The Role of Surgeons in the Current Era of Molecular Therapy

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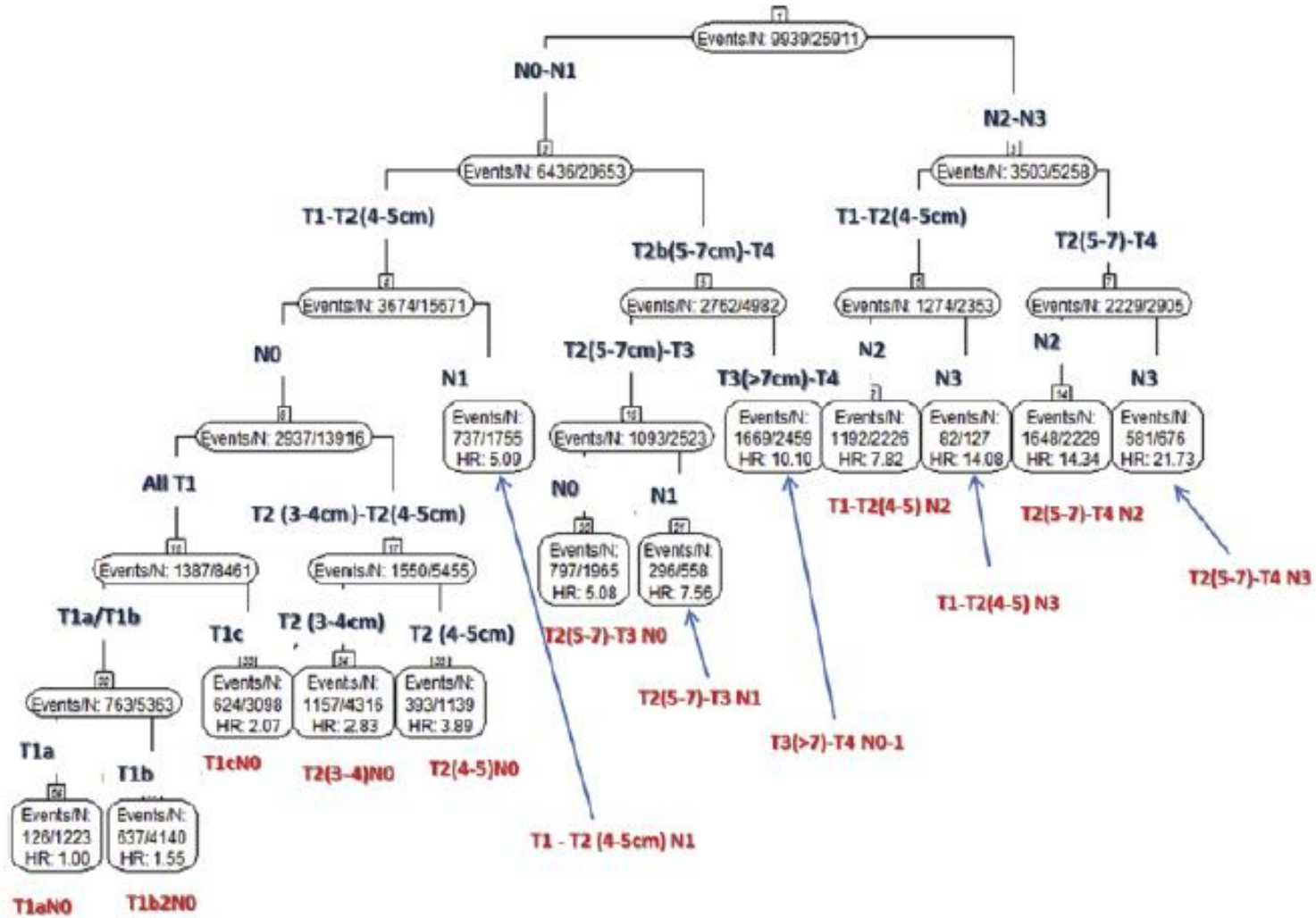
An exciting multidisciplinary landscape

- *Multidisciplinary care of cancer patients is increasingly essential*
- Molecular testing and PD-L1 status will increasingly be used to make *a priori* surgical treatment decisions

What are we trying to achieve?

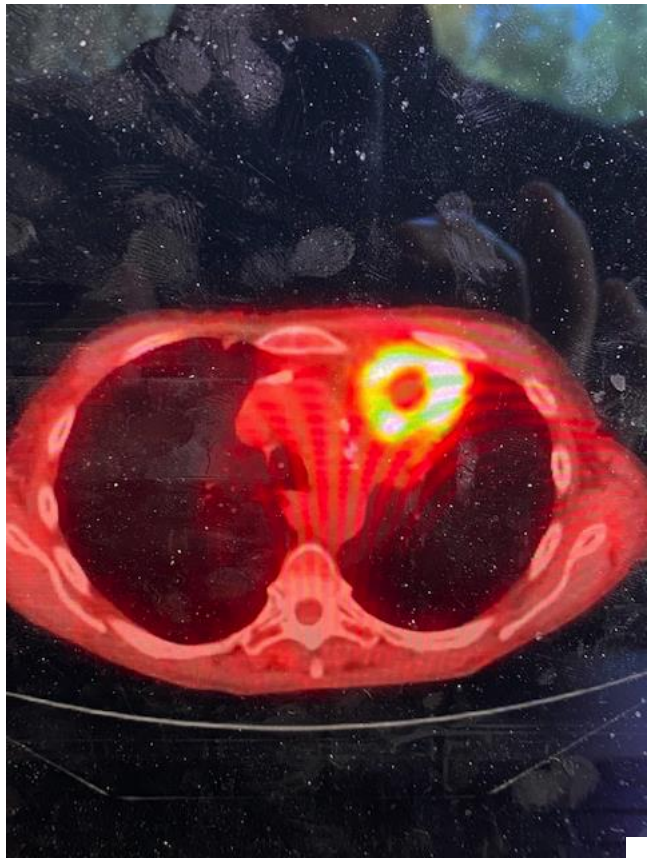
- Perfect oncologic result
  - Staging: as many lymph nodes assessed as possible
  - Negative margins with no tumor left
- Minimal physiologic result
  - Sparing lung
    - Segmentectomy for selected patients
  - Minimizing pain and suffering
    - Robotic surgery

IASLC 8th Edition Staging Proposals



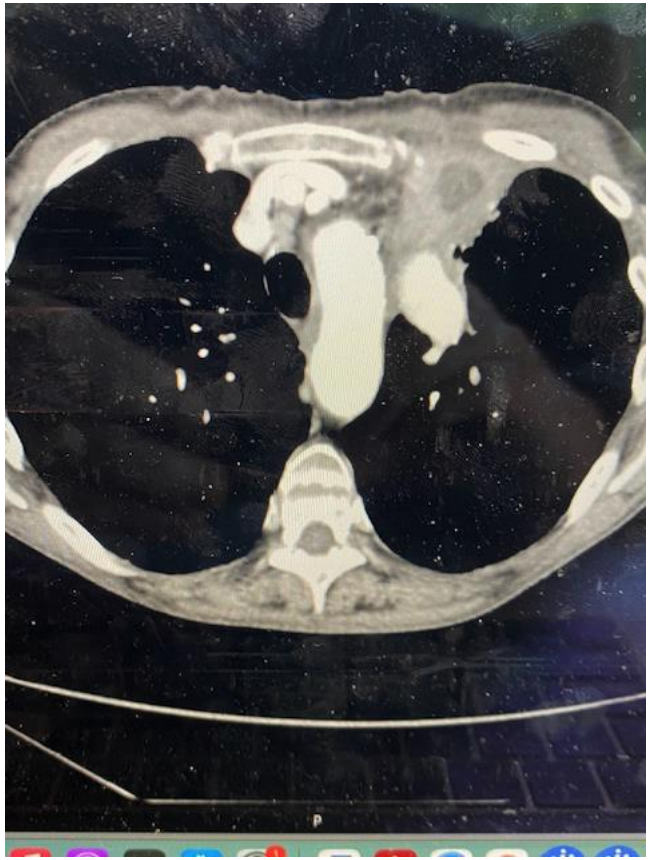
Case

- 77yo lady with large LUL lesion found on chest CT for pneumonia. She is active and can easily walk up 2 flights of stairs. Pulmonology saw her and diagnosed squamous cell cancer on bronchoscopic biopsy. EBUS-guided biopsies of 4L, 4R, and 7 were negative. PDL-1 TPS was 3%.



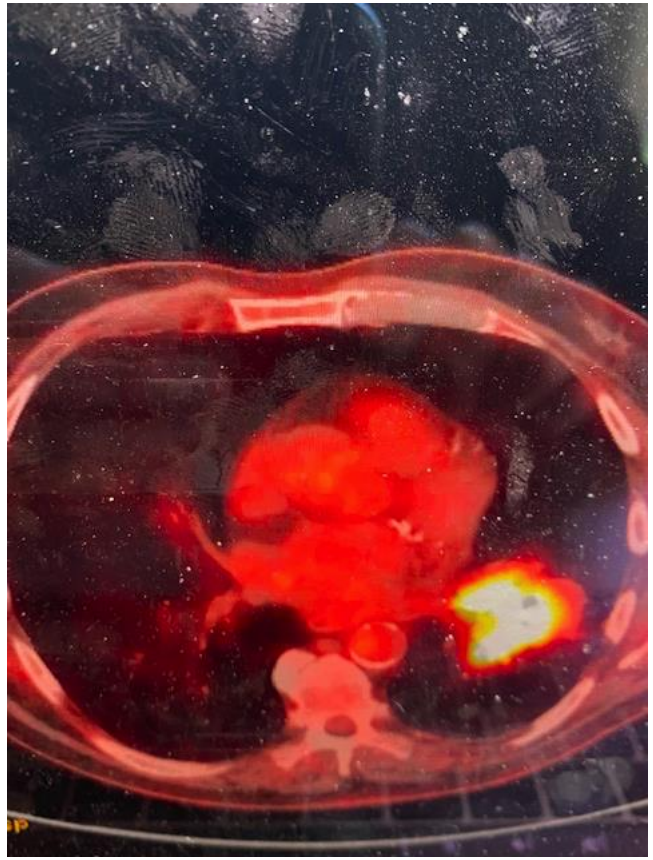
Induction chemoimmunotherapy

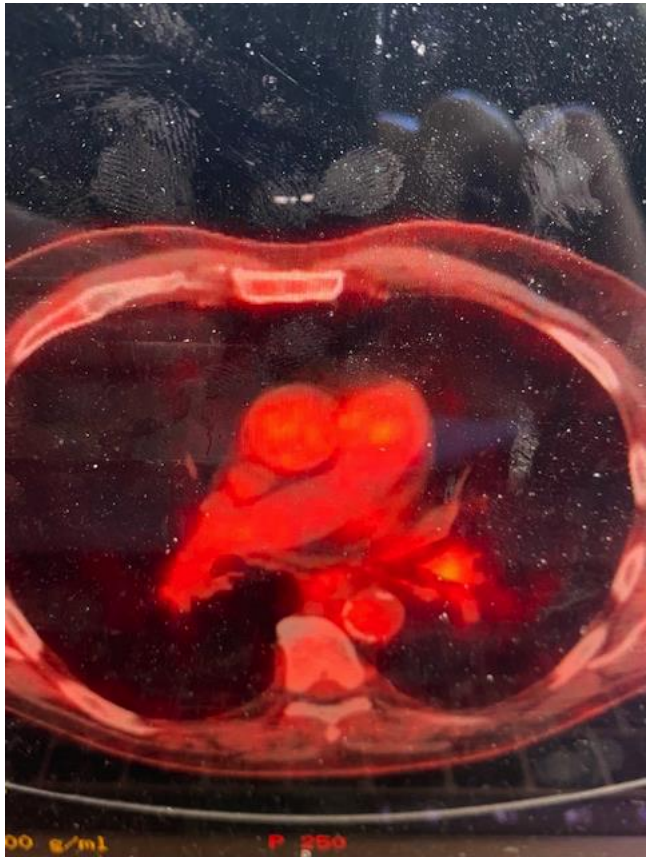
- She underwent 3 cycles of cisplatin-based chemotherapy along with pembrolizumab, which she tolerated well. We performed a robotic left upper lobectomy with focal chest wall resection of intercostal muscle.
- Path: ypT3N2 (2 level 5 nodes positive)



Another case

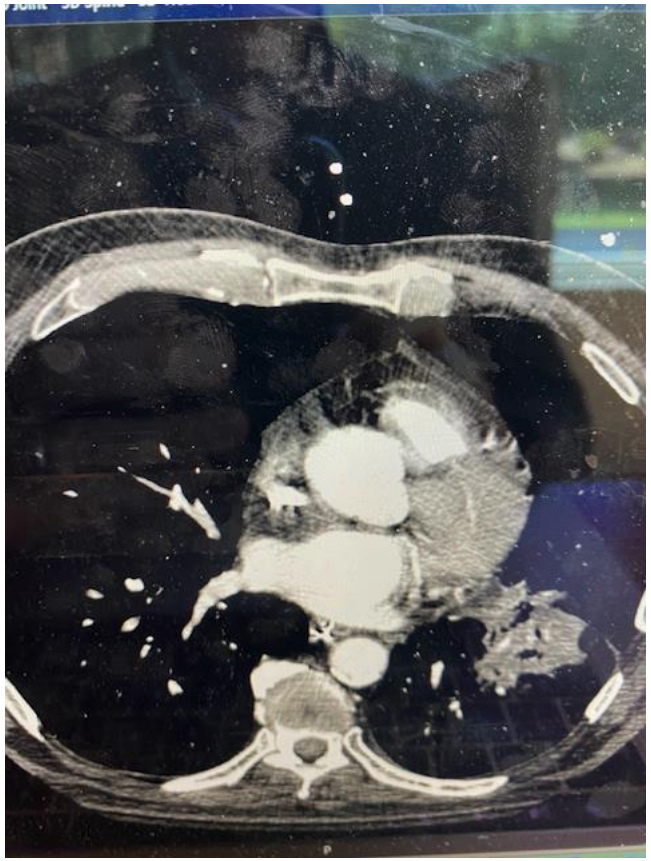
- 75yo man with clinical stage II LLL squamous tumor. He is healthy and able to tolerate 4 METS. PDL-1 TPS 30%





Induction Chemo/IO

- He received 3 cycles of carbo/pemetrexed and pembrolizumab, which he tolerated well. We performed a robotic L lower lobectomy, and he had a complete response.



Basic NSCLC Treatment Strategies

IA & small IB	II and non-N2 IIIA	IIIA N2	IIIB/C
Resection ± adjuvant treatment	*Resection + adjuvant treatment*	*Neoadjuvant treatment + resection, resection + adjuvant, definitive CRT*	*Definitive chemotherapy/RT + I/O*

IA	**IIA**	**IIIA**	**IIIB**
IB **IIA**	**IIA/IIB**	**IIIA**	**IIIB**
IIB	**IIIA**	**IIIA**	**IIIC**
IIIA	**IIIA**	**IIIB**	**IIIC**
IVA/B/C	**IVA/B/C**	**IVA/B/C**	**IVA/B/C**

IVA/B/C
I/O, Chemotherapy ± I/O, targeted therapy

Non-N2 IIIA
Resection + adjuvant tx

IIIA N2
Potential neoadjuvant + resection, determined by bulk of nodal dx

IIIB/C
Definitive chemo/XRT + I/O

NCCN Guidelines® for Non-Small Cell Lung Cancer (Version 3.2022). © 2022 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, g
Postmus, et al. Ann Oncol 2017

Outline

- Role of minimally-invasive techniques
- Role of sublobar resection
- Role of adjuvant/neoadjuvant therapy in surgical patients

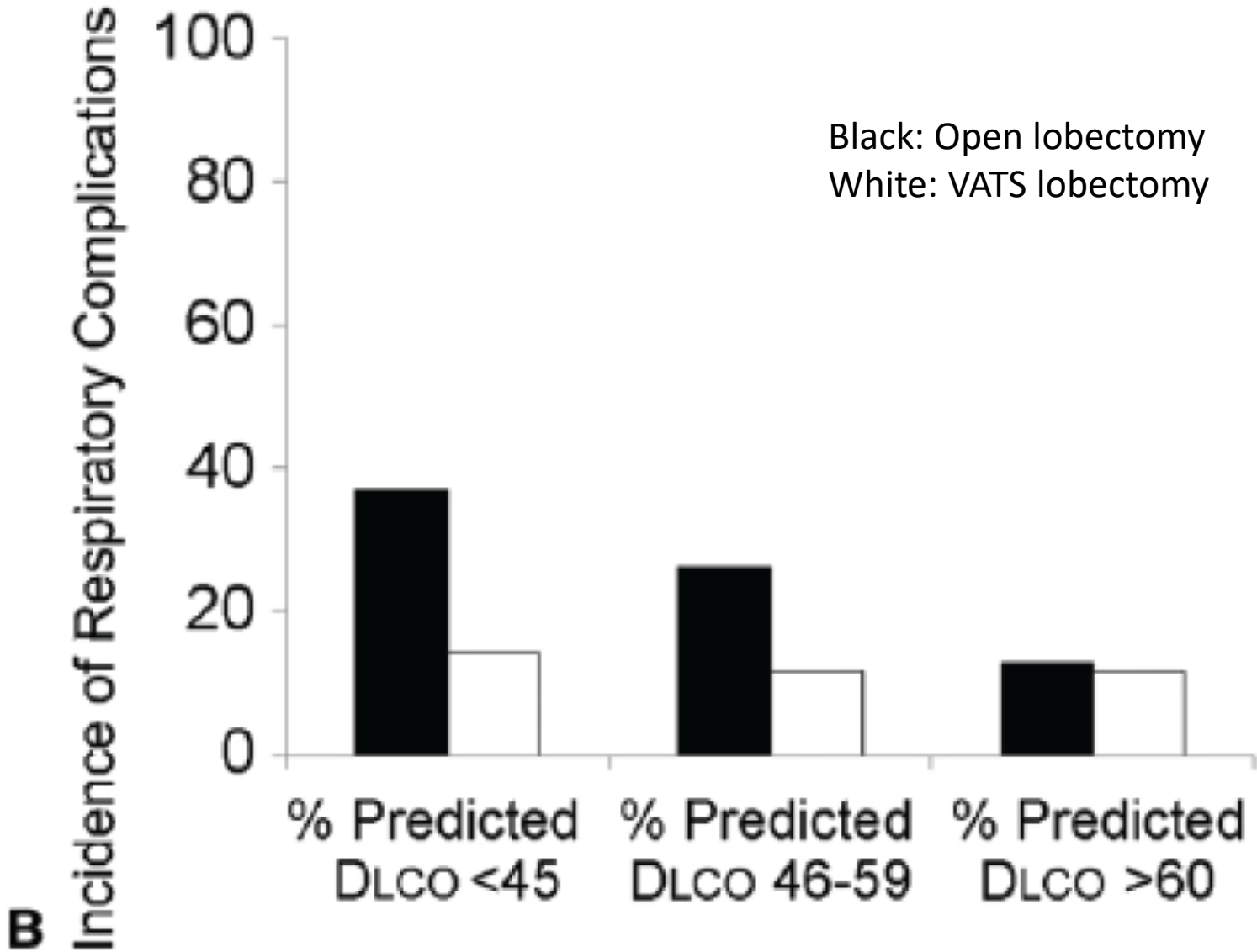
VATS/Minimally-invasive Definition

- Absence of rib spreading
- Visualization by camera

Importance of minimally-invasive resection

- Less pain
- Decreased LOS
- Earlier return to work
- Better tolerance of adjuvant therapy

Importance of Minimally-Invasive Approach

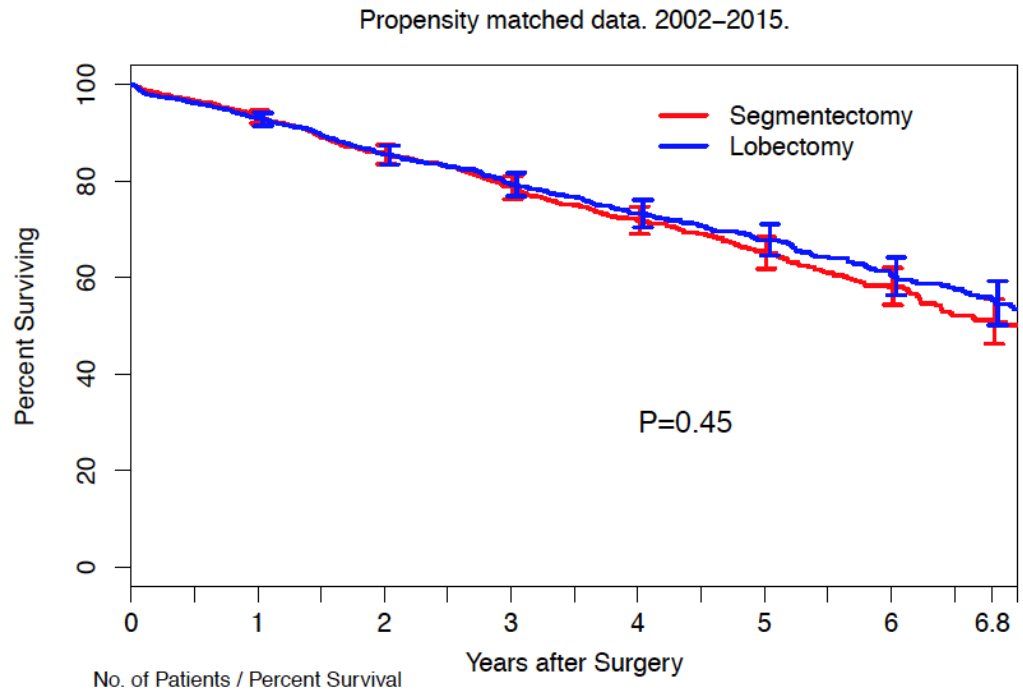


Black: Open lobectomy
White: VATS lobectomy

STS-Medicare data

- Linked STS database to Medicare to explore long-term outcomes
- 14286 stage IA patients
  - 1654 segmentectomy, 12632 lobectomy
- 2 analyses: Cox survival model and propensity matched groups (1654 pairs)

Procedure Lobectomy Segmentectomy	 1.00 1.10 (0.94,1.28)	0.2361	 1.00 1.04 (0.89,1.20)	0.6374
Approach Open VATS	 1.00 0.77 (0.71,0.83)	 <.0001	 1.00 0.86 (0.80,0.94)	 0.0006



No. of Patients / Percent Survival

Segmentectomy	1476	1186/93.5	918/85.6	683/78.9	484/71.8	317/65.3	169/58.1	102/50.7
Lobectomy	1476	1168/93.1	888/85.5	649/79.3	466/73.4	321/67.8	187/60.5	119/55.5

CALGB 140503

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 9, 2023 VOL. 388 NO. 6

Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer

Nasser Altorki, M.D., Xiaofei Wang, Ph.D, David Kozono, M.D., Ph.D., Colleen Watt, B.S., Rodney Landrenau, M.D., Dennis Wigle, M.D., Ph.D., Jeffrey Port, M.D., David R. Jones, M.D., Massimo Conti, M.D., Ahmad S. Ashrafi, M.D., Moishe Liberman, M.D., Ph.D., Kazuhiro Yasufuku, M.D., Ph.D., Stephen Yang, M.D., John D. Mitchell, M.D., Harvey Pass, M.D., Robert Keenan, M.D., Thomas Bauer, M.D., Daniel Miller, M.D., Leslie J. Kohman, M.D., Thomas E. Stinchcombe, M.D., and Everett Vokes, M.D.

CALCB 140503

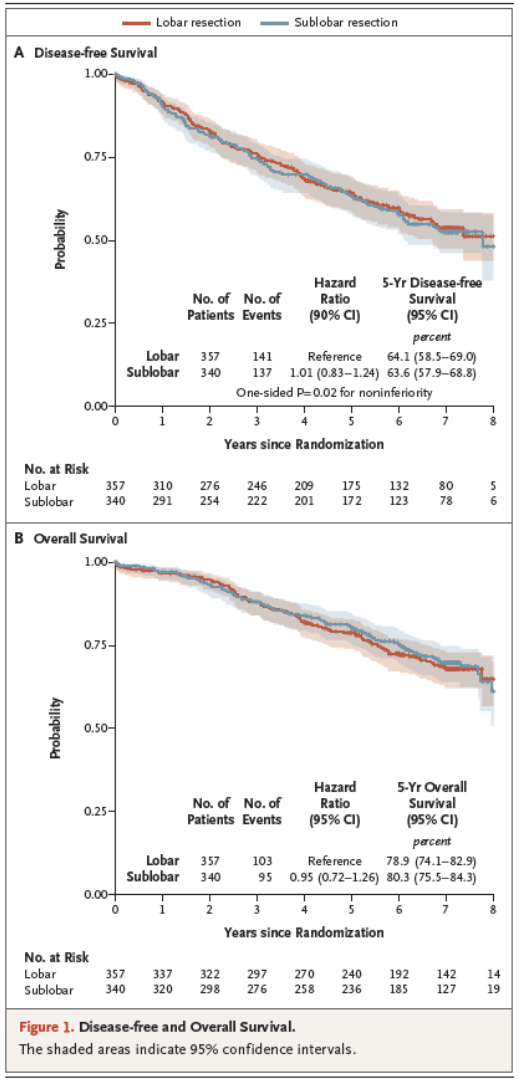


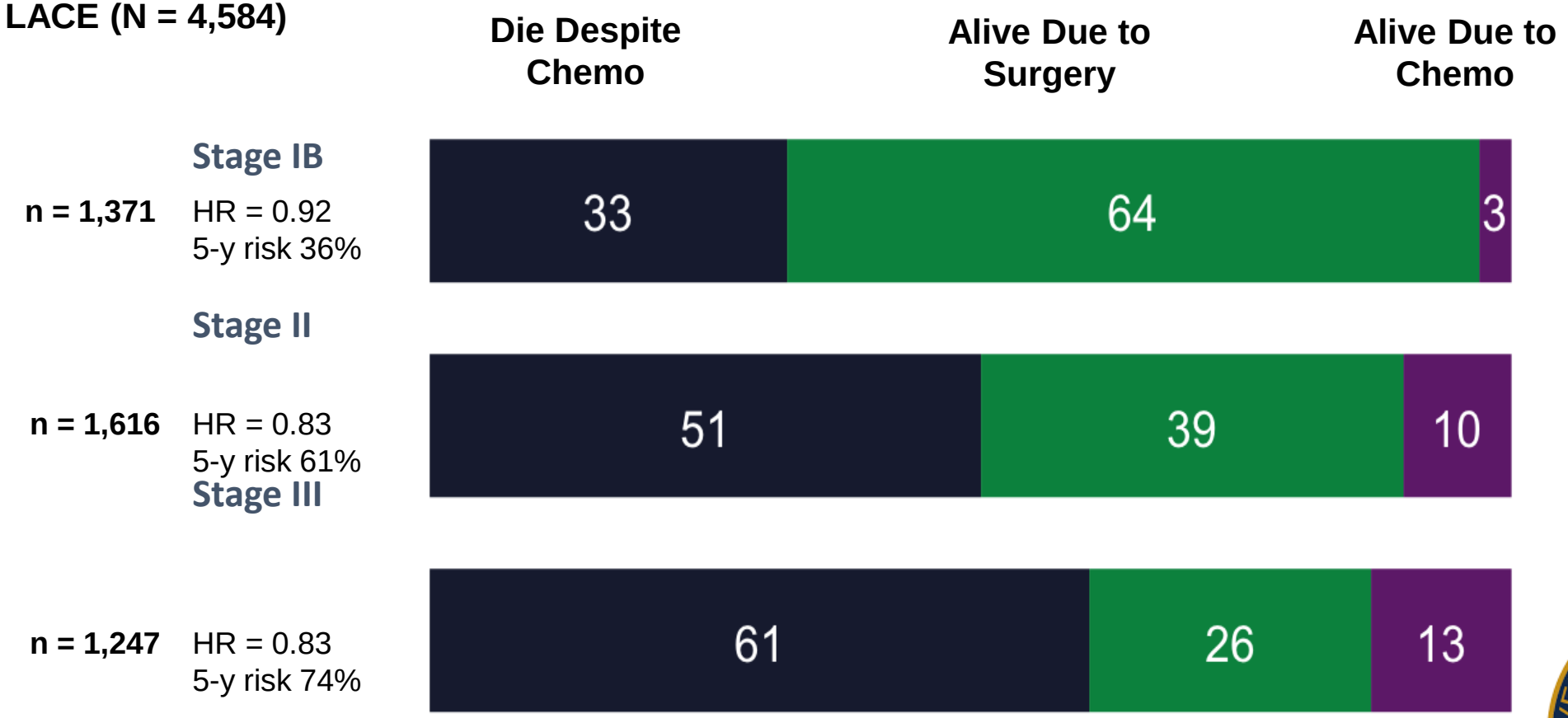
Figure 1. Disease-free and Overall Survival.
The shaded areas indicate 95% confidence intervals.

- T1aN0 patients
- Outer third of lung
- Intraoperative confirmation of N0 status

What about higher stages?

Adjuvant Chemotherapy

LACE (N = 4,584)



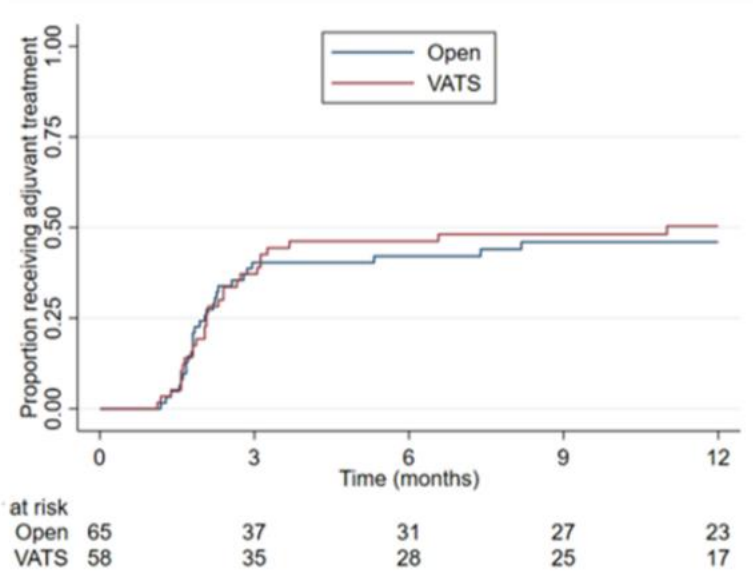
Note: 6th TNM edition staging was used.

Low rates of adjuvant therapy: VIOLET

Outcome	Randomised to VATS (n=247)	Randomised to open surgery (n=255)	HR (95% CI)	p value
Received adjuvant treatment	34/216 (15.7%)	39/216 (18.1%)		
Received adjuvant treatment (eligible subset [a])	28/55 (50.9%)	28/61 (45.9%)		
Time to uptake of adjuvant treatment (months)	-	-	HR=0.90 (0.50, 1.61)	0.716
Time to uptake of adjuvant treatment (eligible subset [a]) (months)	11.0 (2.1, -)	- (2.0, -)	HR=1.12 (0.62, 2.02)	0.716

Data are n/N (%). Analyses are adjusted for operating surgeon.

a Eligible if i) N1-2 disease and M0 disease after surgery, or ii) T2b to 4, N0 and M0 after surgery.



Median (IQR) time to adjuvant treatment (months) for eligible:

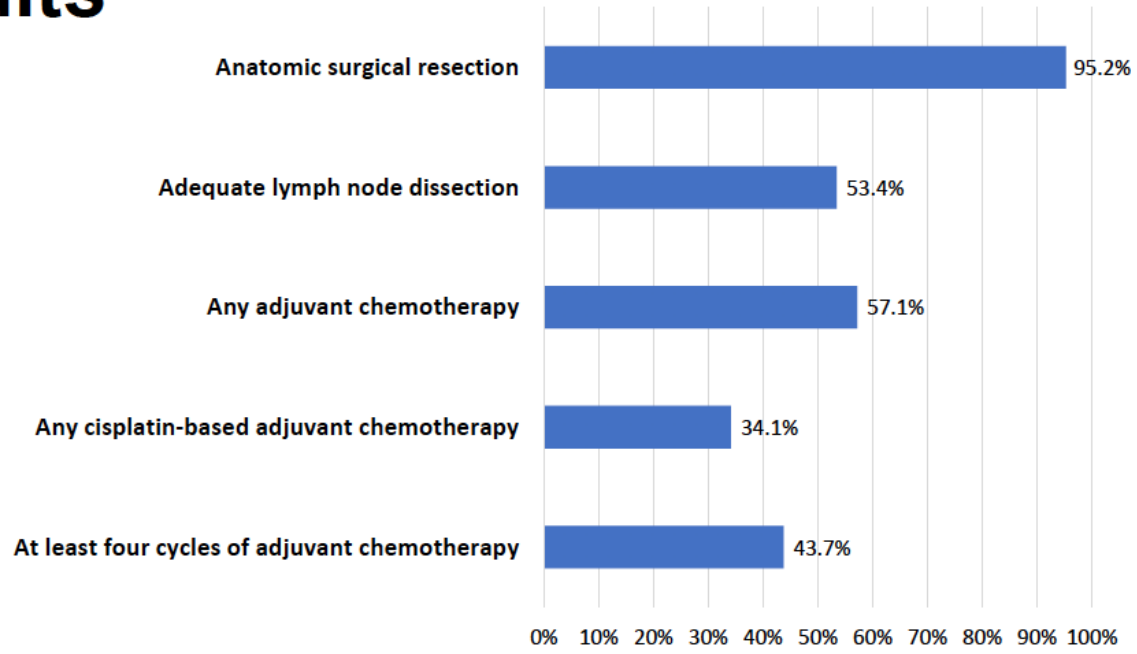
Open: n=28, Median= 1.89, IQR=(1.68, 2.43)
VATS: n=28, Median= 2.07, IQR=(1.63, 2.89)

More bad news

Rates of Guideline-Concordant Surgery and Adjuvant Chemotherapy in the U.S. ALCHEMIST Study (ALLIANCE)

Presenter: Kenneth L. Kehl, MD, MPH
Dana-Farber Cancer Institute
United States

Results

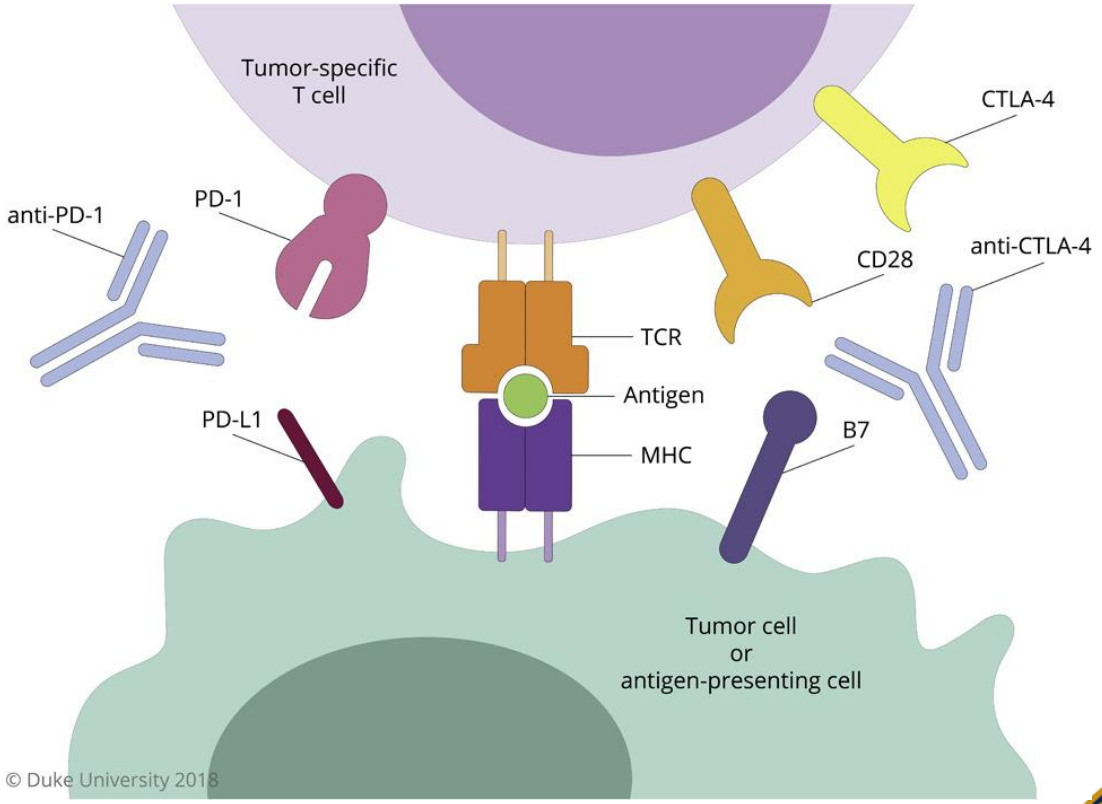


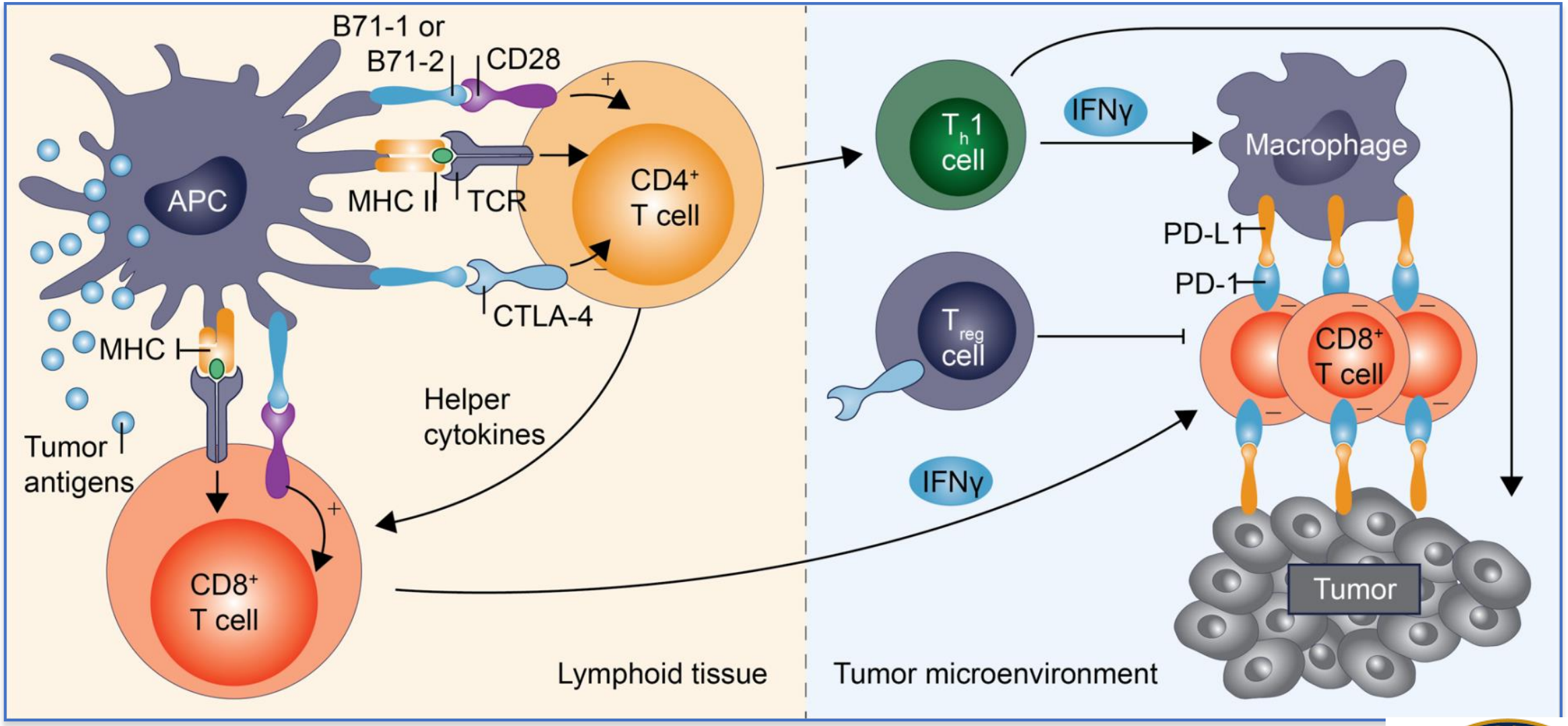
No association between socioeconomic factors and care process outcomes

IASLC | 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Ways to Enhance Anti-Tumor Immunity

- Vaccines
  - Peptide/Protein/Tumor cell lysates
  - Viral
  - Dendritic Cell
- Small molecule agonists and inhibitors
  - IDO
  - TGF-beta
- Cytokines
  - IL-2
- Immune checkpoint modulation
  - CTLA-4
  - PD-1, PD-L1
- Cellular therapy
  - CAR T cells

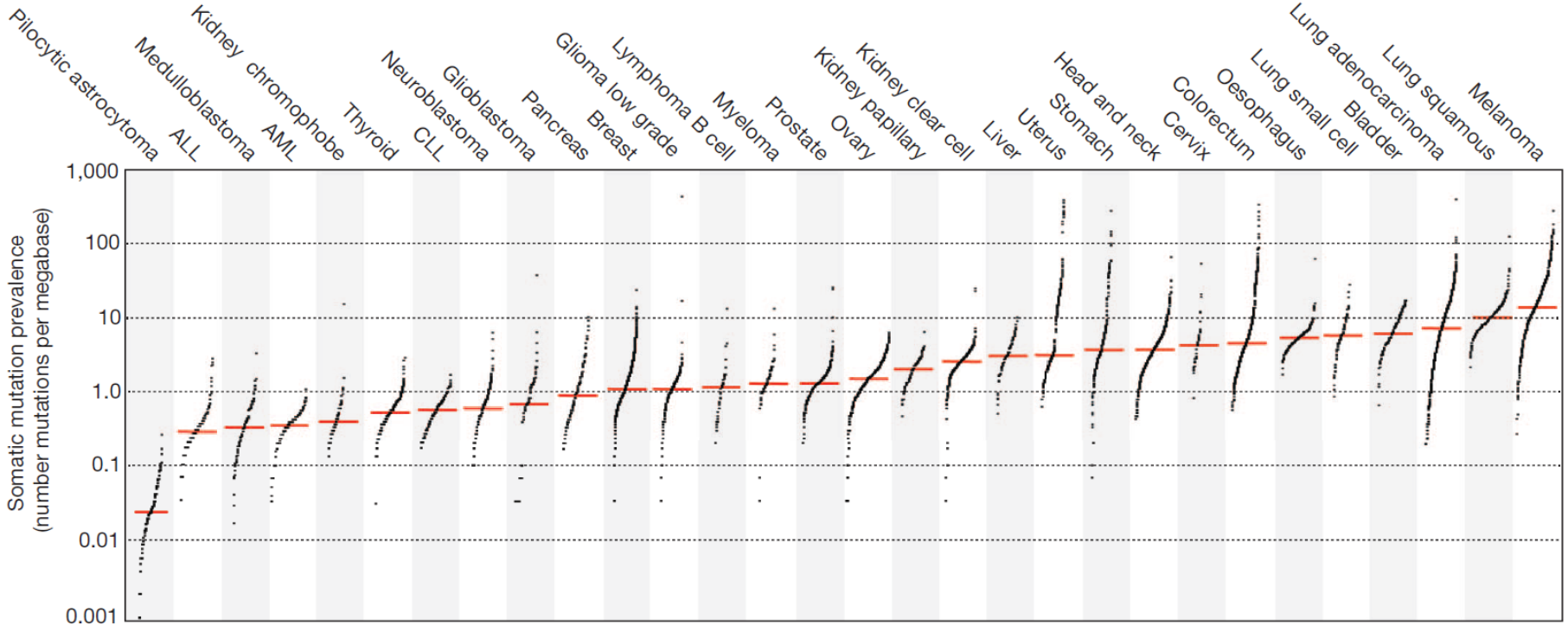



B71-1 or
B71-2
CD28
APC
MHC II
TCR
CD4+
T cell
CTLA-4
MHC
Tumor
antigens
Helper
cytokines
CD8+
T cell
Lymphoid tissue
Th1
cell
IFNγ
Macrophage
PD-L1
PD-1
Treg
cell
CD8+
T cell
IFNγ
Tumor
Tumor microenvironment

Current Immune Checkpoint Inhibitors

Drug	Mechanism
Ipilimumab	Anti–CTLA-4
Nivolumab	Anti–PD-1
Pembrolizumab	
Cemiplimab-rwlc	
Atezolizumab	Anti–PD-L1
Avelumab	
Durvalumab	

Mutational Burden and Immunotherapy Response



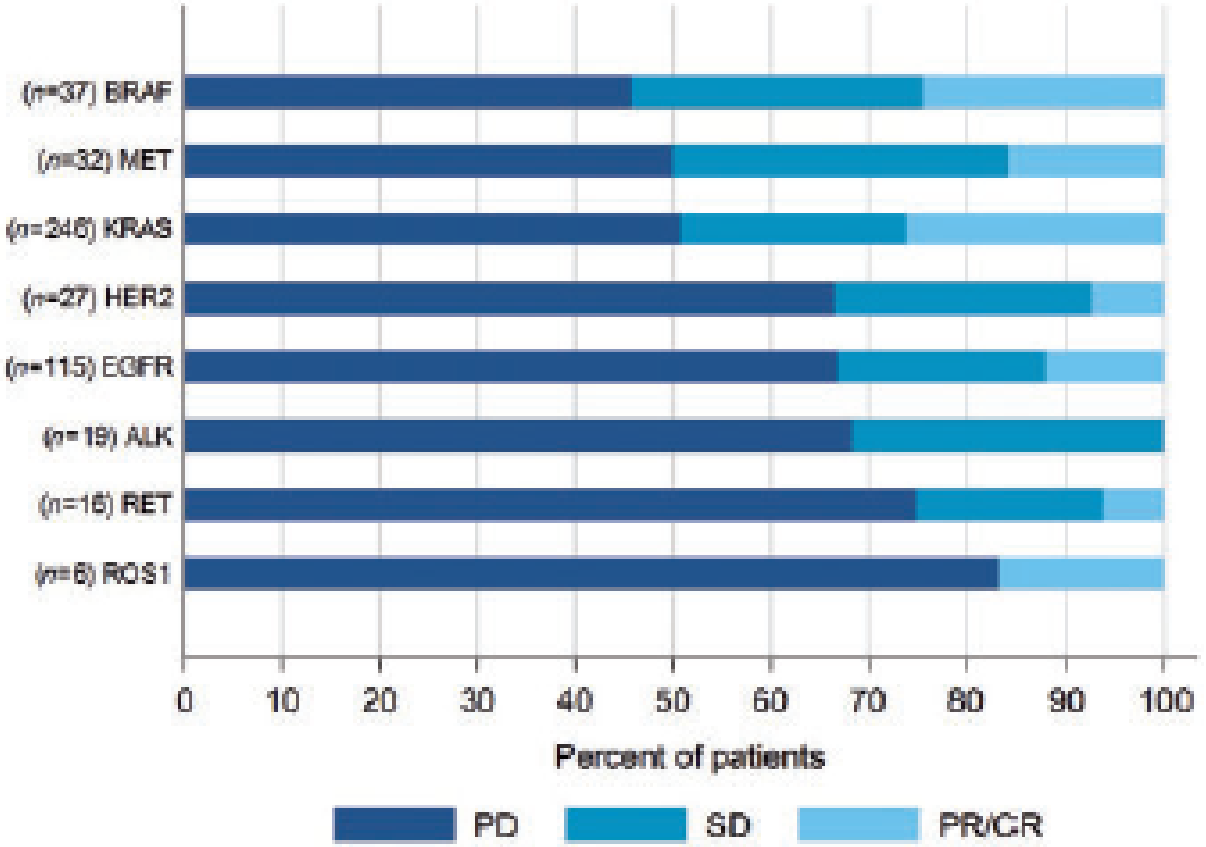
- Tumors with higher mutational burden tend to be more responsive to immunotherapy

Alexandrov LB et al, Nature, 201

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

Annals of Oncology 30: 1321–1328, 2019

J. Mazieres[1*], A. Drilon[2], A. Lusque[3], L. Mhanna[1], A. B. Cortot[4], L. Mezquita[5], A. A. Thai[6], C. Mascaux[7], S. Couraud[8], R. Veillon[9], M. Van den Heuvel[10], J. Neal[11], N. Peled[12], M. Früh[13], T. L. Ng[14], V. Gounant[15], S. Popat[16], J. Diebold[17], J. Sabari[2], V. W. Zhu[18], S. I. Rothschild[19], P. Bironzo[20], A. Martinez-Marti[21], A. Curioni-Fontecedro[22], R. Rosell[23,24], M. Lattuca-Truc[25], M. Wiesweg[26], B. Besse[5], B. Solomon[6], F. Barlesi[7], R. D. Schouten[10], H. Wakelee[11], D. R. Camidge[14], G. Zalcman[15], S. Novello[20], S. I. Ou[18], J. Milia[1] & O. Gautschi[27]



Adaura: adjuvant osimertinib

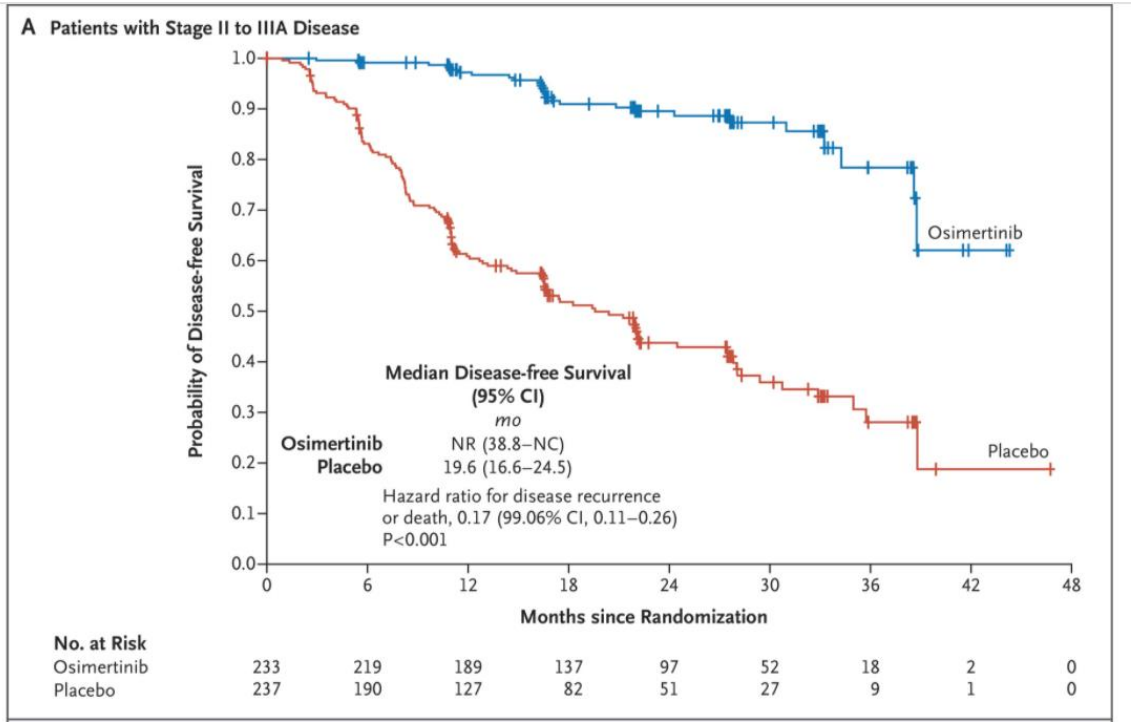
The NEW ENGLAND JOURNAL of MEDICINE

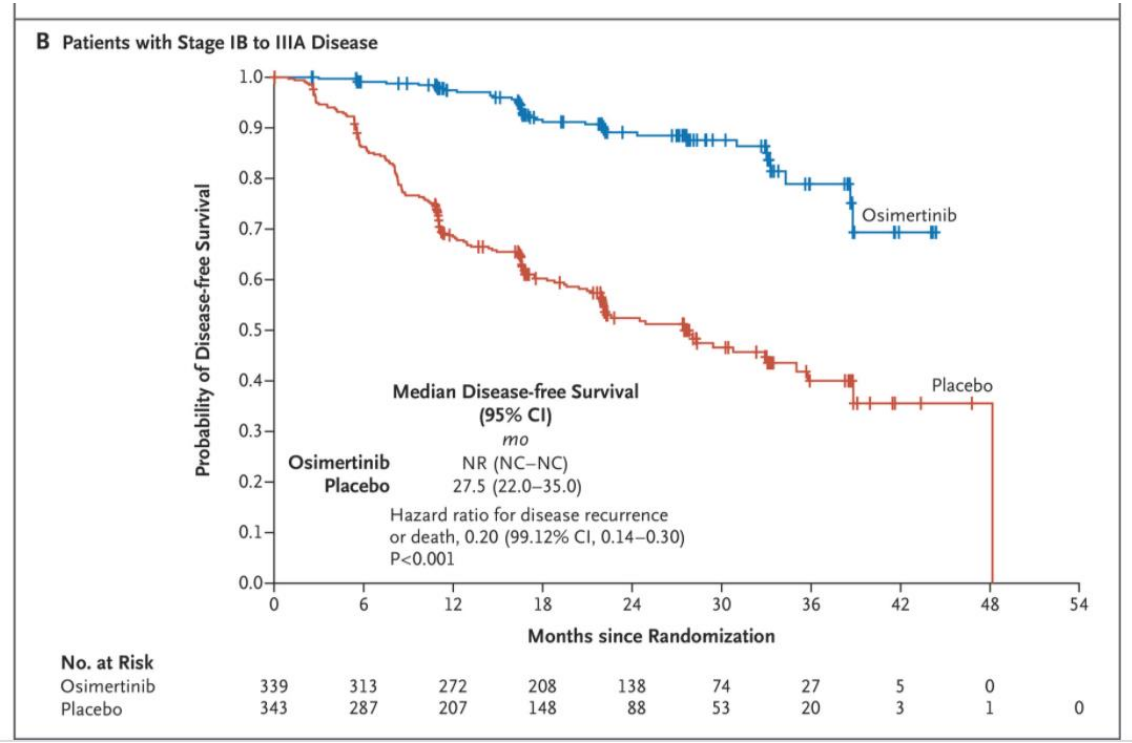
ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

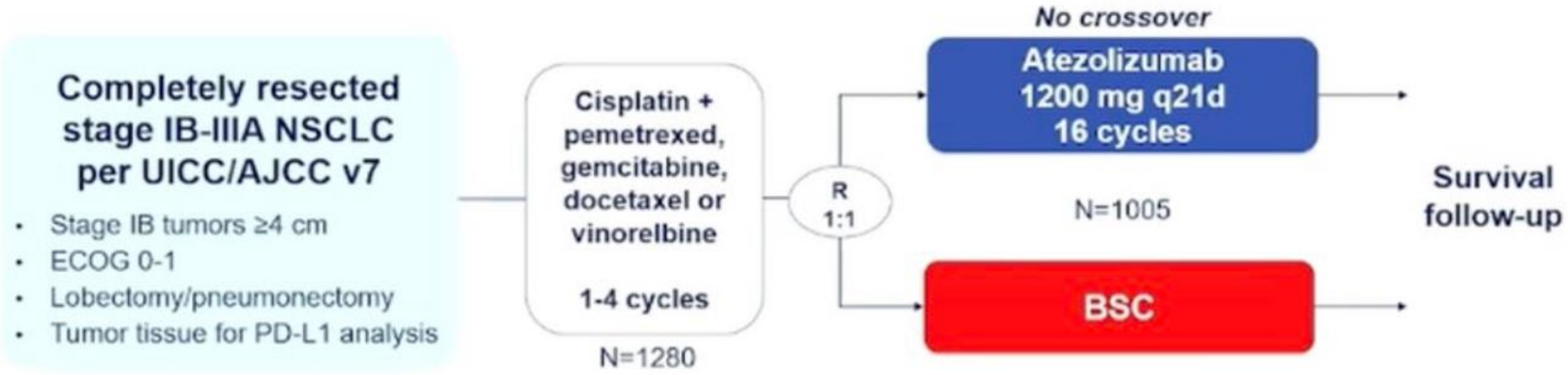
Adaura


A Patients with Stage II to IIIA Disease
Probability of Disease-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
Median Disease-free Survival
(95% CI)
mo
Osimertinib NR (38.8–NC)
Placebo 19.6 (16.6–24.5)
Hazard ratio for disease recurrence
or death, 0.17 (99.06% CI, 0.11–0.26)
P<0.001
0 6 12 18 24 30 36 42 48
Months since Randomization
No. at Risk
Osimertinib 233 219 189 137 97 52 18 2 0
Placebo 237 190 127 82 51 27 9 1 0


B Patients with Stage IB to IIIA Disease
Probability of Disease-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
Median Disease-free Survival
(95% CI)
mo
Osimertinib NR (NC–NC)
Placebo 27.5 (22.0–35.0)
Hazard ratio for disease recurrence
or death, 0.20 (99.12% CI, 0.14–0.30)
P<0.001
0 6 12 18 24 30 36 42 48 54
Months since Randomization
No. at Risk
Osimertinib 339 313 272 208 138 74 27 5 0
Placebo 343 287 207 148 88 53 20 3 1 0

Adjuvant Immunotherapy in NSCLC?

IMpower010: study design



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

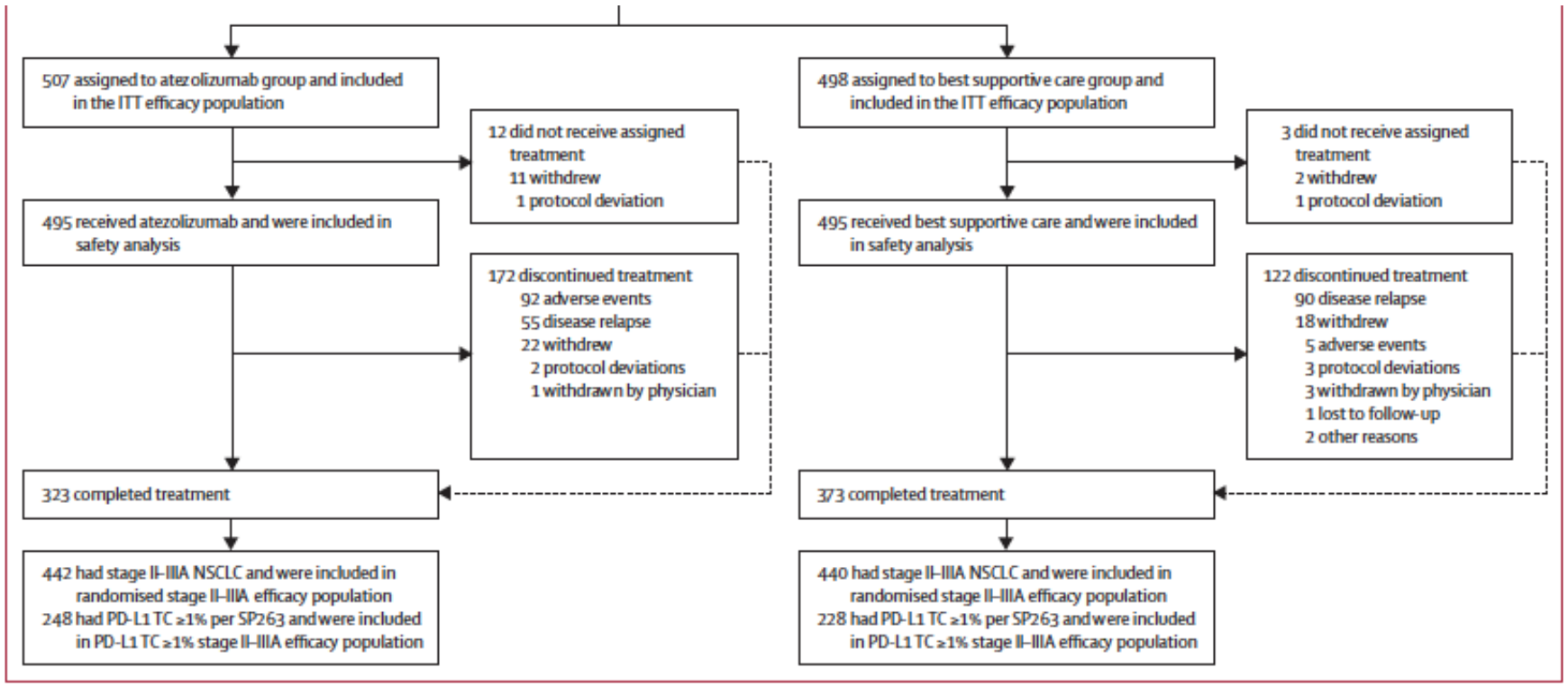
Felip E, et al. Lancet 2021;398:1344-1357.

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a]Per SP142 assay.

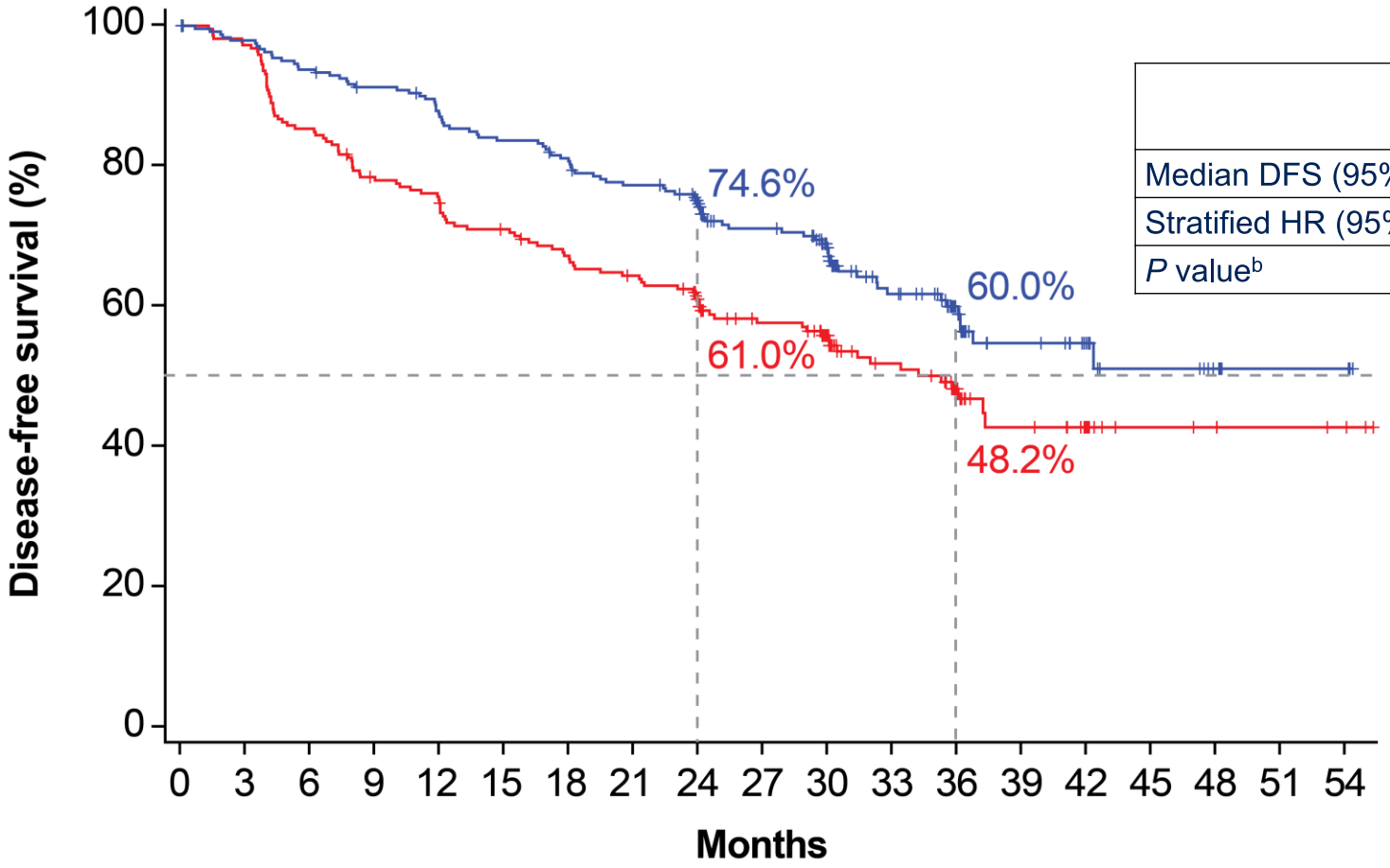
Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

www.thelancet.com Vol 398 October 9, 2021



IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

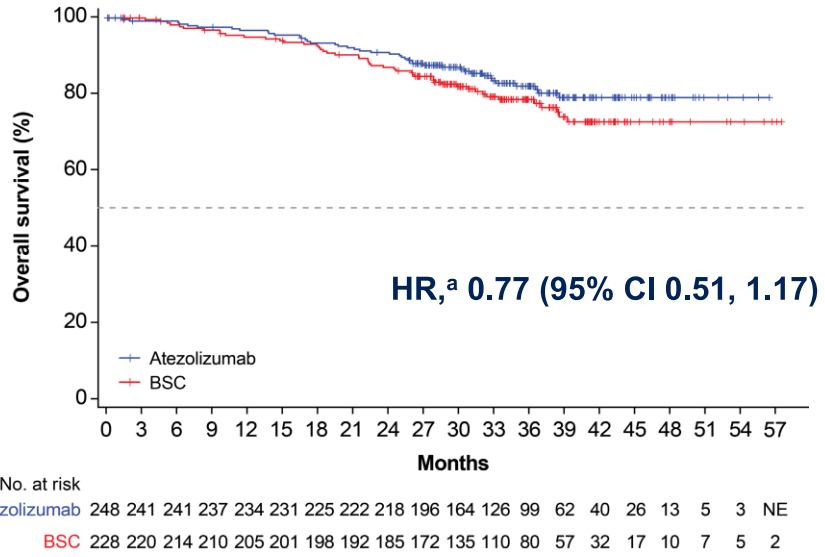
Median follow-up: 32.8 mo (range, 0.1-57.5)

Felip E, et al. Lancet 2021;398:1344-1357.

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

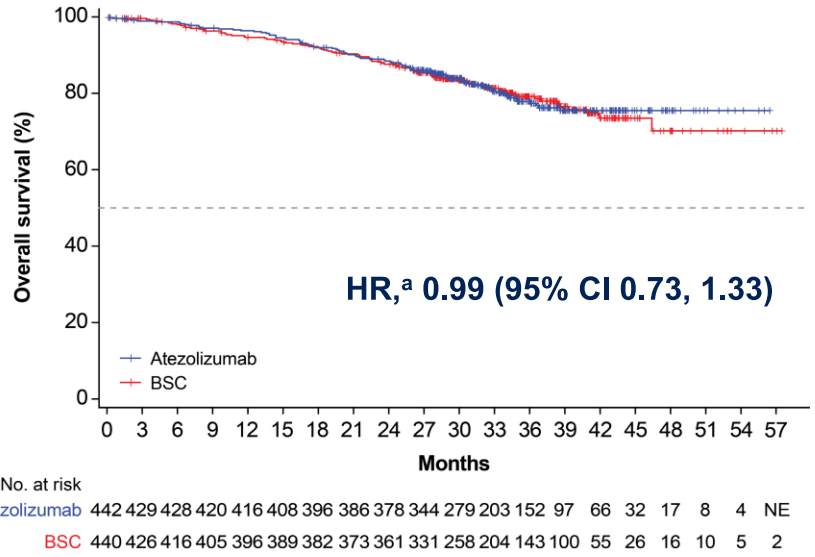
IMpower010: early OS data at interim DFS analysis

PD-L1 TC ≥ 1% stage II-IIIA



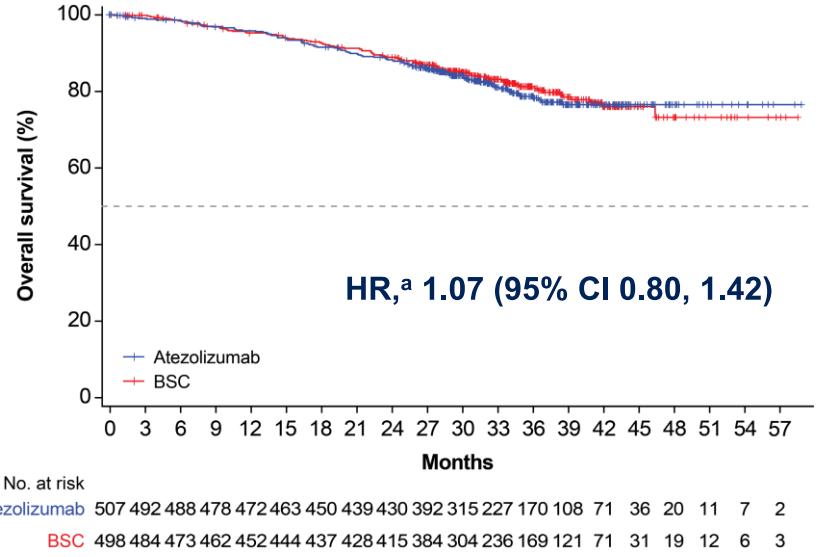
No. at risk																			
Atezolizumab	248	241	241	237	234	231	225	222	218	196	164	126	99	62	40	26	13	5	3	NE
BSC	228	220	214	210	205	201	198	192	185	172	135	110	80	57	32	17	10	7	5	2

All-randomized stage II-IIIA



No. at risk																			
Atezolizumab	442	429	428	420	416	408	396	386	378	344	279	203	152	97	66	32	17	8	4	NE
BSC	440	426	416	405	396	389	382	373	361	331	258	204	143	100	55	26	16	10	5	2

ITT



No. at risk																			
Atezolizumab	507	492	488	478	472	463	450	439	430	392	315	227	170	108	71	36	20	11	7	2
BSC	498	484	473	462	452	444	437	428	415	384	304	236	169	121	71	31	19	12	6	3

- OS data were immature at this pre-planned DFS interim analysis
  - OS in the ITT population was not formally tested
  - A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Felip E, et al. Lancet 2021;398:1344-1357.

IMpower010: immune-mediated AEs[a]

imAEs occuring in ≥1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any grade	Grade 3-4	Any grade	Grade 3-4
Any immune-mediated AEs	256 (51.7)[b]	39 (7.9%)	47 (9.5)	5 (0.6)
Rash	91 (18.4)	7 (1.4)	11 (2.2)	0
Hepatitis (diagnosis and laboratory abnormalities)	86 (17.4)	20 (4.0)	22 (4.4)	1 (0.2)
Hepatitis (laboratory abnormalities)	81 (16.4)	16 (3.2)	21 (4.2)	1 (0.2)
Hepatitis (diagnosis)	7 (1.4)	4 (0.8)	1 (0.2)	0
Hypothyroidism	86 (17.4)	0	3 (0.6)	0
Hyperthyroidism	32 (6.5)	2 (0.4)	4 (0.8)	0
Pneumonitis	19 (3.8)[c]	4 (0.8)	3 (0.6)	0
Infusion-related reaction	7 (1.4)	1 (0.2)	0	0
Adrenal insufficiency	6 (1.2)	2 (0.4)	0	0

imAEs occuring in <1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	Any Grade	Grade 3-4	Any grade	Grade 3-4
Meningoencephalitis	4 (0.8)	3 (0.6)	0	0
Colitis	4 (0.8)	2 (0.4)	1 (0.2)	0
Diabetes mellitus	4 (0.8)	0	1 (0.2)	0
Myositis (myositis and rhabdomyolysis)	4 (0.8)	0	1 (0.2)	0
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Encephalitis	2 (0.4)	2 (0.4)	0	0
Severe cutaneous adverse reaction	2 (0.4)	0	0	0
Autoimmune hemolytic anemia	2 (0.4)	0	0	0
Myocarditis	2 (0.4)[c]	0	0	0
Meningitis	2 (0.4)	1 (0.2)	0	0
Guillain-Barre syndrome	1 (0.2)	1 (0.2)	0	0
Ocular inflammatory toxicity	1 (0.2)	0	1 (0.2)	1 (0.2)
Hypophysitis	1 (0.2)	0	0	0
Nephritis	1 (0.2)	0	0	0
Vasculitis	0	0	1 (0.2)	1 (0.2)

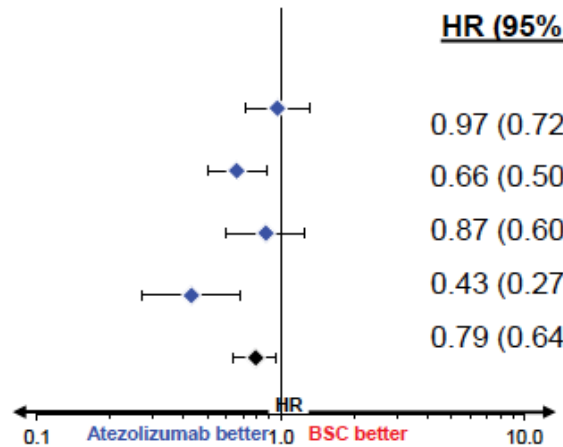
Felip E, et al. Lancet 2021;398:1344-1357.

Clinical cutoff: January 21, 2021. [a] Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). [b] Includes 2 (0.4%) Grade 5 events. [c] Includes 1 (0.2%) Grade 5 event.

DFS by PD-L1 status[a]

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Felip ESMO2021

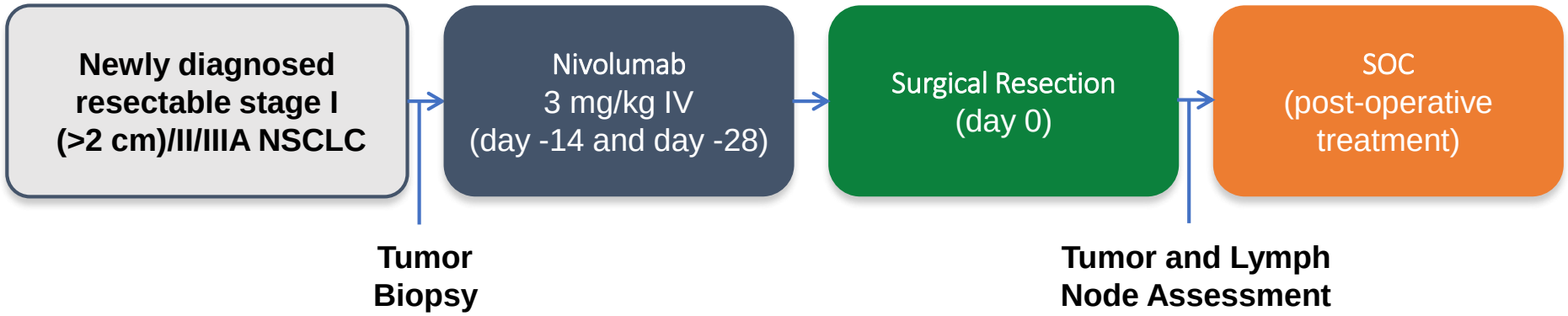
Induction Therapy Rationale

- Patients presenting with advanced disease may be understaged
- More likely to experience systemic failure
- More likely to receive full-dose and -cycle chemotherapy when given preoperatively relative to adjuvant delivery
- Those who get “downstaged” have improved survival, lower distant metastasis
- Does not increase surgical complications

Induction Therapy

- Intact tumor vasculature: enhances local chemotherapy delivery, oxygenation augments responsive to radiation therapy
- Radiation field: Smaller and more accurate, improved tolerance
- Tumor downstaging facilitates curative (R0) and parenchymal-sparing resections
- Identifies patients with biologically aggressive disease for whom surgery should be avoided

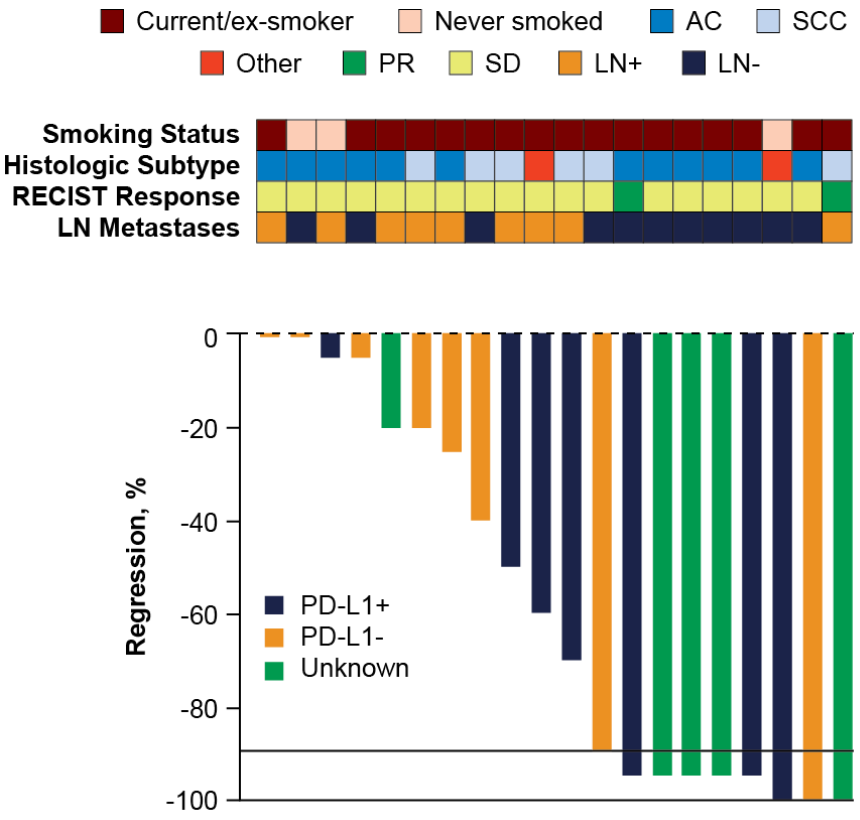
Induction Nivolumab (Forde et al 2018)



- **Primary endpoints:** Safety and feasibility
- **Also evaluated:** Tumor pathological response; expression of PD-L1; mutational burden; and mutation-associated, neoantigen-specific T-cell responses

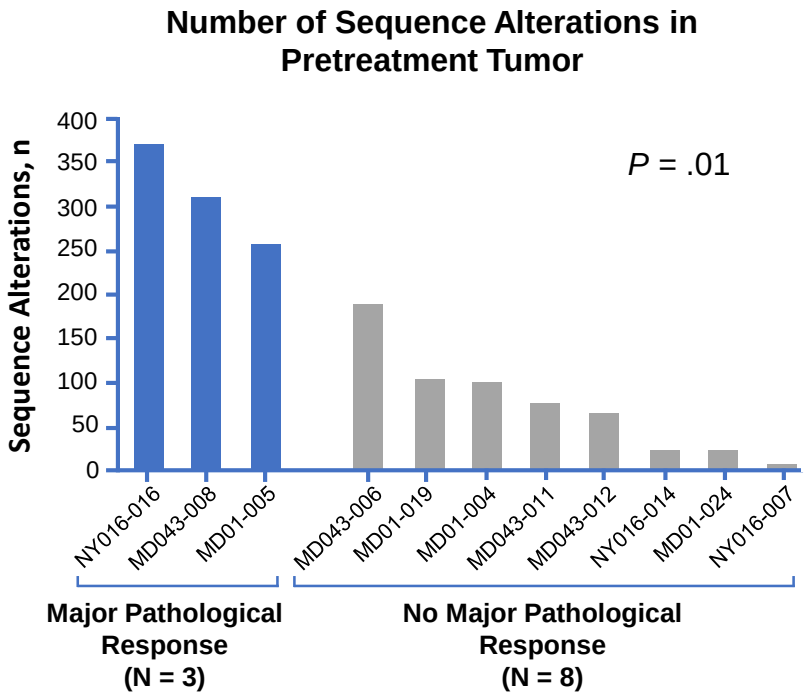
1. Forde PM et al. *N Engl J Med*. 2018;378:1976-1986.

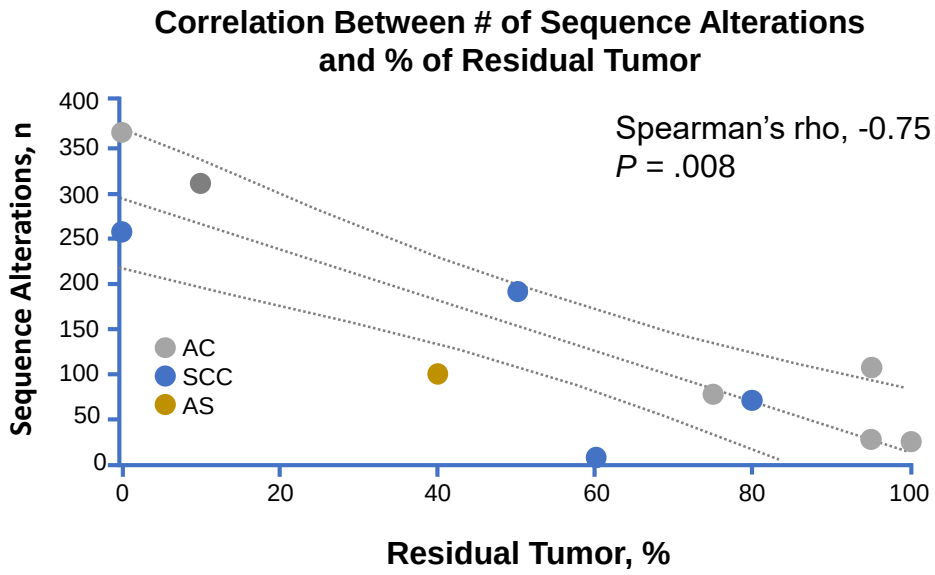
Forde et al. 2018



- Major pathological response occurred in 9/20 resected tumors (45%; 95% CI, 23-68)
- Responses occurred in both PD-L1–positive/–negative tumors

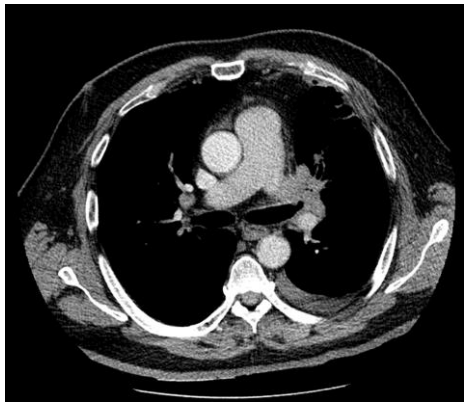
Tumor Mutational Burden

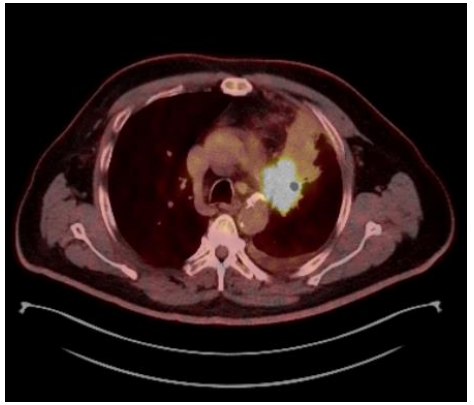




Neoadjuvant immunotherapy: The foundation trials

Study	Stage	N	Backbone	Published	MPR/CPR	Percent undergoing resection
JHU/MSKCC	IB-IIIA	21	Nivo x 2	NEJM 2018	45% / 15%	20 (95%)
NEOSTAR	I-IIIA	23 21	Nivo x 2 Nivo/Ipi	Nat Med 2021	17% / 9% 33% / 29%	39 (89%)
LCMC3	IB-IIIA	101	Atezo x 2	-	19% / 5%	90 (89%)
Weill Cornell	IB-IIIA	60	Durva x 2 Durva + SBRT x 2	Lancet Oncol 2021	6.7% / 0 53% / 31%	52 (87%)
Columbia / MGH	IB-IIIA	30	Atezo + carbo/tax	Lancet Oncol 2020	57% / 33%	29 (97%)
NADIM	IIIA	46	Nivo + carbo/tax	Lancet Oncol 2020	83% / 63%	41 (89%)





Checkmate 816

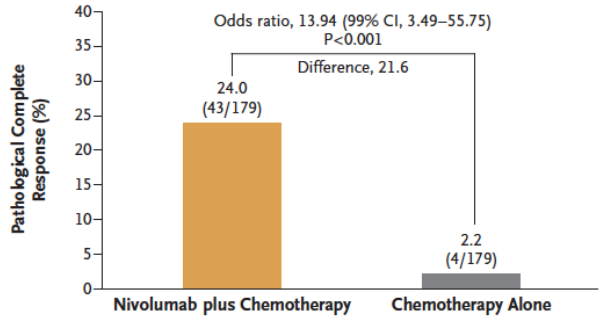
ORIGINAL ARTICLE

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. 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*

pCR

A

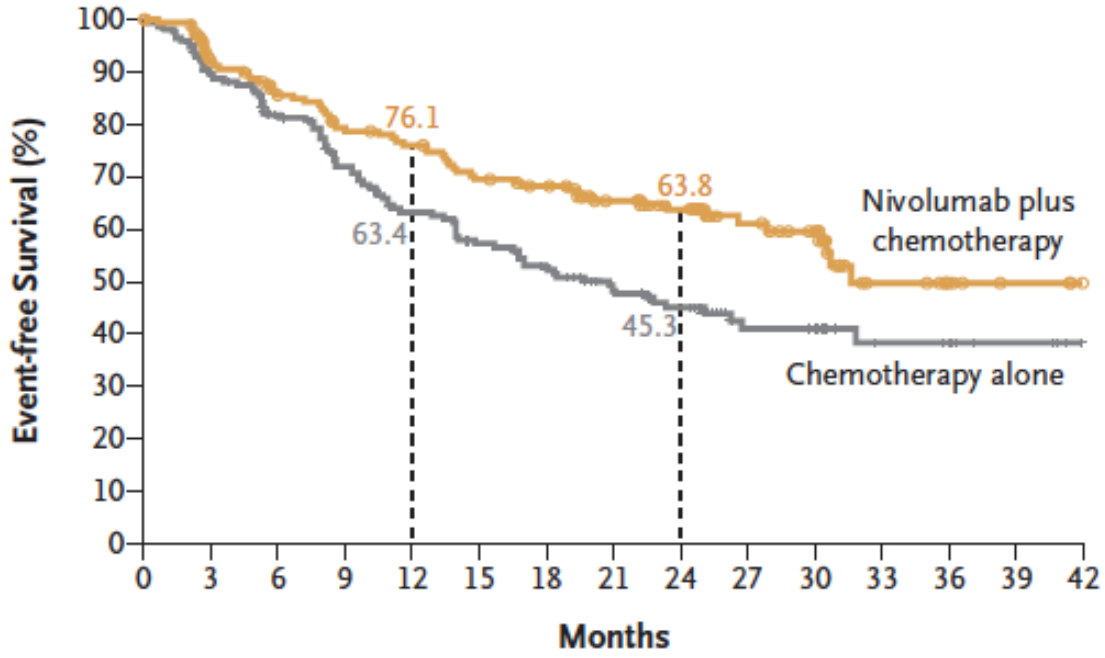


B

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (–7.3 to 31.4)
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)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)

Event-free Survival

A



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

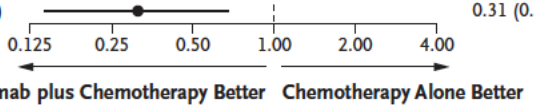
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

B

Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



OS

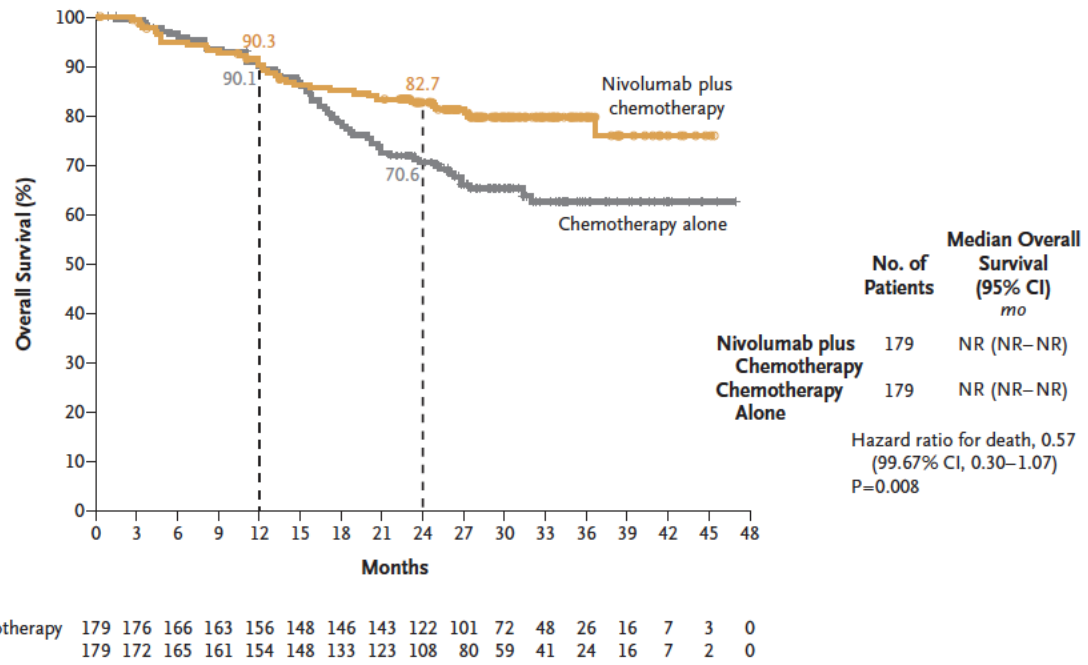


Figure 3. Overall Survival.

The 95% confidence interval of the hazard ratio was 0.38 to 0.87. At this first prespecified interim analysis, the P value for overall survival did not cross the boundary for statistical significance (0.0033).

Table 2. Adverse Events.*

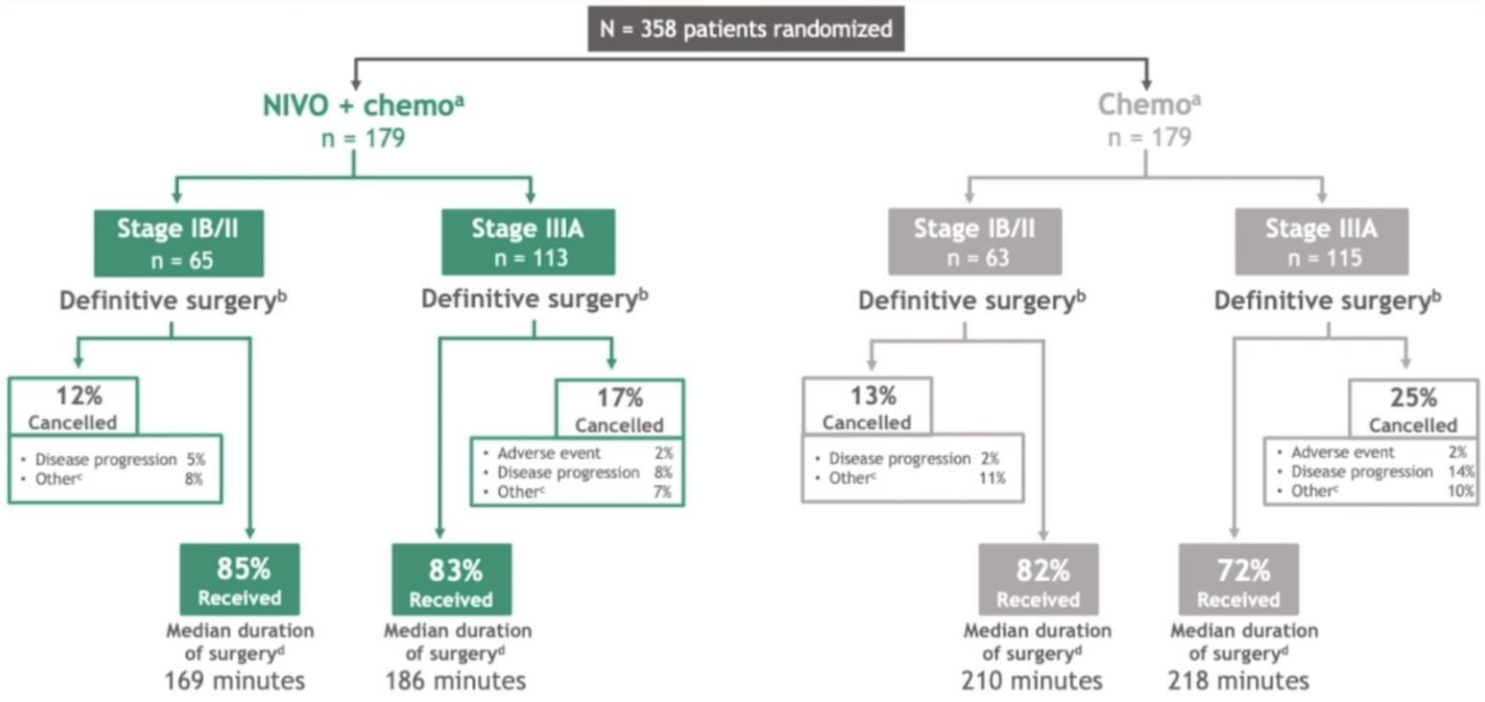
Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

What does that mean for us?
IMPROVED surgical outcomes

Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab + platinum-doublet chemotherapy vs chemotherapy alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer

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

Surgery summary: by baseline stage of disease



[a]1 patient with stage IV in each arm; [b]Patients with definitive surgery not reported: NIVO + chemo, 3% (stage IB/II), 0 (stage IIIA); chemo, 5% (stage IB/II), 3% (stage IIIA); [c]Other reasons included patient refusal, unresectability, and poor lung function; [d]Patients (n) with reported duration of surgery: NIVO + chemo, 46 (stage IB/II), 76 (stage IIIA); chemo, 47 (stage IB/II), 74 (stage IIIA); IQR for median duration of surgery: NIVO + chemo, 126.0-275.0 (stage IB/II) and 134.5-245.5 (stage IIIA); chemo, 150.0-267.0 (stage IB/II) and 147.0-290.0 (stage IIIA).

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2021 ASC
ANNUAL MEETI

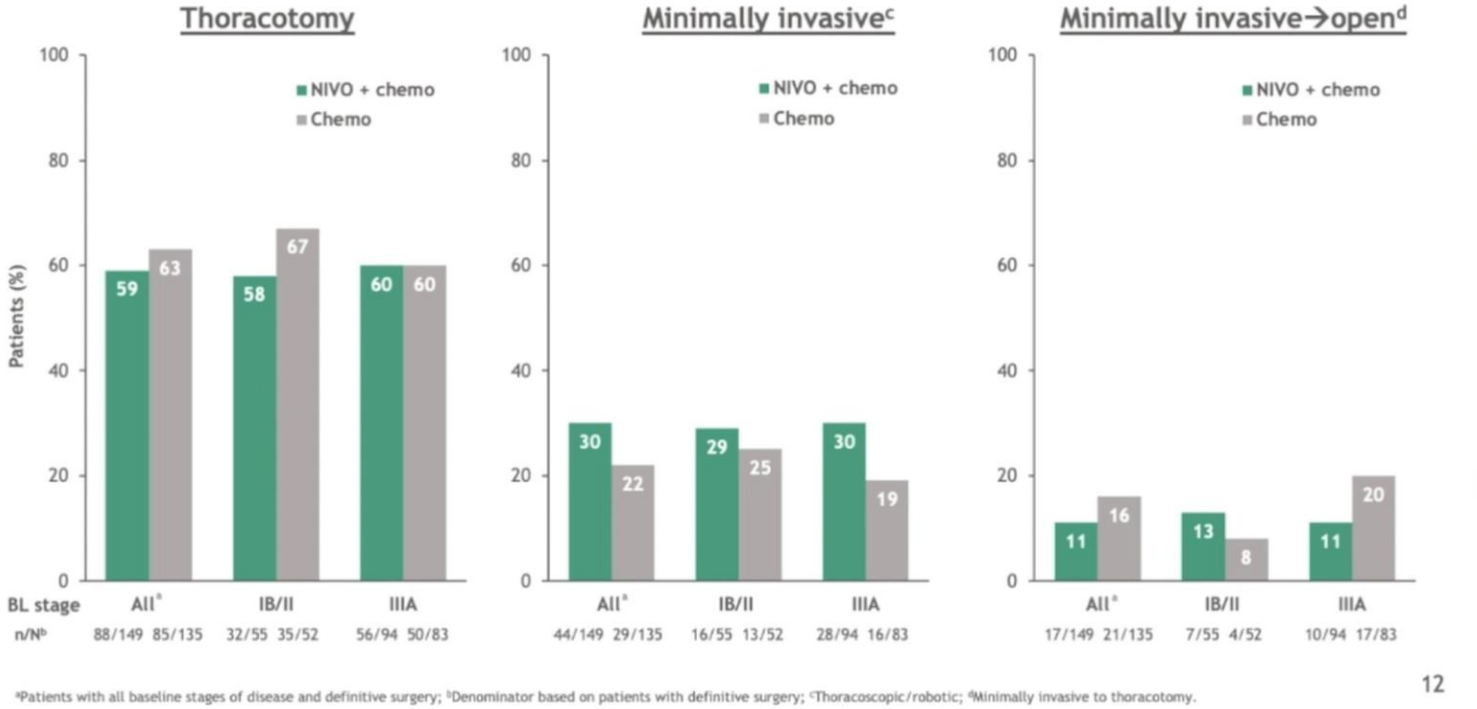
Confidential: with permission from Dr. Spicer

IMPROVED surgical outcomes

Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab + platinum-doublet chemotherapy vs chemotherapy alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer

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

Surgical approach by baseline stage of disease



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

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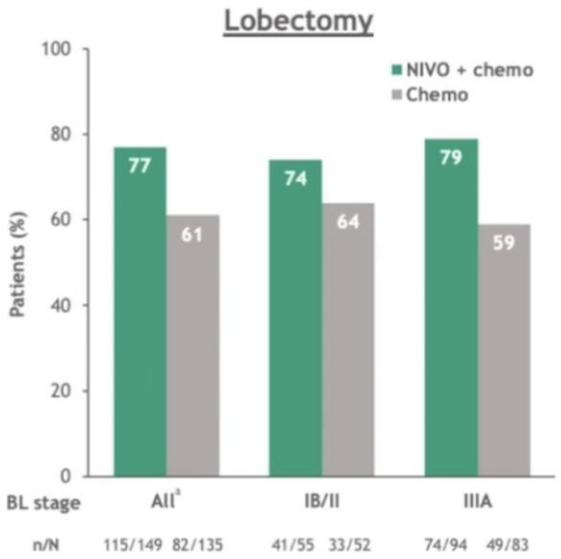
2021 ASCO ANNUAL MEETING

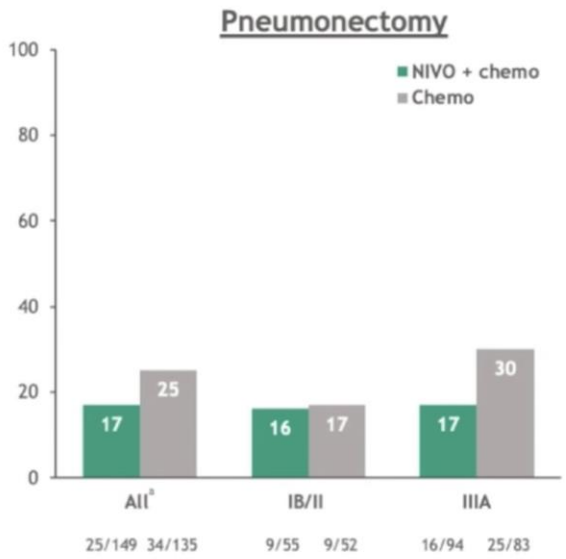
IMPROVED surgical outcomes

Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab + platinum-doublet chemotherapy vs chemotherapy alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer

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

Type of surgery by baseline stage of disease





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

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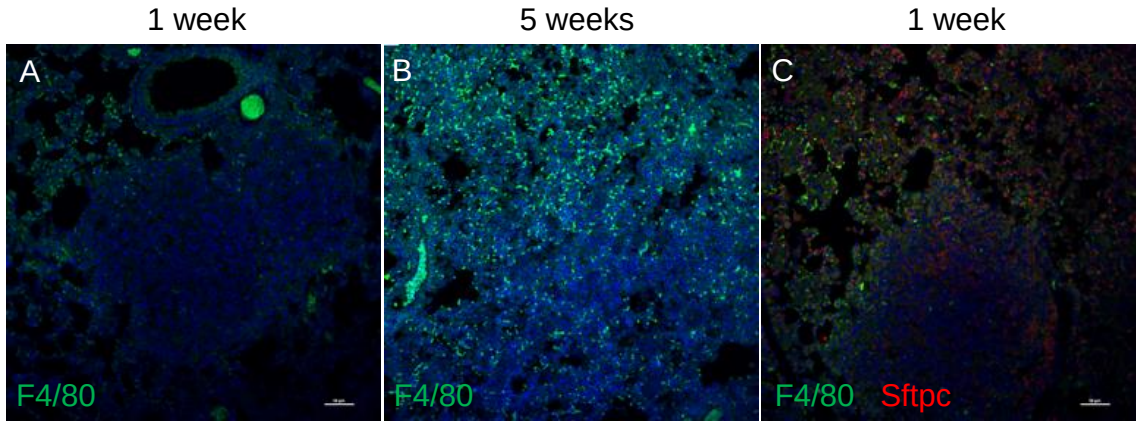
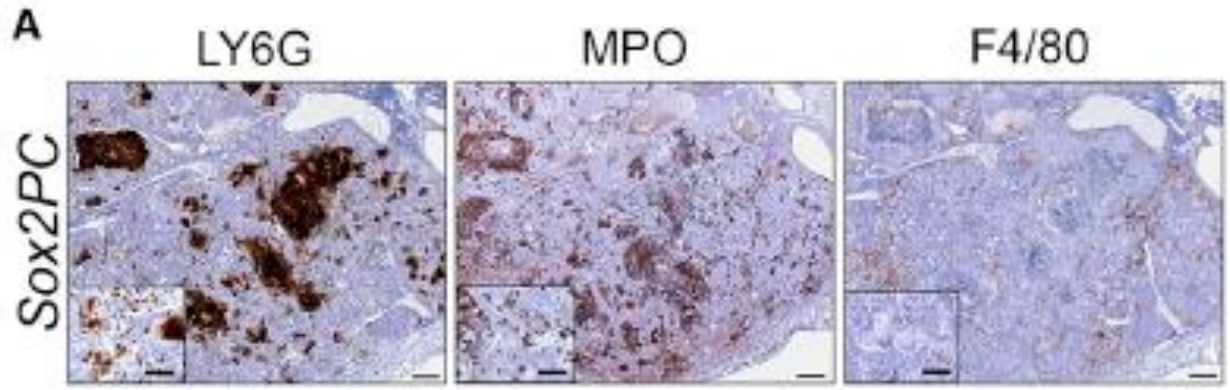
2021 ASCO ANNUAL MEETING

Future

- Predictors of response: ctDNA, tertiary lymphoid structures
- Macrophage repolarization or inhibition for adenocarcinoma?
- Neutrophil inhibition in squamou cell cancer?





Conclusions

- Neoadjuvant and adjuvant immunotherapy options are expanding
- Neoadjuvant chemo-immunotherapy does not appear to compromise (and may enhance) surgical safety
- We still await mature data on effect of these strategies on overall survival
- Identification of which patients are most likely to benefit and determination of appropriate duration of therapy remain key questions