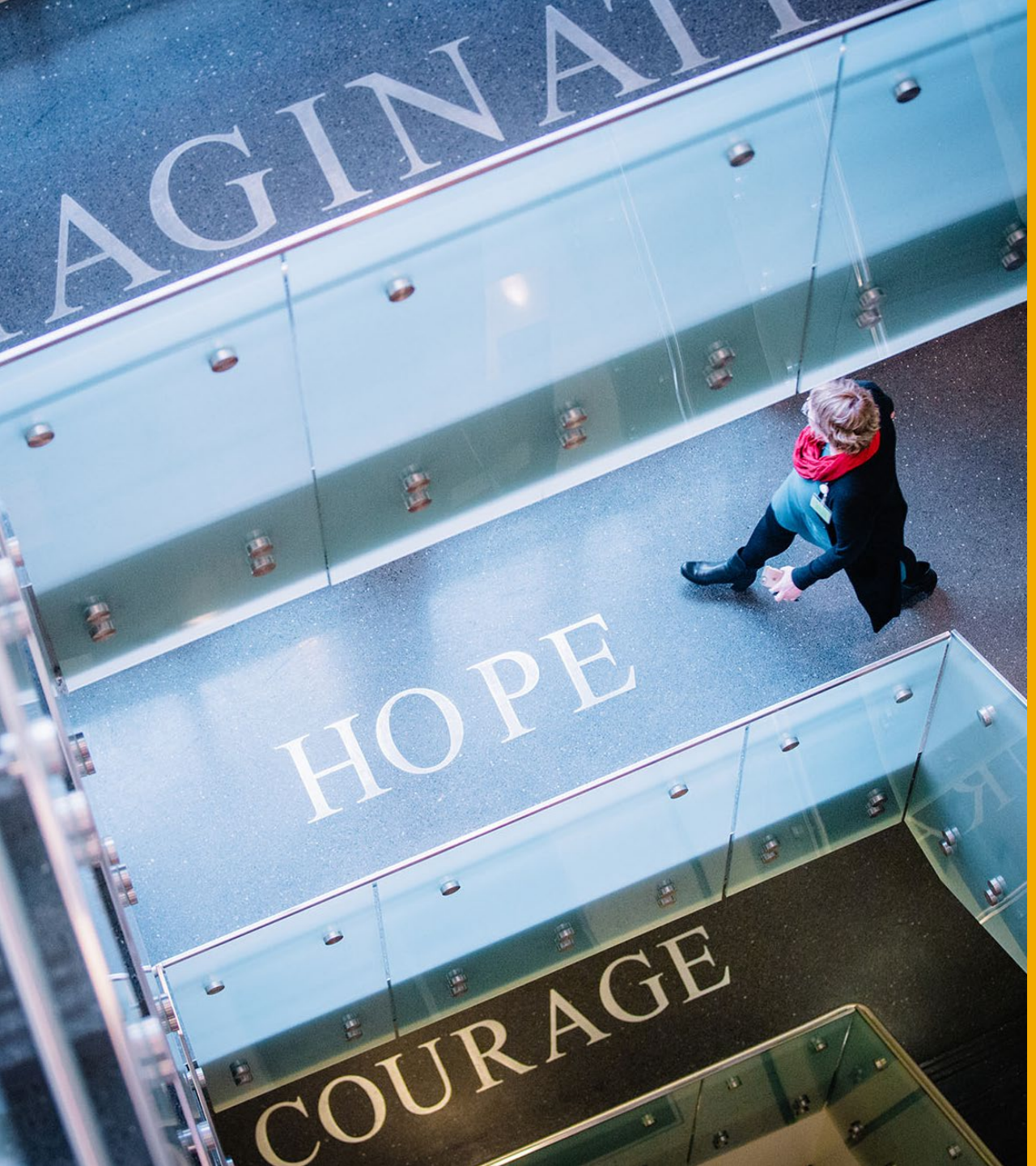

OPTIMAL THERAPY FOR RESECTABLE NSCLC:

NEOADJUVANT

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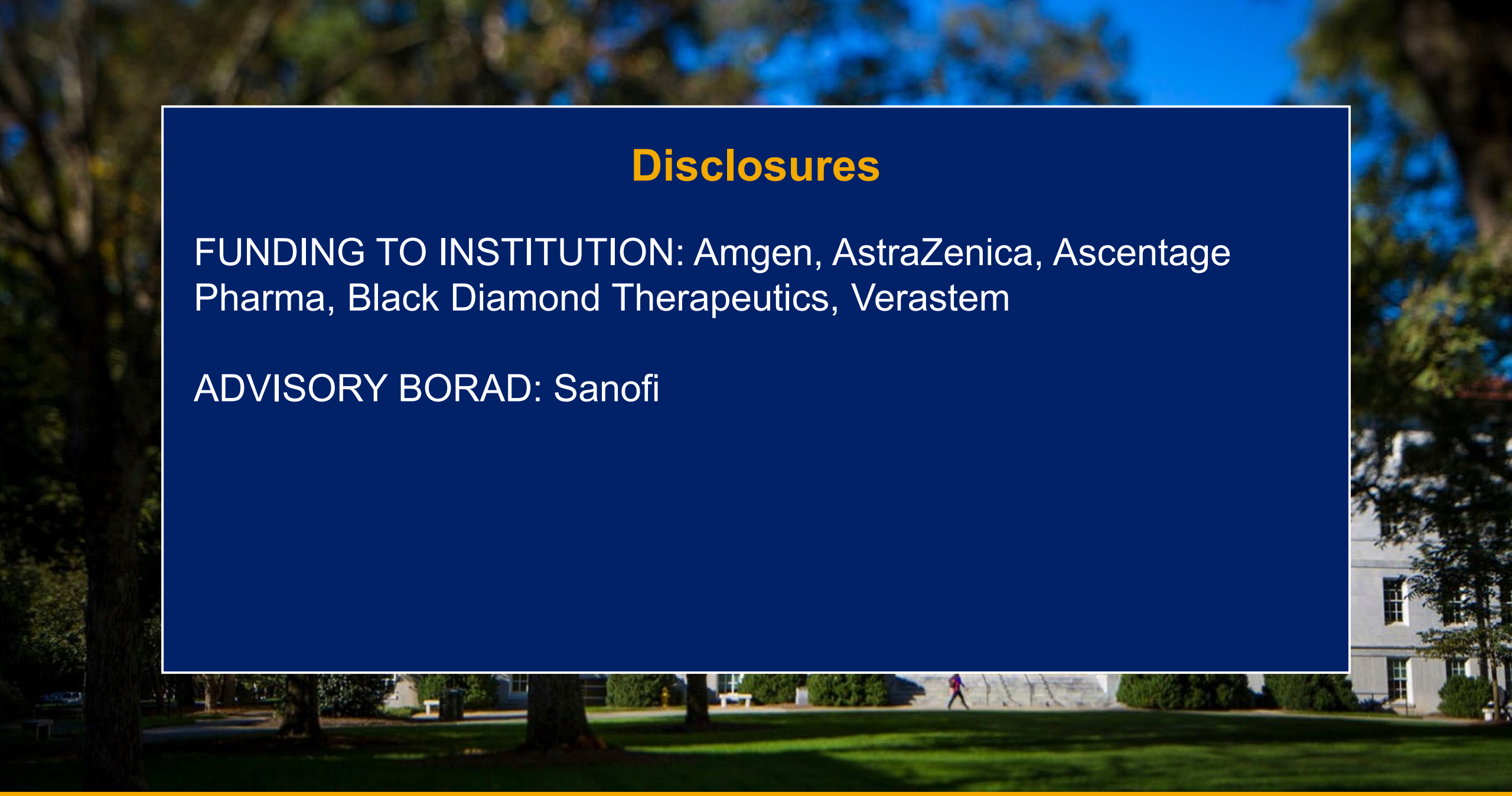
Emory University School of Medicine

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

NCI Designated Comprehensive Cancer Center



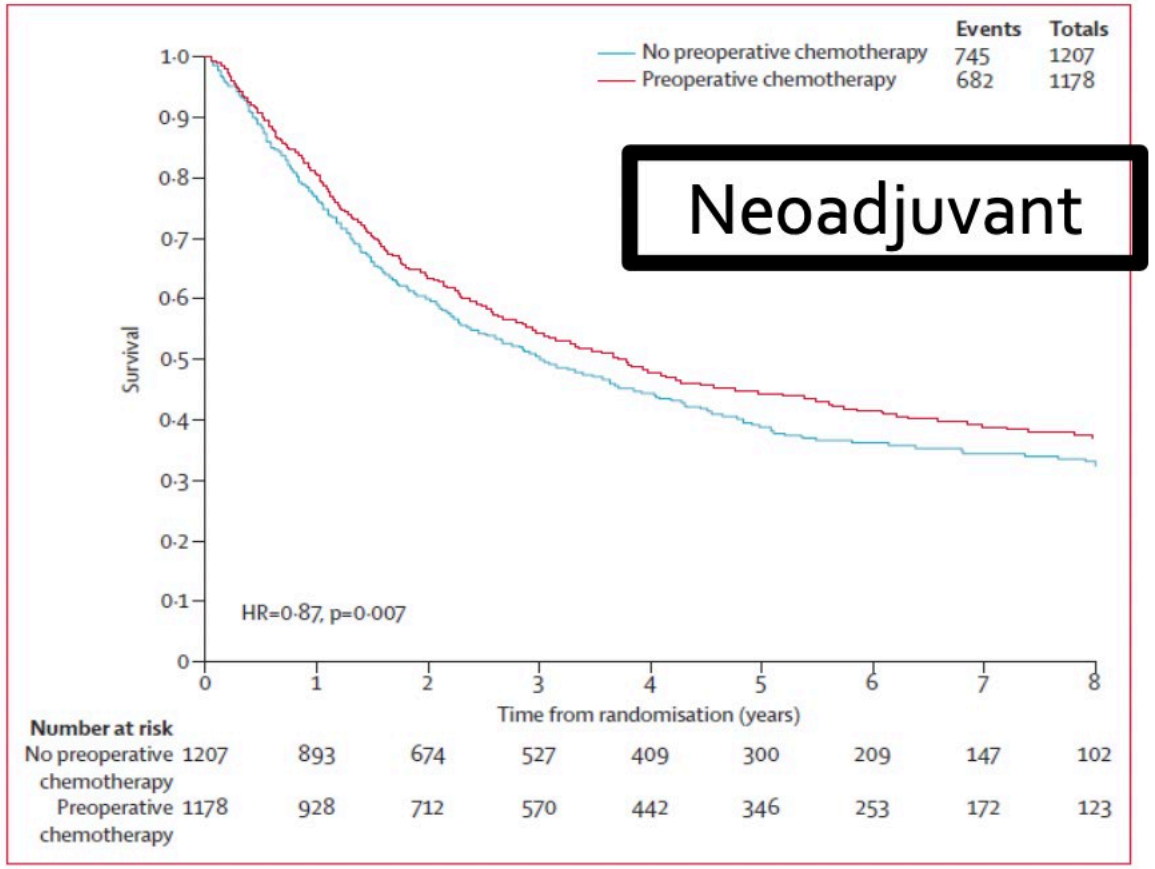
Disclosures

FUNDING TO INSTITUTION: Amgen, AstraZenica, Ascentage Pharma, Black Diamond Therapeutics, Verastem

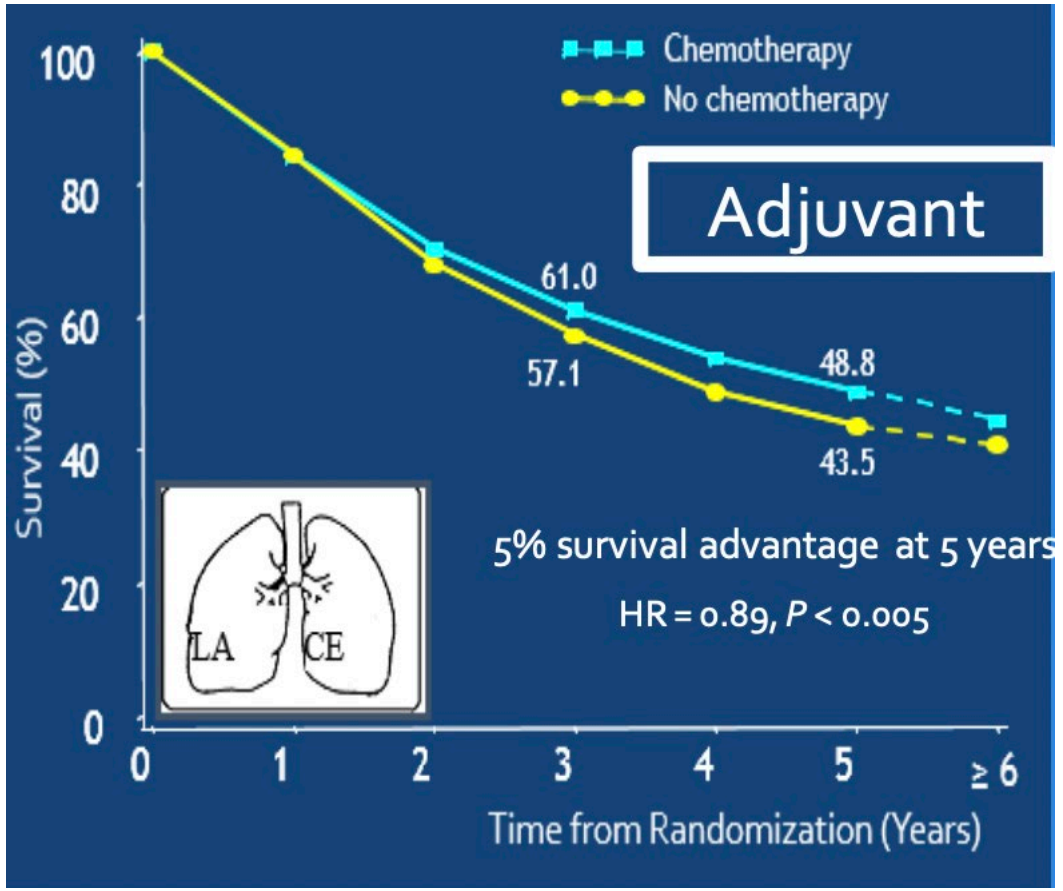
ADVISORY BORAD: Sanofi

Not for debate:

- Chemotherapy is not enough (either pre- or post-op)



NSCLC Meta-Analysis Group. Lancet Oncology 2014



Pignon et al. JCO 2006

Inherent differences in Adjuvant v Neoadjuvant approach

Adjuvant:

- Prioritizes local treatment
- Patients with adverse surgical outcomes not represented in trials
- 30% do not complete adjuvant systemic therapy

Neoadjuvant:

- Prioritizes systemic treatment
- Treatment complications may preclude surgery/ surgical outcomes
- 15% do not have tumor resected

? Is definitive therapy or systemic therapy the priority

?Is this different with better systemic therapies

? Which approach leads to the best survival outcomes

What is Dr. Steuer going to argue?

1. Surgeons prefer to operate first / inertia with current work-flow

2. Surgical implications of immunotherapy:
   -Inflammation, increased OR time

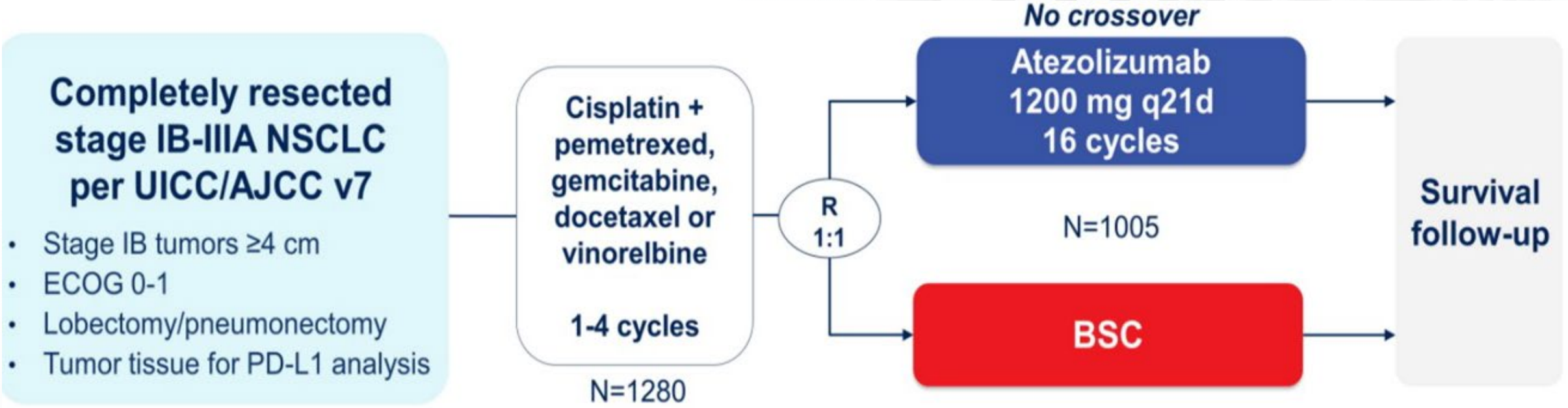
3. Why risk delays or missed surgery when we can give immunotherapy in the adjuvant setting?

PERIOPERATIVE IMMUNOTHERAPY TRIALS

	Study (Primary Endpoint)	Patient population
Neoadjuvant	CheckMate 816 (pCR, EFS)* FDA approval 3/22	Excludes EGFR/ALK
Neoadjuvant/adj	Checkmate 77T (EFS)	Excludes EGFR/ALK
Neoadjuvant/adj	Aegean (pCR, EFS)	Excludes EGFR/ALK
Neoadjuvant/adj	KEYNOTE 671 (EFS, OS)	May include EGFR/ALK
Neoadjuvant/adj	IMpower030 (EFS)	Excludes EGFR/ALK
Adjuvant	IMpower010 (DFS)* FDA approval 10/21	May include EGFR/ALK
Adjuvant	PEARLS/KN 091 (DFS) FDA approval 01/23	May include EGFR/ALK
Adjuvant	BR.31 (DFS in PD-L1 TC ≥ 25%	May include EGFR/ALK
Adjuvant	ANVIL (DFS, OS)	Excludes EGFR/ALK

Forde et al. NEJM 2022; Cascone et al. ASCO 2021; Felip et al. Lancet 2021;
Paz-Ares et al. ESMO Virtual Plenary 2022.ga aco

IMpower010: Adjuvant atezolizumab



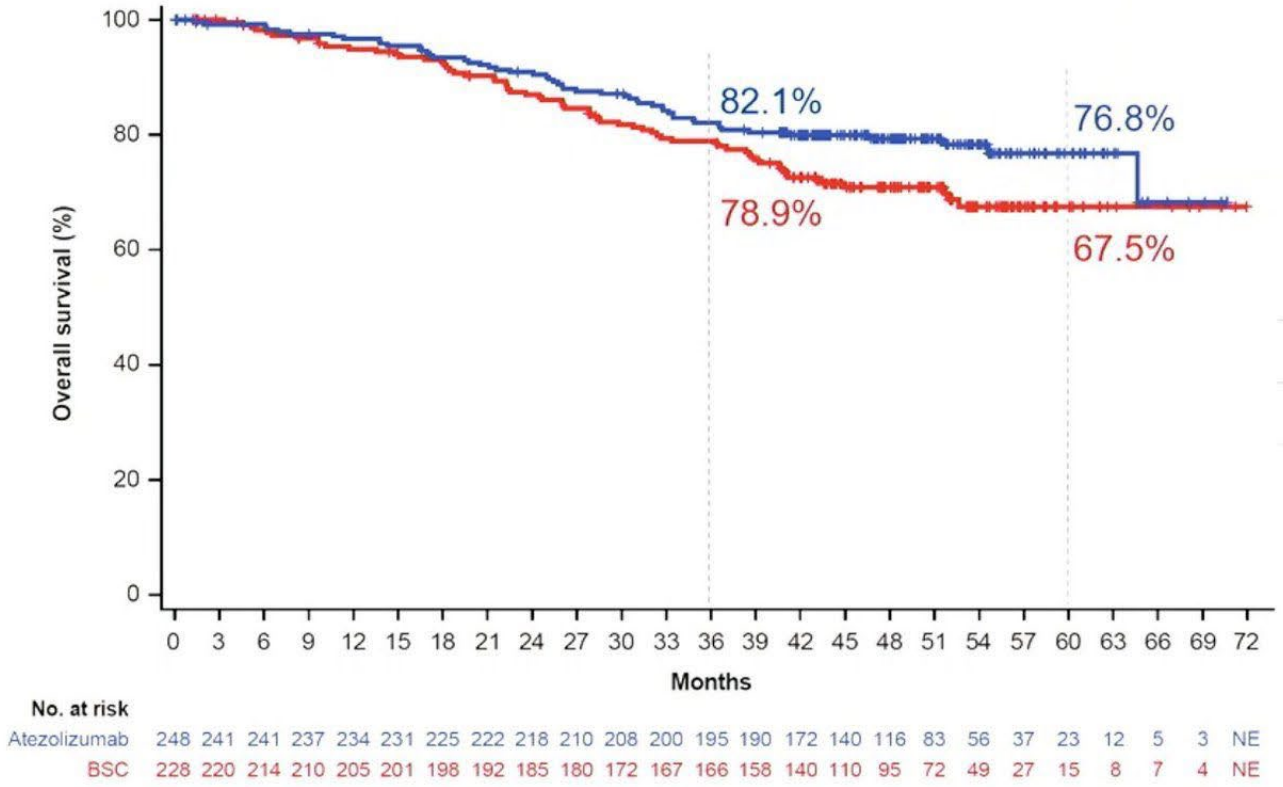
Primary endpoint: DFS in PD-L1 >1%

Felipe et al, Lancet 2021

IMpower010: OS results

Results of OS IA: PD-L1 TC ≥1%[a] (stage II-IIIA)

(data cutoff: 18 Apr '22, median follow-up: 46 months)



	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49	1.03)

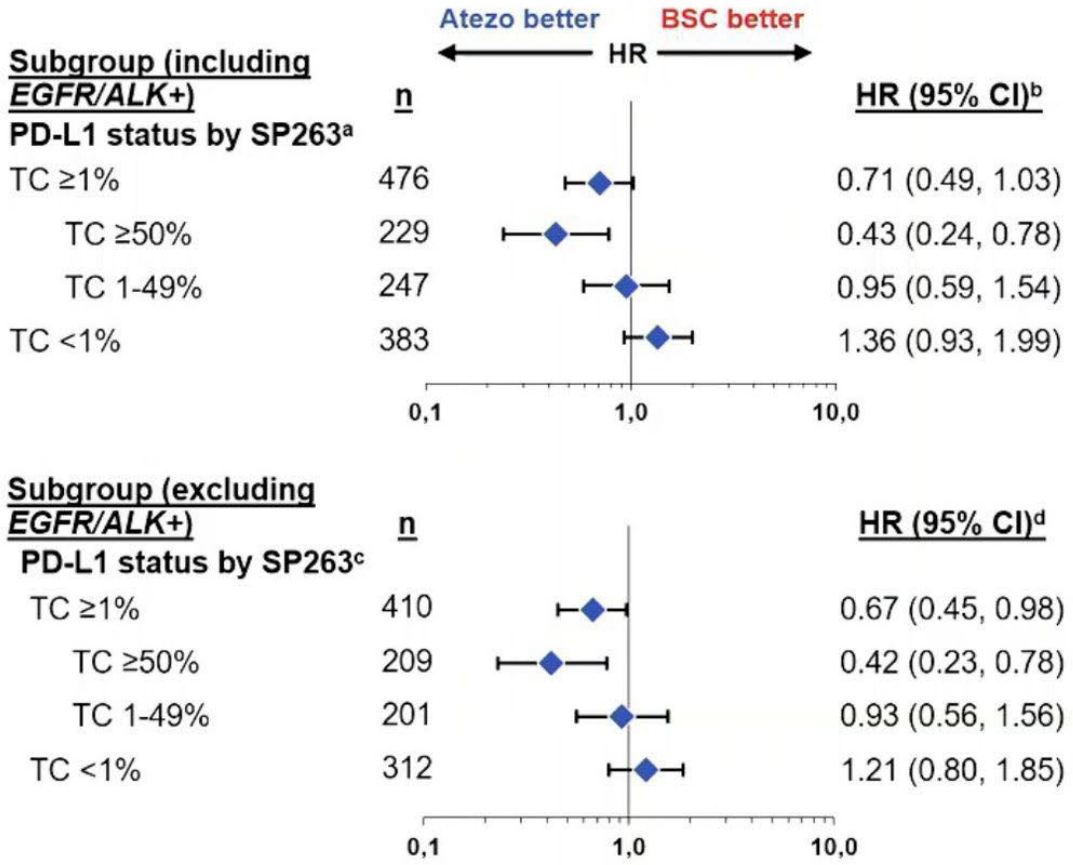
mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

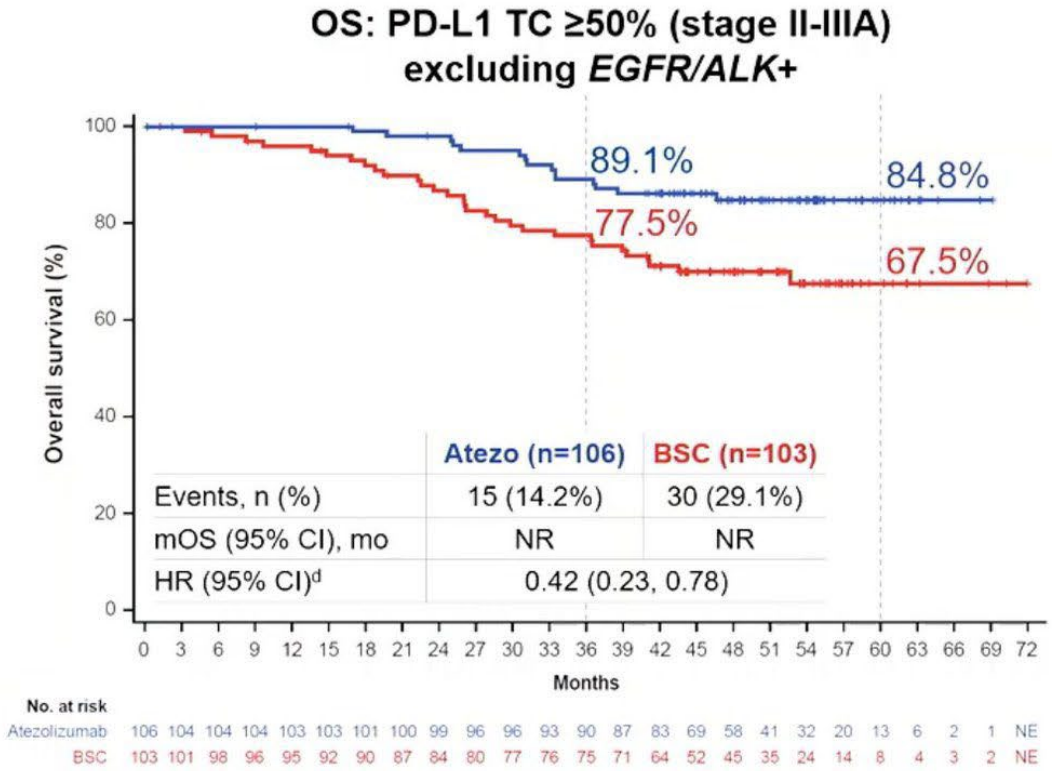
Felipe et al, WCLC 2022

IMpower010:

OS by biomarker status (stage II-IIIA)

(data cutoff: 18 Apr '22)



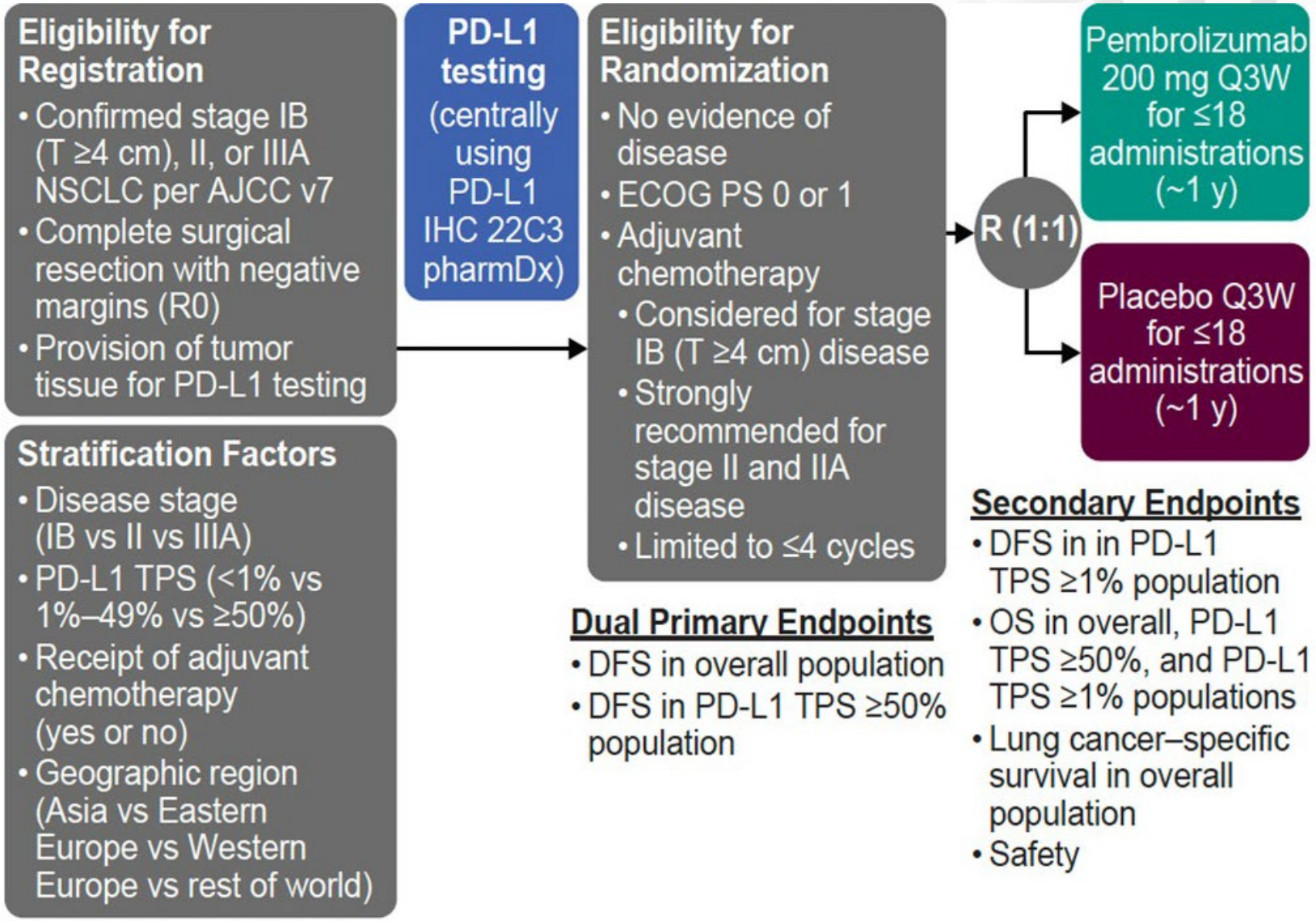


[a] 23 patients had unknown PD-L1 status. [b] Stratified for PD-L1 TC ≥1%; unstratified for all other subgroups. [c] 21 patients had unknown PD-L1 status. [d] Unstratified.

Felipe et al, WCLC 2022

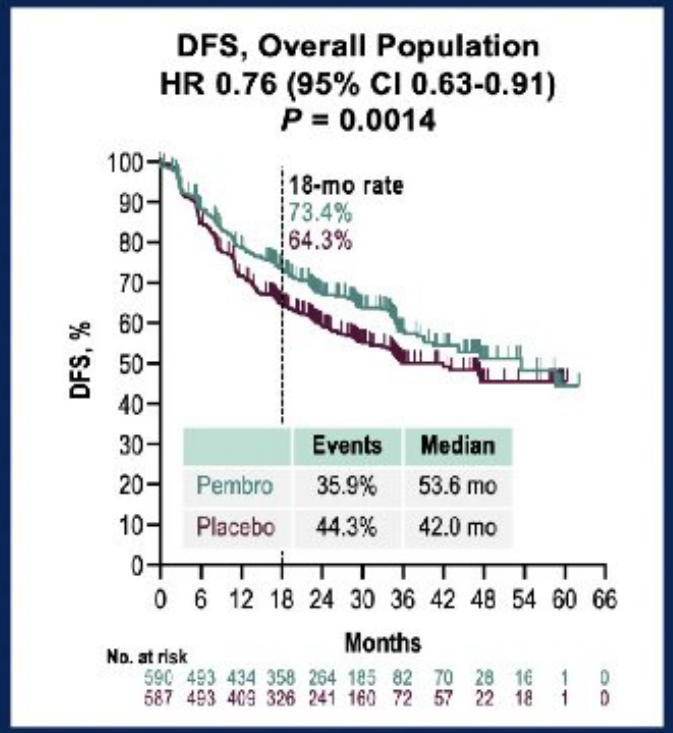
IMpower010 OS IA. https://bit.ly/3InK8SP
Presented by Dr Enriqueta Felip

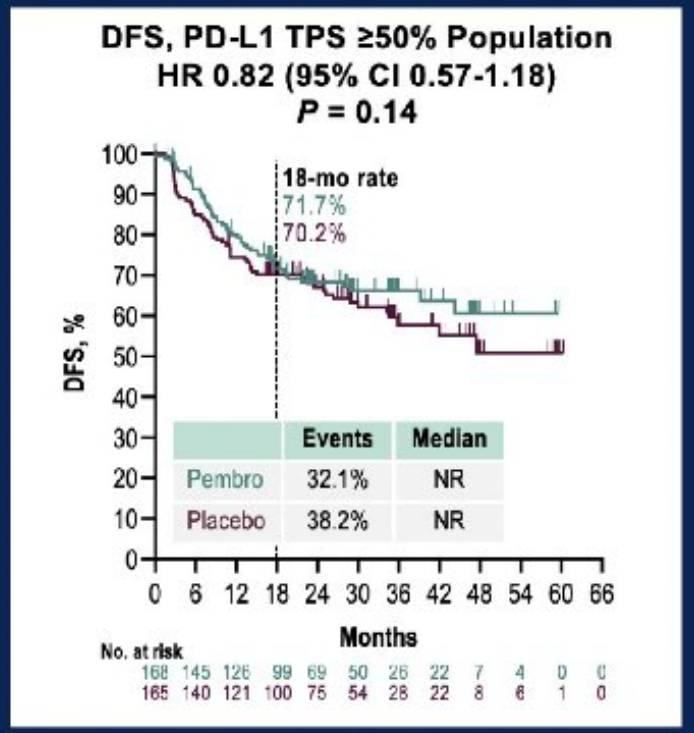
Keynote-091: adjuvant pembrolizumab



Keynote-091: DFS results

PEARLS/KEYNOTE-091:
Primary Results From the Protocol-Specified Second Interim Analysis (IA2)



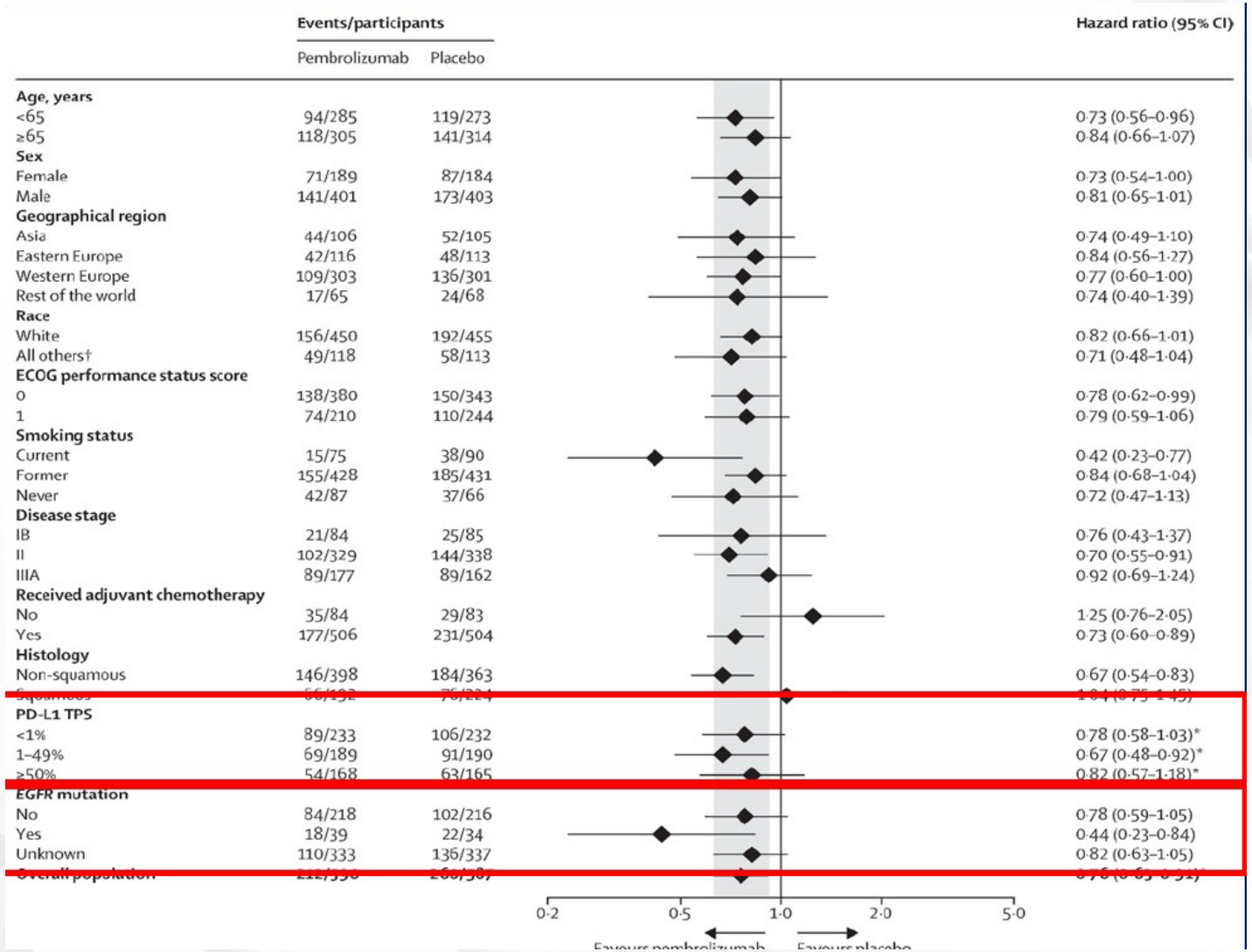


- DFS benefit generally consistent across most protocol-specified subgroups, including PD-L1 TPS <1% (HR 0.78, 95% CI 0.58-1.03) and 1-49% (HR 0.67, 95% CI 0.48-0.92)

Note:
14% of patients in both arms did not receive adjuvant chemotherapy

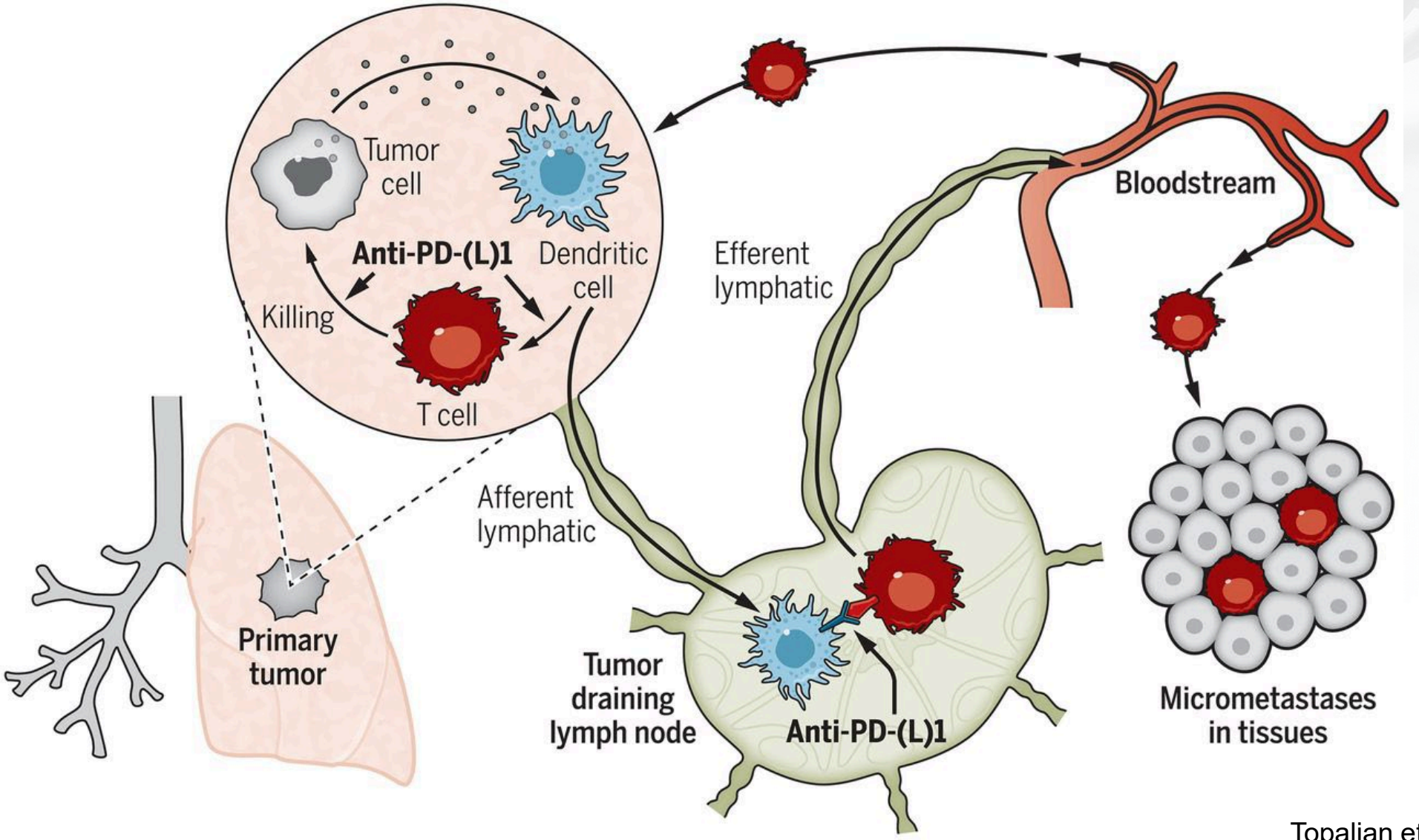
J Patel, ASCO 2022

Keynote-091: DFS results



O Brien et al. Lancet 2022

Why may timing of immunotherapy matter?



Tumor present=

1. More antigen
2. Activate the tumor–specific TILs already in the tumor
3. Better T cell priming at the level of the dendritic cell

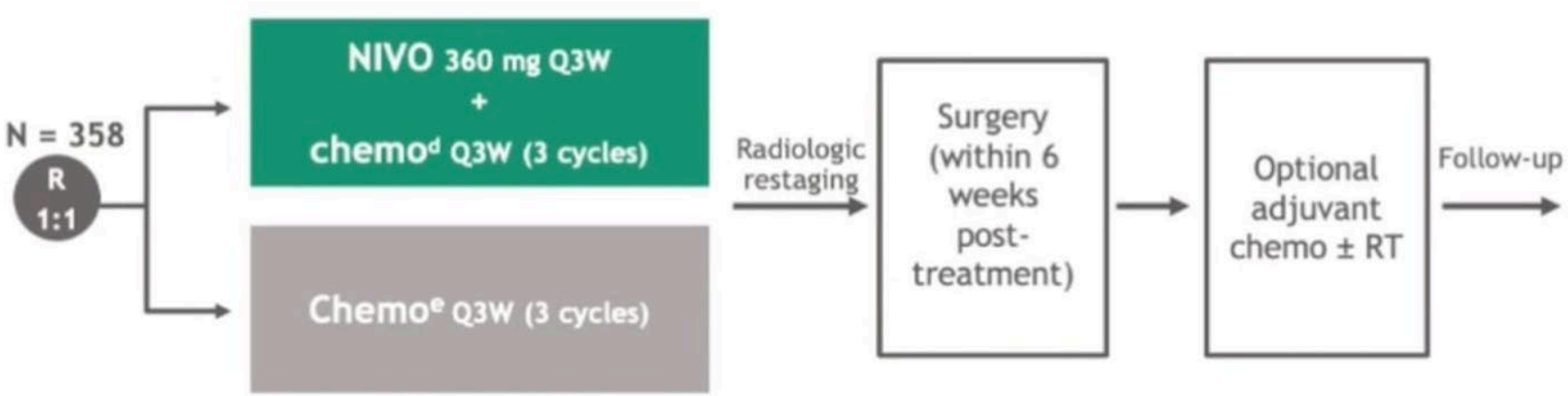
Topalian et al., SCIENCE 2020:367(647)

CHECKMATE 816

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints

- pCR by BIPR
- EFS by BICR

Key secondary endpoints

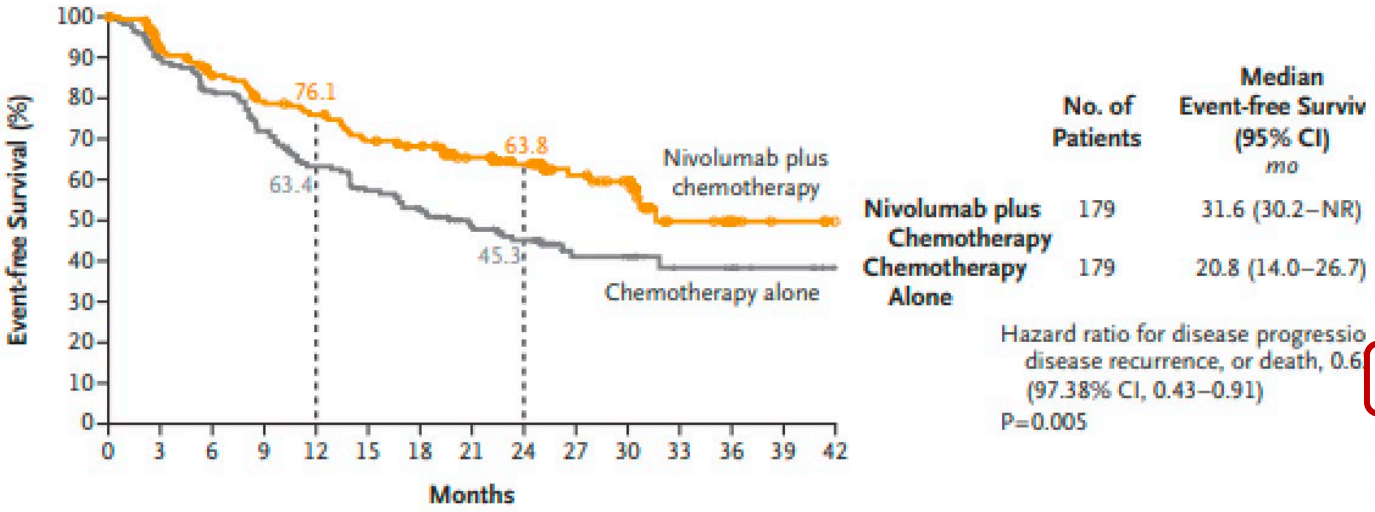
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included

- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Forde et al. NEJM 2022

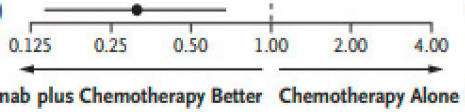
CHECKMATE 816: EFS BENEFIT



	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)

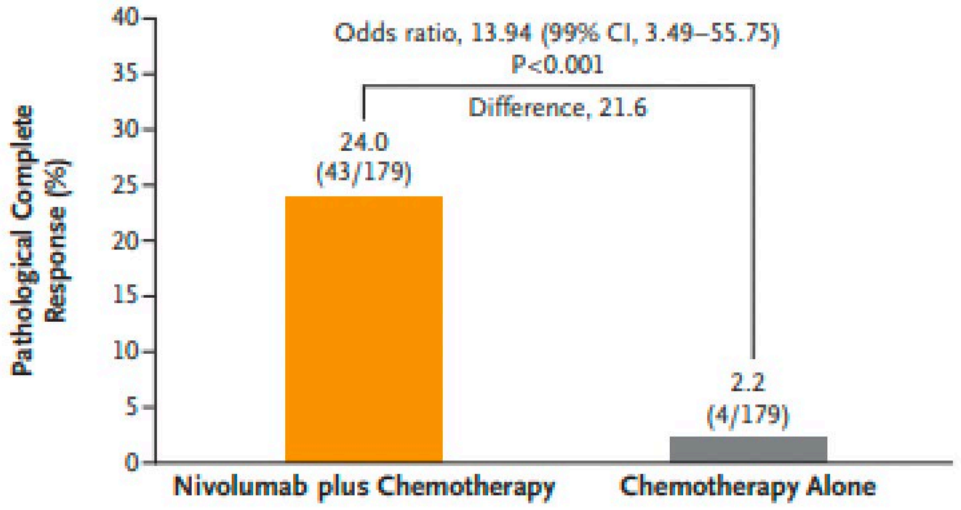
Hazard ratio for disease progressio
disease recurrence, or death, 0.6
(97.38% CI, 0.43–0.91)
P=0.005

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



Forde et al. NEJM 2022

CHECKMATE 816: PATH CR



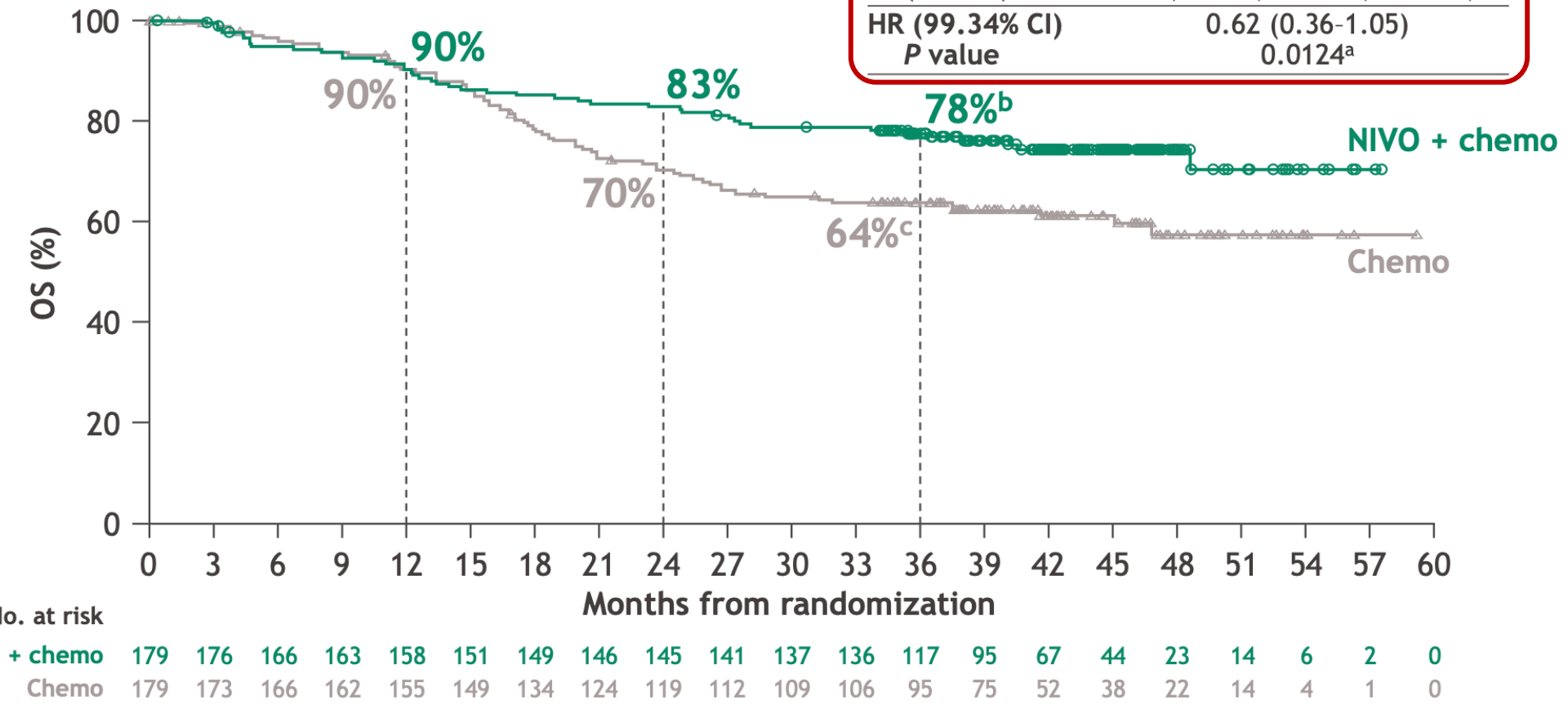
Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		percentage points
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
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)

Forde et al. NEJM 2022

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

Not yet mature

	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

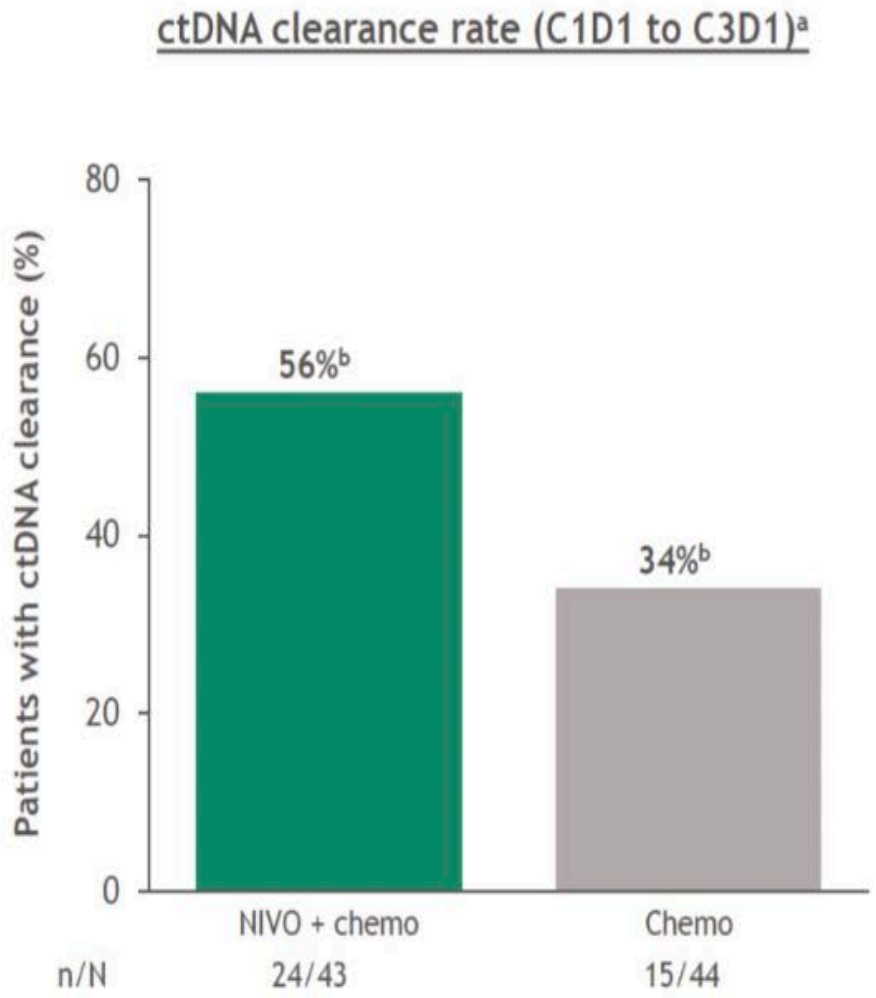
NIVO + chemo	179	176	166	163	158	151	149	146	145	141	137	136	117	95	67	44	23	14	6	2	0
Chemo	179	173	166	162	155	149	134	124	119	112	109	106	95	75	52	38	22	14	4	1	0

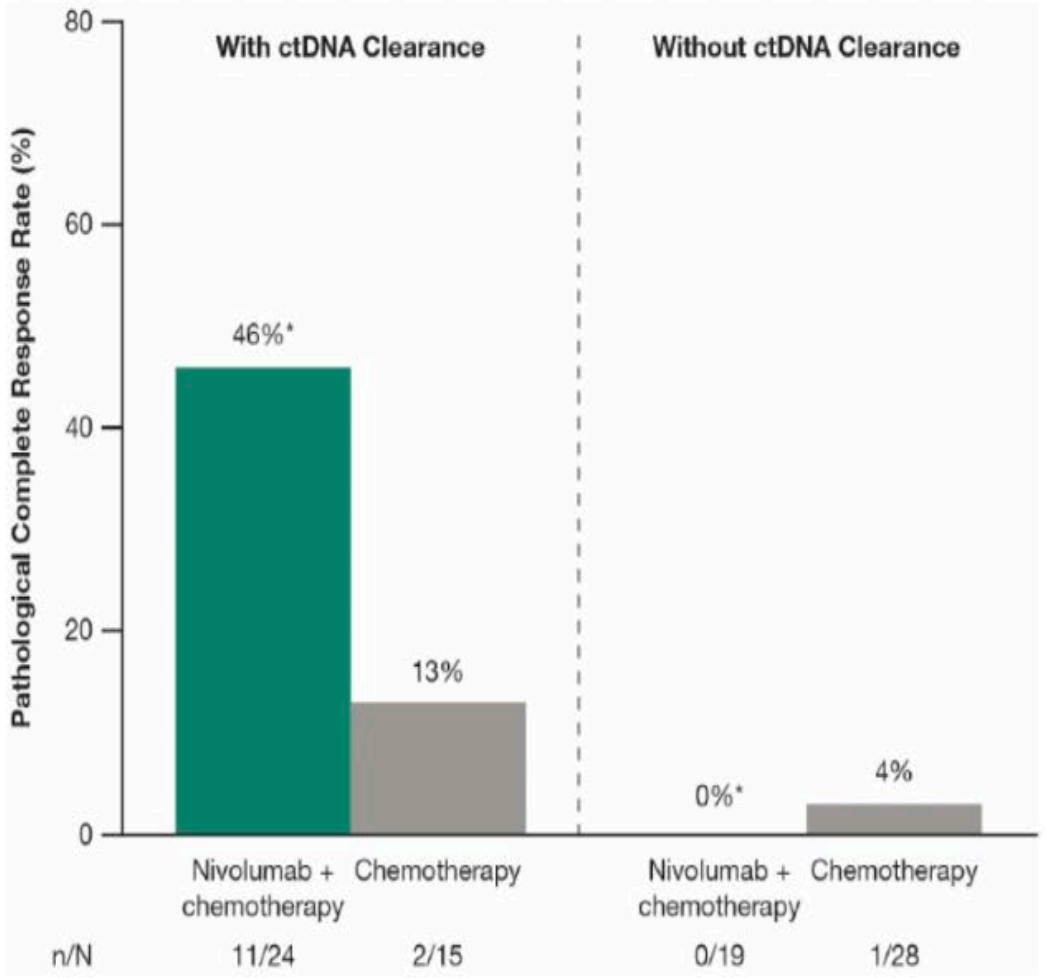
Minimum/median follow-up: 32.9/41.4 months.

[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.

Forde et al. ELCC 2023 oral

CTDNA CLEARANCE AND ASSOCIATION WITH PCR IN CHECKMATE-816





Forde PM et al. *NEJM* 2022

CHECKMATE 816: SAFETY

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)

Forde et al. NEJM 2022

DEBUNKING SURGICAL CONCERNS

CheckMate 816 (NIVO + chemo in resectable NSCLC): 3-y efficacy and safety by definitive surgery status

Subsequent therapy summary

Patients, n (%)	With definitive surgery		Without definitive surgery	
	NIVO + chemo (n = 149)	Chemo (n = 135)	NIVO + chemo (n = 30)	Chemo (n = 44)
Any subsequent therapy	32 (22)	59 (44)	17 (57)	28 (64)
Subsequent radiotherapy	14 (9)	26 (19)	11 (37)	18 (41)
Subsequent surgery	4 (3)	7 (5)	1 (3)	1 (2)
Subsequent systemic therapy	26 (17)	52 (38)	15 (50)	23 (52)
Immunotherapy	14 (9)	31 (23)	1 (3)	16 (36)
Targeted therapy	10 (7)	23 (17)	5 (17)	4 (9)
Chemotherapy	23 (15)	28 (21)	14 (47)	19 (43)

Numerically, more patients who got chemo alone did not get surgery than chemo + IO

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

Spicer et al.[2] ASCO 2023

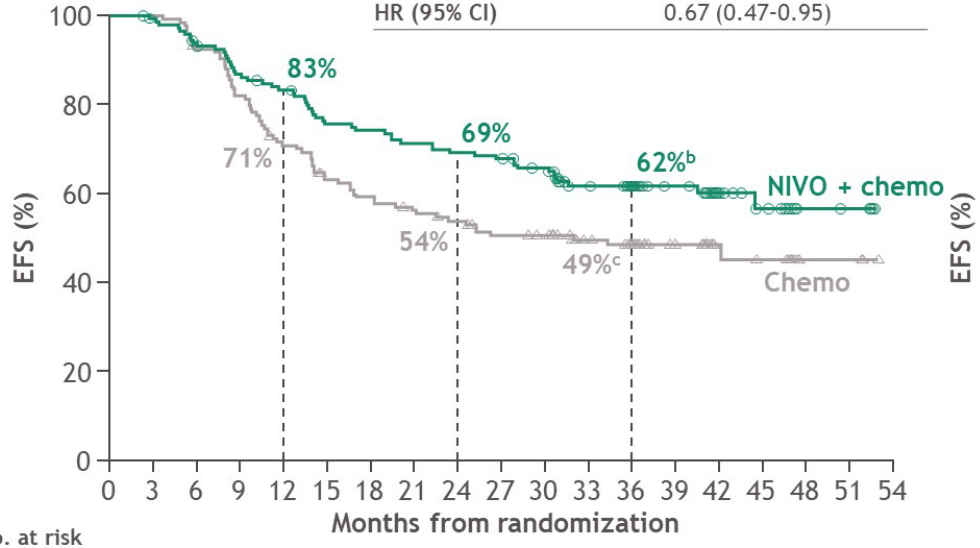
PATIENTS WHO DON'T GET TO SURGERY HAVE POOR OUTCOMES

CheckMate 816 (NIVO + chemo in resectable NSCLC): 3-y efficacy and safety by definitive surgery status

EFS[a] by definitive surgery status

With definitive surgery

	NIVO + chemo (n = 149)	Chemo (n = 135)
Median EFS, mo (95% CI)	NR (44.4-NR)	31.8 (18.0-NR)
HR (95% CI)	0.67 (0.47-0.95)	

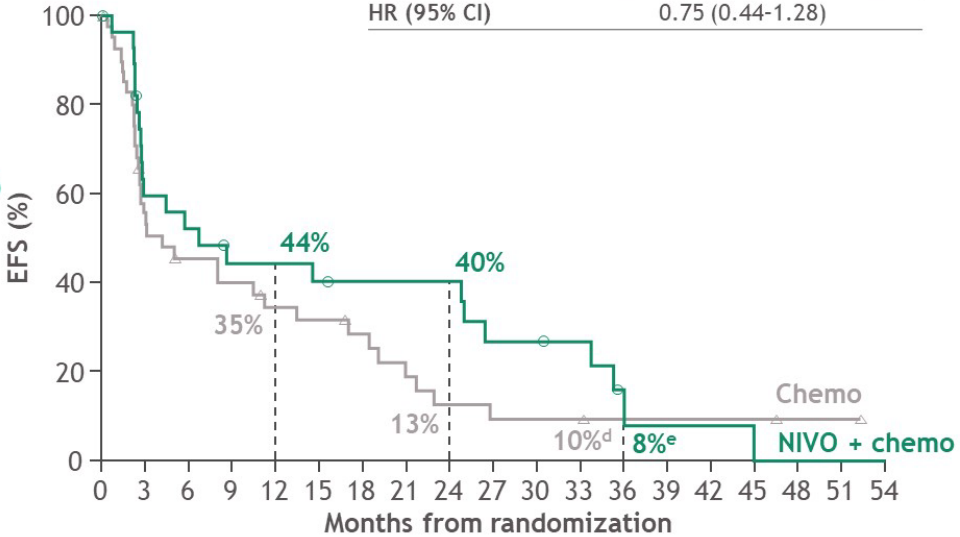


No. at risk

NIVO + chemo	149	146	134	125	119	107	105	101	98	96	90	71	60	40	22	15	7	6	0
Chemo	135	135	125	110	94	82	77	72	68	62	60	48	39	26	14	12	3	3	0

Without definitive surgery

	NIVO + chemo (n = 30)	Chemo (n = 44)
Median EFS, mo (95% CI)	6.7 (2.7-24.9)	4.1 (2.5-11.2)
HR (95% CI)	0.75 (0.44-1.28)	



	30	16	14	11	11	10	9	9	9	6	6	5	1	1	1	0	0	0	0
	44	21	17	15	12	11	9	6	4	3	3	3	2	2	2	2	1	1	0

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

[a]Secondary definition: time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, or death due to any cause; patients receiving subsequent therapy were not censored. [b-e]95% CI: [b]53-69; [c]40-57; [d]2-22; [e]1-28.

Spicer et al. ASCO 2023

ADDITION OF NIVOLUMAB DOES NOT INCREASE SURGICAL AES

CheckMate 816 (NIVO + chemo in resectable NSCLC): 3-y efficacy and safety by definitive surgery status

Safety summary[a]

Patients, n (%)	With definitive surgery				Without definitive surgery			
	NIVO + chemo (n = 149)		Chemo (n = 135)		NIVO + chemo (n = 27)		Chemo (n = 41)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs[b]	142 (95)	68 (46)	133 (98)	58 (43)	23 (85)	8 (30)	40 (98)	21 (51)
TRAEs[b]	129 (87)	56 (38)	120 (89)	48 (36)	18 (67)	7 (26)	39 (95)	19 (46)
All AEs leading to discontinuation[b]	16 (11)	8 (5)	13 (10)	5 (4)	2 (7)	2 (7)	7 (17)	2 (5)
TRAEs leading to discontinuation[b]	16 (11)	8 (5)	11 (8)	5 (4)	2 (7)	2 (7)	6 (15)	1 (2)
All SAEs[b]	23 (15)	16 (11)	15 (11)	11 (8)	7 (26)	3 (11)	9 (22)	6 (15)
Treatment-related SAEs[b]	17 (11)	13 (9)	11 (8)	9 (7)	4 (15)	2 (7)	7 (17)	5 (12)
Surgery-related AEs[c]	67 (45)	17 (11)	66 (49)	20 (15)	—	—	—	—
Treatment-related deaths[d]	0		1 (1)[e]		0		2 (5)[f]	

[a]AEs per CTCAE v4.0 and MedDRA v25.0. [b]Includes events reported between the first dose and 30 days after the last dose of neoadjuvant study treatment. [c]Includes events reported within 90 days after definitive surgery. [d]Treatment-related deaths occurring at any time after the first dose of neoadjuvant study treatment. [e]Due to pneumonia. [f]Due to pancytopenia, diarrhea, and acute kidney injury (all in 1 patient) and enterocolitis (n = 1).

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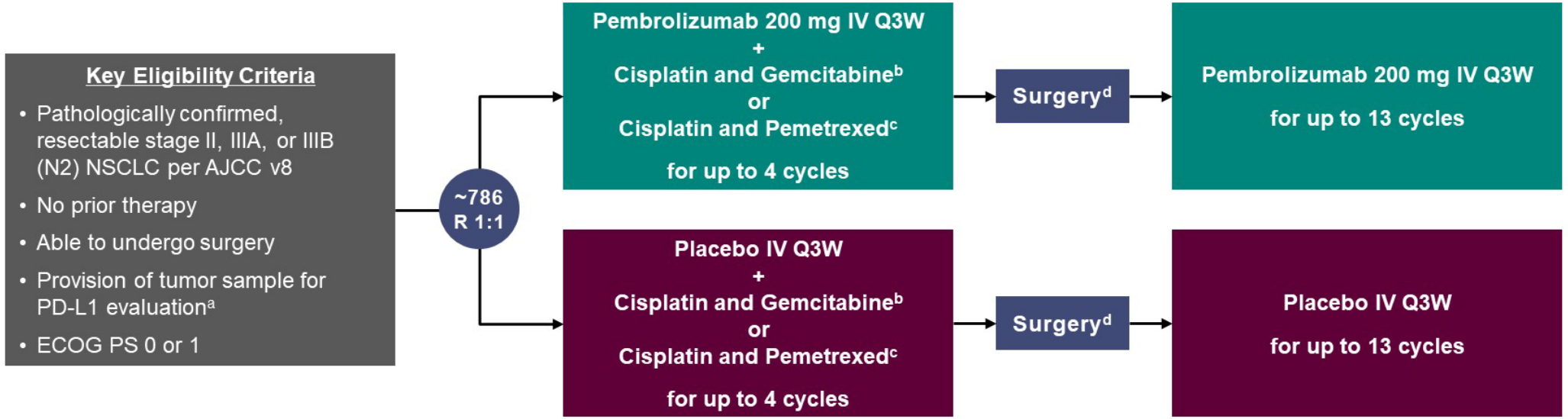
KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

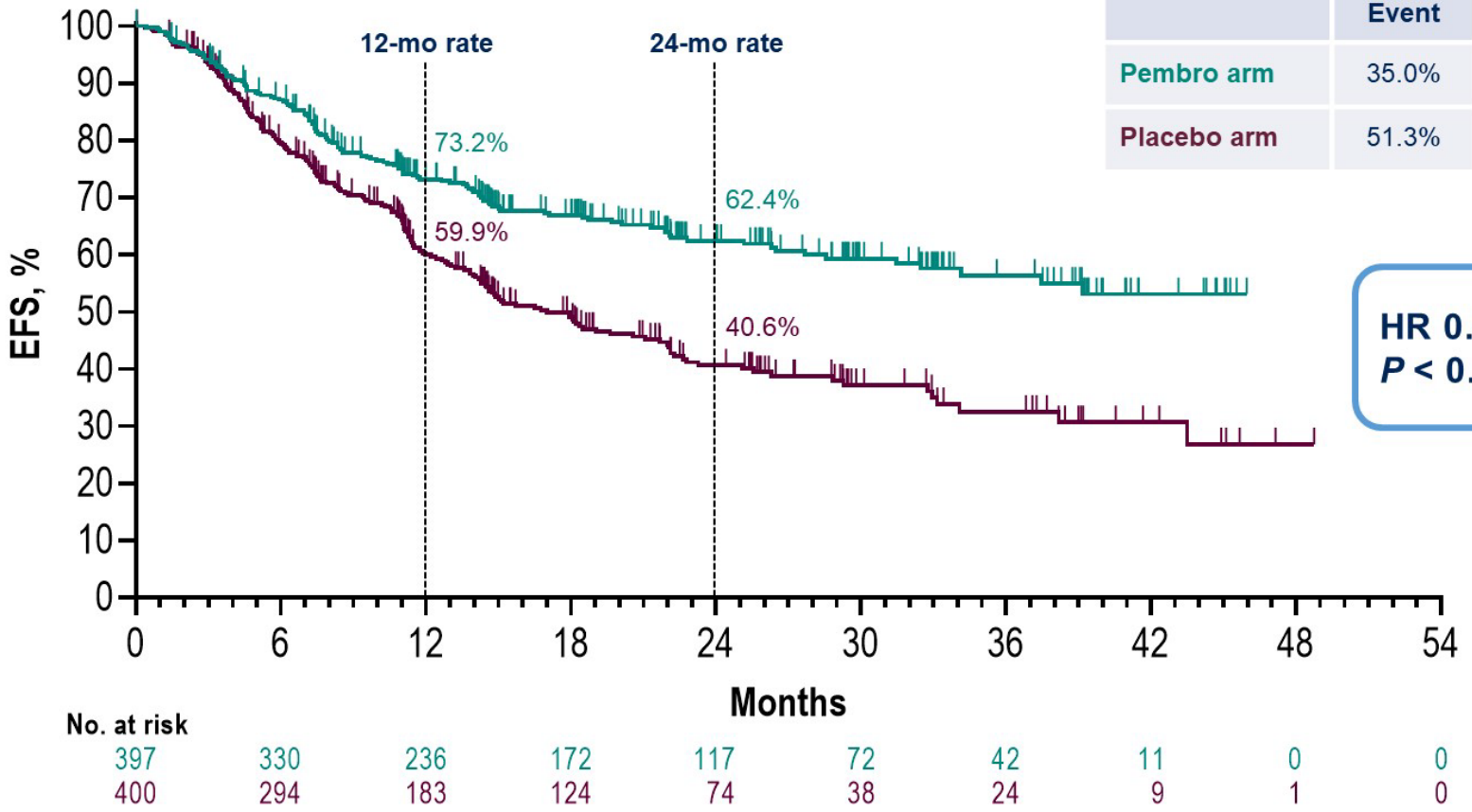
Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

KEYNOTE-671: NEOADJ. CHEMO +PEMBRO

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)

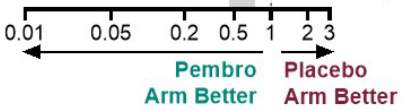
HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

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]).

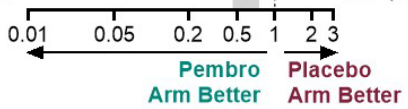
KEYNOTE-671: NEOADJ CHEMO + PEMBRO

Event-Free Survival in Subgroups

Subgroup	Events/participants		Hazard ratio (95% CI)
	Pembro Arm	Placebo Arm	
Overall	139/397	205/400	0.58 (0.46-0.72)
Age			
<65 y	74/221	113/214	0.53 (0.39-0.71)
≥65 y	65/176	92/186	0.64 (0.46-0.88)
Sex			
Female	31/118	55/116	0.44 (0.28-0.68)
Male	108/279	150/284	0.63 (0.49-0.80)
Race			
White	85/250	123/239	0.54 (0.41-0.72)
All others	46/134	70/145	0.62 (0.42-0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45-0.99)
Not east Asia	96/274	148/279	0.54 (0.41-0.69)
Smoking status			
Current	37/96	57/103	0.52 (0.34-0.78)
Former	84/247	128/250	0.57 (0.43-0.75)
Never	18/54	20/47	0.68 (0.36-1.30)
Histology			
Nonsquamous	73/226	107/227	0.58 (0.43-0.78)
Squamous	66/171	98/173	0.57 (0.41-0.77)



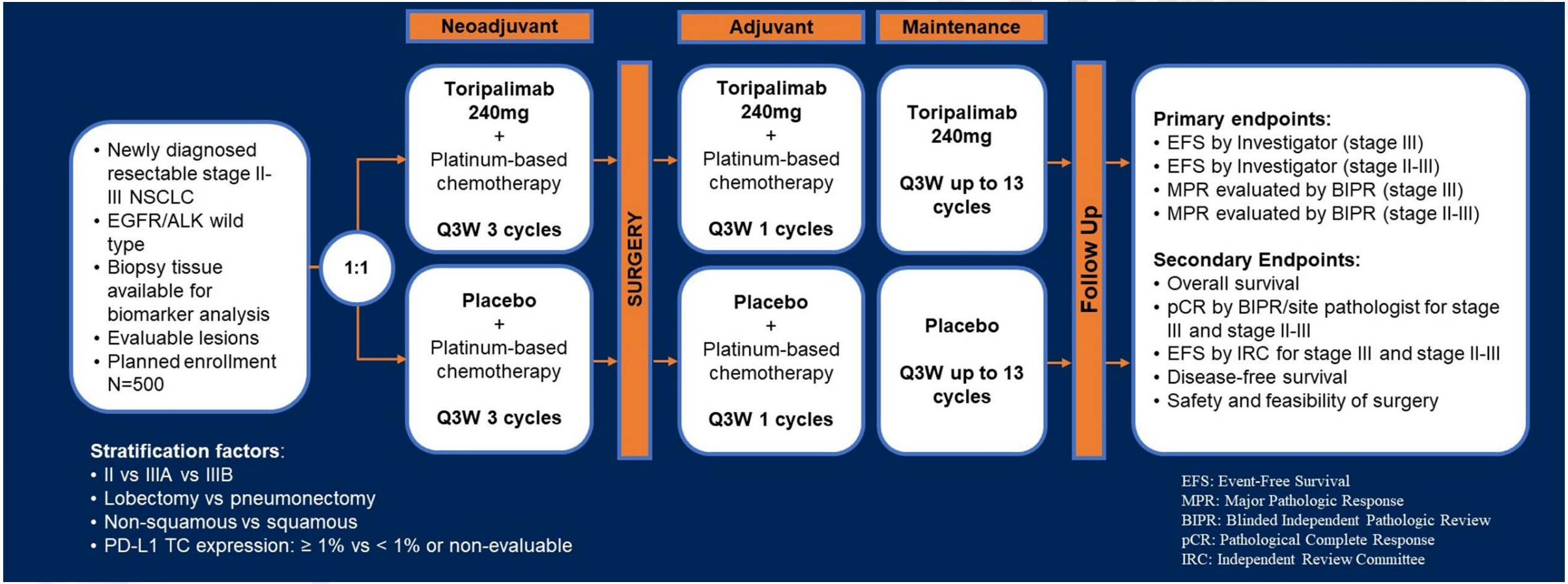
Subgroup	Events/participants		Hazard ratio (95% CI)
	Pembro Arm	Placebo Arm	
Overall	139/397	205/400	0.58 (0.46-0.72)
Pathologic stage			
II	34/118	48/121	0.65 (0.42-1.01)
IIIA	80/217	124/225	0.54 (0.41-0.72)
IIIB	25/62	33/54	0.52 (0.31-0.88)
pN status			
pN0	51/148	70/142	0.57 (0.40-0.82)
pN1	25/81	33/71	0.60 (0.36-1.01)
pN2	63/168	102/187	0.57 (0.42-0.78)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55-1.07)
1-49%	44/127	62/115	0.51 (0.34-0.75)
≥50%	32/132	63/134	0.42 (0.28-0.65)
***EGFR* mutation**			
No	31/111	64/127	0.48 (0.31-0.74)
Yes	1/14	10/19	0.09 (0.01-0.74)
Unknown	107/272	131/254	0.64 (0.49-0.83)
***ALK* translocation**			
No	29/104	76/133	0.41 (0.26-0.62)
Unknown	106/281	128/258	0.63 (0.49-0.82)



Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA1: July 29, 2022.

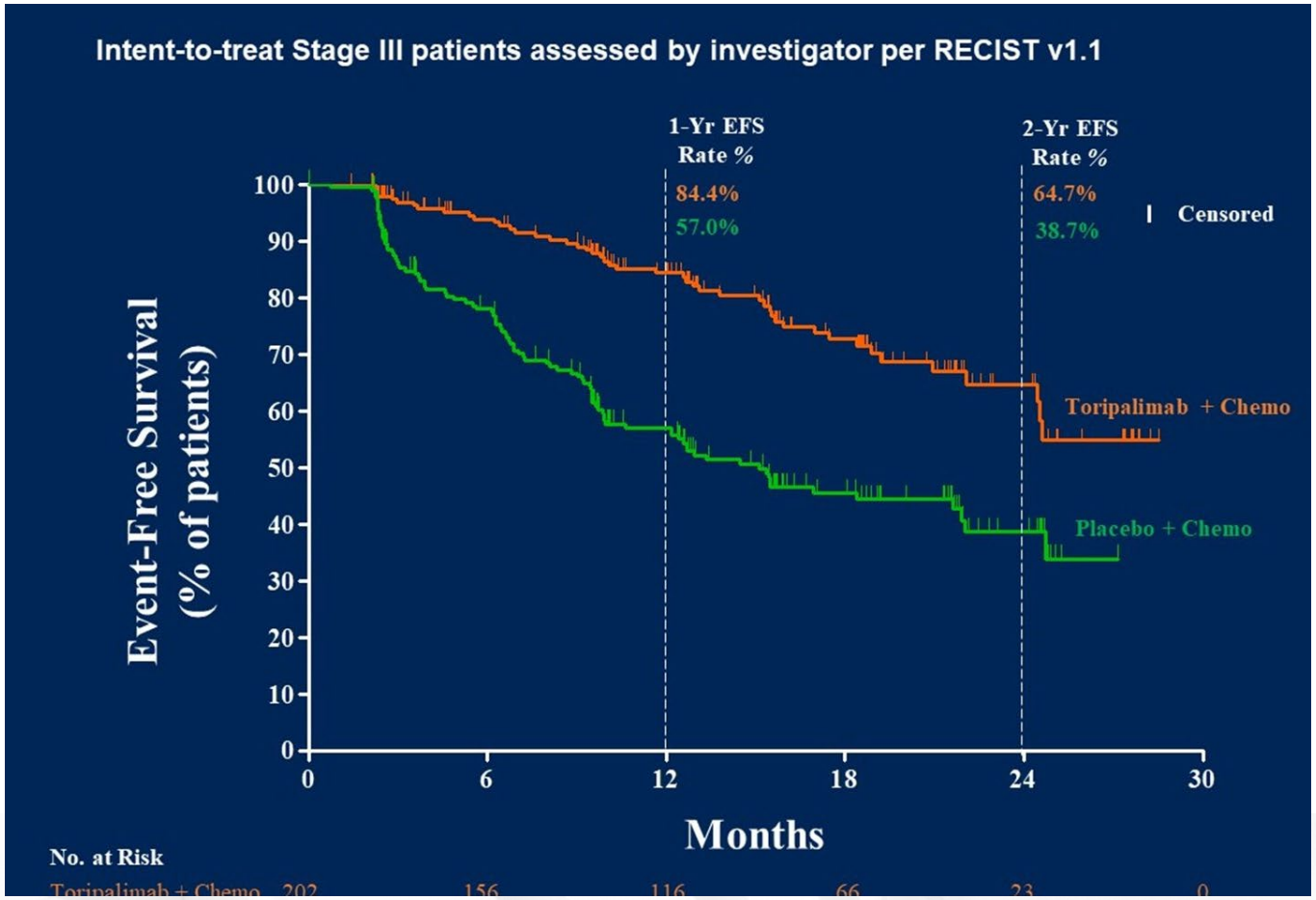
PRESENTED BY: Dr. Heather Wakelee

NEO-TORCH: peri-operative toripalimab + chemo



Shun et al, ASCO virtual Plenary, 2023

NEO-TORCH: peri-operative toripalimab + chemotherapy



	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	47/202	NE (24.4, NE)
Placebo + Chemo	97/202	15.1 (10.6, 21.9)

Median follow-up: 18.25 months

HR 0.40 (95%CI 0.277, 0.565)

two-sided P<0.0001

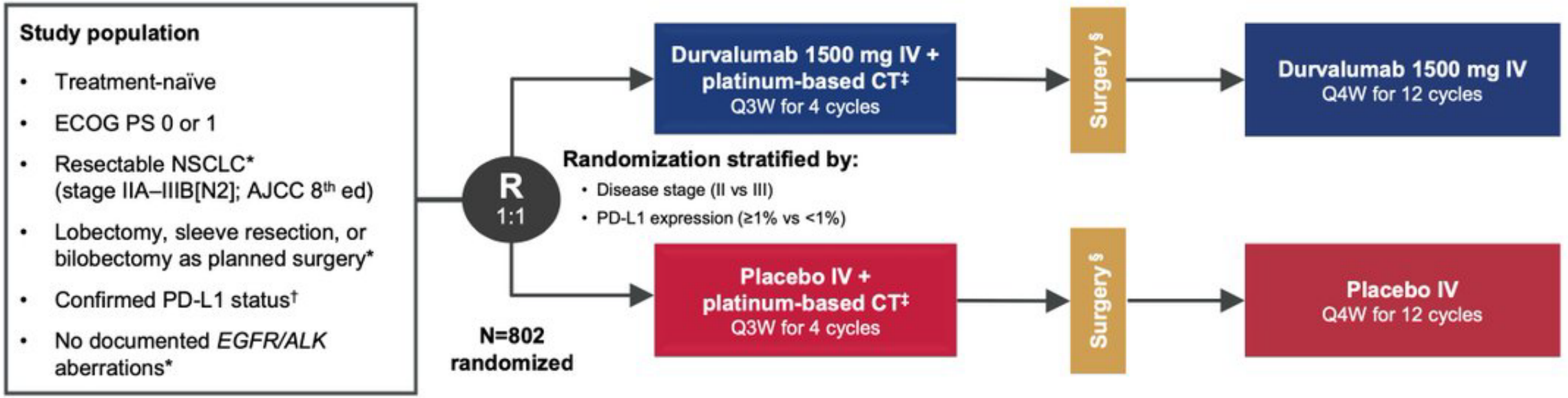
2-sided efficacy boundary: 0.01683

Does the number of cycles and timing of chemo-io matter?

3 chemo-IO pre-op, 1 post op

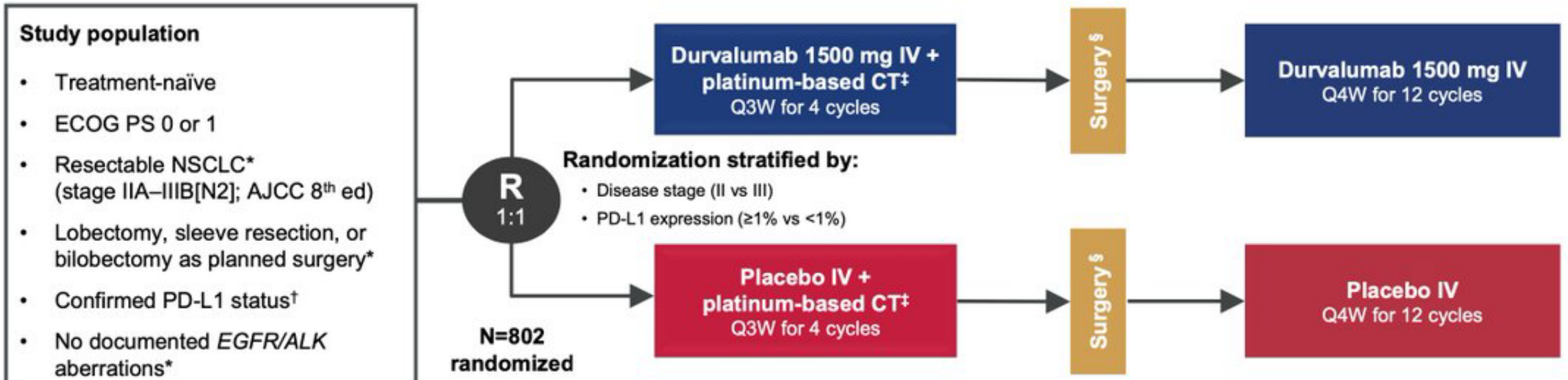
Shun et al, ASCO virtual Plenary, 2023

AEGEAN: peri-operative durvalumab + chemo



Haymach, AACR, 2023

AEGEAN: peri-operative durvalumab + chemo



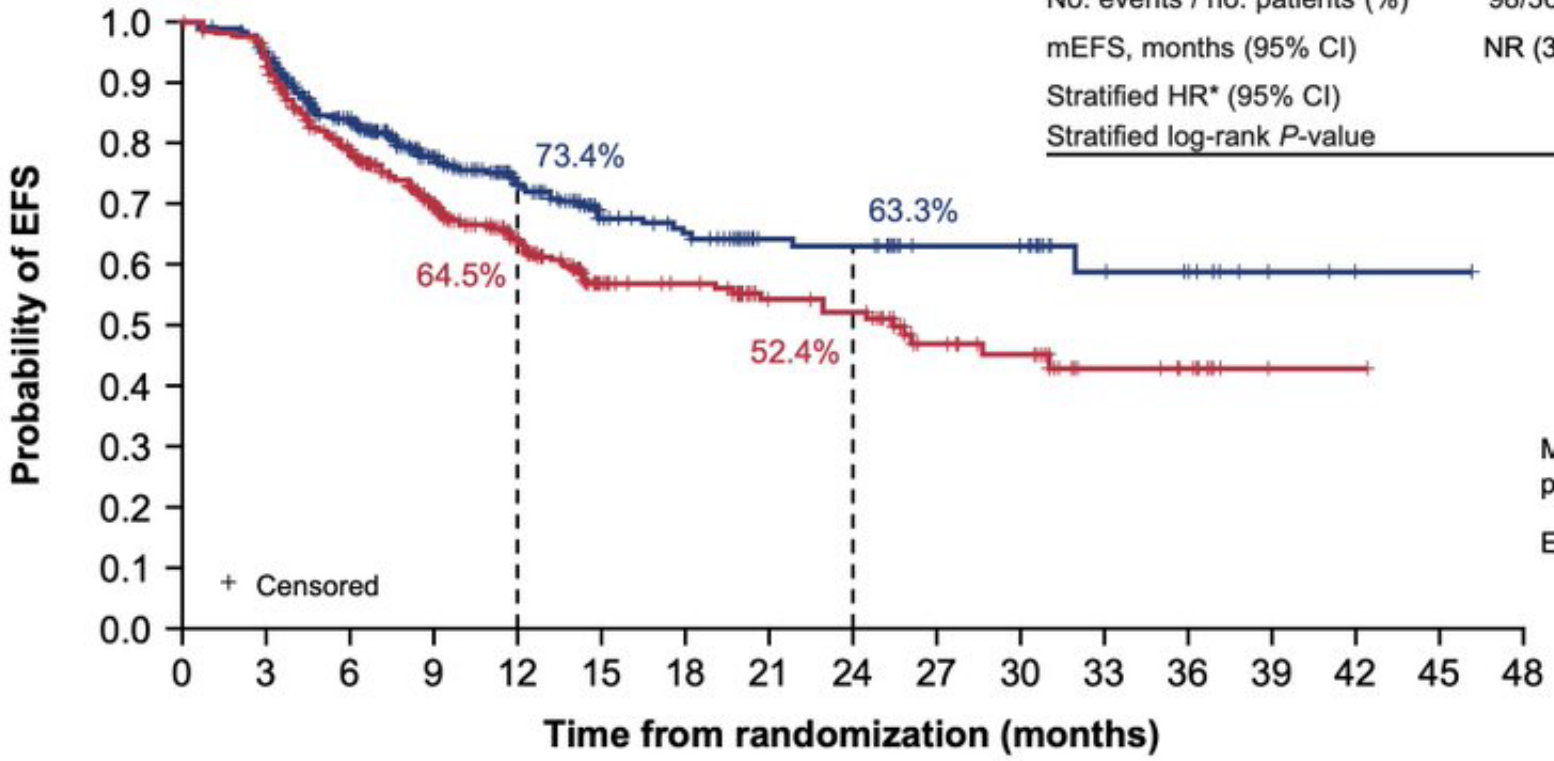
TNM classification†		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5

		Durva.	Placebo
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6

Haymach, AACR, 2023

AEGEAN: peri-operative durvalumab + chemo

	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)

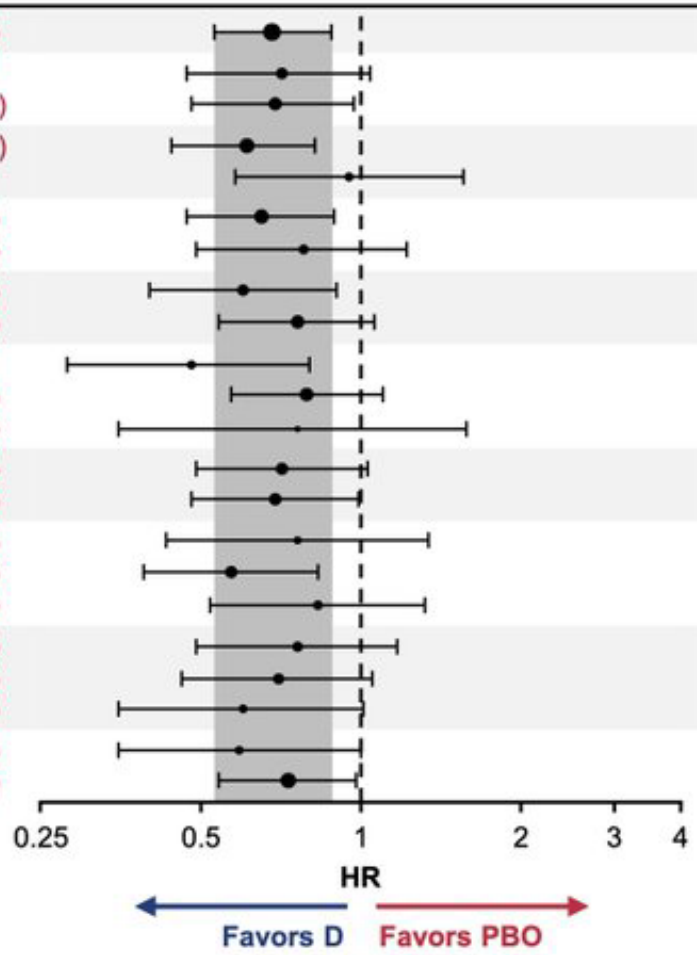
EFS maturity: 31.9%

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

Haymach, AACR, 2023

AEGEAN: peri-operative durvalumab + chemo

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)



DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

Haymach, AACR, 2023

Overall Survival Results Summary (Interim Analyses)

Immunotherapy Setting	Trial	Median f/u	HR (95% CI)	P value
Neoadjuvant + Adjuvant	KEYNOTE-671	25.2 mo	0.73 (0.54, 0.99)	0.02124
	Neotorch	18.2 mo	0.62 (0.381, 0.999)	0.0502
Neoadjuvant	CheckMate 816	41.4 mo	0.62 (0.36, 1.05)	0.0124
Adjuvant	IMpower010	45-46 mo	ITT Stage IB-IIIA: 0.995 (0.78, 1.28) Stage II-IIIA: 0.95 (0.74, 1.24) Stage II-IIIA, PD-L1 TPS ≥1%: 0.71 (0.49, 1.03)	0.9661 N/A N/A
	KEYNOTE-091	35.6 mo	0.87 (0.67, 1.15)	0.17

Wakelee H, et al, ASCO Annual Meeting, 2023; Lu S, et al, ASCO Plenary Series, April 2023; Forde P, et al, ELCC Annual Meeting, 2023; Felip E, et al, WCLC Annual Meeting, 2022; O'Brien M, et al, *Lancet Oncol*. 2022 Oct;23(10):1274-1286.

PRESENTED BY: Mark M. Awad, MD, PhD, Dana-Farber Cancer Institute, Boston, MA

Benefits of neoadjuvant immunotherapy approach

1. Improved overall survival, especially relevant for resectable N2 disease

2. Minimal surgical risks

3. Provides benefit regardless of PD-L1 status

Practice change may not be convenient, but in this case is necessary

Key Questions remain for perioperative treatment NSCLC:

1. Can we omit chemotherapy?
   - Patients want this
   - Currently no proven overall survival benefit of IO alone in peri-operative setting

2. Role of PD_L1
   - Neoadjuvant chemo-nivo: All PD-L1 included in CM816 approval
   - Adjuvant atezo: PD_L1> 1% approved

3. Can we “downstage” patients?
   - Currently need to determine surgical resectability up-front

4. What about common and less common driver mutations?
   - Some trials address EGFR and ALK, but we have so many other drivers