Perioperative immunotherapy in early-stage lung cancer

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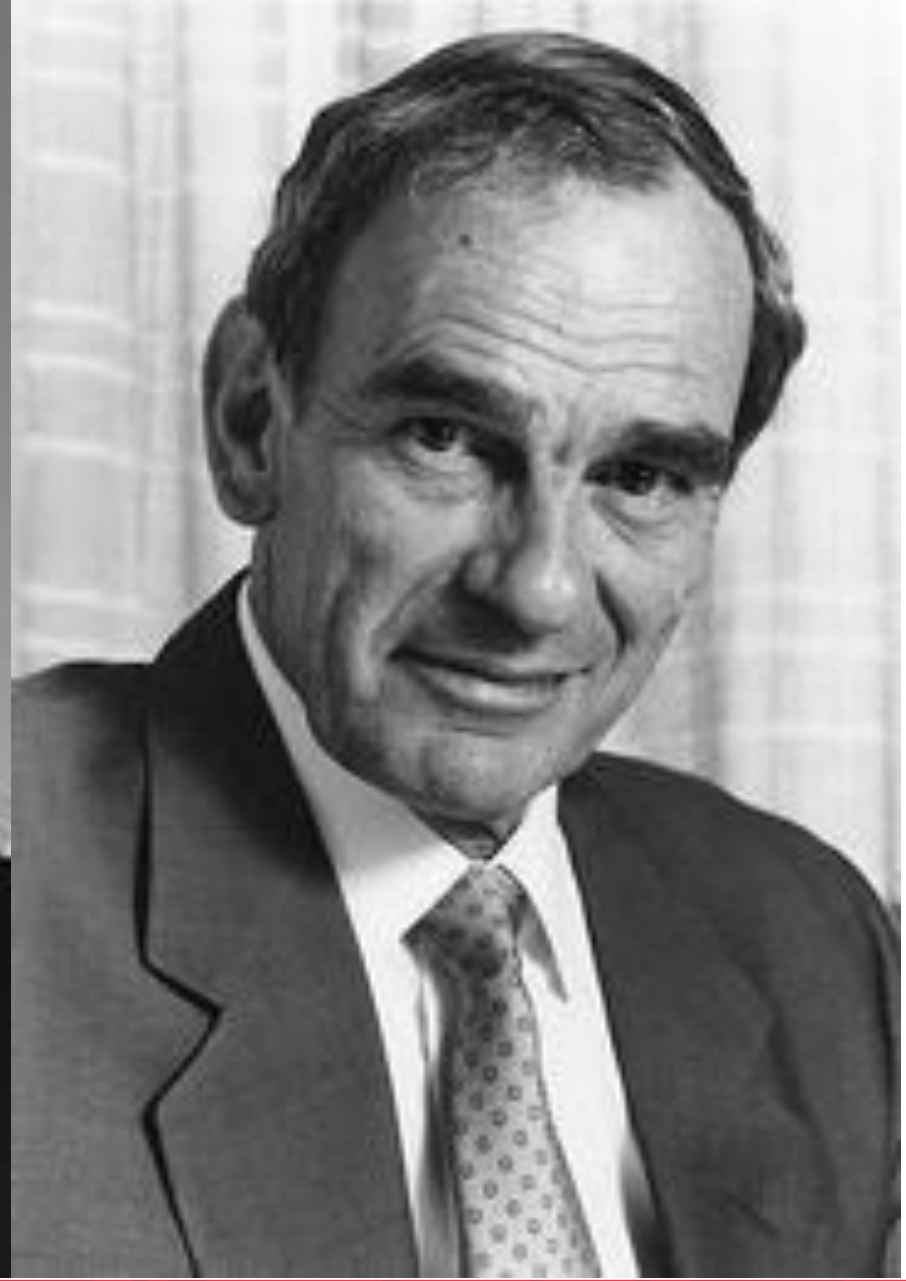
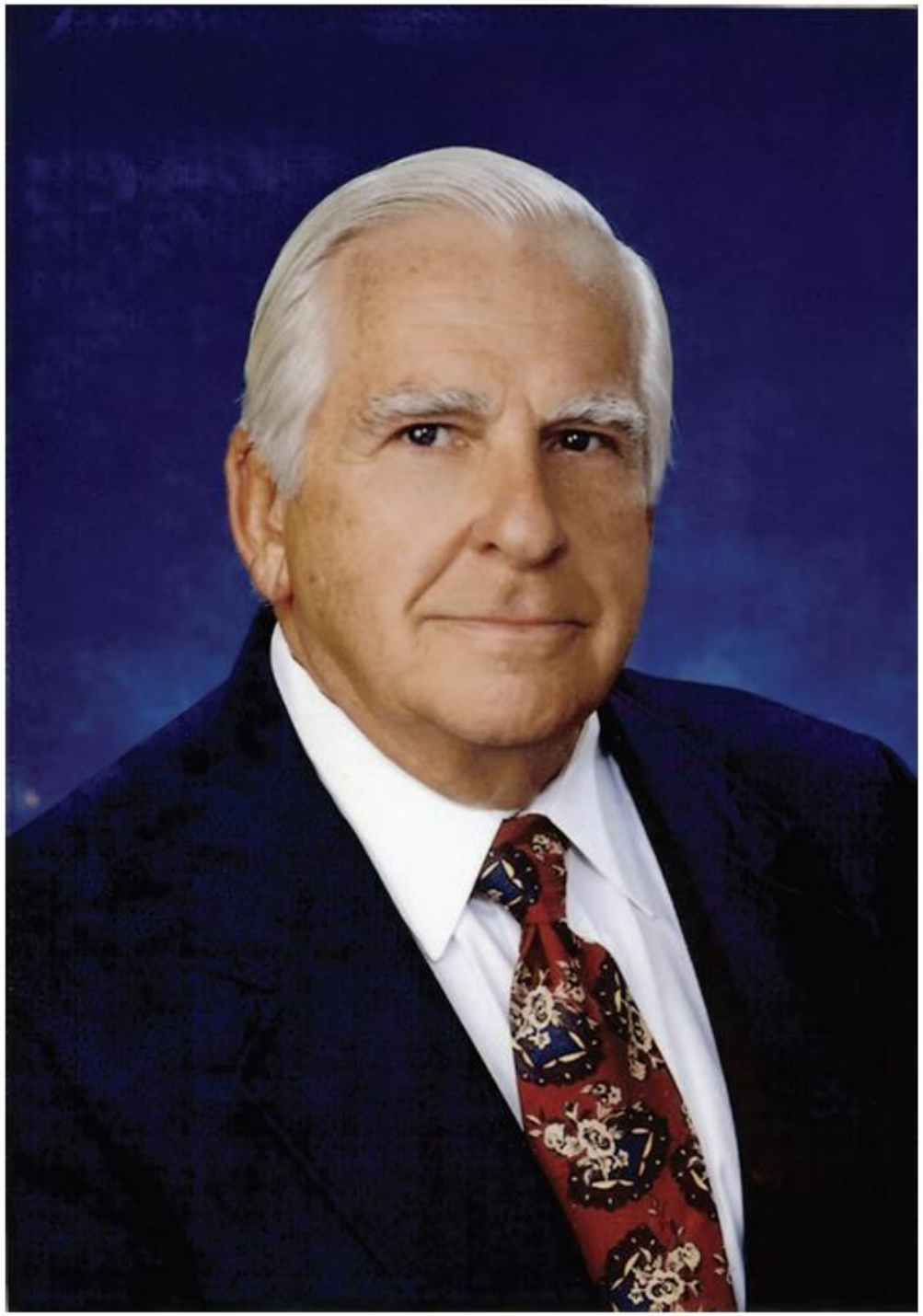
McGill | Department of Surgery

Conflicts of interest

Commercial Interest	Relationship(s)
AstraZeneca, Merck, Roche, BMS, Novartis, Chemocentryx, Amgen, Protalix Biotherapeutics, Xenetic Biosciences, Regeneron, Eisai, Peerview, OncLive, Medscape, Pfizer, Foresight Diagnostics	Consulting, advisory role or honoraria
AstraZeneca, BMS, Merck, Roche, CLS Therapeutics, Protalix Biotherapeutics, Pfizer, Regeneron	Grant to institution
BMS, Novartis, Roche, Merck, AstraZeneca	Clinical trial leadership role





A SYSTEM FOR THE CLINICAL STAGING OF LUNG CANCER*

By CLIFTON F. MOUNTAIN, M.D.,† DAVID T. CARR, M.D.,‡
and W. A. D. ANDERSON, M.D.§
HOUSTON, TEXAS; ROCHESTER, MINNESOTA; AND MIAMI, FLORIDA

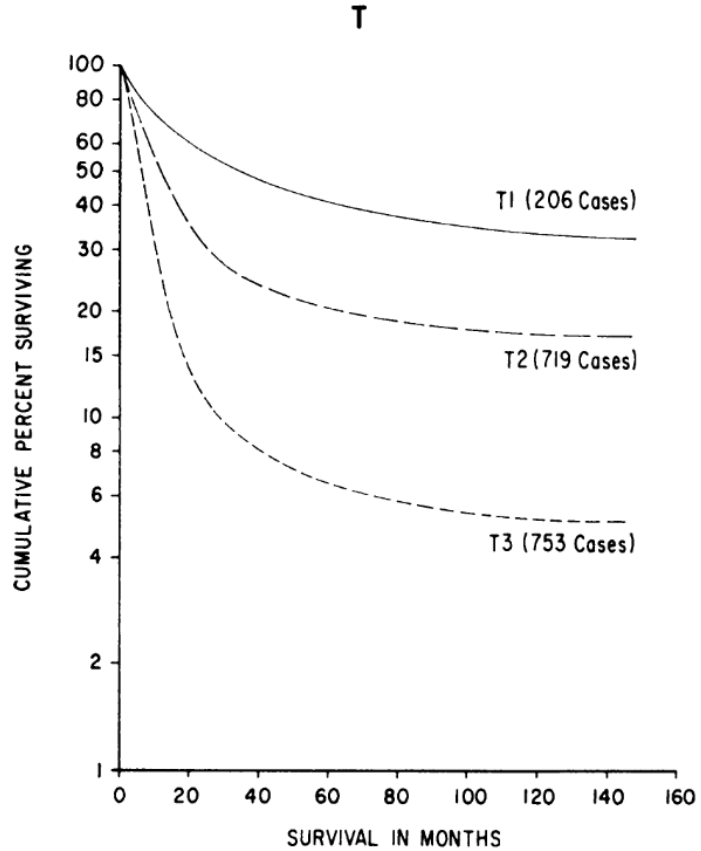


FIG. 2. Survival in lung cancer stratified by the anatomic extent of the primary tumor (T factor), excluding undifferentiated small cell carcinoma.

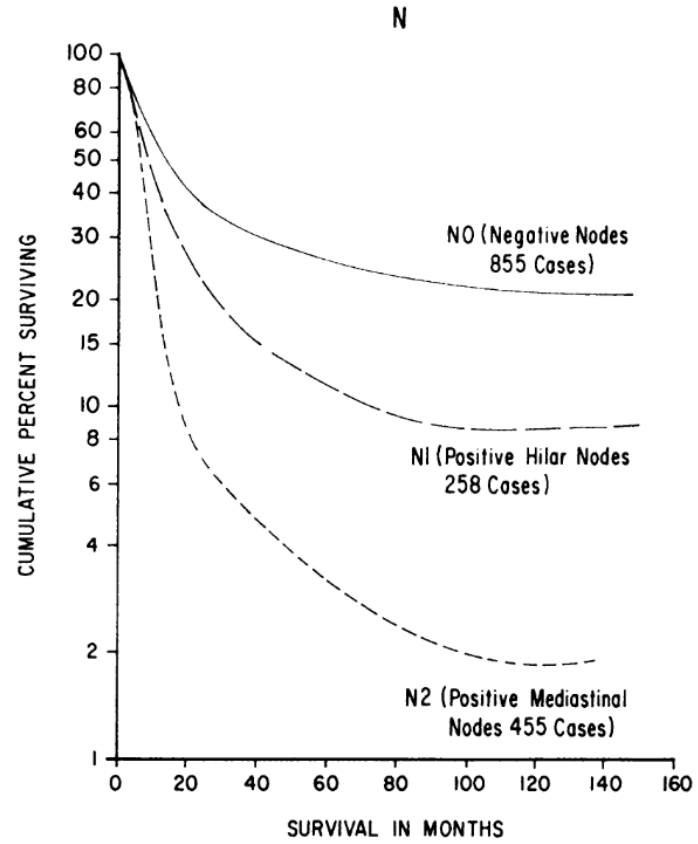
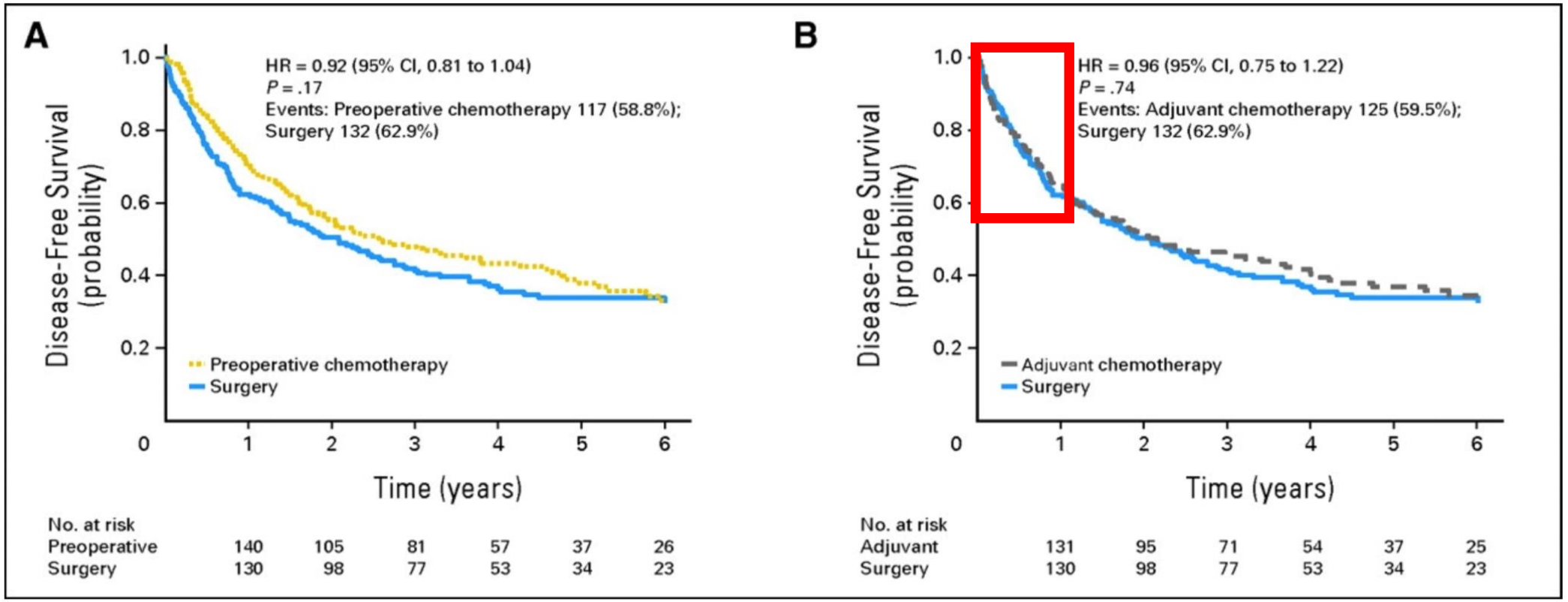


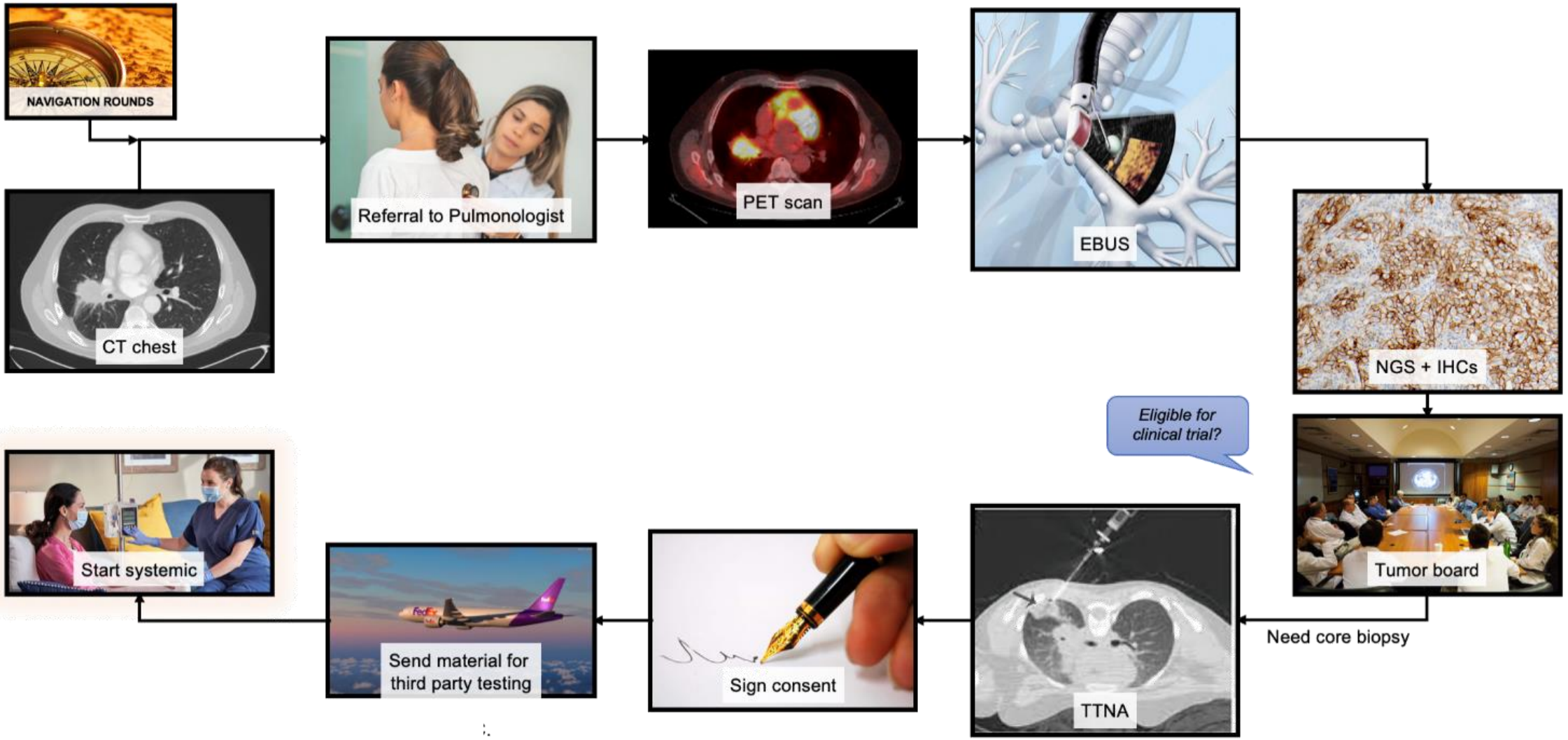
FIG. 3. Survival in lung cancer stratified by the extent of regional lymph node involvement (N factor), excluding undifferentiated small cell carcinoma.

What do we know about surgery for locally advanced NSCLC?

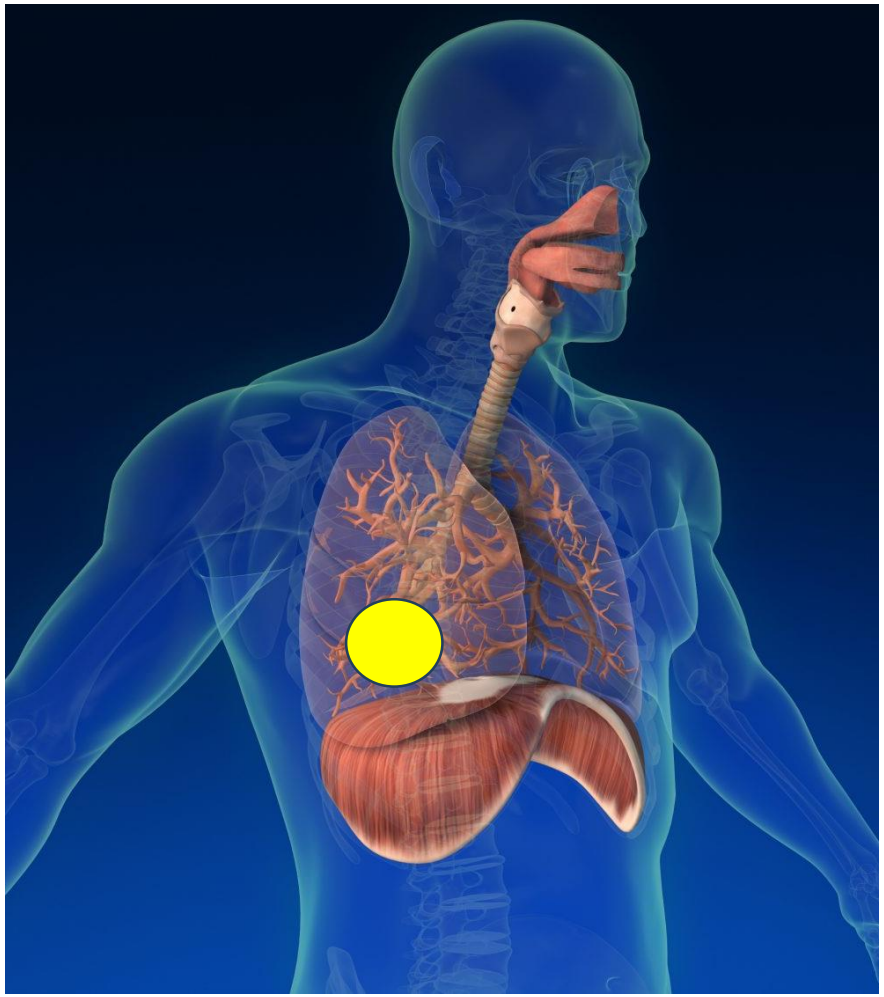


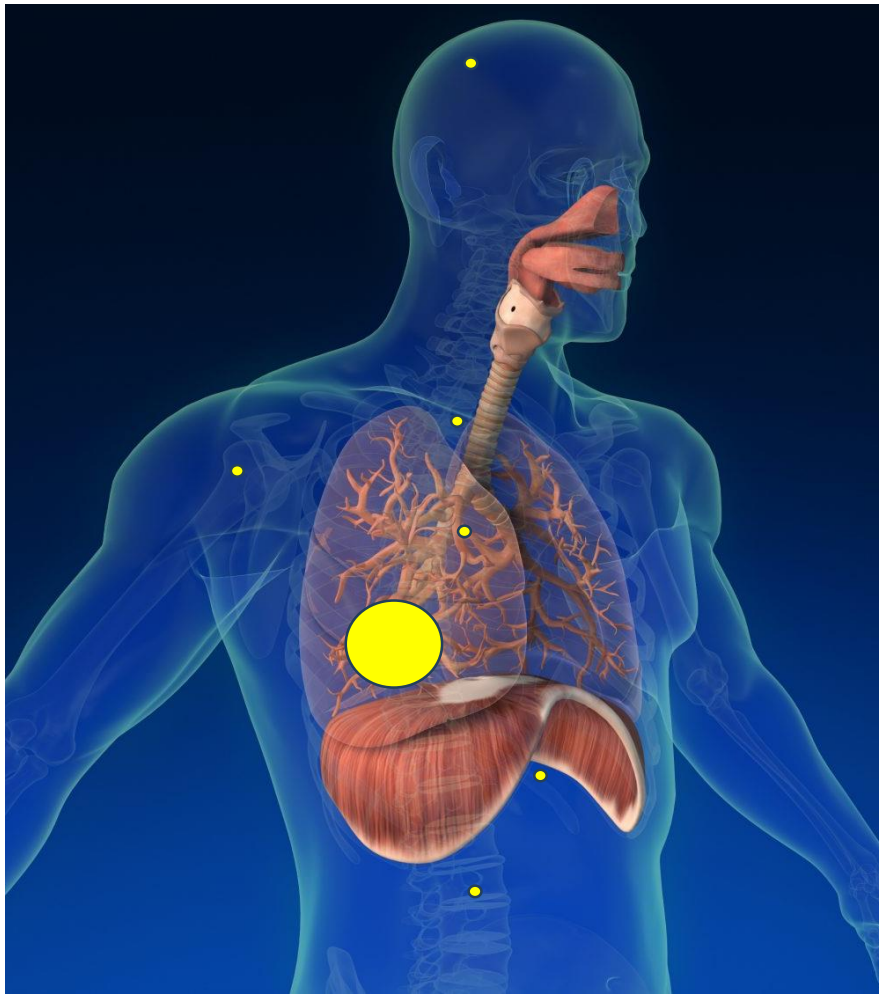
Felip et al, JCO 2010

Establishing TNM stage is a complex endeavour



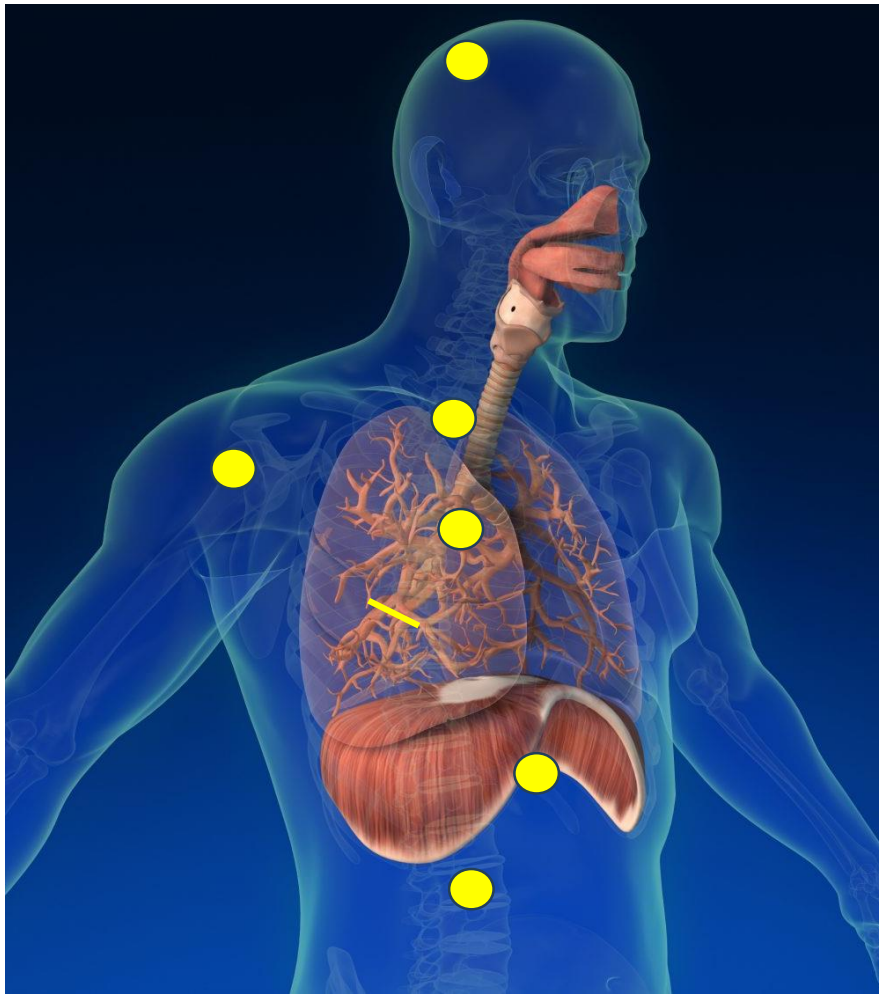
Despite our best efforts, current tech yields two indistinguishable patients in our clinics





Both patients had a contrast infused CT chest/abdo/pelvis, PET, EBUS and brain MRI!

Surgery has tremendous potential for cure, but also in isolation can be futile and harmful



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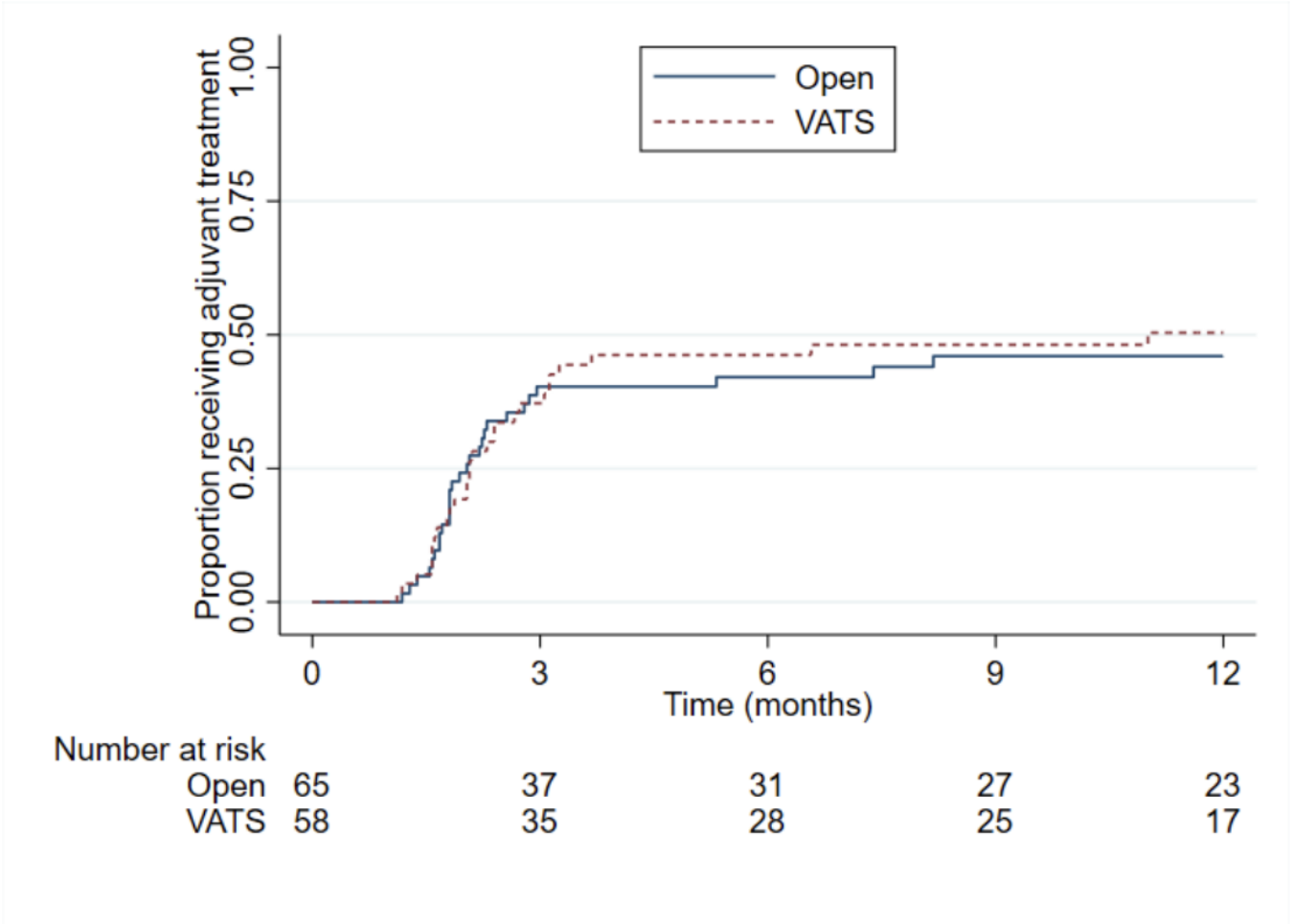
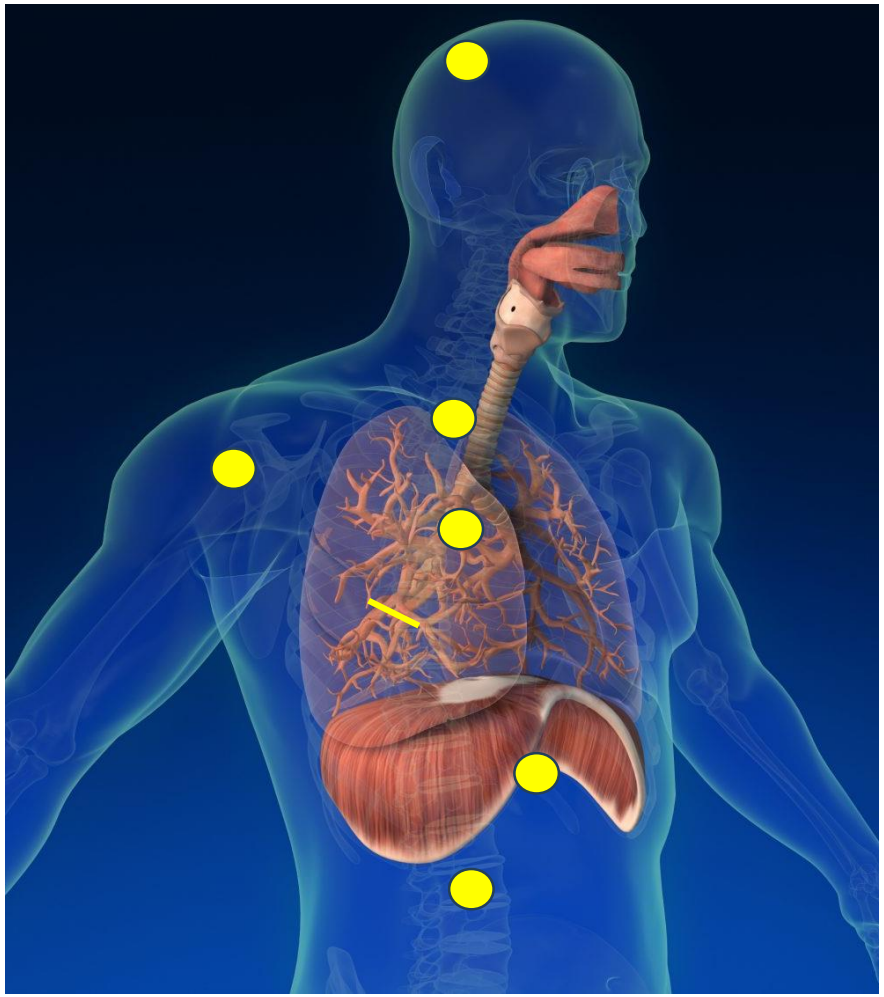
Indicated adjuvant therapy is inconsistently delivered…

Supplementary Figure S29 Uptake of adjuvant treatment: eligible cohort





Lim et al, NEJM Evidence 2022

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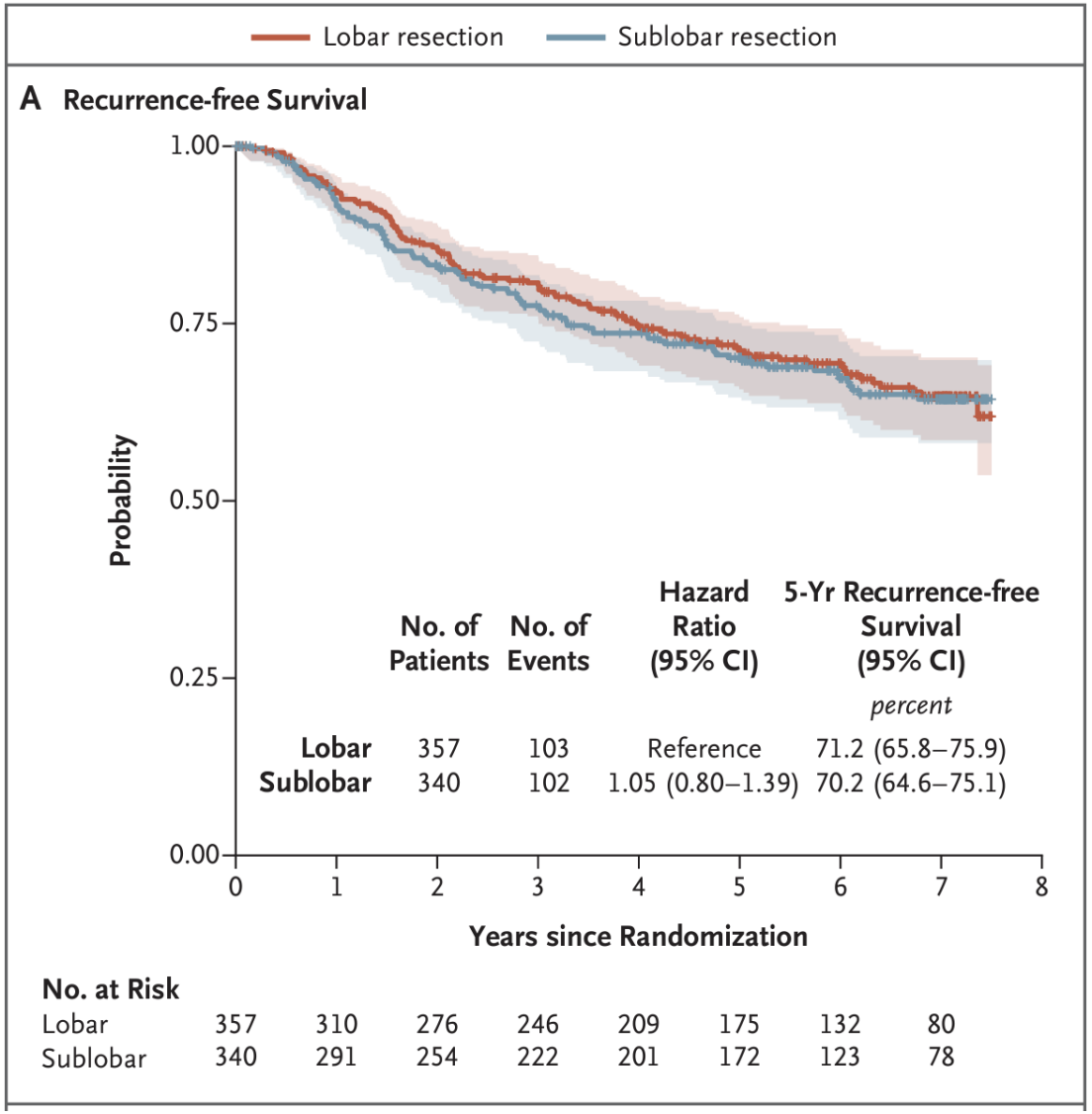
If TNM lung cancer staging and surgery were perfect…

We would not see this:



Altorki et al, NEJM 2023

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Osimert

Yi-Lon
Margarita M
Te
Charuwa
Manue
Ajlan Atasoy

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Alectinib in Resected *ALK*-Positive Non–Small-Cell Lung Cancer

Wu Y-L et al. DOI: 10.1056/NEJMoa2310532

Research

JAMA | Original Investigation

Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer

The Neotorch Randomized Clinical Trial

Shun Lu, MD; Wei Zhang, PhD; Lin Wu, PhD; Wenxiang Wang, PhD; Peng Zhang, PhD; and the Neotorch Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran,
Biswas,
nn,

NAL of MEDICINE

AUGUST 10, 2023 VOL. 389 NO. 6

rioperative Pembrolizumab
Stage Non–Small-Cell Lung Cancer

, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff,
O. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari,
J.D. Spicer, for the KEYNOTE-671 Investigators*

Because most of the time, we are operating on micrometastatic disease AND surgery is a really good form of local consolidative therapy!!!

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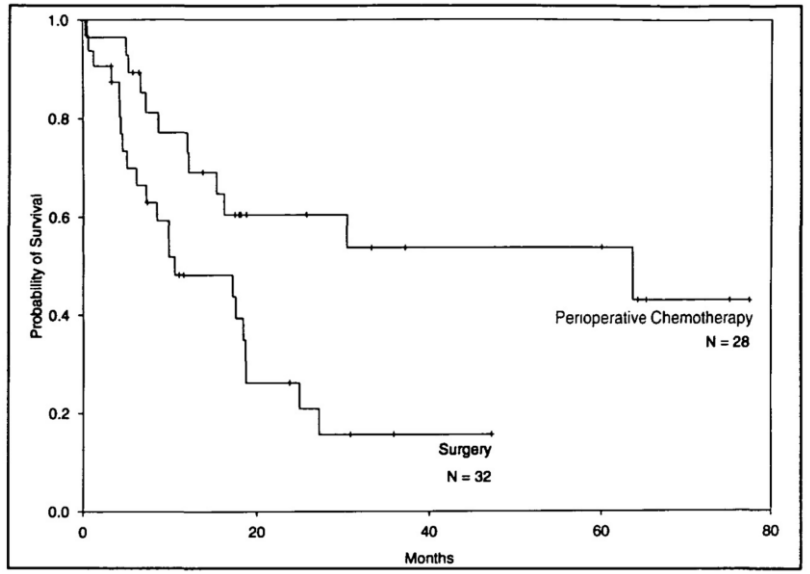
First evidence that effective systemic therapy changes outcomes is now 30 years old

A Randomized Trial Comparing Perioperative Chemotherapy and Surgery With Surgery Alone in Resectable Stage IIIA Non–Small-Cell Lung Cancer

*Jack A. Roth, Frank Fossella, Ritsuko Komaki, M. Bernadette Ryan, J. B. Putnam, Jr., Jin Soo Lee, Hari Dhingra, Louis De Caro, Marvin Chasen, Malcoln McGavran, E. Neely Atkinson, Waun Ki Hong**

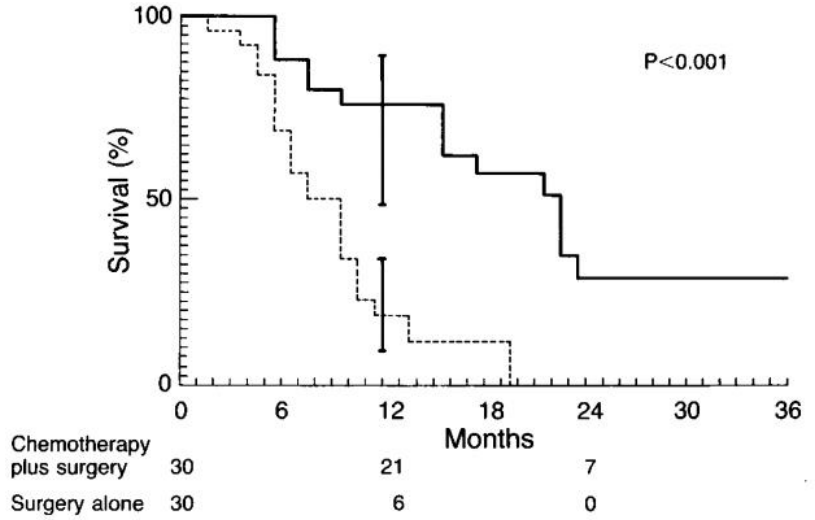


The New England Journal of Medicine

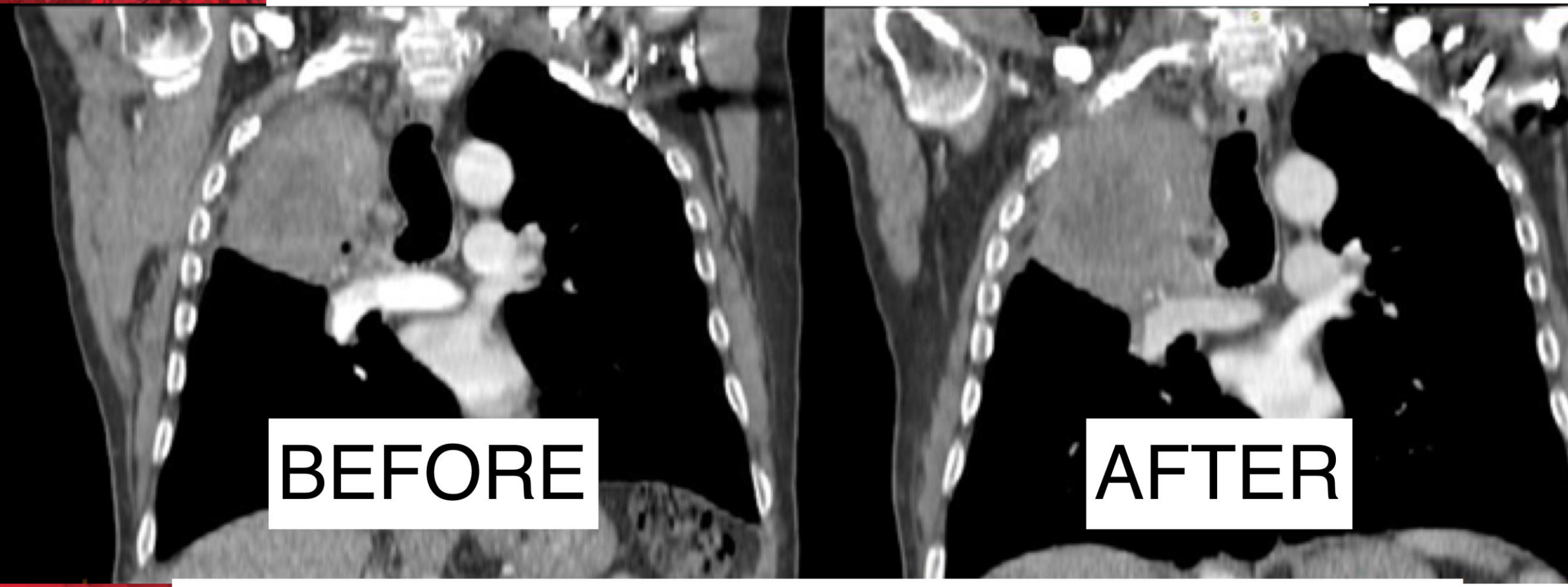
Volume 330 JANUARY 20, 1994 Number 3

A RANDOMIZED TRIAL COMPARING PREOPERATIVE CHEMOTHERAPY PLUS SURGERY WITH SURGERY ALONE IN PATIENTS WITH NON–SMALL-CELL LUNG CANCER

Rafael Rosell, M.D., Ph.D., José Gómez-Codina, M.D., Ph.D., Carlos Camps, M.D., José Maestre, M.D., Ph.D., José Padille, M.D., Antonio Cantó, M.D., José Luis Mate, M.D., Shanrong Li, M.D., Jorge Roig, M.D., Ph.D., Angel Olazábal, M.D., Ph.D., Mercedes Canela, M.D., Ph.D., Aurelio Ariza, M.D., Ph.D., Zdeněk Skácel, M.D., José Morera-Prat, M.D., Ph.D., and Albert Abad, M.D., Ph.D.



Checkmate 816 ➔ PD1+CTLA4



Open RUL: ypT4N1 squamous cell ca

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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[a] study design

Key Eligibility Criteria

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

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

R

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

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

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

Exploratory analysis populations[g]

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

Primary analysis (NIVO + chemo vs chemo)

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory analysis (NIVO + IPI vs chemo)

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

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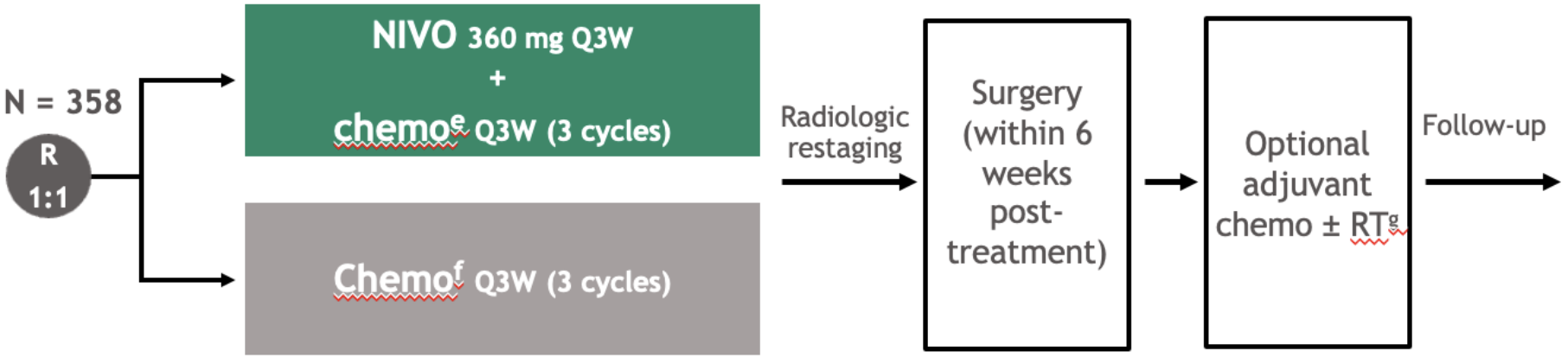
CheckMate 816 study design[a]

Key eligibility criteria

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

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



Primary endpoints
- pCR by BIPR
- EFS[h] by BICR

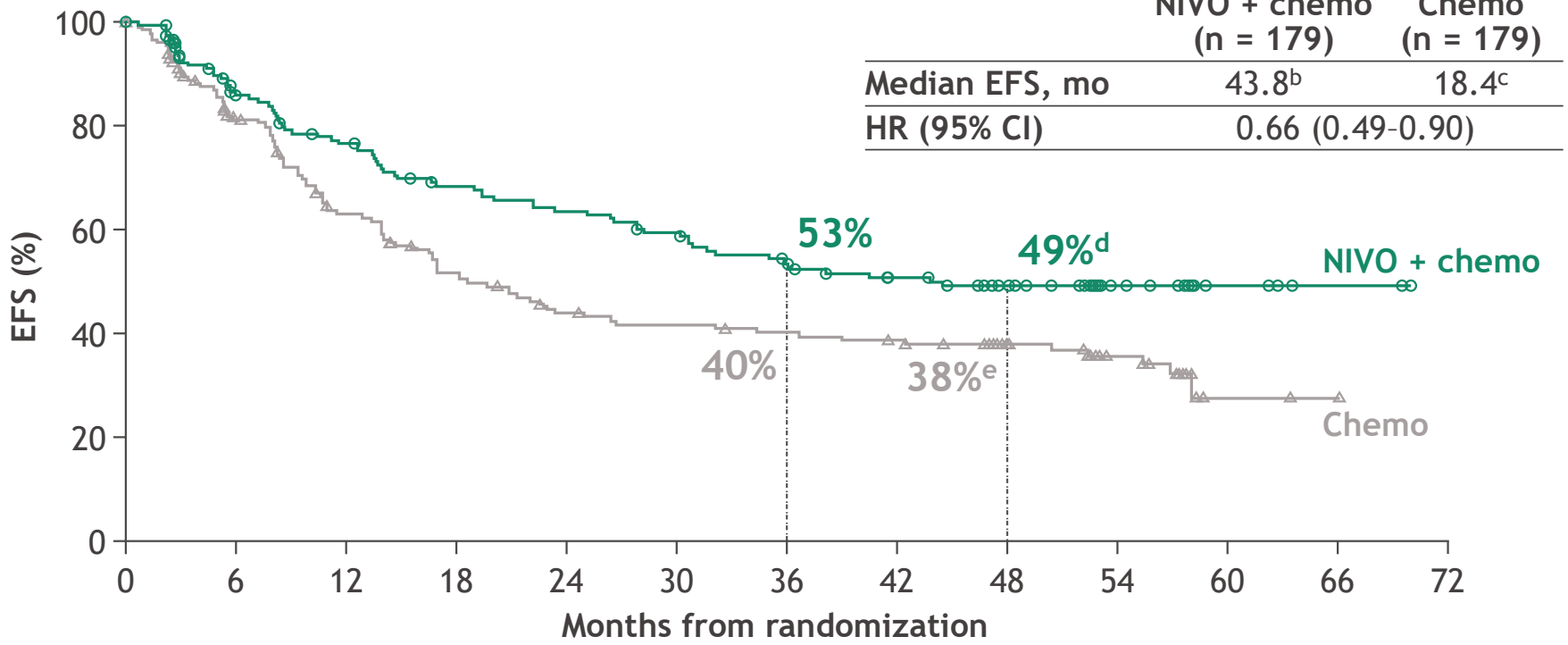
Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory analysis
- EFS by pCR status

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.

Spicer et al, ASCO 2024

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Subsequent anti-cancer therapy[a]

Patients, n (%)	Concurrently randomized patients		Patients with EFS events[b]	
	NIVO + chemo (n = 179)	Chemo (n = 179)	NIVO + chemo (n = 75)	Chemo (n = 101)
Any subsequent therapy	52 (29)	89 (50)	40 (53)	72 (71)
Radiotherapy	24 (13)	42 (24)	17 (23)	35 (35)
Surgery	5 (3)	9 (5)	5 (7)	7 (7)
Systemic therapy	44 (25)	75 (42)	33 (44)	63 (62)
Chemo	40 (22)	47 (26)	30 (40)	39 (39)
Immunotherapy	18 (10)	48 (27)	16 (21)	42 (42)
VEGFR inhibitors	12 (7)	16 (9)	11 (15)	15 (15)
EGFR/ALK TKIs	5 (3)	11 (6)	2 (3)	10 (10)
Other targeted therapy	0	4 (2)[c]	0	3 (3)[d]
Other systemic therapy	1 (1)	8 (4)	0	6 (6)

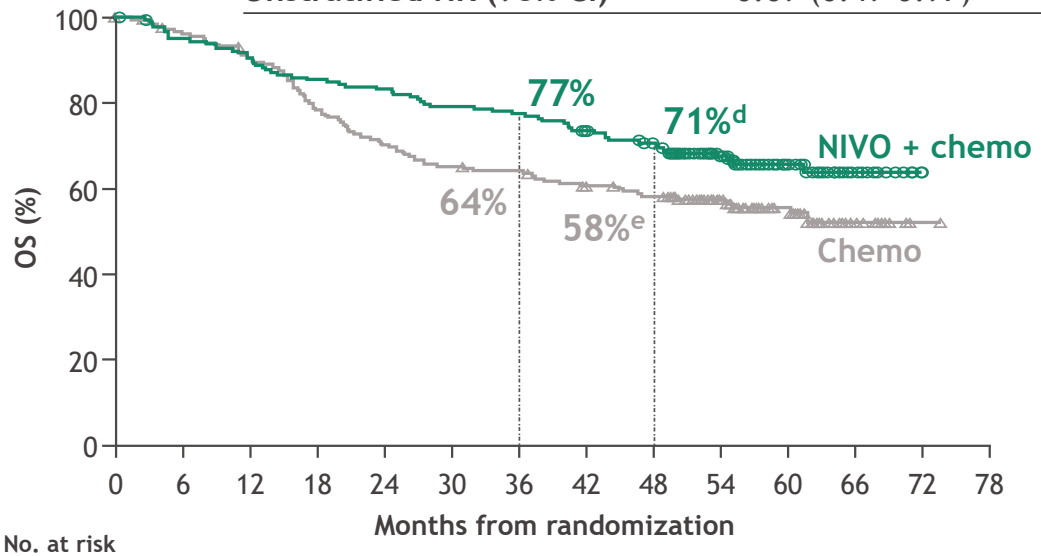
[a]Subsequent therapy was defined as therapy started on or after the first study treatment dosing date (randomization date if the patient was never treated), outside of protocol-specified adjuvant therapy. Patients may have received ≥ 1 type of subsequent therapy. [b]EFS events shown here are per investigator evaluation (not BICR). [c]Included amivantamab, capmatinib, entrectinib, pralsetinib, and regorafenib (n = 1 for each). [d]Included amivantamab, capmatinib, entrectinib, and pralsetinib (n = 1 for each).

Spicer et al, ASCO 2024

OS and lung cancer-specific survival: 4-year update

OS

	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)	

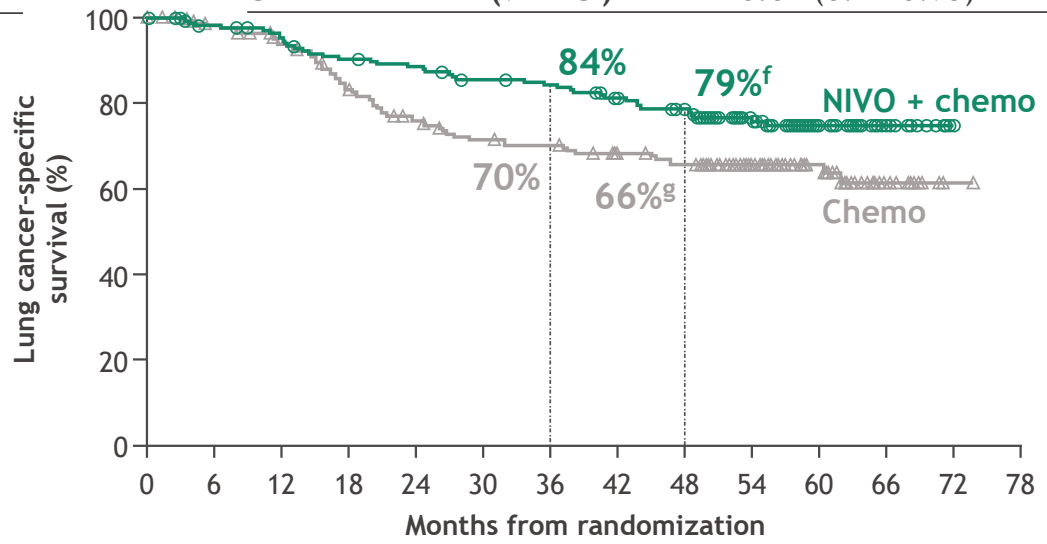


No. at risk

179	168	160	151	147	140	137	129	120	84	41	14	0	0
179	169	158	138	123	114	111	103	97	68	36	12	1	0

Lung cancer-specific survival[h]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median lung cancer-specific survival, mo	NR	NR
Unstratified HR (95% CI)	0.62 (0.41–0.93)	



179	168	160	151	147	140	137	129	120	84	41	14	0	0
179	169	158	138	123	114	111	103	97	68	36	12	1	0

- Patients in the NIVO + chemo arm who had pCR continued to have improved OS vs those who did not (HR [95% CI], 0.08 [0.02–0.34]; **4-year OS rates, 95% vs 63%**)

Minimum/median follow-up, 49.1/57.6 months.
[a]Reasons for OS events (deaths) in all treated patients in the NIVO + chemo vs chemo arms (N = 176 in each arm) were disease (23% vs 33%), study drug toxicity (0% vs 2%), unknown (3% vs 3%), and other (7% vs 5%). [b]Significance boundary for OS (0.0164) was not met at this interim analysis. [c–g]95% CI: [c]50.4–NR; [d]63–77; [e]50–65; [f]72–84; [g]58–72. [h]Exploratory analysis; events were deaths with noted reason of "disease" per investigator assessment.

Spicer et al, ASCO 2024

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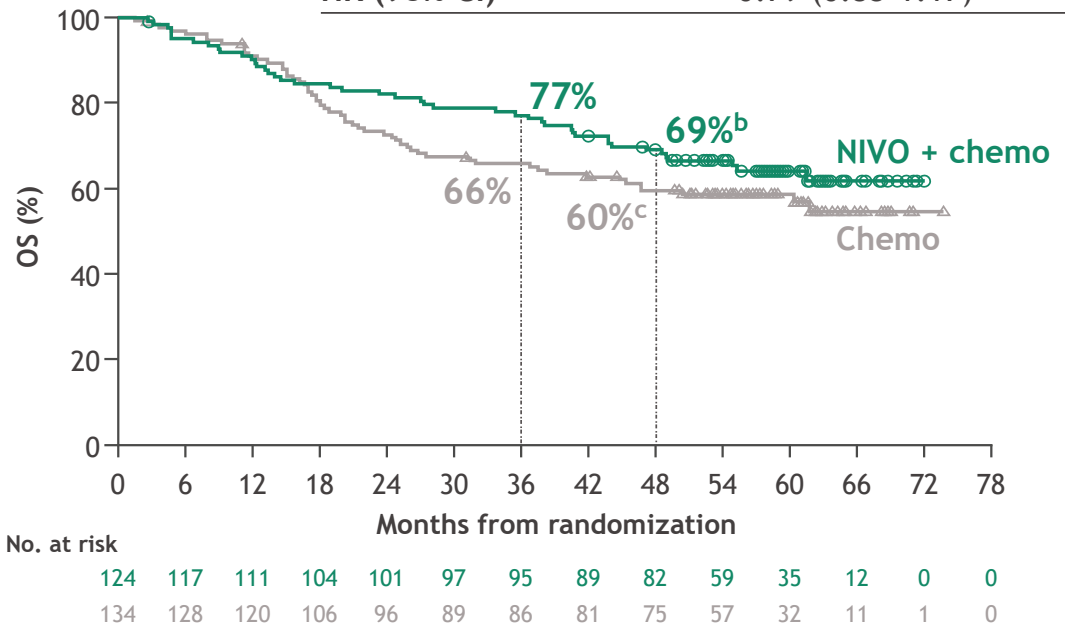
OS by neoadjuvant platinum chemo received

Cisplatin

	NIVO + chemo (n = 124)	Chemo (n = 134)
Median OS, mo	NR	NR[a]
HR (95% CI)	0.79 (0.53-1.17)	

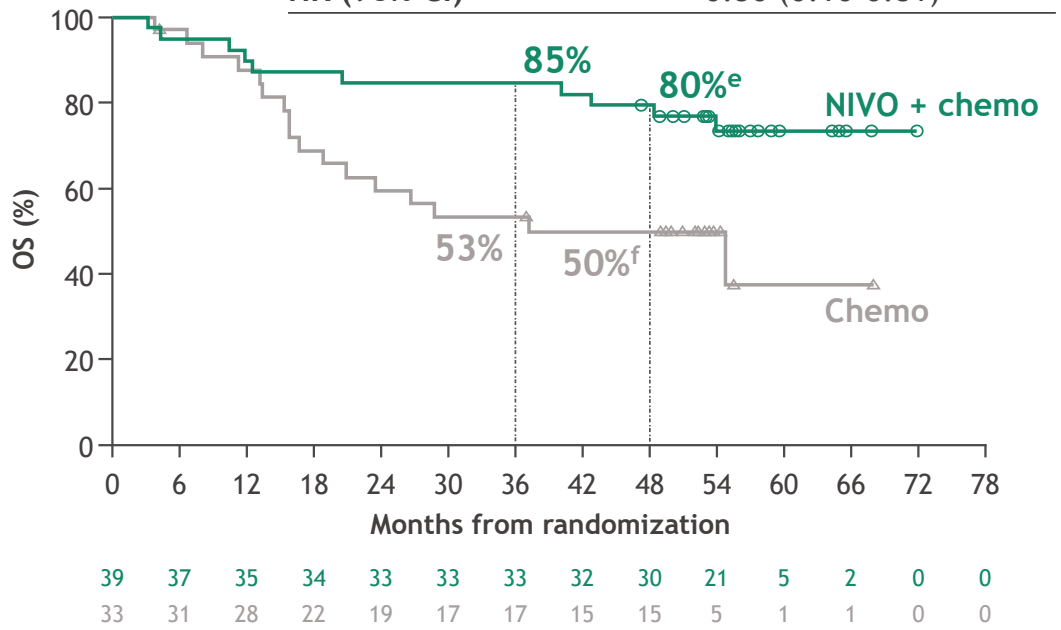


No. at risk

124	117	111	104	101	97	95	89	82	59	35	12	0	0
134	128	120	106	96	89	86	81	75	57	32	11	1	0

Carboplatin

	NIVO + chemo (n = 39)	Chemo (n = 33)
Median OS, mo	NR	37.2[d]
HR (95% CI)	0.36 (0.16-0.81)	



39	37	35	34	33	33	33	32	30	21	5	2	0	0
33	31	28	22	19	17	17	15	15	5	1	1	0	0

Minimum/median follow-up, 49.1/57.6 months.
[a-f]95% CI: [a]50.4-NR; [b]60-76; [c]51-68; [d]16.8-NR; [e]63-89; [f]32-66.

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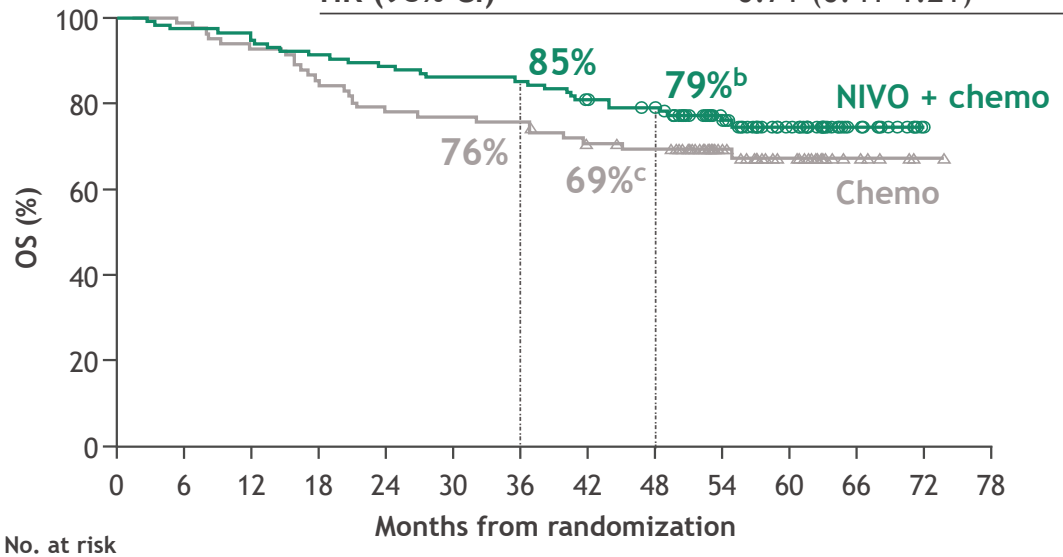
OS by extent of resection[a]

Lobectomy

	NIVO + chemo (n = 115)	Chemo (n = 82)
Median OS, mo	NR	NR
HR (95% CI)	0.71 (0.41–1.21)	

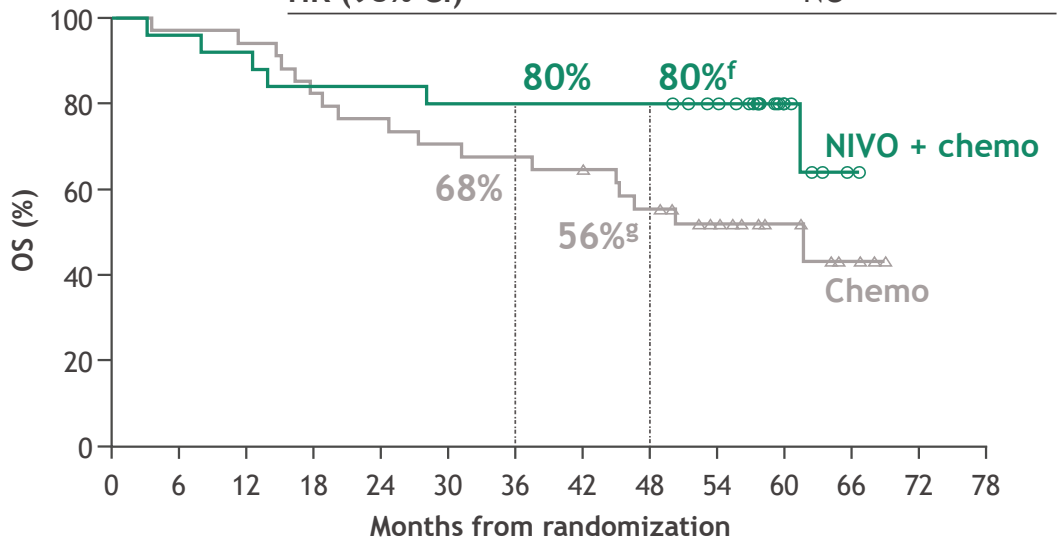


No. at risk

115	112	109	105	102	99	98	92	87	58	33	13	0	0
82	81	76	70	64	63	62	56	54	33	20	6	1	0

Pneumonectomy

	NIVO + chemo (n = 25)	Chemo (n = 34)
Median OS, mo	NR[d]	61.8[e]
HR (95% CI)	NC	



25	24	23	21	21	20	20	20	20	17	7	1	0	0
34	33	32	28	26	24	23	22	18	13	7	3	0	0

- 4-year EFS rates were 56%[h] with NIVO + chemo vs 43%[i] with chemo in patients with lobectomy (HR, 0.59; 95% CI, 0.39–0.90) and 57%[j] vs 40%[k] in patients with pneumonectomy (HR, NC)

Minimum/median follow-up, 49.1/57.6 months.
HRs were NC if there was an insufficient number of events (< 10 per arm). [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]). [b-k]95% CI: [b]70-86; [c]58-78; [d]61.5-NR; [e]31.2-NR; [f]58-91; [g]37-70; [h]46-65; [i]32-54; [j]33-75; [k]22-56.

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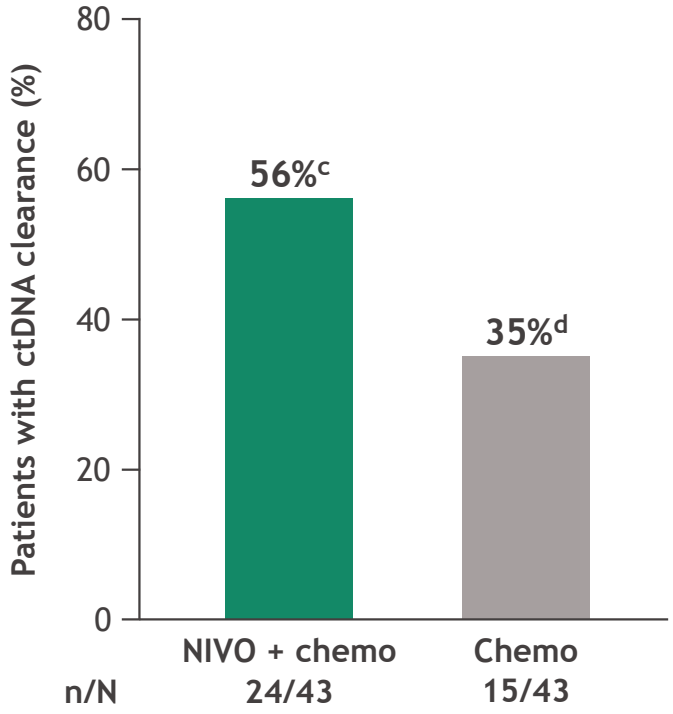
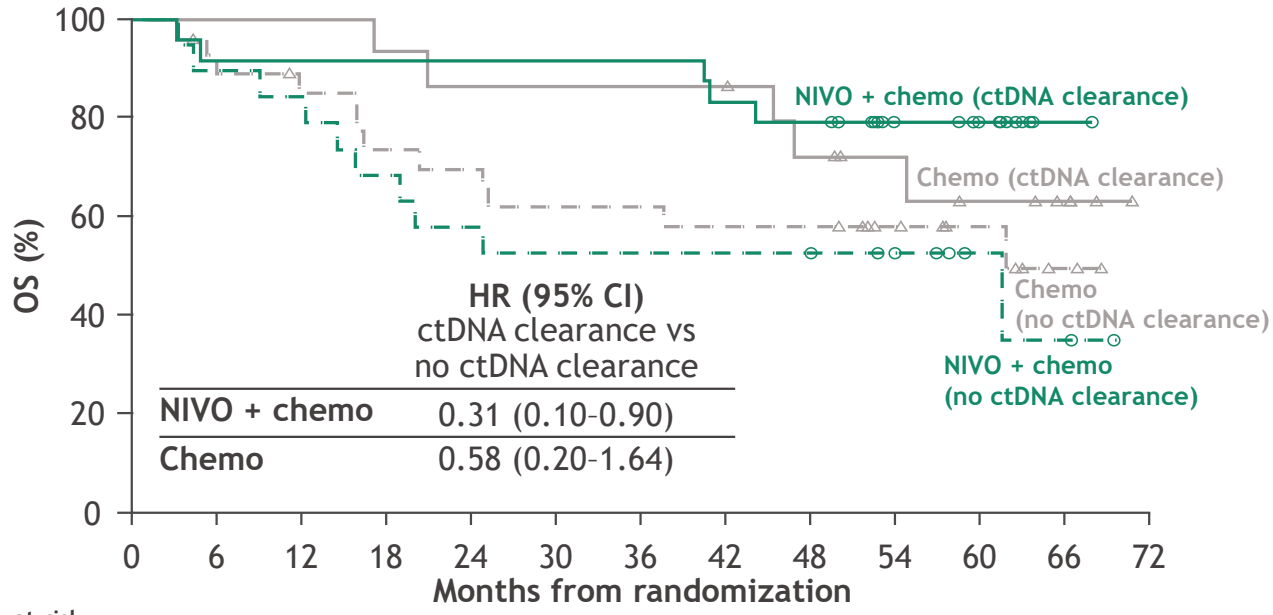
ctDNA clearance rate and OS by ctDNA clearance

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

ctDNA clearance rate[1,b]



OS



No. at risk													
ctDNA clearance	24	22	22	22	22	22	22	20	19	12	9	2	0
ctDNA clearance	15	15	15	14	13	13	13	13	10	8	6	4	0
No ctDNA clearance	19	17	16	13	11	10	10	10	9	7	3	2	0
No ctDNA clearance	28	24	22	19	18	16	16	15	15	11	7	2	0

Minimum/median follow-up, 49.1/57.6 months.
[a]The main reasons for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma. [b]ctDNA clearance was defined as pre-surgical change from detectable ctDNA levels before cycle 1 to undetectable ctDNA levels before cycle 3. Analysis was performed using a WES tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring). [c,d]95% CI: [c]40-71; [d]21-51. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.

Spicer et al, ASCO 2024

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Safety summary[a]

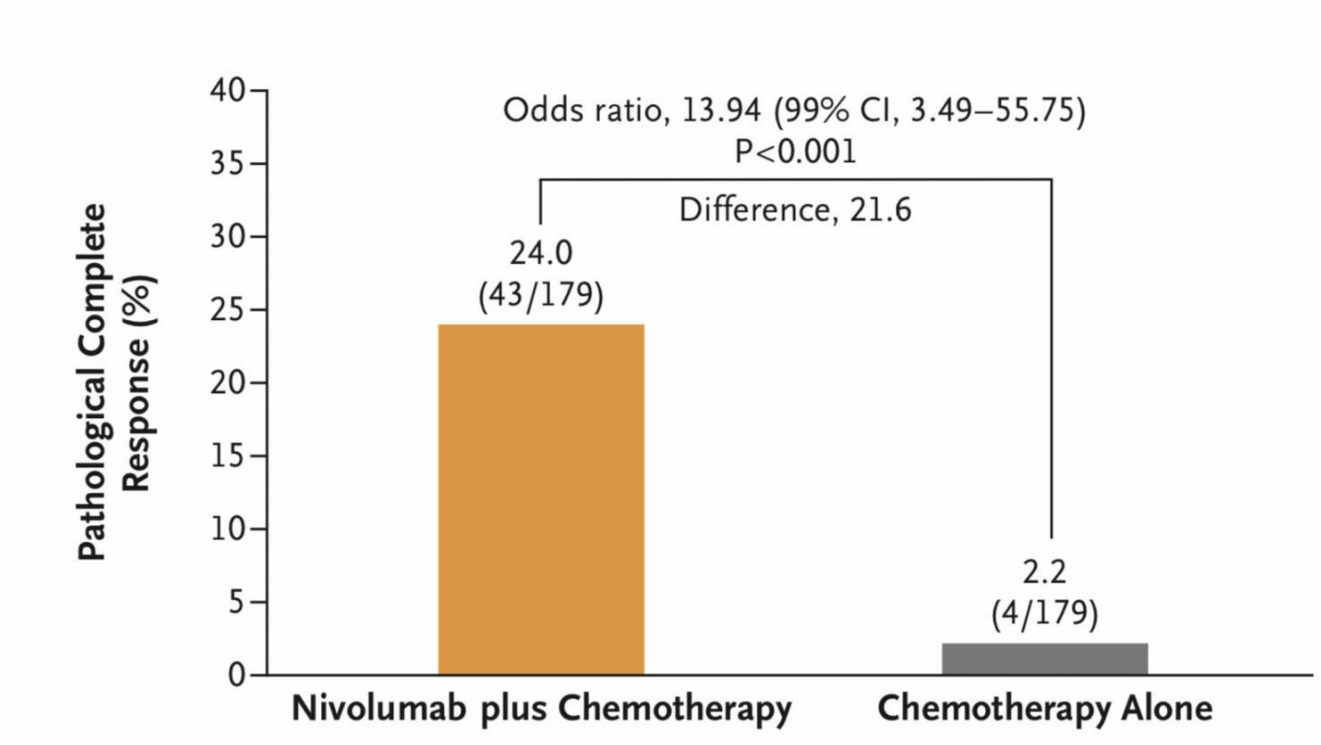
Patients, n (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs[b]	165 (94)	76 (43)	173 (98)	79 (45)
TRAEs[b]	147 (84)	63 (36)	159 (90)	67 (38)
All AEs leading to discontinuation[b]	19 (11)	10 (6)	20 (11)	7 (4)
TRAEs leading to discontinuation[b]	19 (11)	10 (6)	17 (10)	6 (3)
All SAEs[b]	30 (17)	19 (11)	24 (14)	17 (10)
Treatment-related SAEs[b]	21 (12)	15 (8)	18 (10)	14 (8)
Surgery-related AEs[c]	67 (45)	17 (11)	66 (49)	20 (15)
Treatment-related deaths[d]	0		3 (2)[e]	

- Grade 5[f] surgery-related AEs occurred in 2 patients in the NIVO + chemo arm (1 each due to pulmonary embolism and aortic rupture); both were unrelated to study drug

[a]AEs per CTCAE v4.0 and MedDRA v26.1. [b]Includes events reported between the first neoadjuvant dose and 30 days after the last dose of neoadjuvant study treatment. [c]Includes events reported within 90 days after definitive surgery. Percentages calculated from treated patients who had definitive surgery (n = 149 in the NIVO + chemo arm; n = 135 in the chemo arm). [d]Treatment-related deaths occurring at any time after the first dose of neoadjuvant study treatment. [e]Due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis (n = 1), and pneumonia (n = 1). [f]AEs that led to death within 24 hours of onset.

Spicer et al, ASCO 2024

Medical oncologists can achieve RO!



Forde et al, NEJM 2022

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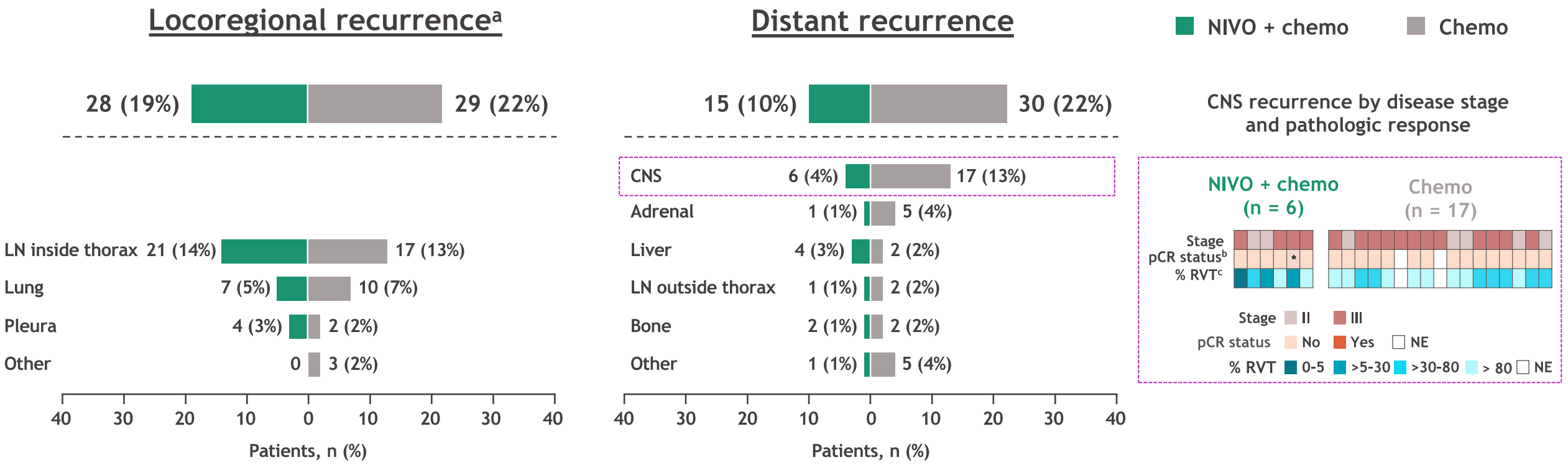
19% locoregional failure in CM816



Forde et al, ELCC 2023

De facto, resectability is defined by our ability to achieve locoregional control with surgery

Need to fully define the patterns of locoregional progression, to understand to what extent they represent a failure of surgical technique

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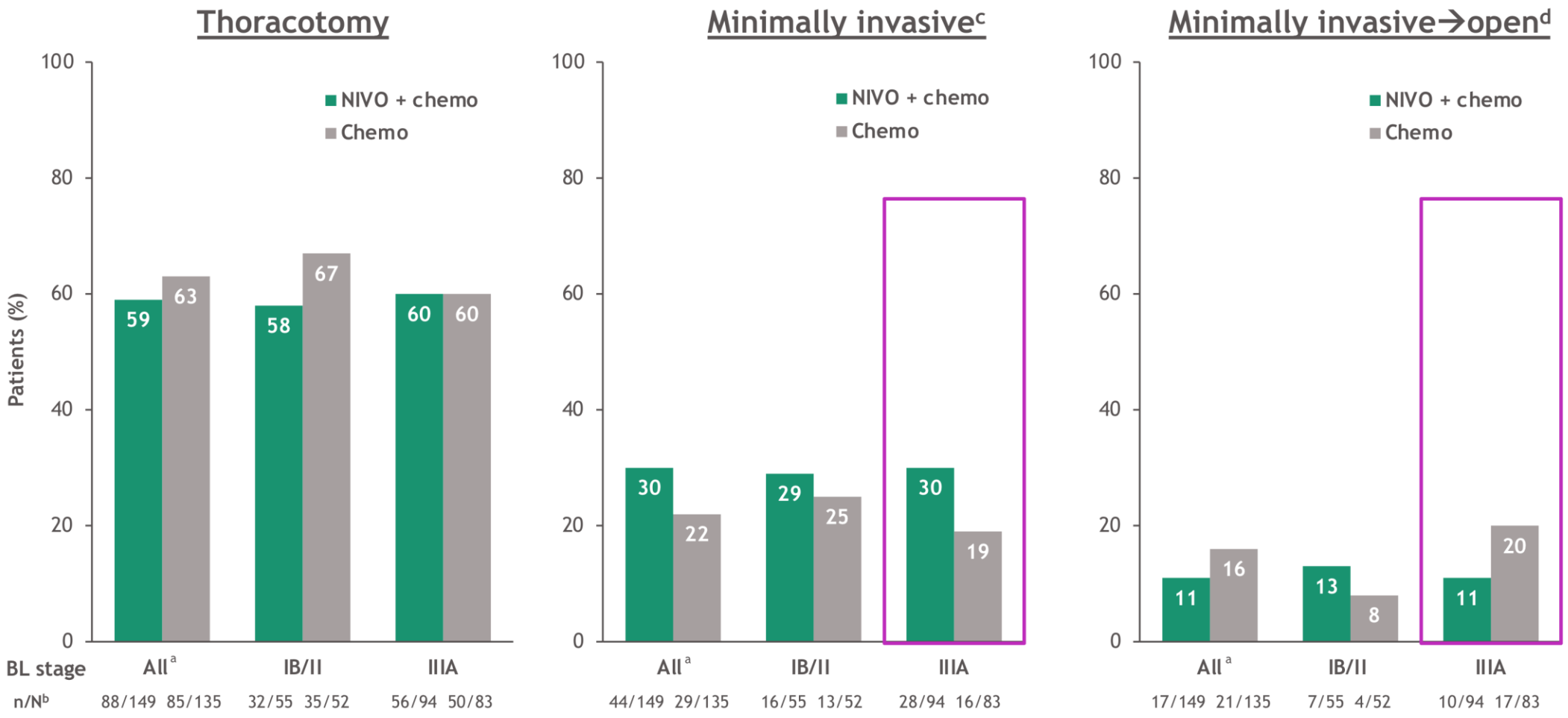
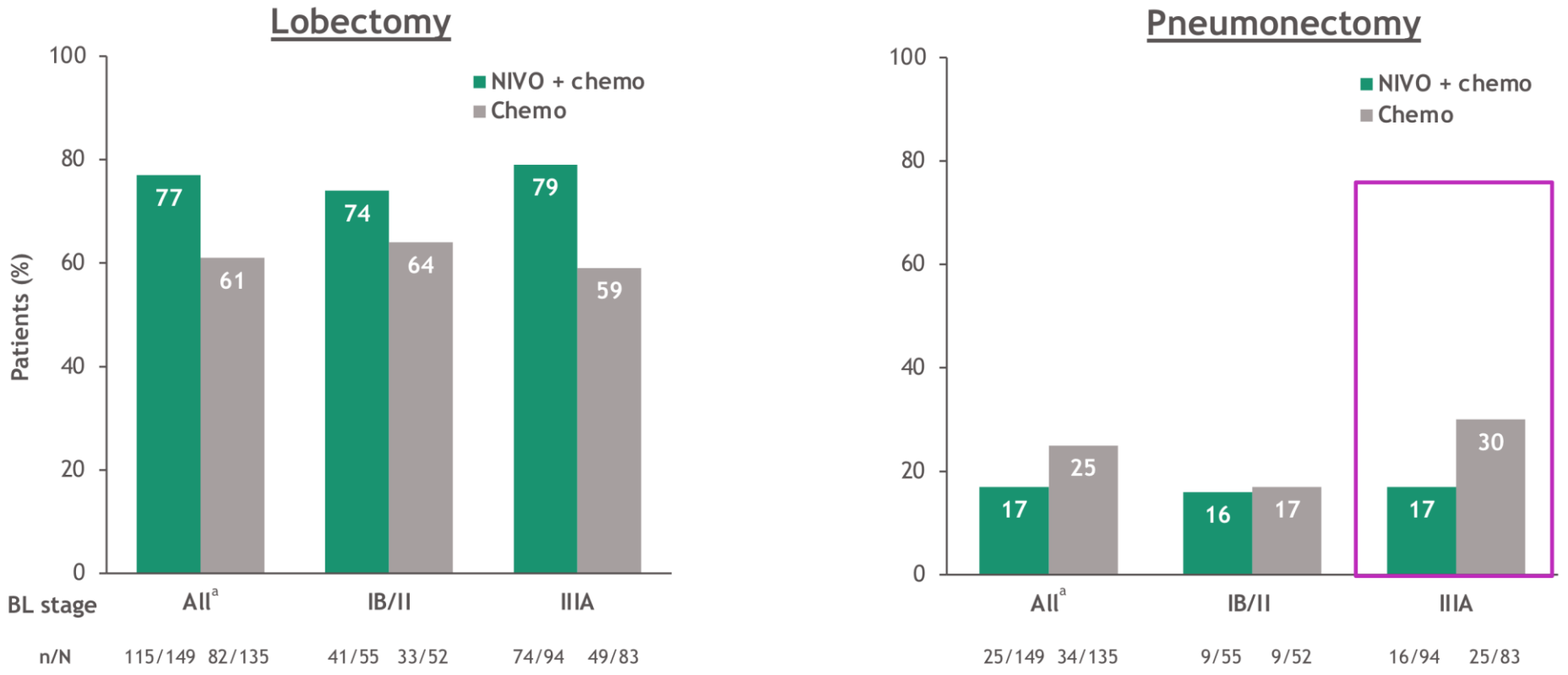
Surgical approach by baseline stage of disease



[a]Patients with all baseline stages of disease and definitive surgery; [b]Denominator based on patients with definitive surgery; [c]Thoracoscopic/robotic; [d]Minimally invasive to thoracotomy.

Spicer et al, ASCO 2022

Type of surgery by baseline stage of disease

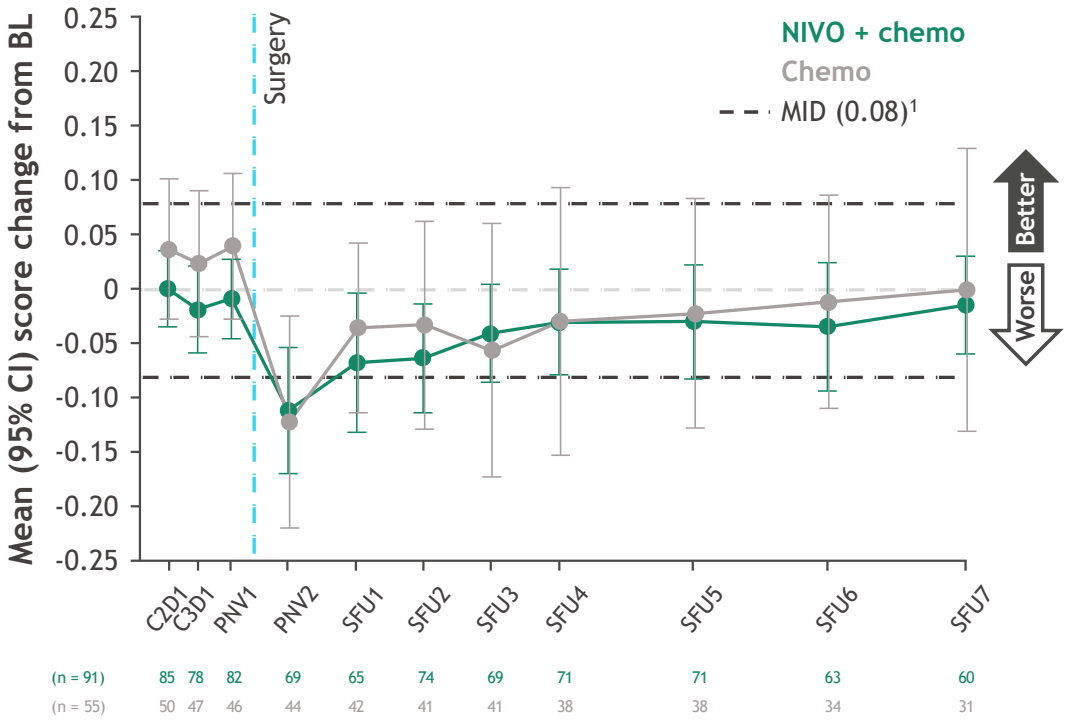


Patients may have had > 1 surgery type. Patient numbers (n/N) for stage IB/II and stage IIIA, respectively, for bilobectomy (NIVO + chemo: 1/55, 2/94; chemo: 2/52, 2/83), sleeve lobectomy (NIVO + chemo: 2/55, 0/94; chemo: 5/52, 5/83), and other (NIVO + chemo: 13/55, 11/94; chemo: 12/52, 9/83). [a]Patients with all baseline stages of disease with surgery.

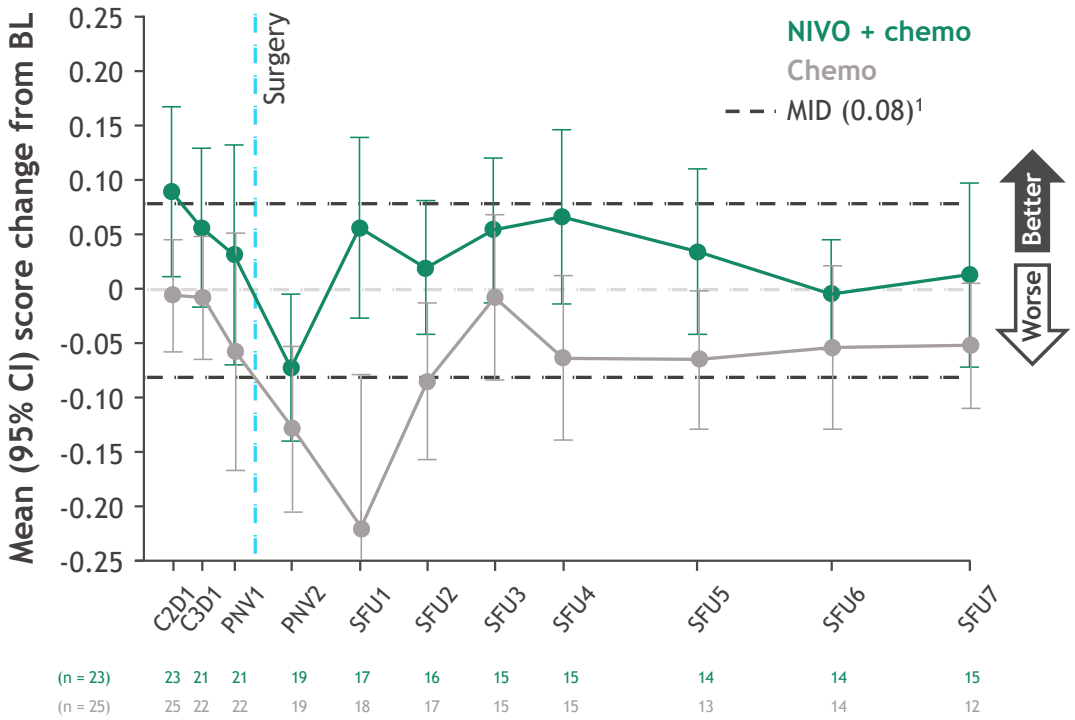
Spicer et al, ASCO 2022

EQ-5D UI mean change from baseline by type of surgery

Lobectomy



Pneumonectomy



The EQ-5D-3L UK UI ranges from -0.594 to 1 with a higher score indicating a more favorable health state. Patients included in this analysis had definitive surgery and did not receive adjuvant therapy. Patients may have had ≥ 1 type of surgery. 1. Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70.

Spicer et al, AATS 2024

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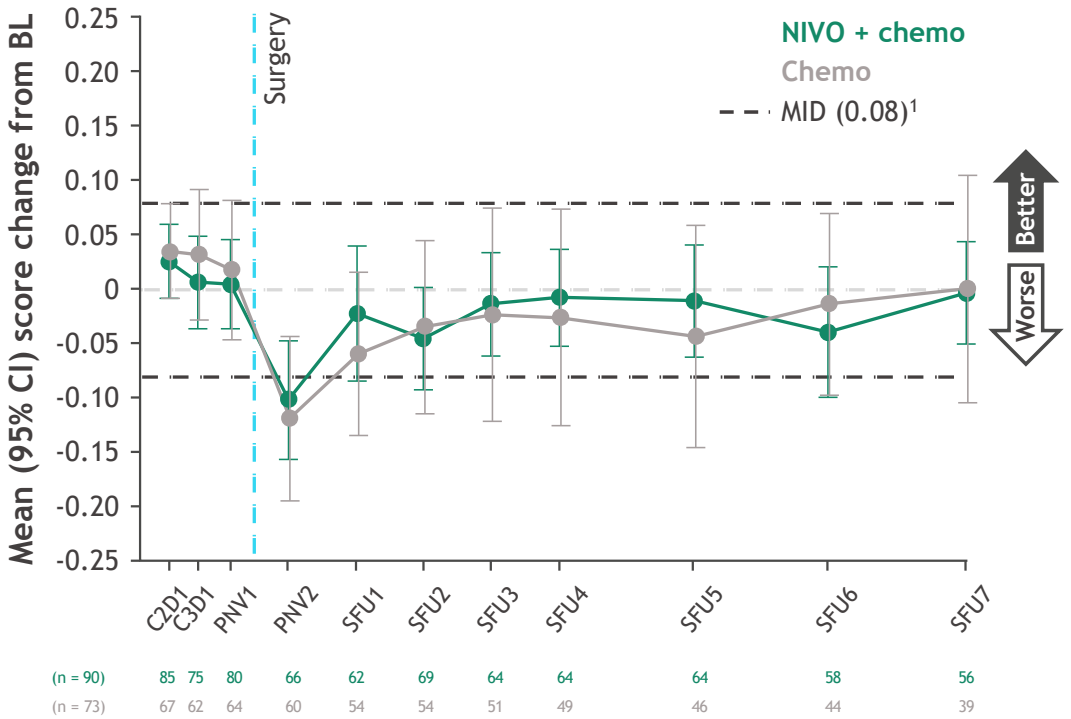
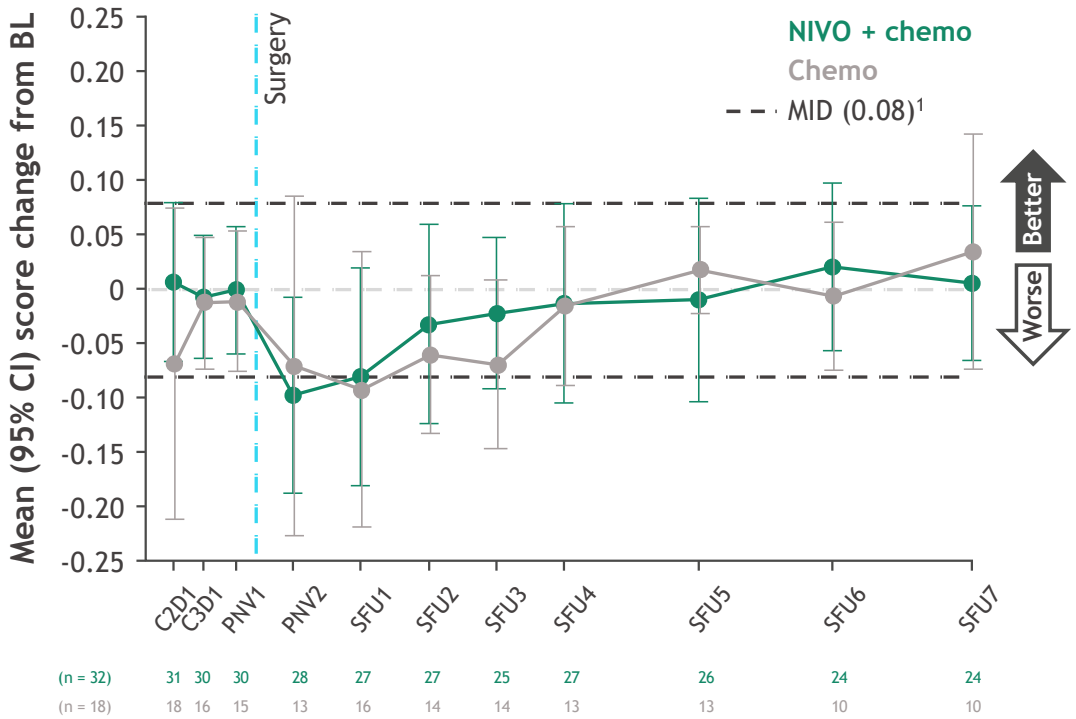
EQ-5D UI mean change from baseline by surgical approach

Thoracotomy/ minimally invasive to thoracotomy



Minimally invasive[a]



The EQ-5D-3L UK UI ranges from -0.594 to 1 with a higher score indicating a more favorable health state. Patients included in this analysis had definitive surgery and did not receive adjuvant therapy. Patients may have had ≥ 1 surgical approach. [a]Includes minimally invasive-thoracoscopic/robotic approaches. 1. Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70.

Spicer et al, AATS 2024

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Key points from CM816

- Pure neoadjuvant chemo-immunotherapy offers prolonged survival advantage
- No measurable increase in toxicity compared to chemotherapy alone
- OS is improved regardless of platinum employed
- OS is improved regardless of extent of surgery (pneumonectomy is viable option)
- ctDNA clearance may inform likelihood of PCR and could provide decisional endpoint in future trial design
- Measurable surgical benefits in an open label design
- Rapid return to baseline QoL without impact of surgical access or extent of resection

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	CM816 (CTx-Nivo)	77T (CTx-Nivo)	AEGEAN (CTx-Durva)	Neotorch (CTx-Tori)	KN671 (CTx-Pembro)	Rationale-315 (CTx-Tisli)
N	358 1:1	461 1:1	740 1:1	404 1:1	797 1:1	453 1:1
Endpoints	PCR, EFS	EFS	PCR, EFS	MPR, EFS	EFS, OS	MPS, EFS
Stages (AJCC 8)	II-IIIB	II-IIIB	II-IIIB	III	II-IIIB	II-IIIA
Systemic plan	Neoadj	Periadj	Periadj	Periadj	Periadj	Periadj
Surgery	83%	78%	81%	82%	82%	84.1%
90-d mortality	3.4%	N/A	N/A	N/A	4%	1.6%
R0 rate	83%	89%	95%	96%	92%	95%
EFS @ 2 years	65%	70% (18 mo)	63.3%	67%	62%	68%
OS @ 2 years	82.7% (HR 0.57)	N/A	N/A	81.2% (HR 0.62)	82% (HR 0.72)	88.6% (HR 0.62)

Immunotherapy for locally advanced resectable NSCLC is here to stay!

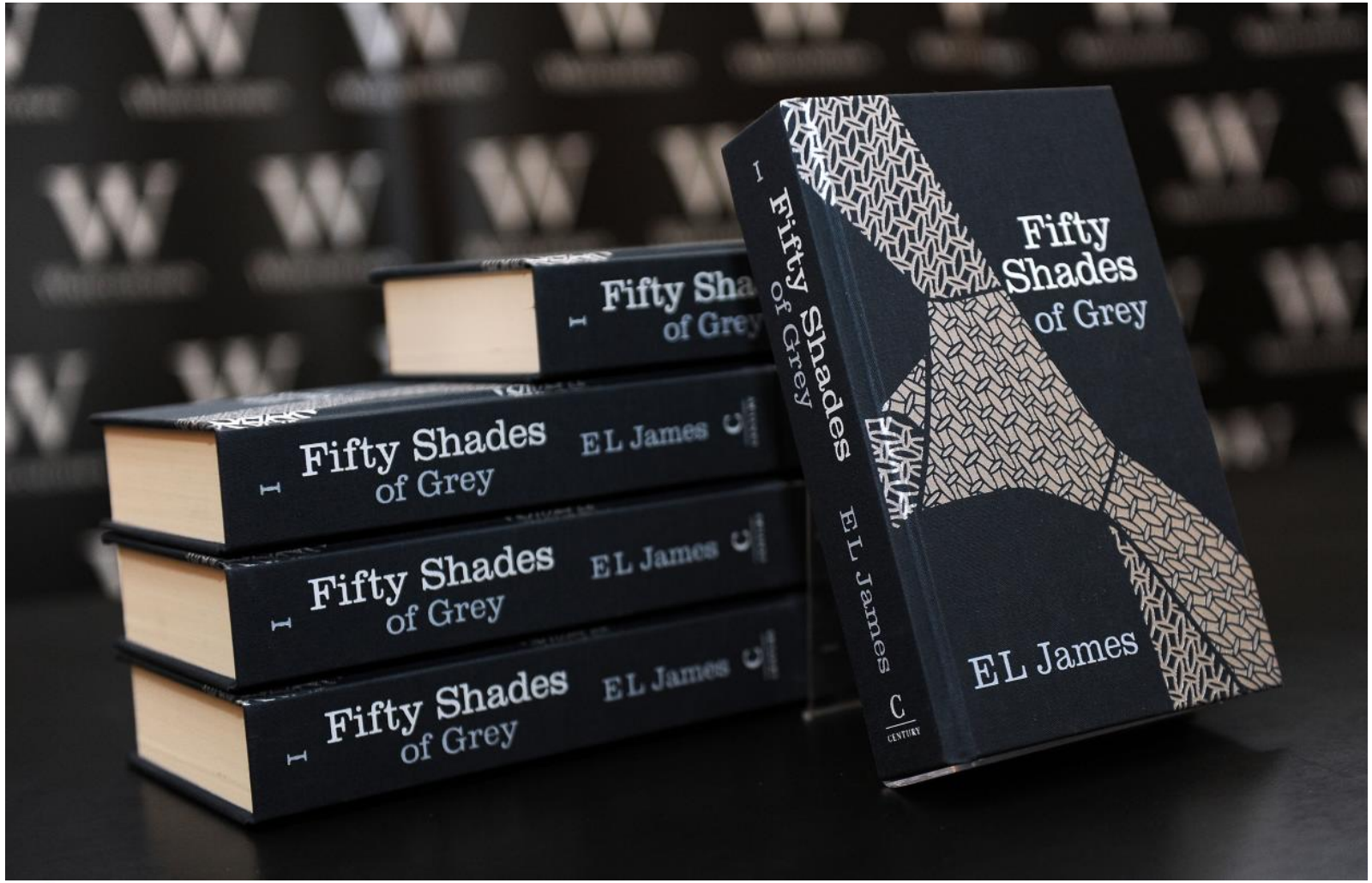
	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY[¶]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE*[§]	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined

[¶]**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed

[§]Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Does stage define resectability or is it defined by a matrix of individualized factors?



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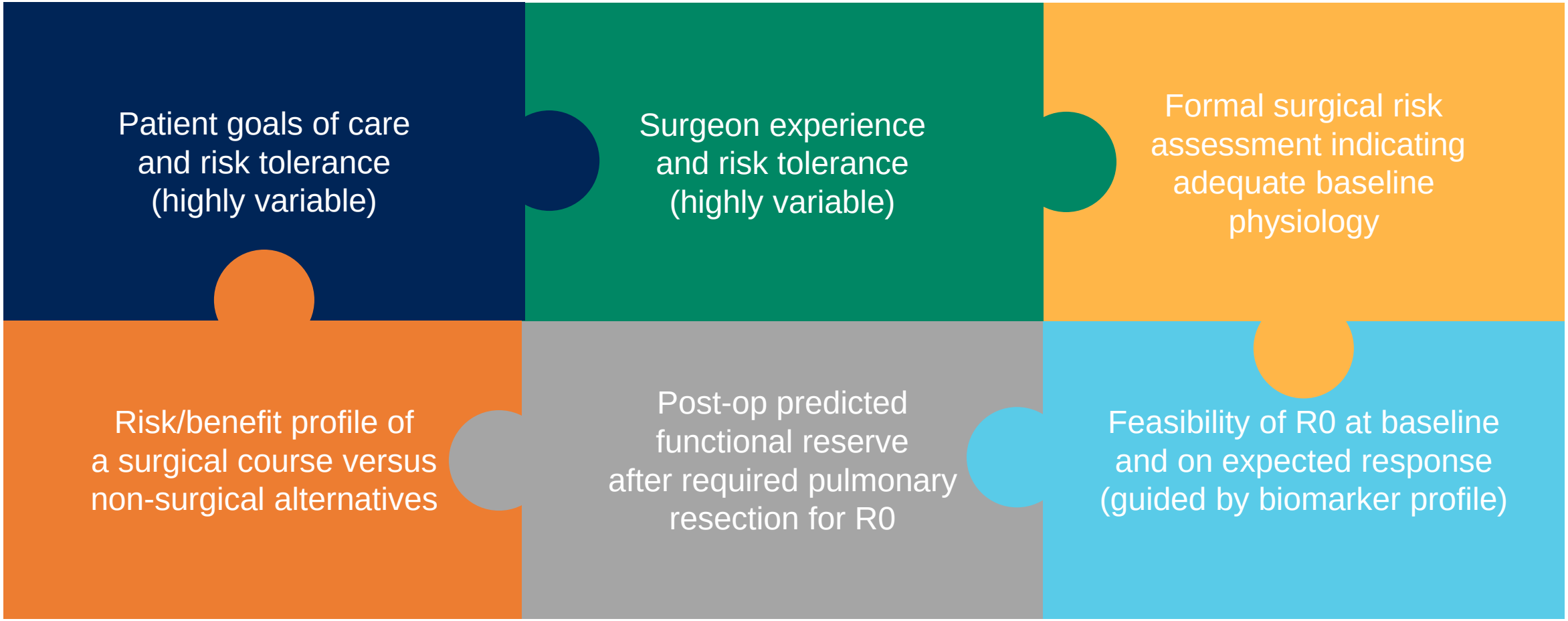
Department of Surgery

Resectability Criteria



R Manochakian, MD, FASCO, J Spicer, MD, PhD, FRCPC, H Park, MD, MPH, A Dingemans MD PhD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Nivolumab in Resectable Lung Cancer

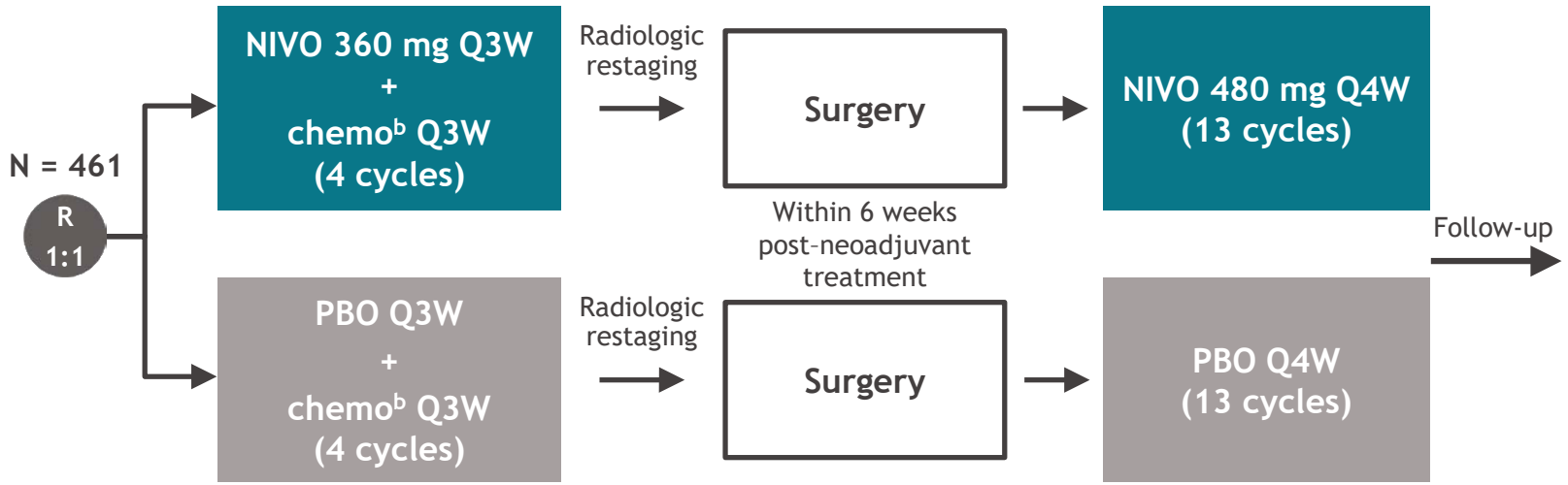
T. Cascone, M.M. Awad, J.D. Spicer, J. He, S. Lu, B. Sepesi, F. Tanaka, J.M. Taube, R. Cornelissen, L. Havel,* N. Karaseva, J. Kuzdzal, L.B. Petruzelka, L. Wu, J.-L. Pujol, H. Ito, T.-E. Ciuleanu, L. de Oliveira Muniz Koch, A. Janssens, A. Alexandru, S. Bohnet, F.V. Moiseyenko, Y. Gao, Y. Watanabe, C.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

CheckMate 77T[a] study design

Key eligibility criteria

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

Stratified by histology (NSQ vs SQ), disease stage (II vs III), and tumor PD-L1 ☎ 🗁❖🖫🗁vs not evaluable/indeterminate)



Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR by BIPR
- MPR by BIPR
- OS
- Safety

Exploratory analyses
- **Clinical outcomes by clinical stage III N2 or non-N2 status**

Database lock date: September 6, 2023; median follow-up (range): 25.4 months (15.7-44.2).

[a]NCT04025879. [b]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel.

Cascone et al, NEJM 2024

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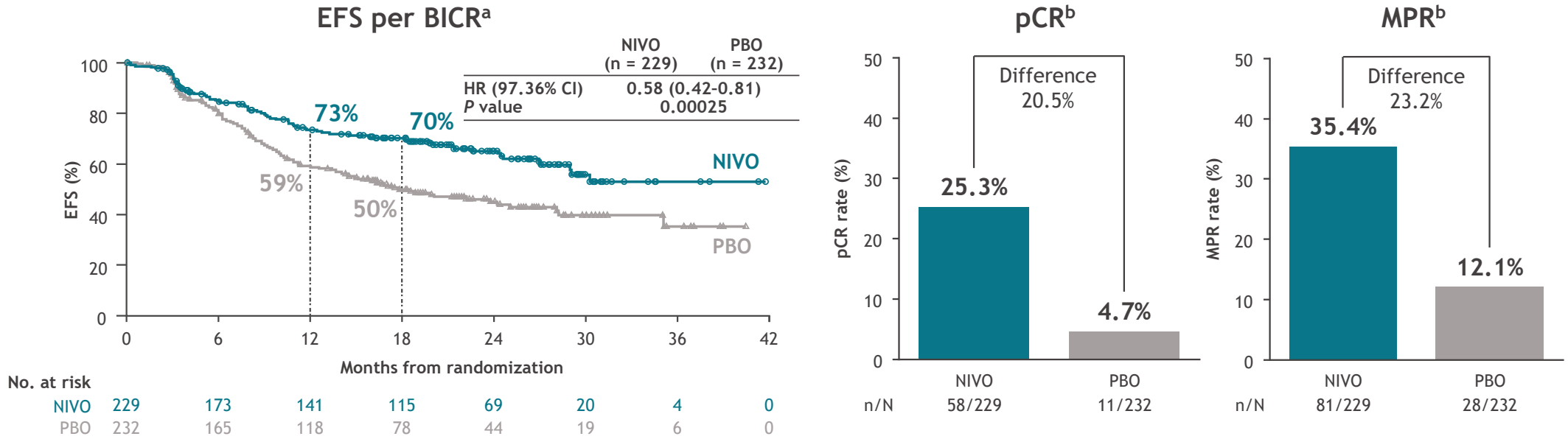
Background

- In the phase 3 CheckMate 77T study, perioperative NIVO showed significant EFS improvement vs PBO in patients with stage II–IIIB resectable NSCLC; pCR and MPR rates were also improved[1]



- Stage IIIA–B resectable NSCLC is historically associated with poor survival; 5-year OS rates range from 24%–41%[2]

Here, we report clinical outcomes from CheckMate 77T for patients with baseline stage III N2 and non-N2 NSCLC

[a]Follow-up, median (range): 25.4 (15.7–44.2) months. [b]From The New England Journal of Medicine, Cascone T, et al, Perioperative nivolumab in resectable lung cancer, 2024;390:1756-1769. Copyright © 2024 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. 1. Cascone T, et al. *N Engl J Med*. 2024;390:1756-1769. 2. Goldstraw P, et al. *J Thorac Oncol* 2016;11:39–51.

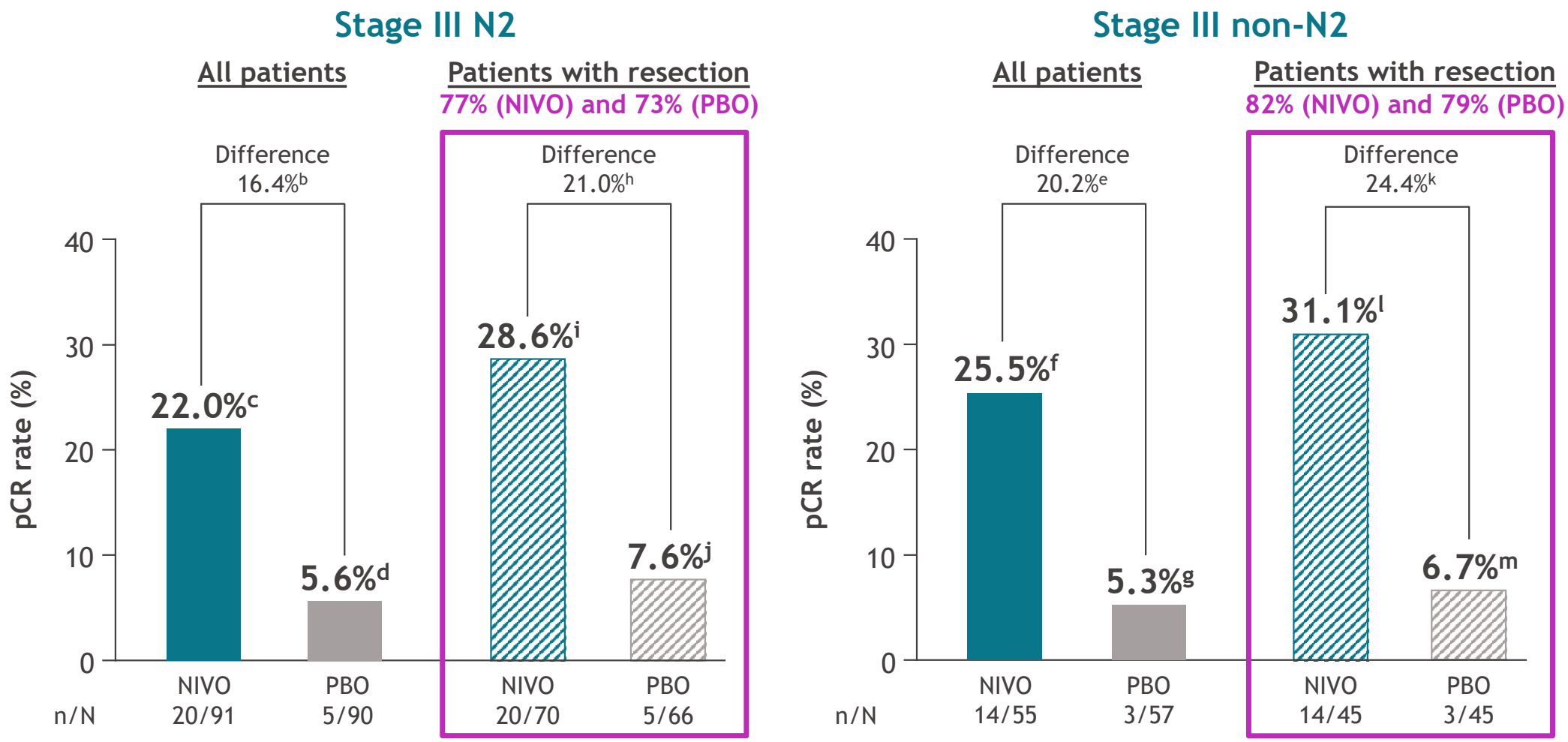
Baseline patient characteristics

	Stage III N2[a]		Stage III non-N2[a,b]	
	NIVO (n = 91)	PBO (n = 90)	NIVO (n = 55)	PBO (n = 57)
Median age, years (range)	66 (37-78)	64 (39-86)	66 (46-81)	65 (35-80)
Male, n (%)	61 (67)	61 (68)	43 (78)	42 (74)
Geographic region, n (%)				
North America	9 (10)	7 (8)	7 (13)	7 (12)
Europe	50 (55)	54 (60)	31 (56)	31 (54)
Asia	25 (28)	17 (19)	15 (27)	12 (21)
Rest of the world[c]	7 (8)	12 (13)	2 (4)	7 (12)
ECOG PS, n (%)				
0	67 (74)	59 (66)	31 (56)	33 (58)
1	24 (26)	31 (34)	24 (44)	24 (42)
Disease stage III, n (%)				
IIIA	48 (53)	57 (63)	55 (100)	57 (100)
IIIB	43 (47)	33 (37)	0	0
Histology, n (%)				
Squamous	40 (44)	38 (42)	31 (56)	34 (60)
Non-squamous	51 (56)	52 (58)	24 (44)	23 (40)
Smoking status, n (%)				
Current/former	79 (87)	79 (88)	52 (94)	55 (96)
Never	12 (13)	11 (12)	3 (6)	2 (4)
Tumor PD-L1 expression, n (%)				
Not evaluable	2 (2)	4 (4)	1 (2)	1 (2)
< 1%	41 (45)	35 (39)	24 (44)	28 (49)
[illegible]	48 (53)	51 (57)	30 (54)	28 (49)
1-49%	36 (40)	29 (32)	15 (27)	17 (30)
[illegible]	12 (13)	22 (24)	15 (27)	11 (19)

[a]Of patients in the ITT population (NIVO, n = 229; PBO, n = 232), 40% and 39% in the NIVO and PBO arms, respectively, had stage III N2 NSCLC, and 24% and 25% had stage III non-N2 NSCLC. [b]2 patients in each arm had stage III N3 NSCLC and were not included in the non-N2 population. [c]Includes Argentina, Australia, Brazil, and Mexico.

Cascone et al, NEJM 2024

pCR[a]



[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes. [b-m]95% CI: [b]6.5-26.5; [c]14.0-31.9; [d]1.8-12.5; [e]6.9-33.5; [f]14.7-39.0; [g]1.1-14.6; [h]8.1-33.3; [i]18.4-40.6; [j]2.5-16.8; [k]8.3-39.6; [l]18.2-46.6; [m]1.4-18.3.

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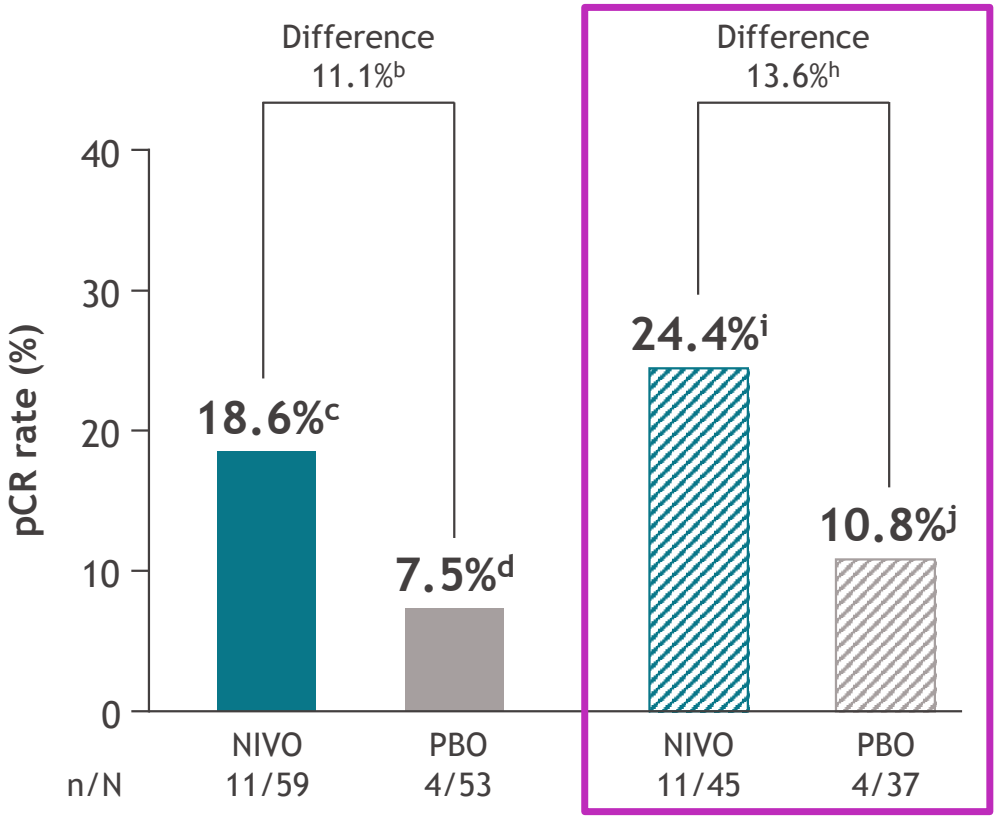
pCR

Stage III single-station N2[a]

All patients

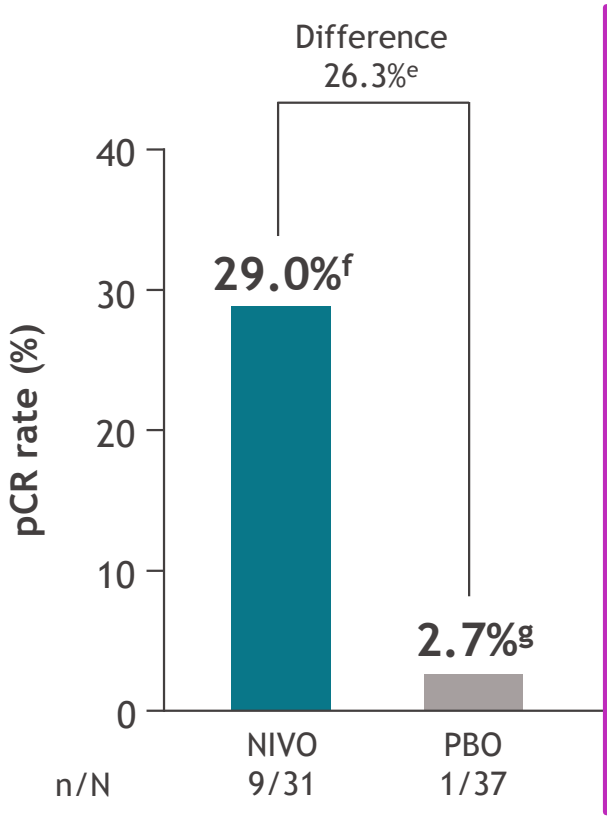


Patients with resection

76% (NIVO) and 70% (PBO)

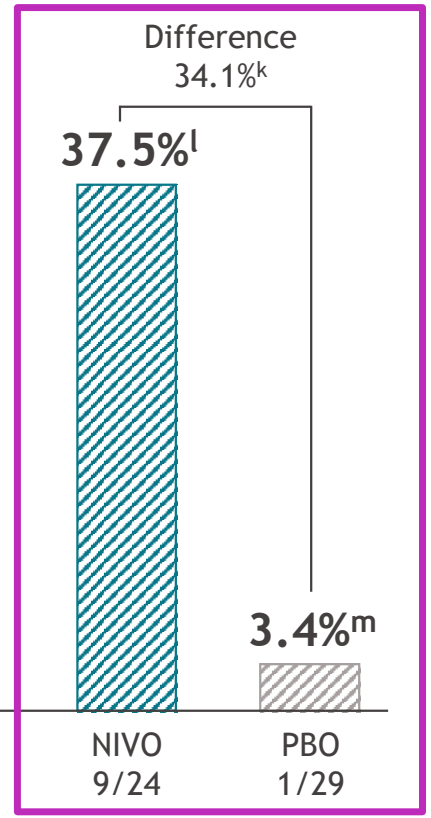
Stage III multi-station N2[a]

All patients



Patients with resection

77% (NIVO) and 78% (PBO)



[a]N2 subcategory was not reported in 1 patient in the NIVO arm. [b-m]95% CI: [b]1.9-23.7; [c]9.7-30.9; [d]2.1-18.2; [e]9.3-44.0; [f]14.2-48.0; [g]0.1-14.2; [h]3.6-29.3; [i]12.9-39.5; [j]3.0-25.4; [k]12.7-54.0; [l]18.8-59.4; [m]0.1-17.8.

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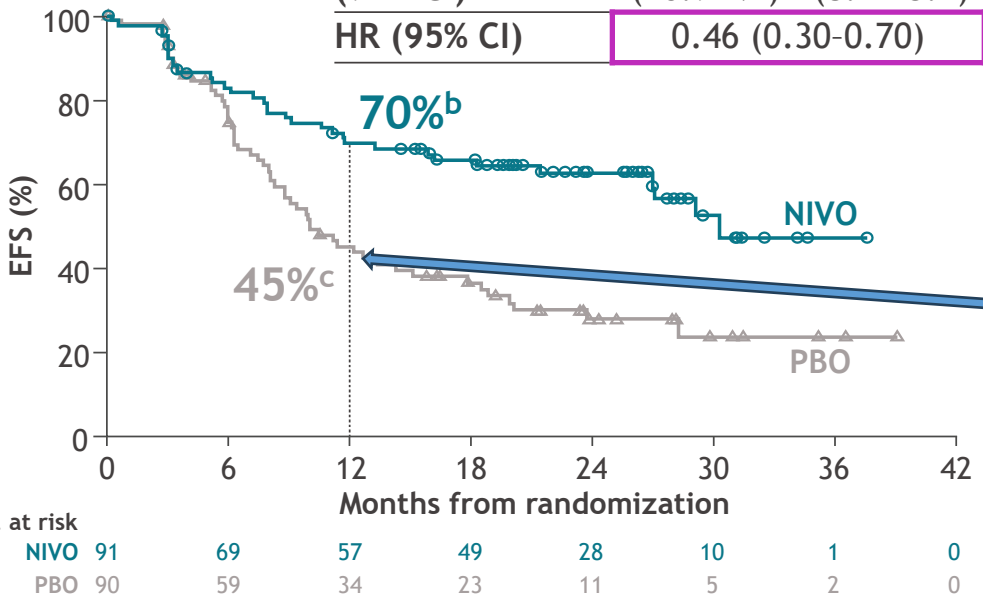
EFS from randomization[a]

Stage III N2

	NIVO (n = 91)	PBO (n = 90)
Median EFS, mo (95% CI)	30.2 (26.9-NR)	10.0 (8.1-15.1)
HR (95% CI)	0.46 (0.30-0.70)	

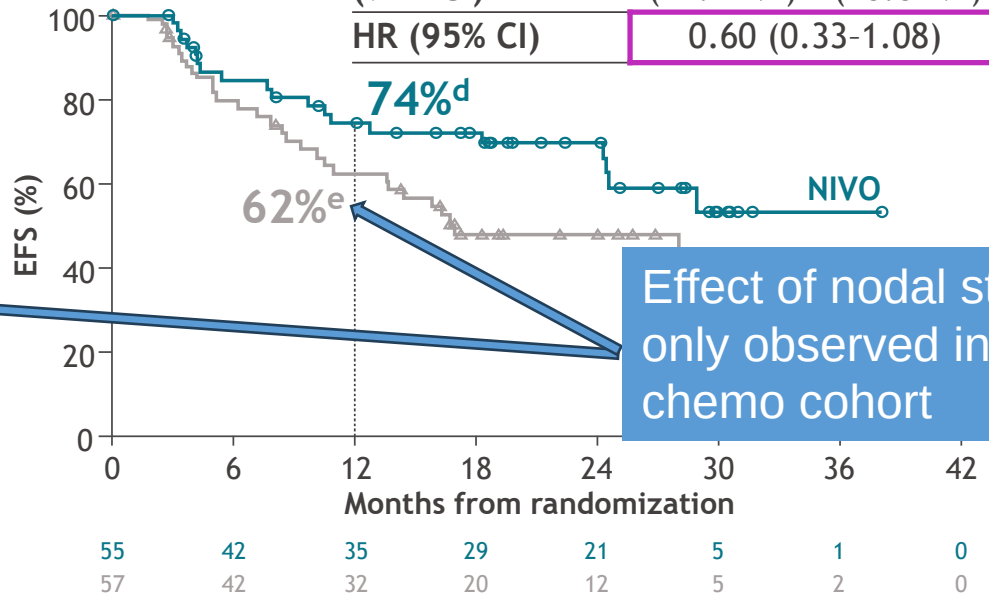


No. at risk

NIVO	91	69	57	49	28	10	1	0
PBO	90	59	34	23	11	5	2	0

Stage III non-N2

	NIVO (n = 55)	PBO (n = 57)
Median EFS, mo (95% CI)	NR (24.2-NR)	17.0 (10.6-NR)
HR (95% CI)	0.60 (0.33-1.08)	



NIVO	55	42	35	29	21	5	1	0
PBO	57	42	32	20	12	5	2	0

Effect of nodal staging only observed in chemo cohort

EFS HRs from randomization: 0.49[f] (single-station N2) and 0.43[g] (multi-station N2)[h]

Median follow-up (range): 25.4 months (15.7-44.2). [a]Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. [b-g]95% CI: [b]58-78; [c]34-55; [d]60-84; [e]48-74; [f]0.29-0.84; [g]0.21-0.88. [h]N2 subcategory was not reported in 1 patient in the NIVO arm.

Cascone et al, NEJM 2024

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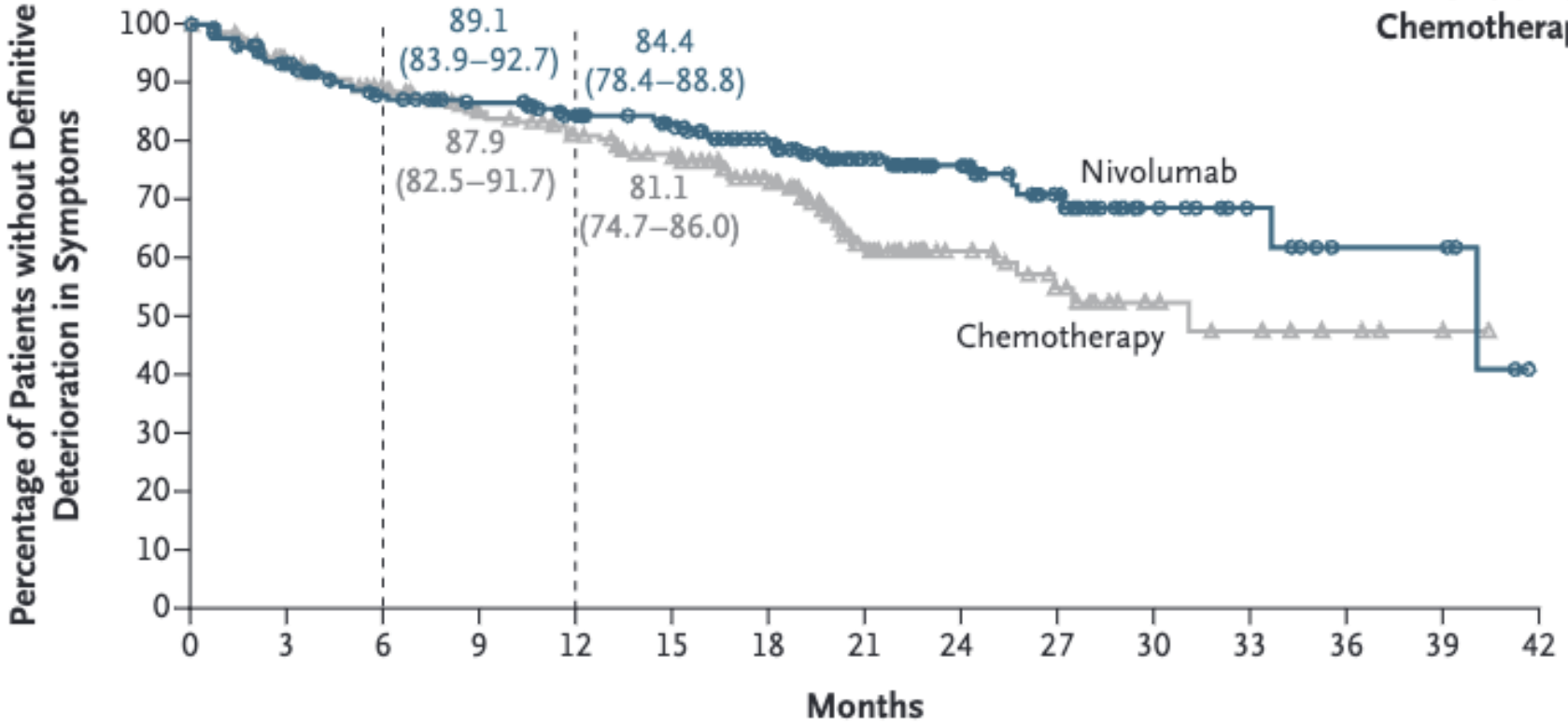
B TTDD in Disease-Related Symptoms, According to NSCLC-SAQ Total Scores



	No. of Patients	Median TTDD (95% CI)
		mo
Nivolumab	229	40.0 (33.6–NR)
Chemotherapy	232	31.1 (25.0–NR)

Hazard ratio for TTDD, 0.66 (95% CI, 0.45–0.98)

No. at Risk

Nivolumab	229	182	159	150	137	129	105	72	52	36	16	10	5	5	0
Chemotherapy	232	188	163	148	135	124	90	48	33	24	12	9	4	1	0

Cascone et al, NEJM 2024

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Key points from 77T

- Perioperative Nivolumab offers comparable EFS results to neoadjuvant Nivolumab.
- Patient level comparisons will be required to provide insight into contribution of adjuvant Nivolumab
- High PCR rates regardless of N2 positivity or extent of involvement (multi-N2)
- **Peri-operative Nivolumab removed stage effects of N2 involvement**
- **Hence, biology trumps anatomical staging which in turn will dictate the role of surgery**
- QoL is prolonged via the receipt of peri-operative Nivolumab

A first in 30 years of resectable lung cancer research

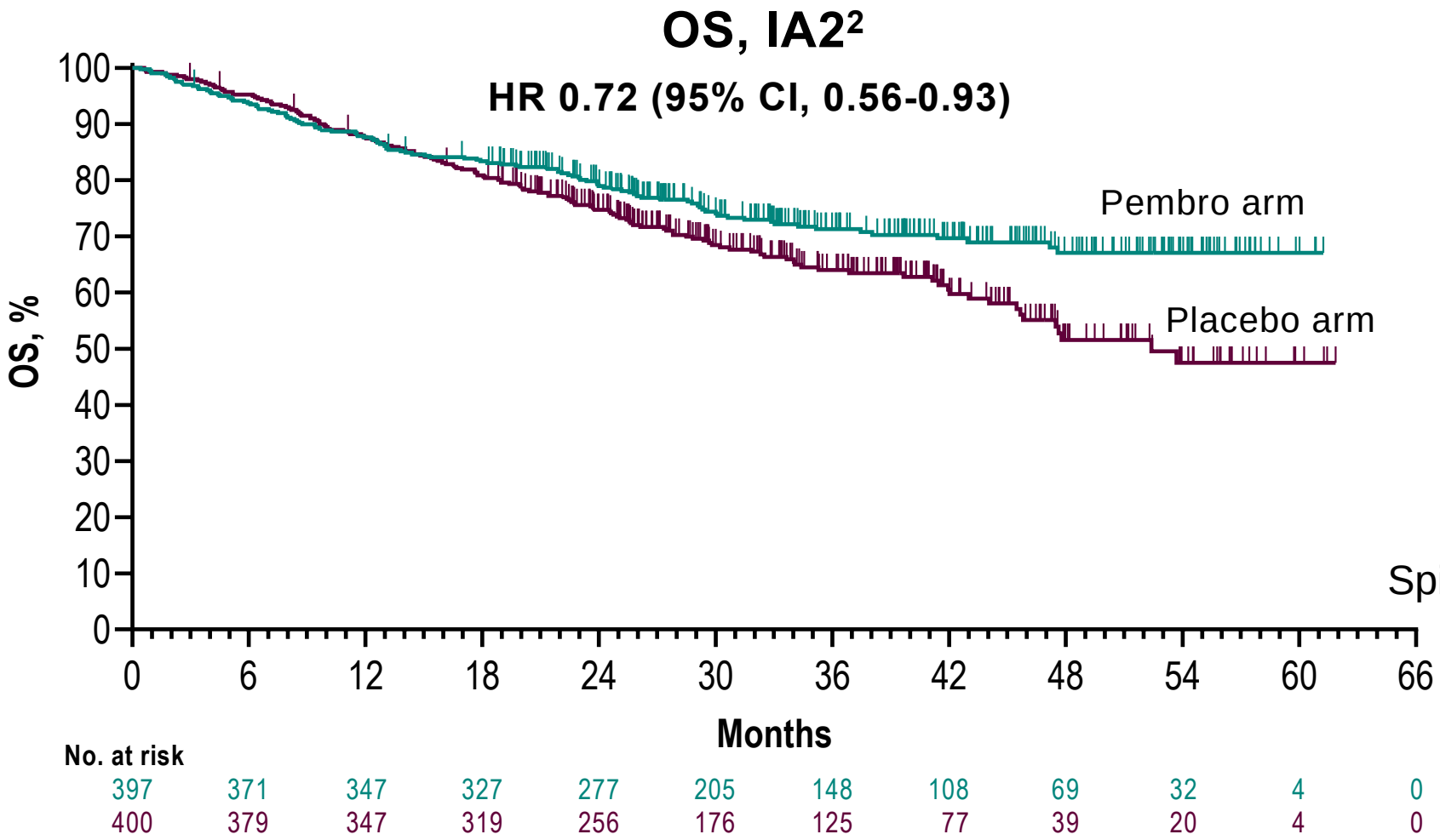
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 10, 2023 VOL. 389 NO. 6

Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*

NCCN level 1A recommendation for KN671 peri-operative pembrolizumab with neoadjuvant chemotherapy

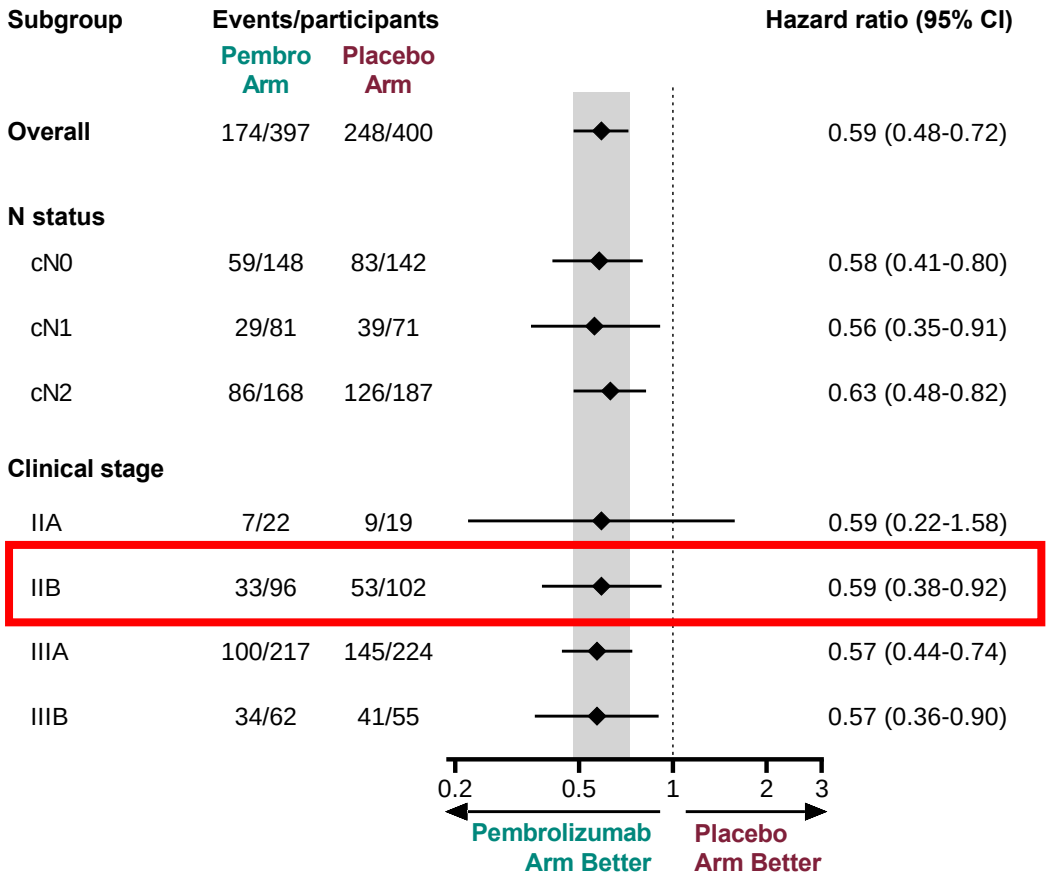


Spicer et al, ESMO 2023

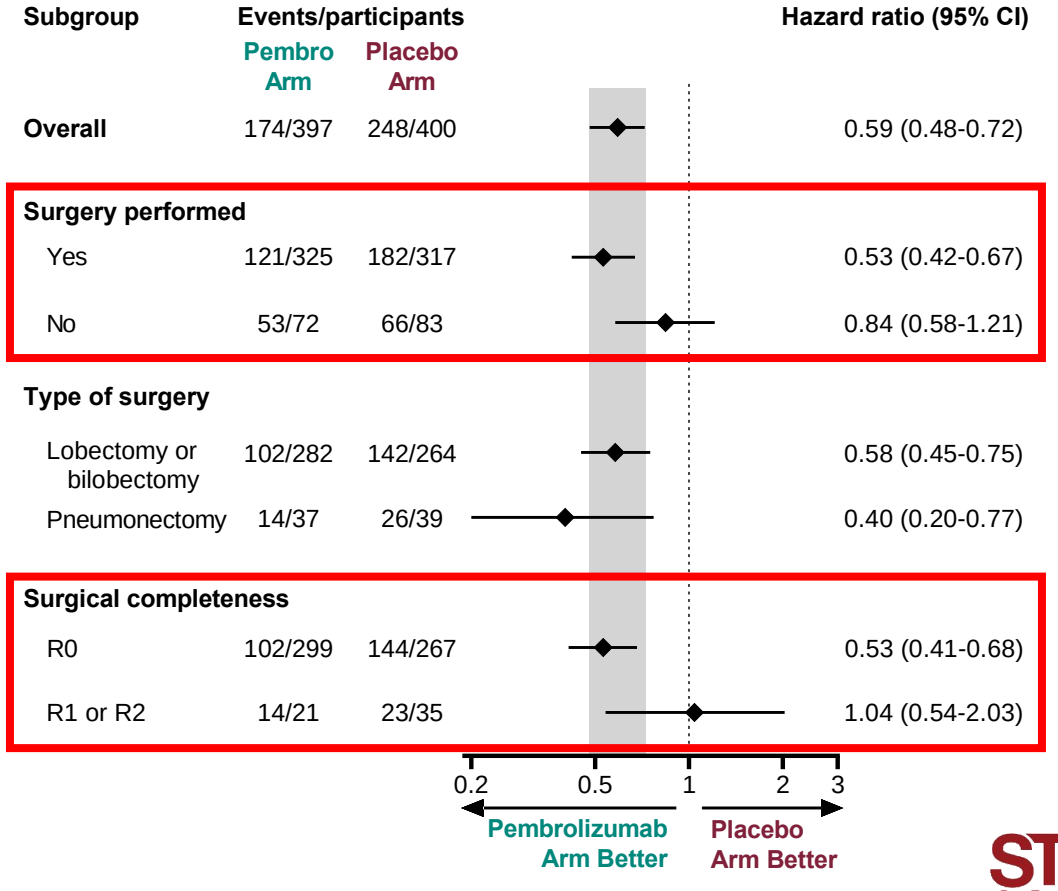
Completing surgery and achieving a complete resection are essential components

Post Hoc Analysis of EFS in Surgically Relevant Subgroups

Baseline Characteristics



Post Randomization Factors



Data cutoff date for IA2: July 10, 2023.

Spicer et al, STS 2024

Doing so safely is a primordial concern

All-Cause Mortality Within 30 and 90 Days of Surgery, Surgical Population

Spicer et al, STS 2024

	Pembro Arm	Placebo Arm
All participants who underwent surgery	**n = 325**	**n = 317**
Within 30 days	6 (1.8%)[a]	2 (0.6%)[b]
Within 90 days	13 (4.0%)[c]	5 (1.6%)[d]
Participants who underwent lobectomy or bilobectomy	**n = 282**	**n = 264**
Within 30 days	4 (1.4%)	2 (0.8%)
Within 90 days	10 (3.5%)	4 (1.5%)
Participants who underwent pneumonectomy	**n = 37**	**n = 39**
Within 30 days	2 (5.4%)[e]	0
Within 90 days	3 (8.1%)[e]	1 (2.6%)[f]

[a]Pulmonary embolism (n = 2) and pulmonary hemorrhage due to arterial injury during surgery, pulmonary sepsis, respiratory failure, and septic shock (n = 1 each); all attributed to surgery. [b]Pneumonia and respiratory failure (n = 1 each); both attributed to surgery. [c]Additional deaths that occurred from days 31-90: malignant neoplasm progression (n = 3) and cardiac arrest, pulmonary hemorrhage, immune-mediated lung disease, and unexplained death (n = 1 each); none attributed to surgery; immune-mediated lung disease attributed to study drug. [d]Additional deaths that occurred from days 31-90: acute respiratory failure, malignant neoplasm progression, and septic shock (n = 1 each); none attributed to surgery or study drug. [e]Deaths within 30 days occurred in 1 of 23 participants with a left-sided tumor and 1 of 14 participants with a right-sided tumor; within 90 days, 1 additional participant with a right-sided tumor died. [e]Death occurred in 1 of 24 participants with a right-sided tumor.
Data cutoff date for IA2: July 10, 2023.

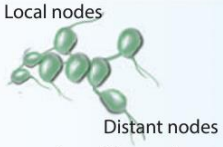
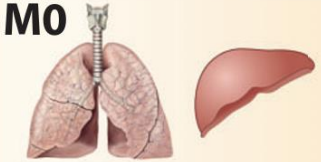
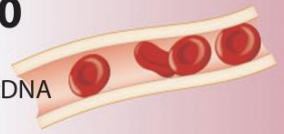
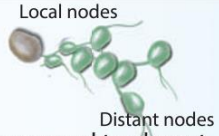
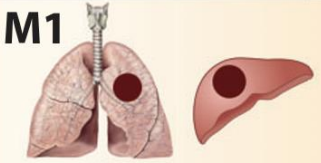
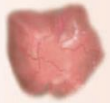
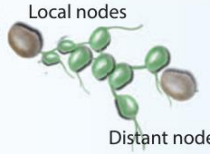
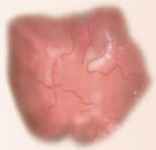
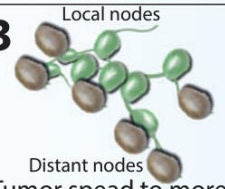
STS 2024

Key points from KN671

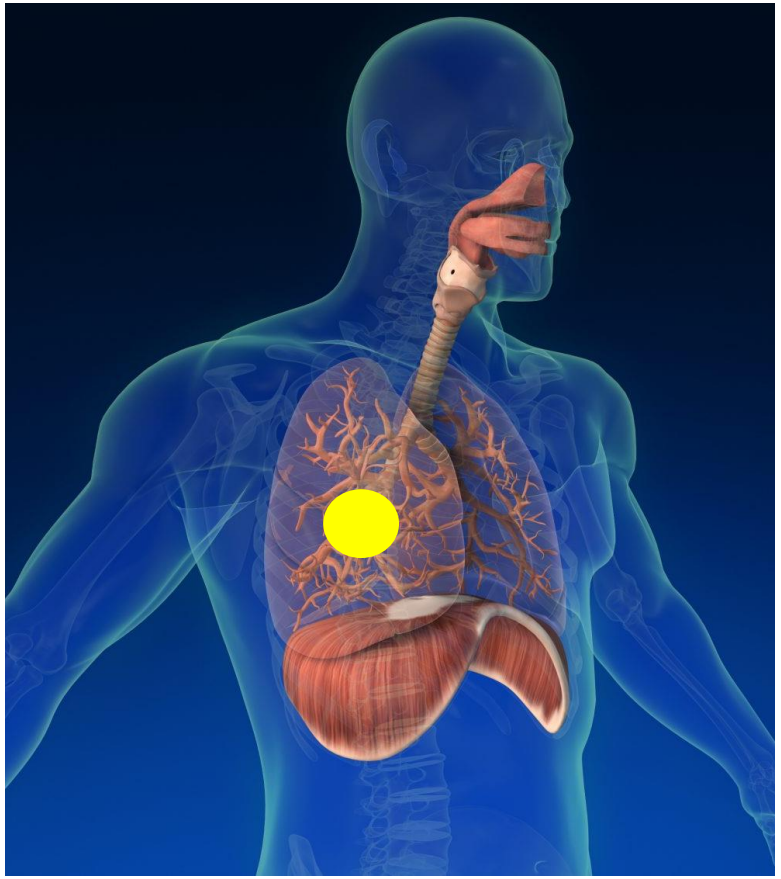
- Perioperative Pembrolizumab improves OS
- Stage II patients benefit to same extent as stage III patients
- Benefits most pronounced in patients who undergo surgery
- R0 resection is necessary to experience benefit from the addition of peri-operative pembrolizumab

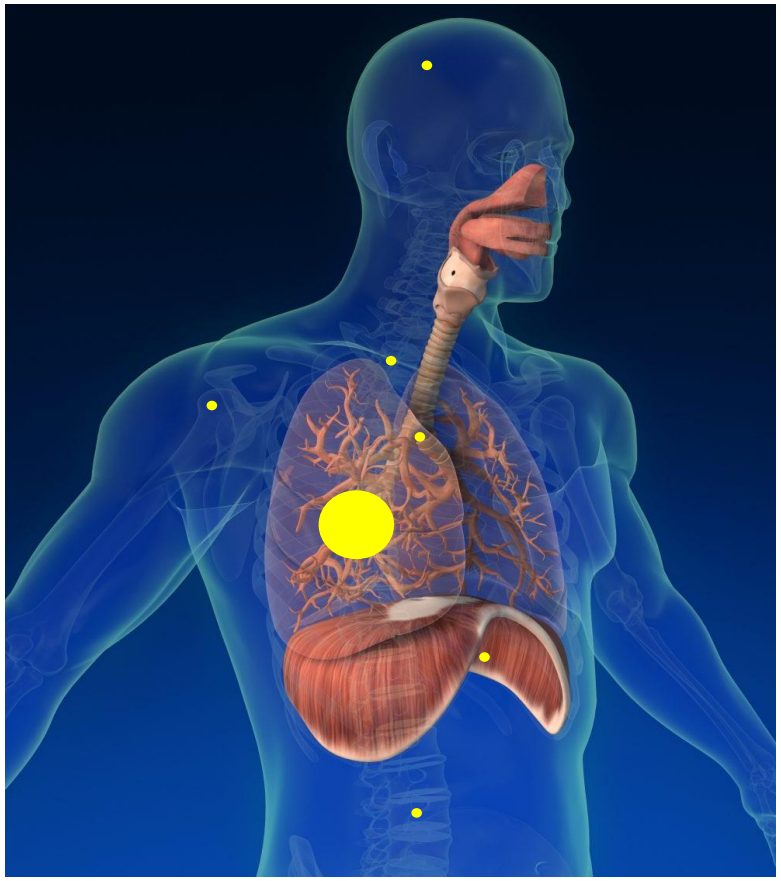
Summary of unmet needs

Key unmet need #1: Detection of micrometastasis to avoid unnecessary systemic therapy

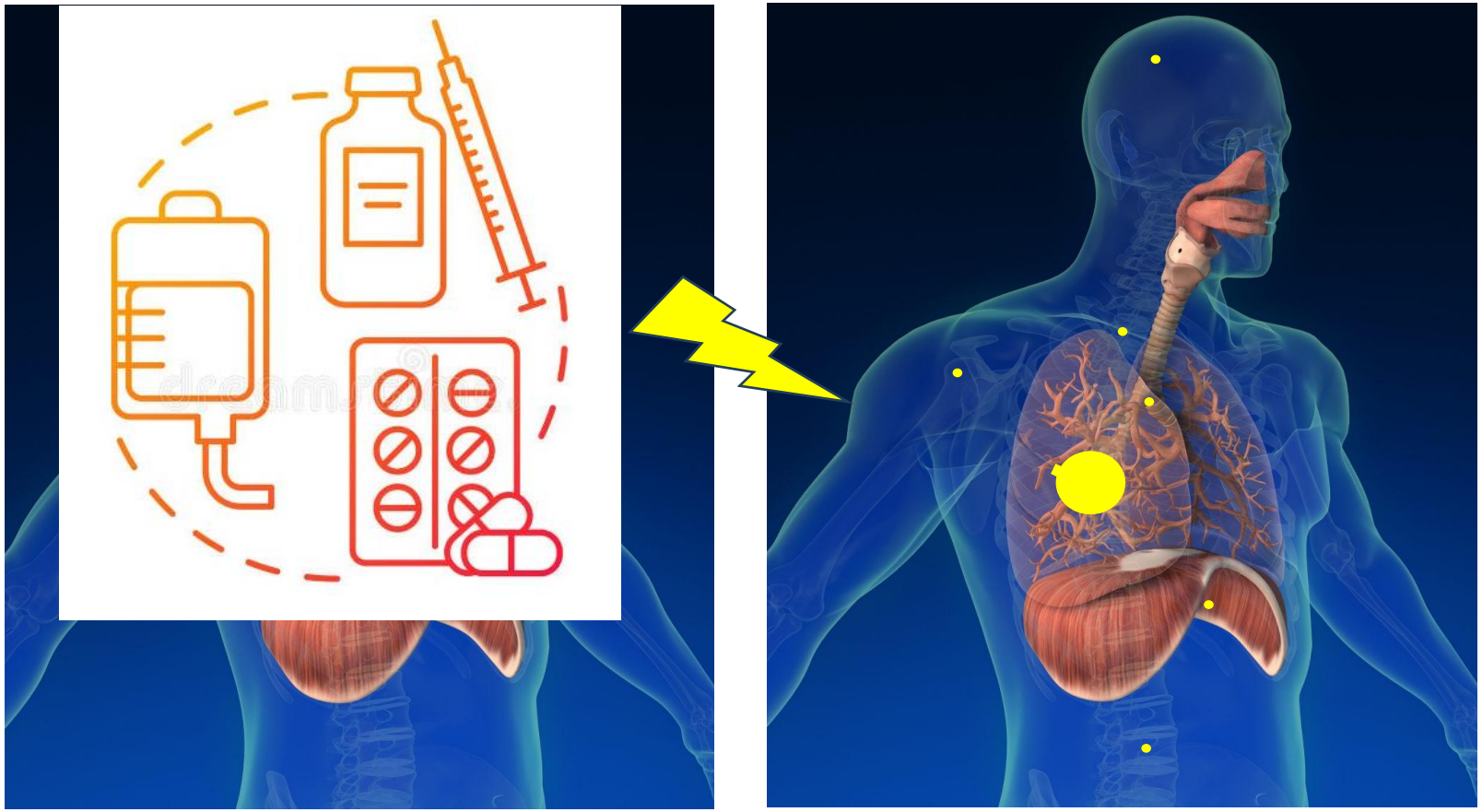
T Tumor Size	N Lymph Node	M Metastasis	B Blood
T1  Tumor size/local invasion	**N0**  No regional lymph node invasion	**M0**  No distant metastasis	**B0**  No ctDNA mutations in blood
T2  Tumor size/local invasion	**N1**  Tumor spead to closest or small number of regional lymph nodes	**M1**  Distant metastasis	**B1**  ctDNA mutations in blood (can be further defined with more detailed quantification in the future)
T3  Tumor size/local invasion	**N2**  Tumor spead to an extent between N1 and N3		
T4  Tumor of any size that invades to other organs	**N3**  Tumor spead to more distant or regional numerous lymph nodes		

Key unmet need #1: Detection of micrometastasis to avoid unnecessary systemic therapy

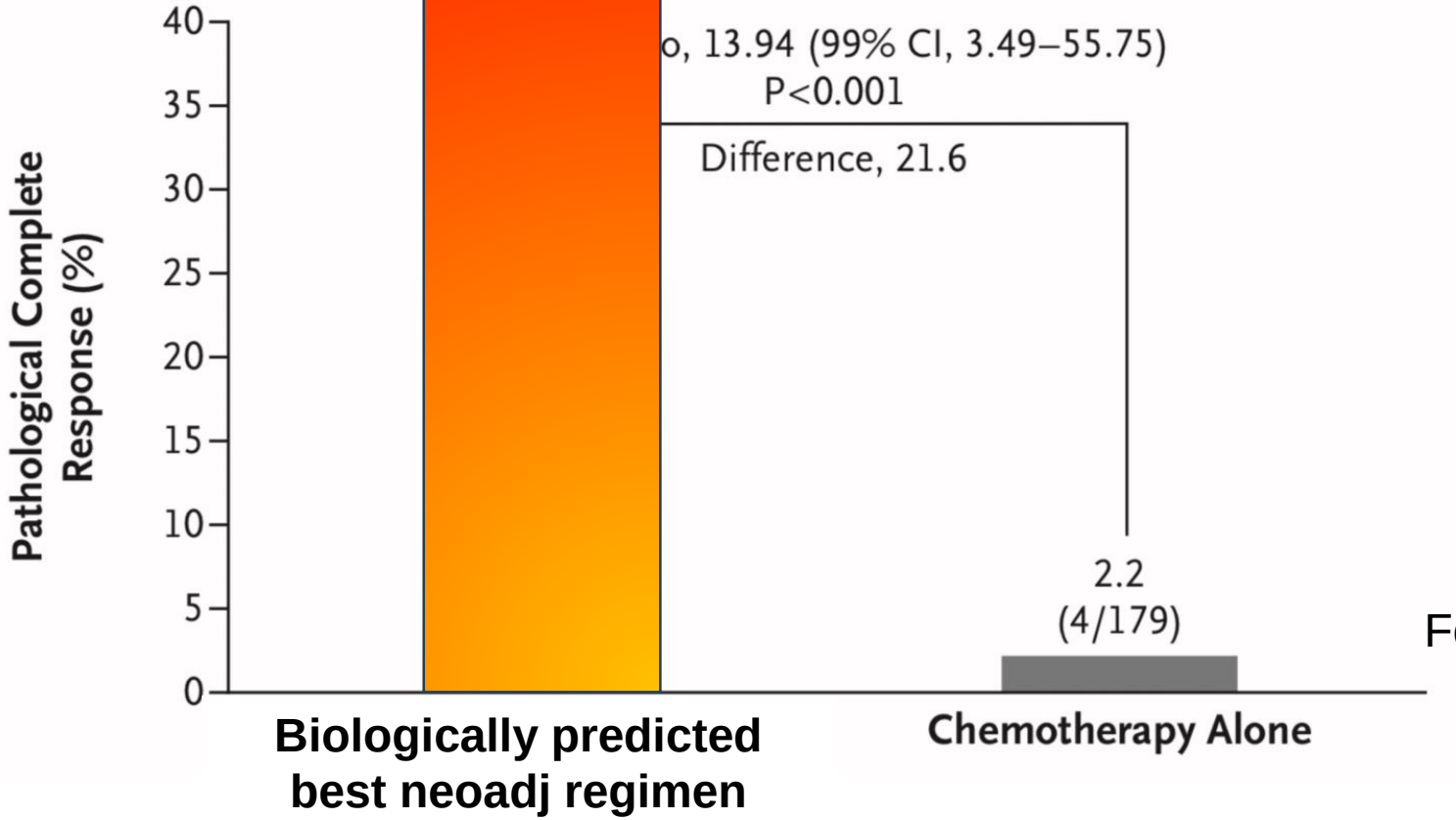




Key unmet need #2: Assignment of micrometastatic patients to biologically tailored systemic therapy



Key unmet need #3: Improve ablative potential of systemic therapies via biomarker driven selection



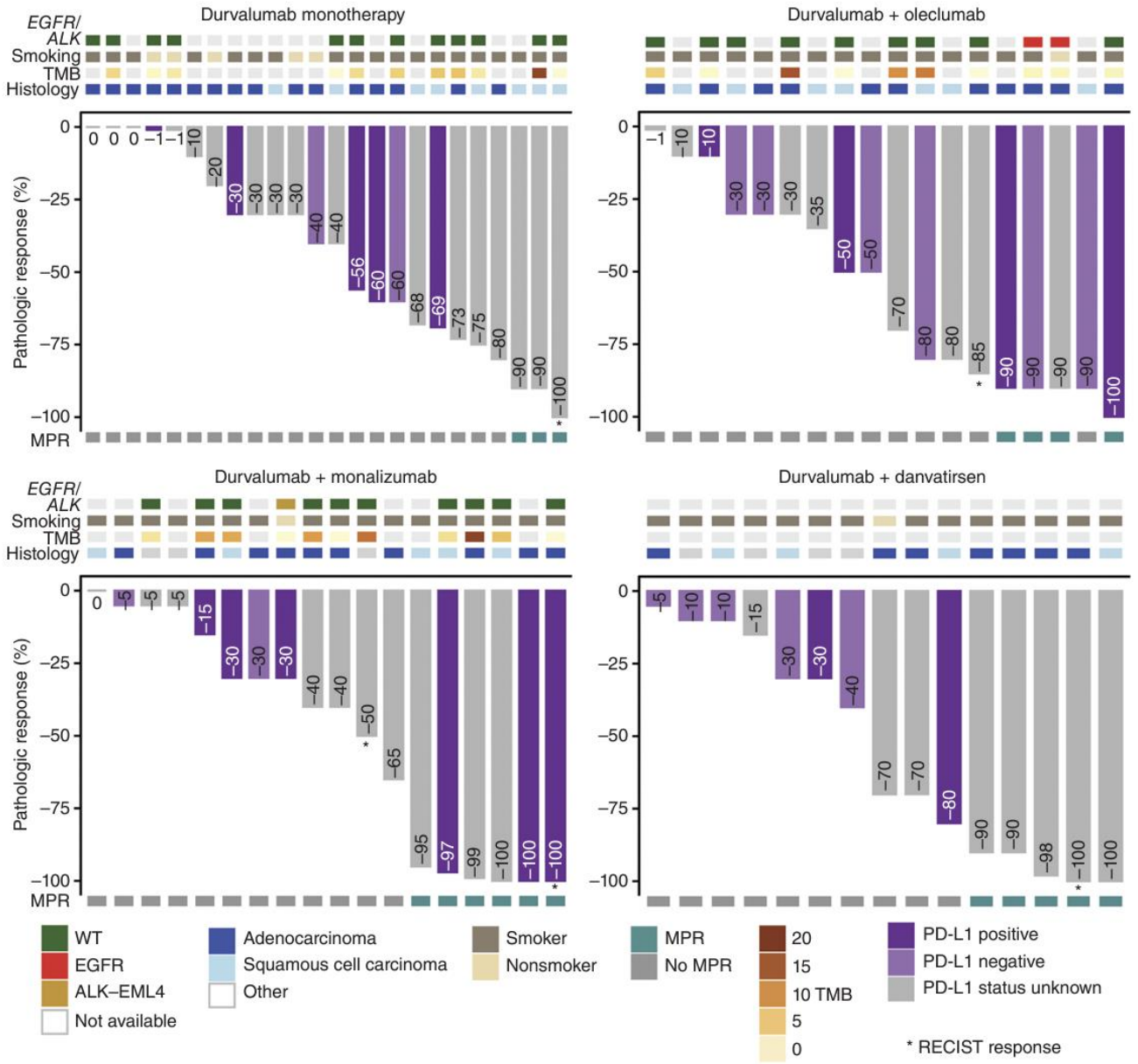
Forde et al, NEJM 2022

NeoCOAST is a proof-of-concept window of opportunity trial designed to perform signal finding by pathological response

RESEARCH ARTICLE

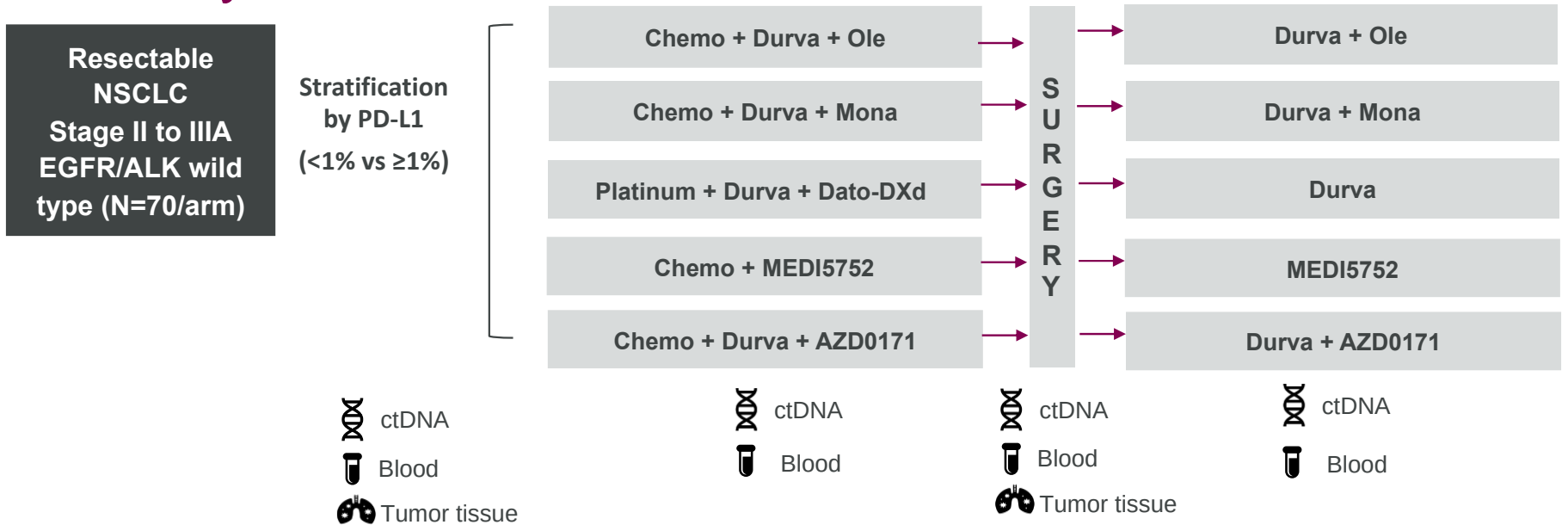
Neoadjuvant Durvalumab Alone or Combined with Novel Immuno-Oncology Agents in Resectable Lung Cancer: The Phase II NeoCOAST Platform Trial

Tina Cascone[1], Gozde Kar[2], Jonathan D. Spicer[3], Rosario García-Campelo[4], Walter Weder[5], Davey B. Daniel[6], David R. Spigel[6], Maen Hussein[7], Julien Mazieres[8], Julio Oliveira[9], Edwin H. Yau[10], Alexander I. Spira[11], Valsamo Anagnostou[12], Raymond Mager[13], Oday Hamid[13], Lin-Yang Cheng[13], Ying Zheng[13], Jorge Blando[13], Tze Heng Tan[14], Michael Surace[13], Jaime Rodriguez-Canales[13], Vancheswaran Gopalakrishnan[13], Bret R. Sellman[13], Italia Grenga[15], Yee Soo-Hoo[13], Rakesh Kumar[13], Lara McGrath[15], and Patrick M. Forde[12]



Next iteration is underway…

Comprehensive translational profiling of tumor, ctDNA, and pharmacodynamic biomarkers in NeoCOAST-2



Biomarker analyses

- FFPE tumor for PD-L1, TROP2, CD73, others to determine patients most likely to benefit
- Longitudinal blood and tumor to provide insights to MoA and associations with response

ctDNA clearance

- Detect early signals of clinical benefit, including patients who will experience pCR
- Identify patients with improved EFS/OS despite not experiencing pCR

ctDNA MRD Profiling

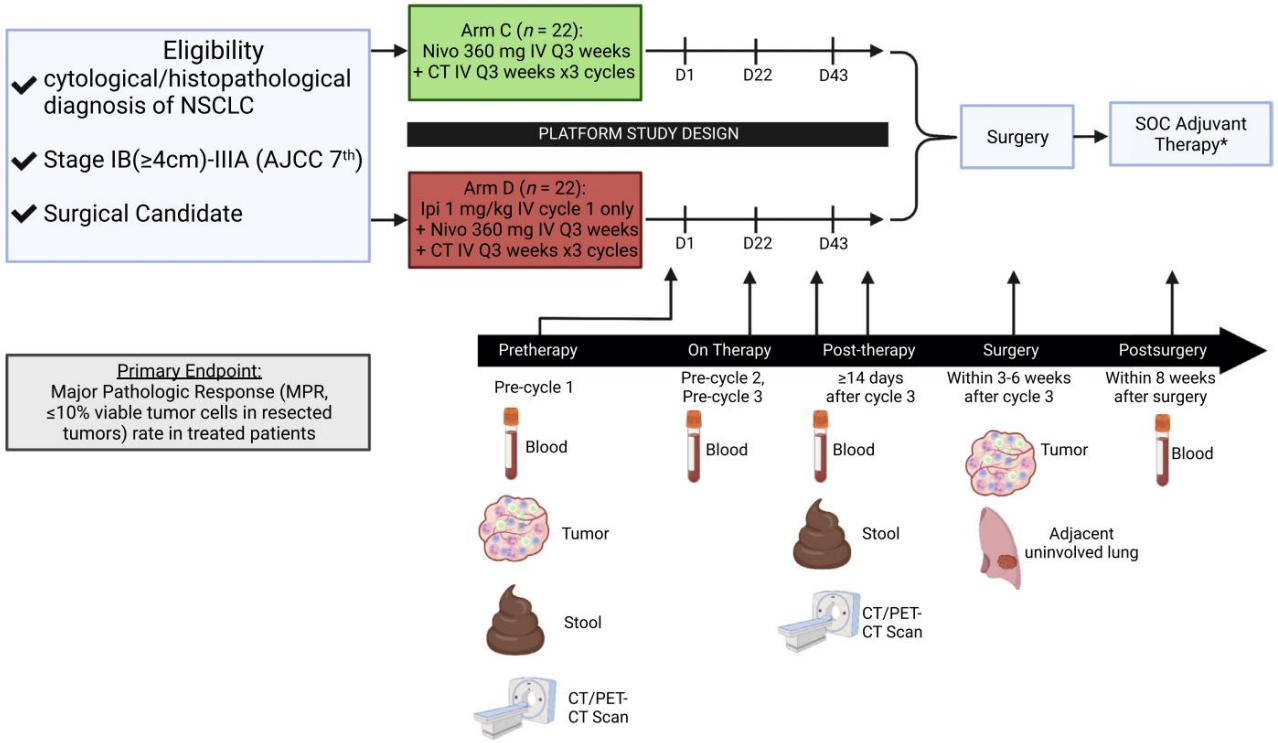
- Identify patients with high risk of recurrence

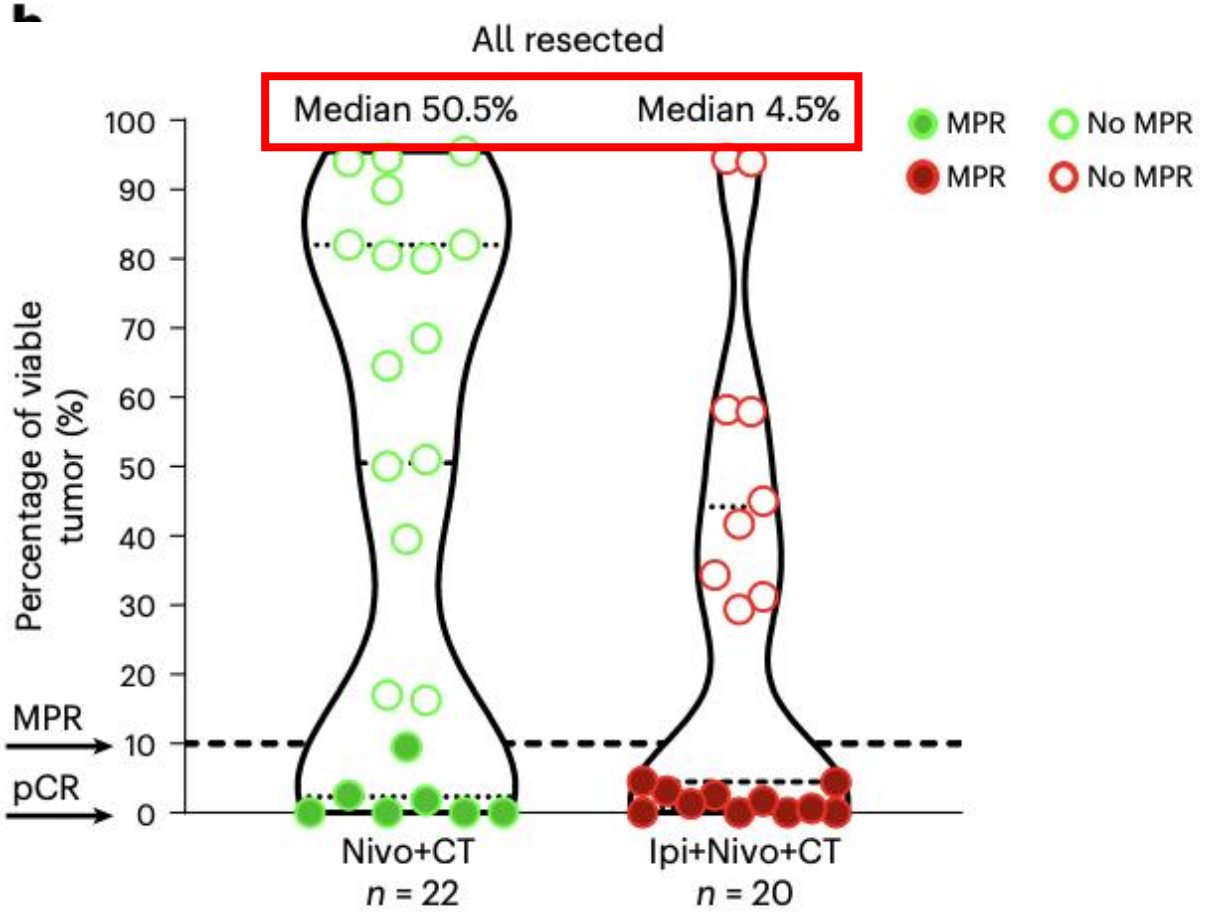
nature medicine

Article

https://doi.org/10.1038/s41591-022-02189-0

Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial

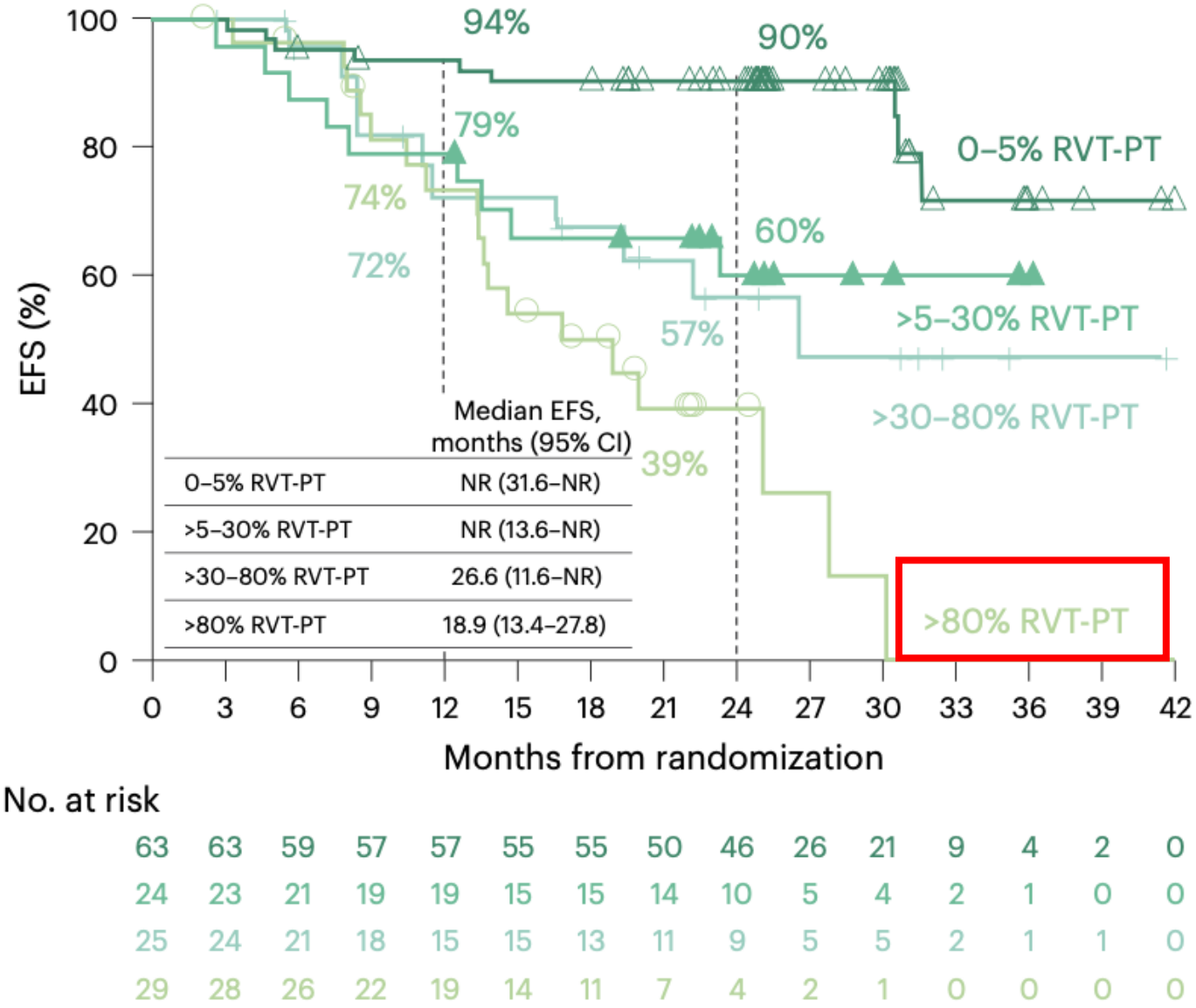




Cascone et al, Nat Med 2023

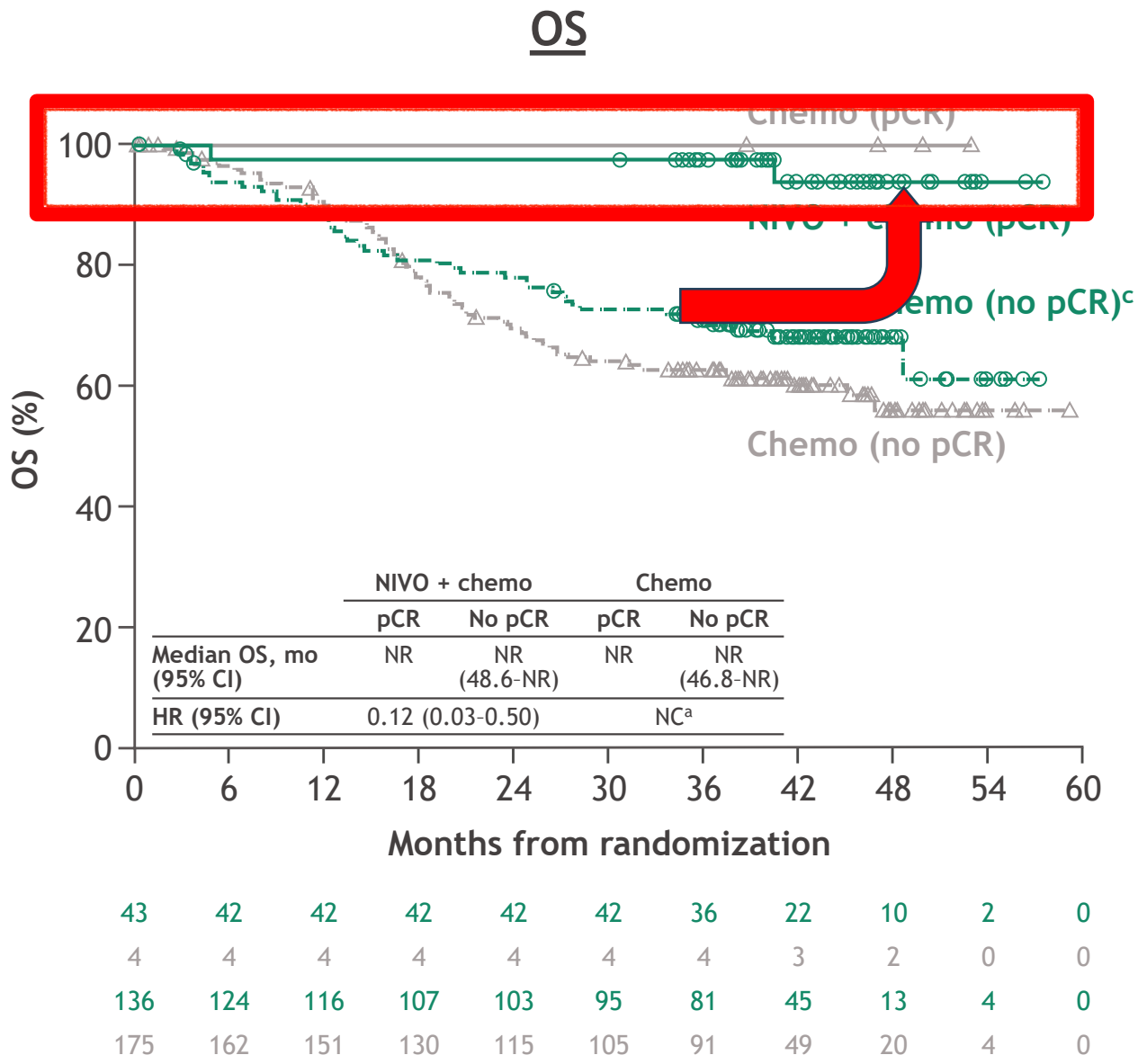
McGill

Key unmet need #4: How do we rescue patients with poor pathological response to neoadjuvant Tx



Deutsch et al, Nat Med 2023

Key unmet need #4: How do we rescue patients with poor pathological response to neoadjuvant Tx



Accurate risk prediction is the path to efficient and useful adjuvant therapy

Article

Single-cell spatial landscapes of the lung tumour immune microenvironment

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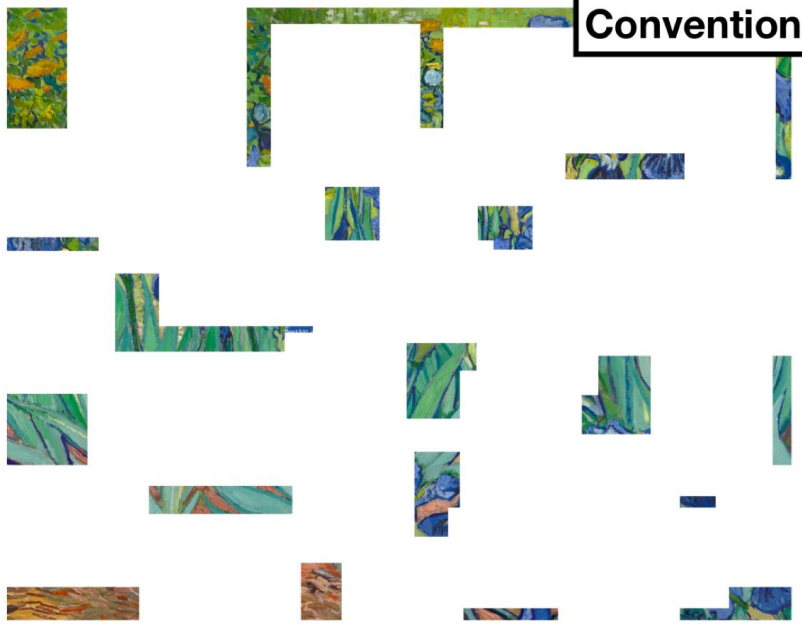
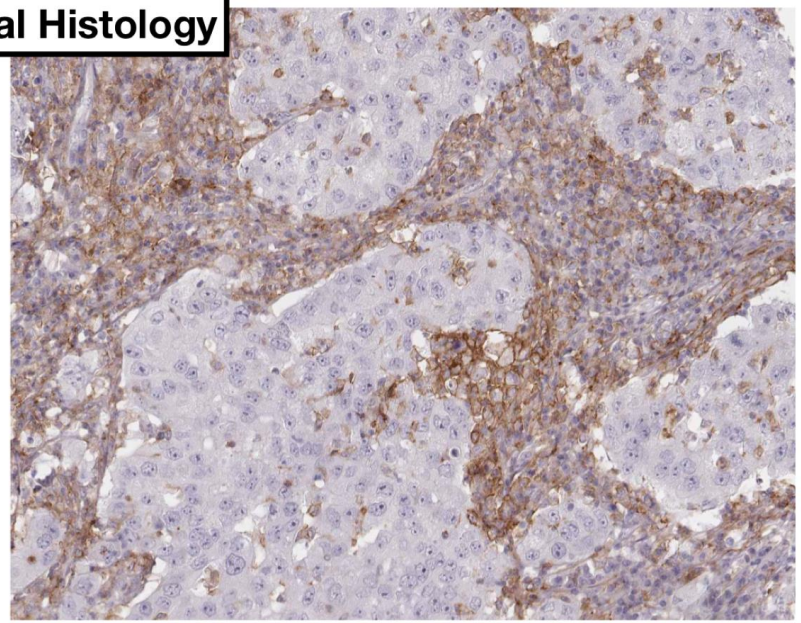
Open access

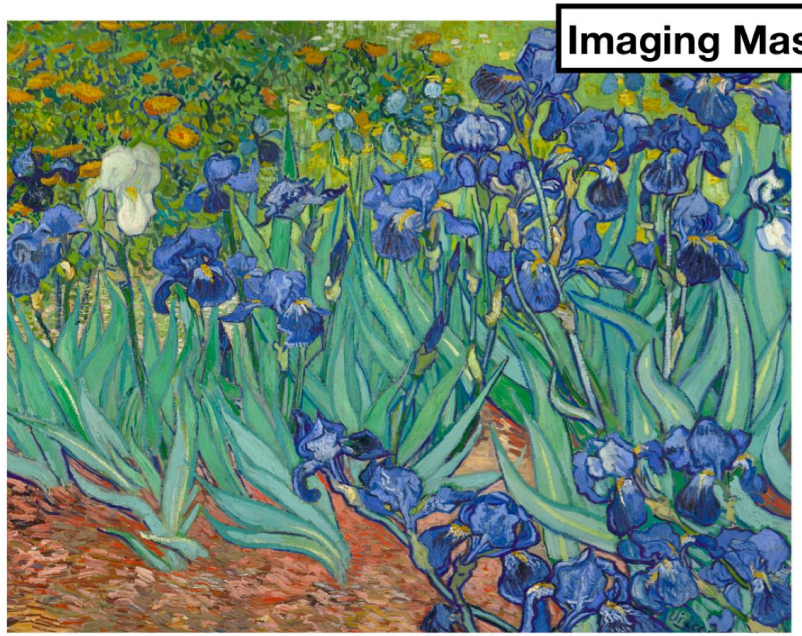
Mark Sorin[1,2,13], Morteza Rezanejad[3,4,13], Elham Karimi[1,13], Benoit Fiset[1], Lysanne Desharnais[1,2], Lucas J. M. Perus[1,5], Simon Milette[1,5], Miranda W. Yu[1,5], Sarah M. Maritan[1,6], Samuel Doré[1,2], Émilie Pichette[7], William Enlow[8], Andréanne Gagné[8], Yuhong Wei[1], Michele Orain[8], Venkata S. K. Manem[8,9], Roni Rayes[1], Peter M. Siegel[1,6,10], Sophie Camilleri-Broët[11], Pierre Olivier Fiset[11], Patrice Desmeules[8], Jonathan D. Spicer[1,6,12], Daniela F. Quail[1,5,6]✉, Philippe Joubert[8]✉ & Logan A. Walsh[1,2]✉

McGill

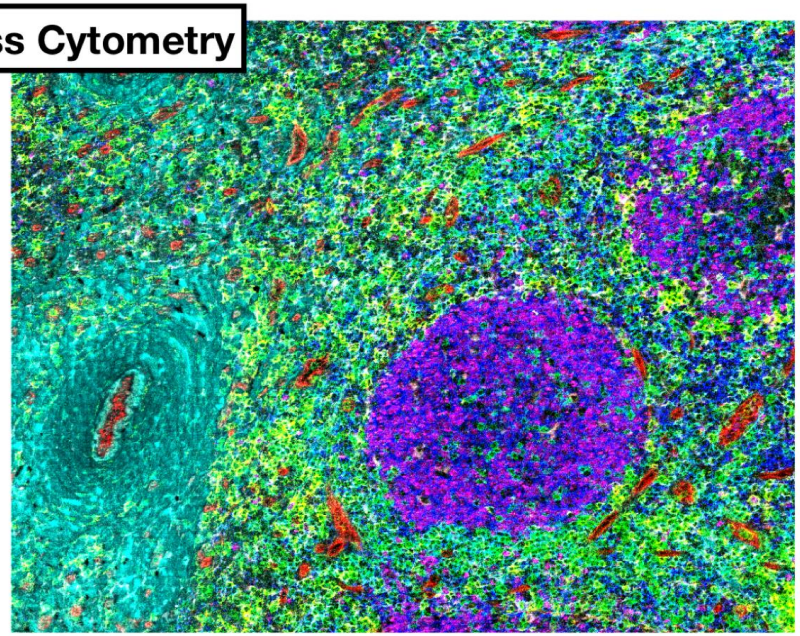


Conventional Histology





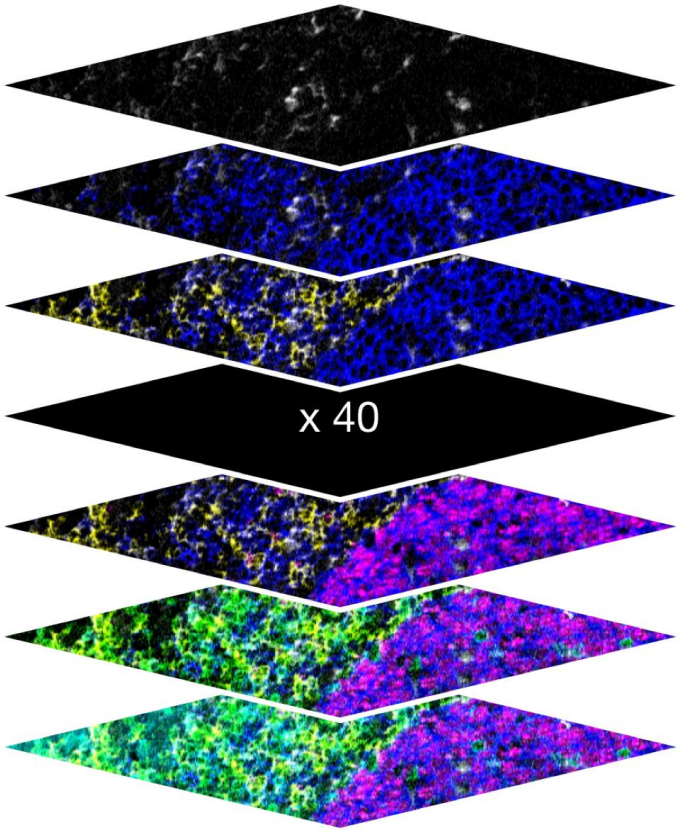
Imaging Mass Cytometry

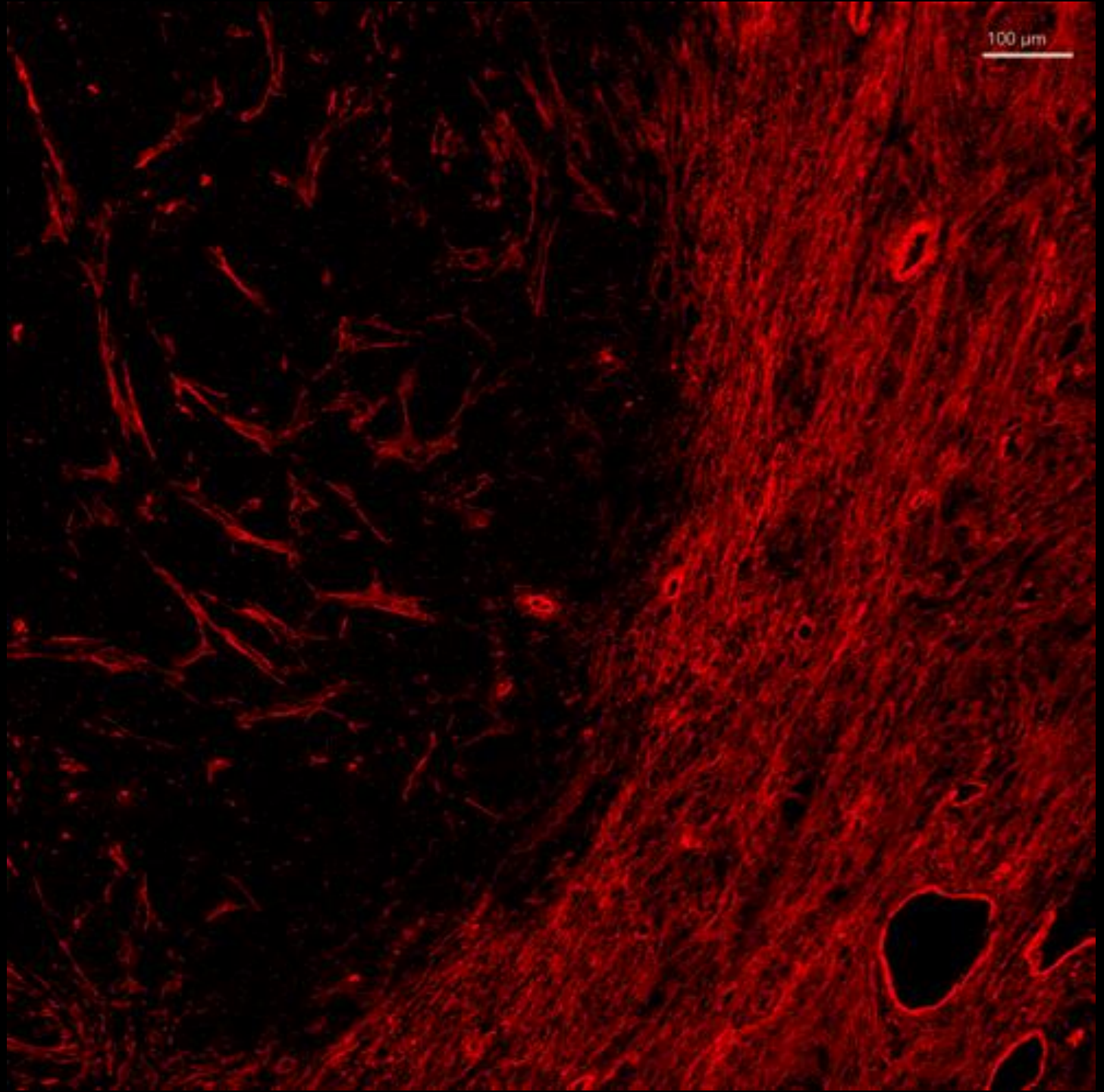


Three Minute Thesis // *Simon Milette*

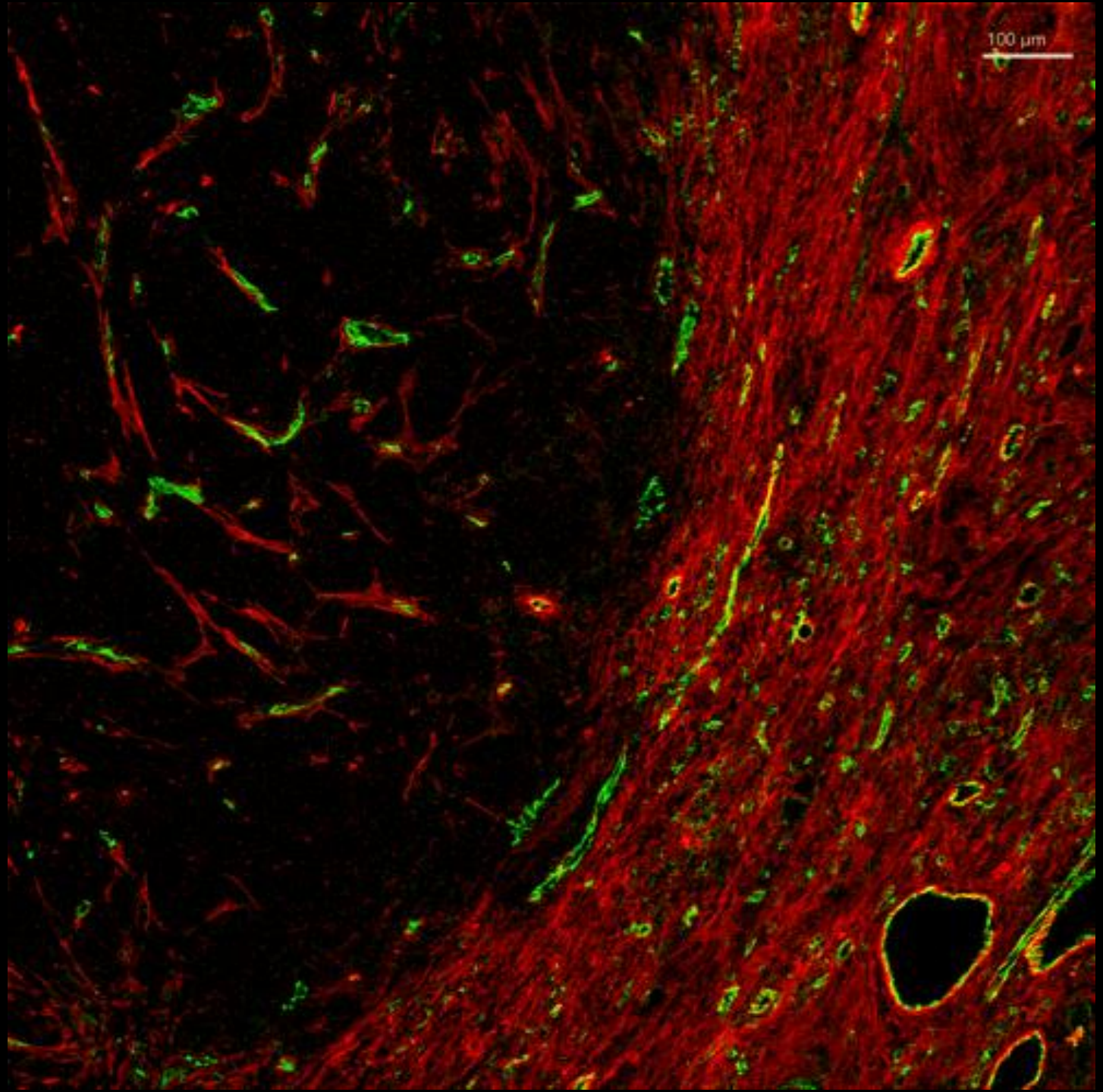
Seeing the Big Picture —
Imaging the immune response to lung malignancies using highly multiplexed mass cytometry

// *C.R.P. Research Day*



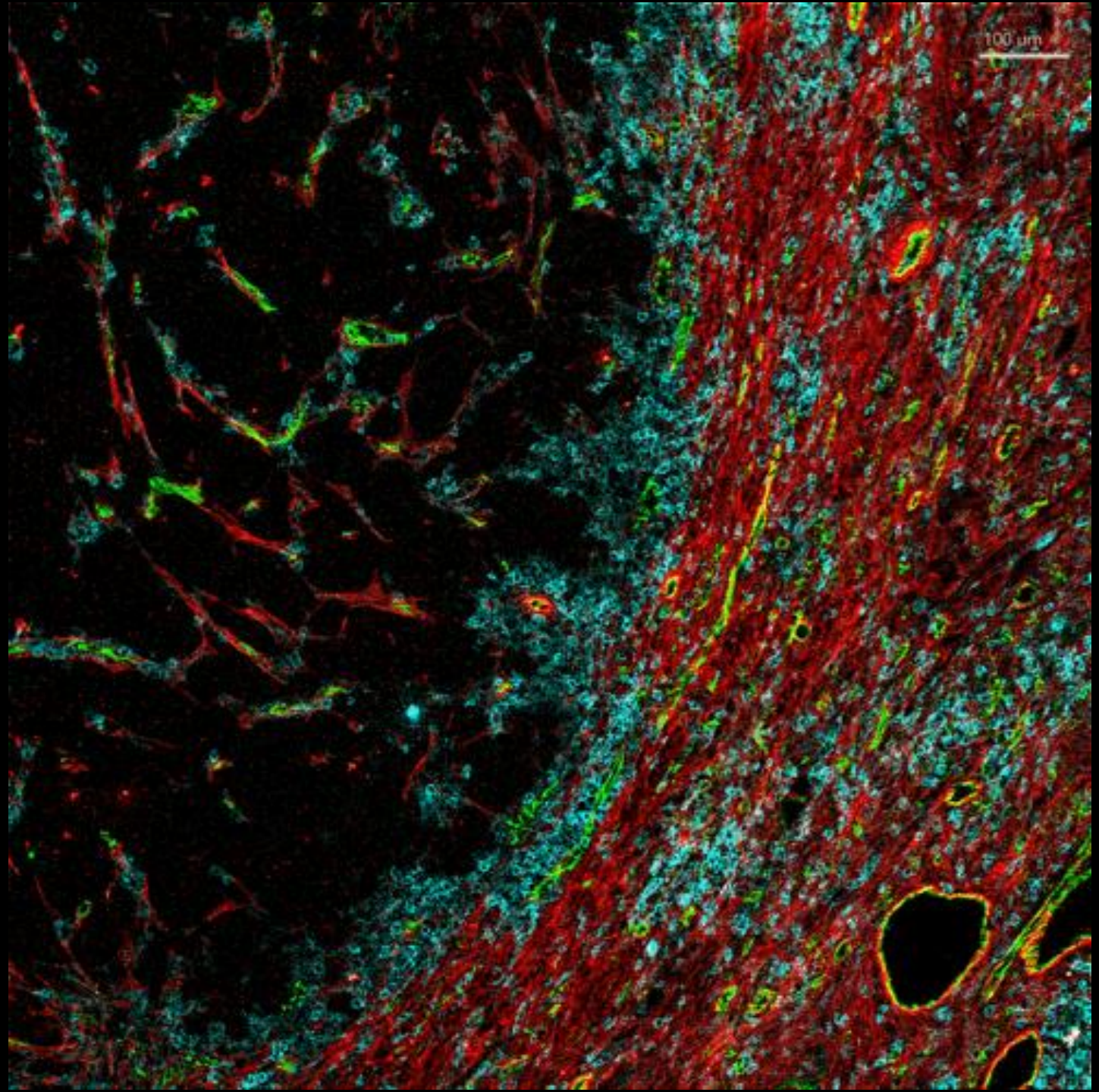


SMA



SMA

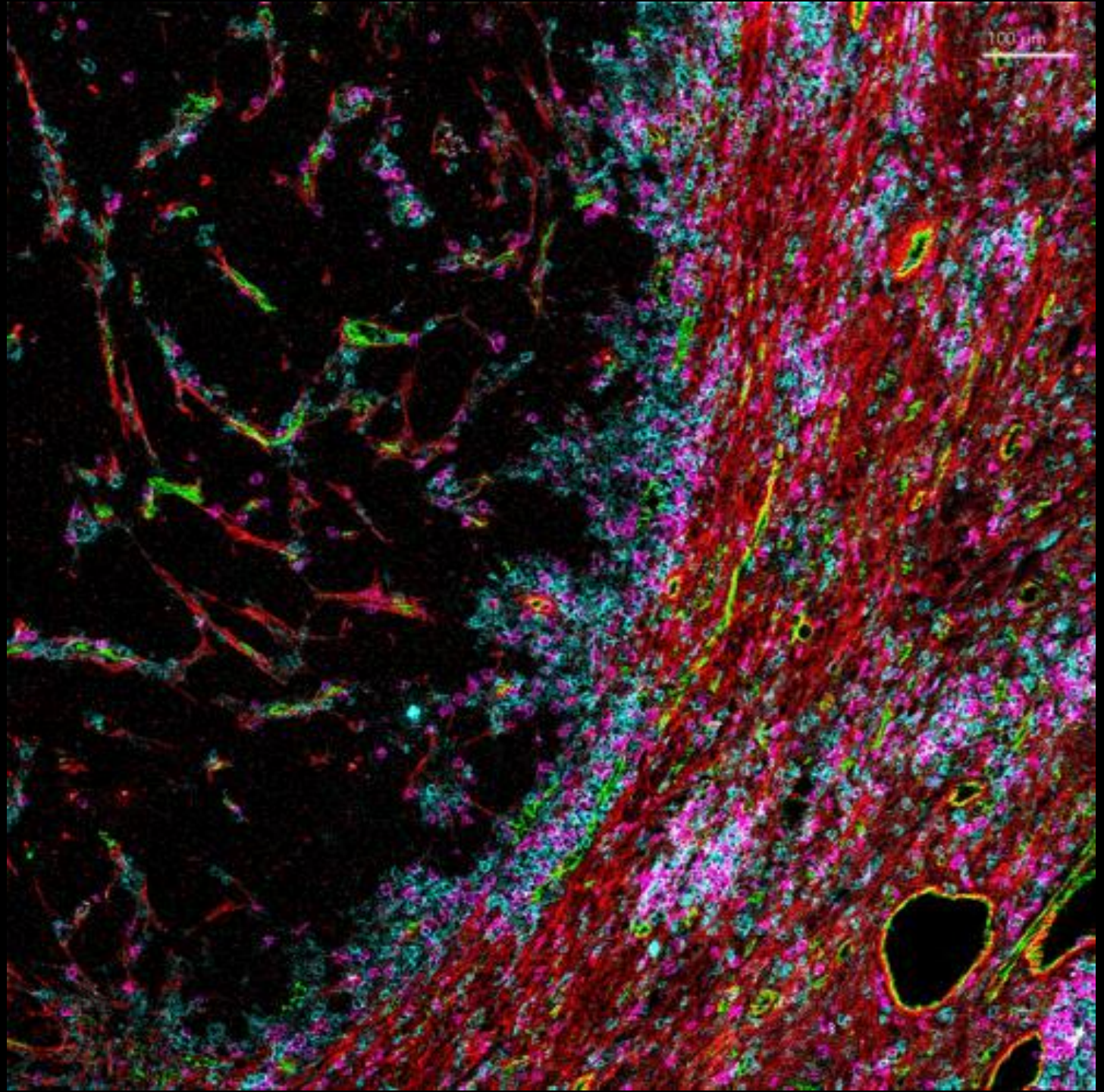
CD31



SMA

CD31

CD4

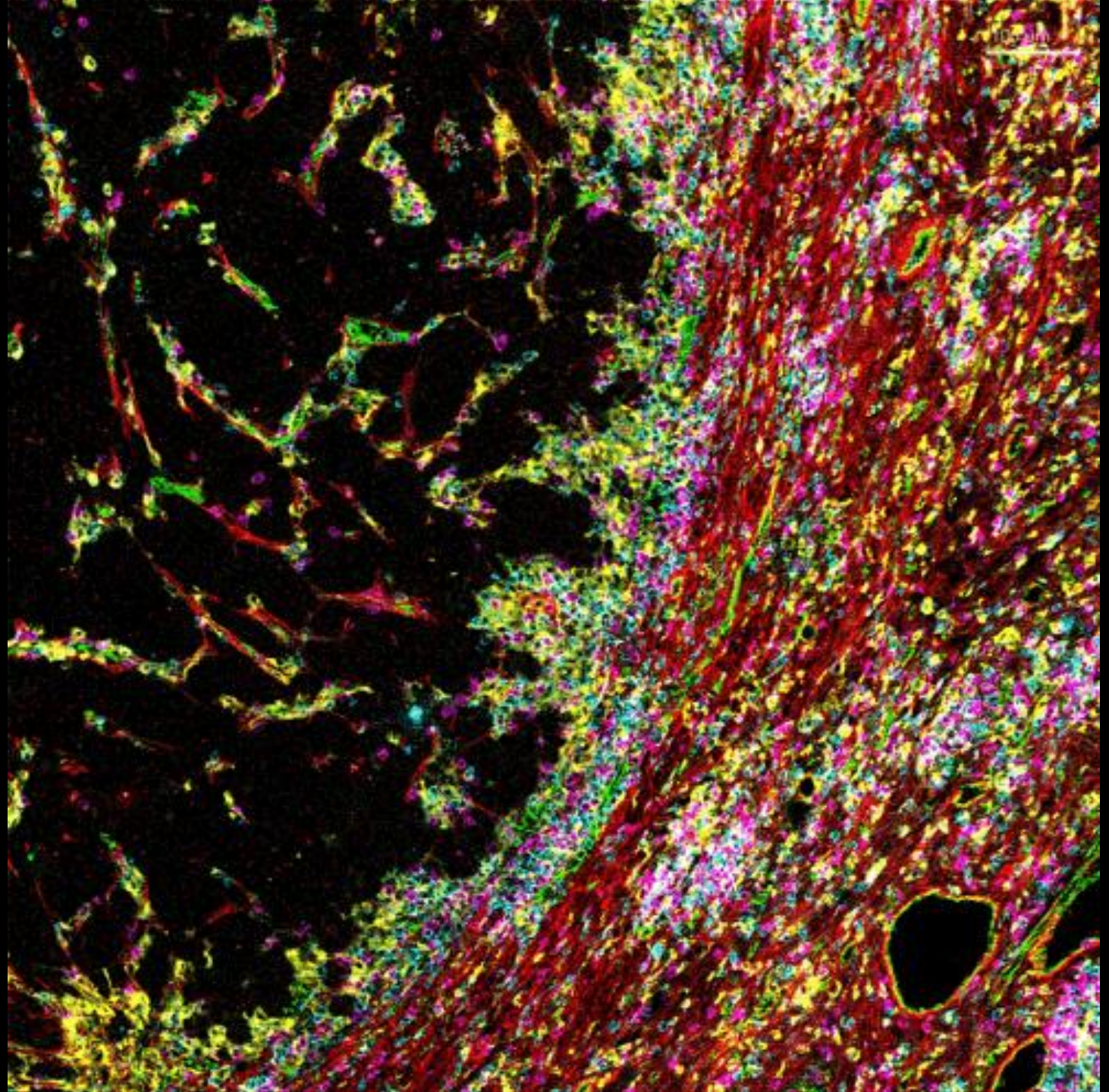


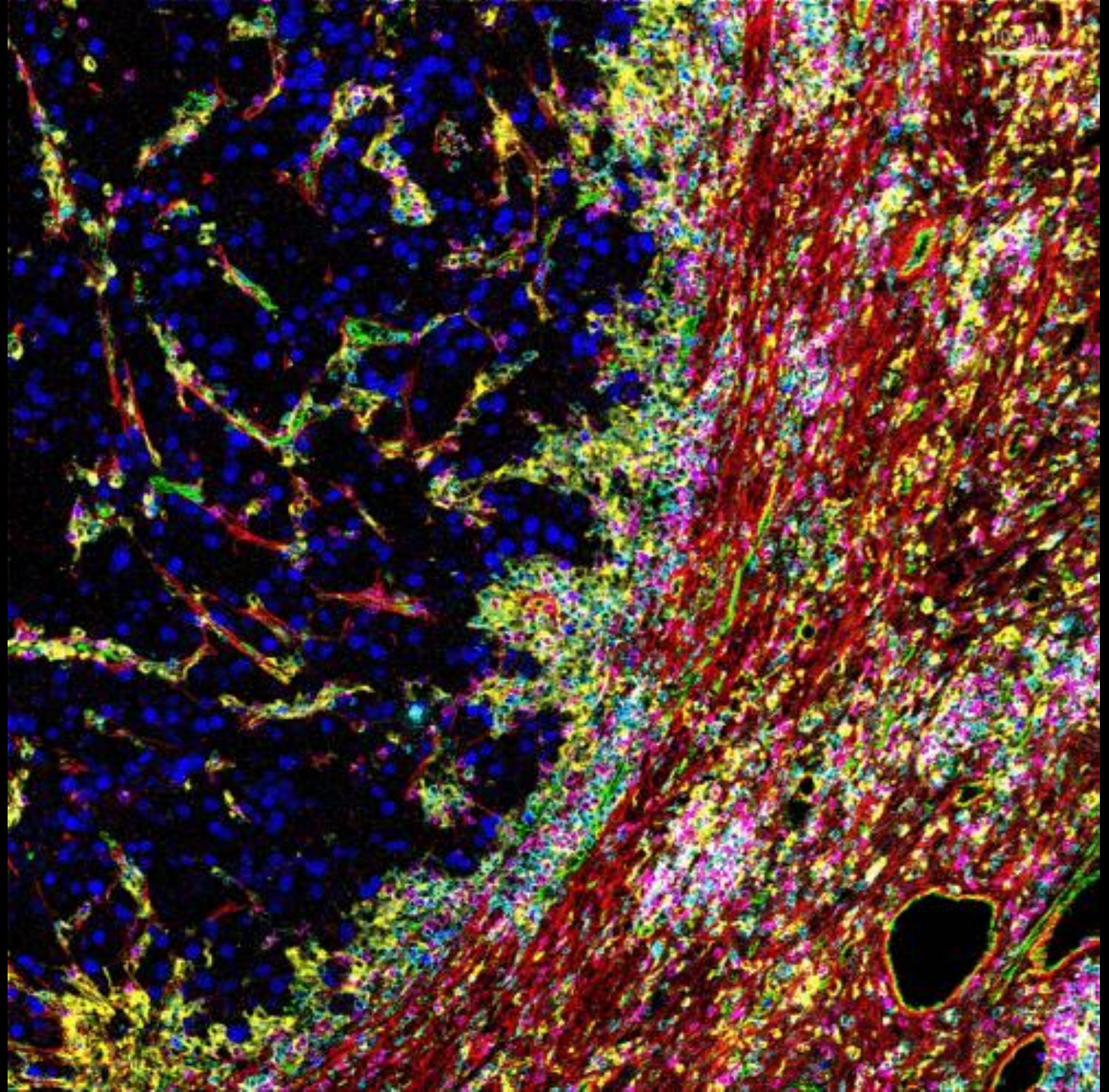
SMA

CD31

CD4

CD8a


SMA
CD31
CD4
CD8a
CD68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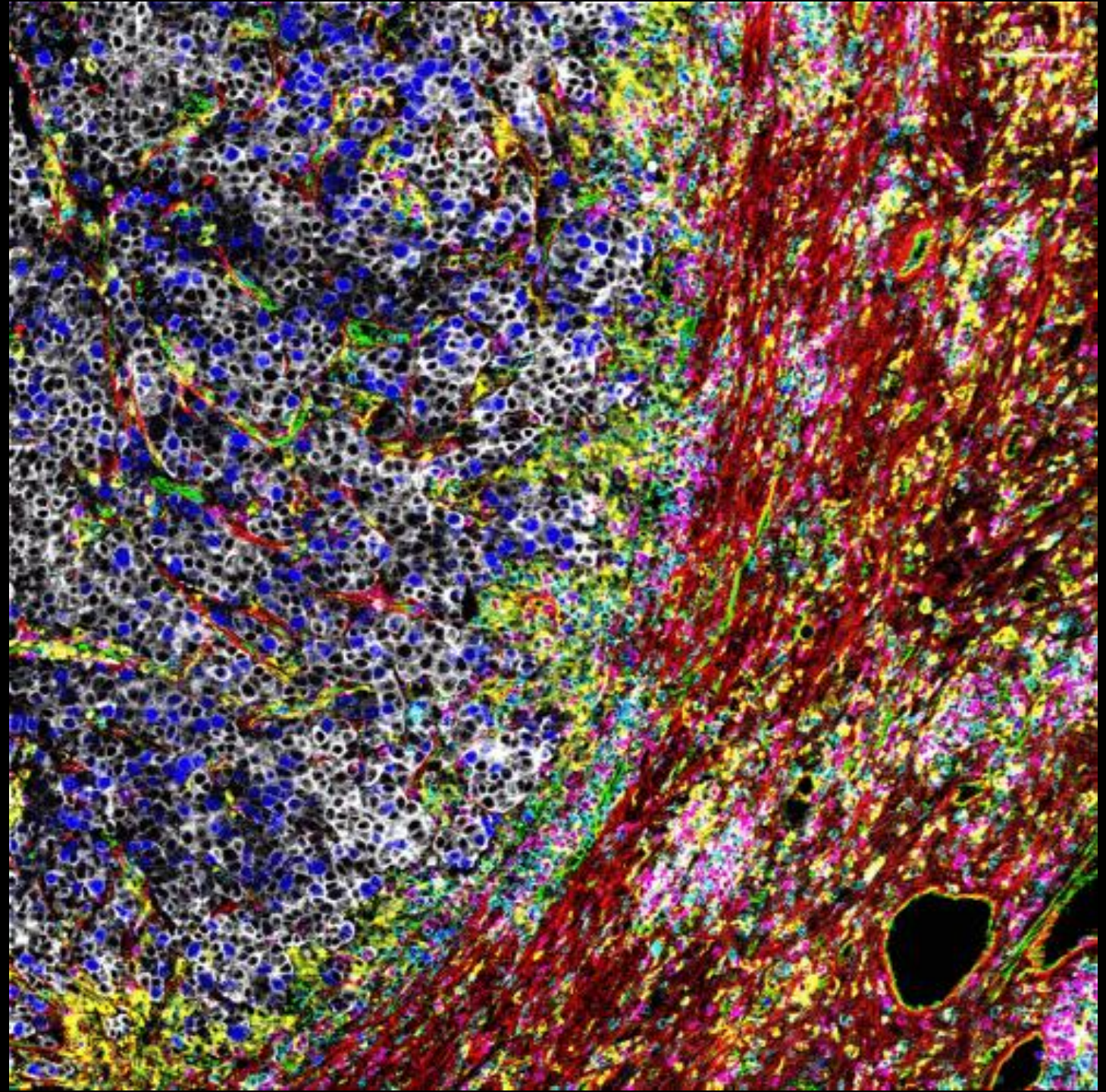
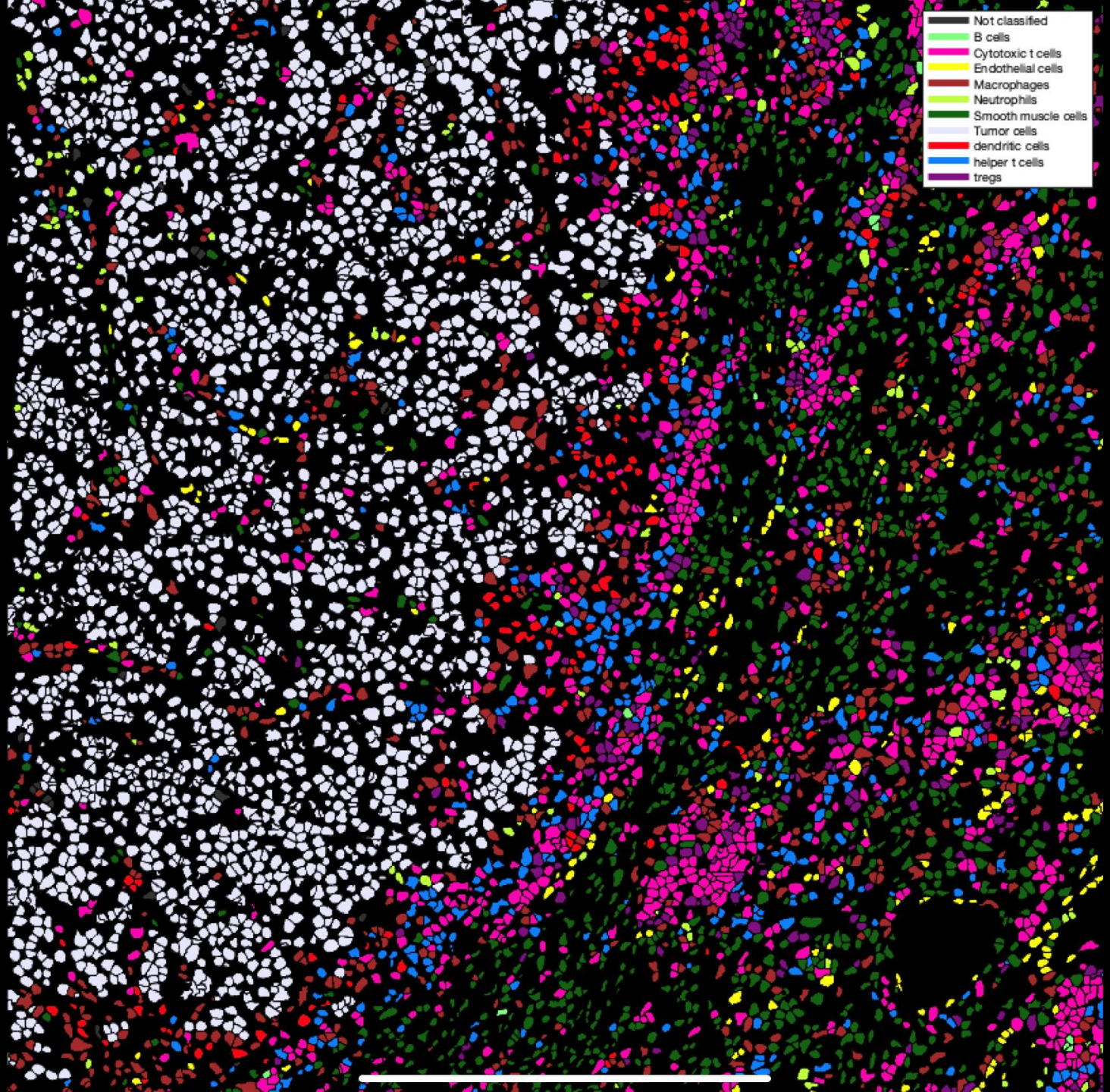
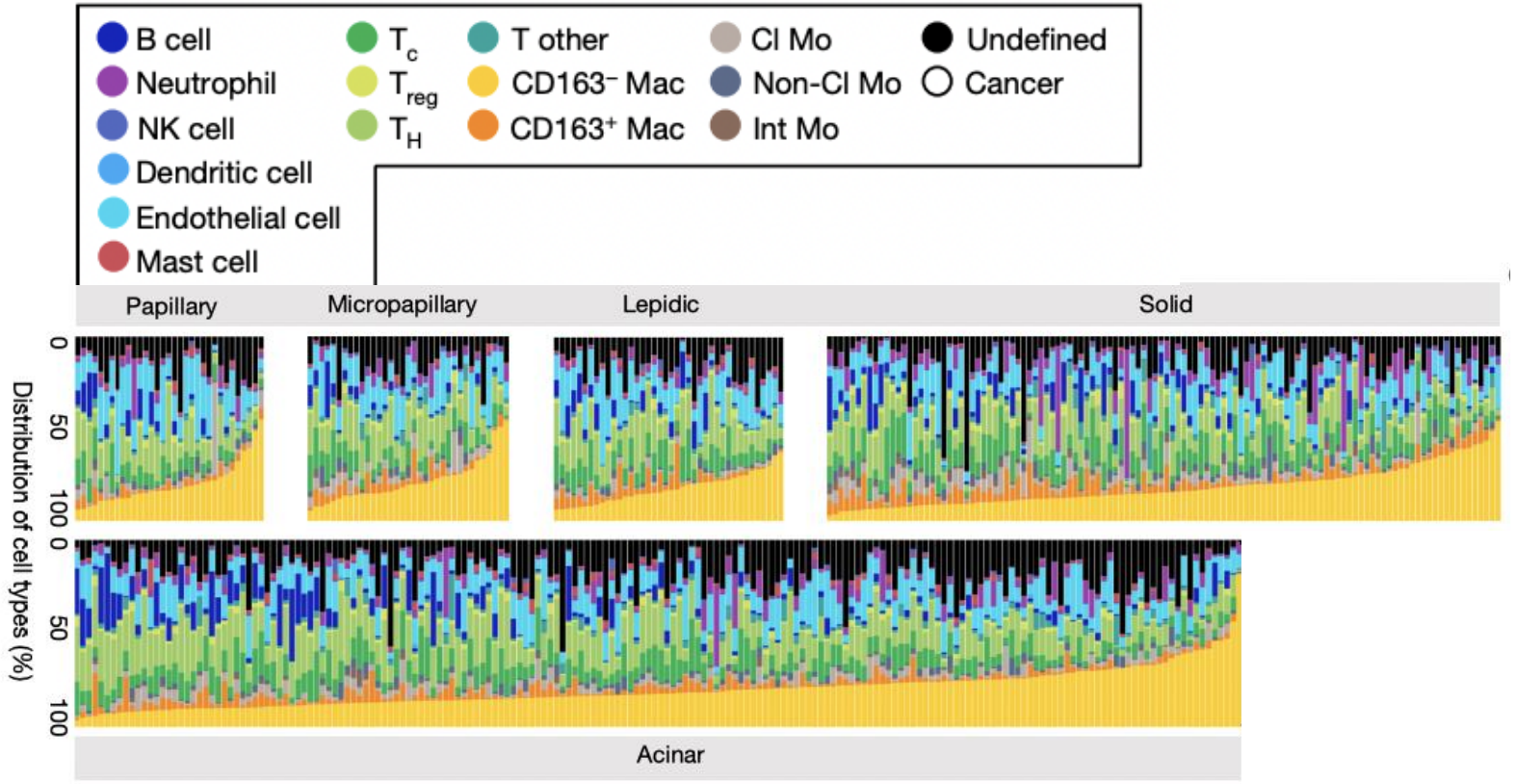
CD8a
CD68
Ki67

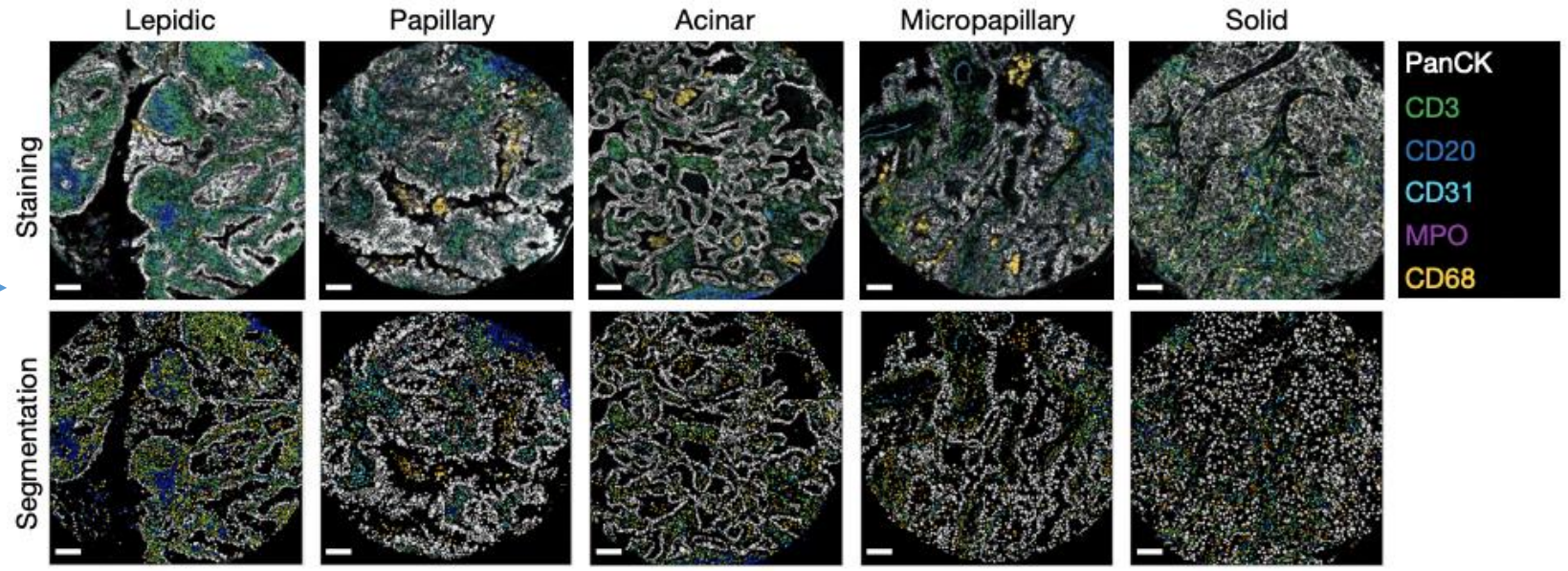


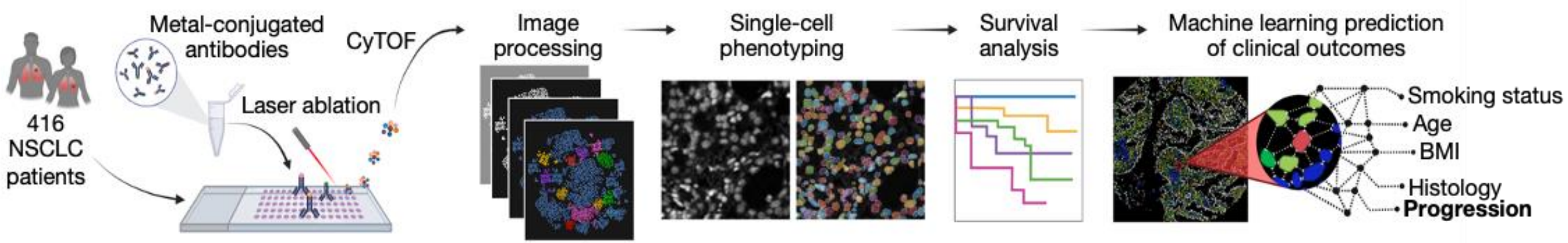
SMA
CD31
CD4
CD8a
CD68
Ki67
PanCK


Not classified
B cells
Cytotoxic t cells
Endothelial cells
Macrophages
Neutrophils
Smooth muscle cells
Tumor cells
dendritic cells
helper t cells
tregs



Extensive characterization of the Tumor-Immune MicroEnvrionment of lung adeno ca





- Stage I adeno ca
- 1 mm^2 FFPE section
- 4 µm thickness
- 36 mAb panel for immune/stromal/tumoral lineage ID

Progression
@ 3 years

YES

AUC > 0.95

NO

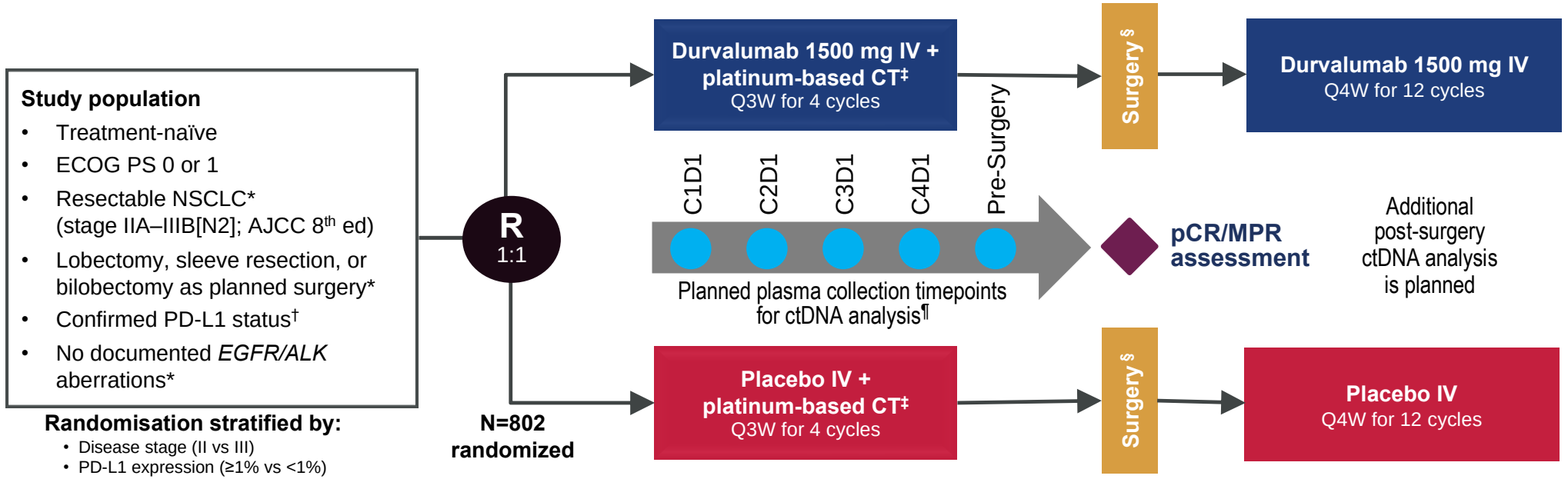
Key unmet need #5: Can we omit surgery if we can predict PCR accurately?

ctDNA assessments during neoadjuvant therapy

AEGEAN Study Design

Reck et al, ESMO 2023

Phase 3, global, randomised, double-blind, placebo-controlled study



- Plasma samples were collected at protocol-specified timepoints, including prior to each neoadjuvant treatment cycle and before surgery
- Analysis was performed using Invitae Personalized Cancer Monitoring™, a tumour-informed MRD assay[1]
  - Patient-specific tumour-informed panels were designed to include 16-50 variants, identified by whole exome sequencing of treatment-naïve diagnostic biopsies only (rather than on-study surgical resections) to avoid selection bias

MADRID 2023 ESMO congress

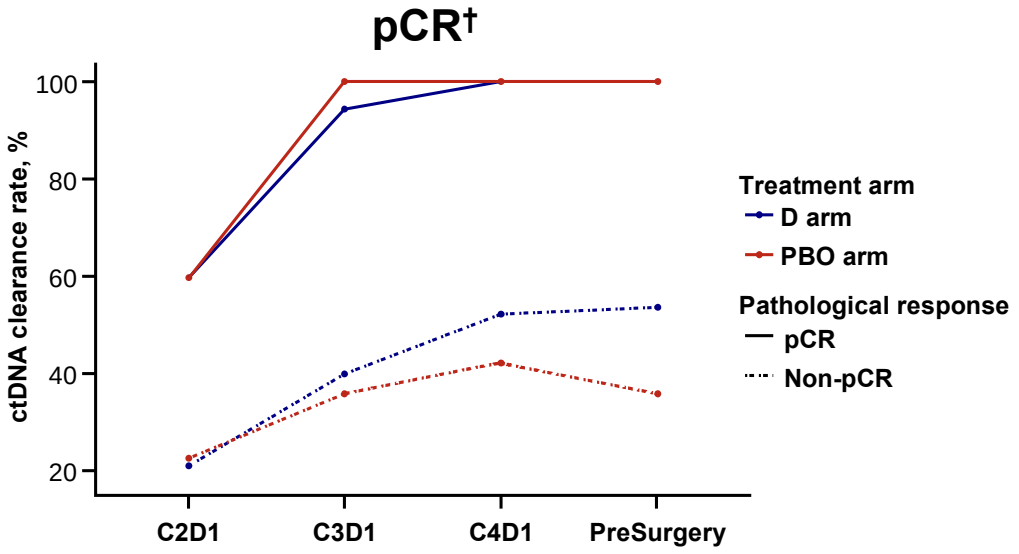
*The protocol was amended while enrolment was ongoing to exclude (1) patients with tumours classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy was permitted where indicated per local guidance. ¶Not all patients had samples available at all timepoints. AJCC, American Joint Committee on Cancer; CT, chemotherapy; ctDNA, circulating tumour DNA; CXDX, cycle X day X; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MPR, major pathologic response; MRD, molecular residual disease; pCR, pathologic complete response; QXW, every X weeks; R, randomisation.

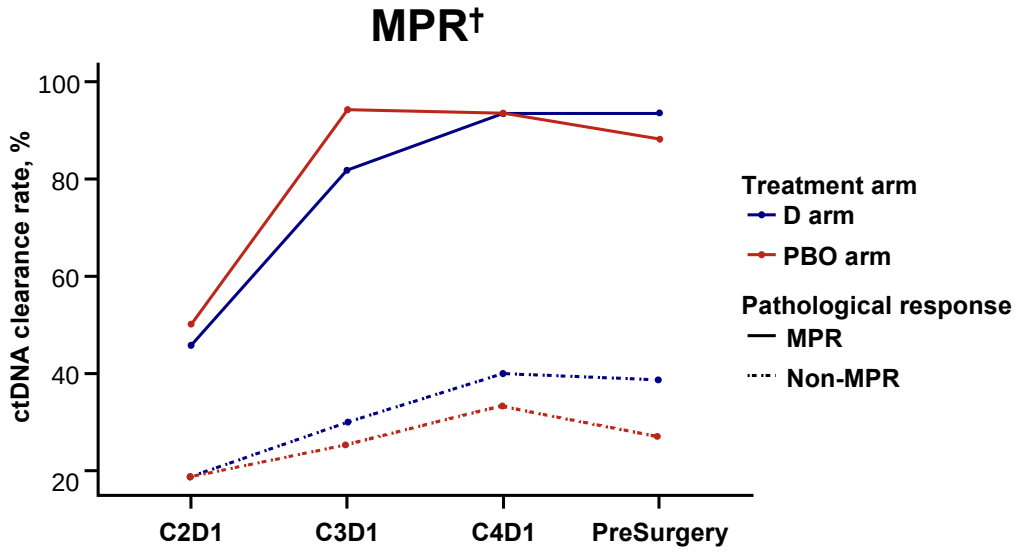
1. Zhao J, et al. Mol Diagn Ther. 2023 Aug 26. Online ahead of print.

ctDNA clearance dynamics track with PCR

Association of ctDNA Clearance with pCR/MPR and Its Predictive Utility

- Among patients who were ctDNA-positive at baseline (C1D1), all patients achieving pCR and >90% of all patients achieving MPR had ctDNA clearance at C4D1*





- Patients without ctDNA clearance were unlikely to achieve pCR (NPV > 84.0% at C2D1 in both arms)
- Patients who achieved ctDNA clearance in the D arm vs the PBO arm were more likely to achieve pCR (PPV = 50.0% vs 14.3% at C2D1)

Predictive value of ctDNA clearance at different timepoints for pCR

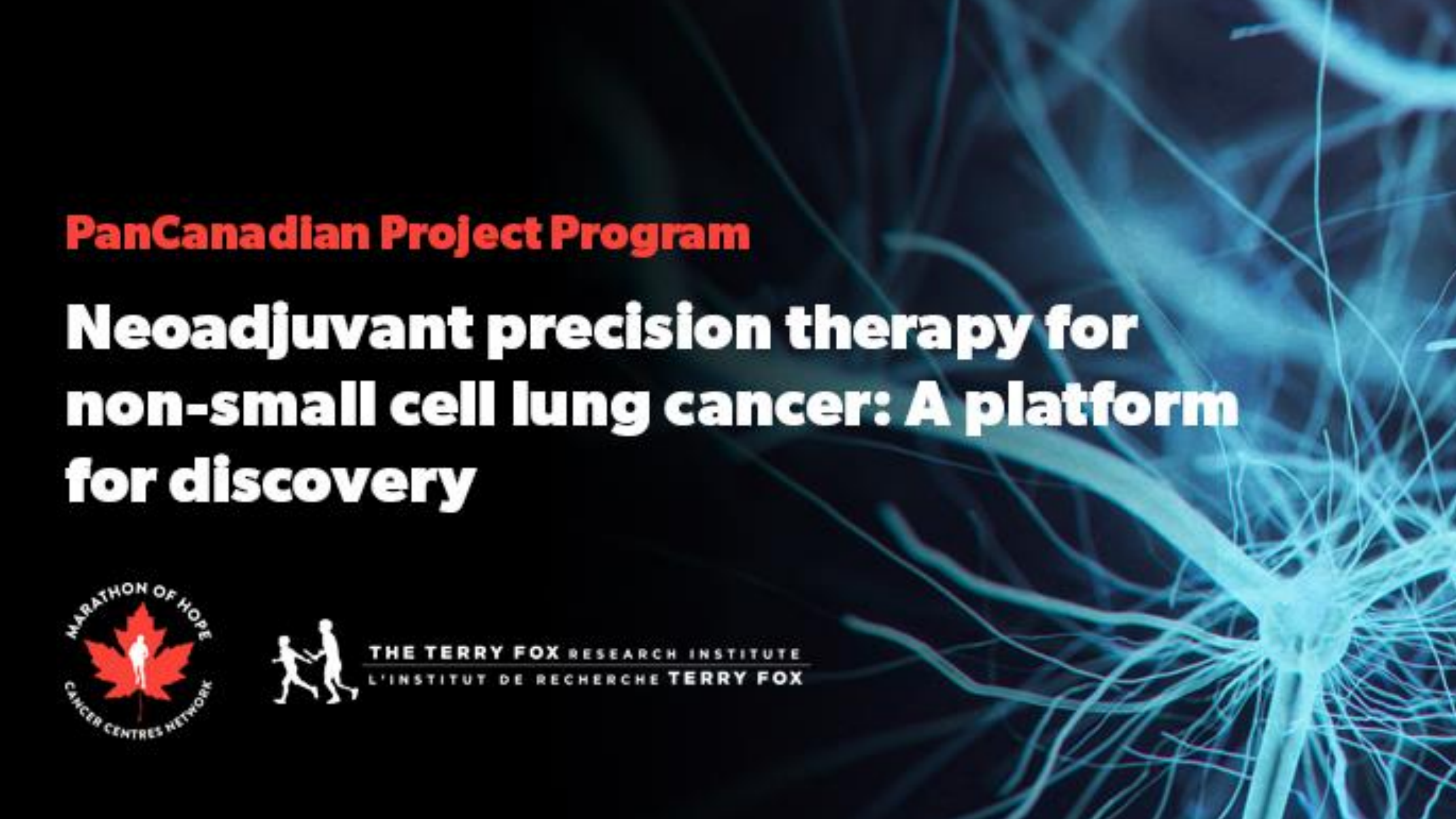
D arm	pCR	
	PPV	NPV
C2D1	50.0%	84.9%
C3D1	43.6%	97.1%
C4D1	40.5%	100.0%
PreSurgery	41.5%	100.0%

PBO arm	pCR	
	PPV	NPV
C2D1	14.3%	96.9%
C3D1	18.2%	100.0%
C4D1	18.2%	100.0%
PreSurgery	19.4%	100.0%

*In the BEP, pCR (25.6% vs 6.3%) and MPR (44.4% vs 18.8%) rates were higher in the D arm vs the PBO arm.
†The plots include all evaluable patients at each timepoint.
NPV, negative predictive value; PPV, positive predictive value.

PanCanadian Project Program

Neoadjuvant precision therapy for non-small cell lung cancer: A platform for discovery



Take home messages

- Embrace change and don’t get too comfortable!
- ”Skate to where the puck is going, not where is has been”
  - Wayne Gretzky
- We have only seen the tip of the iceberg
- A robust understanding of medical oncology is required for modern high level lung cancer surgery
- We must leverage both the curative potential of surgery and its unique potential for discovery

Questions?

McGill | Department of Surgery