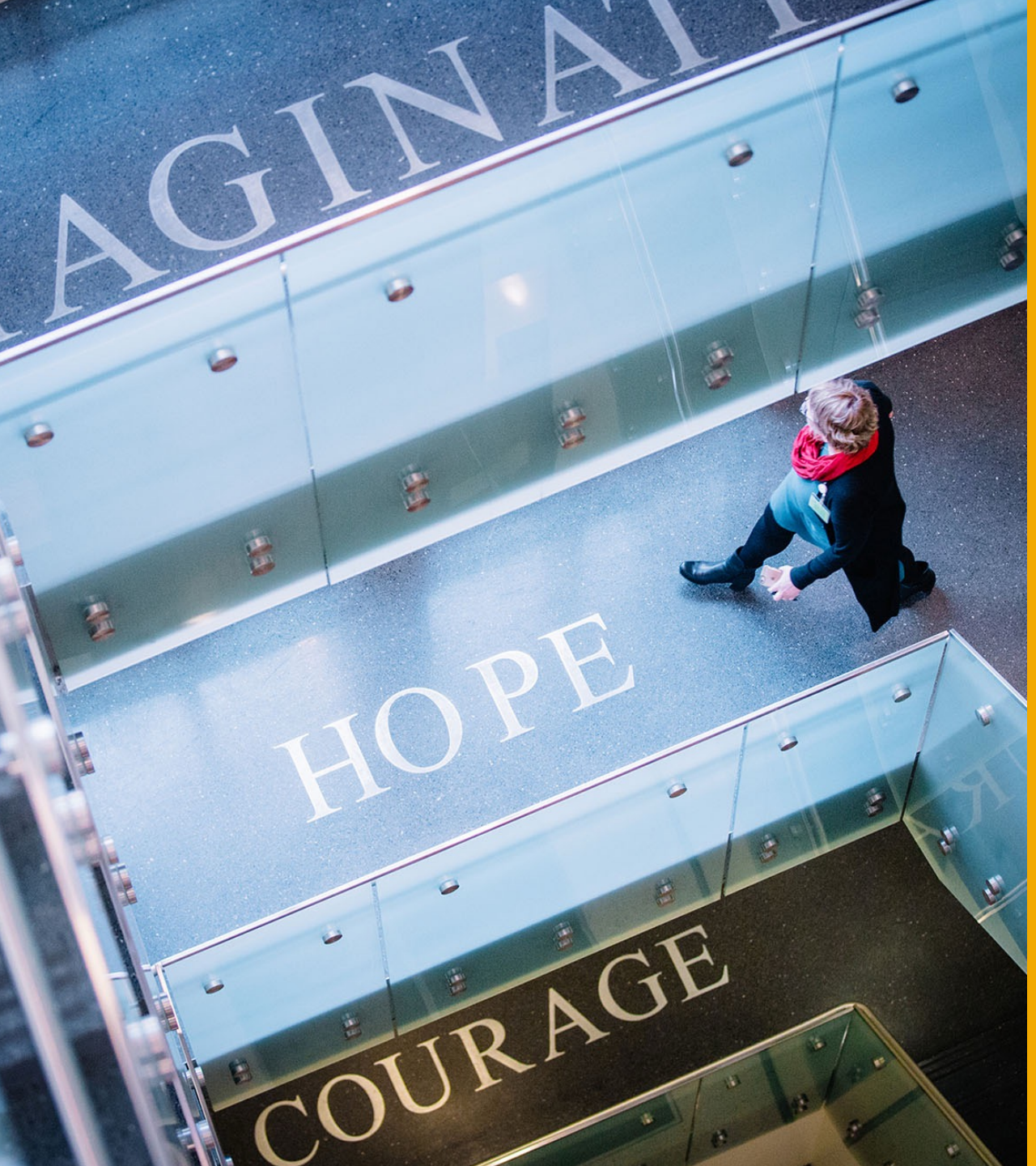

IMMUNOTHERAPY FOR EARLY STAGE LUNG CANCER

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

Disclosures – 24 months

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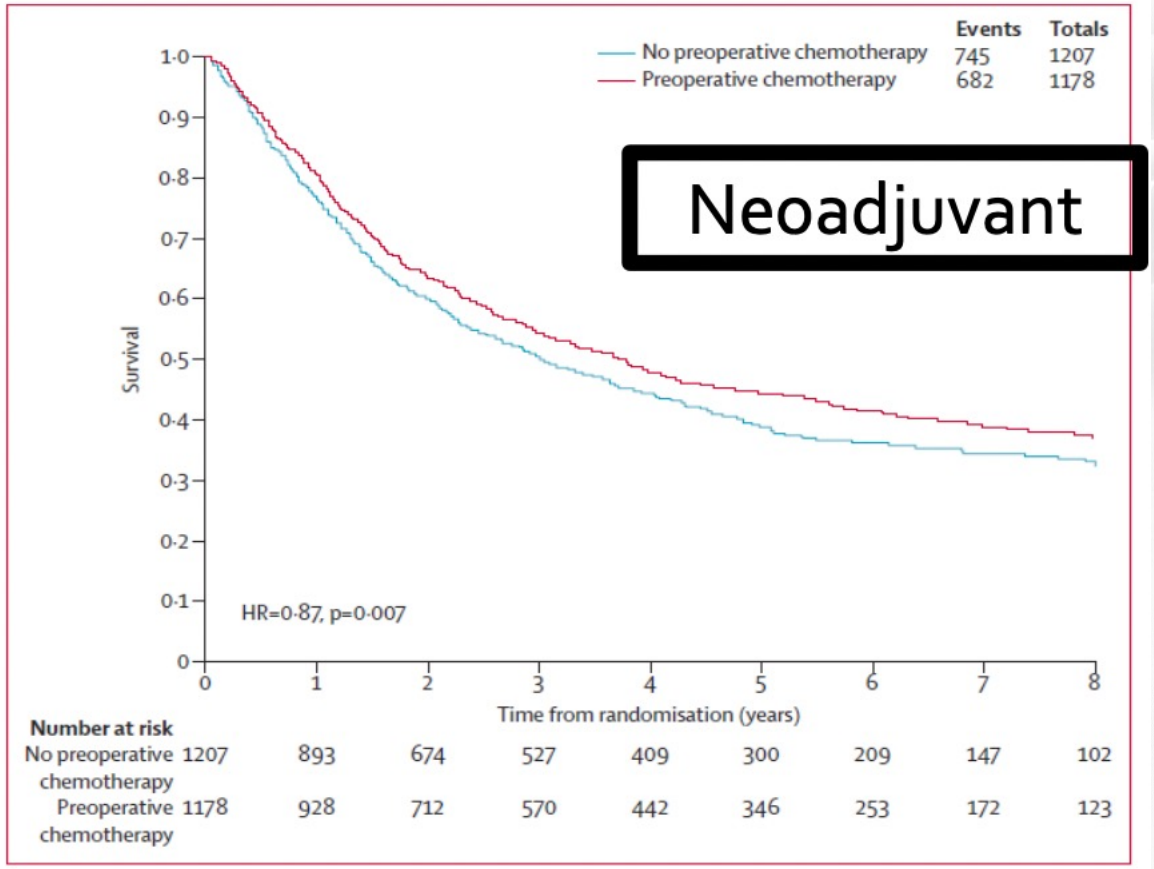
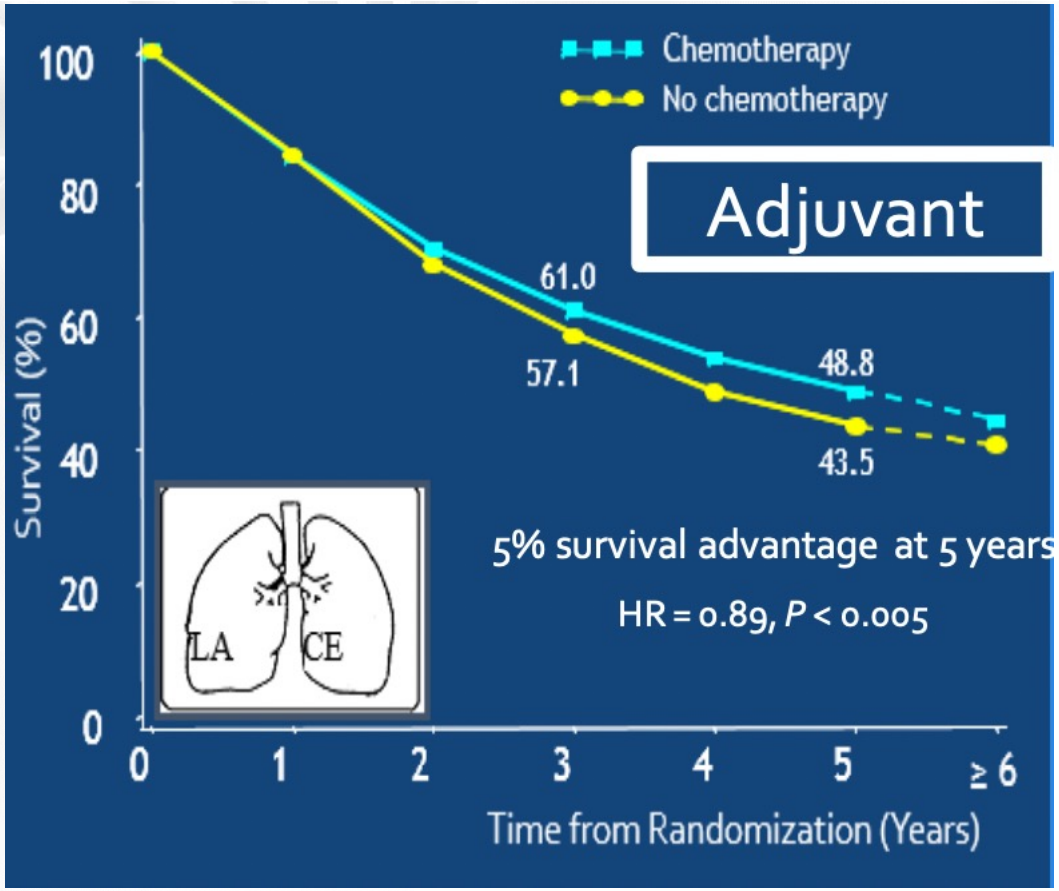
ADVISORY BORAD: AstraZenica, Eli Lilly, Sanofi, Amgen, Novocure, Catalyst

Neoadjuvant versus adjuvant chemotherapy

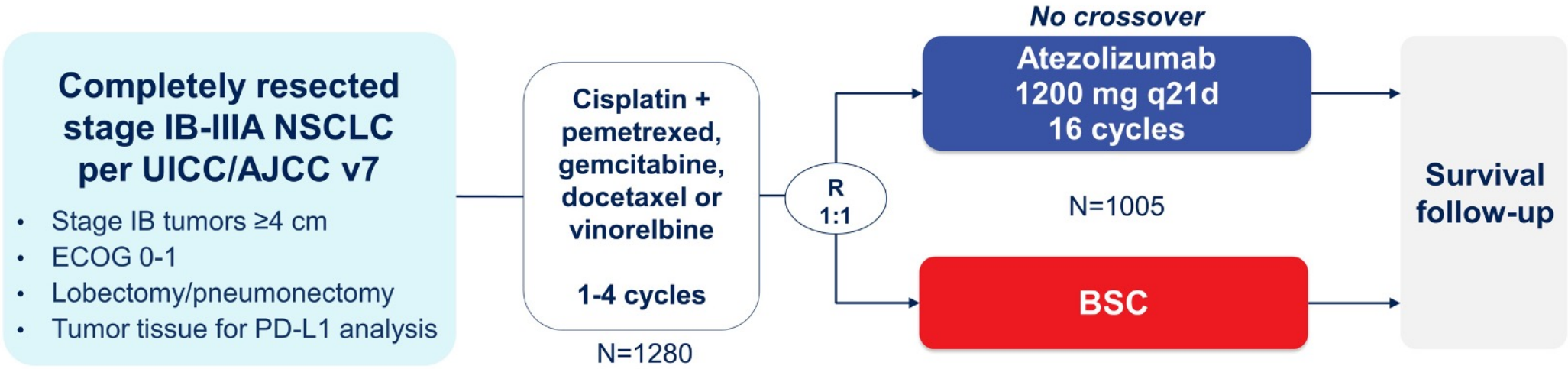
~30% of patients with NSCLC present with resectable disease at the time of diagnosis
Perioperative chemotherapy have led to modest improvements in overall survival
Pathological complete responses are uncommon (<5%)





Forde et al. NEJM 2022; Arriagada et al. Lancet 2010; NSCLC Meta-Analysis Group. Lancet Oncology 2014; Pignon et al. JCO 2006

IMPOWER010: ADJUVANT ATEZOLIZUMAB VS BSC



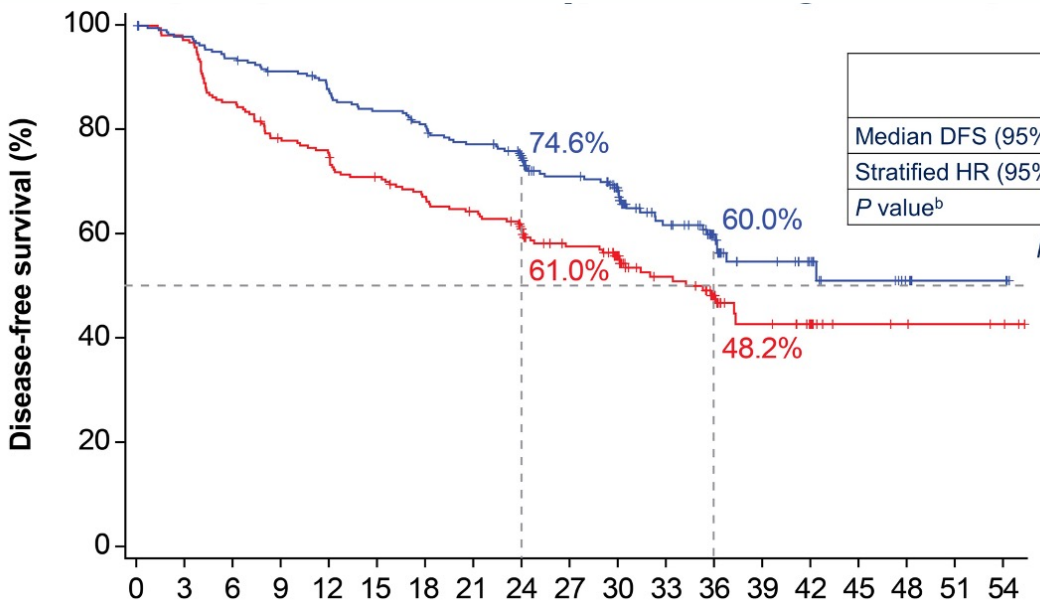
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

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

Wakelee et al. ASCO 2021

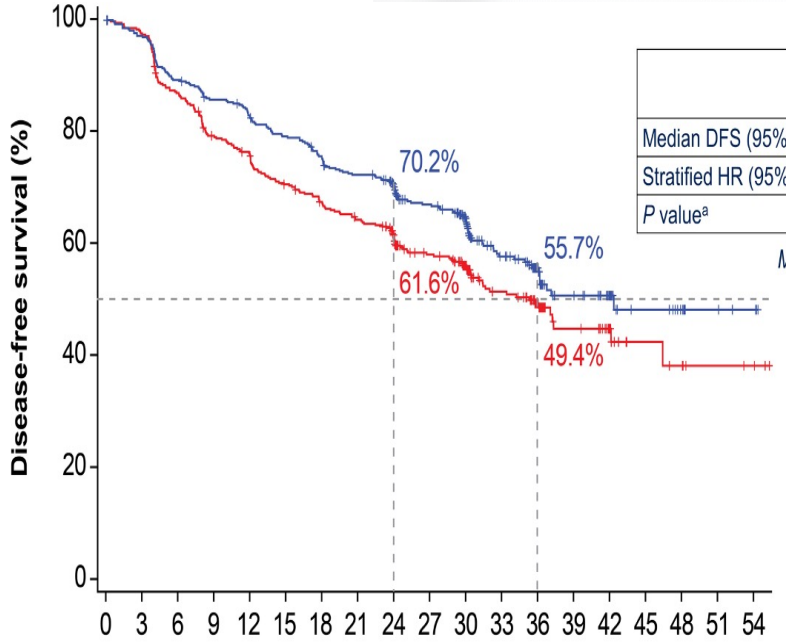
IMPOWER010: DFS IN THE PD-L1 ≥ 1% STAGE II-IIIA POPULATION



	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)

DFS in the all-randomized stage II-IIIA population



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

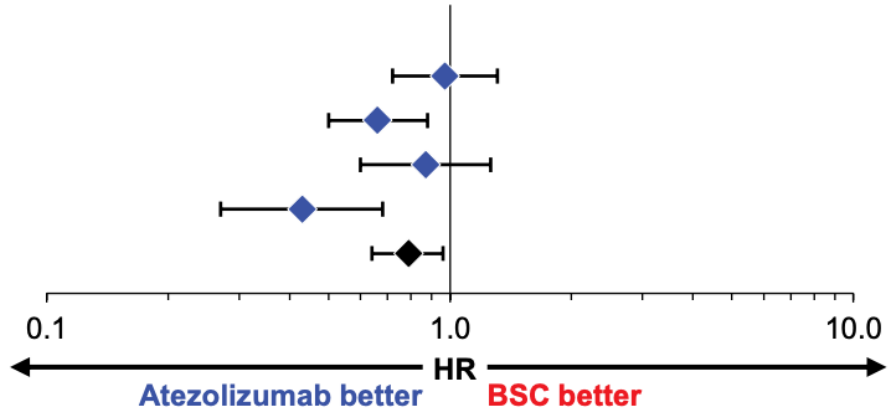
Median follow-up: 32.2 mo (range, 0-57.5)

Wakelee et al. ASCO 2021

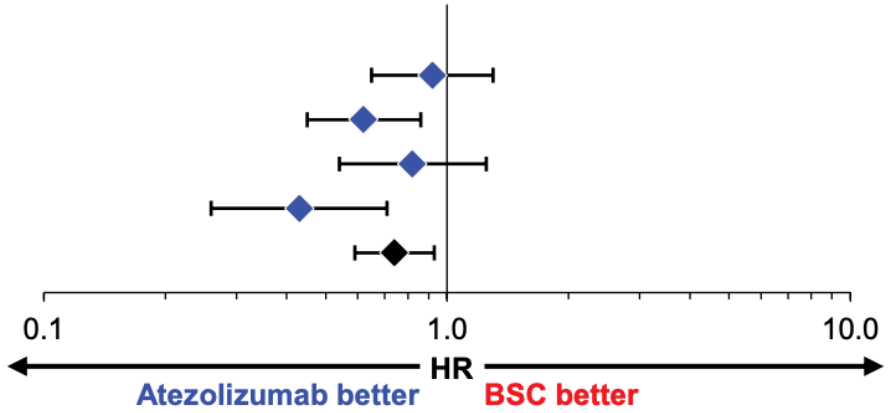
IMPOWER010: DFS BY PD-L1 STATUS

All-randomized 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)



Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)

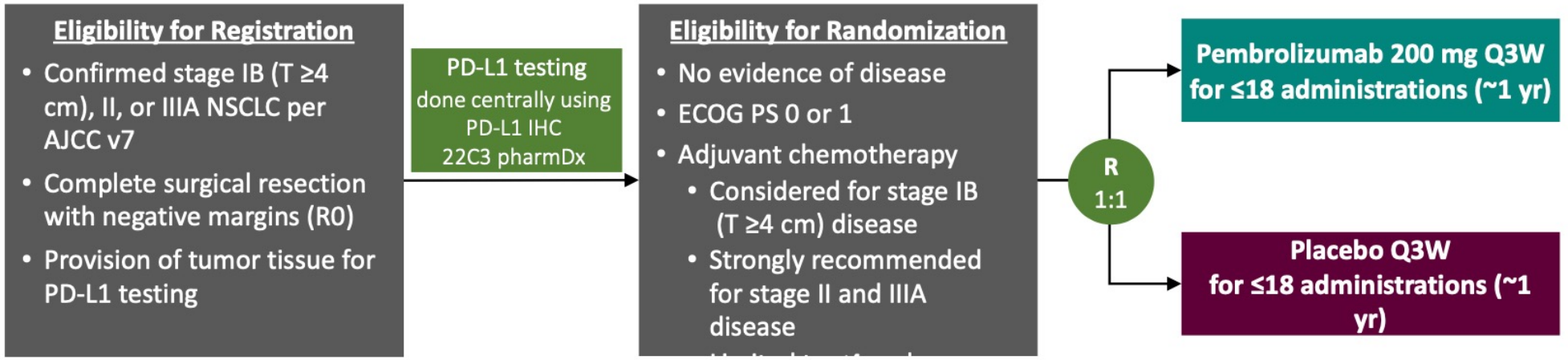


Clinical cutoff: 21 January 2021. [a] Per SP263 assay.

Felipe et al. ESMO 2021

PEARLS/KEYNOTE 091

Randomized, Triple-Blind, Phase 3



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

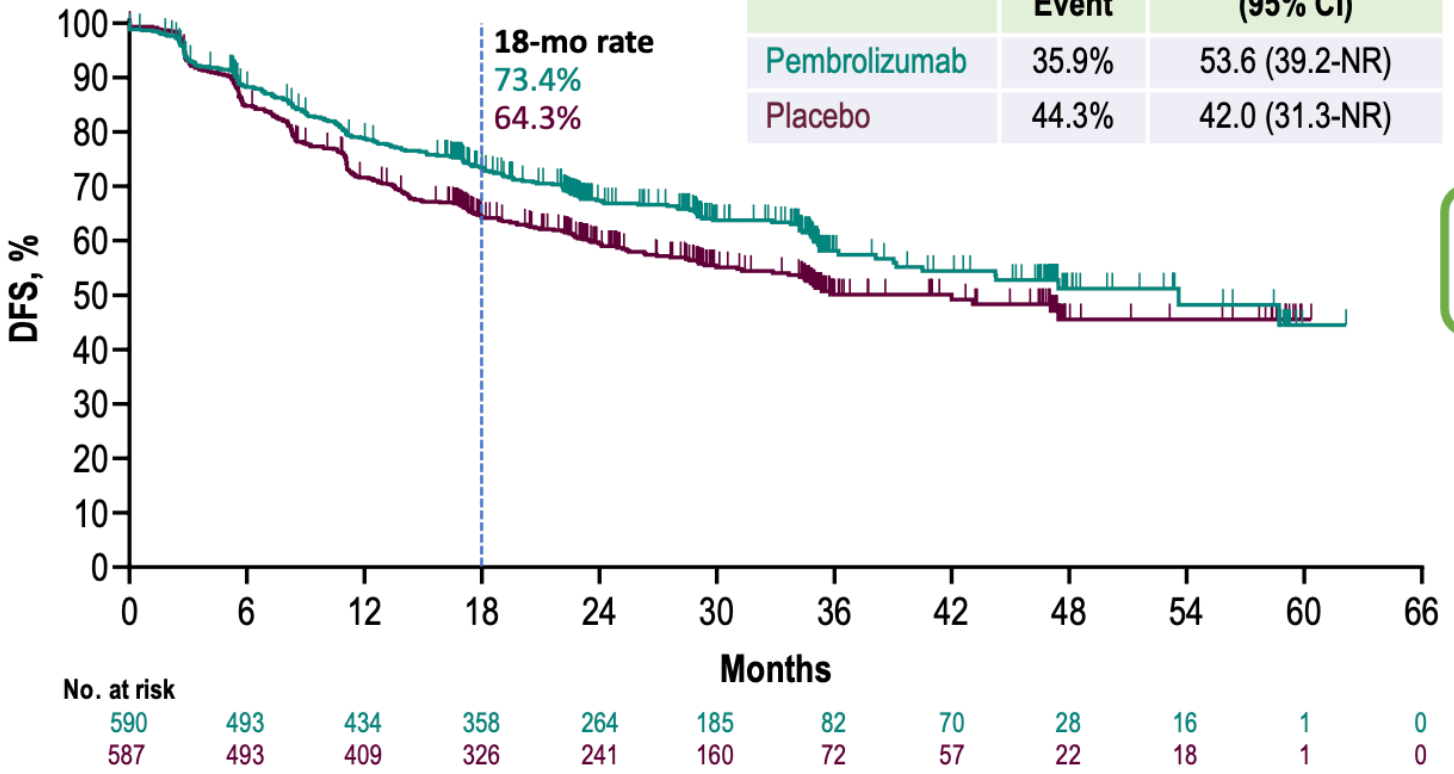
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Paz-Ares et al. ESMO Virtual Plenary 2022

PEARLS/KEYNOTE 091: DFS OVERALL POPULATION



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

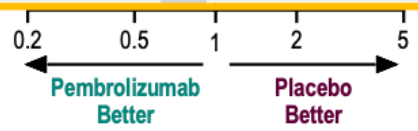
HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

PEARLS/KEYNOTE 091: DFS KEY SUBGROUPS

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Age		
<65 years	213/558	0.73 (0.56-0.96)
≥65 years	259/619	0.84 (0.66-1.07)
Sex		
Female	158/373	0.73 (0.54-1.00)
Male	314/804	0.81 (0.65-1.01)
Geographic region		
Asia	96/211	0.74 (0.49-1.10)
Eastern Europe	90/229	0.84 (0.56-1.27)
Western Europe	245/604	0.77 (0.60-1.00)
Rest of world	41/133	0.74 (0.40-1.39)
ECOG performance status		
0	288/723	0.78 (0.62-0.99)
1	184/454	0.79 (0.59-1.06)
Smoking status		
Current	53/165	0.42 (0.23-0.77)
Former	340/859	0.84 (0.68-1.04)
Never	79/153	0.72 (0.47-1.13)

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Pathologic stage		
IB	46/169	0.76 (0.43-1.37)
II	246/667	0.70 (0.55-0.91)
IIIA	178/339	0.92 (0.69-1.24)
Received adjuvant chemotherapy		
No	64/167	1.25 (0.76-2.05)
Yes	408/1010	0.73 (0.60-0.89)
Histology		
Nonsquamous	330/761	0.67 (0.54-0.83)
Squamous	142/416	1.04 (0.75-1.45)
PD-L1 TPS		
<1%	195/465	0.78 (0.58-1.03)
1-49%	160/379	0.67 (0.48-0.92)
≥50%	117/333	0.82 (0.57-1.18)
***EGFR* mutation**		
No	186/434	0.78 (0.59-1.05)
Yes	40/73	0.44 (0.23-0.84)
Unknown	246/670	0.82 (0.63-1.05)



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

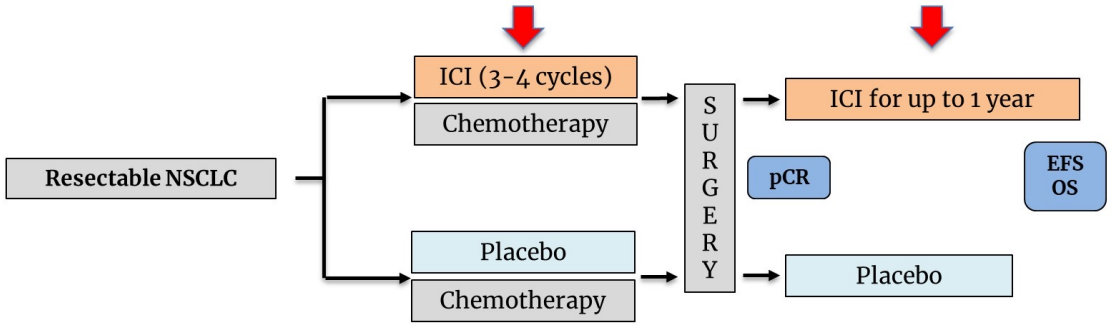
Peri-operative Phase III Trials

	Checkmate816	Keynote671	Aegean	CheckMate 77T
Eligibility	Stage IB-IIIA (AJCC7)	Stage II-IIIB (AJCC8) N2 42%	Stage II-IIIB (AJCC8) N2 49%, multi 9%	Stage II-IIIB (AJCC8, multi N2)
Cycles of neoadjuvant Chemo-IO	3 cycles nivo+ 79% cisplatin 21% carbo doublet	4 cycles pembro+ cisplatin doublet	4 cycles of durva+ 27 % Cisplatin 73% Carbo doublet	4 cycles nivo + 22% cisplatin 78% carboplatin doublet
Adjuvant Regimen	None	Pembrolizumab q 3 weeks for 13 cycles	Durvalumab q 4 weeks for 12 cycles	Nivolumab q 4 weeks for 12 cycles
Pathologic CR	24% vs 2%	*30.2% vs 11.0% (secondary)*	17.2% vs. 4.3%	*25.3% vs. 4.7% (secondary)*
EFS median (mos)	43.8 vs 18.4 (HR 0.66)	47.2 vs 18.3 (HR 0.59)	NR vs 30 months (HR 0.69)	46.6 vs 16.9 (HR 0.61)
OS	*Median NR, HR 0.72*	Not mature	*Not mature*	*Not Reached, HR 0.85*

Forde et al. NEJM 2022; Forde et al. NEJM 2025, Wakelee et al., NEJM 2023; Spicer et al. Lancet 2024, Heymach et al, NEJM, 2023; Cascone et al. NEJM, 2024

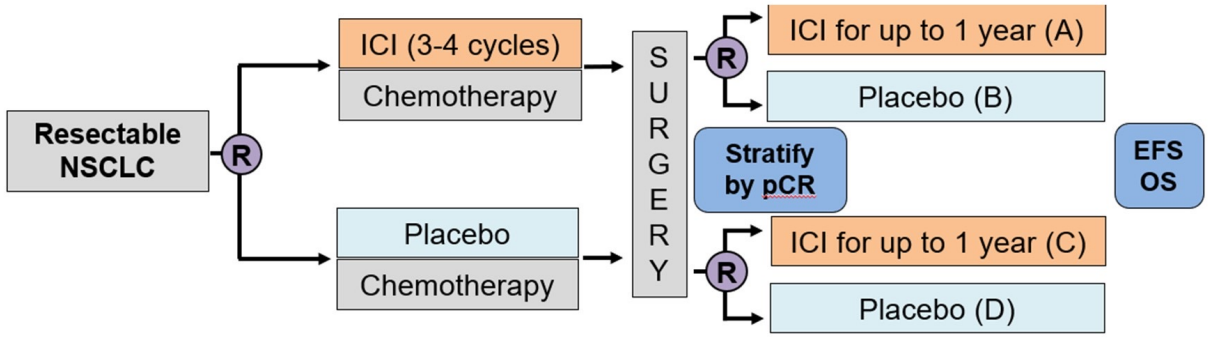
TBD: who needs the adjuvant component?

Contribution of Phase of Treatment



- Do patients need the neoadjuvant, adjuvant, or both phases to benefit?
  - Not addressable by design.
- Patients potentially exposed to **overtreatment.**
  - **Clinical, time, and financial toxicities.**
- **Maximum Therapy ≠ Optimal Therapy.**

SMART* Design



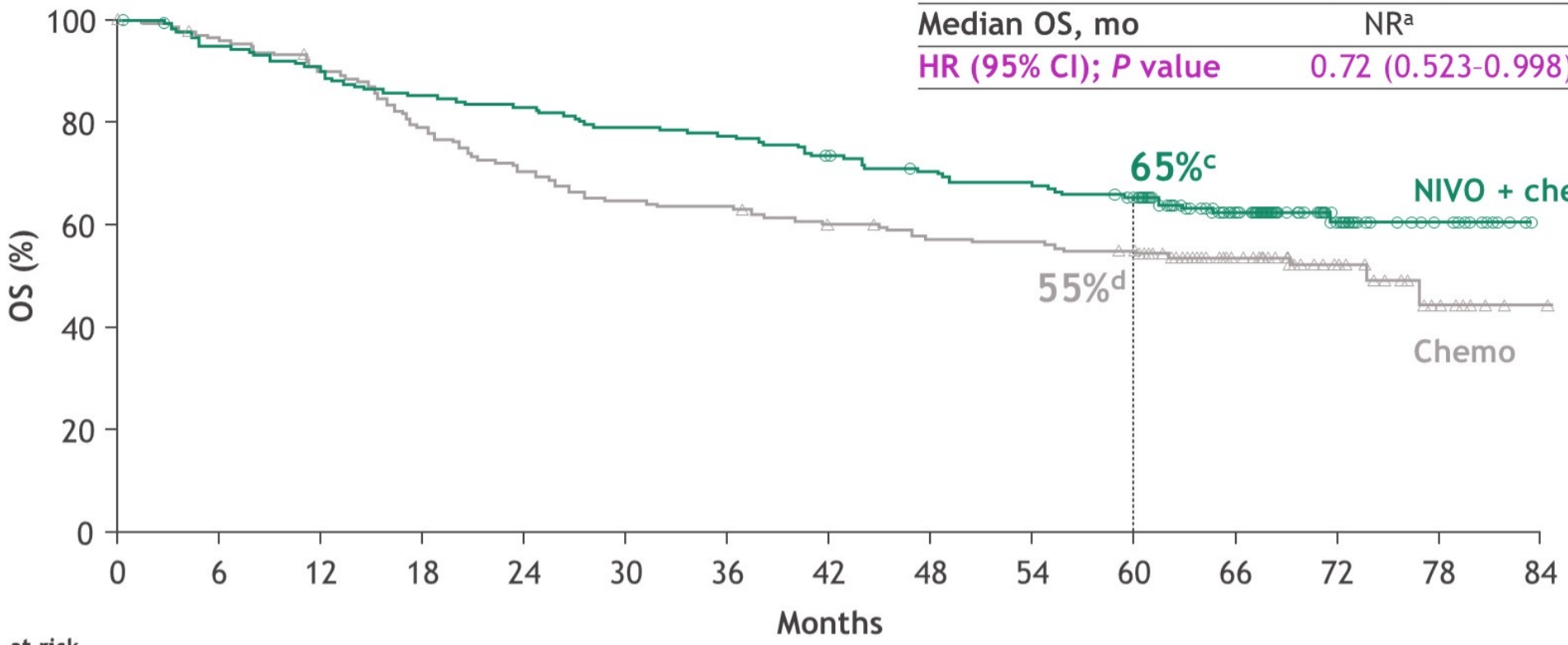
- **Allows for >1 clinical question.**
- **Allows for factor stratification at 2nd randomization (e.g., by PCR).**
- **Operationally challenging.**

***Sequential Multiple Assignment Randomized Trial**

Bernardo Haddock Lobo Goulart, ASCO 2024

CheckMate 816
Final analysis: OS with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo	NR[a]	73.7[b]
HR (95% CI); *P* value	0.72 (0.523-0.998); 0.0479	



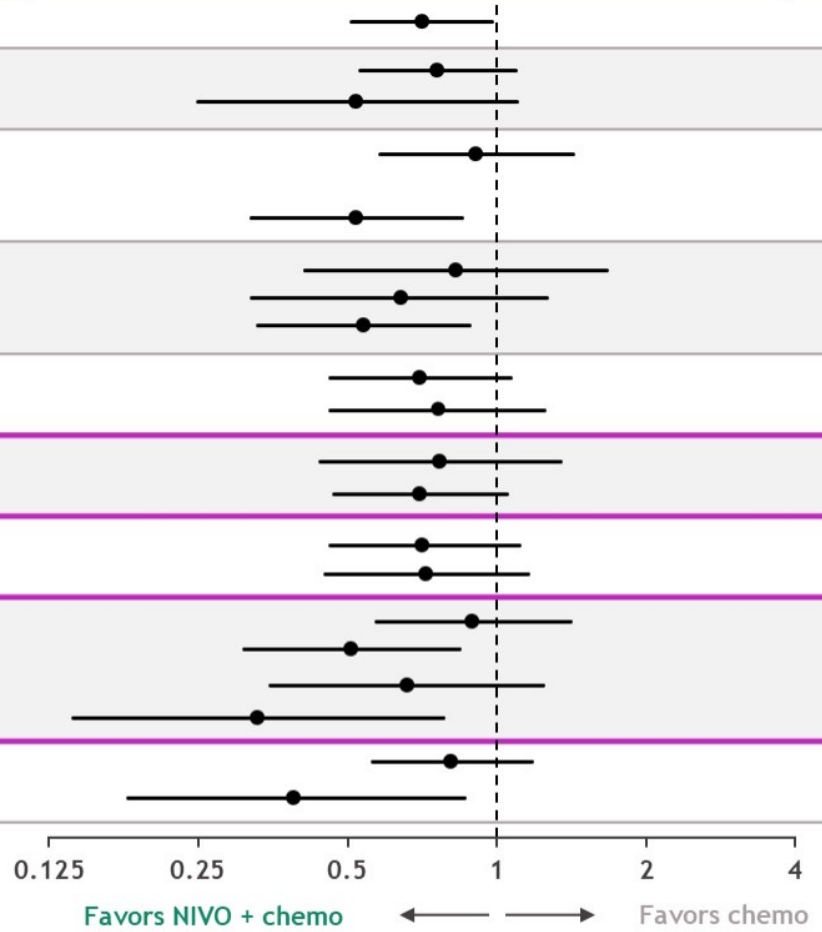
No. at risk															
NIVO + chemo	179	168	159	151	147	140	137	129	122	117	111	67	29	9	0
Chemo	179	170	159	139	124	114	112	104	98	97	91	58	29	6	1

Minimum/median follow-up: 59.9/68.4 months.
[a-d]95% CI: [a]NR; [b]47.3-NR; [c]58-72; [d]47-62.

Forde et al., ASCO 2025

CheckMate 816
OS analysis by key subgroups

	Median OS, mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	73.7		0.71
Male (n = 255)	NR	61.8		0.76
Female (n = 103)	NR	NR		0.52
White (n = 169)	NR	73.7		0.91
Black or African American (n = 7)	NR	20.9		
Asian (n = 179)	NR	76.8		0.52
North America (n = 91)	NR	73.7		0.83
Europe (n = 66)	NR	38.3		0.64
Asia (n = 177)	NR	76.8		0.54
ECOG PS 0 (n = 241)	NR	76.8		0.70
ECOG PS 1 (n = 117)	71.6	45.3		0.76
Stage IB-II (n = 126)	NR	76.8		0.77
Stage IIIA (n = 229)	NR	73.7		0.70
Squamous (n = 182)	NR	73.7		0.71
Nonsquamous (n = 176)	NR	NR		0.72
PD-L1 < 1% (n = 155)	NR	61.8		0.89
PD-L1 ≥ 1% (n = 178)	NR	73.7		0.51
PD-L1 1%-49% (n = 98)	NR	73.7		0.66
PD-L1 ≥ 50% (n = 80)	NR	76.8		0.33
Cisplatin (n = 258)	NR	76.8		0.81
Carboplatin (n = 72)	NR	37.2		0.39



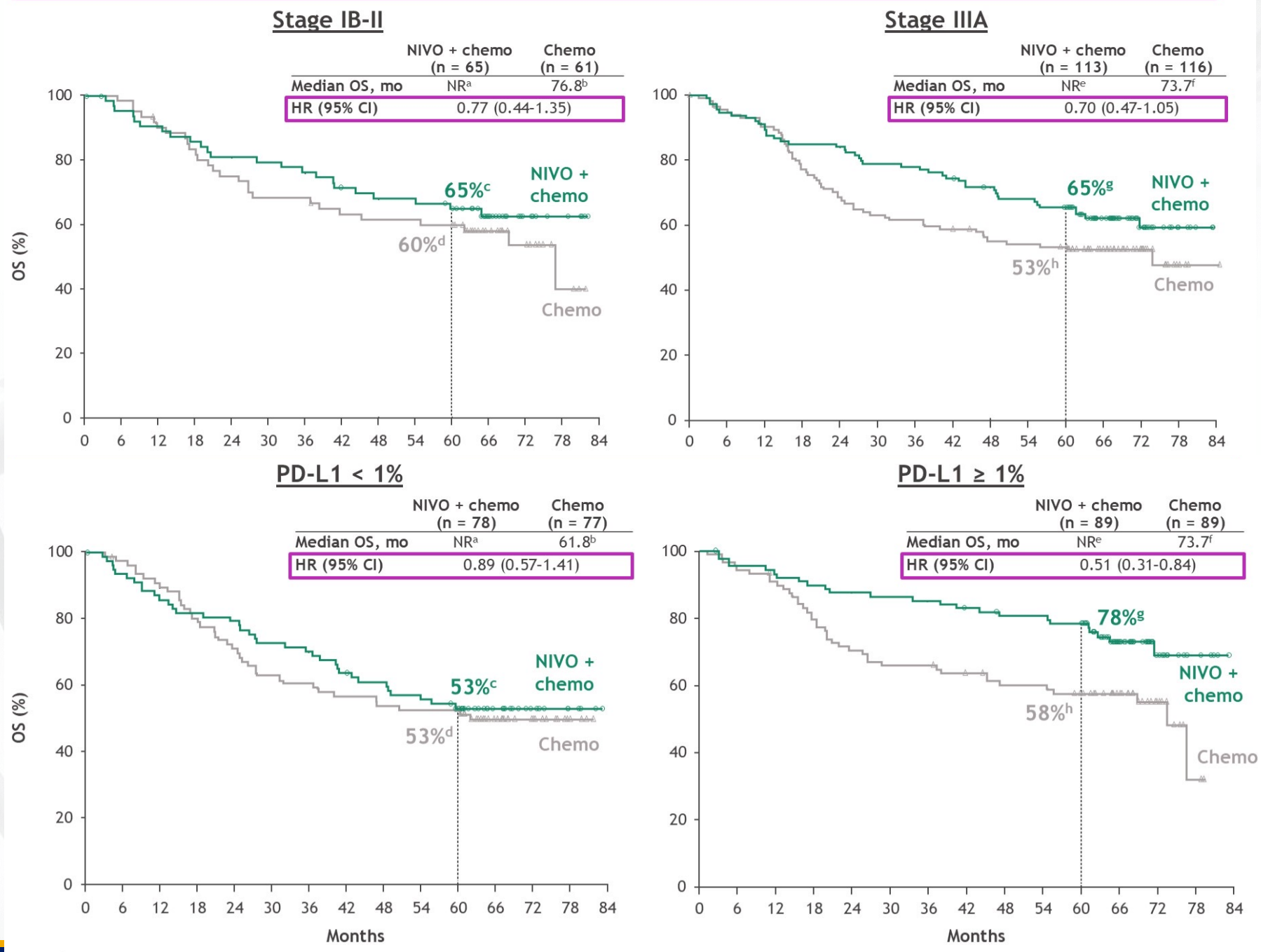
Minimum/median follow-up: 59.9/68.4 months.
HRs were NC if there was an insufficient number of events (< 10 per arm).

Forde et al., ASCO 2025

CHECKMATE 816:

OS BY STAGE

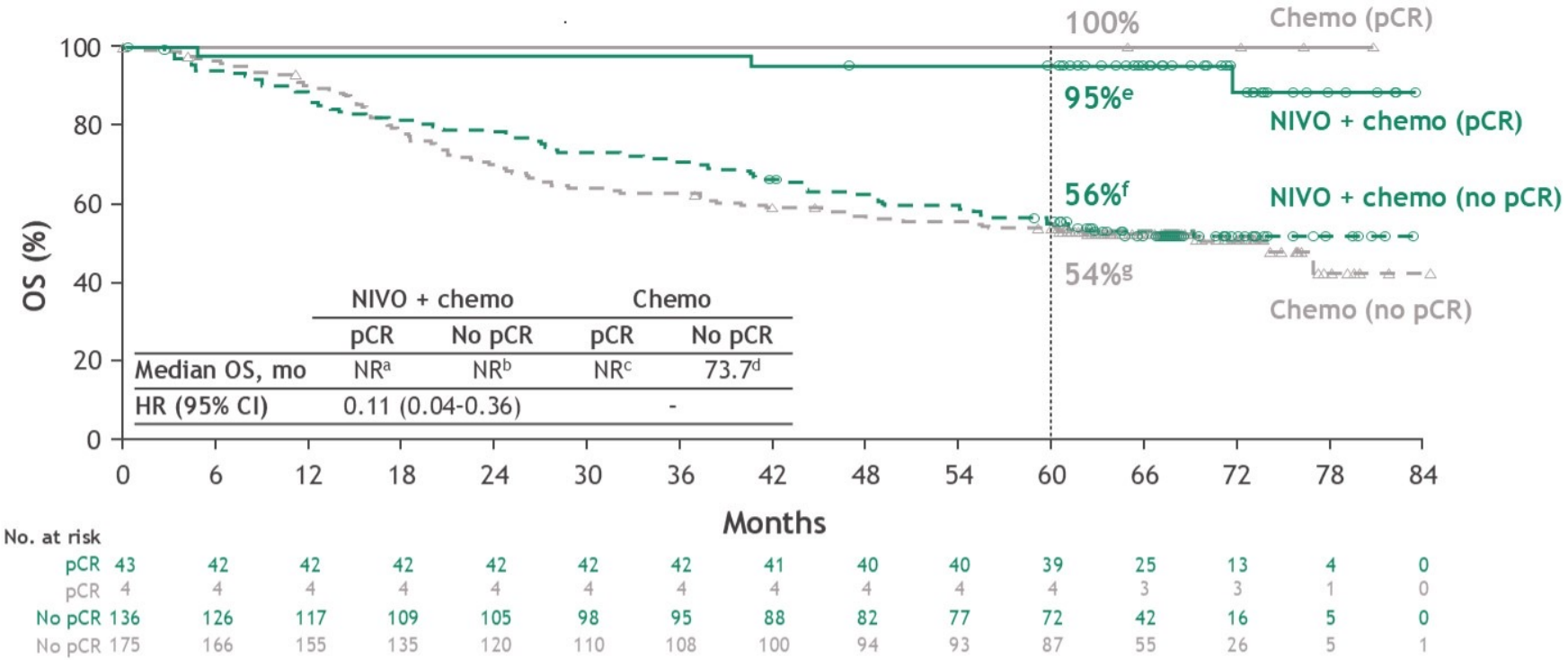
OS BY PD-L1



Forde et al., ASCO 2025

CheckMate 816
Exploratory analysis: OS by pCR status

- Among concurrently randomized patients, 43/179 (24%) patients in the NIVO + chemo arm and 4/179 (2%) patients in the chemo arm had pCR[1]



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo	NR[a]	NR[b]	NR[c]	73.7[d]
HR (95% CI)	0.11 (0.04-0.36)		-	

No. at risk															
pCR	43	42	42	42	42	42	42	41	40	40	39	25	13	4	0
pCR	4	4	4	4	4	4	4	4	4	4	4	3	3	1	0
No pCR	136	126	117	109	105	98	95	88	82	77	72	42	16	5	0
No pCR	175	166	155	135	120	110	108	100	94	93	87	55	26	5	1

In the NIVO + chemo arm:

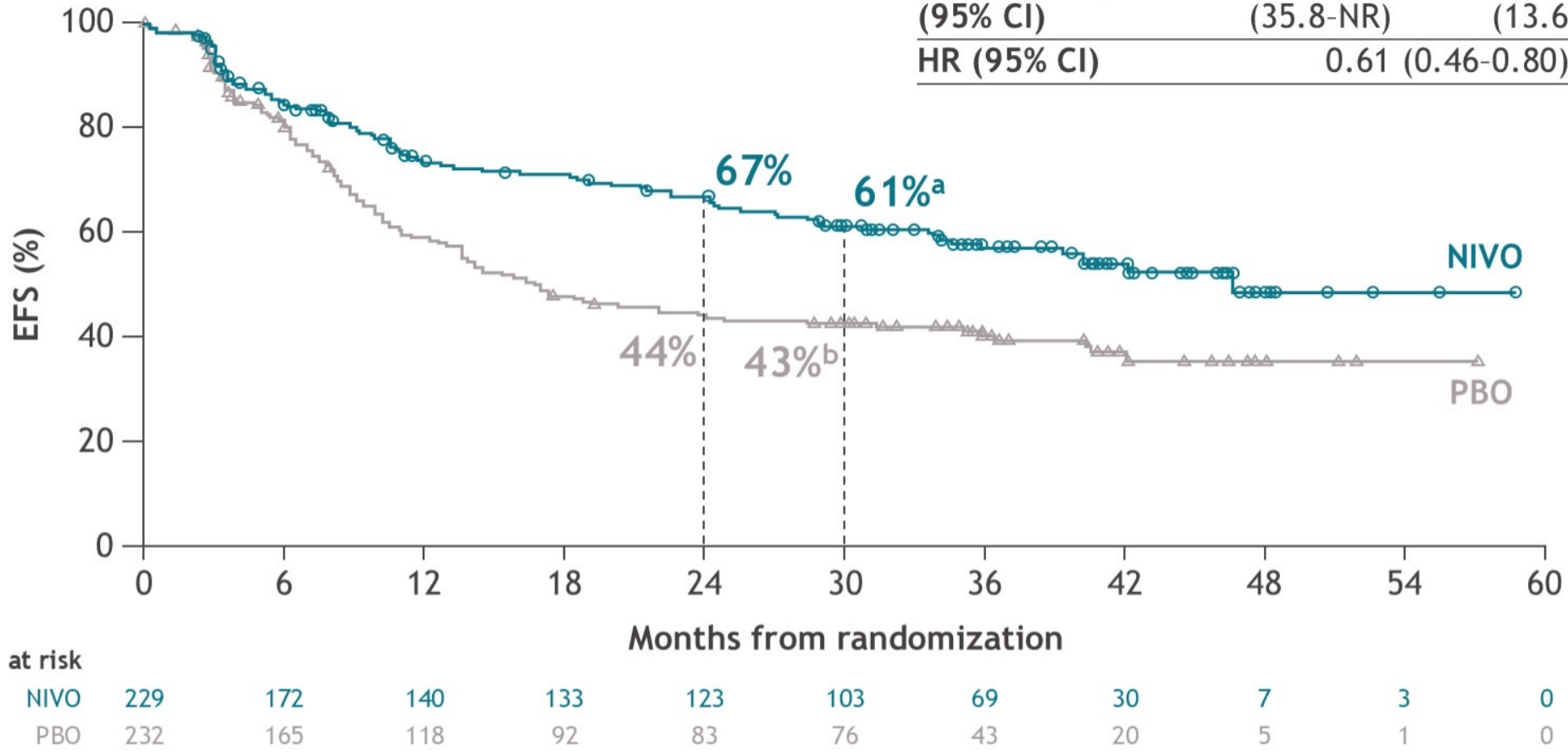
- Among patients with pCR, death occurred in 3 patients; none were due to disease[h]
- Among patients with no pCR, there were a total of 62 (46.6%) deaths; 44 (33.1%) were due to disease[i]

Minimum/median follow-up: 59.9/68.4 months.
HRs were NC if there was an insufficient number of events (< 10 per arm). [a-g]95% CI: [a]NR; [b]53.9-NR; [c]NR; [d]46.7-NR; [e]83-99; [f]47-64; [g]46-61. [h]In the chemo arm, there were no deaths in patients with pCR. [i]In the chemo arm, there were 82 (47.7%) deaths; 60 (34.9%) were due to disease. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.

Forde et al., ASCO 2025

CheckMate 77T
EFS per BICR

	NIVO (n = 229)	PBO (n = 232)
Median EFS, mo (95% CI)	46.6 (35.8-NR)	16.9 (13.6-28.2)
HR (95% CI)	0.61 (0.46-0.80)	

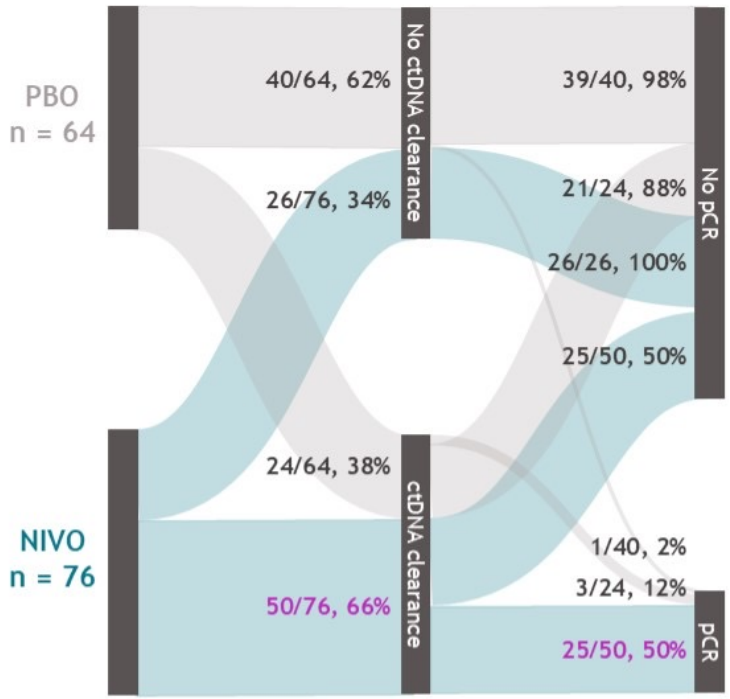


Database lock date: December 16, 2024; median follow-up (range): 41.0 months (31.3-59.8).

Provencio ASCO 2025

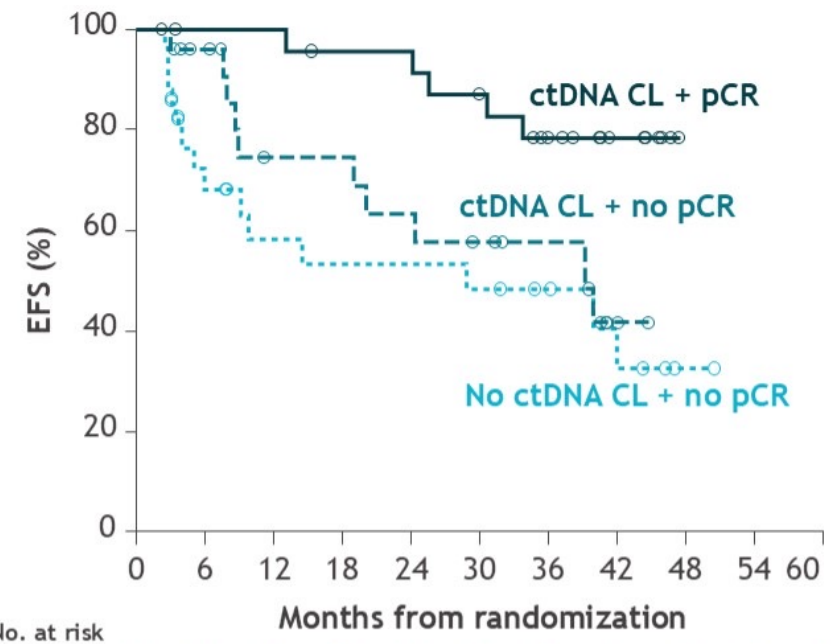
EFS by ctDNA clearance[a] and pCR status

Association between ctDNA clearance and pCR



NIVO

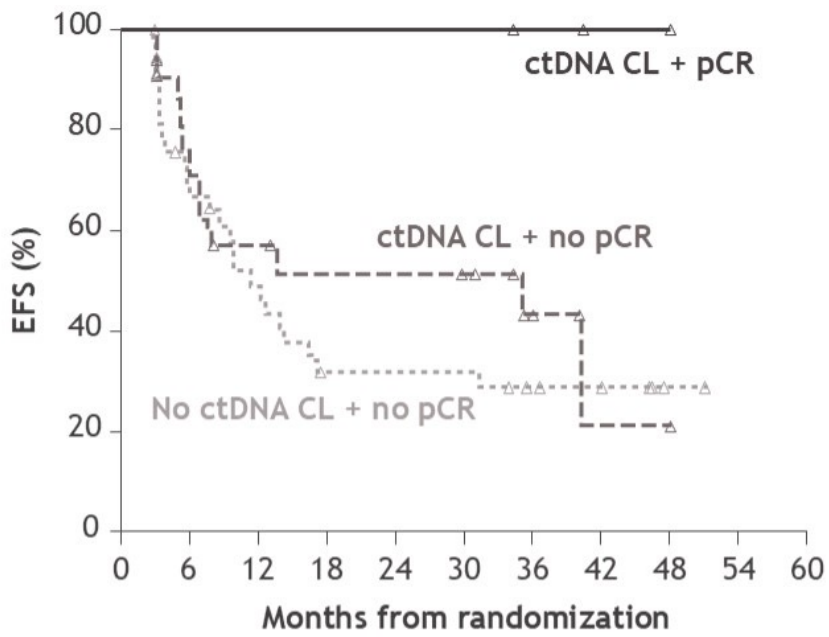
	ctDNA CL + pCR vs ctDNA CL + no pCR	ctDNA CL + pCR vs No ctDNA CL + no pCR	ctDNA CL + no pCR vs No ctDNA CL + no pCR
HR (95% CI)	0.29 (0.10-0.85)	0.23 (0.08-0.65)	0.70 (0.31-1.59)



No. at risk											
ctDNA CL + pCR	25	24	24	22	22	20	14	7	0	0	0
ctDNA CL + no pCR	25	20	13	13	11	9	7	2	0	0	0
No ctDNA CL + no pCR	26	17	12	11	11	10	8	5	1	0	0

PBO

	ctDNA CL + pCR vs ctDNA CL + no pCR	ctDNA CL + pCR vs No ctDNA CL + no pCR	ctDNA CL + no pCR vs No ctDNA CL + no pCR
HR (95% CI)	NC	NC	0.77 (0.39-1.54)



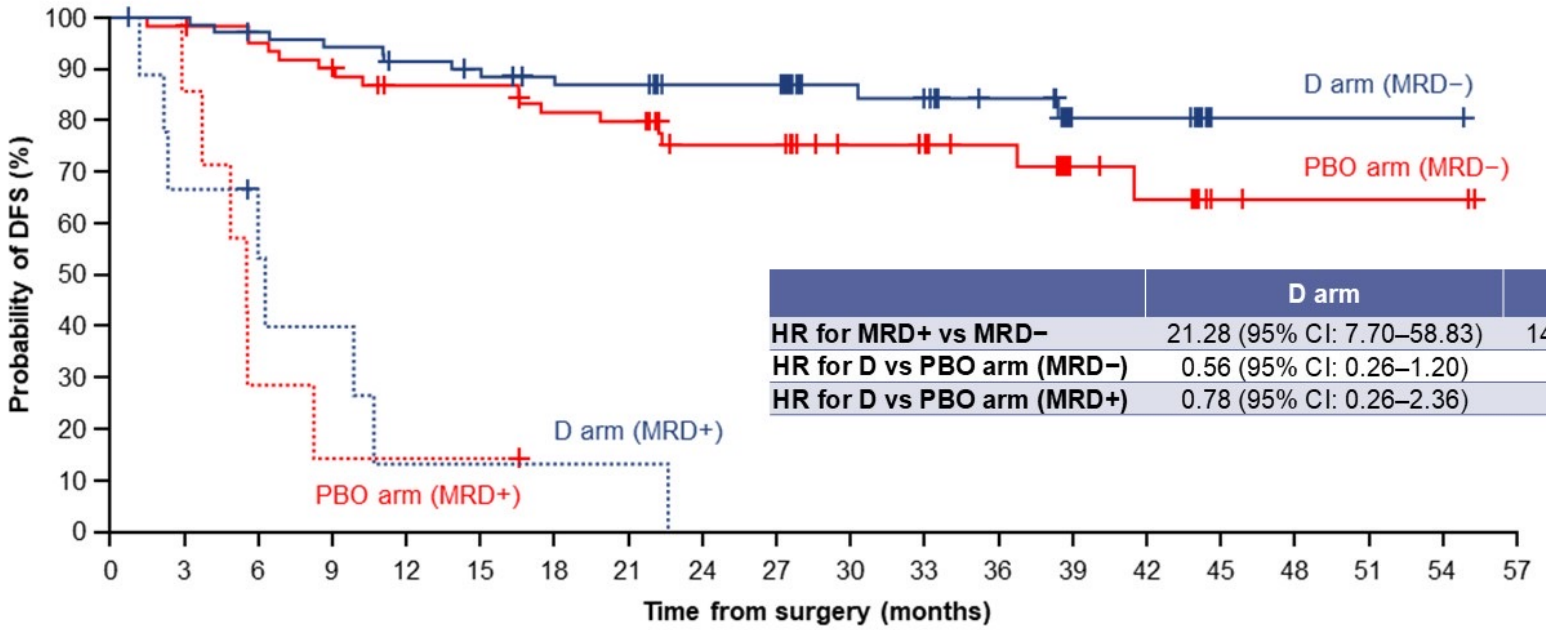
	3	3	3	3	3	3	2	1	1	0	0
	21	16	11	9	9	8	4	1	1	0	0
	39	23	17	10	10	10	7	5	1	0	0

Provencio ASCO 2025

AEGEAN: perioperative durvalumab

Association of MRD at the Post-surgical Landmark with DFS*

- Among MRD-evaluable patients (n=168, total across both arms), 10.1% were MRD+ at the post-surgical landmark†
- DFS outcomes were worse in MRD+ vs MRD− patients, with trends favoring the D vs PBO arm[1]
- Overall, 12-month DFS rates were 14.3% (95% CI: 2.4–36.3) vs 89.3% (95% CI: 82.6–93.5) in all MRD+ vs MRD− patients, respectively



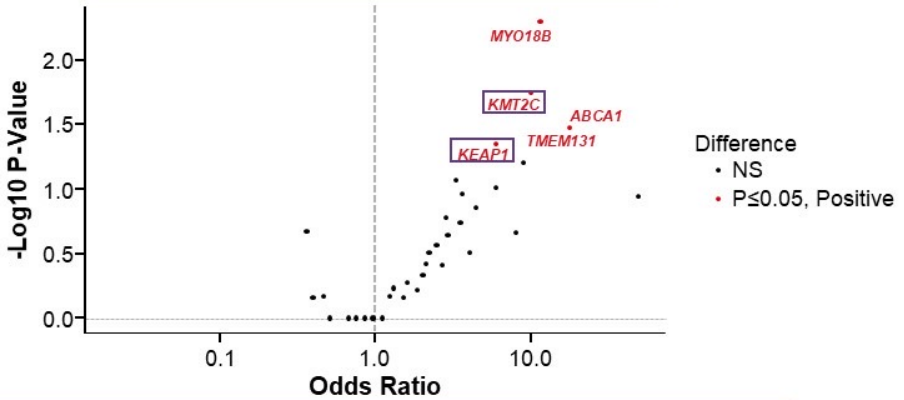
	D arm	PBO arm
HR for MRD+ vs MRD−	21.28 (95% CI: 7.70–58.83)	14.29 (95% CI: 4.94–41.36)
HR for D vs PBO arm (MRD−)	0.56 (95% CI: 0.26–1.20)	–
HR for D vs PBO arm (MRD+)	0.78 (95% CI: 0.26–2.36)	–

Reck et al., ASCO 2025

Exploratory Exome-wide Analysis to Identify Candidate Mutations Associated with MRD Status

- Within the D arm, mutated genes associated with MRD+ status included *KMT2C* and *KEAP1*

Association of Gene Mutation Status with MRD Status within the D arm*

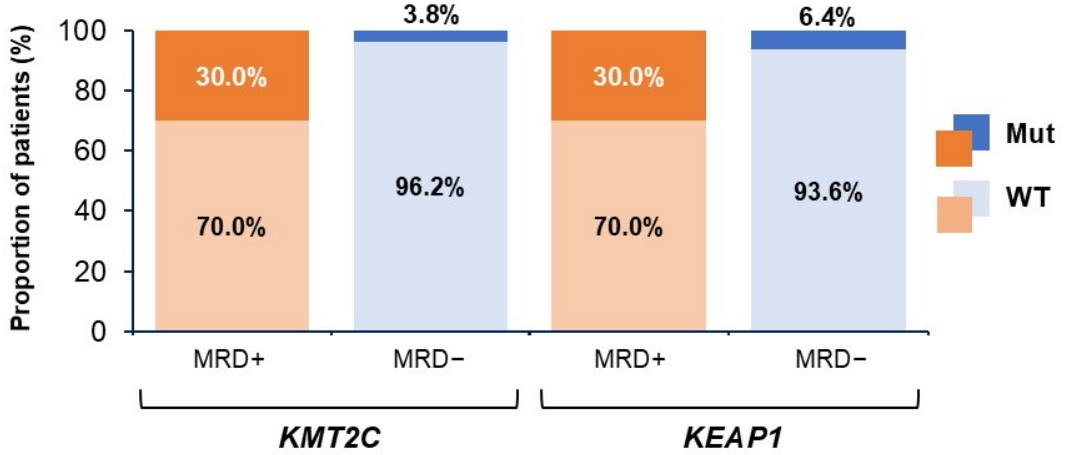


	D arm		PBO arm		Regardless of Tx	
	OR	P	OR	P	OR	P
ABCA1	17.917	0.033	0	1	4.822	0.114
TMEM131	17.917	0.033	0	1	3.189	0.188
MYO18B	11.656	0.005	0	1	4.280	0.038
KMT2C	10.165	0.018	0	0.587	2.260	0.209
KEAP1	6.042	0.044	0	1	3.345	0.107

- Within the PBO arm, mutated genes associated with MRD+ status included *SLC4A4*, *F5*, and *GRM7*

- Within the D arm, a higher proportion of MRD+ vs MRD− patients had *KMT2C* (30.0% vs 3.8%) and *KEAP1* (30.0% vs 6.4%) mutations

Prevalence of *KMT2C* and *KEAP1* Mutations in MRD-evaluable Patients within the D arm



- 62.5% (15/24) and 47.6% (10/21) of patients with *KMT2C* and *KEAP1* mutations, respectively, had persistent ctDNA at all evaluable neoadjuvant timepoints

*The odds ratio (OR) and P value refer to an association between MRD and mutation status, as determined by Fisher's exact test. Mut, patients with *KMT2C* or *KEAP1* mutations; NS, not significant; WT, patients without *KMT2C* or *KEAP1* mutations, i.e., wild type.

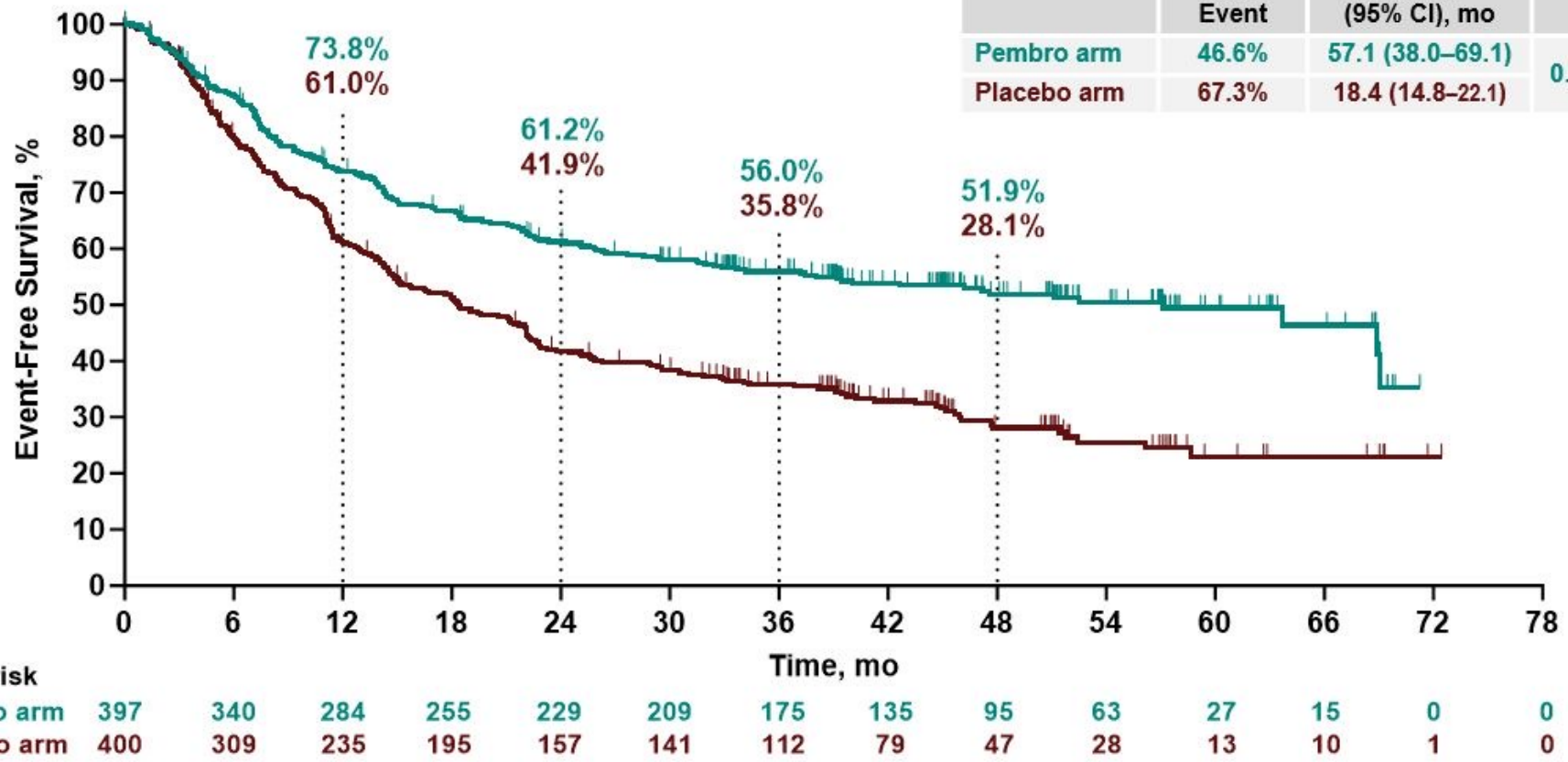
PRESENTED BY: Martin Reck, MD, PhD

Keynote 671

Event-Free Survival[a]

Median Follow-Up: 41.1 (range, 0.4–75.3) months

	Pts w/ Event	Median (95% CI), mo	HR (95% CI)
Pembro arm	46.6%	57.1 (38.0–69.1)	0.57 (0.47–0.69)
Placebo arm	67.3%	18.4 (14.8–22.1)	



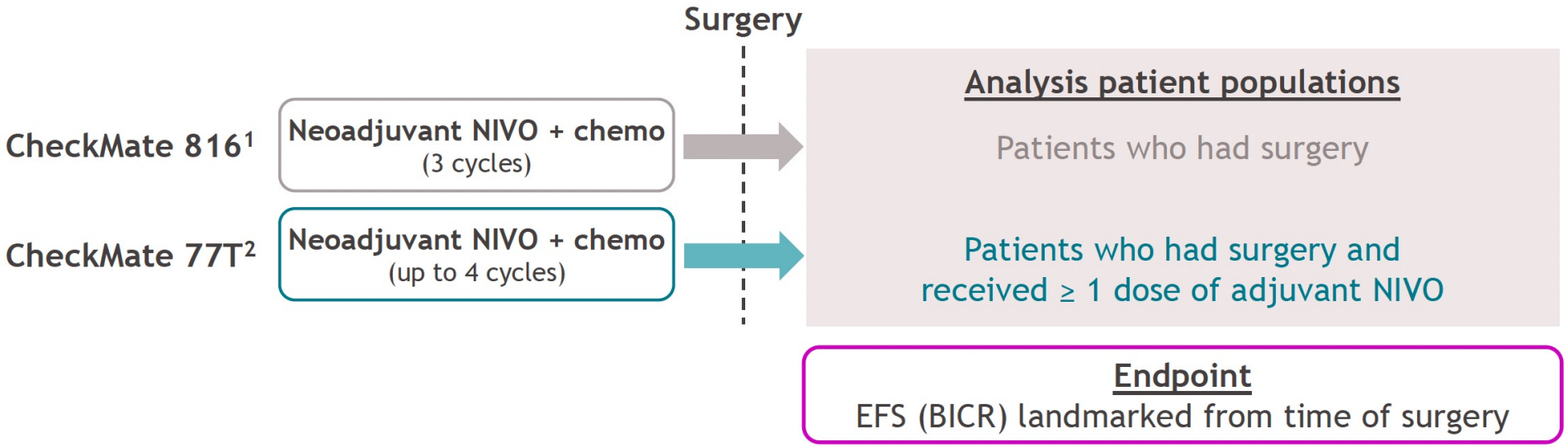
No. at risk													
Pembro arm	397	340	284	255	229	209	175	135	95	63	27	15	0	0
Placebo arm	400	309	235	195	157	141	112	79	47	28	13	10	1	0

[a]Event-free survival defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST version 1.1 by investigator assessment, or death from any cause.
Data cutoff date: August 19, 2024.

EsMO, 2024

PATIENT LEVEL COMPARISON OF CM-816 AND CM 77T

Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



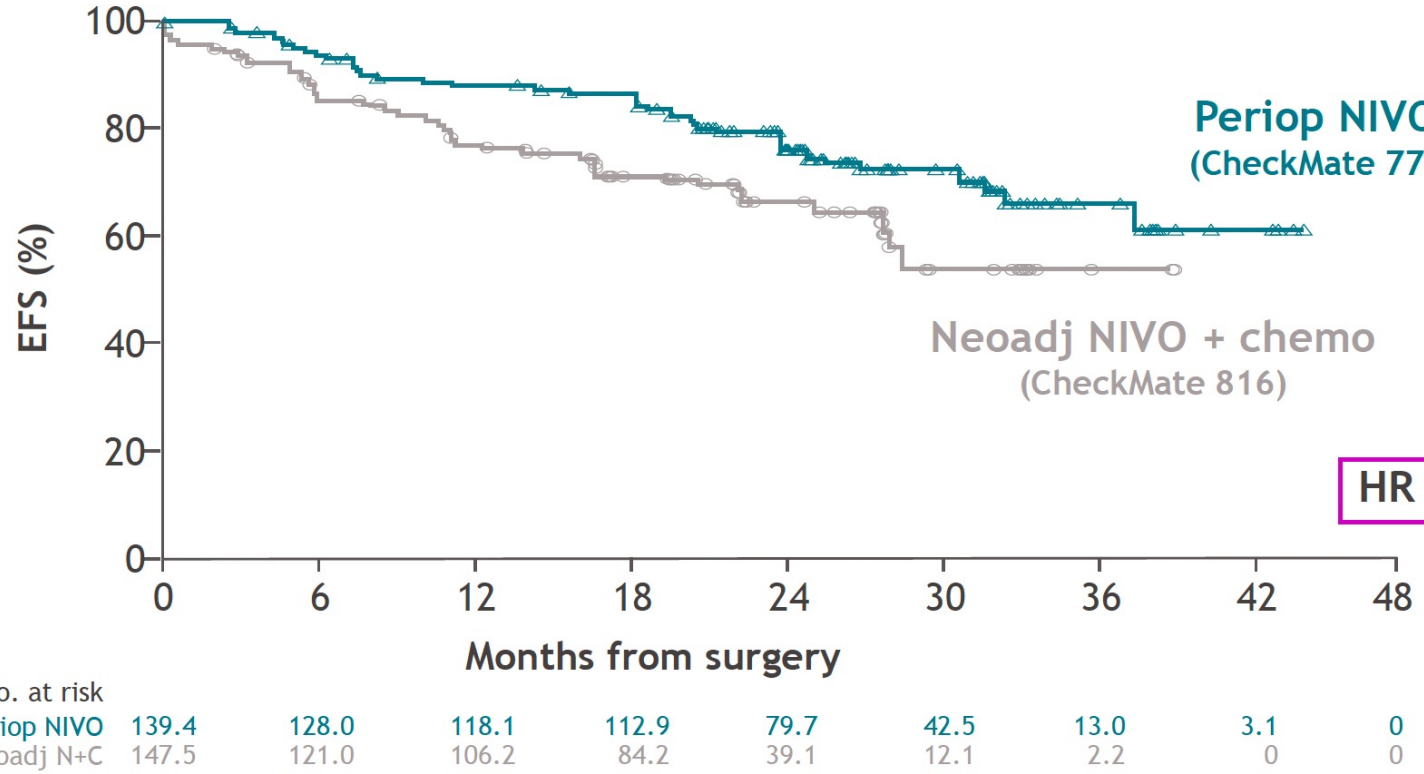
- In lieu of a head-to-head trial, exploratory propensity score weighting analyses (ATT[a] and ATE[b]) were performed to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics[c] between study populations and reducing the confounding effects of these factors
  - Subgroup analyses were not weighted due to smaller sample sizes
- Median duration of follow-up[d]: 29.5 months (CheckMate 816) and 33.3 months (CheckMate 77T)

[a]Average treatment effect for the treated (ATT): a weight of 1 was applied to patients in the perioperative NIVO arm of CheckMate 77T; varying weights were applied to patients in the CheckMate 816 NIVO + chemo arm to make them comparable to those in the perioperative NIVO arm in CheckMate 77T based on propensity scores. [b]Average treatment effect (ATE): varying weights were applied to all patients in the populations of interest from CheckMate 77T and CheckMate 816 to make them comparable to one another based on propensity scores. [c]Sex, race, clinical stage, tumor histology, PD-L1 expression, age, ECOG PS, and smoking status. [d]Database locks: CheckMate 816, October 20, 2021; CheckMate 77T, April 26, 2024. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Cascone T, et al. *N Engl J Med* 2024;390:1756-1769.

Forde et al., World Lung, 2024

PATIENT LEVEL COMPARISON OF CM-816 AND CM 77T

Landmark EFS (BICR) from definitive surgery

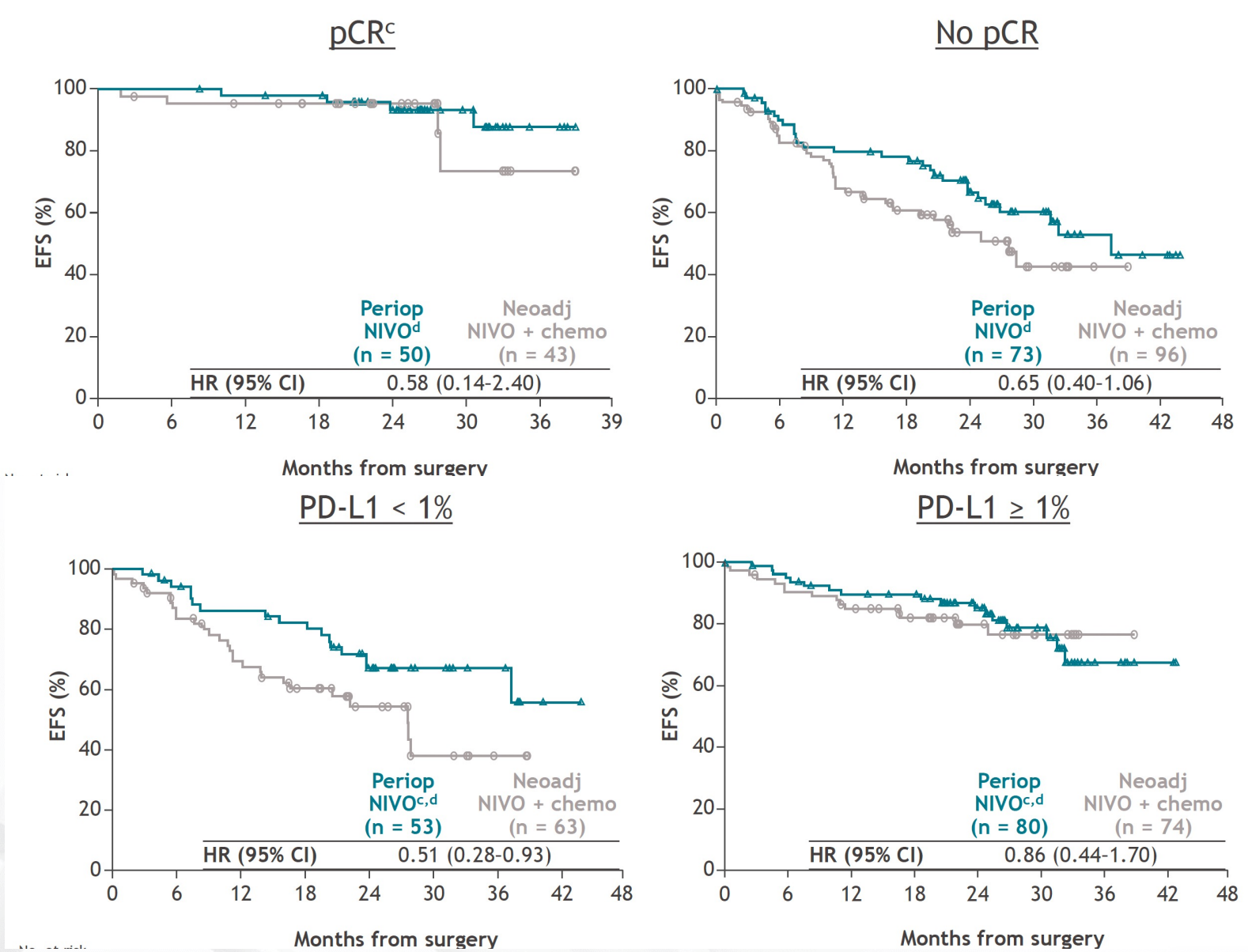


	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Forde et al., World Lung, 2024

PATIENT LEVEL COMPARISON OF CM-816 AND CM 77T: LANDMARK EFS



Forde et al., World Lung, 2024

ALCHEMIST ADJUVANT CHEMO-IO TRIAL (ACCIO)

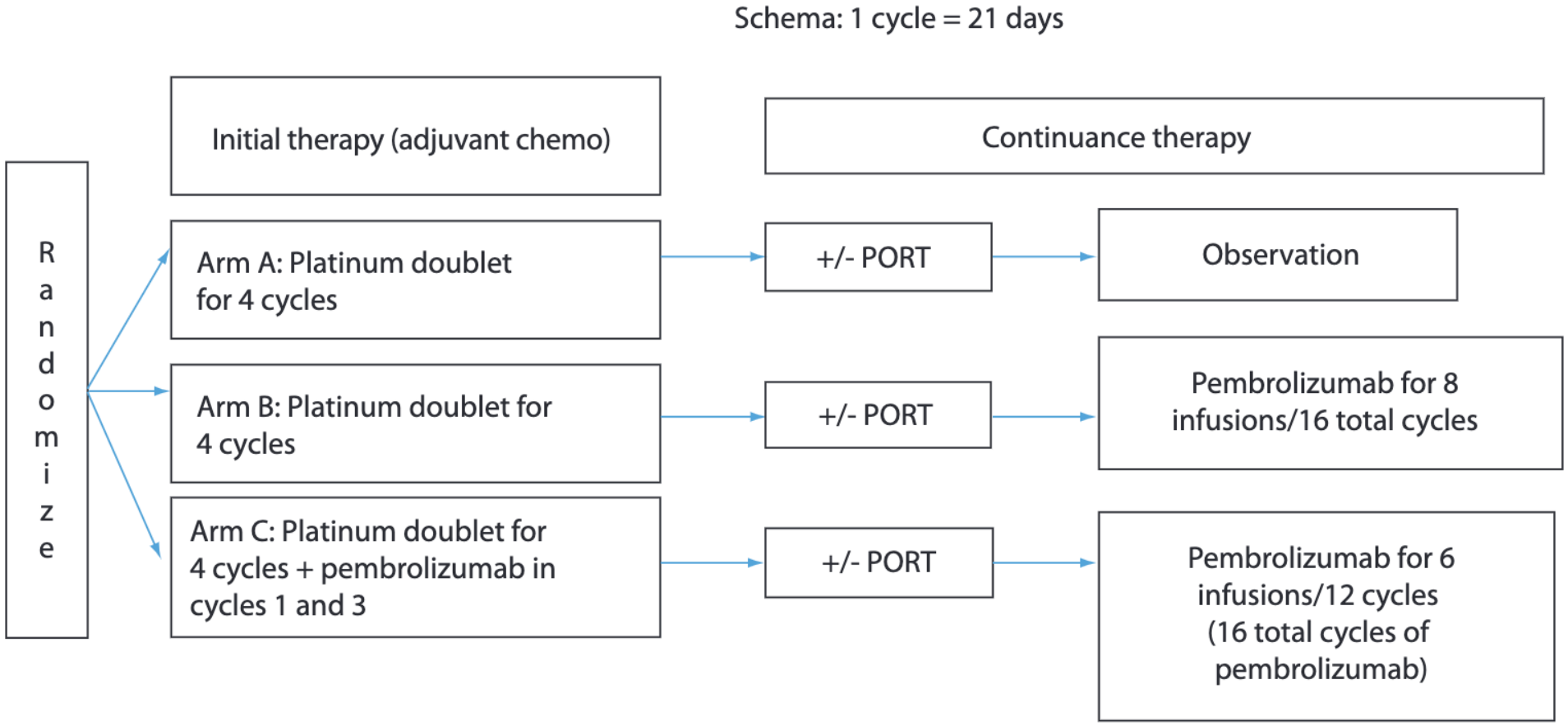
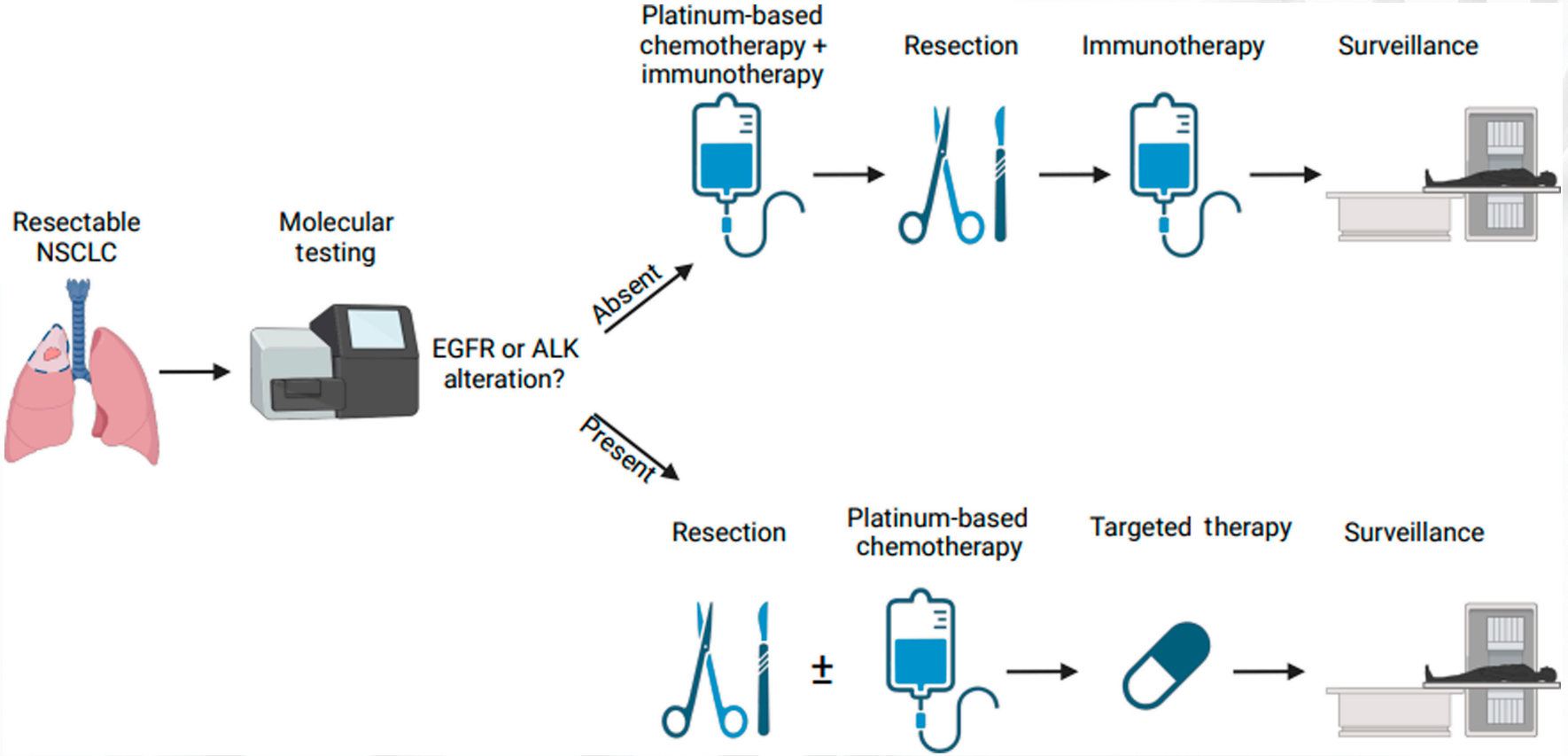


Figure 1. Schema of the ACCIO trial including three arms. Pembrolizumab dosing is every 6 weeks. Sequential and concurrent arms each include about 1 year of pembrolizumab.
PORT: Postoperative radiation therapy.

Sands et al., Immunotherapy (2021) 13(9), 727–734

What about non- EGFR or ALK driver mutated NSCLC?



Immunotherapy responsive mutations:
- BRAF
- KRAS (without STK11, KEAP1)

Less immunotherapy responsive?
- ROS1
- RET
- HER2
- etc

Voruganti et. Al., ASCO ED Book 2025

Summary: Immunotherapy in Early-Stage Lung Cancer

1 neoadjuvant-only option: Chemo + nivolumab x 3 cycles

3 perioperative options: Durvalumab, Nivolumab, and pembrolizumab

MRD and path CR are predictive

Ongoing trials to help determine role of adjuvant component and add agents in the setting of no pathologic complete response

For patients who are up staged at surgery:
Current SOC is platinum doublet chemo followed by pembro or atezolizumab
Awaiting trial of combination chemo-pembro

Thank you to our clinical team:

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