ESMO ON AIR

Non-metastatic non-small-cell lung cancer

ESMO DEEP DIVE WEBINAR SERIES: LUNG CANCER

Enriqueta Felip, *Chair*

Vall d'Hebron Institute of Oncology (VHIO)

Spain

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Programme

5 March 2025

5 min	**Welcome and introduction** Enriqueta Felip
15 min	**Surgery – controversies and challenges (e.g. Pancoast, N2..)** Jonathan Spicer
15 min	**Radiation – opportunities, future directions** Corinne Finn
15 min	**Systemic therapy – key challenges moving from trials into practice** Federico Cappuzzo
15 min	**QnA and Discussion** All speakers

Enriqueta Felip
Chair
Vall d'Hebron University Hospital
Vall d'Hebron Institute of Oncology (VHIO)
Barcelona

Jonathan Spicer
Speaker
McGill University

Corinne Faivre-Finn
Speaker
University of Manchester

Federico Cappuzzo
Speaker
National Cancer Institute Regina Elena

Learning objectives

- To acquire a deeper understanding of the clinical course of lung cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for lung cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO DEEP DIVE: LUNG CANCER

SURGERY – CONTROVERSIES AND CHALLENGES

Jonathan Spicer, MD PhD

McGill University Health Center, Montreal, Canada

ESMO WEBINAR SERIES

CONFLICTS OF INTEREST

Commercial Interest	Relationship(s)
AstraZeneca, Merck, Roche, BMS, Novartis, Chemocentryx, Amgen, Protalix Biotherapeutics, Xenetic Biosciences, Regeneron, Eisai, Peerview, OncLive, Medscape, Pfizer	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

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*

Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

Jonathan D Spicer, Marina C Garassino*, Heather Wakelee, 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 E Chaft, Silvia Novello, Jing Yang, Ashwini Arunachalam, Steven M Keller, Ayman Samkari, Shugeng Gao, on behalf of the KEYNOTE-671 Investigators†*

ORIGINAL ARTICLE

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

Masahiro Tsuboi, M.D., Roy S. Herbst, M.D., Ph.D., Thomas John, M.B., B.S., Ph.D., Terufumi Kato, M.D., Margarita Majem, M.D., Ph.D., Christian Grohé, M.D., Jie Wang, M.D., Ph.D., Jonathan W. Goldman, M.D., Shun Lu, M.D., Wu-Chou Su, M.D., Filippo de Marinis, M.D., Frances A. Shepherd, M.D., Ki Hyeong Lee, M.D., Ph.D., Nhieu Thi Le, M.D., Arunee Dechaphunkul, M.D., Dariusz Kowalski, M.D., Ph.D., Lynne Poole, M.Sc., Ana Bolanos, M.D., Yuri Rukazenkov, M.D., Ph.D., and Yi-Long Wu, M.D., for the ADAURA Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

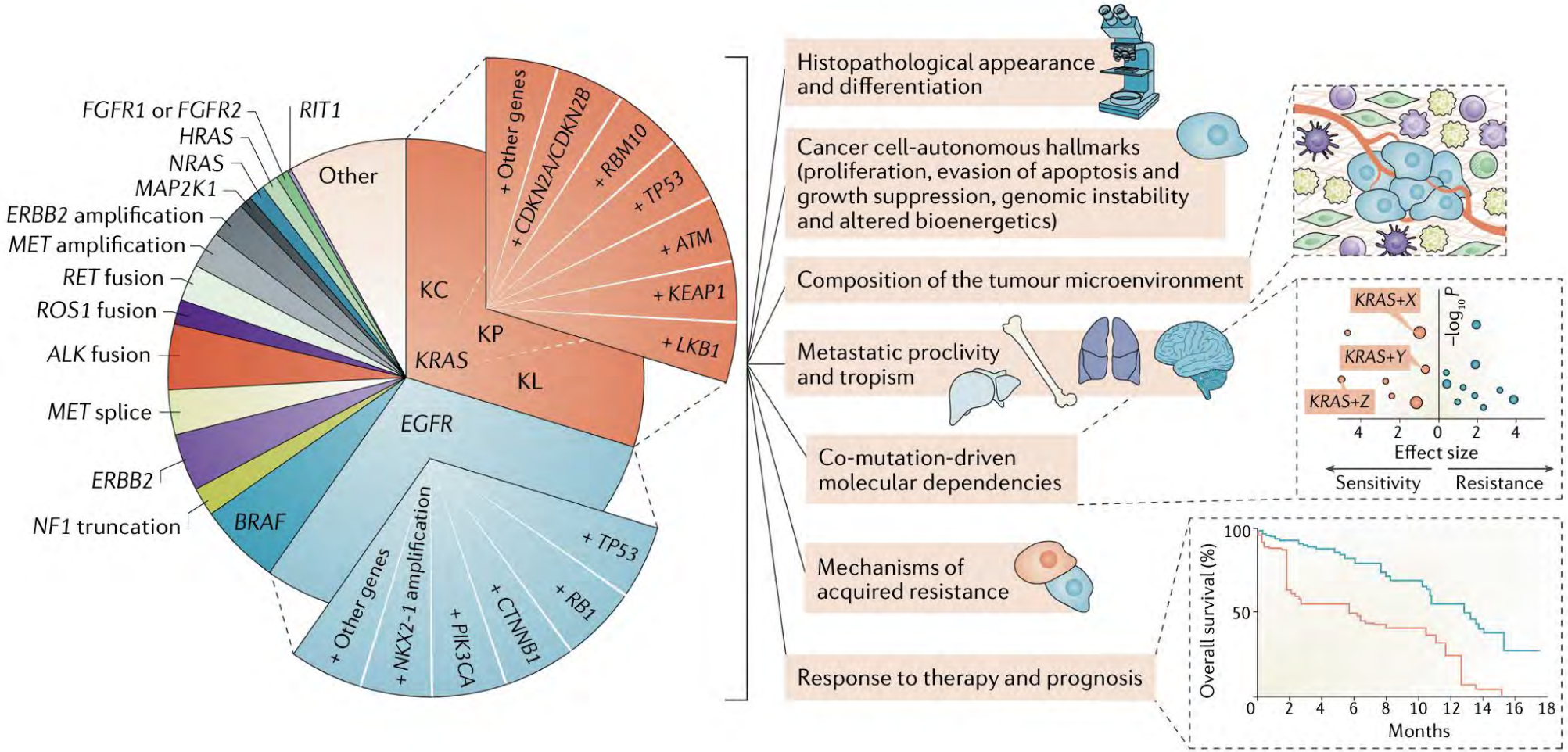
ESTABLISHED IN 1812 APRIL 11, 2024 VOL. 390 NO. 14

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

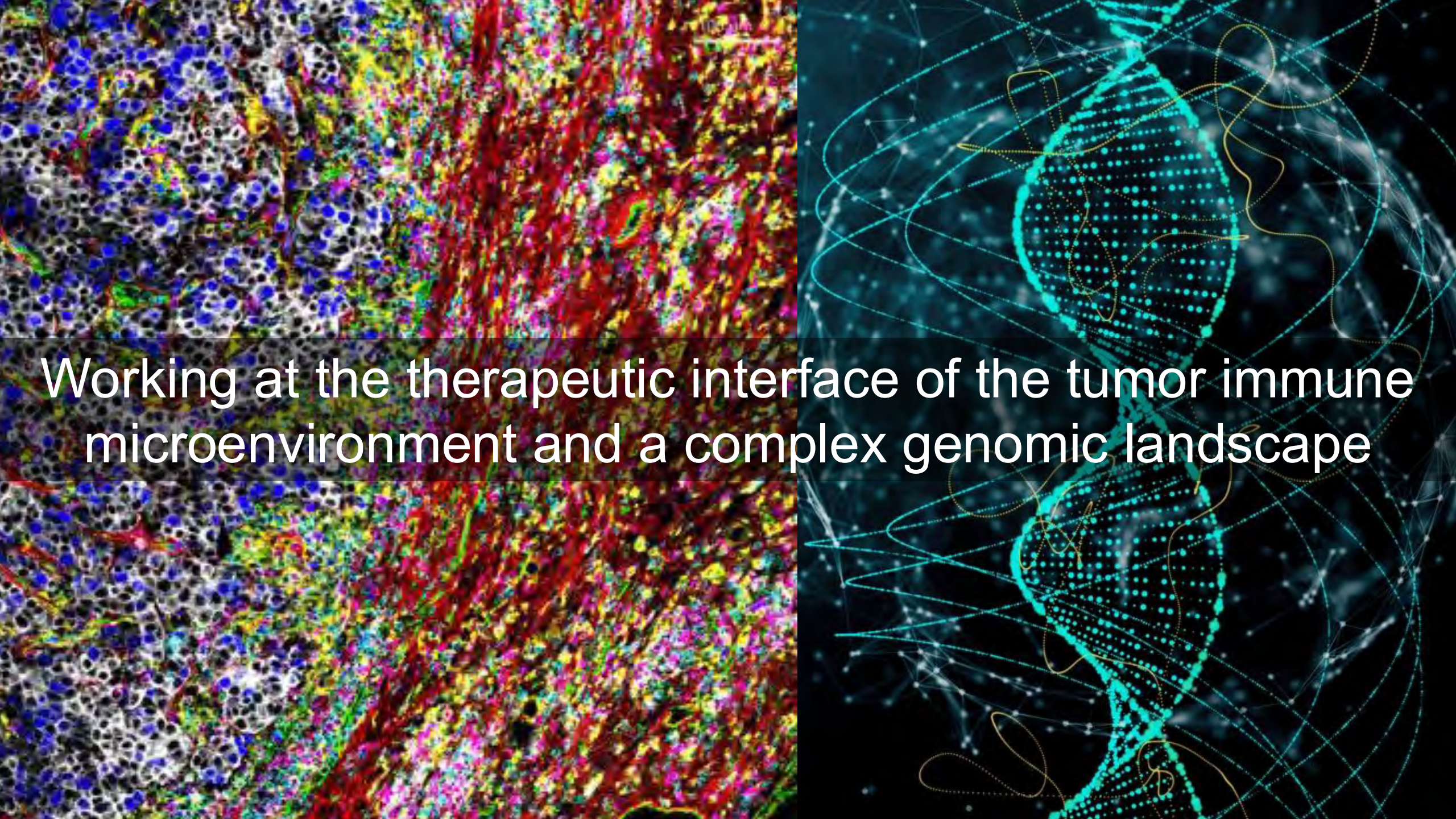
Yi-Long Wu, M.D., Rafal Dziadziuszko, M.D., Ph.D., Jin Seok Ahn, M.D., Ph.D., Fabrice Barlesi, M.D., Ph.D., Makoto Nishio, M.D., Ph.D., Dae Ho Lee, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., Wenzhao Zhong, M.D., Ph.D., Hidehito Horinouchi, M.D., Ph.D., Weimin Mao, M.D., Ph.D., Maximilian Hochmair, M.D., Filippo de Marinis, M.D., M. Rita Migliorino, M.D., Igor Bondarenko, M.D., Ph.D., Shun Lu, M.D., Qun Wang, M.D., Tania Ochi Lohmann, Ph.D., Tingting Xu, M.D., Andres Cardona, M.Sc., Thorsten Ruf, M.D., Johannes Noe, Ph.D., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the ALINA Investigators*

Early-stage landscape has now changed forever…

NSCLC IS A COLLECTION OF MOLECULARLY-DEFINED RARE DISEASES: IO VS TARGETS VS BOTH?



Skoulidis & Heymach, Nat Rev Cancer, 2019


Working at the therapeutic interface of the tumor immune microenvironment and a complex genomic landscape

ATTITUDES TO SHIFTING STANDARDS

SPECIAL ARTICLE

IASLC

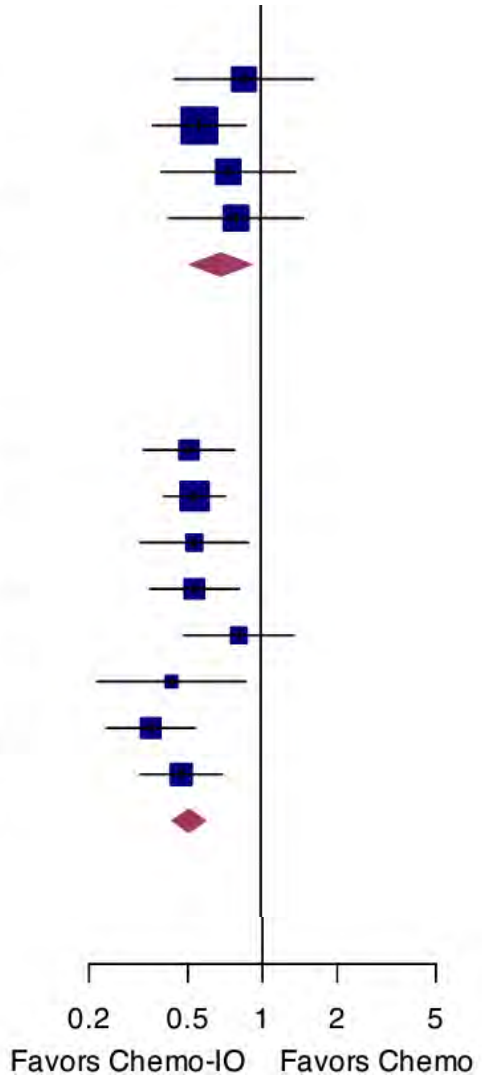
Neoadjuvant and Adjuvant Treatments for Early Stage Resectable NSCLC: Consensus Recommendations From the International Association for the Study of Lung Cancer

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,*]

Recommendation 7	Neoadjuvant chemoimmunotherapy is strongly preferred to upfront surgery for medically operable patients with resectable clinical stage IIIA or IIIB NSCLC at first presentation, irrespective of PD-L1 expression level.	94	79
Recommendation 15	Neoadjuvant chemoimmunotherapy followed by surgery is preferred to upfront surgery for medically operable patients with technically resectable clinical stage II NSCLC at first presentation, regardless of PD-L1 expression level.	65	55

NEOADJ/PERIOP CHEMO-IO IMPROVES EFS IN STAGE II

Stage II				
Forde 2022%	Stage II	65	62	0.87 [0.48; 1.56]
Wakelee 2023	Stage II	118	121	0.59 [0.40; 0.88]
Heymach 2023	Stage II	104	110	0.76 [0.43; 1.34]
Cascone 2023	Stage II	81	81	0.81 [0.46; 1.43]
Random effects model		**368**	**374**	**0.71 [0.55; 0.92]**
Heterogeneity: I^2 = 0%, τ^2 = < 0.1, p = 0.68				
Stage III				
Forde 2022	Stage III	113	115	0.54 [0.37; 0.80]
Wakelee 2023a	Stage III	217	224	0.57 [0.44; 0.74]
Wakelee 2023b	Stage III	62	55	0.57 [0.36; 0.90]
Heymach 2023a	Stage III	173	165	0.57 [0.39; 0.83]
Heymach 2023b	Stage III	88	98	0.83 [0.52; 1.32]
Provencio 2023	Stage III	57	29	0.47 [0.25; 0.88]
Lu 2023	Stage III	202	202	0.39 [0.27; 0.57]
Cascone 2023	Stage III	146	149	0.51 [0.36; 0.72]
Random effects model		**1058**	**1037**	**0.54 [0.48; 0.62]**
Heterogeneity: I^2 = 0%, τ^2 = < 0.1, p = 0.47				

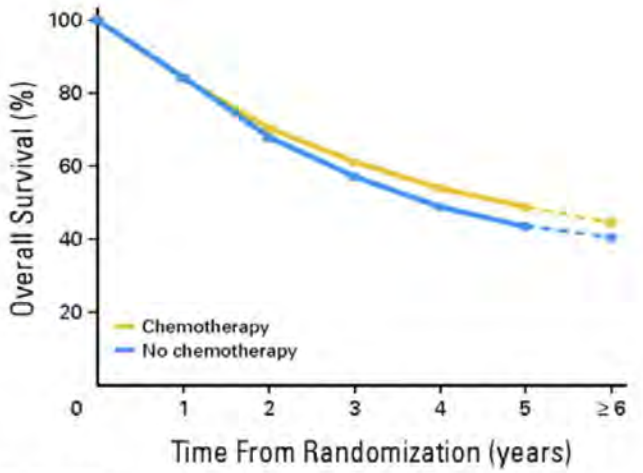


Sorin et al, JAMA Onc 2024

HOW QUICKLY WE FORGET…

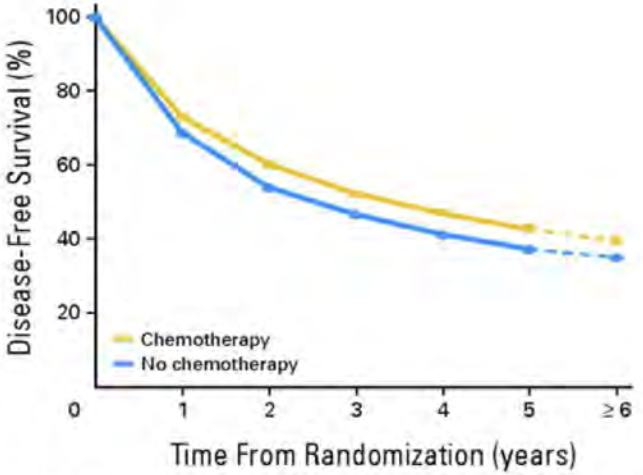
Basis for the SoC of adjuvant chemotherapy: LACE meta analysis w/ HR 0.83

A

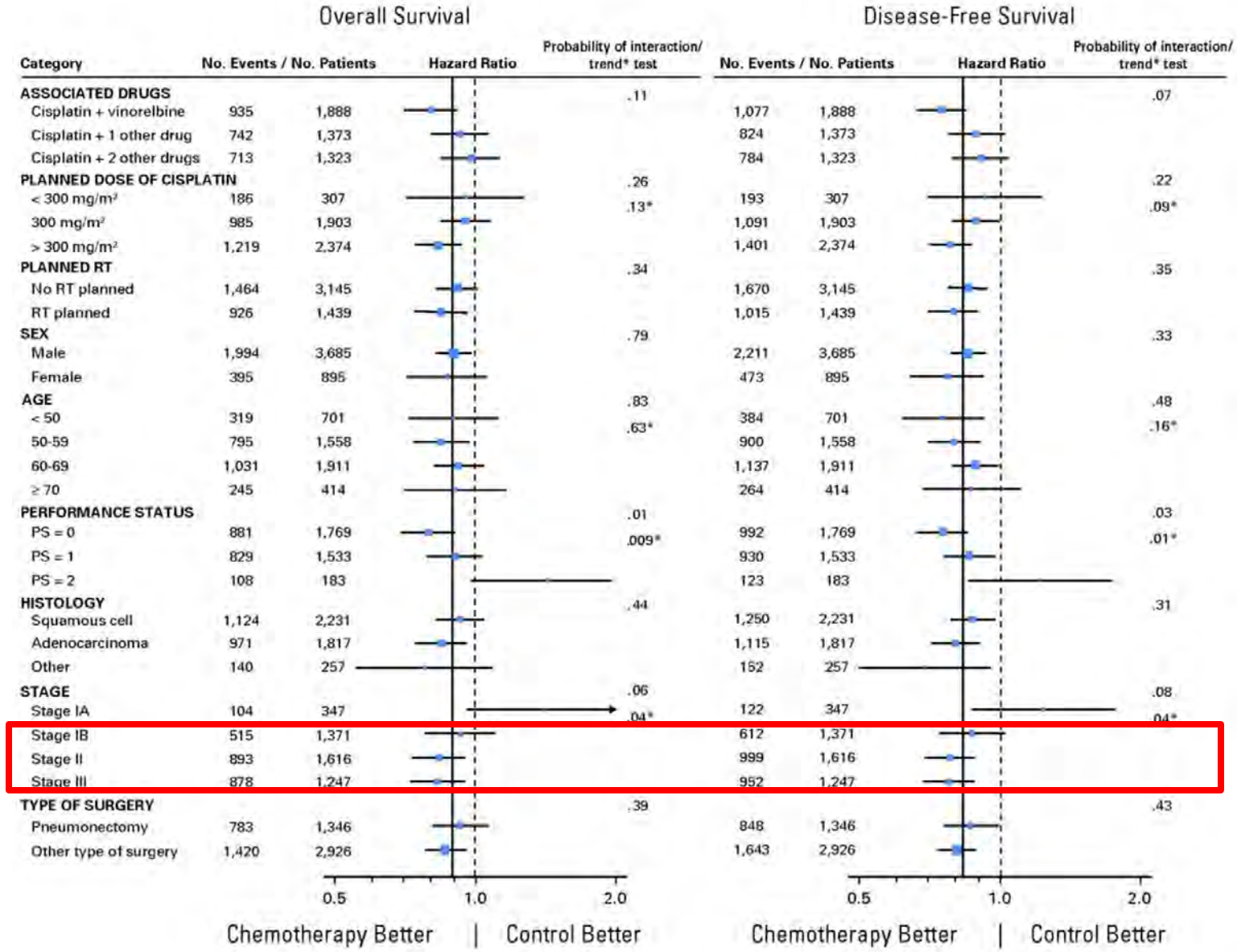


Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

B

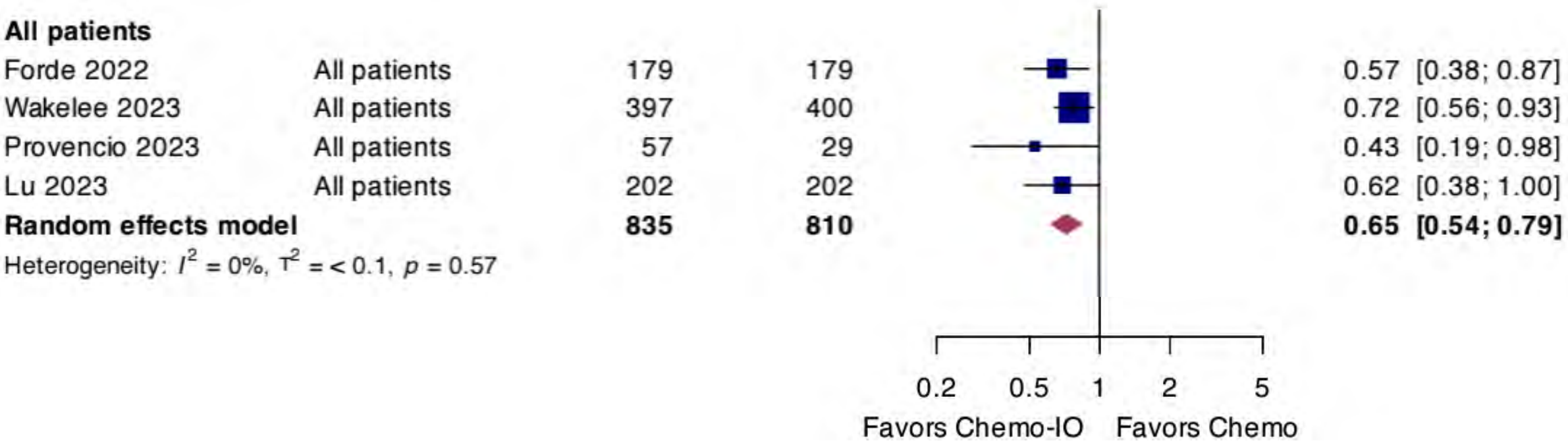


Events / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	1,222 / 4,341	163 / 1,396	35 / 610
Chemotherapy	1,047 / 4,627	159 / 1,606	59 / 708



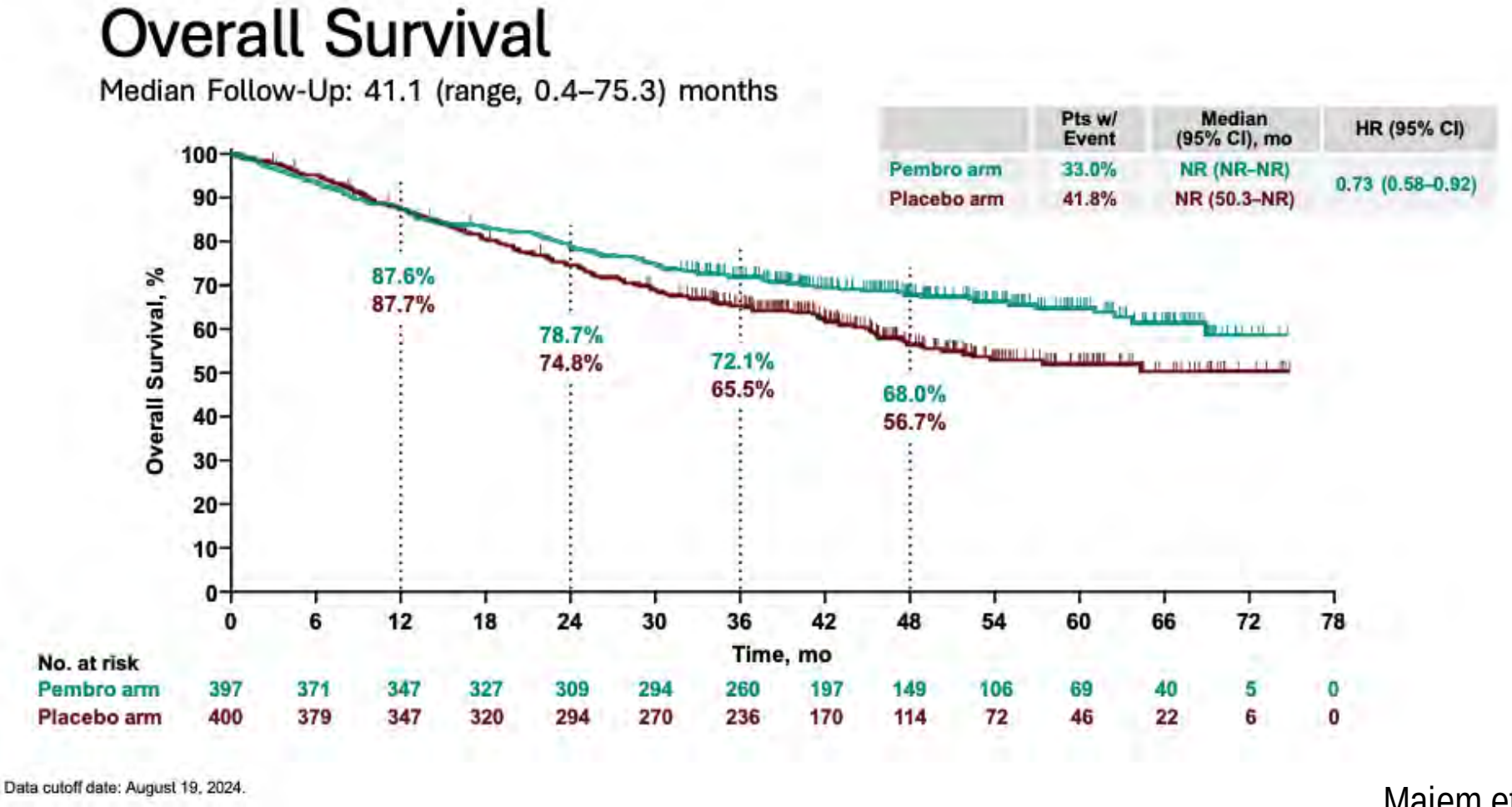
NEOADJ/PERIOP CHEMO-IO IMPROVES OS!

Neoadj/periop improves OS in ITT population (N=1645 pts)



Sorin et al, JAMA Onc 2024

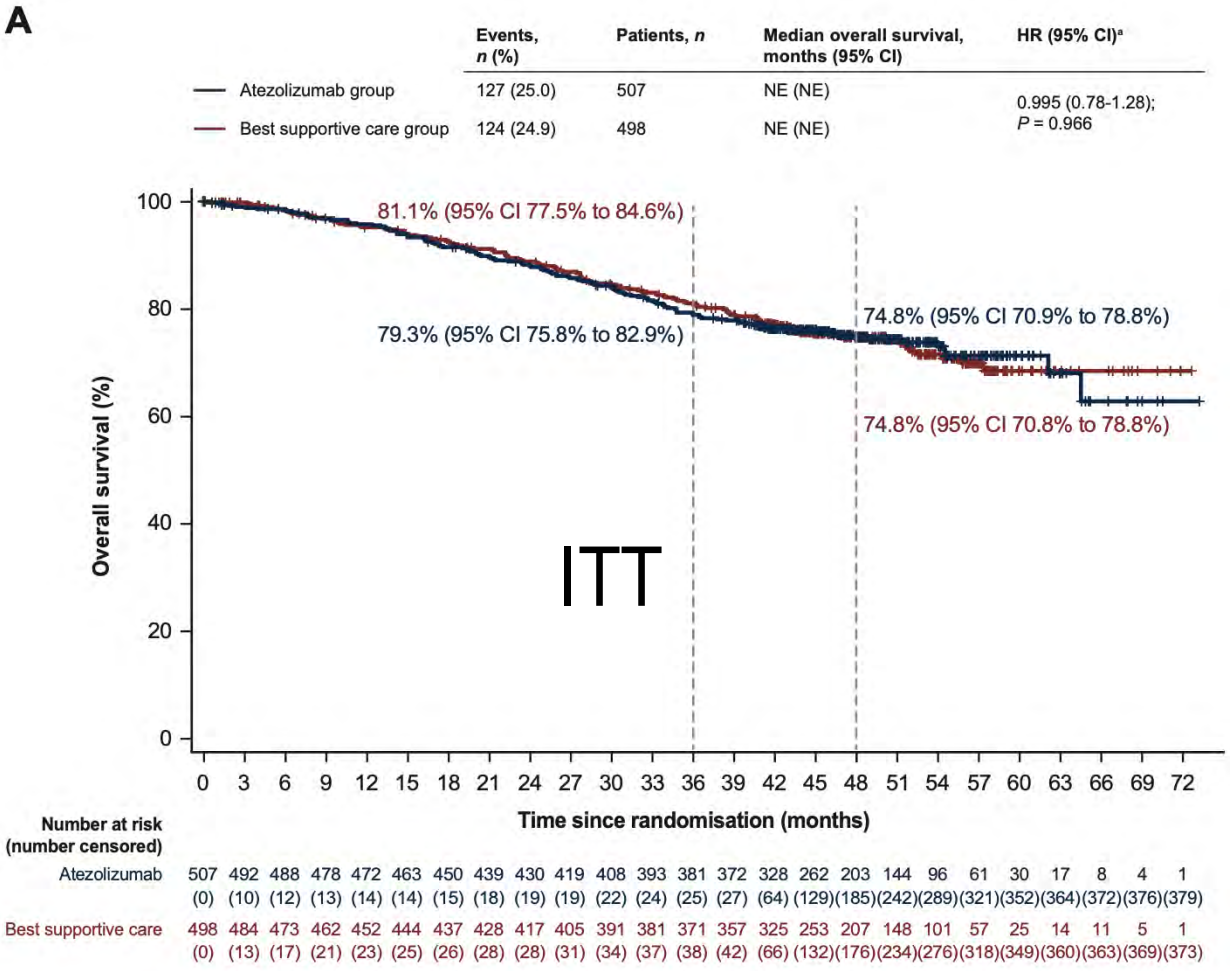
KN671 - FIRST NEOADJ/PERIOP TO SHOW OS BENEFIT IN ITT



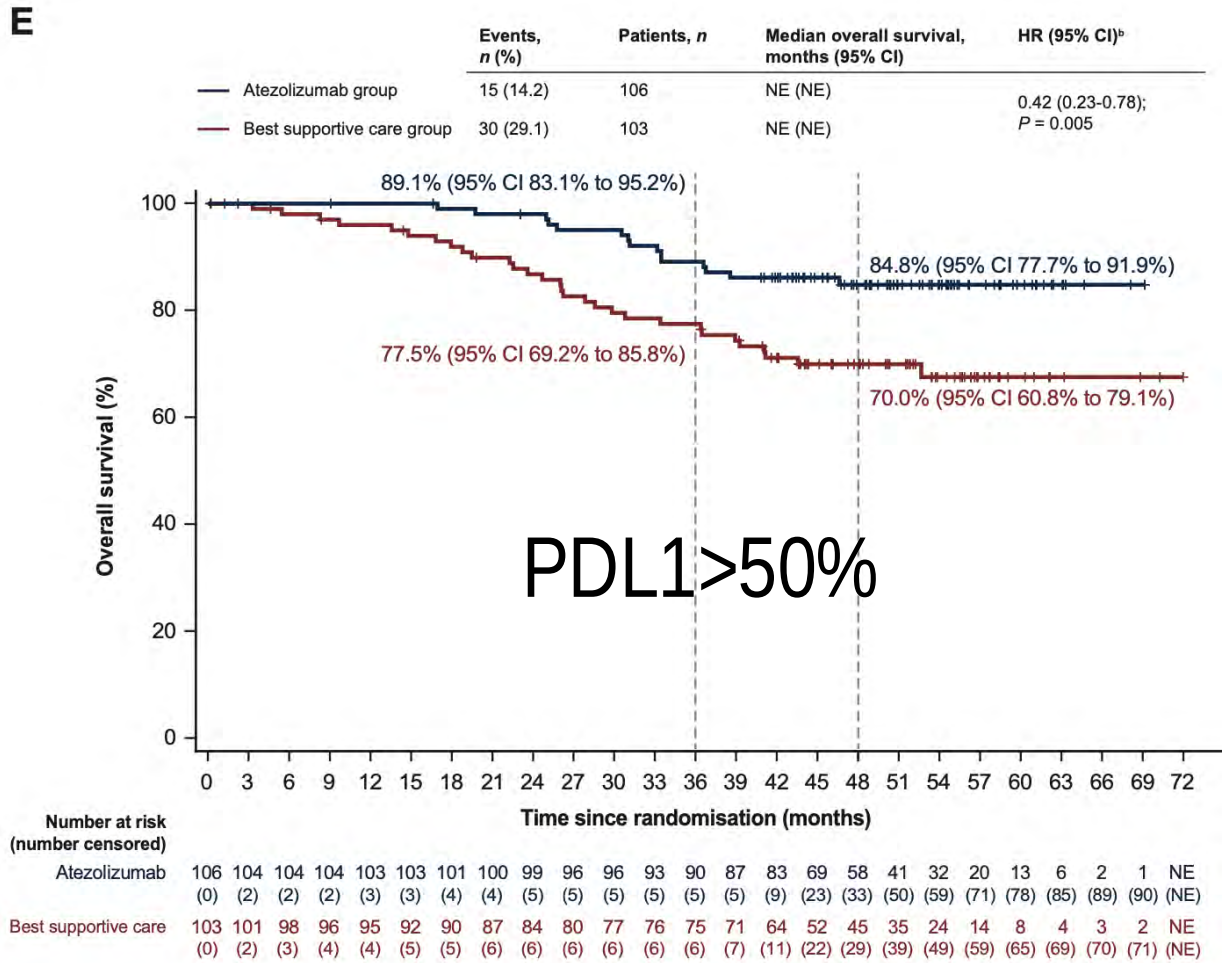
Majem et al, ESMO-IO 2024

WHAT'S THE DATA ON OS FOR ADJUVANT IO?

A

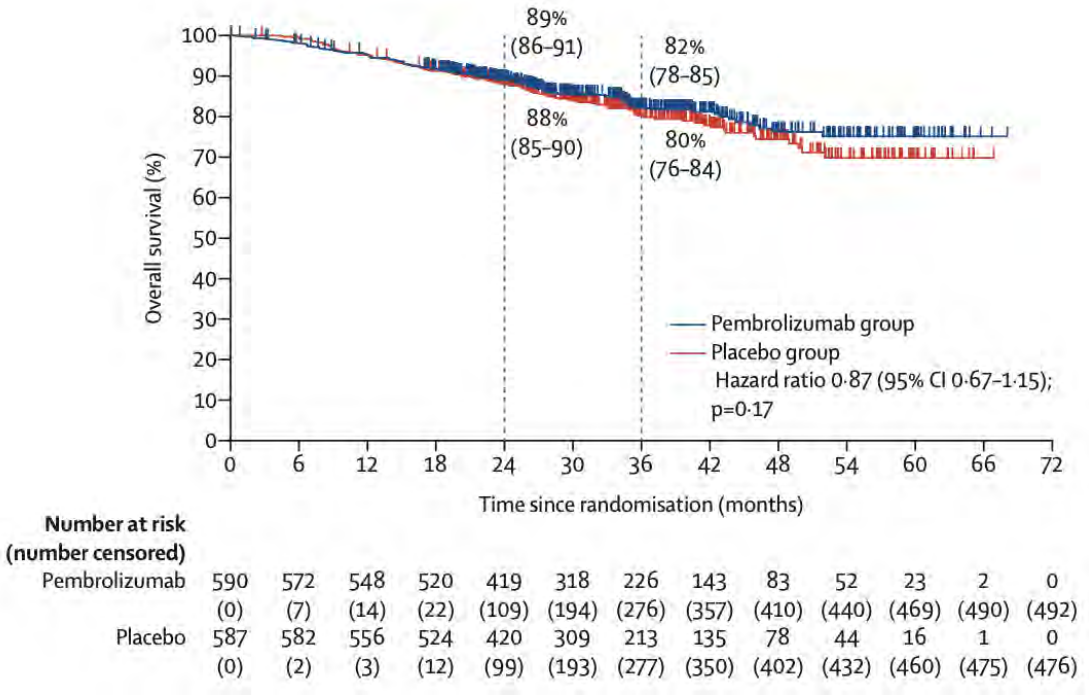


E

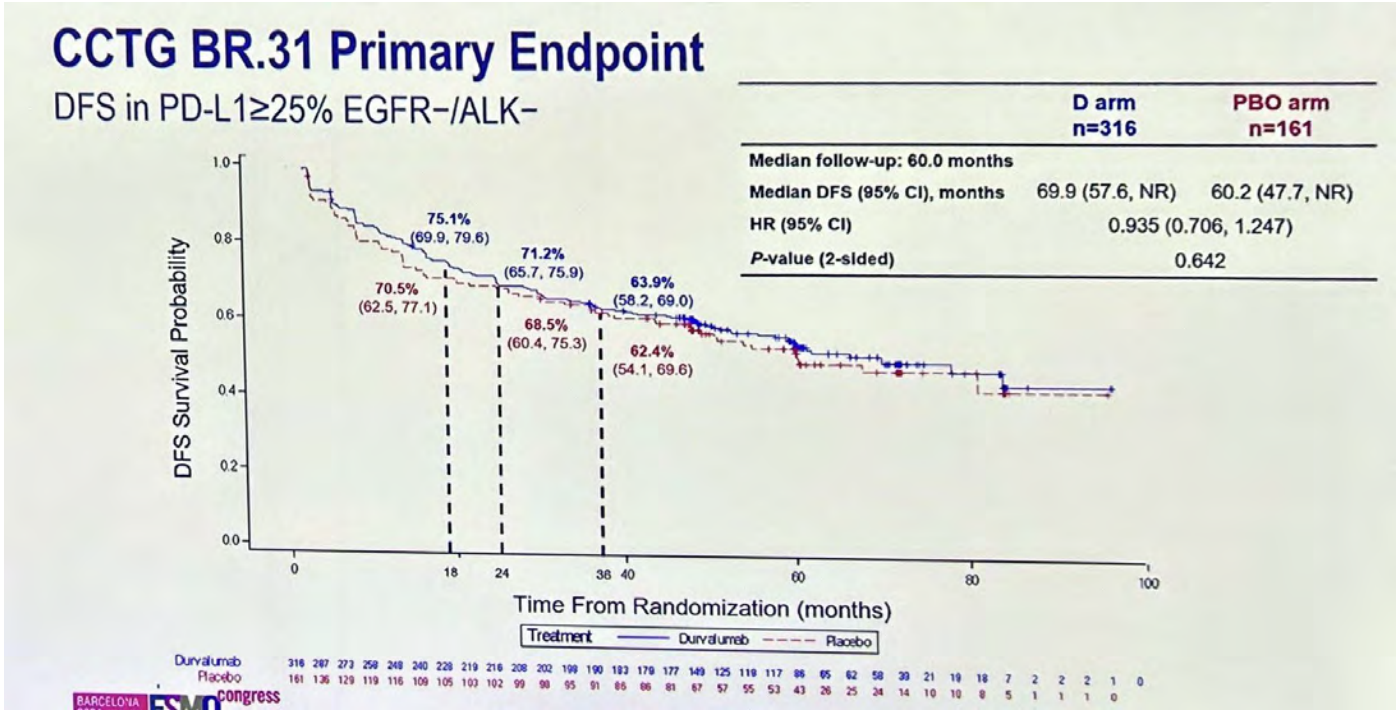


Felipe et al , Ann Onc 2023

OS IMPROVEMENT WITH ADJUVANT IO LACKS PROMISE

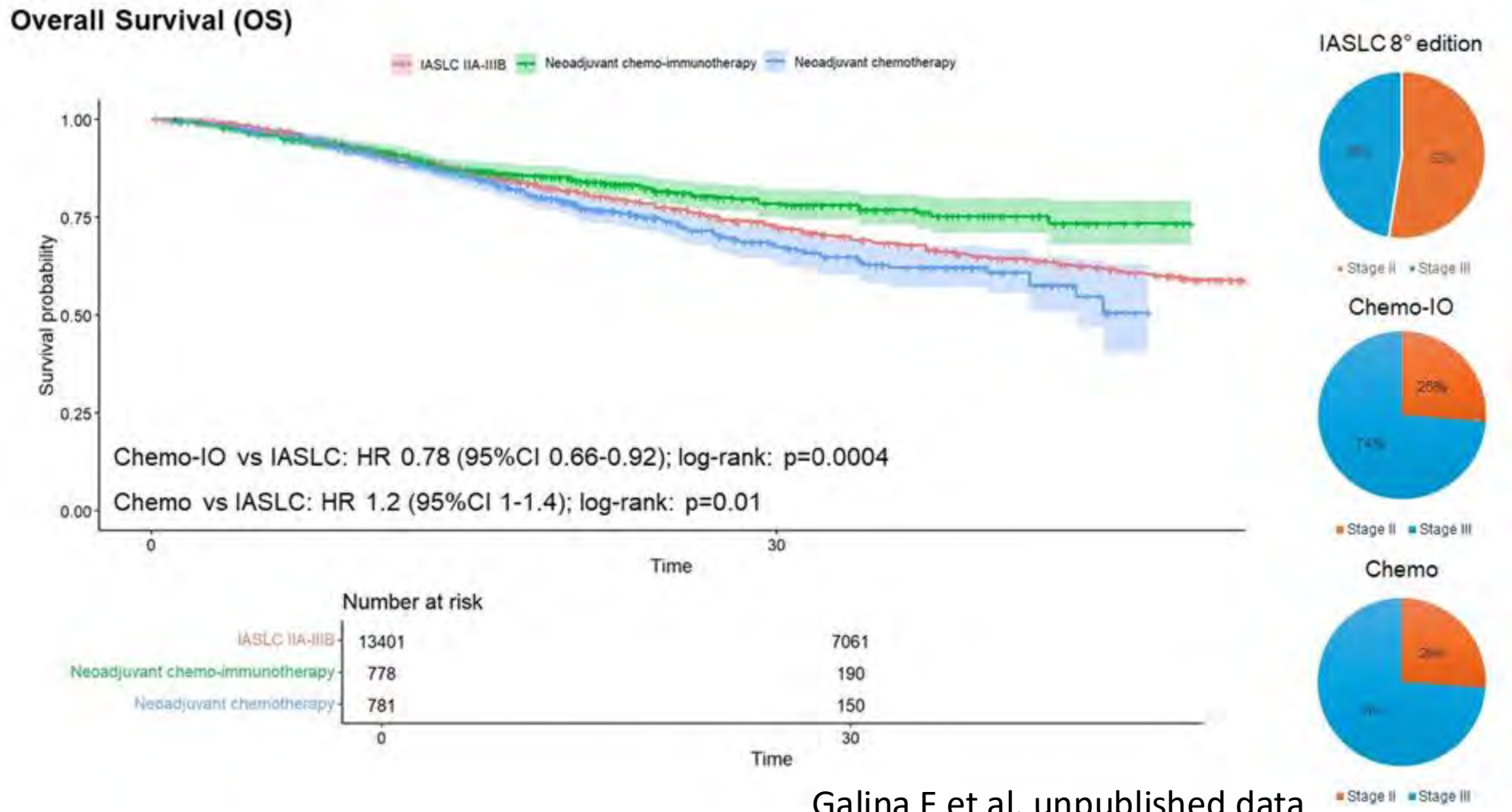


O'Brien et al, Lancet Oncol 2022



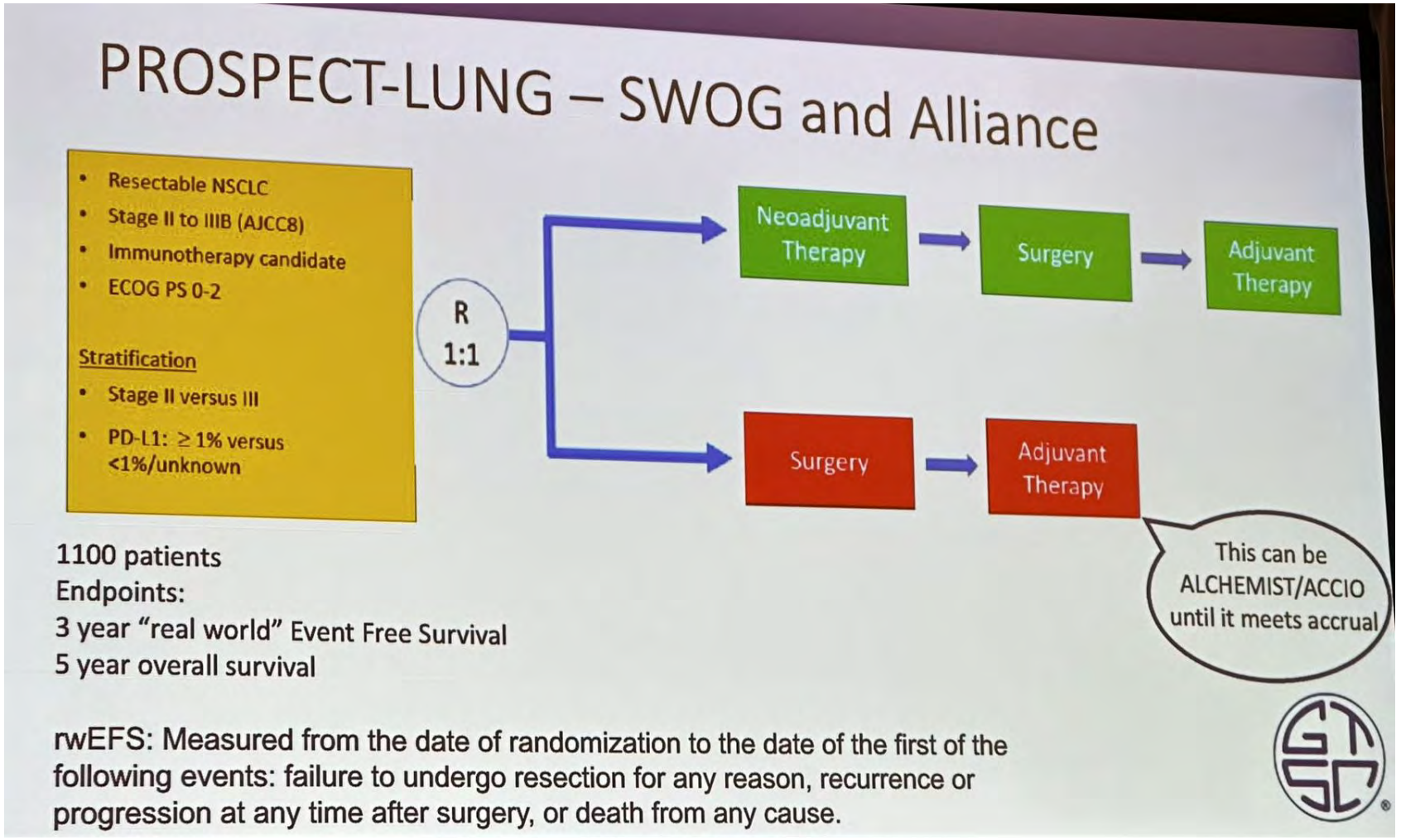
Goss et al, ESMO 2024

HARD FOR UP-FRONT SURGERY TO SURPASS NEOADJ/PERI-OP

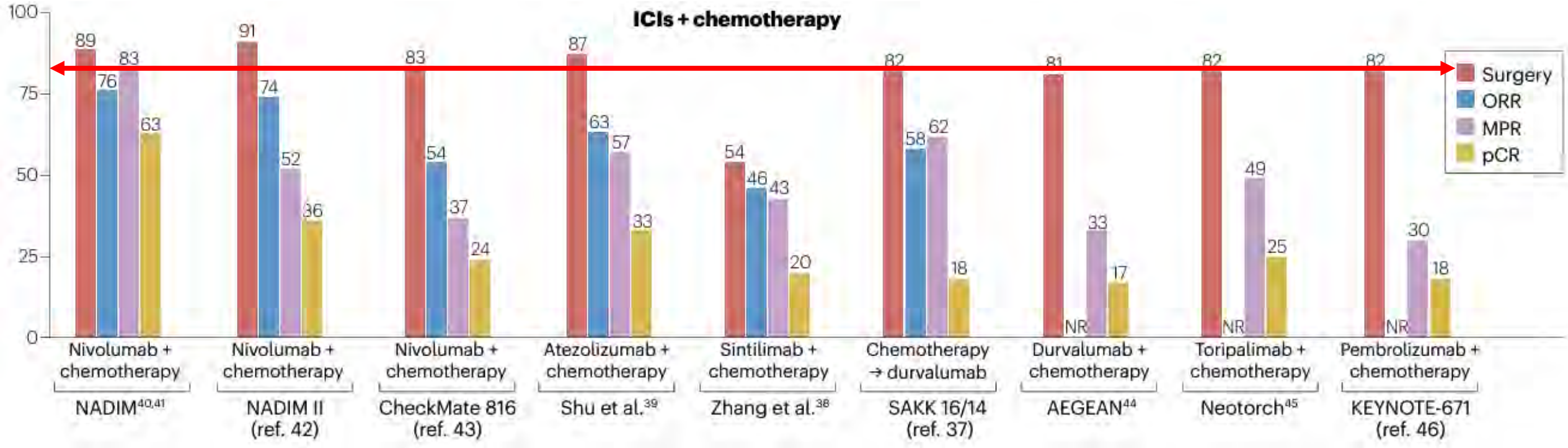


Galina F et al, unpublished data

EQUIPOISE STILL EXISTS IN THE FIELD



BUT WHAT ABOUT ATTRITION TO SURGERY?



Mountzios, Nat Rev Clin Onc, 2023

Surgical attrition in neoadj trial pts @ McGill

- 24 pts enrolled on CM816
- 20 pts enrolled on KN671
- 2 pts enrolled on NeoCOAST
- 6 pts enrolled on NeoCOAST2
- 6 pts enrolled in IIT of neoadj IO for stage I-IIA
- 12 pts enrolled in J1414
- 2 pts on NeoADAURA

McGill

Surgical attrition in neoadj trial pts @ McGill

- 24 pts enrolled on CM816
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- 2 pts enrolled on NeoCOAST
- 6 pts enrolled on NeoCOAST2
- 6 pts enrolled in IIT of neoadj IO for stage I-IIA
- 12 pts enrolled in J1414
- 2 pts on NeoADAURA

- 72 patients enrolled all resected ➔ Surgical attrition = 0%

In NADIM2, surgical attrition for chemo-Nivo was 7%.

Provencio et al, NEJM 2023

McGill

RESECTABILITY REMAINS IN THE CENTER OF THE DEBATE

	N0	N1	N2 SINGLE	N2 MULTI	N2 BULKY	N2 INVASIVE
T1-2	N/A	N/A	POTENTIALLY RESECTABLE (95%)	NO AGREEMENT (50%)	UNRESECTABLE (75%)	UNRESECTABLE (84%)
T3 SIZE	N/A	RESECTABLE (83%)[a]	POTENTIALLY RESECTABLE (87%)	NO AGREEMENT (39%)	UNRESECTABLE (80%)	UNRESECTABLE (88%)
T3 SATELLITE	N/A	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (79%)	NO AGREEMENT (34%)	UNRESECTABLE (84%)	UNRESECTABLE (91%)
T3 INVASION	N/A	POTENTIALLY RESECTABLE (89%)	NO AGREEMENT (71%)[b]	NO AGREEMENT (28%)[c]	UNRESECTABLE (87%)	UNRESECTABLE (92%)
T4 SIZE	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (90%)	NO AGREEMENT (66%)	UNRESECTABLE (77%)	UNRESECTABLE (88%)	UNRESECTABLE (93%)
T4 SATELLITE	POTENTIALLY RESECTABLE (78%)	NO AGREEMENT (71%)[b]	NO AGREEMENT (44%)	UNRESECTABLE (85%)	UNRESECTABLE (92%)	UNRESECTABLE (94%)
T4 INVASION	NO AGREEMENT (62%)[b]	NO AGREEMENT (57%)[b]	NO AGREEMENT (34%)[c]	UNRESECTABLE (90%)	UNRESECTABLE (95%)	UNRESECTABLE (94%)

Houda et al, Lung Cancer 2024

WHAT ABOUT A SURGICAL SOCIETY?

EXPERT CONSENSUS DOCUMENT

The Society of Thoracic Surgeons Expert Consensus on the Multidisciplinary Management and Resectability of Locally Advanced Non-small Cell Lung Cancer

Samuel S. Kim, MD,[1] David T. Cooke, MD,[2] Biniam Kidane, MD, MSC,[3] Luis F. Tapias, MD,[4] John F. Lazar, MD,[5] Jeremiah W. Awori Hayanga, MD,[6] Jyoti D. Patel, MD,[7] Joel W. Neal, MD, PhD,[8] Mohamed E. Abazeed, MD, PhD,[9] Henning Willers, MD,[10] and Joseph B. Shrager, MD[11,12]

TABLE 2 Consensus Summary of Surgical Resectability for Non-small Cell Lung Cancer[a]

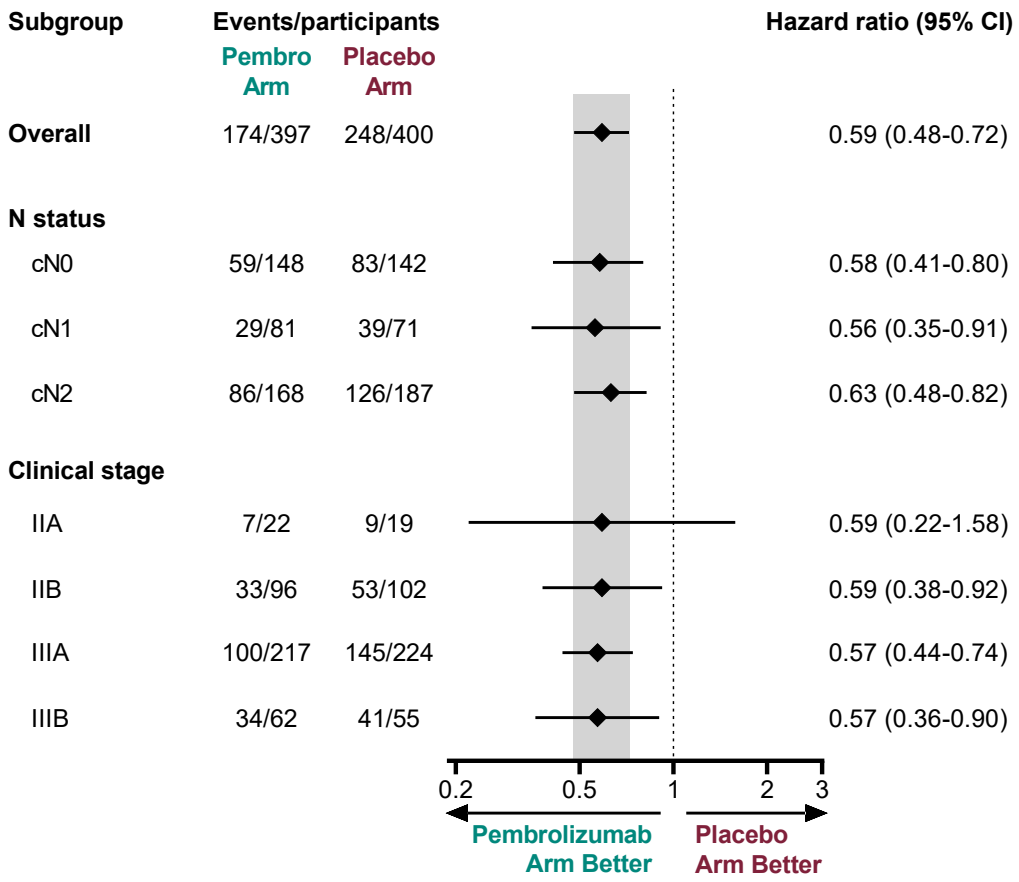
			Nonbulky		Bulky	
Variable	N0	N1	N2 Single	N2 Multstation	N2 Single	N2 Multistation
T1/T2	Resectable	Resectable	Resectable	Potentially resectable	Potentially resectable	Unresectable
T3	Resectable	Resectable	Resectable	Potentially resectable	Potentially resectable	Unresectable
T3 (Pancoast)	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable
T4 size	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable
T4 satellite	Potentially resectable	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable
T4 invasion	Potentially resectable	Potentially resectable	Unresectable	Unresectable	Unresectable	Unresectable

[a]This table represents a general recommendation for the surgical management of locally advanced lung cancer. Every case is unique, and in selected "unresectable" patients, surgical resection may be considered after a multidisciplinary discussion in the institutions with expertise.

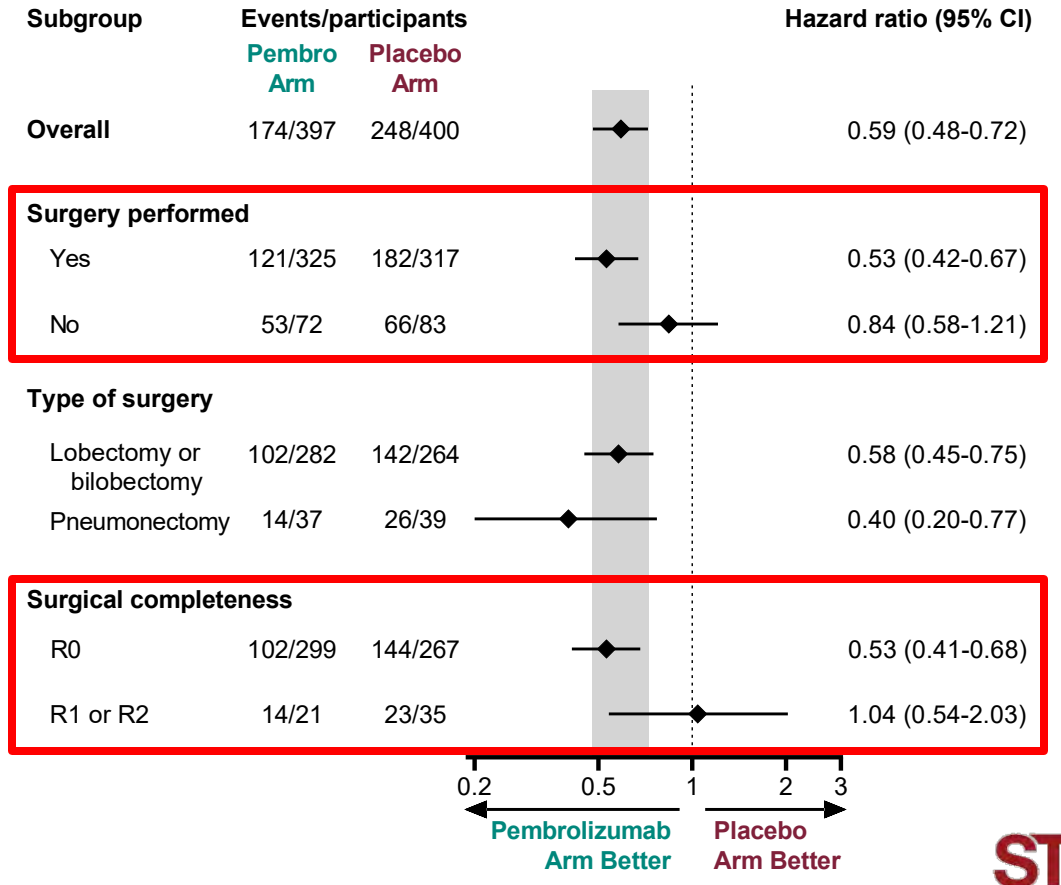
KEY RESPONSIBILITIES OF THE SURGEON: SELECT RESECTABLE PTS, RESECT THEM, GET R0!

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

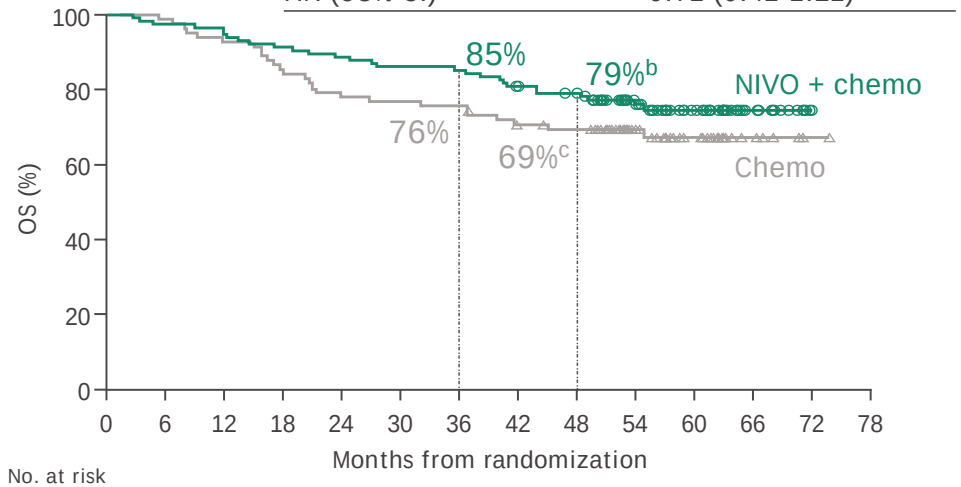
RESECT WHAT NEEDS TO BE RESECTED: EXTENT DOES NOT IMPACT OS EVEN IF PNEUMONECTOMY IS REQUIRED

CheckMate 816: 4-y survival update

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)	

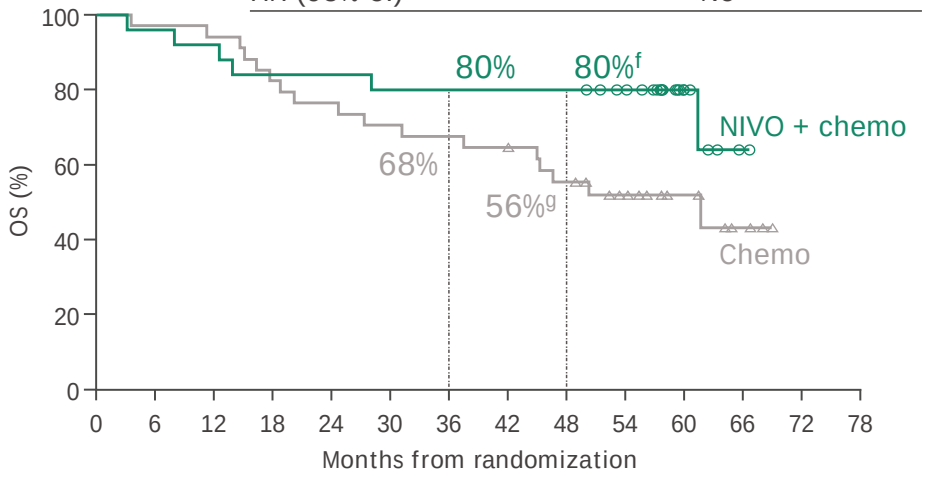


No. at risk

NIVO + chemo	115	112	109	105	102	99	98	92	87	58	33	13	0	0
Chemo	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	



No. at risk

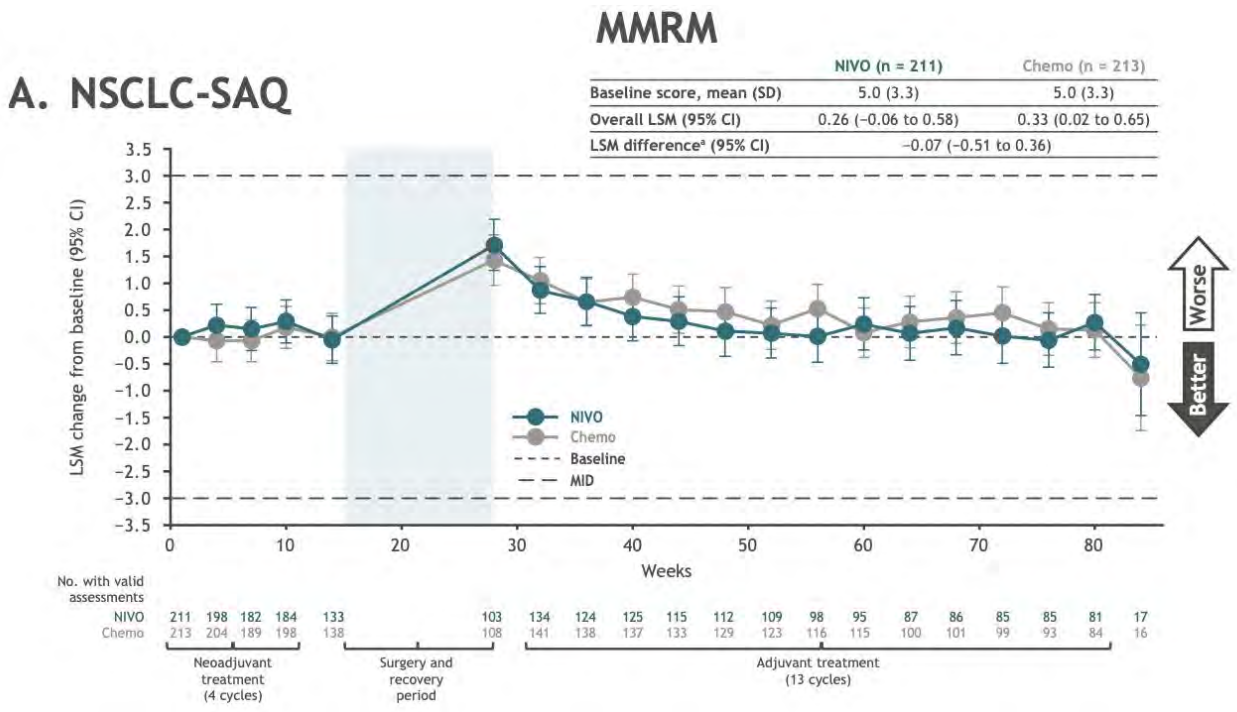
NIVO + chemo	25	24	23	21	21	20	20	20	20	17	7	1	0	0
Chemo	34	33	32	28	26	24	23	22	18	13	7	3	0	0

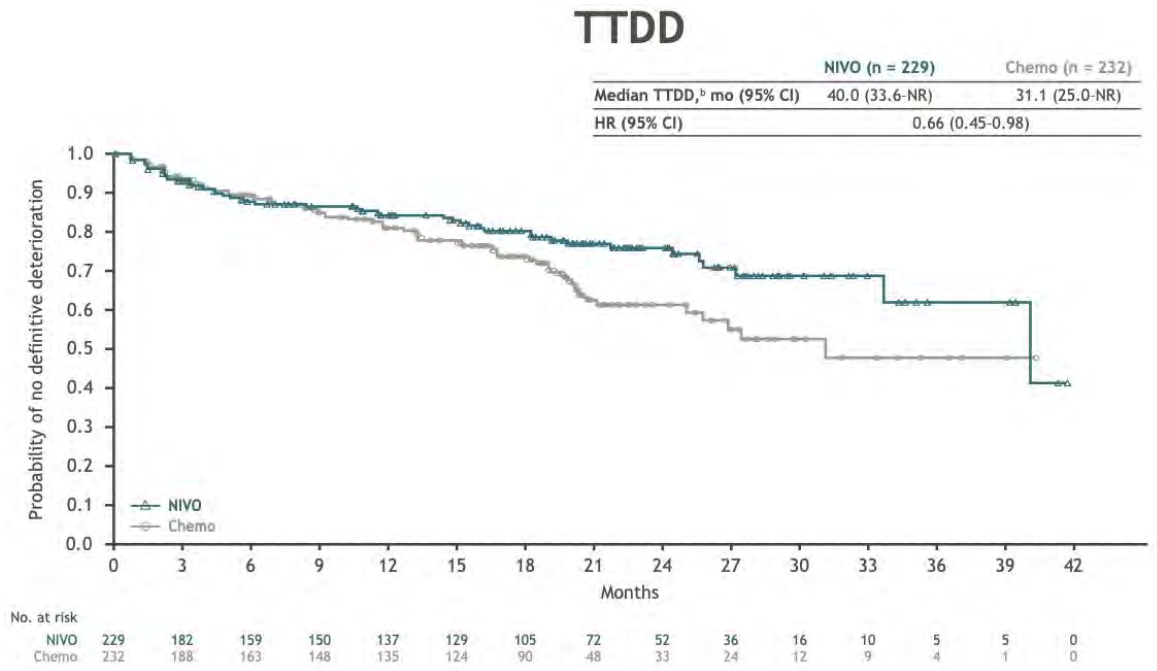
- 4-year EFS rates were 56%[h] with NIVO + chemo vs 43%[i] with chemo in patients with lobectomy (HR, 0.59; 95% CI, 0.39-0.90) and 57%[j] vs 40%[k] in patients with pneumonectomy (HR, NC)

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.

Spicer et al, ASCO 2024

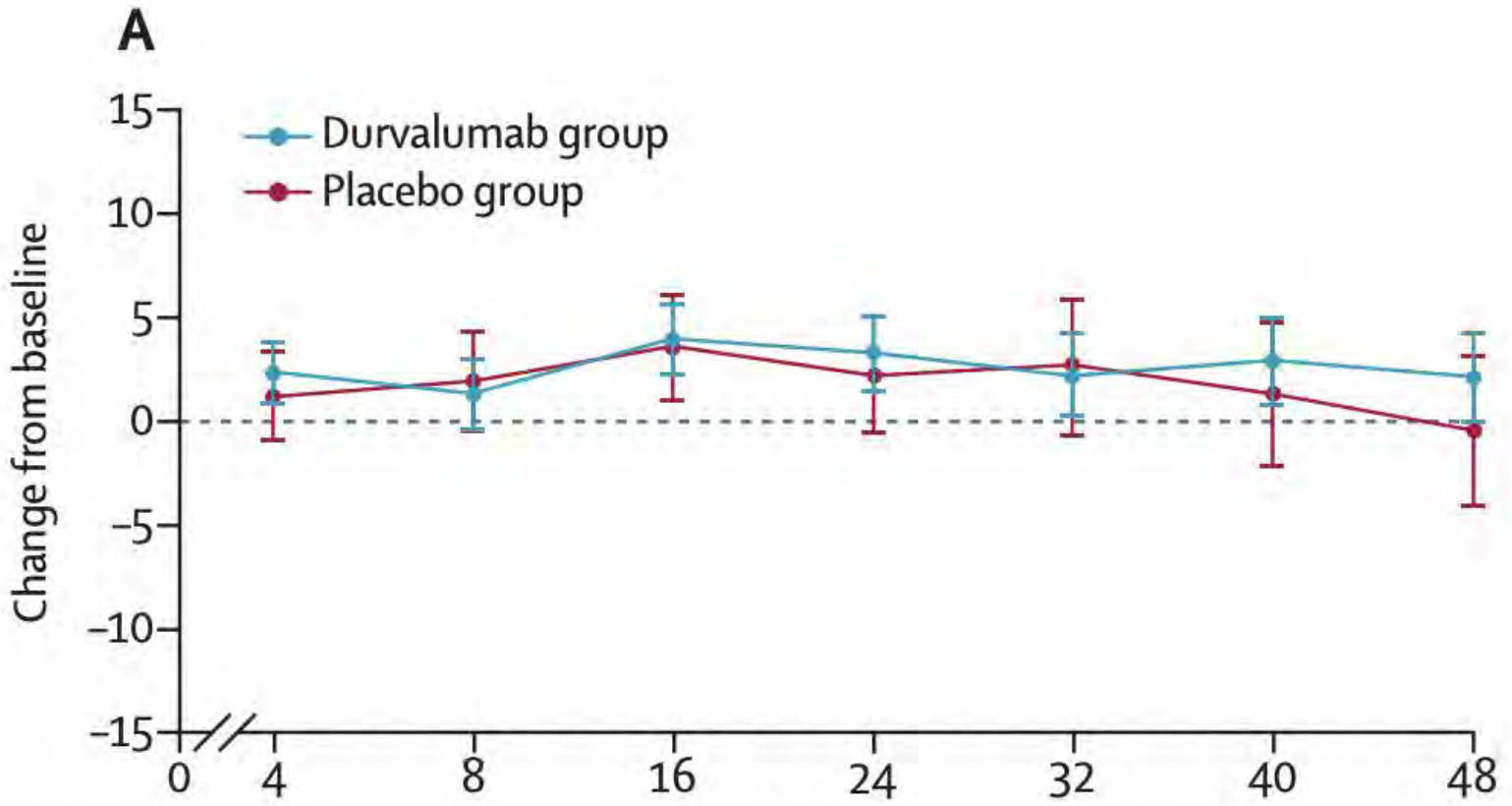
HRQOL THROUGHOUT THERAPEUTIC PHASE WITH LONG-TERM PROLONGATION OF QOL





Spicer et al, ELCC 2024

FOR REFERENCE THESE ARE THE PATIENT REPORTED **OUTCOMES FOR PACIFIC ON PHYSICAL FUNCTION…**

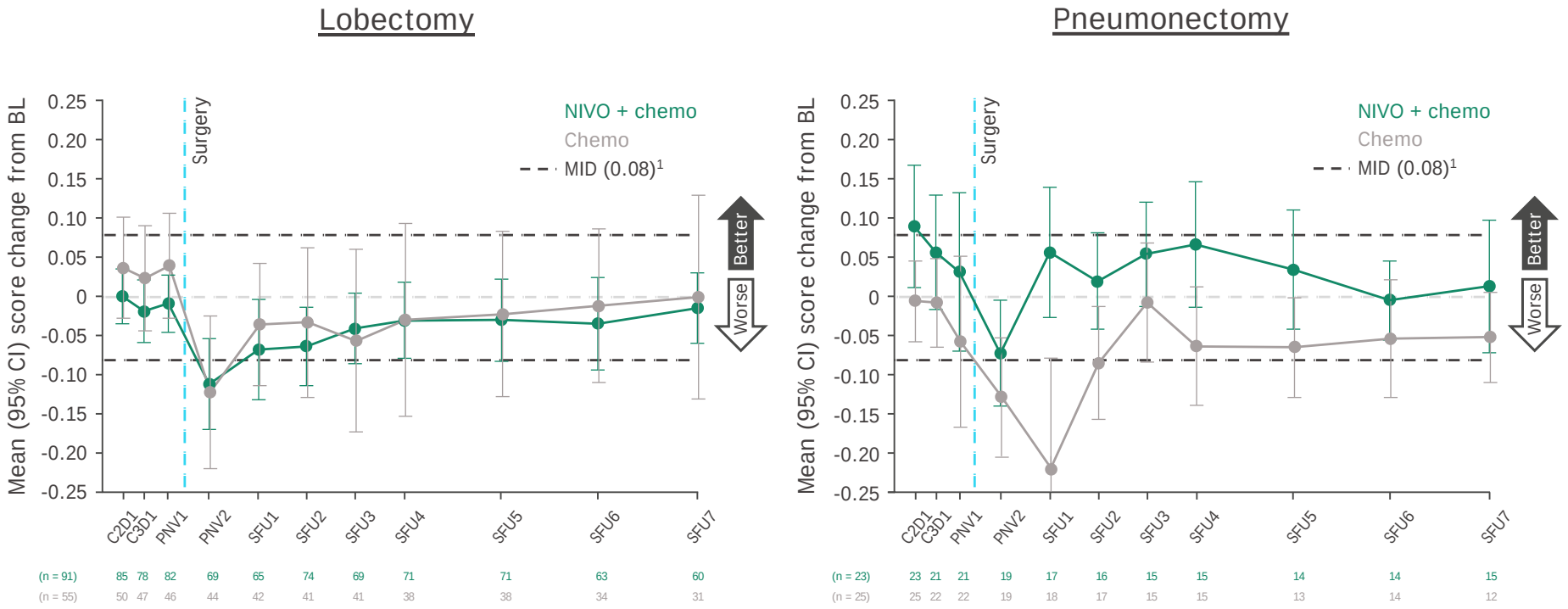


Number of patients	647	538	437	382	332	298	272
Durvalumab group	439	367	306	274	248	220	205
Placebo group	208	171	131	108	84	78	67

Hui et al, Lancet Onc 2019

NO DETECTABLE IMPACT OF EXTENT OF SURGERY ON HRQOL

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



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

What did the CM816 and other periop protocols say about resectability?

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Group (ECOG) Performance Status 0-1 (Appendix 3)

b) P Participants with histologically confirmed Stage IB (≥ 4 cm), II, IIIA (N2) NSCLC (per the 8th American Joint Committee on Cancer (AJCC) (Rami-Porta, 2015) with disease that is considered resectable.[49]

c) Measurable disease according to RECIST version 1.1

d) Participants must have a tumor tissue sample available for PD-L1 IHC testing performed by a third-party analyzing lab during the screening period:

i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment.

ii) Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies obtained by EBUS is not considered adequate for biomarker review and randomization. Core needle biopsies obtained by EBUS are acceptable for randomization.

e) Absence of major associated pathologies that increase the surgery risk to an unacceptable level

f) Mediastinal lymph node samples at levels 4 (bilaterally) and 7 are required for clinical staging to assess nodal involvement in participants with mediastinal adenopathy on PET/CT. Mediastinoscopy, thoracostomy, or EBUS are all acceptable for such assessment.

g) Pulmonary function capacity capable of tolerating the proposed lung resection according to the surgeon.

6.2 Exclusion Criteria

1) Medical Conditions

a) Presence of locally advanced unresectable regardless of stage or metastatic disease (stage IV). Staging assessment should include sample of lymph nodes at levels 4, bilaterally, and level 7 to rule out stage IIIB disease.

b) Participants with known EGFR mutations or ALK translocation. If testing is done, an FDA-approved assay should be used, and testing will be performed locally.

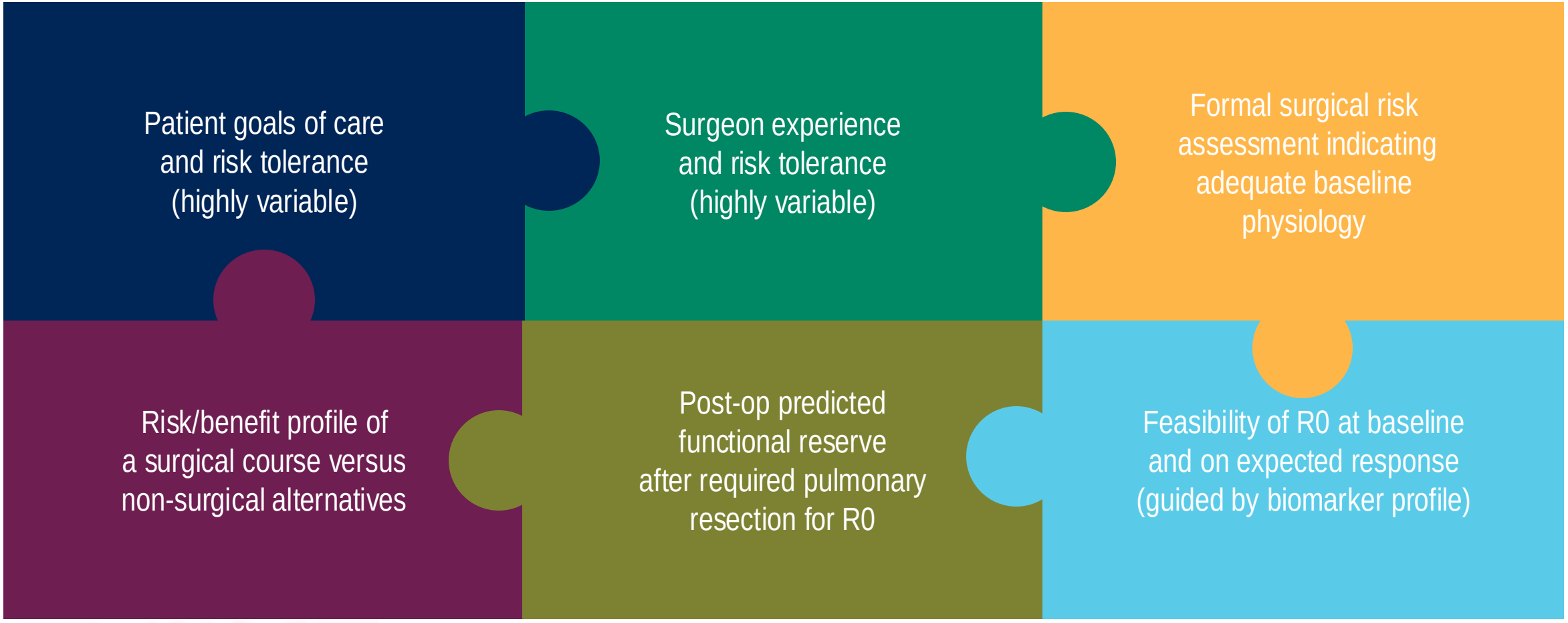
c) Participants with brain metastases are excluded from this study and all participants with stage II disease or higher should have brain imaging (either MRI brain or CT brain with contrast) 28 days prior to randomization.

d) Participants with ≥ Grade 2 peripheral neuropathy

e) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

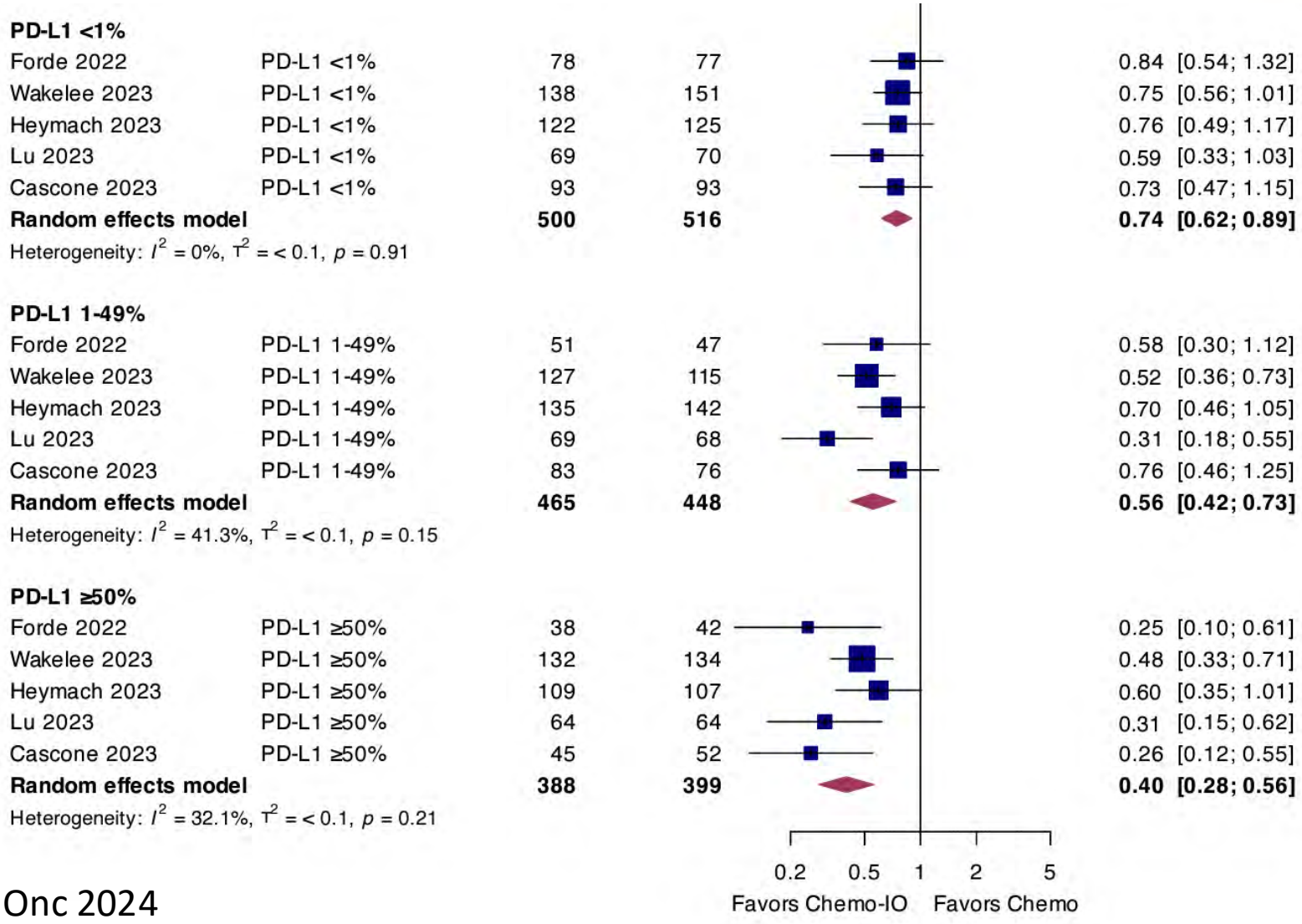
f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid

My resectability criteria



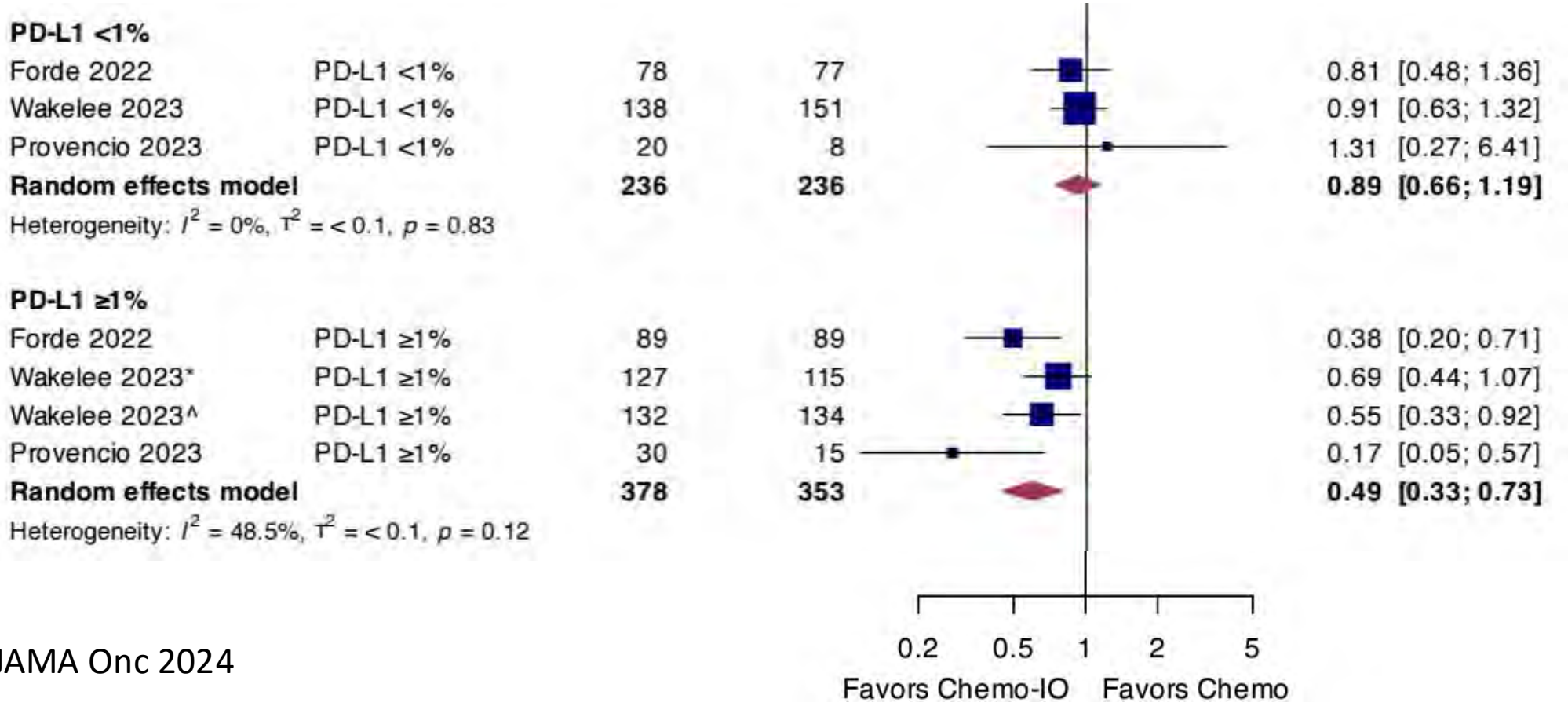
(note absence of stage)

IS PDL1 TPS PART OF THE DECISION TREE?
IMPACT ON EFS…



Sorin et al, JAMA Onc 2024

CLEAR UNMET NEED IS PDL1 NEGATIVE POPULATION WHERE OS BENEFIT IS CONSISTENTLY EQUIVOCAL DESPITE CONSISTENT EFS BENEFIT



Sorin et al, JAMA Onc 2024

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

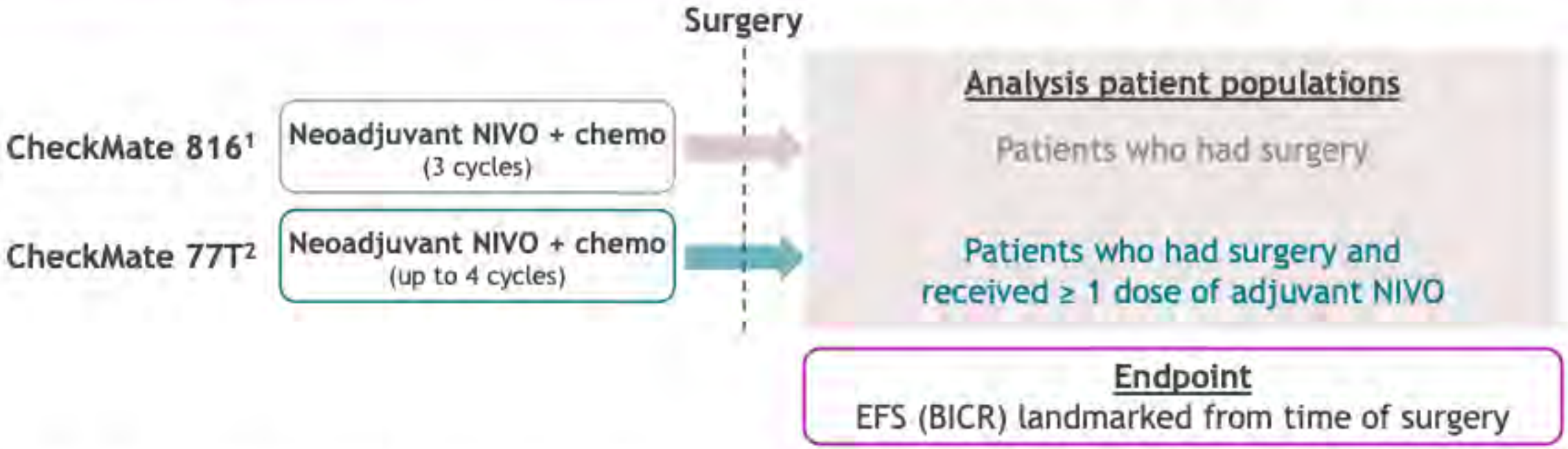
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

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

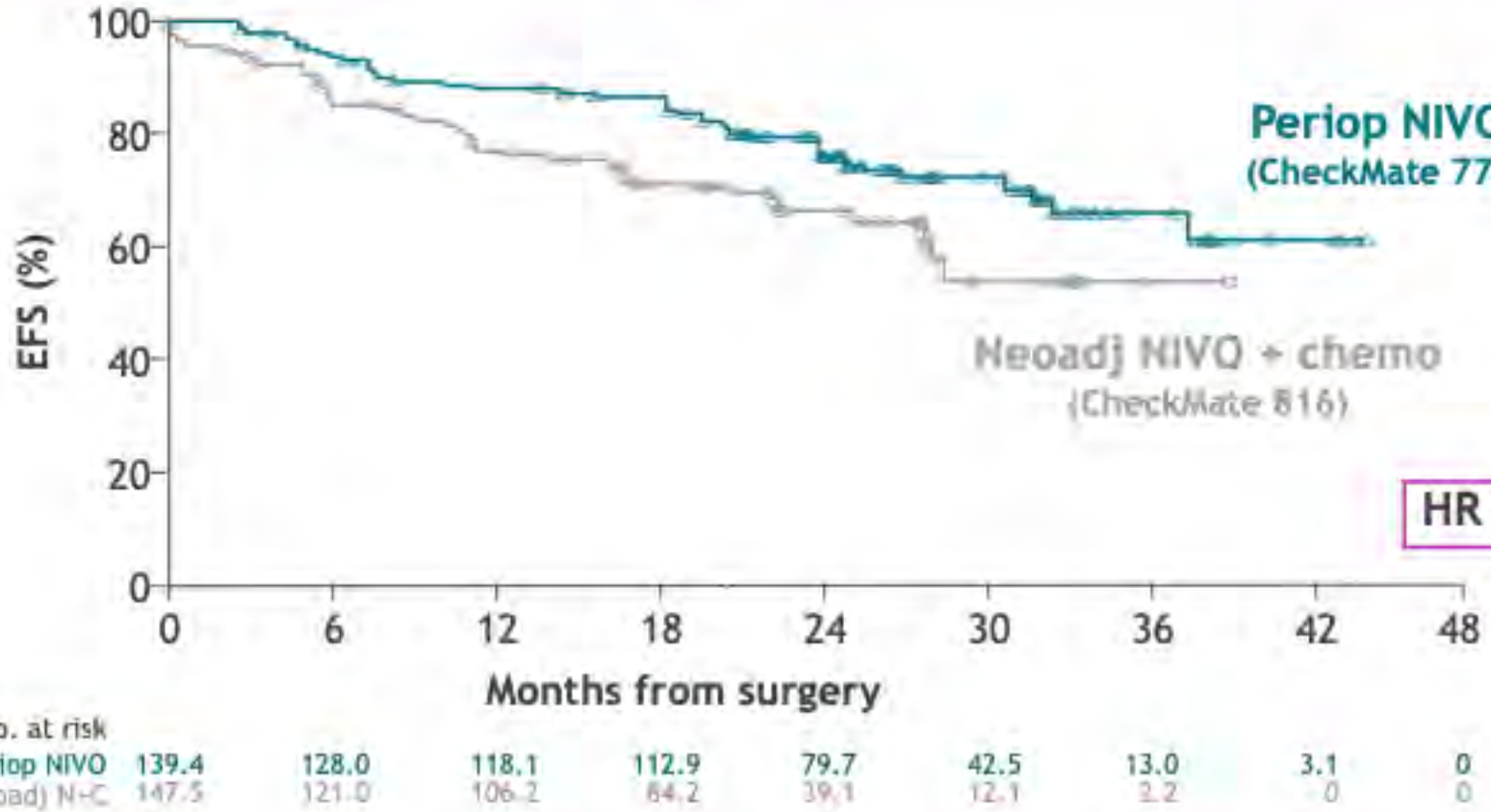
Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



- 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



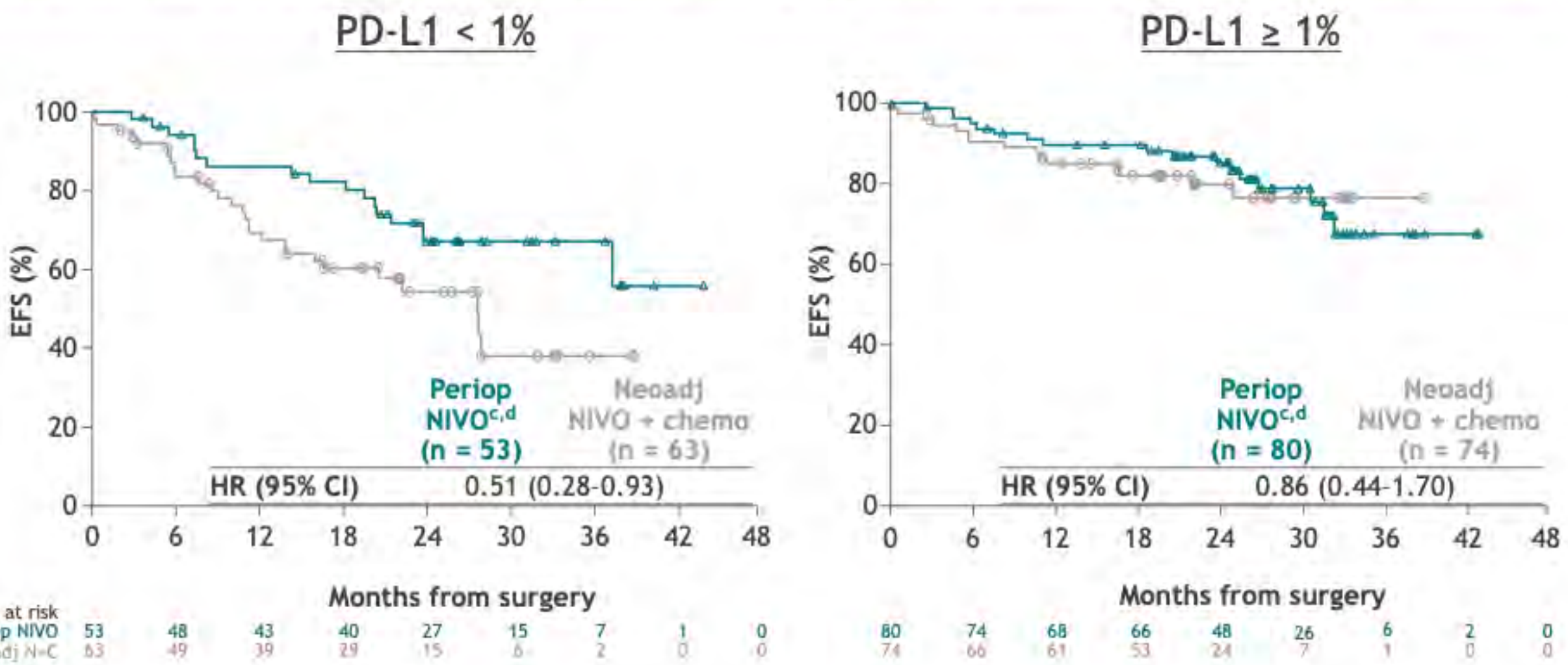
Weighted (ATE)[b]		
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

- 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).

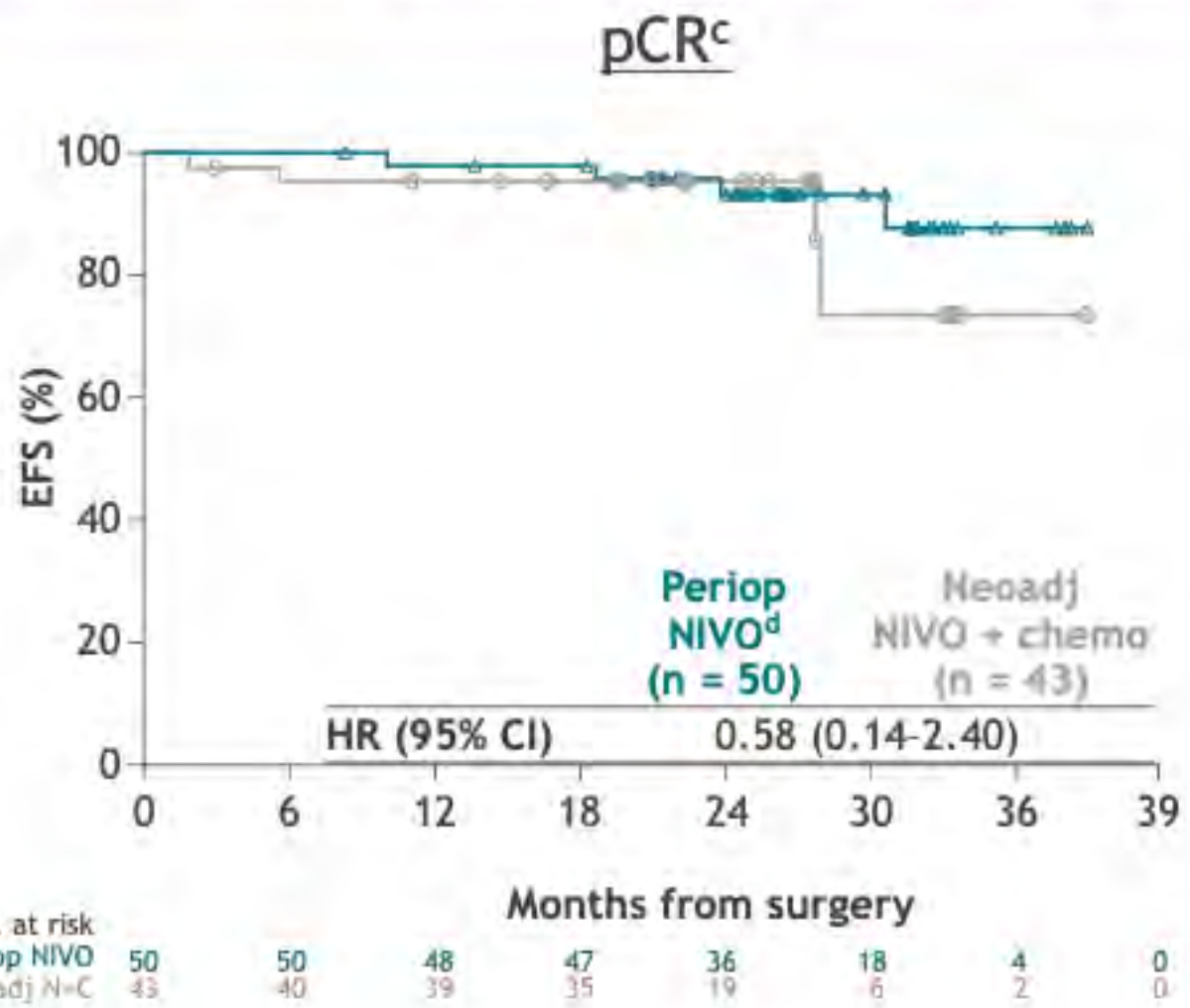
In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) was 13.0 (1-13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for periop NIVO vs neoadj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

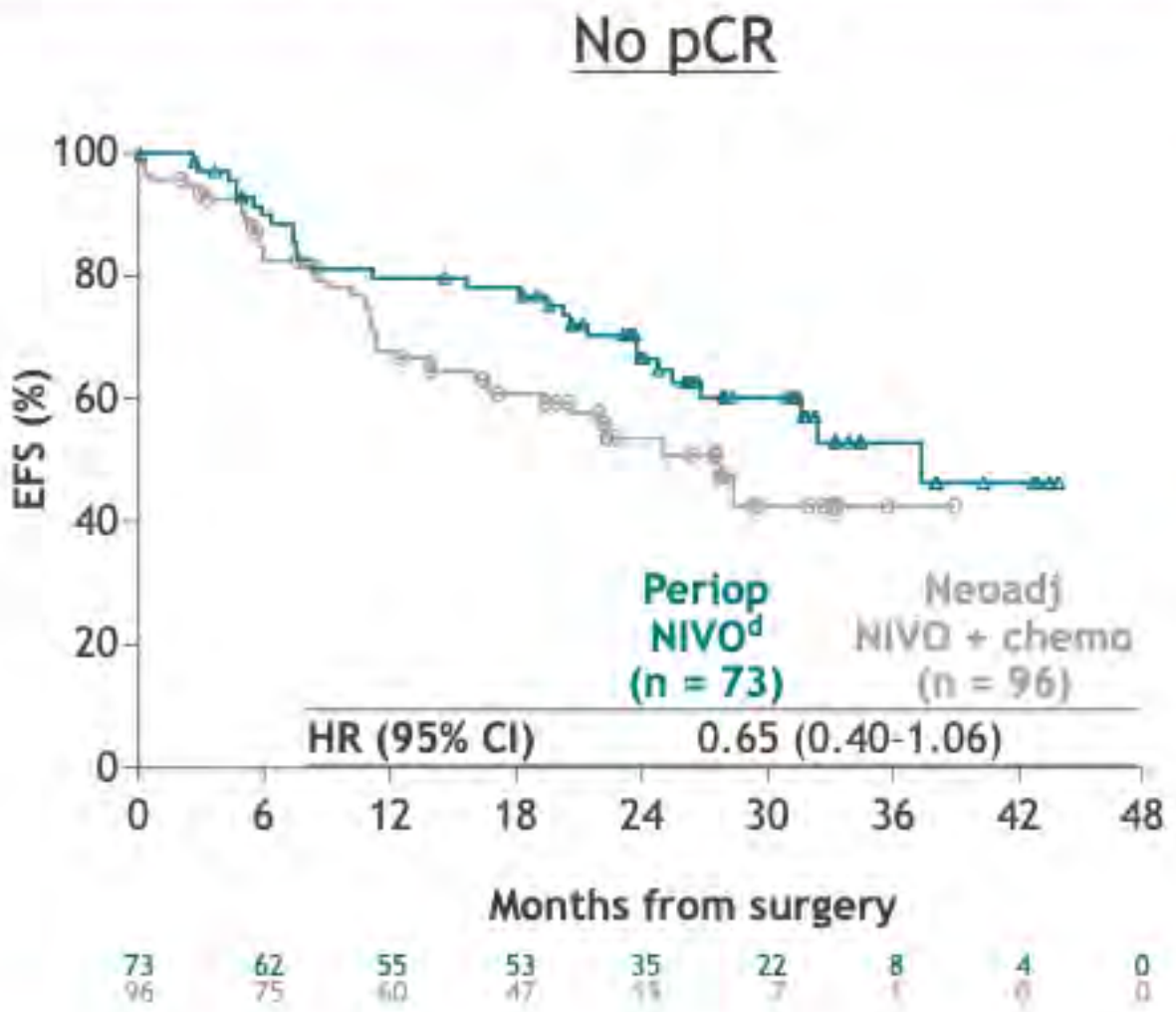
Landmark EFS (analysis population) by tumor PD-L1 expression[a,b]



Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable PD-L1 expression were excluded. [b]Unweighted analyses. [c]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [d]Completed adjuvant treatment: < 1%, 33 patients (62%) and ≥ 1%, 51 patients (64%). Median number of doses (range): < 1%, 13 (1-13) and ≥ 1%, 13 (1-13).

Landmark EFS[a] (analysis population) by pCR status[a,b]





Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable pCR status were excluded. [b]Unweighted analyses. [c]pCR rates in this analysis population: perioperative NIVO, 40.7%; neoadjuvant NIVO + chemo, 30.5%. [d]Includes only patients who received ≥ 1 dose of adjuvant NIVO.

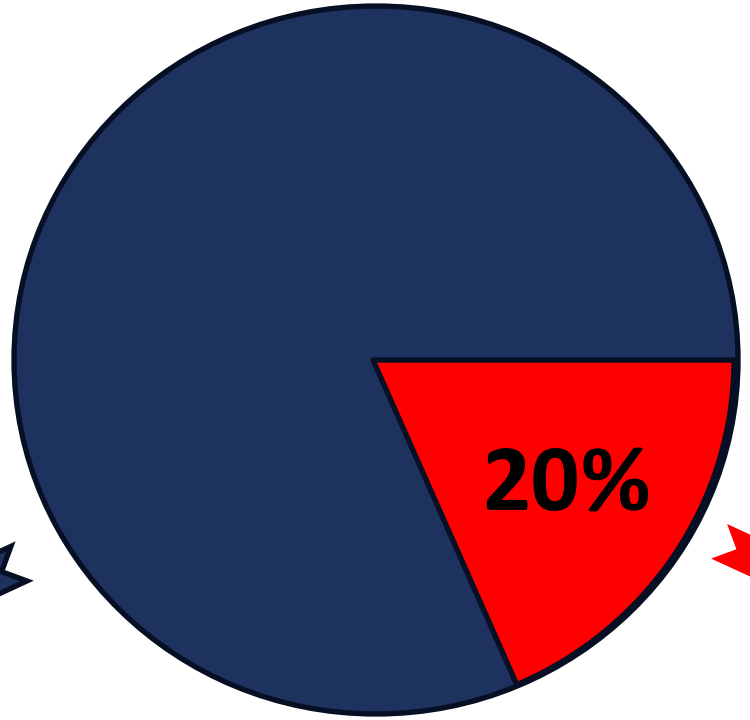
End of story?
Peri-op is best?

CHECKMATE 77T

Post-op cohort

N=178pts

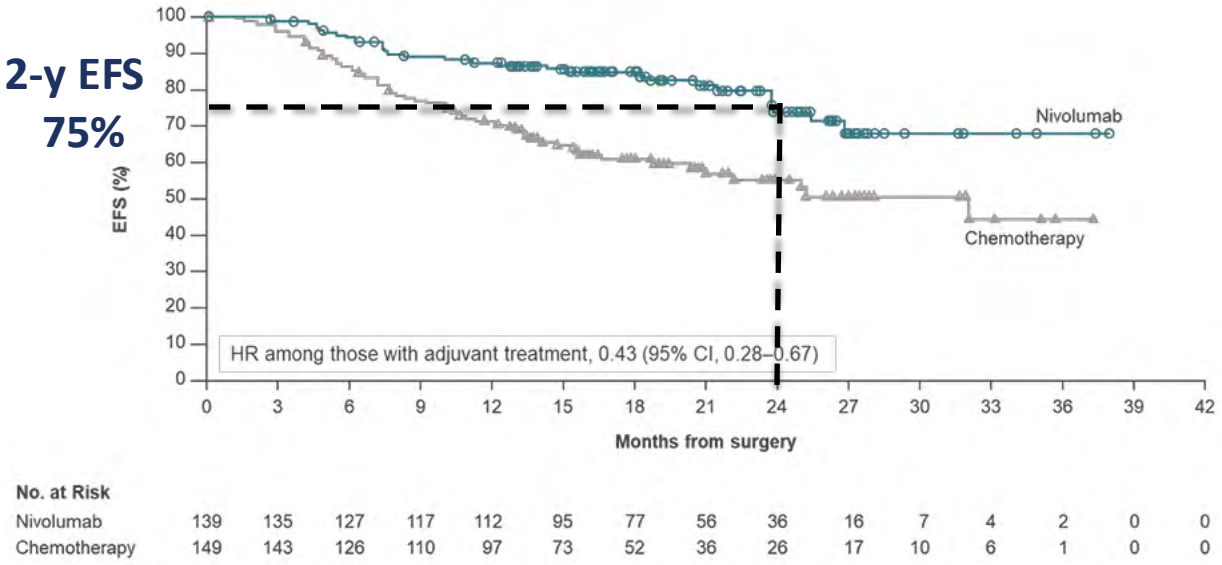
78% of ITT pop



EXCLUDED FROM THE ANALISYS!!!

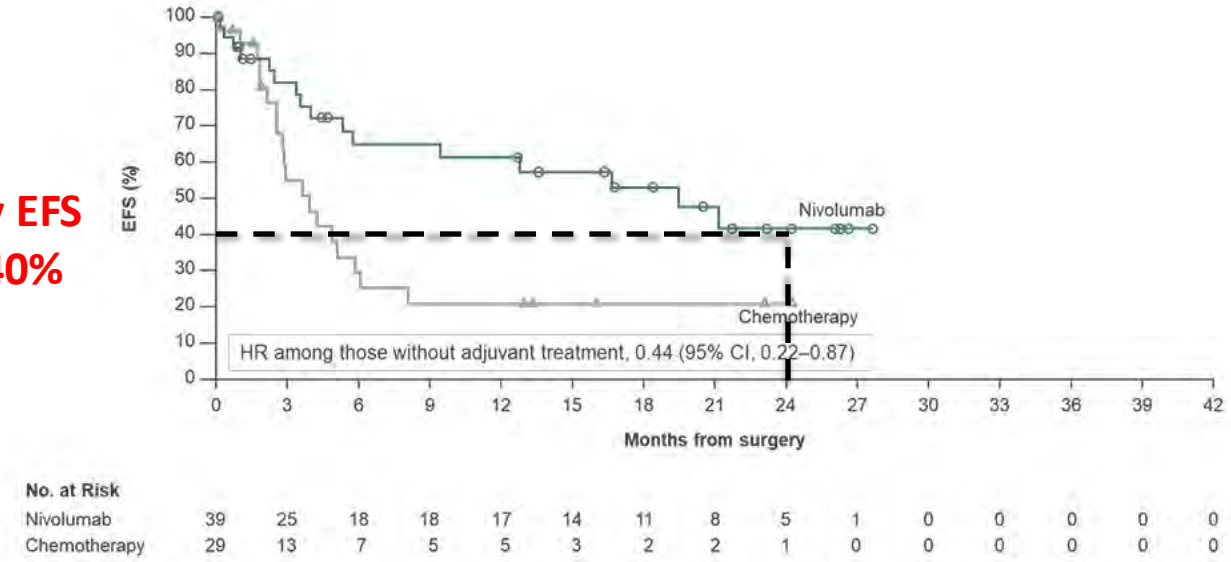
GOT ADJUVANT

2-y EFS 75%



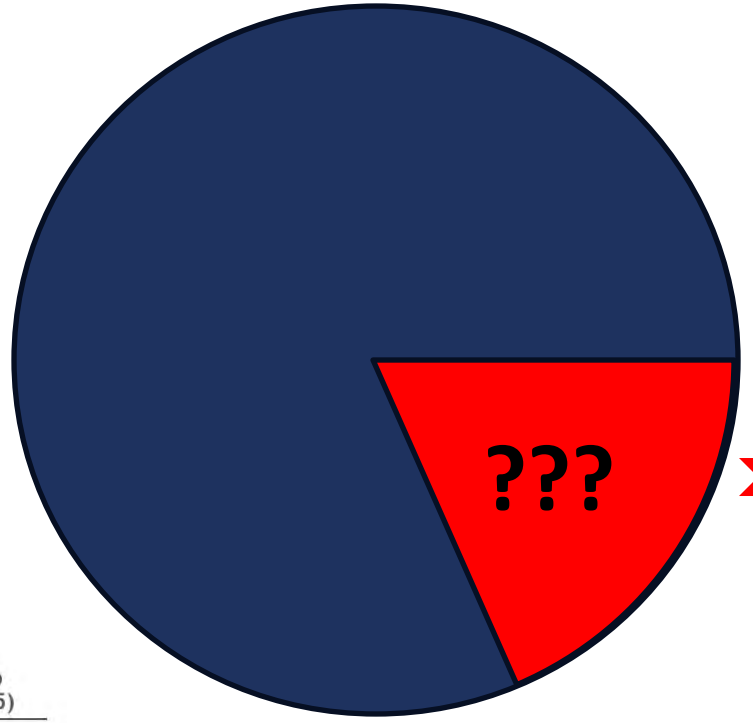
DIDN'T GET ADJUVANT

2-y EFS 40%

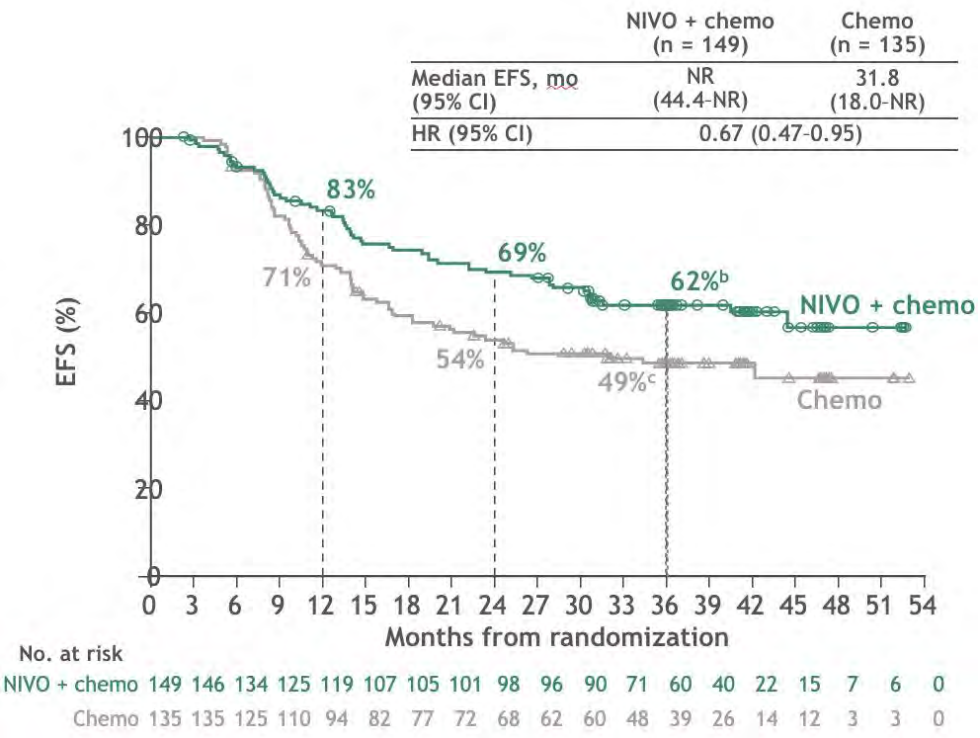


Cascone et al, NEJM 2024

CHECKMATE 816
Post-op cohort
N=149 pts
83% of ITT pop



NOT EXCLUDED!



Is the EFS difference between 77T pts who got adj versus all resected 816 patients driven by 1 year of adj Nivo???

Spicer et al, ASCO 2023

Neoadj vs Peri-op? Remains TBD!

What would an ITT analysis look like?

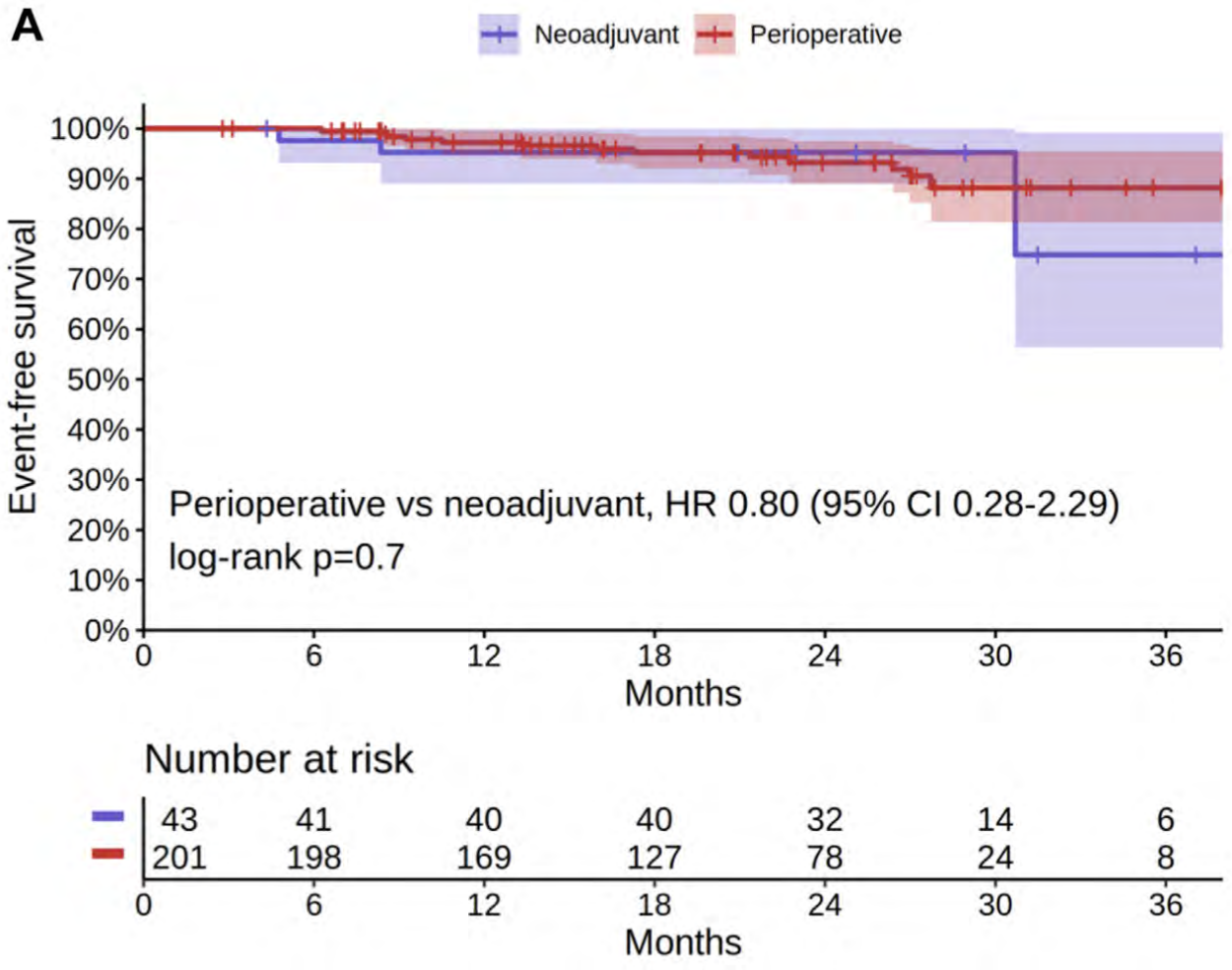
IASLC

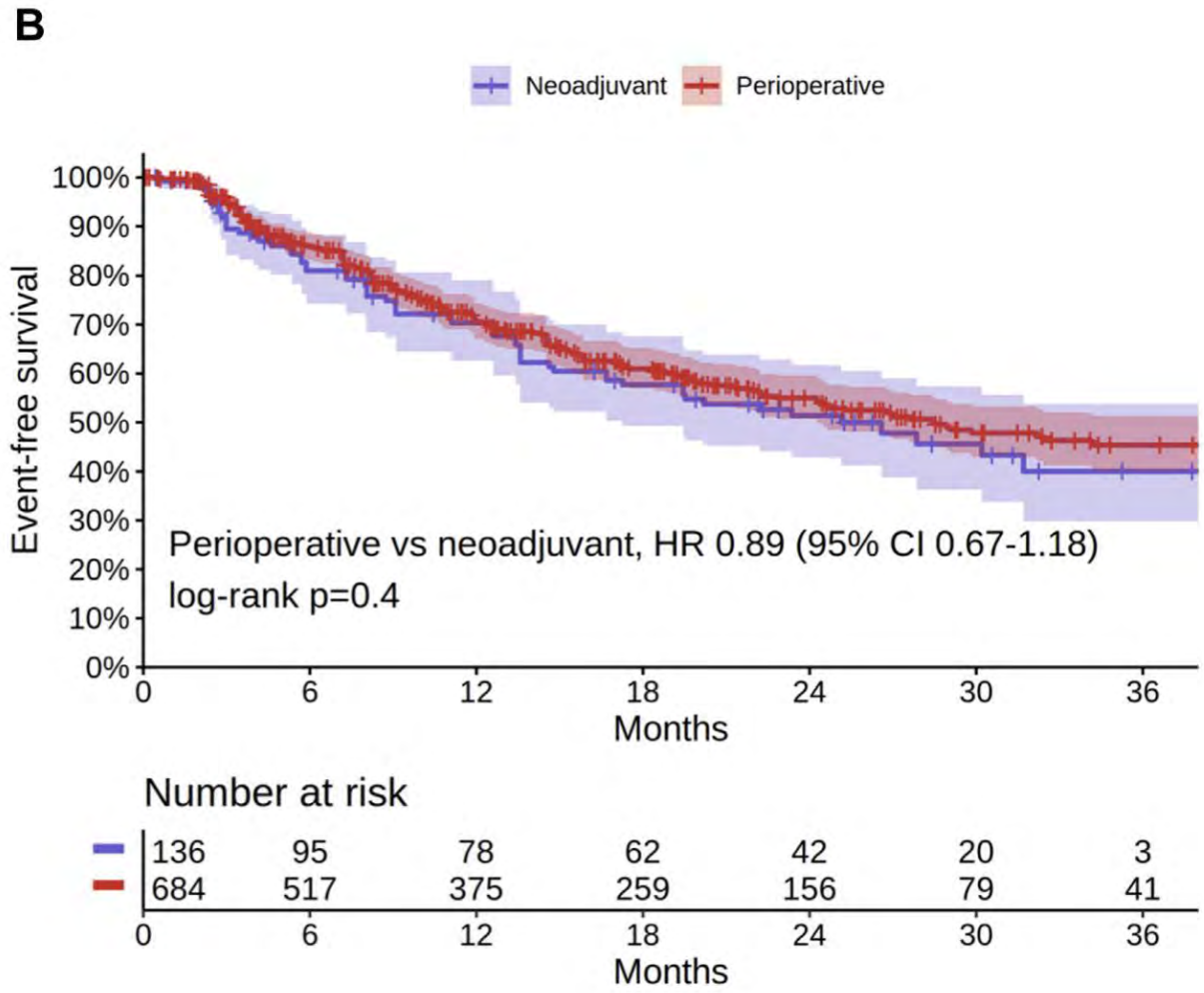
ORIGINAL ARTICLE

Improved Event-Free Survival After Complete or Major Pathologic Response in Patients With Resectable NSCLC Treated With Neoadjuvant Chemoimmunotherapy Regardless of Adjuvant Treatment: A Systematic Review and Individual Patient Data Meta-Analysis

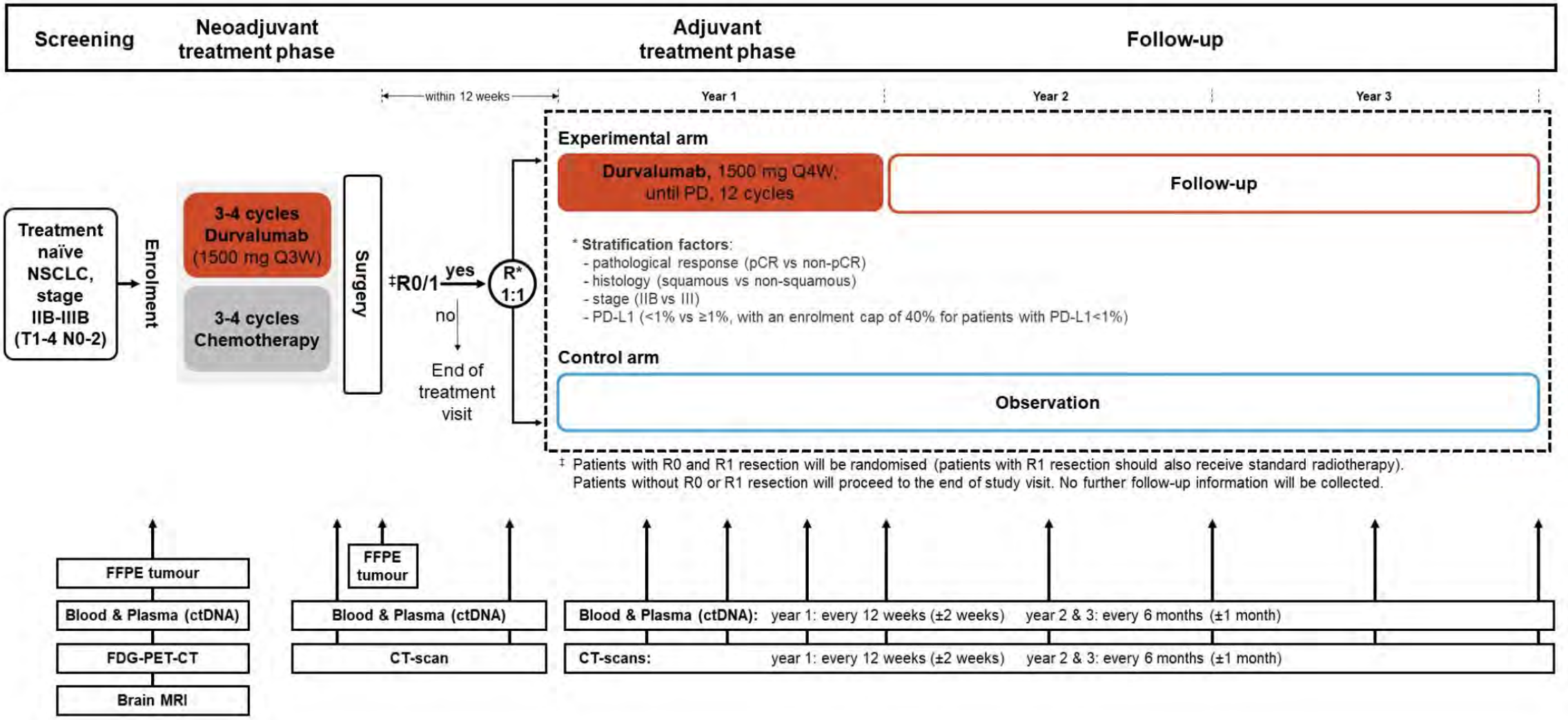
Daniele Marinelli, MD,[a] Antonio Nuccio, MD,[b,c] Alessandro Di Federico, MD,[d,e] Francesca Ambrosi, MD,[f,g] Pietro Bertoglio, MD,[h,i] Eleonora Faccioli, MD,[j] Roberto Ferrara, MD,[b,c] Alessandra Ferro, MD,[k] Raffaele Giusti, MD,[l] Francesco Guerrera, MD,[m,n] Marco Mammana, MD,[j] Alessandra Pittaro, MD,[o] Matteo Sepulcri, MD,[p] Giuseppe Viscardi, MD,[q] Filippo Tommaso Gallina, MD[r,s,*]

ON INTENT TO TREAT ANALYSIS THE DIFFERENCES CANNOT BE DETECTED

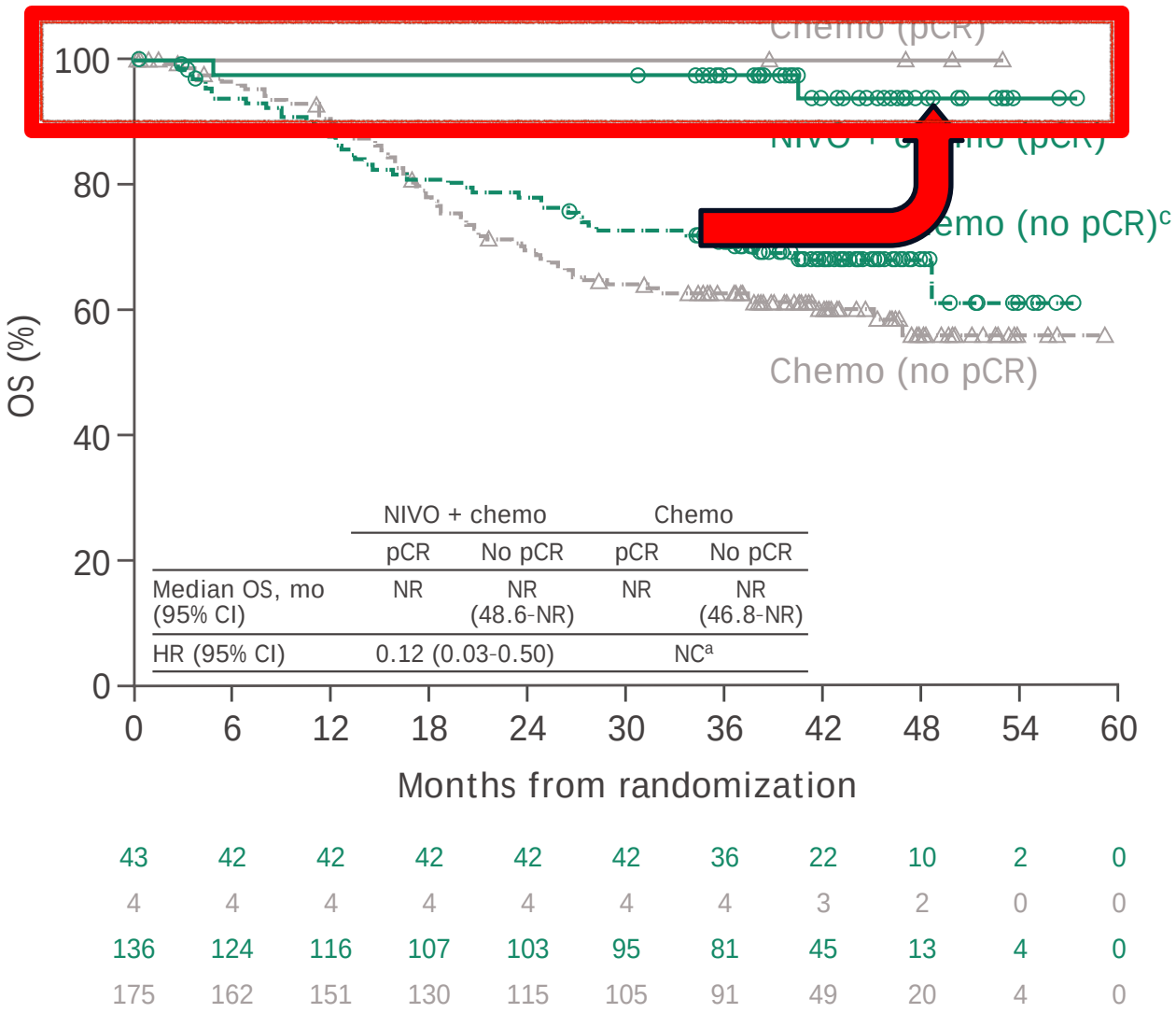




THIS TRIAL WILL RESOLVE THE QUESTION, BUT WILL IT BE TOO LATE???



WHY I THINK WE NEED TO FOCUS ON NEOADJ…



Because promise of PCR ➔ 95% OS @ 4 years (CM816)

And opportunity for adjuvant escalation

Spicer et al, ASCO 2024

Bristol Myers Squibb

Corporate/Financial News

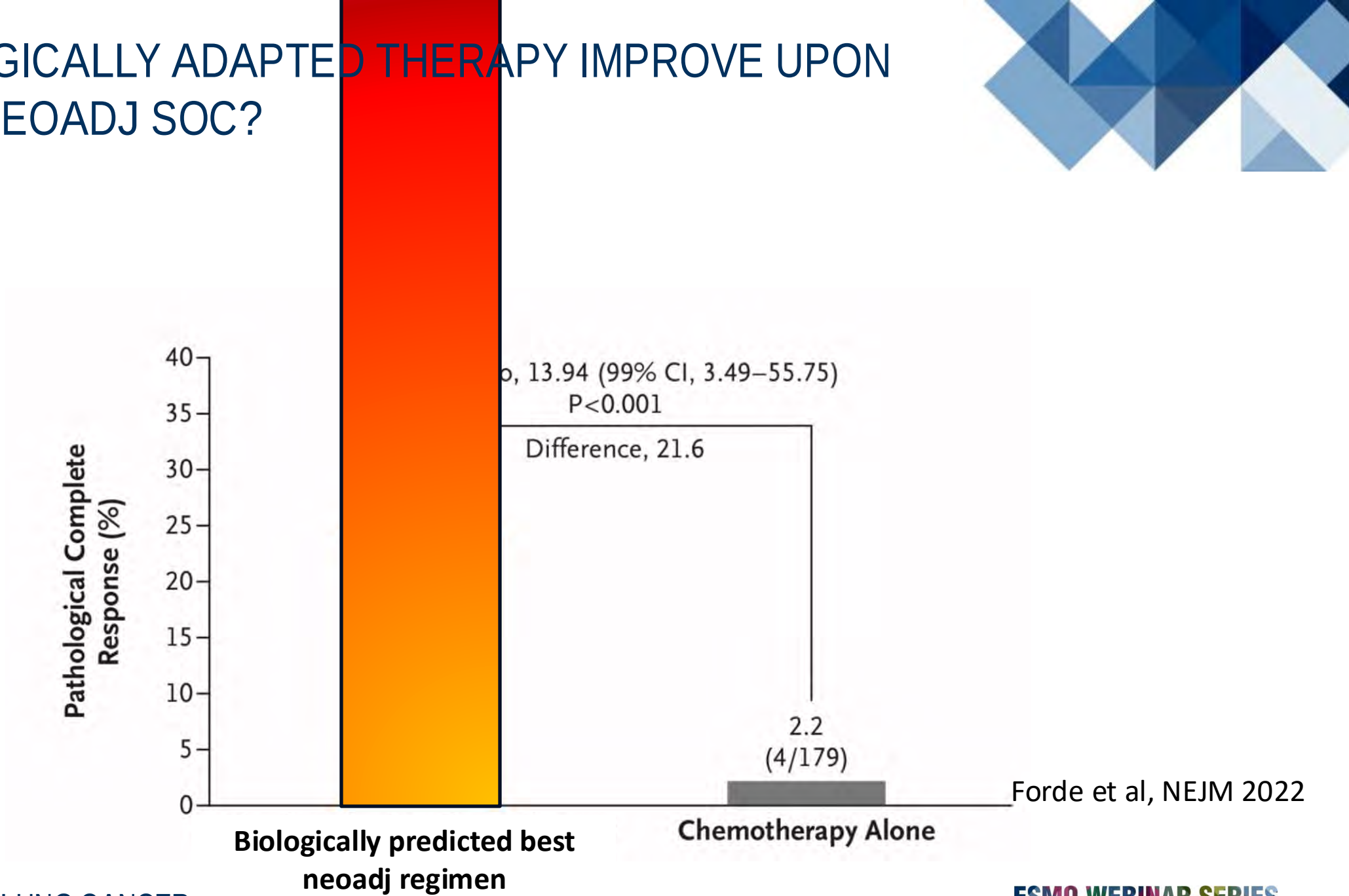
Corporate news details

February 19, 2025

See all press releases Sign up for email alerts

Bristol Myers Squibb Announces Opdivo® Plus Chemotherapy as the First and Only Neoadjuvant-Only Immuno-Oncology Therapy to Demonstrate Statistically Significant and Clinically Meaningful Overall Survival in Resectable Non-Small Cell Lung Cancer

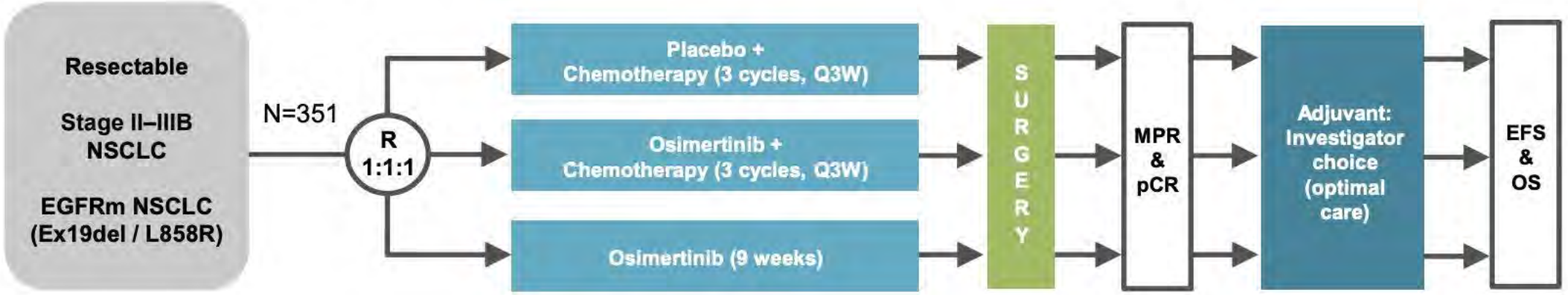
CAN BIOLOGICALLY ADAPTED THERAPY IMPROVE UPON CURRENT NEOADJ SOC?



Forde et al, NEJM 2022

Study design

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



Stratification:

- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:

1. Placebo QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2

Open-label (sponsor-blind) treatment arm:

3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:

- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

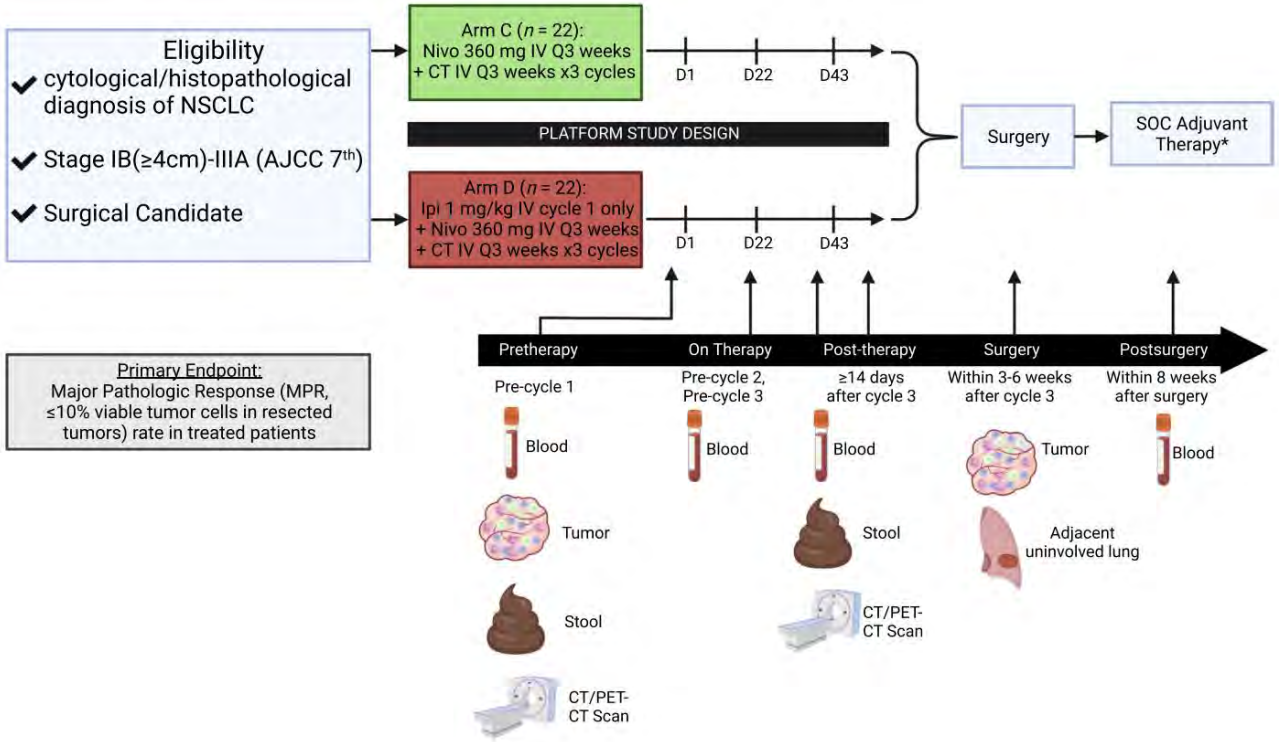
AUC, area under plasma concentration-time curve; Ex19del, Exon 19 deletion; EFS, event-free survival; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; R, randomization, Q3W, every three weeks; QD, once per day; MPR, major pathological response; pCR, complete pathological response; OS, overall survival

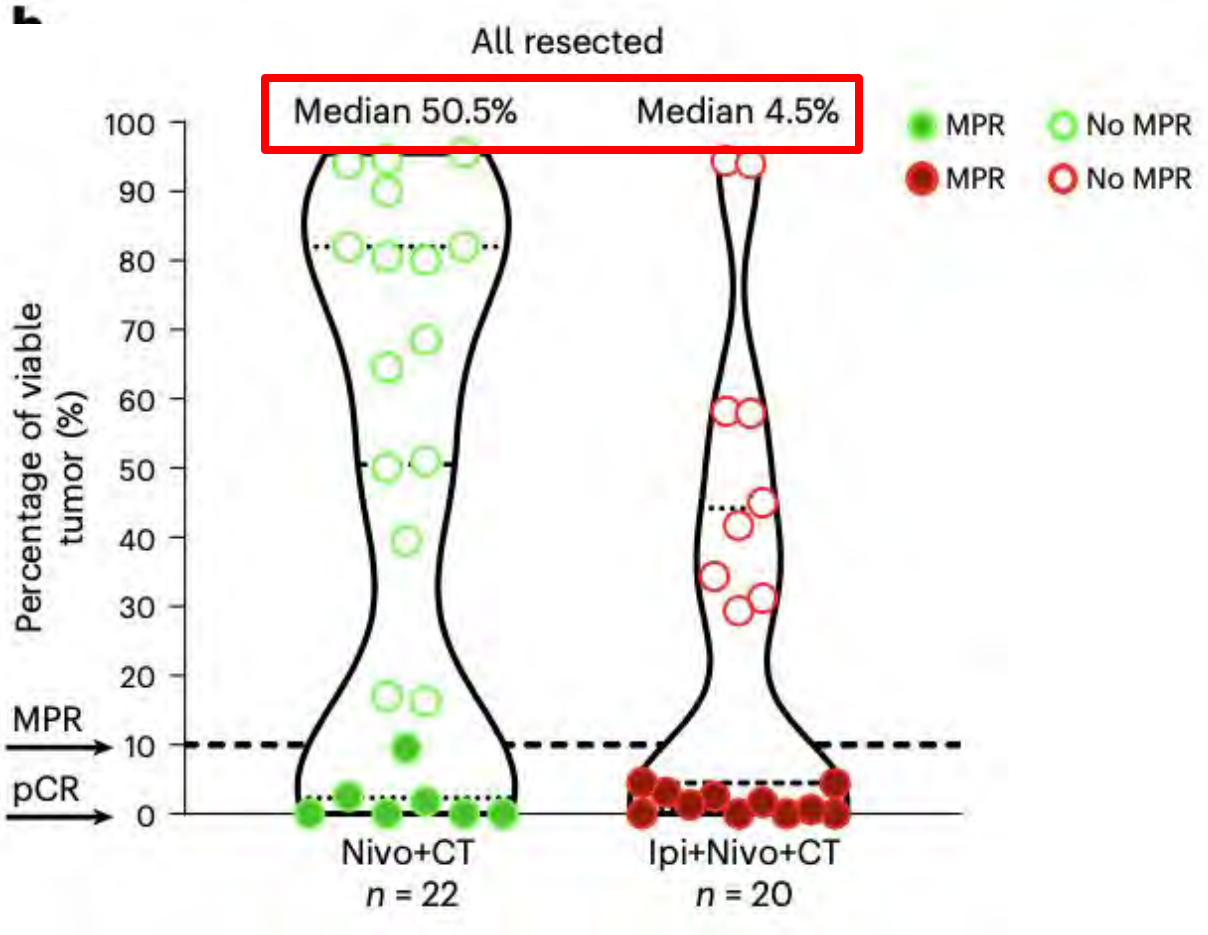
nature medicine

Article

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

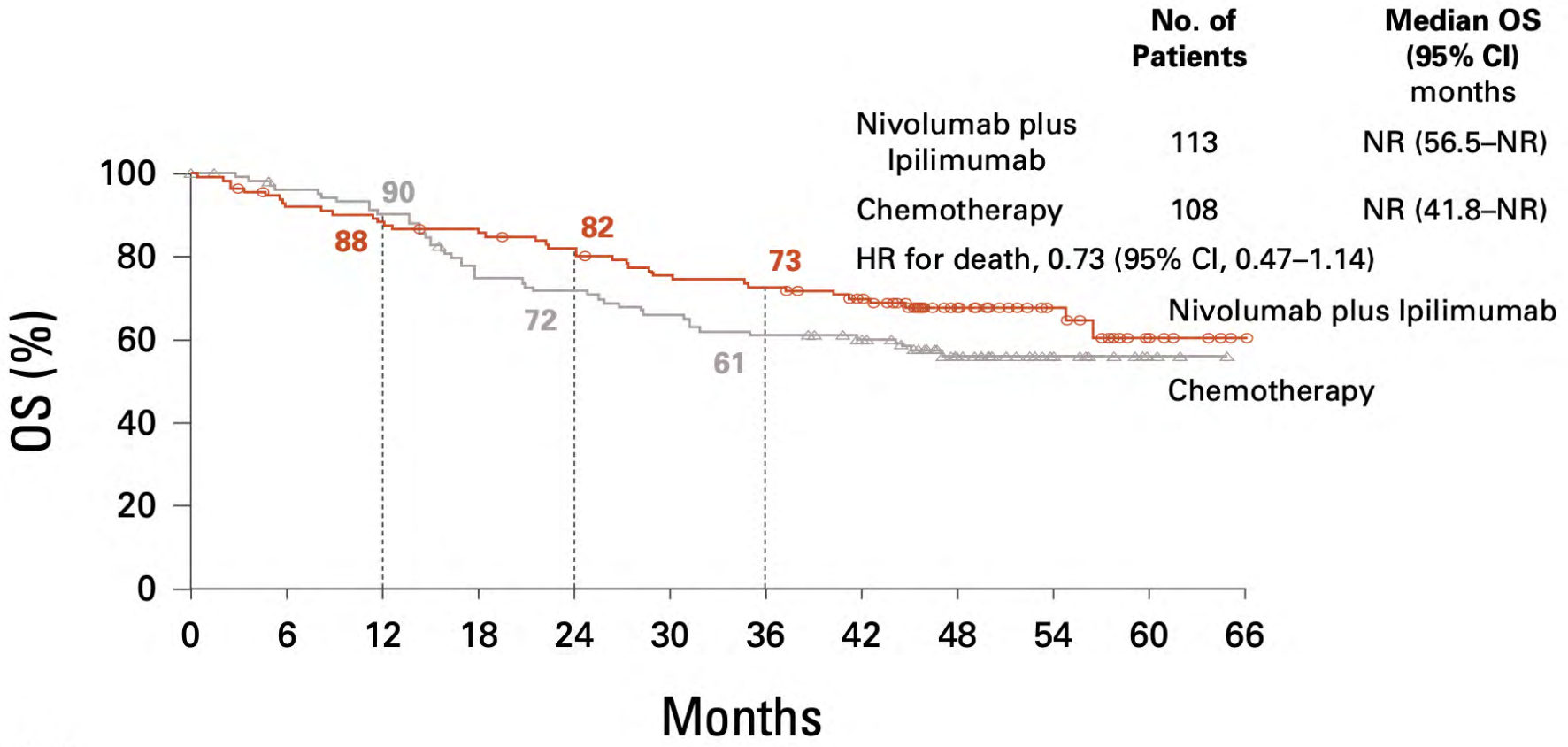
Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial





Cascone et al, Nat Med 2023

BECAUSE PATH RESPONSE BEGETS OS BENEFIT…



Awad, JCO 2024

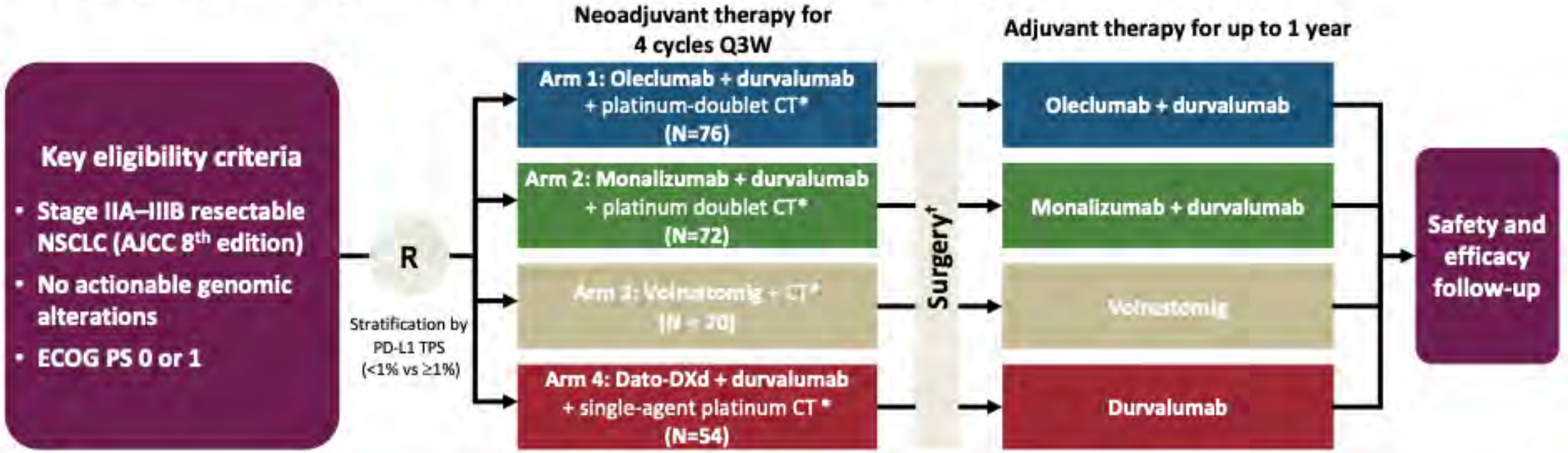
PL02.07

NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Tina Cascone,[1] Florian Guisier,[2] Laura Bonanno,[3] Moishe Liberman,[4] Olivier Bylicki,[5] Amelia Insa,[6] Lorenzo Livi,[7] Romain Corre,[8] Thomas Egenod,[9] Agata Bielska,[10] Alula Yohannes,[11] Ray Mager,[11] Yun He,[10] Adam Dowson,[12] Lara McGrath,[10] Rakesh Kumar,[11] Italia Grenga,[10] Jonathan Spicer,[13] Patrick Forde[14]

[1]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Univ Rouen Normandie, LITIS Lab QuantIF team EA4108, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, F-76000 Rouen, France; [3]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy; [4]Division of Thoracic Surgery, University of Montréal, Montréal, Québec, Canada; CETOC - CHUM Endoscopic Tracheobronchial and Oesophageal Center, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada; [5]Respiratory Medicine Department, Hôpital d'Instruction des Armées Sainte-Anne, Toulon, France; [6]Medical Oncology Department, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain; [7]Department of Radiation Oncology, University of Florence, Florence, Italy; [8]Department of Medical Oncology, CH de Cornouaille, Quimper, France; [9]Department of Thoracic Oncology, Dupuytren University Hospital, Limoges, France; [10]AstraZeneca, Waltham, MA, USA; [11]AstraZeneca, Gaithersburg, MD, USA; [12]AstraZeneca, Cambridge, UK; [13]Department of Thoracic Surgery, McGill University, Montreal, QC, Canada; [14]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

NeoCOAST-2: open-label, multi-arm platform study



Primary endpoints
- pCR rate
- Safety and tolerability

Key secondary endpoints
- mPR rate and EFS
- Feasibility to surgery

Statistical considerations
- This study was not powered to make direct statistical comparisons between arms.
- Descriptive statistics are summarised and presented.
- The primary intent was to look for preliminary efficacy signals by calculating pCR rates and their confidence intervals.

*Carboplatin + paclitaxel for squamous tumor histology, pemetrexed + cisplatin or carboplatin for non-squamous tumor histology.
†Within 40 days of the last dose of neoadjuvant treatment.
CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; EFS, event-free survival; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; R, randomised; TPS, tumour proportion score.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Baseline patient characteristics

n (%)	Arm 1 Oleclumab + durvalumab + CTx* N=76	Arm 2 Monalizumab + durvalumab + CTx* N=72	Arm 4 Dato-DXd + durvalumab + CT* N=54
Median age, years (range)	66.5 (30–79)	66.0 (48–83)	65.0 (38–81)
Female/Male, n (%)	29 (38.2) / 47 (61.8)	29 (40.3) / 43 (59.7)	22 (40.7) / 32 (59.3)
Race, n (%)			
Asian	7 (9.2)	5 (6.9)	5 (9.3)
Black or African American	1 (1.3)	0	0
White	48 (63.2)	43 (59.7)	37 (68.5)
Not reported	20 (26.3)	24 (33.3)	12 (22.2)
ECOG PS 0/1, n (%)	45 (61.6) / 28 (38.4)†	49 (69.0) / 22 (31.0)‡	36 (66.7) / 18 (33.3)
PD-L1 <1% / PD-L1 ≥1% TPS, n (%)	24 (31.6) / 52 (68.4)	24 (33.3) / 48 (66.7)	13 (24.1) / 41 (75.9)
Stage, n (%)§			
IIA	7 (9.2)	7 (9.7)	2 (3.8)
IIB	16 (21.1)	19 (26.4)	13 (24.5)
IIIA	40 (52.6)	33 (45.8)	27 (50.9)
IIIB	13 (17.1)	13 (18.1)	11 (20.8)
Histology, n (%)			
Adenocarcinoma	50 (65.8)	46 (63.9)	33 (61.1)
Squamous cell carcinoma	24 (31.6)	20 (27.8)	17 (31.5)
Other	2 (2.6)	6 (8.3)	4 (7.4)

- The majority of patients received carboplatin compared with cisplatin: in Arm 1, n=53 vs n=21; in Arm 2, n=55 vs n=16; and in Arm 4, n=47 vs n=7 patients received carboplatin vs cisplatin

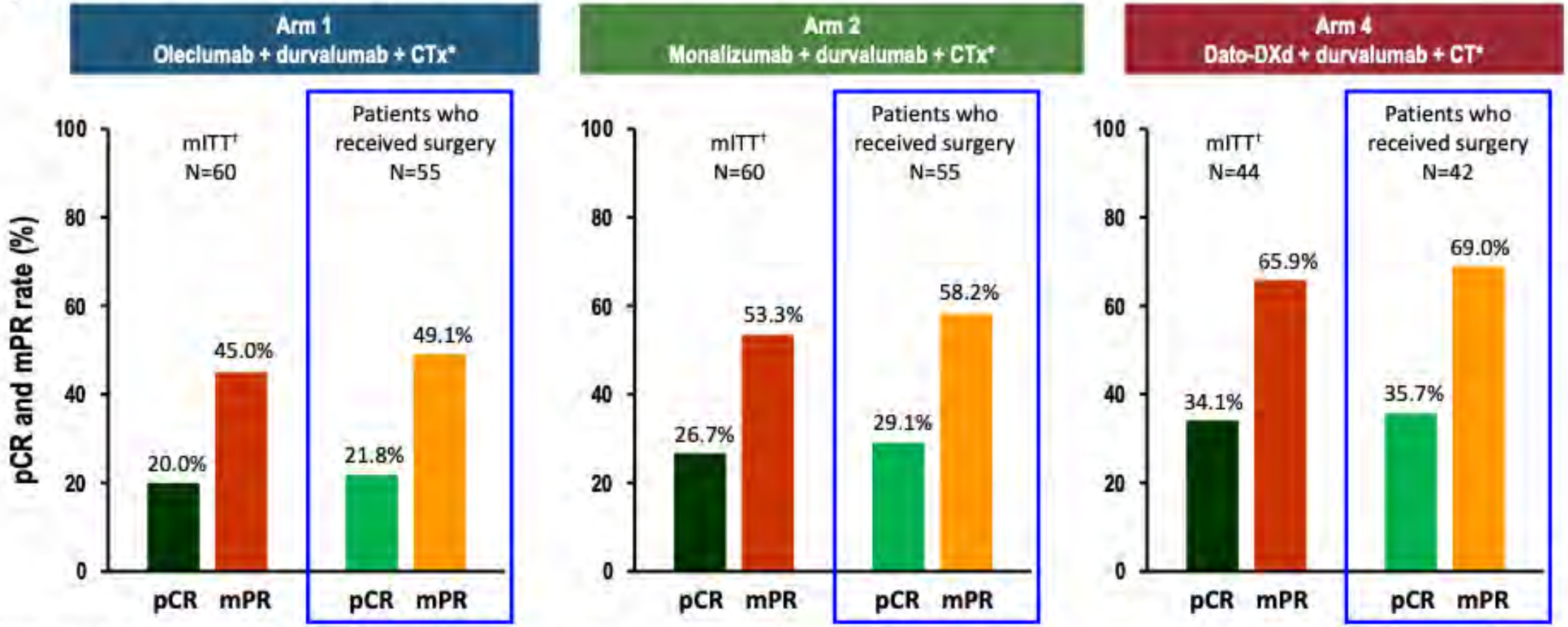
Data cut-off: 17 June 2024

*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT; †Data missing for 3 patients; ‡Data missing for 1 patient; §Data missing for 1 patient in Arm 4.

CT(x), chemotherapy(s); D, durvalumab; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TPS, tumour proportion score.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

pCR and mPR rates across treatment arms



Pathological assessment performed locally and/or centrally

Data cut-off: 17 June 2024

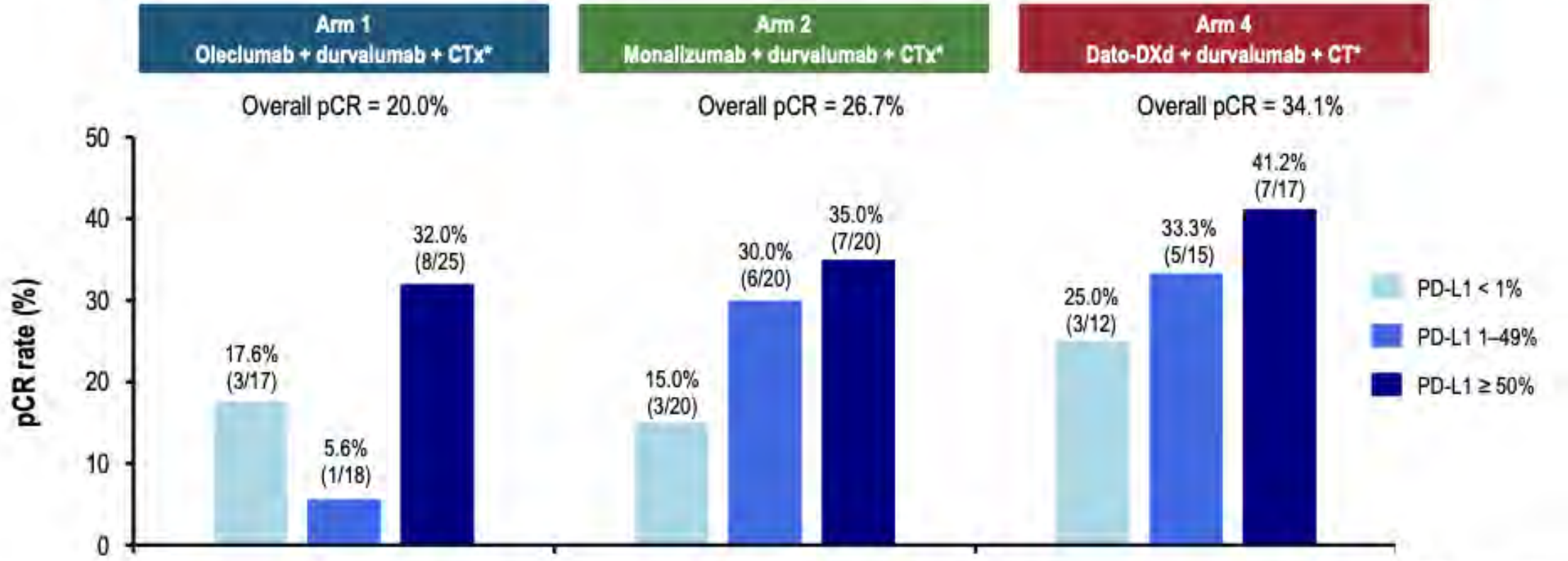
*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT.

†The modified intention-to-treat population includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at the data cut-off, including those who were unable to receive or complete surgery.

CT(x), chemotherapy(s); Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat population; mPR, major pathological response; pCR, pathological complete response.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

pCR rates across baseline PD-L1 subgroups



Data cut-off: 17 June 2024

Based on the modified intention-to-treat population which includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at the DCO, including those who were unable to receive or complete surgery. Baseline PD-L1 status is assessed using central (Ventana SP263) or local testing (Ventana SP263, pharmDx 28-8, or pharmDx 22C3). Central results are reported for patients who have central results, otherwise local results are reported.

In AEGEAN, pCR rates were 9.0%, 16.3% and 27.5% in PD-L1 <1%, PD-L1 1–49% and PD-L1 ≥50% subgroups, respectively (Heymach et al. *N Engl J Med* 2023;389;1672–84).

*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT.

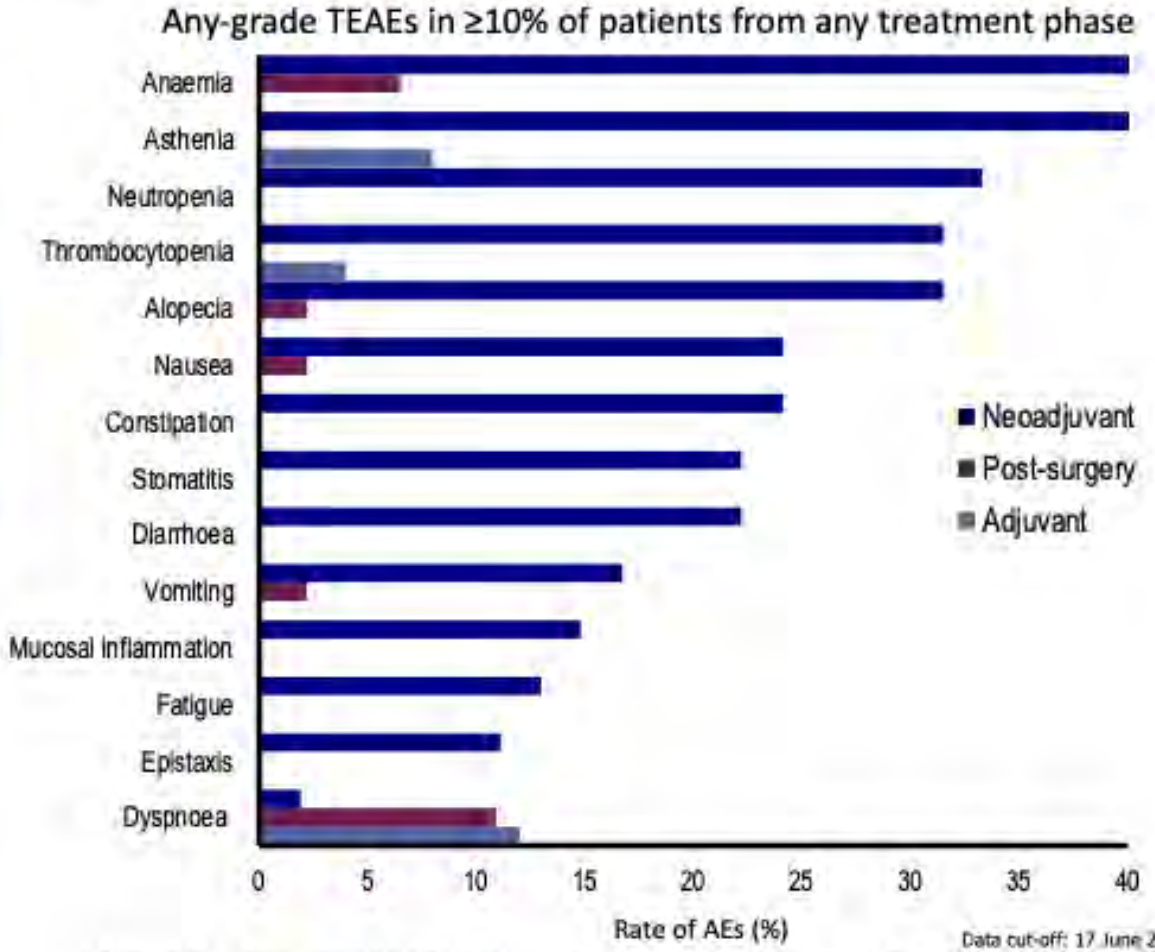
CT(x), chemotherapy(s); Dato-DXd, datopotamab deruxtecan; pCR, pathological complete response; PD-L1, programmed cell death ligand 1.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Safety profile of Arm 4: Dato-DXd + durvalumab + single-agent platinum CT

n (%)	Neoadjuvant N=54	Post-surgery N=46	Adjuvant N=25
Any TEAE	53 (98.1)	24 (52.2)	11 (44.0)
Any TRAE	52 (96.3)	6 (13.0)	5 (20.0)
Grade ≥3 TEAE	13 (24.1)	4 (8.7)	1 (4.0)
Grade ≥3 TRAE	10 (18.5)	0	0
AE leading to discontinuation	4 (7.4)	0	0
SAE	10 (18.5)	7 (15.2)	1 (4.0)
Any SAE with outcome of death	0	1 (2.2)	0

- One death in the post-surgery phase was due to idiopathic pulmonary fibrosis unrelated to treatment.*

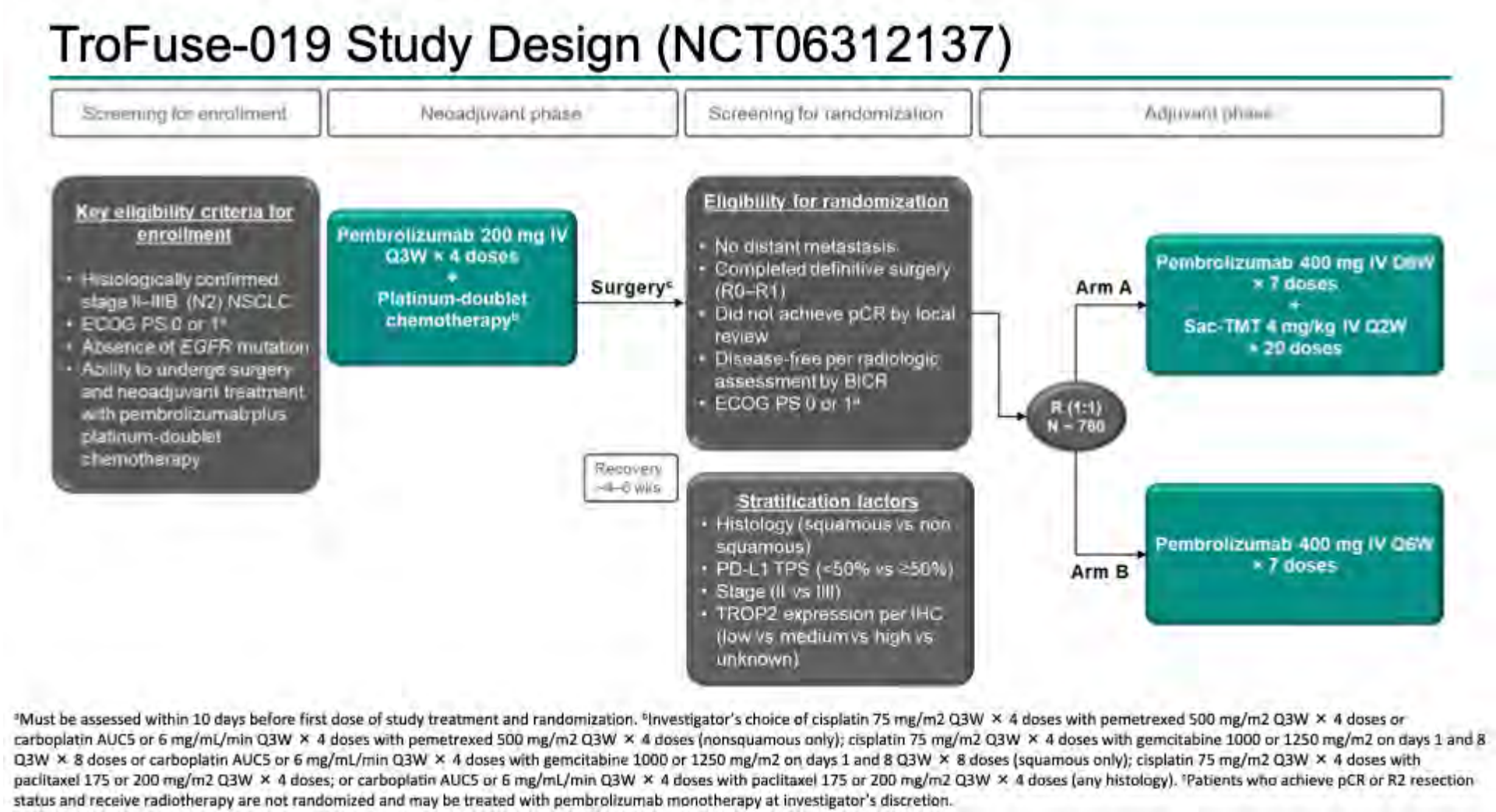


Data cut-off: 17 June 2024

Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
*Unrelated per principal investigator, independent adjudication is pending.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

ADC NOW IN THE PHASE 3 REALM OF RESECTABLE NSCLC, **ALBEIT AS AN ADJUVANT ESCALATION STRATEGY…**

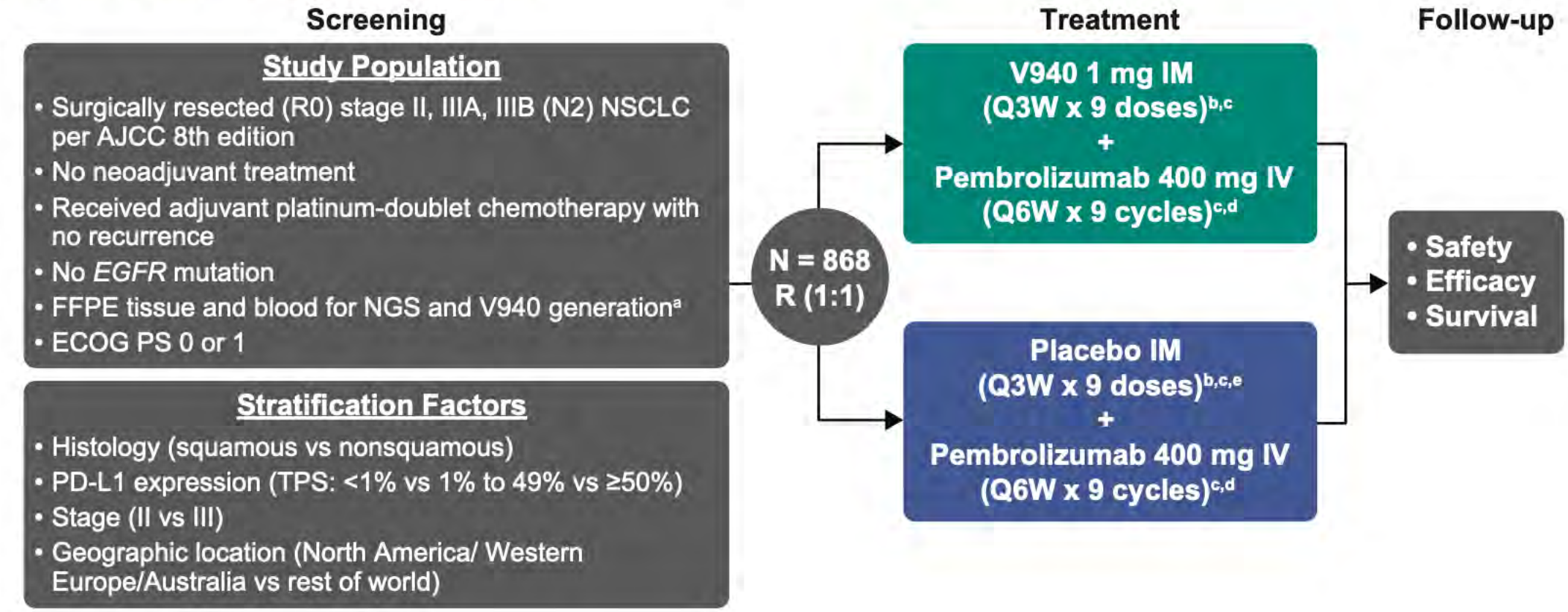


[a]Must be assessed within 10 days before first dose of study treatment and randomization. [b]Investigator's choice of cisplatin 75 mg/m2 Q3W × 4 doses with pemetrexed 500 mg/m2 Q3W × 4 doses or carboplatin AUC5 or 6 mg/mL/min Q3W × 4 doses with pemetrexed 500 mg/m2 Q3W × 4 doses (nonsquamous only); cisplatin 75 mg/m2 Q3W × 4 doses with gemcitabine 1000 or 1250 mg/m2 on days 1 and 8 Q3W × 8 doses or carboplatin AUC5 or 6 mg/mL/min Q3W × 4 doses with gemcitabine 1000 or 1250 mg/m2 on days 1 and 8 Q3W × 8 doses (squamous only); cisplatin 75 mg/m2 Q3W × 4 doses with paclitaxel 175 or 200 mg/m2 Q3W × 4 doses; or carboplatin AUC5 or 6 mg/mL/min Q3W × 4 doses with paclitaxel 175 or 200 mg/m2 Q3W × 4 doses (any histology). [c]Patients who achieve pCR or R2 resection status and receive radiotherapy are not randomized and may be treated with pembrolizumab monotherapy at investigator's discretion.

Lee et al, CSCO 2024

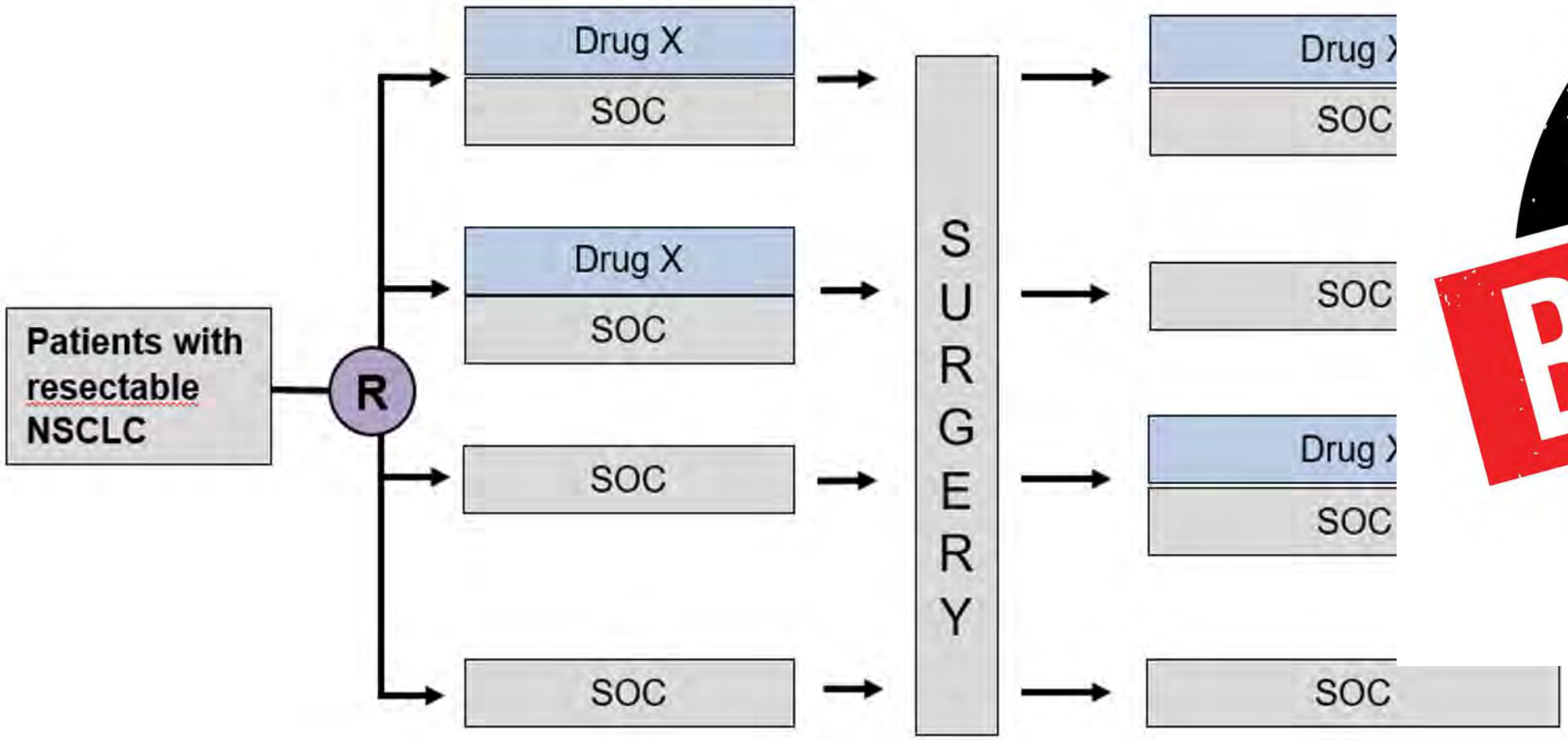
INDIVIDUALIZED NEOANTIGEN THERAPY NOW IN RESECTABLE NSCLC FOR ADJUVANT AND PERIOP

Figure. INTerpath-002 study design



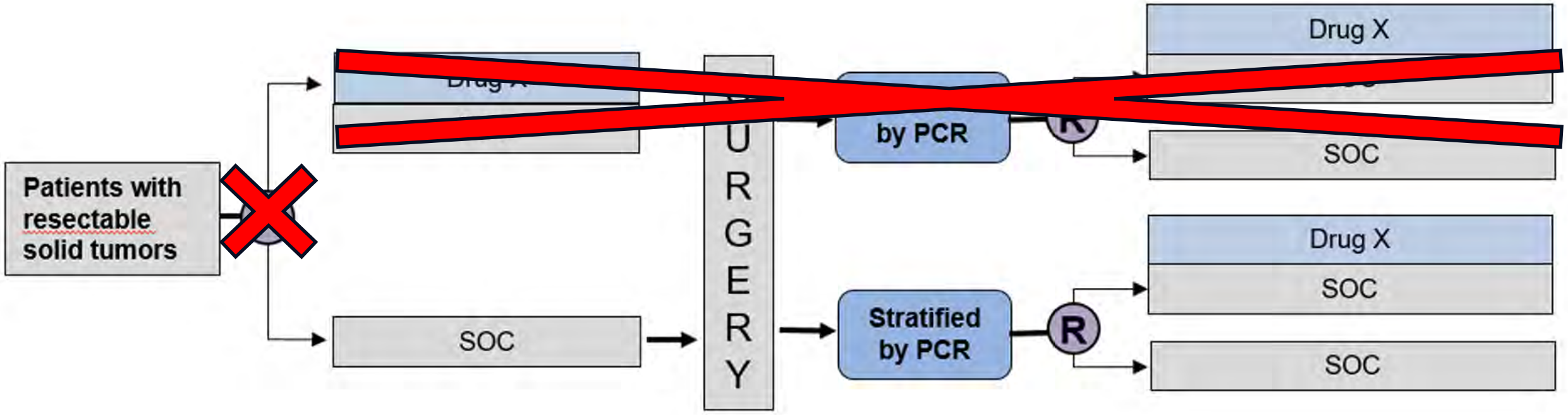
Spicer et al, AACR 2024

MY FEARS FOR THE FUTURE OF RESECTABLE NSCLC TRIALS



Expensive study! If most patient friendly option wins, company loses!

MY FEARS FOR THE FUTURE OF RESECTABLE NSCLC TRIALS



Expensive study! So why bother with the commercially risky design…

MAJOR CHALLENGES

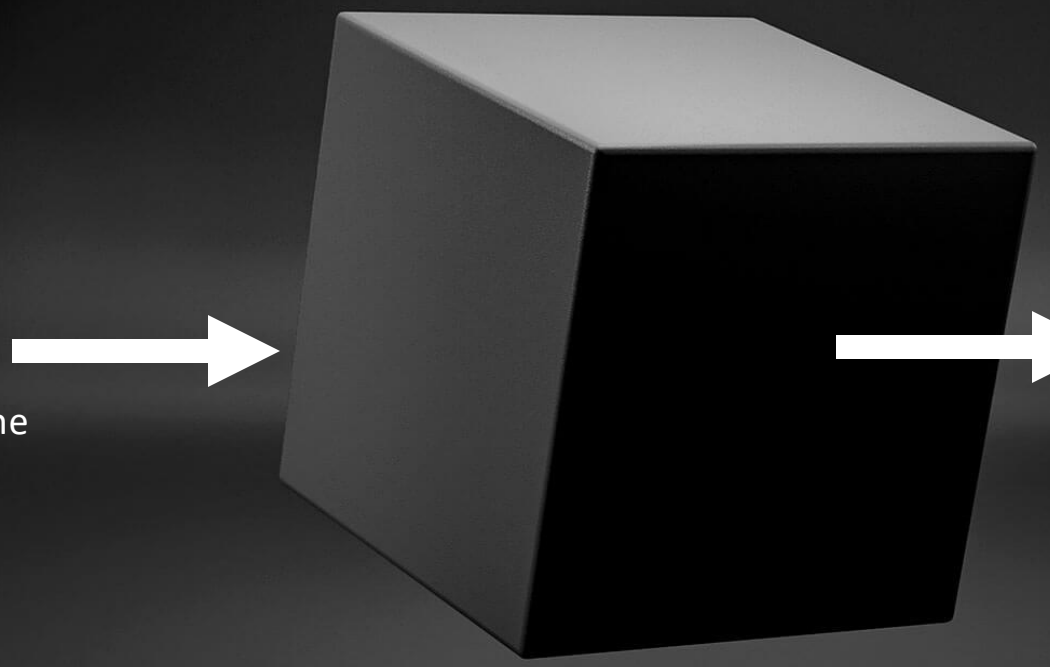
- Shifting standards that lack consensus: Can we find a way to all pull in the same direction?
- Increasing diagnostic precision means more subgroups and challenging accruals
- Multiple competing strategies may yield positive results in overlapping subgroups
- How to manage patient interests when these collide with commercial imperatives!

AI Predictions

Image generated by ChatGPT, OpenAI, 2024

Integration of key data from:

- Clinical characteristics
- Molecular details
- Imaging Response
- ctDNA response
- Post-induction tumor-immune interface pattern
- High throughput PDO screen
- Adverse-event profile



Next step?

Rad Tx

Targeted Tx

ADC

PD1 mAb

mRNA Tx

PD1-CTLA4 bispecific

PD1-VEGF bispecific

No Tx needed

Questions?

McGill | Department of Surgery

ESMO ON AIR

ESMO Deep Dive Webinar

Non-metastatic Non-small Cell Lung Cancer: Multidisciplinary State of the Art
Radiation – opportunities, future directions

Prof Corinne Faivre-Finn

The Christie NHS Foundation Trust

University of Manchester

UK

5th March 2025

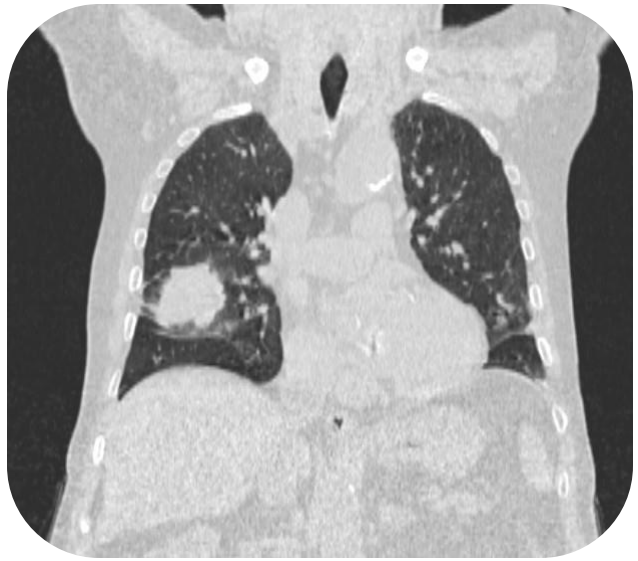
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

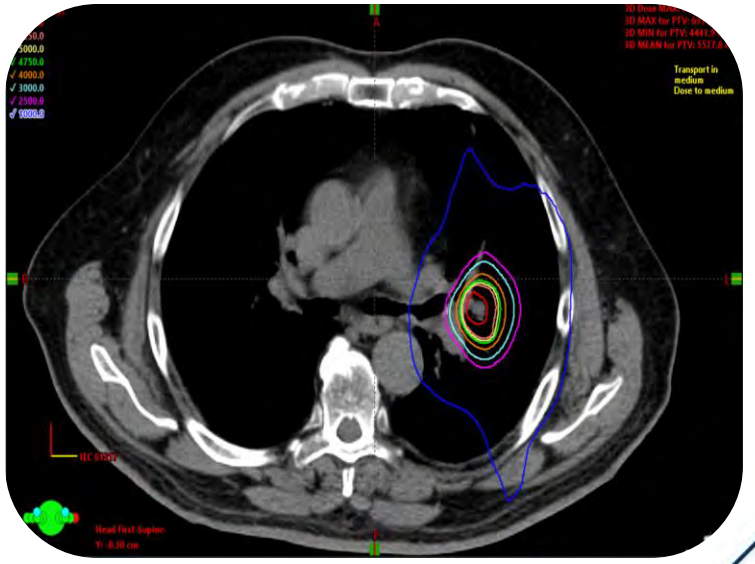
Declaration of Interest

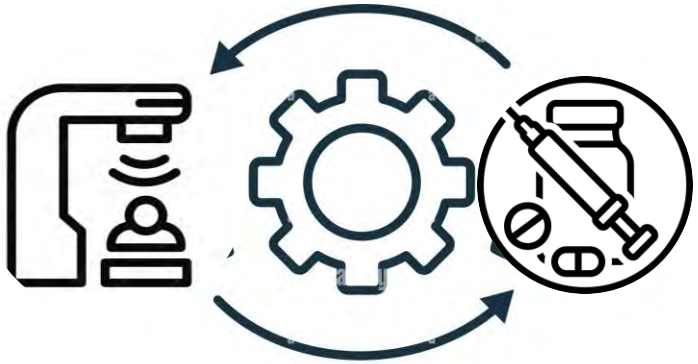
Research funding - AstraZeneca (to the institution)

Research funding – Elekta (to the institution)

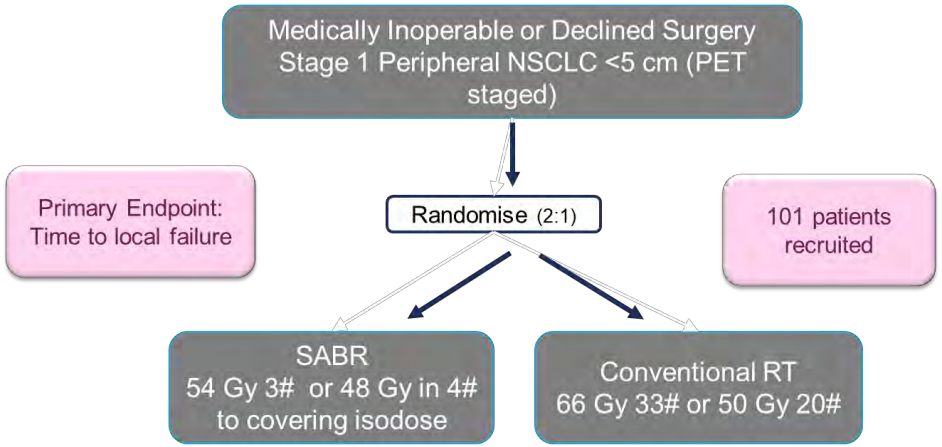
Early-stage NSCLC

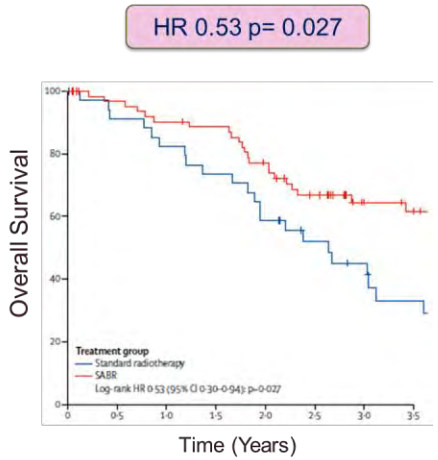






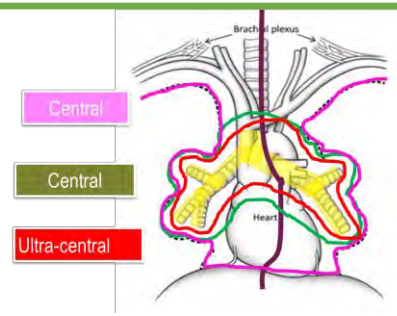
SABR is Standard of Care for
'Medically Inoperable' early stage NSCLC

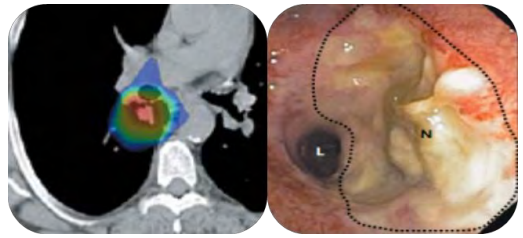


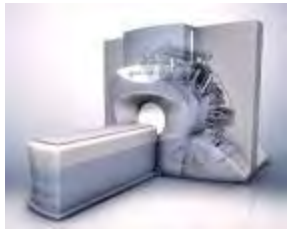


Ball. Lancet Oncol 2019

Local control – 80-90%







Central and Ultra-central SABR Outcomes

Study	Definition of Ultra-central	Dose/Fractionation	2-yr Local Control	Toxicity
Nestle: Lungtech EORTC, 2023 (n=31)	Withing 2cm or touching PBT or adjacent to mediastinal or pericardial pleura	60Gy/8F	78.6% (3yrs)	Grade 3:22.6% Grade 5: 6.5%
Giulianie: Sunset, 2023 (n=30)	PTV overlapping PBT, oesophagus, pulmonary vein/artery	60Gy /8F 120% hotspot	86.9% (3yr)	Grade 3: 3.3% Grade 5: 3.3%
HILUS Phase II, 2021 (n=65)	≤ 1 cm from PBT	56 Gy/8 fx (100%) 150% hotspot	83%	Grade 3+: 34% Grade 5: 15%
Breen, 2021 (n=110)	GTV abutting PBT, trachea; PTV overlap PBT, trachea; GTV ≤ 1 cm from PBT	50 Gy/5 fx (57%) 60 Gy/8 fx (15%) 48 Gy/4 fx (13%)	84%	Grade 5 (4%)
RTOG 0813, 2019 (n=120)	≤ 2cm from PBT	50-60 Gy/5 fx	87.9-89.4%	7.2% DLTs
Raman, 2018 (n=26)	PTV overlapping PBT, trachea, esophagus, pulmonary vein/artery	60 Gy/8 fx (77%) 50 Gy/10 fx (12%)	100%	Grade 2-3: 7.9% Grade 4-5: 0%
Tekatli, 2016 (n=47)	PTV overlapping trachea or main bronchi	60 Gy/12 fx 140% hotspot	78%	Grade 3+: 38% Grade 5: 13%
Li, 2014 (n=82)	Dose constraints for 50 Gy in 4 fx not met	70 Gy/10 fx (100%)	96.2%	Grade 3: 3.6% Grade 5: 1.2%

Q1- Can we reduce the toxicity of SABR?

SABR vs Surgery

*Pooled analysis STARS and ROSEL **n=58***
Chang. Lancet Oncol 2015

	ROSEL	STARS	Z4099
Eligibility criteria	Operable non-central stage IA	Operable stage IA, IB (≤ 4 cm)	'Borderline' operable, stage I <3cm
Primary end-point	Local & regional control, QoL treatment costs at 2- and 5-years	OS at 3 years	OS at 3 years
Secondary end-points	OS, pulmonary functions, QALYs, total costs	DSS at 3 years Local PFS at 3 years; toxicities	LRR, DFS, toxicities, pulmonary function
Total enrolled	22 (of 920)	36 (of 1030)	10 (of 420)

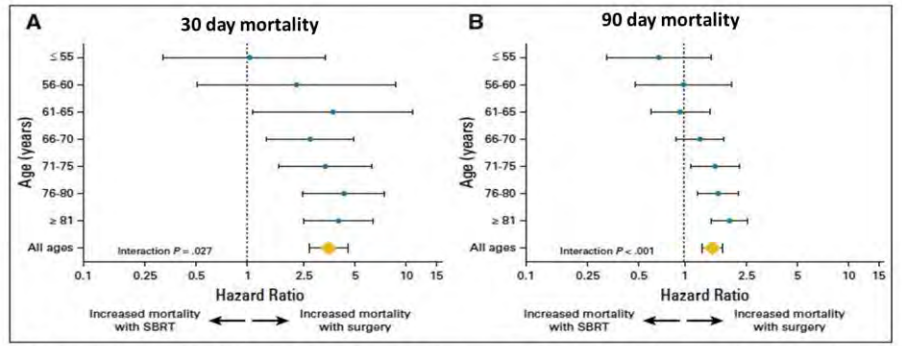
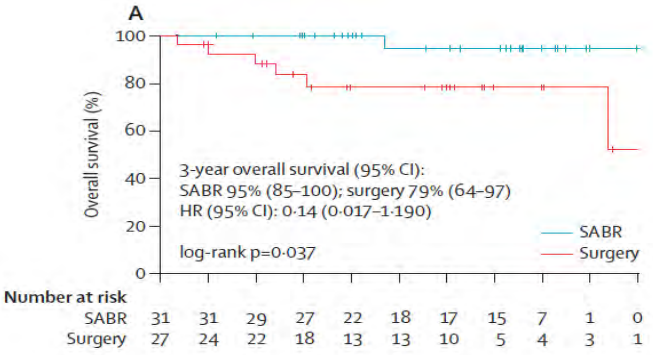
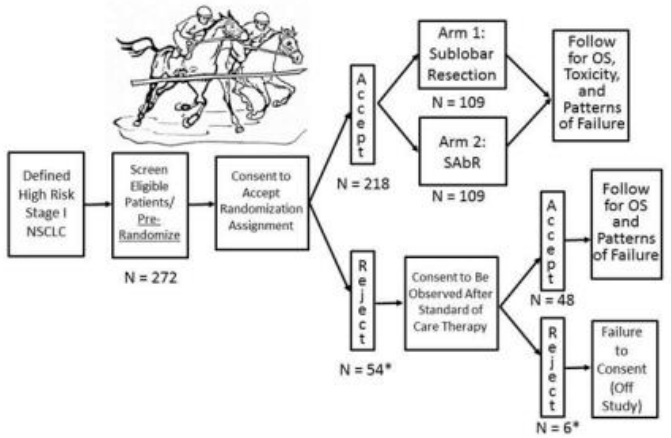


Fig 3. Forest plots depicting multivariable adjusted hazard ratios of mortality by age group at (A) 30 days, and (B) 90 days postintervention, surgery versus stereotactic body radiotherapy (SBRT).

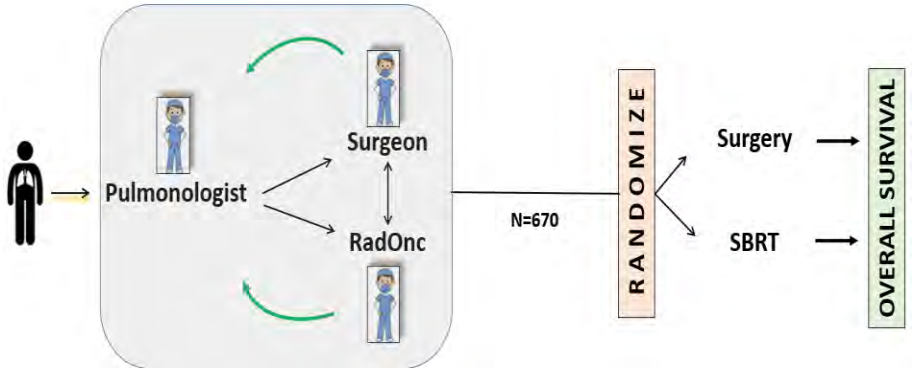


Q2- Can SABR be an alternative to surgery?

STABLMATES NCT02468024



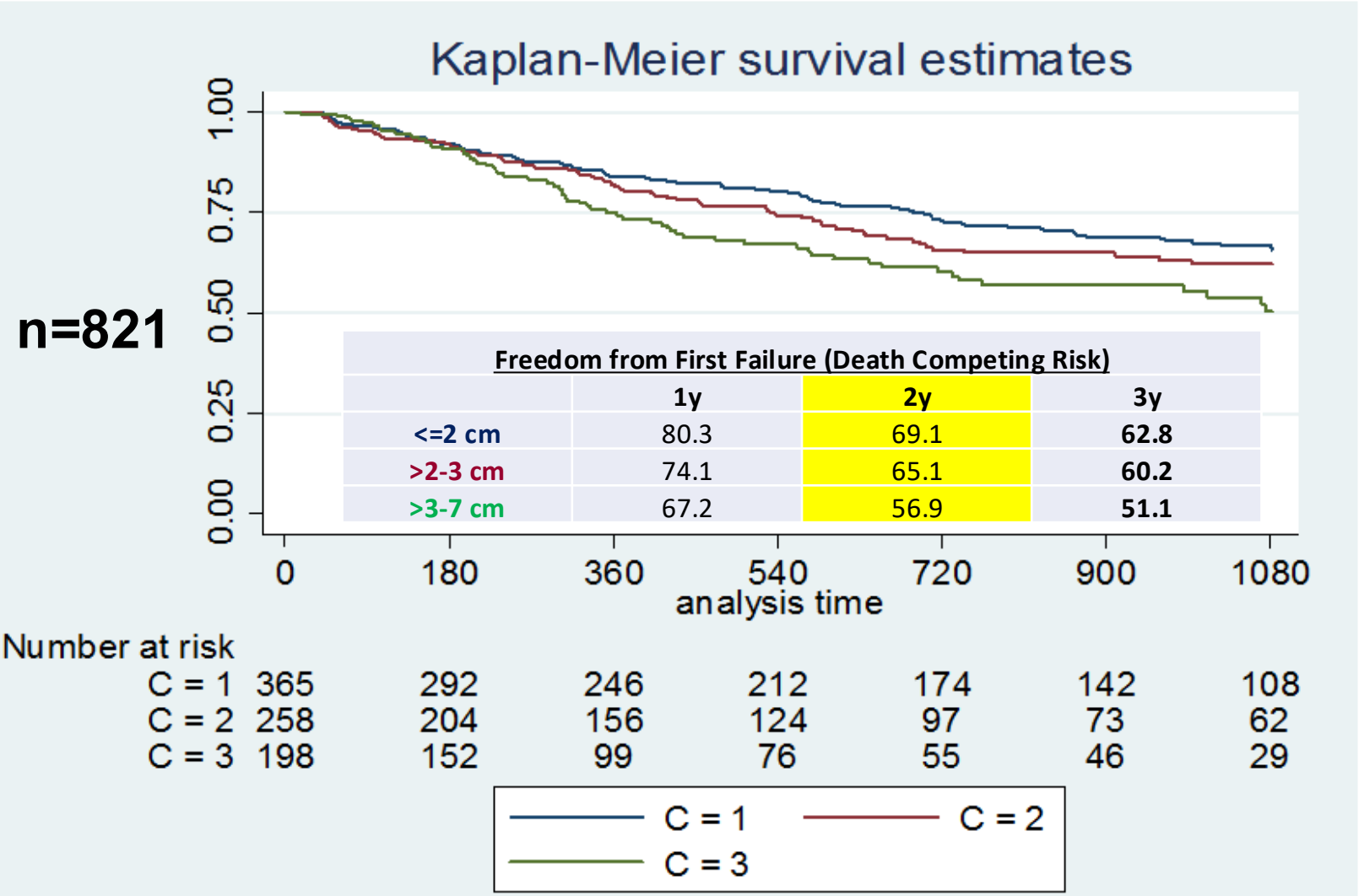
VALOR NCT02984761



Completed accrual

430/670 randomised

Risk of treatment failure-Real world evidence



Freedom from First Failure (Death Competing Risk)

	1y	2y	3y
<=2 cm	80.3	69.1	**62.8**
>2-3 cm	74.1	65.1	**60.2**
>3-7 cm	67.2	56.9	**51.1**

- ↑ tumour size
  = ↑ rate of failure
- Majority of failures within first 2 years post SABR
- Majority are distant failures

- Chemotherapy too toxic in this population
- IO has a tolerable toxicity profile

Rationale for adjuvant IO

North American Conference on Lung Cancer 2019 Abstr GS04

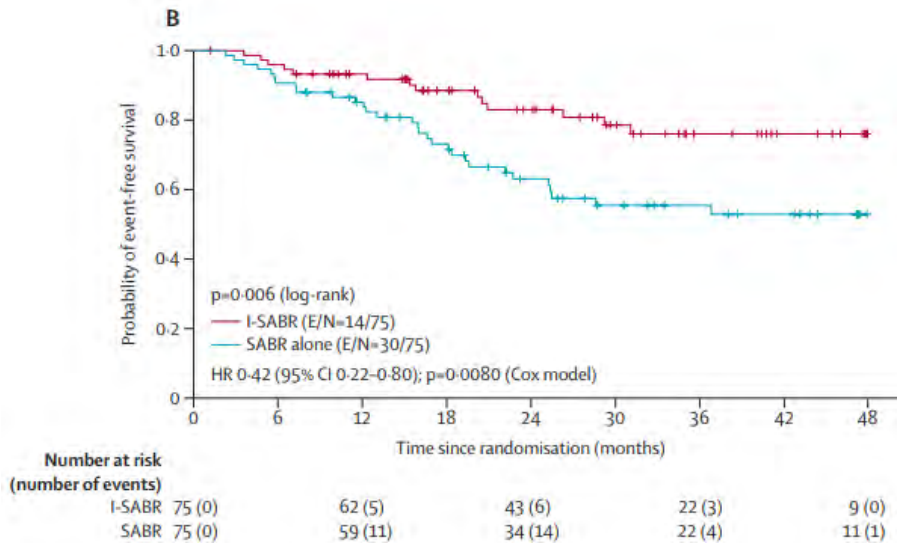
Role of adjuvant systemic therapies

Q3- Can IO reduce the risk of metastatic disease in patients without driver mutations ?

Q4- Can EGFR TKIs reduce the risk of metastatic disease in patients with driver mutations ?

I-SABR phase 2 trial

SABR +/- 4 cycles of Nivolumab



Chang. Lancet 2023

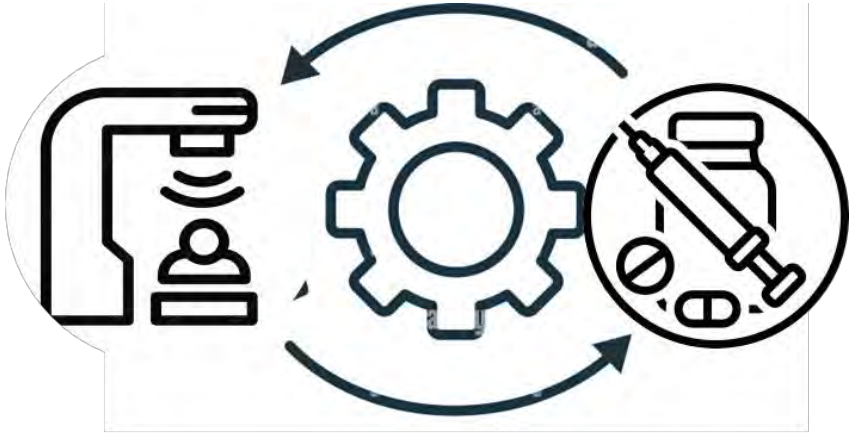
Ongoing Phase III Trials of SBRT ± Checkpoint Inhibitors for NSCLC Stage IA-IB

Stage I NSCLC (Inoperable or Refuse Surgery)		
PACIFIC 4	**Keynote 867**	**SWOG 1914**
SBRT ± durvalumab (24 months)	SBRT ± pembrolizumab (17 cycles)	SBRT ± atezolizumab (8 cycles)
Primary Outcome= PFS Secondary Outcome = OS	Primary Outcome= EFS Secondary Outcome = OS	Primary Outcome = OS Secondary Outcome = PFS
Sample Size = 706	Sample Size = 530	Sample Size = 480
Opened March 2019	**Opened June 2019**	**Opened March 2020**
NCT03833154	NCT03924869	NCT04214262

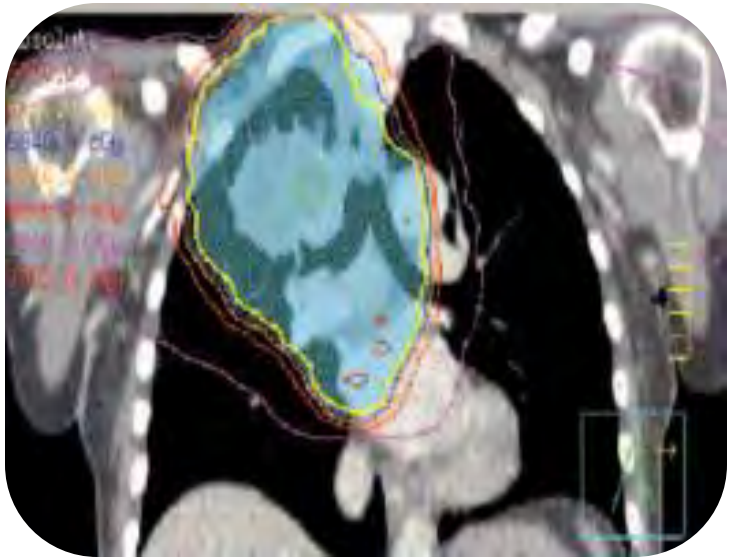
Need for larger phase 3 study, excluding driver mutations, double-blinded or placebo-controlled, with masked independent central review of imaging

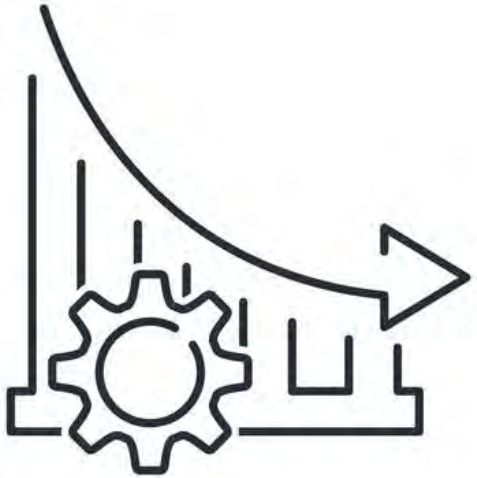
Q5- can PDL1 be used as a biomarker?

Locally advanced NSCLC



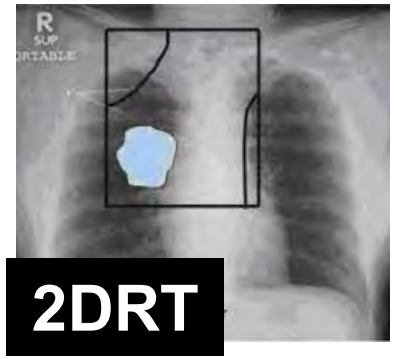
Drug-RT combination

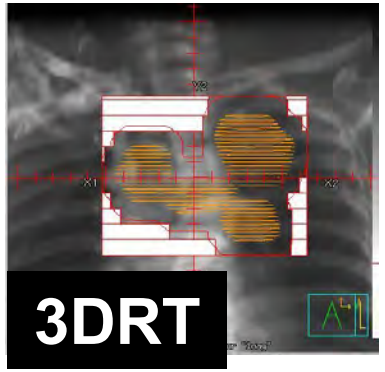


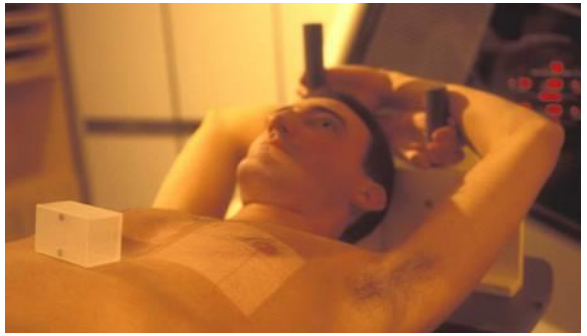


De-escalation of RT

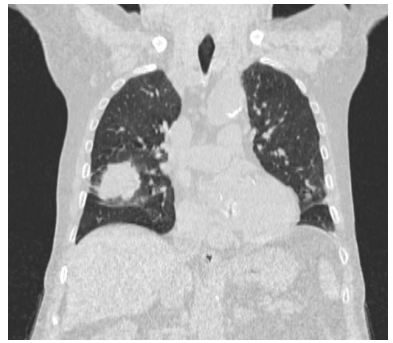
Importance of the quality of RT

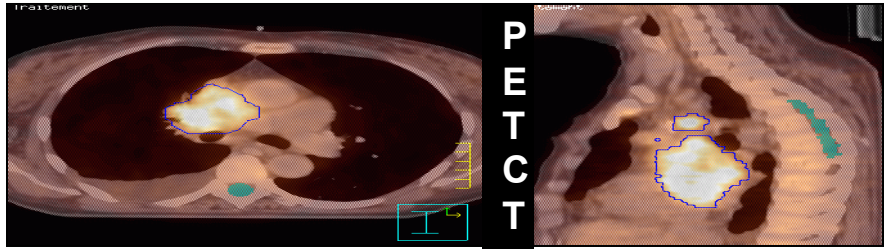


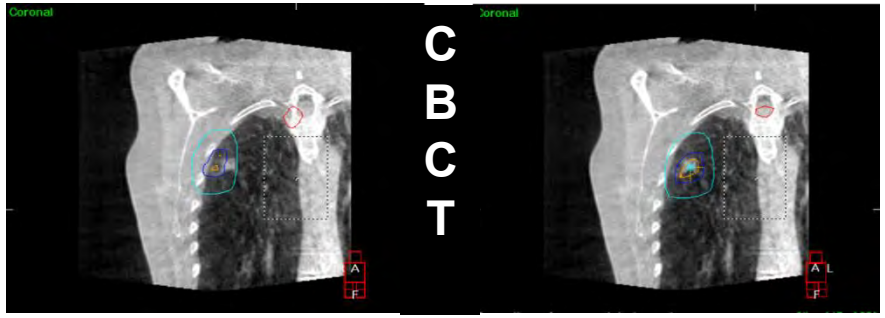


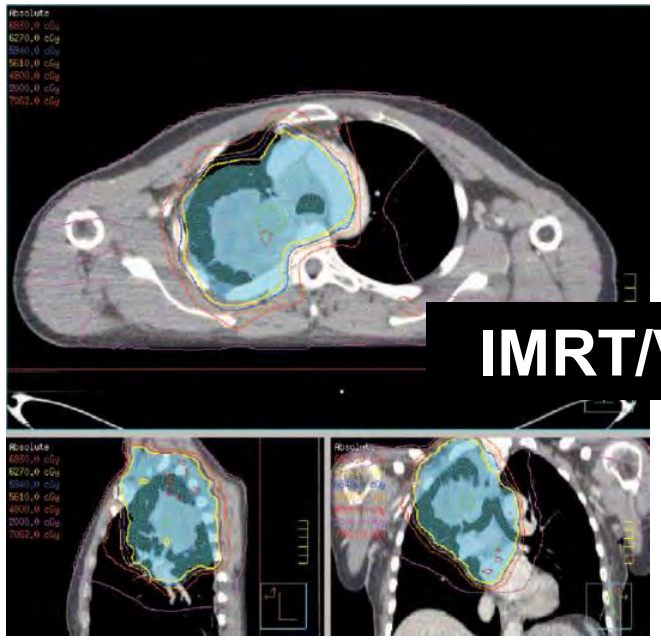


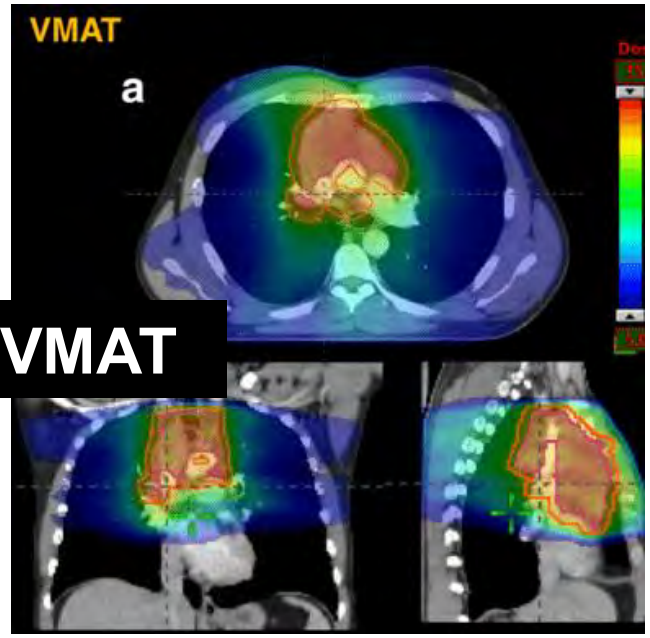
4DCT











Impact on toxicity of CTRT

Study Year publication	N	Inclusion	Staging PET-CT	Treatment regimen in standard CRT arm	RT technique	Toxicity
RTOG 9410 2011	610	Inoperable stage II-III	0	63 Gy cisplatin-vinblastine	2DRT	Grade ≥3 oesophagitis 22% Grade ≥3 acute RP 4% Grade 5 toxicity 2%
Auperin meta analysis 2010	603 concurrent 602 sequential	Unresectable stage III	0	60 Gy (2 tirals), 66 Gy (1 trial), 66 Gy in 24 fractions (1 trial), 56 Gy split course (1 trial), 48.5 Gy (split course of 36 Gy in 12 fractions, 7 days' rest, 12.5 Gy in 5 fractions) Single agent low-dose cisplatin (2 trials), cisplatin-based doublet (3 trials), carboplatin (1 trials)	3DCRT in 1 trial Remainder 2DRT	Grade ≥3 oesophagitis 18% (concurrent CRT) Rates of acute pneumonitis and grade 5 toxicity NR
PROCLAIM 2016	598	Unresectable Non squamous stage III	82%	60-66 Gy etoposide-cisplatin Consolidation in both arms	25% IMRT (remainder 3DCRT)	Grade ≥3 oesophagitis 15.5% Grade ≥3 pneumonitis 1.8/2.6 % Grade 5 toxicity 1.7/1%
RTOG 0617 2015	424 analysable for RT end-point	Unresectable stage III	91%	60 Gy concurrent carboplatin-paclitaxel followed by 2 cycles consolidation	46/47% IMRT in 60/74 Gy arms (remainder 3DCRT)	Grade ≥3 oesophagitis 7% Grade ≥3 pneumonitis 7% Grade 5 toxicity 3%
KCSG-LU05-04 2015	437	Unresectable stage III	92%	66 Gy concurrent docetaxel-cisplatin Arm A: CRT - observation	Not reported	Grade ≥3 oesophagitis 9.5% Grade ≥3 pneumonitis 1.2% Grade 5 toxicity 3.6% during CRT, 2.9% during consolidation

Impact of local control on overall survival

CHART

Saunders et al. Lancet 2010

- 60 Gy/30# OD vs. 54 Gy/36# TDS
- HR local progression 0·77 (p=0·027, 95% 0·61–0·97)
- HR death 0·76 (p=0·004, 95% CI 0·63–0·92)

NSCLCCG Meta-analysis

Auperin et al. JCO 2010

(6 trials, 1205 patients)

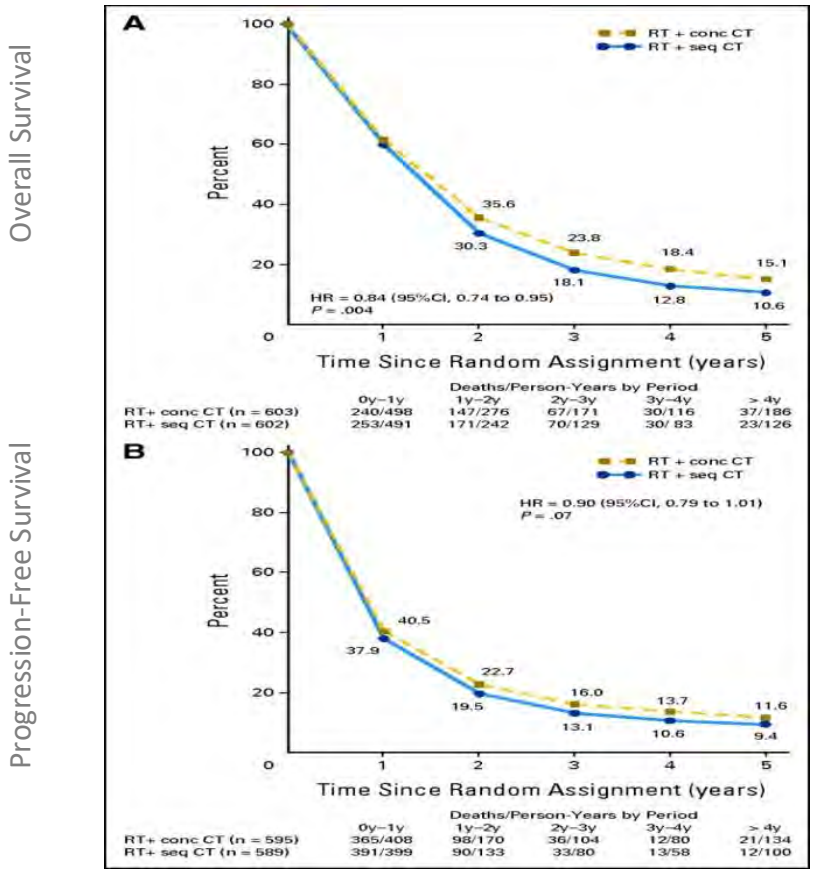
- HR death 0.83 (p=0.04); absolute benefit survival 4.5% at 5 years
- HR loco-regional progression 0.77; 95% CI 0.62 to 0.95; p= 0.01); absolute survival benefit 6% at 3 years

RTOG Meta-analysis

Machtay et al. JTO 2012

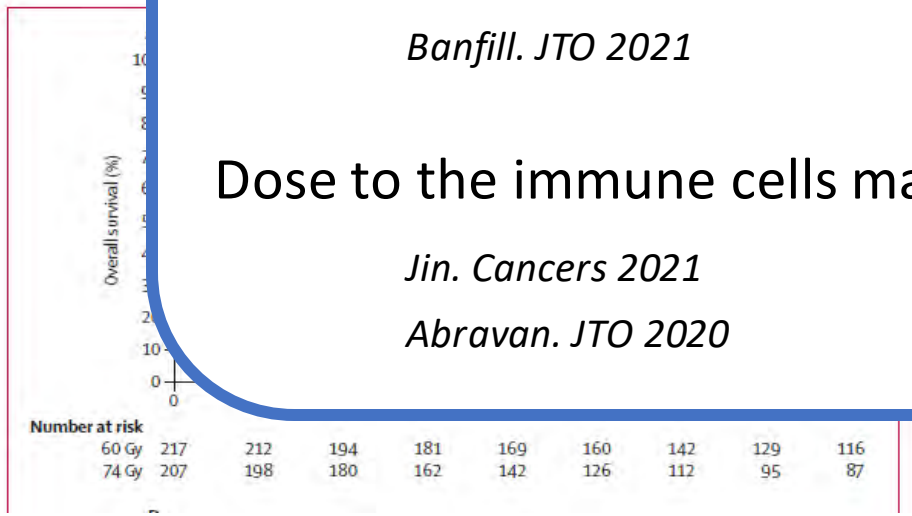
(7 trials, 1390 patients)

- Improved local control correlates with improved overall survival (p<0.0001)



Failure of dose escalation - RTOG 0617

STRATIFY	Concurrent Treatment	Consolidation Treatment
RT Technique 1.3D-CRT 2.IMRT		
Zubrod 1.0 2.1		
PET Stag 1.No 2.Yes		
Histology 1.Squamo 2.Non-Squamou		



What have we learnt?

Heart dose matters

Bradley. Lancet Oncol 2015

Mcwilliam. EJC 2017

Stam. Radiother Oncol 2017

Vivekanandan. *Int J Radiat Oncol Biol Phys 2017*

Banfill. JTO 2021

Dose to the immune cells matters

Jin. Cancers 2021

Abravan. JTO 2020

		Gy
		onths –25·0)
Oesophagitis G3+	7%	15%
Treatment-related deaths	2	8

Bradley. Lancet Oncol 2015

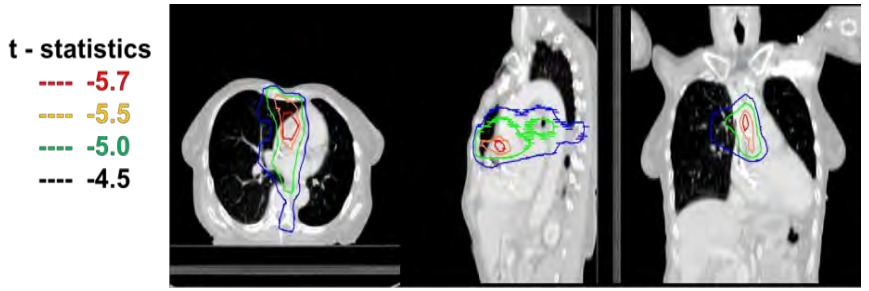
Radiation dose to heart base linked with poorer survival in lung cancer patients

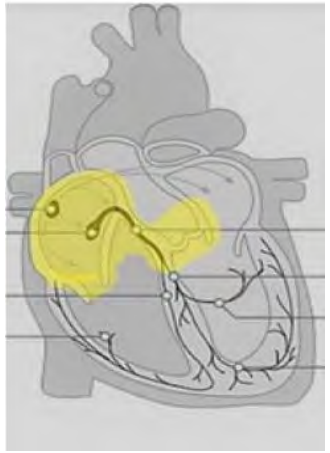
Alan McWilliam [a,b,*], Jason Kennedy [b], Clare Hodgson [c], Eliana Vasquez Osorio [a], Corinne Faivre-Finn [a,b,1], Marcel van Herk [a,b,d,1]

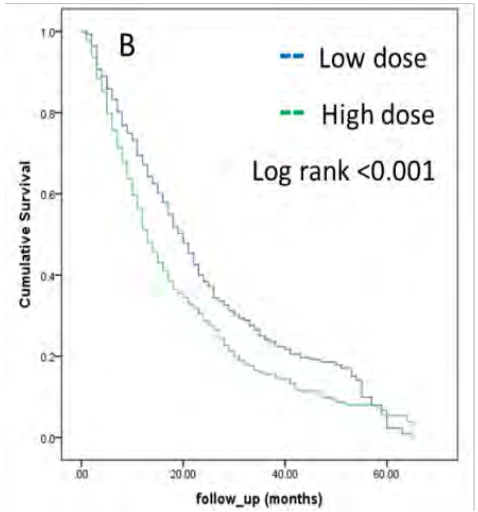
European Journal of Cancer 85 (2017) 106–113

Image-based data mining

- 1101 patients
- NSCLC
- Curative intent RT, 55Gy/20#







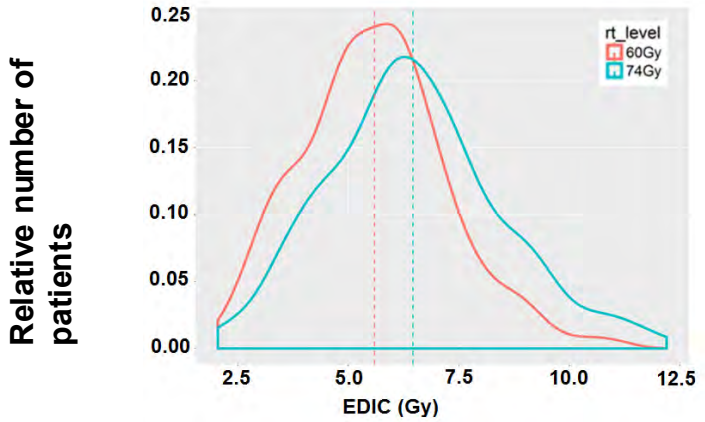
		Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Dose to defined region (> 16.3 Gy)		1.51 (1.01 – 2.27)	0.04	1.21 (1.02 – 1.44)	0.029
Tumour size (> median)		2.27 (1.55 – 3.32)	<0.001	1.67 (1.43 – 1.95)	<0.001
Age		1.03 (1.01 – 1.05)	0.005	1.02 (1.01 – 1.02)	0.045
Gender (female vs. male)		1.68 (1.19 – 2.36)	0.003	-	-
Induction Chemotherapy (yes vs. no)		0.97 (0.62 – 1.52)	0.88	-	-
T-Stage			0.03	-	-
	T1	1.45 (0.92 – 2.29)	0.11		
	T2	2.19 (1.24 – 3.87)	0.007		
	T3	2.31 (1.19 – 4.50)	0.014		
N-stage			0.003		<0.001
	N0	0.66 (0.41 – 1.06)	0.085	0.90 (0.72 – 1.14)	
	N1	1.76 (1.08 – 2.85)	0.022	1.45 (1.20 – 1.75)	
	N2	1.86 (0.85 – 4.07)	0.12	1.64 (1.21 – 2.22)	

Validated in external datasets
RTOG0617 and PET-plan trials

Base of the heart identified as the anatomical area associated with poor survival

Reduction of RT dose to base of heart investigated in the prospective RAPID-RT study

Importance of radiation dose to immune cells

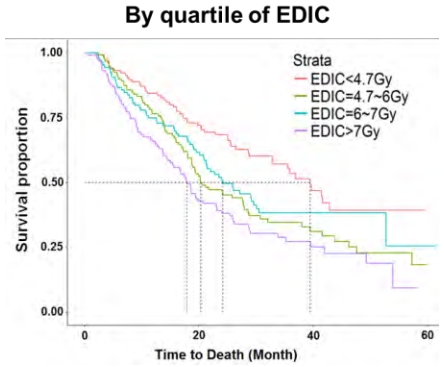


EDIC ranged from 2.05-12.20 Gy
EDIC was significantly lower for the 60-Gy vs 74-Gy arm (p <0.0001)

EDIC-Effective Dose to the Immune Cells (RTOG017)

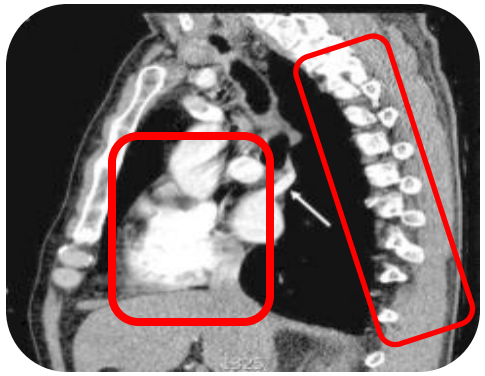
Covariate	Comparison	HR (95%CI)	p-value
Esophagitis grade 3	Grade <3 (RL) vs Grade≥3	1.55 (1.13, 2.13)	0.006
Received full chemo	No (RL) vs Yes	0.65 (0.47, 0.90)	0.01
EDIC	Continuous	1.17 (1.09, 1.25)	<0.0001

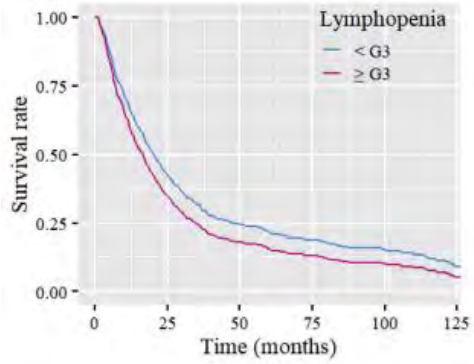
EDIC is the strongest significant factor for OS



Jin. Cancers 2021

Impact of G3 lymphopenia on survival





Parameters	SCLC Cohort (n = 317) HR (Univariate)	SCLC Cohort (n = 317) Adjusted HR (Multivariable)	NSCLC Cohort (n = 584) HR (Univariate)	NSCLC Cohort (n = 584) Adjusted HR (Multivariable)
Sex				
Female	160 (50.5) –	–	263 (45.0) –	–
Male	157 (49.5) 1.18 (0.92-1.52, $p = 0.185$)	–	321 (55.0) 1.21 (1.01-1.44, $p = 0.038$)	–
Age, y				
Mean (SD)	63.8 (8.9) 1.02 (1.01-1.04, $p = 0.005$)	1.01 (1.00-1.03, $p = 0.144$)	65.4 (10.1) 1.01 (1.00-1.02, $p = 0.033$)	–
ECOG PS				
0	65 (20.5) –	–	126 (21.6) –	–
1	172 (54.3) 1.54 (1.08-2.18, $p = 0.016$)	–	305 (52.3) 0.99 (0.79-1.25, $p = 0.958$)	–
2	54 (17.0) 2.35 (1.55-3.57, $p < 0.001$)	–	91 (15.6) 1.11 (0.83-1.49, $p = 0.473$)	–
3	12 (3.8) 2.64 (1.35-5.14, $p = 0.004$)	–	21 (3.6) 1.46 (0.91-2.34, $p = 0.112$)	–
NA	14 (4.4) 2.12 (1.13-3.96, $p = 0.019$)	–	40 (6.9) 1.33 (0.92-1.93, $p = 0.131$)	–
Baseline lymphocytes, $\times 10^9$/liter				
Mean (SD)	2.0 (0.9) 0.80 (0.68-0.94, $p = 0.007$)	–	2.0 (4.1) 1.00 (0.98-1.02, $p = 0.932$)	–
Lymphopenia grade 3				
No	174 (54.9) –	–	234 (40.1) –	–
Yes	143 (45.1) 1.39 (1.08-1.78, $p = 0.010$)	1.29 (1.00-1.67, $p = 0.044$)	350 (59.9) 1.17 (0.98-1.40, $p = 0.018$)	1.50 (1.22-1.84, $p < 0.001$)
Chemotherapy				
Radiotherapy only	38 (12.0) –	–	147 (25.2) –	–
Concurrent	188 (59.3) 0.51 (0.35-0.73, $p < 0.001$)	0.46 (0.30-0.69, $p < 0.001$)	292 (50.0) 0.68 (0.55-0.84, $p < 0.001$)	0.61 (0.45-0.82, $p = 0.001$)
Sequential	91 (28.7) 1.24 (0.84-1.83, $p = 0.281$)	1.16 (0.77-1.74, $p = 0.477$)	145 (24.8) 1.22 (0.96-1.55, $p = 0.102$)	1.11 (0.87-1.42, $p = 0.396$)
PTV, ln				
Mean (SD)	5.9 (0.5) 1.90 (1.49-2.43, $p < 0.001$)	2.28 (1.73-3.00, $p < 0.001$)	6.0 (0.5) 1.40 (1.18-1.66, $p < 0.001$)	1.72 (1.43-2.07, $p < 0.001$)
Prescribed dose, Gy				
Mean (SD)	52.5 (7.5) 1.00 (0.99-1.02, $p = 0.987$)	–	59.8 (5.5) 0.96 (0.94-0.98, $p < 0.001$)	0.96 (0.94-0.99, $p = 0.002$)
Radiotherapy duration, d				
Mean (SD)	27.9 (11.8) 1.00 (0.99-1.01, $p = 0.719$)	–	35.6 (9.4) 0.98 (0.97-0.99, $p < 0.001$)	–

Severe lymphopenia is a poor prognostic factor for OS and could be mitigated by minimising thoracic vertebrae V20, MLD, mean heart dose

Abravan. JTO 2020

PACIFIC -randomised, double-blind, placebo-controlled, multi-centre study

- **Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)**
- **18 years or older**
- **WHO PS score 0 or 1**
- **If available, archived pre-cCRT tumor tissue for PD-L1 testing***

All-comers population
(i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
for up to 12 months
N=237

2:1 randomization, stratified by age, sex, and smoking history

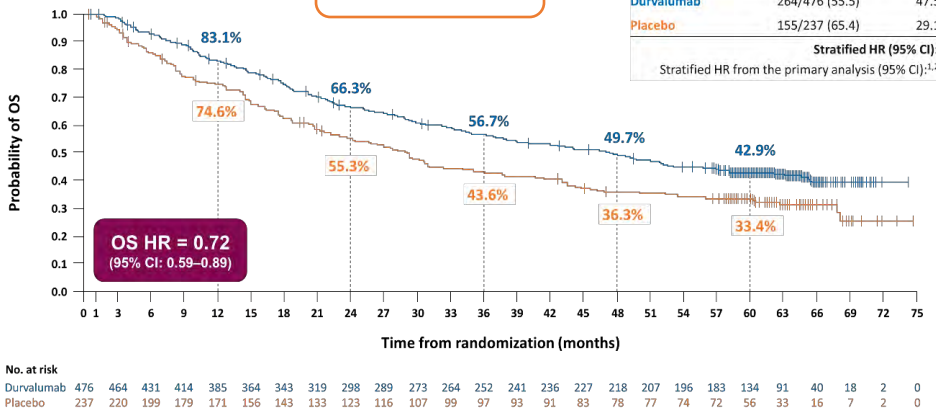
Primary endpoints
- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

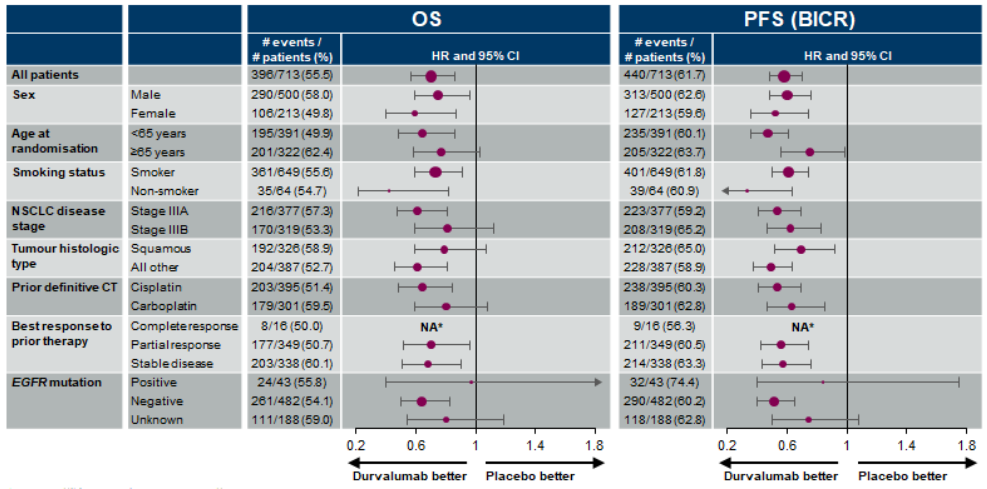
HR 0.72

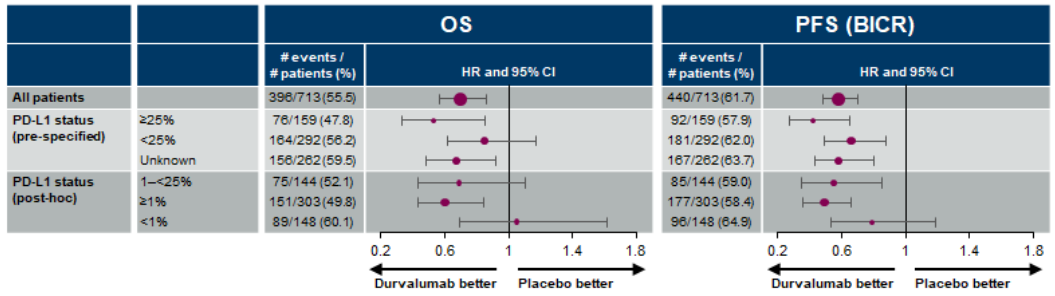
	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)
Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



Unresectability loosely defined

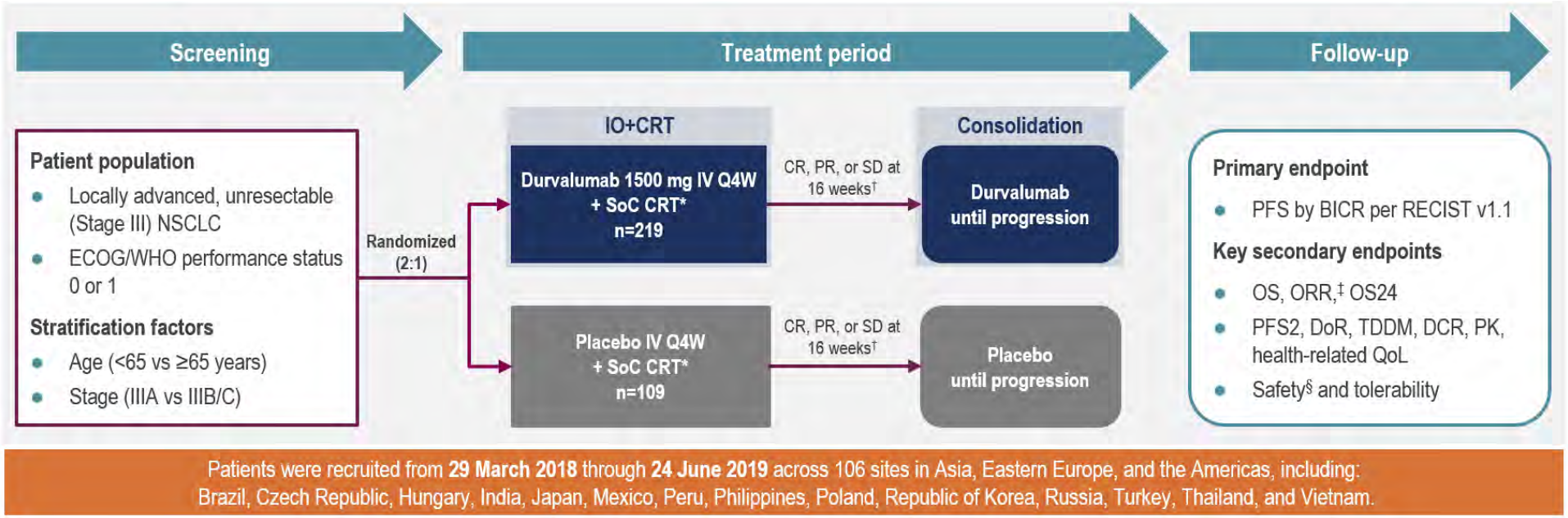




Consistent benefit in most subgroups
FDA-approval in all comers
EMA and NICE-approval in PDL1>1%

Antonia NEJM 2017 & 2018; Faivre-Finn JTO 2021; Spigel JCO 2022

Concurrent IO and consolidation IO - PACIFIC 2



Bradley ELCC 2024

More AEs in the concurrent arm

More discontinuation of CTRT+durvalumab and more discontinuation of durvalumab consolidation due to AEs, particularly in the first 4 months from start of CTRT +/-IO

PL

Time (Months)

Time (Months)

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

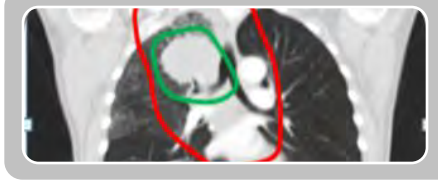
IO in stage 3 NSCLC -Outstanding questions

Timing of CTRT and consolidation IO?

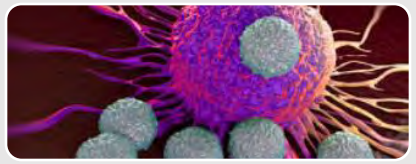
14 days?
42 days?

Optimal duration of IO treatment?

1 year?
2 years?
<1 year?



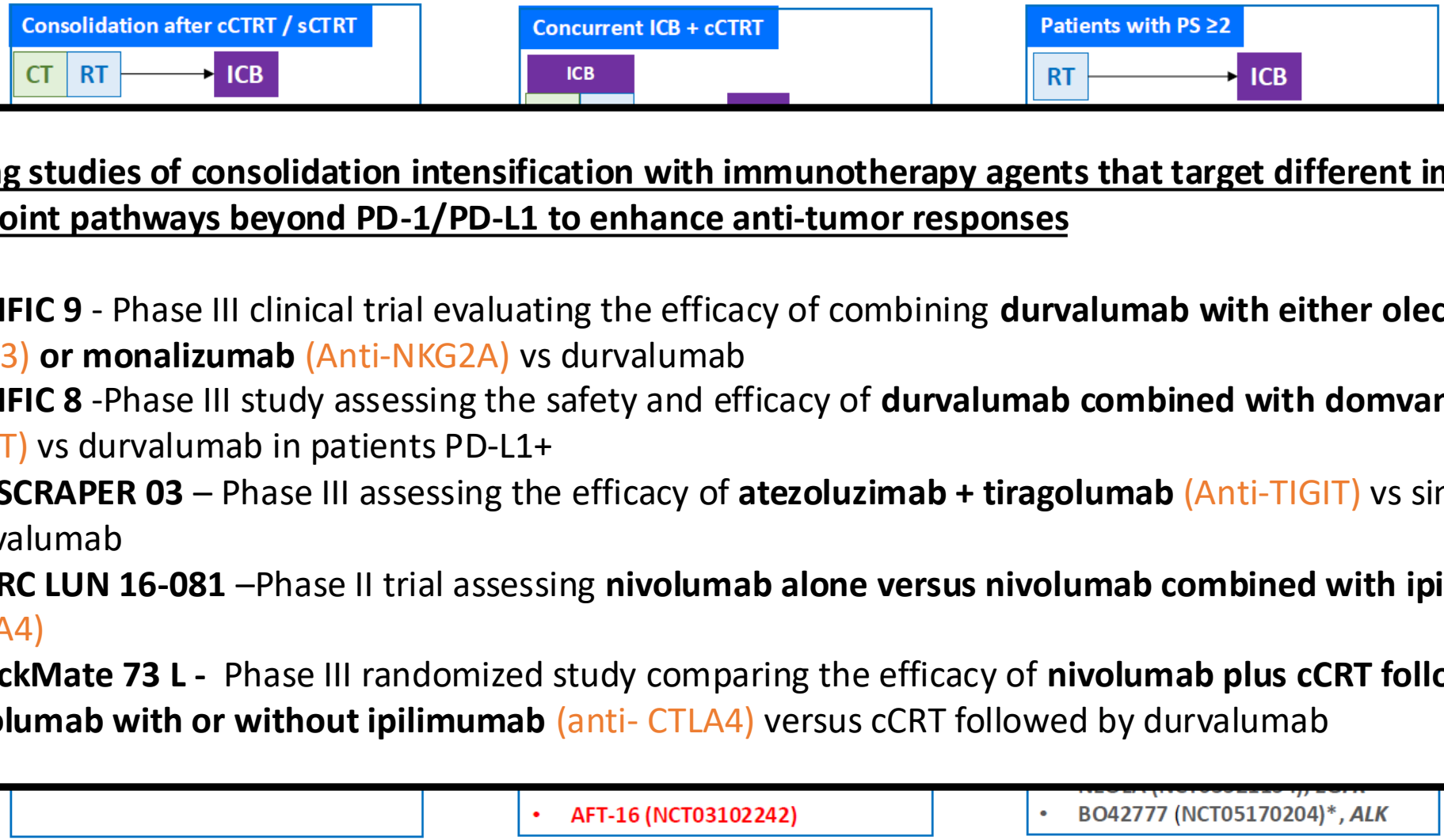
What are the optimal RT dose and schedule to enable adequate priming for immunotherapy? Target volume?



What type of immunotherapy should be used in combination with RT? What is the benefit of immunomodulators in addition to ICIs?

Beyond PDL1- Who are the patients most likely to benefit from consolidation immunotherapy post-CTRT?

Phase II and III clinical trials investigating IO and TKIs in unresectable stage III NSCLC



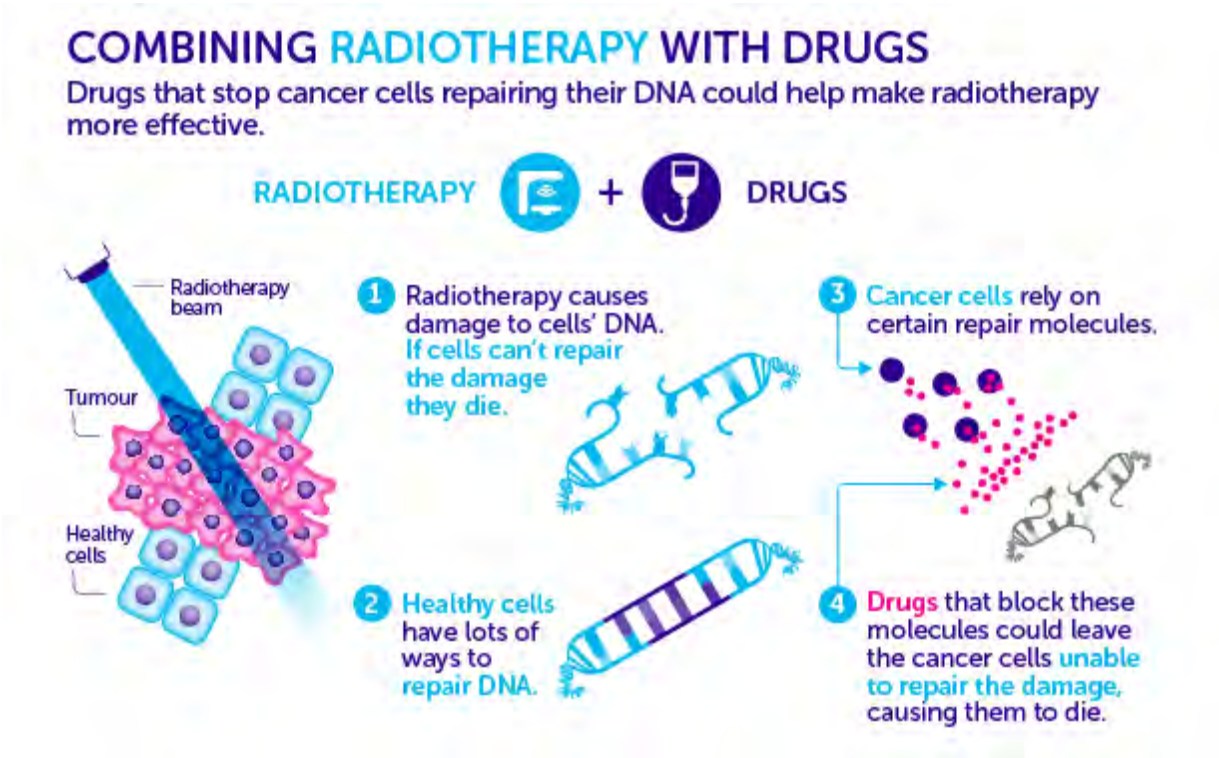
Ongoing studies of consolidation intensification with immunotherapy agents that target different immune checkpoint pathways beyond PD-1/PD-L1 to enhance anti-tumor responses

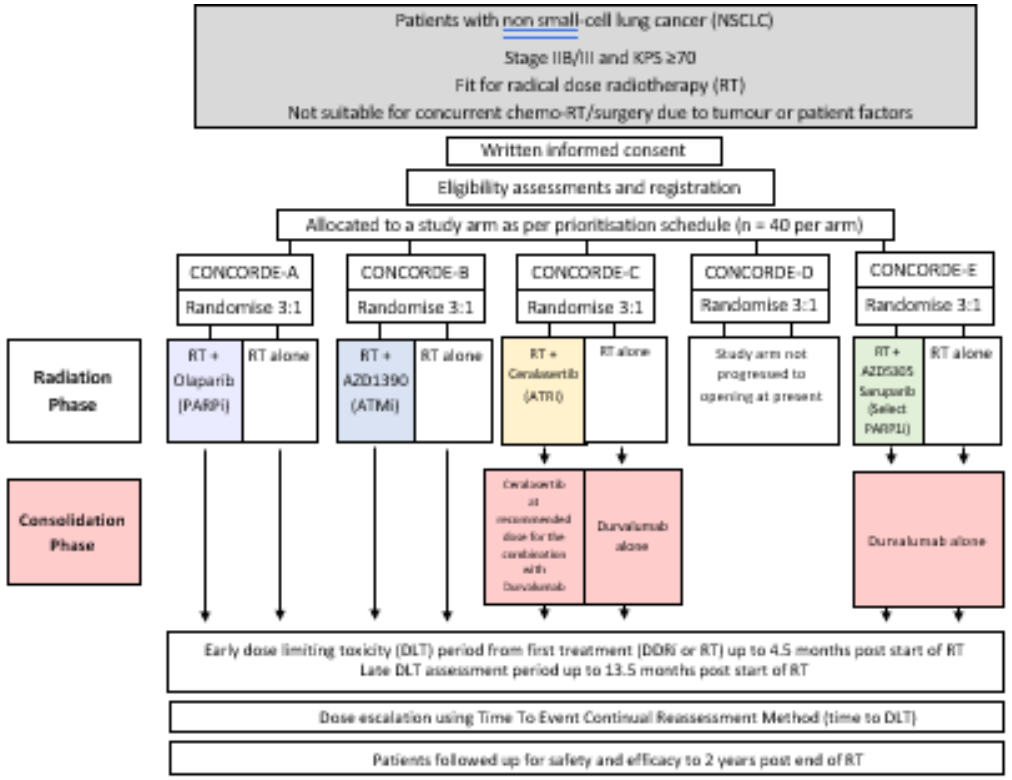
- **PACIFIC 9** - Phase III clinical trial evaluating the efficacy of combining **durvalumab with either oleclumab** (anti-CD73) **or monalizumab** (Anti-NKG2A) vs durvalumab
- **PACIFIC 8** -Phase III study assessing the safety and efficacy of **durvalumab combined with domvanalimab** (Anti-TIGIT) vs durvalumab in patients PD-L1+
- **SKYSCRAPER 03** – Phase III assessing the efficacy of **atezoluzimab + tiragolumab** (Anti-TIGIT) vs single-agent durvalumab
- **BTCRC LUN 16-081** –Phase II trial assessing **nivolumab alone versus nivolumab combined with ipilimumab** (anti-CTLA4)
- **CheckMate 73 L -** Phase III randomized study comparing the efficacy of **nivolumab plus cCRT followed by nivolumab with or without ipilimumab** (anti- CTLA4) versus cCRT followed by durvalumab

*Phase III trials. #In the consolidation patients receive pembrolizumab +/- olaparib. cCTRT: concurrent chemo-radiotherapy. sCTRT: sequential chemo-radiotherapy
ICB: immune checkpoint blockers. TKI: tyrosine kinase inhibitors. In red trials already published / data presented.

Remon –Ther Adv Med Oncol 2022 – Updated 2025

CONCORDE trial





CANCER RESEARCH UK

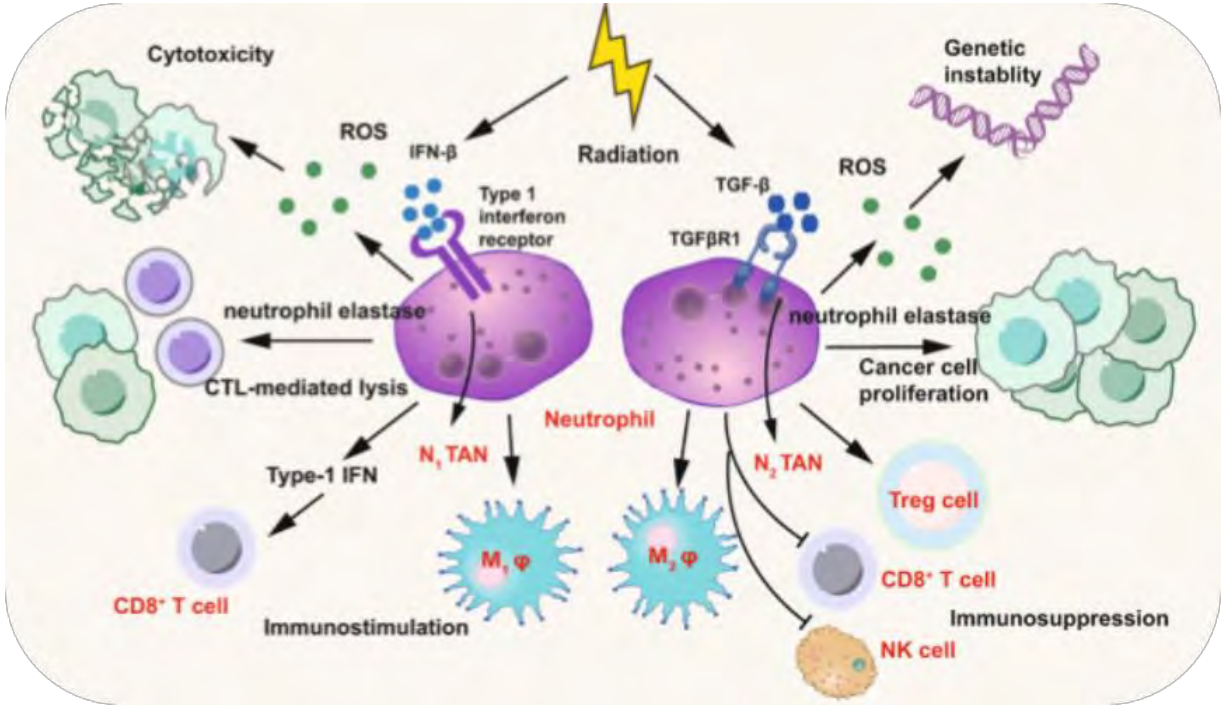
AstraZeneca

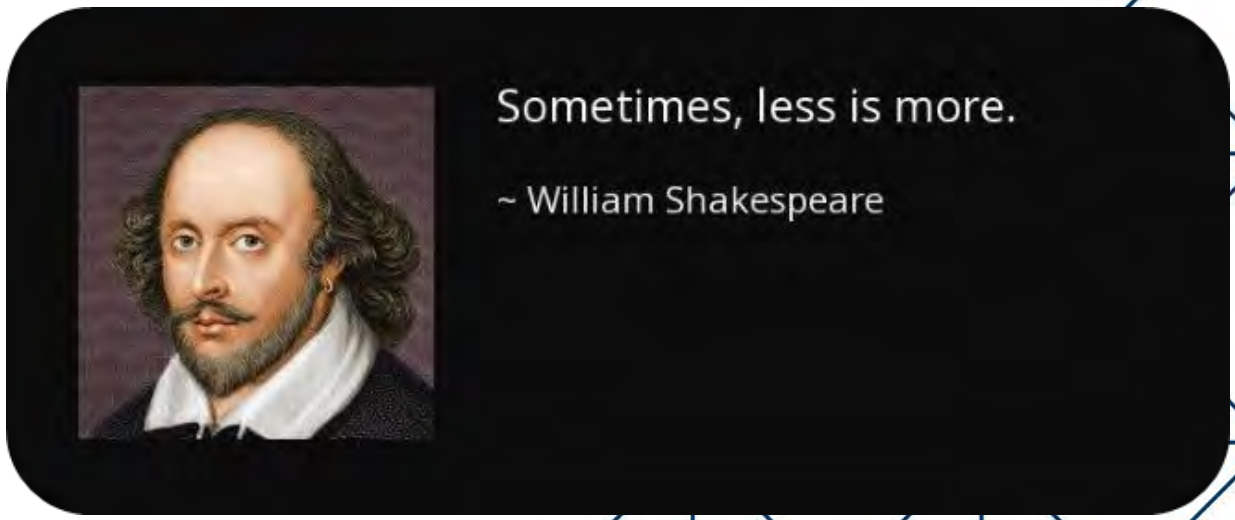
ctru University of Leeds

Walls. Clin Transl Radiat Oncol. 2020

Grey areas

Q1 – Should we de-escalate dose and volume of RT?



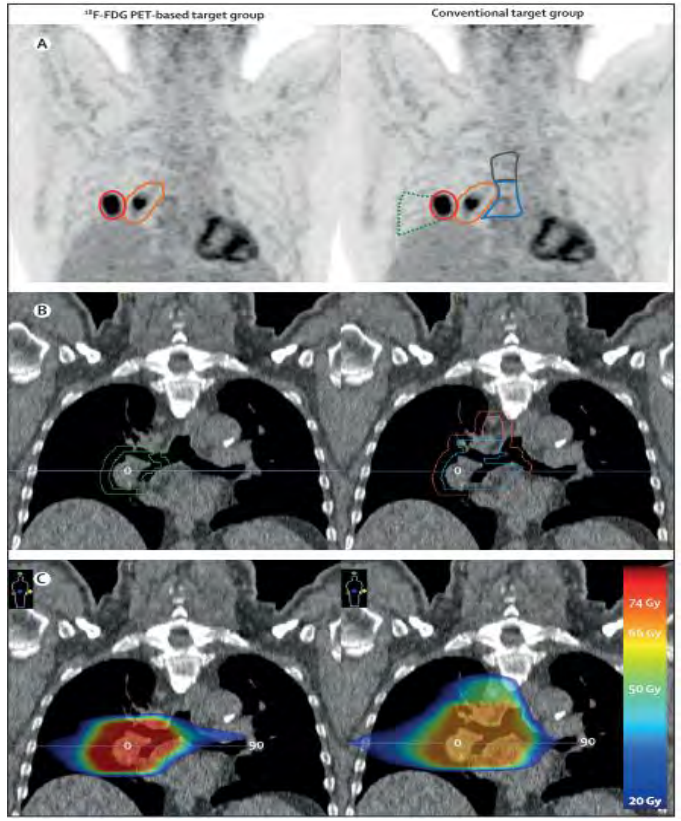


ESMO ON AIR

De-escalation of volume

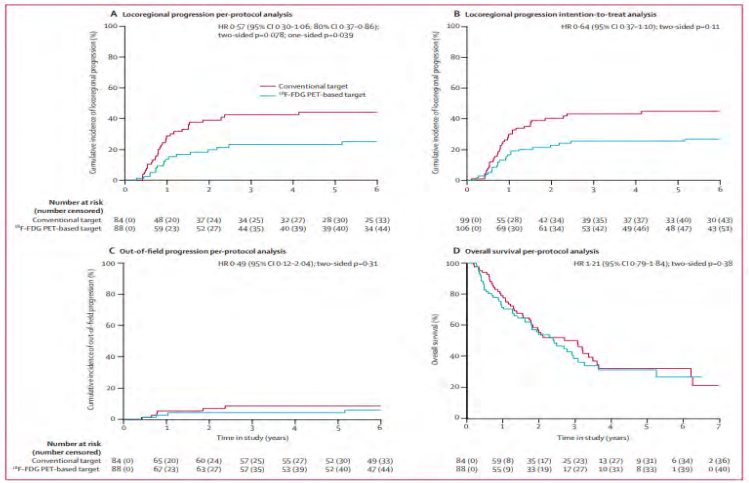
PET PLAN - 205 pts randomised

Target volume delineation informed PET and CT + elective nodal irradiation or by PET alone



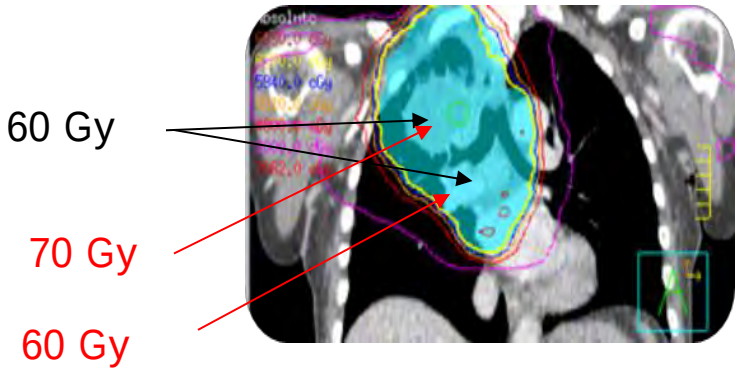
Nestle, Lancet Oncol 2020

Risk of progression in the PET-group non-inferior HR 0·64 [95% CI 0·37-1·10])



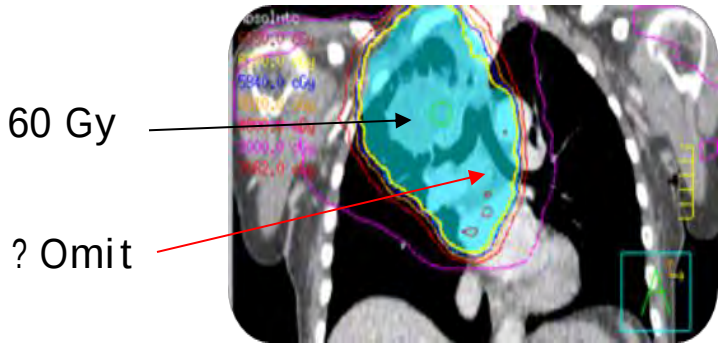
Primary endpoint:
time to locoregional progression

Differential dose to nodes



Reduced oesophageal and lung toxicity
No increase in regional failures

Van Diessen, Radiother Oncol 2020

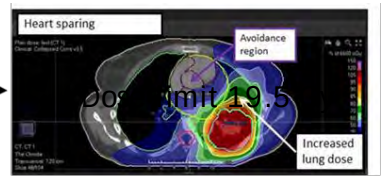


De-escalation of dose to critical structures

Q2 - Can a reduction in dose to heart substructures improve survival ?

Feb 2022

Change heart dose for all lung cancer patients treated at the Christie



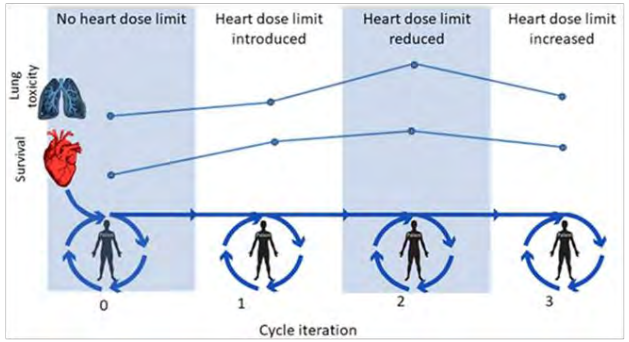
Use real-world routinely collected data to look at impact of change on patient outcomes

April 2023

FUNDED BY NIHR National Institute for Health and Care Research

RAPID-RT trial
Dose limit to base of heart using rapid-learning methodology

Price et al. Clin Oncol 2022

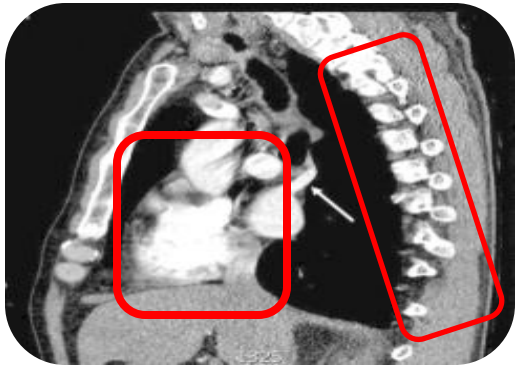


Primary outcome – overall survival;
Secondary outcome - acute toxicity

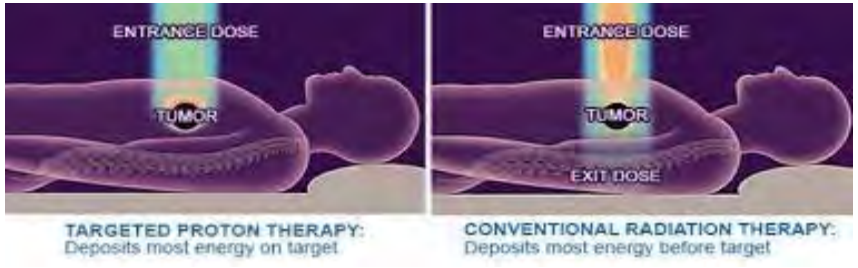
Multiple **rapid learning cycles** will be performed, balancing improved survival vs. side effects

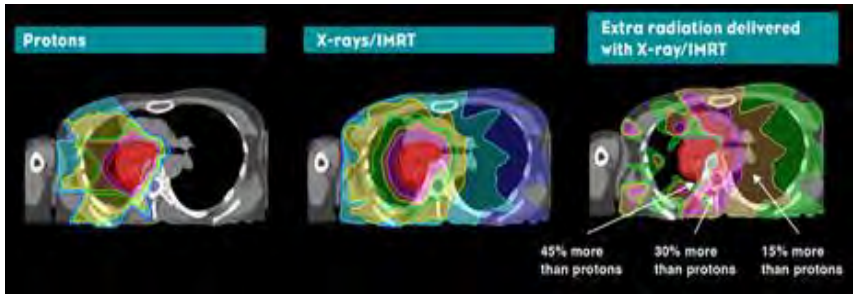
Q3 - Can a reduction in dose to immune cells improve survival ?

BIG CHALLENGE



Role of protons





RCT proton vs photon
No difference in mean lung dose
Reduction in mean heart does
No differences in outcome
Liao. JCO 2018

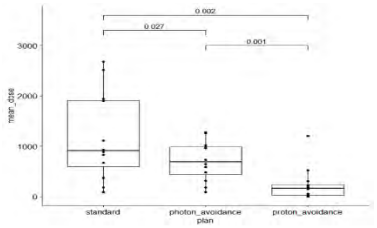
NRG 1308 completed recruitment sept 2023

- 343 patients
- IMRT or PBT
- Severe lymphopenia (SRL) <0.5
- Propensity score matching performed between the IMRT and PBT groups

Heart

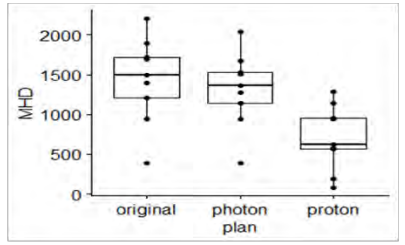
Q4- Can proton spare the cardiac avoidance area?

Mean dose cardiac avoidance area



Mean dose cardiac avoidance area significantly lower with proton

Mean Heart Dose



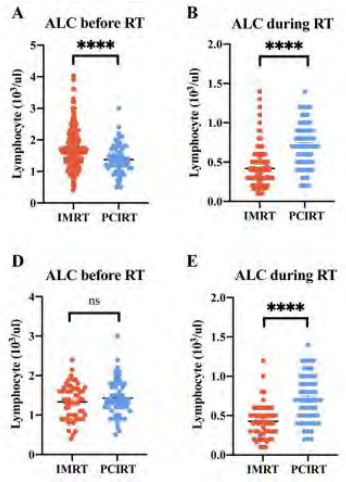
MHD significant lower in proton cardiac avoidance plans (p=0.002)
15Gy v 6Gy

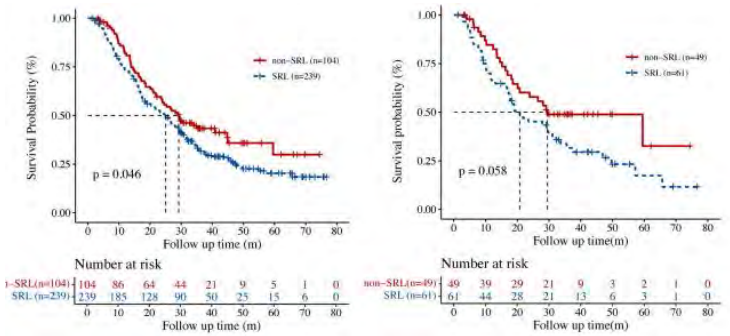
Banfill ESTRO 2021

Immune system

Q5- Can proton reduce the risk of severe lymphopenia ?

Propensity score matching



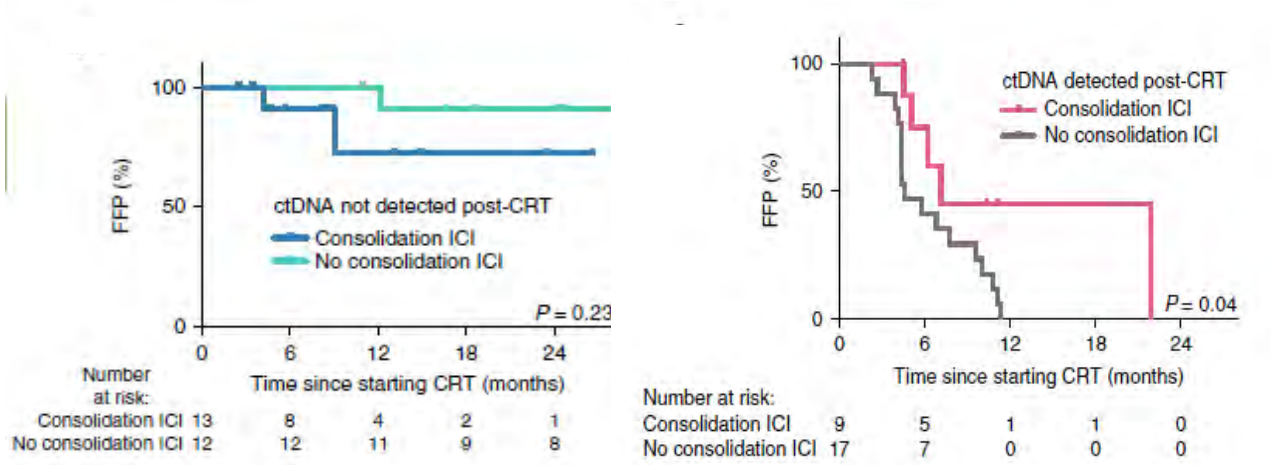


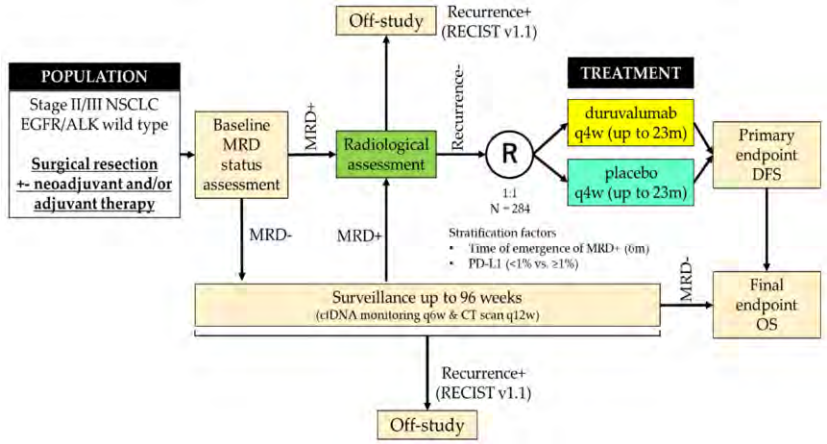
SRL showed significant association with poorer OS

Li. Red J 2022

Risk of severe lymphopenia reduced with proton by limiting thoracic vertebra and aortic doses

Q6- Can we better select patients for IO. Role of ctDNA?



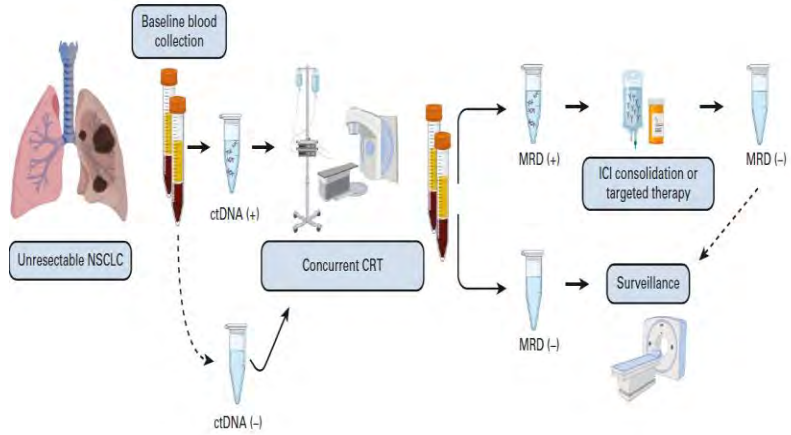


MeRmaiD-2 trial (NCT04642469)
Stage II–III NSCLC post-resection +/- neo/adjuvant therapy
Patients CtDNA+ were randomised to durvalumab or placebo

Could ctDNA be predictive of benefit from CTRT and IO?

218 samples
65 patients treated with concurrent CTRT
28 received consolidation IO
CtDNA-→good outcome independently of the use of consolidation IO
CtDNA+→outcome improved by consolidation IO

Moding et al. Nature Cancer 2020



Pellini . JCO 2022

Conclusions

1. Drug-RT combination is a major opportunity in stage 1-3 NSCLC. New opportunity:ADCs and RT
2. Integration of IO is a major success→strong rationale for de-escalation of RT in IO era
3. Dose and volume de-escalation facilitated by modern RT techniques

Key message: enrol patients in clinical trials

ESMO ON AIR

Key challenges moving from trials into practice in NSCLC

Federico Cappuzzo MD

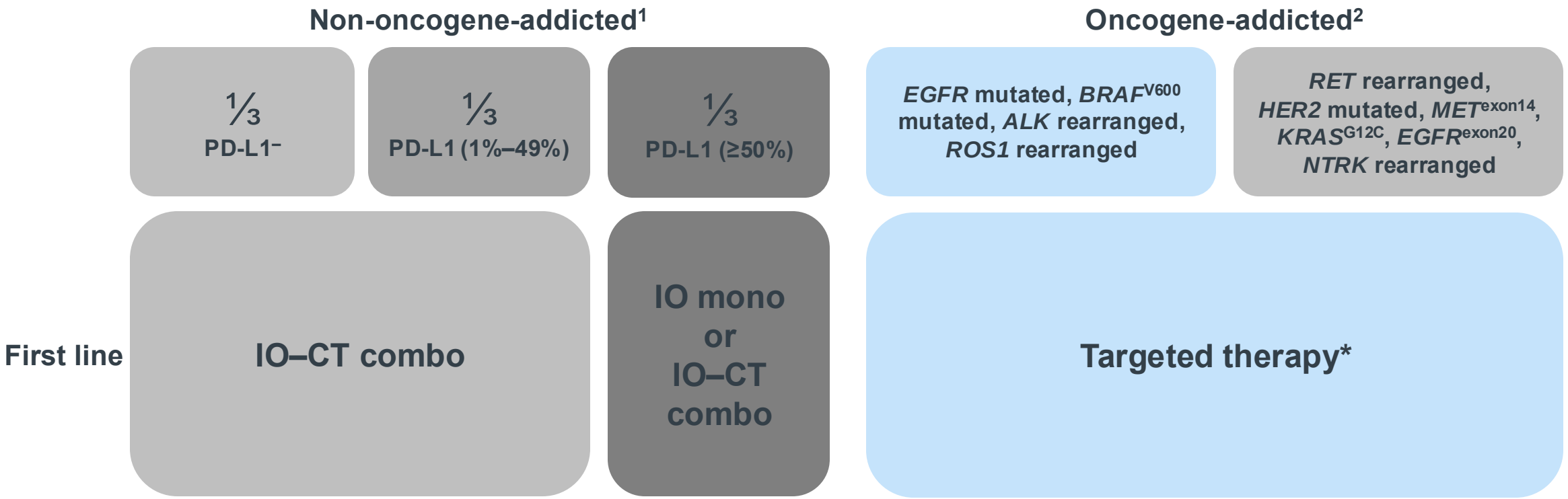
05 March 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Disclosures

- Dr Cappuzzo discloses the following conflicts of interest:
  - Fees for membership of an advisory board or lectures from Roche, AstraZeneca, BMS, Pfizer, Takeda, Lilly, Bayer, Amgen, Sanofi, PharmaMar, Novocure, Mirati, Galecto, OSE, ThermoFisher and MSD

Treatment options for metastatic NSCLC in 2025



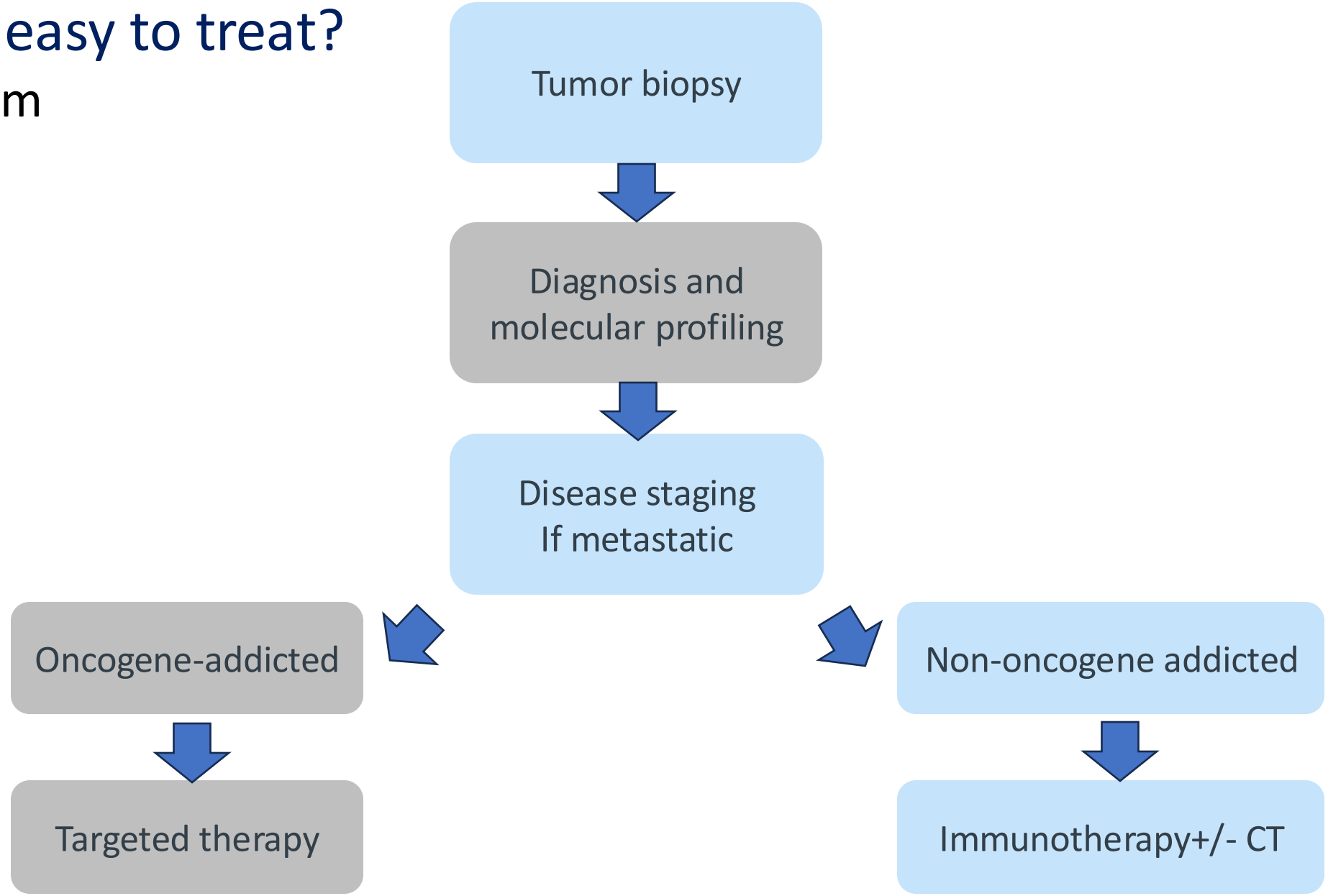
*First-line targeted therapy not approved for all indicated targets.

ALK, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene; CT, chemotherapy; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; IO, immunotherapy; *KRAS*, Kirsten rat sarcoma virus; *MET*, mesenchymal–epithelial transition factor; NSCLC, non–small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection proto-oncogene; *ROS1*, c-ros oncogene 1.

1. Hendriks LE *et al. Ann Oncol* 2023; 34 (4): 358–376. 2. Hendriks LE *et al. Ann Oncol* 2023; 34 (4): 339–357.

Is NSCLC so easy to treat?

Basic algorithm



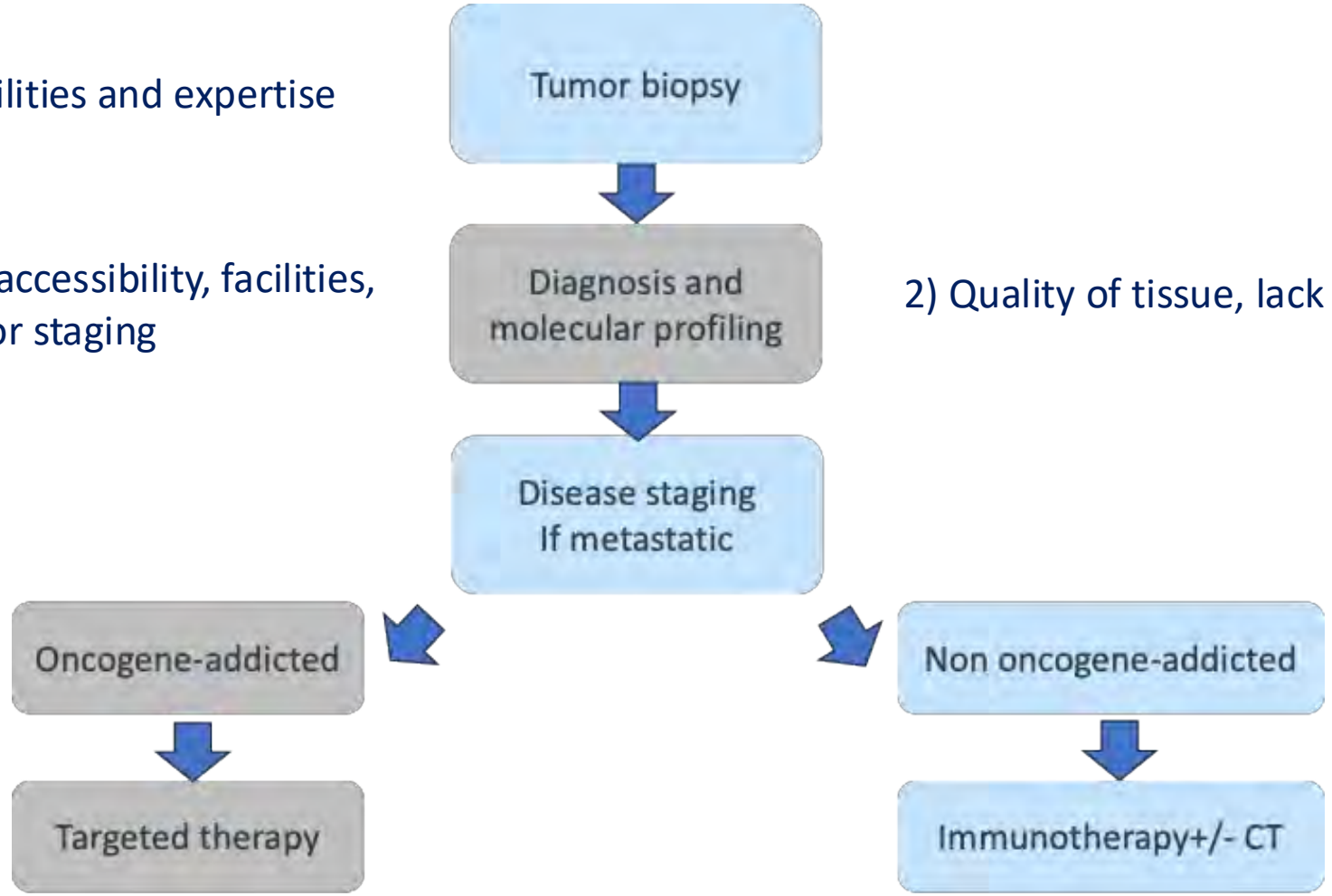
NSCLC is not easy to treat

Issues in clinical practice

1) Facilities and expertise

3) Tissue, pre-analitic, accessibility, facilities, waiting lists and cost for staging

2) Quality of tissue, lack of information

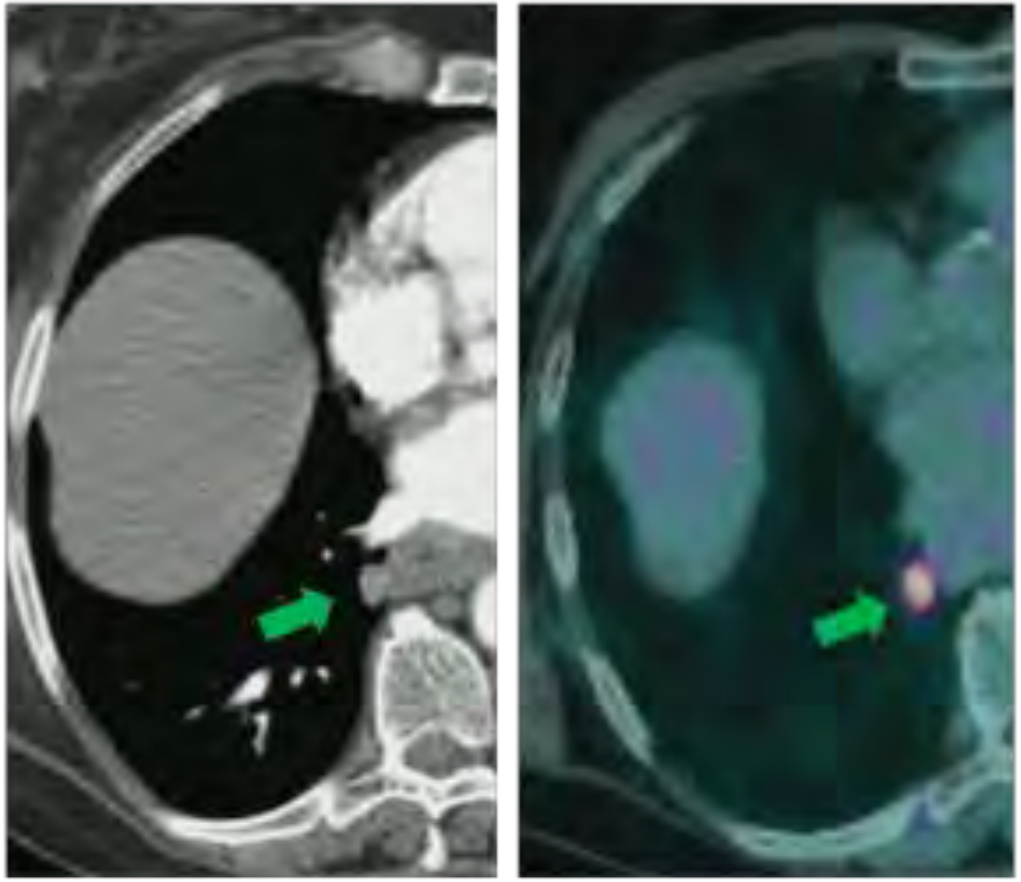


4) Trial related (patient characteristics-age, PS, comorbidities)

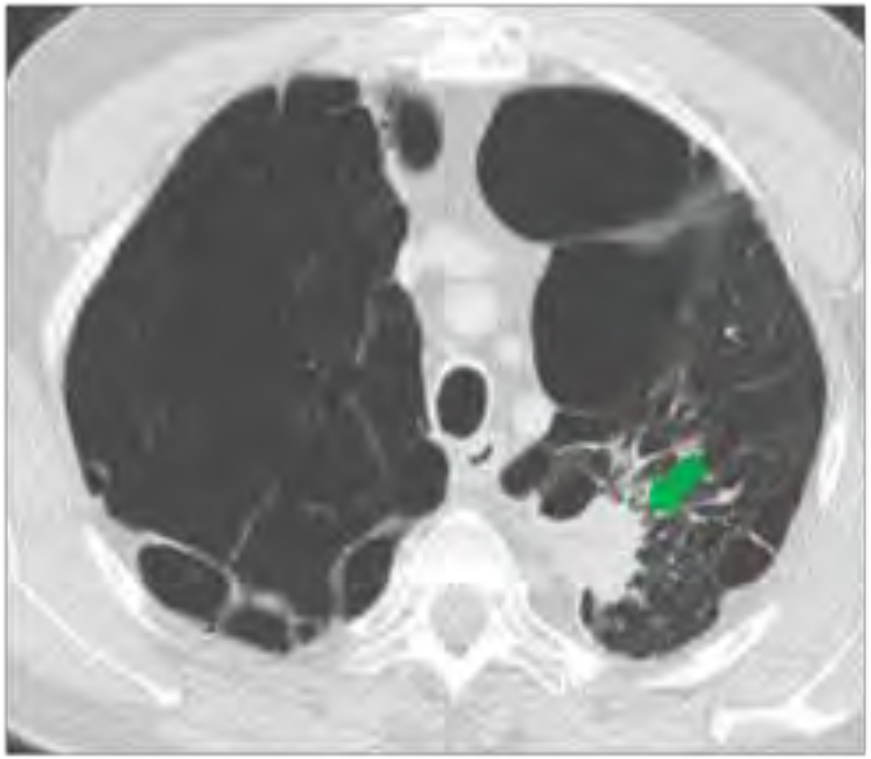
5) Non-trial related (cost/reimbursement, Doctor strategy-sequence Patient preference/bias)

1: Tumor biopsy is often challenging in lung cancer

Center lacks experienced / skilled operators



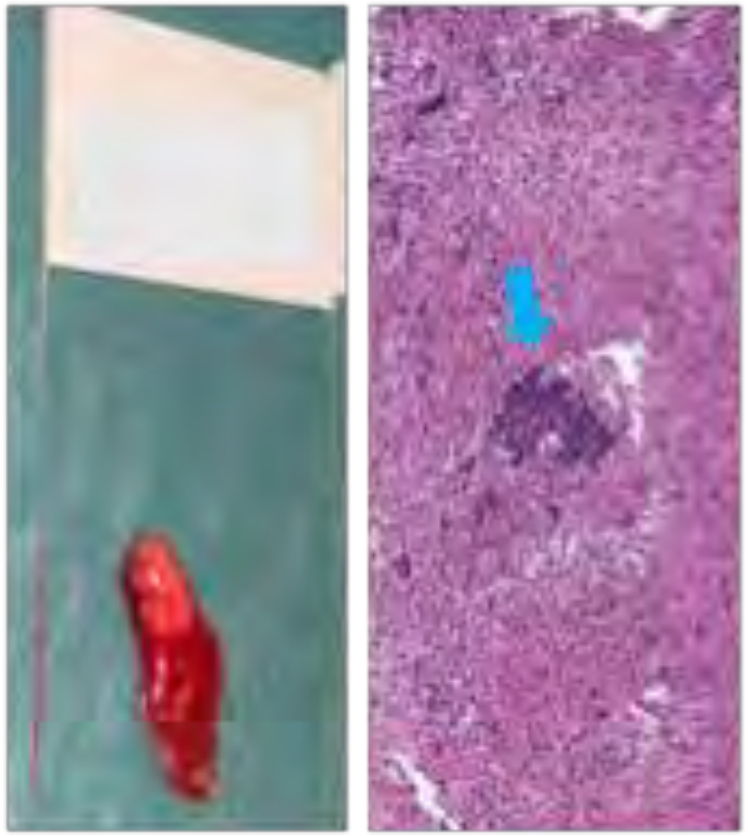
Patient is unfit for undergoing a biopsy
(or the biopsy indicated for that specific lesion)



Courtesy of Prof R. Trisolini

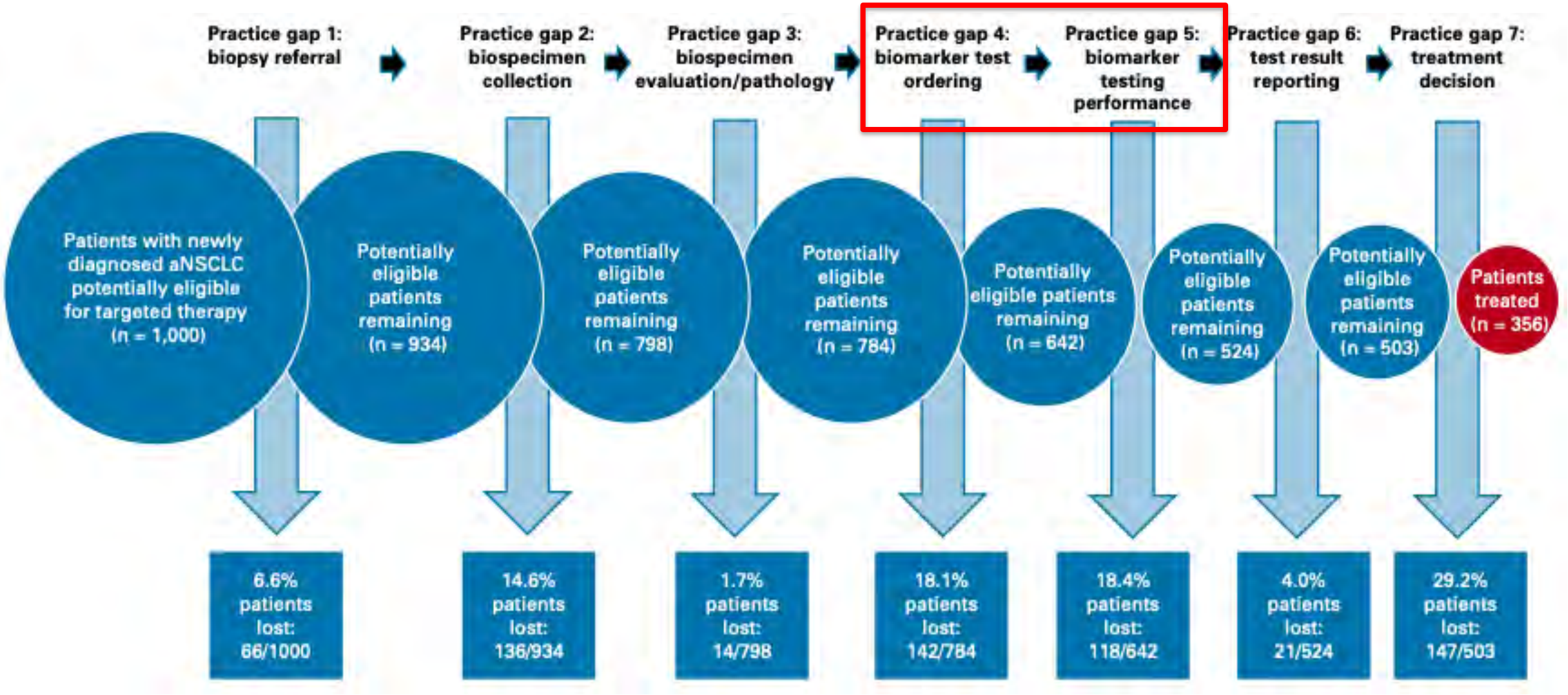
2: Quality of tissue

Biopsy is non-diagnostic or has poor quality or quantity of malignant cells (more common with needle aspiration procedures)



Courtesy of Prof R. Trisolini

Biomarker test ordering or pre-analytic impact on patient loss



Sadik H, et al. JCO Prec Oncol 2022

Accurate staging often not feasible

Clinical trials have too stringent selection criteria

Example of criteria required for a phase III clinical trial

4.2. Inclusion Criteria

Members of all genders, races, and ethnic groups are eligible for this study.

Participants must meet all of the following inclusion criteria to be eligible for participation in this study (no waivers for participant eligibility will be permitted).

1) Participants assigned male at birth and participants assigned female at birth, 18 years of age or older, able to understand and give written informed consent.
2) Life expectancy ≥ 3 months.
3) Pathologically documented NSCLC that meets both of the criteria below:
    a) Have documented evidence of Stage IV NSCLC disease at the time of enrollment (based on AJCC, Eighth Edition).
    b) Have documented negative test results for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations.

    Note: Tumor testing for EGFR or ALK mutations is required if status is unknown (Section 6.3.9).
4) Have no known genomic alterations in ROS proto-oncogene 1 (ROS1), neurotrophic tyrosine receptor kinase (NTRK), proto-oncogene B-raf (BRAF), RET mutations, or other actionable driver oncogenes with approved therapies (actionable genomic alteration). Testing is not required if status is unknown.
5) Provide adequate tumor tissue from locations not radiated prior to biopsy to evaluate PD-L1 status prior to randomization. Formalin-fixed specimens after the participant has been diagnosed with metastatic disease are preferred. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible. Bone biopsies and fine needle aspirates are not suitable tissues. If no tissue is available, a new biopsy will need to be obtained prior to enrollment in the study.
6) Have not received prior systemic treatment for metastatic NSCLC. Participants who received adjuvant or neoadjuvant chemotherapy are eligible if the adjuvant/neoadjuvant chemotherapy was completed at least 12 months prior to the start of study treatment.
7) Measurable disease by CT or MRI as per RECIST v1.1 criteria by investigator assessment (Appendix 7). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8) ECOG PS score of 0 or 1.
9) Organ function requirement:

Organ Function	Status	Parameters
Adequate hematologic counts	Without transfusion or growth factor support within 2 weeks of study drug initiation	Hemoglobin ≥ 9 g/dL, ANC ≥ 1500/mm³, and platelets ≥ 100,000/µL
Adequate hepatic function	–	Bilirubin ≤ 1.5 ULN, AST and ALT ≤ 2.5 ULN or ≤ 5 ULN if known liver metastases, and serum albumin > 3 g/dL
Creatinine clearance	–	At least 45 mL/min (60 mL/min for participants receiving cisplatin) as assessed by the Cockcroft-Gault equation {Cockcroft 1976}

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BMI = body mass index; ULN = upper limit of normal
Estimated creatinine clearance in mL/min calculated using the Cockcroft-Gault equation. In overweight or obese individuals (BMI = 25 or above), use of alternative body weight metrics such as ideal body weight to calculate creatinine clearance, which is likely to provide a more accurate estimate of renal function than total body weight.

10) Participants assigned male at birth and participants assigned female at birth of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4.
11) Willing and able to comply with the requirements and restrictions in this protocol.

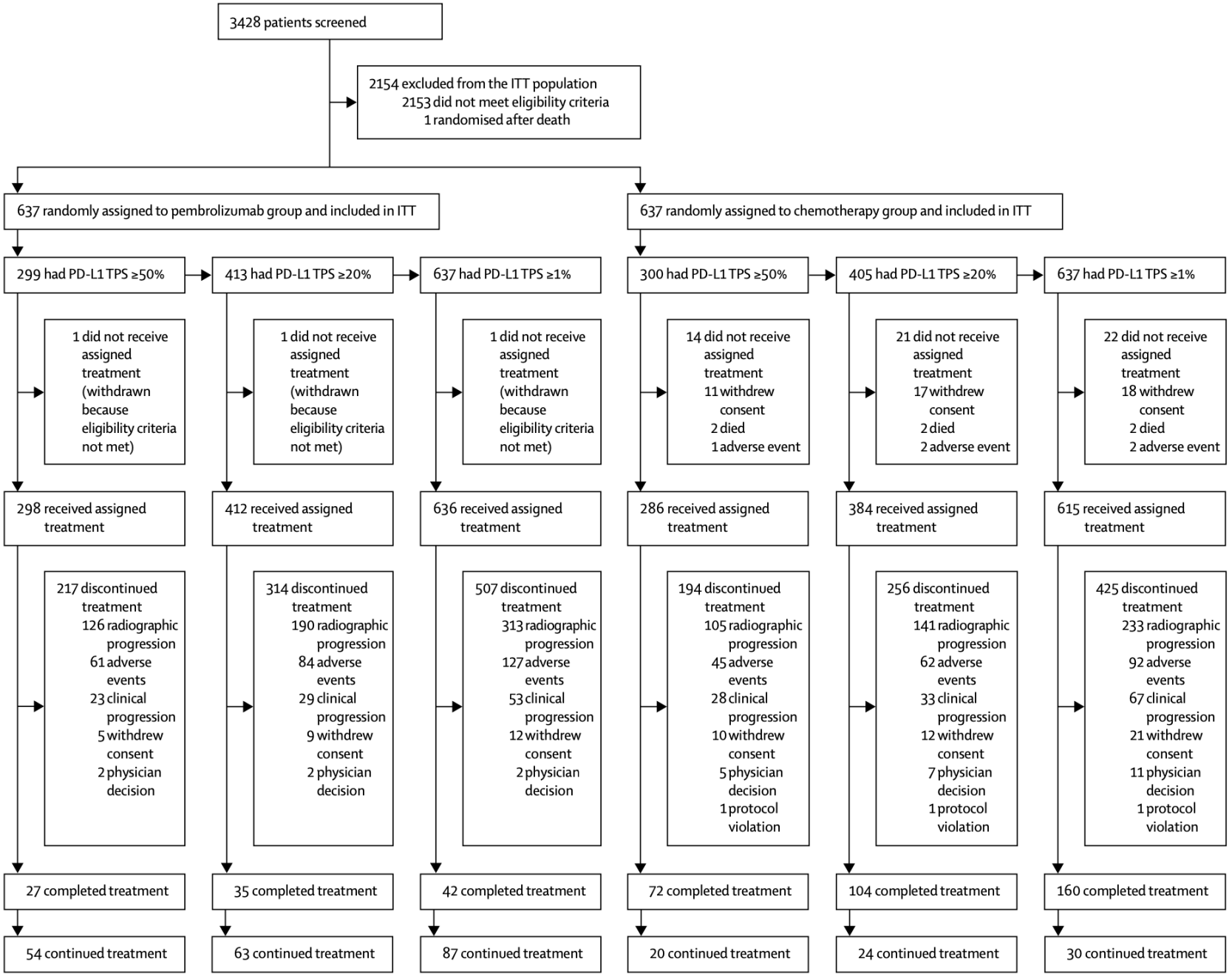
4.3. Exclusion Criteria

Participants who meet any of the following exclusion criteria at screening/Day -1 are not eligible to be enrolled in this study (no waivers for participant eligibility will be offered or permitted):

1) Have mixed small-cell lung cancer (SCLC) and NSCLC histology.
2) Positive serum pregnancy test or participants who are breastfeeding or have plans to breastfeed during the study period and for the required duration of contraception use after the last dose of study drug.
3) Received prior treatment with any anti-PD-1, anti-PD-L1, or any other antibody targeting an immune checkpoint. Participants who received PD-(L)1 inhibitors as a part of treatment for early stage NSCLC including in neoadjuvant/adjuvant setting are not eligible.
4) Known hypersensitivity to the study drug, its metabolites, or formulation excipient.

KEYNOTE 042 trial as an example

Only 37% of screened patients were included in the study



Mok T, et al. Lancet 2019

Certain patient populations are not included/under-represented

- Elderly
- PS ≥ 2
- Patients with comordities
- Brain mets (including specific brain location, number, size)

A way to select a positive population

- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

  No ongoing requirement for corticosteroids as therapy for CNS disease

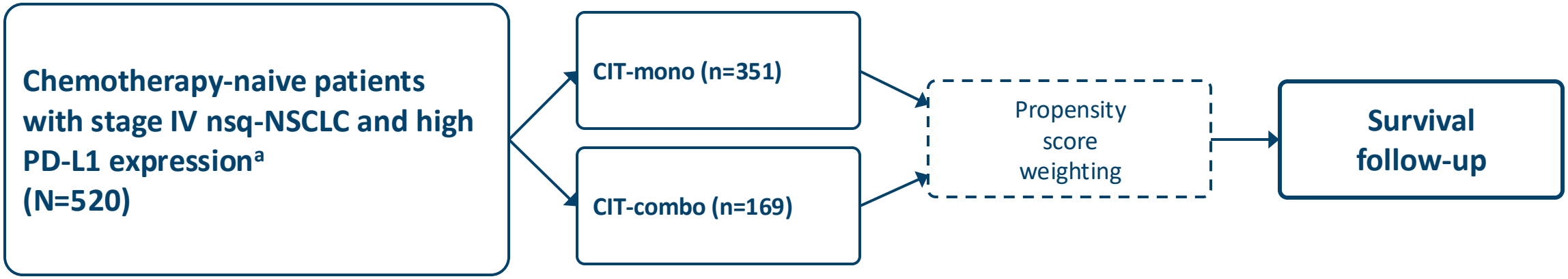
  No stereotactic radiation within 7 days

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.

ETOP study: real world data

- Primary outcome was overall survival (OS) among treatment initiators[1]
- Secondary endpoints included real-world progression-free survival (rwPFS) using a clinician-anchored approach supported by radiology report data[2]
- Subgroup analyses were conducted to evaluate the influence of brain metastases, liver metastases and smoking history



[a] PD-L1–high expression defined as TPS ≥50% by local test. Assay type was balanced between CIT-mono (86% 22C3) and CIT-combo (85% 22C3); remaining patients in each group had "Other/Unknown" assay.

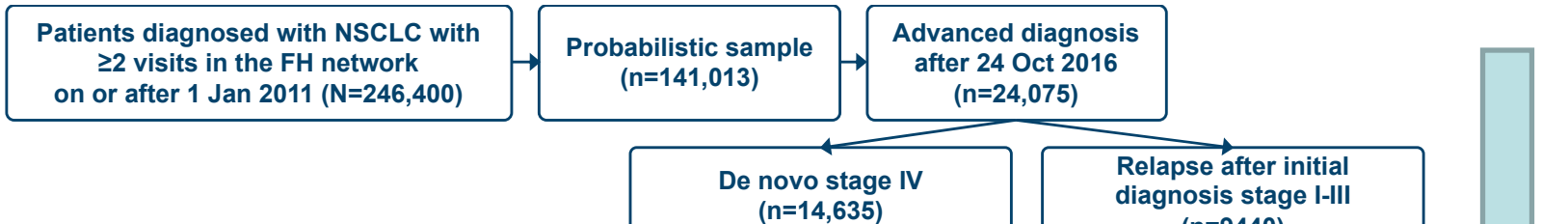
1. Curtis MD, et al. Health Serv Res 2018;53(6):4460-76. 2. Griffith SD, et al. Adv Ther 2019;36(8):2122-36.

Peters S, ESMO Virtual Plenary 2021

Does this study reflect the clinical scenario?

Patient selection

From 24.075 initial cases



Attrition step	De novo stage IV NSCLC	Initial diagnosis stage I-III NSCLC
Receipt of CIT-mono or CIT-combo[a]	5168	2125
Relevant line of therapy started before 28 Feb 2019	3132	1271
Normal laboratory values	2756	1104
ECOG performance status, 0-1	1508	642
PD-L1 ≥1%	975	379
No evidence of ALK, EGFR, ROS1, BRAF	930	352
No structured activity gap	905	347
Evidence of metastatic diagnosis	905	253
Random sample	774	–
Confirmed receipt of treatment in 1L	764	191
Non-squamous histology	594	134
PD-L1 ≥50%	428	92

TO

N=520

[a] CIT-combo included platinum-doublet therapy without bevacizumab; patients participating in a clinical trial were excluded.

- **Only 2,1% of initial cases included onto the analysis**
- **No PS2 patients**
- **No squamous patients**

«selected» real-life

Patient selection: A potential bias in real world data

Prospective, Phase III/IV, Multicenter TAIL Study

- Stage IIIb/IV NSCLC (squamous or non-squamous)
- Progression following 1-2 lines of prior chemotherapy
- Any PD-L1 status
- **Patients typically excluded from clinical trials:**
  - **ECOG PS 2**
  - **Prior anti–PD-1 treatment**
  - **Untreated/treated asymptomatic CNS metastases**
  - **Autoimmune disease**
  - **HBV/HCV/HIV+**
  - **Severe renal impairment**

N = 619

→ Atezolizumab1200 mg IV q3w until loss of clinical benefit, unacceptable toxicity, investigator/patient decision to withdraw, loss of follow-up or death

Primary endpoint (readout ≈ 6 mo after LPI):

- Incidence of SAEs related to atezolizumab[a]
- Incidence of irAEs related to atezolizumab[b]

Secondary endpoints

- OS, OS at 6 and 12 mo, PFS, ORR, DOR
- Safety and efficacy in subgroups

Ardizzoni A et al. ESMO 2019

Baseline Characteristics: special populations still under-represented

Characteristic	All Patients (N = 615)
Median age (min-max), y	64.0 (24-88)
Male, n (%)	370 (60.2)
ECOG PS, n (%)	
0-1	554 (90.1)
2	61 (9.9)
Stage IV at diagnosis, n (%)	581 (94.5)
Histology, n (%)[a]	
Non-squamous	462 (75.1)
Squamous	152 (24.7)
Prior lines of NSCLC therapy, n (%)	
1	398 (64.7)
2	177 (28.8)
> 2	40 (6.5)

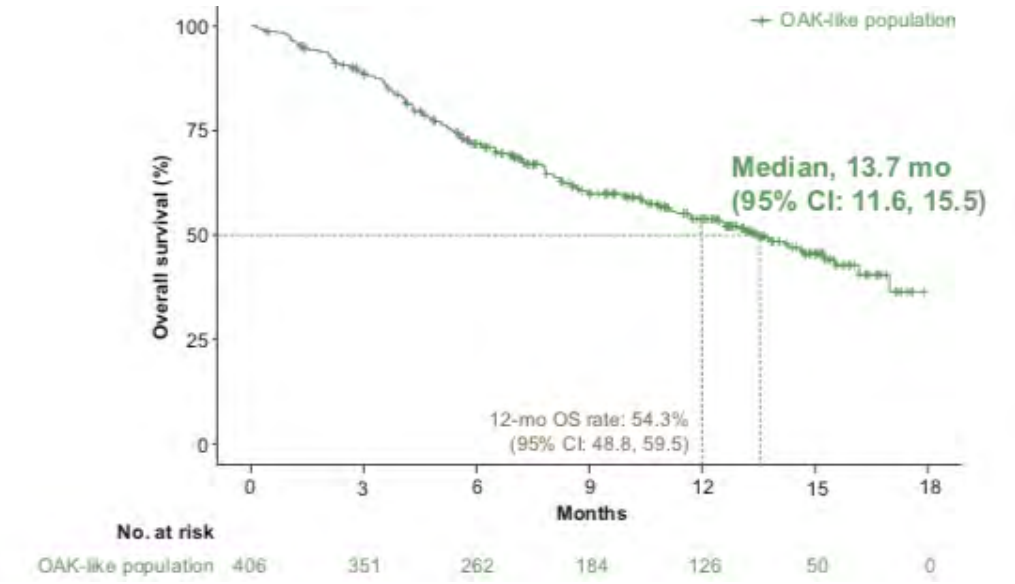
Characteristic	All Patients (N = 615)
Prior chemotherapy, n (%)[b]	611 (99.3)
Prior anti–PD-1 therapy, n (%)[c]	39 (6.3)
≥ 2 prior lines of NSCLC therapy	35 (89.7)
EGFR mutation, n (%)	40 (6.5)
EML4-ALK rearrangement, n (%)	5 (0.8)
PD-L1 expression on TC, n (%)[d]	
Positive (≥ 1%)	213 (34.6)
Negative (< 1%)	168 (27.3)
Unknown	234 (38.1)
CNS metastases, n (%)	89 (14.5)
Renal impairment, n (%)[e]	78 (12.7)
History of autoimmune disease, n (%)	30 (4.9)
OAK-like population, n (%)[f]	406 (66.0)

Ardizzoni A et al. ESMO 2019

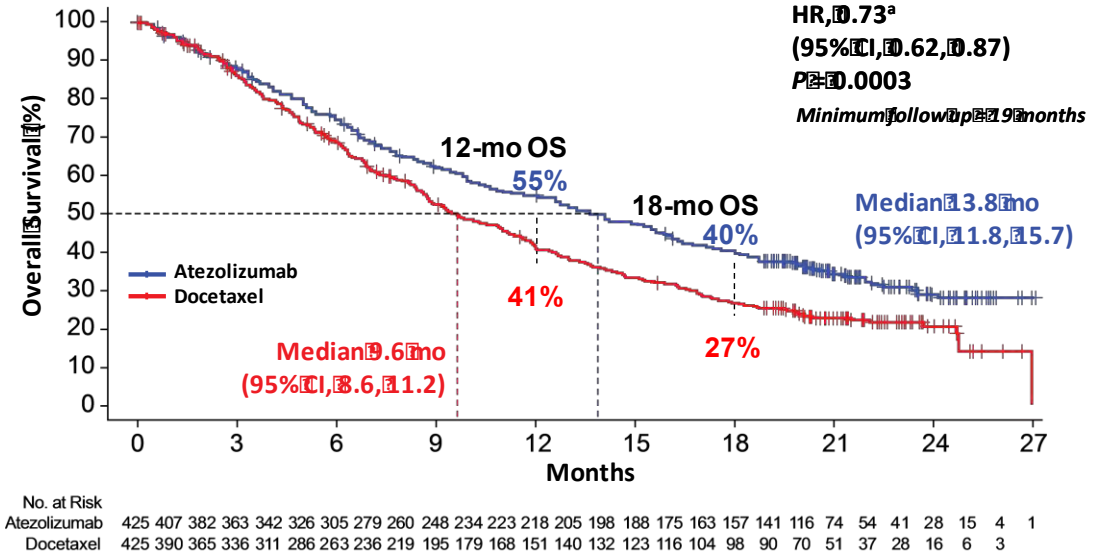
Similar efficacy to clinical trials

Patient subgroup	n	CR, n (%)	PR, n (%)	ORR, % (95% CI)	PFS, mo (95% CI)	OS events, n	OS, mo (95% CI)
All patients	615	3 (0.5)	65 (10.6)	11.1 (8.7,13.8)	2.7 (2.1, 2.8)	312	11.1 (8.9, 12.9)
OAK-like population	406	3 (0.7)	52 (12.8)	13.5 (10.4,17.3)	2.8 (2.7, 3.9)	181	13.7 (11.6, 15.5)

OS in OAK-like patients



OS in OAK trial



Ardizzoni A et al. ESMO 2019

Patient selection: the Nivolumab Italian Expanded Access Program (EAP)

Outcomes from 1959 patients treated within the Italian EAP have been analyzed

- EAP-Squamous Cohort: 371 patients enrolled (Apr – Sept 2015) at 96 Institutions and treated with at least 1 dose of Nivolumab

✓Median follow-up 7.1 months (range 0.1 -16.4 months)

✓Median Nivolumab doses 6 (range 1-22)

- EAP-NonSquamous Cohort: 1588 patients enrolled (Jun 2015 – Apr 2016) at 153 Institutions and treated with at least 1 dose of Nivolumab

✓Median follow-up 8.1 months (range: 1.0–27.4)

✓Median Nivolumab doses 7 (range 1-55)

- Scientific Relevance

✓SQ-NSCLC Italian EAP 10 abstracts presented at International Congress

✓NSQ-NSCLC Italian EAP 11 abstracts presented at International Congress

EAP Squamous cohort: similar patients characteristics to registration trial

Italian EAP Squamous cohort

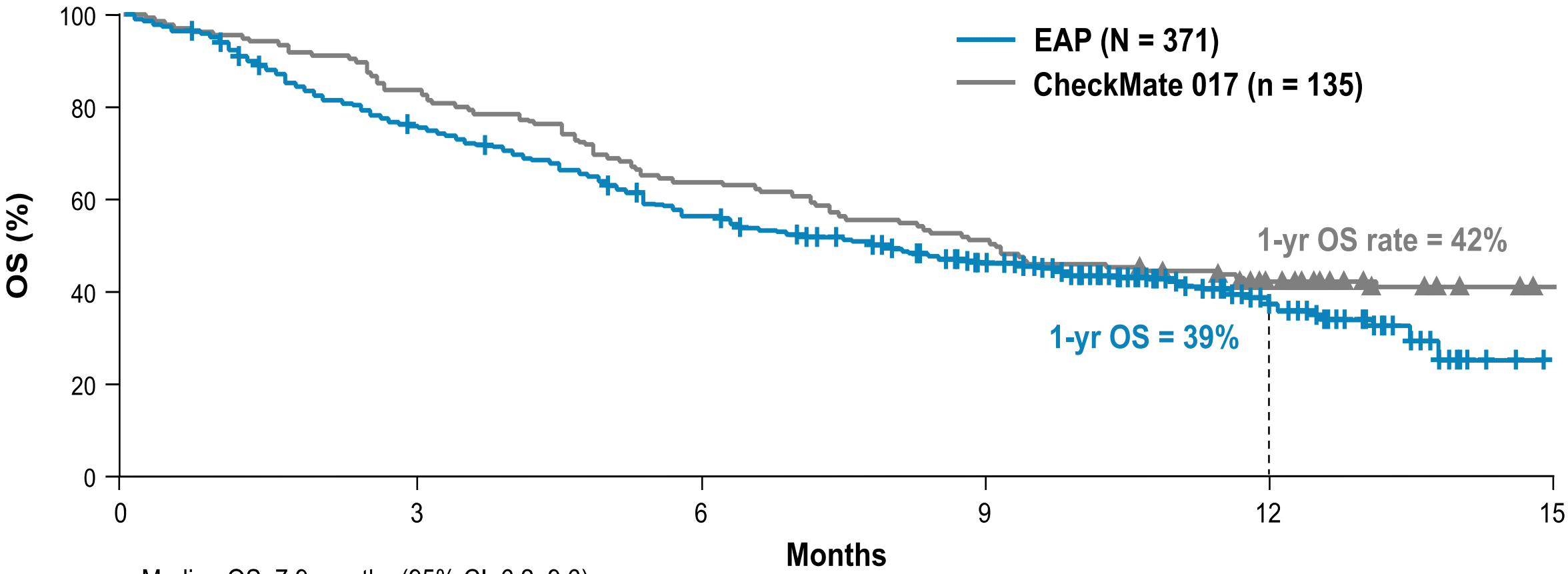
Characteristic	N = 371
Gender, n (%)	
Male	298 (80)
Female	73 (20)
Median age, years (range)	68 (31–91)
≥75, n (%)	70 (19)
Smoking status, n (%)	
Smoker	83 (22)
Former smoker	225 (61)
Never smoker	31 (8)
Unknown	32 (9)
ECOG PS, n (%)	
0	134 (36)
1	215 (58)
2	22 (6)
Metastasis site, n (%)	
CNS	37 (10)
Liver	63 (17)
Bone	120 (32)
Number of prior therapies, n (%)	
1	162 (44)
2	120 (32)
3	68 (18)
≥4	21 (6)

CheckMate 017

Characteristic	Nivolumab (N=135)	Docetaxel (N=137)	Total (N=272)
Age — yr			
Median	62	64	63
Range	39–85	42–84	39–85
Age category — no. (%)			
<65 yr	79 (59)	73 (53)	152 (56)
≥65 to <75 yr	45 (33)	46 (34)	91 (33)
≥75 yr	11 (8)	18 (13)	29 (11)
Sex — no. (%)			
Male	111 (82)	97 (71)	208 (76)
Female	24 (18)	40 (29)	64 (24)
Race — no. (%)†			
White	122 (90)	130 (95)	252 (93)
Black	6 (4)	2 (1)	8 (3)
Asian	4 (3)	2 (1)	6 (2)
Other	1 (1)	2 (1)	3 (1)
Not reported	2 (1)	1 (1)	3 (1)
Disease stage — no. (%)			
IIIB	29 (21)	24 (18)	53 (19)
IV	105 (78)	112 (82)	217 (80)
Not reported	1 (1)	1 (1)	2 (1)
ECOG performance-status score — no. (%)‡			
0	27 (20)	37 (27)	64 (24)
1	106 (79)	100 (73)	206 (76)
Not reported	2 (1)	0	2 (1)
Central nervous system metastasis — no. (%)			
Yes	9 (7)	8 (6)	17 (6)
No	126 (93)	129 (94)	255 (94)
Smoking status — no. (%)			
Current or former smoker	121 (90)	129 (94)	250 (92)
Never smoked	10 (7)	7 (5)	17 (6)
Unknown	4 (3)	1 (1)	5 (2)

Crinò L, et al. WCLC 2016; Brahmer J, et al. NEJM 2015

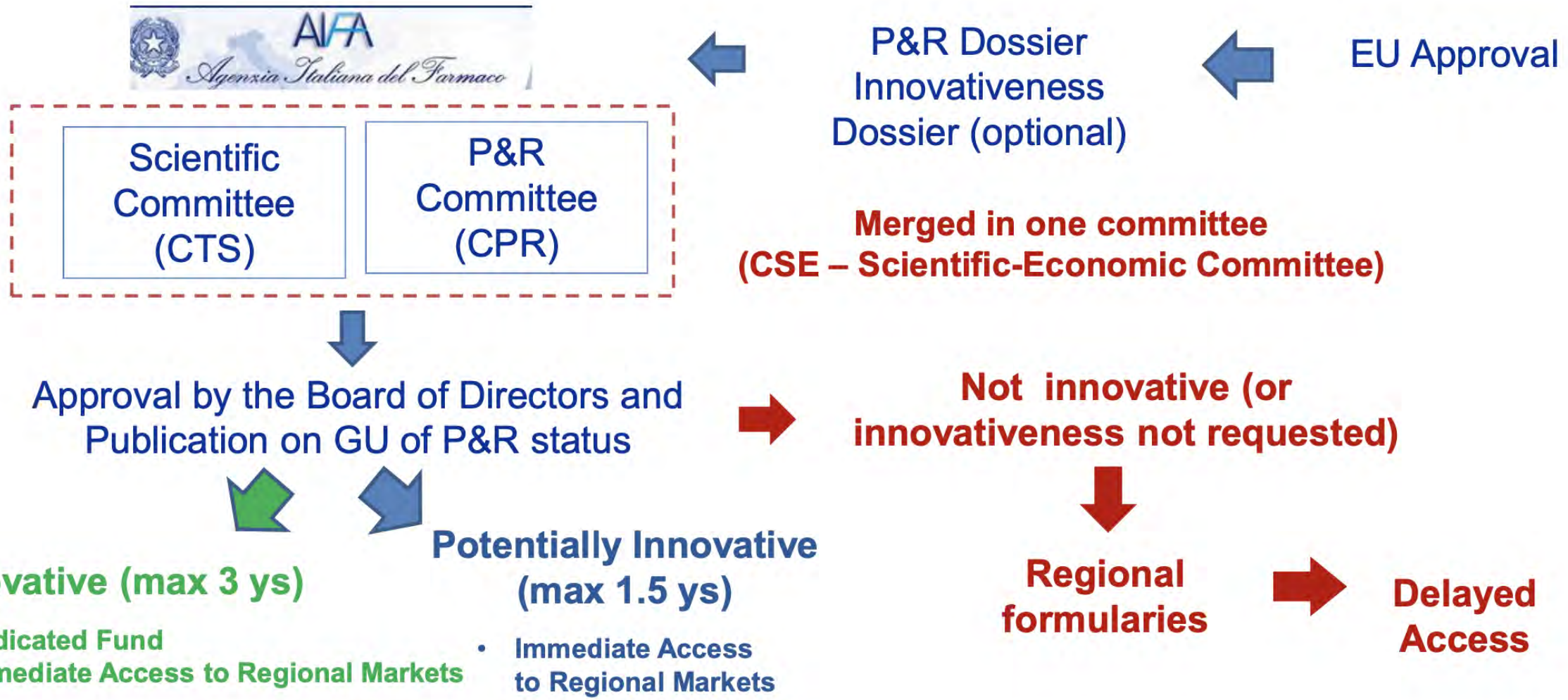
Italian Nivolumab EAP Squamous cohort, OS similar to registration trial



- Median OS: 7.9 months (95% CI: 6.2, 9.6)
- Median follow-up = 7 months

Crinò L, et al. WCLC 2016; Brahmer J, et al. NEJM 2015

Cost/reimbursement is a relevant issue



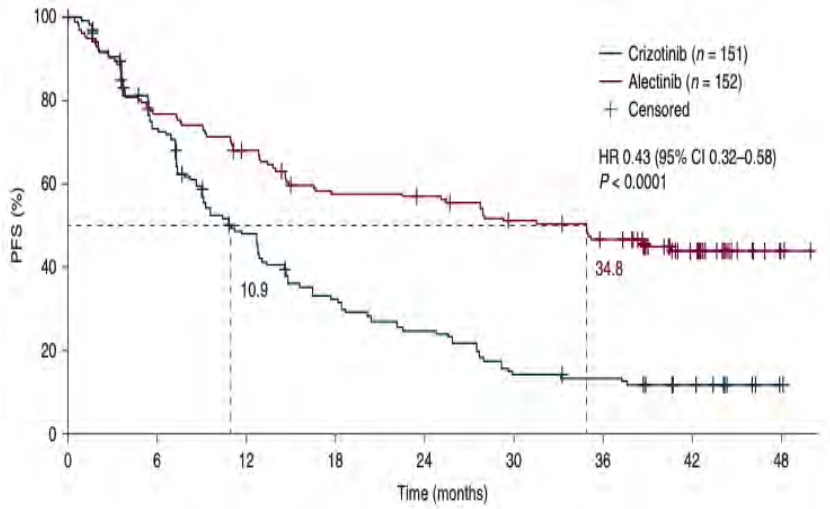
* P&R should be negotiated for any new medicines, indication and formulation
P&R: Pricing and Reimbursement; GU: Gazzetta Ufficiale

Physician strategy : the illusion of a perfect sequencing

ALK+ NSCLC as an example

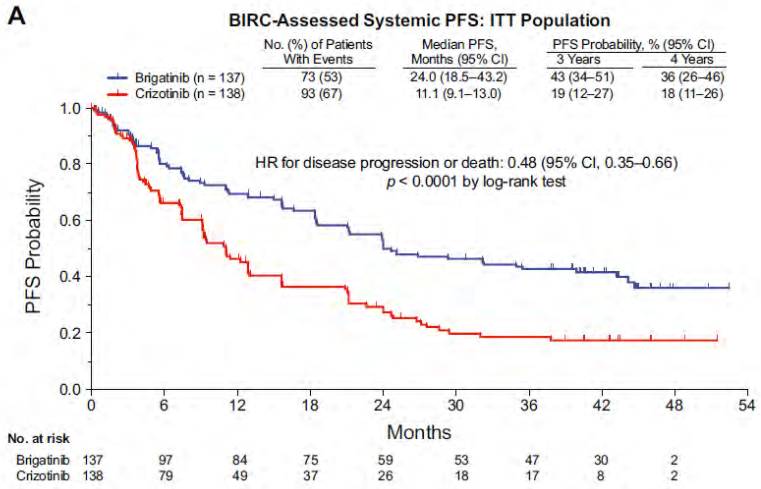
ALEX, Ph. III
Alectinib vs Crizotinib

PFS
(Investigator-assessed)



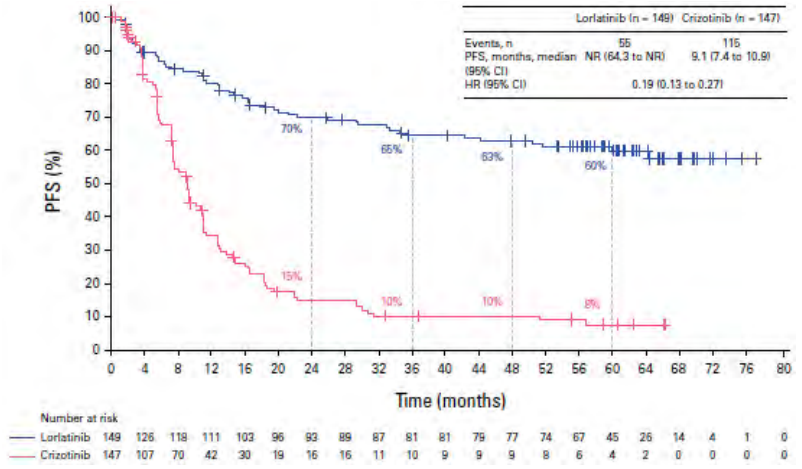
ALTA-1L, Ph. III
Brigatinib vs Crizotinib

PFS
(BIRC-assessed)



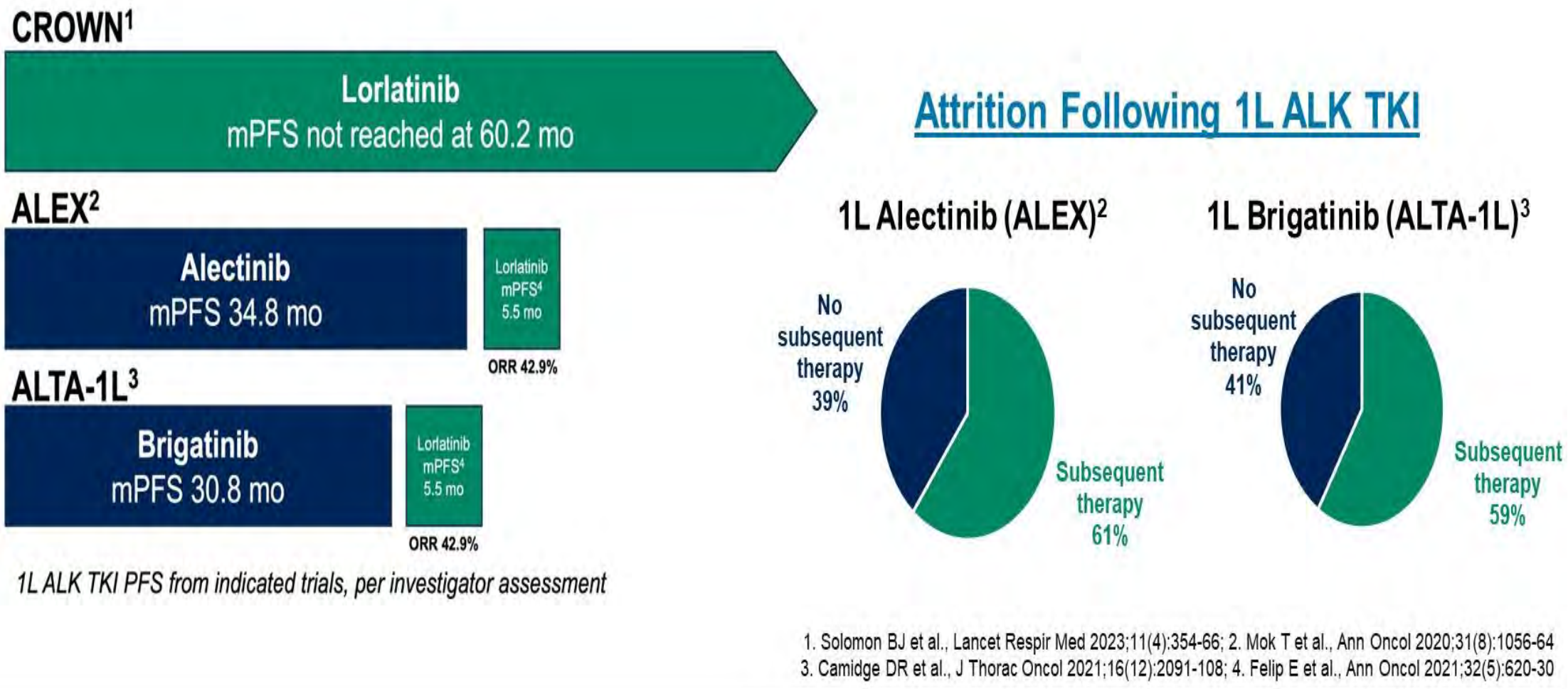
CROWN, Ph. III
Lorlatinib vs Crizotinib

PFS
(BIRC-assessed)



Mok T, et al. Ann Oncol 2020; Camidge R, et al. JTO 2021; Solomon B, et al. JCO 2024

The best FIRST



1. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66; 2. Mok T et al., Ann Oncol 2020;31(8):1056-64
3. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108; 4. Felip E et al., Ann Oncol 2021;32(5):620-30

Chi vuol esser lieto, sia: di doman non c'è certezza - *Let who will be gay, tomorrow, none can tell*

Lorenzo de' Medici, " The Magnificent" - Canzona di Bacco, Florence, 1490

Lin JJ, ASCO 2024

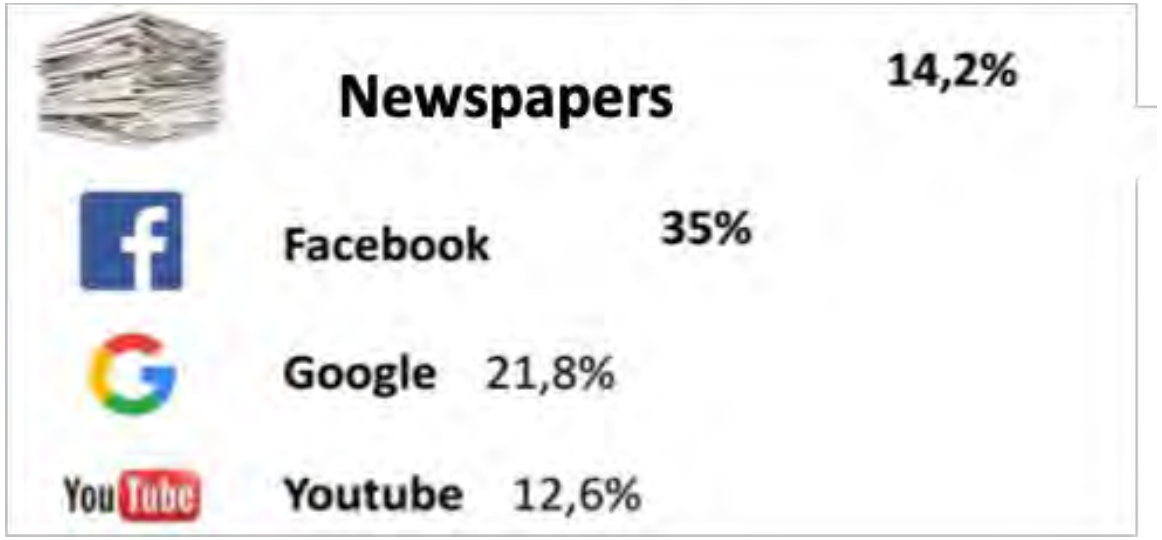
Patient bias: fake news impair therapy acceptance/compliance

The spread of true and false news online

Soroush Vosoughi,[1] Deb Roy,[1] Sinan Aral[2]*

Massachusetts Institute of Technology (MIT)

Source of information in Italy



51° Rapporto Censis 2017

Conclusions

- Clinical practice is different to clinical trial
  - Patients are not selected using the trial criteria
  - Several subpopulations are not or minimally represented (PS2, elderly…)
- In clinical practice several factors interfere with patient journey
  - Issues for diagnosis and staging
  - Biomarker testing
  - Physician and/or patient preference
- Real world data are useful but not enough for depicting all clinical scenarios
  - Selection remains an issue
  - Quality of data often not optimal

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