How I treat Resectable NSCLC: The Benefits of Systemic Therapy

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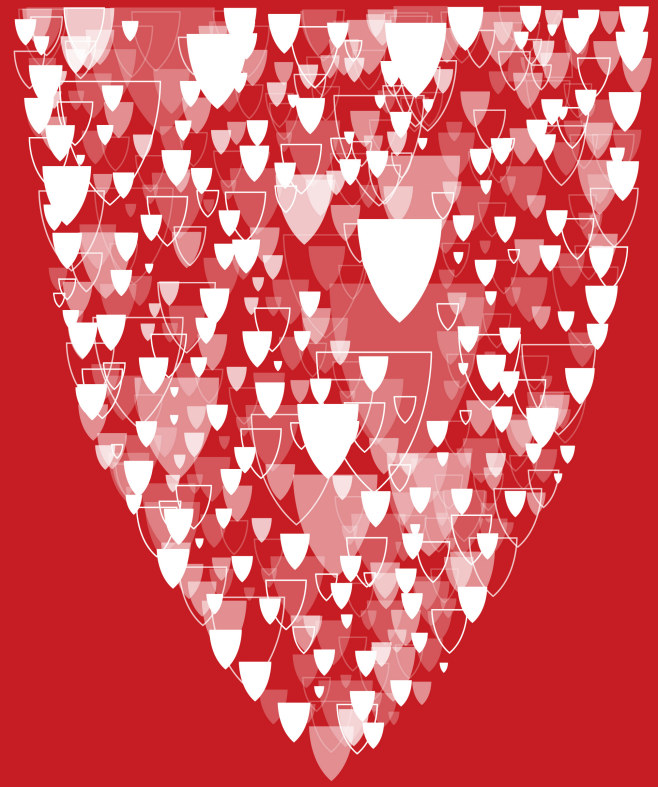
Cleveland | Ohio



Debora Bruno MD, MS
Assistant Professor CRWU
Lead, Thoracic Medical Oncology, UH/Seidman Cancer Center
Case Comprehensive Cancer Center

Objectives

- Review the indications and benefits of perioperative systemic therapy in resectable NSCLC
- Review the indications for genomic and PD-L1 testing in early stage NSCLC and its impact on choice of systemic therapy
- Understand the pros and cons of neoadjuvant and adjuvant chemo-immunotherapy in the context of resectable NSCLC
- Review the indications for targeted therapy in the treatment of early stage NSCLC

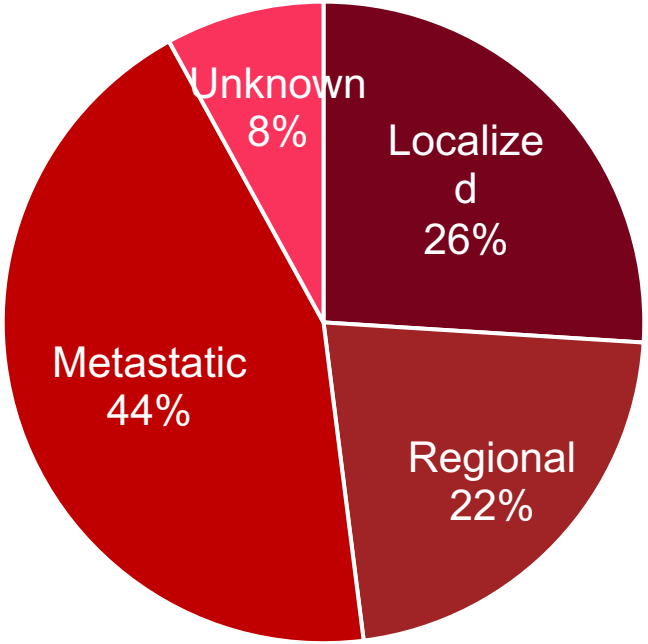
Estimated New Cancer Cases and Deaths: US 2023

Estimated New Cases

Males			Females		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**	**All Sites**	**948,000**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**	**All Sites**	**287,740**	**100%**



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Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48

Resectable NSCLC: 5-year OS

Stage	Clinical	Pathologic
IA1	92%	90%
IA2	83%	85%
IA3	77%	80%
IB	68%	73%
IIA	60%	65%
IIB	53%	56%
IIIA	36%	41%
IIIB	26%	24%

- Micrometastases are highly prevalent and major cause of relapse and death
- Curative treatment for operable NSCLC requires multi-disciplinary approach
- Effective systemic therapies required for long-term survival improvement

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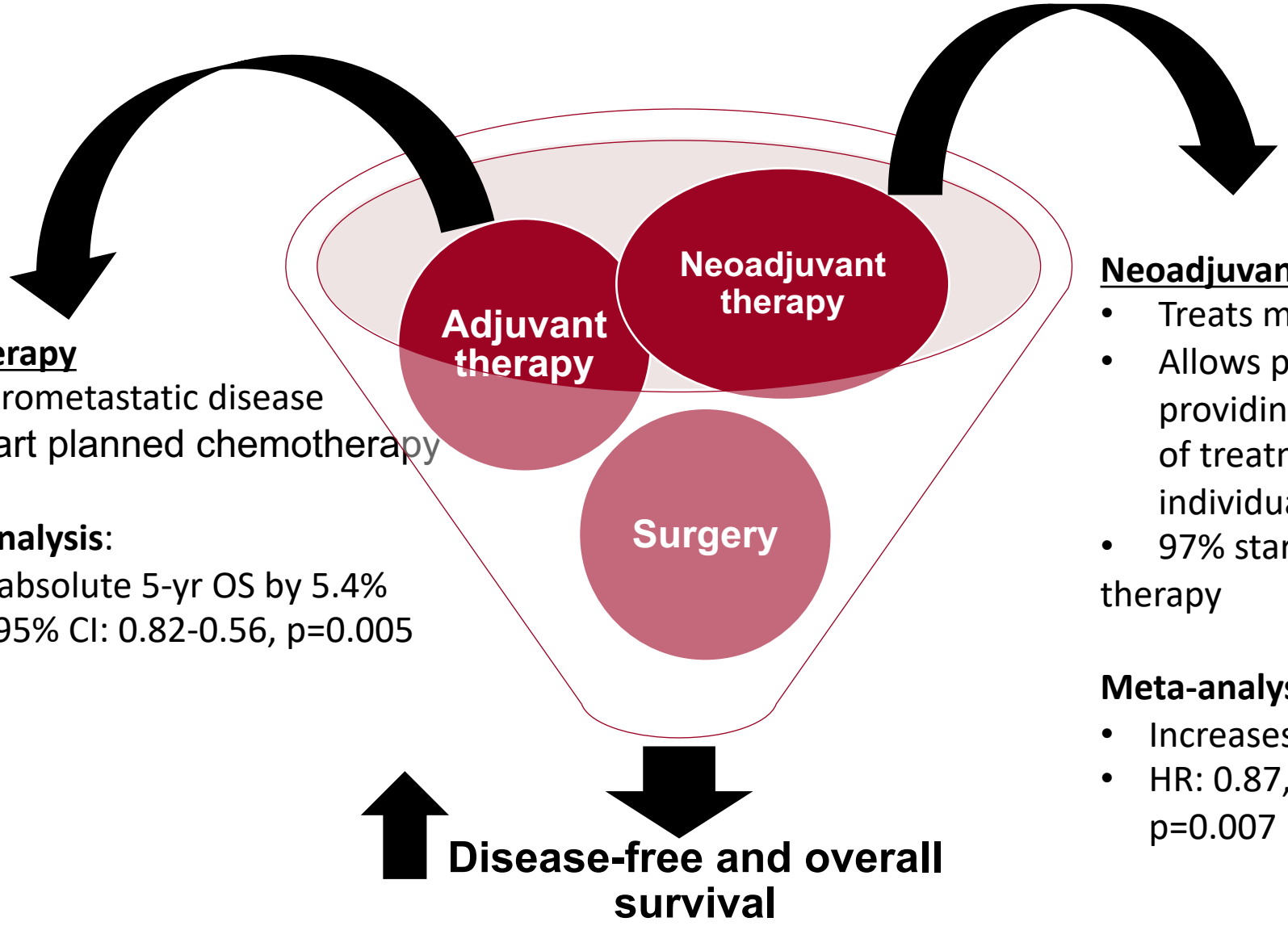
Detterbeck FC, et al. *Chest*. 2017;151(1):193-203.



Adjuvant Therapy

- Treats micrometastatic disease
- 66.2% start planned chemotherapy

LACE Meta-analysis:

- Increases absolute 5-yr OS by 5.4%
- HR: 0.89, 95% CI: 0.82-0.56, p=0.005

Neoadjuvant Therapy

- Treats micrometastatic disease
- Allows prognostication by providing immediate "read out" of treatment efficacy for each individual
- 97% start planned neoadjuvant therapy

Meta-analysis

- Increases absolute 5-yr OS by 5%
- HR: 0.87, 95% CI: 0.78-0.96, p=0.007

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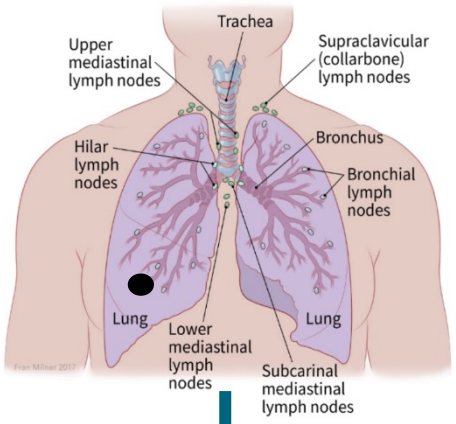
Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559; NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383(9928):1561-1571; Felip E, et al. *J Clin Oncol*. 2010;28(19):3138-3145.

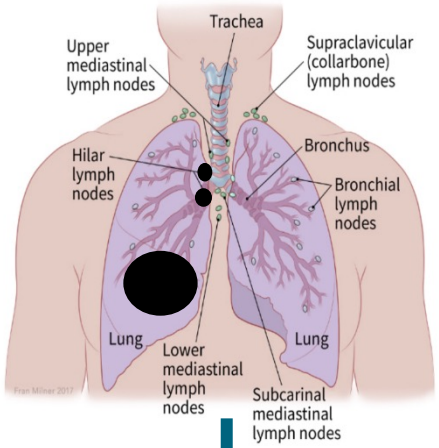
Multidisciplinary Treatment: Resectable NSCLC

Stage IA



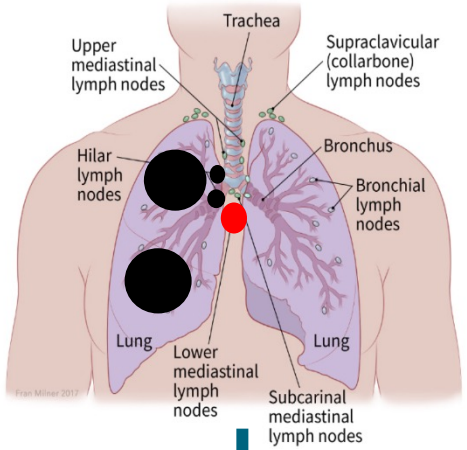
Surgery

Stage IB – IIIA
T1-3, N0-1



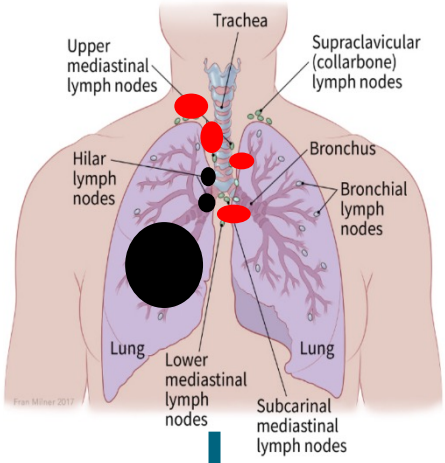
Perioperative chemoimmunotherapy + surgery

Select Stage IIIA-B
(select T4 and N2)



Induction systemic therapy +/- RT followed by surgery followed by adjuvant therapy if indicated

Stage IIIB and IIIC
(most N2, all N3)



Chemo-RT + durvalumab

Neoadjuvant Chemoimmunotherapy in Resectable NSCLC

Case Discussion # 1

79 year-old, 40-pack-year former smoker, presented to ED with cough, chest pain and ongoing severe pain over her shins, relieved by NSAIDs. No weight loss or fatigue. PS ECOG 1

On exam: clubbing

Bronchoscopy with EBUS: 10R and 4R + for adenocarcinoma, TTF-1 +

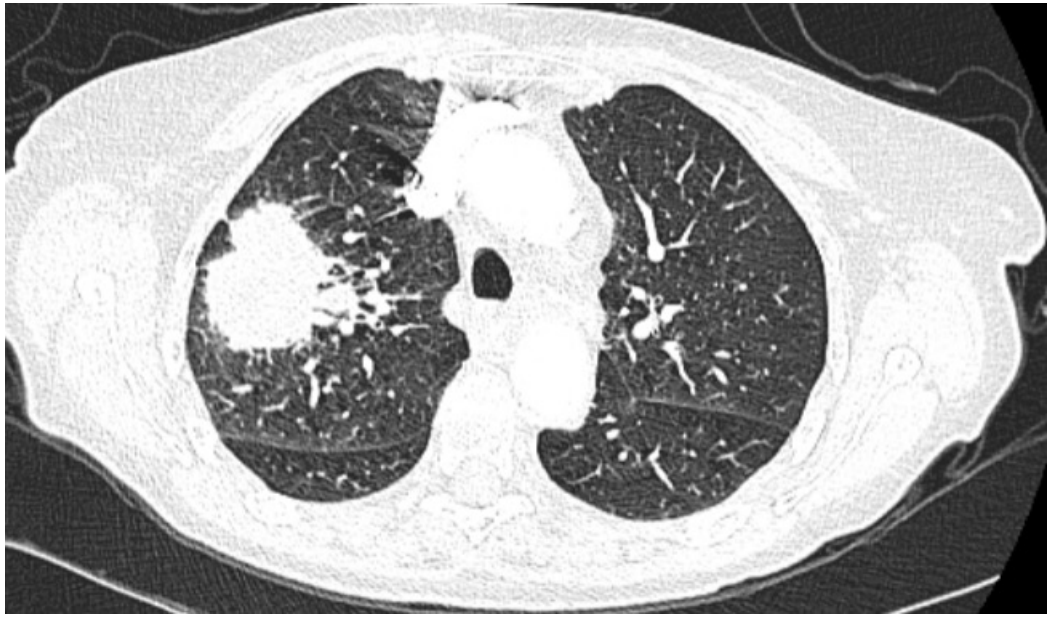
Focused NGS: KRAS G12C

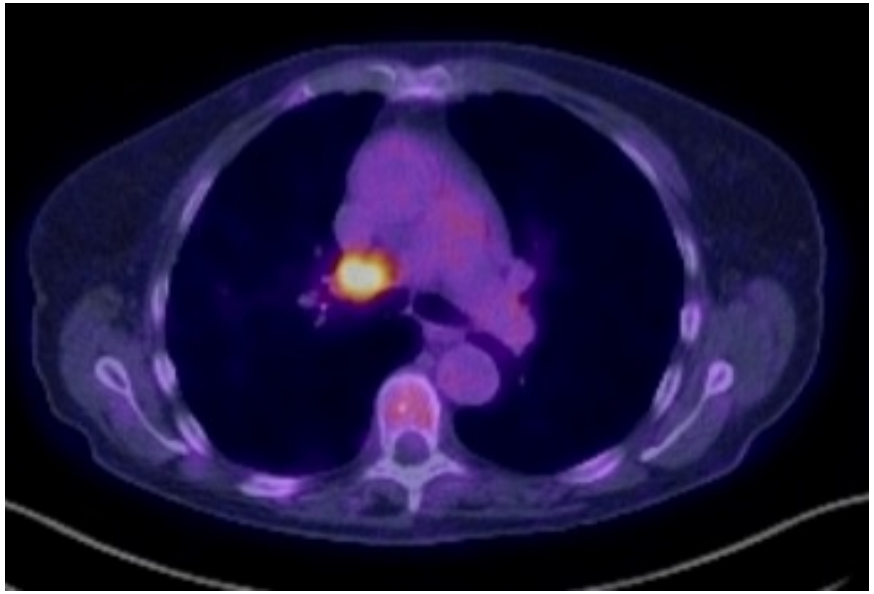
PD-L1 TPS < 1%

Brain MRI negative

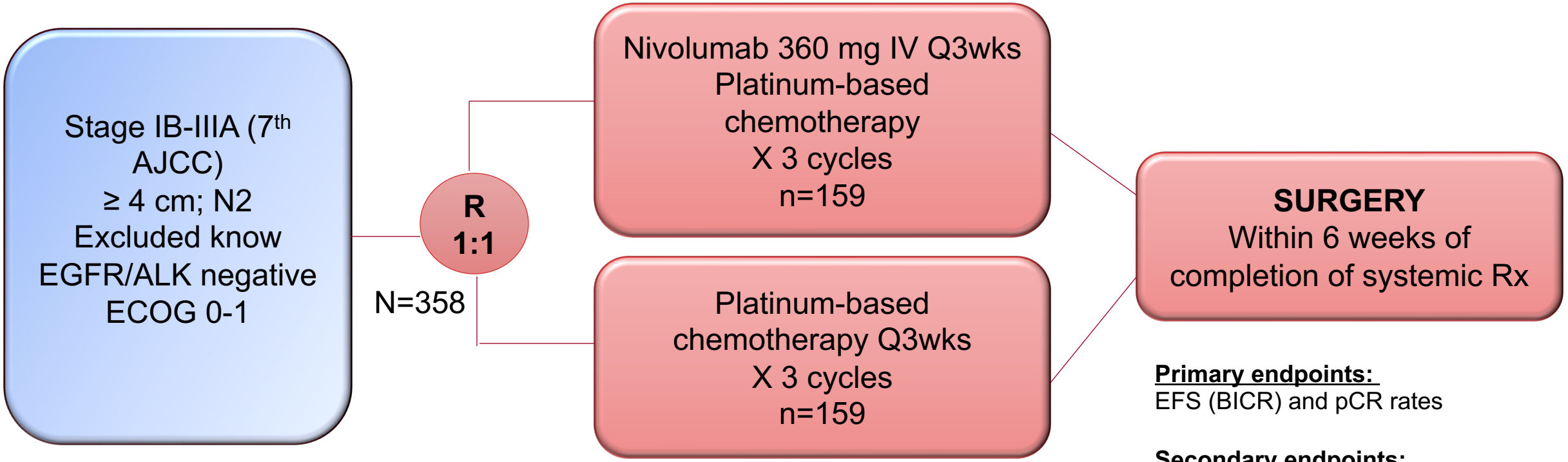
Adequate PFTs

Stage IIIB (cT3 pN2 cM0) NSCLC





CheckMate 816 Study Design



Stratification factors:
Disease stage (IB vs II vs IIIA)
PD-L1 status: < 1% vs ≥1%
Sex

Primary endpoints:
EFS (BICR) and pCR rates

Secondary endpoints:
mPR, OS and TTD or distant metastasis

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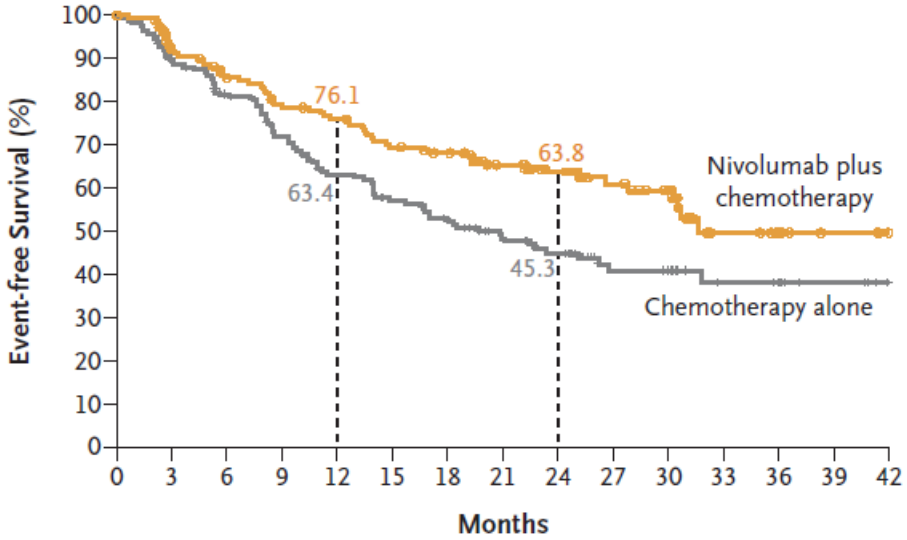
A

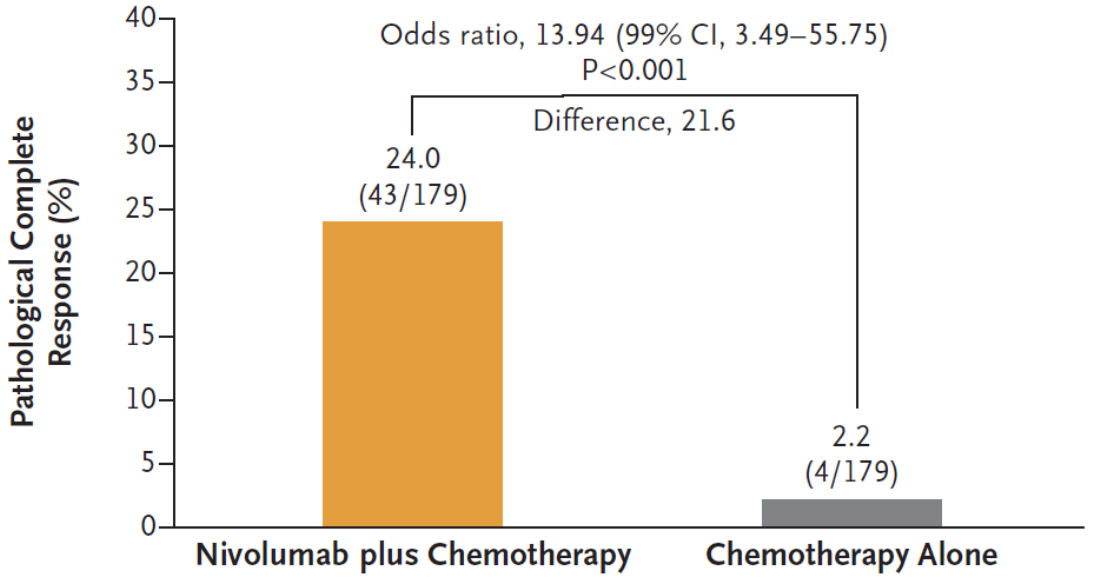


	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

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



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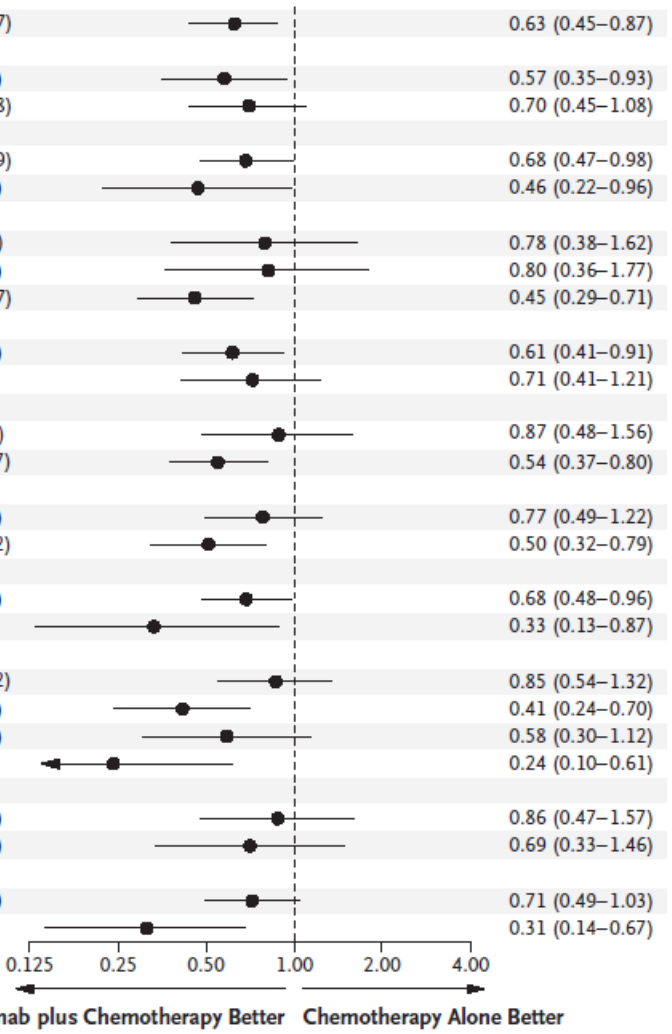
B

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)



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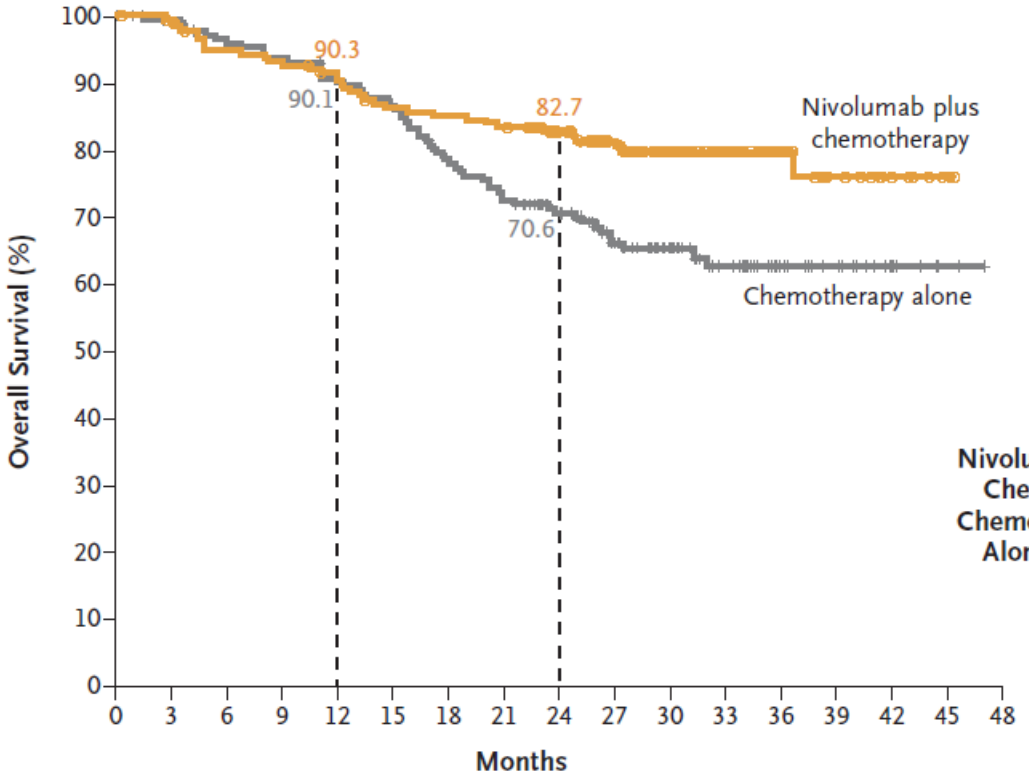

	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

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

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CheckMate 816: Surgical Outcomes

Surgical outcomes	Chemo + Nivolumab n=179	Chemo n=179
Definitive surgery	149 (83%)	135 (75%)
Surgery called - PD	12	17
Minimally invasive surgery	30%	22%
Conversion to open	11%	16%
Lobectomy	77%	61%
Pneumonectomy	17%	25%
R0 resection	83%	78%
Median residual viable tumor	10%	74%
Duration of Surgery (min)	184	217
Length of Hospitalization (days)	10	10.7
Any Grade Surgical AE	41%	47%
Grade 3-4 surgical AE	11%	15%

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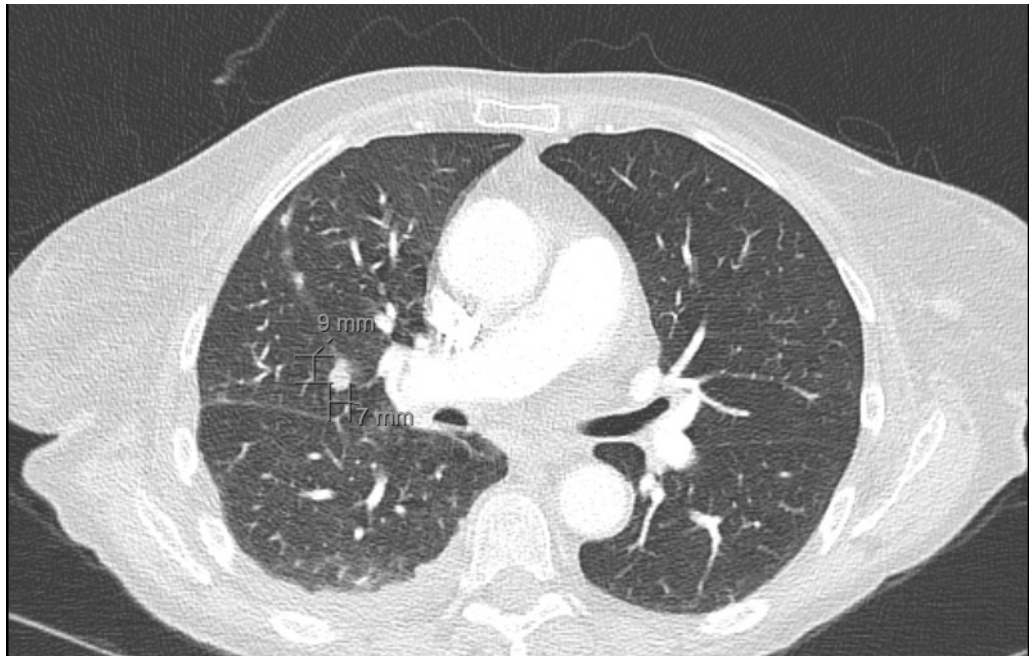
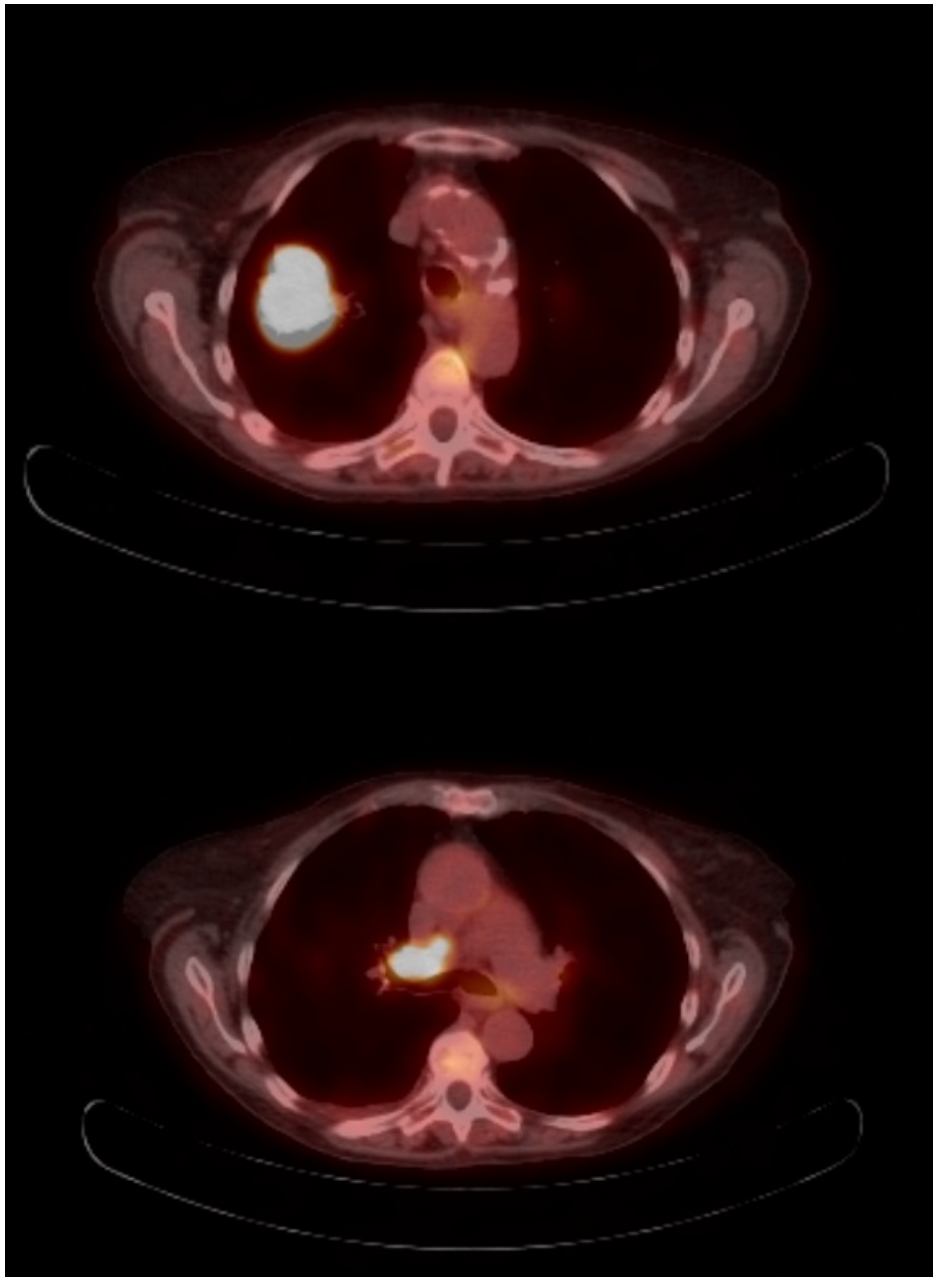
Case Discussion # 1



After 2 cycles of carboplatin/pemetrexed/nivolumab:
Admitted with new onset dyspnea
CT/PE: new pulmonary nodules, including pleural-based (+effusion)
Pleuroscopy: papillary mesothelial hyperplasia with chronic inflammation; no evidence of malignancy
RUL lobectomy: ypT3 ypN1 (1 peribronchial node) – 40% residual tumor – 4R, 9R, 10R, 11R, 7 all negative



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Perioperative Chemoimmunotherapy in Resectable NSCLC

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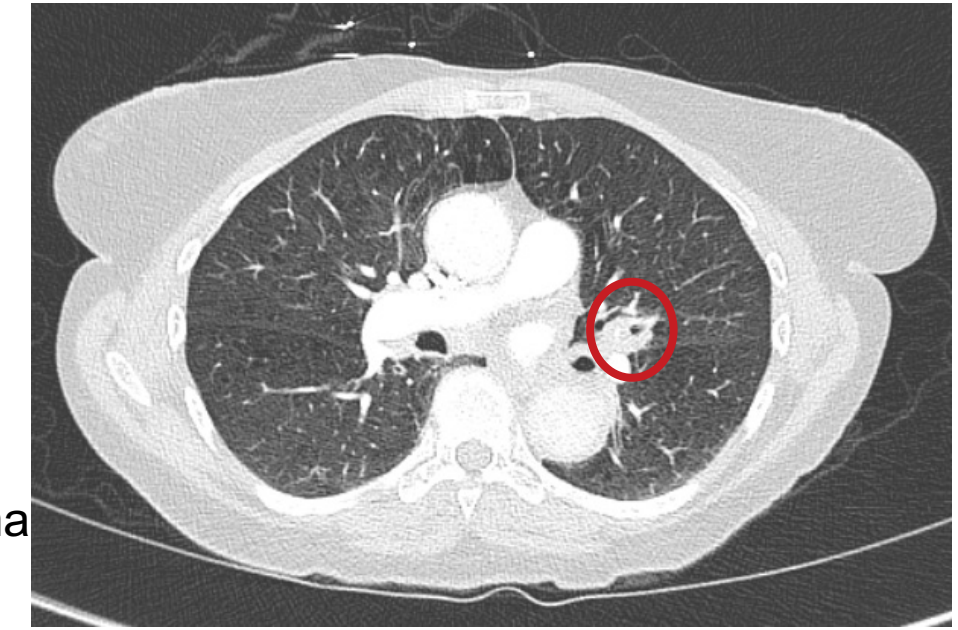
Case Discussion # 2

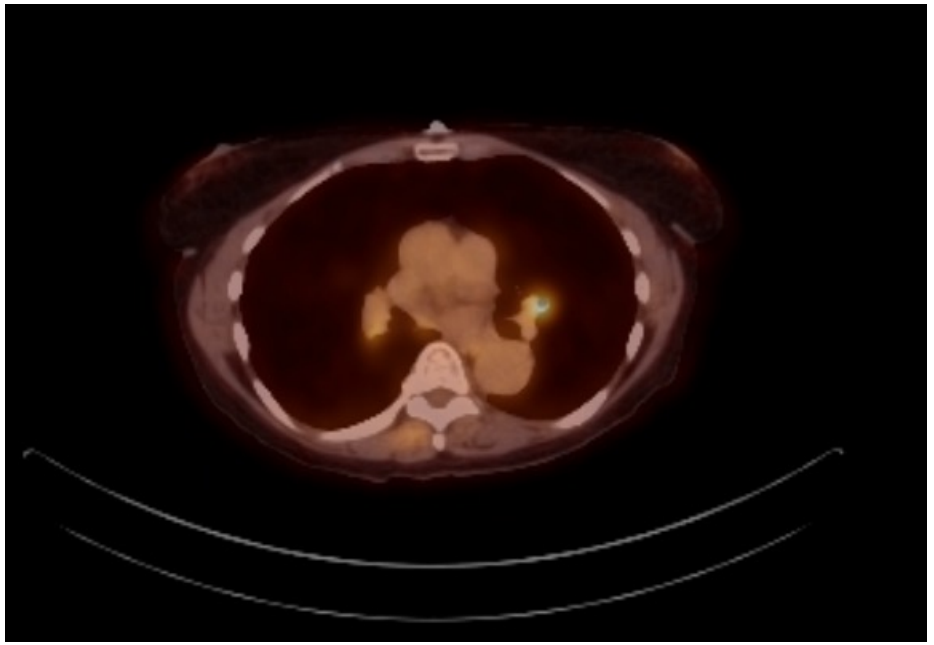
- 69 year-old F, 50 pack-year tobacco use,

undergoes a CTA for new

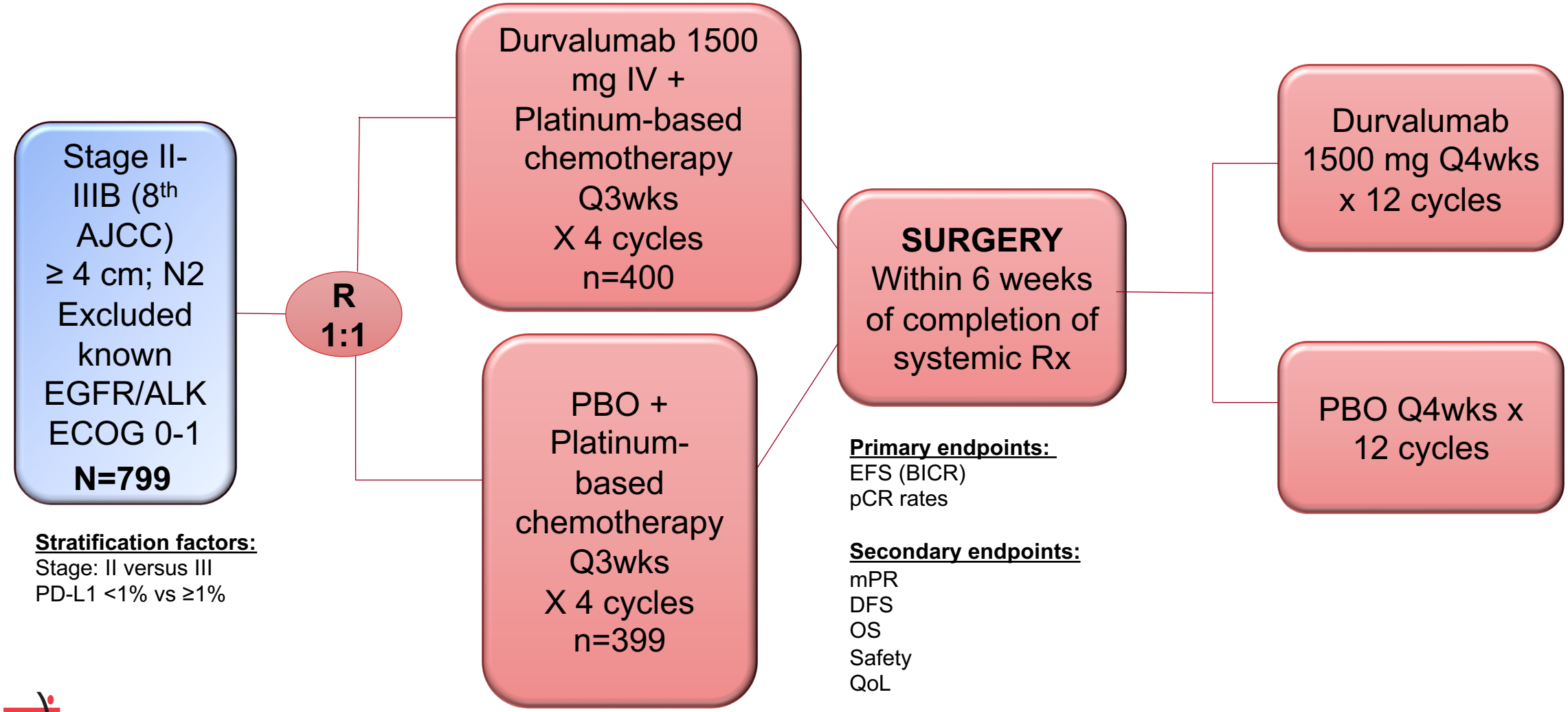
onset dyspnea and chest pain

- Bronchoscopy with EBUS: 11L + squamous cell carcinoma
- Focused NGS: no disease associated alterations
- PD-L1 TPS 55%
- Brain MRI negative
- Adequate PFTs
- Stage IIB (cT1b pN1) NSCLC
- Cycle 1 carboplatin/paclitaxel/nivolumab complicated by
- Gr3 CIPN and neutropenia leading to hospitalization
- After 10 weeks, surgery: ypT0 ypN0 (28 nodes negative)





AEGEAN Study Design



Stratification factors:
Stage: II versus III
PD-L1 <1% vs ≥1%

Primary endpoints:
EFS (BICR)
pCR rates

Secondary endpoints:
mPR
DFS
OS
Safety
QoL

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Heymach JV. Cancer Res, 2023;83 (8_Supplement): CT005

AEGEAN – EFS and pCR/MPR

EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

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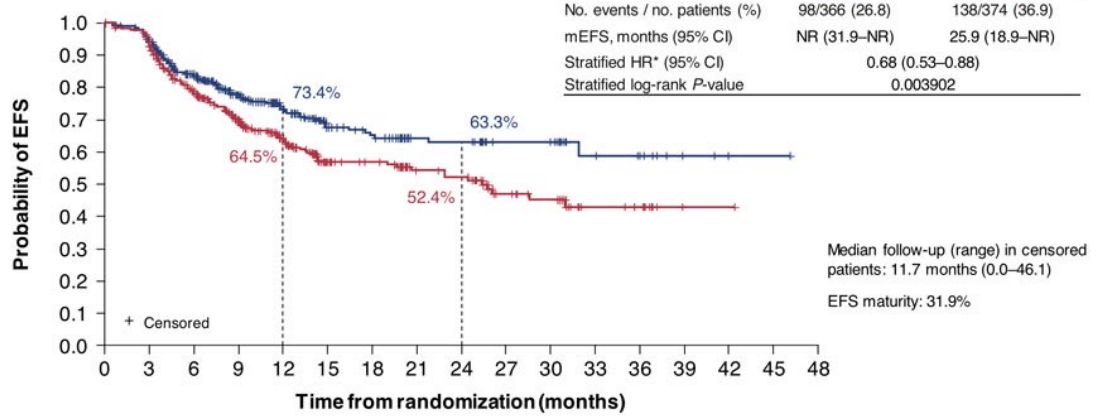
	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

Pathologic response per IASLC 2020 methodology* (mITT)

Final analysis

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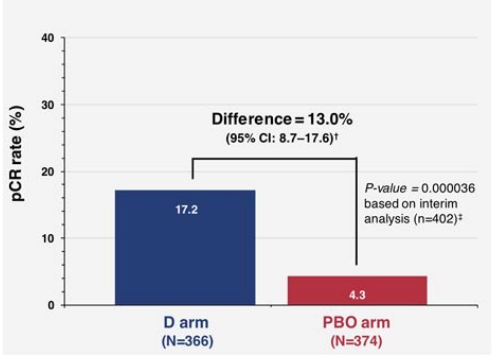
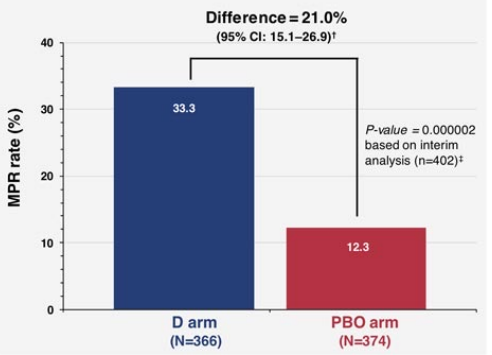
pCR (central lab)



MPR (central lab)



*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

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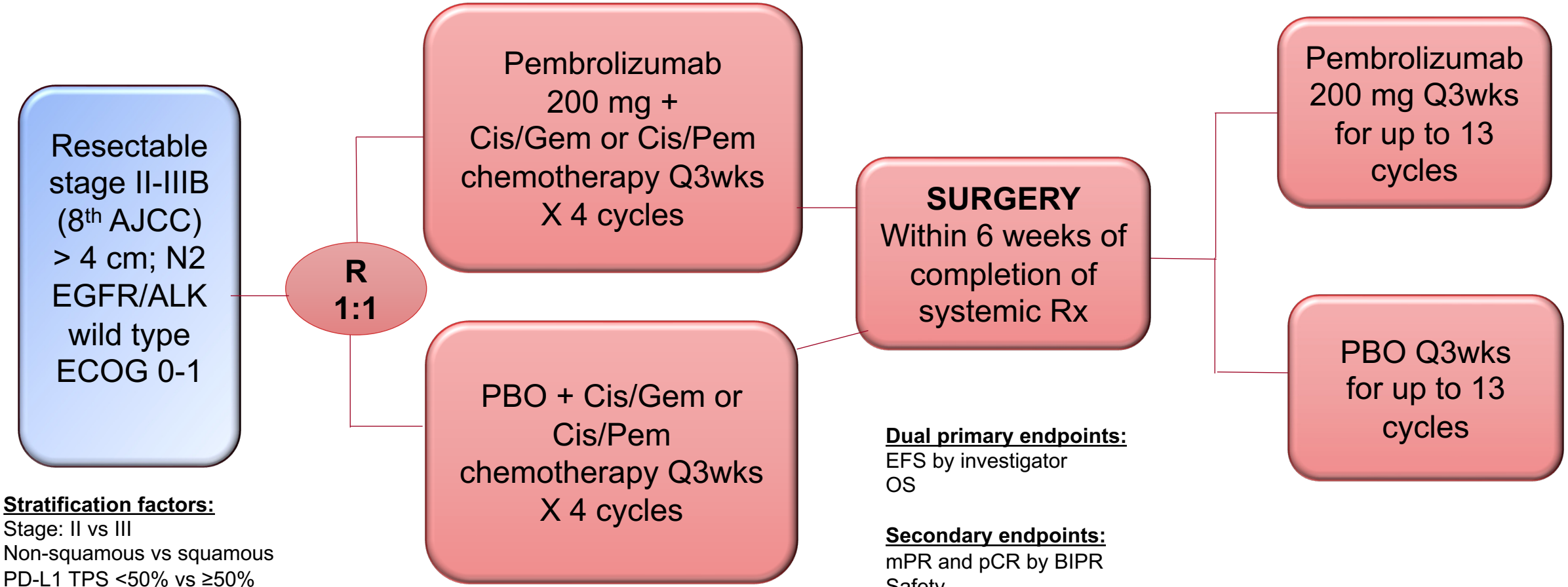
Heymach JV. Cancer Res, 2023;83 (8_Supplement): CT005

KEYNOTE-671 – Study Design



Stratification factors:
Stage: II vs III
Non-squamous vs squamous
PD-L1 TPS <50% vs ≥50%
Geographic region (East Asia vs not East Asia)

Dual primary endpoints:
EFS by investigator
OS

Secondary endpoints:
mPR and pCR by BIPR
Safety

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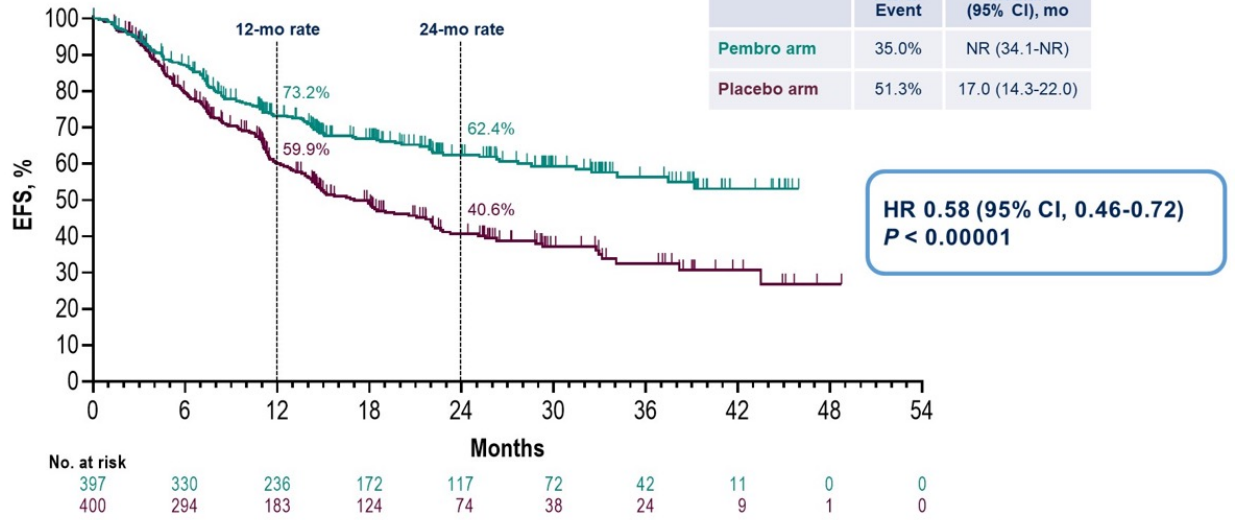
Wakelee H. N Engl J Med, 2023

KEYNOTE-671 – EFS, pCR and MPR

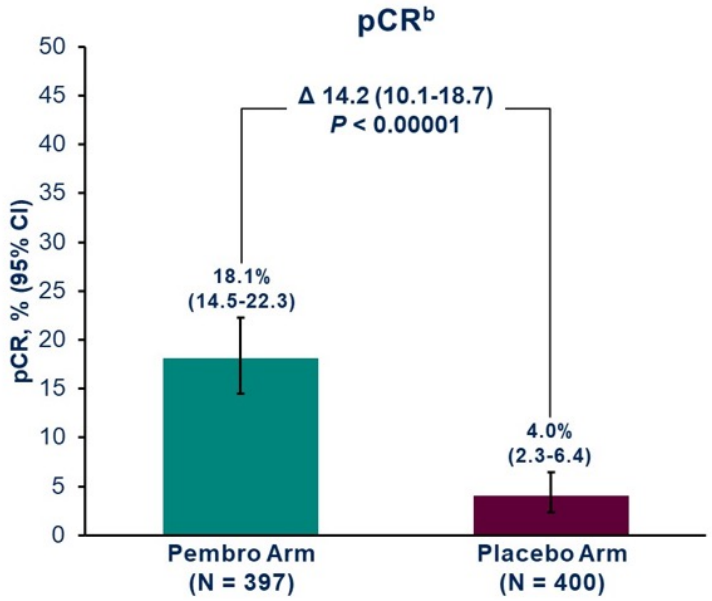
Event-Free Survival

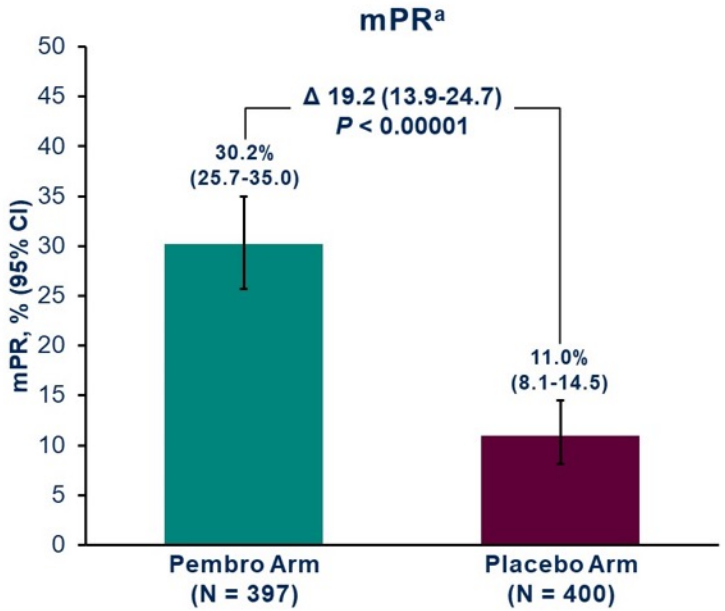


	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

HR 0.58 (95% CI, 0.46-0.72)
P < 0.00001

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).





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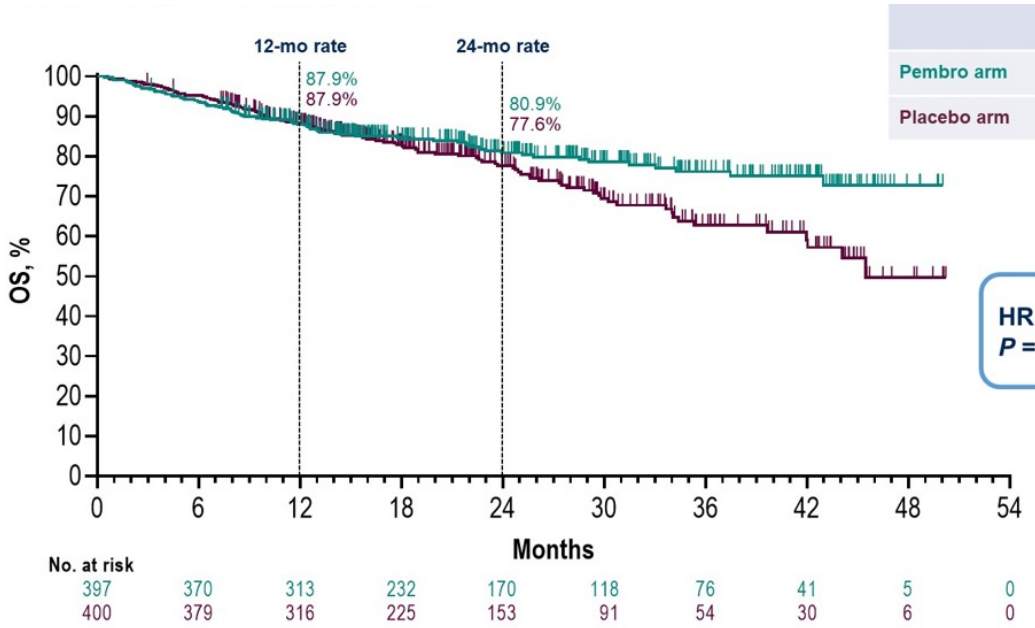
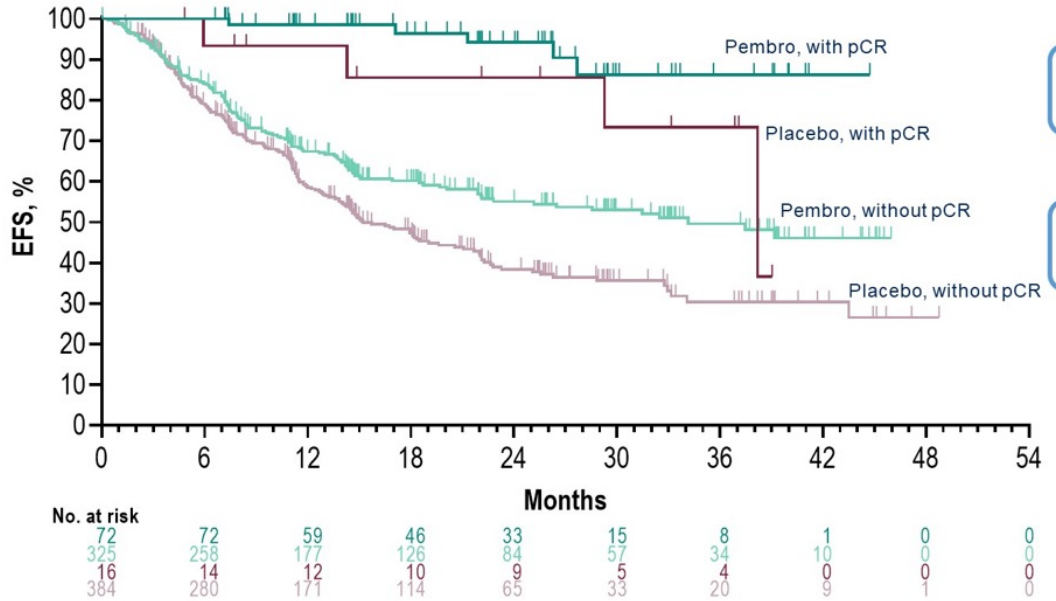
KEYNOTE-671 – OS and EFS by pCR



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**



With pCR
HR 0.33 (95% CI, 0.09-1.22)

Without pCR
HR 0.69 (95% CI, 0.55-0.85)

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The Perils of Cross-Trial Comparison

Outcomes in treatment arms	CheckMate 816 N=179	AEGEAN N=366	KEYNOTE-671 N=397 6.5% known *EGFR/ALK*
Eligibility Criteria	IB-IIIA [N2] (7th AJCC) – tumors >= 4 cm known EGFR/ALK excluded	II-IIIB [N2] (8th AJCC) EGFR/ALK excluded	II-IIIB [N2] (8th AJCC)
III pts Squamous PD-L1 < 1% PD-L1 ≥ 50%	63% 47% 44% 21%	71% 46% 33% 30%	70% 43% 35% 33%
Treatment	3 cycles neoadjuvant chemo-IO **22% carboplatin**	4 cycles neoadjuvant chemo-IO followed by 1 year adjuvant CIT **73% carboplatin**	4 cycles neoadjuvant chemo-IO followed by 1 year adjuvant CIT **No carboplatin allowed**
pCR rates	24%	17.2% [OR 13.0]	18.4%
Surgery	83.2%	81%	82.1%
mEFS	31.6 months [HR 0.63]	NR [HR 0.68]	NR [HR 0.58]
EFS at 24m	64%	63.3%	62.4%
OS at 24 m	83% [HR 0.57]	---	80.9% [HR 0.73]

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Case Study # 3

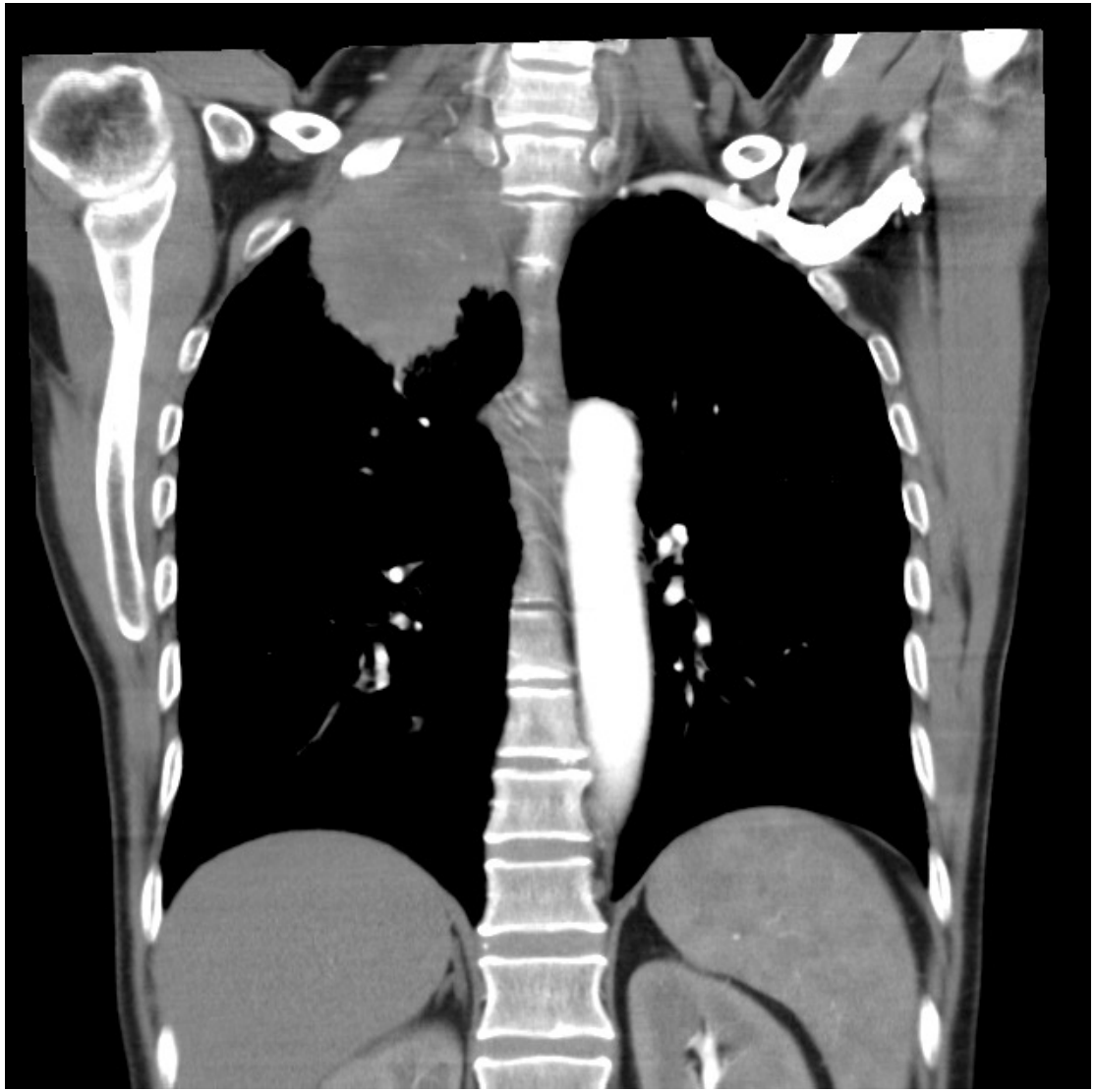
69 year-old male, former smoker, presented with right shoulder and chest pain to the ED and a CTA demonstrated a 6.5 cm RUL mass.

PET scan shows + ipsilateral hilar node

EBUS: 10L + for adenocarcinoma cells. PD-L1 80%. Specimen QNS for NGS.

Brain MRI no ICM

Is this a candidate for neoadjuvant chemo-IO?



Pancoast Tumors and Borderline Resectable

Neoadjuvant and perioperative trials: only readily resectable patients!

Borderline resectable patients may be considered for neoadjuvant chemo-RT vs definitive chemo-RT

Pancoast tumor pts should always be treated with neoadjuvant chemo-RT followed by surgery and then adjuvant CIT

Elligibility for neoadjuvant chemo-IO therapy:

- ✓Stage II-IIIB [N2, single station, non-bulky]
- ✓Readily resectable/operable
- ✓Underwent systematic mediastinal staging
- ✓No contra-indications for CIT
- ✓NGS results available (EGFR/ALK)
- ✓PD-L1 levels will not determine candidacy for neoadjuvant chemo-IO

Adjuvant Immunotherapy in NSCLC

Case Study # 4

55 year-old male, former 10 pack-year smoker, quit 30 years ago, presents to the ED after being involved in an MVA. Chest x-rays show a RLL mass. CT imaging shows a 4.5 cm RLL speculated mass. PET scans shows no extra-thoracic disease.

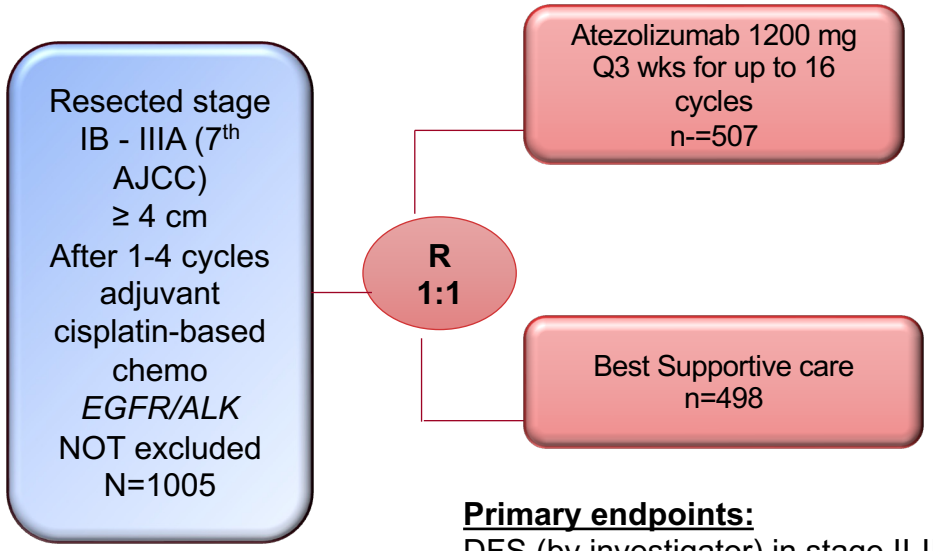
EBUS + 10R for adenocarcinoma cells. Stations 4R, 7 and 4L with lymphoid specimen and all negative for malignant cells. Specimen shows PD-L1 15%. QNS for NGS.

Brain MRI negative for ICM.

Pt comes to you to discuss neoadjuvant therapy.

What are your recommendations?

IMpower 010: Study Design and Patient Characteristics



	PD-L1 TC ≥ 1% II-IIIA		Intention-to-Treat group (IB-IIIA)	
	Atezolizumab n = 248	BSC n = 228	Atezolizumab n = 507	BSC n = 498
Squamous	96 (39%)	85 (37%)	179 (35%)	167 (34%)
Never smokers	51 (21%)	41 (18%)	114 (23%)	108 (22%)
Stage IIIA	117 (47%)	115 (50%)	205 (40%)	208 (42%)
Stage IB			65 (13%)	58 (12%)

Primary endpoints:
DFS (by investigator) in stage II-III pts with PD-L1 ≥ 1%*
DFS (by investigator) in all stage II-III pts
DFS (by investigator) in the ITT stage IB-III pts

* PD-L1 by Ventana SP 263

Stratification factors:
Gender
Histology
Stage: IB vs II vs IIIA
PD-L1

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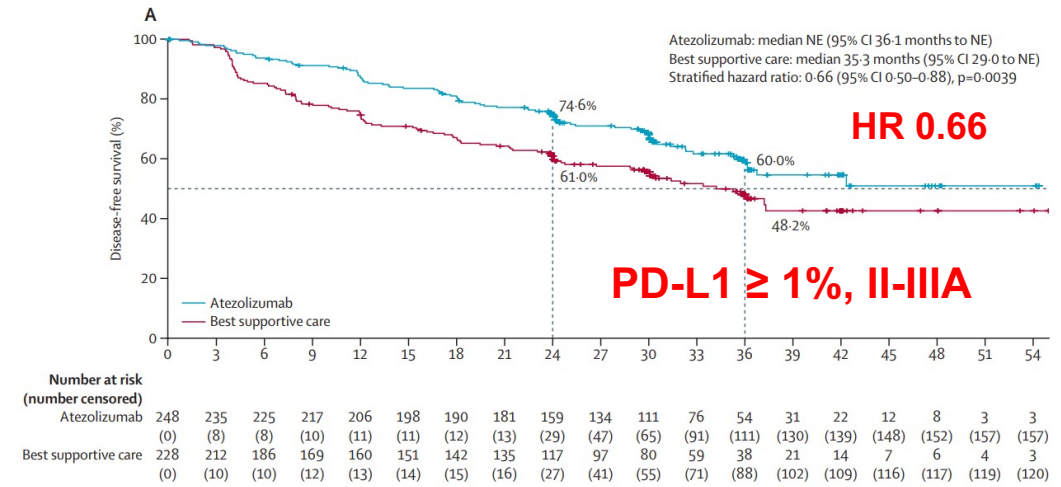
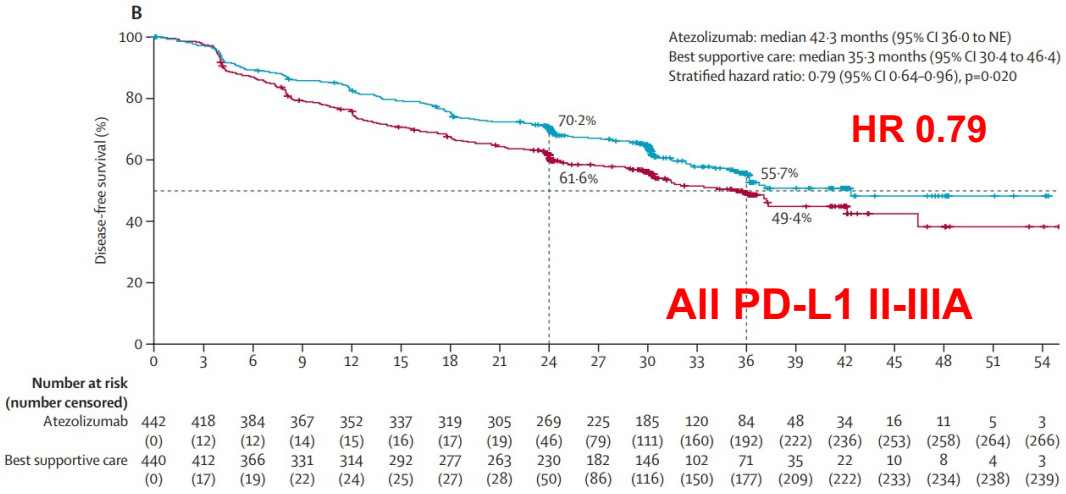
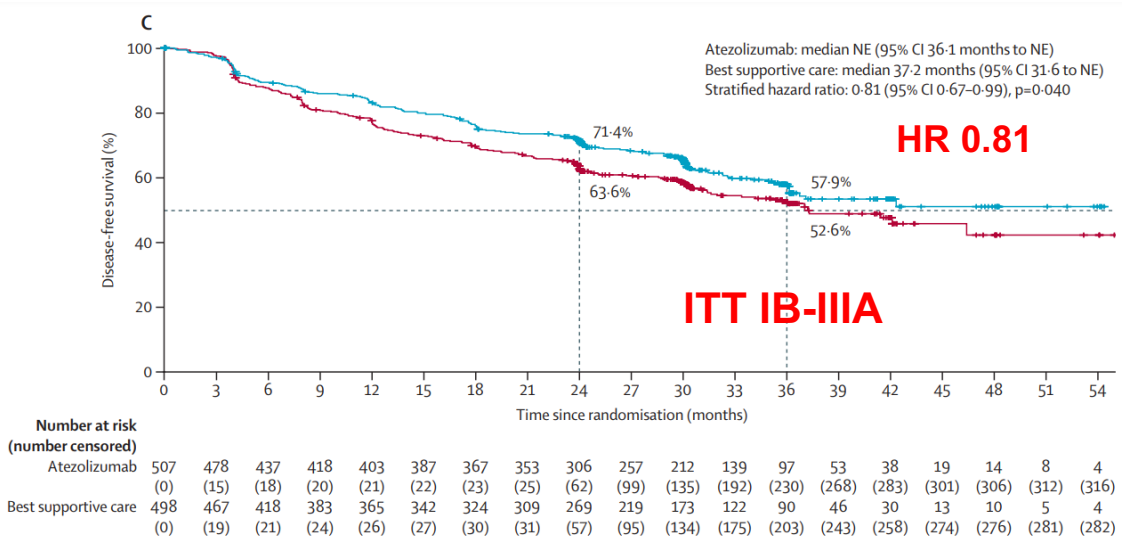
Felip E, N Engl J Med 2021; 398:1344-57

IMpower 010: DFS in II-IIIA PD-L1 ≥ 1%, all PD-L1 II-IIIA and ITT IB-IIIA







PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

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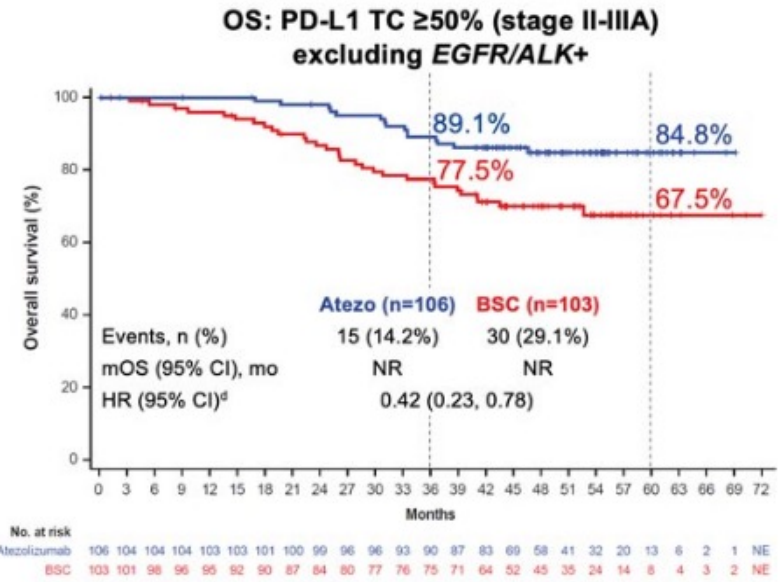
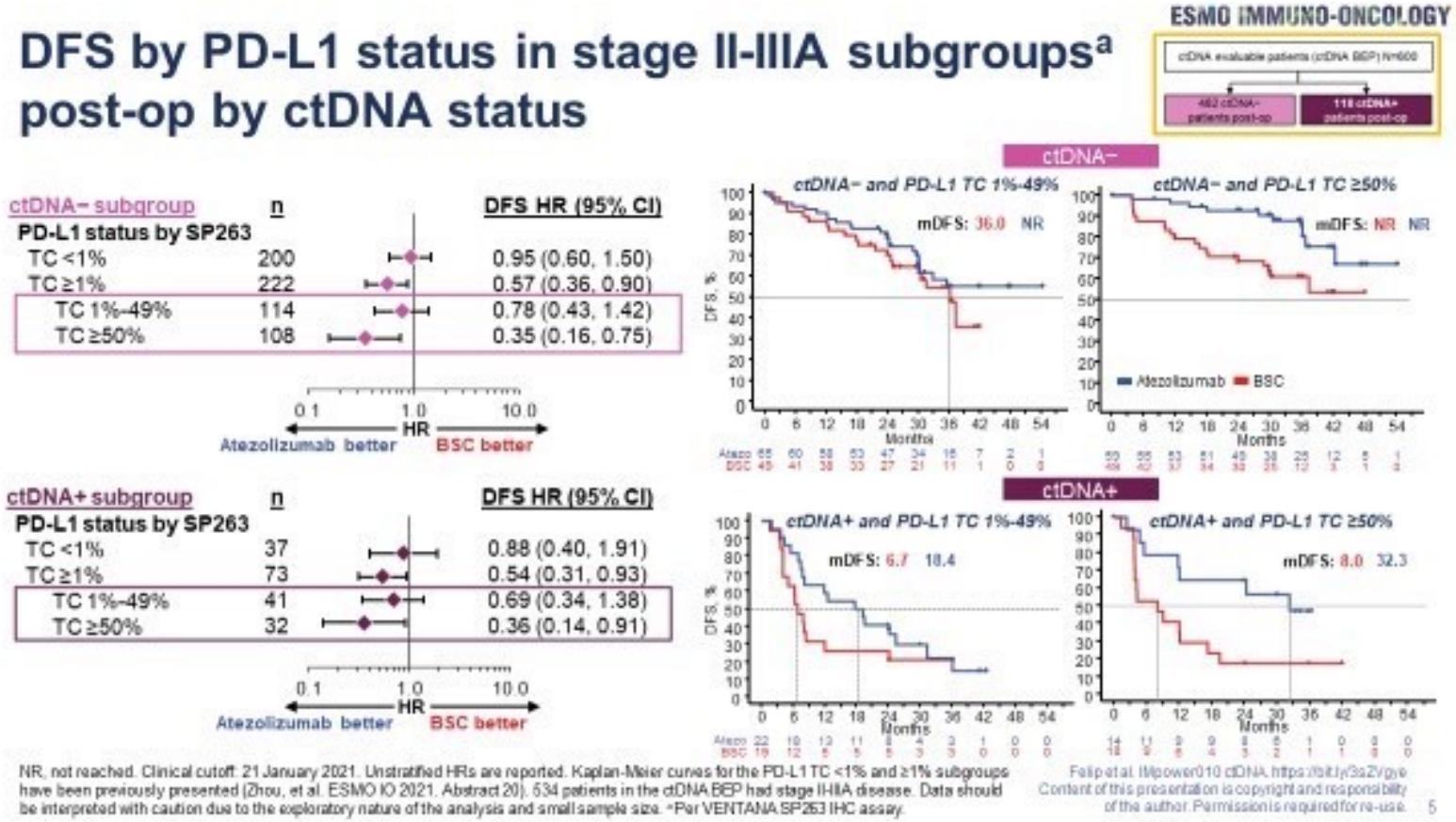
Felip E, N Engl J Med 2021; 398:1344-57

IMpower 010: Overall Survival and DFS by PD-L1 and ctDNA





NR, not reached. Clinical cutoff: 21 January 2021. Unstratified HRs are reported. Kaplan-Meier curves for the PD-L1 TC <1% and ≥1% subgroups have been previously presented (Zhou, et al. ESMO IO 2021. Abstract 20). 534 patients in the ctDNA BEP had stage II-IIIA disease. Data should be interpreted with caution due to the exploratory nature of the analysis and small sample size. [a]Per VENTANA SP263 IHC assay.

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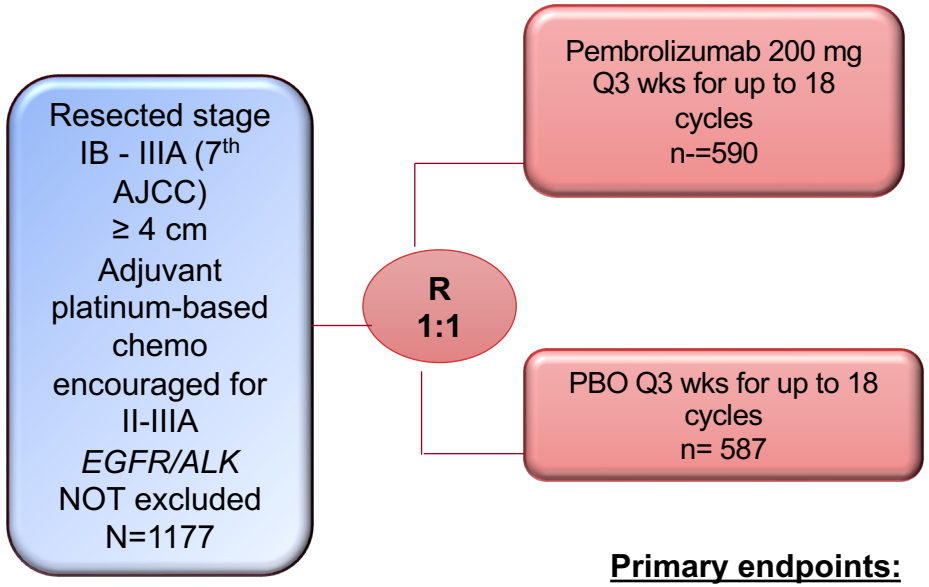
1. Wakalee H. J Thorac Oncol 2022; 17:S2
2. Felip E. Annals of Oncology (2022) 16 (suppl_1): 100100-100100.

PEARLS-KEYNOTE-091: Study Design and Patient Characteristics



Stratification factors:
Adjuvant chemo: yes vs no
Stage: IB vs II vs IIIA
PD-L1 , 1% vs 1-49% vs ≥50%
Region: Asia vs Eastern Europe vs Western Europe vs Rest of the world

Primary endpoints:
DFS in overall population
DFS in PD-L1 ≥ 50%

Secondary endpoints:
DFS in PD-L1 ≥ 1%
OS in overall population
OS in TPS ≥ 50%
OS in TPS ≥ 1%
Lung CA specific survival
Safety

	Overall ITT Population		TPS ≥ 50%	
	Pembrolizumab n = 590	PBO n = 587	Pembrolizumab n = 168	BSC n = 165
Squamous	192 (33%)	224 (38%)	65 (39%)	60 (36%)
Never smokers	87 (15%)	66 (11%)	14 (8%)	13 (8%)
Stage IIIA	177 (30%)	162 (28%)	52 (31%)	50 (30%)
Stage IB	84 (14%)	85 (14%)	21 (13%)	22 (13%)
TPS ≥ 50%	168 (28%)	165 (28%)	168 (100%)	165 (100%)
TPS < 1%	233 (39%)	232 (40%)		

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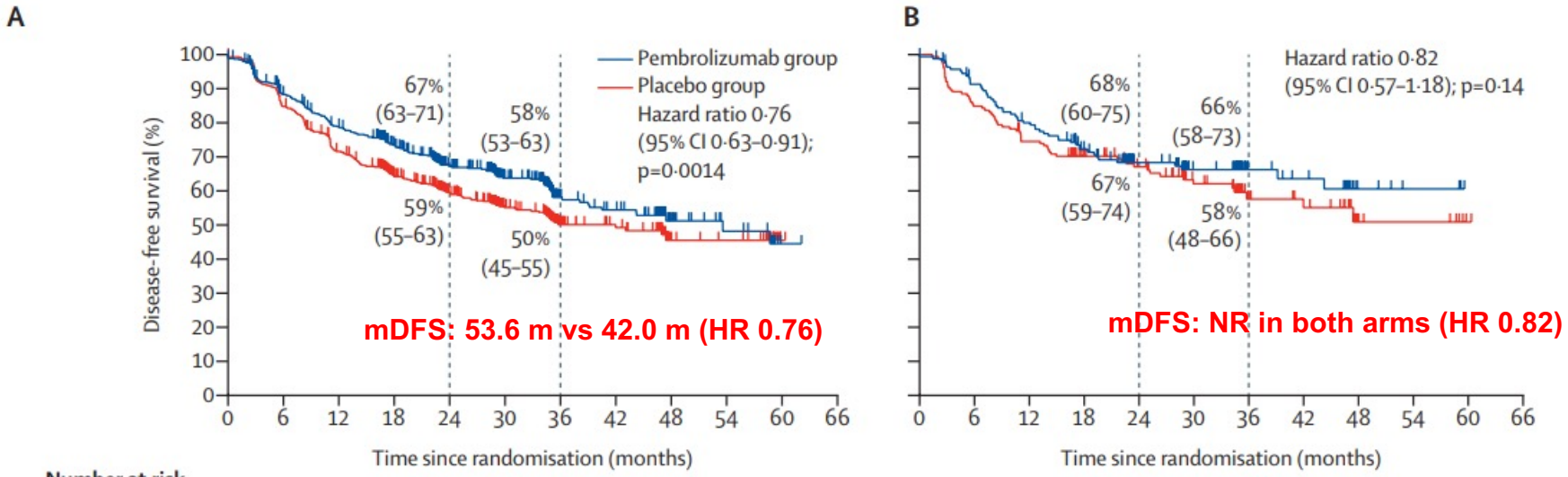
O'Brien M. Lancet, 2022; 23: 1274

PEARLS-KEYNOTE-091: DFS

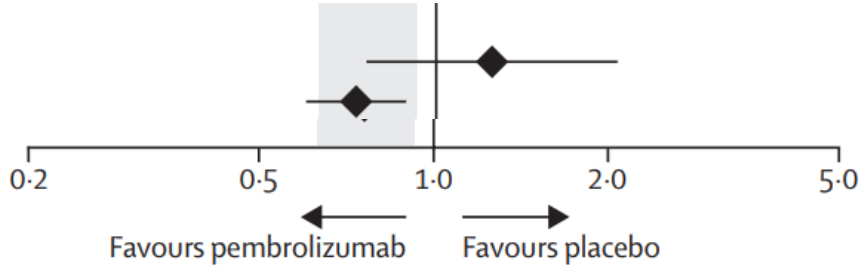


Number at risk (number censored)

Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

	168	145	126	99	69	50	26	22	7	4	0	0
	(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
	165	140	121	100	75	54	28	22	8	6	1	0
	(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)

Received adjuvant chemotherapy			
No	35/84	29/83	1·25 (0·76–2·05)
Yes	177/506	231/504	0·73 (0·60–0·89)



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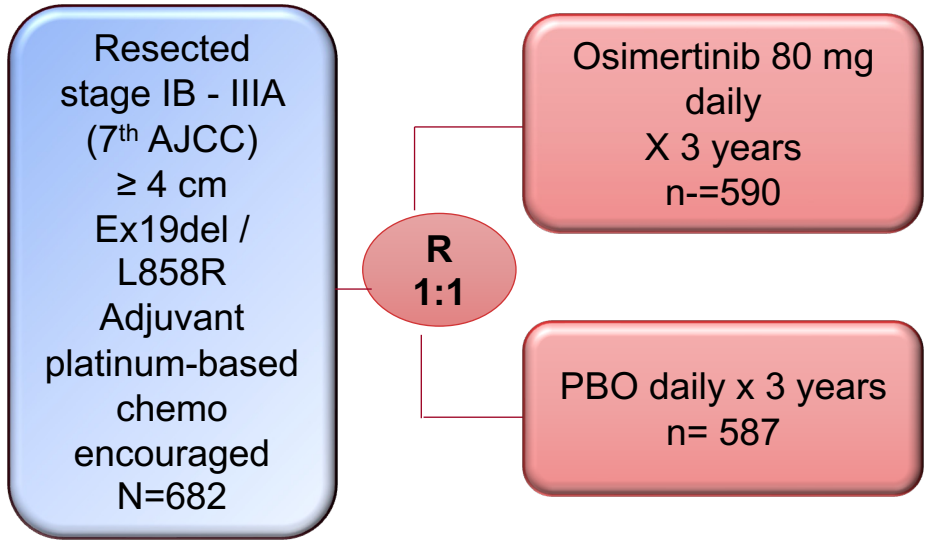
O'Brien M. Lancet, 2022; 23: 1274

ADAURA: Study Design and Patient Characteristics



Stratification factors:
Stage: IB vs II vs IIIA
EGFRm: Ex19del vs L858R
Race: Asian vs non-Asian

Primary endpoint:
DFS by investigator in II-IIIA

Secondary endpoints:
DFS in overall population (IB-IIIA)
Landmark FDA rates
OS
Safety
Health-related QoL

	Osimertinib n = 339	PBO n = 343
N0	41%	42%
N1	29%	28%
N2	31%	30%
Ex19del	55%	55%
L858R	45%	45%
No adjuvant chemotherapy	40%	40%

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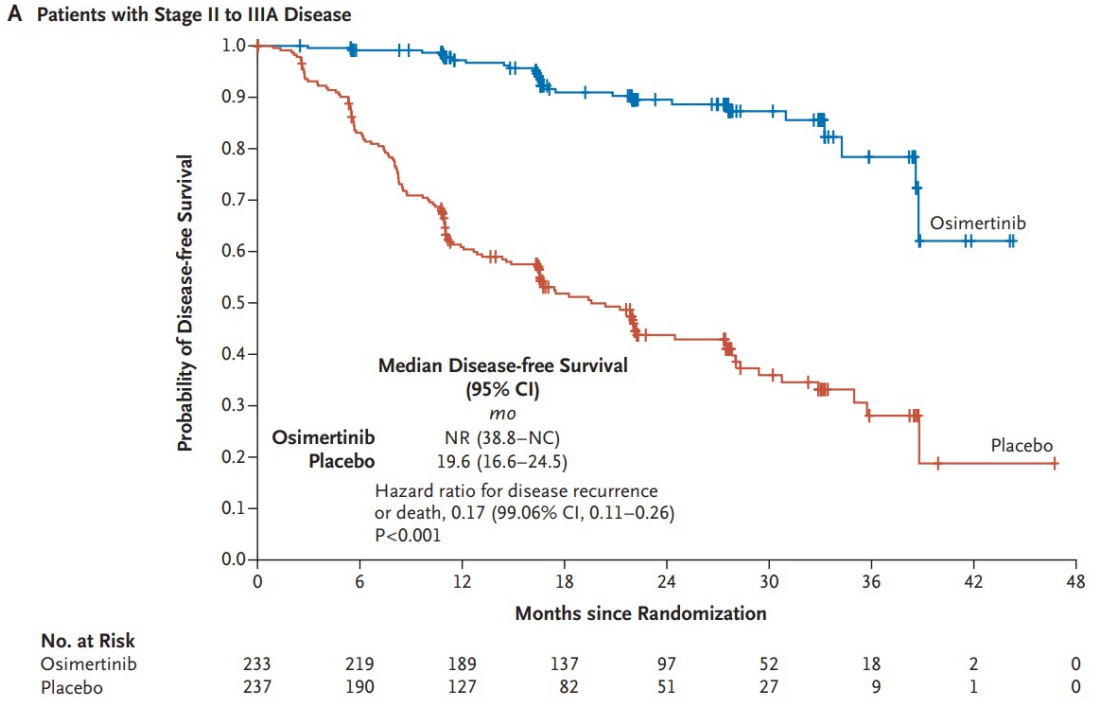
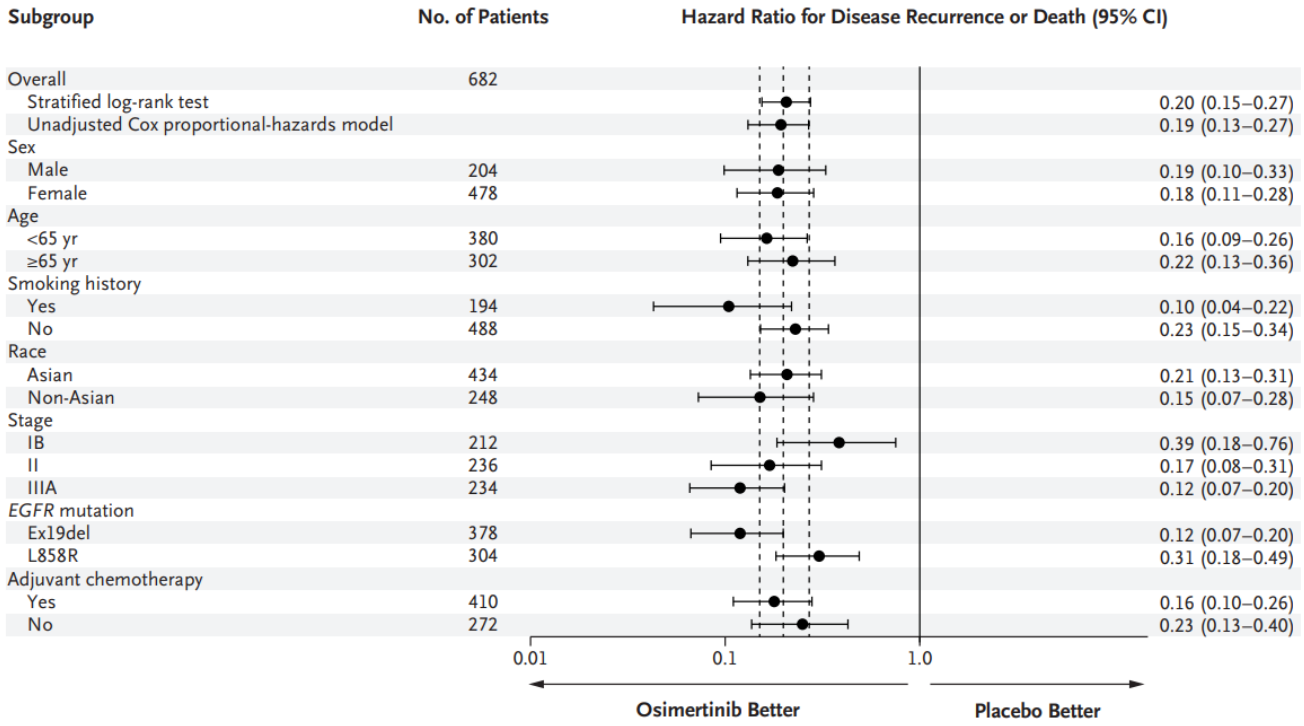
Wu Y-L. N Engl J Med, 2021;383:1711

ADAURA - DFS

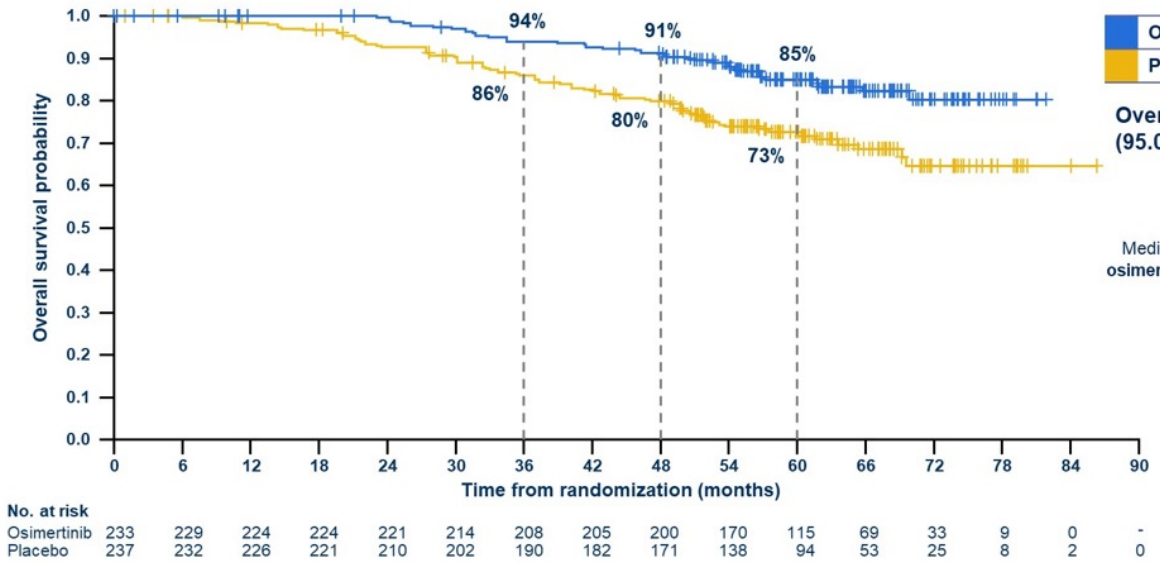




Wu Y-L. N Engl J Med, 2021;383:1711

ADAURA – OS in stage II-IIIA and across subgroups

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

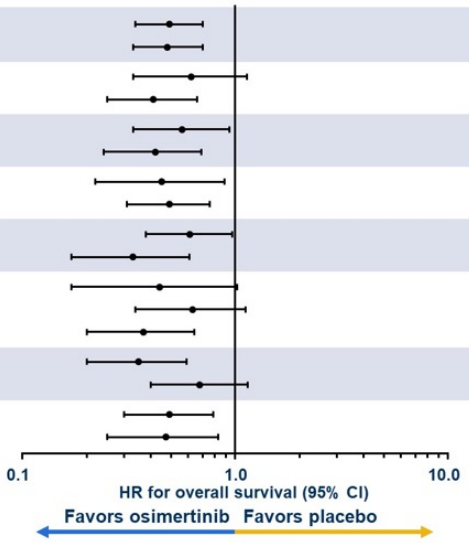
Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

OS across subgroups: patients with stage IB / II / IIIA disease

Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83



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Herbst R. J Clin Oncol, 2023

Case Study # 4

62 year-old female, former 10 pack-year smoker, quit 30 years ago, presents to the ED after being involved in an MVA. Chest x-rays show a RLL mass. CT imaging shows a 4.5 cm RLL speculated mass. PET scans shows no extra-thoracic disease.

EBUS + 10R for adenocarcinoma cells. Stations 4R, 7 and 4L with lymphoid specimen and all negative for malignant cells. Specimen shows PD-L1 15%. QNS for NGS.

Brain MRI negative for ICM.

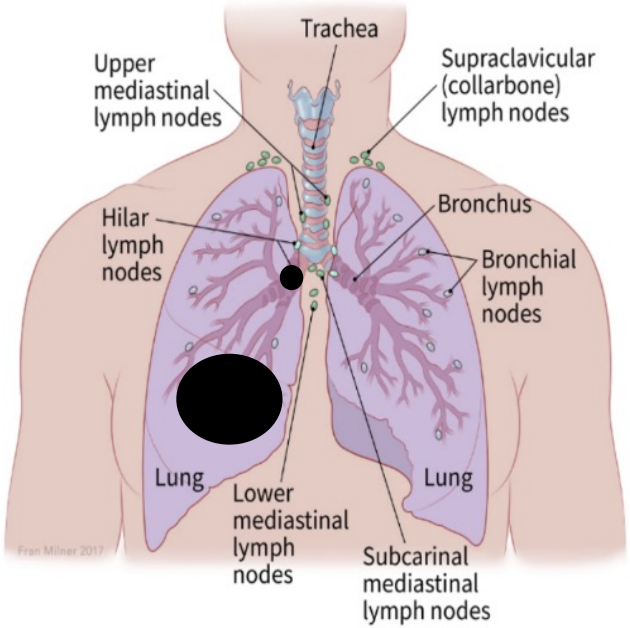
Pt comes to you to discuss neoadjuvant therapy.

What are your recommendations?

Case Study # 4

- ✓ You discuss with the patient undergoing a repeat EBUS/Navigational bronchoscopy for more tissue so NGS can be obtained.
- ✓ Pt declines it. He asks if you can send a blood test to determine if tumor has an AGA.
- ✓ You explain the yield of ctDNA in patients with no clinical metastasis is limited and not recommended in this setting.
- ✓ Case discussed at TB -
- ✓ Pt undergoes a RUL lobectomy: pT2b pN1 (Stage IIB). Surgical specimen NGS: EGFR L858R mutation
- ✓ After 4 cycles of adjuvant cisplatin/pemetrexed, the patient begins adjuvant osimertinib.

Stage IIB



How I Treat Resectable NSCLC

- ✓ Always discuss multi-disciplinary patients at MDT Tumor Board
- ✓ Patients with indications for adjuvant systemic therapy – tumor ≥ 4 cm, + N1, single station/non-bulky N2 station, discuss neoadjuvant chemo-IO– 3 cycles are preferable to 4 – similar pCR rates across trials
- ✓ Need NGS test results to decide neoadjuvant chemo-IO!
- ✓ Do not use ctDNA to test patients with no clinical metastasis – it has very low yield
- ✓ If no NGS available, consider adjuvant therapy only (especially in adenocarcinoma) – as surgical specimen will be tested

How I Treat Resectable NSCLC

- ✓ Always confirm with tissue any radiographic concerns of progression while pts are undergoing neoadjuvant chemo-IO – do NOT rely solely on PET scan results
- ✓ In the adjuvant setting, candidates for immunotherapy should ALWAYS receive platinum-based chemo first!
- ✓ IMpower 010 or KEYNOTE-091? Leave atezolizumab for PD-L1 TPS ≥ 50%
- ✓ Candidates for adjuvant osimertinib and stage II-III should always receive chemotherapy first if able to tolerate it (ECOG 0-1)
- ✓ Borderline operable disease: favor neoadjuvant chemo-RT followed by surgery, followed by immunotherapy or targeted therapy
- ✓ Pancoast tumors: chemo-RT ➡ Surgery ➡ Adjuvant Immunotherapy

Thank you!
Always consider offering a clinical trial to your patients – it may save their lives

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