



CAN WE CONVERT UNRESECTABLE TO RESECTABLE?

Brendon Stiles, MD

Albert Einstein College of Medicine
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March 31, 2023



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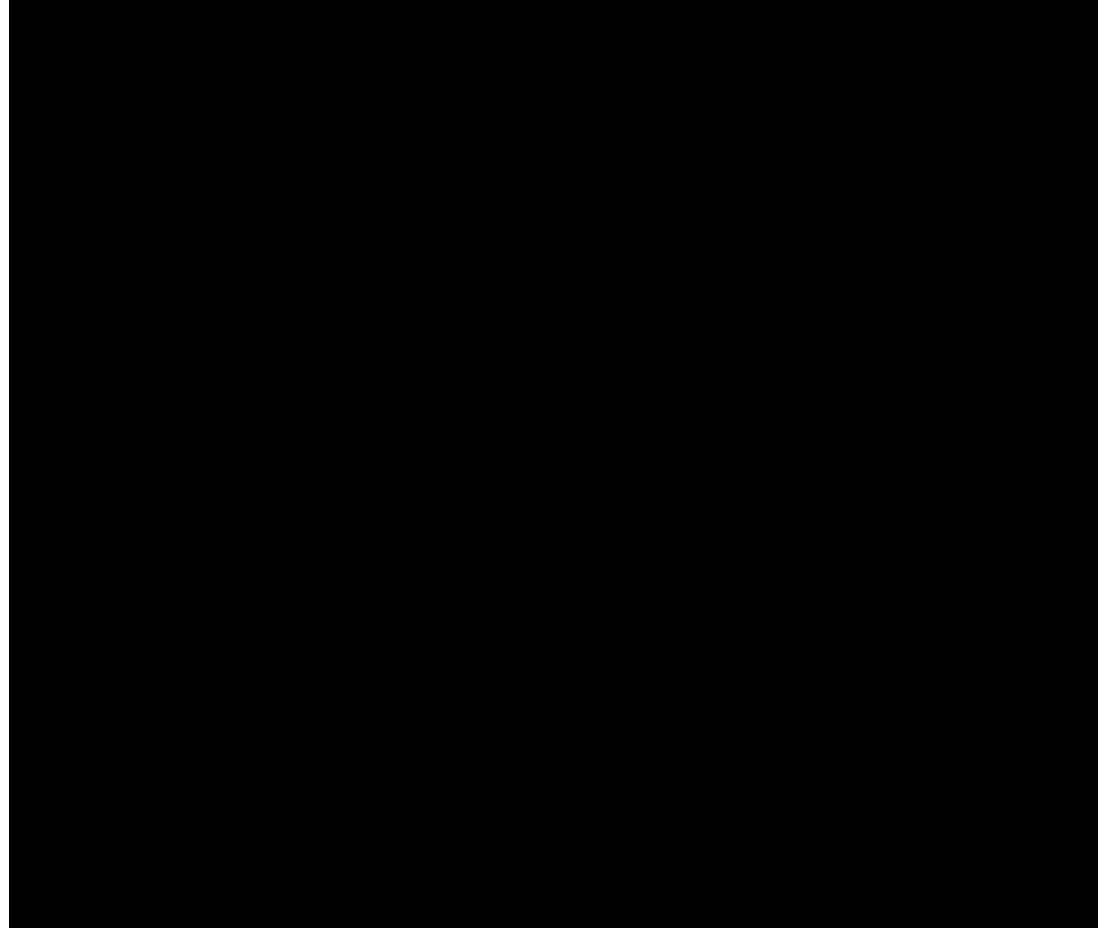
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Case 1



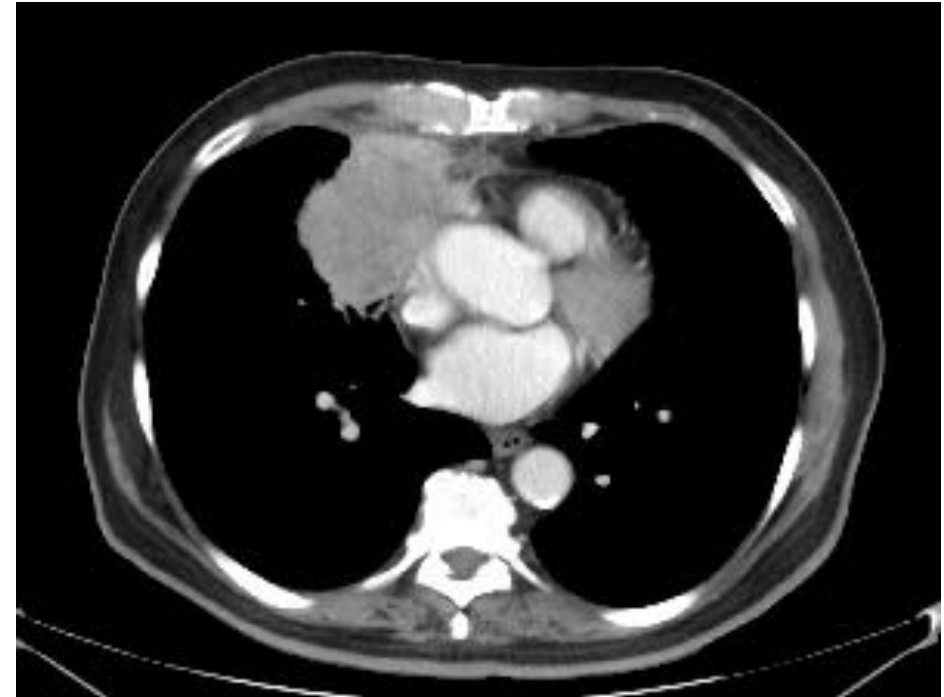
- CT/PET scan: 8.4cm right middle lobe mass with upper lobe invasion and concerns for pericardial/myocardial invasion
- PET: SUV 26.5, paratracheal and bilateral hilar adenopathy, SUV 3.6-7.7
- EBUS negative for multiple stations.
- Core biopsy: Mixed NSCLC with adenocarcinoma and large cell neuroendocrine features
- PD-L1: TPS<1%
- Brain MRI: Normal



Case 1



- Cardiac MRI: contiguous with the right atrium over interface of 4.1 cm, focally causing mass effect on the right atrium, with concern for localized invasion
- Mediastinoscopy/repeat EBUS: Multiple N2/N1 stations negative – final cStage T4N0, IIIA
- No actionable mutations/rearrangements



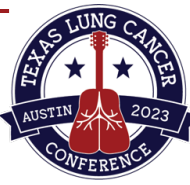
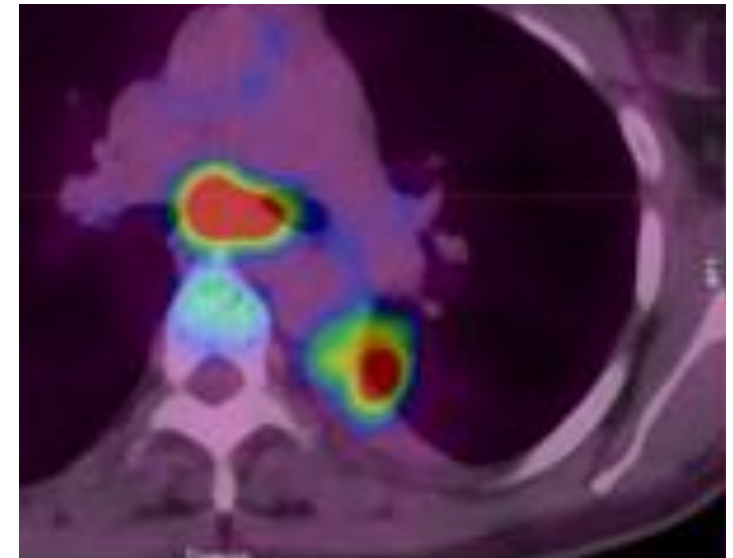
Treatment options



- Upfront surgical exploration and resection, with option for adjuvant systemic treatment
- Neoadjuvant chemotherapy and radiation, followed by surgical resection
- Neoadjuvant chemotherapy and immunotherapy, followed by surgical resection
- Definitive chemoradiation, followed by durvalumab

Case 2

- 51 yo never smoker, presented with hemoptysis
- Excellent performance status
- Found to have left lower lobe adenocarcinoma with endobronchial extension, 6.4 x 5.8 x 9.6 cm
- PET scan:
 - Primary tumor, SUV 15.0
 - Level 7 node, 2.3 x 1.5, SUV 8.0
 - AP window, 1.2 x 0.7 cm, SUV 2.0
- No metastatic disease, brain MRI negative





Further staging and treatment consideration

- Bronch/EBUS confirms + level 7, L4/R4 negative
- Molecular testing demonstrates EGFR L858R mutation
- Clinical T4N2 (bulky), stage IIIB
- Challenging for both surgery and radiation
 - Appears resectable by LLL sleeve lobectomy, but will be challenging and may require pneumonectomy
 - Radiation will also require a very large field

Treatment options



- Neoadjuvant chemotherapy, surgery, adjuvant Osimertinib
- Chemoradiation, followed by Osimertinib
- Chemoradiation, followed by Durvalumab
- Off-label neoadjuvant Osimertinib and reassess

Resectability, like beauty, is in the eye of the beholder



“The establishment of criteria for treatment of carcinoma of the lung, especially operability and resectability, is particularly difficult....

What would have been well accepted criteria of inoperability 15 to 20 years ago no longer hold, and those today may be in doubt in a few years.

Criteria also vary from group to group, among individual surgeons, and, indeed for the same surgeon from time to time depending on his (her) recent experience.”



The Criteria for Operability and Resectability in Lung Cancer

Eugene E. Clifton, MD

Clifton EE, et al. JAMA 1966 Mar 21;195:1031-2

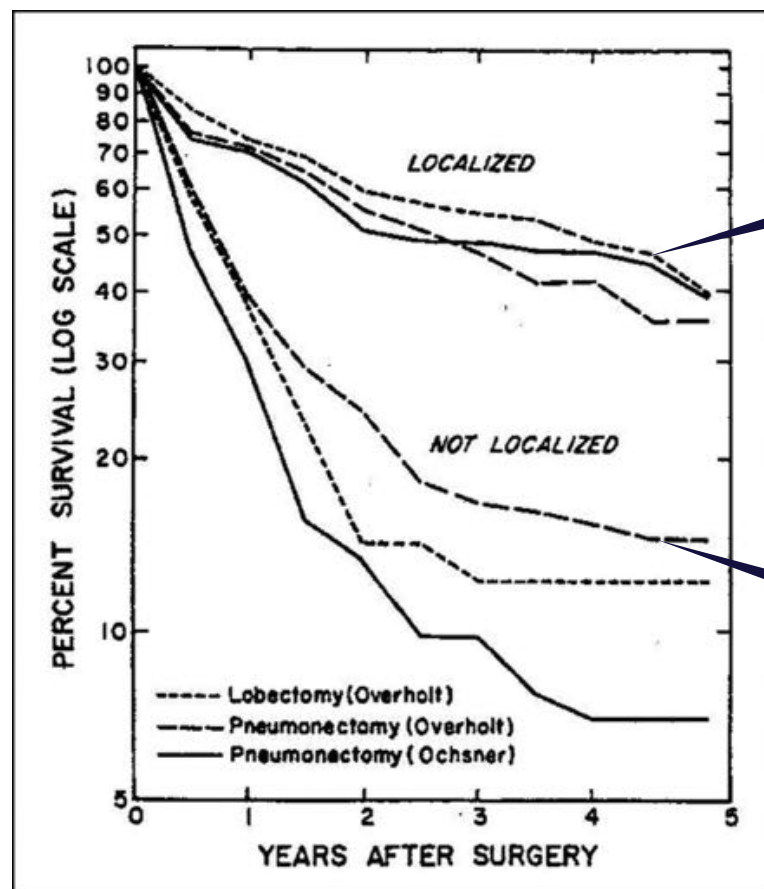
The optimal cancer operation would seemingly be the widest possible resection



“Just as experience with carcinoma in other parts of the body has taught that the number of cures is, in general, directly proportional to the extent of radial removal, so it may be inferred, perhaps, that if the entire lung is removed the patient will have less chance of a recurrence than if only one lobe or a smaller portion is removed”

Graham 1933

But surgeons should bear in mind that the disease may often overcome his or her operation



Lobectomy

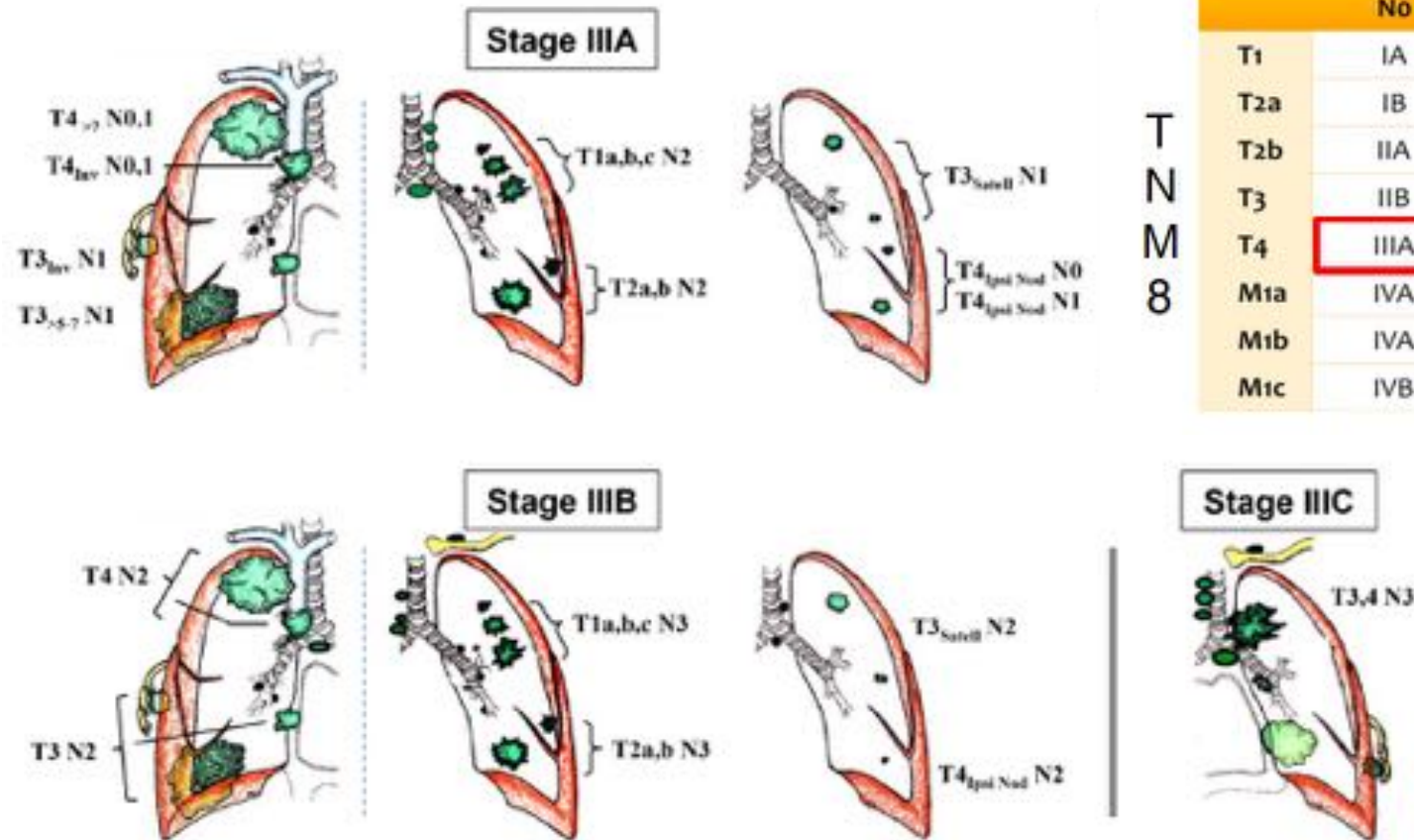
“Without surgical resection, the patient is doomed, but it is pointless to hasten this demise or increase suffering by ill-advised exploration.”

—Richard Overholt

Lobectomy

Shimkin MB, et al. J Thorac Cardiovasc Surg 1962;44:503-19
Reproduced: Horn L, et al. J Clin Oncol 2008;26:3268-75

The question of resectability/operability most often arises for Stage III NSCLC, a heterogeneous disease

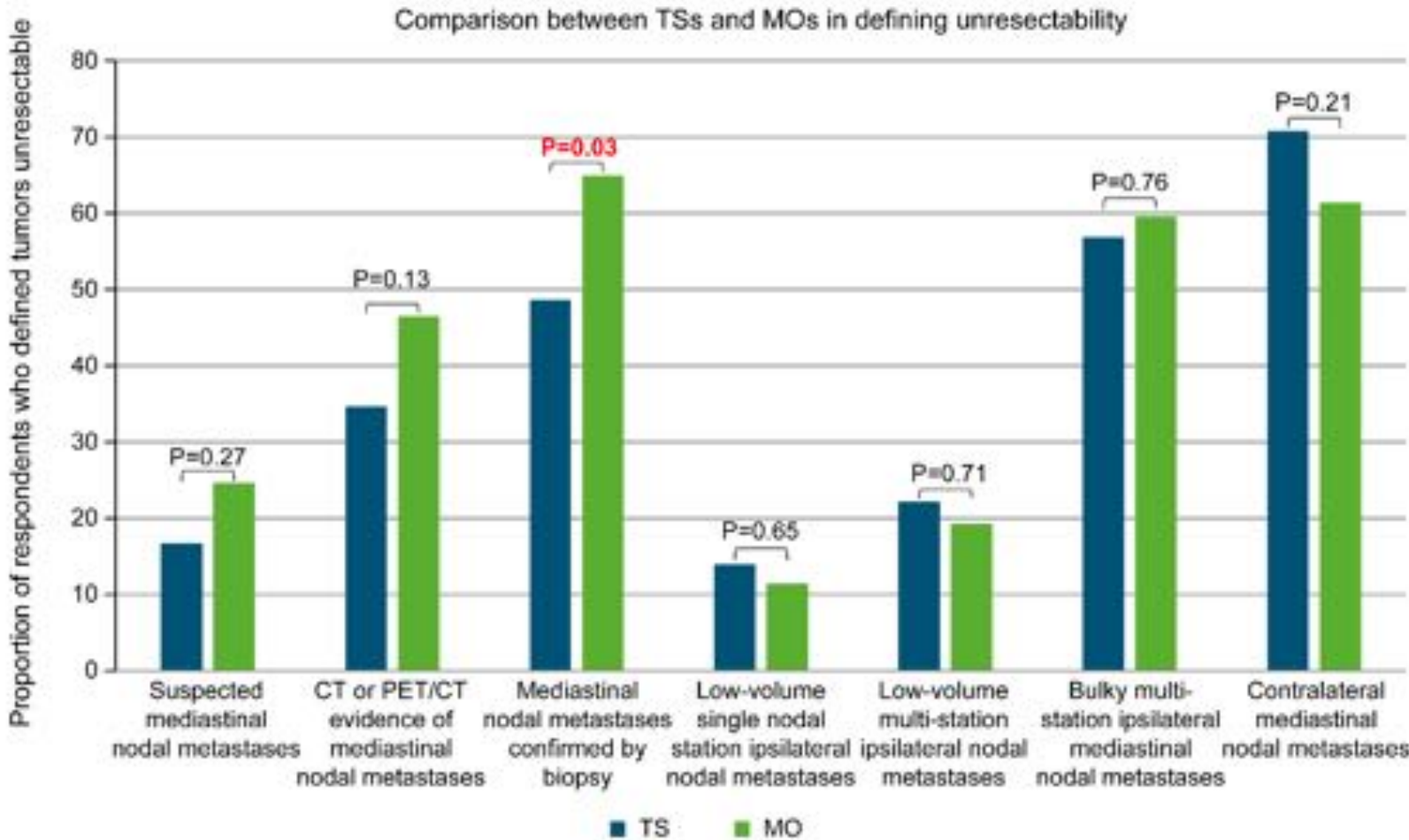
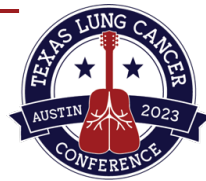


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	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

NSCLC, non-small cell lung cancer
 Detterbeck FC, et al. CHEST 2009;136(1):260-71

Comparison between thoracic surgeons and medical oncologists in the primary definition of unresectability



ASSOCIATION OF COMMUNITY
CANCER CENTERS

IMPROVING CARE FOR PATIENTS
WITH ADVANCED NON-SMALL CELL
LUNG CANCER

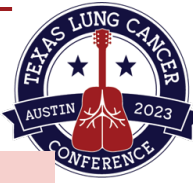
RESULTS FROM A NATIONAL QUALITY SURVEY
FOR THORACIC SURGEONS, RADIATION
ONCOLOGISTS, AND
MEDICAL ONCOLOGISTS

protocols to define unresectable
stage II⁺ tumors compared with
program (79.6% of MDCs
34)

BY BRENDON STILES, MD;
LEIGH M. BOEHMER, PHARM.D;
CANDICE YONG, PH.D;
AND PERCY LEE, MD

acc-cancer.org | Vol 36, No 6, 2023

Key Questions in Managing Stage III



Multidisciplinary patient assessment, treatment planning, and support

Patient Factors

- Performance status
- Weight loss \leq 15%
- Comorbidities
- Pulmonary function (FEV1, DLCO)
- Cardiac function
- Patient preferences
- Social, financial factors

Tumor Factors

- Staging: IIIA vs. III B, C
- N2 bulk, number of stations, extranodal spread?
- Is it technically resectable?
- Extent of resection?
- Can radiation be delivered to curative dose safely?

FEV1, forced expiratory volume in one second

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2018. 2. Yoon SM, et al. World J Clin Oncol 2017;8:1-20

3. Albain K, et al. Lancet 2009;374:379-86; 4. NCCN: Guidelines for Patients, Lung Cancer – 2018. <https://www.nccn.org/patients/guidelines/lung-nscl/>. November 30, 2017. Accessed April 2, 2018. 5. Detterbeck FC, et al. Chest 2017;151:193-203



INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

Speaker: Brendon Stiles, MD, Montefiore Medical Center (@BrendonStilesMD)



@TLCconference #TexasLung23

Common refrains post-PACIFIC



Shankar Siva @_ShankarSiva · Oct 6

There is no more room for an RCT for stage IIIa - surgery does not improve survival over radiotherapy despite 20 years of effort (6 trials, > 1300 patients). With PACIFIC outcomes it's time to put this question to rest - R.I.P. #TSSMN #radonc #lscsm

Adding surgery into the stage III paradigm

6 RCTs, n=1322

OS not different b/w surgery vs radiotherapy (HR=0.92 [95%CI 0.82-1.04], p=0.19, χ^2 -test). Treatment related mortality higher in the surgical arms (risk ratio=3.56, p=0.0005). PFS not different b/w surgery vs radiotherapy were found (HR=0.91 [95%CI: 0.73 - 1.13])

Study	TE	seTE	Hazard Ratio	HR	95%-CI W(random)
RTOG 89-01	-0.21	0.8860		0.81	[0.14; 4.60]
NCI Canada	-0.13	0.4383		0.88	[0.37; 2.08]
EORTC 08941	0.06	0.1099		1.06	[0.85; 1.31]
NTOG	-0.14	0.1168		0.87	[0.69; 1.09]
INT 0139	-0.14	0.1197		0.87	[0.69; 1.10]
ESPAUTIE	-0.21	0.2195		0.81	[0.53; 1.25]
Random effects model				0.92	[0.82; 1.04]

Heterogeneity: I-squared=0%, tau-squared=0, p=0.7806

0.2 0.5 1 2 5
Favors Surgery – Favors (Chemo)RT

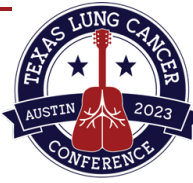
Figure 1: Forest plot: overall survival - randomized prospective studies, experimental: treatment arms with surgery.
*Pottgen, Eberhardt et al. Oncotarget. 2017 Jun 20; 8(25): 41670–41678.

Ben Solomon, Solange Peters, Tom John, MBBS, PhD and 3 others

3 13 24

- Haven't trials shown no benefit to surgery for Stage III disease?
- Following the PACIFIC trial, shouldn't we be less inclined to offer surgical therapy?

Recurrences in the PACIFIC Trial



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiet, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

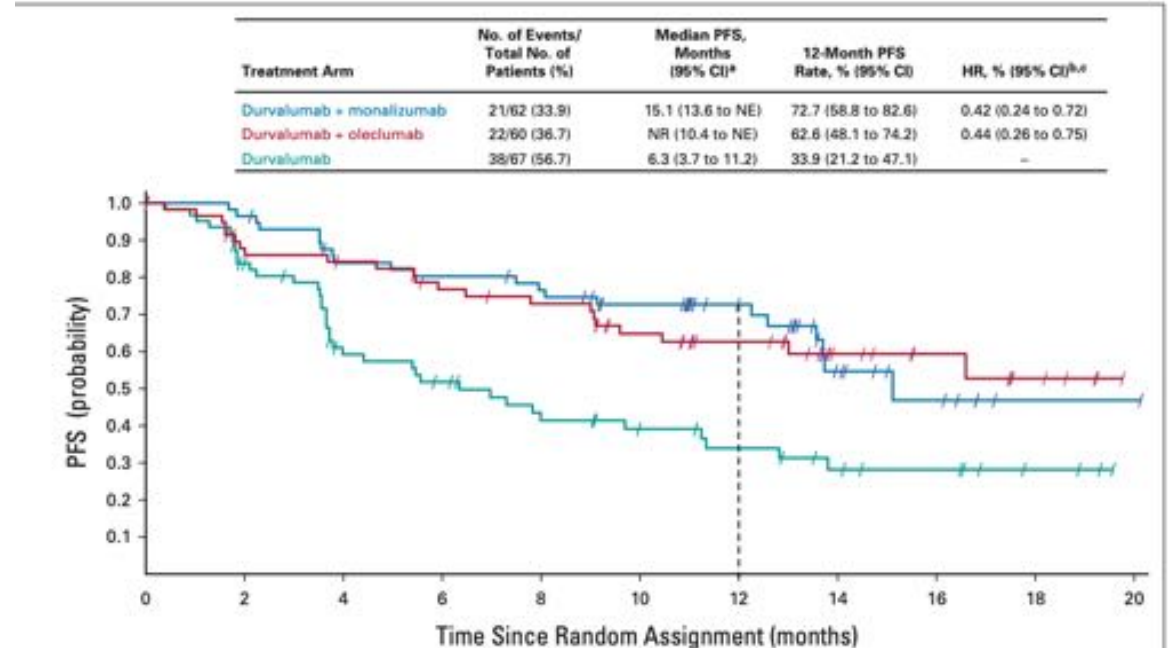
Median f/u 25 months

PFS: 17 vs. 5.6 months

30% with Grade 3 or 4 events

f/u, follow-up; PFS, progression free survival
Antonia S, et al. N Engl J Med 2018;379:2342-50;

Durvalumab Plus Novel Agents for Unresectable, Stage III NSCLC



J Clin Oncol 40:3383-3393. © 2022 by American Society of Clinical Oncology

**85% of progression in
lung/lymph nodes**

Should we give more radiation for “unresectable” tumors?

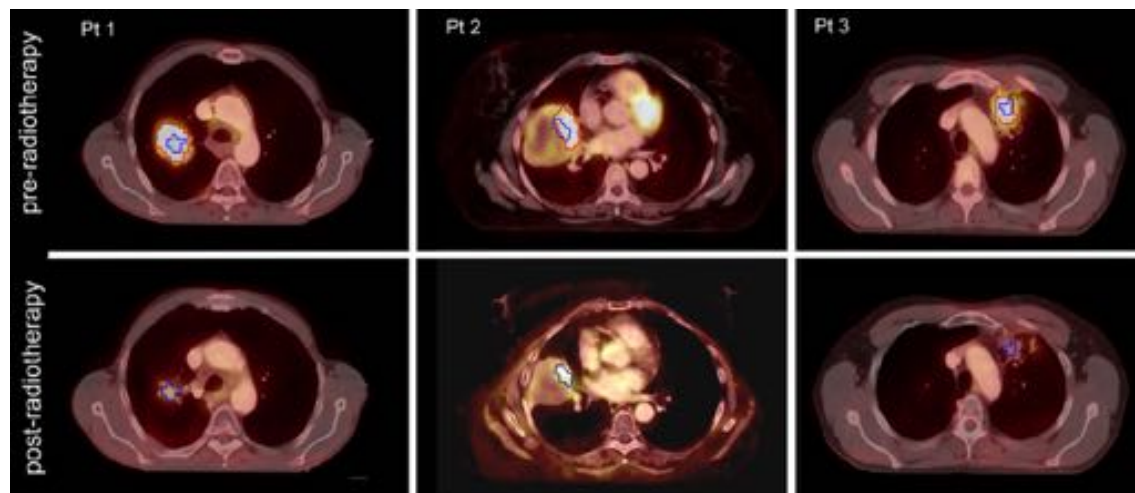


¹⁸F-FDG-PET guided vs whole tumour radiotherapy dose escalation in patients with locally advanced non-small cell lung cancer (PET-Boost): Results from a randomised clinical trial

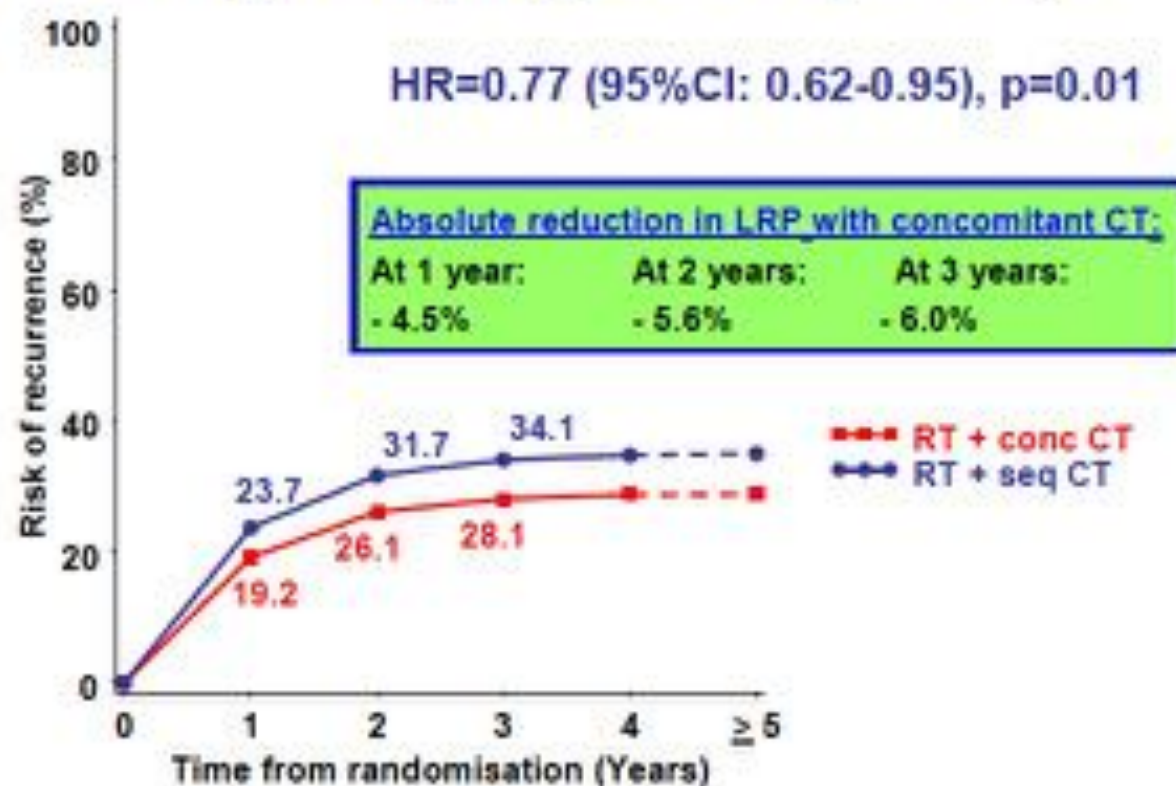


Saskia A. Cooke^{a,*}, Dirk de Ruyscher^b, Bart Reymen^b, Maarten Lambrecht^{c,d}, Gitte Fredberg Persson^{e,f,g}, Corinne Faivre-Finn^h, Edith M.T. Dielemanⁱ, Rolf Lewensohn^{j,k}, Judi N.A. van Diessen^a, Karolina Sikorska^l, Ferry Lalezari^m, Wouter Vogel^{a,n}, Wouter van Elmpt^b, Eugène M.F. Damen^a, Jan-Jakob Sonke^a, José S.A. Belderbos^{a,*}

-Grade ≥ 3 AEs in 54% and 53%



Cumulative incidence of loco-regional progression (5 trials)



Radiotherapy and Oncology 181 (2023) 109492

The neoadjuvant chemo-immunotherapy paradigm

CheckMate 816



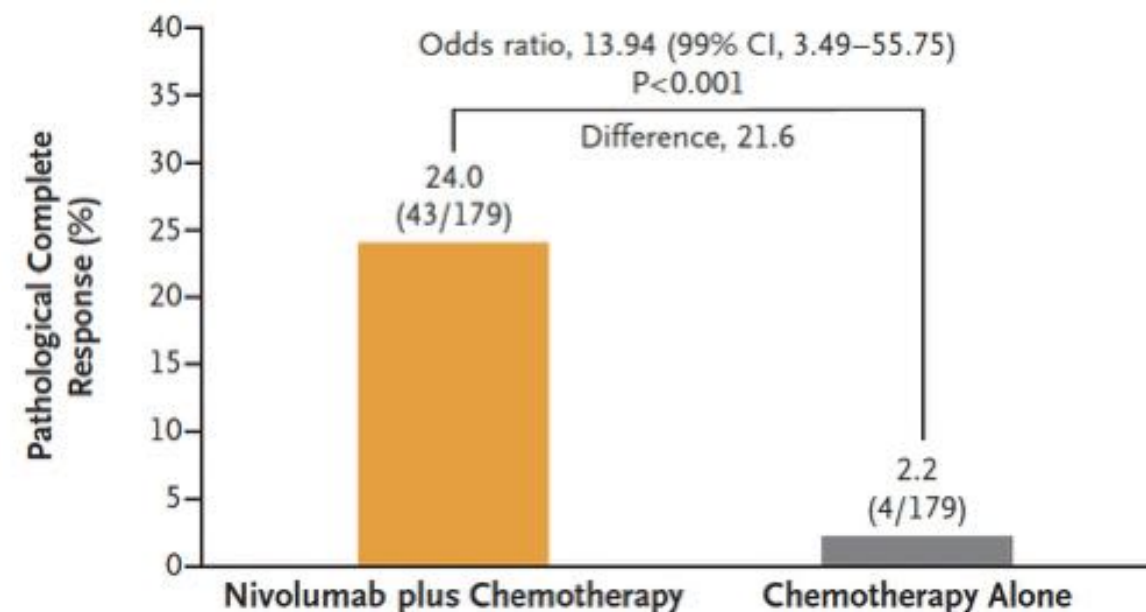
ORIGINAL ARTICLE

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. Saylor, 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*

PD-L1 expression level

<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)



CI, confidence interval; PD-L1, programmed cell death ligand-1
Forde PM, et al. N Engl J Med 2022;386:1973-85

Neoadjuvant chemo-immunotherapy



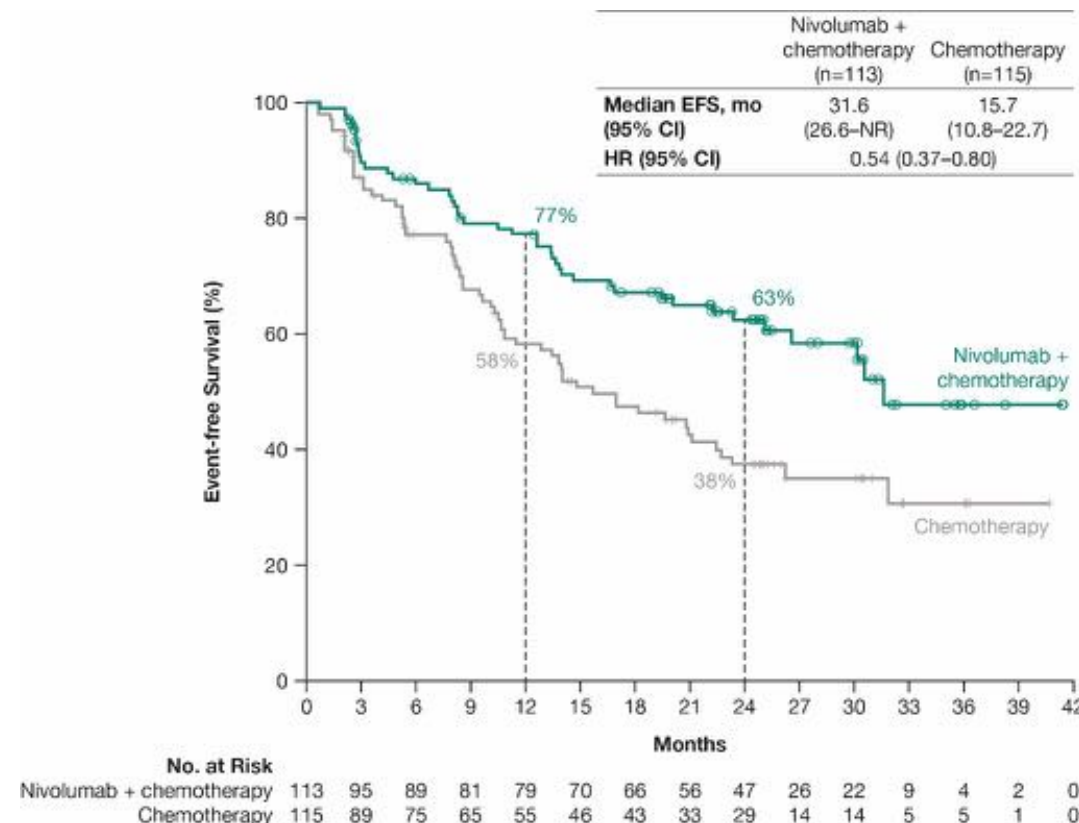
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Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

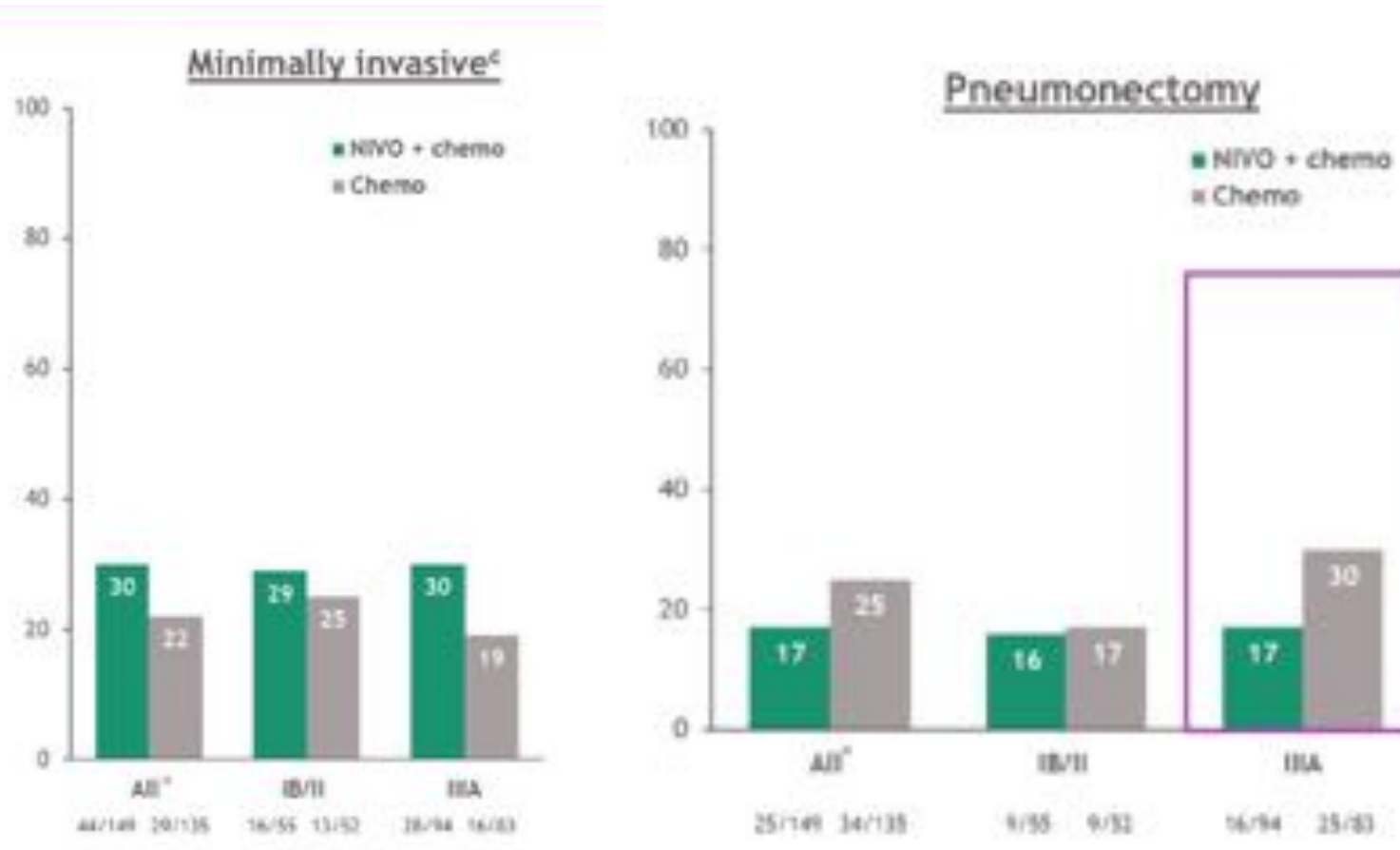
P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen,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

CI, confidence interval; EFS, event free survival; HR, hazard ratio; NR, not reached
Forde PM, et al. N Engl J Med 2022;386:1973-85

Checkmate-816 Stage IIIA



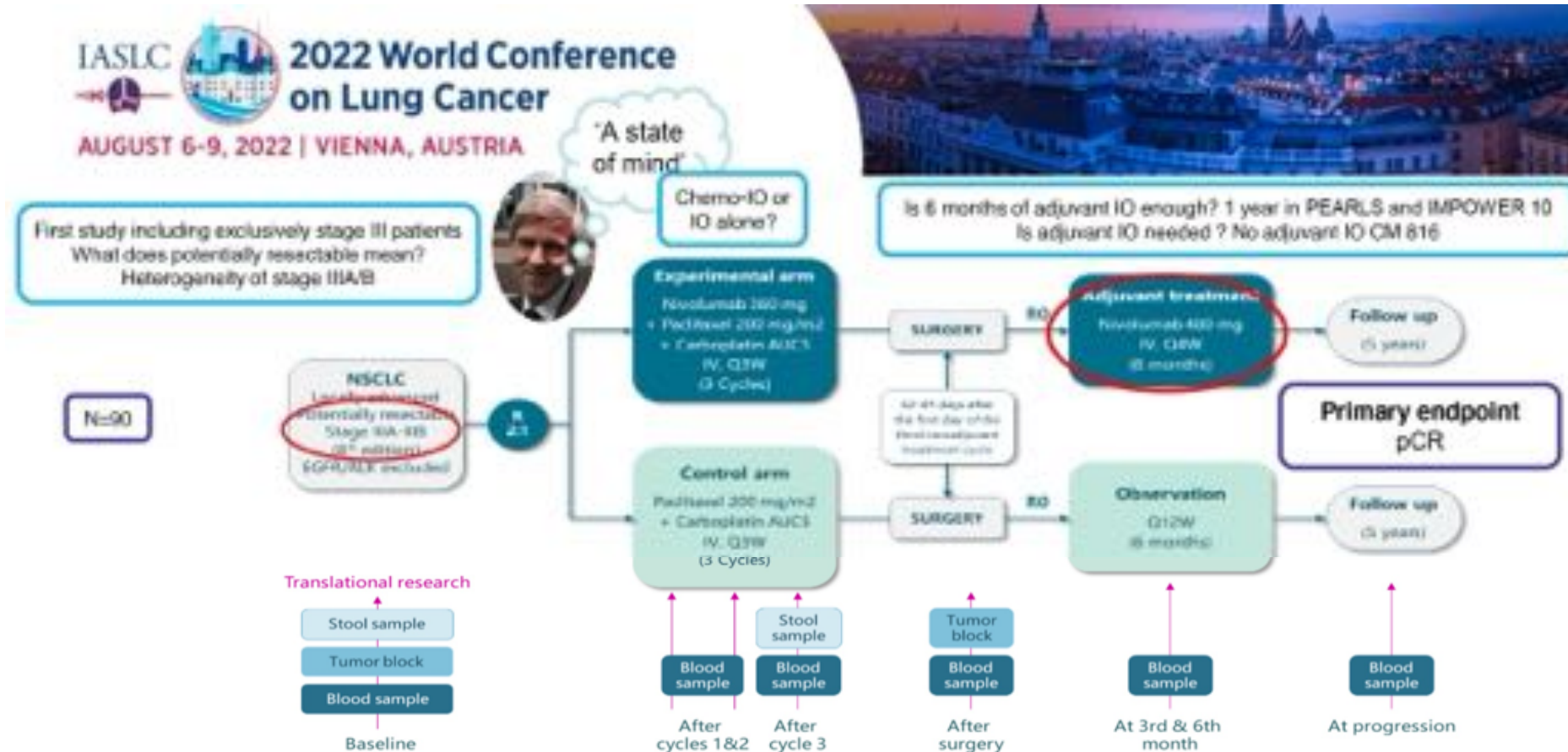
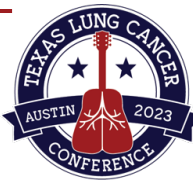
It is a win for the patients, but also for the surgeons?



- **More patients made it to surgery**
(83% vs. 72%, Stage IIIA)
- **Duration of surgery shorter**
(32 minutes, Stage IIIA)
- **More minimally invasive**
(30% vs. 19%, Stage IIIA)
- **Less pneumonectomies**
(17% vs. 30%, Stage IIIA)

Chemo, chemotherapy; NIVO, nivolumab
Spicer J, et al. N Engl J Med 2022;386:1973-85
Figures courtesy of Spicer J, et al. ASCO 2021 (Abstract 8503)

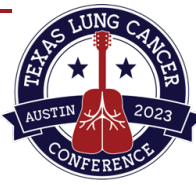
Surgeons must adjust their “state of mind” for Stage III disease: NADIM II



AUC, area under the curve; EGFR, epidermal growth factor receptor; IO, immuno-oncology; NSCLC, non-small cell lung cancer; pCR, pathologic complete response; Q3/4/12/W, every 3/4/12 weeks

Study design: Provencio-Pulla M, et al. WCLC 2022 (Abstract 1988)

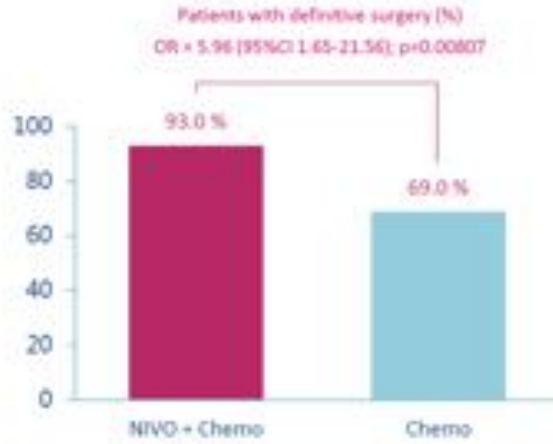
Multi-disciplinary teams should push the boundaries of the definition of resectable Stage III disease: NADIM II



Baseline characteristics

Characteristic	NIVO + Chemo (n = 57)	Chemo (n = 29)
TNM classification (AJCC 8th Ed.)		
T1N2M0	12 (21.1)	4 (13.8)
T2N2M0	16 (28.1)	7 (24.1)
T3N1M0	2 (3.5)	1 (3.5)
T3N2M0	13 (22.8)	5 (19.3)
T4N0M0	6 (10.5)	9 (31.0)
T4N1M0	8 (14.0)	3 (10.3)
Tumor size – Median (range), mm	43 (29-54)	52 (39-75)
Nodal stage – No. (%)		
N0	6 (10.5)	9 (31.0)
N1	10 (17.5)	4 (13.8)
N2	41 (71.9)	16 (55.2)
N2 multiple station	21 (36.8)	10 (34.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; NIVO, nivolumab; NOS, not otherwise specified
Provencio-Pulla M, et al. WCLC 2022 (Abstract 1988)

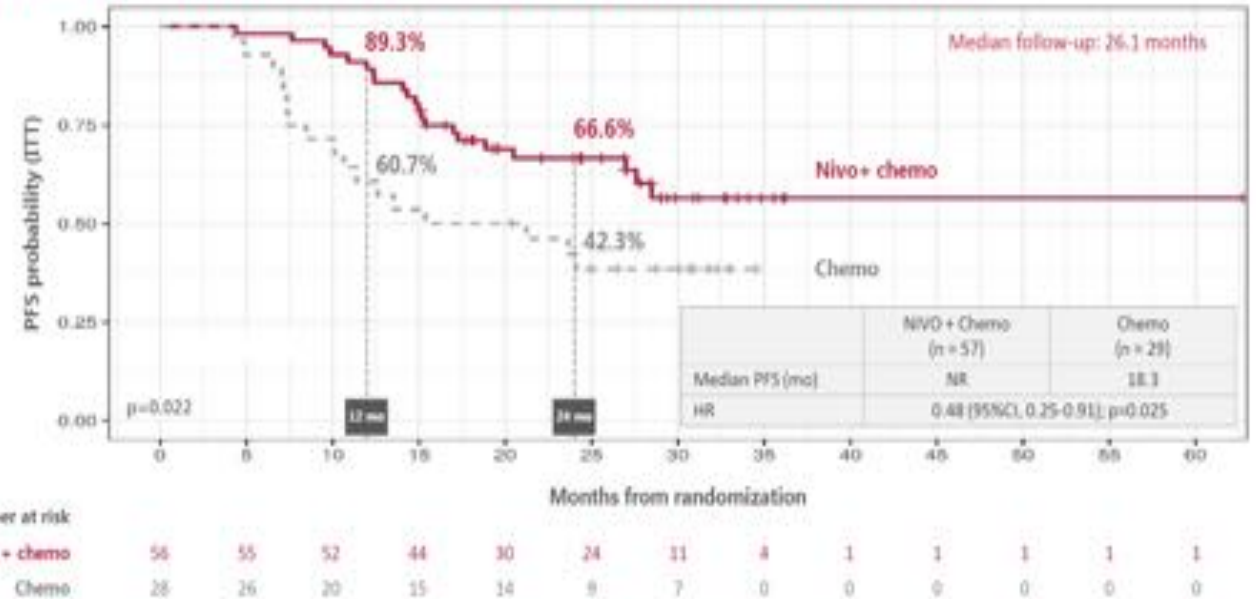


SURGERY SUMMARY

Type of surgery, No. (%)	NIVO + Chemo (n = 53)	Chemo (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right Lower Lobectomy + Segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

Resection degree, No (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)
R0	49 (92.5)	13 (65.0)
Odds Ratio: 6.60 [95% CI 1.67-26.02]; p = 0.007		

SECONDARY ENDPOINTS – Progression-free survival



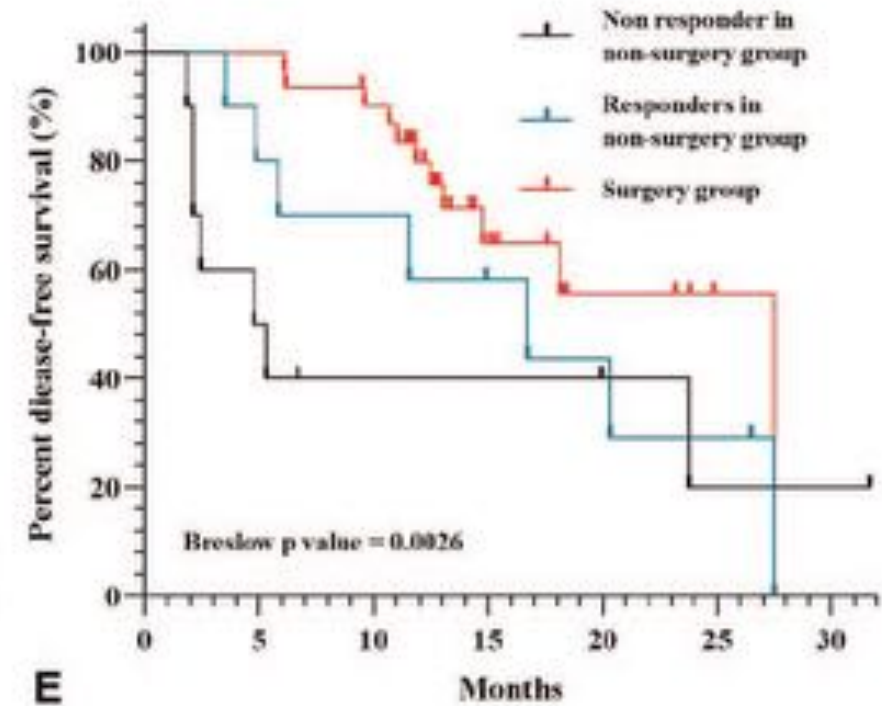
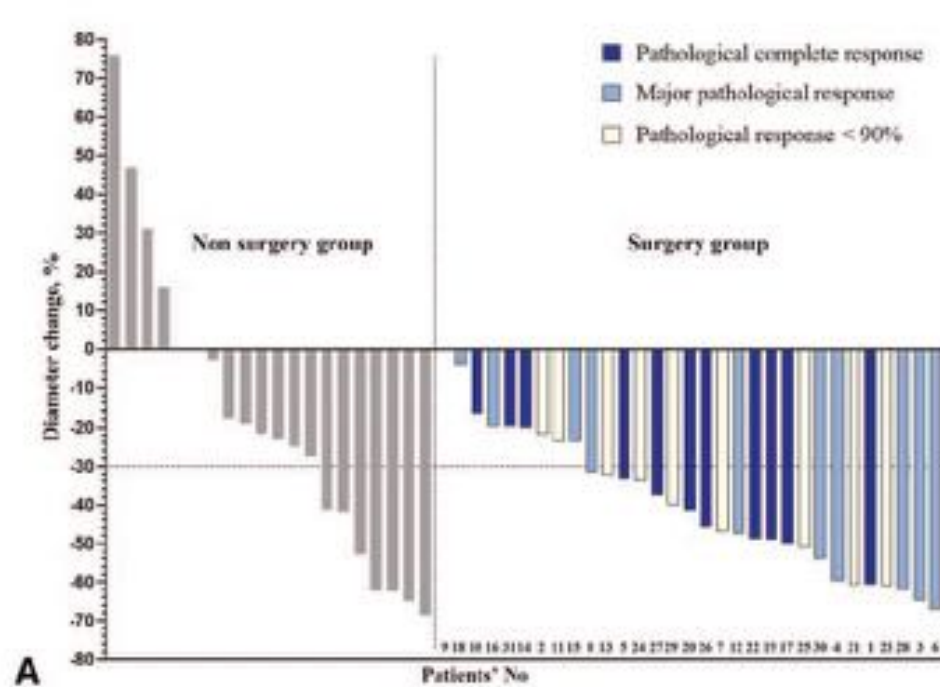
Progression free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; NIVO, nivolumab; OR, overall response; PFS, progression free survival

Provencio-Pulla M, et al. WCLC 2022 (Abstract 1988)

Radical Minimally Invasive Surgery After Immuno-chemotherapy in Initially-unresectable Stage IIIB Non-small cell Lung Cancer

Hongsheng Deng, MD,* Jun Liu, MD,* Xiuyu Cai, MD,† Jiawei Chen, MD,* Gaetano Rocco, MD, FRCSEd,‡
René Horsleben Petersen, MD,§ Alessandro Brunelli, MD,¶ Calvin S. H. Ng, MD,|| Thomas A. D'Amico, MD,**
Wenhua Liang, MD,*✉ and Jianxing He, MD, PhD, FACS*✉



Ann Surg 2022;275:e600-e602

We will learn more from Checkmate-816 about resectability, the role of pneumonectomy, and the need for R0 resection

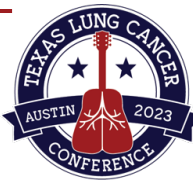


Table S6. Surgical Outcomes Summary by Region.

	Nivolumab plus Chemotherapy				Chemotherapy			
	North America (N = 41)	Europe (N = 41)	Asia (N = 85)	Rest of World ^a (N = 12)	North America (N = 58)	Europe (N = 25)	Asia (N = 92)	Rest of World ^a (N = 12)
	number of patients (percent)							
Patients with cancelled surgery	4 (9.8)	12 (29.3)	9 (10.6)	3 (25.0)	6 (12.0)	7 (28.0)	19 (20.7)	5 (41.7)
Surgical approach ^b								
Thoracotomy	18 (48.6)	26 (89.7)	37 (50.0)	7 (77.8)	23 (57.5)	15 (88.2)	42 (59.2)	5 (71.4)
Minimally invasive ^c	16 (43.2)	1 (3.4)	25 (33.8)	2 (22.2)	13 (32.5)	1 (5.9)	14 (19.7)	1 (14.3)
Minimally invasive to thoracotomy	3 (8.1)	2 (6.9)	12 (16.2)	0	4 (10.0)	1 (5.9)	15 (21.1)	1 (14.3)
Type of surgery ^d								
Pneumonectomy	5 (13.5)	4 (13.8)	14 (18.9)	2 (22.2)	8 (20.0)	7 (41.2)	17 (23.9)	2 (28.6)
Lobectomy	26 (75.7)	23 (79.3)	57 (77.0)	7 (77.8)	31 (77.5)	7 (41.2)	39 (54.9)	5 (71.4)
Sleeve lobectomy	0	0	2 (2.7)	0	0	0	10 (14.1)	0
Bilobectomy	1 (2.7)	2 (6.9)	0	0	0	1 (5.9)	3 (4.2)	0
Other	11 (29.7)	3 (10.3)	10 (13.5)	0	10 (25.0)	3 (17.6)	8 (11.3)	0
R0 (no residual tumor) ^e	24 (54.9)	26 (89.7)	67 (90.5)	7 (77.8)	20 (50.0)	15 (88.2)	63 (86.7)	7 (100.0)

^a Argentina and Turkey.

^b Denominator based on patients with definitive surgery.


^c Thoracoscopic/robotic.

^d Patients may have had more than one surgery type.


Spicer J, et al. N Engl J Med 2022;386:1973-85

Is pneumonectomy still such a terrible thing?

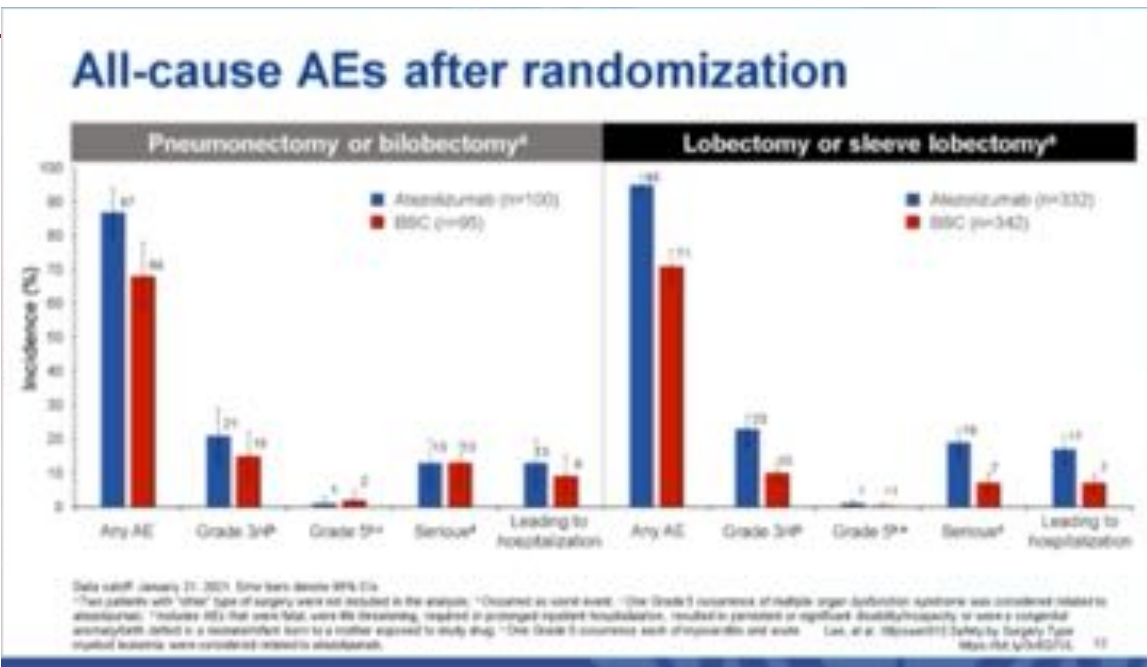
IMpower010



International Thoracic Surgical Oncology Summit



	IMpower010 safety-evaluable randomized Stage II-IIIa population (N=871)	
Type of surgery, n (%)	Atezolizumab (n=433)	BSC (n=438)
Lobectomy or Sleeve lobectomy	332 (77%)	342 (78%)
Bilobectomy	30 (7%)	17 (4%)
Pneumonectomy	70 (16%)	78 (18%)



Adjuvant atezolizumab treatment

	Pneumonectomy or bilobectomy ^a	Lobectomy or sleeve lobectomy ^a
	Atezolizumab (n=100)	Atezolizumab (n=332)
Treatment discontinuation, n (%) ^b	32 (32)	115 (36)
Due to AE	15 (15)	64 (19)
Due to disease relapse	14 (14)	37 (11)
Median treatment duration (range), mo	10.4 (0-13)	10.4 (0-16)
Median doses received, n (range)	16 (1-16)	16 (1-16)

www.thelancet.com Published online September 20, 2021 [https://doi.org/10.1016/S0140-6736\(21\)02098-5](https://doi.org/10.1016/S0140-6736(21)02098-5)

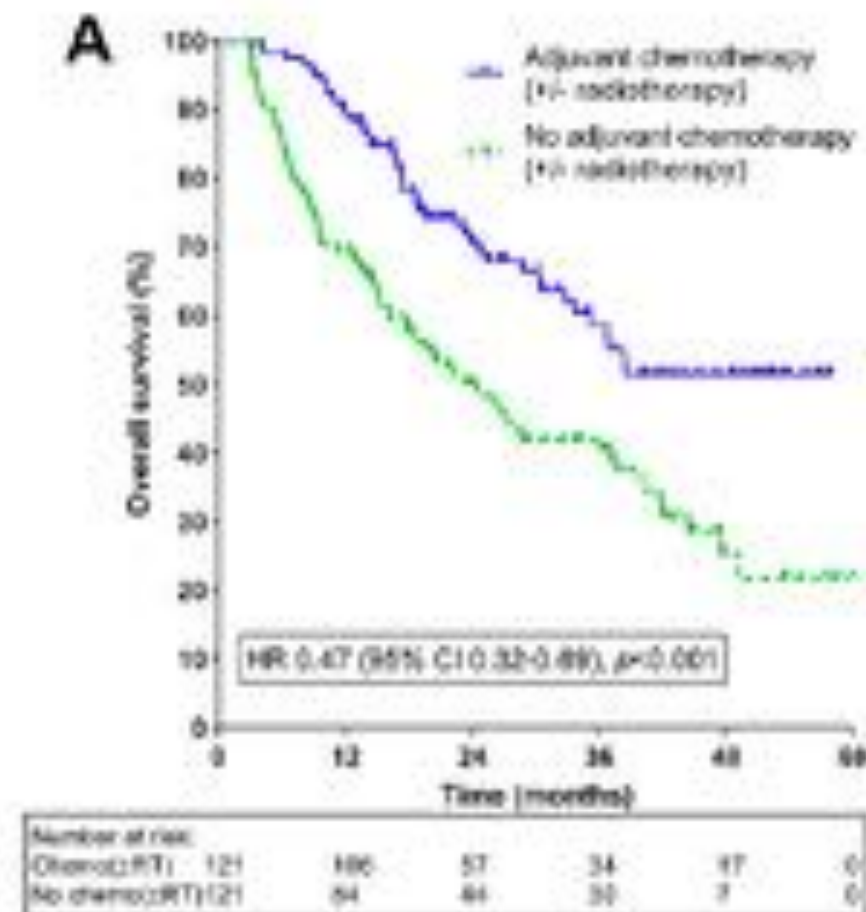
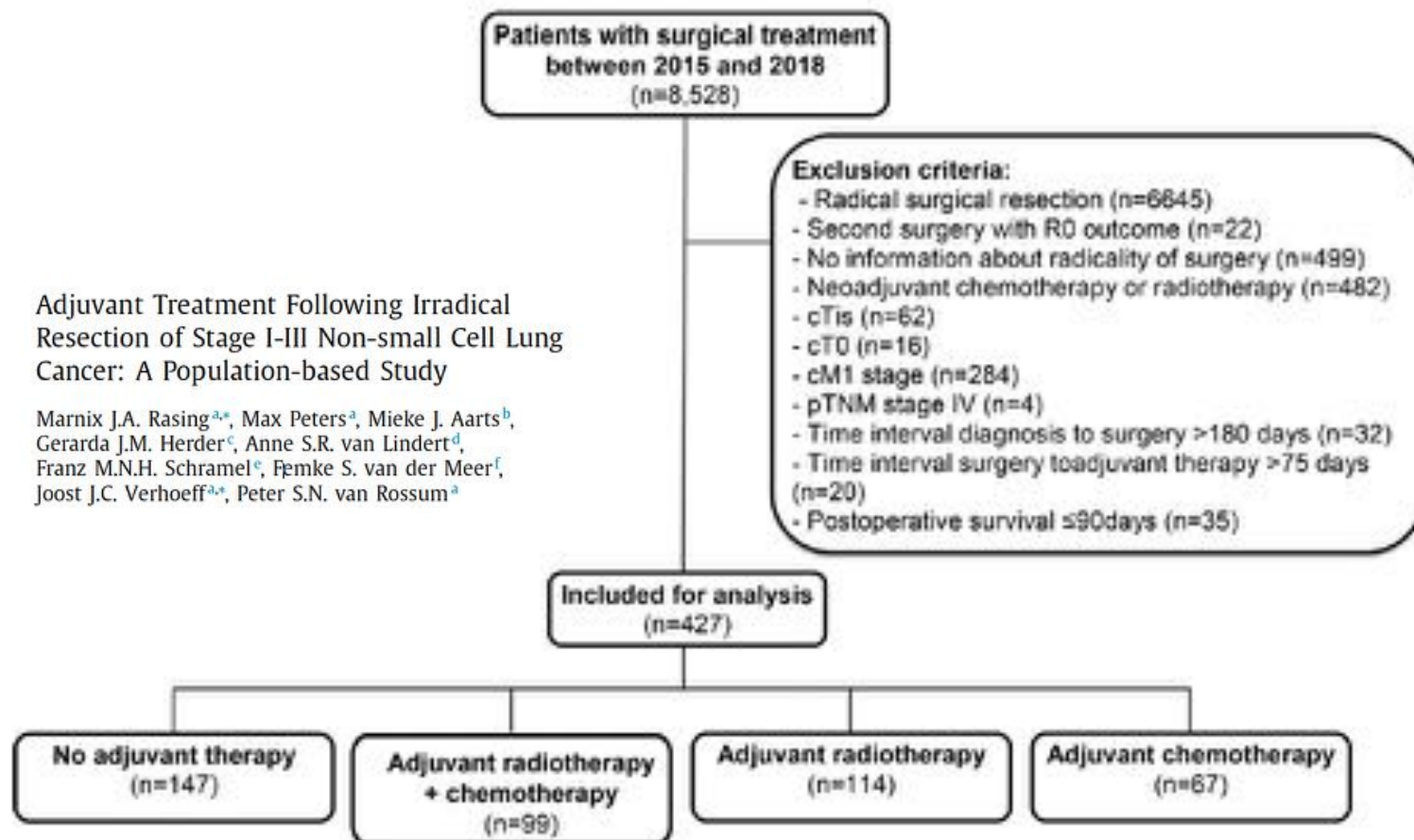
Data cutoff: January 21, 2021. NA, not applicable.
^aTwo patients with "other" type of surgery were not included in the analysis. ^bPatients who discontinued treatment as or after the start of atezolizumab. Lee, et al. IMpower010 Safety by Surgery Type. N Engl J Med. 2021;384:102-114.

What actually does happen if surgeons don't “get it all”?



Adjuvant Treatment Following Irradical Resection of Stage I-III Non-small Cell Lung Cancer: A Population-based Study

Marnix J.A. Rasing^{a,*}, Max Peters^a, Mieke J. Aarts^b, Gerarda J.M. Herder^c, Anne S.R. van Lindert^d, Franz M.N.H. Schramel^e, Femke S. van der Meer^f, Joost J.C. Verhoeff^{a,*}, Peter S.N. van Rossum^a

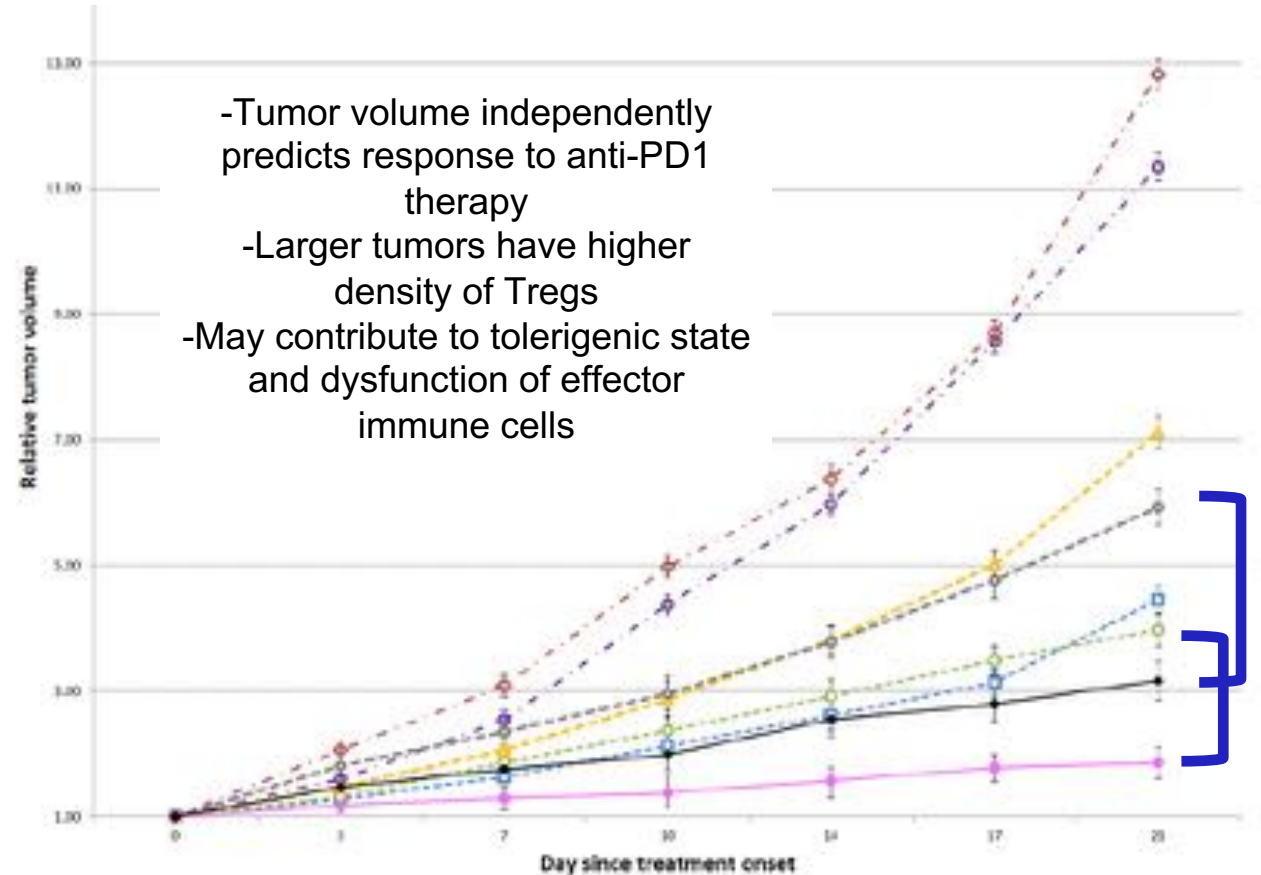
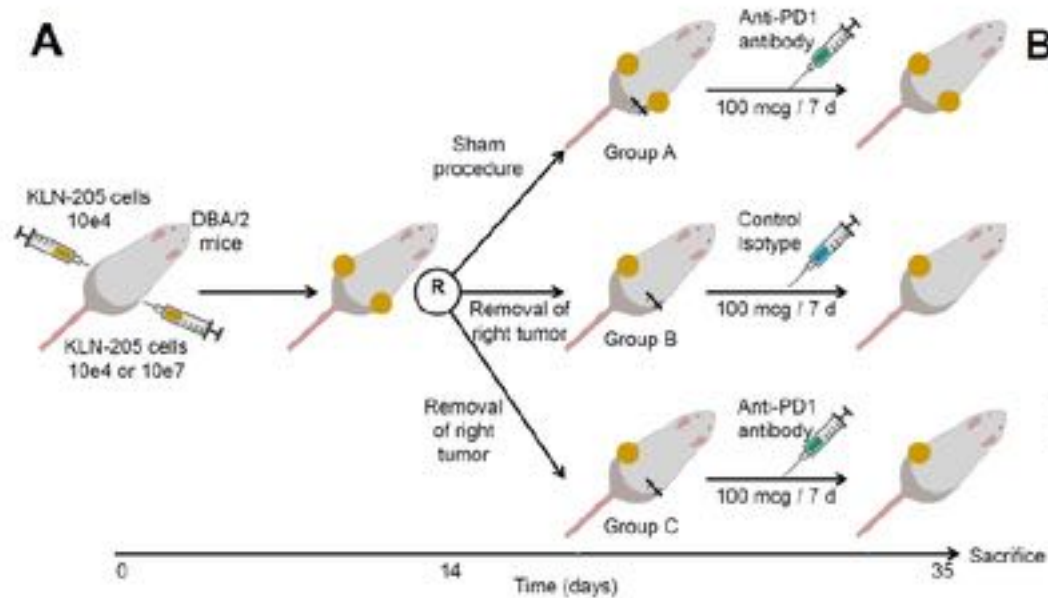


Current Problems in Cancer 46 (2022) 100784

Surgical debulking as an immune primer?

A rationale for surgical debulking to improve anti-PD1 therapy outcome in non small cell lung cancer

Florian Guisier^{1,2,3*}, Stephanie Cousse^{1,2}, Mathilde Jeanvoine^{1,2}, Luc Thiberville^{1,2,3} & Mathieu Salaun^{1,2,3}



Scientific Reports (2019)9:16902

Case 1: Treatment



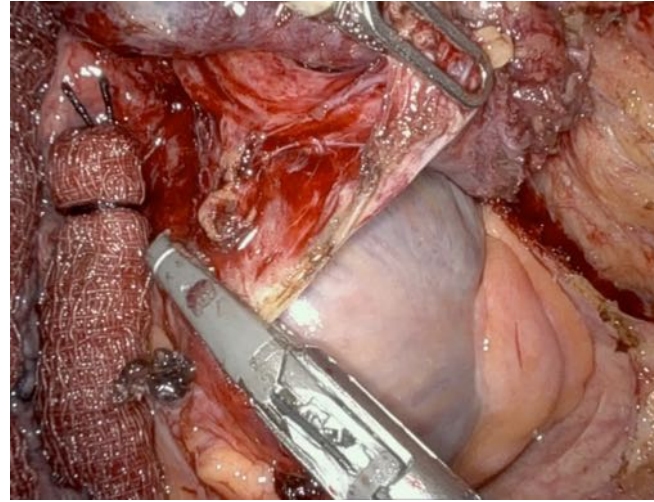
Neoadjuvant therapy: Carbo/Paclitaxel + Nivolumab x 3 cycles

Well tolerated with good response: size decreased to 4.0 x 2.9 cm

Subsequently taken to surgery for robotic exploration and resection

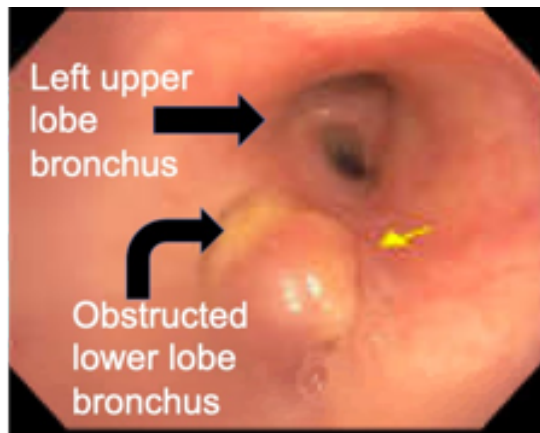
R0 resection performed with right middle lobectomy and en bloc resection of pericardium

Final path: No evidence of residual tumor (pCR), multiple lymph nodes with granulomatous inflammation

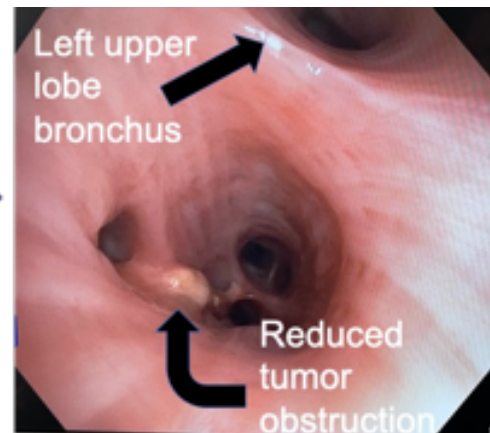


Case 2: Treatment

- Treatment with induction osimertinib for 10 weeks
- Tolerated without major toxicity
- Major clinical response in follow-up imaging
- Obvious reduction in endobronchial burden of disease



Pre-osimertinib



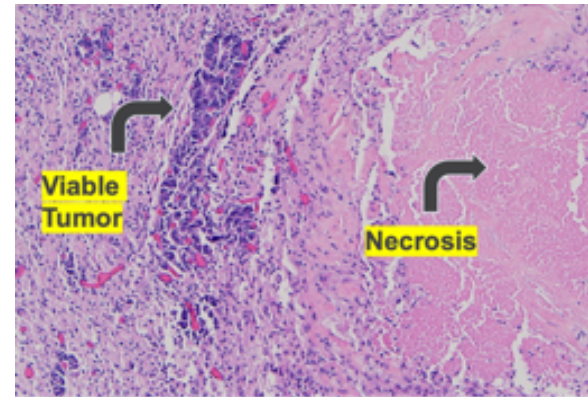
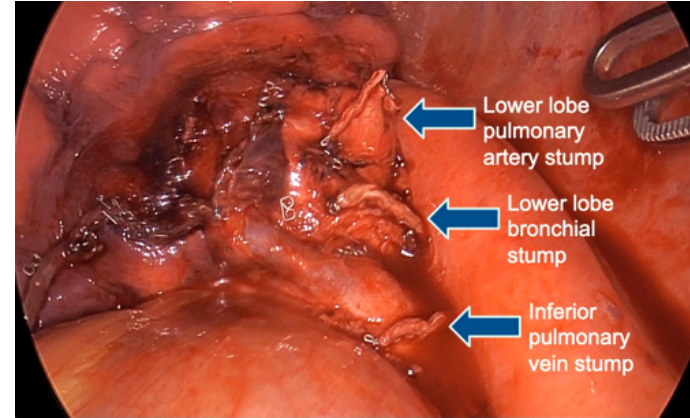
Post-osimertinib



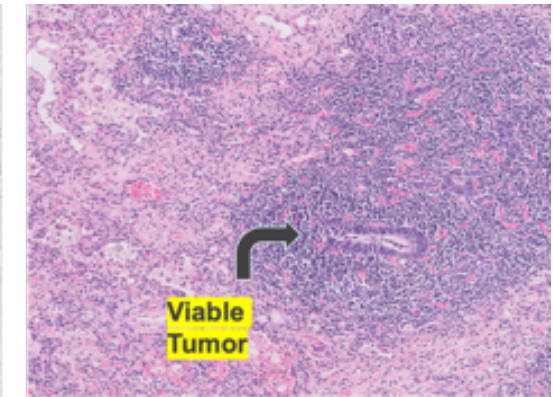
Treatment: Surgical resection



- Performed via standard three-port video-assisted technique
- Uneventful postoperative course
- Discharged POD3
- Final pathology
 - Viable tumor 0.9cm with visceral pleural invasion
 - 1/24 lymph nodes positive: 10% viable tumor in subcarinal node
 - ypT_{2a}N₂



Primary Tumor



Subcarinal Lymph Node

Conclusions



*"If you're looking for
God, he was in
operating room #2"*

-No more!

- We CAN convert "unresectable" to resectable
- Surgical experience and volume are critical, as is multidisciplinary consensus
- *Whether in the eye of the beholder or a state of mind, we will likely see more patients with Stage III NSCLC who undergo surgical resection as part of their multi-modality therapy*
- Neoadjuvant chemotherapy/immunotherapy does not appear to make surgery more difficult and may make it easier
- Surgeons should still (probably) avoid pneumonectomy, but this should be weighed against extent and morbidity of radiation therapy