A Teaching Affiliate of Harvard Medical School

Primer on Circulating Tumor DNA

General Thoracic Surgical Club

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Uma M. Sachdeva, M.D., Ph.D.

Assistant Professor of Surgery

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What is Circulating Tumor DNA?

- Cell free DNA (cfDNA) is fragmented DNA in cell-free component of whole blood
- Typically 160-200 base pairs
- Released through cell death
- Can also be identified in urine, CSF, pleural fluid, saliva
- Normal: 1-10ng/ml, primarily hematopoietic origin, cleared by liver with 2.5 hour half life
- Cancers: 5-10x amount of cfDNA
  - Tumor derived fraction is ctDNA (0.1-50%)
    - Same genomic alterations as parent tumor
    - 143-145bp
- Markers of ctDNA:
  - Fragment size
  - Epigenetic markers (DNA methylation)
  - Genomic mutations (EGFR, ALK, ROS1)

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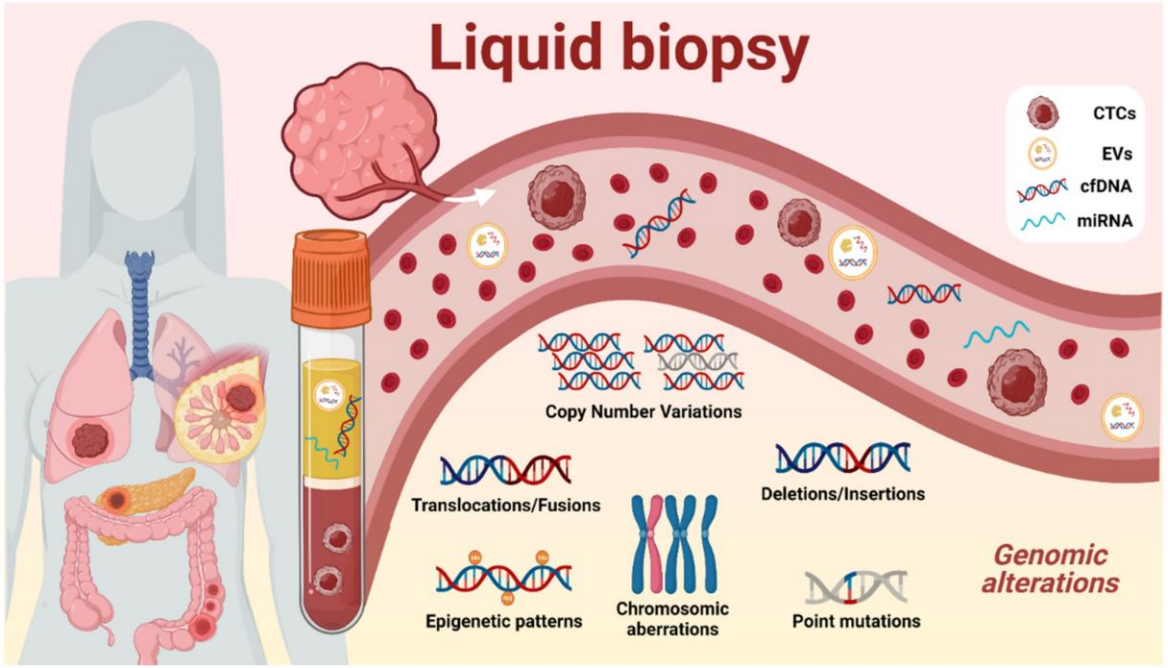
What is a Liquid Biopsy?

- cfDNA
- Extracellular vesicles
- Circulating tumor cells
- miRNAs



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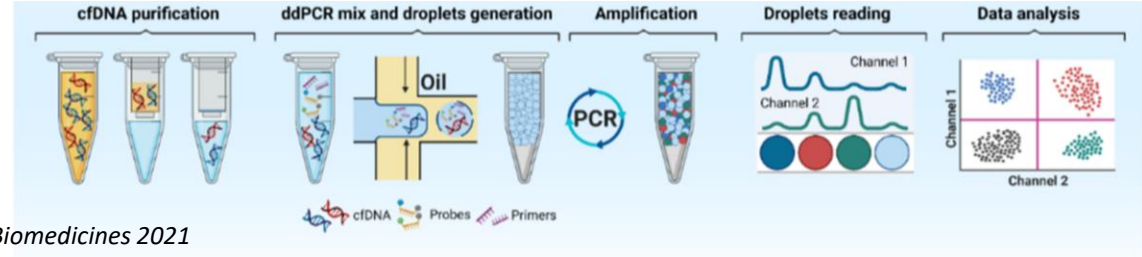
Palacin-Aliana et al, Biomedicines 2021

How is ctDNA Assessed?

- Extracted from plasma portion of serum sample
  - Processing ideally within 1-2 hours to prevent leukocyte death
  - May be confounded by CHIP (Clonal hematopoietic mutations of indeterminate potential) to create false positives
    - Can be accounted for by WBC sequencing and mutation subtraction
- Allele-specific
  - Detect known mutation in single gene or small number of genes
  - Droplet digital PCR (detects mutated allele fraction up to 0.01%) for point mutation or small insertion/deletion
    - One assay per analysis
    - Hot spot mutations, previously identified mutations, known resistance hot spots
    - High sensitivity, low genomic coverage



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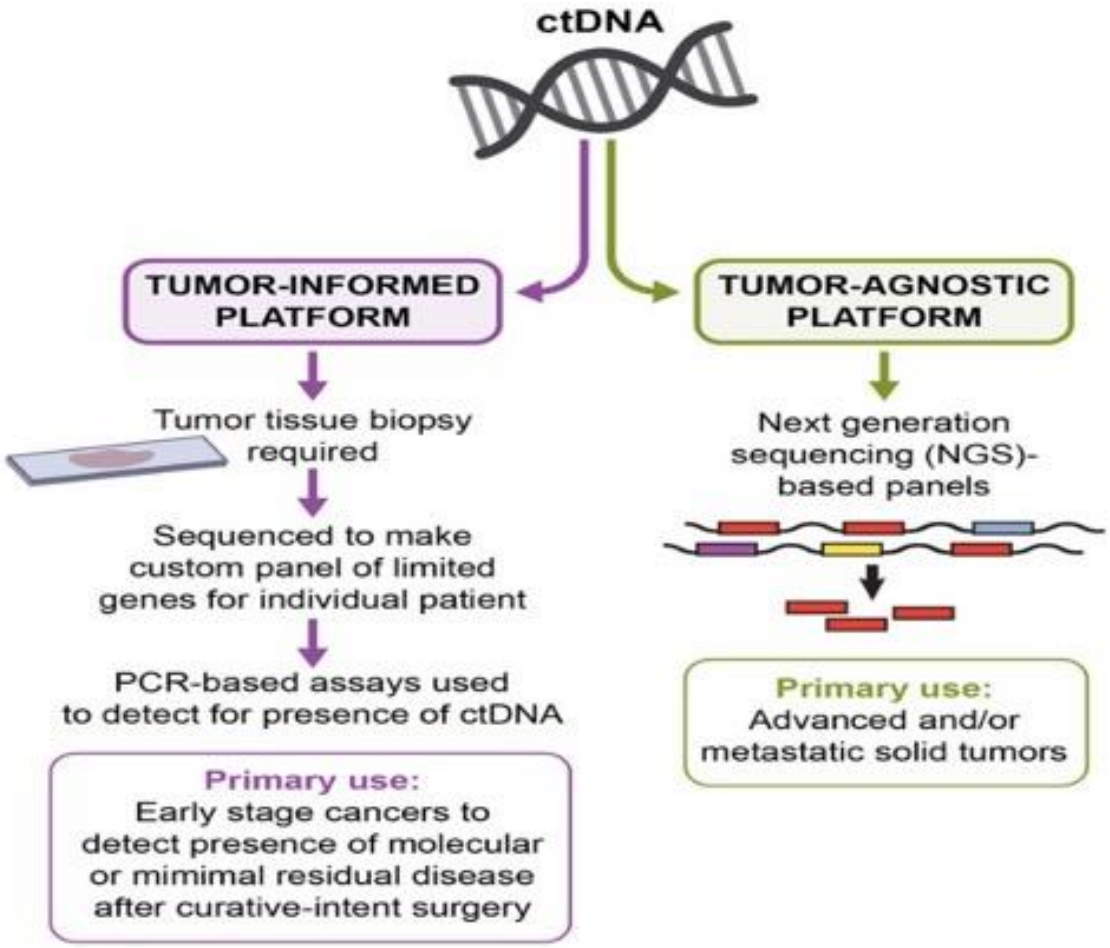
Palacin-Aliana et al, Biomedicines 2021

How is ctDNA Assessed?

- Next Generation Sequencing (NGS, e.g. Guardant360, Signatera)
  - Amplicon based sequencing
    - Up to 100 genes with high sensitivity
    - Disease focused, hot spot, actionable mutation panels, comprehensive panels
  - Hybrid capture sequencing
    - Larger genomic regions (100s of genes to whole exomes)
    - Can detect indels, translocations, chromosomal rearrangements
    - Broader genomic coverage – better molecular profiling, can track multiple clones simultaneously and emergence of new mutations
    - Disease progression, clonal evolution
  - Whole Exome Sequencing
    - Lower sensitivity due to shallow sequencing depths
    - Broad coverage
    - Detects copy number variations, gene fusions

Tumor-Informed vs Tumor Agnostic Approach



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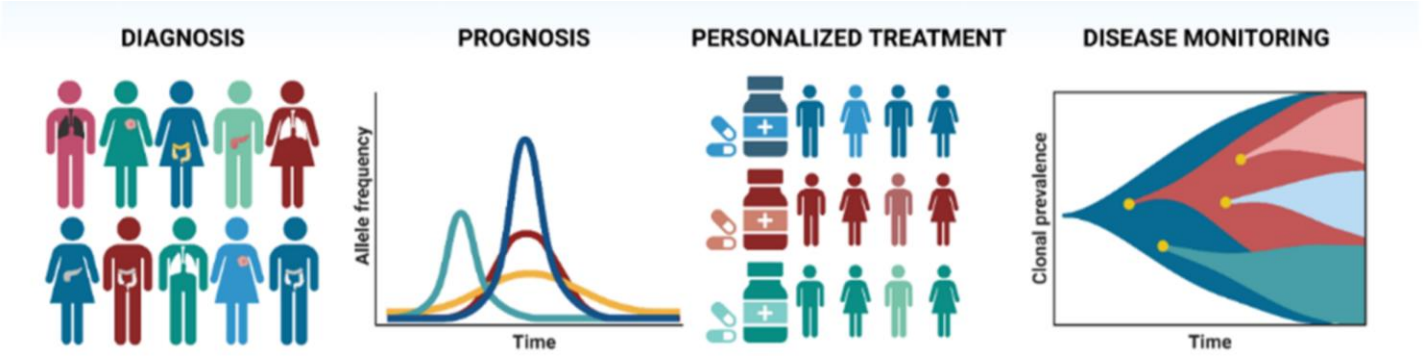
Kasi, ASCO Daily News, 2020

Uses for ctDNA

- Molecular diagnosis without solid-tumor sampling (e.g. EGFR mutations)
- Prognosis following curative intent treatment of early-stage disease (detection of MRD: minimal/microscopic/molecular residual disease)
- Determine need for adjuvant therapy following curative-intent resections (cutting edge, colorectal cancer)
- Early detection of recurrence several months prior to detection by imaging
  - Sensitivity 100,000 cells vs 10,000,000 cells for CT



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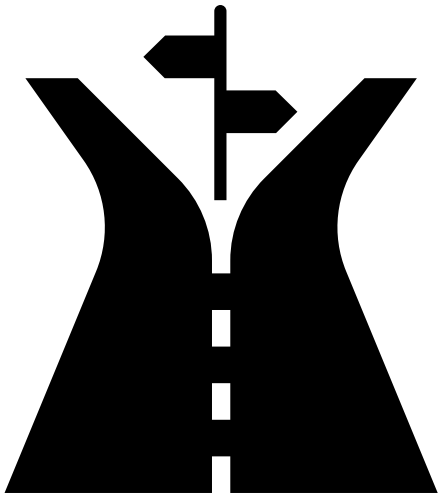
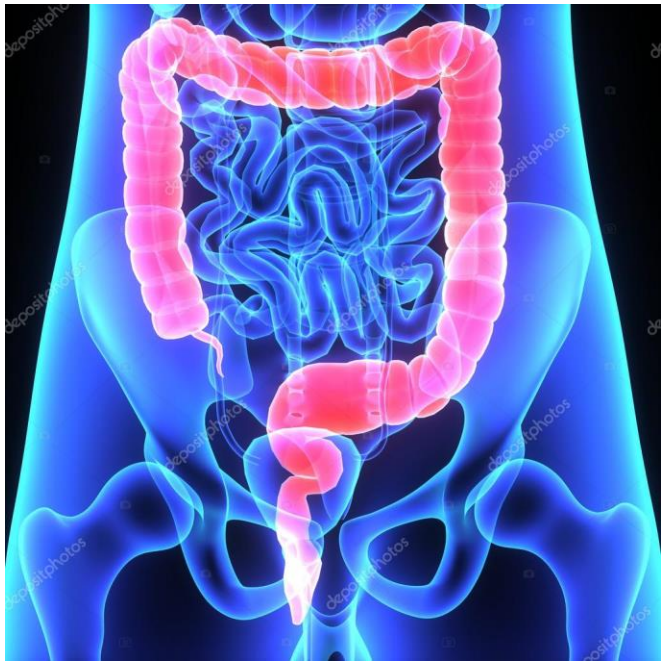
Palacin-Aliana et al, Biomedicines 2021

Detour to Colon Cancer: Leading the Way





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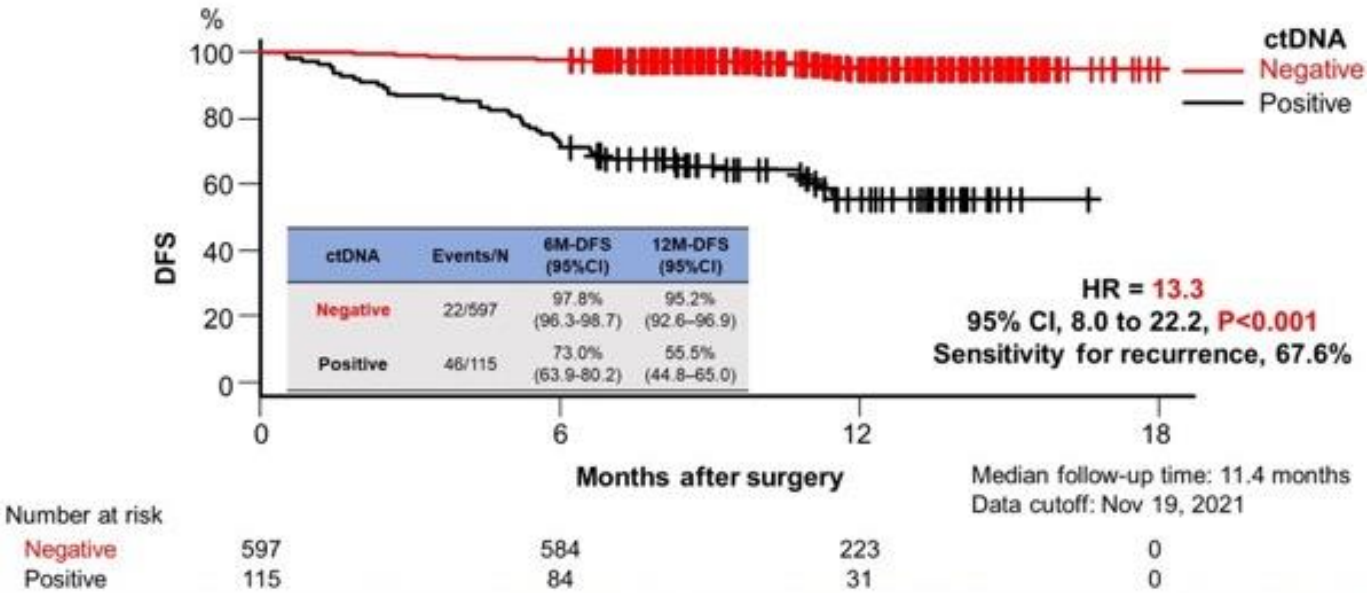
Post-operative ctDNA+ is Prognostic in Colorectal Cancer: CIRCULATE-Japan

- ctDNA assessed 4 weeks after curative intent resection in patients with Stage II-III colon cancer
- DFS assessed
  - Almost 30% recurred within 6 months if ctDNA+ at 4 weeks
  - ctDNA+ was strongest predictor of recurrence in multivariable analysis



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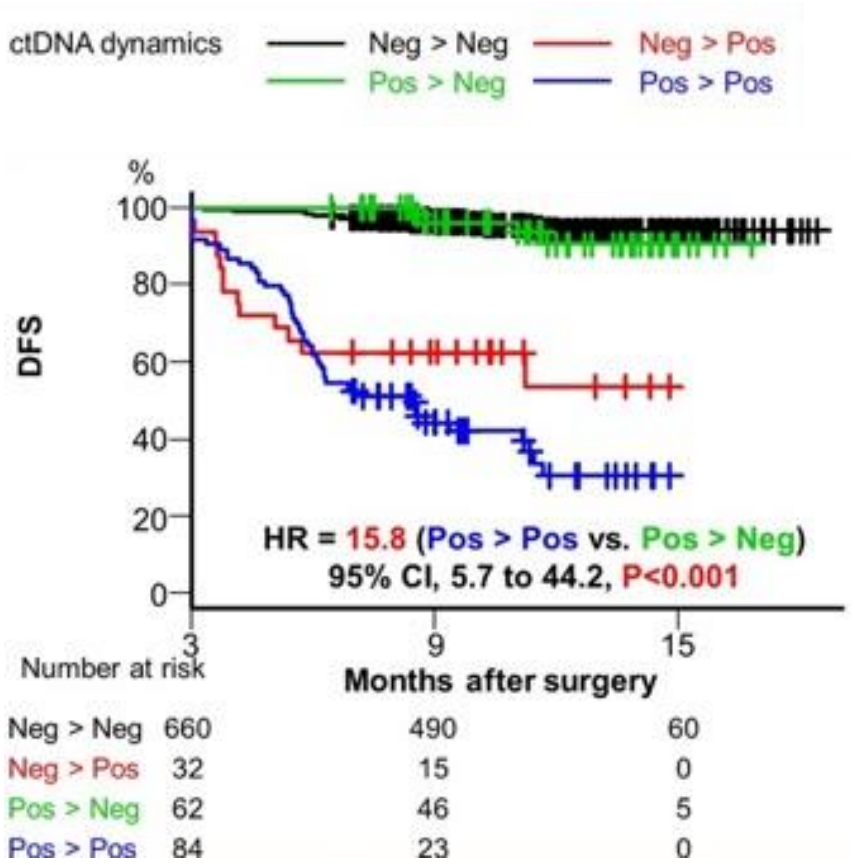
Dr. Masahito Kotaka, ASCO GI 1/2022

ctDNA Clearance Portends Improved Survival in Colon Cancer

- ctDNA assessed at 4 weeks and 12 weeks post-operatively



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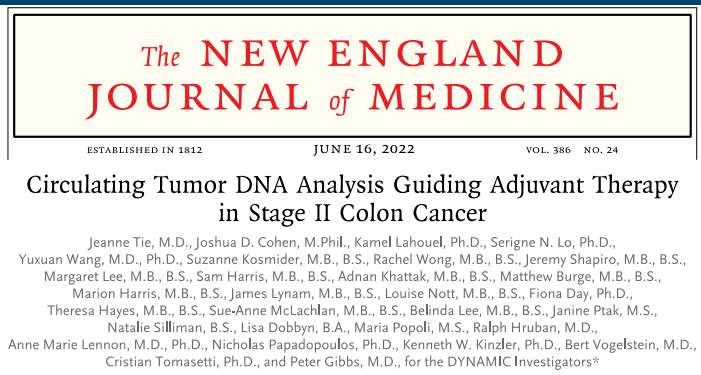
Dr. Masahito Kotaka, ASCO GI 1/2022

ctDNA to Determine Need for Adjuvant Therapy After Curative-Intent Surgery for CRC



- Phase 2 RCT Stage II (T3 or T4, N0, M0) colon cancer
  - Surgical resection curative in 80%
  - No overall survival benefit with adjuvant therapy in trials
  - Adjuvant offered if “high risk” clinicopathologic features
  - DYNAMIC study: ctDNA-guided approach to adjuvant chemotherapy
  - Plasma analysis of ctDNA at week 4 and week 7 after surgery
    - ctDNA arm:
      - Patients with positive ctDNA received single-agent fluoropyrimidine or oxaliplatin-based chemotherapy
      - Patients with negative ctDNA underwent surveillance
    - Standard Management Arm:
      - Treatment decisions based on clinicopathologic criteria
  - Primary endpoint: Recurrence free survival

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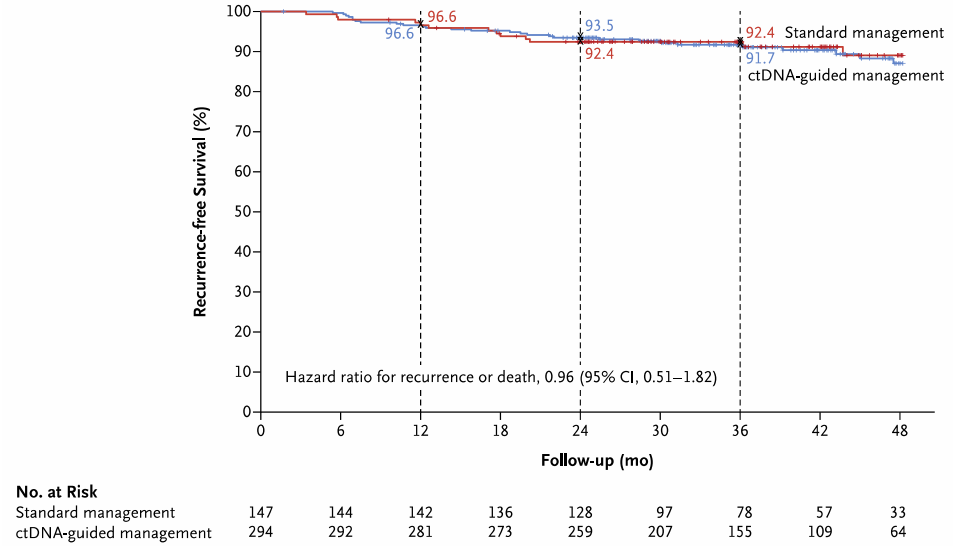
ctDNA Guides Adjuvant Therapy in Colon Cancer

- 28% in standard group received adjuvant chemotherapy vs 15% in ctDNA arm
  - ctDNA arm: 246 ctDNA negative, 45 ctDNA positive



  - *ctDNA decreased number of patients who received adjuvant therapy without increasing rate of recurrence or decreasing survival*
  - *Very low risk of recurrence in ctDNA negative patients with no adjuvant therapy*

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ctDNA in Lung Cancer

- Detection of targetable mutations (Guardant360, etc.)

JAMA Oncology | Original Investigation

Prospective Validation of Rapid Plasma Genotyping for the Detection of *EGFR* and *KRAS* Mutations in Advanced Lung Cancer

Adrian G. Sacher, MD; Cloud Paweletz, PhD; Suzanne E. Dahlberg, PhD; Ryan S. Alden, BSc; Allison O'Connell, BSc; Nora Feeney, BSc; Stacy L. Mach, BA; Pasi A. Jänne, MD, PhD; Geoffrey R. Oxnard, MD

- Monitor treatment efficacy and modify regimen in advanced disease

Heterogeneity and Coexistence of T790M and T790 Wild-Type Resistant Subclones Drive Mixed Response to Third-Generation Epidermal Growth Factor Receptor Inhibitors in Lung Cancer

Zofia Piotrowska
Mathilka Hazar-Rethinam
Coleen Rizzo
Brandon Nadres
Emily E. Van Seventer
Heather A. Shahzade
Inga T. Lennes
Anthony J. Iafrate
Dora Dias-Santagata
Ignaty Leshchiner
Nicholas A. Jessop
Haichuan Hu
Subba R. Digumarthy
Rebecca J. Nagy
Richard B. Lanman
Susan Moody
Matthew J. Niederst
Jeffrey A. Engelman
Aaron N. Hata
Ryan B. Corcoran
Lecia V. Sequist

ascopubs.org/journal/po **JCO™ Precision Oncology**

- Predict recurrence

Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer

D. Gale[1,2†], K. Heider[1,2†], A. Ruiz-Valdepenas[1,2‡], S. Hackinger[3], M. Perry[3], G. Marsico[3], V. Rundell[4], J. Wulff[4], G. Sharma[3], H. Knock[4], J. Castedo[2,5], W. Cooper[1,2], H. Zhao[1,2], C. G. Smith[1,2], S. Garg[6], S. Anand[6], K. Howarth[3], D. Gilligan[5,7], S. V. Harden[7†], D. M. Rassl[2,5], R. C. Rintoul[2,5,8*§] & N. Rosenfeld[1,2,3*§]

[1]Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Cambridge; [2]Cancer Research UK Cambridge Centre, University of Cambridge, Cambridge; [3]Inivata Ltd, The Glenn Berge Building, Babraham Research Park, Babraham, Cambridge; [4]Cambridge Clinical Trials Unit – Cancer Theme, Cambridge; [5]Royal Papworth Hospital NHS Foundation Trust, Cambridge; [6]Cancer Molecular Diagnostics Laboratory, Clifford Allbutt Building, University of Cambridge, Cambridge Biomedical Campus, Cambridge; [7]Addenbrooke's Hospital, Cambridge; [8]Department of Oncology, University of Cambridge Hutchison–MRC Research Centre, Cambridge Biomedical Campus, Cambridge, UK

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Detection of EGFR Mutations

Table 2. Plasma Droplet Digital Polymerase Chain Reaction Assay Sensitivity, Specificity, and Positive Predictive Value

	Sensitivity Analysis			Specificity Analysis			
		No.			No.		
Assay	Sensitivity, % (95% CI)	True Positive[a]	False Negative[b]	Specificity, % (95% CI)	True Negative[c]	False Positive[d]	Positive Predictive Value, % (95% CI)
EGFR exon 19 del							
Newly diagnosed	86 (57-98)	12	2	100 (96-100)	101	0	100 (74-100)
Acquired resistance	81 (64-92)	29	7	100 (85-100)	23	0	100 (88-100)
Overall	82 (69-91)	41	9	100 (97-100)	124	0	100 (91-100)
EGFR L858R							
Newly diagnosed	69 (39-91)	9	4	100 (96-100)	102	0	100 (66-100)
Acquired resistance	78 (52-94)	14	4	100 (91-100)	41	0	100 (77-100)
Overall	74 (55-88)	23	8	100 (97-100)	143	0	100 (85-100)
EGFR T790M							
Acquired resistance	77 (60-90)	27	8	63 (38-84)	12	7	79 (62-91)
KRAS G12X							
Newly diagnosed	64 (43-82)	16	9	100 (94-100)	62	0	100 (79-100)

[a] True positive indicates positive test result in both tissue and plasma.

[b] False negative indicates positive test result in tissue and negative result in plasma.

[c] True negative indicates negative test result in both tissue and plasma.

[d] False positive indicates negative test result in tissue and positive result in plasma.

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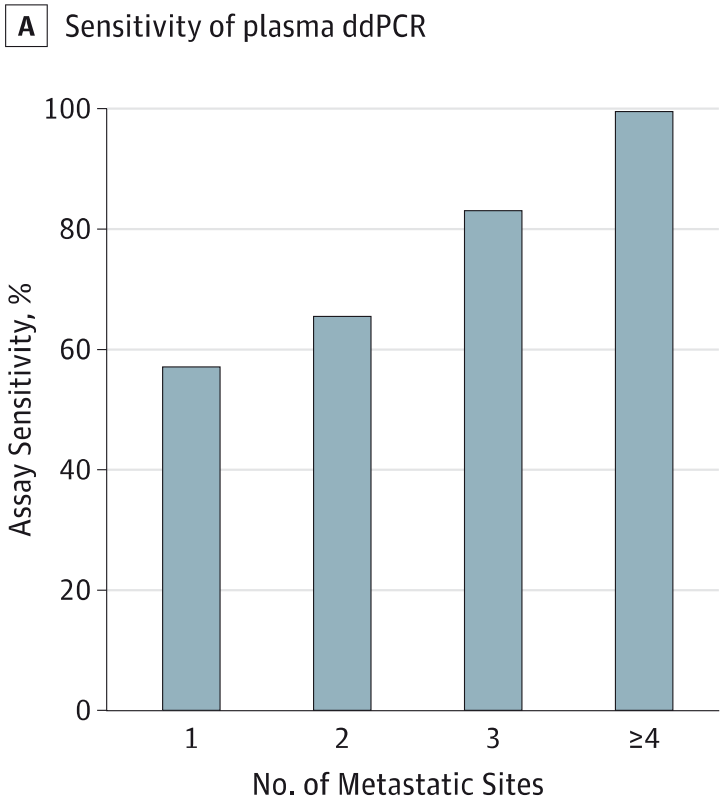
Sacher et al., JAMA Oncology, 2016

Sensitivity Increases with Higher Metastatic Burden



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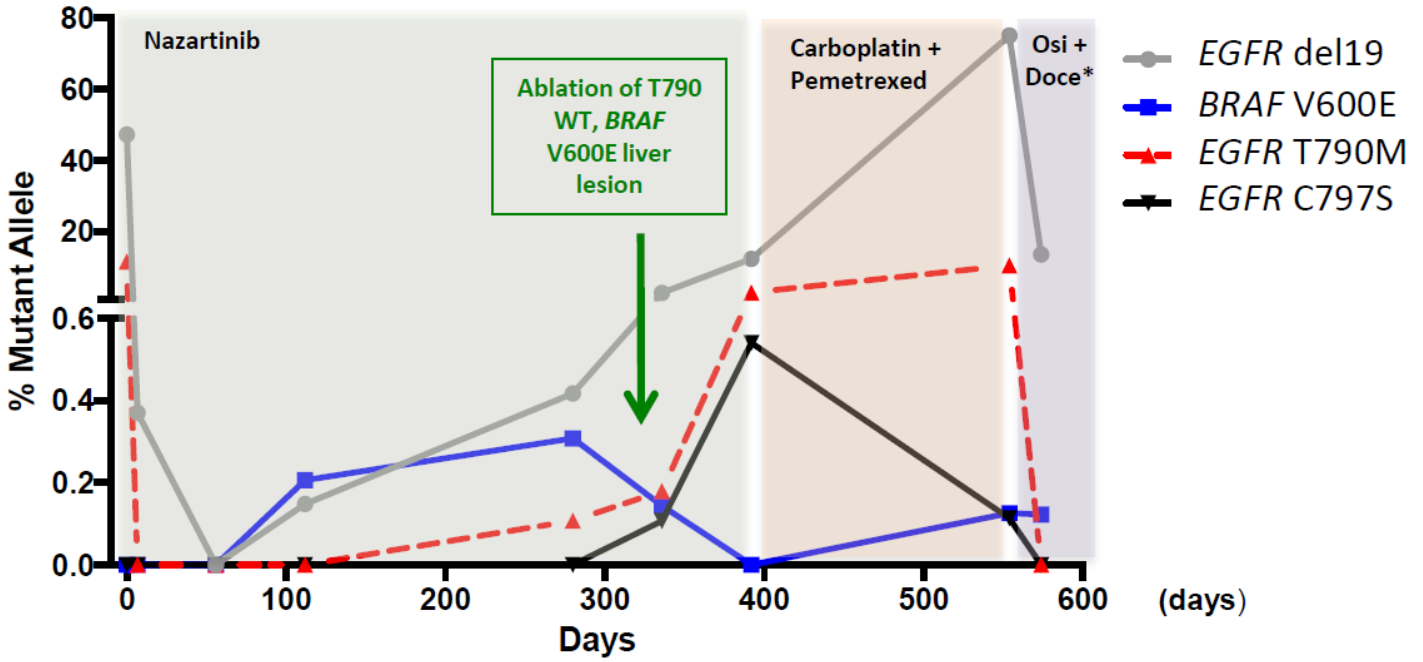
Sacher et al., JAMA Oncology, 2016

ctDNA Analysis Can Guide Changes in Treatment Through Detection of Clonal Shifts



ctDNA actively used in advanced NSCLC to guide TKI therapy and treatment escalation

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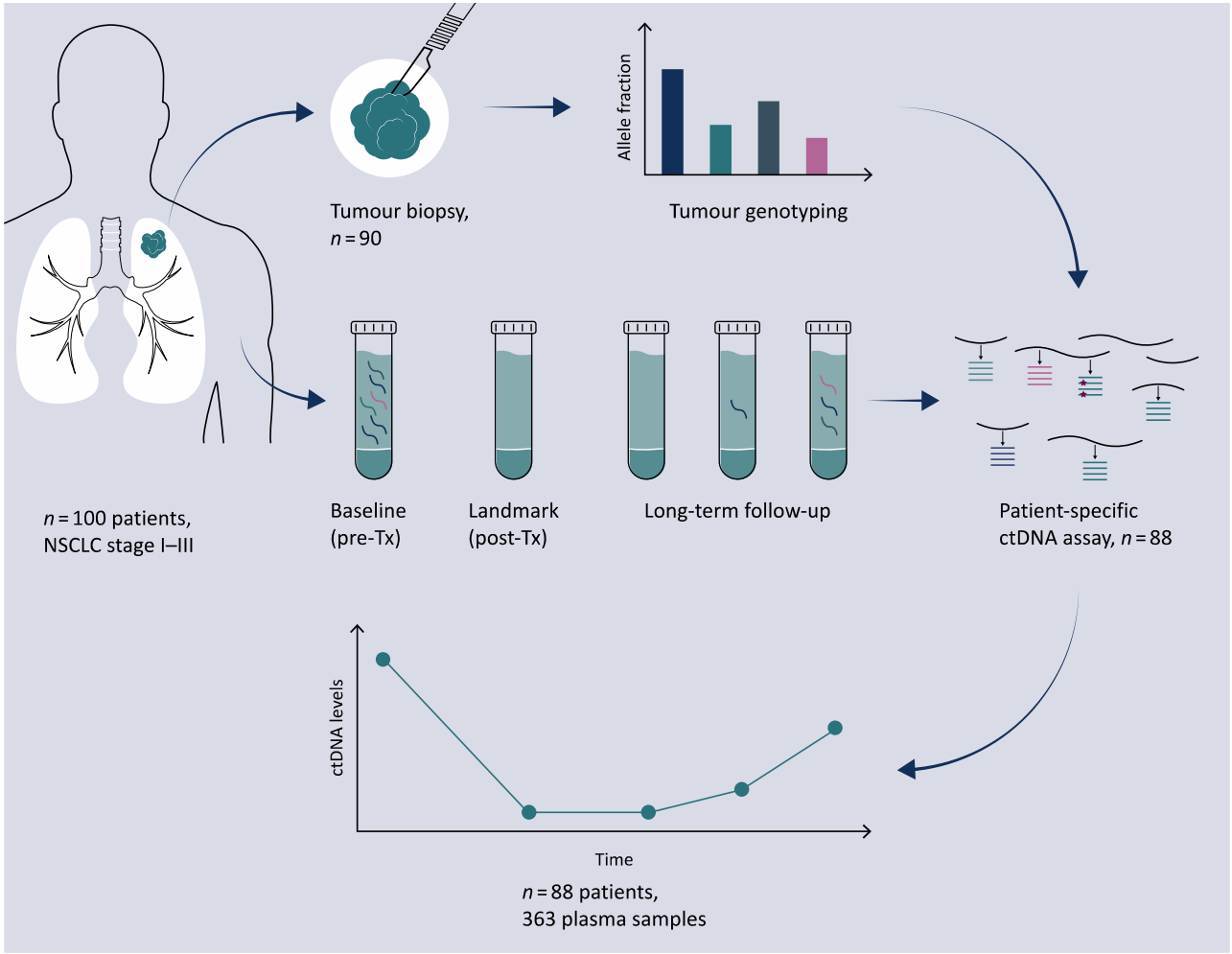
Piotrowska et al., JCO Precision Oncology, 2018

Detection of Early Relapse in NSCLC



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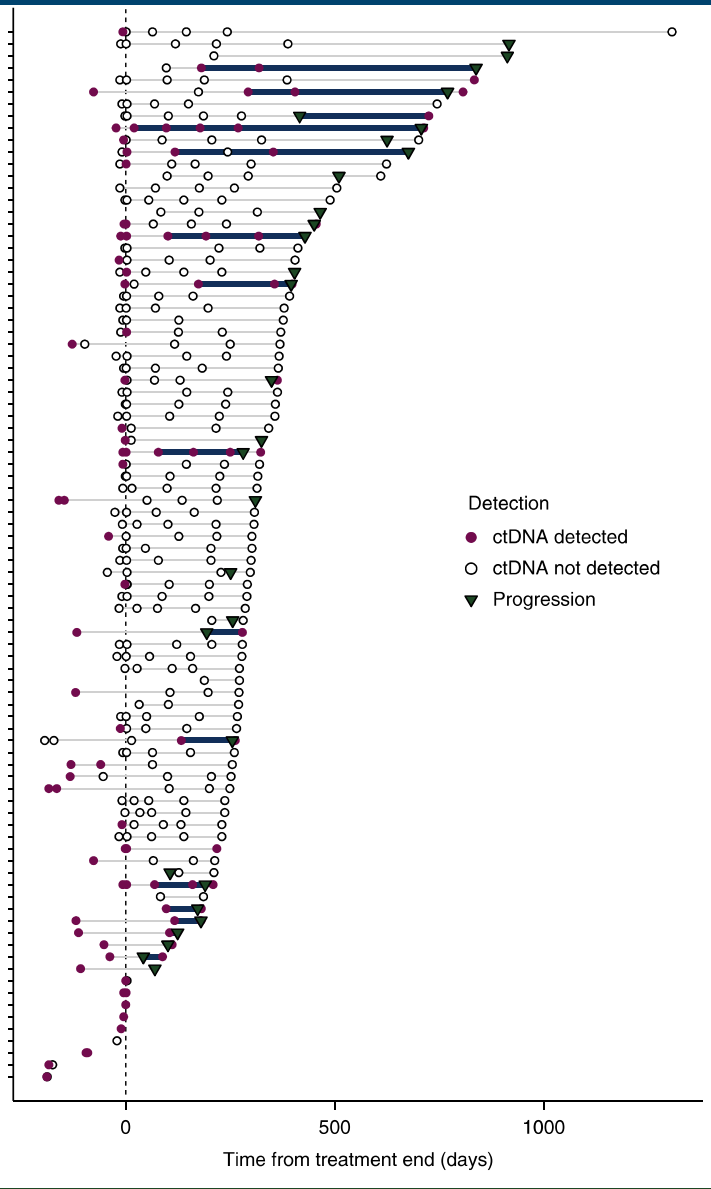
Gale et al., Annals of Oncology, 2022

Detection of Early Relapse in NSCLC



- *ctDNA+ preceded clinical progression*
- *Lead time up to 328 days*

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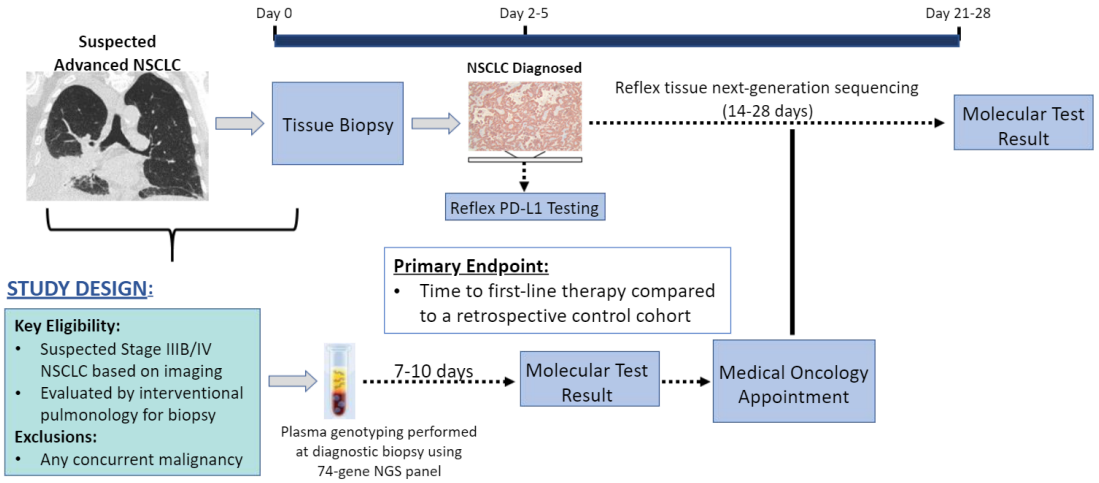
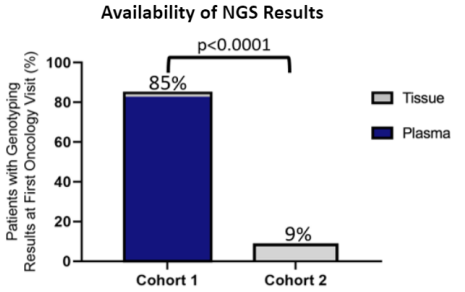
Gale et al., Annals of Oncology, 2022

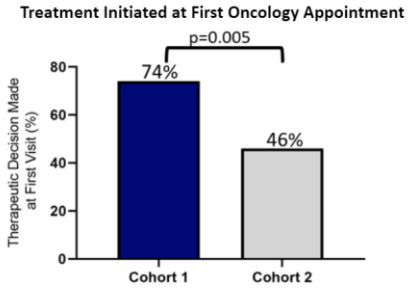
Future Perspectives in Lung Cancer

- TSOG 101 (PI: Isbell)
- Risk stratification of lung nodules/early detection of disease
  - Lung cancer screening population only comprises 30% of diagnosed lung cancers
  - Positive predictive value of LDCT for nodule >7mm is 7%
- Earlier initiation of treatment in patients with targetable mutations



Thompson et al., World Conf on Lung Cancer, 2021





ctDNA in Esophageal Cancer

- Evaluation for MRD post-operatively/predict early recurrence
- Monitor for recurrence
- Assess treatment response in advanced setting
- Detect early emergence of new clones/mutations that may confer resistance phenotypes

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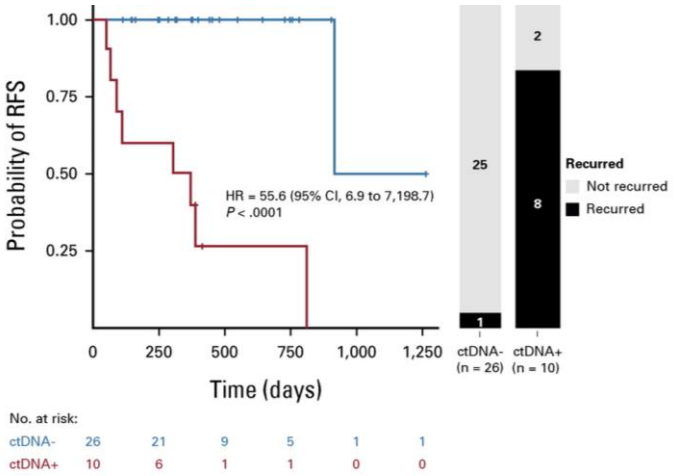
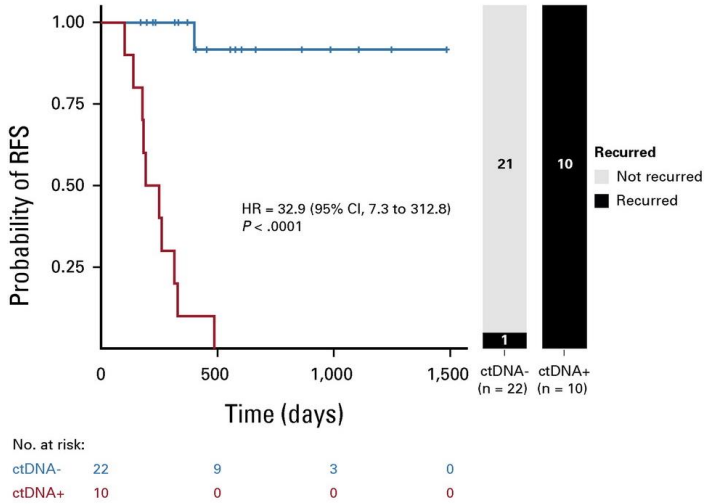
ctDNA+ Anytime Post-Esophagectomy Confers Worse Prognosis

ctDNA detected anytime following curative-intent resection

Esophageal



GE Junction



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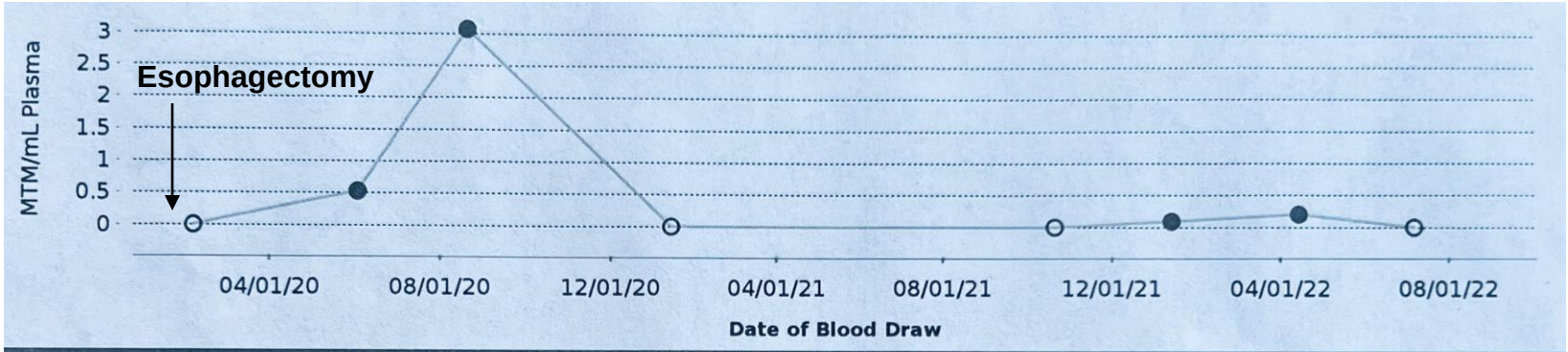
Huffman et al., JCO Precision Oncology 2022

Huffman et al., JCO Precision Oncology 2022

CtDNA in Real-World Scenarios: Case 1



Date	MTM/mL
Jul 07, 2022	0.00
Apr 14, 2022	0.20
Jan 13, 2022	0.09
Oct 21, 2021	0.00
Jan 14, 2021	0.00
Aug 20, 2020	3.07
Jun 03, 2020	0.53
Feb 06, 2020	0.00

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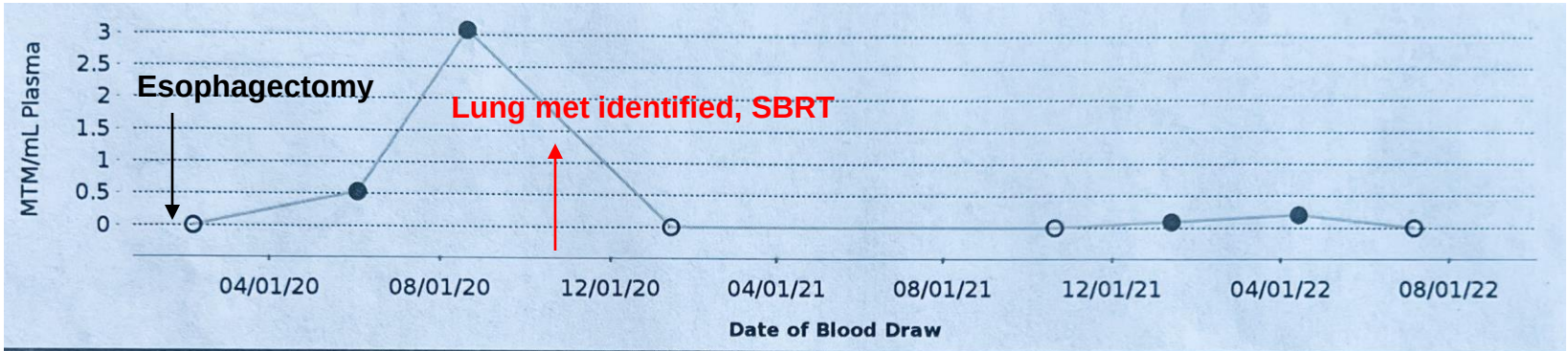

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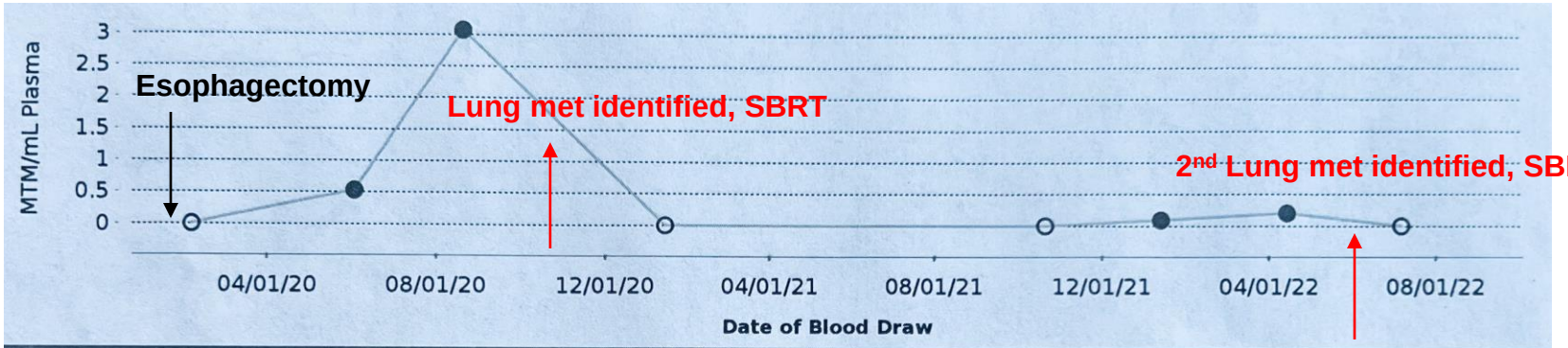

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CtDNA in Real-World Scenarios: Case 2

- 67 year old man, history of prostate cancer s/p radical prostatectomy in 1991
- Esophageal adenocarcinoma, T3N0, proficient MMR, Her2 negative
- Staging workup also showed 8cm right renal mass, biopsy returned RCC
- Treated with 5 cycles carbo/taxol with concurrent radiation, esophagectomy May 2022
- Right nephrectomy December 2022

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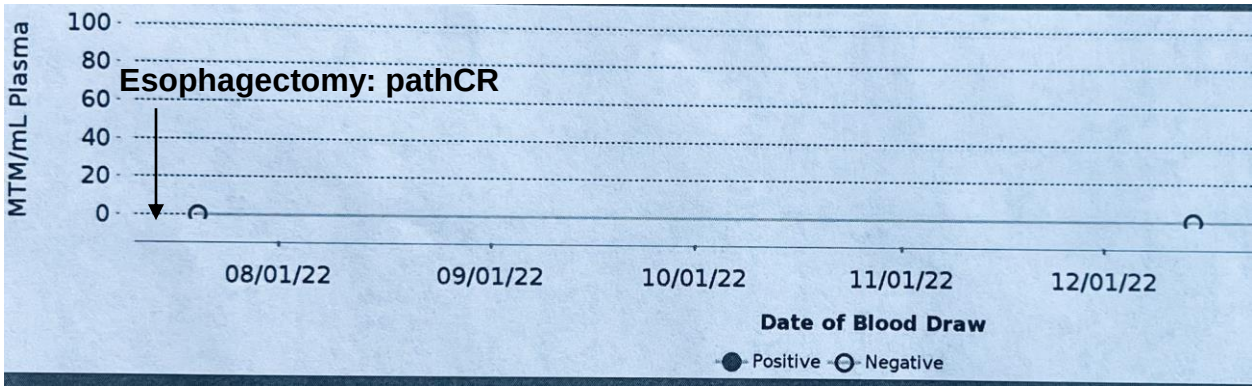
CtDNA in Real-World Scenarios: Case 2



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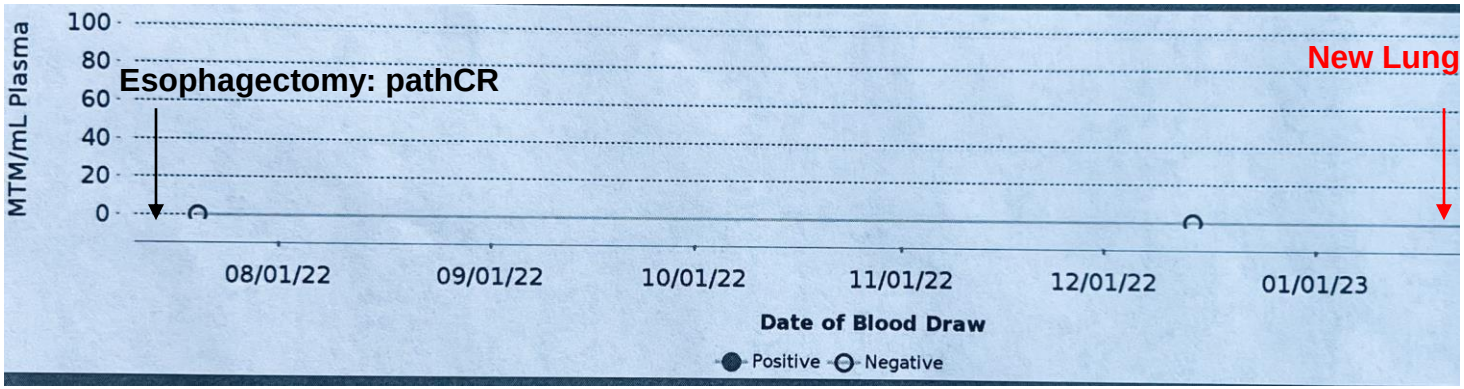
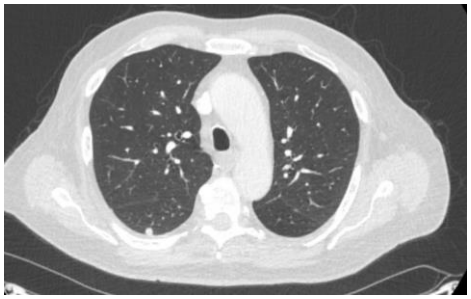
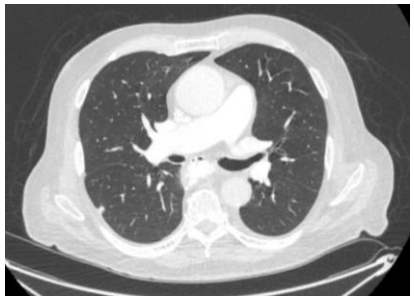
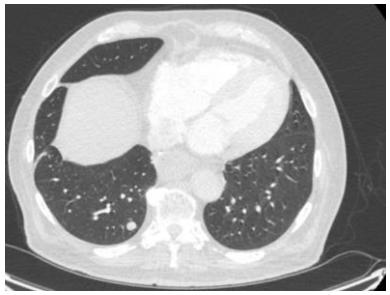
CtDNA in Real-World Scenarios: Case 2









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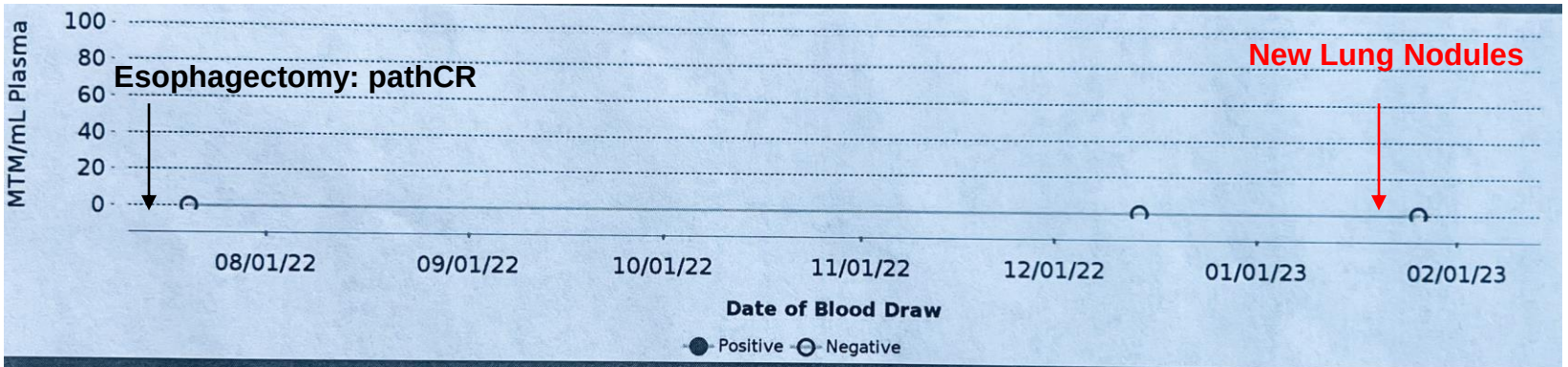
CtDNA in Real-World Scenarios: Case 2



Date	Reported MTM/mL
Jan 26, 2023	0.00
Dec 14, 2022	0.00
Jul 20, 2022	0.00

ctDNA remains negative ⟶ Likely RCC mets

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Conclusions, Ongoing Work, and Future Directions

- ctDNA+ post-operatively is highly predictive of recurrence in multiple cancer types, including NSCLC and esophageal cancer
  - May be useful to determine need for adjuvant therapy
- ctDNA clearance is associated with improved survival in multiple cancer types
  - Long-term follow up of ctDNA as part of standard surveillance protocols
- ctDNA can be utilized in tumor-informed (MRD) and tumor-agnostic (targeted mutations, resistance) approaches
- Liquid biopsies, including ctDNA, will be critically important in advancing treatment, surveillance, and screening paradigms for thoracic malignancies
  - Non-operative management of clinical complete response in ESCC
    - Moving towards EAC?
  - Screening or adjunct to LDCT in NSCLC
  - Novel screening platform for EAC in patients with GERD

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Acknowledgements

- Patients participating in clinical trials
- MGH Division of Thoracic Surgery
- Lecia Sequist, MD
- Sam Klempner, MD

- Questions?

  uma.sachdeva@mgh.harvard.edu

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Neoadjuvant radiation therapy: Drowned in the PACIFIC?

Jonathan Spicer, MD PhD

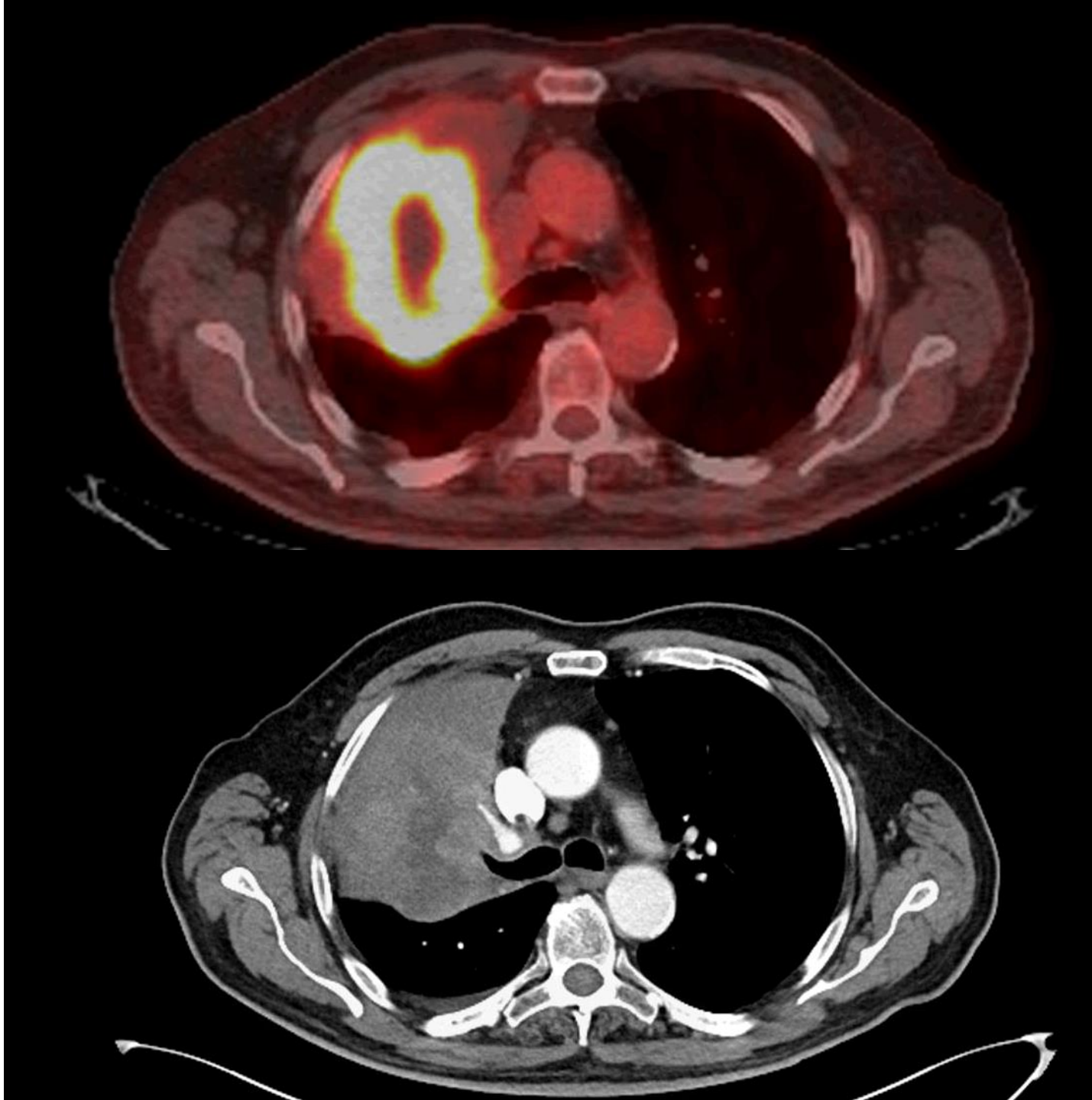
McGill University

Disclosures

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

Resectable?

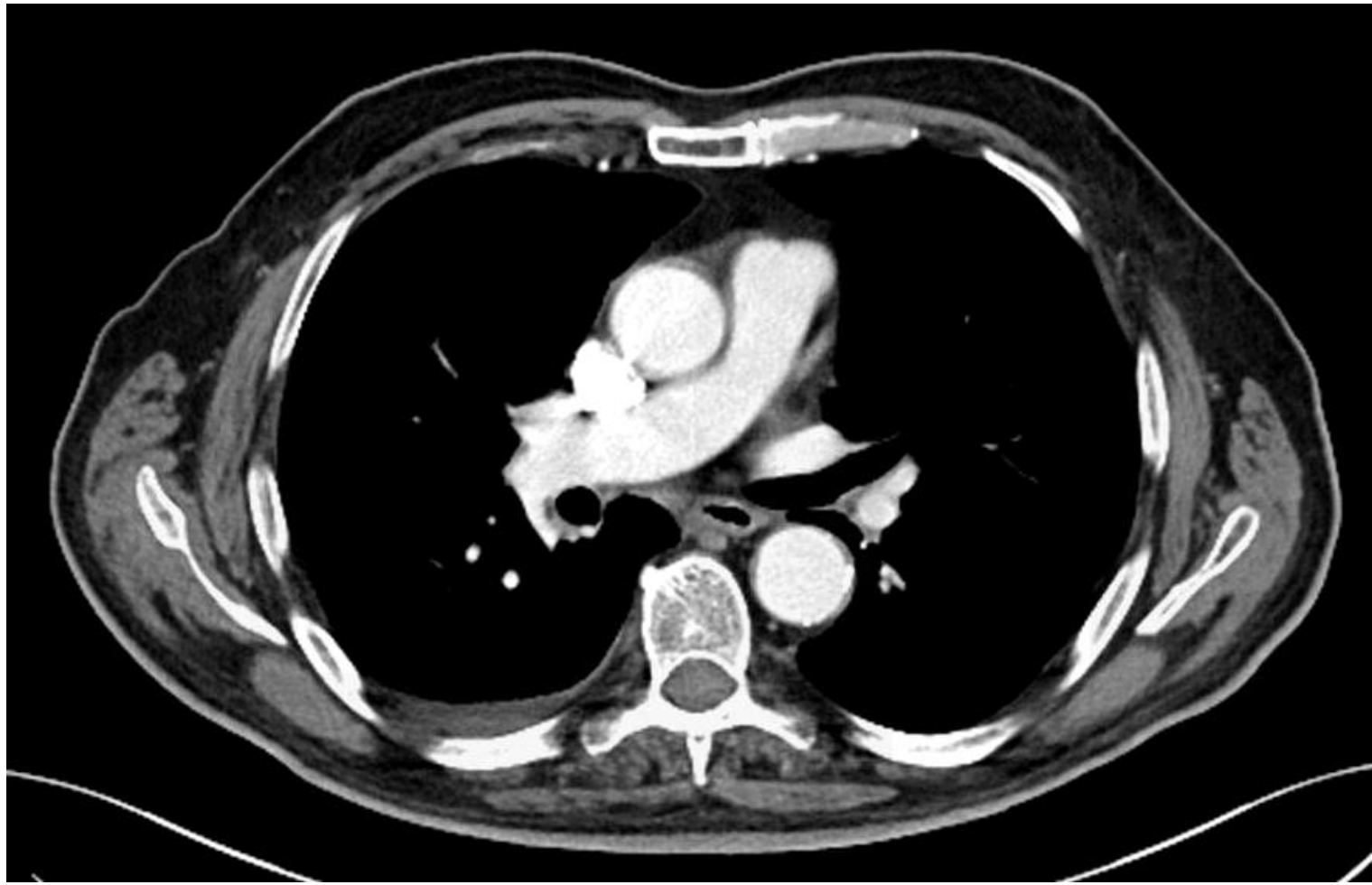
- 75M active smoker cT4N1, adenocarcinoma, no driver mutations on 52 gene NGS panel, PDL1 30%
- CAD, HTN, COPD
- FEV1 76%
- DLCO 63%
- ECOG 1



Maybe? Probably? Potentially!

Proposed operation:

Open thoracotomy, upper lobectomy with bronchial sleeve resection, possible pulmonary artery angioplasty



Resectability begins with operability

- Can my patient undergo an operation?
- What are my patient's goals of care? Do they want an operation?
- What is the required approach?
- What is the extent of surgery required to achieve an R0 resection?
- What is the risk profile of the proposed intervention given my patient's physiology?
- What is risk tolerance of the patient and the treating team?
- What are the competing alternatives?

Many options for this patient

- CRT + IO
- Surgery + adjuvant
- ~~CRT + surgery~~
- ChemoIO + surgery

Why I favour avoiding RT in this setting…

Impact of Neoadjuvant Chemoradiation on Adverse Events After Bronchial Sleeve Resection

Maria Rodriguez, MD, Aaron R. Dezube, MD, Carlos E. Bravo-Iniguez, MD, Sam Fox, BS, Luis E. De León, MD, Jeffrey Tarascio, BA, Sam Freyaldenhoven, MD, Steven J. Mentzer, MD, Scott James Swanson, MD, Raphael Bueno, MD, Matthew M. Rochefort, MD, M. Blair Marshall, MD, and Michael T. Jaklitsch, MD

Table 6. Logistic Regression Model for Airway Complications

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Age, y	0.99	0.95-1.02	.442
Body mass index, kg/m^2	0.97	0.90-1.05	.513
FEV_1, %	1.0	0.96-1.05	.888
Forced vital capacity, %	0.99	0.95-1.04	.727
DLCO, %	0.99	0.96-1.03	.68
Coronary artery disease, yes or no	0.76	0.12-4.63	.766
Neoadjuvant radiation[a] yes or no	11.52	3.52-37.71	<.001
Non-small cell lung cancer,[b] yes or no	2.77	0.72-10.70	.938

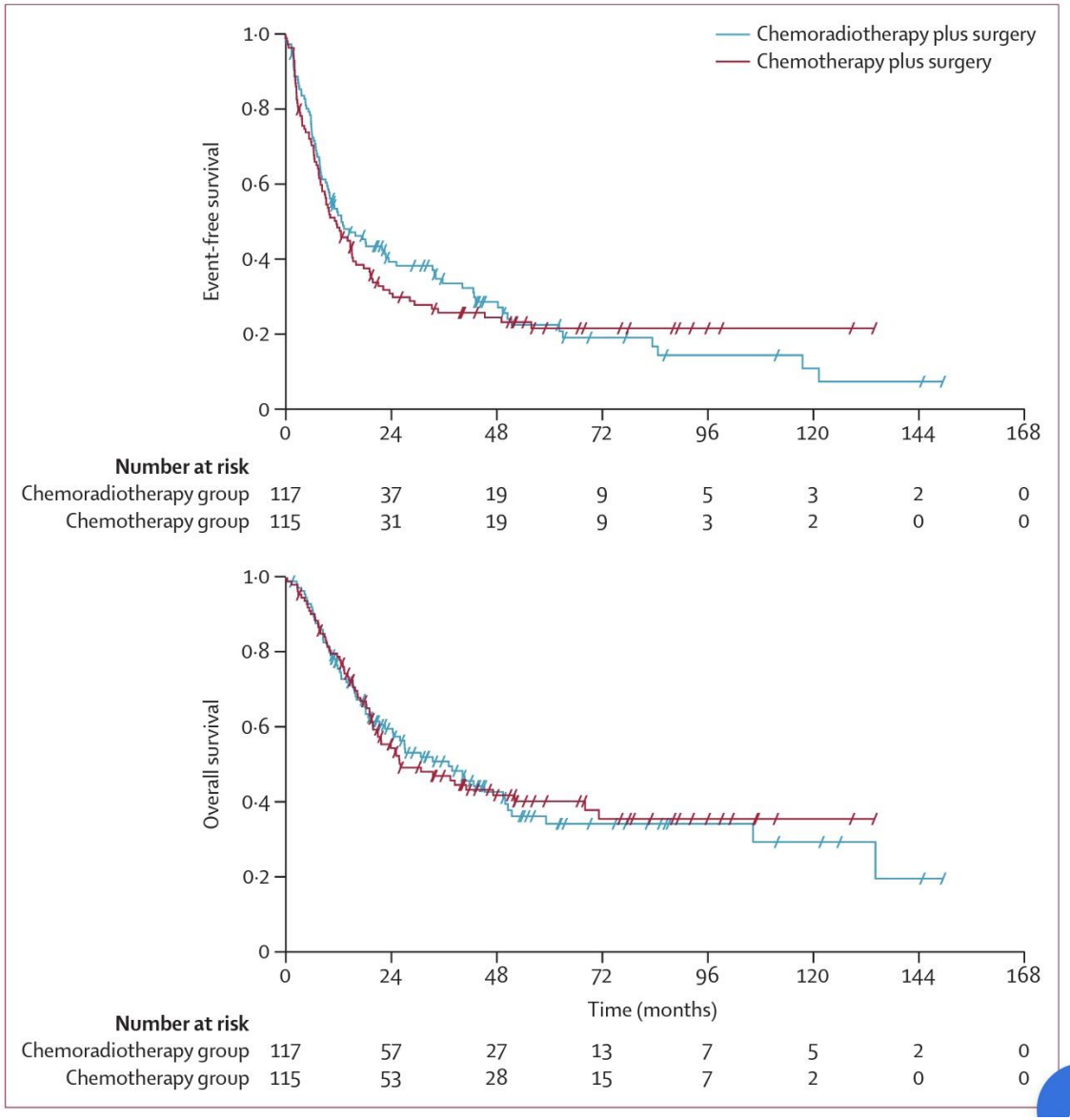
[a]Includes neoadjuvant chemotherapy alone; [b]Includes adenocarcinoma, squamous cell, mucoepidermoid, pleomorphic, and poorly differentiated carcinoma.

DLCO, diffusion capacity of lung for carbon monoxide (mL/min/mm Hg); FEV_1, forced expiratory volume in 1 second.

Why I favour avoiding RT in this setting… (Cont.)

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group



Why I favour avoiding RT in this setting… (Cont.)

Multimodality Therapy for N2 Non-Small Cell Lung Cancer: An Evolving Paradigm

Jonathan D. Spicer, MD, PhD,* Jitesh B. Shewale, BDS, PhD,* David B. Nelson, MD,*
Kyle G. Mitchell, MD, Matthew J. Bott, MD, Eric Vallières, MD, Candice L. Wilshire, MD,
Ara A. Vaporciyan, MD, Stephen G. Swisher, MD, David R. Jones, MD,
Gail E. Darling, MD, and Boris Sepesi, MD

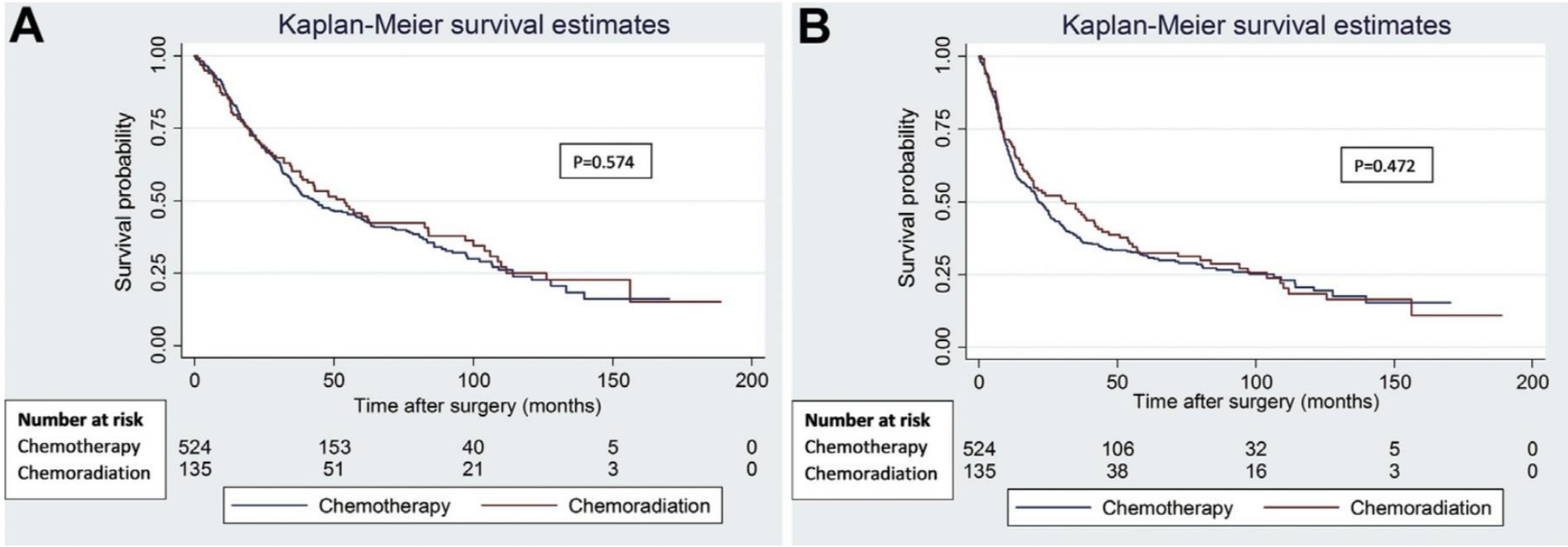
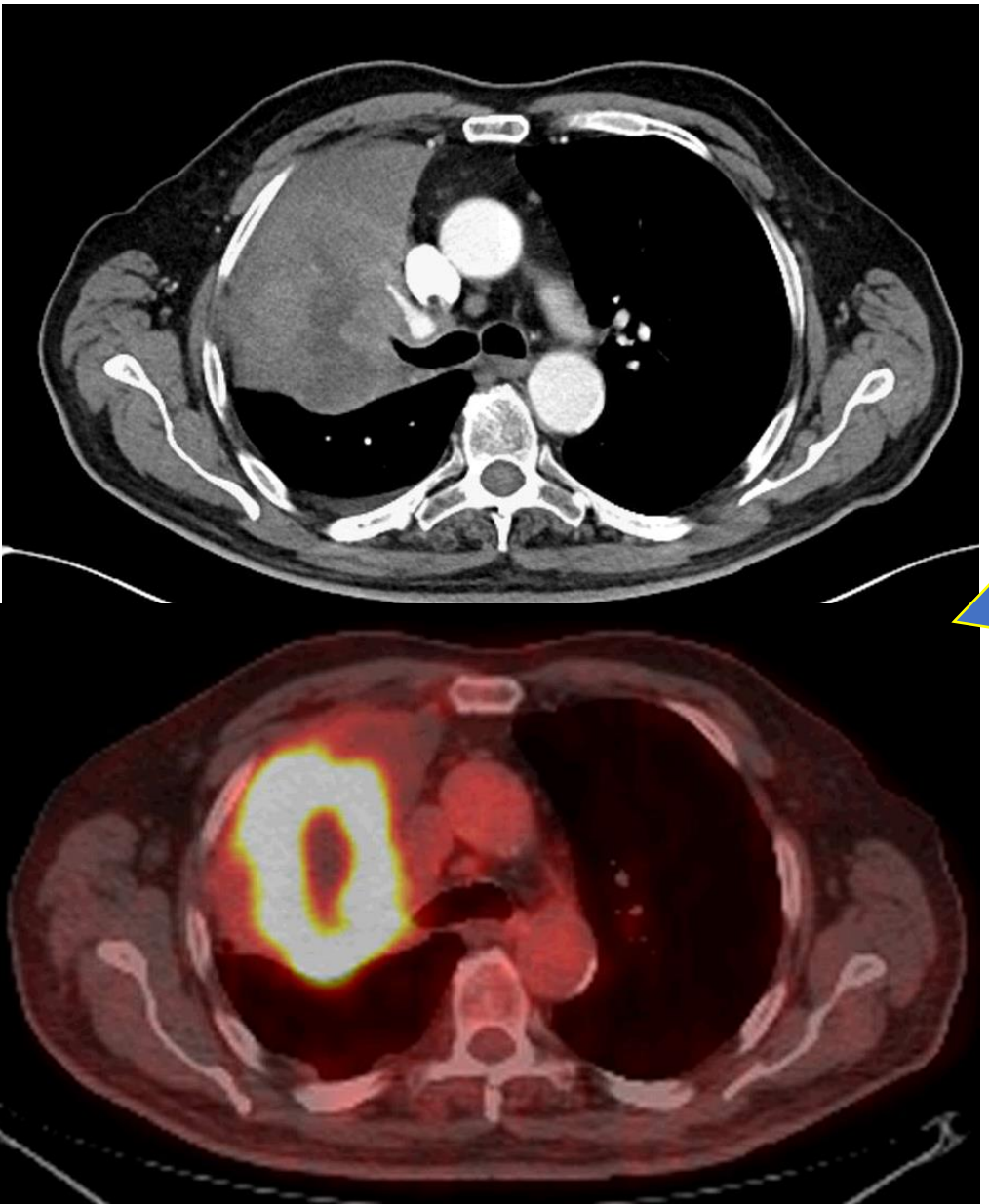
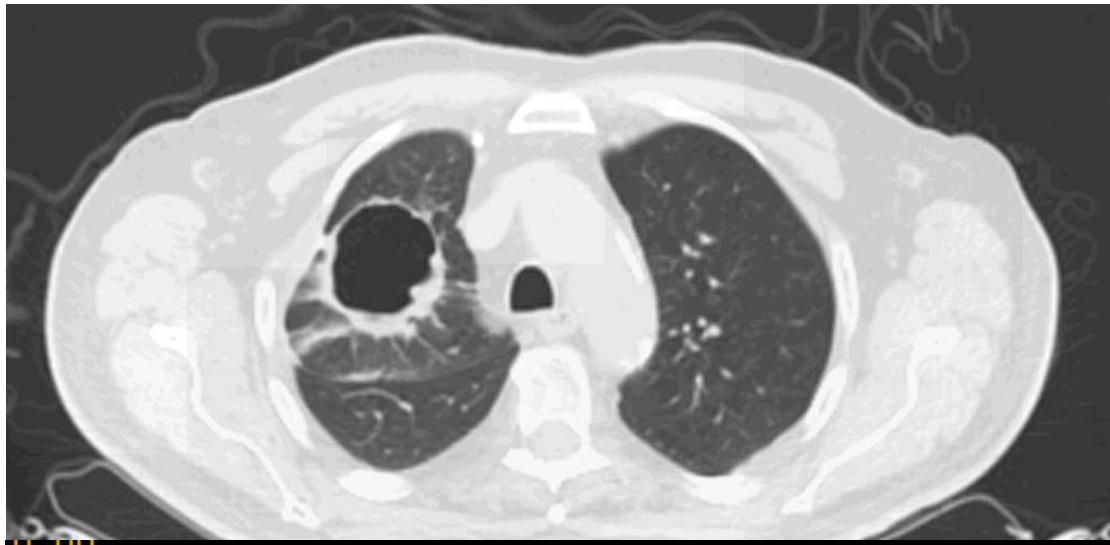


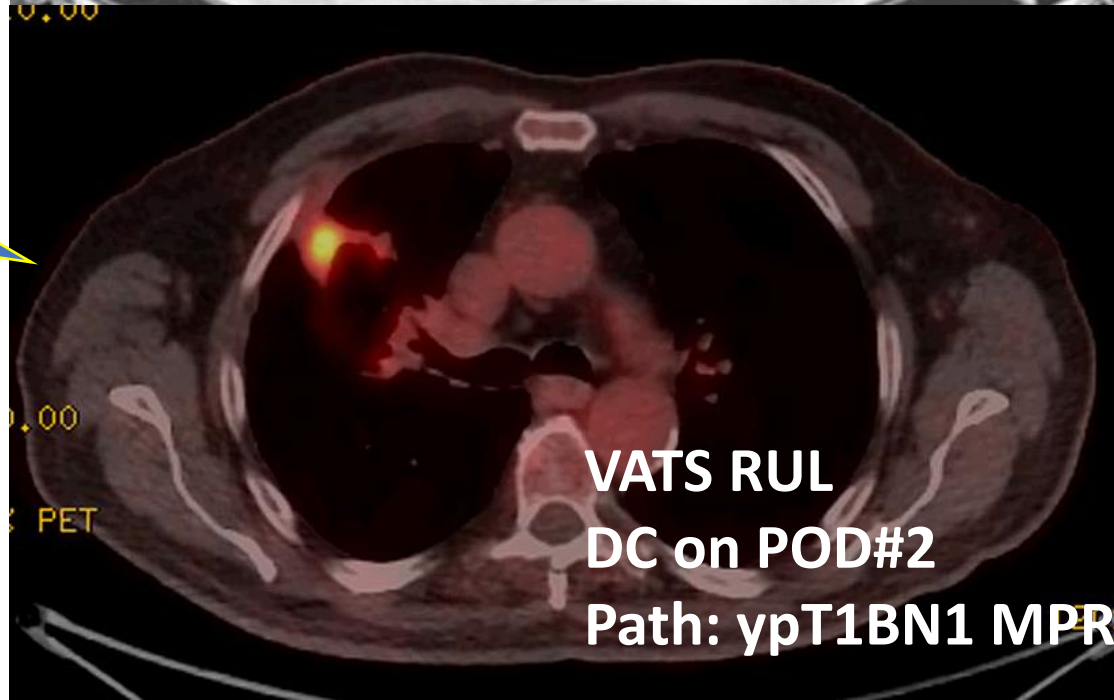
Fig 3. (A) Overall and (B) disease-free survival in patients who underwent lobectomy segregated by induction treatment.

Why I favour avoiding RT in this setting… (Cont.)



Chemo-IO x 3





VATS RUL
DC on POD#2
Path: ypT1BN1 MPR

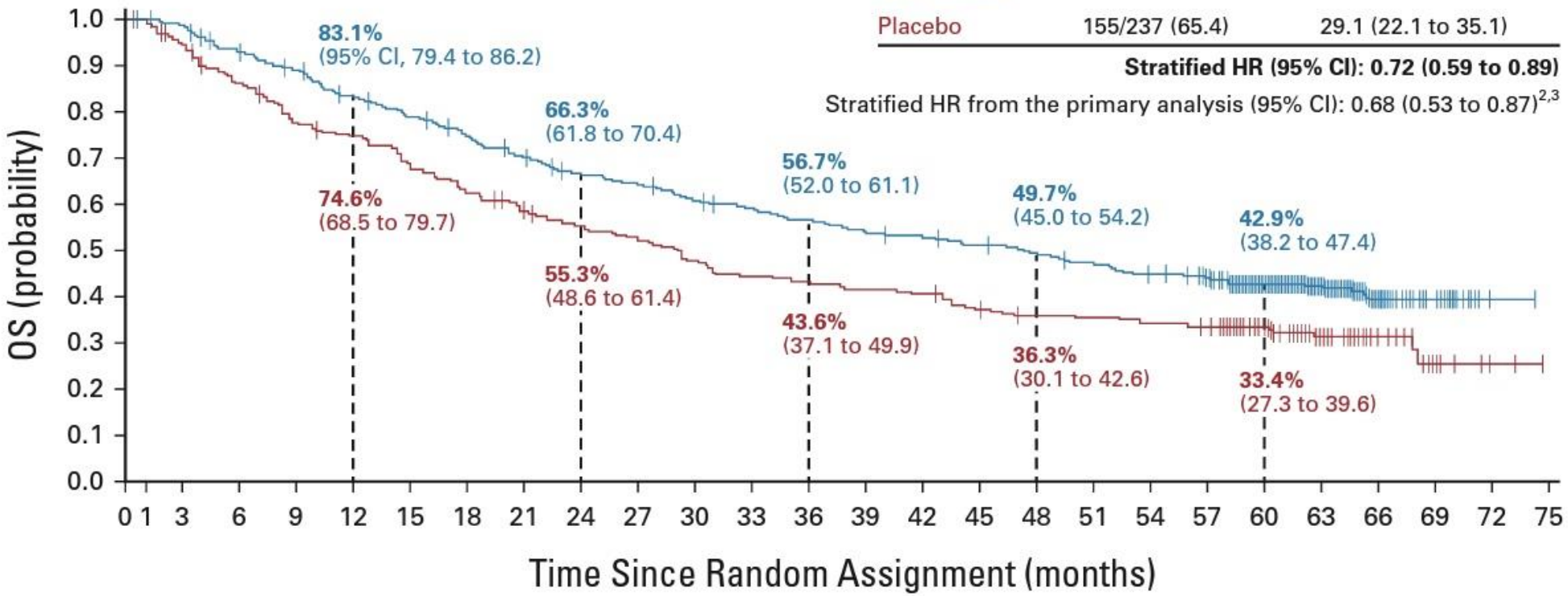
Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

David R. Spigel, MD[1]; Corinne Faivre-Finn, MD, PhD[2]; Jhanelle E. Gray, MD[3]; David Vicente, MD[4]; David Planchard, MD, PhD[5];

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

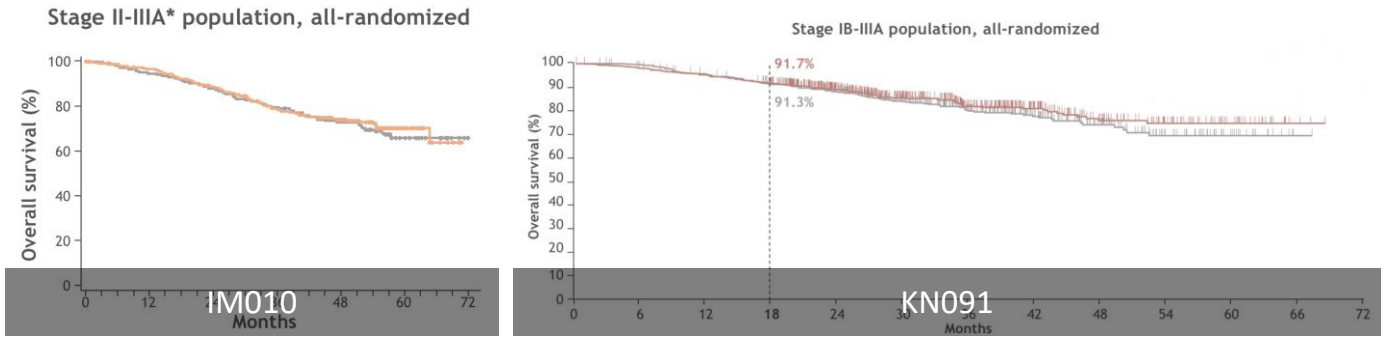
Reading the methods: painful but useful!

METHODS

Study Design

The design of PACIFIC is published elsewhere.[1,2] Patients with a WHO performance status (PS) of 0 or 1 and histologically or cytologically documented stage III (7th edition of the American Joint Committee on Cancer staging manual), unresectable NSCLC who had received concurrent CRT (≥ 2 cycles; total prescription radiation dose typically 60 to 66 Gy in 30 to 33 fractions)[18] without disease progression were randomly assigned 1-42 days after CRT. Patients with unresolved grade > 2 toxicities (Common Terminology Criteria for Adverse Events [AEs] v4.03) or grade ≥ 2 pneumonitis and/or radiation pneumonitis from prior CRT were excluded. Tumor tissue collection was not required nor was enrollment restricted by PD-L1 expression level or oncogenic driver gene aberration status. Additional details of the work-up required to confirm diagnosis are provided in Appendix 1 (online only; also see the Data Supplement [online only]).

PACFIC was an adjuvant study…



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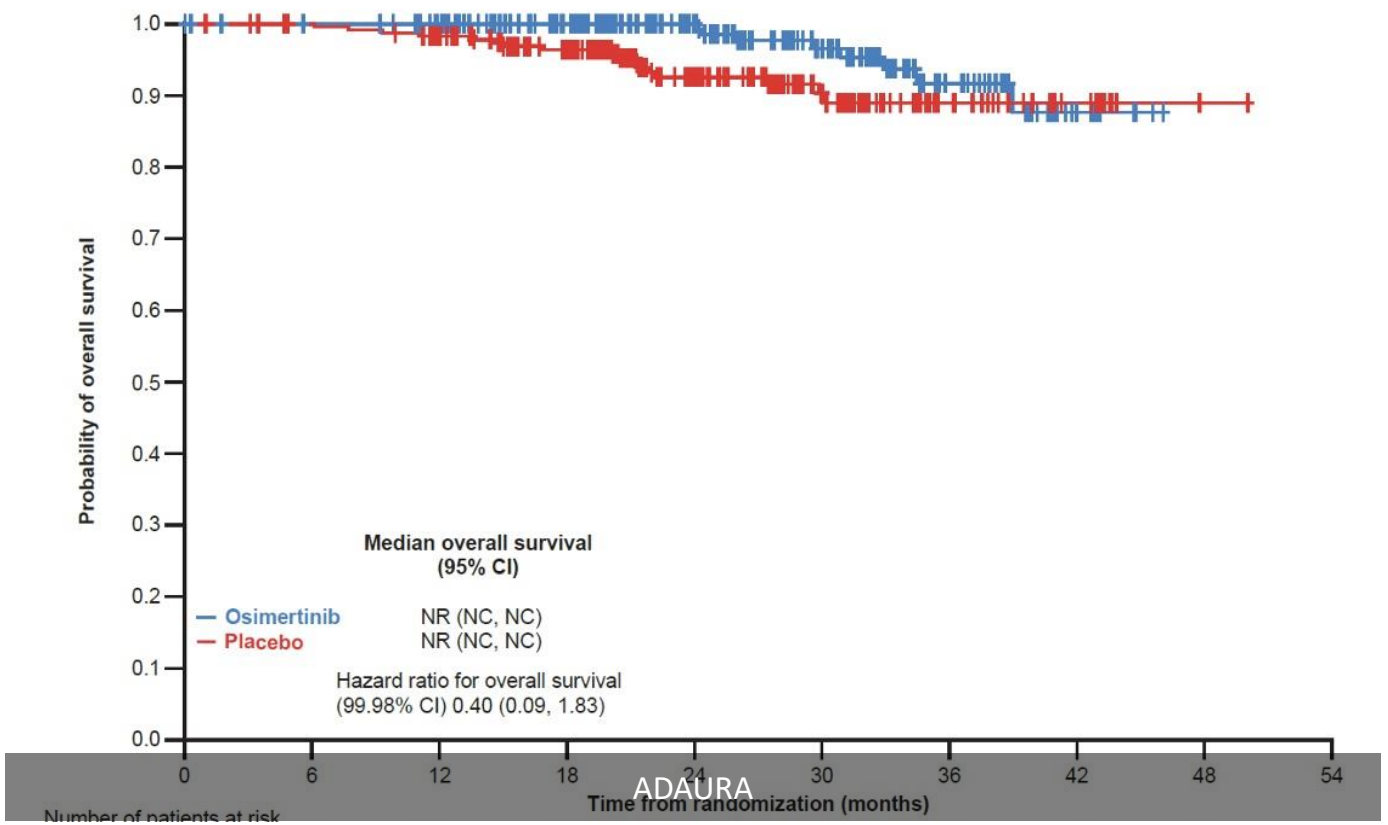
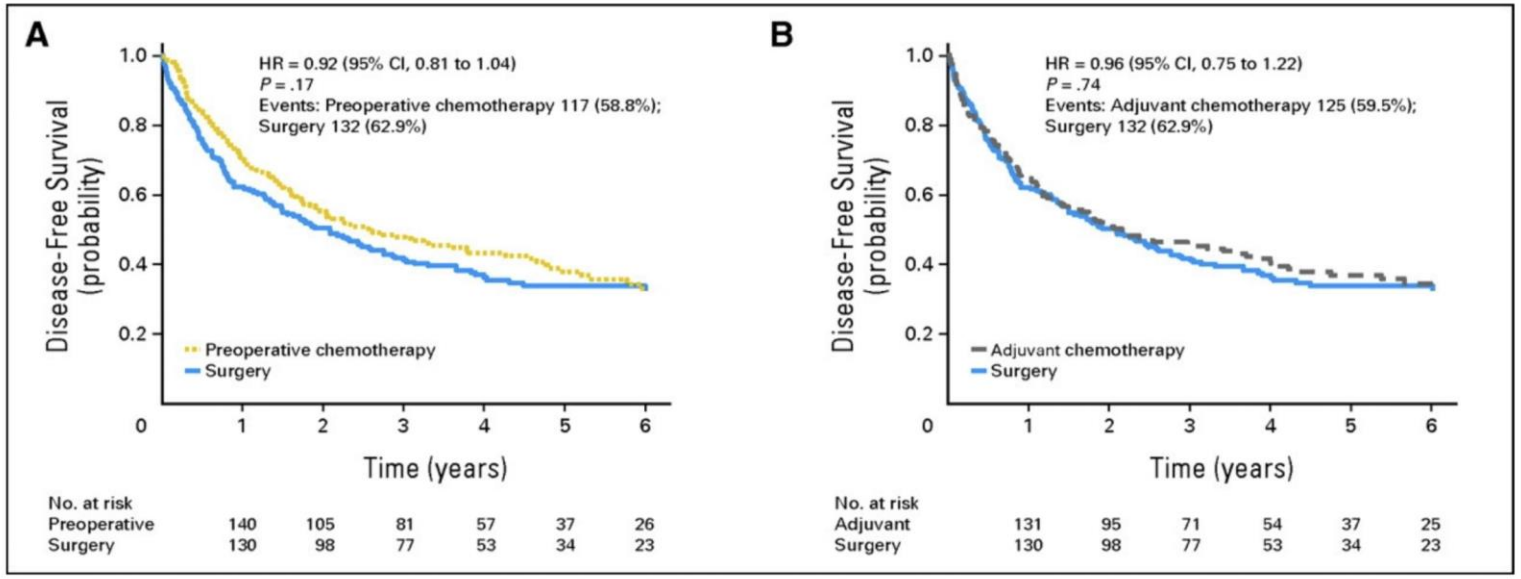


ADAURA

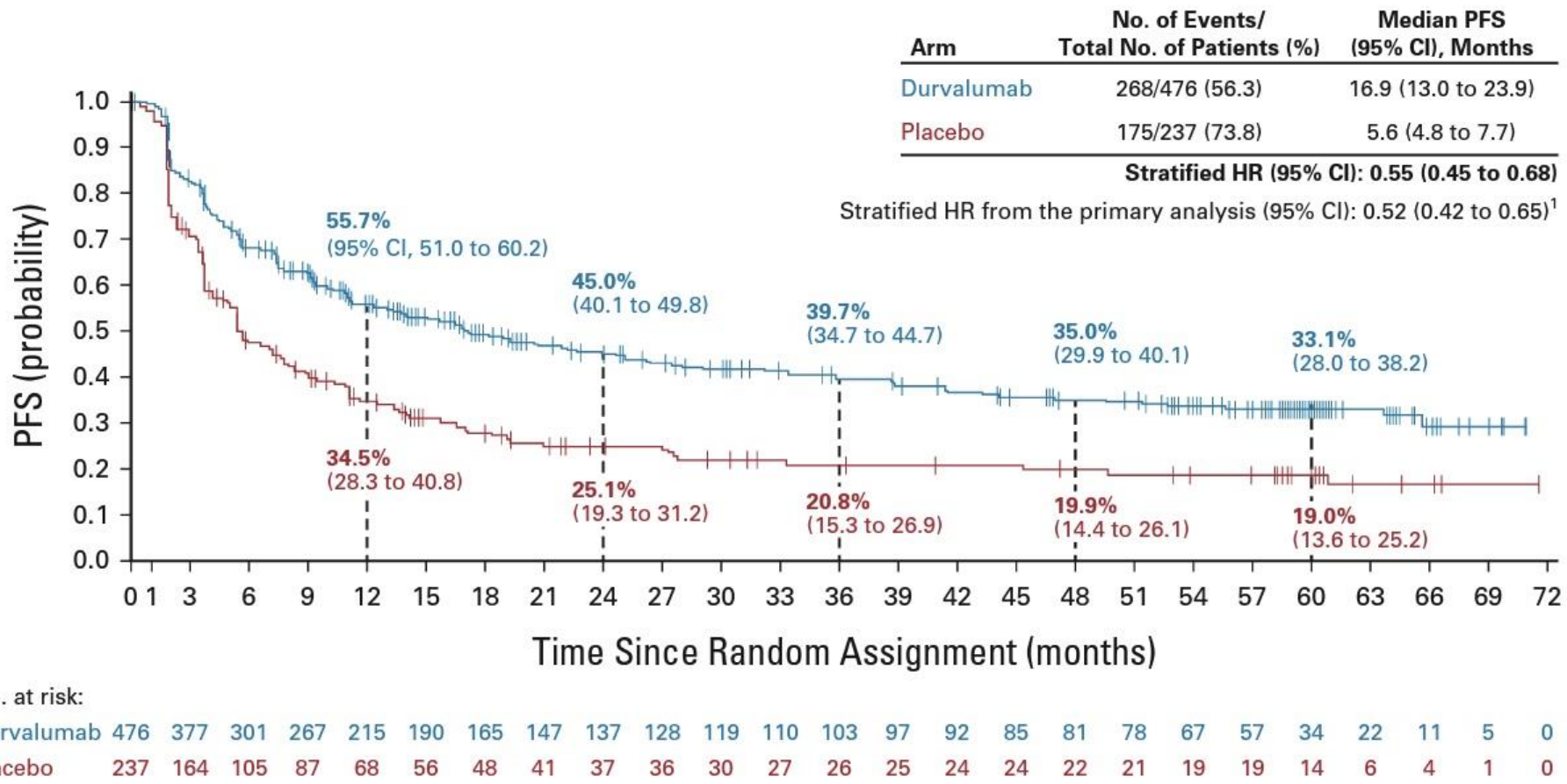
The shape of the curve is different when you start at the real time ZERO

Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non–Small-Cell Lung Cancer

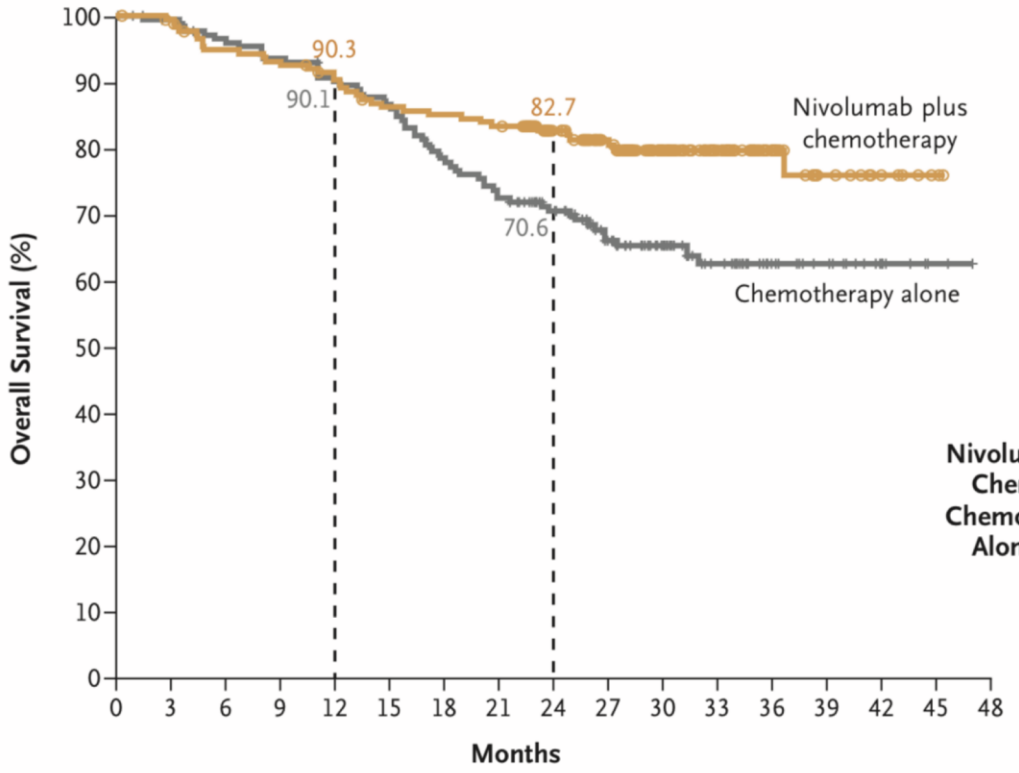
Enriqueta Felip, Rafael Rosell, José Antonio Maestre, José Manuel Rodríguez-Paniagua, Teresa Morán,



IO after CRT seems to be palliating incomplete locoregional control



Chemo-IO + surgery flattens the curve in the first two years after diagnosis



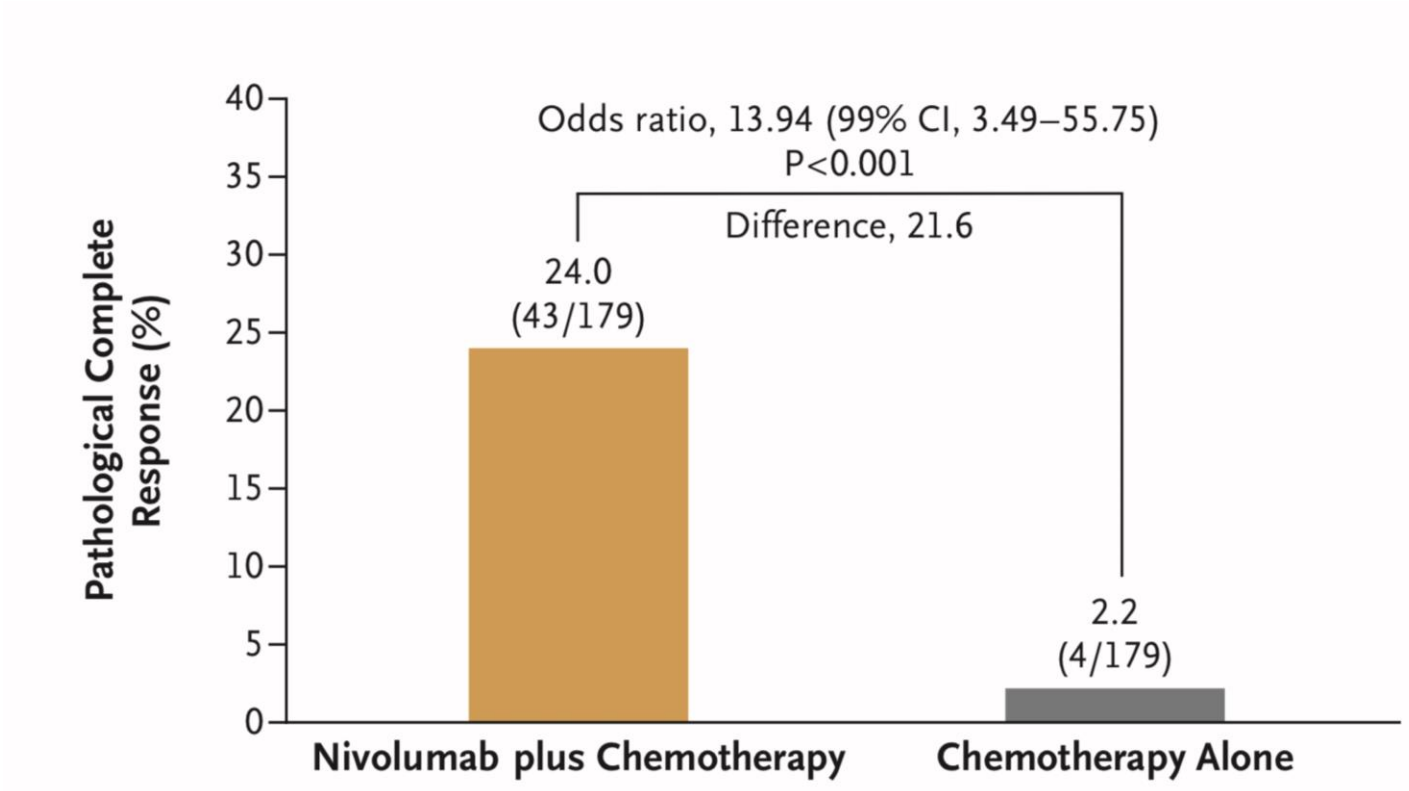
	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

No. at Risk

Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

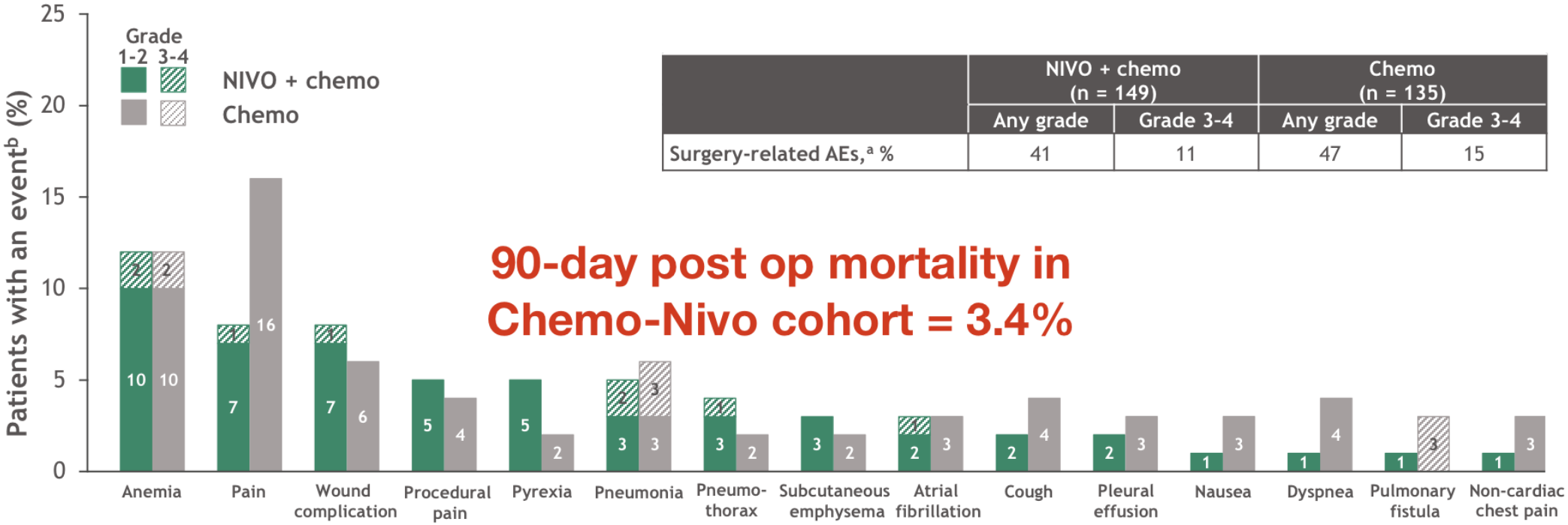
Medical oncologists can achieve RO!



Chemo-IO + surgery is a safe regimen

CheckMate 816: surgical outcomes with neoadjuvant NIVO + chemo in resectable NSCLC

90-Day surgery-related complications summary[a]



	NIVO + chemo (n = 149)		Chemo (n = 135)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Surgery-related AEs,[a] %	41	11	47	15

90-day post op mortality in Chemo-Nivo cohort = 3.4%

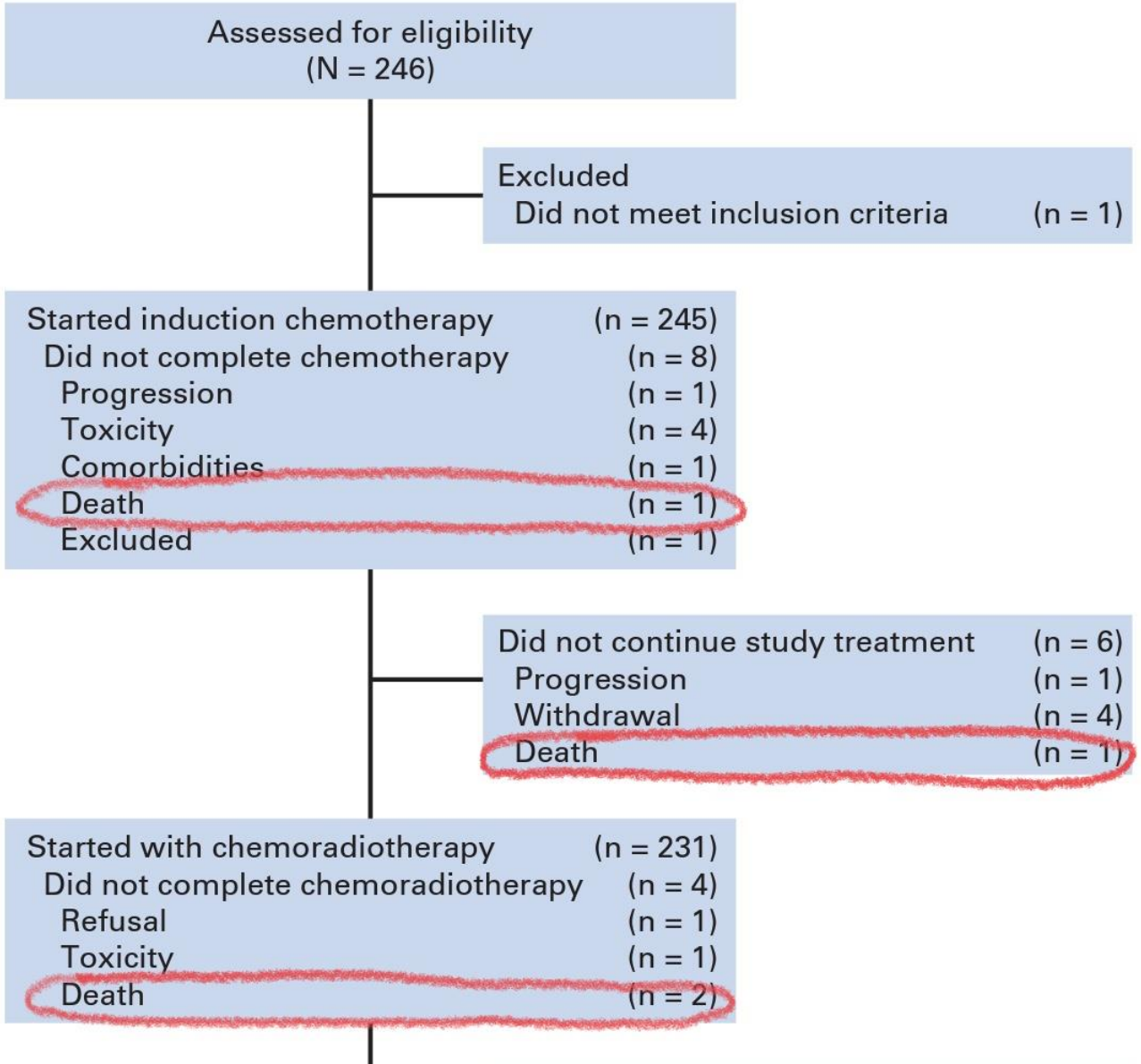
- Grade 5 surgery-related AEs (within 24 hours of AE onset) were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)[c]

[a]Includes events reported up to 90 days after definitive surgery; denominator based on patients with definitive surgery; CTCAE Version 4.0; MedDRA Version 23.0. Two intra-operative complications occurred in the NIVO + chemo arm (1 each of intraoperative hemorrhage and aortic rupture, not study treatment related); [b]Surgery-related AEs with an incidence of ≥ 3%; [c]Grade 5 AEs are defined as events that led to death within 24 hours of AE onset; only aortic rupture in NIVO + chemo arm was confirmed to occur within 24 hours of AE onset post-database lock.

Is CRT that much safer?

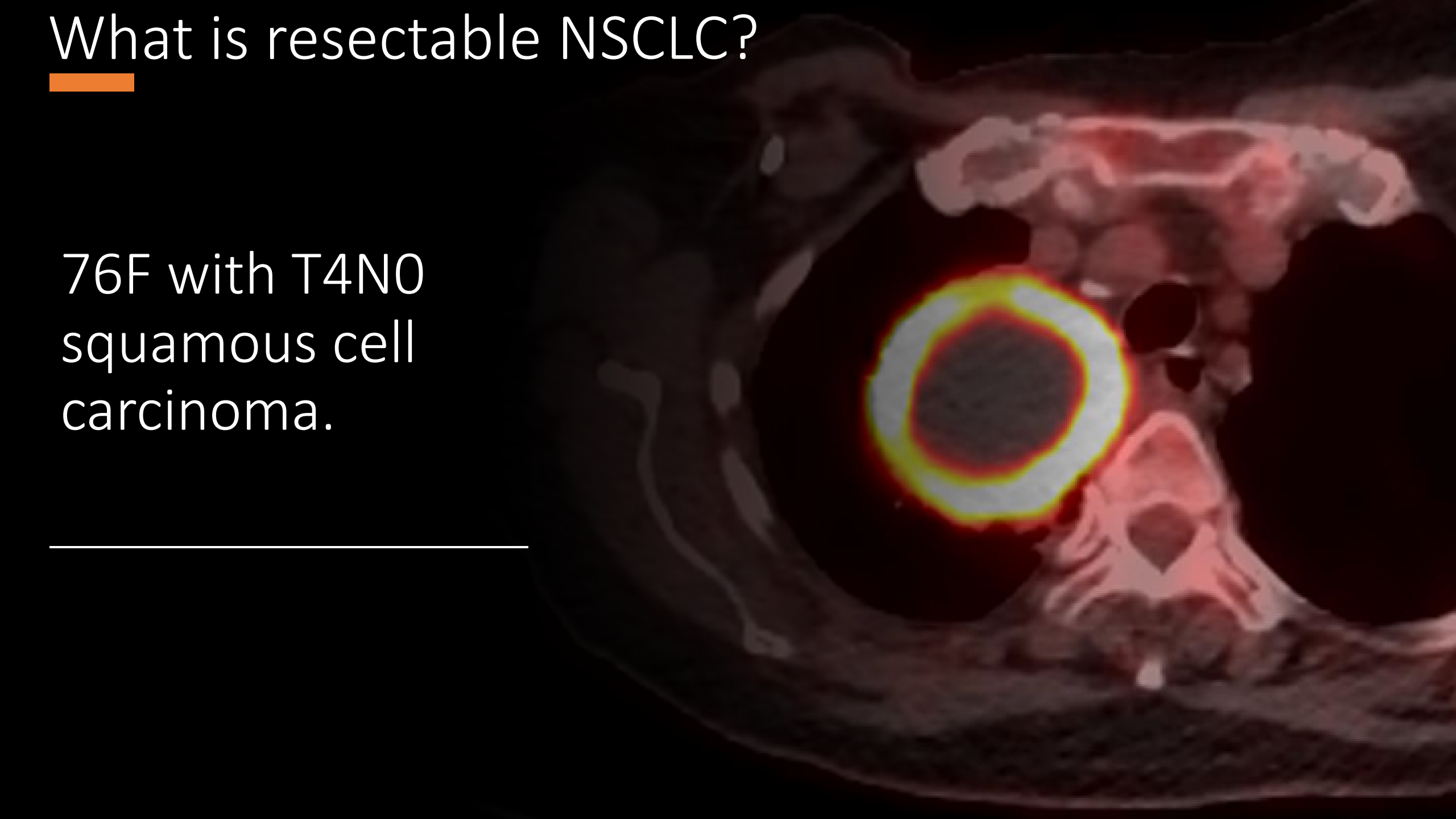
Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

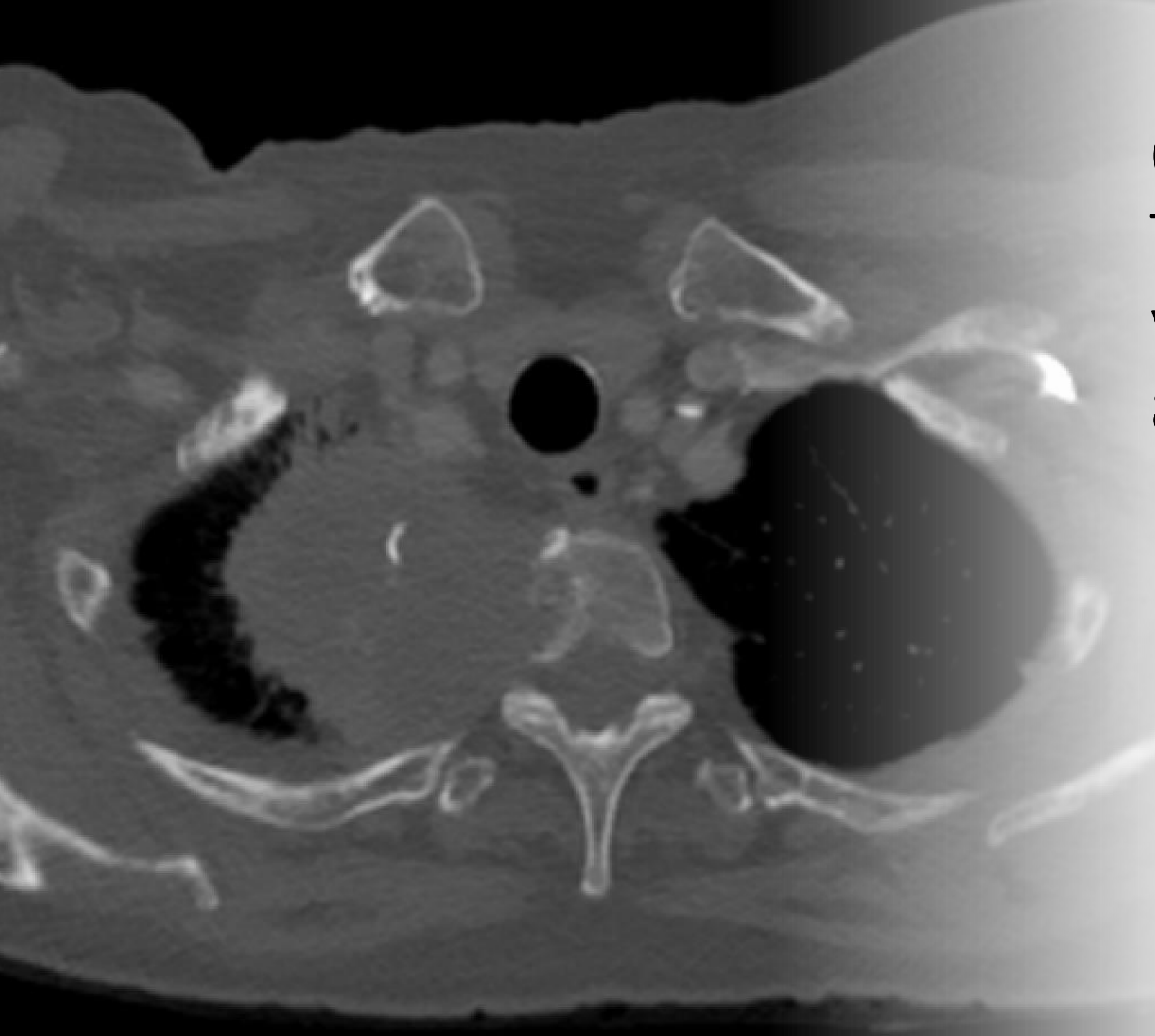
Wilfried Ernst Erich Eberhardt, Christoph Pöttgen, Thomas Christoph Gauler, Godehard Friedel, Stefanie Veit,



What is resectable NSCLC?

76F with T4N0 squamous cell carcinoma.

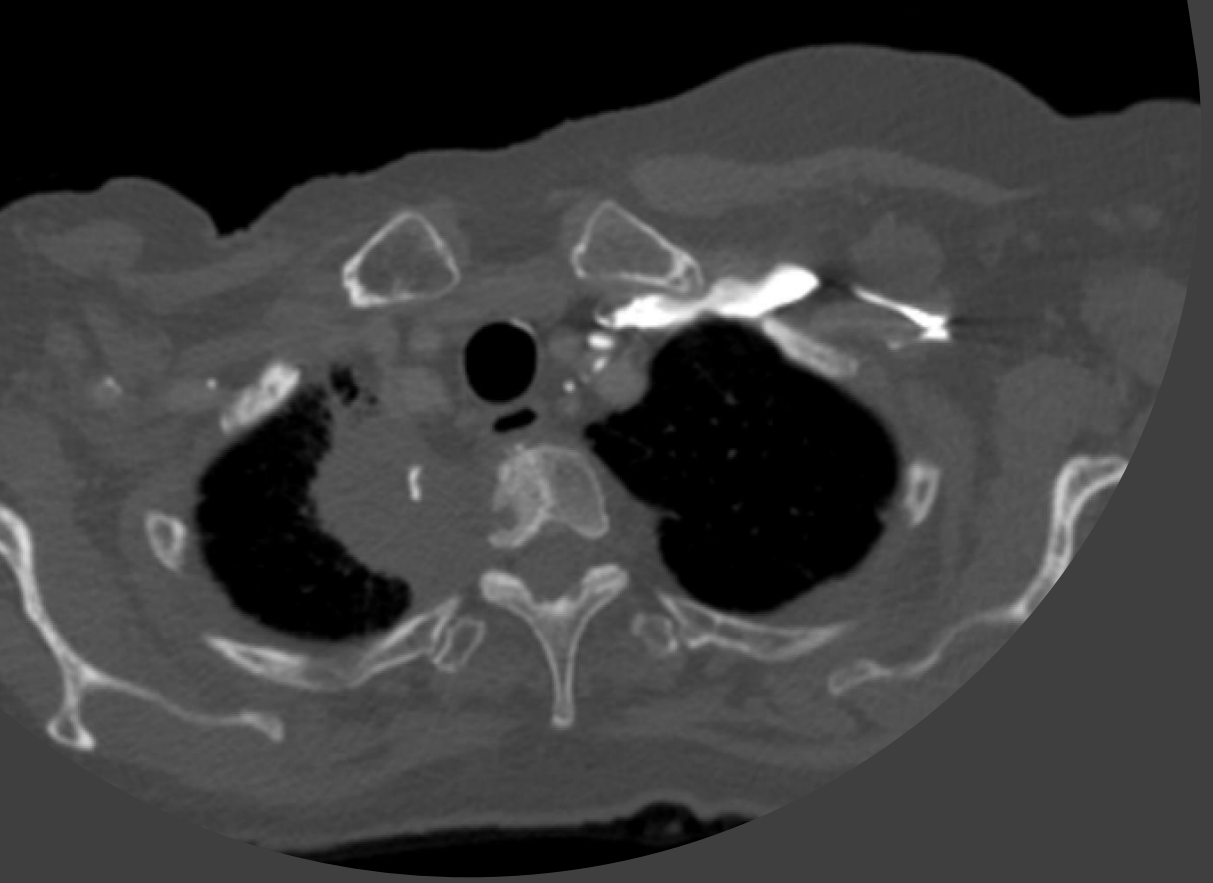


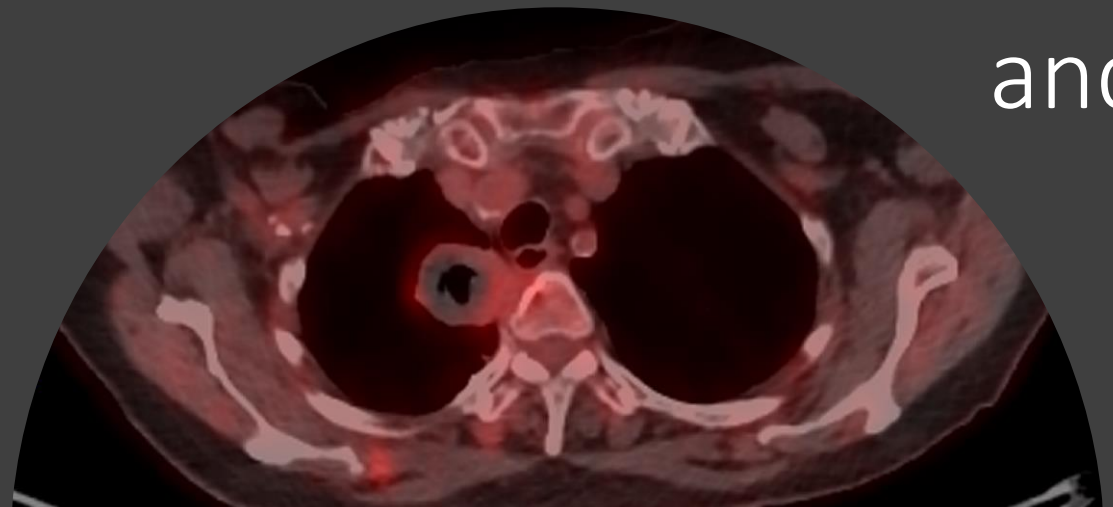


Clear invasion of T2 vertebral body with significant arm pain

Is this resectable disease?

1) Yes
2) No
3) Borderline





- Dramatic response
- Resolution of arm pain after 1st cycle
- Near complete metabolic response
- Recently underwent lobectomy with hemivertebrectomy and spinal stabilization

PCR!

What about NADIM2?

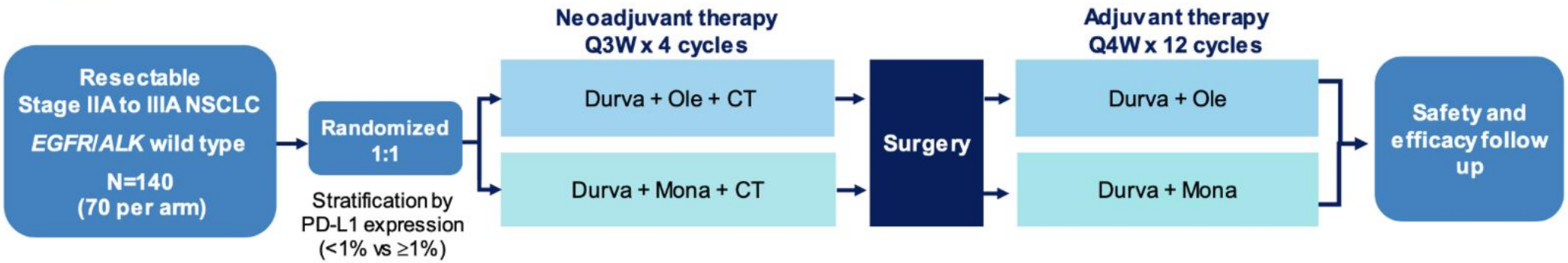
	CM816	NADIM2
Randomized	358 1:1	90 2:1
Endpoints	PCR, EFS	PCR, PFS, OS
Stages	IB-IIIA (AJCC7) or II-IIIB (AJCC8)	IIIA-IIIB (AJCC8)
Systemic therapy plan	Pure neoadjuvant	Periadjuvant (adj = 6 months)
Progress to surgery (CTxIO vs CTx)	83% vs 75%	93% vs 69%
R0 rate (CTxIO vs CTx)	83% vs 78%	93% vs 65%* (OR 6.6, p=0.007)
OS @ 2 years (CTxIO vs CTX)	82.7% vs 70.6%* (HR 0.57, 95% CI 0.38-0.87)	84.7% vs 63.4%*(HR 0.40, 95% CI 0.17-0.034, p=0.034)

What about phase 3 peri-adj IO?

Trial Identifier and Status	Study Title (Planned Accrual)	Stage (Edition)	Backbone	Intervention	Adjuvant Immunotherapy Treatment	Primary Endpoints
NCT02998528 Completed accrual Q4 2019	CheckMate -816 N = 360	IB-IIIA (7th)	3 cycles of cis or carbo + vino/pem/docel/pac	± Nivolumab (nivolumab + ipilimumab)	No	EFS pCR
NCT03425643 Completed accrual	KEYNOTE-671 N = 786	IIA-IIIB (8th)	4 cycles of cis + pem or gem	Pembrolizumab or placebo	13x3-wk cycles of pembrolizumab/ placebo	EFS OS
NCT03456063 Completed accrual	IMpower030 N = 450	II-IIIB (8th)	4 cycles of cis/carbo + nab-pac/pem/gem	Atezolizumab or placebo	16 x 3-wk cycles of atezolizumab or BSC	EFS
NCT03800134 Completed accrual	AEGEAN N = 800	IIA-IIIB (8th)	3-4 cycles of cis + gem or carbon + pac or cis + pem or carbo + perm	Durvalumab or placebo	Adjuvant durvalumab or placebo	pCR EFS
NCT04025879 Completed accrual	CA209-77T N = 452	II-IIIB (8th)	3-4 cycles of cis/carbo + pem/doce or pac	Nivolumab or placebo	Adjuvant nivolumab or placebo	EFS

NeoCOAST-2: Study design

NeoCOAST-2

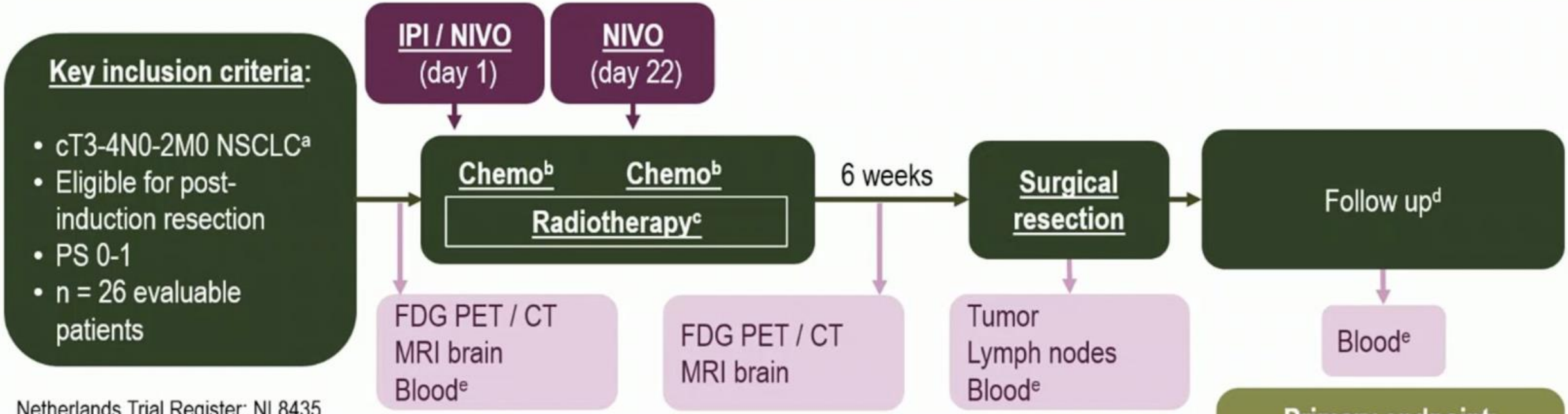


- NeoCOAST-2 (NCT05061550) is a phase 2, randomized study of neoadjuvant durvalumab combined with chemotherapy and either ole or mona, followed by surgery and adjuvant durva plus ole or mona, in patients with resectable, Stage IIA–IIIA NSCLC.[1]
  - Primary endpoints: pCR, safety and tolerability
  - Secondary endpoints: EFS, DFS, OS, and ORR per RECIST v1.1; MPR; feasibility of surgery; pharmacokinetics; immunogenicity; baseline tumor PD-L1 expression; changes in ctDNA
  - Recruitment initiated in January 2022.

ALK, anaplastic large-cell lymphoma kinase; ctDNA, circulating tumor DNA; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; MPR, major pathological response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q3W, once every 3 weeks; Q4W, once every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Cascone T, et al. AACR 2022 (poster CT124).

INCREASE DESIGN



Netherlands Trial Register: NL8435

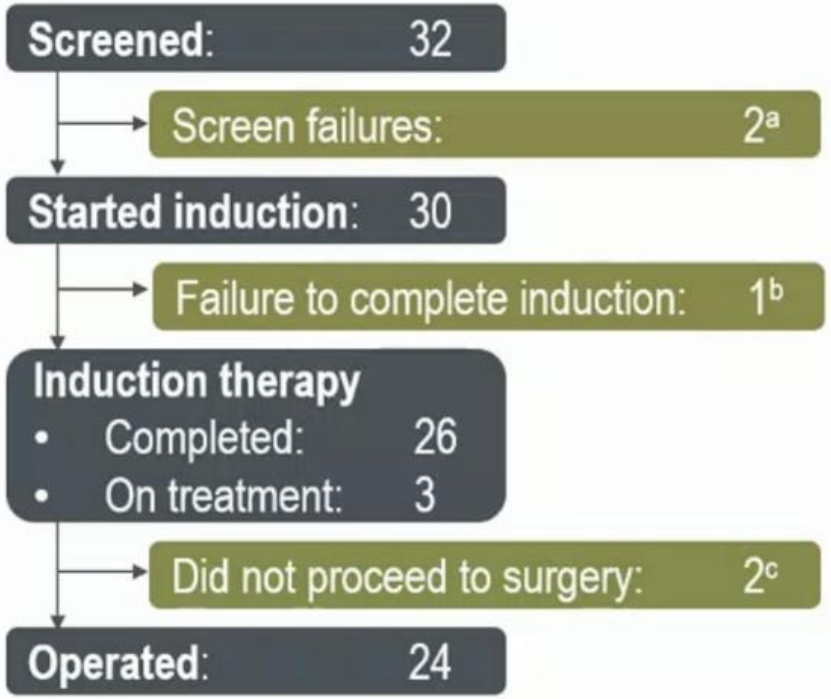
Single-arm, prospective phase II trial with an estimated sample size of 26, for which a pre-specified 60% pCR threshold in the study population was tested against the historical pCR rate of 30% (2-sided α = 5% and 1-ß = 90%). Enrolment commenced in Feb 2020

Primary endpoint:
- pCR / MPR
- safety

Secondary endpoint[f]:
- EFS[g]
- OS

IPI / NIVO = ipilimumab plus nivolumab; NIVO = nivolumab; pCR = pathological complete response; MPR = major pathological response defined as a residual viable tumor cells percentage of 10% or less; EFS = event-free survival; OS = overall survival. ([a]) based on invasion of thoracic wall, vertebra, mediastinum or diaphragm; ([b]) Platinum-doublet chemotherapy was given for two 3-weekly cycles; ([c]) Radiotherapy to a total dose of 50-60 Gy was given in once-daily doses of 2 Gy; ([d]) monitoring was performed using CT-scans of the thorax and blood analysis; ([e]) blood sampling for translational analysis; ([f]) Exploratory endpoints were immune profiling on tumor tissue (baseline and post-resection), tumor-draining lymph nodes, and on blood (PBMC's); ([g]) local and distant failure patterns

PATIENT DISPOSITION & PATIENT CHARACTERISTICS



([a]) 1 patient withdrew consent, 1 patient had an extensive N2 involvement; ([b]) 1 patient died due to COVID-19; ([c]) 1 patient had pleural disease progression, 1 patient achieved a metabolic complete response and the tumor board recommended omission of surgery that would have involved resection of 3 vertebrae, ([d]) from the last delivered radiotherapy fraction.

		n (%)
Age (median, range)		64 (43-73)
Gender	M	14 (44%)
	F	18 (56%)
Smoking	Never	1 (3%)
	Former	12 (38%)
	Current	19 (59%)
Auto-immune disease	Yes	4 (12.5%)
	No	28 (87.5%)
ECOG-PS	0	19 (59%)
	1	13 (41%)
T-descriptor	T3	11 (34%)
	T4	21 (66%)
N-descriptor	N0	19 (59%)
	N1	9 (28%)
	N2	4 (13%)

		n (%)
Pathological classification	Non-sq	22 (73%)
	Squam	8 (27%)
PD-L1 expression	≥50%	12 (63%)
	1-49%	3 (16%)
	<1%	4 (21%)
Chemotherapy cycles received	1	2 (7%)
	2	24 (89%)
	3	1 (4%)
Immunotherapy cycles received	1	2 (7%)
	2	25 (93%)
Radiotherapy delivered dose	50Gy	23 (88.5%)
	60Gy	3 (11.5%)
Time to operation[d] (median, range)		6 (5-9) weeks

PARIS 2022 ESMO congress

Presented by Dr. I. Bahce

AE'S IN 27 PATIENTS WHO UNDERWENT IO-THERAPY

	n (%)
Any TEAE	27 (100%)
• Grade 3-4	22 (81%)
• Serious adverse events	10 (37%)
• Grade 5	1[a] (4%)
Any TRAE	21 (78%)
• Grade 3-4	18 (67%)
• irAE Grade 3-4	5 (19%)
• Grade 5	0 (0%)
• Leading to IO discontinuation	2 (7%)
• Leading to failure to surgery	0 (0%)

Key irAE[c]	Any grade n (%)	Grade 1-2	Grade 3-4
Dermatitis	11 (41%)	9	2
Thyroid disorders	9 (33%)	9	0
Pneumonitis	3 (11%)	2	1
Hepatitis	2 (7%)	0	2
Pancreatitis	1 (4%)	0	1
Allergic reaction	1 (4%)	1	0

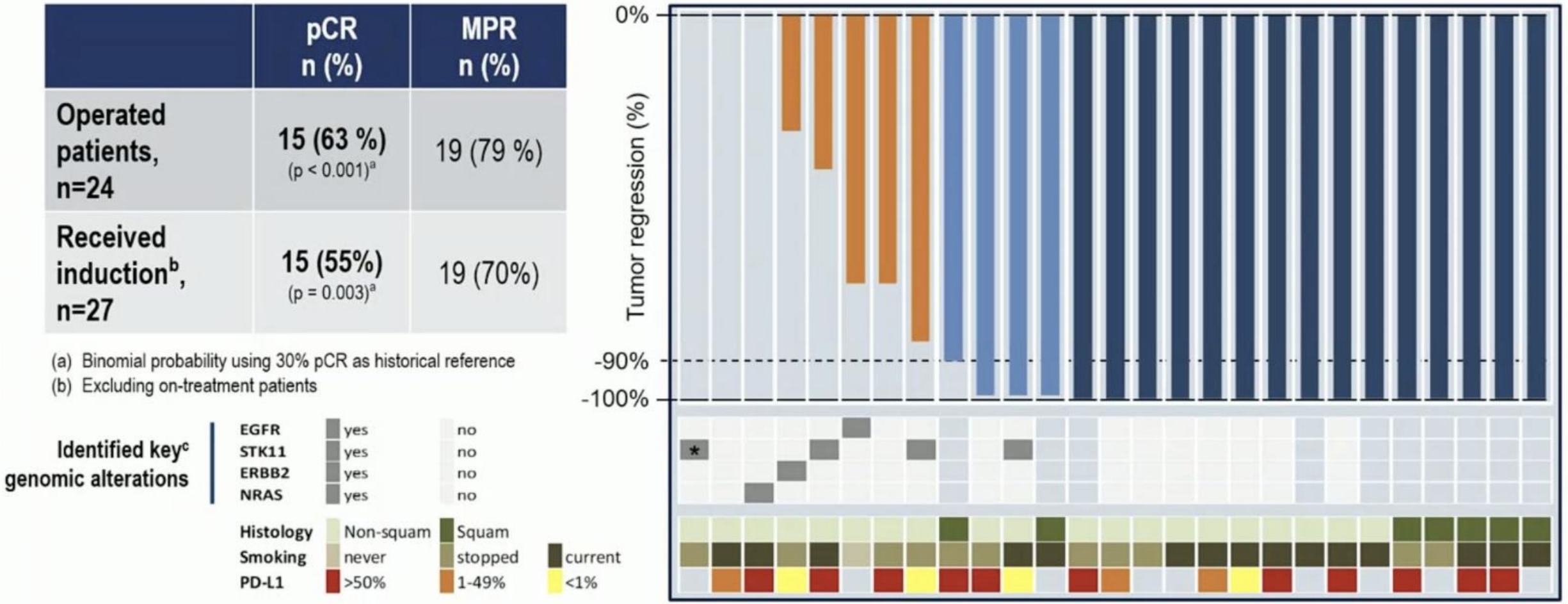
Median follow-up: 14 (range 4-26) months[b]
Grade 3-4 ITT: 56%

IO = immune oncology drugs; TEAE = treatment-emergent adverse events; TRAE = treatment-related adverse events; irAE= immune-related adverse events. ([a]) death from COVID-19 in 1 patient was not considered as treatment related; ([b]) from the first cycle of immunotherapy to data cut-off at 3-May-2022 (abstract deadline); (c) within the 90-days post-surgery timeframe.

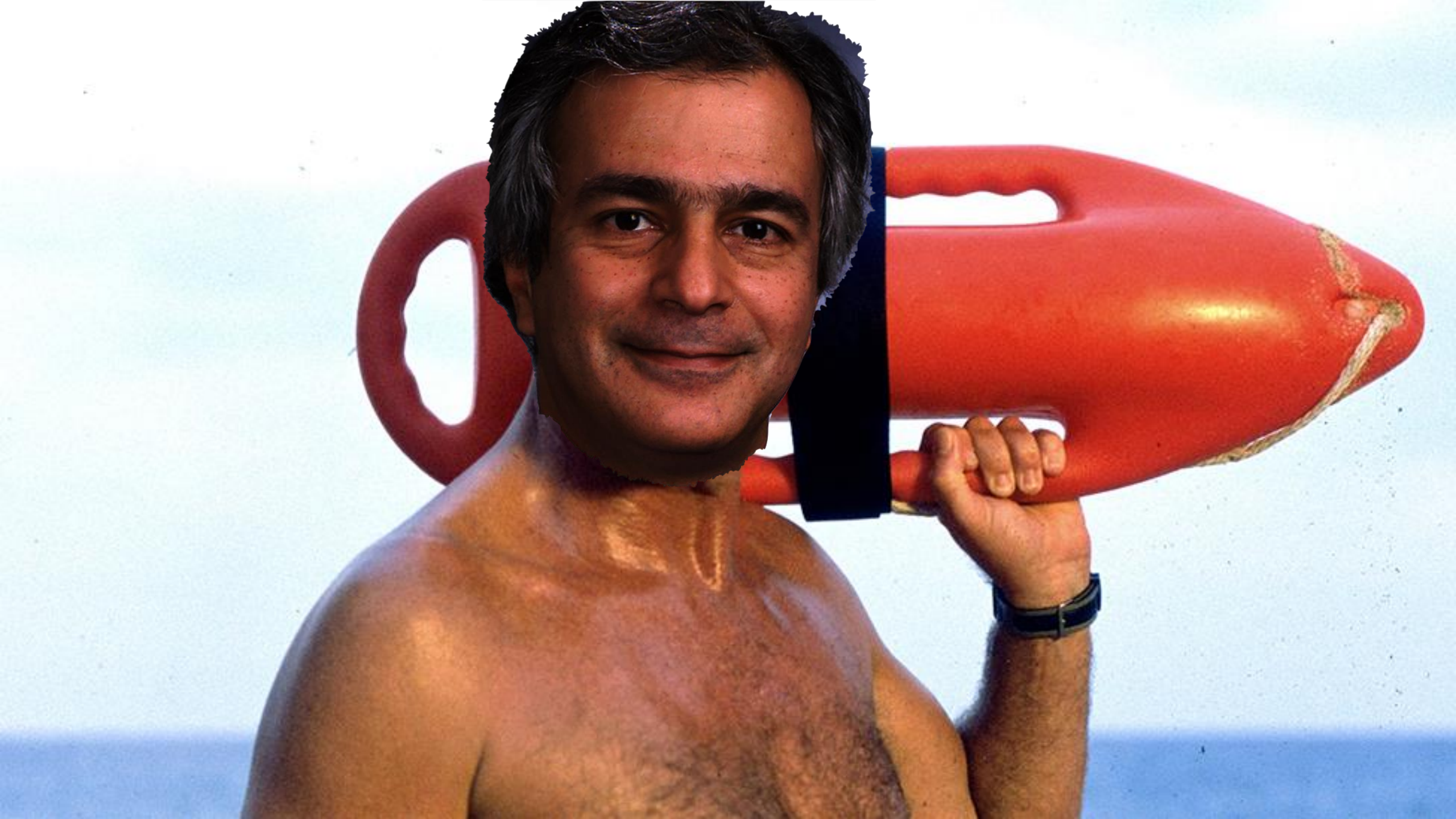
PRIMARY ENDPOINTS: pCR & MPR

	pCR n (%)	MPR n (%)
Operated patients, n=24	15 (63 %) (p < 0.001)[a]	19 (79 %)
Received induction[b], n=27	15 (55%) (p = 0.003)[a]	19 (70%)

(a) Binomial probability using 30% pCR as historical reference
(b) Excluding on-treatment patients

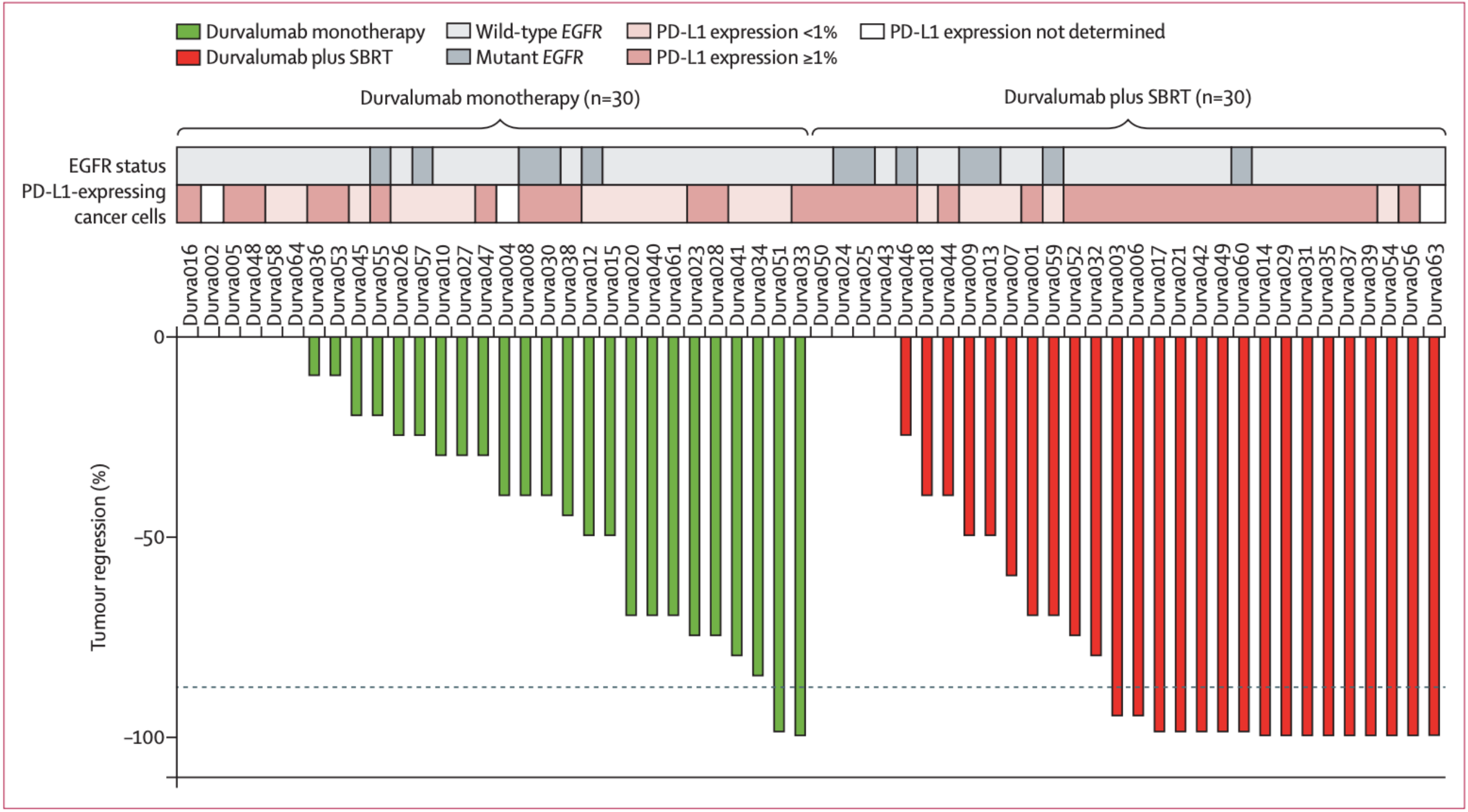


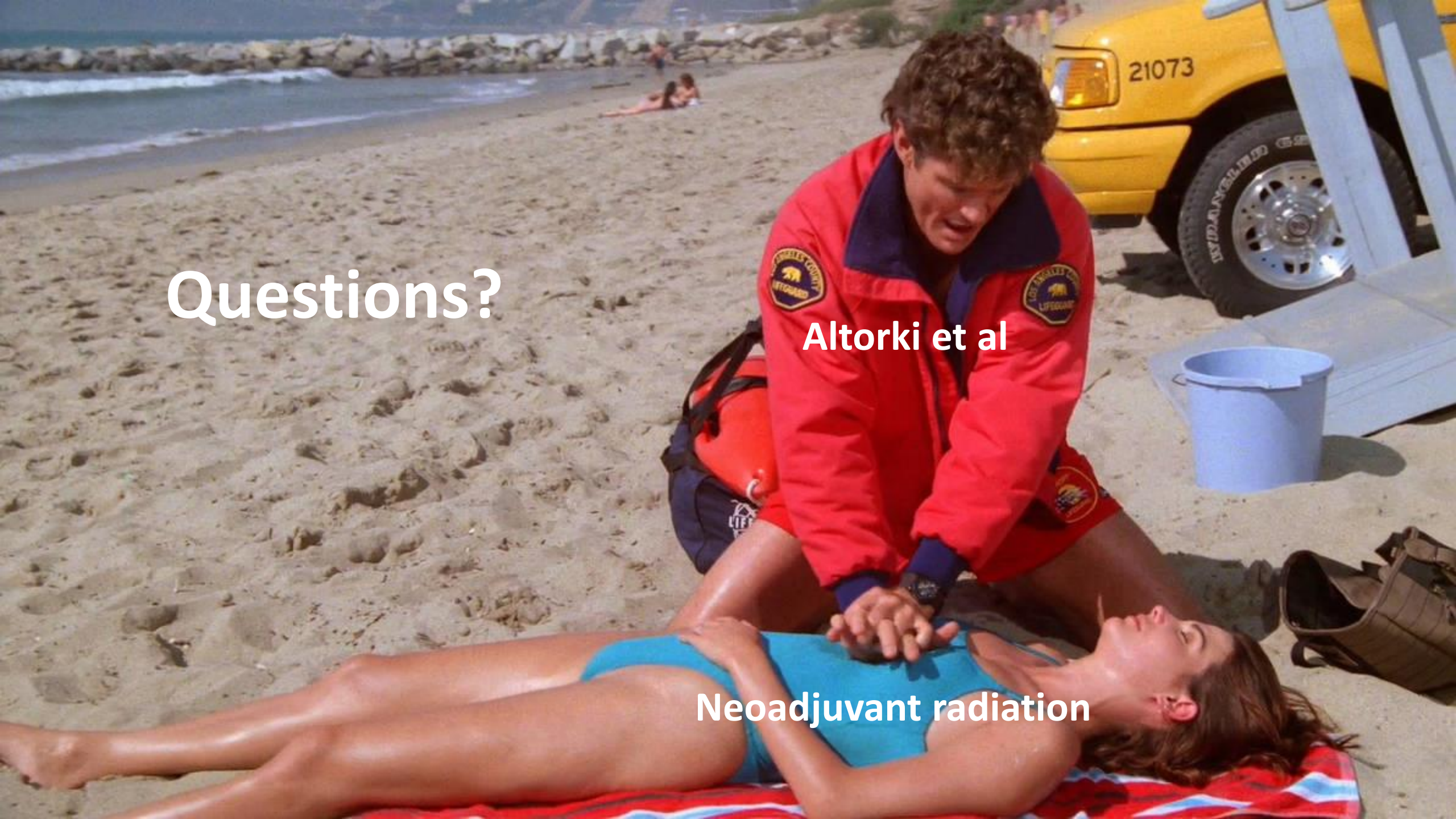
(*) this patient developed pleural metastases during induction therapy and did not receive surgery; ([c]) from a 60+ oncogenic next-generation sequencing panel, only selected genes possibly associated with IO resistance are shown.



Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

Nasser K Altorki, Timothy E McGraw, Alain C Borczuk, Ashish Saxena, Jeffrey L Port, Brendon M Stiles, Benjamin E Lee, Nicholas J Sanfilippo, Ronald J Scheff, Bradley B Pua, James F Gruden, Paul J Christos, Cathy Spinelli, Joyce Gakuria, Manik Uppal, Bhavneet Binder, Olivier Elemento, Karla V Ballman, Silvia C Formenti


Durvalumab monotherapy
Durvalumab plus SBRT
Wild-type EGFR
Mutant EGFR
PD-L1 expression <1%
PD-L1 expression ≥1%
PD-L1 expression not determined
Durvalumab monotherapy (n=30)
Durvalumab plus SBRT (n=30)
EGFR status
PD-L1-expressing cancer cells
Durva016 Durva002 Durva005 Durva048 Durva058 Durva064 Durva036 Durva053 Durva045 Durva055 Durva026 Durva057 Durva010 Durva027 Durva047 Durva004 Durva008 Durva030 Durva038 Durva012 Durva015 Durva020 Durva040 Durva061 Durva023 Durva028 Durva041 Durva034 Durva051 Durva033 Durva050 Durva024 Durva025 Durva043 Durva046 Durva018 Durva044 Durva009 Durva013 Durva007 Durva001 Durva059 Durva052 Durva032 Durva003 Durva006 Durva017 Durva021 Durva042 Durva049 Durva060 Durva014 Durva029 Durva031 Durva035 Durva037 Durva039 Durva054 Durva056 Durva063
0
−50
−100
Tumour regression (%)



Questions?

Altorki et al

Neoadjuvant radiation

Clinical Pearls I Will Never Publish

General Thoracic Surgery Club 2023

Rishi Reddy, Elliot Servais, Josh Sonett, Stephanie G. Worrell

Clinical Pearls I'll Never Publish

Rishi Reddy, MD, MBA
University of Michigan, Professor of Thoracic Surgery
Jose Jose Alvarez Endowed Professor of Thoracic Oncology Research
Chair-UM Comprehensive Robotic Surgery Program
Director-Center for Surgical Innovation, Dept of Surgery

Our post Transhiatal Esophagectomy Leak Rate was never 3%

- Our leak rate is an honest 20-25%
- My key factors for leak include:
  1) Gastric conduit blood flow
  2) Microbiome
  3) Increased coughing causing transition “pressure” at thoracic inlet

  4) NOT TENSION

Our residents perform ≥90% of robotic cases

- Simulation is key to understand how to use the robot, even if not familiar with operation
- Planned out graduated responsibility based on resident experience and robotic capability
- Dual console is key
- M2 medical students and Surgical scrubs are my bedside assists (no formal First Assist, no FA port)

I miss doing VATS lobectomies

- I enjoy robotic operations
- I am a much better laparoscopic surgeon (suturing, etc.) with the robot
- I am concerned about losing the ability to safely perform non-robotic laparoscopic and thoracoscopic cases

D 50W Pleurodesis

Robert J McKenna Jr. MD
St John's Cancer Institute
Stanford University

D 50 W
Impact of Prolonged Air Leak

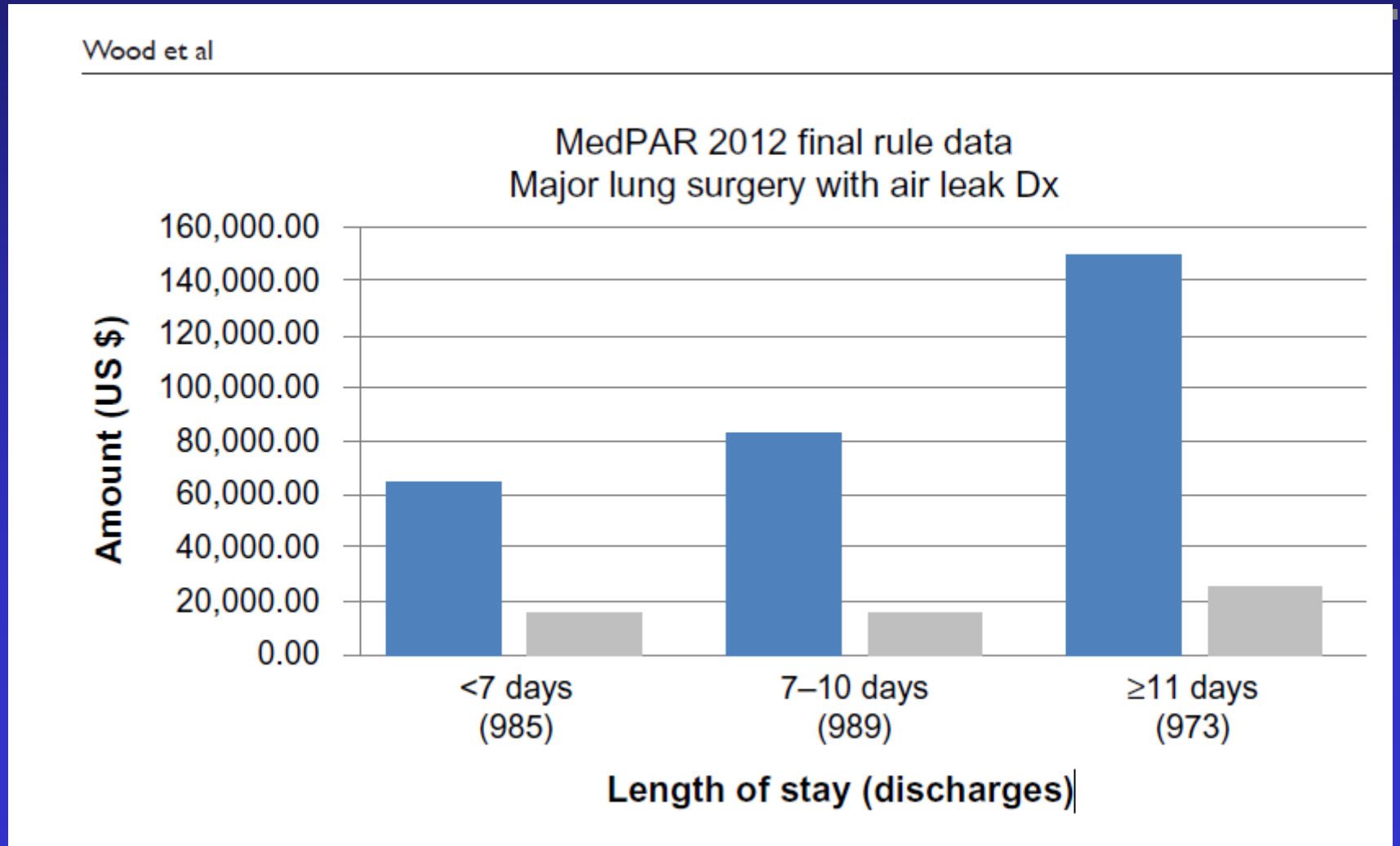
Add. Costs for PAL 13,000 pounds

Length of Stay

No PAL 5 days

PAL 10 days

D 50 W
Impact of Prolonged Air Leak



D 50W Pleurodesis Protocol

- Pleurodesis on POD 1-3
- Lidocaine 1%, 50-200 ml D 50W,
- Clamp CT 2 hrs
- Change position q 15 minutes
- Up to 3 attempts

D 50W Pleurodesis Complications

- **Pain (Lidocaine)**
- **How to avoid Hyperglycemia:**
  - **NPO 3 hr pre and post**
  - **Not for Diabetics**

D 50W Pleurodesis Results

In 39 of 46 (80%), pleurodesis stops the air leak

Varela Eur J Cardiothorac Surg

D 50W Pleurodesis Billing Code

32560 Bedside chemical pleurodesis ($347. 21, (RVU= 1.54)

32650 VATS chemical pleurodesis ($735.96. RVU= 10.83). That gets billed as return to OR that counts against hurts STS database rating

Beth Israel Lahey Health
Lahey Hospital & Medical Center

Tufts University School of Medicine

Clinical Pearls I'll Never Publish

Elliot Servais, MD, FACS

Section Chief, Thoracic Surgery

Lahey Hospital & Medical Center

Associate Professor of Surgery

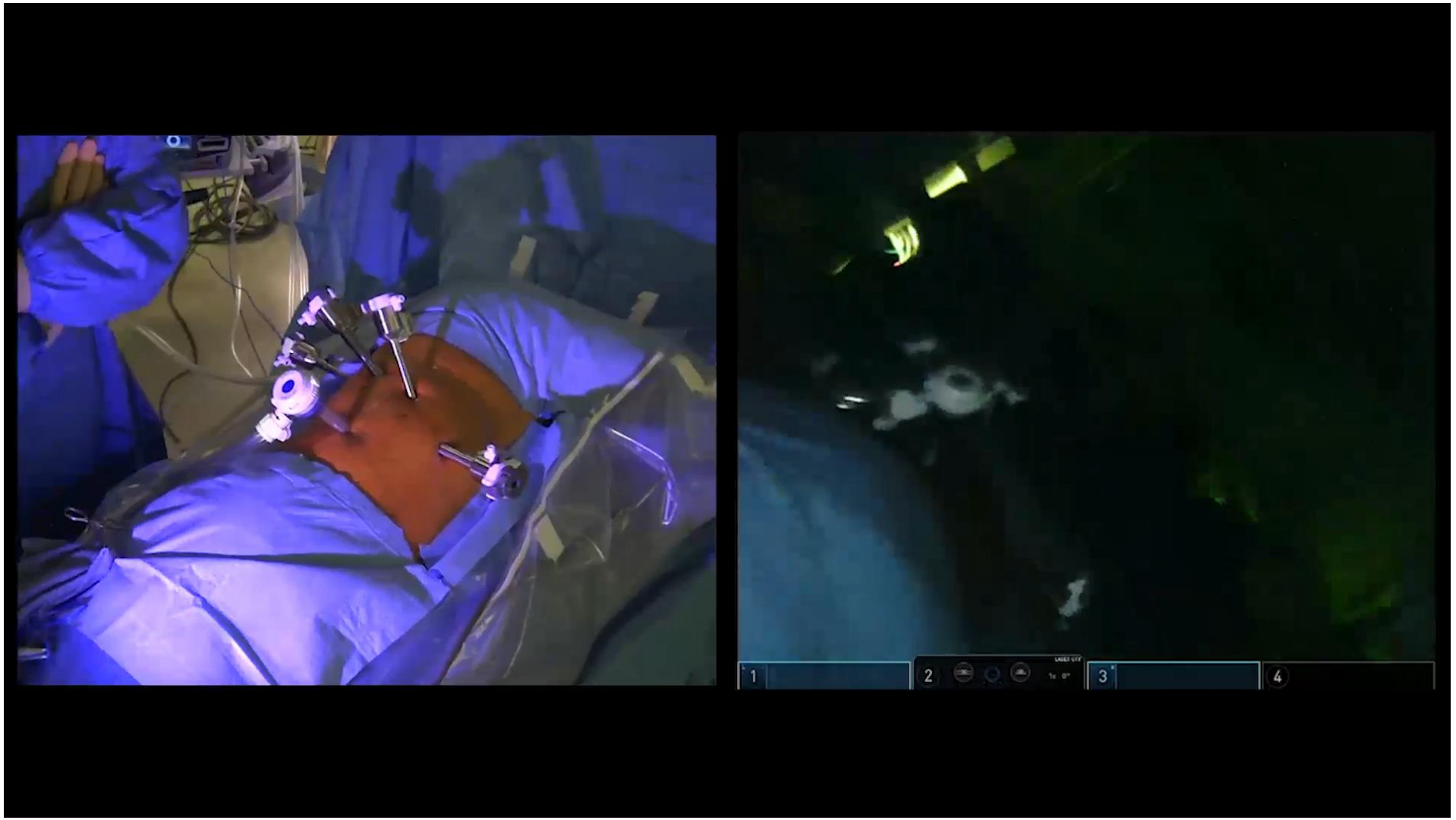
Tufts University School of Medicine

INTUITIVE SURGICAL®

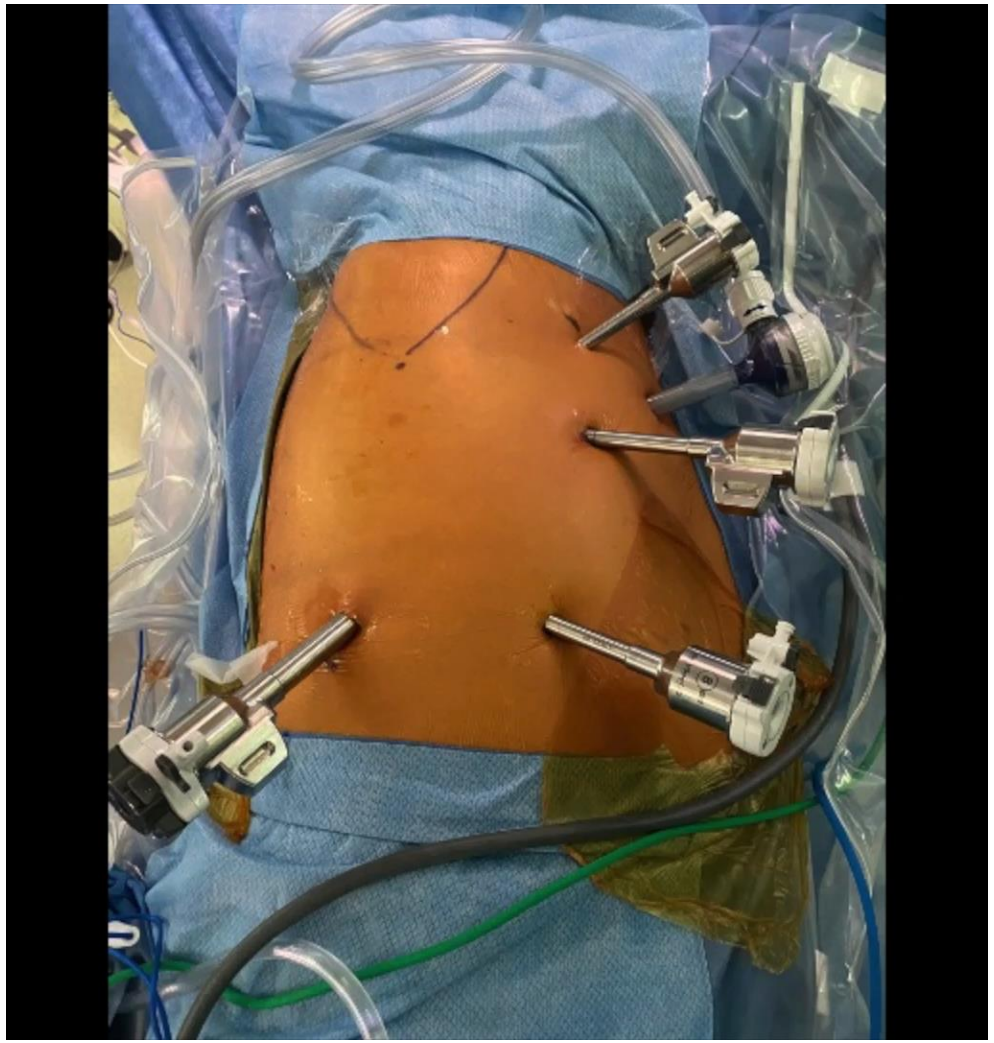
Robotic setup

- ✧ Goals:
  - ✧ Safety
  - ✧ Minimize collisions (internal & external)
  - ✧ Efficiency
  - ✧ Reproducible
  - → We never target
  - → It’s all about the camera arm position!!

Pulmonary cases



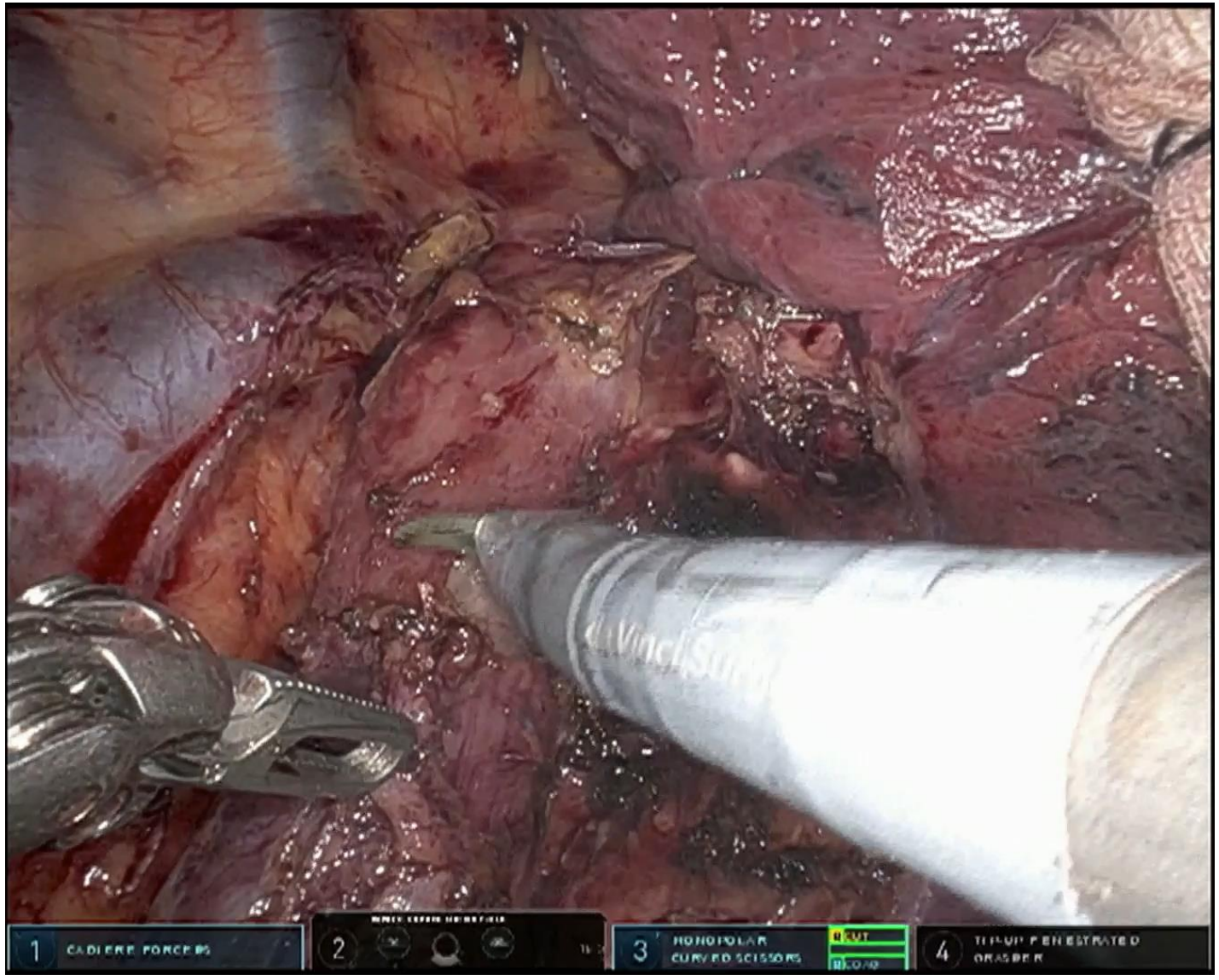
RAMIE - chest



RAMIE

- ✧ Goals:
  - ✧ Achieve the PERFECT proximal esophageal division for Ivor Lewis
  - ✧ Avoid the retracted or pooching mucosa
  - ✧ Autonomy
- ✧ I’ve tried many alternatives
  - ✧ The robotic shears are too darn short!!
  - → Robotic vessel sealer

RAMIE – Dividing the Goose

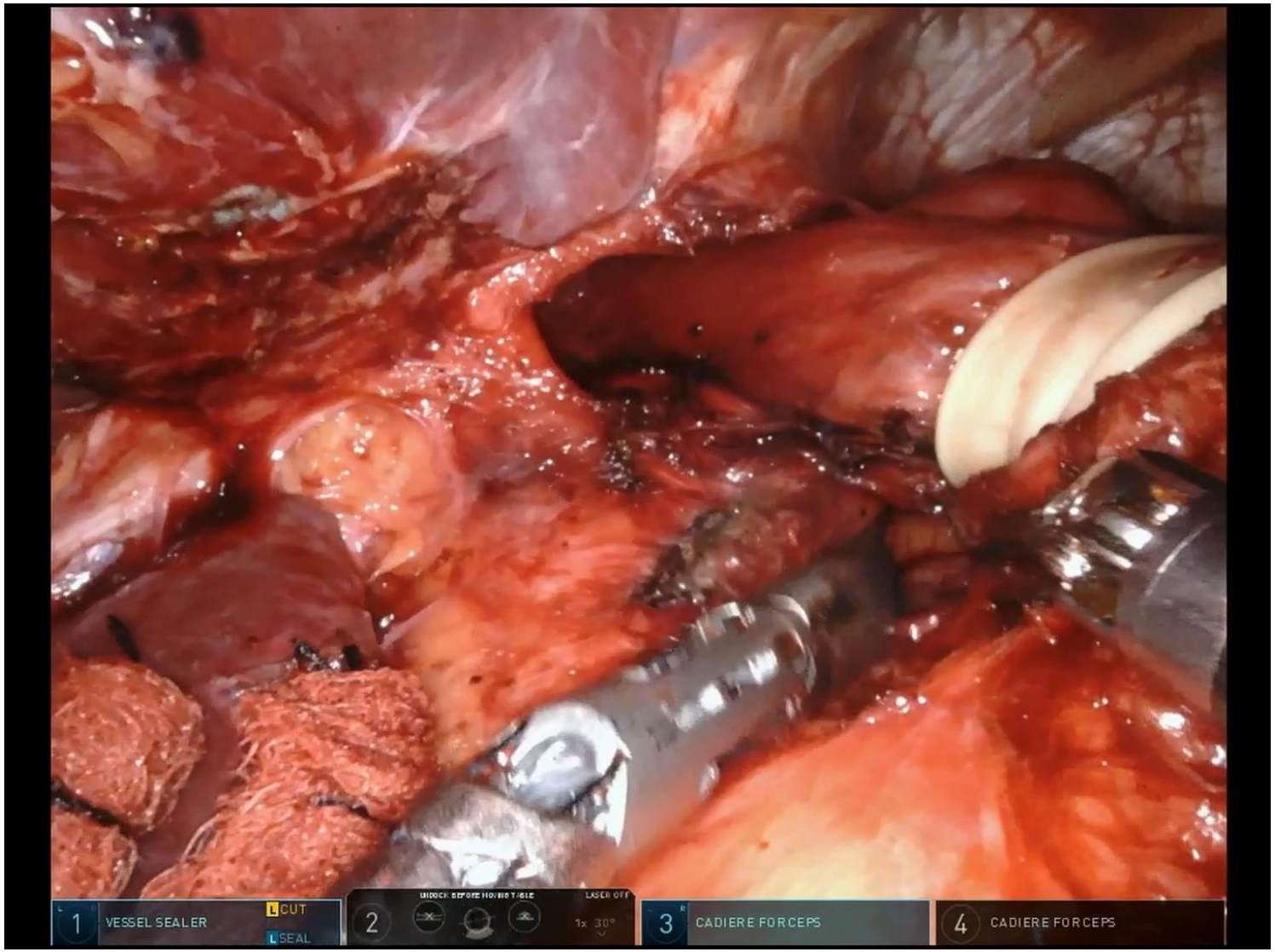


Redo fundoplication/PEH

- ✧ “The stapler is your friend”
  - Taking down prior Nissen with stapler
  - Functional conversion of Nissen to Toupet

Redo fundoplication/PEH

The stapler is your friend



Clinical Pearls I Will Never Publish

General Thoracic Surgery Club

Stephanie G. Worrell

March 10 2023

The Safe Robotic Case

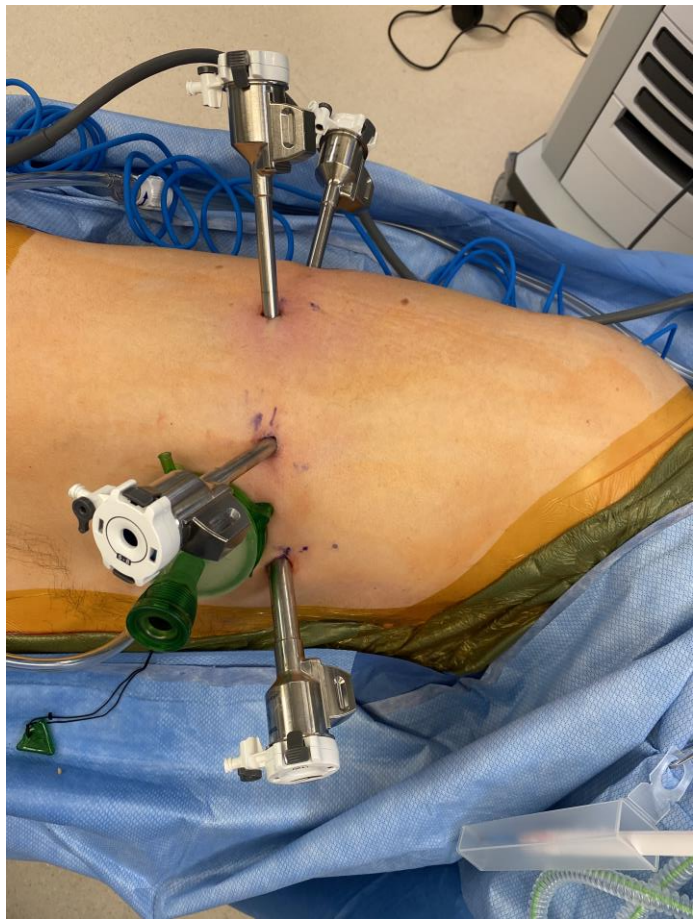
- The first few cases you do at a new place will determine what type of surgeon you are in the eyes of your colleagues
- Many clinical pearls are made from some disaster you experienced

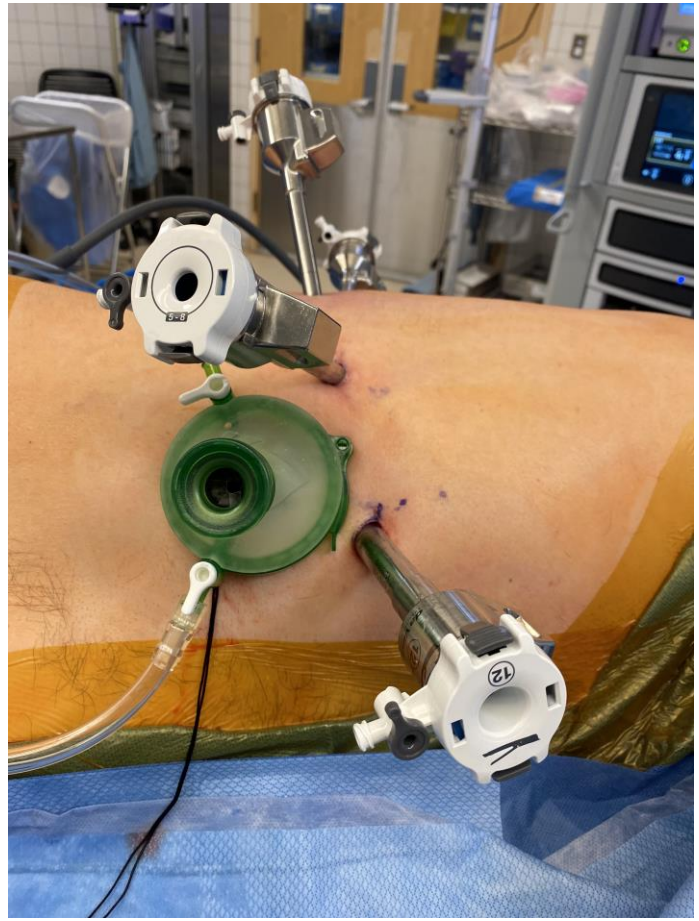
My mis-steps

- Started with a right upper lobectomy
  - Peripheral cT1bN0 NSCLC
  - Wedge resection followed by completion lobectomy with MLND
  - Resection went well, difficulty with specimen extraction
  - Resulted in a take back for bleeding
  - Patient did well, still discharged POD#3

More access

- Don’t have to scrub back in to increase extraction site
- Ease of sponge stick placement
- Easy to pass in cigarette rolls, suction and take out lymph nodes
- Maintain CO2



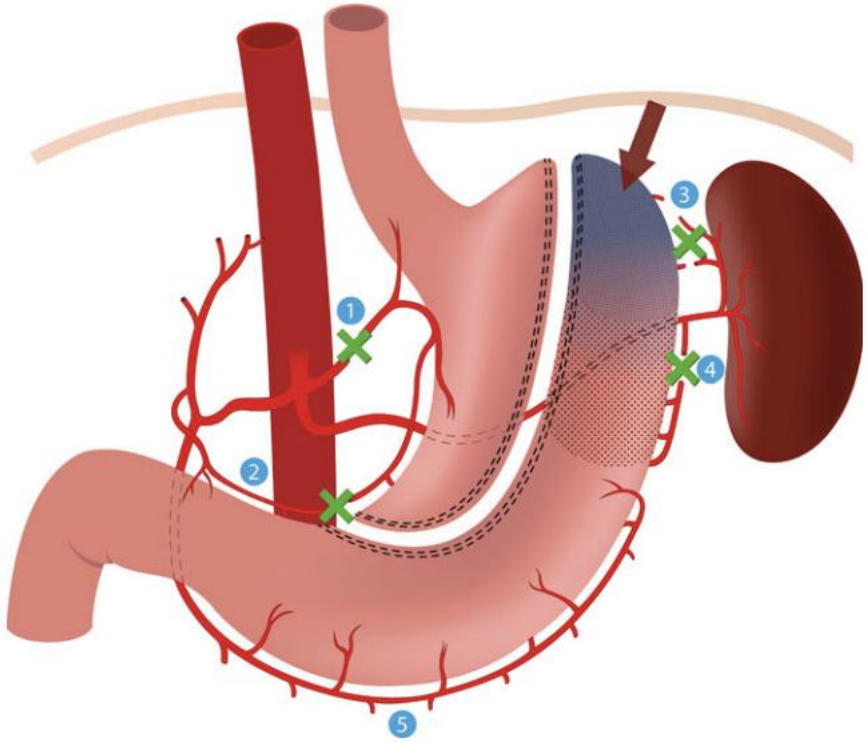


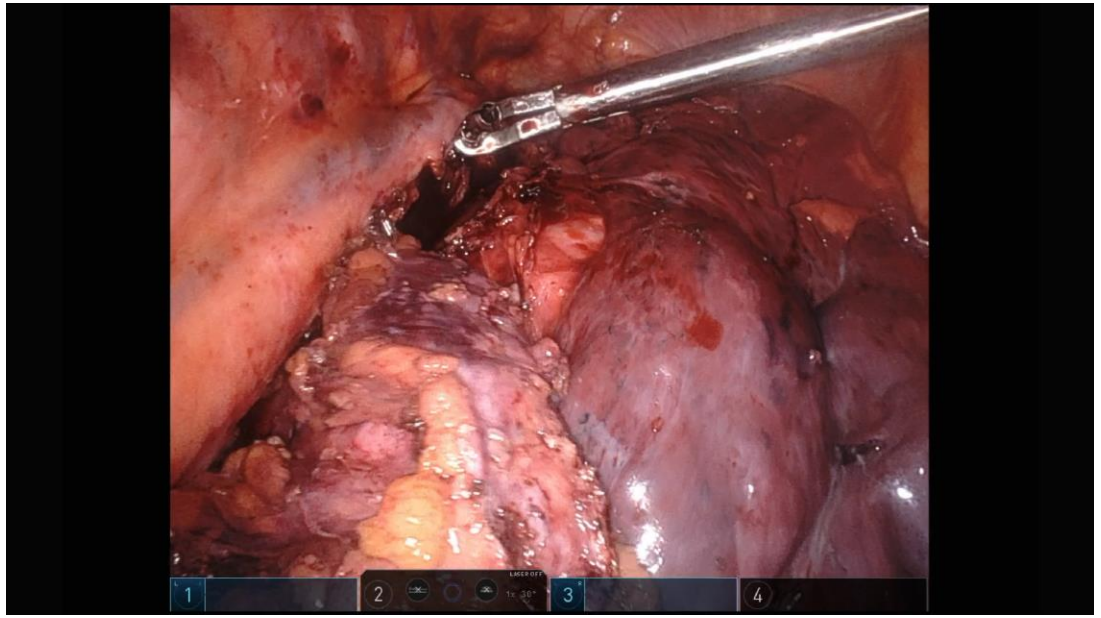
Some pearls don’t require a disaster

Esophagectomy

- Long term outcomes are related to a number of distinct maneuvers during a long operation
- Pyloric intervention, extent of kocherization of the duodenum, closure of the hiatal opening, width of the conduit, proximal location of the anastomoses, width of the anastomoses
- A straight conduit is a very important part of appropriate function

Anatomically correct gastric conduit

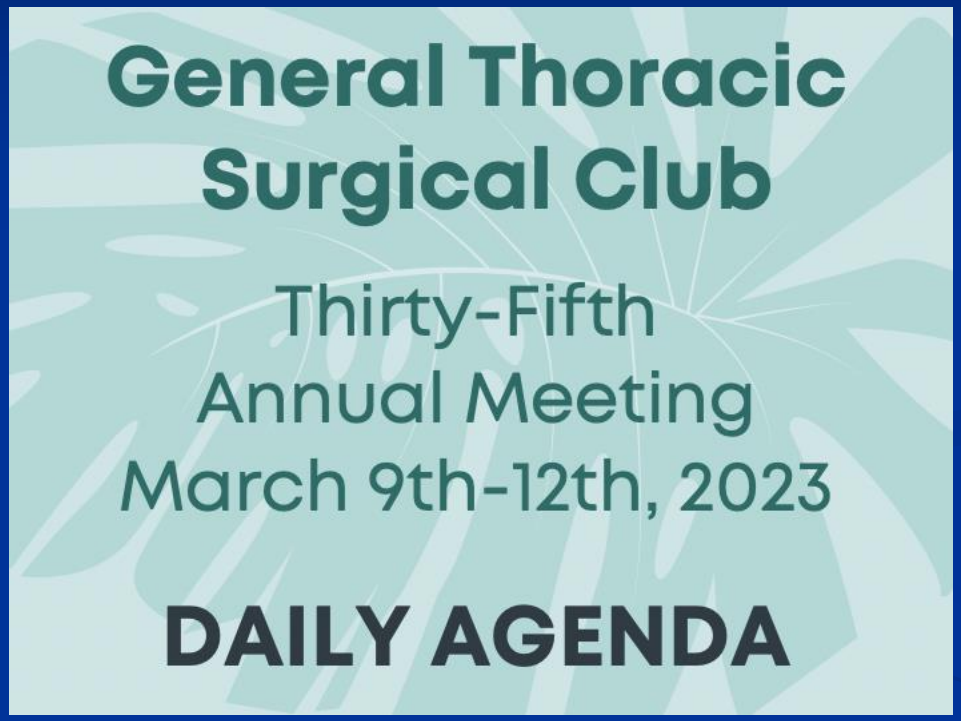




Clinical Pearls I'll Never Publish

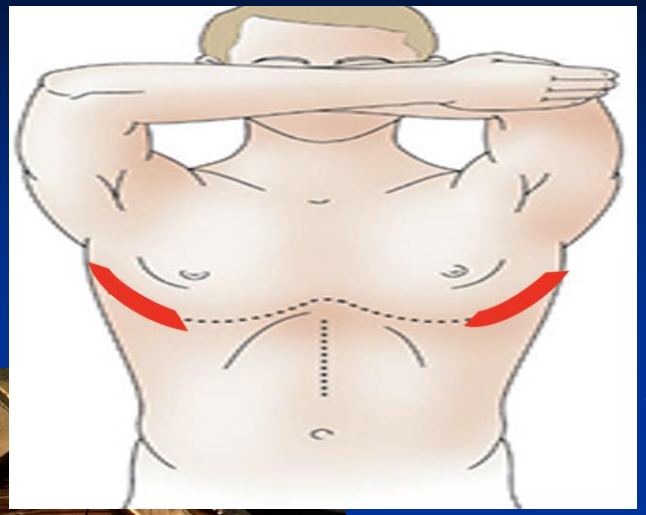
Joshua Sonett, MD
Professor of Surgery
Chief General Thoracic Surgery
Director Price Family Center
for Comprehensive Chest Care
Columbia University
New-York Presbyterian Hospital

Clinical Pearls I'll Never Publish

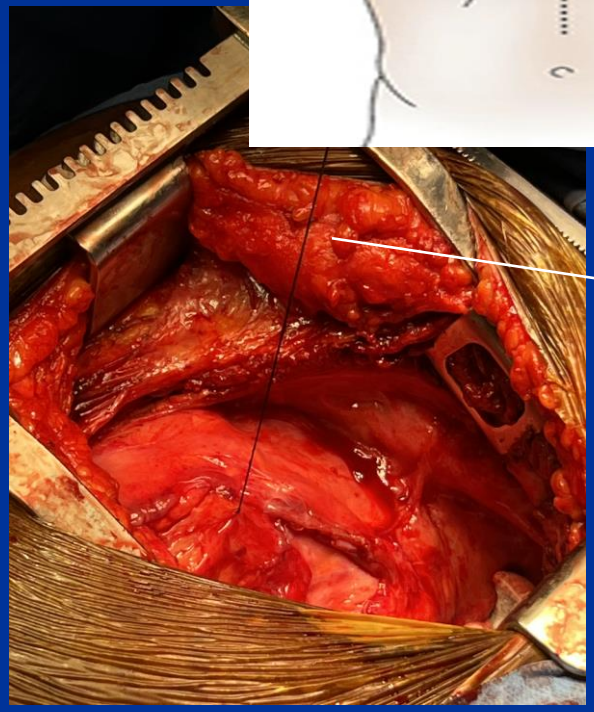


Disclosures: Medtronic Consultant

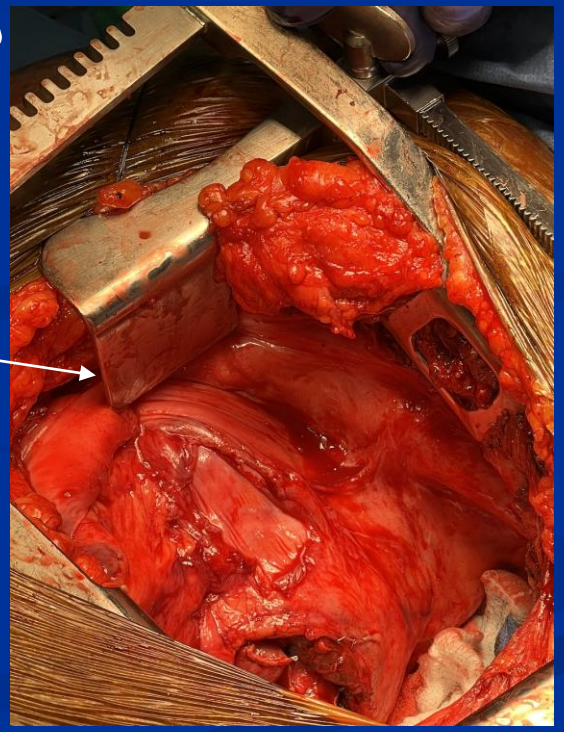
Tips and Tricks I'll Never Publish



Resident/Attending

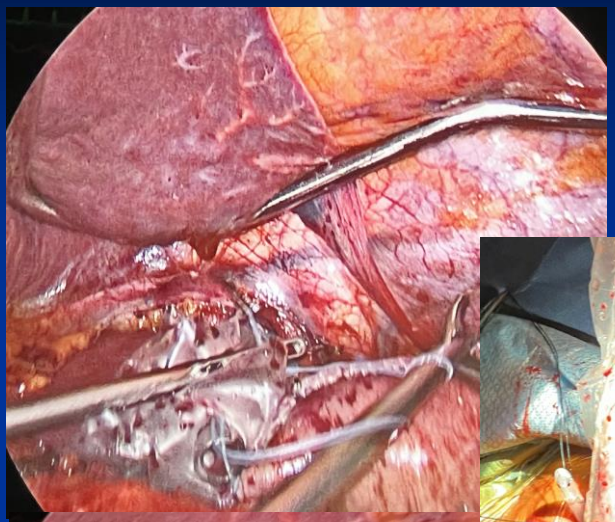


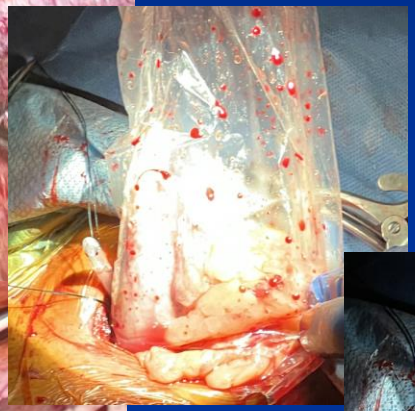
Pericardial stich to rotate Hilum

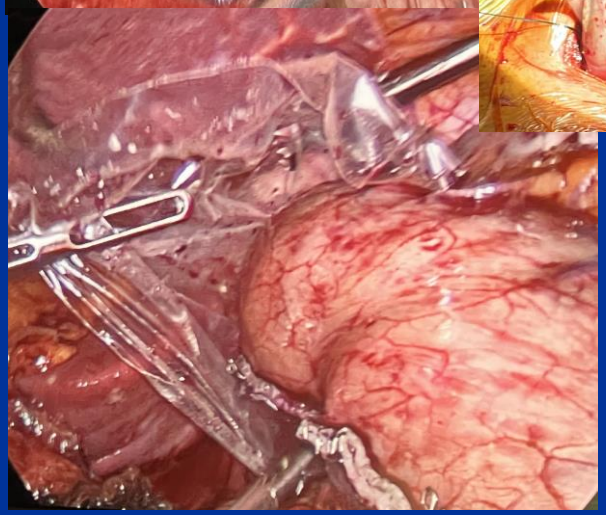


Left Axillary Exposure Lung Transplant

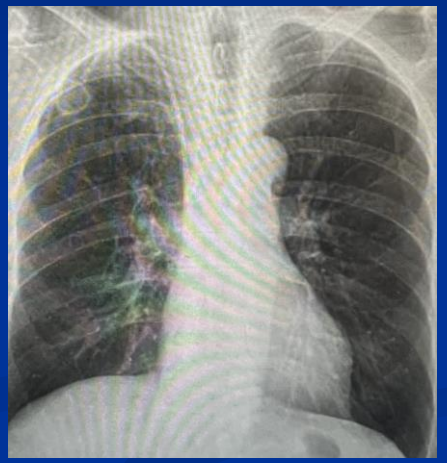
Tips and Tricks I'll Never Publish

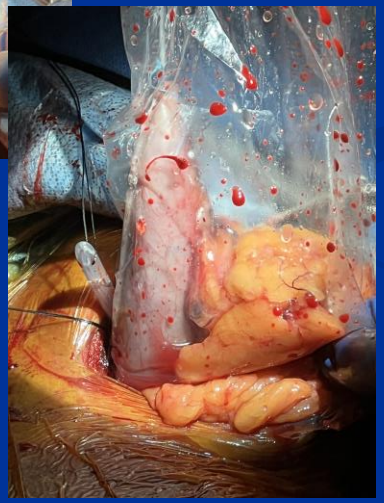


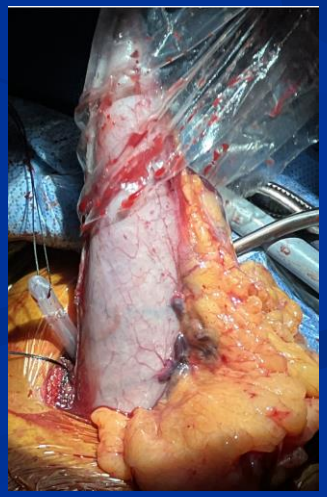




Slippy Slide to bring conduit
To Neck in MIE.







MIE MCkewon, Bringing Stomach to Neck

Clinical Pearls I'll Never Publish

- **Anyone can learn to operate**

- **Residents Learn more from you by**
  - How you treat and interact with your patients
  - How you advocate for your patients
  - How you interact in your work environment

Best Clinical Pearl Received
Walter Pories Med School Graduation
Pearls Lecture 1988