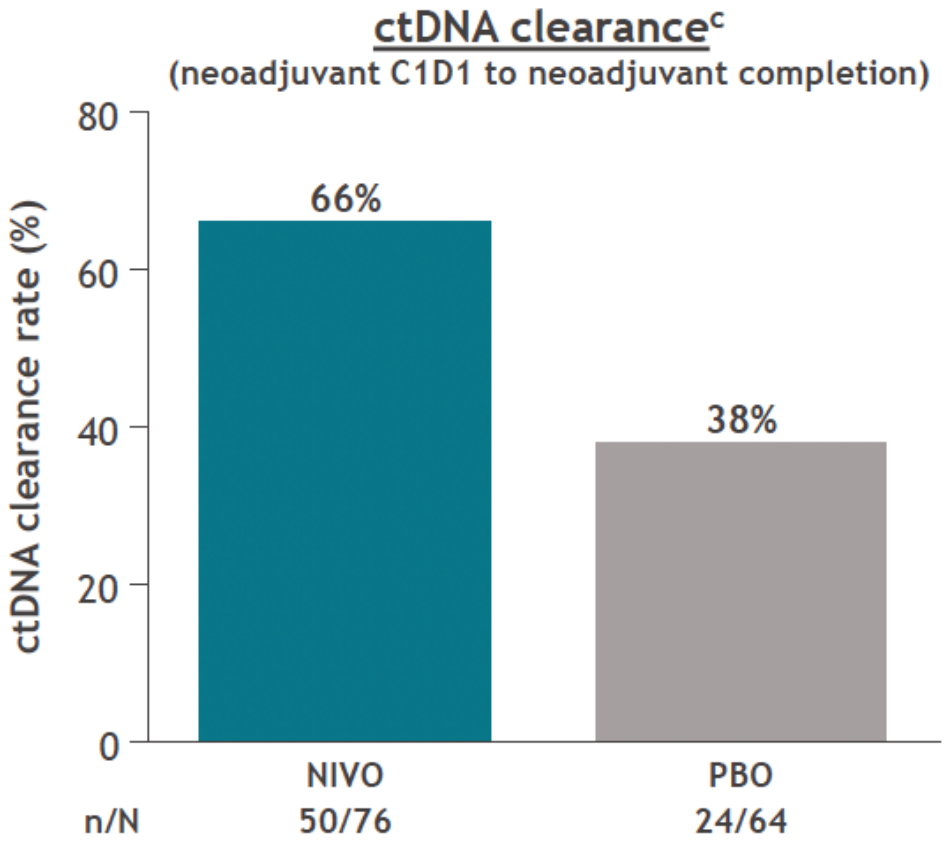
ctDNA clearance rate and OS by ctDNA clearance

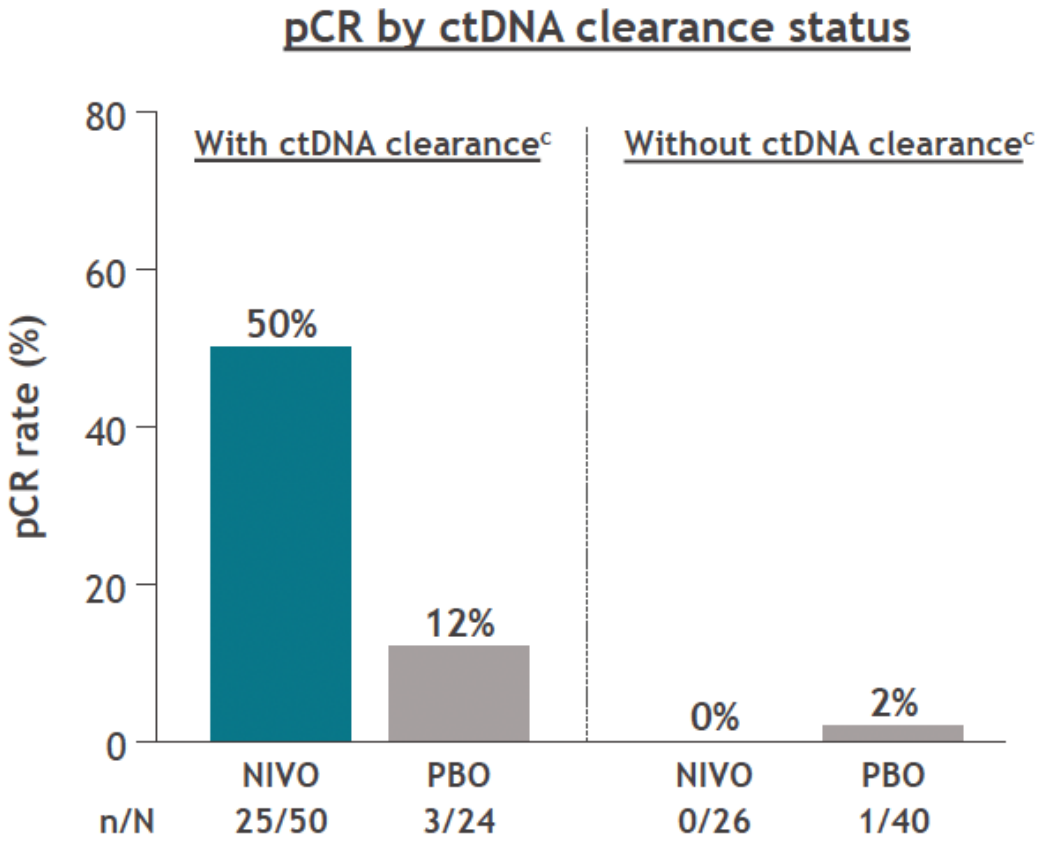
- Among concurrently randomized patients, 89 (25%) had evaluable ctDNA levels, and 86 (24%) had detectable ctDNA levels at baseline[1,a]



ctDNA clearance is prognostic

50% of ctDNA clearance is seen in absence of pCR in CM7T





- Among patients with ctDNA clearance, the EFS HR was 0.38 (95% CI, 0.16-0.88); 2-year EFS rates were 81% (NIVO) vs 58% (PBO)
- Among patients without ctDNA clearance, the EFS HR was 0.74 (95% CI, 0.39-1.42); 2-year EFS rates were 50% (NIVO) vs 31% (PBO)

Provencio, ESMO 2024

MRD tests are specific, but not sensitive enough to guide any de-escalation decisions today

PPV = 80-99%
NPV = 70-80%
Sensitivity = 25-40%
Specificity = 95-100%

Aggregated hypotheses
Assumptions: Recurrence rate at 2yrs = 30%

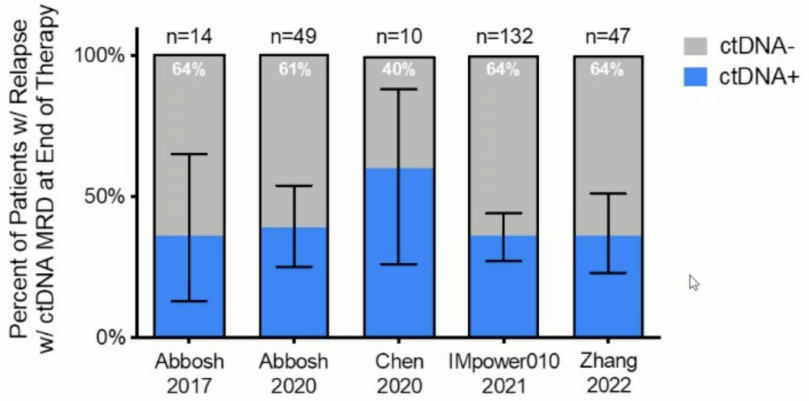
GRAIL Galleri

GUARDANT Reveal/Infinity

燃石医学 Burning Rock Dx OverC

DELFI Delfi-TF

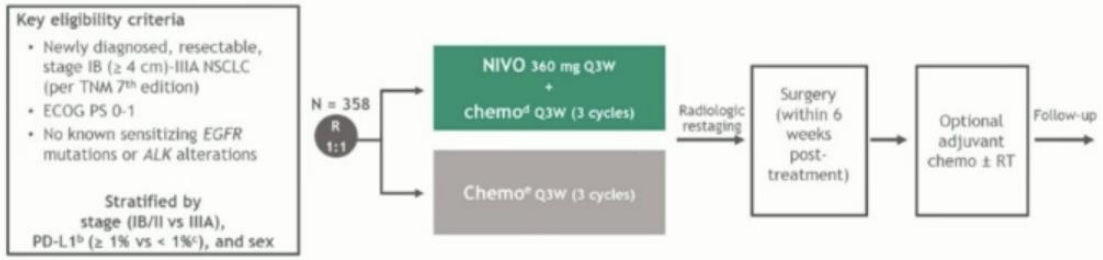
….and have significants false negative rates!



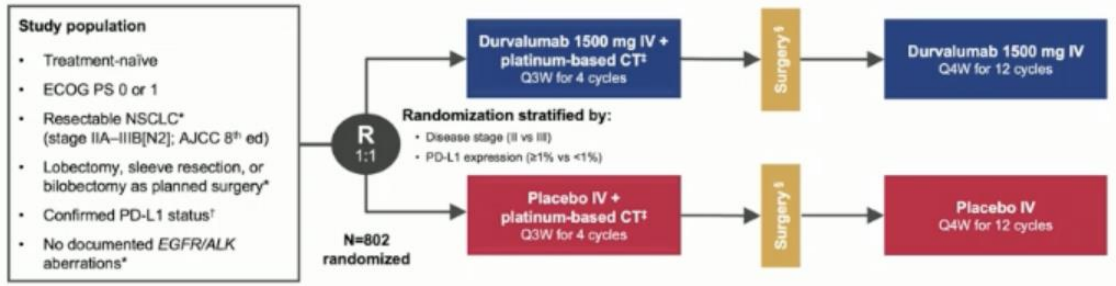
1st generation ctDNA MRD assays have high false negative rates

What data do we have in NSCLC: phase III global trials

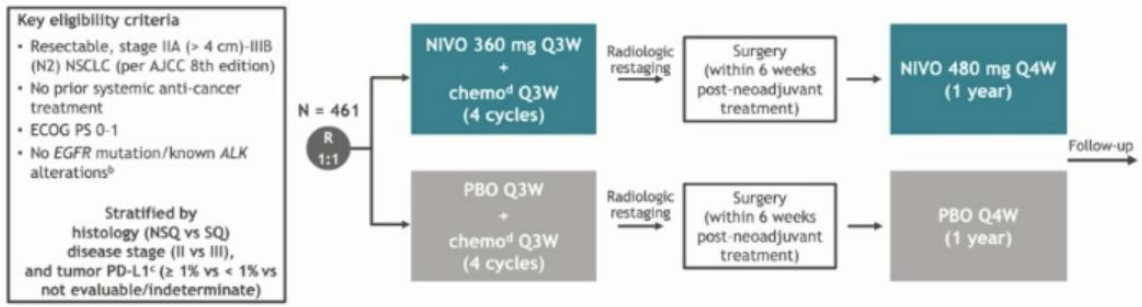
CheckMate-816



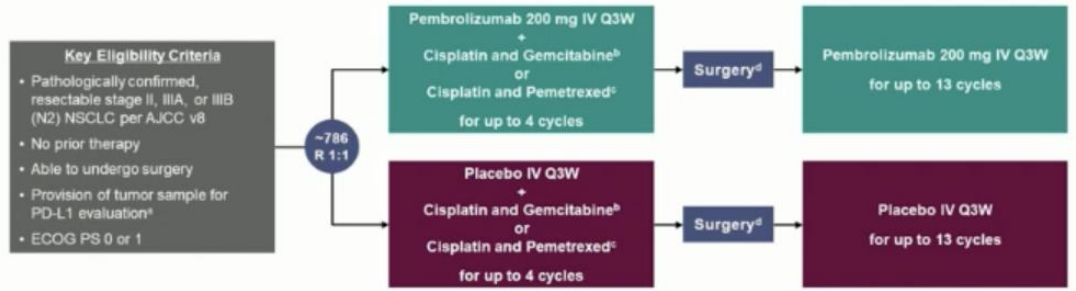
AEGEAN



CheckMate-77T



KEYNOTE-671



Differences in preoperative pathological confirmation of lymph nodes, brain imaging, cisplatin vs. carboplatin, pCR criteria, EFS definition

Neo-Adjuvant or peri-operative trials: a basis for discussion

Trials	stage	n	Stratification	Neo-adjuvant	adjuvant	Main objectives
CheckMate 816[1] Phase III R1:1	IB (≥4cm), II, IIIA (7th ed.) ALK/EGFR -	179 179	IB,II vs IIIA PD-L1 (< 1 vs ≥1%, PharmDx Dako 28-8) Sex	Chemo. + Nivo. (x3) Chemo. (x3)	Optional chemo. (x4) Optional chemo. (x4)	**EFS** **pCR**
KEYNOTE-671 [2] Phase III R1:1	II, IIIA, IIIB[N2] (8th ed.) ALK/EGFR -	397 400	II vs. III PD-L1-TPS (<50% vs. ≥50%, PharmDx, 22C3), Nonsquamous vs squamous East Asia vs Other	Gem-cis. or Pem-cis (x4) + Pembro. (x4) + Placebo (x4)	Pembro. (1 year) Placebo (1 year)	**EFS** **pCR**
AEGEAN [3] Phase III R1:1	II, IIIA, IIIB[N2] (8th ed.) ALK/EGFR -	366 374	II vs III PD-L1 (<1% vs ≥1%)	Chemo. + Durva. (x4) Chemo. + Placebo(x4)	Durva. (1 year) Placebo (1 year)	**pCR** **EFS**
CheckMate 77T[6] Phase III R1:1	IIA (> 4 cm), IIIB[N2] (8th ed.) ALK/EGFR -	229 232	Nonsquamous vs squamous II vs III PD-L1 (<1% vs. ≥1% vs NE or ND PharmDx Dako 28-8)	Chemo. + Nivo. (x4) Chemo. + Placebo (x4)	Nivo. (1 year) Placebo (1 year)	**EFS**

* Neotorch, results for stage III only

** Statistical hierarchical test: EFS stage III ➳ EFS stage II, III ➳ MPR stage III ➳ MPR stage II, III ➳ OS stage III ➳ OS stage II, III

U.S. FOOD & DRUG ADMINISTRATION

DFS and EFS are listed as surrogate endpoints that were the basis of drug approvals or licensure by the FDA[1]

Time from randomisation to any of the following:

- First recurrence of NSCLC
- Occurrence of new primary NSCLC
- Death from any cause

DFS (adjuvant)

Absence of any viable tumour at the time of surgical resection

pCR

EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

DFS and EFS are also accepted endpoints by the EMA[2]

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

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

MALCOLM WILLETT

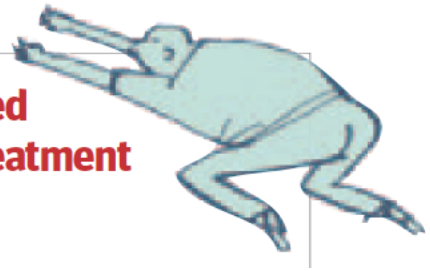
THE IDOLATRY OF THE SURROGATE

Easier to measure surrogate outcomes are often used instead of patient important outcomes such as death, quality of life, or functional capacity when assessing treatments. **John Yudkin, Kasia Lipska, and Victor Montori** argue that our obsession with surrogates is damaging patient care

BMJ | 14 JANUARY 2012 | VOLUME 344

Since they respond sooner than outcomes that are important to patients, surrogates are better suited as end points in clinical trials that need to be completed quickly and at low cost

Surrogate markers are not intrinsically flawed. When interpreted appropriately, they can be helpful in risk stratification and in treatment

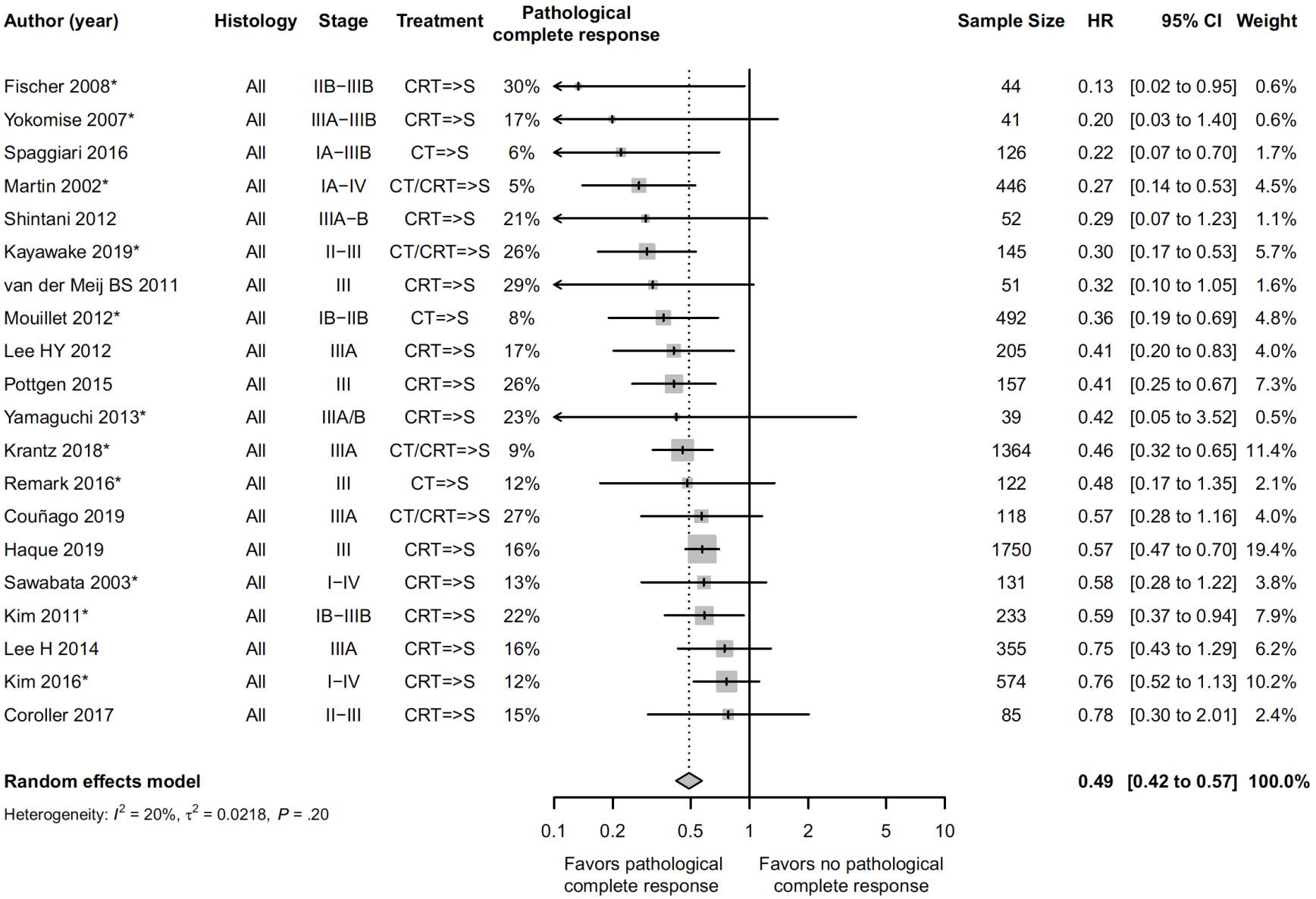


SACRO CUORE DON CALABRIA
I R C C S

Pathological response in resectable non–small cell lung cancer: a systematic literature review and meta-analysis

Nathalie A. Waser, PhD,[1,*] Melanie Quintana, MSc,[2] Bernd Schweikert, PhD,[3] Jamie E. Chaft, MD,[4] Lindsay Berry, PhD,[2] Ahmed Adam, MPH,[1] Lien Vo, PharmD, MPH,[5] John R. Penrod, PhD,[5] Joseph Fiore, PharmD,[5] Donald A. Berry, PhD,[2] Sarah Goring, MSc[1]

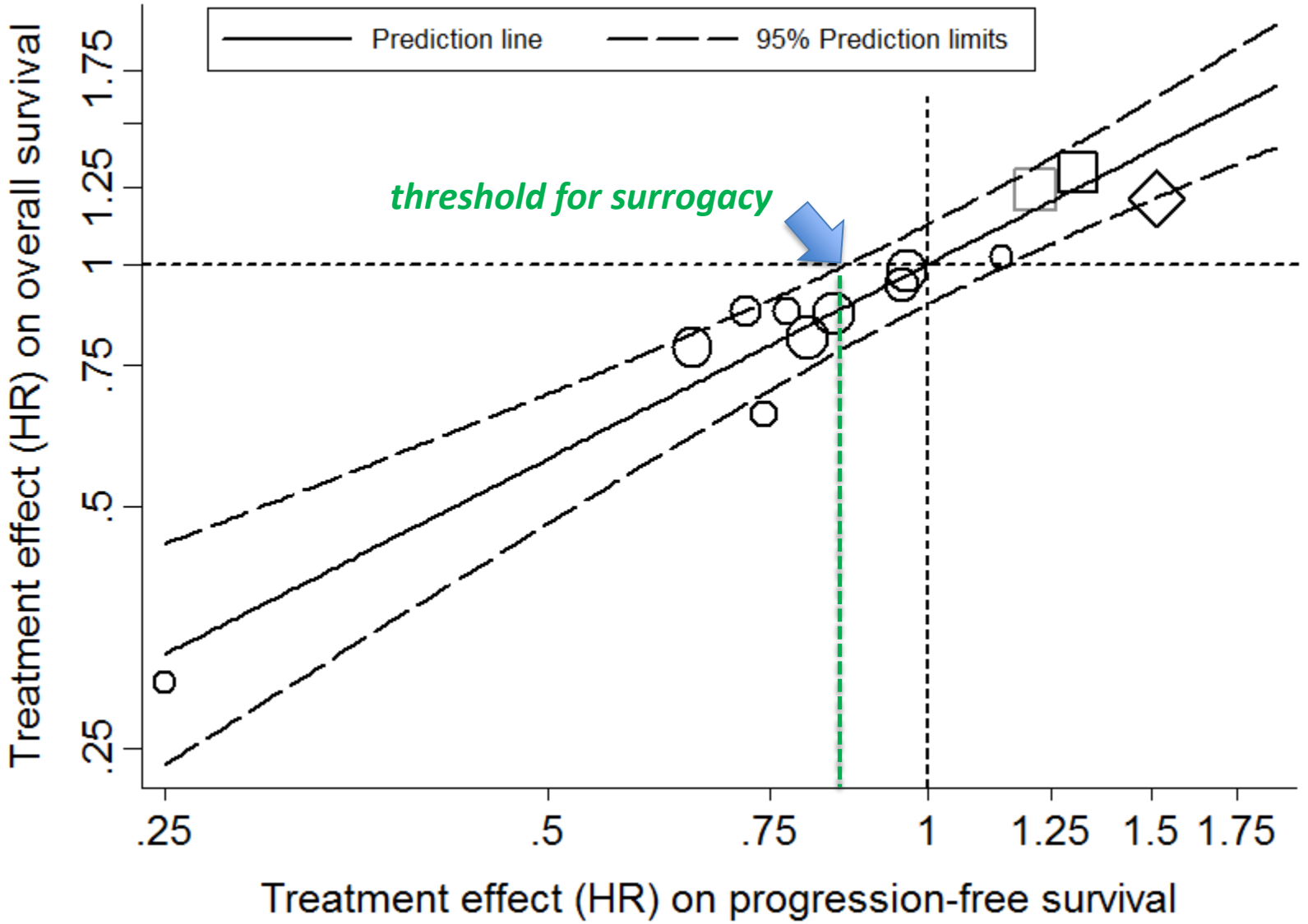
JNCI Cancer Spectrum, 2024, **8(3)**, pkae021



Patient level analysis

(association between the expression of the intermediate endpoint and the reference final endpoint)

TRIAL LEVEL CORRELATION BETWEEN EFFECTS



Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

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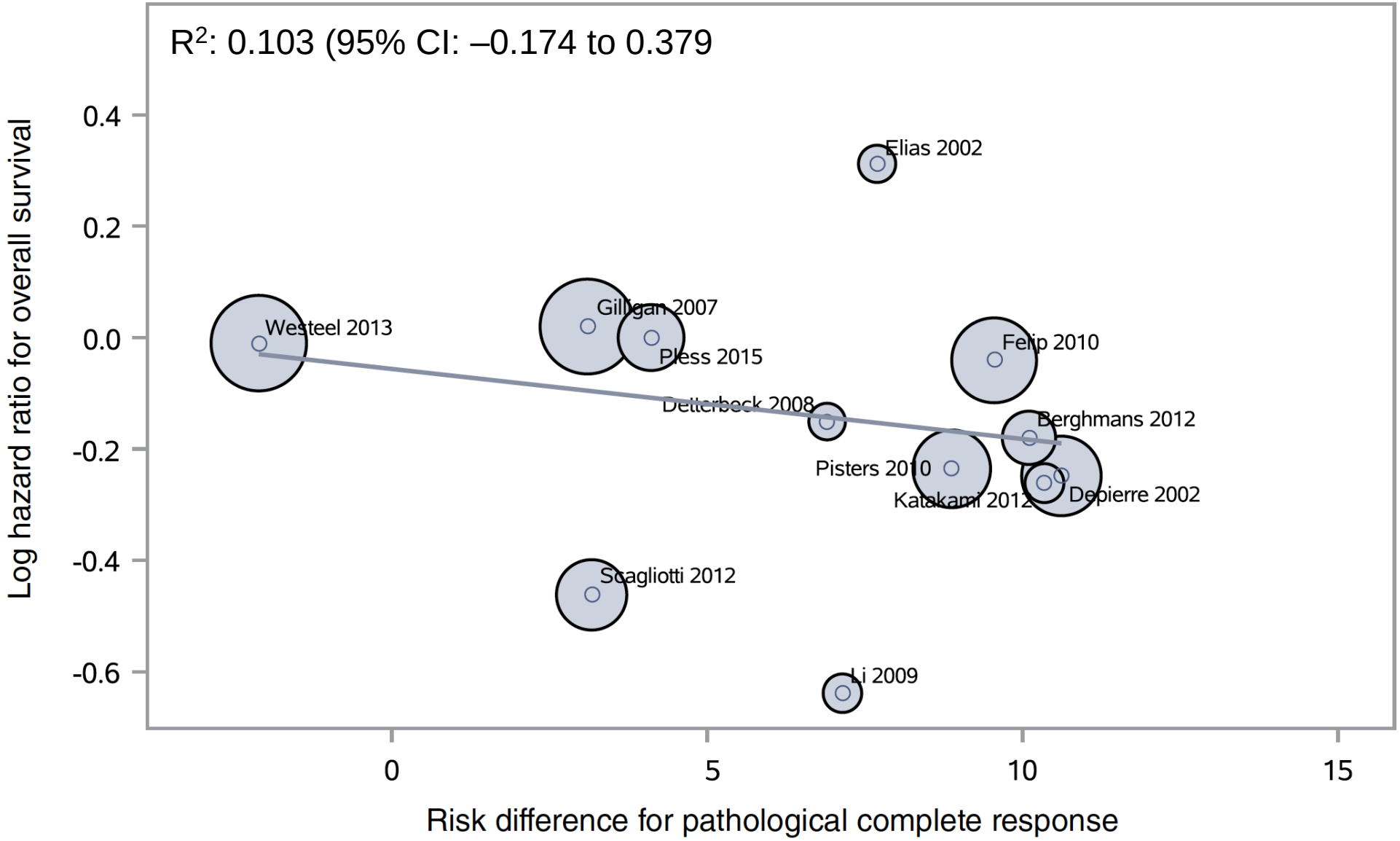

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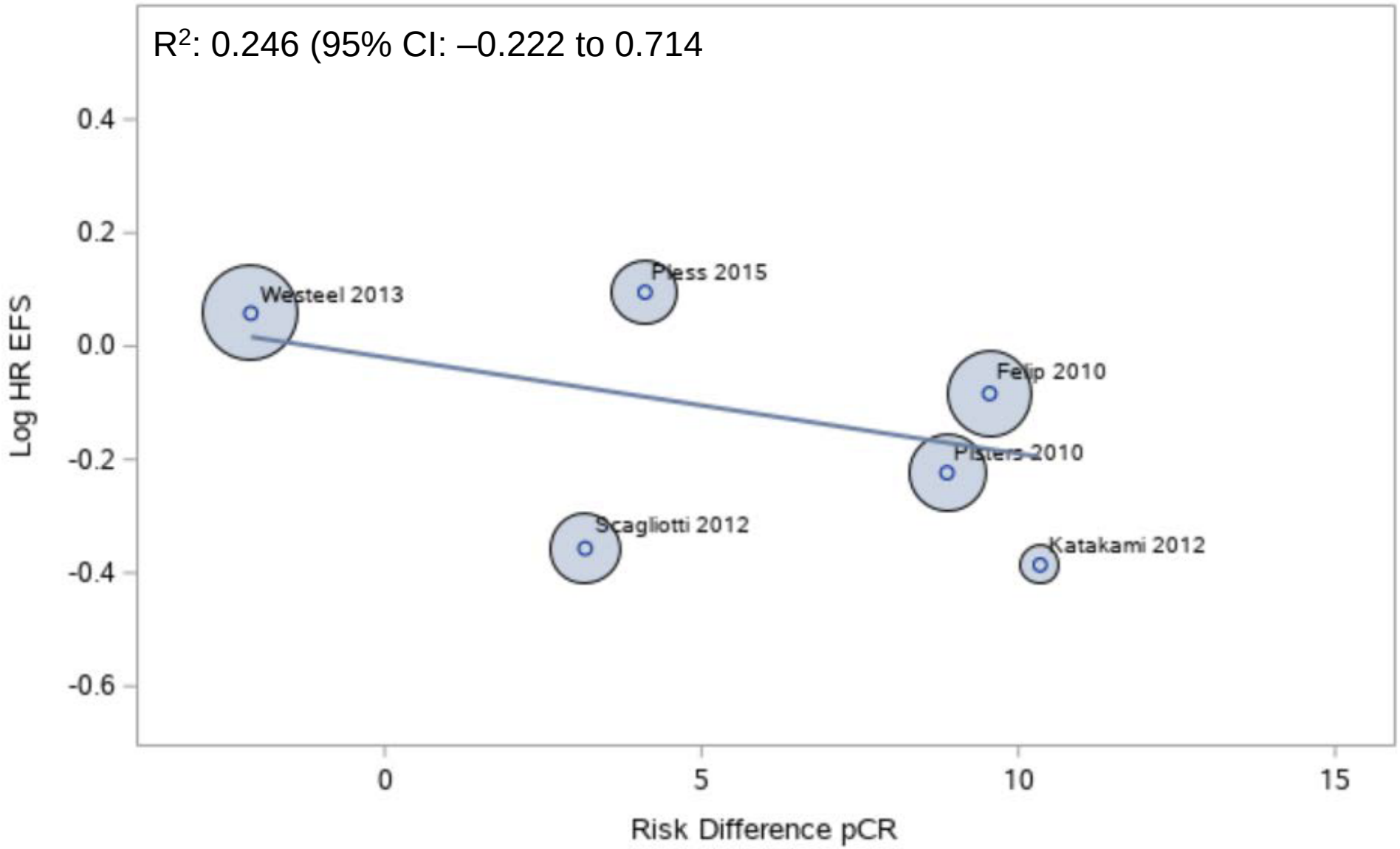

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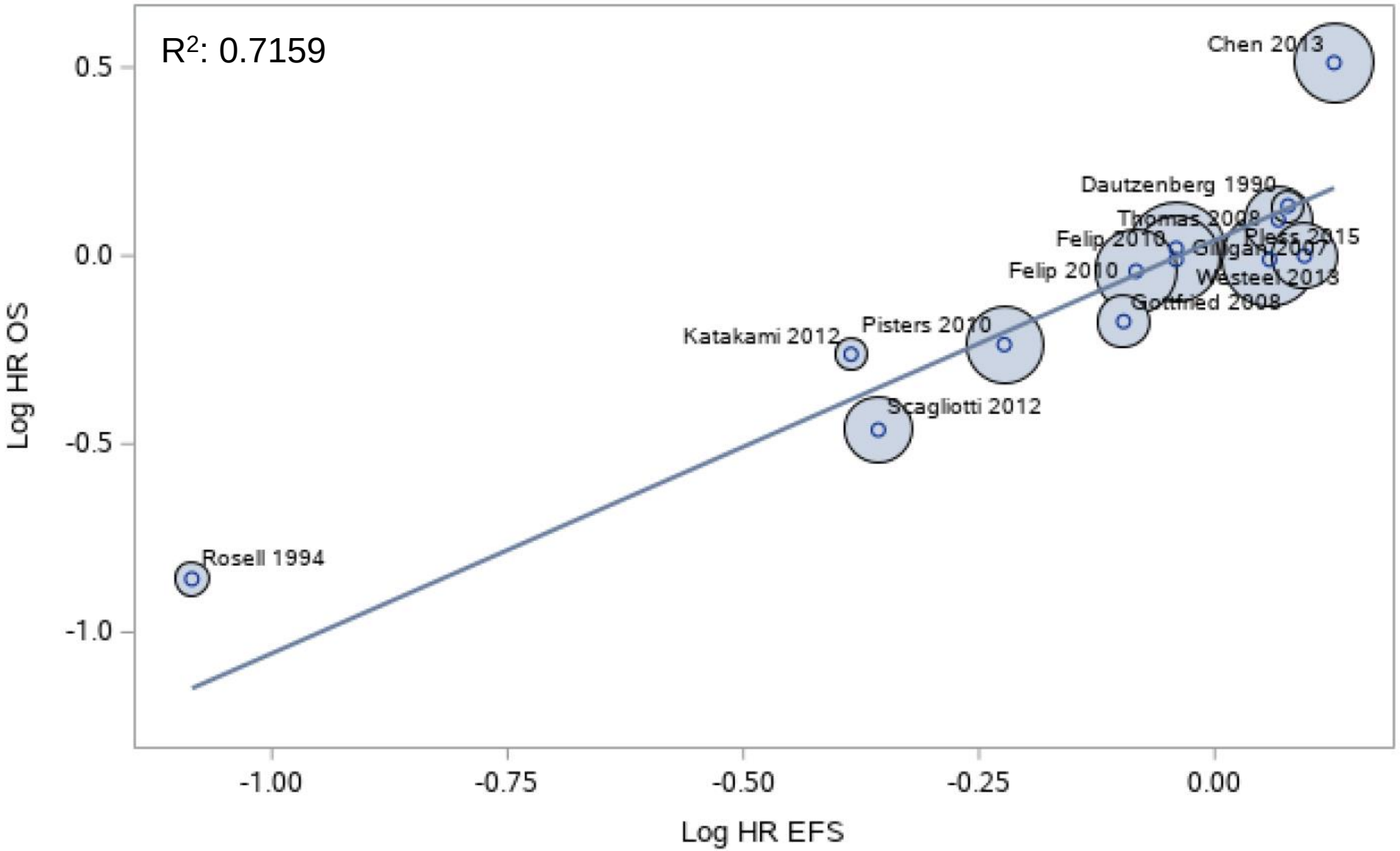

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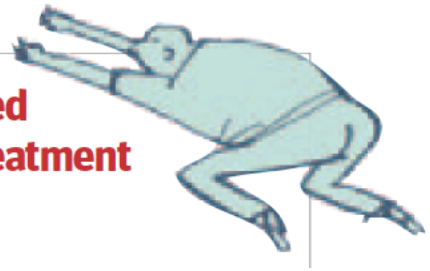


In order to fully engage our patients in treatment decisions, we must understand how therapies affect outcomes that are important to them. Surrogate end-points will not provide us with these answers.

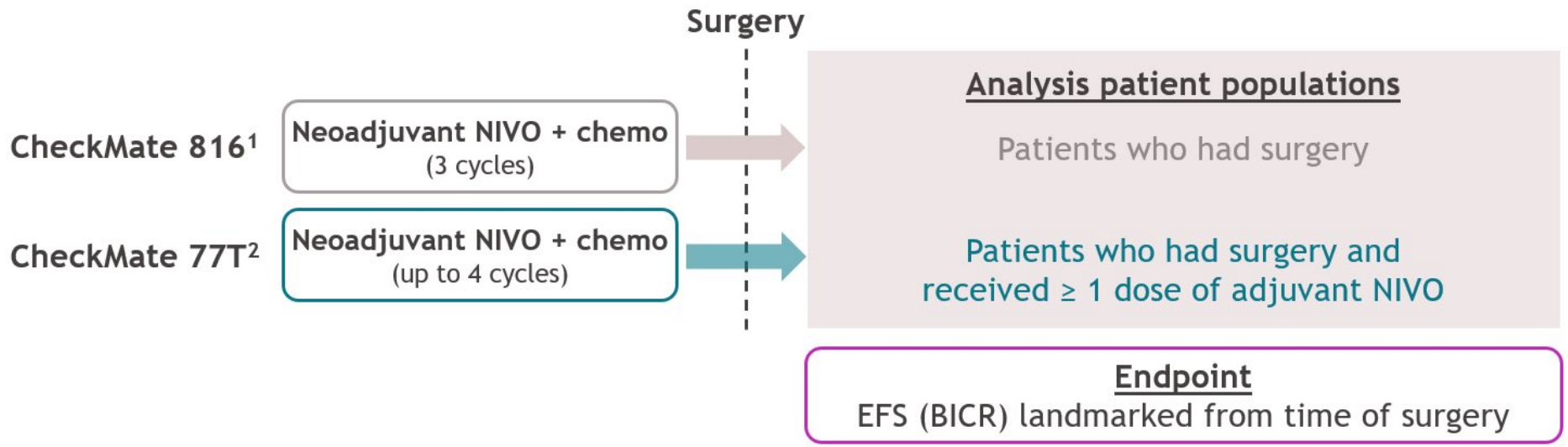
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,[1] Solange Peters,[2] Jessica Donington,[3] Stephanie Meadows-Shropshire,[4] Phuong Tran,[4] Stefano Lucherini,[5] Cinthya Coronado Erdmann,[6] Hong Sun,[6] Tina Cascone[7]

[1]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD, USA; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]The University of Chicago, Chicago, IL, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]Bristol Myers Squibb, Uxbridge, UK; [6]Bristol Myers Squibb, Boudry, Switzerland; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presentation number 3589

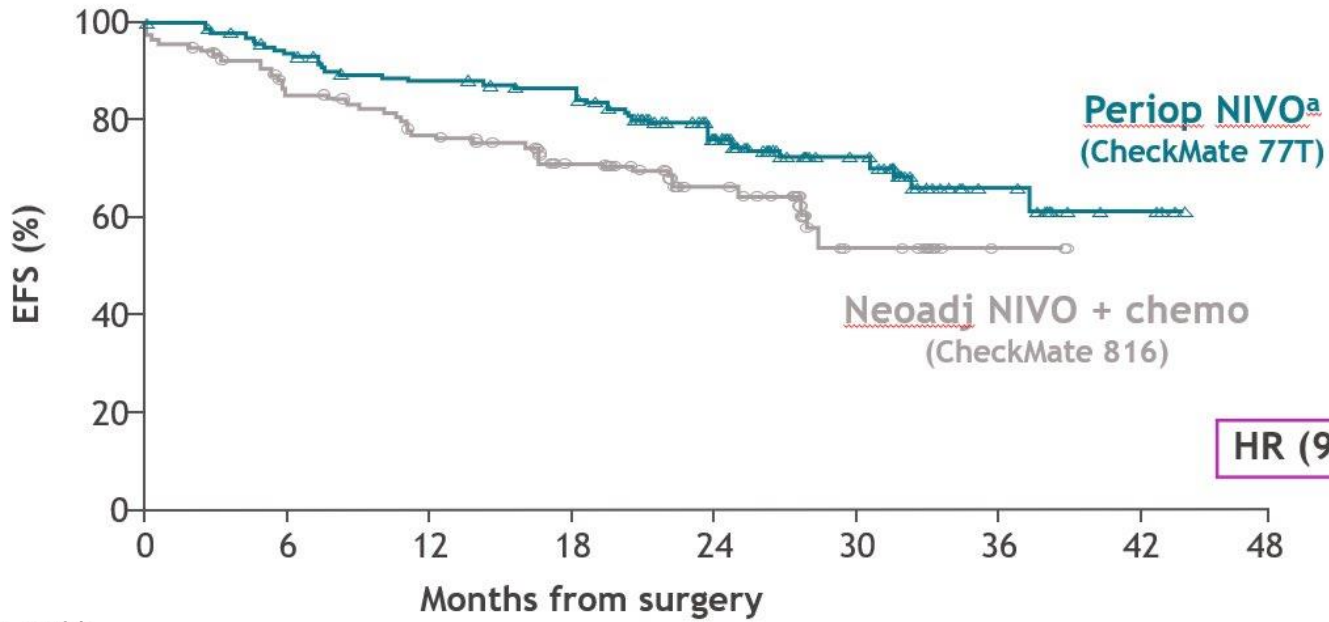
Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



- In lieu of a head-to-head trial, exploratory propensity score weighting analyses (ATT[a] and ATE[b]) were performed to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics[c] between study populations and reducing the confounding effects of these factors
  - Subgroup analyses were not weighted due to smaller sample sizes
- Median duration of follow-up[d]: 29.5 months (CheckMate 816) and 33.3 months (CheckMate 77T)

[a]Average treatment effect for the treated (ATT): a weight of 1 was applied to patients in the perioperative NIVO arm of CheckMate 77T; varying weights were applied to patients in the CheckMate 816 NIVO + chemo arm to make them comparable to those in the perioperative NIVO arm in CheckMate 77T based on propensity scores. [b]Average treatment effect (ATE): varying weights were applied to all patients in the populations of interest from CheckMate 77T and CheckMate 816 to make them comparable to one another based on propensity scores. [c]Sex, race, clinical stage, tumor histology, PD-L1 expression, age, ECOG PS, and smoking status. [d]Database locks: CheckMate 816, October 20, 2021; CheckMate 77T, April 26, 2024. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Cascone T, et al. *N Engl J Med* 2024;390:1756-1769.

Landmark EFS (BICR) from definitive surgery



No. at risk									
Periop NIVO	139.4	128.0	118.1	112.9	79.7	42.5	13.0	3.1	0
Neoadj N+C	147.5	121.0	106.2	84.2	39.1	12.1	2.2	0	0

	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [b]ATE: varying weights were applied to all patients in both neoadjuvant NIVO + chemo arm (CheckMate 816) and perioperative NIVO (CheckMate 77T) to make them comparable to one another. [c]N values fractional due to weighting. [d]ATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T).

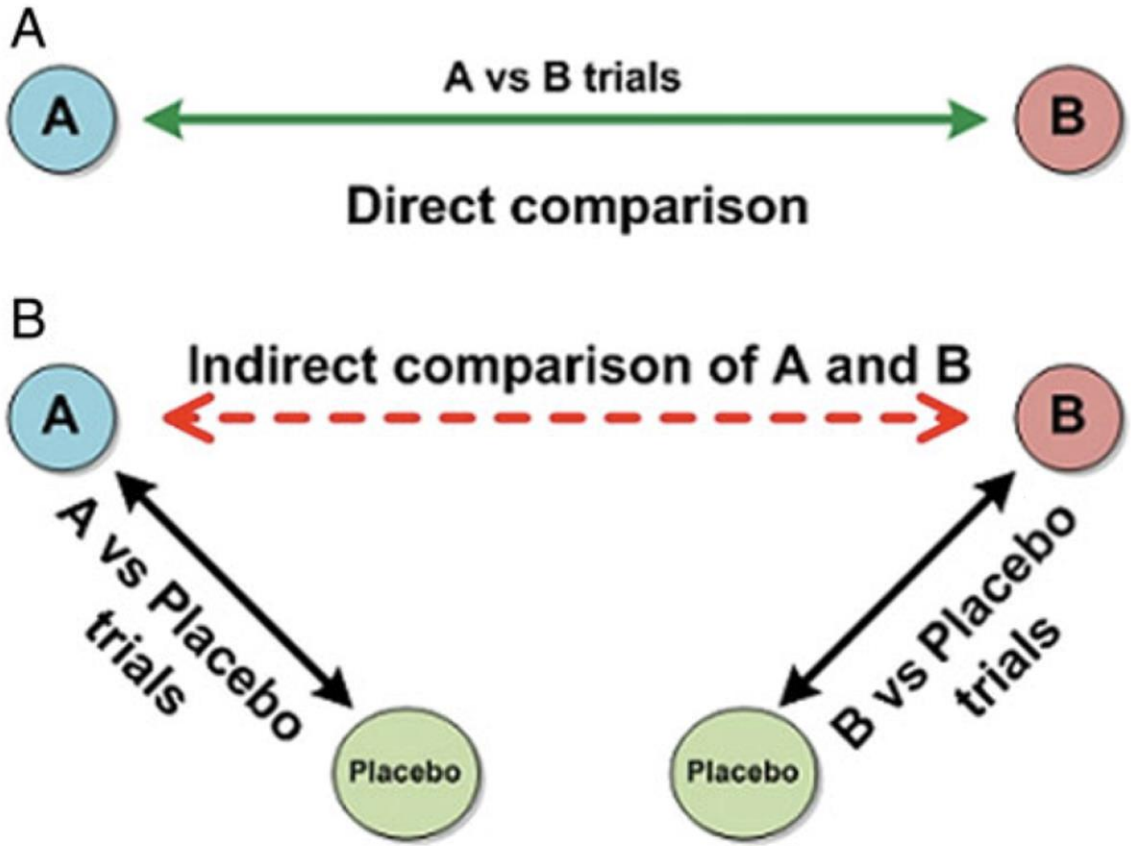
In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) was 13.0 (1-13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for periop NIVO vs neoadj NIVO + chemo: HR = 0.82 (95% CI, 0.55-1.21).

Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.



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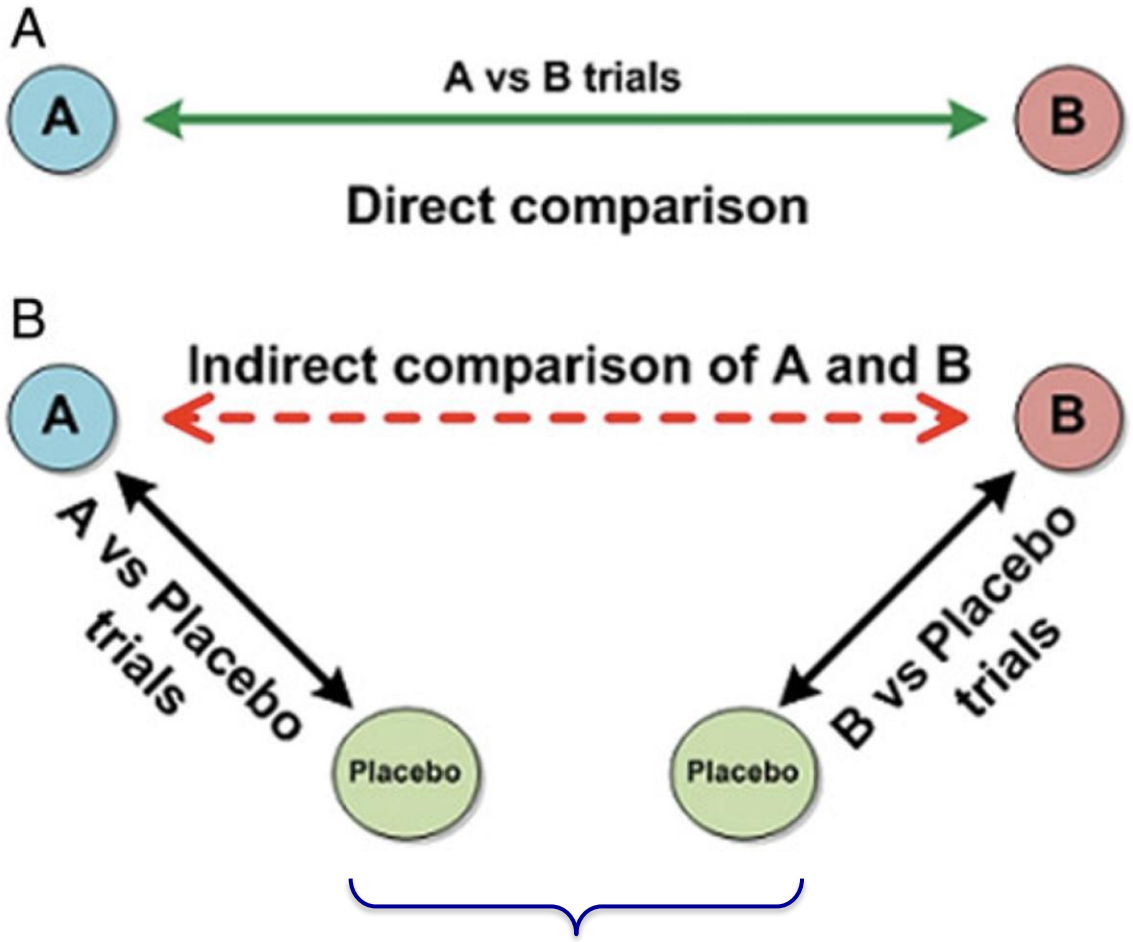

Similarity Assumption

trials must be comparable on effect modifiers to obtain an unbiased pooled estimate.

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HTA

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WHAT FACTORS DETERMINE SIMILARITY?

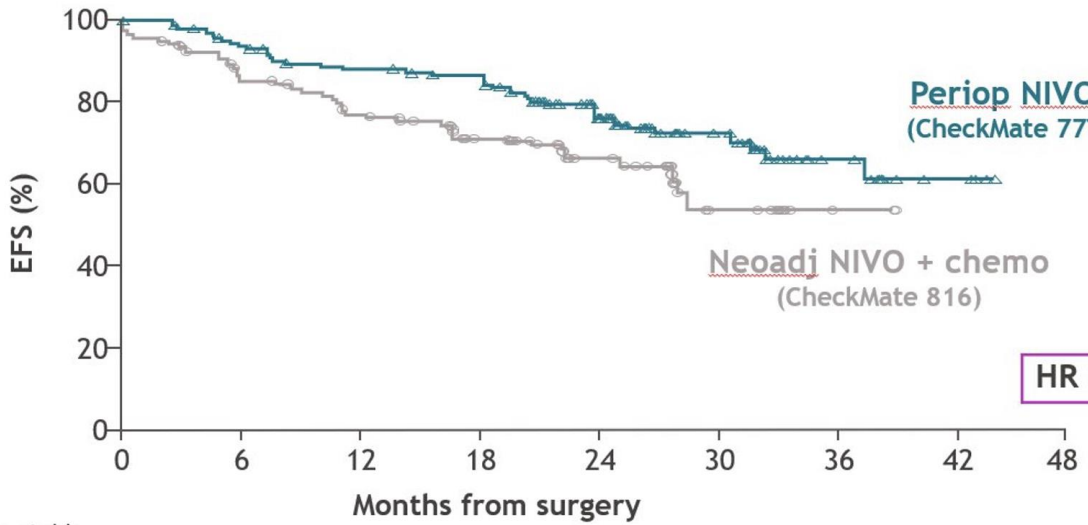
- Included trials should be “comparable” in terms of key factors that could affect the outcome of treatment
- If differences in patient or study characteristics would not be expected to influence treatment effect, the assumption of similarity is not violated
- **There are no statistical methods to test for similarity**
- Must use clinical knowledge and best judgement to assess appropriate comparability

Population-adjusted Indirect Comparisons

- Population-adjusted Indirect Comparisons use patient-level data from a trial of a given treatment (referred to as the index trial) to derive a comparison of outcomes with competing treatments, based on published information from similarly designed studies, after adjusting for differences in the characteristics of the populations.
- *in other words*: individual patient data (IPD) in one or more trials are used to adjust for between-trial differences in the distribution of variables that influence outcome

https://www.nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf.

Landmark EFS (BICR) from definitive surgery



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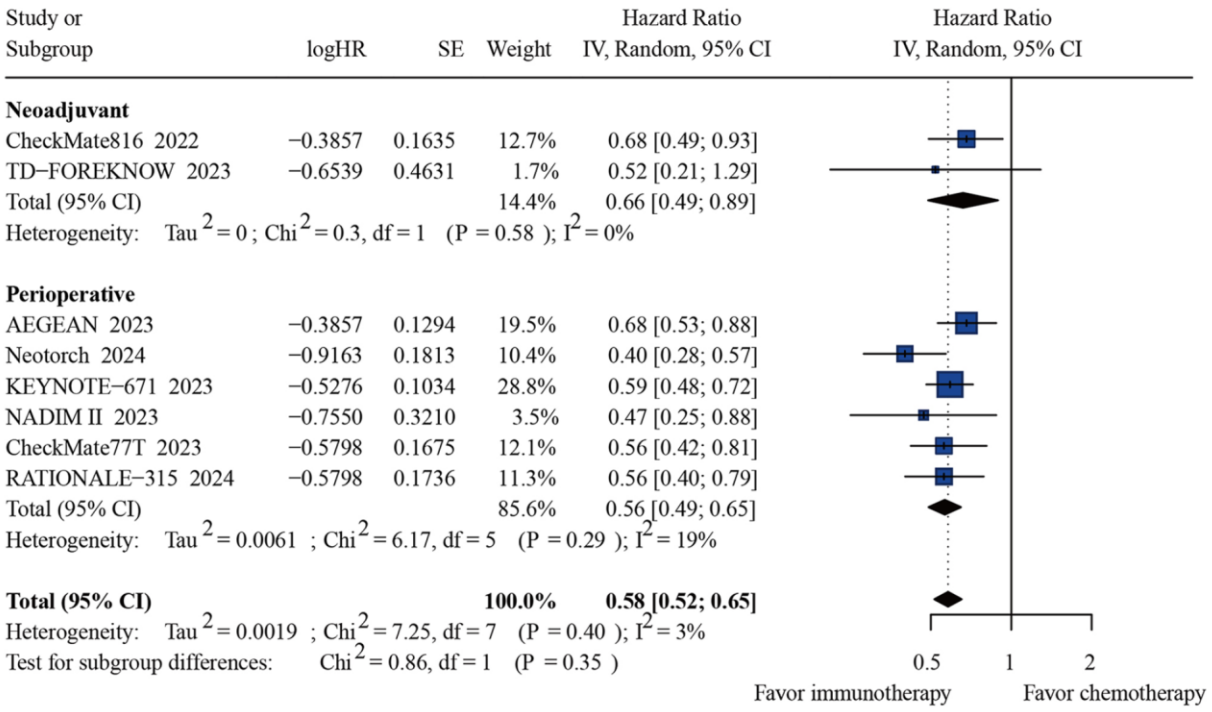
Efficacy and safety of perioperative, neoadjuvant, or adjuvant immunotherapy alone or in combination with chemotherapy in early-stage non-small cell lung cancer: a systematic review and meta-analysis of randomized clinical trials

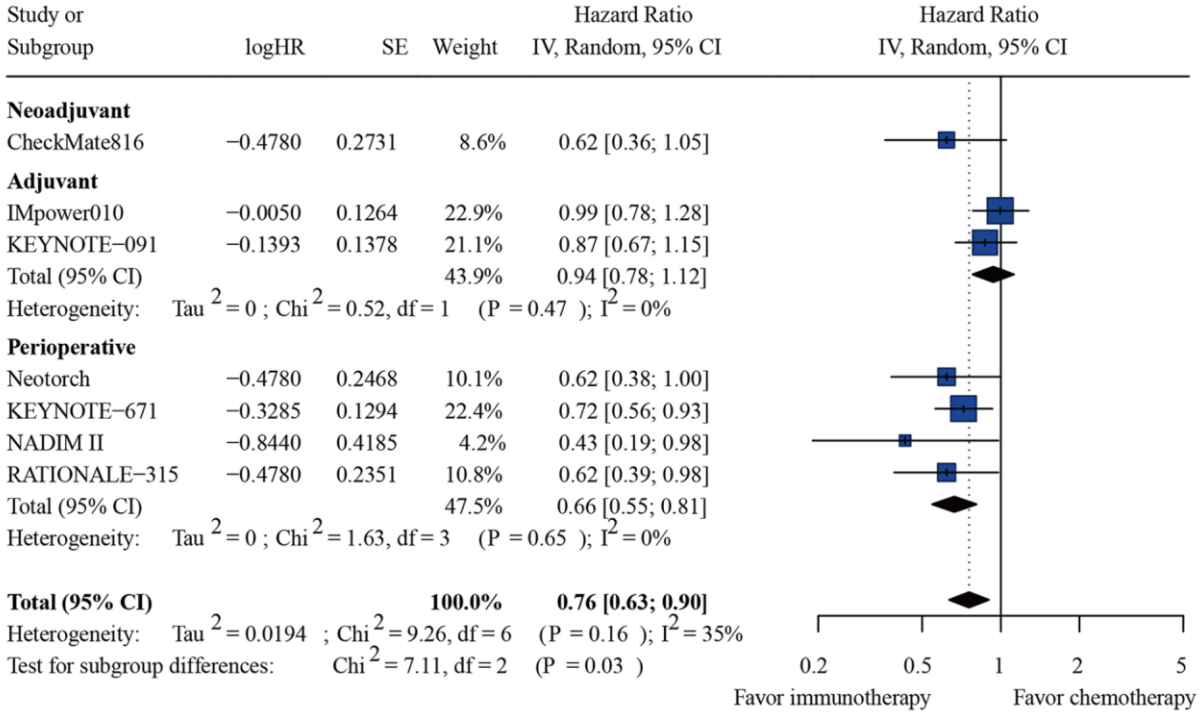
Yunchang Meng*, Qingfeng Zhang*, Ranpu Wu, Huijuan Li, Zhaofeng Wang, Yang Yao, Xinjing Li, Zhangxuan Chen, Yanzhuo Gong and Hongbing Liu

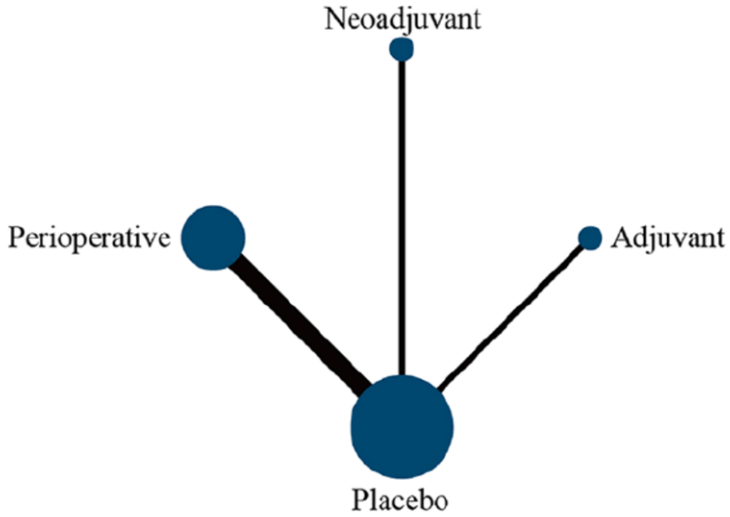
Ther Adv Med Oncol 2024, Vol. 16: 1–18

Event-Free Survival



Overall Survival





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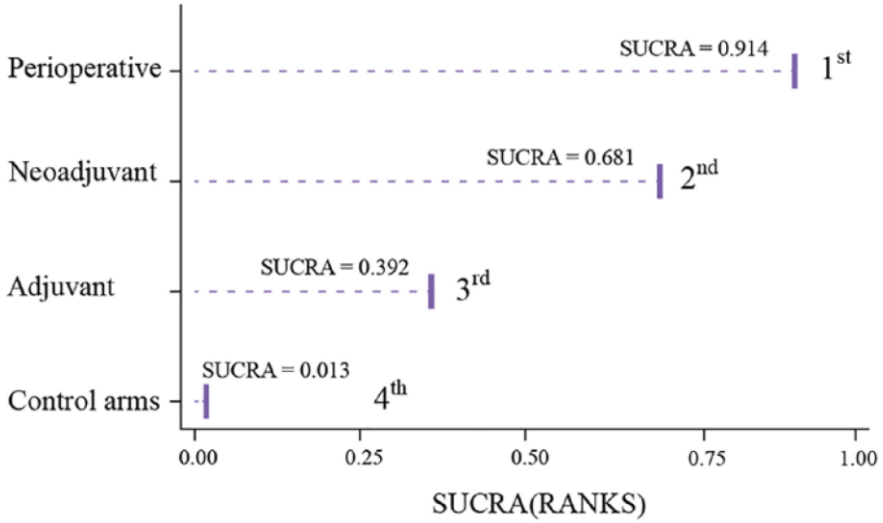

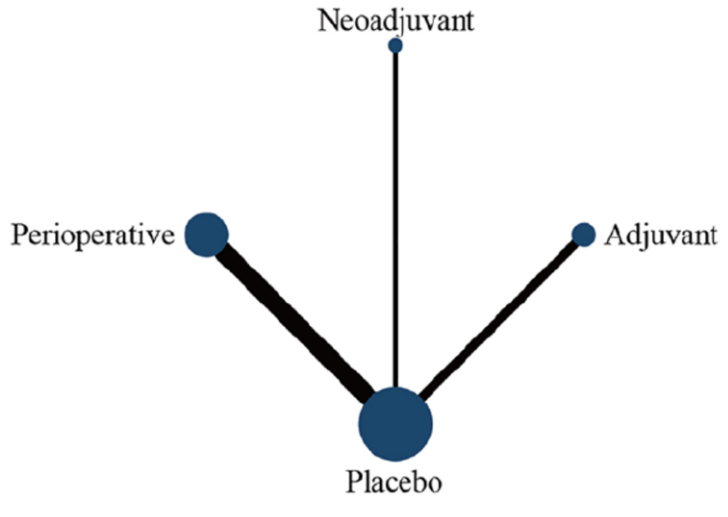

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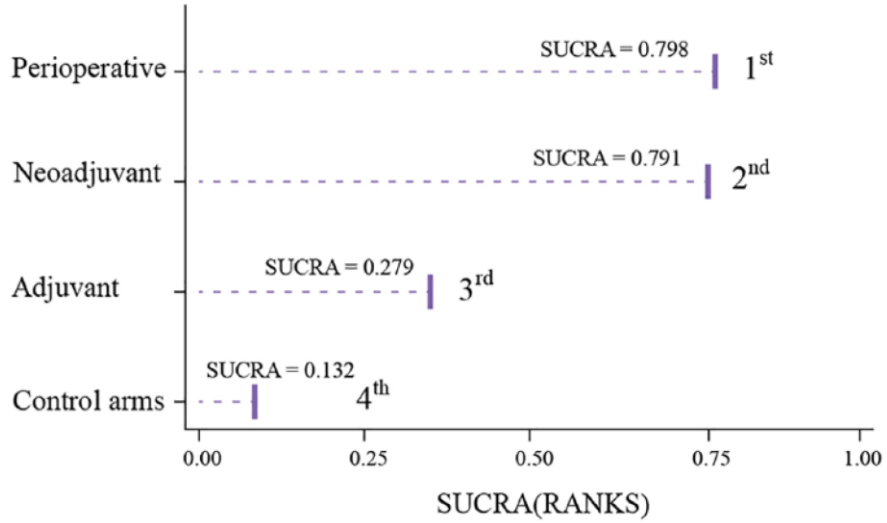

AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Grazie per l’attenzione!