Neoadjuvant and Perioperative immunotherapy for NSCLC

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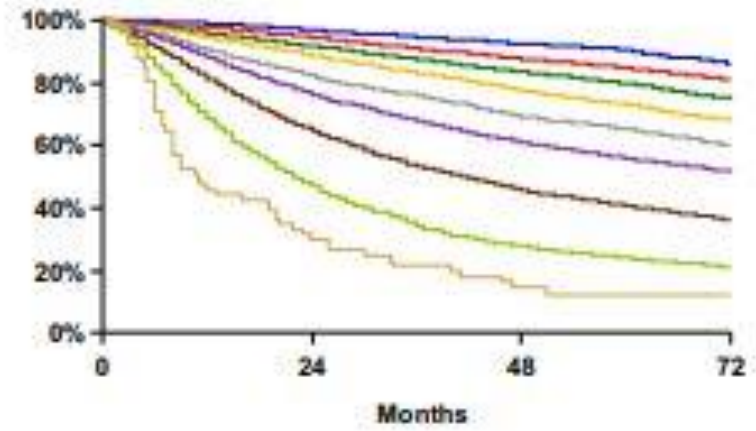
Operable Non-Small cell Lung Cancer : The Unmet Need



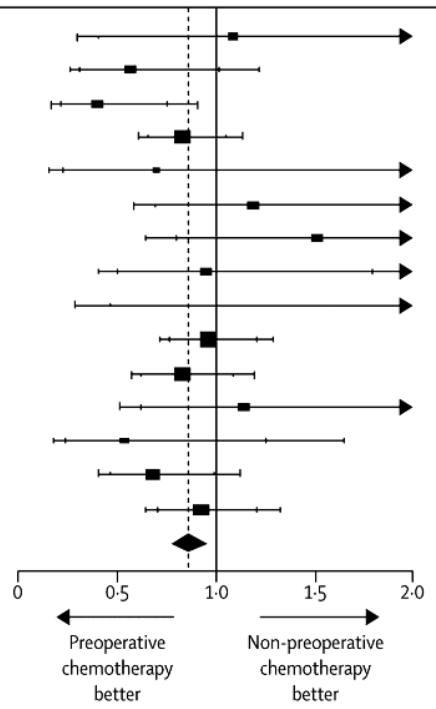
Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

SEER Program. Cancer Stat Facts: Lung and Bronchus Cancer. Accesed on 7th July 2021
Goldstraw et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51

Operable Non-Small cell Lung Cancer: *Prior to* the era of novel therapies

Analysis of 15 RCTs of preoperative chemotherapy in stage IB-IIIA NSCI

	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG S9900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**

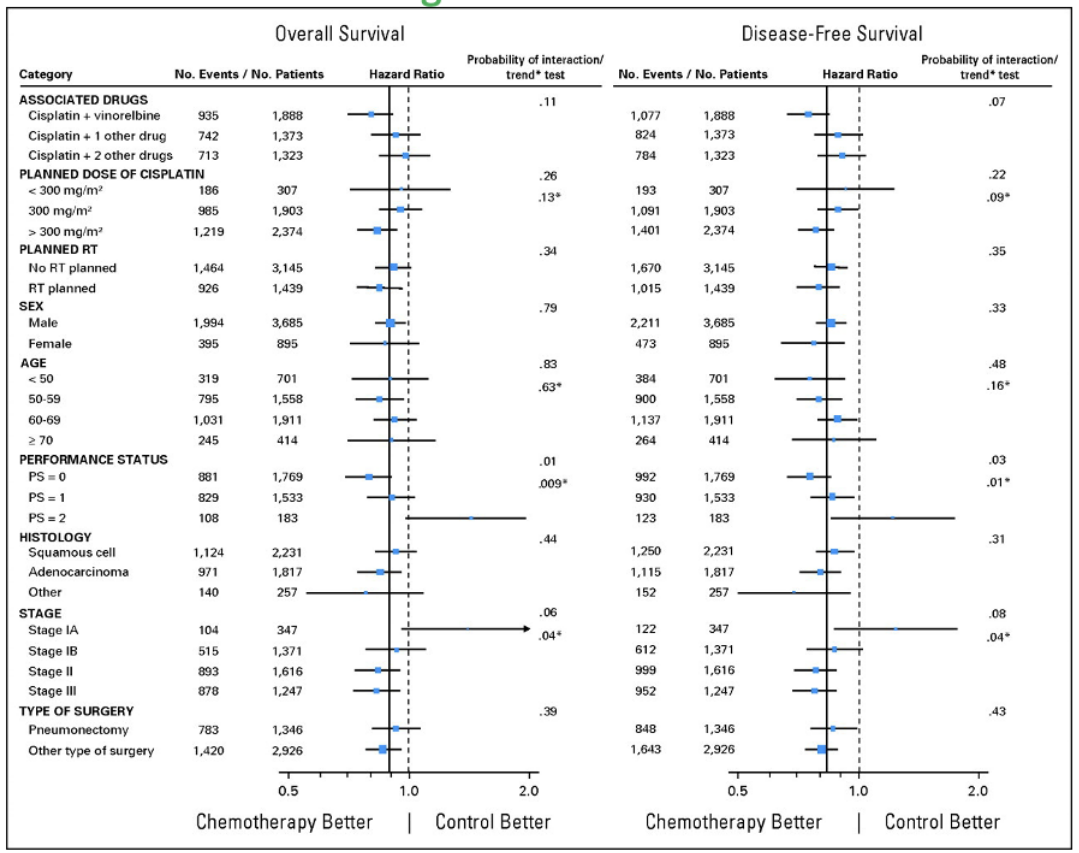


Overall HR
0·87 (0·78–0·96). p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

Neo adjuvant chemotherapy improves OS, RFS and time to distant m
ABSOLUTE SURVIVAL IMPROVEMENT OF ~ 5%

NSCLC Meta analysis Colaborative Group. The Lancet 2014.383(9928);P1561-1571

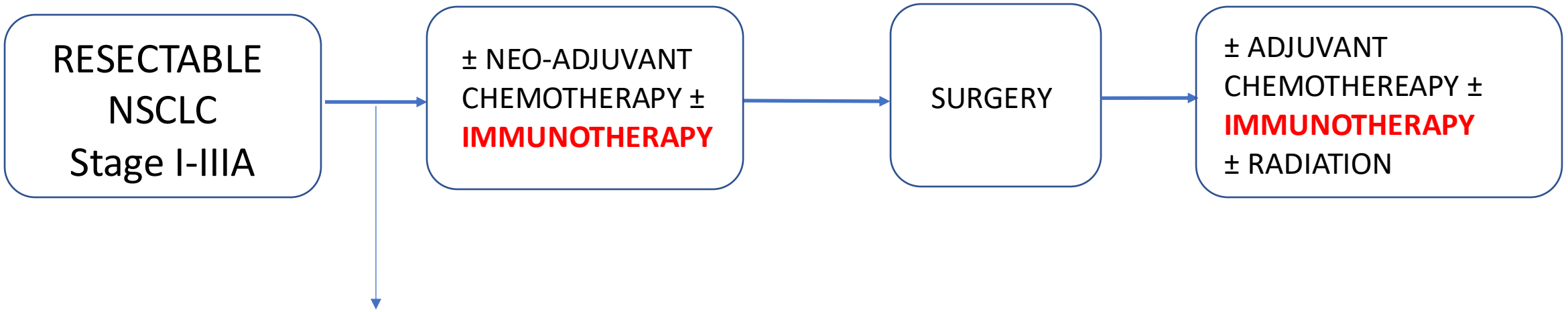
LACE Meta-Analysis of 5 RCTs of adjuvant chemotherapy in stage IB-IIIA NSCLC



Adjuvant chemotherapy improves OS and DFS
ABSOLUTE SURVIVAL IMPROVEMENT OF ~ 5% in 5 years

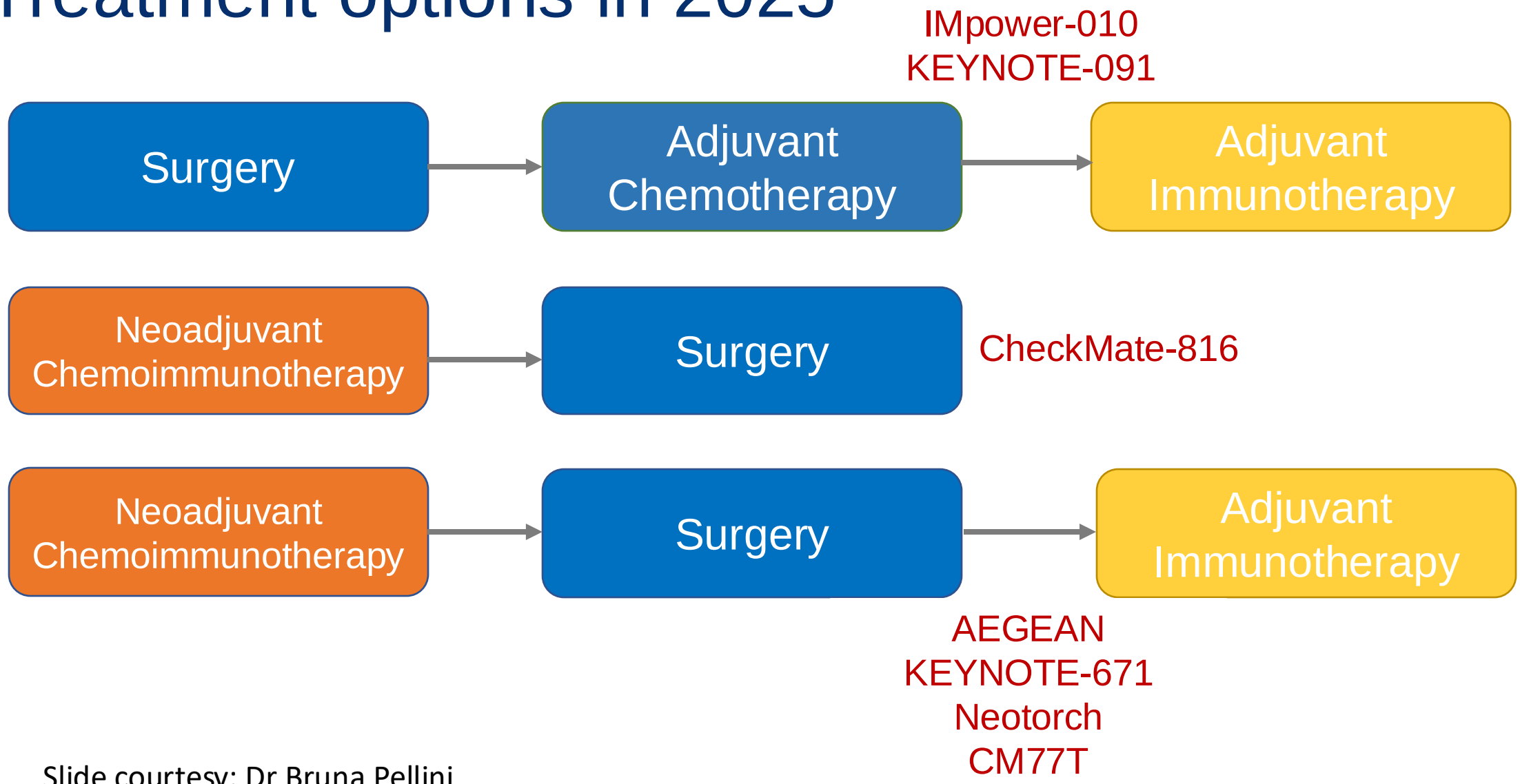
Pignon et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20; 26(21):3552-9.

Operable Non-Small cell Lung Cancer IN 2025
Change in Treatment paradigm



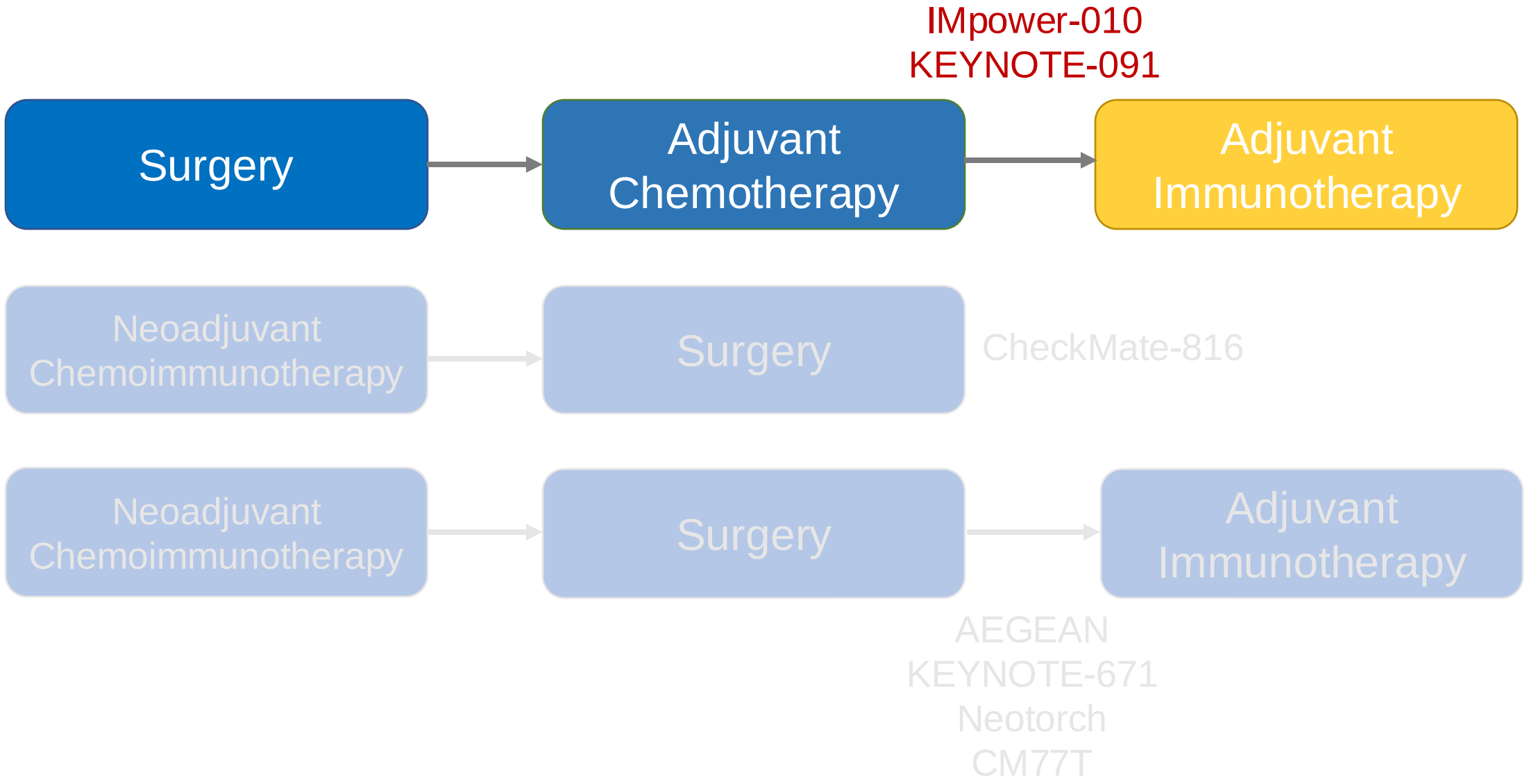
Multidisciplinary Tumor board discussion
Tumor testing for mutations – EGFR/ALK and PD-L1

Immunotherapy for Resectable NSCLC Treatment options in 2025



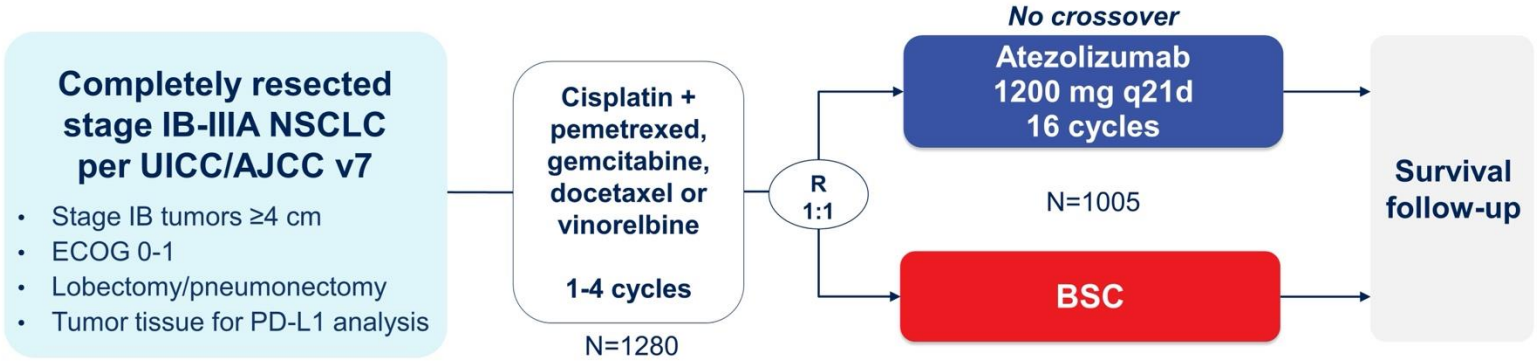
Slide courtesy: Dr Bruna Pellini

Treatment options:



Adjuvant IO/CT: IMPOWER 010

IMpower010: study design



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

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

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

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

Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

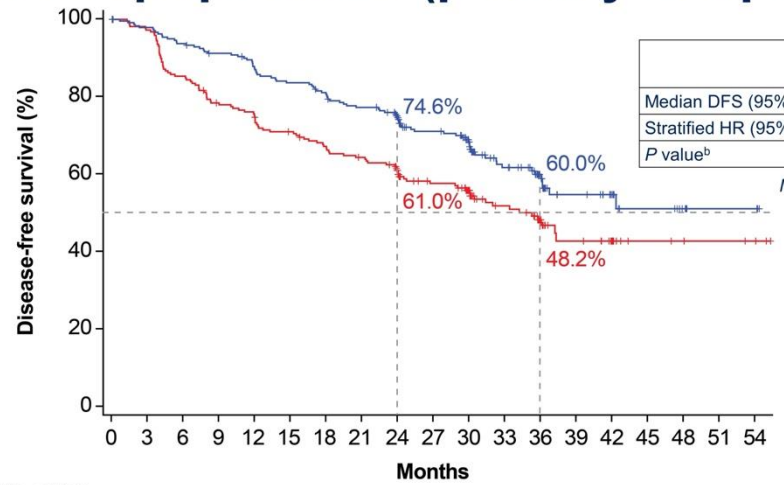
IMpower 010: baseline characteristics

Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIA)		All randomized (stage II-IIIA)		ITT (stage IB-IIIA)	
		Atezo (n=248)	BSC (n=228)	Atezo (n=442)	BSC (n=440)	Atezo (n=507)	BSC (n=498)
Median (range) age,	**62 (26-84)**	61 (34–82)	62 (26–84)	62 (33–82)	62 (26–84)	62 (33–83)	62 (26–84)
Age ≥65 y, n (%)	**382 (38.0)**	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	**672 (66.9)**	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	**738 (73.4)**	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75.5)
Asian	**242 (24.1)**	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	**25 (2.5)**	8 (3.2)	6 (2.6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
Histology, non-SQ	**659 (65.6)**	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	**123 (12.2)**	–	–	–	–	65 (12.8)	58 (11.6)
IIA	**295 (29.4)**	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	**174 (17.3)**	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	**413 (41.1)**	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Tobacco use, n (%)							
Never	**222 (22.1)**	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108 (21.7)
Current/previous	**783 (77.9)**	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC≥1%, n (%)[a]	**535 (54.6)**	248 (100)	228 (100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)

Dr. Heather A. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; https://bit.ly/33t6JJ; Felip Lancet 2021

Adjuvant Atezolizumab extends DFS

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



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

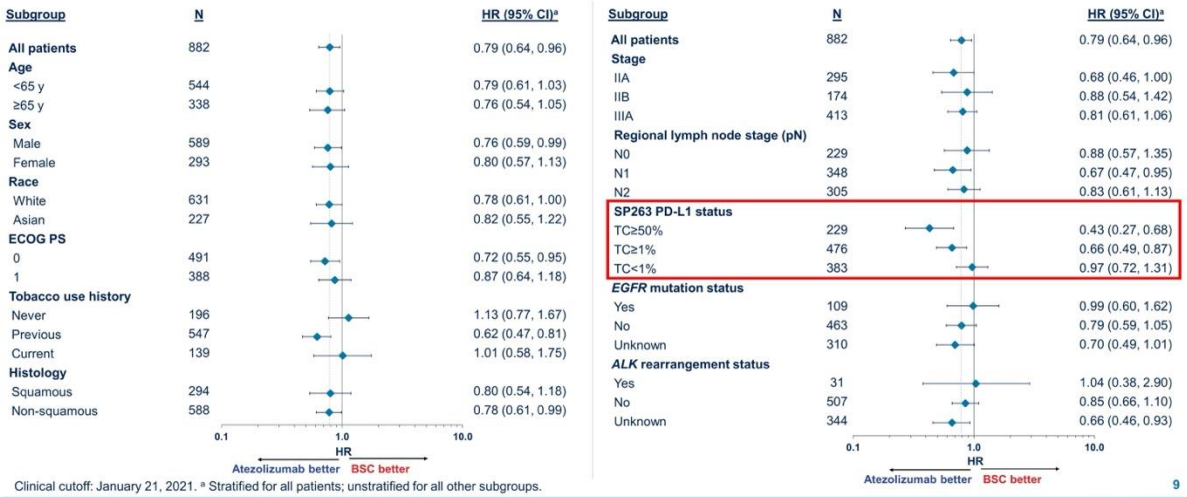
Median follow-up: 32.8 mo (range, 0.1-57.5)

No. at risk

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

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

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population

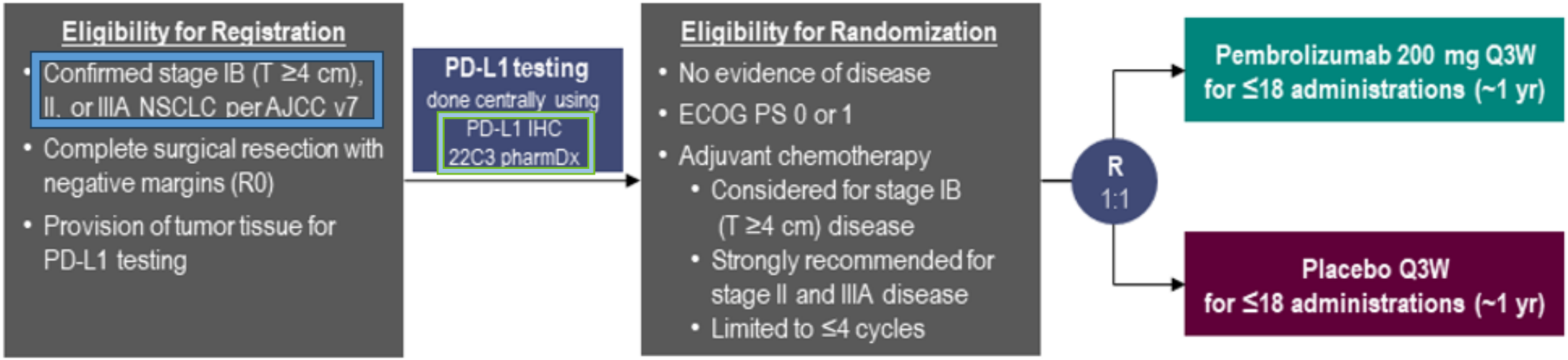


Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

2021 ASCO ANNUAL MEETING

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial



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

ESMO VIRTUAL PLENARY

ClinicalTrials.gov number, NCT02504372.

Paz-Ares KEYNOTE-091 ESMO Plenary 2022

Baseline Characteristics, Overall Population

	Pembrolizumab (N = 590)	Placebo (N = 587)
Age, median (range)	65 y (31-87)	65 y (37-85)
Male	401 (68.0%)	403 (68.7%)
Geographic region		
Asia	106 (18.0%)	105 (17.9%)
Eastern Europe	116 (19.7%)	113 (19.3%)
Western Europe	303 (51.4%)	301 (51.3%)
Rest of world	65 (11.0%)	68 (11.6%)
ECOG PS 1	210 (35.6%)	244 (41.6%)
Current/former smoker	503 (85.3%)	521 (88.8%)
***EGFR* mutation**[a]	39 (6.6%)	34 (5.8%)
***ALK* translocation**[b]	7 (1.2%)	7 (1.2%)
Nonsquamous histology	398 (67.5%)	363 (61.8%)
Pathologic stage[c]		
IB	84 (14.2%)	85 (14.5%)
II	329 (55.8%)	338 (57.6%)
IIIA	177 (30.0%)	162 (27.6%)
Received adjuvant chemotherapy		
Yes	506 (85.8%)	504 (85.9%)
No	84 (14.2%)	83 (14.1%)
PD-L1 TPS		
<1%	233 (39.5%)	232 (39.5%)
1-49%	189 (32.0%)	190 (32.4%)
≥50%	168 (28.5%)	165 (28.1%)

[a] *EGFR* status unknown for 333 (56.4%) in pembro arm and 337 (57.4%) in placebo arm.
[b] *ALK* status unknown for 357 (60.5%) in pembro arm and 390 (66.4%) in placebo arm.
[c] 2 (0.3%) participants in the placebo group had stage IV disease.

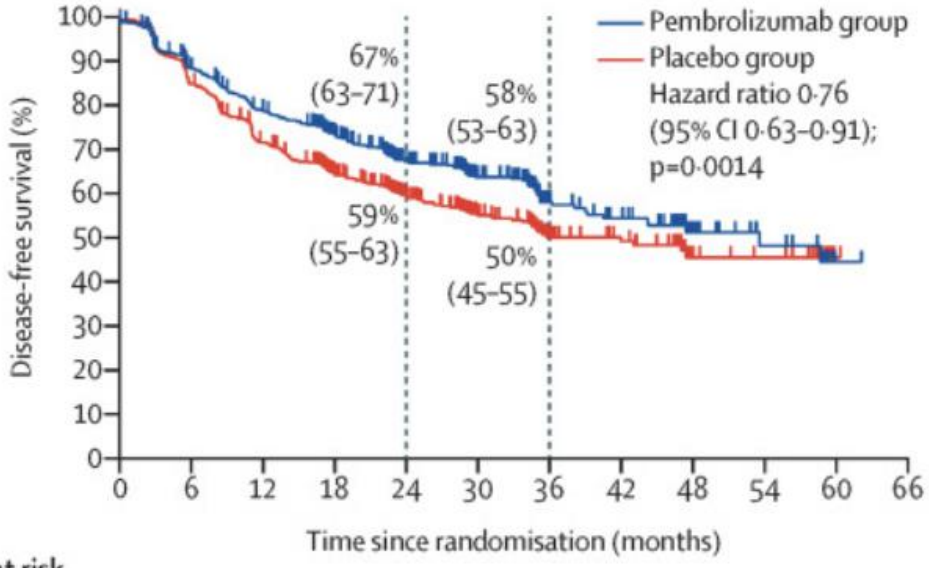
ESMO VIRTUAL PLENARY

Data cutoff date: September 20, 2021

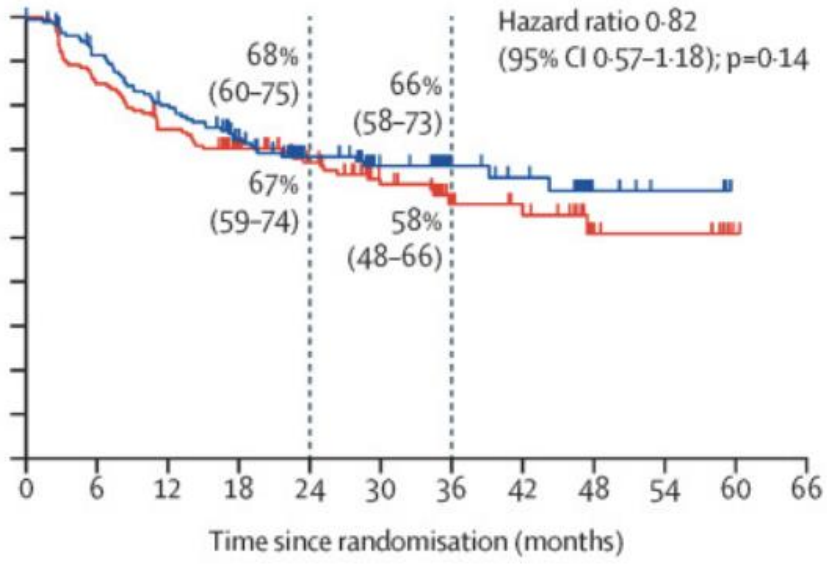
Paz-Ares KEYNOTE-091 ESMO Plenary 2022

PEARLS: Adjuvant Pembrolizumab vs placebo

DFS : All comer PD-L1 22C3.



DFS: PD-L1>/=50%



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)

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

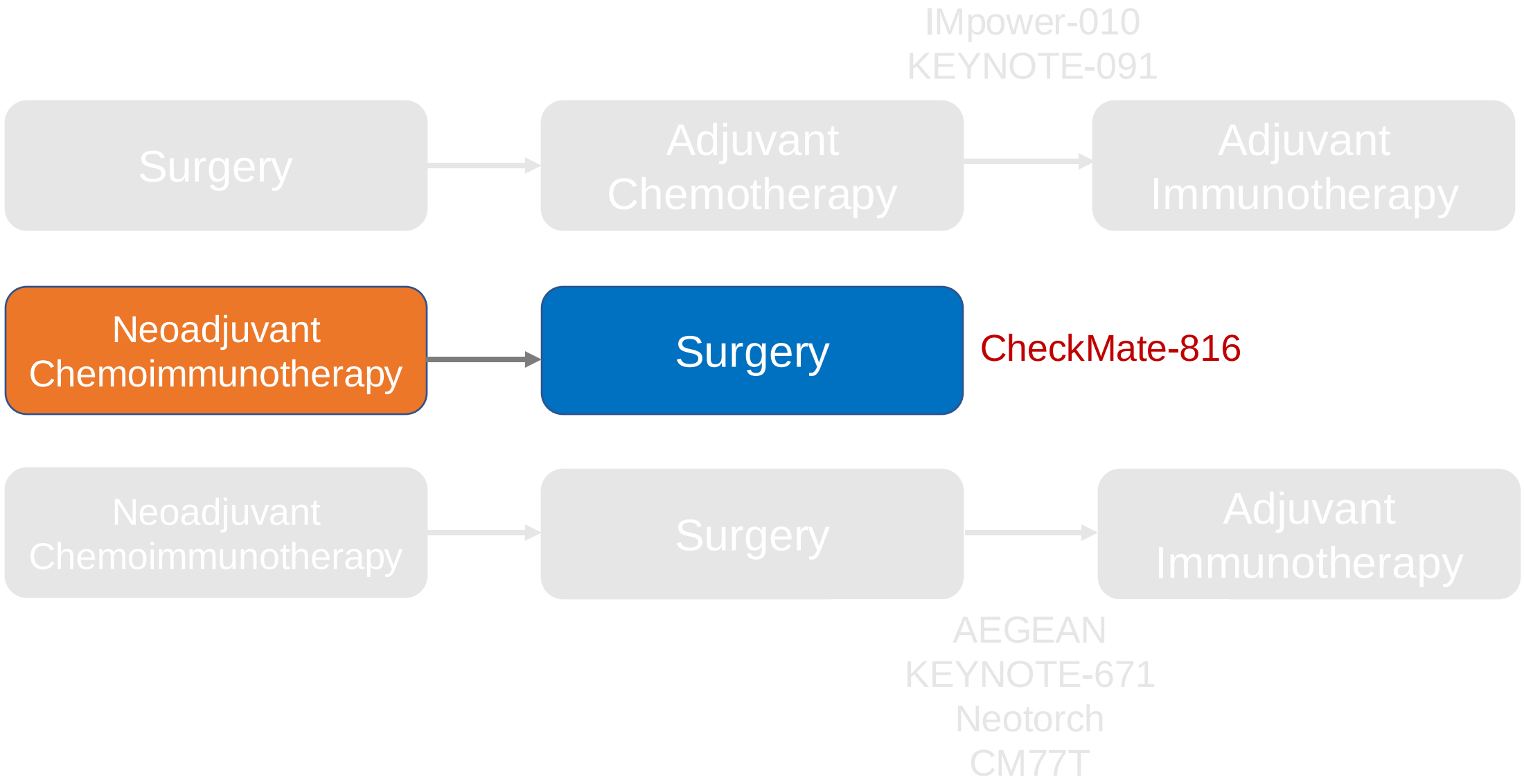
DFS in Key Subgroups, Overall Population

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)

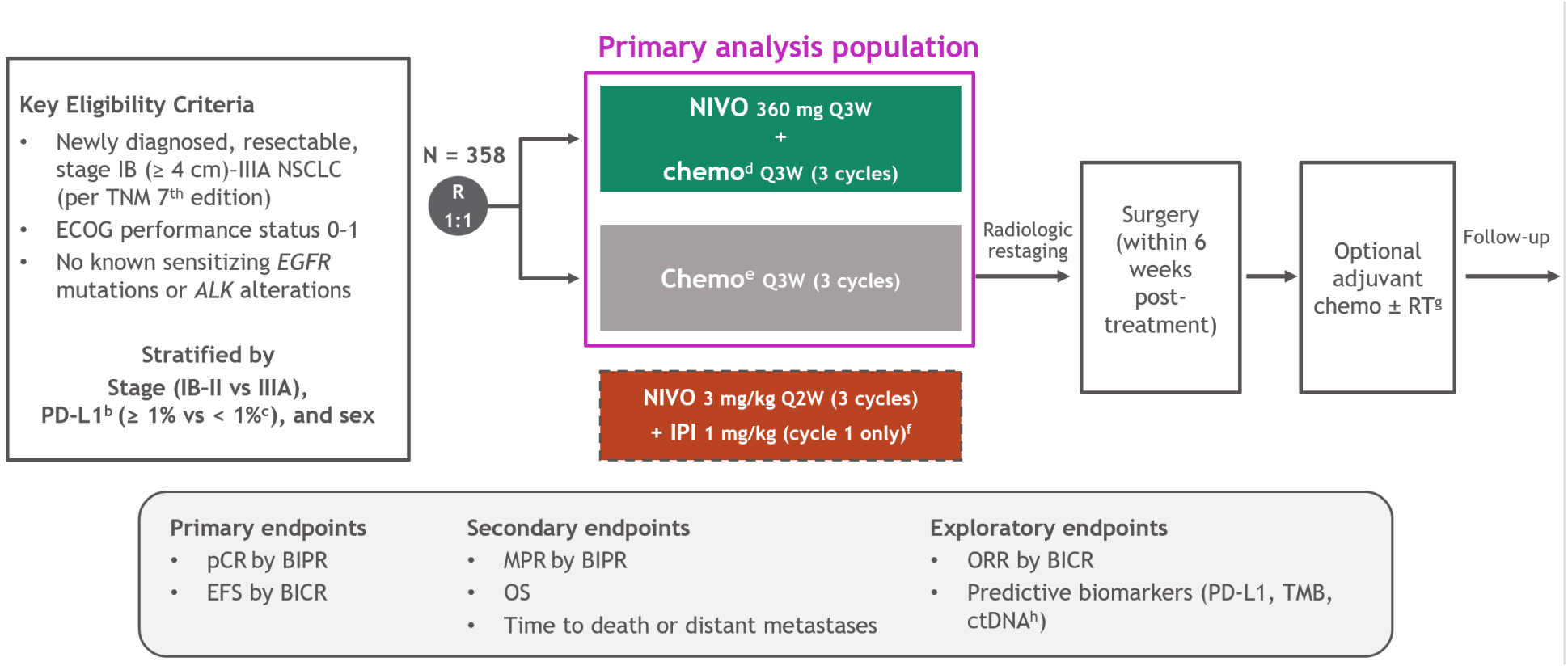
Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Pathologic stage		
IB	46/169	0.76 (0.43-1.37)
II	246/667	0.70 (0.55-0.91)
IIIA	178/339	0.92 (0.69-1.24)
Received adjuvant chemotherapy		
No	64/167	1.25 (0.76-2.05)
Yes	408/1010	0.73 (0.60-0.89)
Histology		
Nonsquamous	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

Treatment options:



CheckMate 816: Study design



Forde et al. Presented at AARC 2021

CheckMate 816: Baseline Characteristics

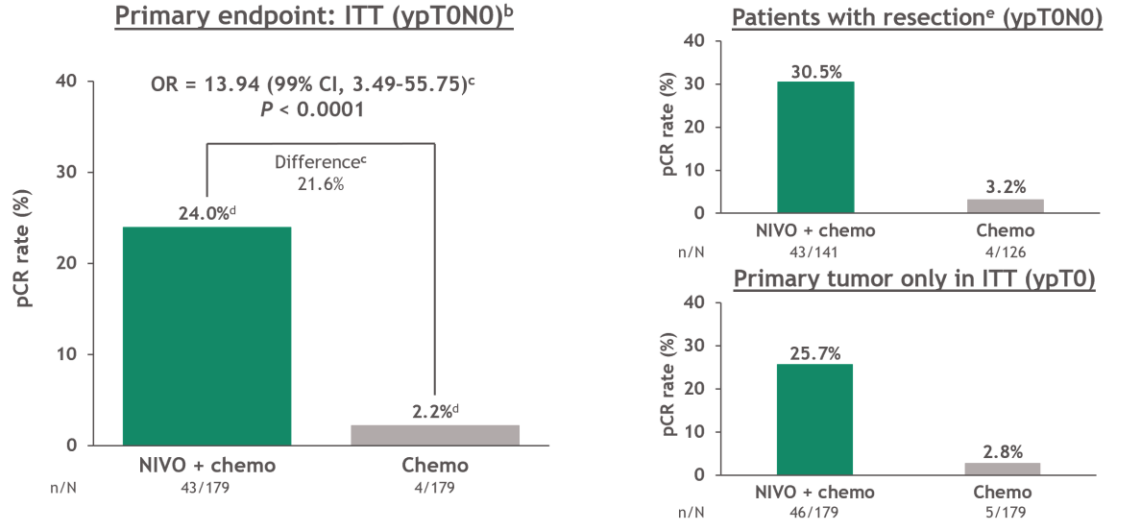
	NIVO + Chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41–82)	65 (34–84)
Female, %	28	29
Region, %*		
North America	23	28
Europe	23	14
Asia	48	51
Stage, %†		
IB–II‡	36	35
IIIA	63	64
Histology, %		
Squamous	49	53
Nonsquamous	51	47
Smoking status, %§		
Current / former	89	88
Never	11	11

	NIVO + Chemo (n = 179)	Chemo (n = 179)
Tumor PD-L1 expression, %¶		
Not evaluable	7	7
<1%	44	43
≥1%	50	50
1%–49%	28	26
≥50%	21	24
TMB, %¶		
Not evaluable / not reported//	51	50
<12.3 mut/Mb	27	30
≥12.3 mut/Mb	22	21

*Rest of the world: 7% of patients in each of the NIVO + chemo and chemo arms. †Disease stage by CRF, with TNM 7th edition used for classification; 1 patient in each of the NIVO + chemo and chemo arms had stage IV disease. ‡Stage IB, IIA, IIB disease: 6%, 17%, and 14% of patients in the NIVO + chemo arm, and 4%, 18%, and 13% in the chemo arm, respectively. §Smoking status unknown: 1 patient in chemo arm. ¶Percentages are based on ITT. //TMB was not analyzed for patients in China, and these patients are included in the "not reported" category.
Abbreviations: ITT, intention to treat; NICO, nivolumab; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.
Forde PM, et al. Abstract CT003. Presented at: 2021 AACR; April 10–15, 2021. Graphic courtesy of Patrick Forde, MBBCh.

Slide courtesy of Forde P. TTLC 2022

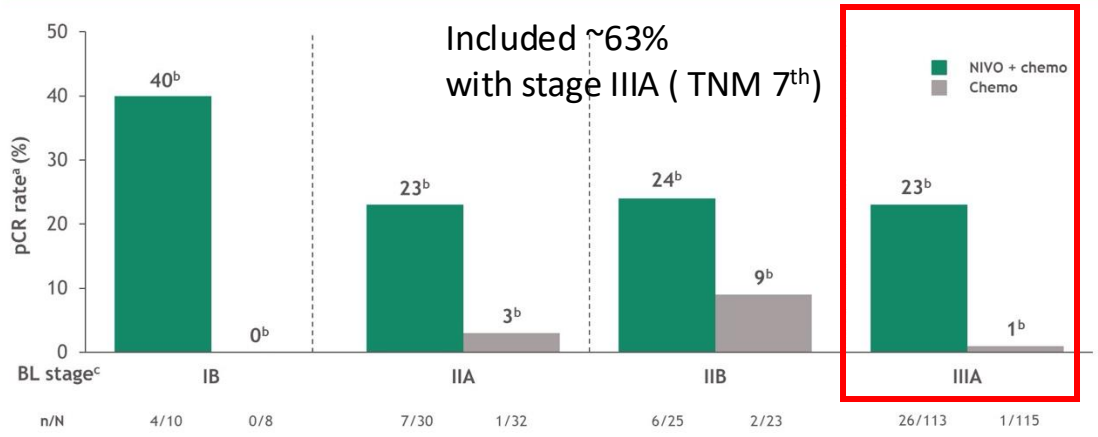
Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo



pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

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

pCR by baseline stage of disease



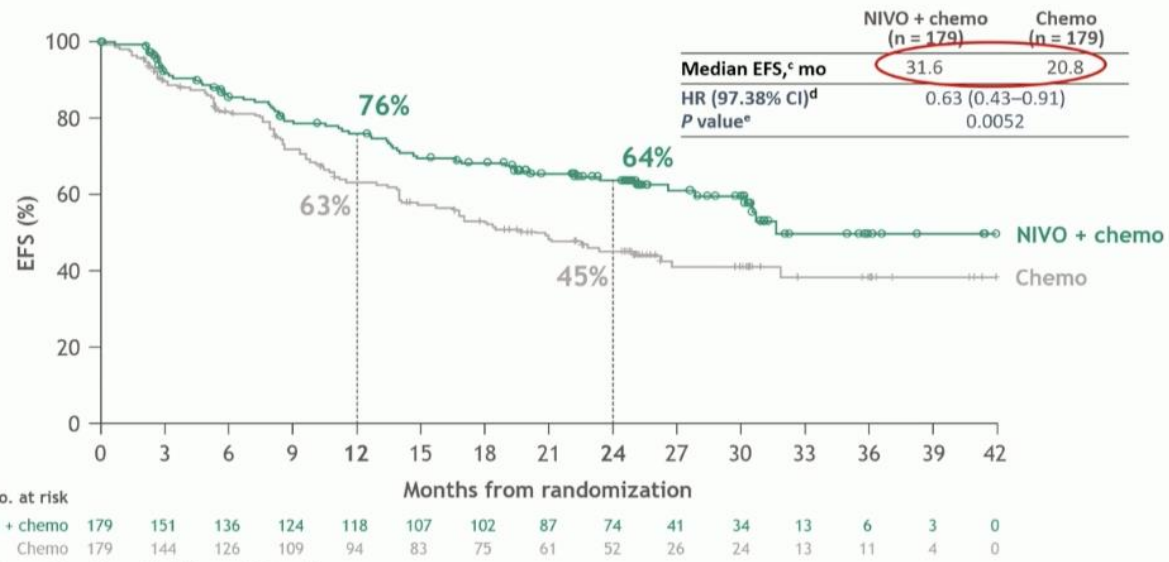
Included ~63%
with stage IIIA (TNM 7th)

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

[a]Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR; [b]95% CI: NIVO + chemo, chemo (stage): 12.2-73.8, 0.0-36.9 (IB); 9.9-42.3, 0.1-16.2 (IIA); 9.4-45.1, 1.1-28.0 (IIB); 15.6-31.9, 0.0-4.7 (IIIA); [c]Baseline stage of disease by CRF, TNM 7th edition used for classification; [d]pCR rate in patients with radiographic down-staging: 31% with NIVO + chemo vs 7% with chemo; pCR rate in patients without radiographic down-staging: 22% with NIVO + chemo vs 1% with chemo.

10

Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo

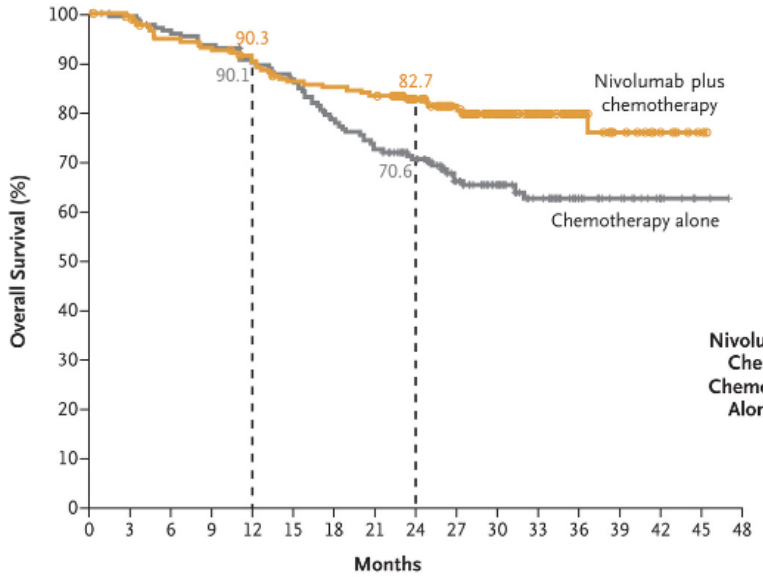


Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2–NR (NIVO + chemo) and 14.0–26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

5

OS

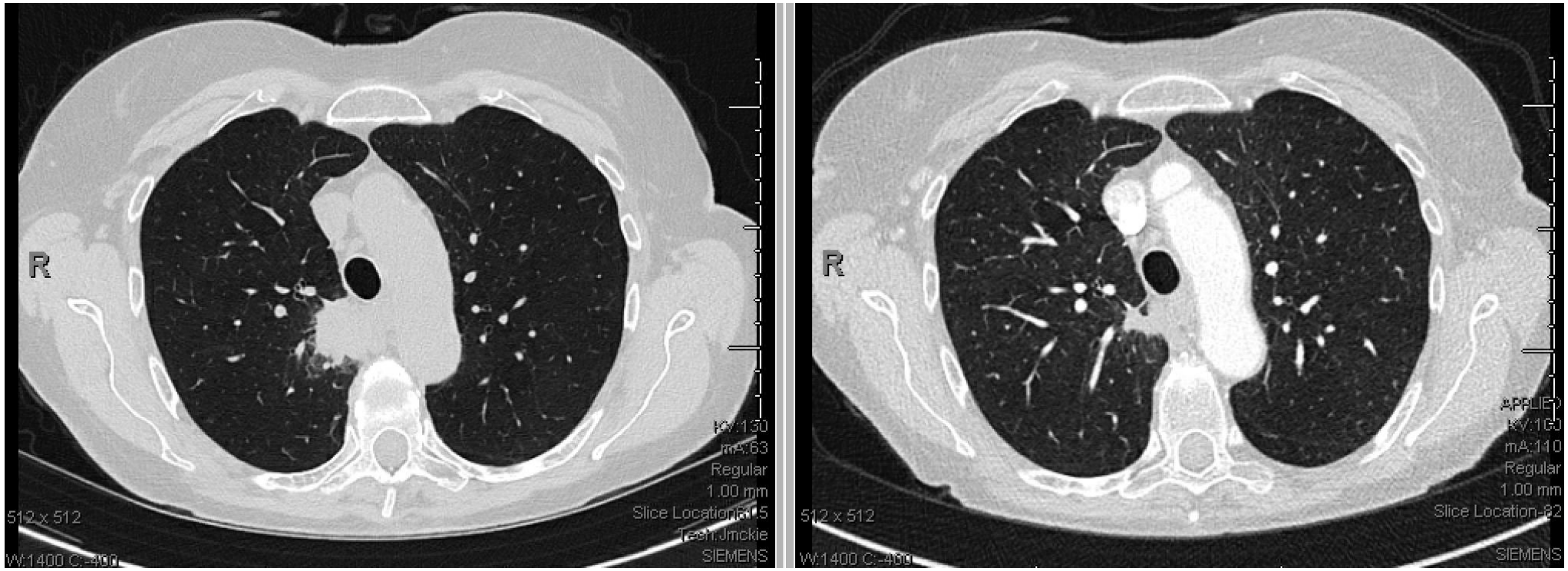


	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

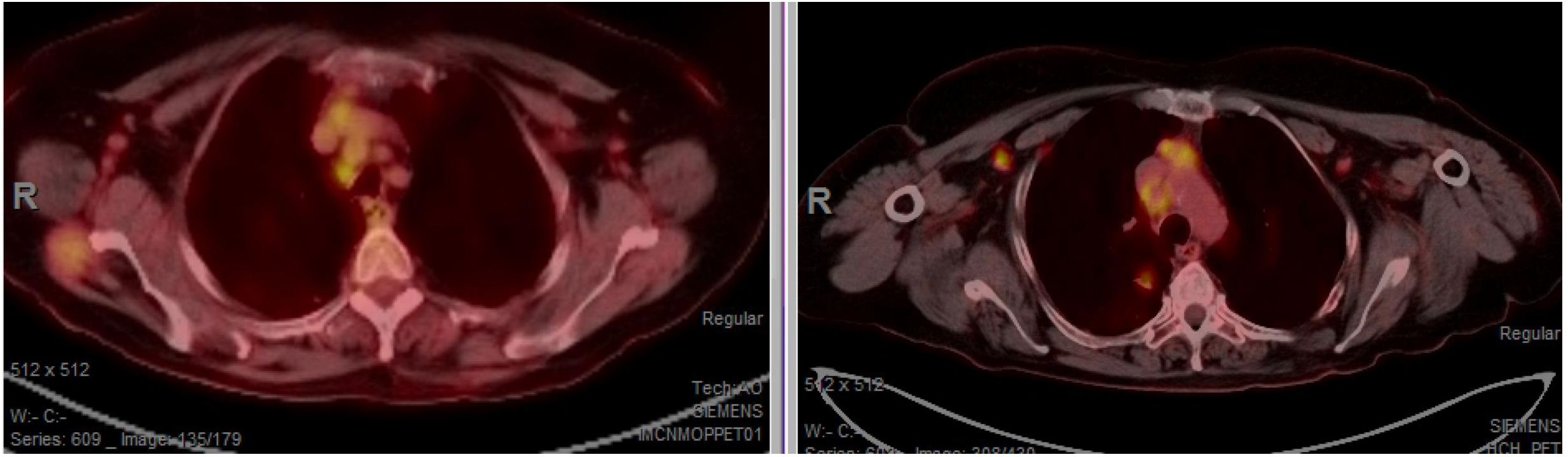
Forde et al. Presented at AACR 2021, N Engl J Med. 2022

CM 816 regimen: The real world success



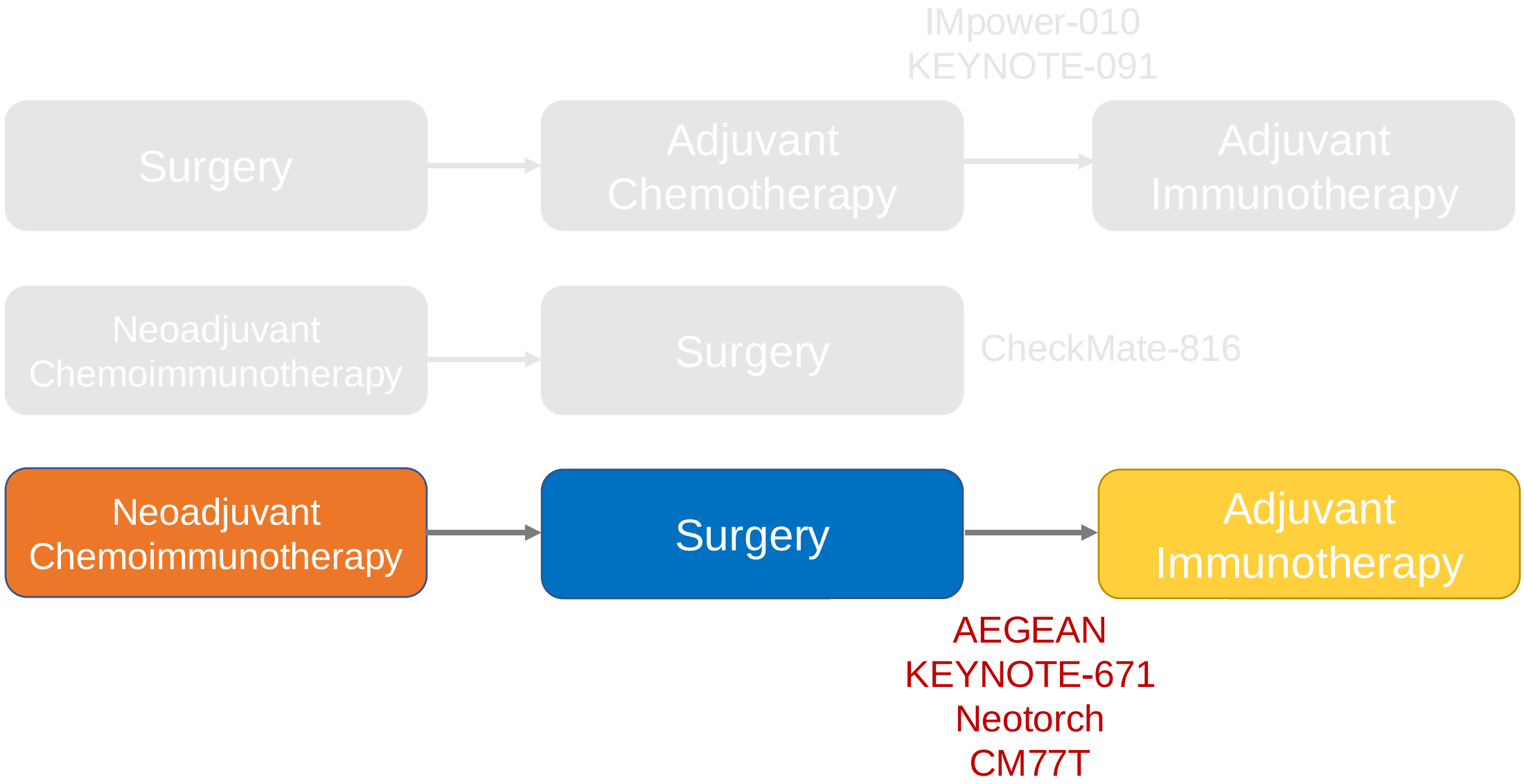
81 y/o female with stage IIIA single station N2 positive NSCLC s/p 3 cycles of NA chemotherapy plus immunotherapy

CM 816 regimen: The real-world failures

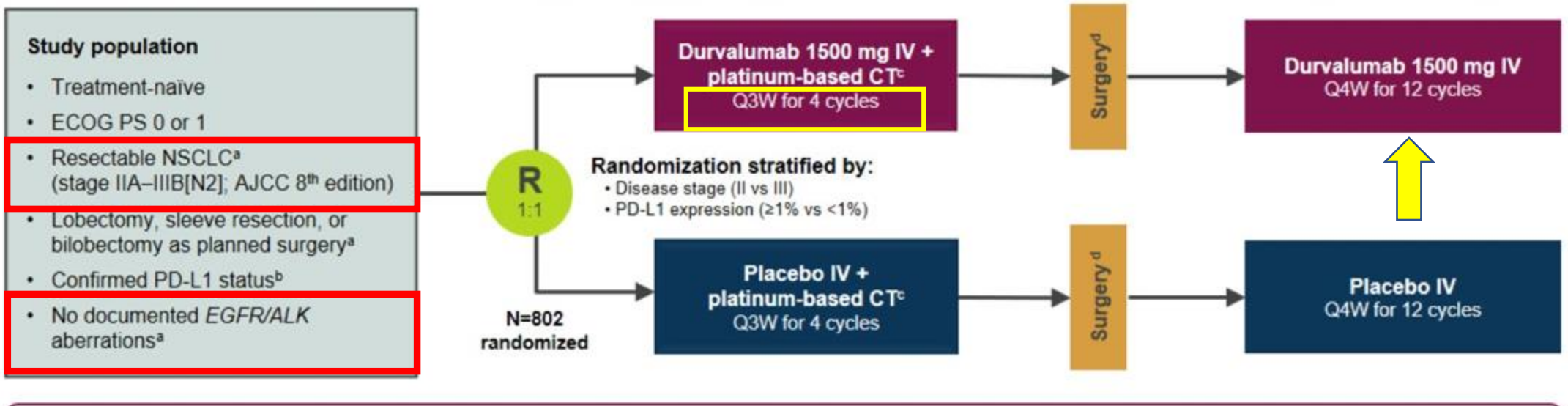


64 y/o female with stage IIIA single station N2 positive NSCLC s/p 3 cycles of NA chemotherapy plus immunotherapy

Treatment options:



AEGEAN: Study design



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented EGFR/ALK aberrations[e]

Primary:
- pCR by central lab (per IASLC 2020)
- EFS using BICR (per RECIST v1.1)

Key secondary:
- MPR by central lab (per IASLC 2020)
- DFS using BICR (per RECIST v1.1)
- OS

Heymach JV.2023 AACR; *Cancer Res* 15 April 2023; 83 (8_Supplement): CT005

AEGEAN: Baseline characteristics

- Baseline characteristics were largely balanced between the study arms
- The planned neoadjuvant CT doublet regimen was carboplatin-based for >70% of patients

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

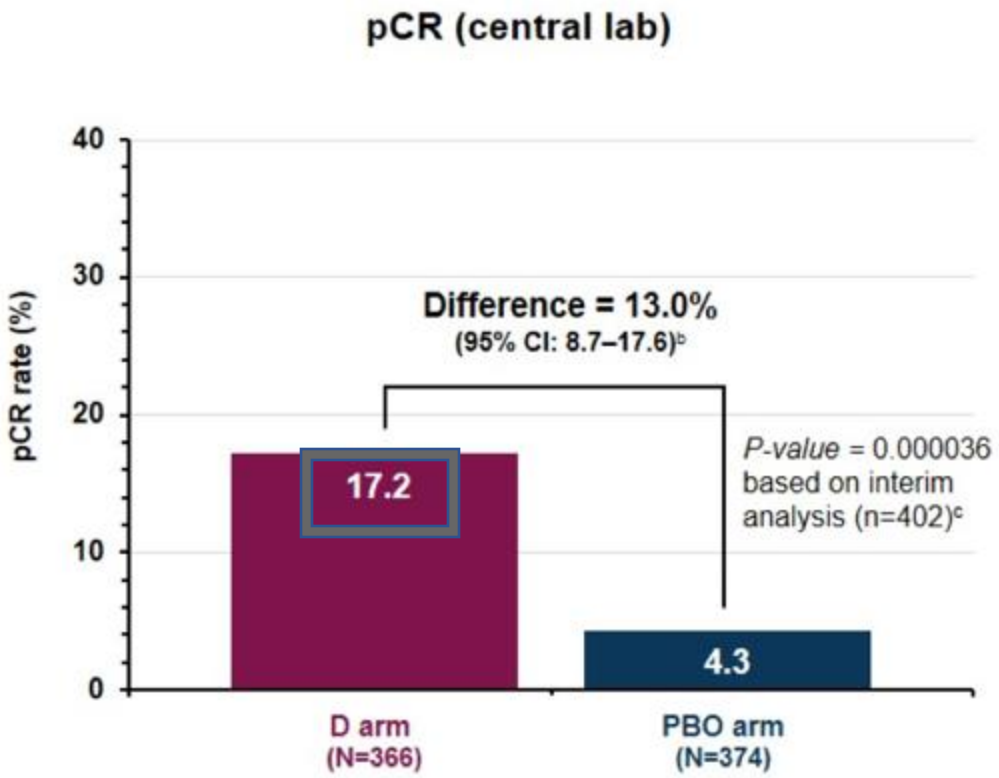
Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race‡, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
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
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

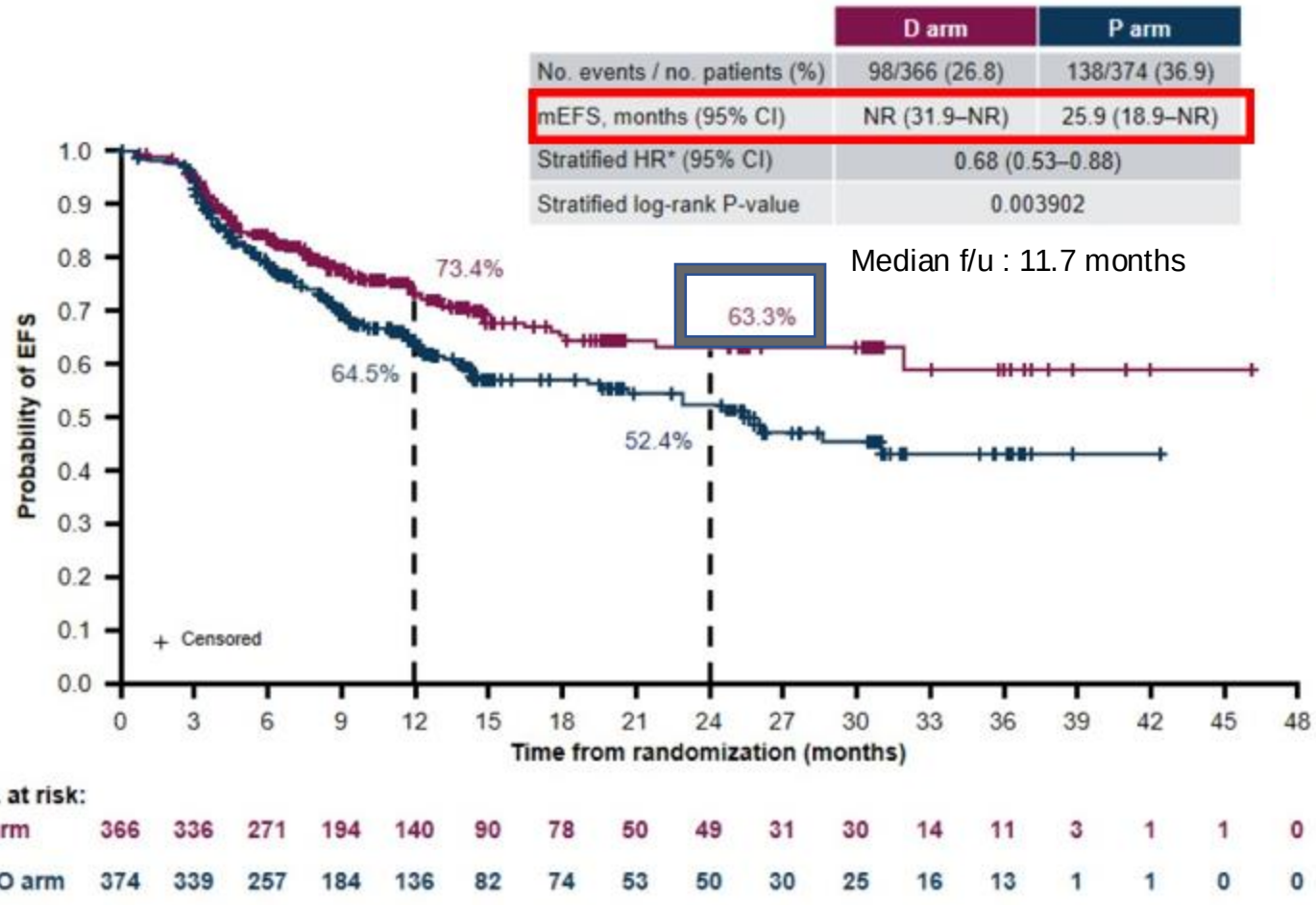
DCO = Nov 10, 2022. *Characteristics with missing/other responses are histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology) and disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the electronic case report form [eCRF]). †All patients were M0 except one patient in the D arm who was classified as M1 (NOS). ‡Race was self-reported per the eCRF. NOS, not otherwise specified; TC, tumor cells.

Cancer Res 15 April 2023; 83 (8_Supplement): CT005

Slide adapted from Heymach JV. 2023 AACR.

AEGEAN: pCR and EFS

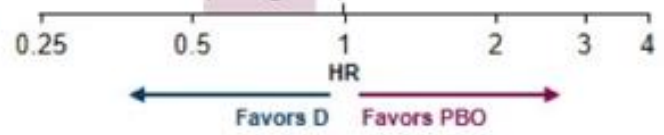




Heymach JV. 2023 AACR.
Cancer Res 15 April 2023; 83 (8_Supplement): CT005

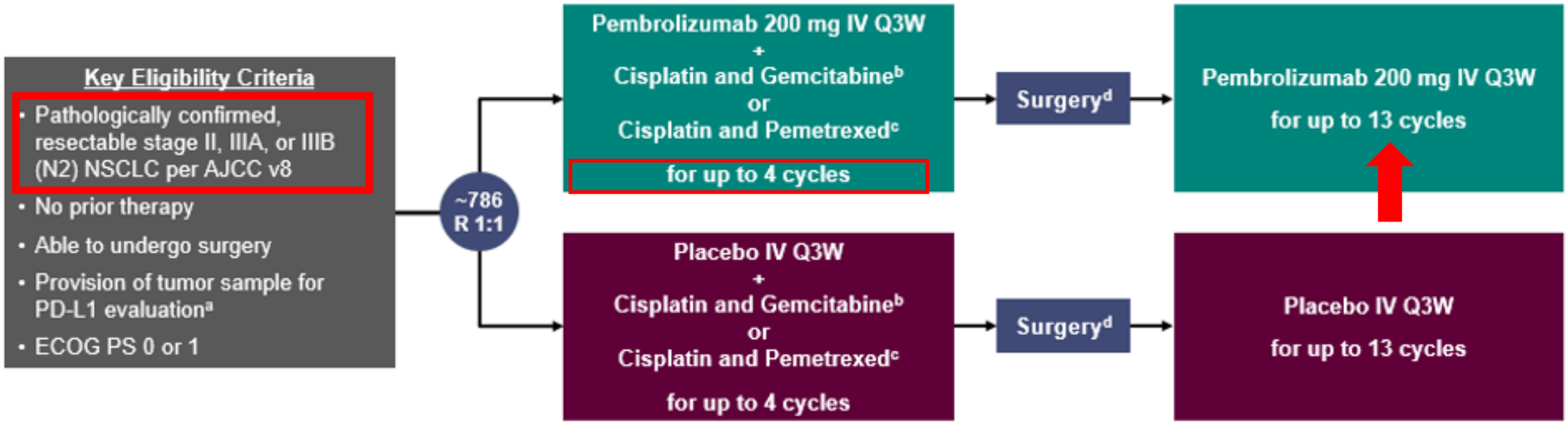
AEGEAN: EFS subgroup analysis

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[a]	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 edition)	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[b]	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)



Heymach JV et al. *Cancer Res* 15 April 2023; 83 (8_Supplement): CT005

KEYNOTE-671: Trial design



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

Wakelee H et at. *N Engl J Med*. 2023;389(6):491-503.

KEYNOTE-671: Baseline Characteristics

	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Median age (range), years	63 (26-83)	64 (35-81)
Male	279 (70.3%)	284 (71.0%)
Race		
American Indian or Alaska Native	1 (0.3%)	0
Asian	124 (31.2%)	125 (31.3%)
Black or African American	6 (1.5%)	10 (2.5%)
Multiple	3 (0.8%)	10 (2.5%)
White	250 (63.0%)	239 (59.8%)
Missing data	13 (3.3%)	16 (4.0%)
Geographic region		
East Asia	123 (31.0%)	121 (30.3%)
Not east Asia	274 (69.0%)	279 (69.8%)
ECOG PS		
0	253 (63.7%)	246 (61.5%)
1	144 (36.3%)	154 (38.5%)
Histology		
Nonsquamous	226 (56.9%)	227 (56.8%)
Squamous	171 (43.1%)	173 (43.3%)

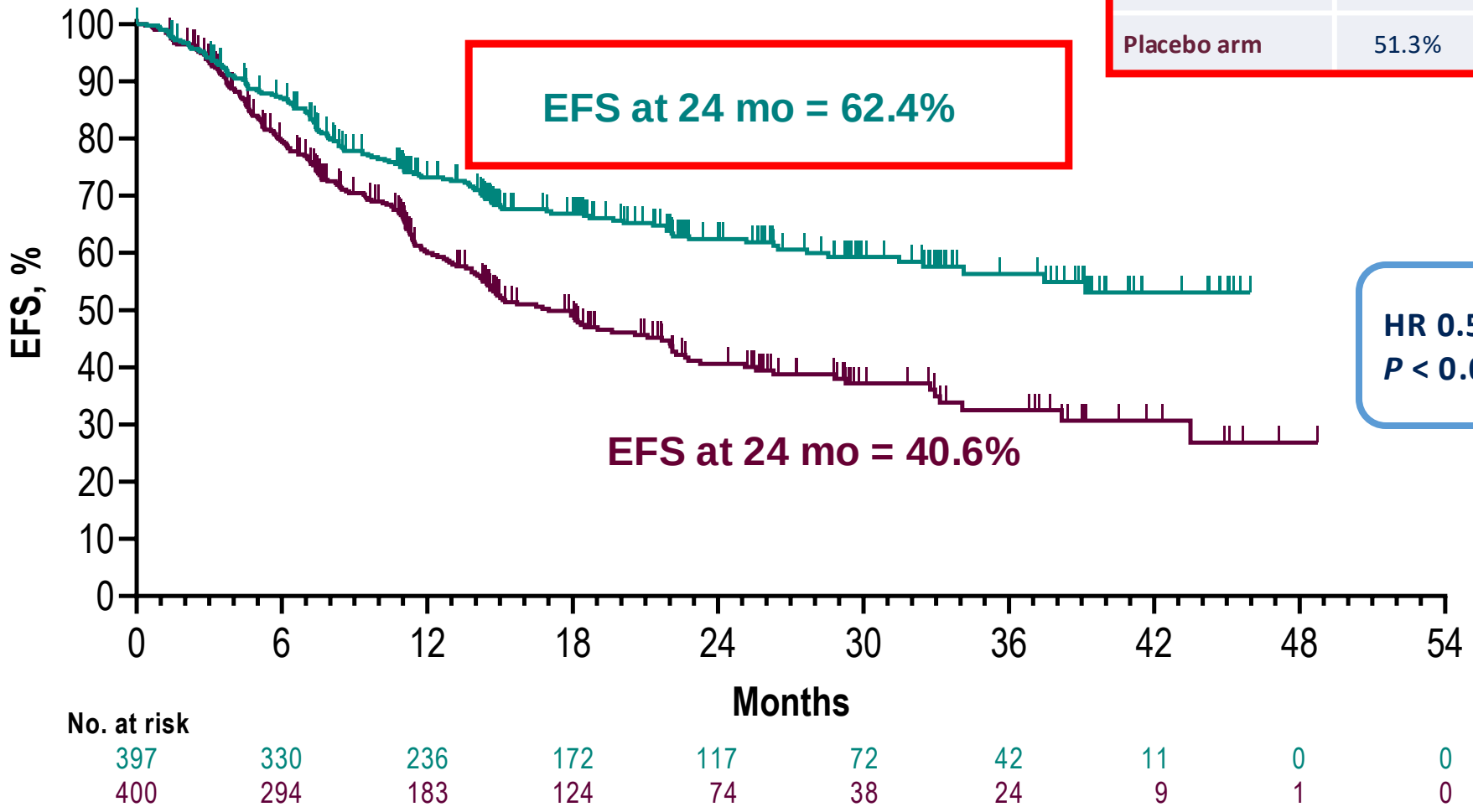
	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Smoking status		
Current	96 (24.2%)	103 (25.8%)
Former	247 (62.2%)	250 (62.5%)
Never	54 (13.6%)	47 (11.8%)
Disease stage at baseline (per AJCC v8)		
II	118 (29.7%)	121 (30.3%)
IIIA	217 (54.7%)	225 (56.3%)
IIIB	62 (15.6%)	54 (13.5%)
pN status		
N0	148 (37.3%)	142 (35.5%)
N1	81 (20.4%)	71 (17.8%)
N2	168 (42.3%)	187 (46.8%)
PD-L1 TPS		
≥50%	132 (33.2%)	134 (33.5%)
1-49%	127 (32.0%)	115 (28.8%)
<1%	138 (34.8%)	151 (37.8%)
Known *EGFR* mutation[a]	14 (3.5%)	19 (4.8%)
Known *ALK* translocation[a]	12 (3.0%)	9 (2.3%)

Slide courtesy of Wakelee H et al. ASCO 2023

Wakelee H et at. *N Engl J Med*. 2023;389(6):491-503.

KEYNOTE-671: EFS

	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)

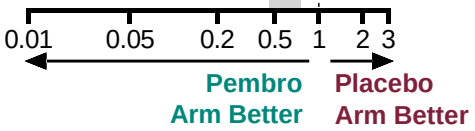


HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

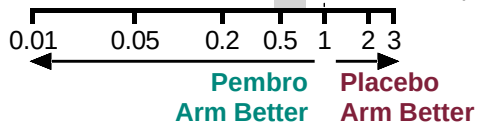
Wakelee H et at. *N Engl J Med*. 2023;389(6):491-503.

KEYNOTE-671: EFS subgroup analysis

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)

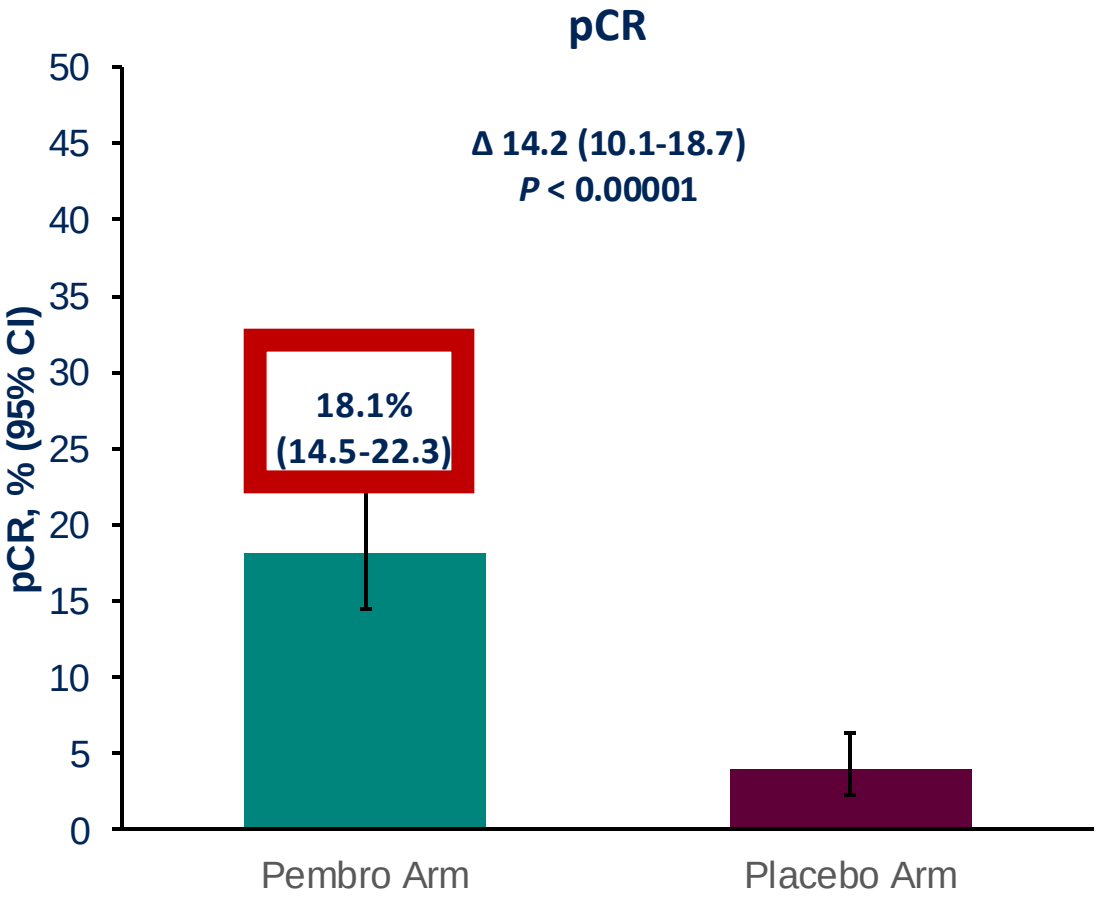


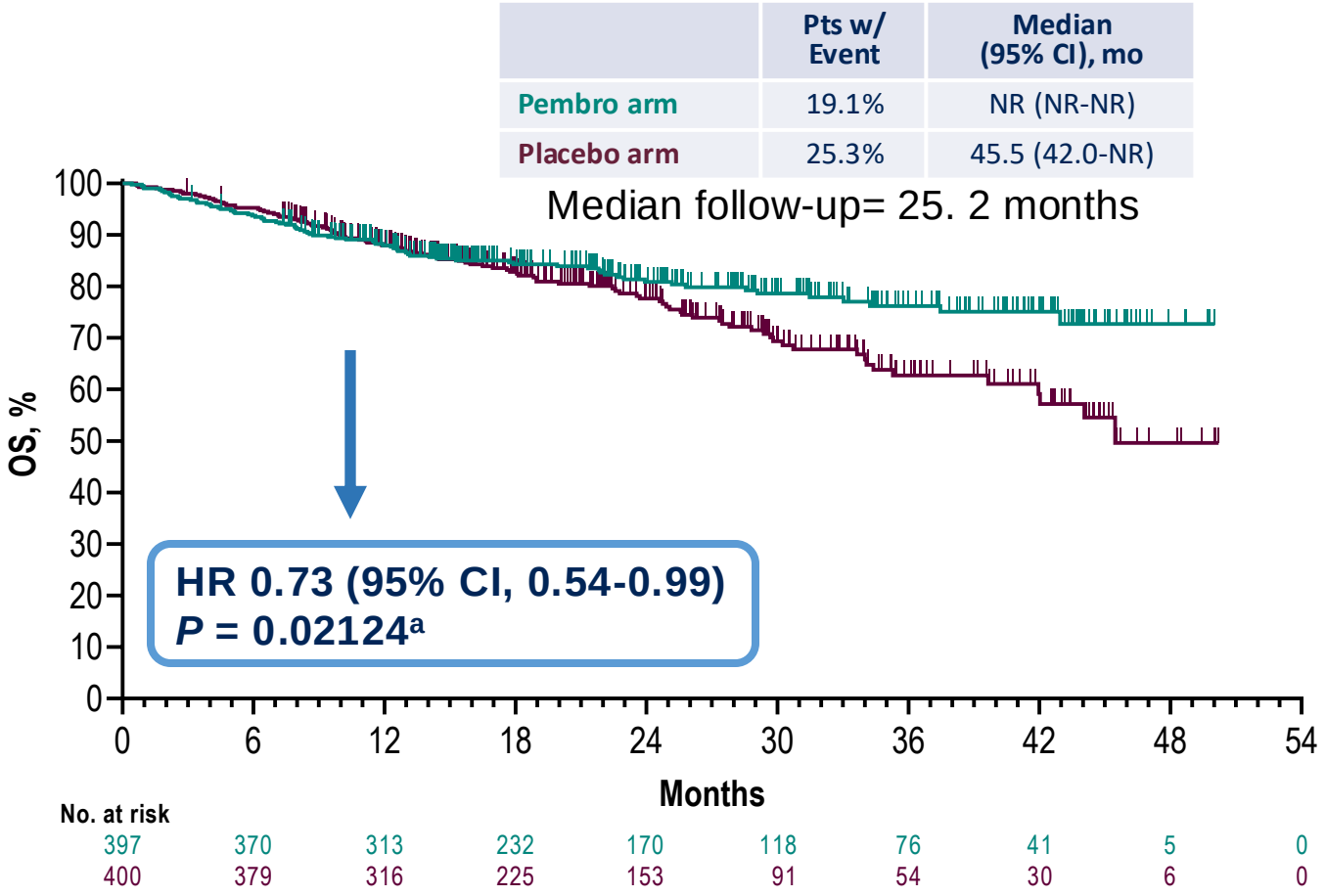
Subgroup	Events/participants		Hazard ratio (95% CI)
	Pembro Arm	Placebo Arm	
Overall	139/397	205/400	0.58 (0.46-0.72)
Pathologic stage			
II	34/118	48/121	0.65 (0.42-1.01)
IIIA	80/217	124/225	0.54 (0.41-0.72)
IIIB	25/62	33/54	0.52 (0.31-0.88)
pN status			
pN0	51/148	70/142	0.57 (0.40-0.82)
pN1	25/81	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)



Wakelee H et at. *N Engl J Med*. 2023;389(6):491-503.

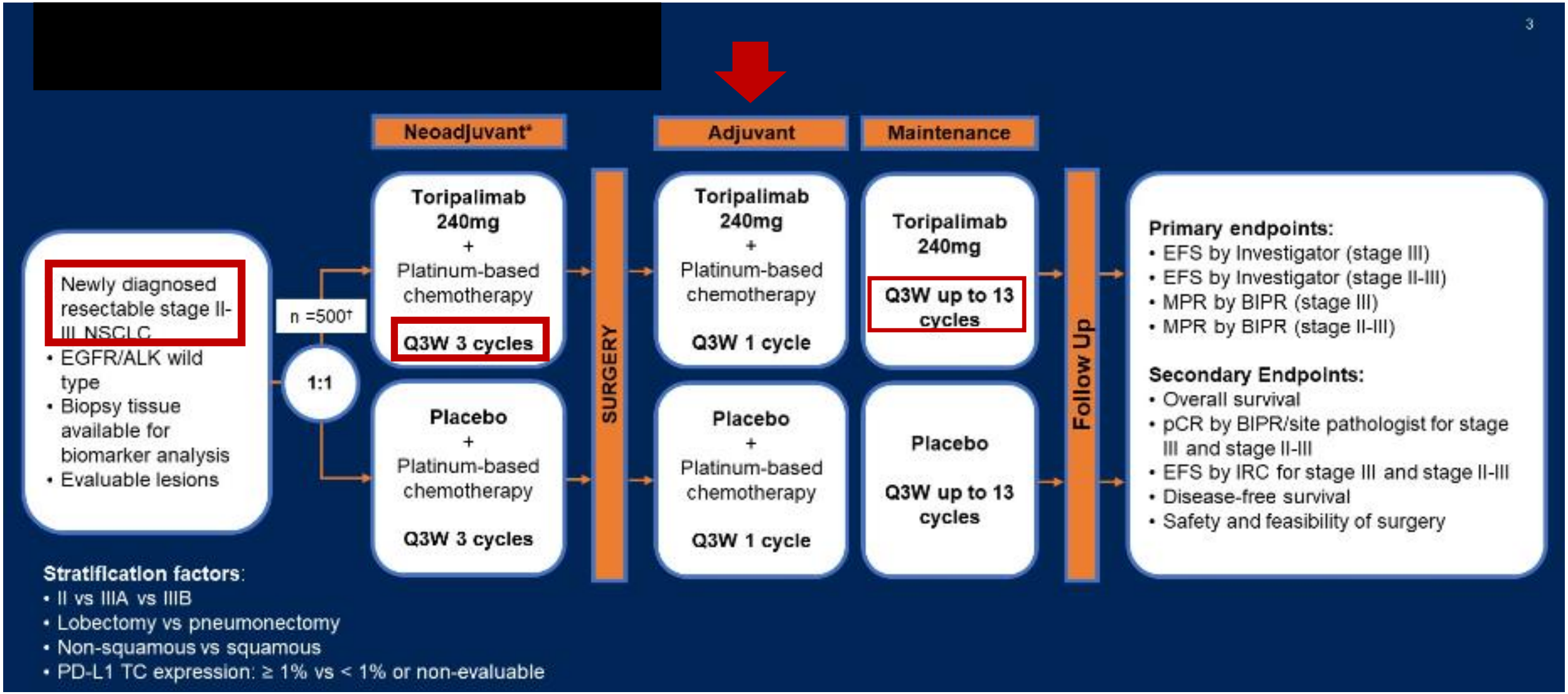
KEYNOTE-671: pCR and OS





Wakelee H et at. *N Engl J Med*. 2023;389(6):491-503.

Neotorch: Study Design



Lu S et al. J Clin Oncol 41, 2023 (suppl 16; abstr 8501)

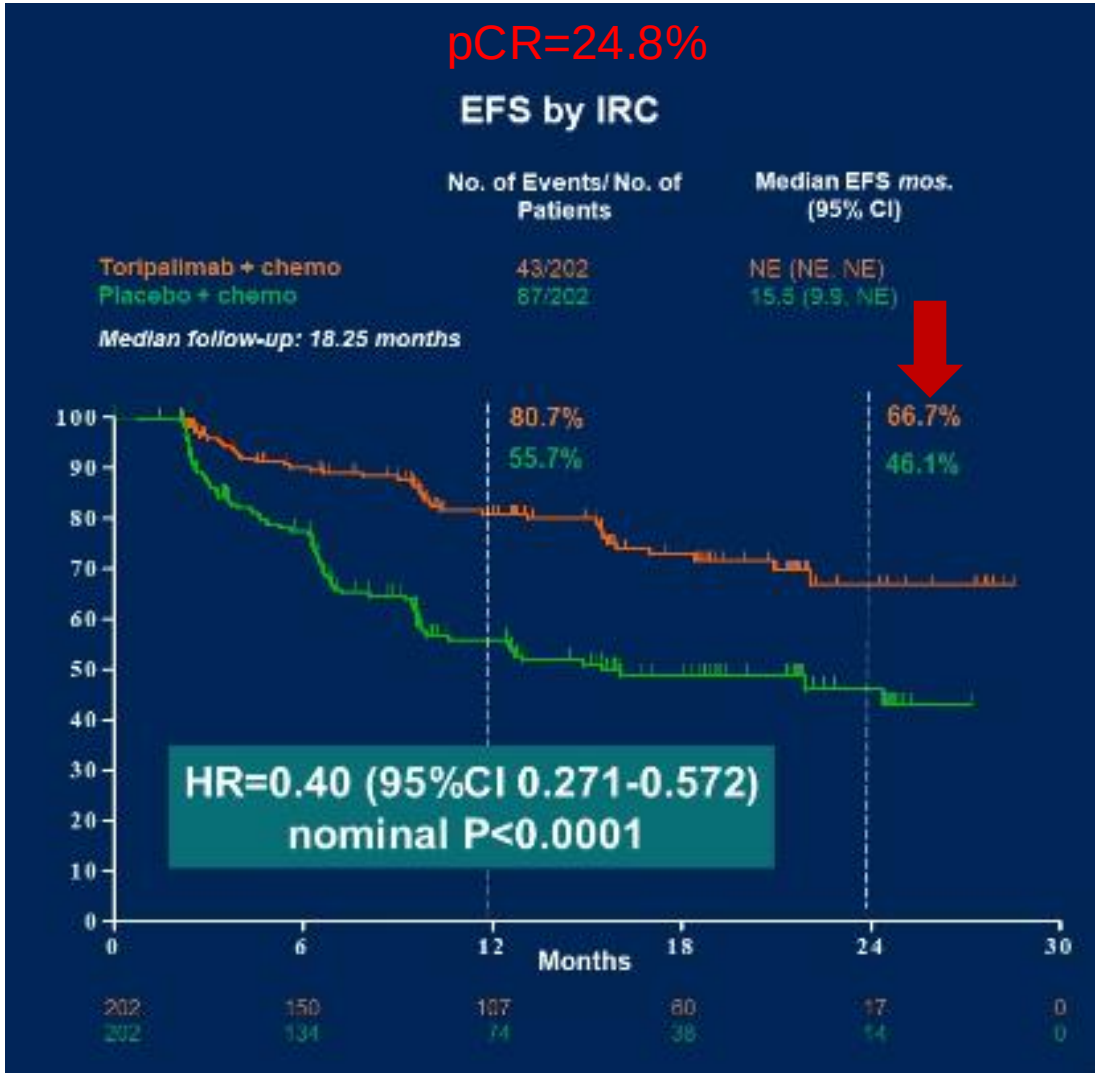
Neotorch

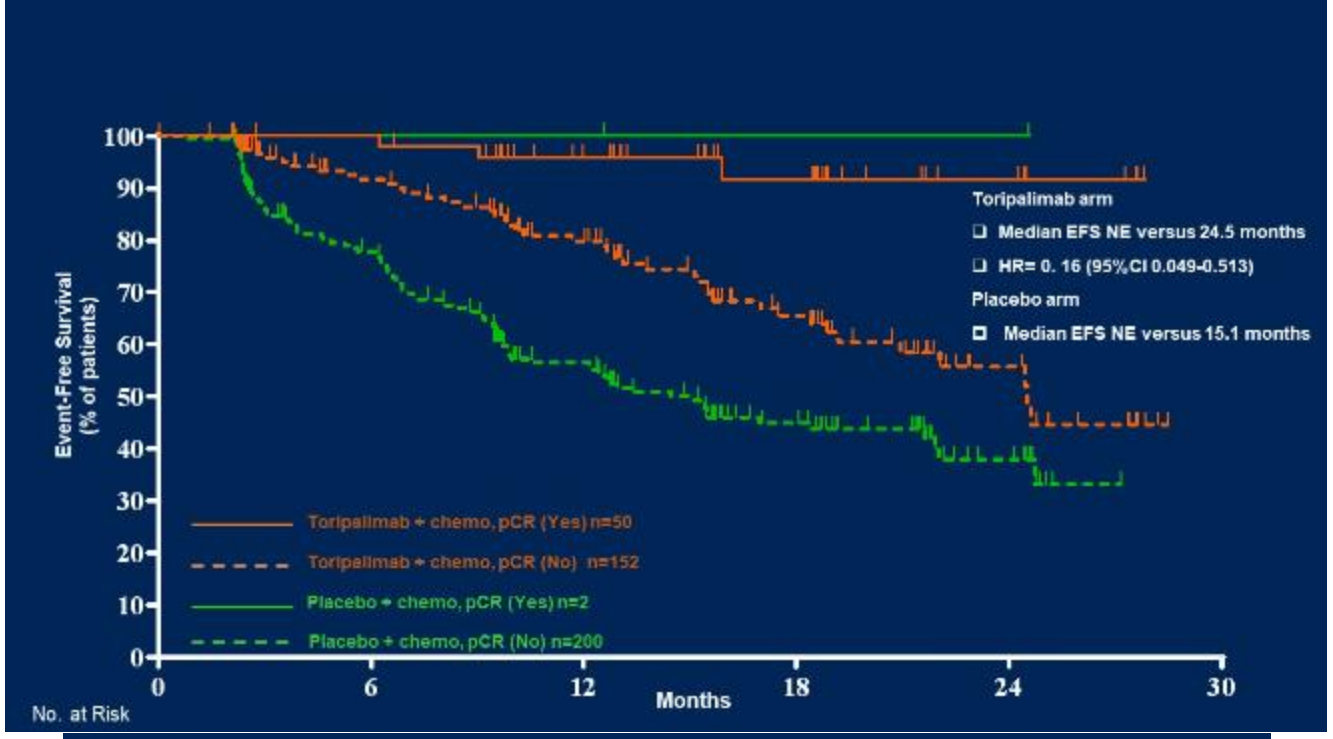
Baseline Characteristics of Stage III Patients

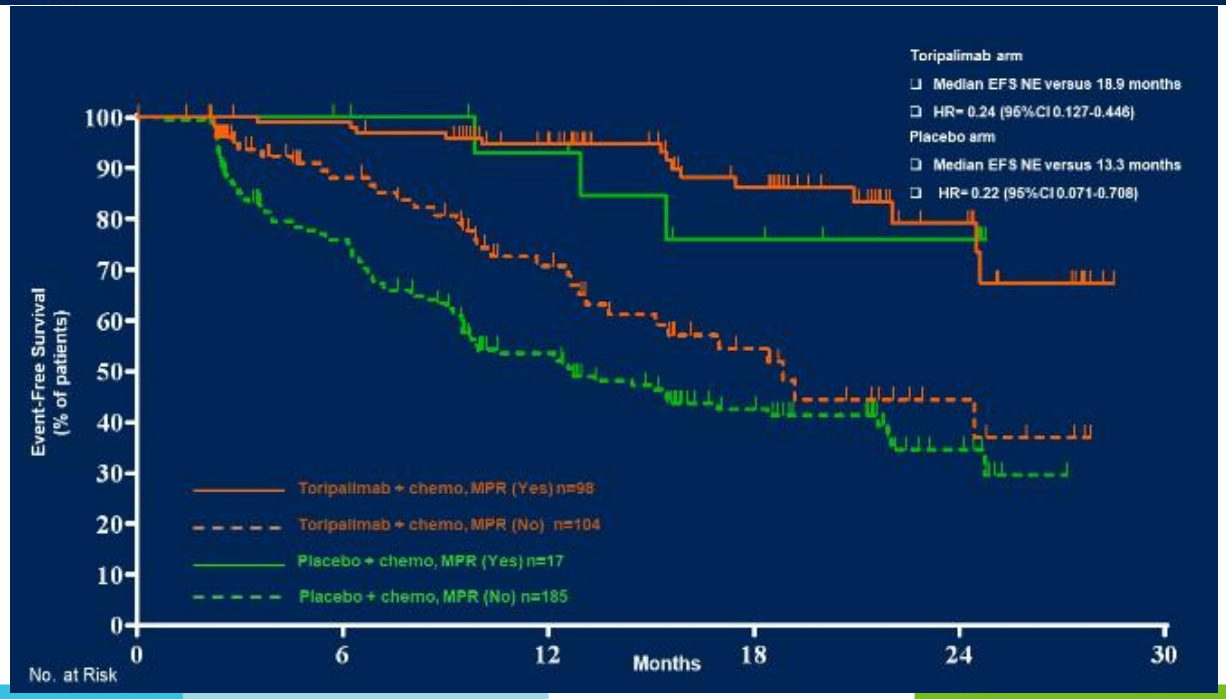
		Toripalimab + chemo n = 202	Placebo + chemo n = 202	Total n = 404
Median age, years (range)		62 (31-70)	61 (29-70)	62 (29-70)
Age < 65 years, n (%)		140 (69.3)	138 (68.3)	278 (68.8)
Gender, n (%)	Male	181 (89.6)	189 (93.6)	370 (91.6)
Smoking status, n (%)	Non-smoker	28 (13.9)	21 (10.4)	49 (12.1)
	Smoker	30 (14.9)	23 (11.4)	53 (13.1)
	Former	144 (71.3)	158 (78.2)	302 (74.8)
ECOG PS, n (%)	0	70 (34.7)	73 (36.1)	143 (35.4)
	1	132 (65.3)	129 (63.9)	261 (64.6)
Histology, n (%)	Non-squamous	45 (22.3)	45 (22.3)	90 (22.3)
	Squamous	157 (77.7)	157 (77.7)	314 (77.7)
PD-L1 expression, n (%)	TC ≥ 1%	133 (65.8)	132 (65.3)	265 (65.6)
	TC＜1% or non-evaluable	69 (34.2)	70 (34.7)	139 (34.4)
Stage*, n (%)	IIIA	136 (67.3)	136 (67.3)	272 (67.3)
	IIIB	65 (32.2)	64 (31.7)	129 (31.9)
N stage^, n(%)	N0	17(8.4)	18(8.9)	35(8.7)
	N1	46(22.8)	39(19.3)	85(21.0)
	N2	138(68.3)	145(71.8)	283(70.0)

Lu S et al. J Clin Oncol 41, 2023 (suppl 16; abstr 8501)

Neotorch: pCR and EFS

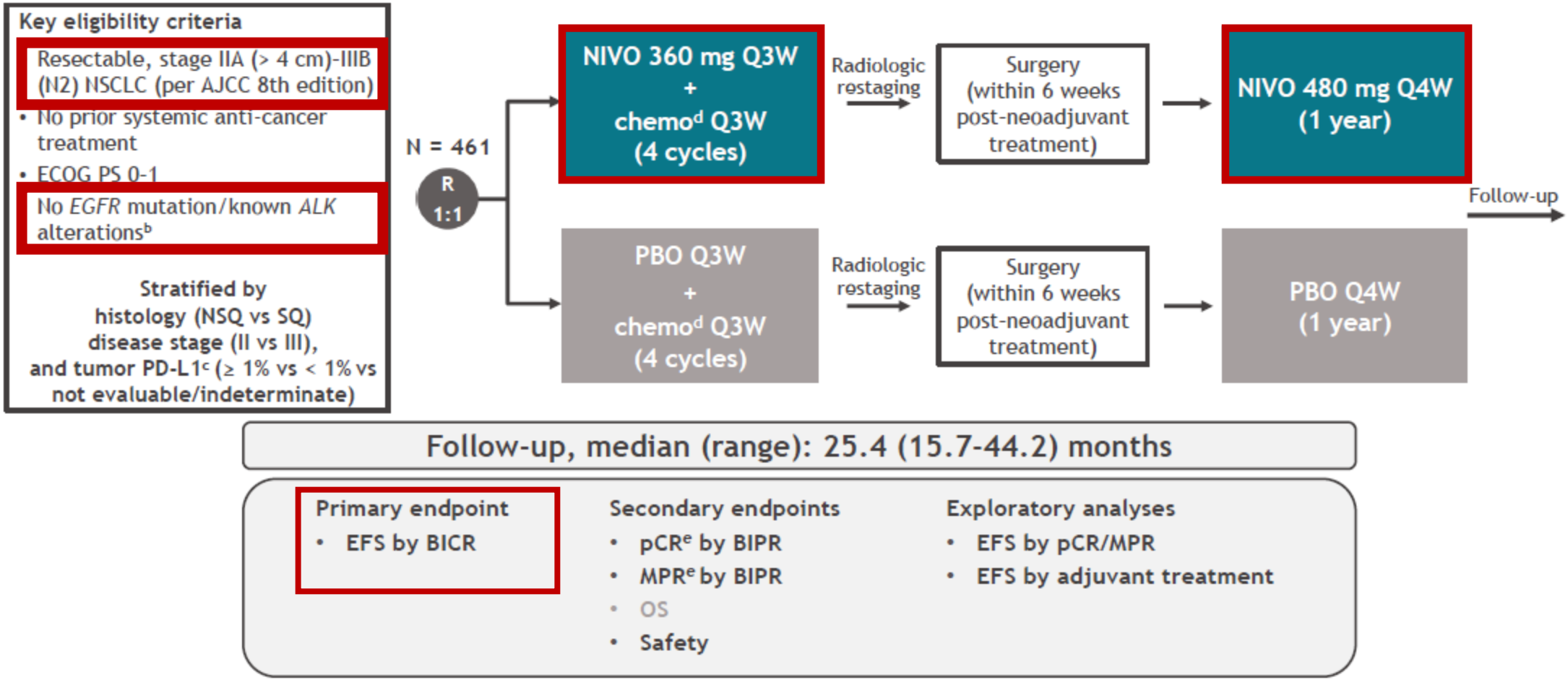






Lu S et al. J Clin Oncol 41, 2023 (suppl 16; abstr 8501)

CM77T: Study Design



Cascone T. LBA1. 2023 ESMO.

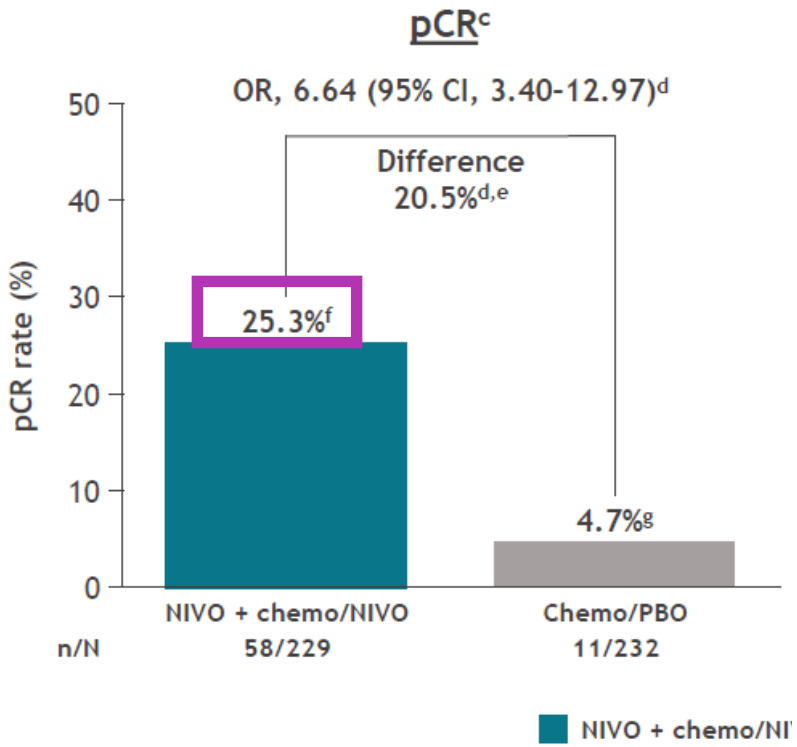
CM77T: Baseline characteristics

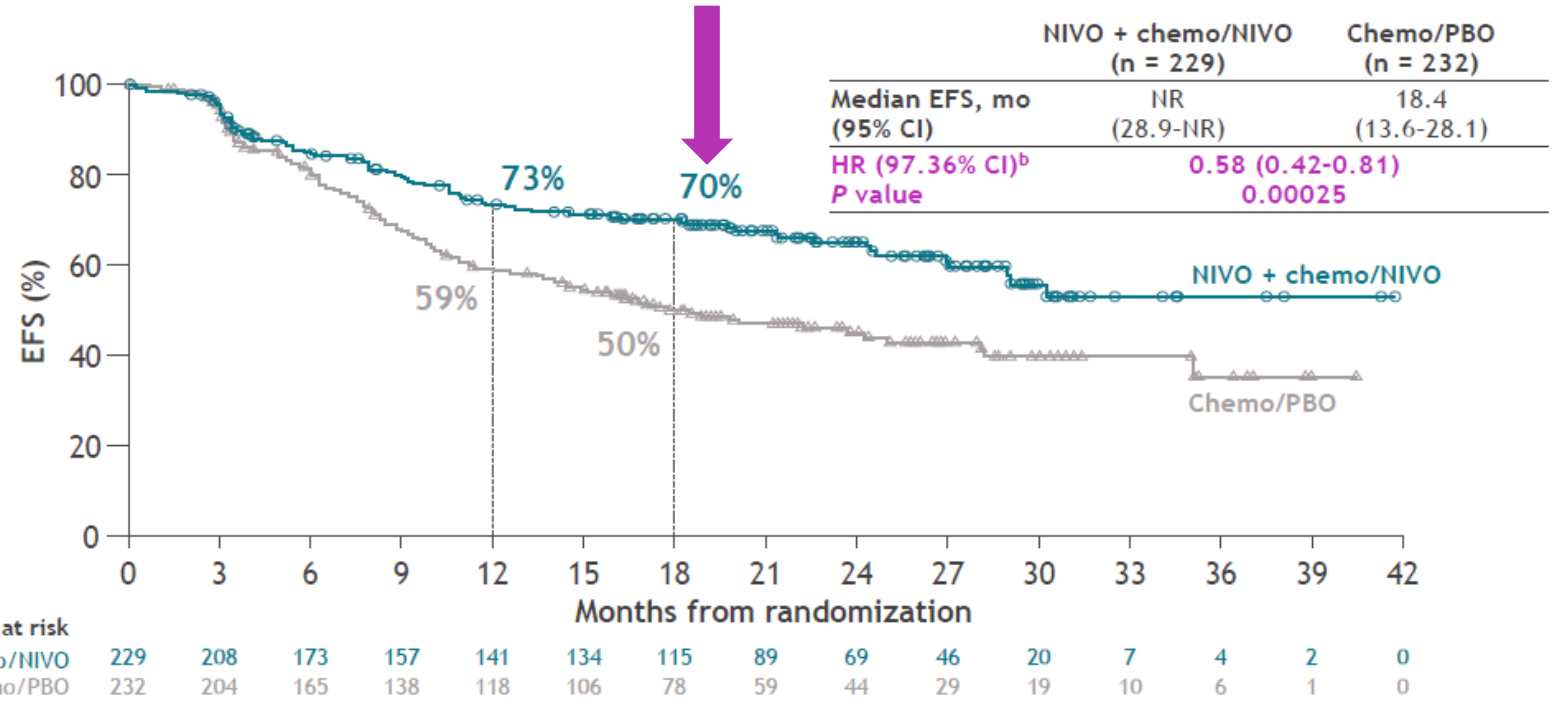
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)[a]
Median age, years (range)	66 (37-83)	66 (35-86)
Male, n (%)	167 (73)	160 (69)
Geographic region, n (%)		
North America	23 (10)	21 (9)
Europe	123 (54)	127 (55)
Asia	65 (28)	50 (22)
Rest of the world[b]	18 (8)	34 (15)
ECOG PS, n (%)		
0	147 (64)	141 (61)
1	82 (36)	91 (39)
Disease stage,[c] n (%)		
IIA-B[d]	81 (35)	81 (35)
IIIA-B[e]	146 (64)	149 (64)
Histology, n (%)		
Squamous	116 (51)	118 (51)
Non-squamous	113 (49)	114 (49)

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)[a]
Smoking status, n (%)		
Current/former	212 (93)	205 (88)
Never	17 (7)	27 (12)
Tumor PD-L1 expression,[f] n (%)		
Not evaluable	8 (4)	11 (5)
< 1%	93 (41)	93 (40)
≥ 1%	128 (56)	128 (55)
1-49%	83 (36)	76 (33)
≥ 50%	45 (20)	52 (22)
Platinum therapy type, n (%)		
Cisplatin	55 (24)	42 (18)
Carboplatin	167 (73)	180 (78)

Cascone T. LBA1. 2023 ESMO.

CM77T: pCR and DFS



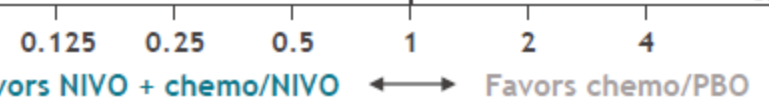


Cascone T. LBA1. 2023 ESMO.

CM77T: EFS analysis by subgroups

EFS analysis by key subgroups

	Median EFS,[a] mo		Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)	
Overall (N = 461)	NR	18.4	0.59 (0.44-0.79)
< 65 years (n = 202)	NR	16.7	0.55 (0.36-0.85)
≥ 65 years (n = 259)	NR	20.1	0.61 (0.41-0.91)
Male (n = 327)	NR	16.7	0.53 (0.37-0.75)
Female (n = 134)	30.2	18.8	0.71 (0.41-1.20)
North America (n = 44)	30.2	9.4	0.59 (0.25-1.38)
Europe (n = 250)	NR	23.7	0.61 (0.40-0.92)
Asia (n = 115)	NR	13.9	0.47 (0.26-0.86)
ECOG PS 0 (n = 288)	NR	20.1	0.57 (0.39-0.83)
ECOG PS 1 (n = 173)	29.0	17.3	0.61 (0.39-0.97)
Stage II (n = 162)	NR	NR	0.81 (0.46-1.43)
Stage III (n = 297)	30.2	13.4	0.51 (0.36-0.72)
N0 (n = 167)[b]	NR	NR	0.80 (0.48-1.32)
N1 (n = 108)[b]	NR	28.1	0.58 (0.29-1.16)
N2 (n = 182)[b,c]	30.2	10.0	0.46 (0.30-0.70)
Single-station (n = 112)	30.2	10.0	0.49 (0.29-0.84)
Multi-station (n = 69)	NR	10.0	0.43 (0.21-0.88)
Squamous (n = 234)	NR	17.0	0.46 (0.30-0.72)
Non-squamous (n = 227)	28.9	18.4	0.72 (0.49-1.07)
Current/former smoker (n = 417)	NR	17.0	0.54 (0.40-0.74)
Never smoker (n = 44)	19.7	25.0	1.32 (0.54-3.20)
PD-L1 < 1% (n = 186)[d]	29.0	19.8	0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8	0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	30.2	28.1	0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0	0.26 (0.12-0.55)
Cisplatin (n = 97)	27.0	15.8	0.61 (0.35-1.08)
Carboplatin (n = 347)	NR	17.3	0.53 (0.37-0.75)



Median follow-up (range): 25.4 months (15.7-44.2).
[a]Per BICR. [b]Nodal status was N3 in 4 patients. [c]N2 subcategory was not reported in 1 patient.Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression (median 10% across both arms).

KEY PHASE III IMMUNOTHERAPY STUDIES IN RESECTABLE NSCLC

	Adjuvant		Neoadjuvant	Perioperative therapy			
	IMP-010	KN-091	CM816	AEGEAN	KN671	Neotorch	CM77T
Primary endpoint	DFS	DFS	EFS, pCR	EFS, pCR	EFS, OS	EFS, MPR	EFS
Non-Squamous (%)	64.7	67.5	51	53.6	56.9	22.3	49
PD-L1 ≥1% (%)	57.4	60.5	50	66.7	65.2	65.8	56
Stage IIIA (%)	40.4	30	63	47.3	54.7	67.3	45
Stage IIIB (%)	-	-	-	24.0	15.6	32.2	19
Median Follow-up	32.2	35.6	21	11.7	25.2	NA	15.7
pCR (%)	NA	NA	24	17.2	18.1	24.8	25.3
MPR (%)	NA	NA	36.9	33.3	30.2	48.5	35.4
EFS at 2y (%)	74.6	67	63.8	63.3	62.4	66.7	~63*
OS at 2y (%)	~88%*	89	82.7	-	80.9	81.2	-
Grade 3≥ AEs (%)	24	33	11.9	32.3	44.9	63.4	32
FDA approval	Oct 2021	Jan 2023	Mar 2022	Aug 2024	Oct 2023	-	Oct 2024

Slide adapted from a slide courtesy Dr Bruna Pellini

Take Home Points and Future Directions

Patients with resectable NSCLC II-IIIB should be be considered for therapy with either adjuvant, neoadjuvant or a combination of neoadjuvant and adjuvant (perioperative) chemotherapy and immunotherapy

UNASWERED CLINICAL QUESTIONS

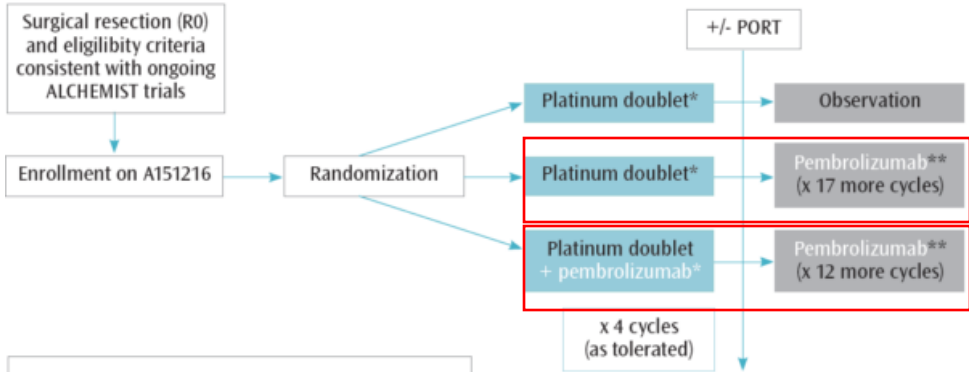
- Should stage IA with specific HR features be treated with novel therapies?
- Would you consider omitting surgical resection and consider observation alone in a patient with path CR after CM 816 therapy?
- What is an optimal duration of treatment with perioperative novel therapies?
- What is the optimal therapy of a patient with no response to neoadjuvant chemotherapy plus immunotherapy?
- Should adjuvant immunotherapy be considered in patients who have received neoadjuvant chemo + immunotherapy prior to resection?
- Neoadjuvant vs Adjuvant therapy?
- Perioperative immunotherapy in NSCLC with driver mutations?

LOGISTICS

- Access to rapid perioperative tumor tissue molecular testing.
- For assessment of pCR or MPR – processes like pathological assessment and specimen processing need to be standardized.
- Development and standardization of biological biomarkers for identification of high-risk patients.
- Prompt recognition of treatment related adverse events with perioperative novel therapies to avoid surgical delays.
- Access to novel therapies after regulatory approvals.

Next steps in Adjuvant IO: Concurrent CT+IO, ctDNA assessment

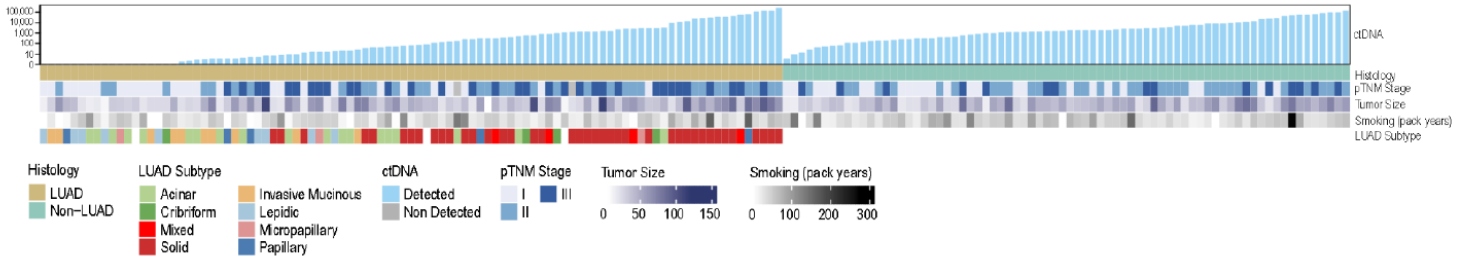
ALCHEMIST CHEMO IO



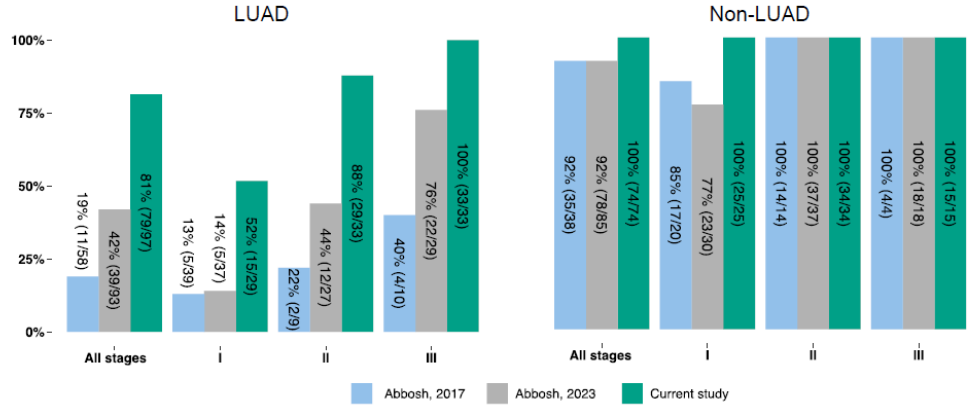
Primary endpoint: DFS and OS

Bulletin of the American College of Surgeons. ALCHEMIST trial has potential to improve outcomes after lung cancer resection by Jacob Sands et al

Pre-operative detection of ctDNA using NeXT Personal



- ctDNA detected from 1.7 to 253,826 PPM
- Pre-operative ctDNA detected in **81%** of LUAD and **100%** of non-LUAD patients
- Includes **52%** of pTNM stage I LUAD patients



MADRID 2023 ESMO congress

PAVING THE WAY FOR NOVEL THERAPIES IN RESECTED NSCLC

Diagnosis of resectable NSCLC

Preoperative Risk stratification and personalization of therapy:
Tumor genotyping , PD-L1 and TMB

Low risk

SURGERY

Post operative Risk assessment
- Surgical tumor evaluation for predictive biomarkers: MPR, pCR
- Biological risk stratification using cfDNA

High risk

NEO-ADJUVANT CHEMOTHERAPY + IMMUNOTHERAPY ± **Novel agents**

High risk

± ADJUVANT IMMUNOTHERAPY ± CHEMOTHEREAPY ± WITHOUT RADIATION
+ Novel agents

Low risk

SURVEILLENCE
(CtDNA + Imaging)


THANK YOU