Biomarker Testing and Systemic Treatment for Resectable Non-small Cell Lung Cancer

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Disclosure

Astra Zeneca Advisory Board

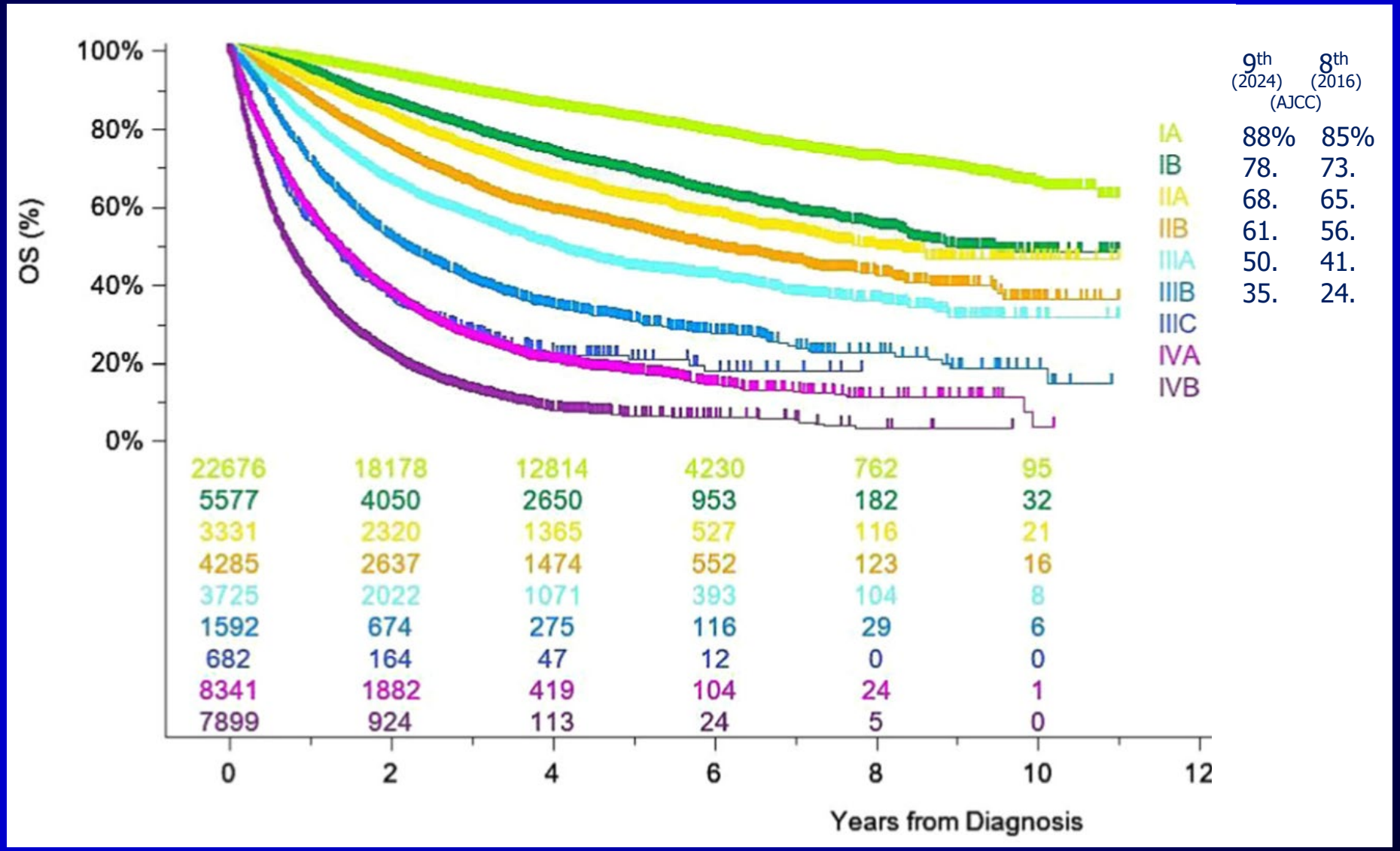
Learning Objectives

Describe recent advances in systemic treatment after Complete resection in NSCLC

Understand why systemic therapy depends on biomarker Testing in resected NSCLC

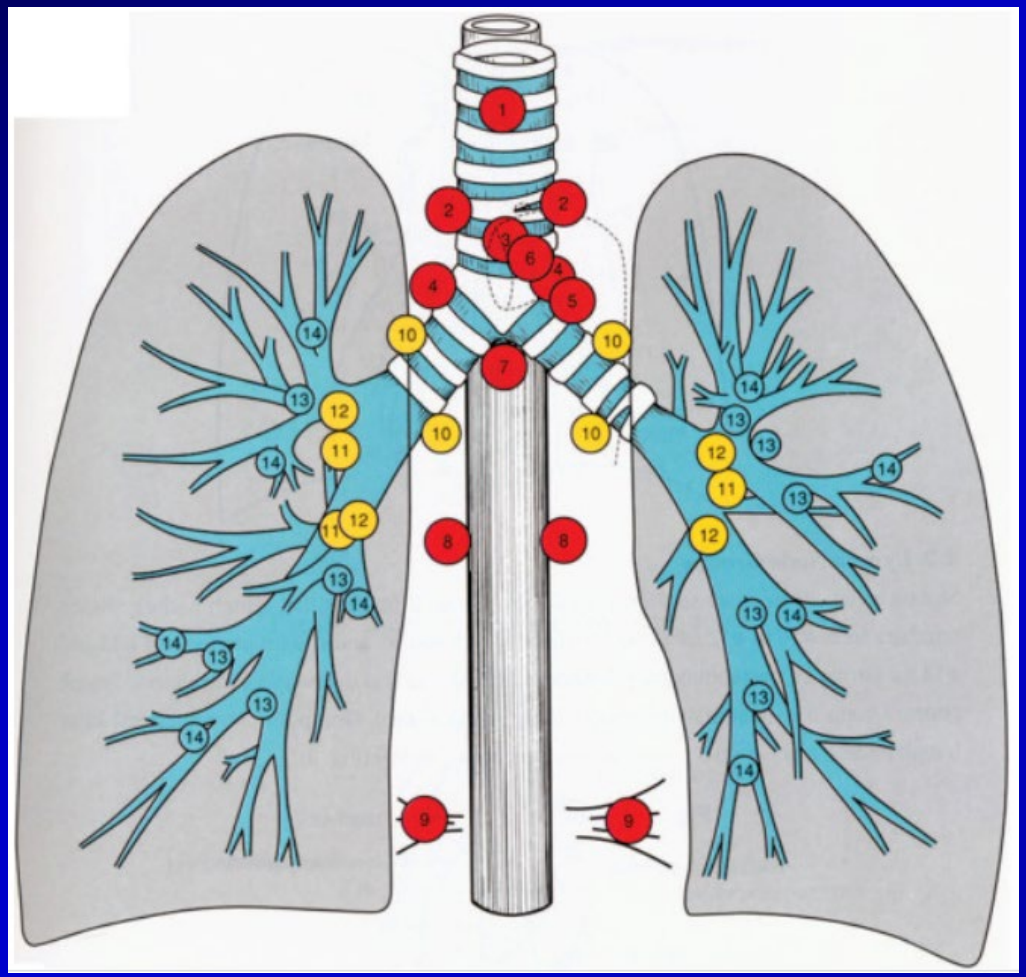
Learn the timing of biomarker testing in resected NSCLC

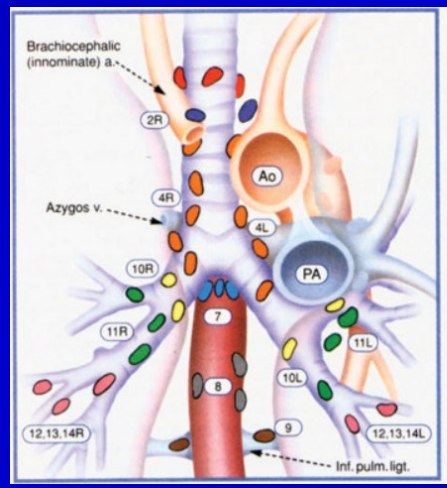
Progresses has been made to cure



	9th (2024) (AJCC)	8th (2016)
IA	88%	85%
IB	78.	73.
IIA	68.	65.
IIB	61.	56.
IIIA	50.	41.
IIIB	35.	24.

NSCLC are Staged Based on What We See (TNM) But We Can not See Micromets





Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

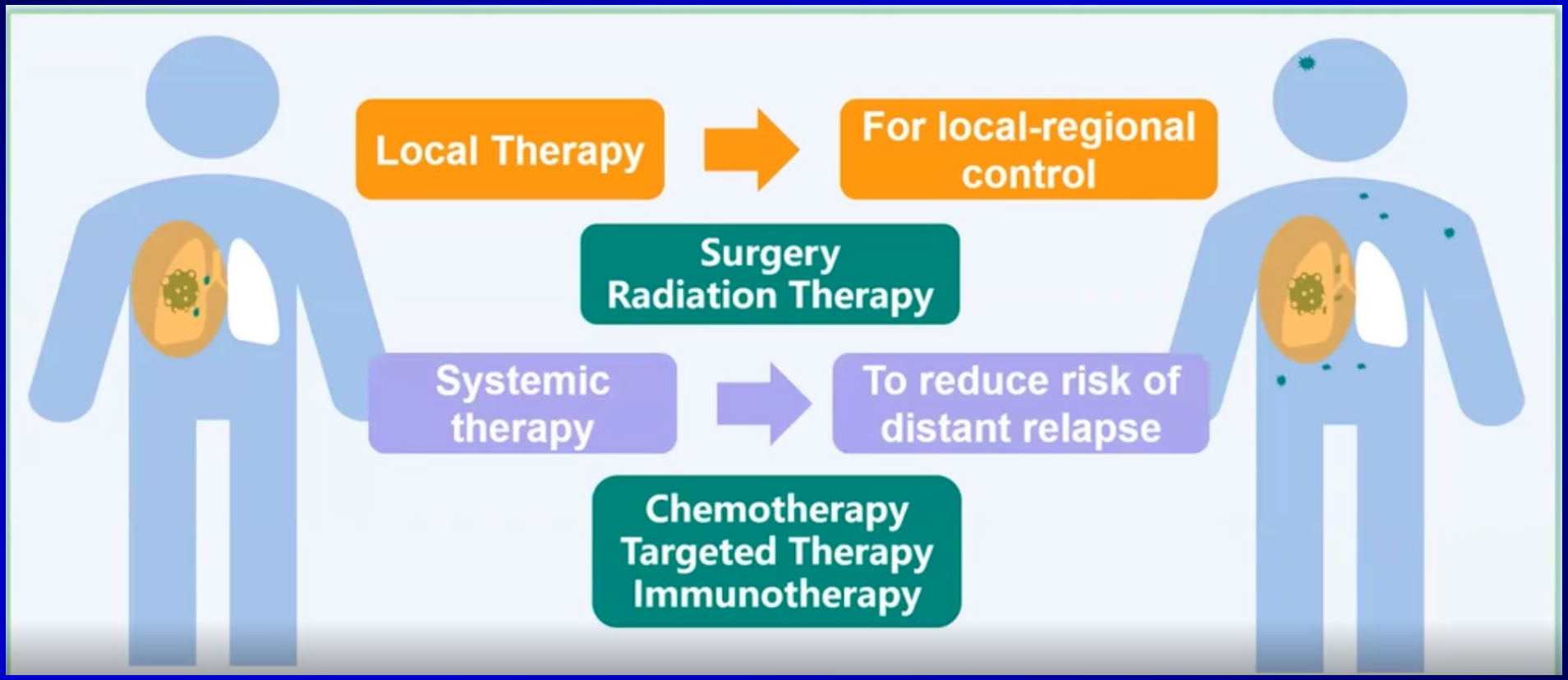
The Three Pillars of Oncological Treatment

Surgery: Addressing local recurrence better with lobectomy and nodal dissection for early occult metastasis to the nodes

Radiation: Addressing local tumor only, can be offered to those who do not like surgery or less robust to go through surgery

Systemic Treatment: Addressing remote metastasis In addition to boost efficacy of local radiation Control of remote mets esp in the brain is very attractive.

Early occult metastasis (can not see) contributes to failure



Systemic Treatment Depends on Biology Based on Biomarker Testing

AGA positive, actionable: EGFR mutation or ALK fusion
TKI with or without chemotherapy first. (2-3 years)

AGA negative, But PD-L1 expressing tumor,
Chemotherapy followed by immune checkpoint inhibitor
For one year

AGA, negative and PD-L1 negative
Chemotherapy only. 4 cycles of platinum doublet
per histology

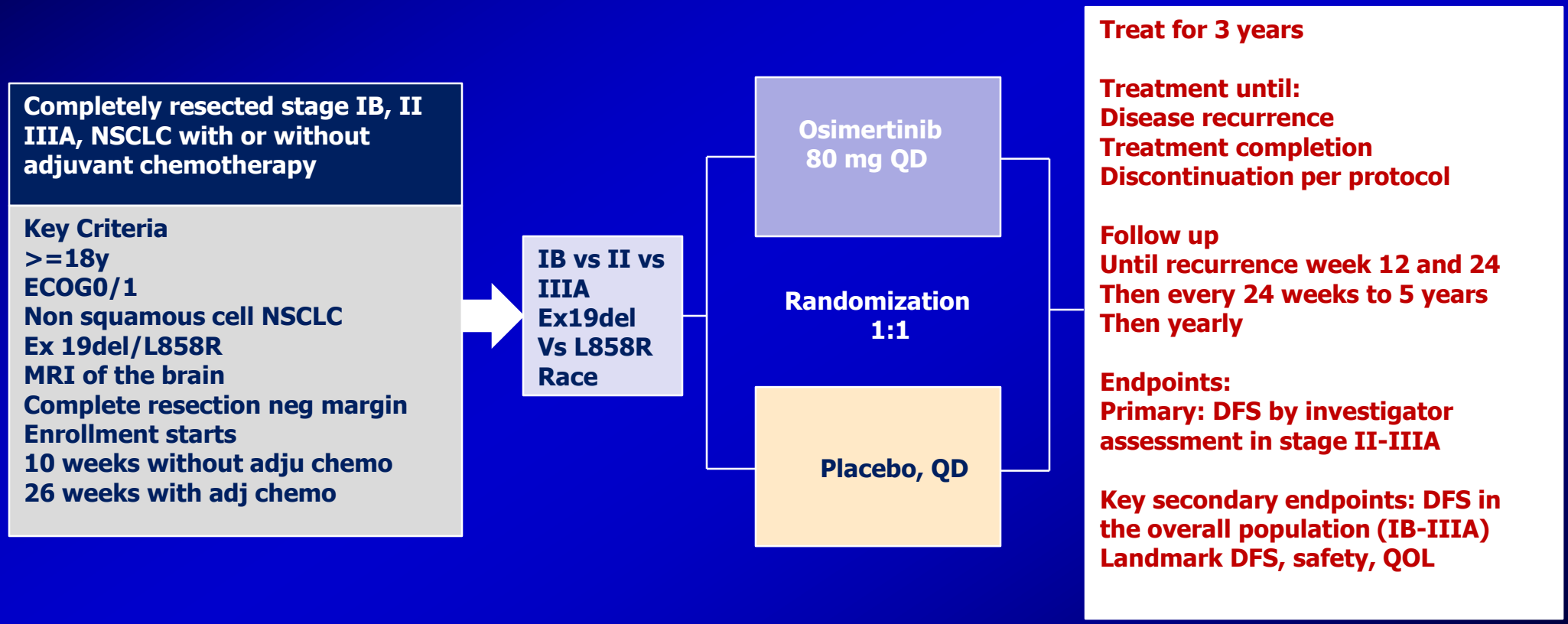
Adjuvant for EGFR+ Lung Cancer after Resection: The ADAURA phase 3

Does it help when you give osimertinib after Platinum doublet for stage II-IIIa lung cancer Treated with surgical resection if EGFR mut+?

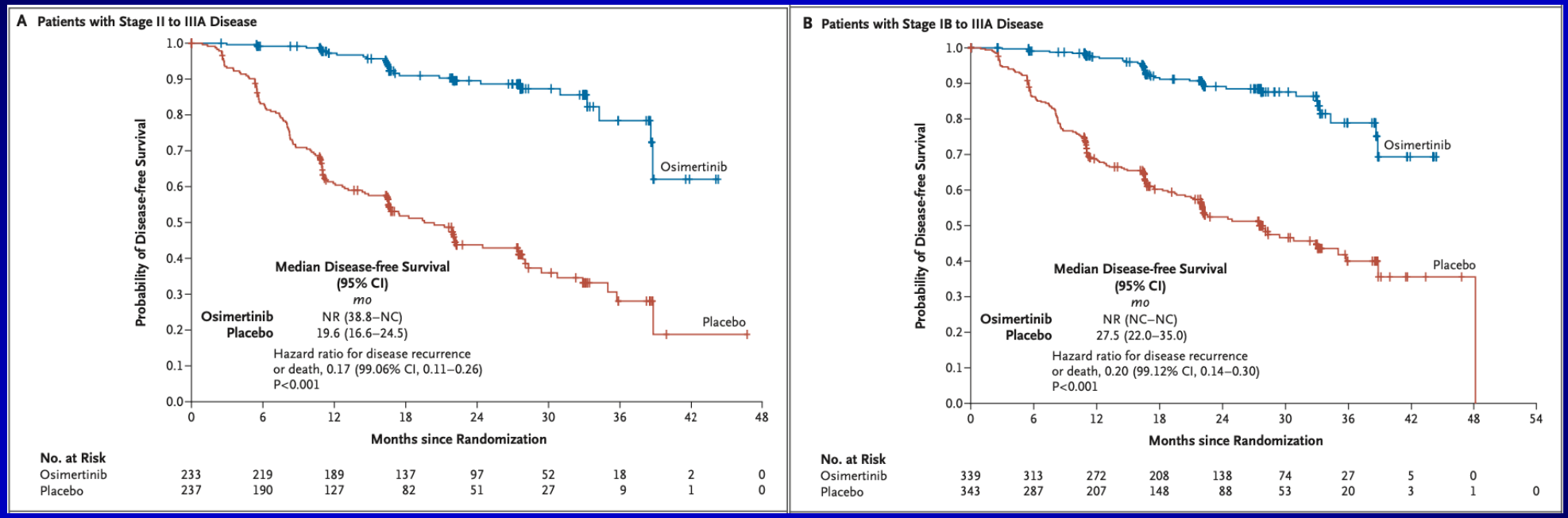
Phase 3, randomized, placebo control 1:1, ~340 Patients each. 1º ?DFS 2º ?DFS, ?OS ?Safety

Wu YL et al NEJM Oct 29, 2020; 38(18)1711-32

Adjuvant Osimertinib Improved PFS of EGFR Mutated NSCLC (ADAURA)



Probability of Disease Free Survival



Wu YL et al NEJM Oct 29, 2020; 38(18)1711-32

CNS Disease Free Survival

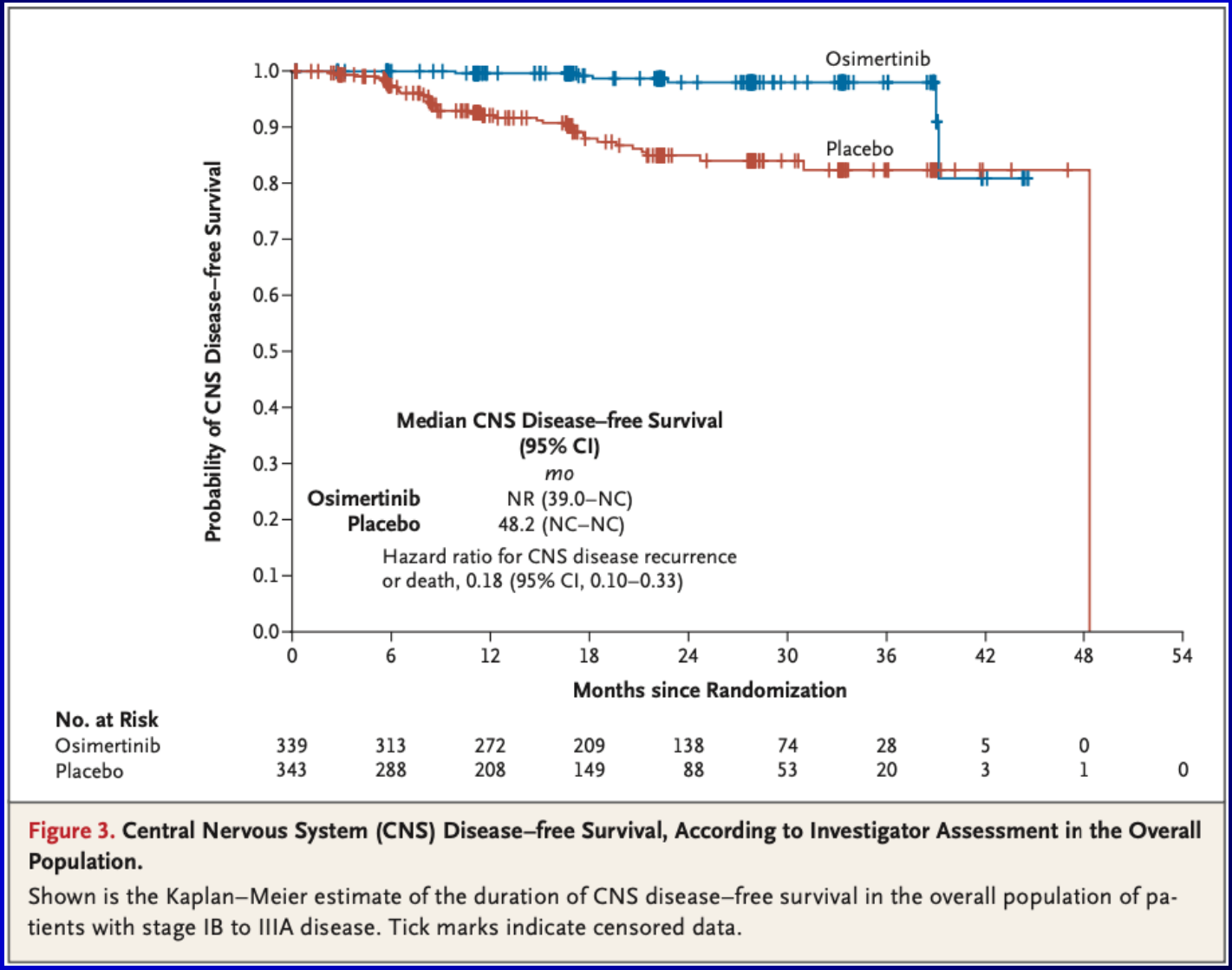
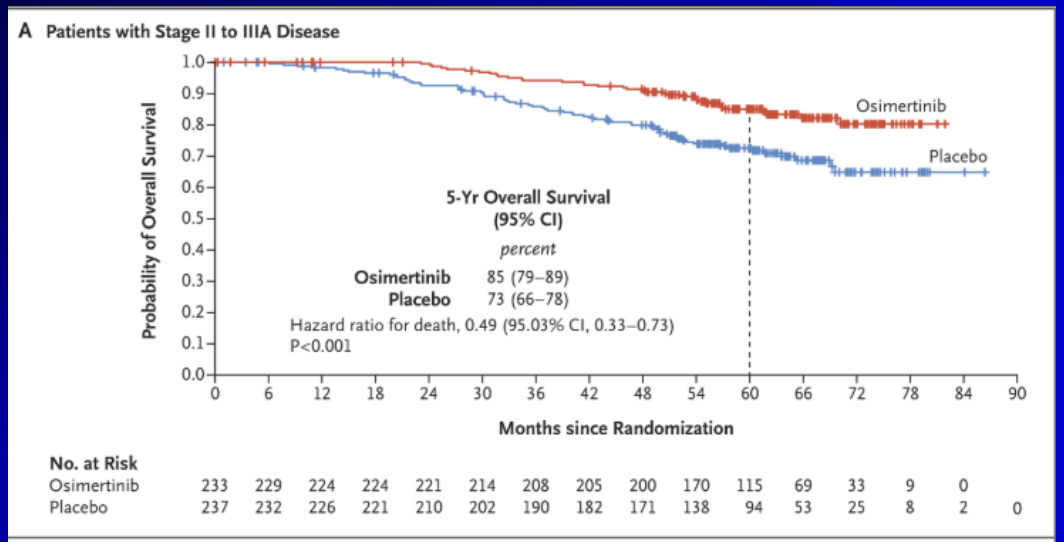
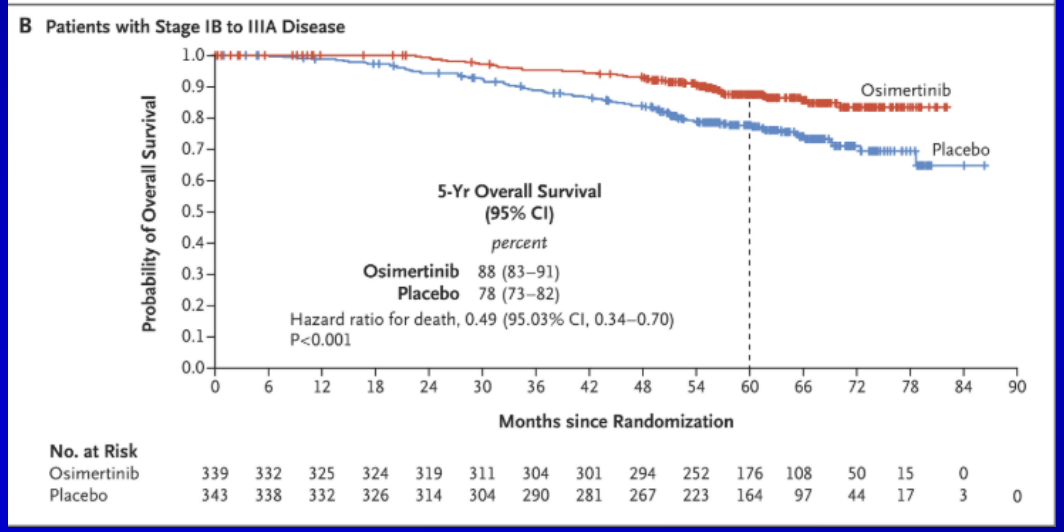


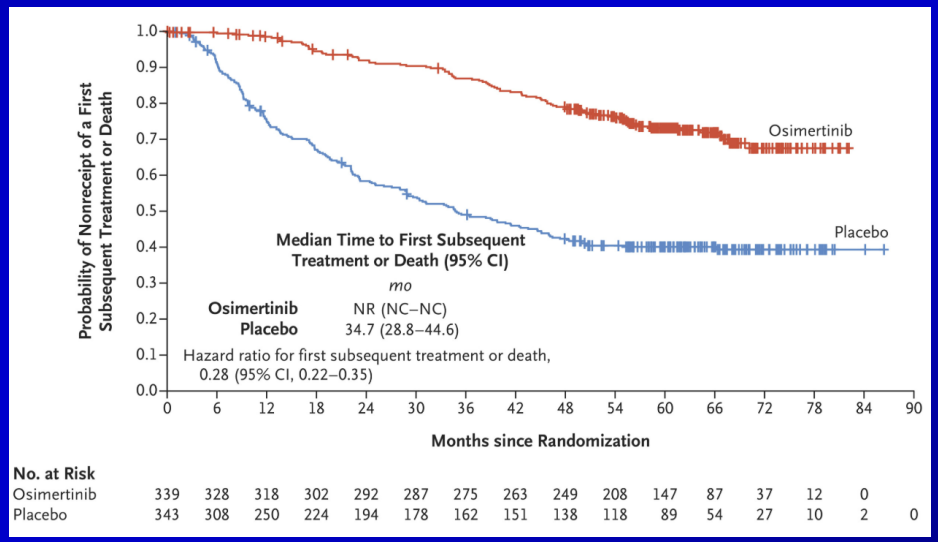
Figure 3. Central Nervous System (CNS) Disease–free Survival, According to Investigator Assessment in the Overall Population.

Shown is the Kaplan–Meier estimate of the duration of CNS disease–free survival in the overall population of patients with stage IB to IIIA disease. Tick marks indicate censored data.

OS and Time to First Subsequent Treatment



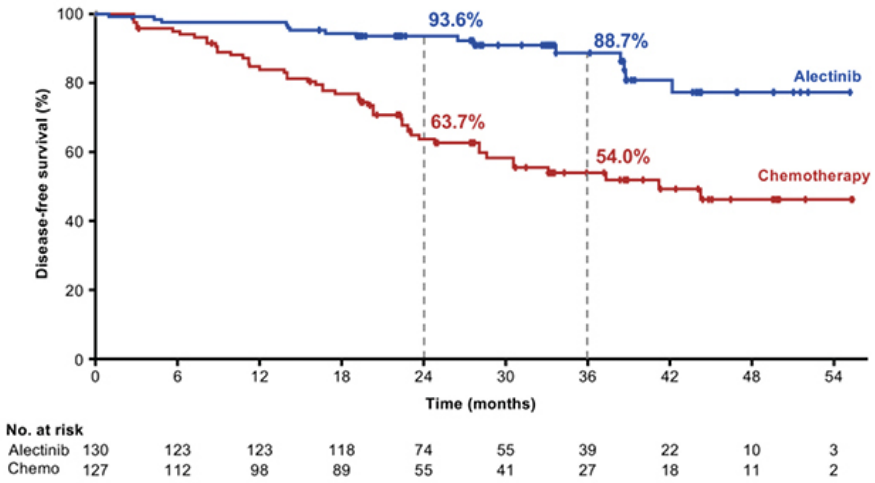




Masahiro T et al NEJM 2023

ALINA Trial, Alectinib improve PFS

Disease-free survival: ITT (stage IB-IIIA)*



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p‡<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported §

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023; *Per UICC/AJCC 7th edition; ‡Stratified log rank; §2 events in the alectinib arm, 4 events in the chemo arm; one patient in chemo died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first.

Ben Soloman ESMO 2023

Impower 010 Trial

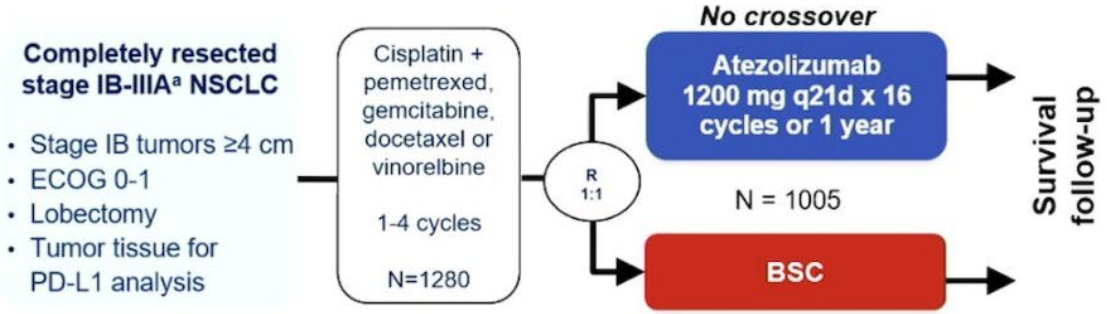
The role of immune checkpoint inhibitor in resected NSCLC stage Ib to IIIa whose tumors express PD-L1 With atezolizumab (anti-PD-L1)

Phase 3, open labeled, randomized ~500 each group 1:1, atezo q3w for 17 cycles

Felip E. et al; Lancet 2021; 398; 1344-57

Adjuvant Atezolizumab Improve OS in PD-L1>1% NSCLC

IMpower010: Phase III randomised trial of atezolizumab vs BSC in early-stage NSCLC



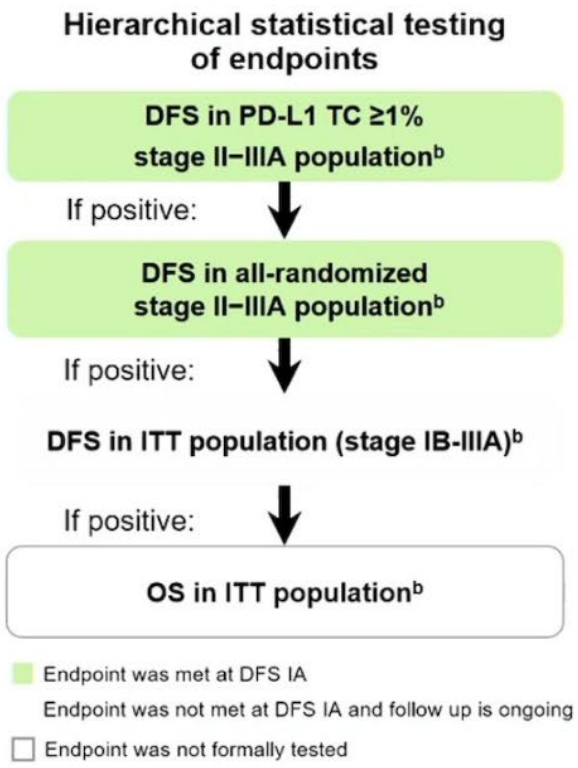
Stratification factors
- Sex | Stage | Histology | PD-L1 status

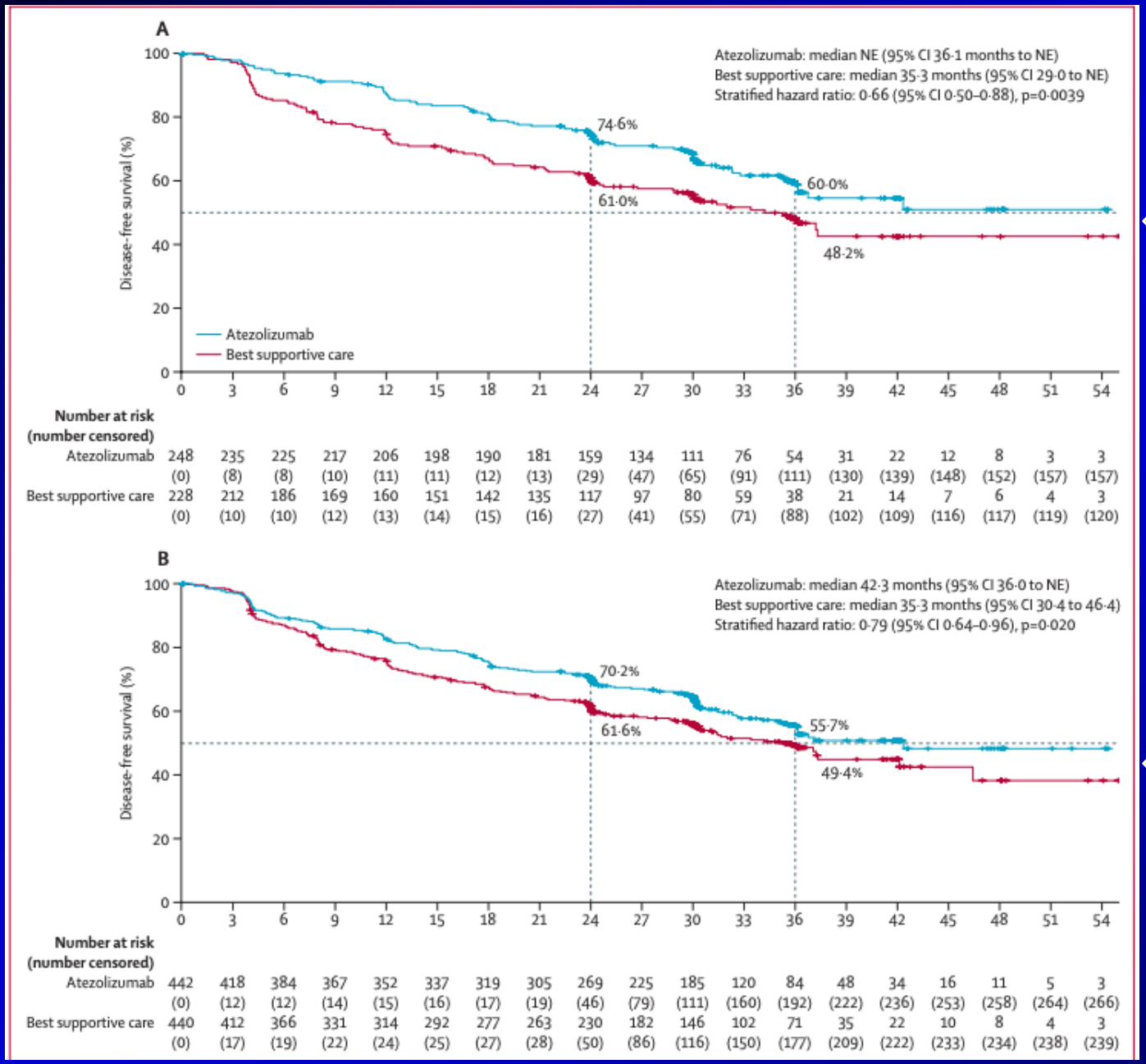
Primary endpoint
- Investigator-assessed DFS tested hierarchically

Key secondary endpoints
- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS

Key exploratory endpoints
- OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

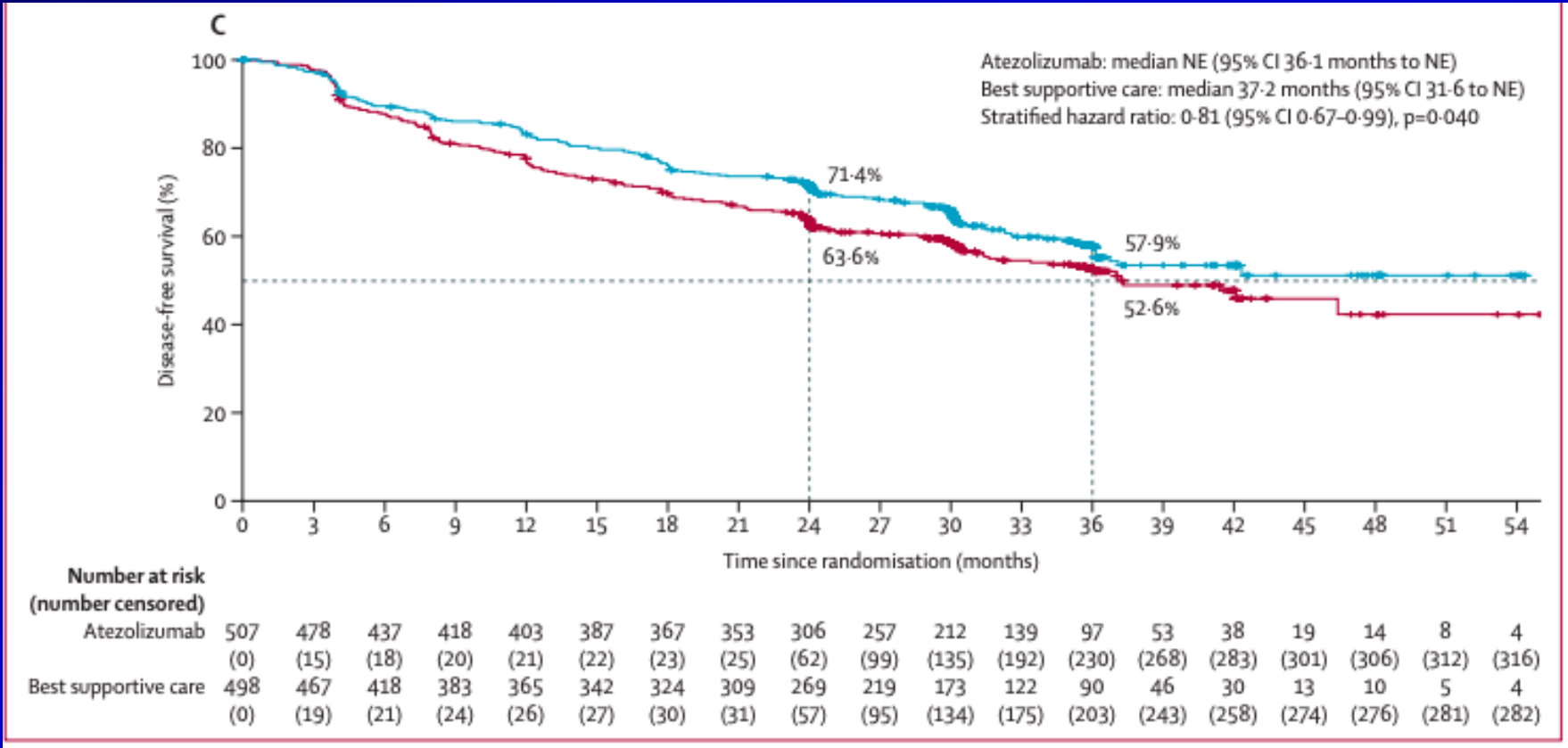




PD-L1>1%

All Patients

Intention to Treat Population



Felip E. et al; Lancet 2021; 398; 1344-57

Safety Profile Impower 010

	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Data are n (%). *Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

Table 2: **Safety summary in the safety evaluable population**

Two additional trials in the adjuvant settings

Keynote 091 (pembrolizumab)

BR-31 (Durvalumab)

Advantages of neoadjuvant chemoimmune

Addressing systemically micrometastasis before surgery
Less remote failure

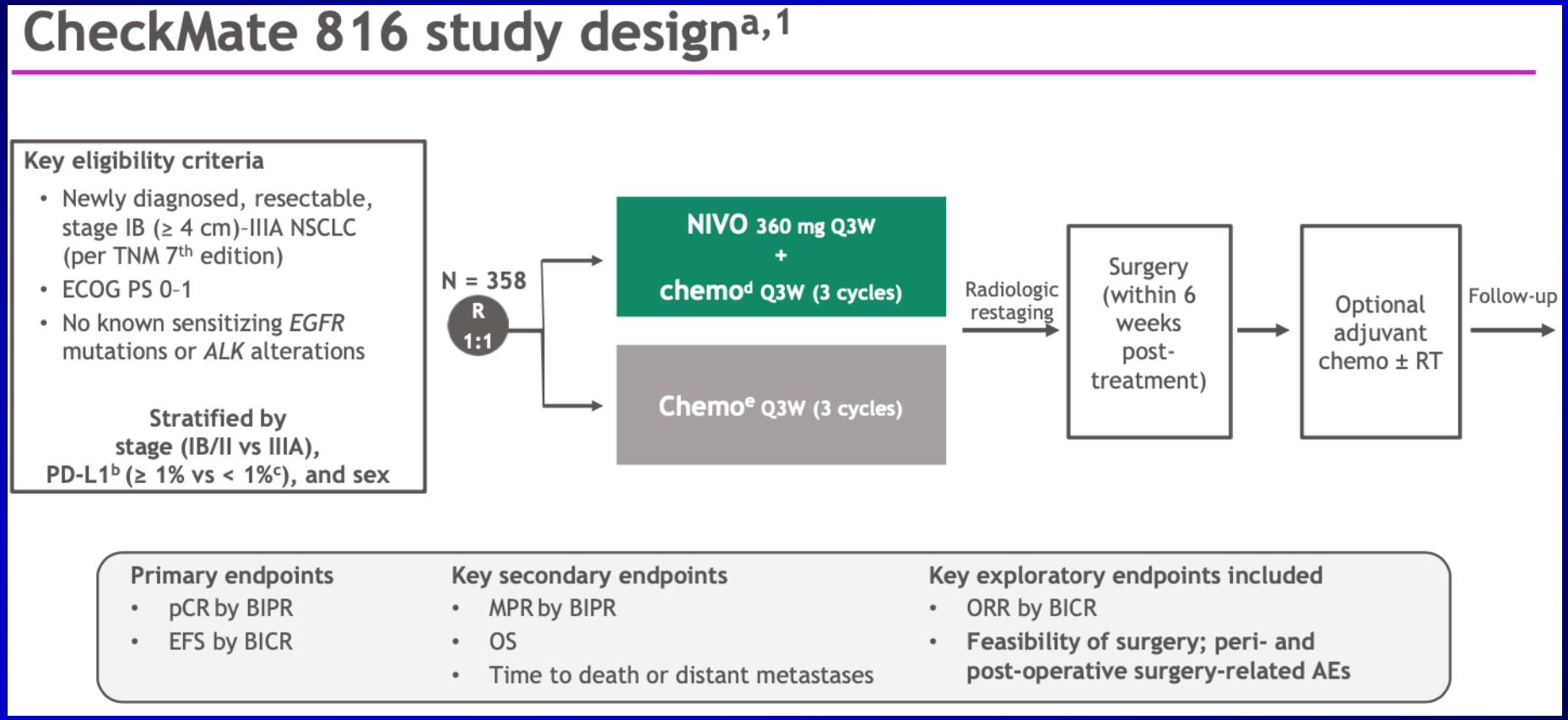
Potential downstaging making resection easier with
Less margin problems

Test response to combined chemo and immune therapy
Which is more powerful than either alone

Easier to give, to a uncompromised immune system

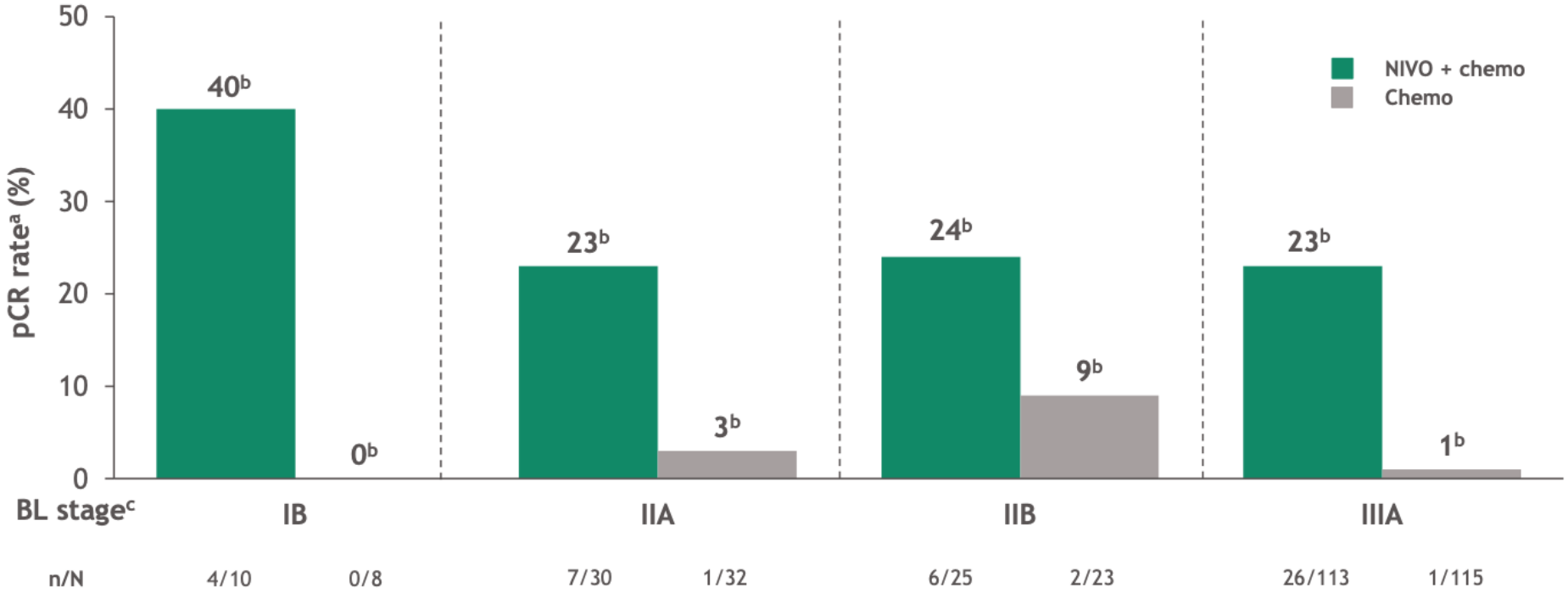
Better compliance to treatment

Study Design CheckMate 816



Pathological Complete Response

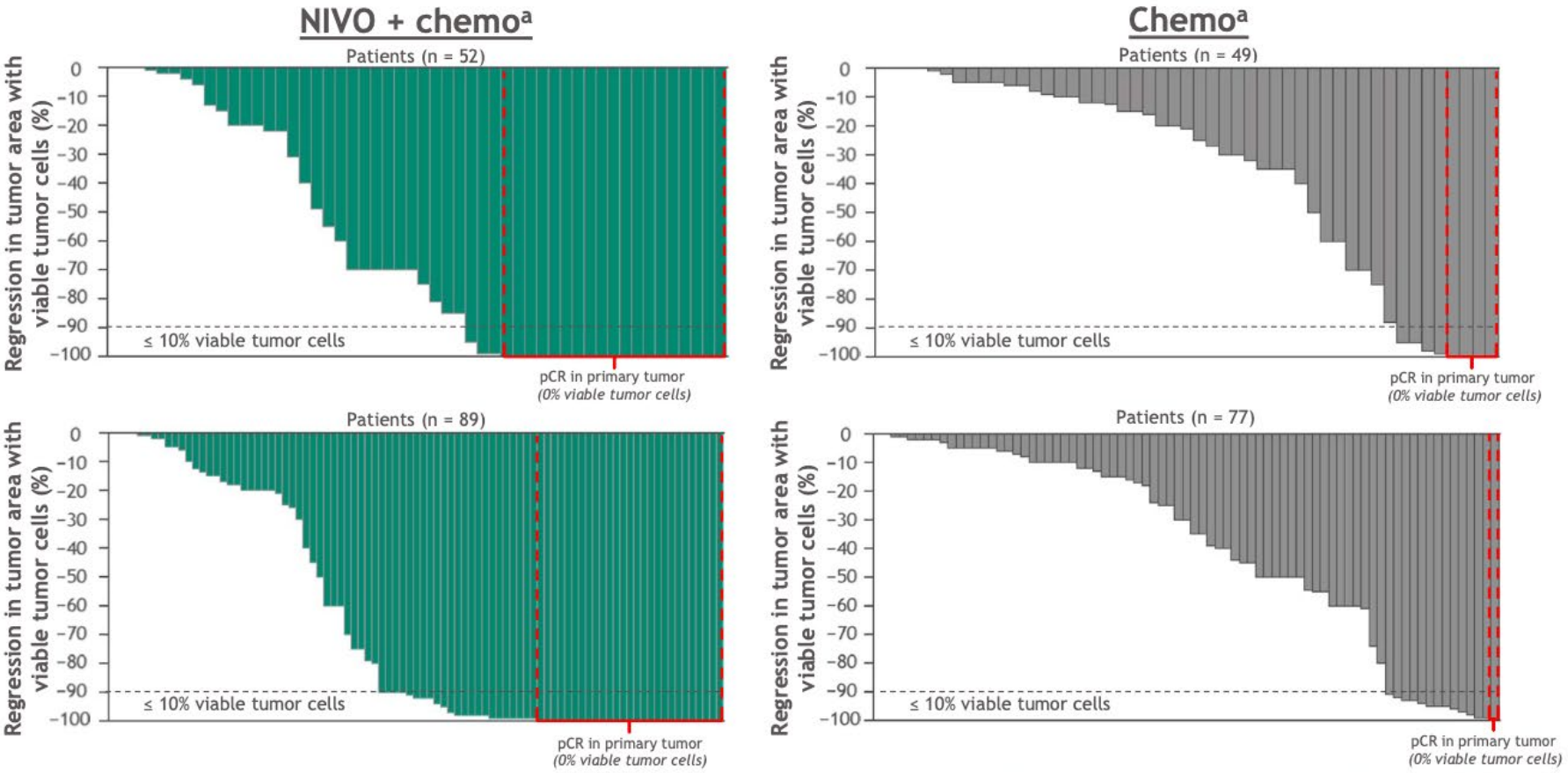
pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

Depth of Response to Treatment by Stage

Depth of pathological regression in primary tumor by stage[a]

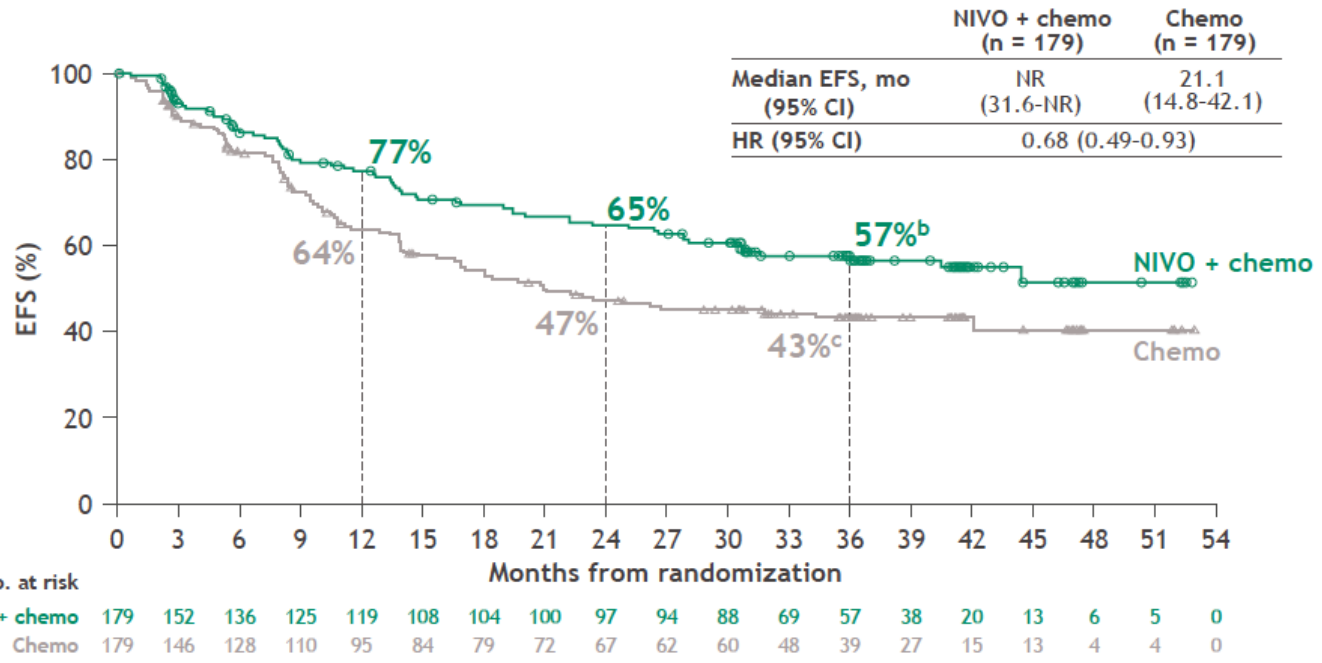


- The median residual viable tumor percentage in stage IB/II and IIIA was 28% and 8% with NIVO + chemo vs 79% and 70% with chemo, respectively

Improved EFS

CheckMate 816: 3-y efficacy/safety update and biomarker analyses

EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]



Minimum/median follow-up: 32.9/41.4 months.

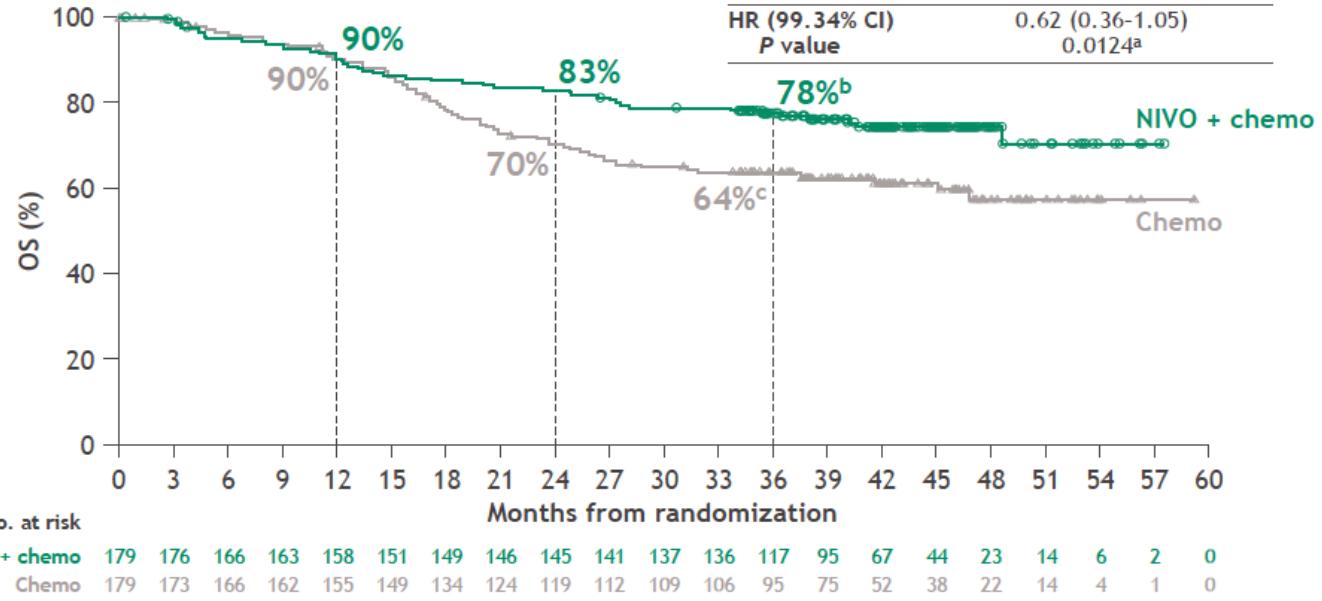
[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48-64; [c]35-51.

Improved OS with Neoadjuvant IO/CT

CheckMate 816: 3-y efficacy/safety update and biomarker analyses

OS with neoadjuvant NIVO + chemo vs chemo: 3-year update

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR-NR)	NR (46.8-NR)
HR (99.34% CI)	0.62 (0.36-1.05)	
P value	0.0124[a]	



No. at risk

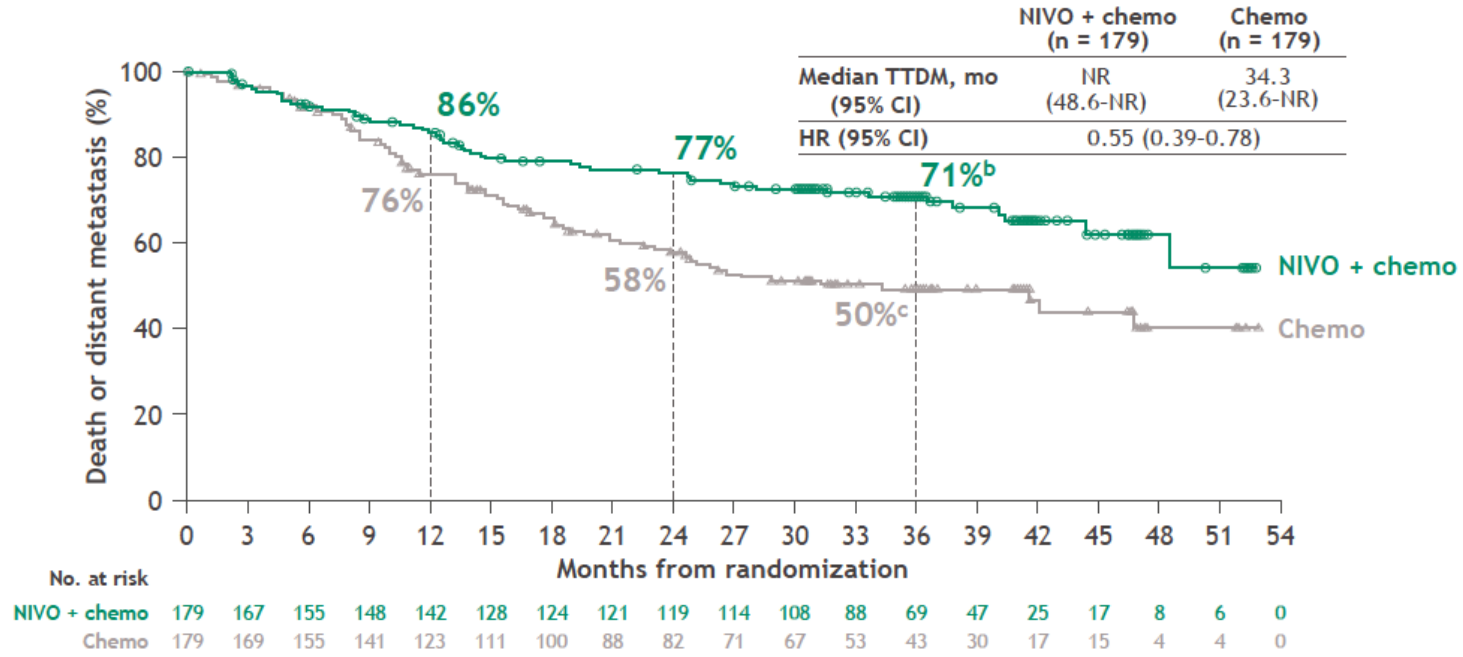
NIVO + chemo	179	176	166	163	158	151	149	146	145	141	137	136	117	95	67	44	23	14	6	2	0
Chemo	179	173	166	162	155	149	134	124	119	112	109	106	95	75	52	38	22	14	4	1	0

Minimum/median follow-up: 32.9/41.4 months.

[a]Significance boundary for OS was not crossed at this interim analysis. [b,c]95% CIs for 3-year OS rates: [b]71-83; [c]56-70.

Delayed Time to Distant Metastasis

TTDM[a] with neoadjuvant NIVO + chemo vs chemo: 3-year update



Minimum/median follow-up: 32.9/41.4 months.

[a]Time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis per BICR. [b,c]95% CI for 3-year TTDM rates: [b]63-77; [c]41-57.

Perioperative/Sandwich Treatment

Checkmate 77T. Nivolumab

Keynote 671. Pembrolizumab

Aegean. Durvalumab

Neotorch. Torpalimab

Rationale 315. Tislelizumab

Checkmate 77T, with a new design

CheckMate 77T[a] study design

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)

N = 461

R 1:1

NIVO 360 mg Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → NIVO 480 mg Q4W (1 year) → Follow-up

PBO Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → PBO Q4W (1 year) → Follow-up

Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

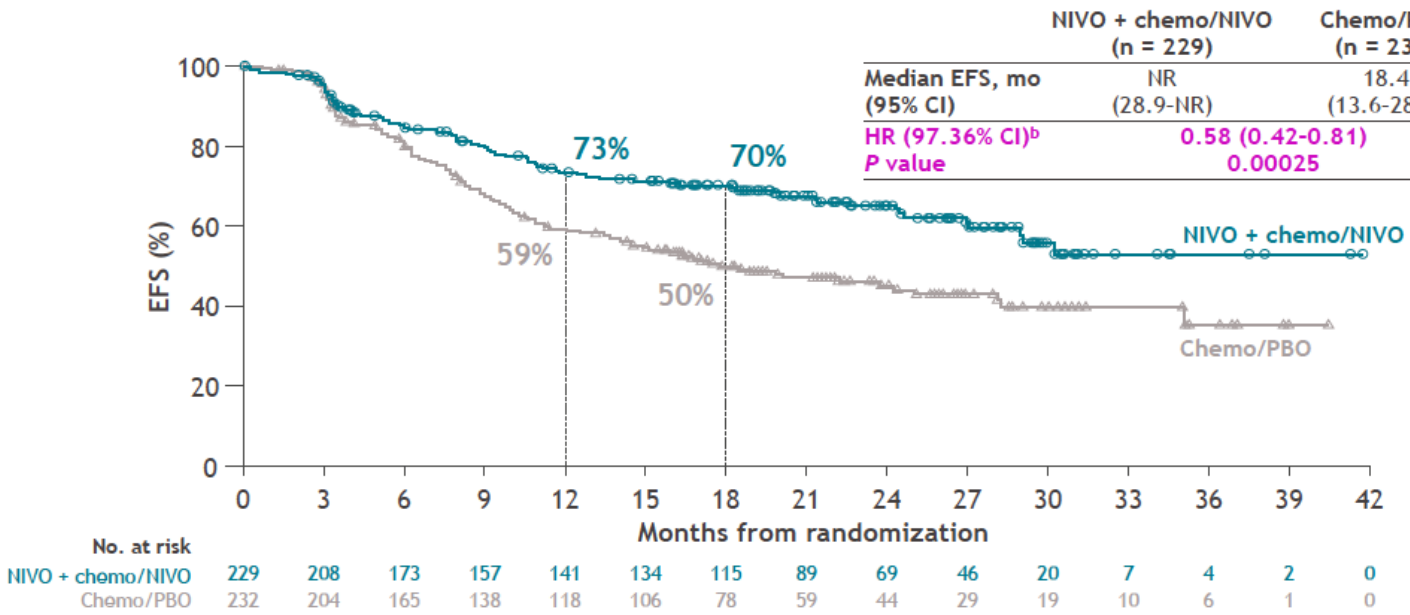
Database lock date: September 6, 2023.

[a]NCT04025879. [b]*EGFR* testing was mandatory in all patients with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority-approved assays. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [e]Assessed per immune-related pathologic response criteria.[1] BICR, blinded independent central review; BIPR, blinded independent pathological review. 1. Cottrell TR, et al. *Ann Oncol* 2018:29:1853-1860.

EFS improved in Checkmate 77T

CheckMate 77T: perioperative NIVO in resectable NSCLC

Primary endpoint:
EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

Median follow-up (range): 25.4 months (15.7-44.2).

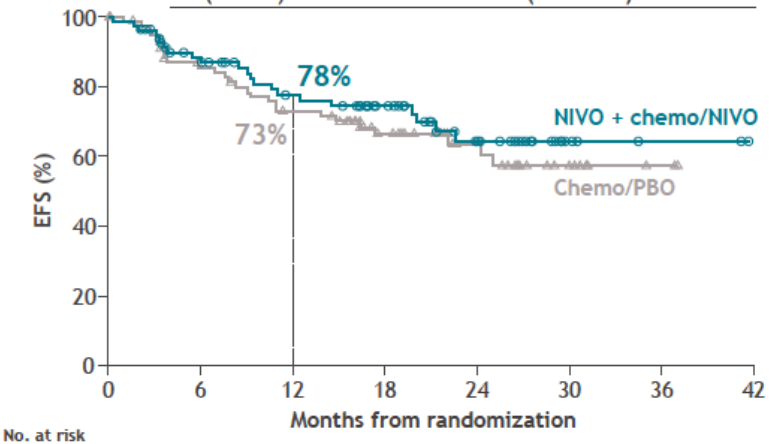
[a]Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b]Unstratified HR (95% CI), 0.59 (0.44-0.79).

Benefit across disease stage

EFS by baseline disease stage

Stage II

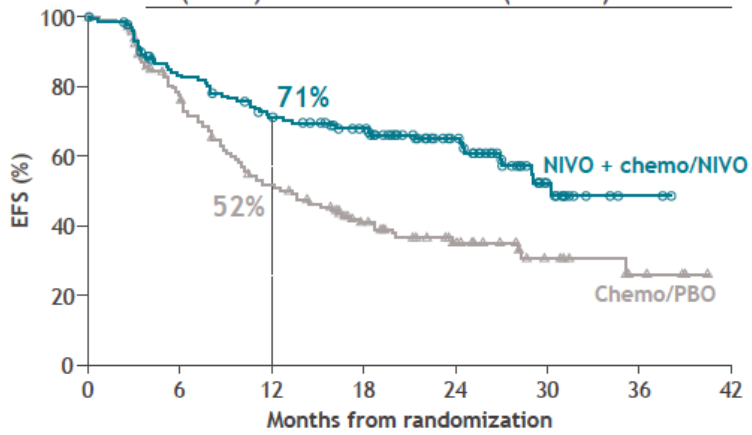
	NIVO + chemo/NIVO (n = 81)	Chemo/PBO (n = 81)
Median EFS, mo (95% CI)	NR (22.6-NR)	NR (24.2-NR)
HR (95% CI)	0.81 (0.46-1.43)	



No. at risk								
NIVO + chemo/NIVO	81	62	49	37	20	5	2	0
Chemo/PBO	81	63	51	34	20	8	2	0

Stage III

	NIVO + chemo/NIVO (n = 148)	Chemo/PBO (n = 149)
Median EFS, mo (95% CI)	30.2 (26.9-NR)	13.4 (9.8-17.7)
HR (95% CI)	0.51 (0.36-0.72)	



NIVO + chemo/NIVO	148	111	92	78	49	15	2	0
Chemo/PBO	149	102	67	44	24	11	4	0

Median follow-up (range): 25.4 months (15.7-44.2).

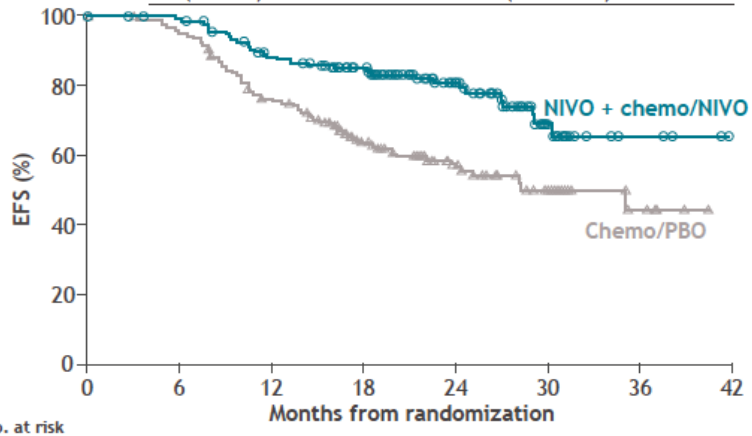
Benefit of Adjuvant Treatment

CheckMate 77T: perioperative NIVO in resectable NSCLC

Exploratory analysis: EFS by adjuvant treatment status

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	

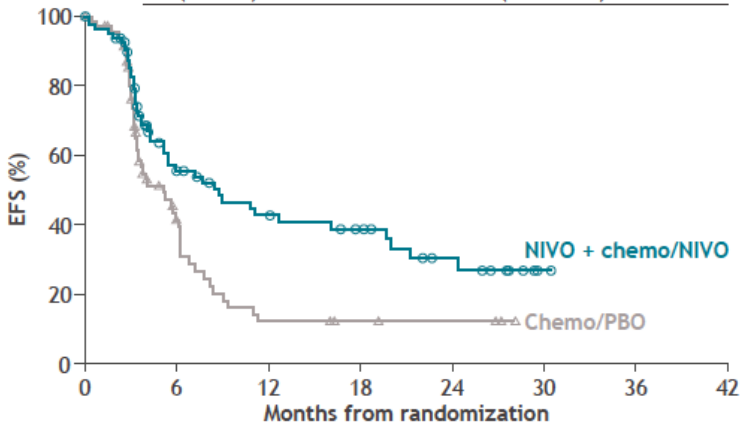


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

No adjuvant

	NIVO + chemo/NIVO (n = 87)	Chemo/PBO (n = 80)
Median EFS, mo (95% CI)	8.8 (5.2-19.7)	5.2 (3.4-6.2)
HR (95% CI)	0.55 (0.37-0.83)	



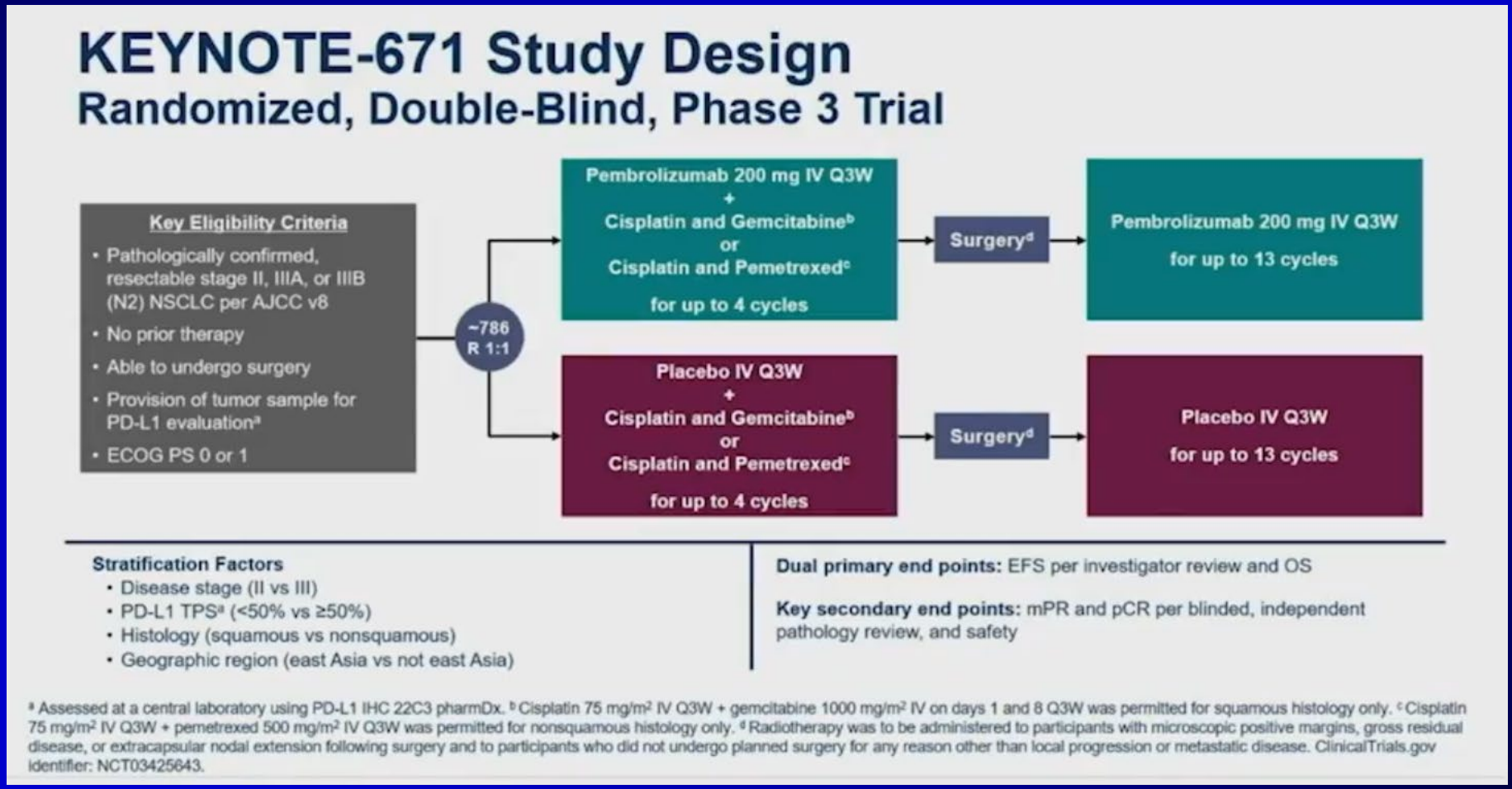
NIVO + chemo/NIVO	87	34	23	18	9	1	0	0
Chemo/PBO	80	21	6	4	3	0	0	0

- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

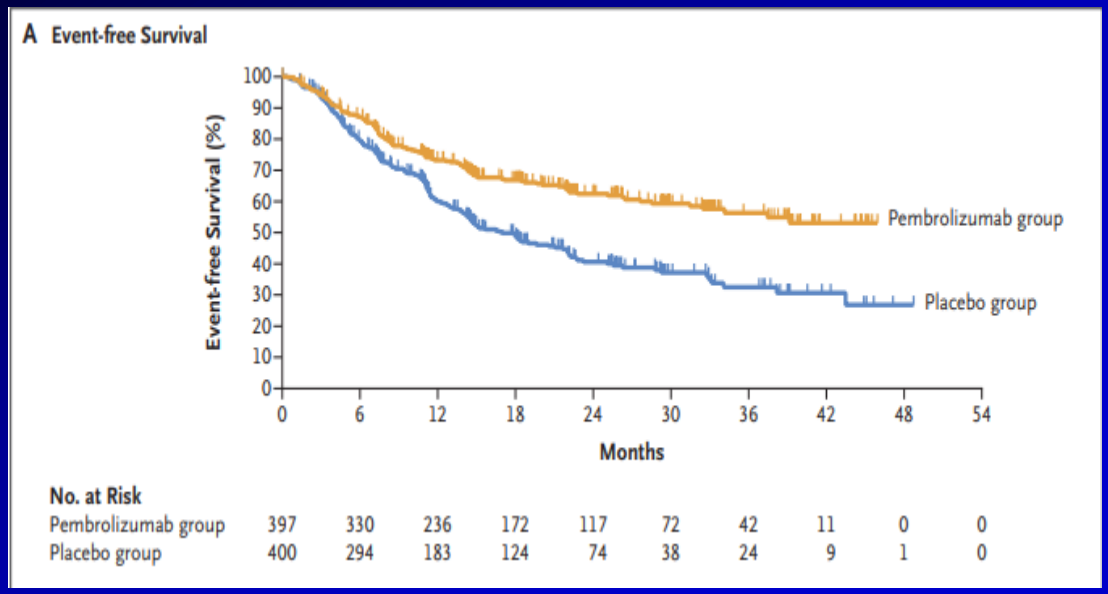
Median follow-up (range): 25.4 months (15.7-44.2).

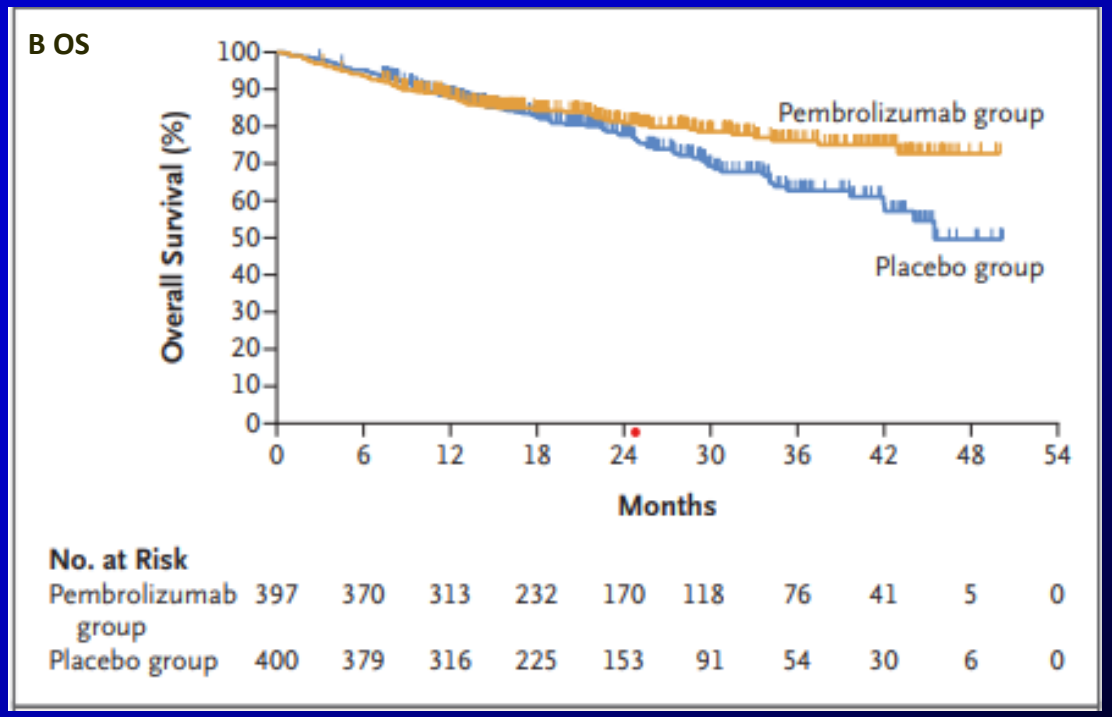
[a]HR (95% CI), 0.17 (0.11-0.27) in those who received adjuvant treatment vs those who did not in the NIVO + chemo/NIVO arm and 0.15 (0.10-0.22) in the chemo/PBO arm.

Perioperative Pembrolizumab in NSCLC



Survival Analysis NEJM 2023

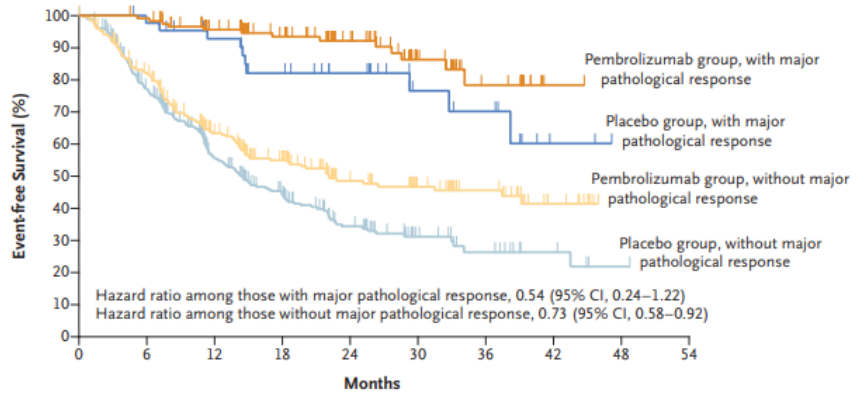




EFS Survival Analysis for Keynote 671

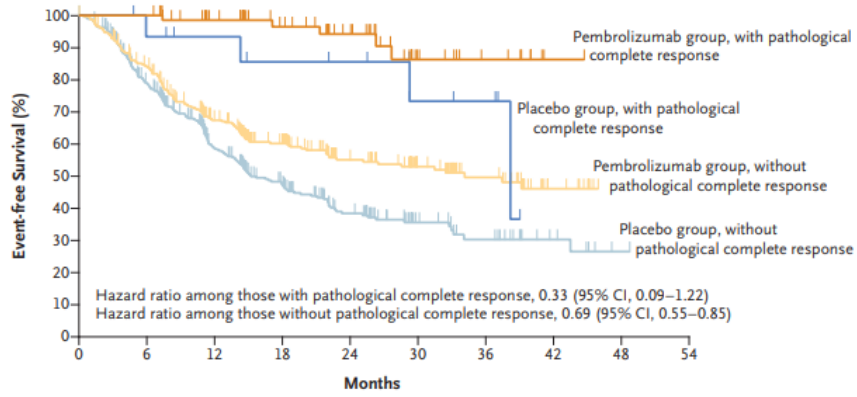
Survival Analysis NEJM 2023

A Event-free Survival According to Major Pathological Response



No. at Risk										
With major pathological response										
Pembrolizumab group	120	117	99	79	60	30	15	1	0	0
Placebo group	44	42	36	28	22	12	10	2	0	0
Without major pathological response										
Pembrolizumab group	277	213	137	93	57	42	27	10	0	0
Placebo group	356	252	147	96	52	26	14	7	1	0

B Event-free Survival According to Pathological Complete Response



No. at Risk										
With pathological complete response										
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

Timing of Biomarker Testing

As soon as enough tissue is available
Takes 2-3 weeks to complete

Can tell more about the prognosis, treatment algorithm
Existance of actionable driver vs none (e.g. EGFR, ALK)

Tell us about the PD-L1 level, usefulness as adjuvant
And likelihood to respond to neoadjuvant immuno

Tell us about multifocal synchronous vs metastasis
Regardless squamous or adenocarcinoma

Appropriateness to start IO therapy

Why Testing Before Planning Systemic?

Trials	IMPower 010	KN- 091	BR-31	CM-816	AEGEAN	Neotorch	KN-671	CM-77T	RATIONAL E 315
Timing	Adjuvant	Adjuvant	Adjuvant	neodjuvant	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative
Sample size	1005	1177	1415	358	802	500	786	461	453
ICI Agent	Atezo	Pembro	Durva	Nivo	Durva	Torpalimab	Pembro	Nivo	Tisle
Chemo agents	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet	Platinum doublet
IO #	16	18	12	3	16	17	13	16	11-12
Stage Range	Ib-IIIa >4cm	Ib-IIIa >4cm	Ib-IIIa >4cm	Ib-IIIa resectable	II-IIIb Resectable	II-IIIb Resectable	II-IIIb resectable	II-IIIb resectable	II-IIIa resectable
Stage II/III %	59/41	72/28	62/38	63/64	27/73	20/80	30/70	35/65	41/59
Primary EP	DFS	DFS PD-L1> 50%	DFS PD-L1 >25%	pCR, EFS	MPR, EFS	MPR, EFS	EFS, OS	EFS	MPR, EFS
Driver + EGFR/ALK	15%	7.5%	14%	Not documented	No doc mutation	WT	No	No Doc EGFR/ ALK	WT

(Adjuvant chemo) Indications

- Stage Ia (~T1a), (T2a = Ib size <=4cm) is not given.
- Stage II-IIIa given. Stage IIa = T2b (>4cm)
- Given after complete resection with node dissection.
- Within 4-6 weeks after resection.
- Good performance.
- 4 cycles of platinum containing doublets (cis preferred). But substitute cisplatin with carboplatin if renal Insuf.

Considered in stage I patient (Ib)

Poor differentiation
Lymph vascular invasion
Visceral pleural invasion
Not lobectomy (wedge or segmentectomy)
Unknown nodal status
Some histology such as micropapillary

Young and multiple factors
Use gene panel

Adjuvant Chemo in Early Stages

- Adjuvant chemotherapy with cisplatin-based regimens results in 5-15% improvement in absolute survival for patients with resected stages Ib-IIIA NSCLC
- Survival benefit in stage Ib disease is unproven
- Neo-adjuvant strategy has several advantages over adjuvant chemotherapy, though the two approaches have not been compared against each other.

  International adjuvant lung cancer trial (IALT)