Immunotherapy in resectable NSCLC

Dr Akshay Raut

SR Pulmonary Medicine

Outline

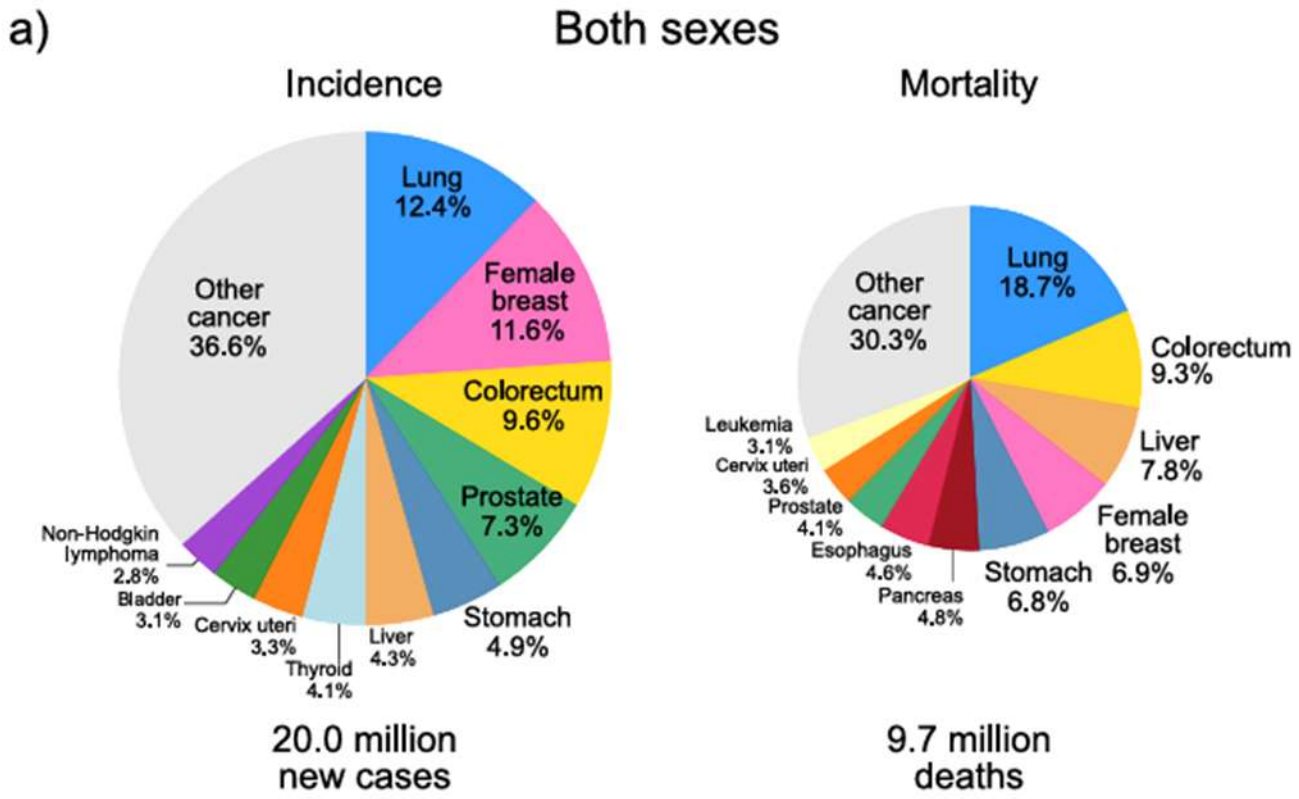
- **Introduction & Epidemiology**
- **Immunotherapy in neoadjuvant setting**
- **Immunotherapy in perioperative setting**
- **Immunotherapy in adjuvant setting**
- **Overview of trials**
- **Selection of strategy**
- **Optimal duration & Biomarkers**
- **Ongoing trials**

Introduction & Epidemiology

- Lung cancer is the Mc cancer across the globe (12.4% of all cancers)
- Leading cause of death among all cancer subtypes in both men and women (18.7%)
- NSCLC composes the largest majority (~85%) of lung cancer cases and includes adenocarcinoma (50%), squamous cell carcinoma (30%), and large cell carcinoma (5%)
- Approximately 44.8% of NSCLC patients present with stage IV metastatic disease at initial diagnosis, while 22.3% and 28.1% of patients had either regional lymph node involvement or localized disease only

Freddie Bray et al, Global Cancer statistics 2022; GLOBOCAN
Siegel RL, et al Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12–49
Howlader N et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med. 2020;383:640–9

Introduction & Epidemiology



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- Approximately 20-25 % of patients with NSCLC have resectable disease
- 30 to 55% of patients who undergo curative surgery have recurrence and ultimately die of their disease
- The absolute difference in 5-year recurrence-free and overall survival with neoadjuvant chemotherapy as compared with surgery alone is only 5 to 6 % only
- In the absence of a driver mutation, the multimodality approach to the treatment of NSCLC relies on chemotherapy, immunotherapy, surgery, and radiation therapy

Pignon, J. P. et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J. Clin. Oncol. 26, 3552–3559 (2008)

GLOBOCAN India statistics 2018[S1]	
Number of new cancer cases	1.16 million
Cancer deaths	784,821
Number of prevalent cancer cases (5-y)	2.26 million
Lung cancer	5.9% of all cancer cases (fourth most common)
Lung cancer incidence	67,795
Lung cancer mortality	63,475 (8.1% of all cancer deaths)
Projected incidence, 2020[S2]	
All sites	1,392,179
Males	679,421
Females	712,758
Lung cancer	98,278
Males	71,788
Females	26,490

- EGFR mutations and ALK rearrangements in India is 30% and 10%, respectively
- The number of patients who are eligible for surgery or undergo surgery varies between 1.5% and 5.3%
- Lung cancer accounts for 5.9% of all cancers and 8.1% of all cancer-related deaths

Navneet Singh et al. Lung Cancer in India Journal of Thoracic Oncology, 2021

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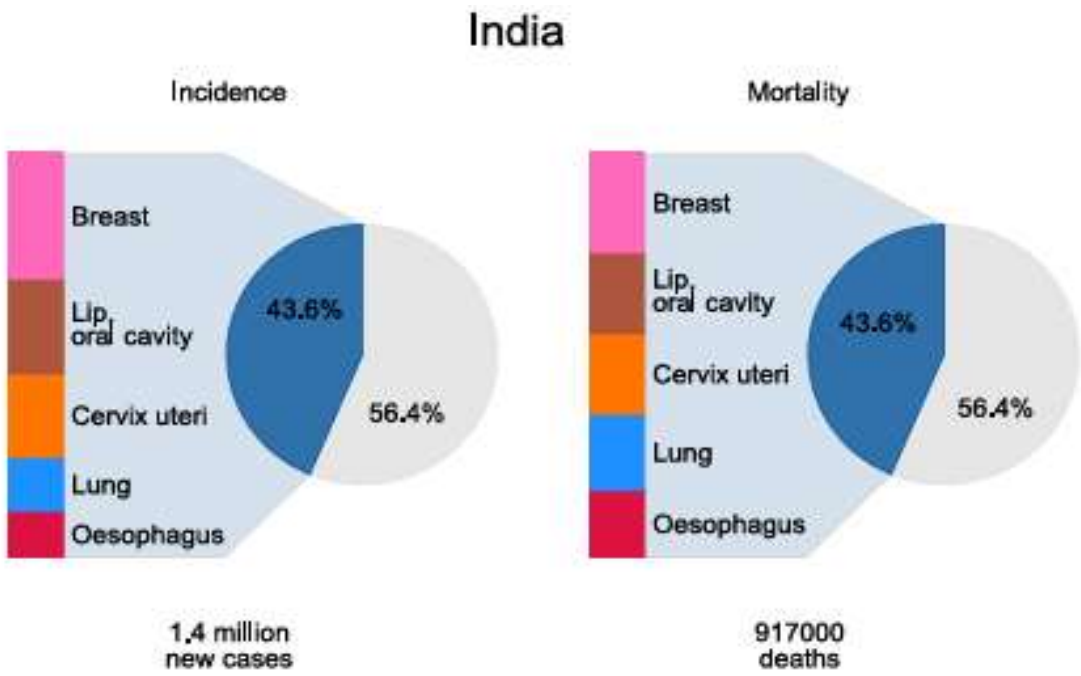

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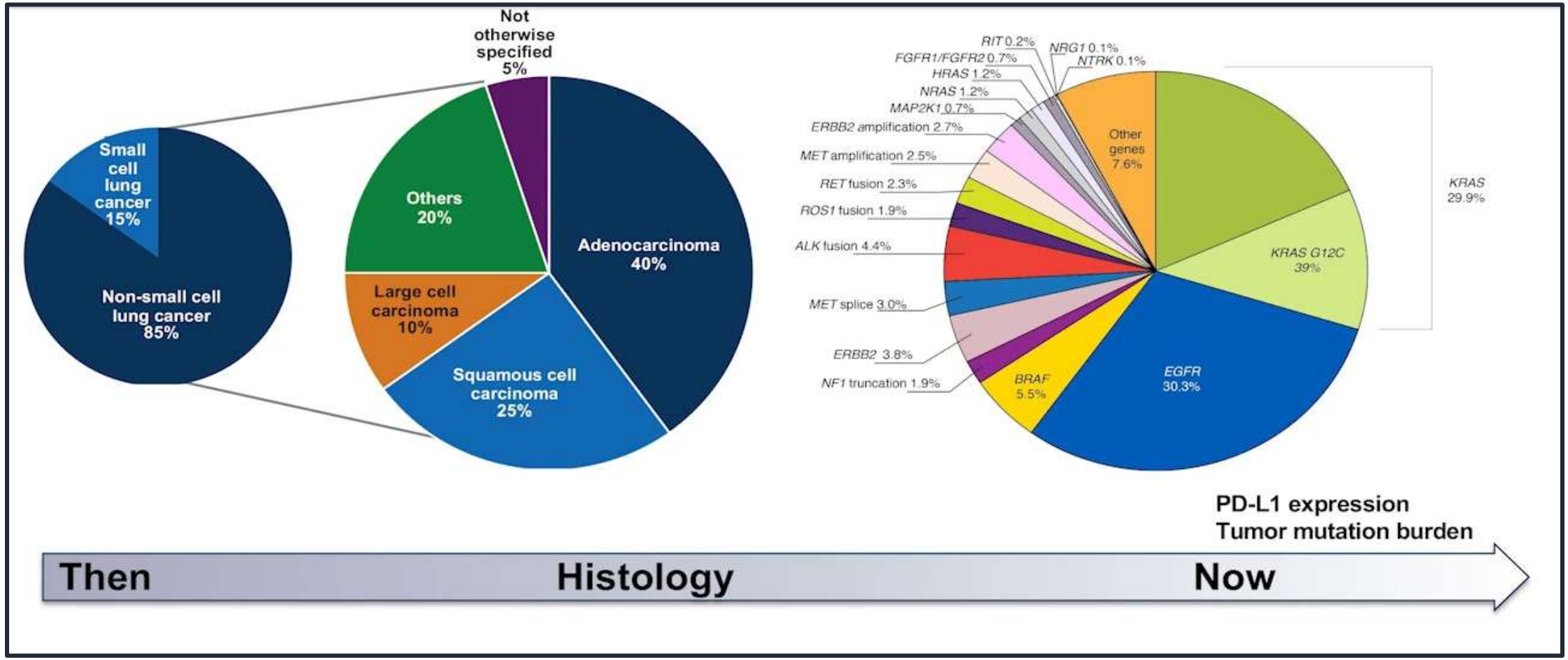
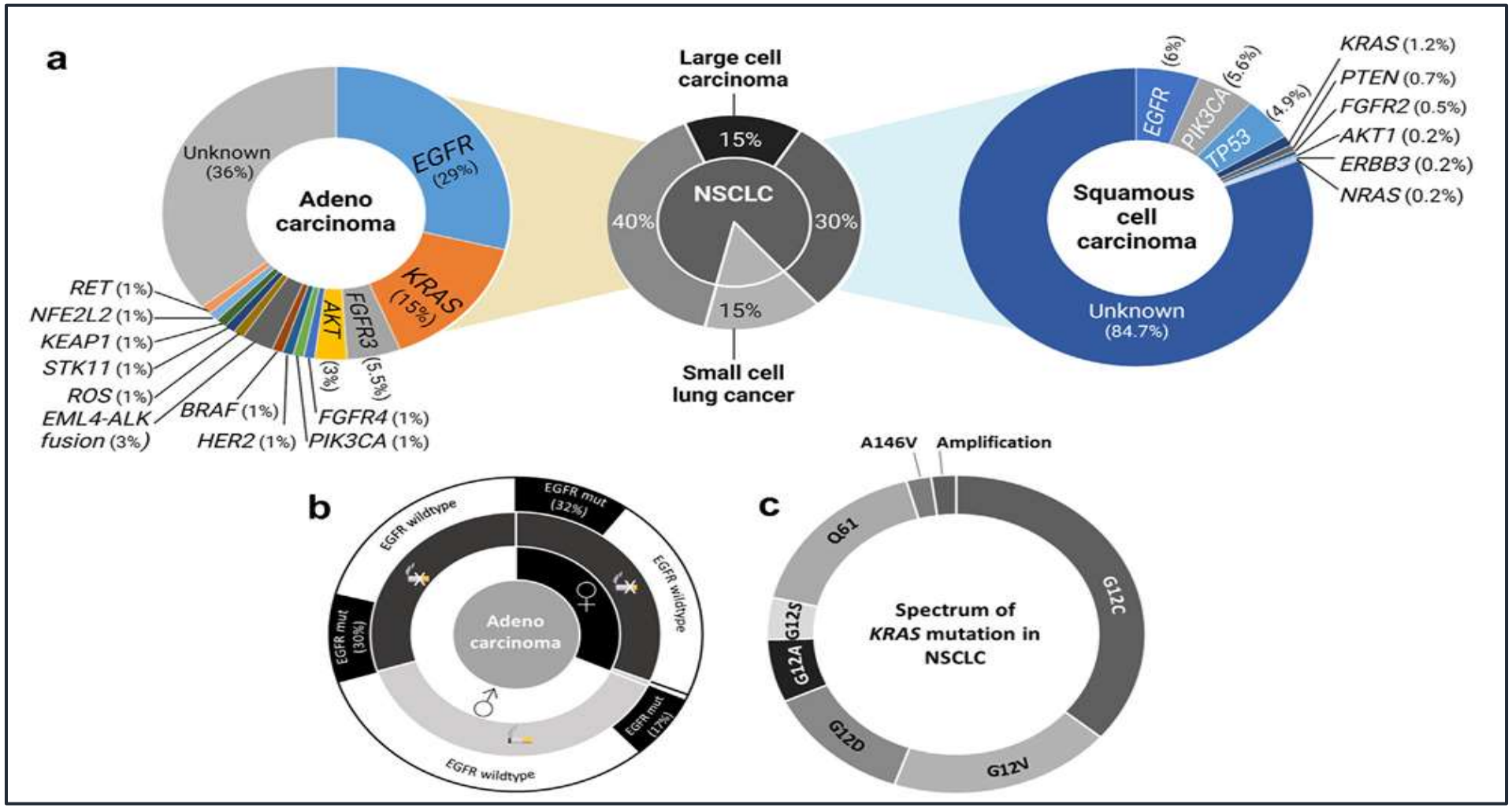
Freddie Bray et al, Global Cancer statistics 2022; GLOBOCAN

Landscape of Lung Cancer



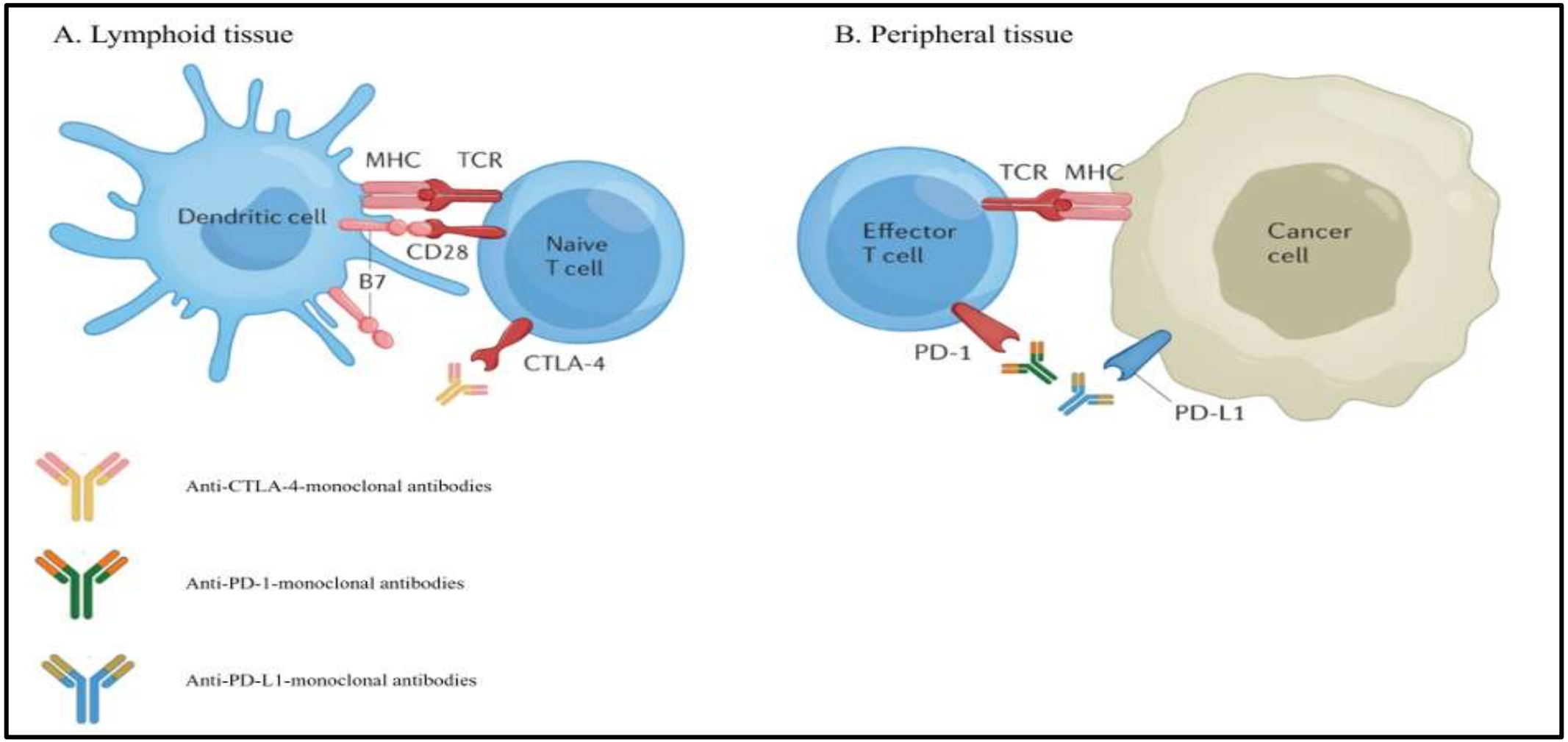
Addeo A, et al Immunotherapy in non-small cell lung cancer harboring driver mutations. Cancer Treat Rev. 2021 May;96:102179.

Genomic landscape of lung cancer in the Indian subcontinent



Vanita Noronha et al. Uniqueness of Lung Ca in Southeast Asia, The Lancet Regional Health- Southeast Asia 2024;27: 100430

Immune checkpoint inhibitors (ICI)



Kuhlman JJ et al. Curative immunotherapy-based strategies for non metastatic NSCLC. Explor Target Antitumor Ther. 2024

Immunotherapy: How Does It Work?

Immune Checkpoint Inhibitors Block T-Cell Inhibitory Signals

PD-1/PD-L1 Checkpoint Inhibition

PD-1 pathway inhibits signaling downstream of TCR

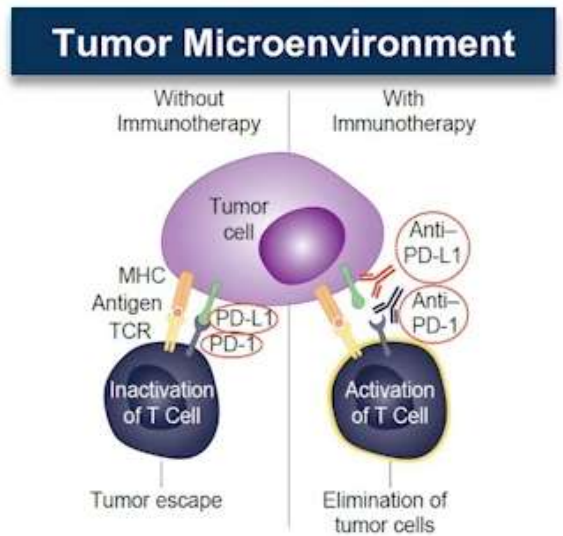
- TCR triggered by antigen presented by tumor cell
- Negative regulatory receptor PD-1 expressed and PD-L1 reactively expressed
- PD-L1 binds to PD-1

T cell inactivated

Tumor escape

Anti–PD-1 therapies used in NSCLC

Nivolumab
Pembrolizumab
Cemiplimab-rwlc



STOP

GO

Anti–PD-1 or anti–PD-L1 monoclonal antibodies block the interaction and negative regulation

T cell activated

Tumor attack

Anti–PD-L1 therapies used in NSCLC

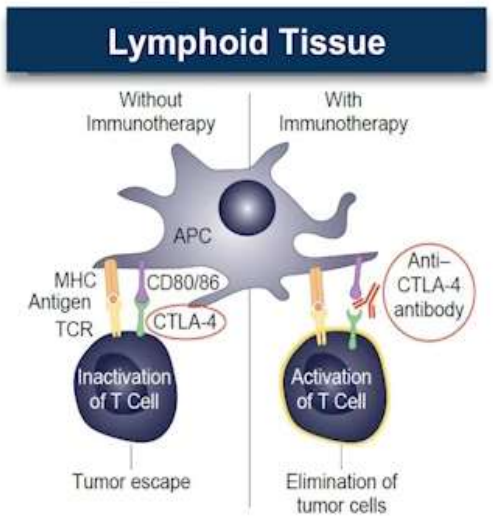
Atezolizumab
Durvalumab

CTLA-4 Checkpoint Inhibition

CTLA-4 is a negative regulator of co-stimulation required for activation of an antitumor T cell in a lymph node upon recognition of tumor antigen

T cell inactivated

Tumor escape



STOP

GO

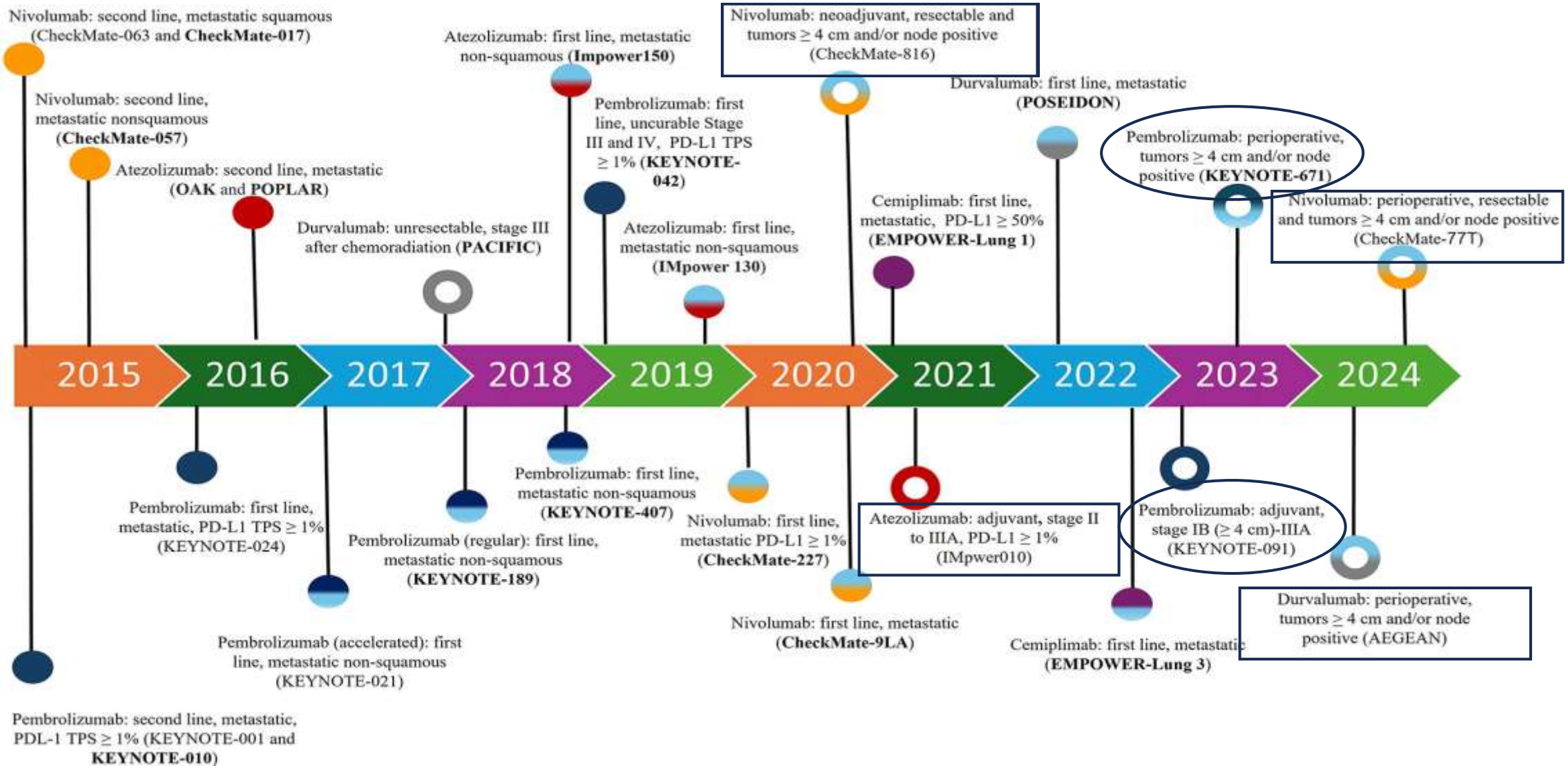
Anti–CTLA-4 monoclonal antibodies block negative regulation by CTLA-4

T cell activated

Tumor attack

Anti–CTLA-4 therapies used in NSCLC

Ipilimumab
Tremelimumab



Kuhlman JJ et al. Curative immunotherapy-based strategies for non metastatic NSCLC. Explor Target Antitumor Ther. 2024

- Event-free survival (EFS) - The time from randomization to the first documentation of disease progression leading to the inability to operate, postoperative progression, and local or distant recurrence or death of any cause, whichever occurred first
- Major pathological response (MPR) - Defined as 10% or less viable tumor cells in the tumor bed evaluated by blinded, independent pathological review
- The pathological complete response (pCR) - Defined as no residual tumor cells in the lungs and lymph nodes

- Overall survival (OS) - Defined as the time from randomization to death for any reason
- Disease-free survival (DFS) - Defined as the time from surgery to the first documentation of disease progression, local or distant recurrence, and death for any reason, whichever occurred first

Neoadjuvant, Adjuvant and Perioperative IO-Based Combination Therapy

Treatment setting	Setting overview and rationale	Endpoints
Neoadjuvant *(Treatment prior to surgery)*	 *Earliest opportunity to eradicate micrometastases, increased treatment compliance, evaluation of surrogate endpoints*[1–4]	EFS, pCR, MPR, OS, TTDM
+		
Adjuvant *(Treatment after surgery)*	 *Reduced time to surgery, longer treatment duration*[5]	DFS, OS, LCSS
=		
Perioperative *(Treatment before and after surgery)*	 *May couple rationale for neoadjuvant and adjuvant therapy, and for continuous IO treatment throughout the surgical setting*[6]	EFS, DFS, OS, pCR, MPR

Neoadjuvant/Perioperative Trials

Phase II

Forde et al.		Nivolumab x 2 doses	SURGERY	
Shu et al.		Atezolizumab + Chemo x 4 cycles		
LCMC3		Atezolizumab x 2 doses		Optional atezolizumab x 1 year
NEOSTAR		Nivolumab + Chemo +/- Ipilimumab x 3 cycles		Optional Chemo
NADIM I		Nivolumab + Chemo x 3 cycles		Nivolumab x 1 year
NADIM II		Nivolumab + Chemo x 3 cycles		Nivolumab x 6 months
SAKK 16/14	Chemo x 3 cycles	Durvalumab x 2 doses		Durvalumab x 1 year
Altorki et al.		SBRT x 3; Durvalumab x 2		

Phase III

CheckMate 816		Nivolumab + Chemo x 3 cycles		Optional chemo or radiation
KEYNOTE-671		Pembrolizumab + Chemo x 4 cycles		Pembrolizumab x 1 year
AEGEAN		Durvalumab + Chemo x 3 cycles		Durvalumab x 1 year
NEOTORCH		Toripalimab + Chemo x 3 cycles		Chemo x 1 cycle / Toripalimab x 1 year
CheckMate 77T		Nivolumab + Chemo x 4 cycles		Nivolumab x 1 year

Adjuvant Trials

IMpower010				SOC Chemo / Atezolizumab x 1 year
PEARLS				SOC Chemo / Pembrolizumab x 1 year

Immunotherapy in neoadjuvant setting

Immunotherapy for earlier-stage resectable NSCLC (Neoadjuvant setting)

Study	Population	Intervention	Outcome
Forde et al **Neoadjuvant PD-1 Blockade in Resectable Lung Cancer – Pilot study** Single arm phase1b/II NEJM 2018	Untreated, surgically resectable early (stage I, II, or IIIA) NSCLC	N=21 Nivolumab (3 mg/kg) iv every 2 wks, with surgery planned ≈ 4 weeks after the first dose	20 underwent Sx, rates of MPR and pCR were 45% and 15%, 5-year RFS and OS rates were 60% and 80%
LCMC 3 study To investigate the efficacy and safety of **atezolizumab as neoadjuvant therapy in patients with stages IB - IIIB resectable NSCLC** A phase II multicentre single-arm study	Patients with stage IB to IIIB resectable NSCLC and ECOG PS - 0/1 without EGFR/ALK alteration	N = 181 Atezolizumab 1200 mg iv every 3 wks for 2 cycles or less followed by resection With optional adjuvant Atezolizumab	MPR was 20% (pCR 6%), and landmark 3-year DFS and OS were 72% and 80%, respectively

Study	Population	Intervetion	Outcome
CheckMate 816 Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer open-label, phase 3 trial NEJM 2022	Stage **IB to IIIA resectable NSCLC**	N=358, neoadjuvant nivo 360 mg plus chemo 3 cycles q3w(179 patients) or chemo 3 cycles q3w (179 patients) Followed by Sx within 6 wks post-treatment	The **median EFS** was **31.6 mo** (95% CI, 30.2 to NR) with nivo plus chemo and **20.8 mo** (95% CI, 14.0 to 26.7) with chemo alone (HR for disease progression, disease recurrence, or death, **0.63**; 97.38% CI, 0.43 to 0.91; p =0.005) The % of patients with a **pCR** was **24.0%** (95% CI, 18.0 to 31.0) and **2.2%**. (95% CI, 0.6 to 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 to 55.75; p < 0.001)
NEOSTAR Trial **Randomized phase II** Neoadjuvant chemo plus nivo with or without ipilimumab in operable NSCLC Platform trial – Neoadj Nivo + CT, and Nivo + Ipi + CT Nature 2021-22	Previously Untreated stage I –IIIA NSCLC	22 patients in each arm Arm A - neoadjuvant nivo (3 mg/kg i.v.), q14d on D1, D15 and D29 and Arm B - nivo + ipi (ipi 1 mg kg−1 i.v. on D1 only) Arm C – Nivo + CT Arm D – Nivo + Ipi + CT	The **MPR** in nivo + ipi grp (**38%**) vs in nivo-alone grp (**22%**) (PCR 2/6) When chemo was added, MPR rates increased to 50% and 32% in patients who received nivo + ipi and nivo, respectively (PCR 4/4) The 2-year EFS was 73% for nivo+ chemo and 77% for dual ICI + chemo

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer – CheckMate 816

- International, open-labeled, phase III trial
- Untreated resectable stage IB (≥4 cm) to IIIA NSCLC, with ECOG PS – 0 or 1
- Pts with ALK translocation or EGFR mutations were excluded
- Patients were randomly assigned in a 1:1 ratio

Forde et al Neoadjuvant Nivolumab plus chemotherapy in resectable lung cancer- NEJM 2022

- Patients in both groups could receive up to four cycles of adjuvant chemotherapy, radiotherapy, or both
- Two primary endpoints – **EFS** , **pCR**
- 83.2% in the nivo + CT group and 75.4% in the CT-alone group underwent definitive surgery
- R0 resection (no residual tumor) was performed in 83.2 % in nivo + CT group and 77.8 in CT-alone group

Forde et al Neoadjuvant Nivolumab plus chemotherapy in resectable lung cancer- NEJM 2022

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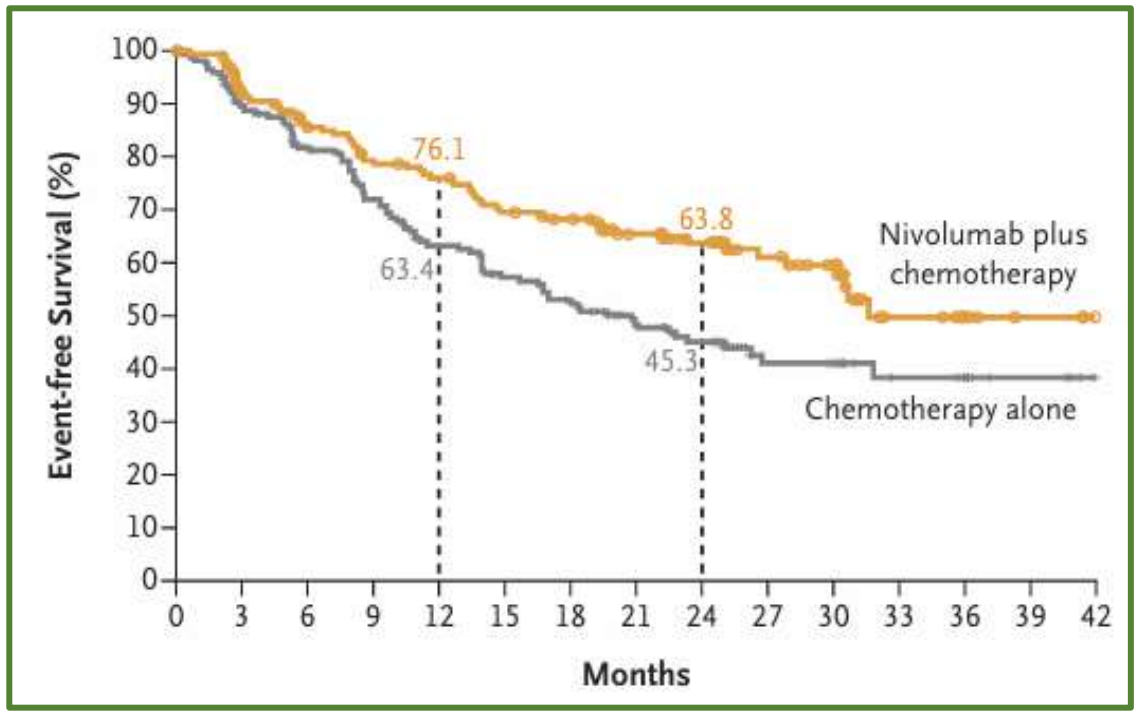

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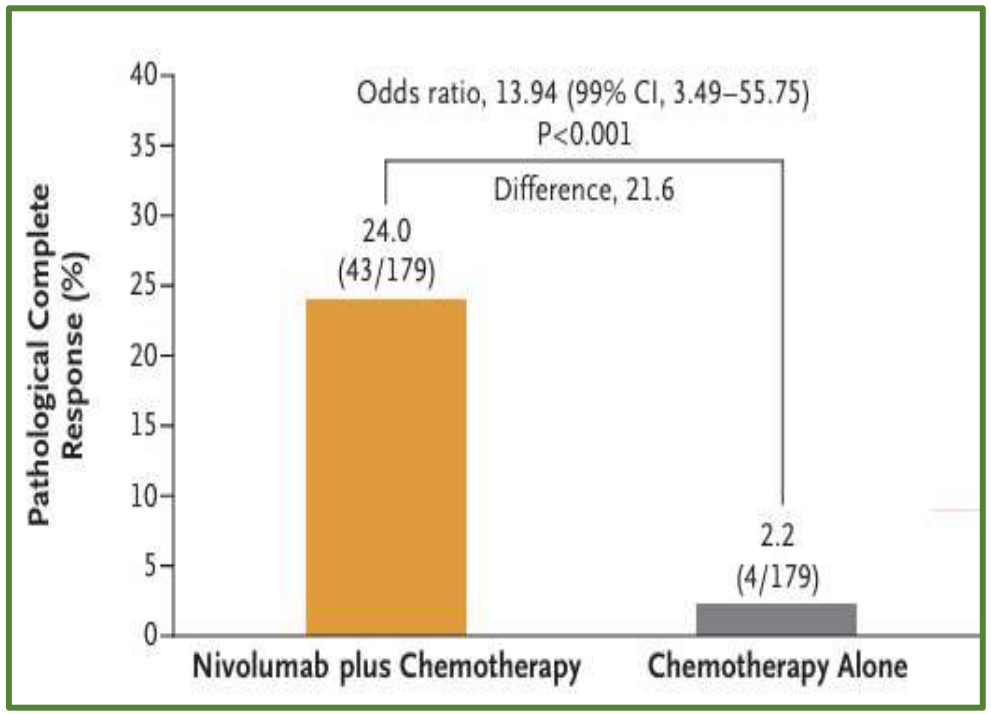
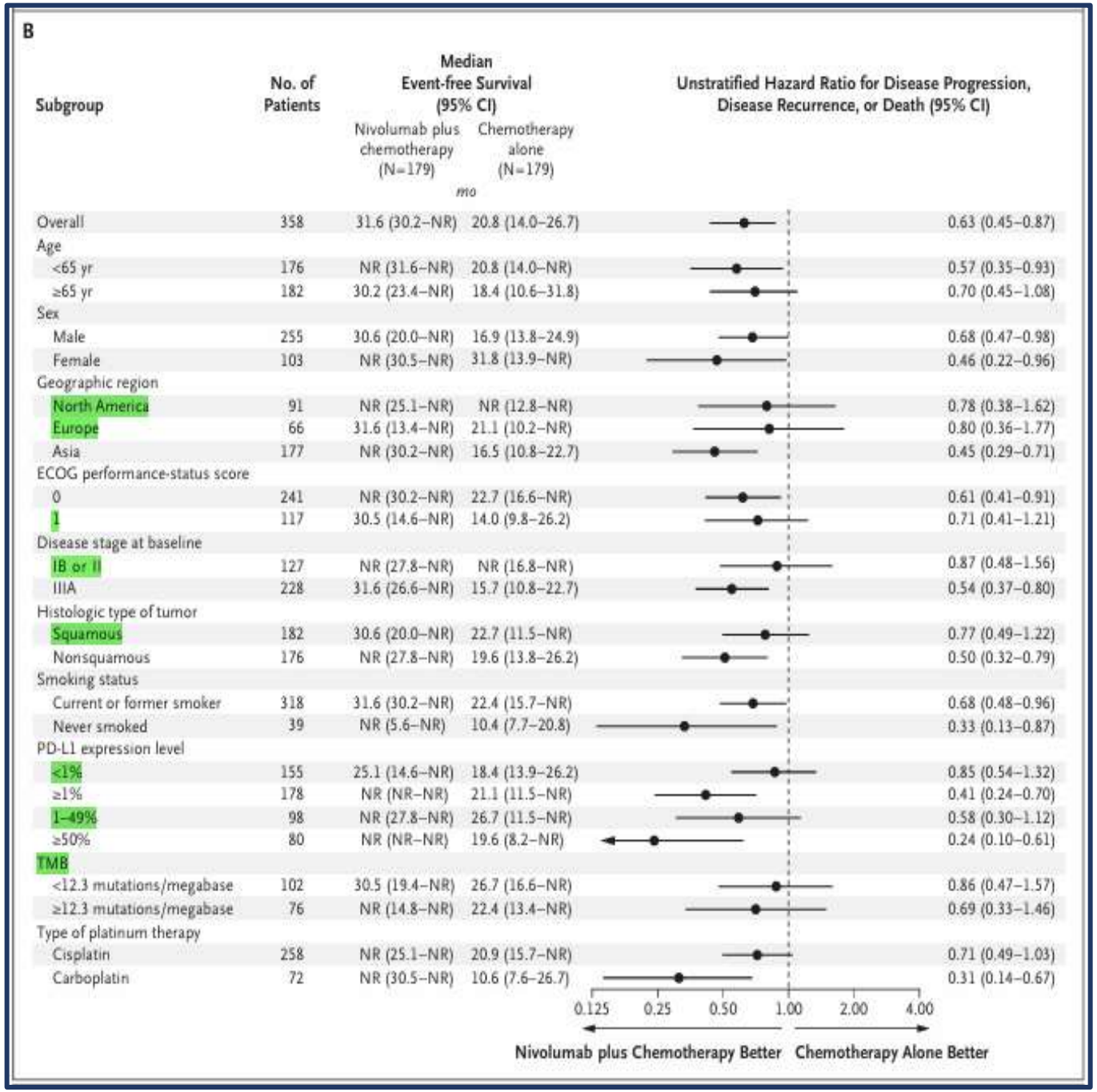
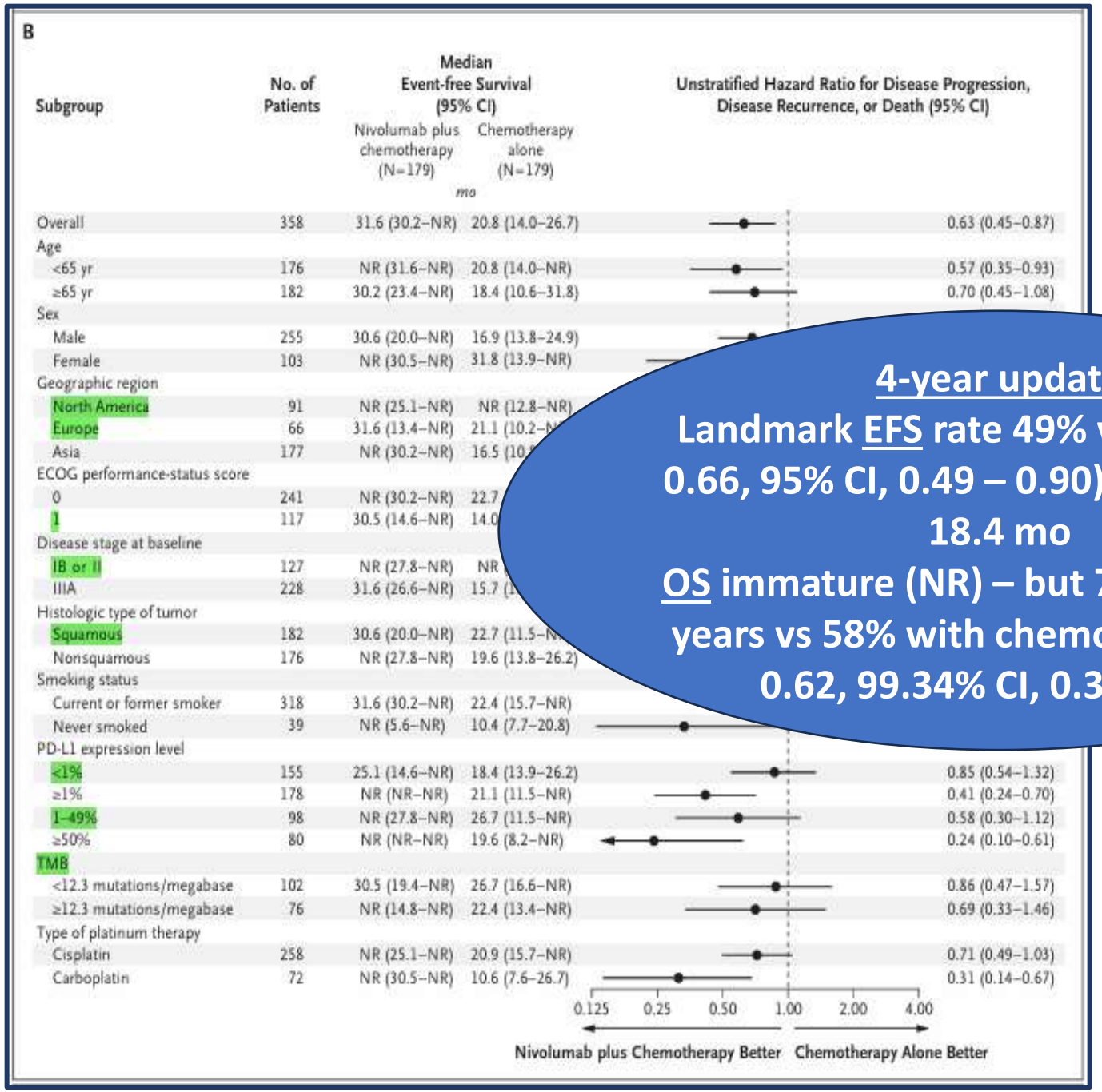


Median EFS 95% CI - 31.6 (30.2–NR) – Nivo + CT
20.8 (14.0–26.7) – CT- alone
HR - 0.63 (97.38% CI, 0.43–0.91), P = 0.005

Forde et al Neoadjuvant Nivolumab plus chemotherapy in resectable lung cancer- NEJM 2022



- Median OS was not reached in either groups - (HR for death, 0.57; 99.67% CI, 0.30 to 1.07; P = 0.008)
- **The % of patients with ctDNA clearance was higher with nivo + CT (56%; 95% CI, 40 to 71) than with CT alone (35%; 95% CI, 21 to 51)**
- **Patients with ctDNA clearance before the last cycle of neoadjuvant Rx were more likely to have pCR than patients with detectable ctDNA (46% vs 0%)**



4-year update

Landmark EFS rate 49% vs 38% (HR – 0.66, 95% CI, 0.49 – 0.90) – 43.8 mo vs 18.4 mo

OS immature (NR) – but 71% alive at 4 years vs 58% with chemo alone (HR – 0.62, 99.34% CI, 0.36 -1.05)

- At 1 yr % of patients without disease progression/recurrence – 76.1% vs 63.4%
- At 2 years - 63.8% and 45.3%
- …% vs. 8.9%; OR - 5.70; 95% CI -
- …t reached in either …death, 0.57; 99.67% CI, …07; P = 0.008)
- The % of patients with ctDNA clearance was higher with nivo + CT (56%; 95% CI, 40 to 71) than with CT alone (35%; 95% CI, 21 to 51)

Immunotherapy in perioperative setting

Immunotherapy in perioperative setting

Study	Population	Interventon	Outcome
NADIM I Neoadjv CT and nivolumab in resectable NSCLC - an open-label, multicentre, single-arm, phase 2 trial – LANCEL ONCOL 2020	**N = 46** Treatment-naive stage **IIIA** NSCLC with ECOG PS 0 or 1	Neoadjuvant iv paclitaxel (200 mg/m^2) and carboplatin (**AUC 6,** 6mg/ml/min) plus nivolumab (360 mg) q3w × 3 cycles before Sx, f/b adjuvant iv nivolumab for **1 year** (240 mg q2w for 4 mo, f/b 480 mg q4w for 8 mo)	The primary end-point of **PFS** at 2 years was **77%** **MPR of 83% and a pCR of 63%** 5-year PFS was 65·0% (95% CI 49·4–76·9), and OS was 69·3%
NADIM II Perioperative Nivolumab and Chemotherapy in Stage III NSCLC - open-label, phase 2 trial NEJM 2023	**N = 86, 2:1 ratio (57:29)** Previously untreated stage **IIIA or IIIB** NSCLC with ECOG PS 0 or 1	Experimental Grp - Nivolumab (360 mg), paclitaxel (200 mg/m2), and carboplatin (**AUC 5,** 5mg/ml/min) as neoadjuvant Rx q3w × 3 cycles f/b Sx If R0 resections - adjuvant Rx with nivolumab 480 mg q4w × **6 mo** Control group received paclitaxel and carboplat f/b surgery, and then 3 observation visits	The **pCR** rate was higher in the nivolumab + CT group (**37% vs 7%)** The nivolumab + CT group had significantly better **2-year PFS (67% vs 41%**; hazard ratio [HR], 0.47 [95% CI, 0.25-0.88]) and **OS** (**85% vs 64%;** HR, 0.43 [95% CI, 0.19-0.98]) 2/3 rd completed adjuvant Rx – Post hoc OS - HR, 0.29 [95% CI, 0.05-1.76]

Study	Population	Intervention	Outcome
SAKK 16/14 Durvalumab in Addition to Neoadjv CT in Patients With Stage IIIA(N2) NSCLC—A Multicenter Single-Arm Phase II Trial	N = 68 Pathologically proven, locally advanced T1-3N2M0, stage IIIA(N2) NSCLC, ECOG 0 or 1	Neoadjuvant 3 cycles of cisplatin (100mg/m2) and docetaxel (85mg/m2) q3w f/b 2 doses of durvalumab (750mg q2w).Durvalumab was continued for 1 year (26 cycles) after surgery	MPR and pCR were achieved in 62% and 18% 1-year EFS and OS were 73% and 91%

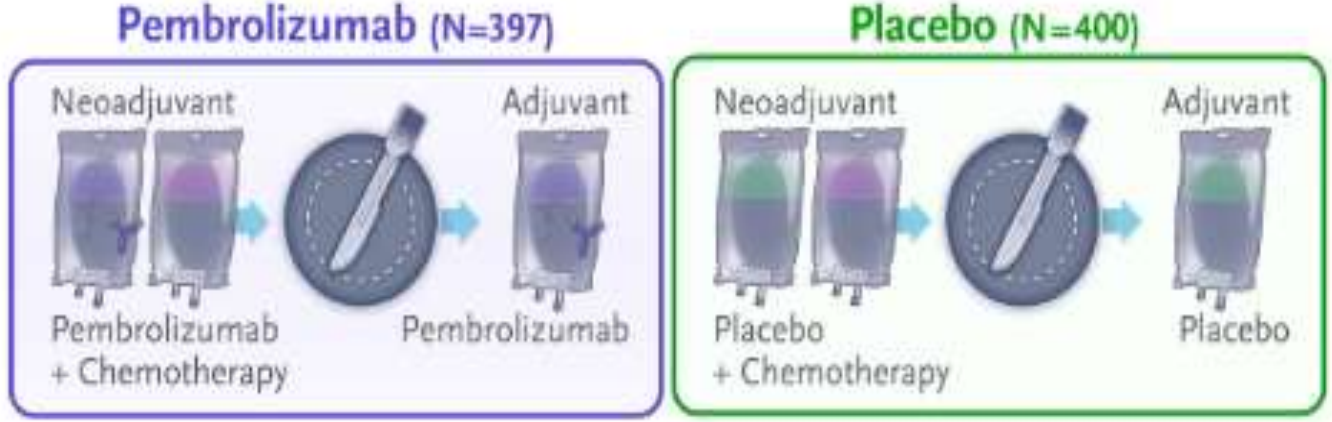
Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*

NEJM 2023

Grp 1- Neoadjv pembrolizumab (200 mg)+ CT q3w 4 cycles
f/b Sx, f/b Adjuvant pembro (200 mg) iv q3w for 13 cycles
Grp 2- Plus neoadjv CT – Cis + gem or cis + peme – 4 cycles
F/b Sx within 20 wks of 1st dose
Adjuvant placebo iv q3w for 13 cycles

Phase 3, double-blind, placebo-controlled, RCT
N = 797

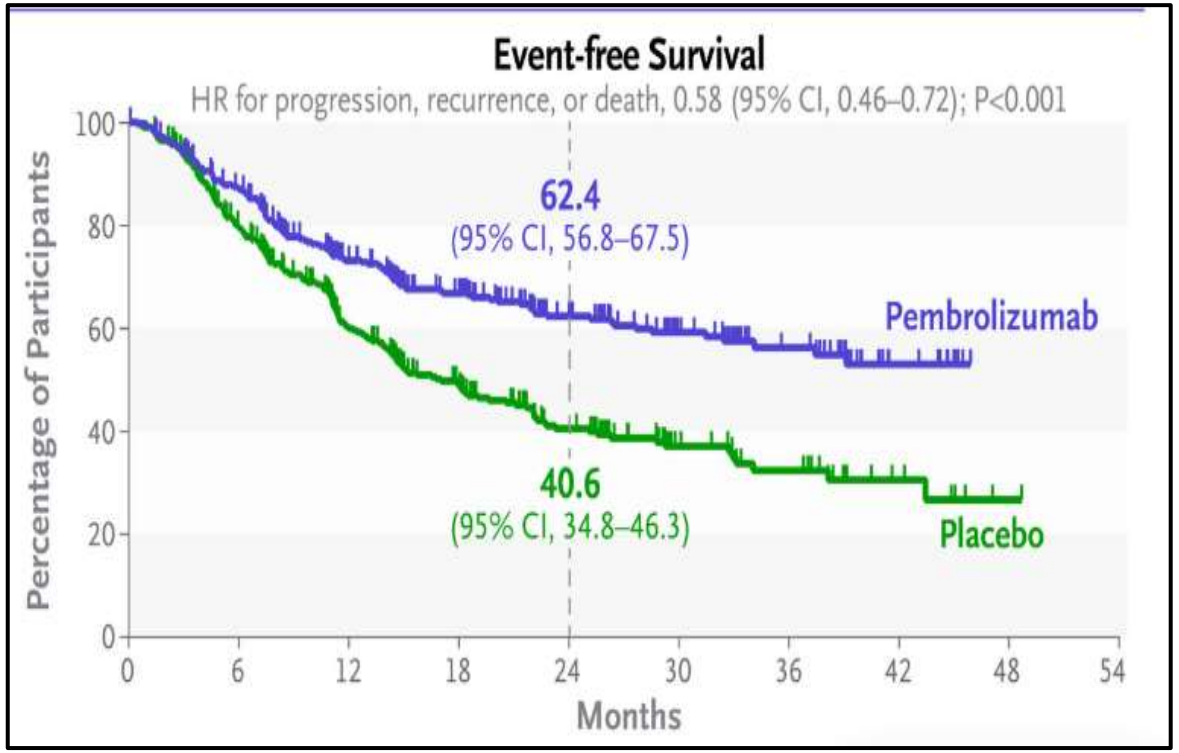


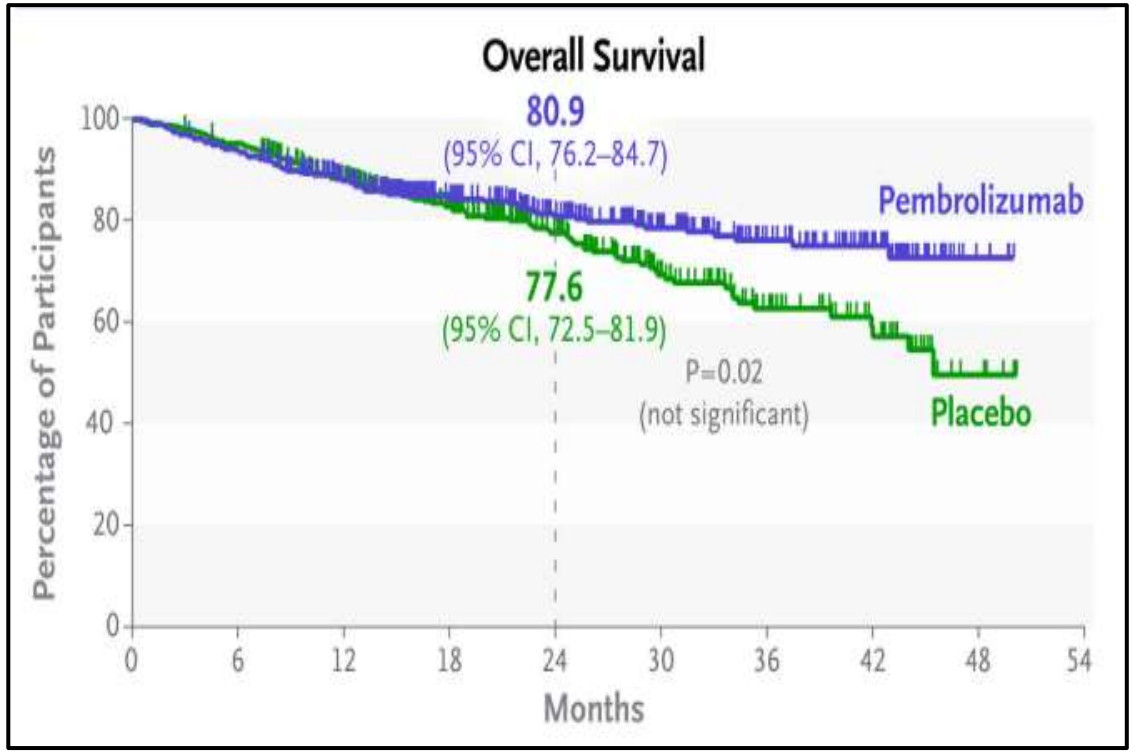
Primary end points – EFS and OS

Secondary end points – MPR, pCR, safety

H. Wakelee et al. Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer, NEJM 2023;389:491-503

- In pembrolizumab grp -325 (82.1%) underwent Sx, and 290 (73.2%) received at least one dose of adjuvant pembrolizumab
- In placebo grp -317 (79.4%) underwent Sx, and 267 (66.9%) received at least one dose of adjuvant placebo





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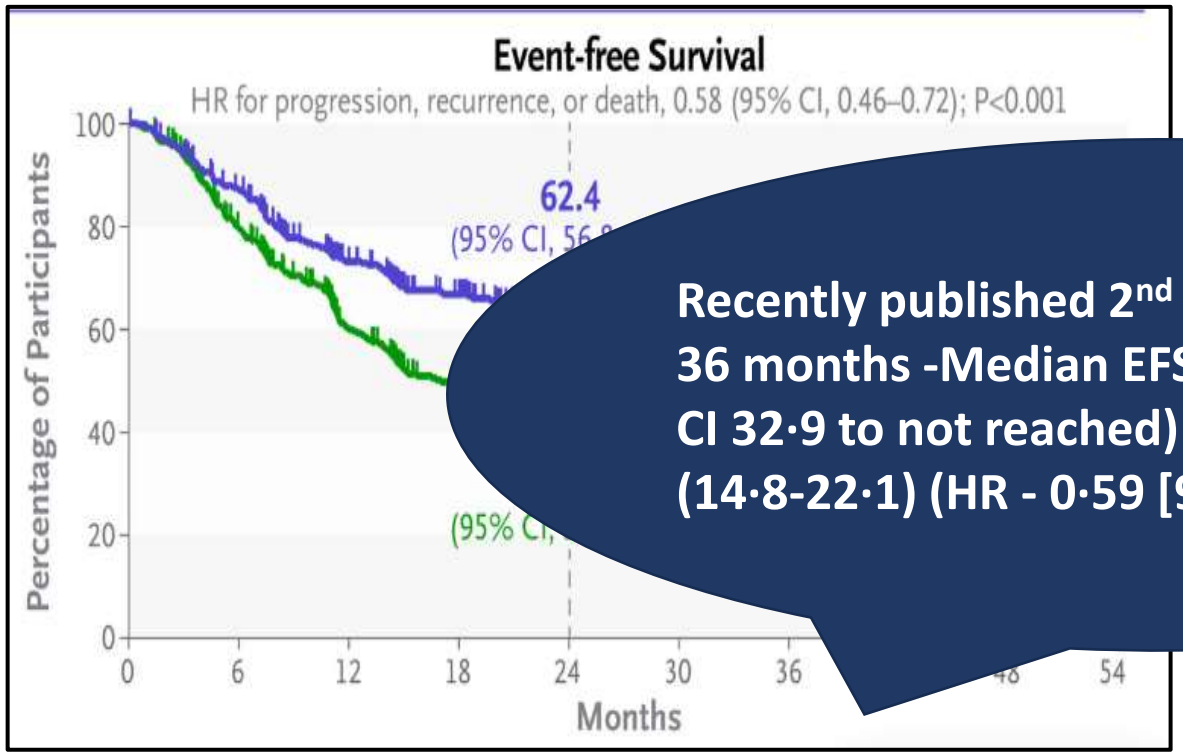
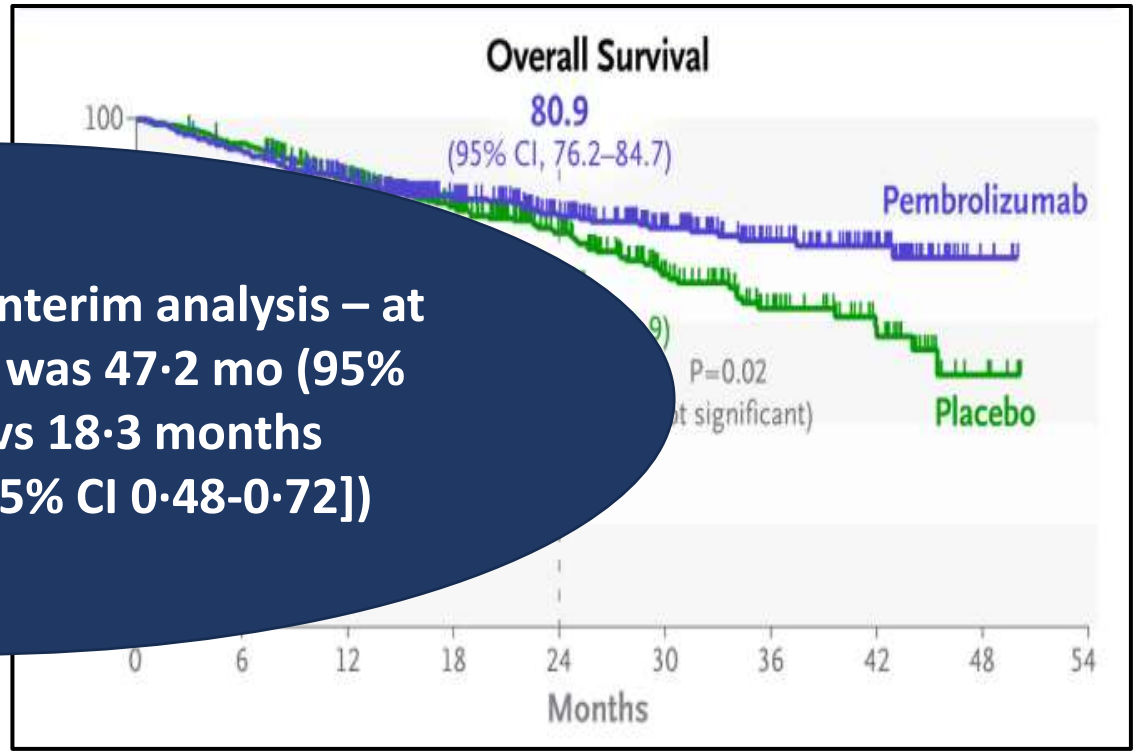


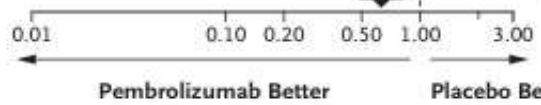
Recently published 2nd interim analysis – at 36 months -Median EFS was 47·2 mo (95% CI 32·9 to not reached) vs 18·3 months (14·8-22·1) (HR - 0·59 [95% CI 0·48-0·72])

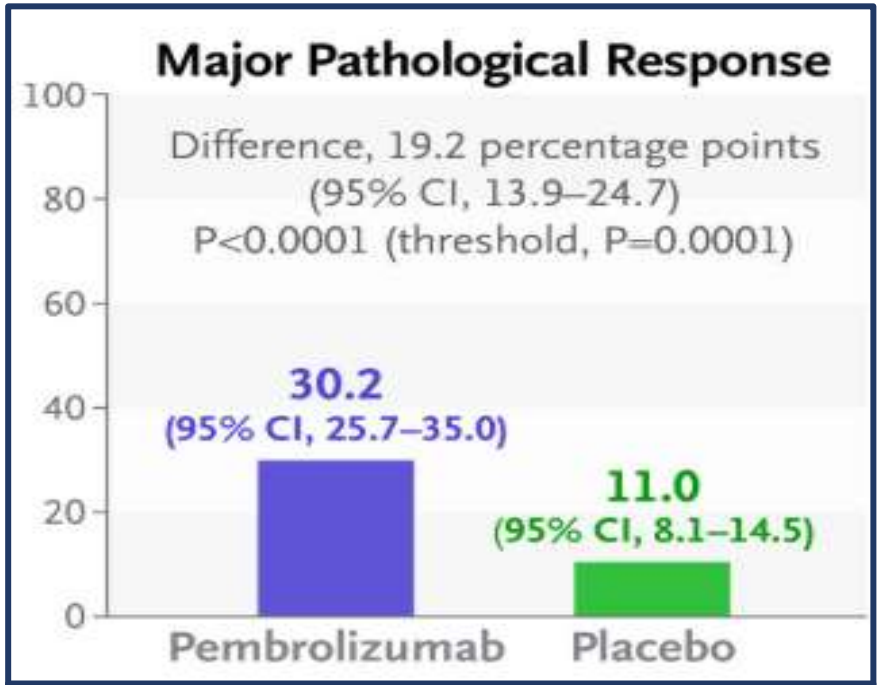


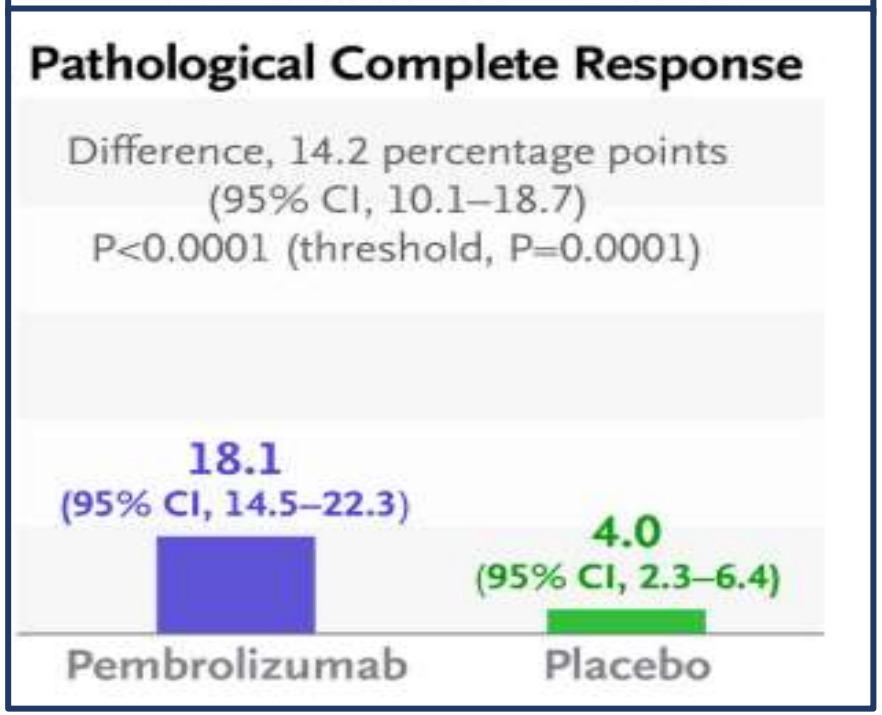
H. Wakelee et al. Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer, NEJM 2023;389:491-503

B Subgroup Analysis of Event-free Survival

Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)
	no. of events/no. of participants		
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	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)
Other	46/134	70/145	0.62 (0.42–0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45–0.99)
Other	96/274	148/279	0.54 (0.41–0.69)
Smoking status			
Current smoker	37/96	57/103	0.52 (0.34–0.78)
Former smoker	84/247	128/250	0.57 (0.43–0.75)
Never smoked	18/54	20/47	0.68 (0.36–1.30)
Pathological stage			
II	34/118	48/121	0.65 (0.42–1.01)
III	105/279	157/279	0.54 (0.42–0.70)
Histologic features			
Nonsquamous	73/226	107/227	0.58 (0.43–0.78)
Squamous	66/171	98/173	0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
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)

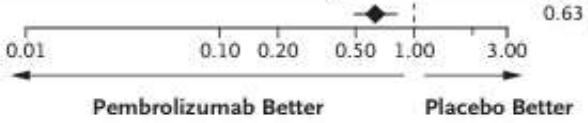




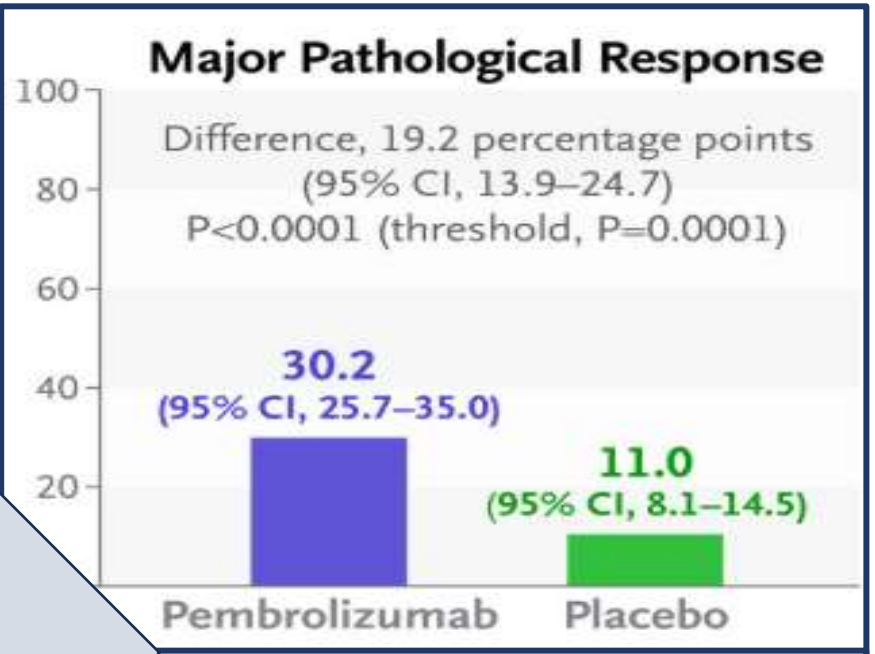


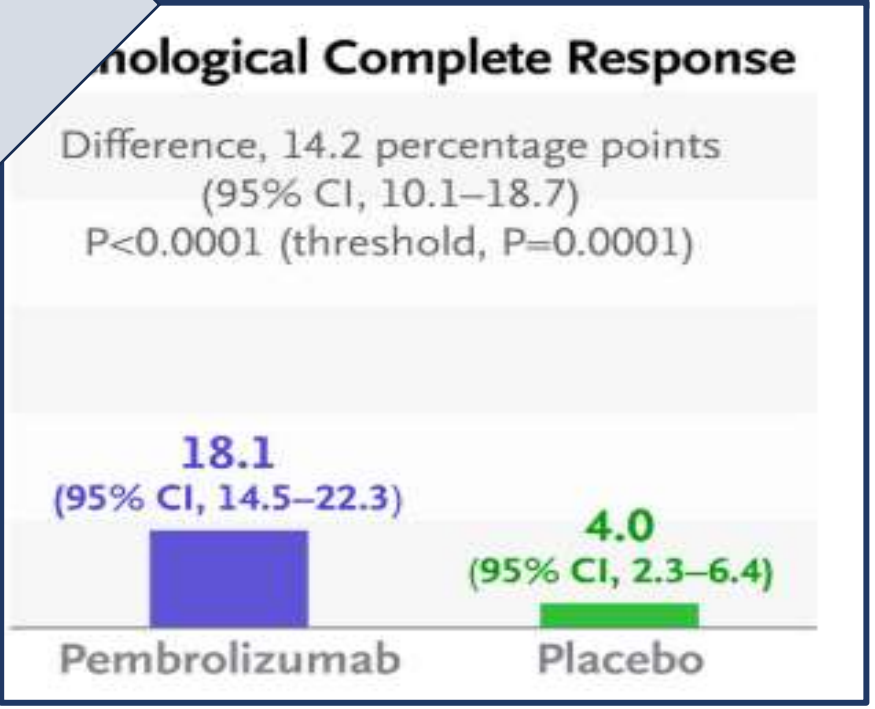
B Subgroup Analysis of Event-free Survival

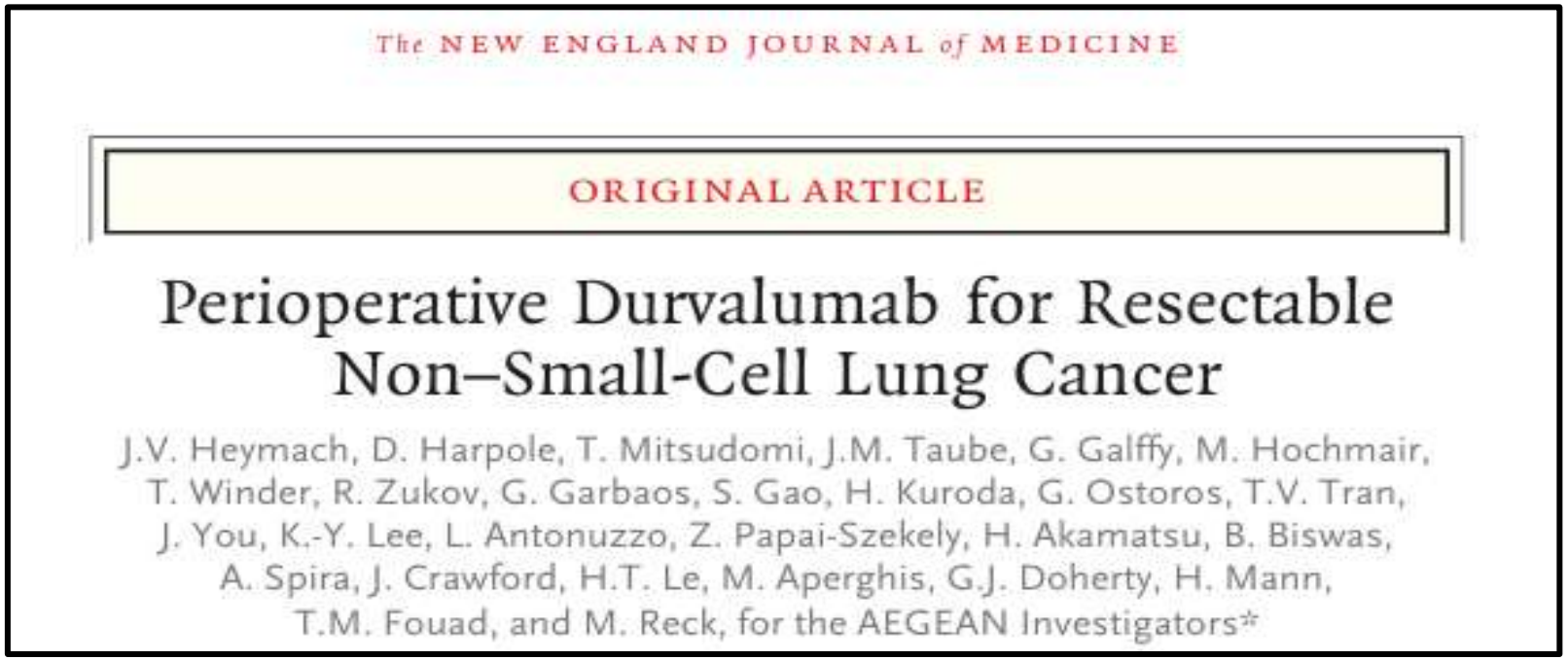
Subgroup	Pembrolizumab Group (no. of events/no. of participants)	Placebo Group (no. of events/no. of participants)	Hazard Ratio for Event or Death (95% CI)
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	65/176	92/186	0.64 (0.46–0.88)
Sex			
Female	31/118	55/116	(0.28–0.68)
Male	108/279	150/284	49–0.80)
Race			
White	85/250	123/239	72)
Other	46/134	70/145	
Geographic region			
East Asia			
Other			
Smoking status			
Current smoker			
Former smoker			
Never smoked			
Pathological stage			
II			
III			
Histologic features			
Nonsquamous			
Squamous			
PD-L1 TPS (50% cutoff)			
<50%			
≥50%	32/132	63/134	
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	.07)
≥1%	76/259	125/249	–0.63)
PD-L1 TPS			
<1%	63/138	80/151	(0.55–1.07)
1–49%	44/127	62/115	.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)



Recently published second interim analysis, the OS benefit in the pembrolizumab arm with 71% survival at 36 months vs 64% in the placebo arm (HR 0.72; 95% CI 0.56–0.93; one-sided P = 0.0052)



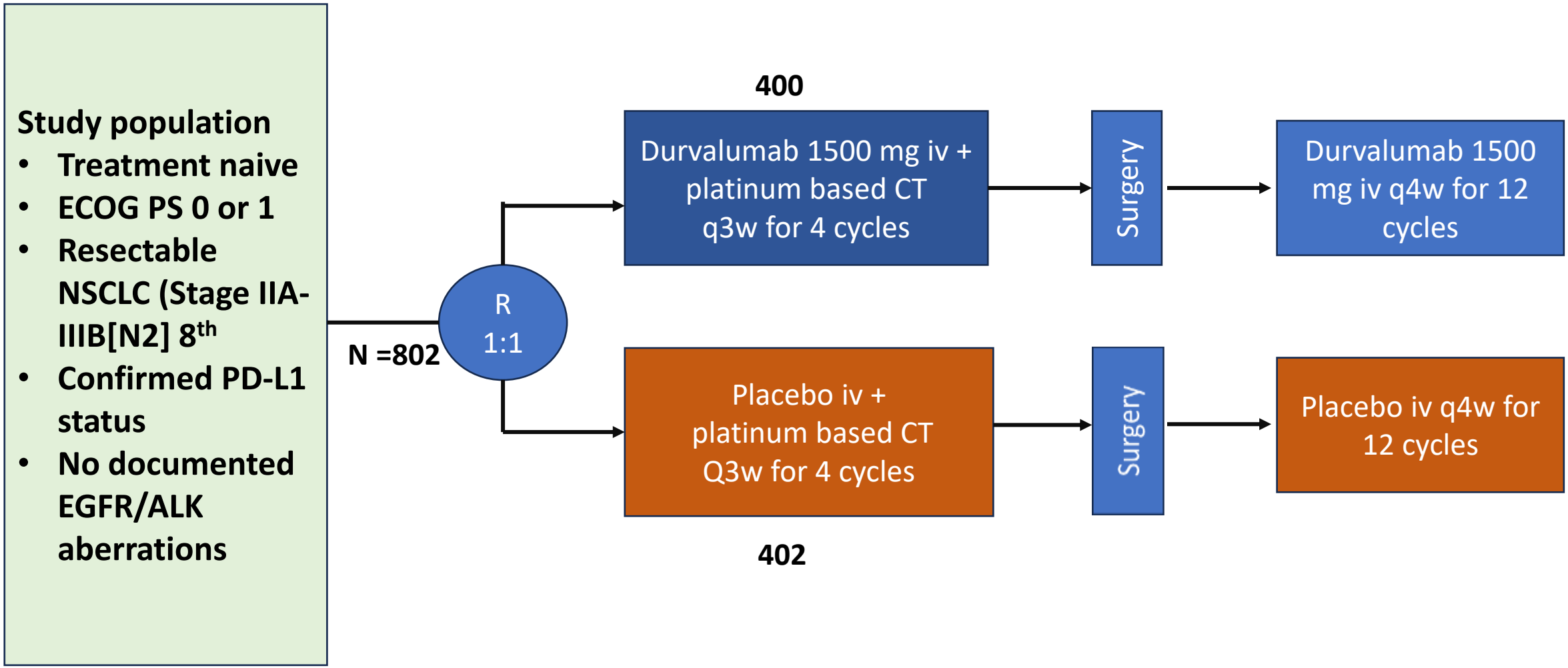




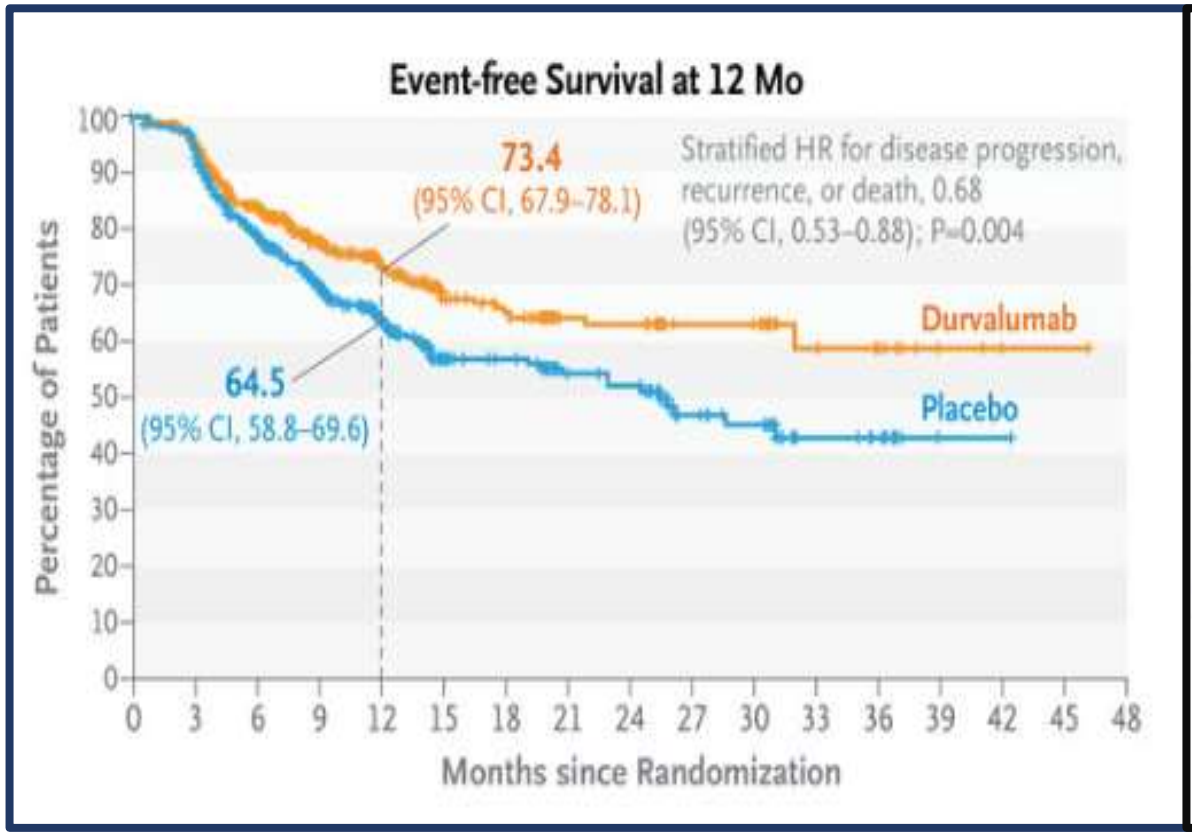
N = 802, 1:1
400 vs 402 (Placebo)
previously untreated, resectable NSCLC (stage IIA to IIIB disease)

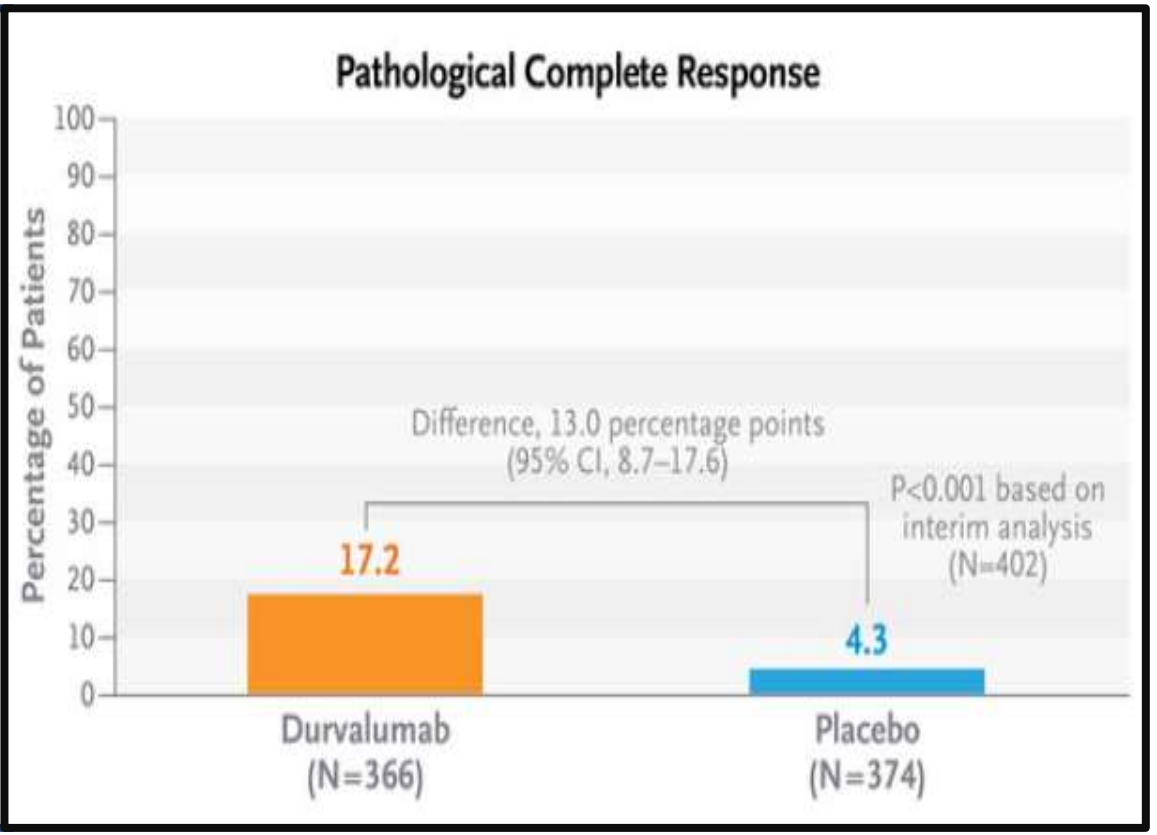
Primary end points – EFS and pCR
Secondary end points – MPR, DFS, OS

J.V. Heymach et al. Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer, NEJM 2023, 389;18



J.V. Heymach et al. Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer, NEJM 2023, 389;18

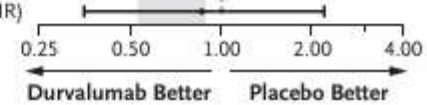




J.V. Heymach et al. Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer, NEJM 2023, 389;18

B Subgroup Analysis

Subgroup	No. of Patients	Median Event-free Survival (95% CI) Durvalumab	Placebo	Hazard Ratio for Disease Progression, Recurrence, or Death (95% CI)
		mo		
All patients	740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization				
<65 yr	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
≥65 yr	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 performance-status score				
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)
Geographic region				
Asia	305	NR (NR–NR)	22.9 (13.9–NR)	0.62 (0.41–0.93)
Europe	281	31.9 (31.9–NR)	NR (14.3–NR)	0.75 (0.49–1.14)
North America	86	NR (21.8–NR)	24.5 (10.0–NR)	0.69 (0.27–1.62)
South America	68	16.5 (13.0–NR)	11.0 (7.1–NR)	0.71 (0.33–1.53)
Smoking status				
Current smoker	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
Former smoker	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
Never smoked	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histologic features				
Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
Nonsquamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage				
II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
Lymph node station				
N2 single	273	NR (NR–NR)	22.8 (12.6–NR)	0.61 (0.39–0.94)
N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.69 (0.33–1.38)
PD-L1 expression at baseline				
Tumor cell <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
Tumor cell 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
Tumor cell ≥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)
EGFR-mutation positive	51	30.8 (11.4–NR)	19.6 (14.3–NR)	0.86 (0.35–2.19)



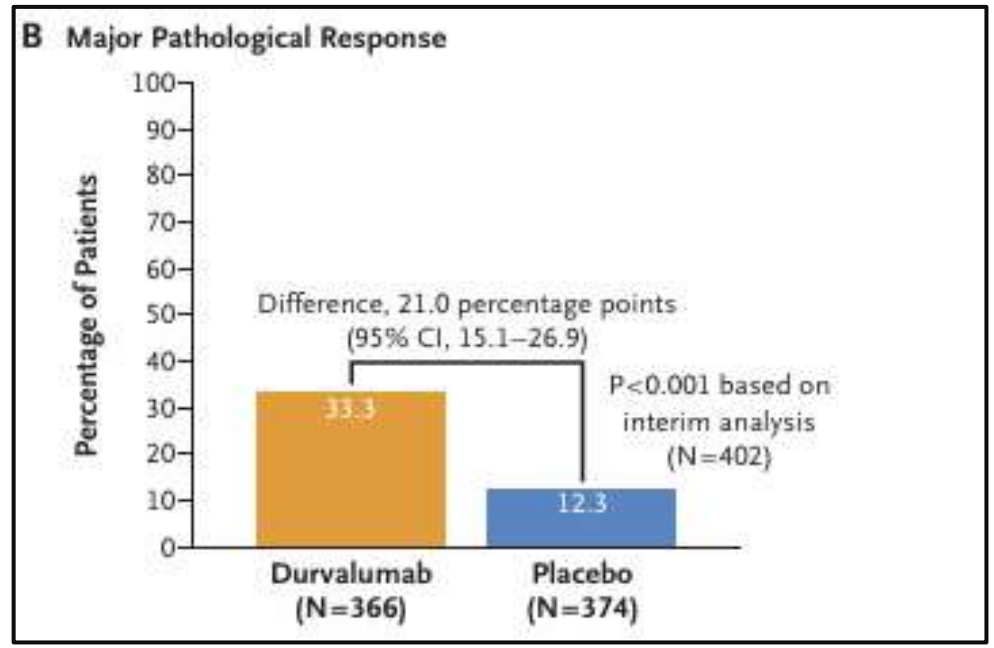


TABLE Summary of End Points of Phase III Neoadjuvant or Perioperative Trials in Resectable Non-small Cell Lung Cancer

	CheckMate 816		KEYNOTE-671		AEGEAN	
Variable	Nivolumab (n = 179)	Control (n = 179)	Pembrolizumab (n = 397)	Control (n = 400)	Durvalumab (n = 400)	Control (n = 402)
Completed neoadjuvant therapy	94	85	75	74	85	87
Underwent surgery	83	75	82	79	81	81
Minimally invasive surgery approach	30	22	NR	NR	49	47
R0 rate	83	78	92	84	95	91
Pathologic complete response rate	24	2	18	4	17	4
Major pathologic response rate	37	9	30	11	33	12
Completed adjuvant therapy	NA	NA	40	35	24	21
Ongoing adjuvant therapy	NA	NA	11	11	23	24
Discontinued adjuvant treatment	NA	NA	22	20	19	19
Did not receive any adjuvant treatment	NA	NA	27	33	34	37
2-year event-fee survival	64	45	62	41	63	52
2-year overall survival	83	71	71[a]	64[a]	NR	NR

Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non–Small Cell Lung Cancer - The Neotorch Randomized Clinical Trial

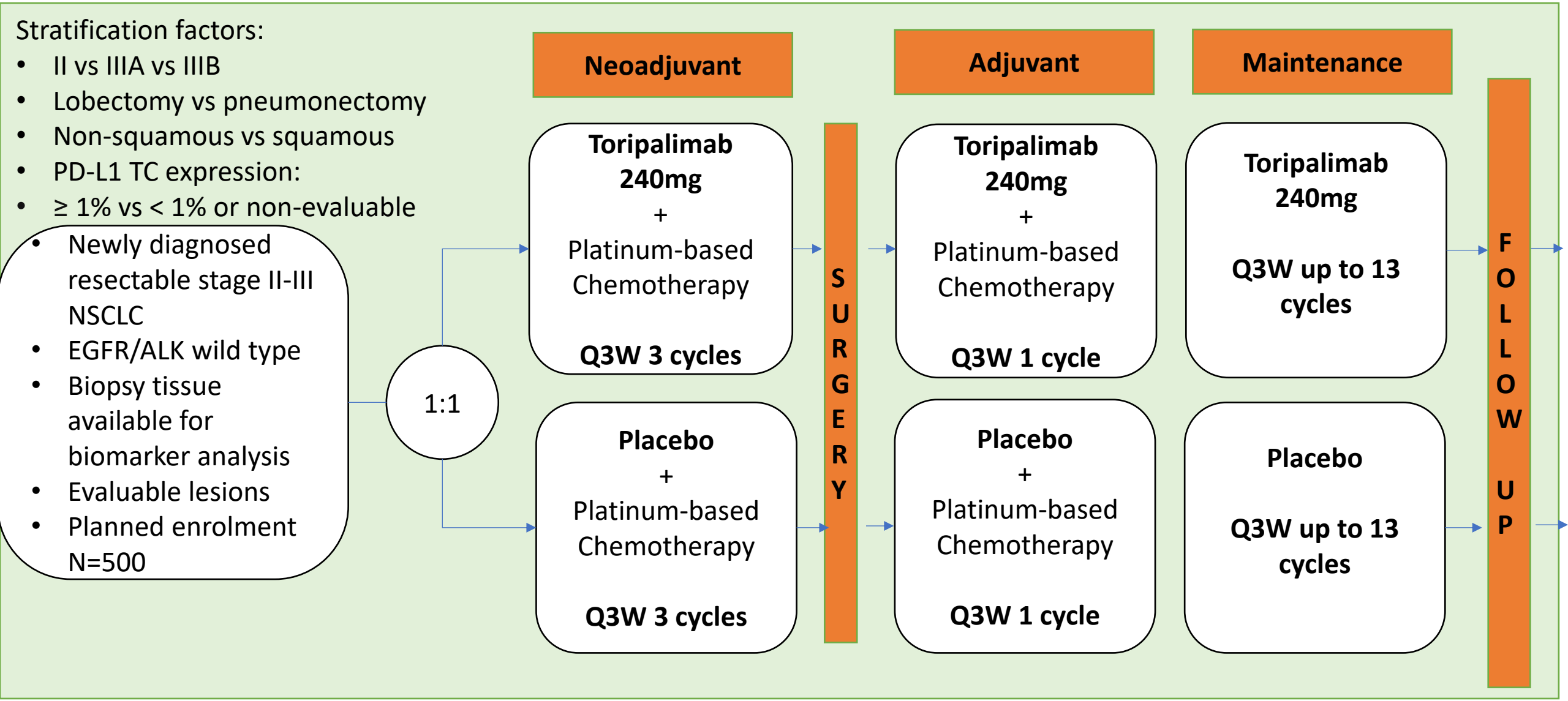
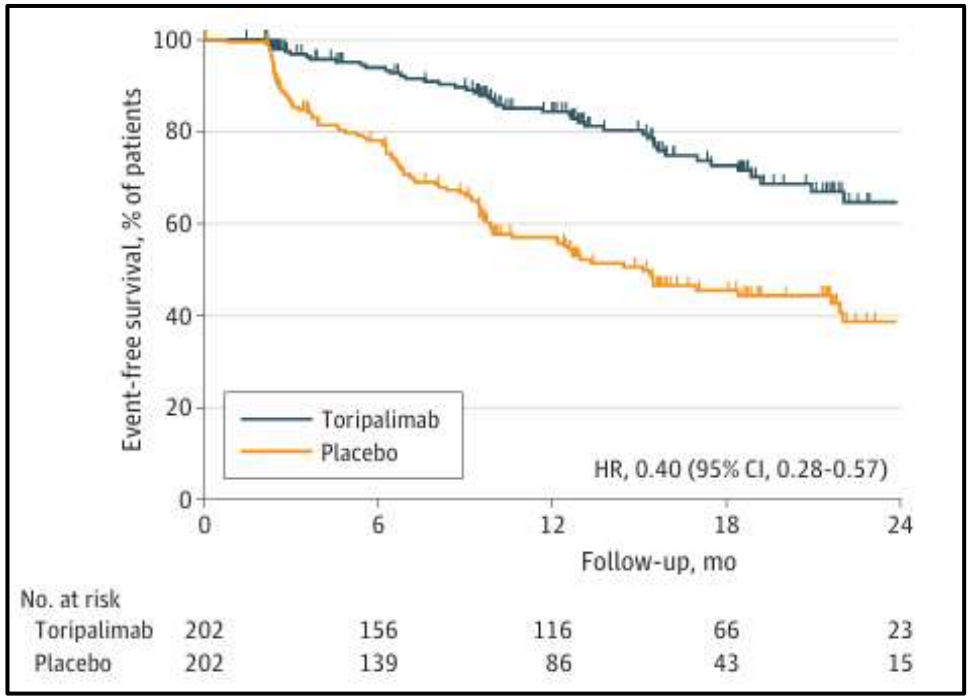


Table 2. Primary and Secondary Outcomes as of November 30, 2022

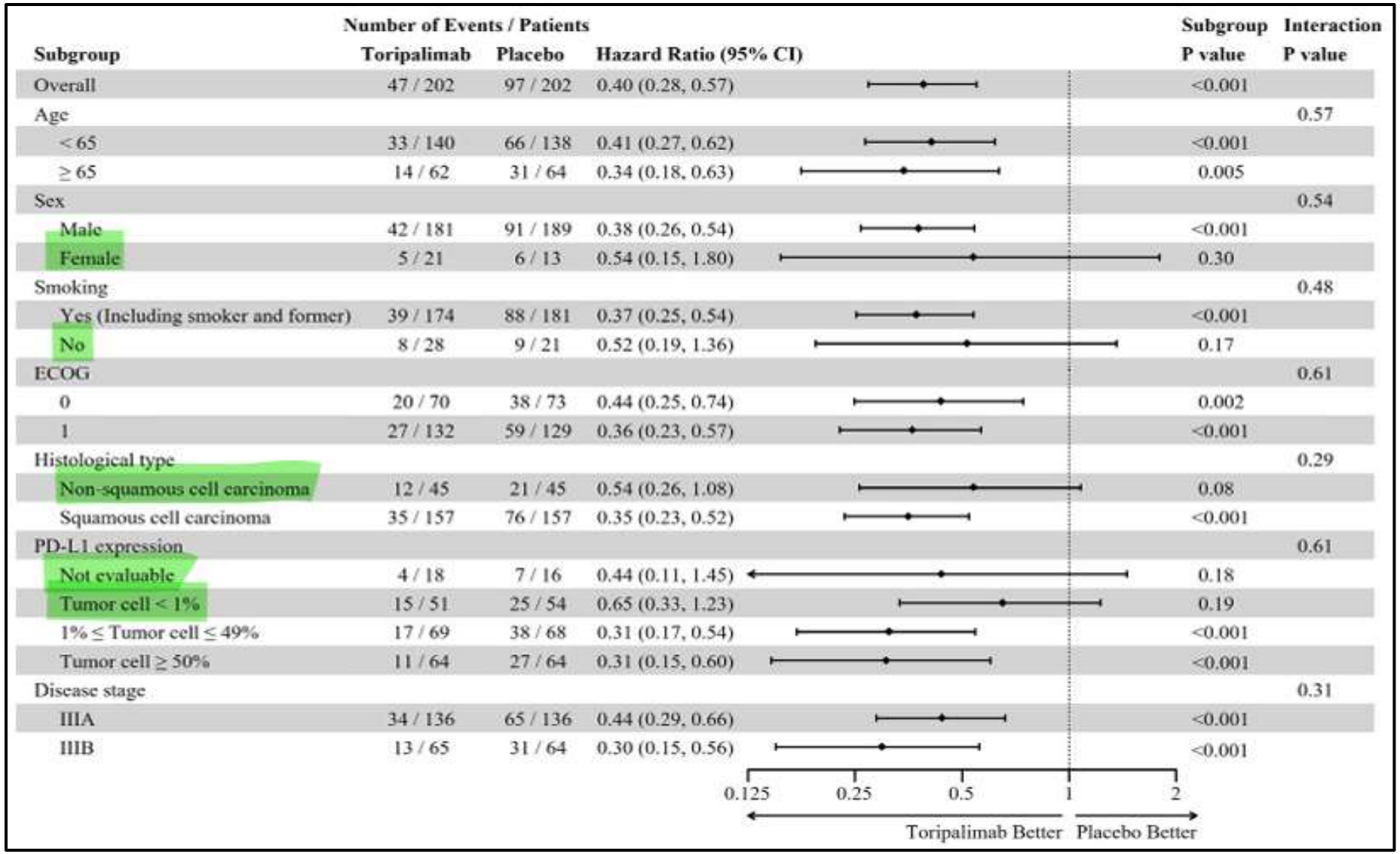
	Toripalimab + chemotherapy (n = 202)	Placebo + chemotherapy (n = 202)	Between-group difference (95% CI)[a]	Hazard ratio (95% CI)[b]	*P* value
Primary outcomes[c]					
Event-free survival, median (95% CI), mo[d]	NE (24.4-NE)	15.1 (10.6-21.9)		0.40 (0.28-0.57)	<.001[e]
Major pathological response rate (95% CI), %[f]	48.5 (41.4-55.6)	8.4 (5.0-13.1)	40.2 (32.2-48.1)		<.001[g]
Secondary outcomes					
Overall survival, median (95% CI), mo[d]	NE (NE-NE)	30.4 (29.2-NE)		0.62 (0.38-1.00)	.05[e]
Event-free survival, median (95% CI), mo[d,h]	NE (NE-NE)	15.5 (9.9-NE)		0.40 (0.27-0.57)	<.001[e]
Pathological complete response rate (95% CI), %[f]					
Assessed by blinded, independent pathological review	24.8 (19.0-31.3)	1.0 (0.1-3.5)	23.7 (17.6-29.8)		<.001[g]
Assessed by local pathologists	28.2 (22.1-35.0)	1.0 (0.1-3.5)	27.2 (20.8-33.5)		<.001[g]
Disease-free survival among patients who underwent surgery, median (95% CI), mo[d]	(n = 166)	(n = 148)			
Assessed by the independent review committee	NE (NE-NE)	22.0 (14.2-NE)		0.49 (0.31-0.76)	.001[e]
Assessed by the investigators	NE (22.0-NE)	19.3 (12.9-NE)		0.50 (0.33-0.76)	<.001[e]
Tumor response rate after receiving neoadjuvant treatment, % (95% CI)[f]					
Objective response[i]	64.4 (57.3-71.0)	32.7 (26.3-39.6)	31.5 (22.2-40.9)		<.001[g]
Disease control[j]	93.6 (89.2-96.5)	83.2 (77.3-88.1)	8.5 (3.0-14.0)		.002[g]

EFS



Shun Lu et al. Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non–Small Cell Lung Cancer JAMA.2024;331(3):201-211

Subgroup analysis of EFS



Subgroup	Number of Events / Patients: Toripalimab	Placebo	Hazard Ratio (95% CI)	Subgroup P value	Interaction P value
Overall	47 / 202	97 / 202	0.40 (0.28, 0.57)	<0.001	
Age					0.57
< 65	33 / 140	66 / 138	0.41 (0.27, 0.62)	<0.001	
≥ 65	14 / 62	31 / 64	0.34 (0.18, 0.63)	0.005	
Sex					0.54
Male	42 / 181	91 / 189	0.38 (0.26, 0.54)	<0.001	
Female	5 / 21	6 / 13	0.54 (0.15, 1.80)	0.30	
Smoking					0.48
Yes (Including smoker and former)	39 / 174	88 / 181	0.37 (0.25, 0.54)	<0.001	
No	8 / 28	9 / 21	0.52 (0.19, 1.36)	0.17	
ECOG					0.61
0	20 / 70	38 / 73	0.44 (0.25, 0.74)	0.002	
1	27 / 132	59 / 129	0.36 (0.23, 0.57)	<0.001	
Histological type					0.29
Non-squamous cell carcinoma	12 / 45	21 / 45	0.54 (0.26, 1.08)	0.08	
Squamous cell carcinoma	35 / 157	76 / 157	0.35 (0.23, 0.52)	<0.001	
PD-L1 expression					0.61
Not evaluable	4 / 18	7 / 16	0.44 (0.11, 1.45)	0.18	
Tumor cell < 1%	15 / 51	25 / 54	0.65 (0.33, 1.23)	0.19	
1% ≤ Tumor cell ≤ 49%	17 / 69	38 / 68	0.31 (0.17, 0.54)	<0.001	
Tumor cell ≥ 50%	11 / 64	27 / 64	0.31 (0.15, 0.60)	<0.001	
Disease stage					0.31
IIIA	34 / 136	65 / 136	0.44 (0.29, 0.66)	<0.001	
IIIB	13 / 65	31 / 64	0.30 (0.15, 0.56)	<0.001	

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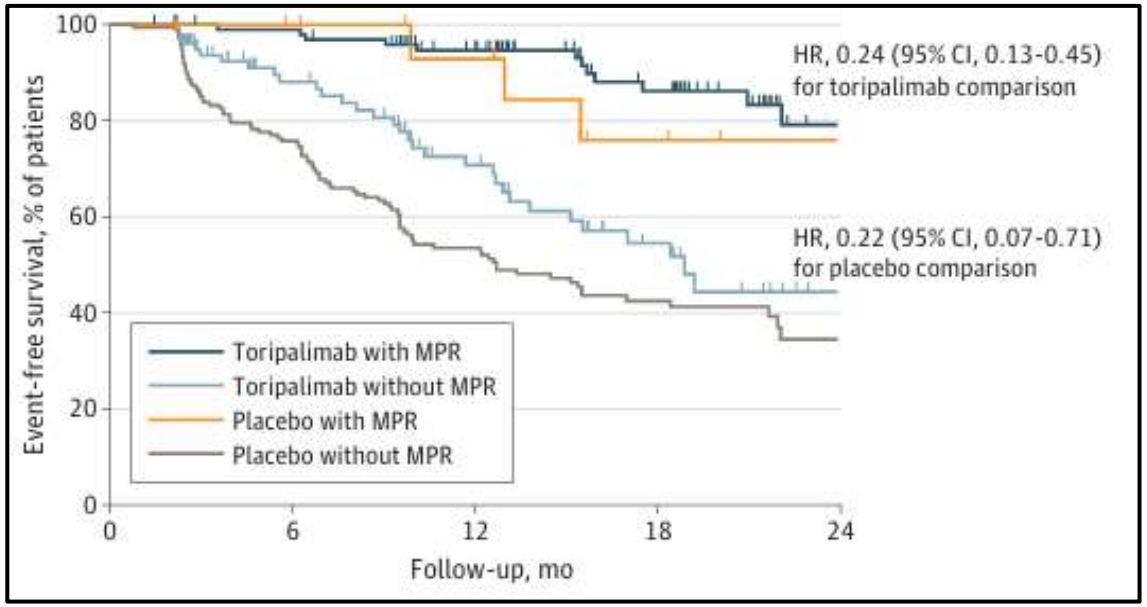
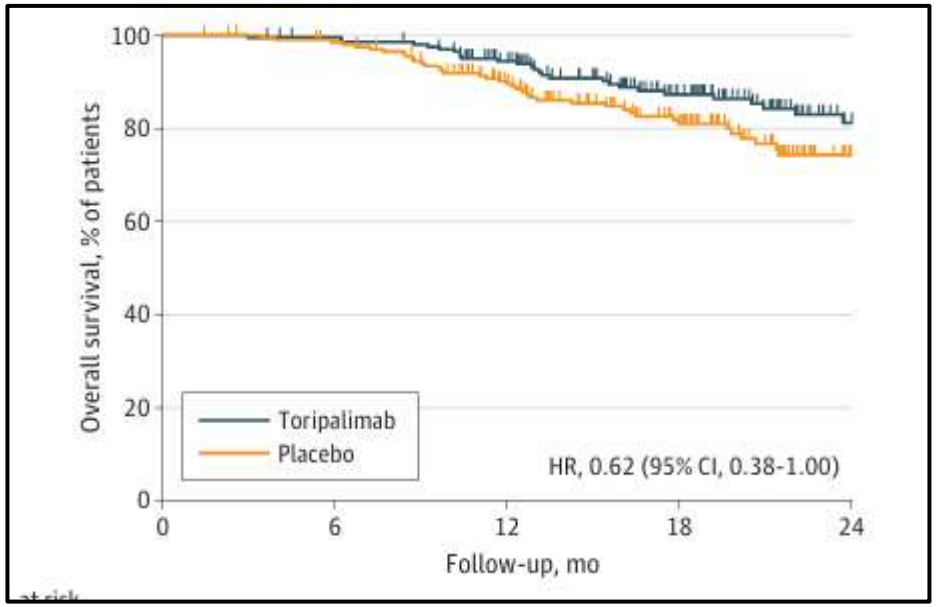
EFS in MPR subgroups



OS



MPR rate – 48.5% in ICI + CT vs 8.4% in CT arm

pCR rate – 24.8% in ICI + CT vs 1% in CT arm

Shun Lu et al. Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non–Small Cell Lung Cancer JAMA.2024;331(3):201-211

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

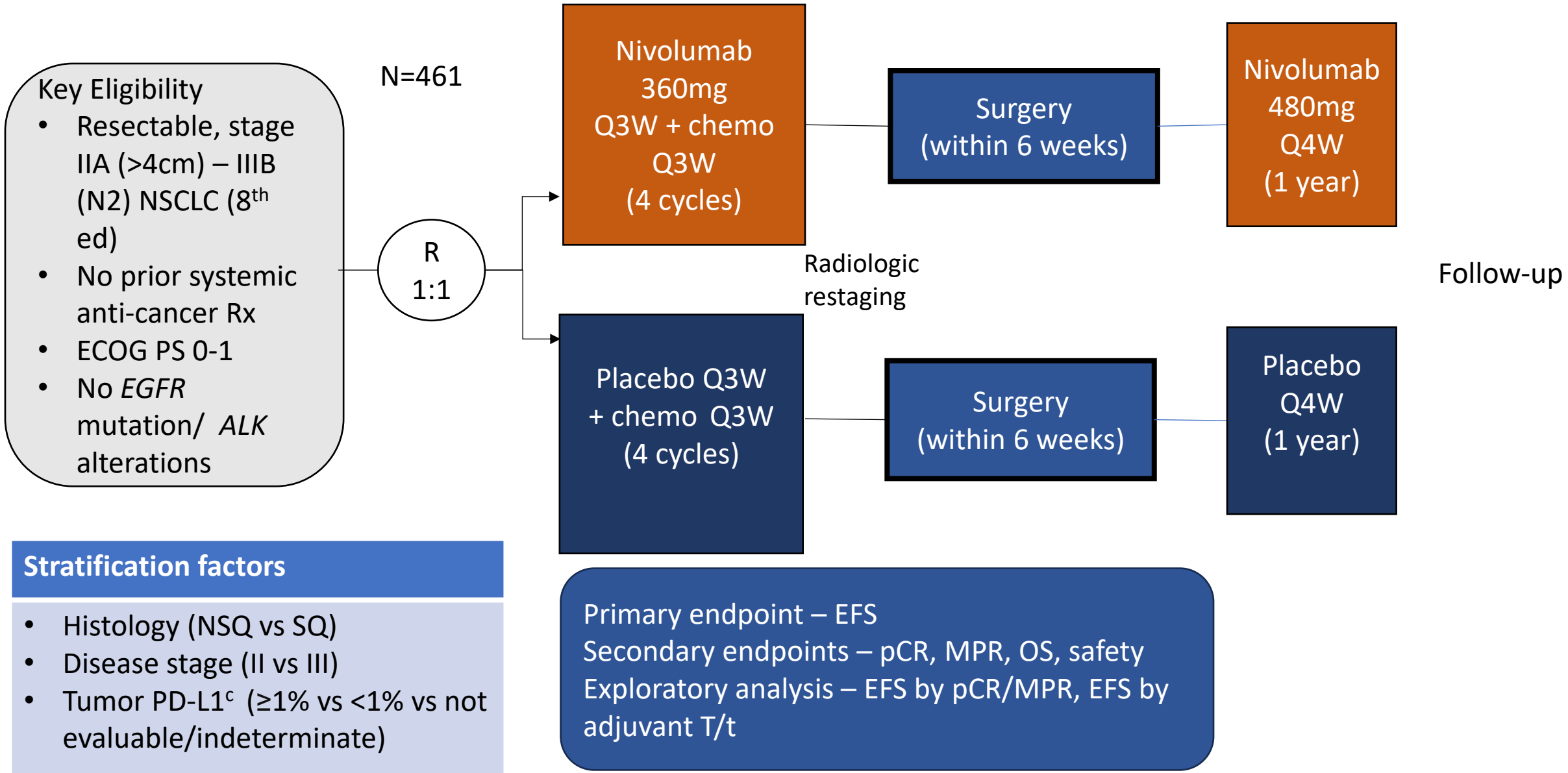
Perioperative Nivolumab in Resectable Lung Cancer

CheckMate 77T

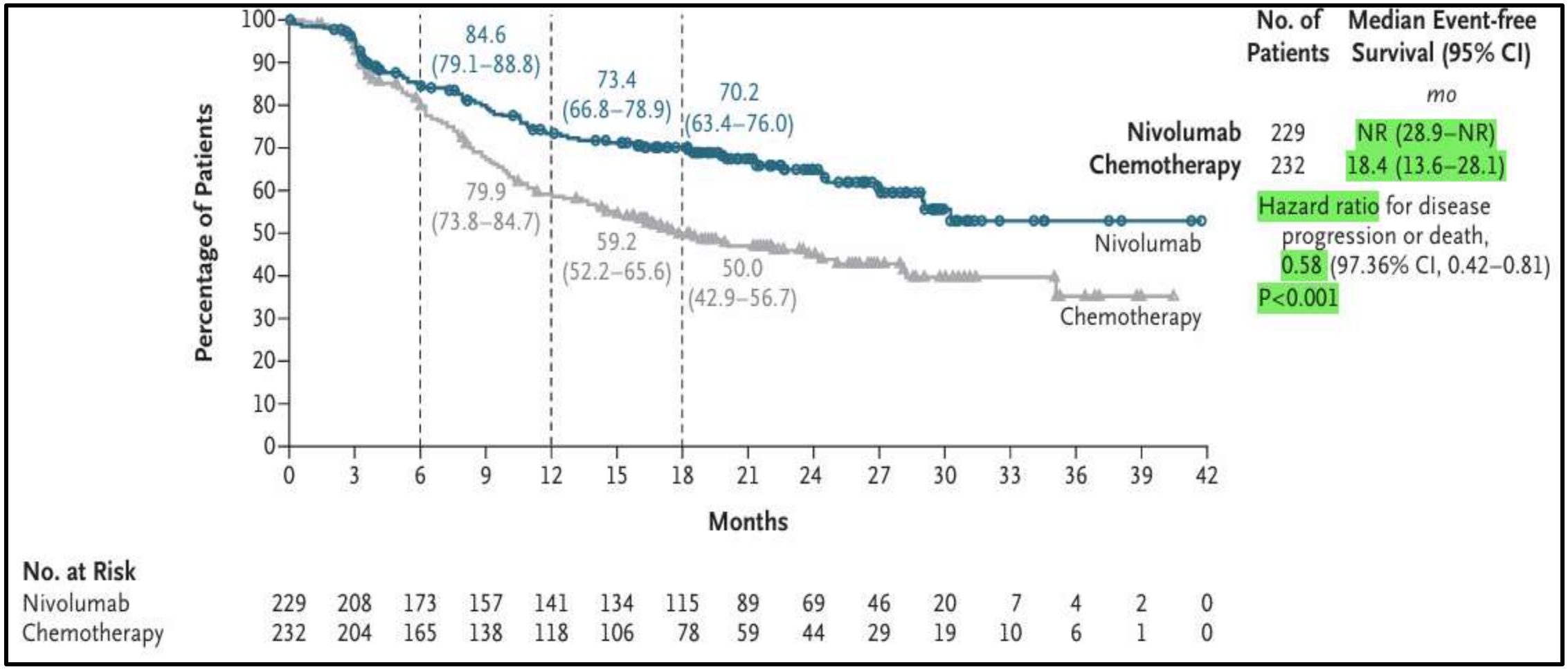
T. Cascone, M.M. Awad, J.D. Spicer, J. He, S. Lu, B. Sepesi, F. Tanaka, J.M. Taube, R. Cornelissen, L. Havel,* N. Karaseva, J. Kuzdzal, L.B. Petruzelka, L. Wu,

- Phase 3, double-blind, RCT that evaluated neoadjuvant nivolumab plus CT f/b adjuvant nivolumab (i.e., perioperative nivolumab) as compared with neoadjuvant placebo plus chemotherapy f/b adjuvant placebo in patients with resectable NSCLC (stage IIA – IIIB)

T. Cascone et al. Perioperative Nivolumab in Resectable Lung CancerN Engl J Med 2024;390:1756-69.


Key Eligibility
• Resectable, stage IIA (>4cm) – IIIB (N2) NSCLC (8th ed)
• No prior systemic anti-cancer Rx
• ECOG PS 0-1
• No *EGFR* mutation/ *ALK* alterations
N=461
R
1:1
Nivolumab 360mg Q3W + chemo Q3W (4 cycles)
Surgery (within 6 weeks)
Nivolumab 480mg Q4W (1 year)
Radiologic restaging
Follow-up
Placebo Q3W + chemo Q3W (4 cycles)
Surgery (within 6 weeks)
Placebo Q4W (1 year)
Stratification factors
• Histology (NSQ vs SQ)
• Disease stage (II vs III)
• Tumor PD-L1[c] (≥1% vs <1% vs not evaluable/indeterminate)
Primary endpoint – EFS
Secondary endpoints – pCR, MPR, OS, safety
Exploratory analysis – EFS by pCR/MPR, EFS by adjuvant T/t

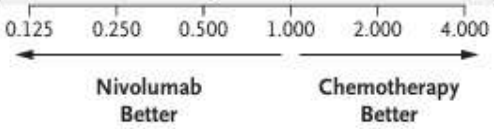
EFS

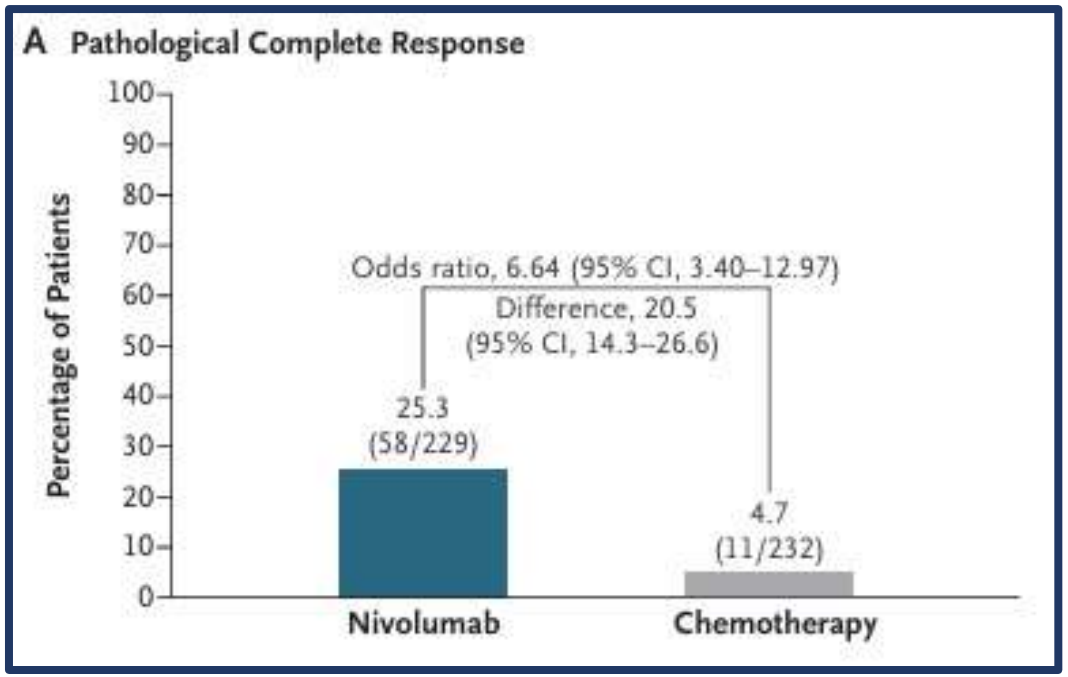


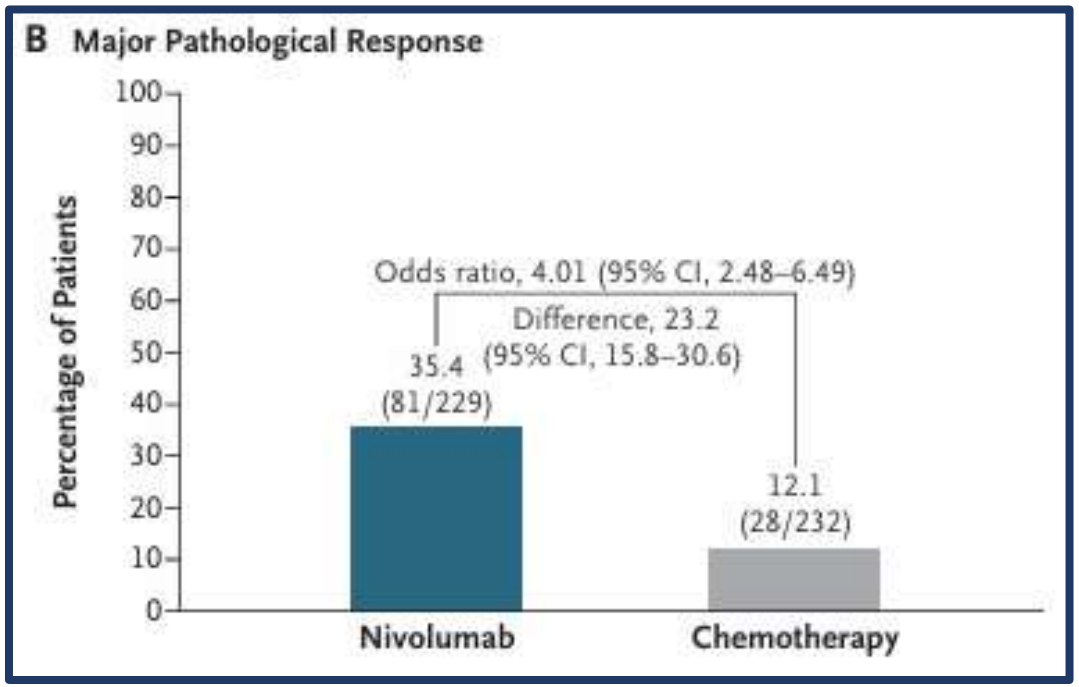
T. Cascone et al. Perioperative Nivolumab in Resectable Lung CancerN Engl J Med 2024;390:1756-69.

B Subgroup Analyses for Event-free Survival

Subgroup	No. of Patients	Median Event-free Survival (mo) Nivolumab (N=229)	Median Event-free Survival (mo) Chemotherapy (N=232)	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
Overall	461	NR (28.9–NR)	18.4 (13.6–28.1)	0.59 (0.44–0.79)
Age				
<65 yr	202	NR (24.4–NR)	16.7 (11.0–28.2)	0.55 (0.36–0.85)
≥65 yr	259	NR (28.9–NR)	20.1 (11.2–NR)	0.61 (0.41–0.91)
Sex				
Male	327	NR (28.9–NR)	16.7 (10.2–NR)	0.53 (0.37–0.75)
Female	134	30.2 (19.7–NR)	18.8 (14.7–35.1)	0.71 (0.41–1.20)
Geographic region				
North America	44	30.2 (7.9–NR)	9.4 (6.2–22.0)	0.59 (0.25–1.38)
Europe	250	NR (27.0–NR)	23.7 (15.1–NR)	0.61 (0.40–0.92)
Asia	115	NR (24.2–NR)	13.9 (8.1–NR)	0.47 (0.26–0.86)
ECOG performance-status score				
0	288	NR (27.0–NR)	20.1 (12.6–NR)	0.57 (0.39–0.83)
1	173	29.0 (22.6–NR)	17.3 (10.6–35.1)	0.61 (0.39–0.97)
Baseline disease stage				
II	162	NR (22.6–NR)	NR (24.2–NR)	0.81 (0.46–1.43)
III	297	30.2 (26.9–NR)	13.4 (9.8–17.7)	0.51 (0.36–0.72)
Node stage				
N0	167	NR (24.2–NR)	NR (15.8–NR)	0.80 (0.48–1.32)
N1	108	NR (24.4–NR)	28.1 (17.0–NR)	0.58 (0.29–1.16)
N2	182	30.2 (26.9–NR)	10.0 (8.1–15.1)	0.46 (0.30–0.70)
Single-station	112	30.2 (18.2–NR)	10.0 (6.5–18.4)	0.49 (0.29–0.84)
Multistation	69	NR (13.2–NR)	10.0 (8.0–18.8)	0.43 (0.21–0.88)
Tumor histology				
Squamous	234	NR (NR–NR)	17.0 (10.2–NR)	0.46 (0.30–0.72)
Nonsquamous	227	28.9 (21.4–NR)	18.4 (13.6–28.1)	0.72 (0.49–1.07)
Smoking status				
Current or former smoker	417	NR (29.0–NR)	17.0 (11.4–28.1)	0.54 (0.40–0.74)
Never smoked	44	19.7 (3.7–NR)	25.0 (13.9–NR)	1.32 (0.54–3.20)
Tumor PD-L1 expression				
<1%	186	29.0 (21.4–NR)	19.8 (13.9–NR)	0.73 (0.47–1.15)
≥1%	256	NR (28.9–NR)	15.8 (9.3–35.1)	0.52 (0.35–0.78)
1–49%	159	30.2 (20.0–NR)	28.1 (11.0–NR)	0.76 (0.46–1.25)
≥50%	97	NR (NR–NR)	8.0 (6.3–23.7)	0.26 (0.12–0.55)
Neoadjuvant platinum chemotherapy				
Cisplatin	97	27.0 (21.3–NR)	15.8 (8.8–28.1)	0.61 (0.35–1.08)
Carboplatin	347	NR (29.0–NR)	17.3 (12.6–35.1)	0.53 (0.37–0.75)



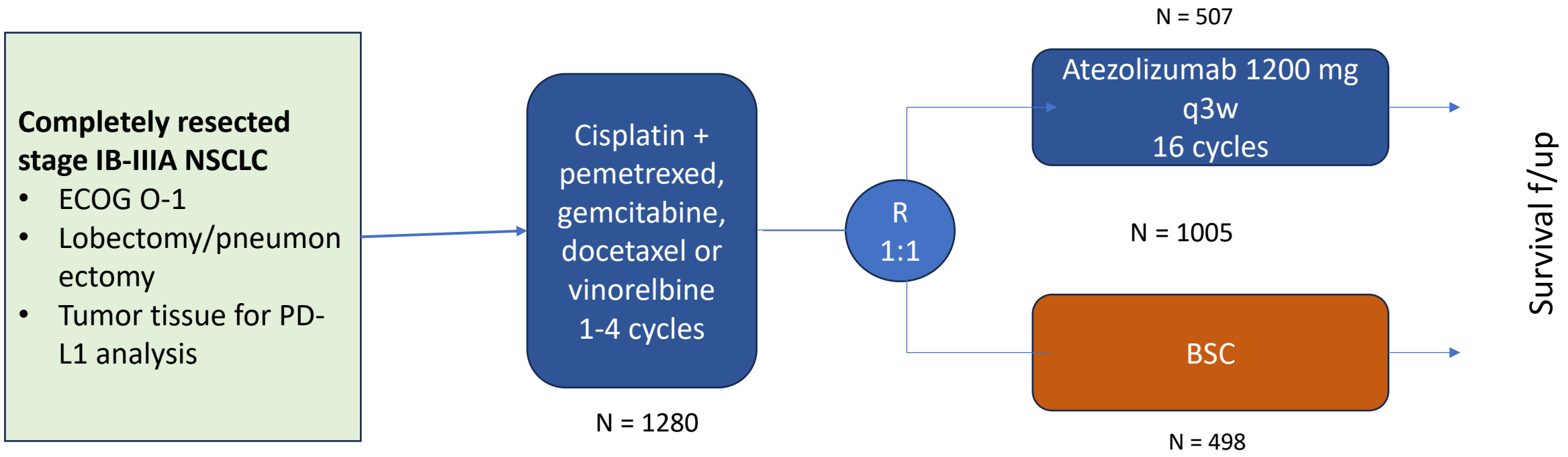




Immunotherapy in adjuvant setting

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**



Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase

*Enriqueta Felip … nnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez- … nio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McClelar … elee, for the IMpower010 Investigators**

Stratification factors

- Male/Female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status

Complet… stage IB-IIIA NSCLC

- ECOG O-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine 1-4 cycles

N = 1280

R 1:1

N = 507

Atezolizumab 1200 mg q3w 16 cycles

N = 1005

BSC

N = 498

Survival f/up

Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

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Completely resected stage IB-IIIA NSCLC
- ECOG O-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

ge... docetaxel or vinorelbine 1-4 cycles

N = 1280

1:1

Ate...

N = 1005

BSC

N = 498

Primary endpoints

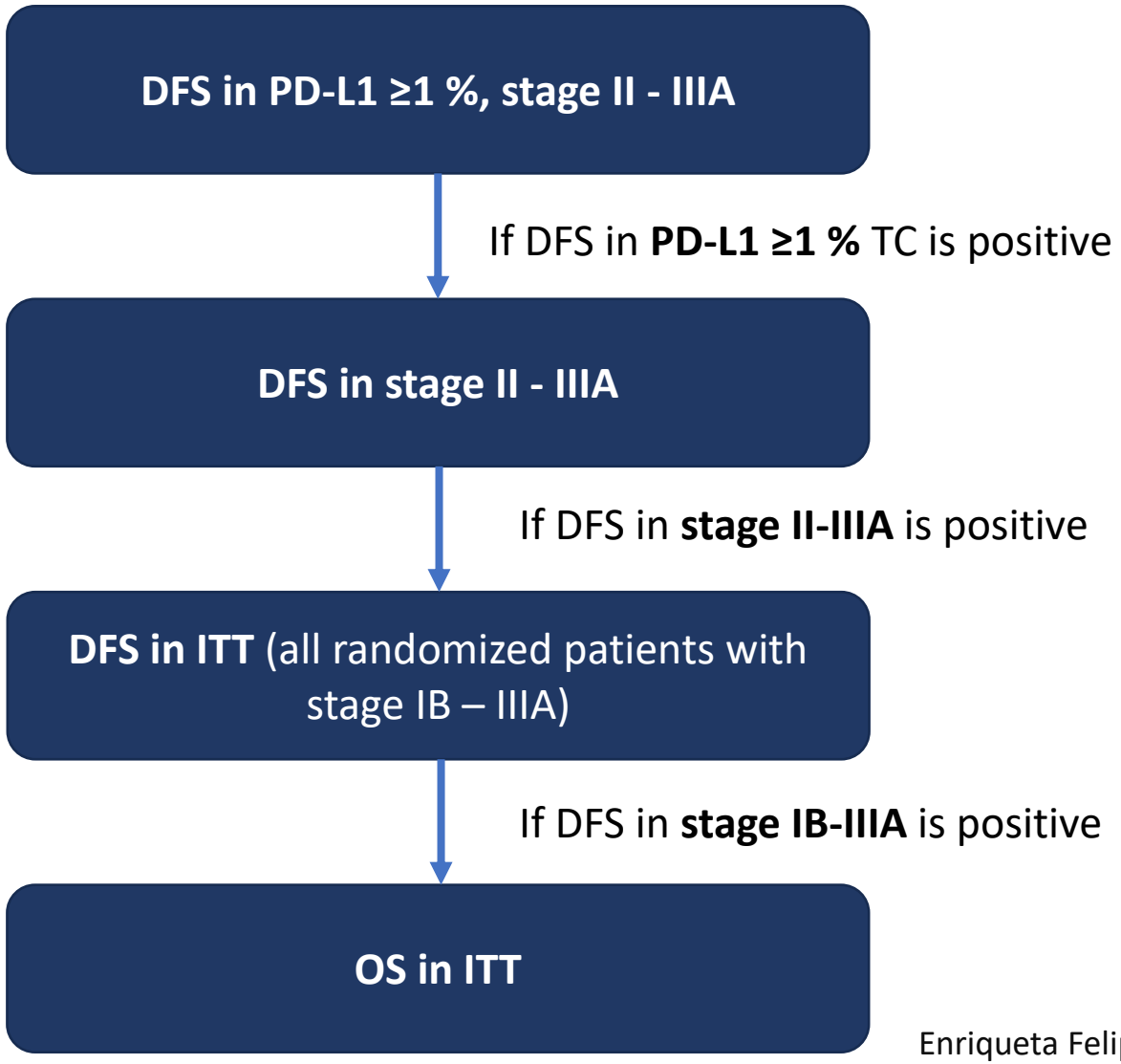
Investigator-assessed DFS tested hierarchically
- PD-L1 TC ≥ 1% stage II-IIIA population
- All randomized stage II-IIIA population
- ITT population (stage IB-IIIA)

Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥ 50% stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

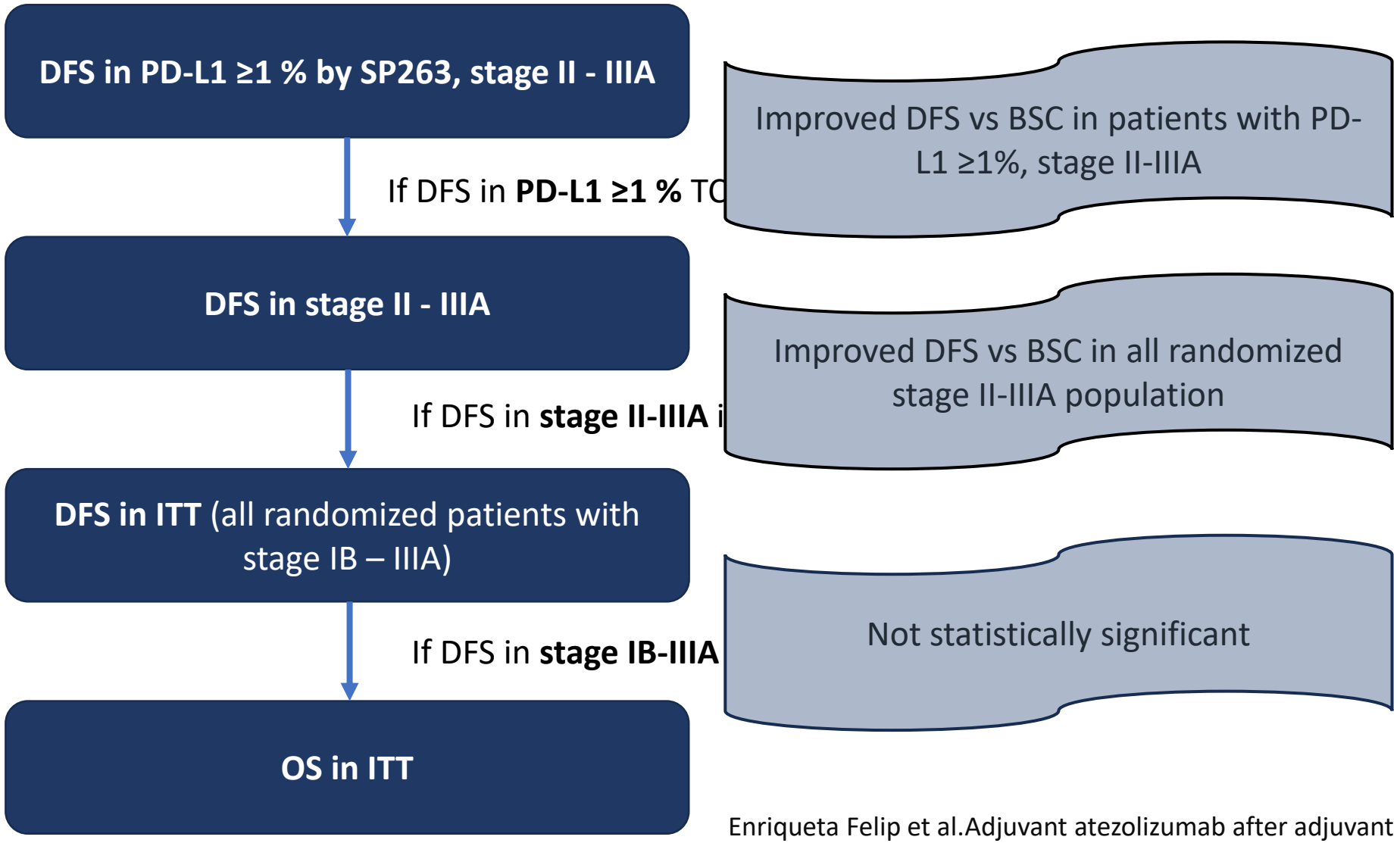
Survival ...

Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;



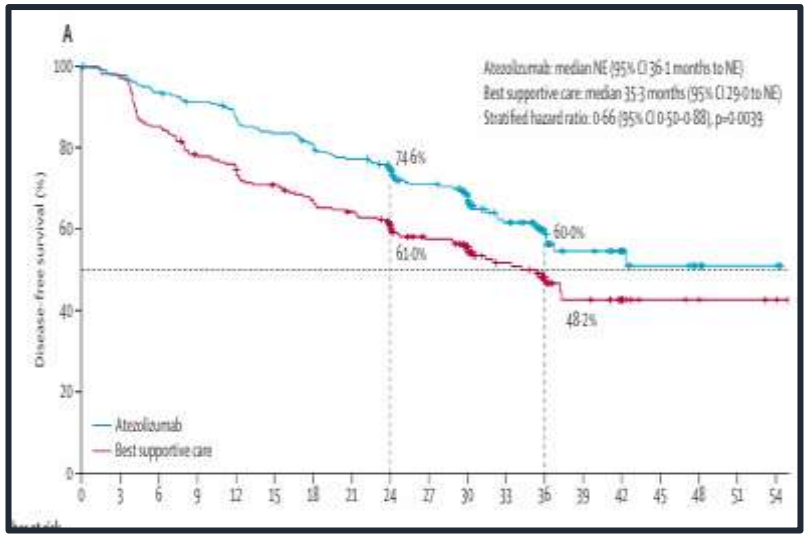
The primary DFS endpoint was tested hierarchically in 3 primary analysis populations

Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;

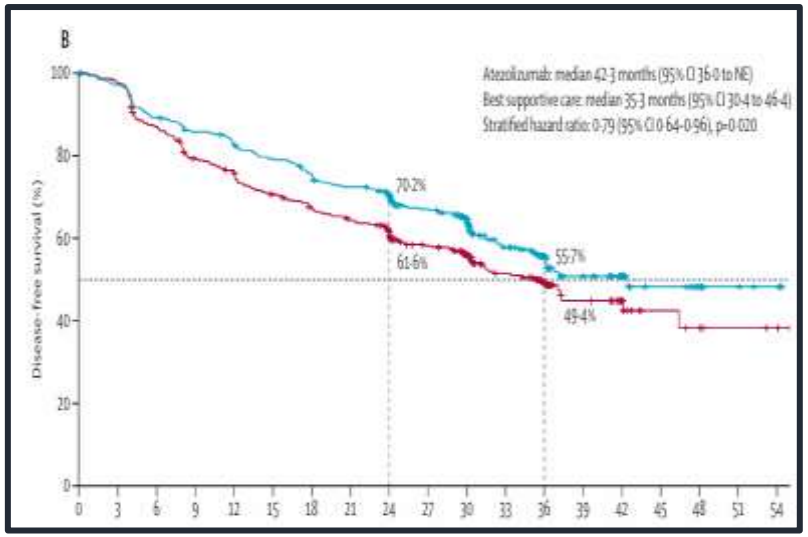


Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;

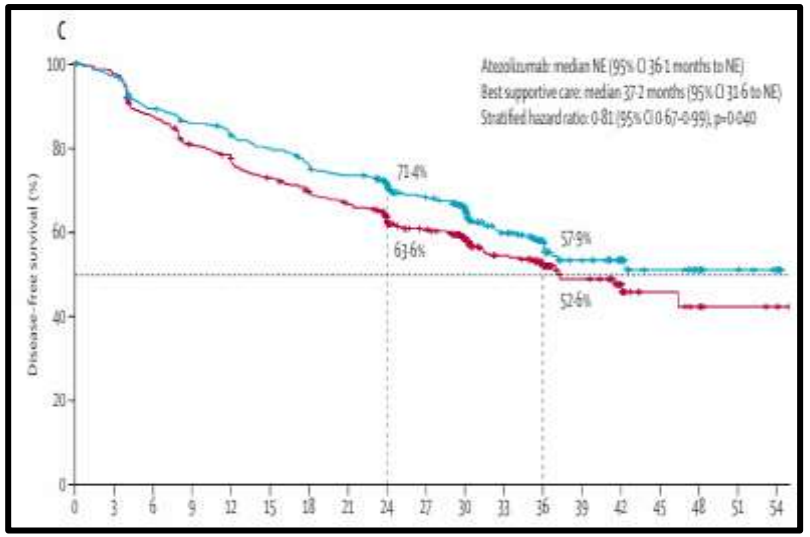
PD-L1 TC ≥1% stage IIA-IIIA population



All randomized stage IIA-IIIA population



ITT (randomized stage IB-IIIA) population



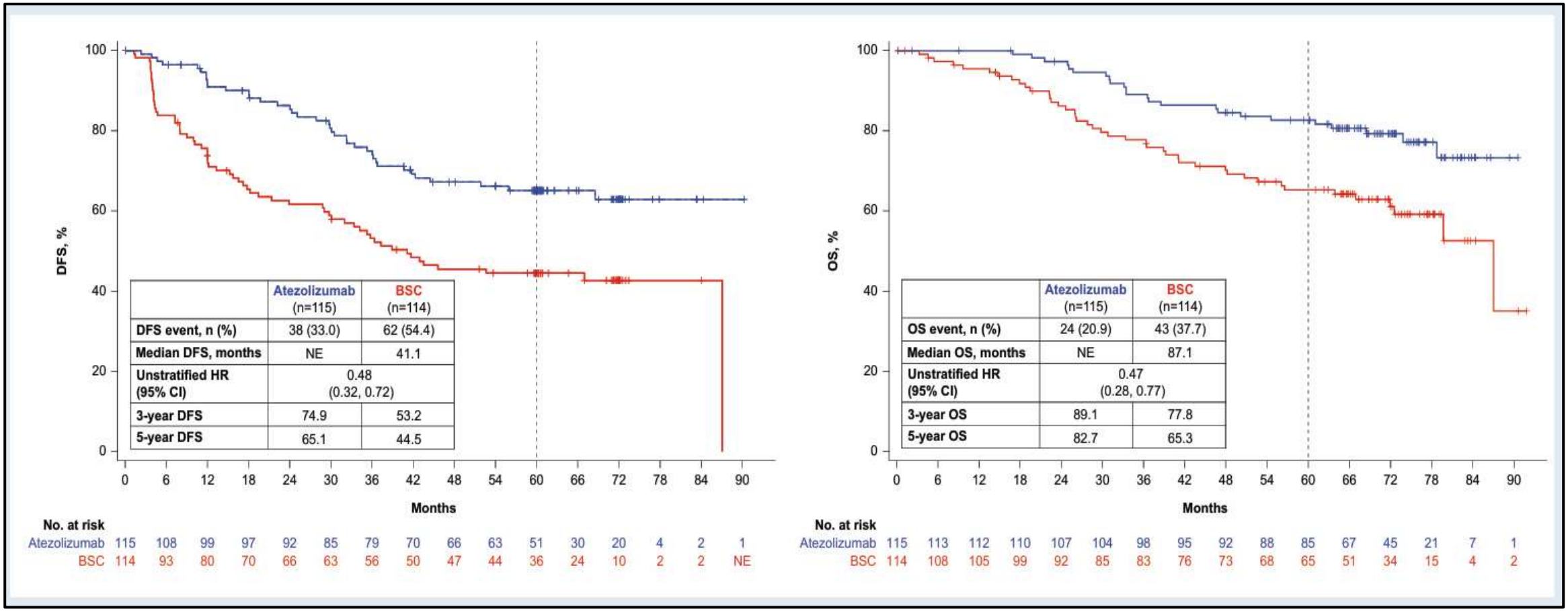
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

	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[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Enriqueta Felip et al.Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer, Lancet 2021;

DFS and OS in the stage II-IIIA PD-L1 TC ≥50% population



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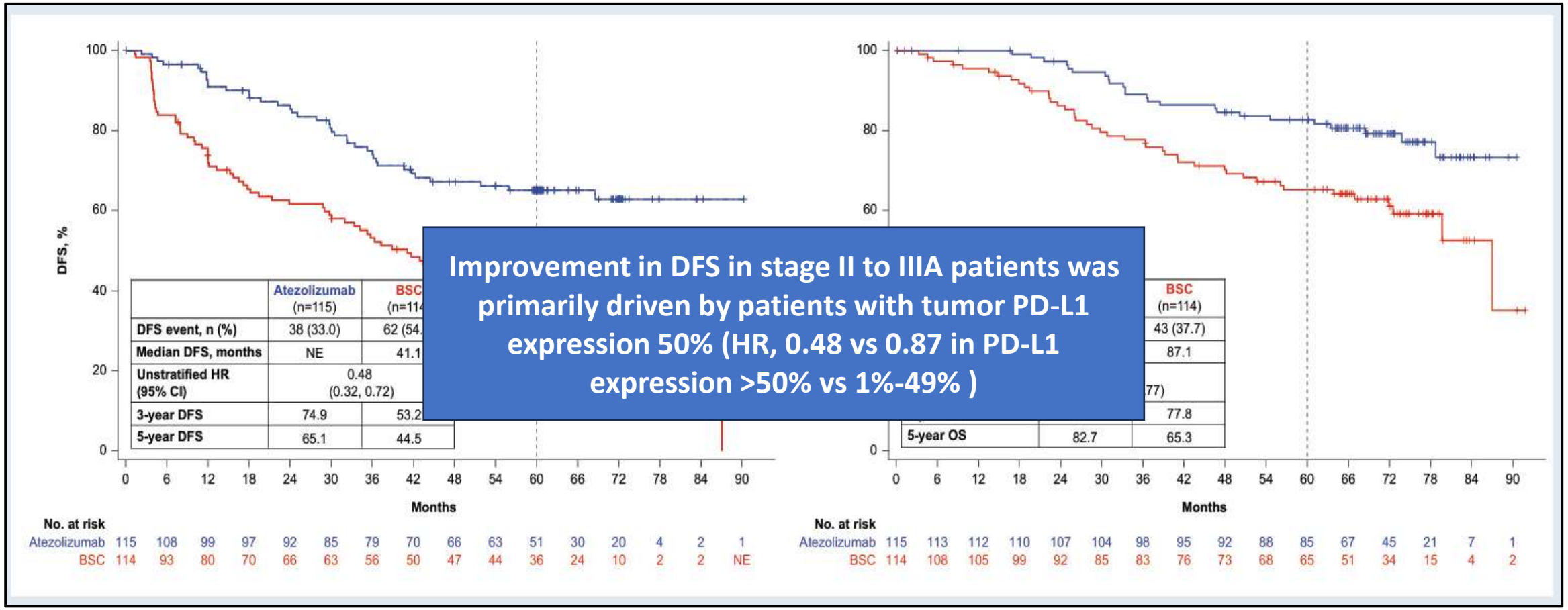
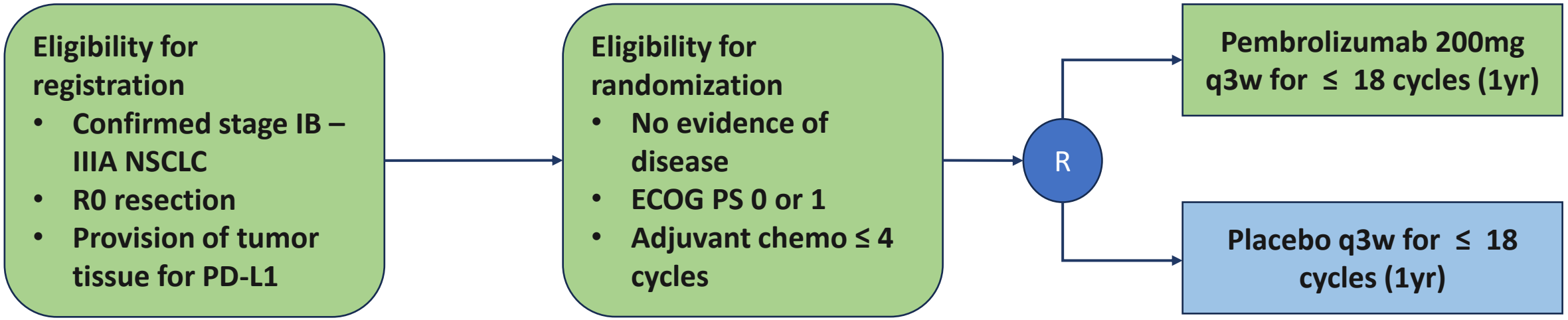
DFS and OS in the stage II-IIIA PD-L1 TC ≥50% population



Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

Mary O'Brien, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡*



Mary O'Brian et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected IB–IIIA non-small-cell lung cancer, Lancet Oncol 2022; 23: 1274–86

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a r… blind, phase 3 trial

Mary …
Marti…
Rolf S…

Stratification factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥ 50%)
- Adjuvant chemo – yes/no
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Primary end points
- DFS in overall population
- DFS in PD-L1 ≥ 50%

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

E… reg…
- Confirmed stage IB – IIIA NSCLC
- R0 resection
- Provision of tumor tissue for PD-L1

Eligibility for randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemo ≤ 4 cycles

R

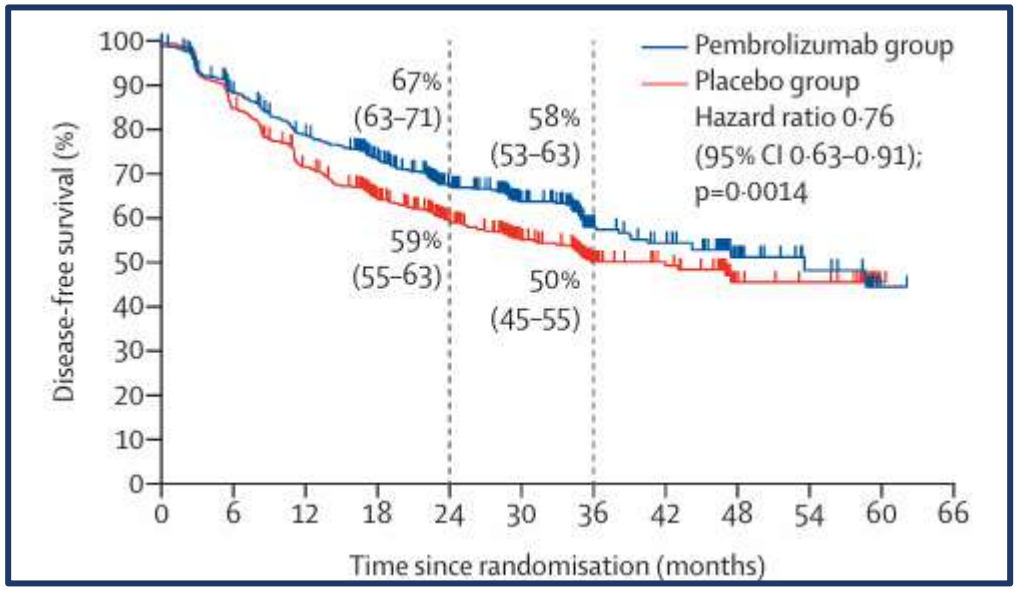
…200mg …ycles (1yr)

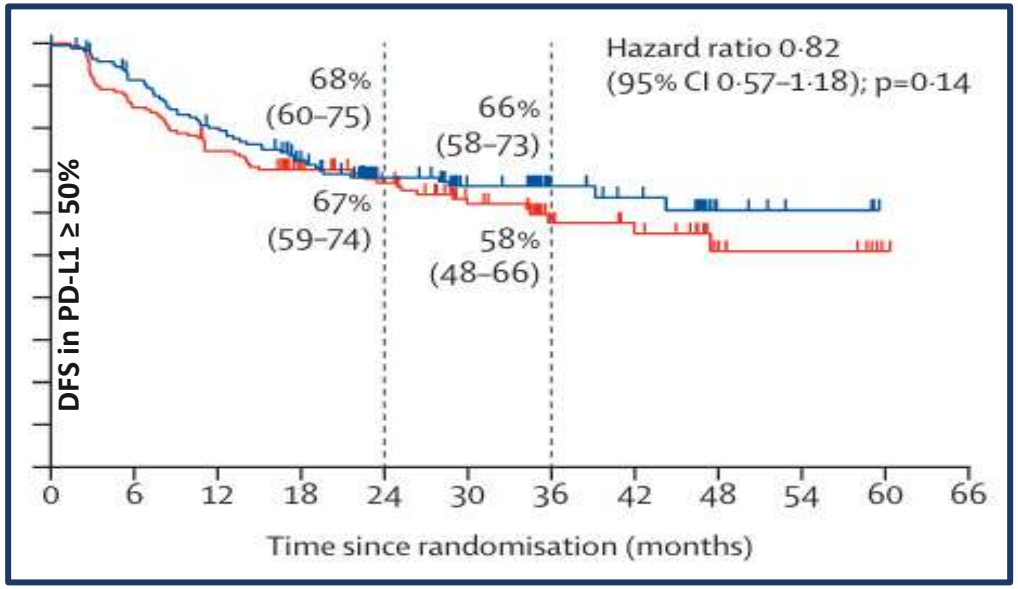
Placebo q3w for ≤ 18 cycles (1yr)

Mary O'Brian et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected IB–IIIA non-small-cell lung cancer, Lancet Oncol 2022; 23: 1274–86

	Pembrolizumab (n = 590)	Placebo (n = 587)
Median age, y (range)	65 (31-87)	65 (37-85)
Male, n (%)	401 (68.0)	403 (68.7)
Geographic location		
Asia, n (%)	106 (18.0)	105 (17.9)
Eastern Europe, n (%)	116 (19.7)	113 (19.3)
Western Europe, n (%)	303 (51.4)	301 (51.3)
Rest of world, n (%)	65 (11.0)	68 (11.6)
ECOG PS 1, n (%)	210 (35.6)	244 (41.6)
Current/former smoker, n (%)	503 (85.3)	521 (88.8)
EGFR mutation,[a] n (%)	39 (6.6)	34 (5.8)
ALK translocation,[b] n (%)	7 (1.2)	7 (1.2)

	Pembrolizumab (n = 590)	Placebo (n = 587)
Nonsquamous histology, n (%)	398 (67.5)	363 (61.8)
Pathologic stage[c]		
IB, n (%)	84 (14.2)	85 (14.5)
II, n (%)	329 (55.8)	338 (57.6)
IIIA, n (%)	177 (30.0)	162 (27.6)
Received adjuvant chemotherapy		
Yes, n (%)	506 (85.8)	504 (85.9)
No, n (%)	84 (14.2)	83 (14.1)
PD-L1 TPS		
<1%, n (%)	233 (39.5)	232 (39.5)
1%-49%, n (%)	189 (32.0)	190 (32.4)
≥50%, n (%)	168 (28.5)	165 (28.1)





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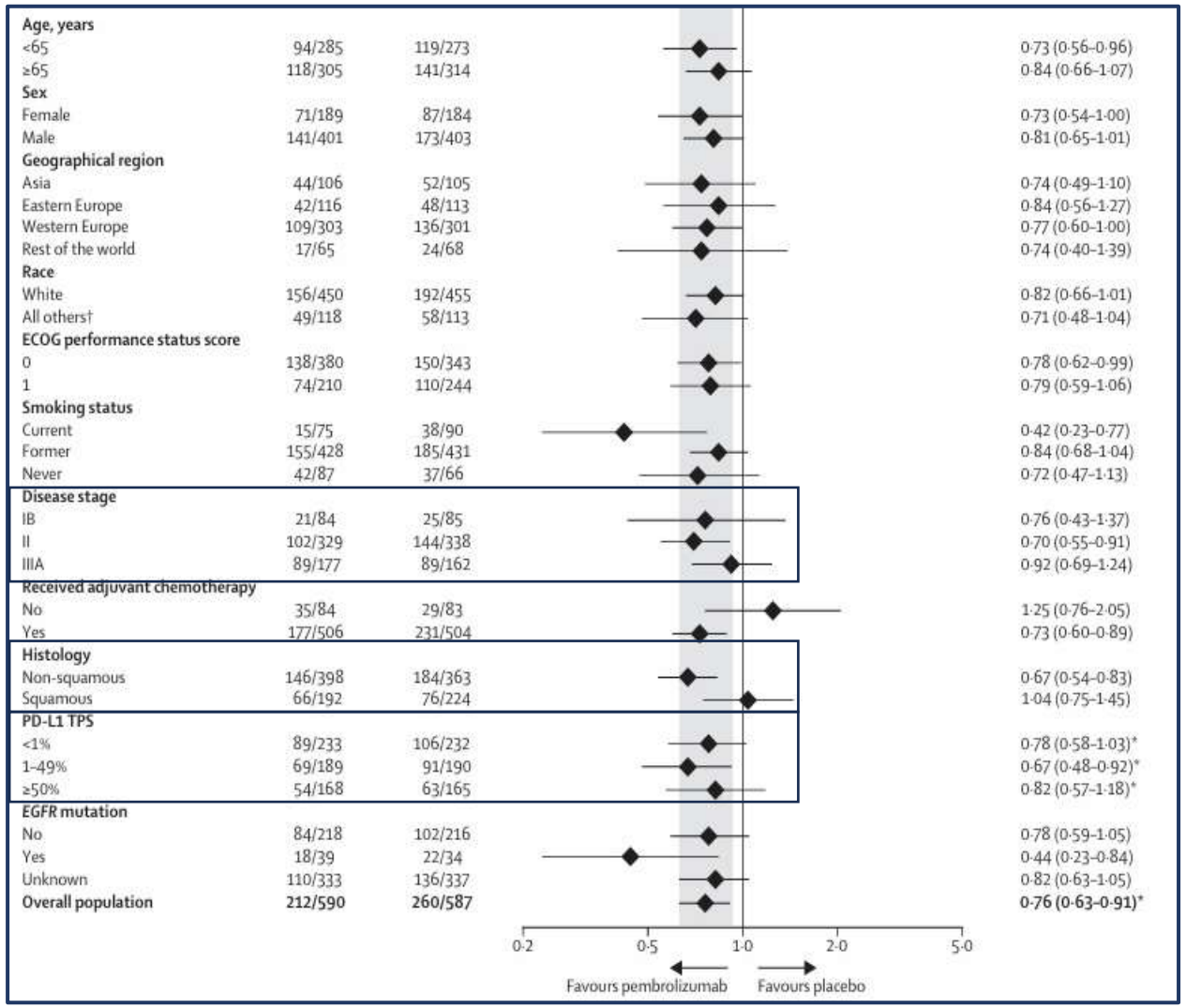
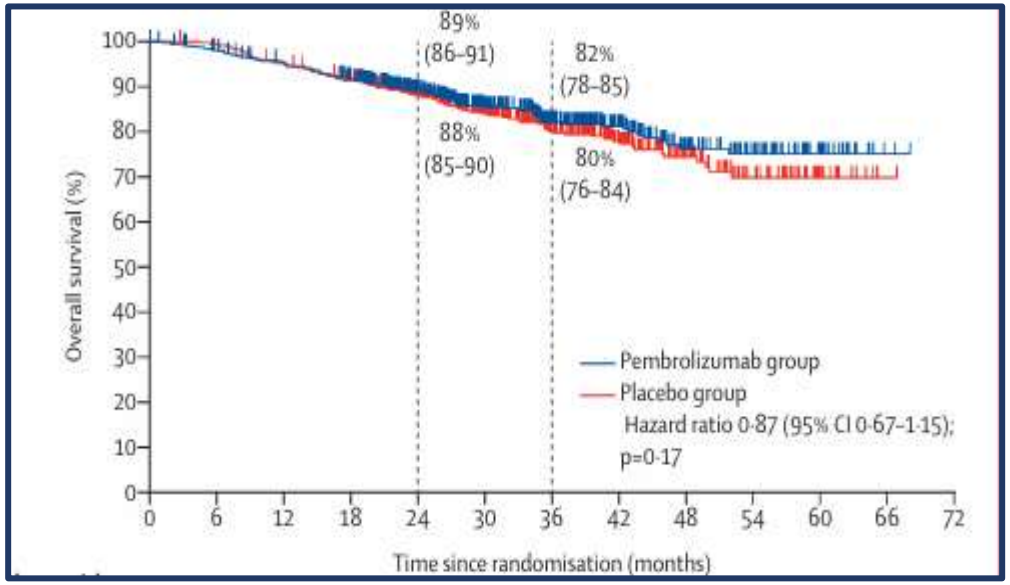




Mary O'Brian et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected IB–IIIA non-small-cell lung cancer, Lancet Oncol 2022; 23: 1274–86

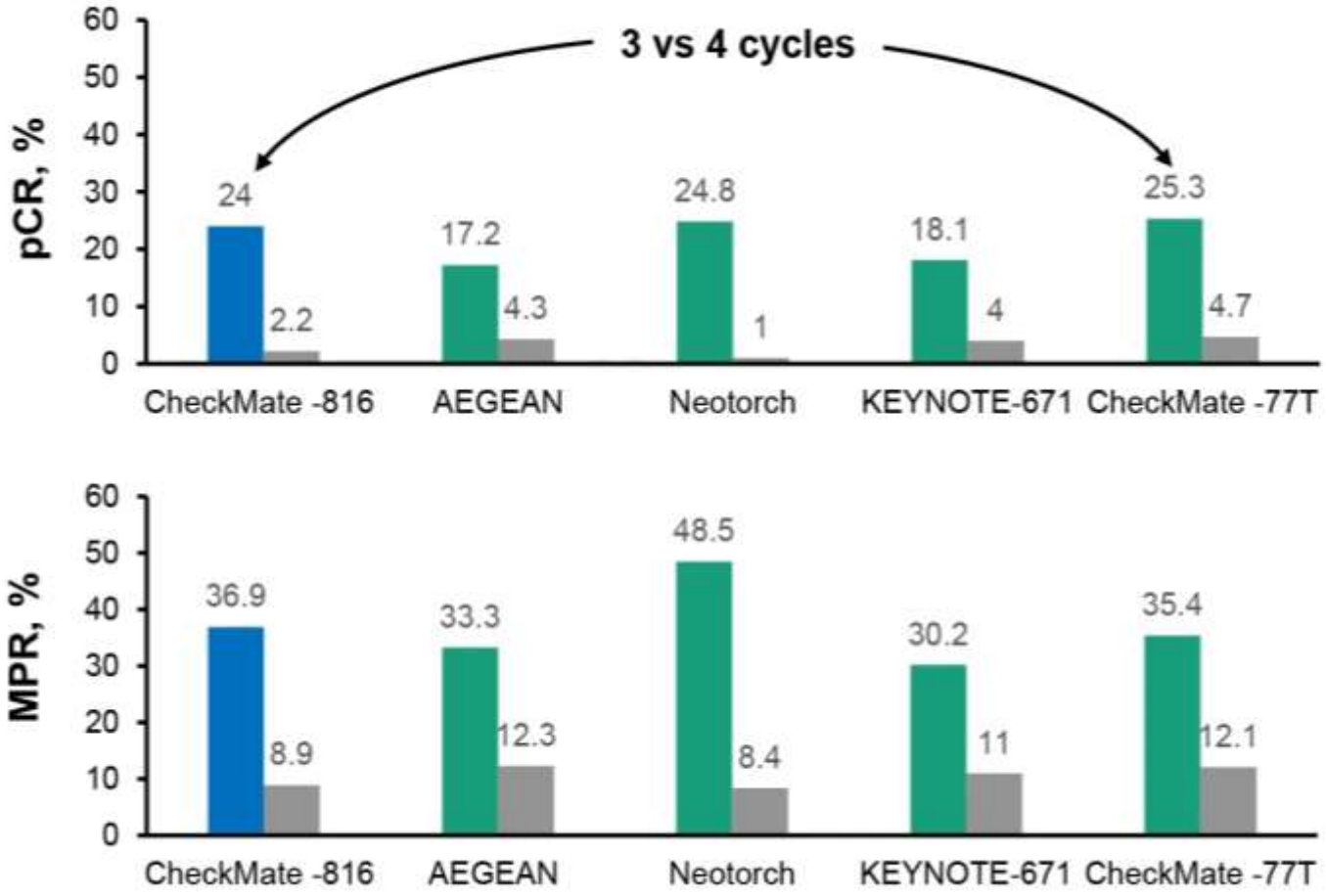
Agent	**Pembrolizumab[1]**	**Atezolizumab[2]**	
Comparator(s)	**Placebo**	**Best supportive care***	
Study	**PEARLS/KEYNOTE-091** NCT02504372	**IMpower010** NCT02486718	**IMpower010** **≥5-year follow-up data[3]**
Population	Resected stage IB (T ≥4 cm) to IIIA NSCLC (N=1,010)	Resected stage IB (T ≥4 cm) to IIIA NSCLC (N=1,005)	
Efficacy	Median FU: 37.4 months Pembrolizumab (n=506) **mDFS: 58.7 months** Placebo group (n=504) **mDFS: 34.9 months**	Median FU: 32.8 months Atezolizumab (n=507) **mDFS: NE** BSC (n=498) **mDFS: 35.3 months** (stage II–IIIA NSCLC and PD-L1 ≥1%)	Median FU: 65.0 months Atezolizumab (n=248) **mDFS: 68.5 months** BSC (n=228) **mDFS: 37.3 months** (stage II–IIIA NSCLC and PD-L1 ≥1%)

Overview of Trials

Overview of Key Immunotherapy Strategies and Trials

Trial	IMpower010[1]	KEYNOTE-091[2]	CheckMate -816[3]	AEGEAN[4]	Neotorch[5]	KEYNOTE-671[6]	CheckMate -77T[7]	RATIONALE-315[8]
Timing	Adjuvant	Adjuvant	Neoadjuvant	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative
Size	1,005	1,177	358	802	500	797	461	453
Agent I/O	Atezolizumab (PD-L1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Durvalumab (PD-L1)	Toripalimab (PD-1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Tislelizumab (PD-1)
Cycles, N	16	18	3	16	17	13	16	12
Inclusion	Completely resected IB (>4 cm)-IIIA (7th)	Completely resected IB (>4 cm)-IIIA (7th)	Resectable IB (>4 cm)-IIIA (7th)	Resectable II-IIIB (8th) by lobectomy	Resectable II-IIIB (8th)	Resectable II-IIIB (8th)	Resectable II-IIIB/ (8th)	Resectable II-IIIA (8th)
Stage IB+II/III, %	59 / 41	72 / 28	36 / 64	29 / 71	20 / 80	30 / 70	35 / 65	41 / 59
Primary endpoint	DFS hierarchical	DFS, DFS in PD-L1 ≥50%	pCR, EFS	pCR, EFS	MPR, EFS	EFS, OS	EFS	EFS, MPR
Chemotherapy	Cisplatin doublet	Platinum doublet encouraged	Platinum doublet	Platinum-based	Platinum-based	Cisplatin doublet	Platinum doublet	Platinum doublet
EGFR/ALK	Included (15%)	Included (7.4%)	No documented mutation, WT: Asia	No documented mutation	WT	Included (7%)	No *EGFR*, no documented *ALK*	WT

Felipe E et al. Lancet. 2021;398:1344-1357
O'Brian et al. Lancet Onc. 2022,23
Wakelee H et al. NEJM. 2023

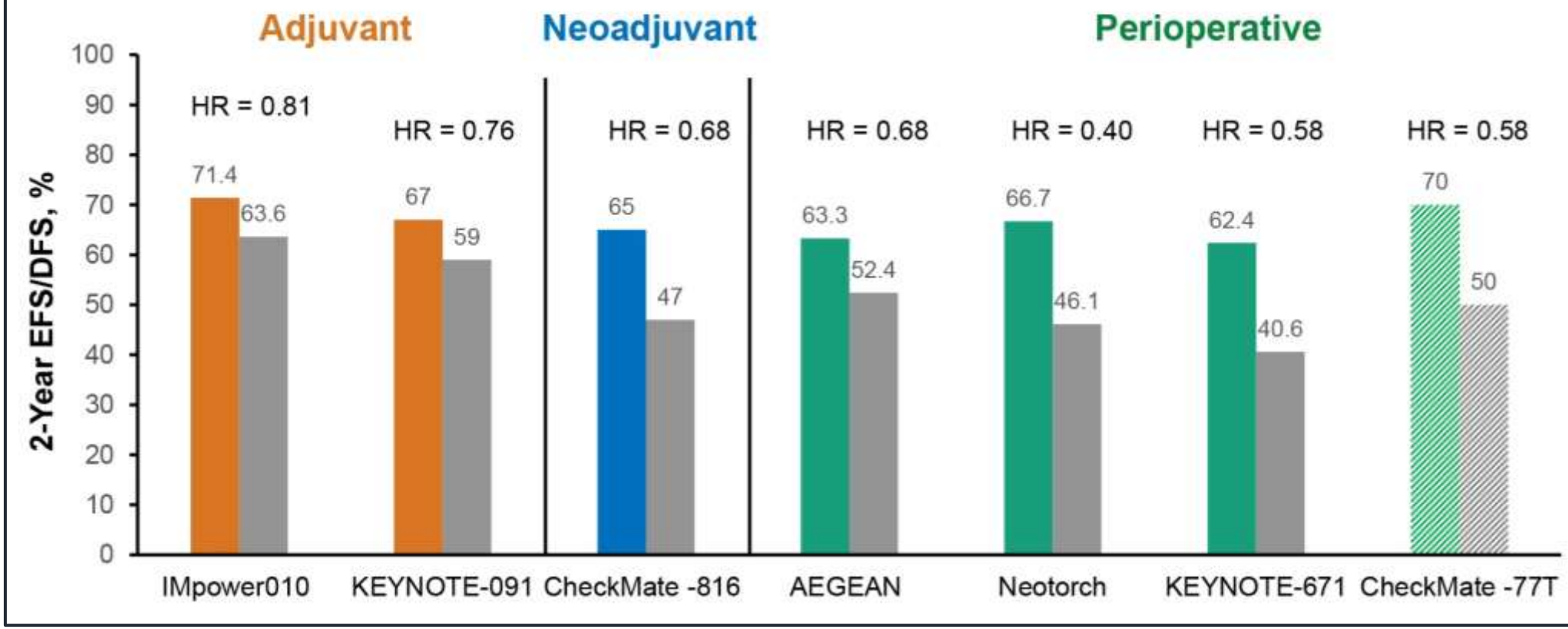


pCR
Pathologic Complete Response
(No Viable Tumour at Resection)

MPR
Major Pathologic Response
(10% Viable Tumour at Resection)

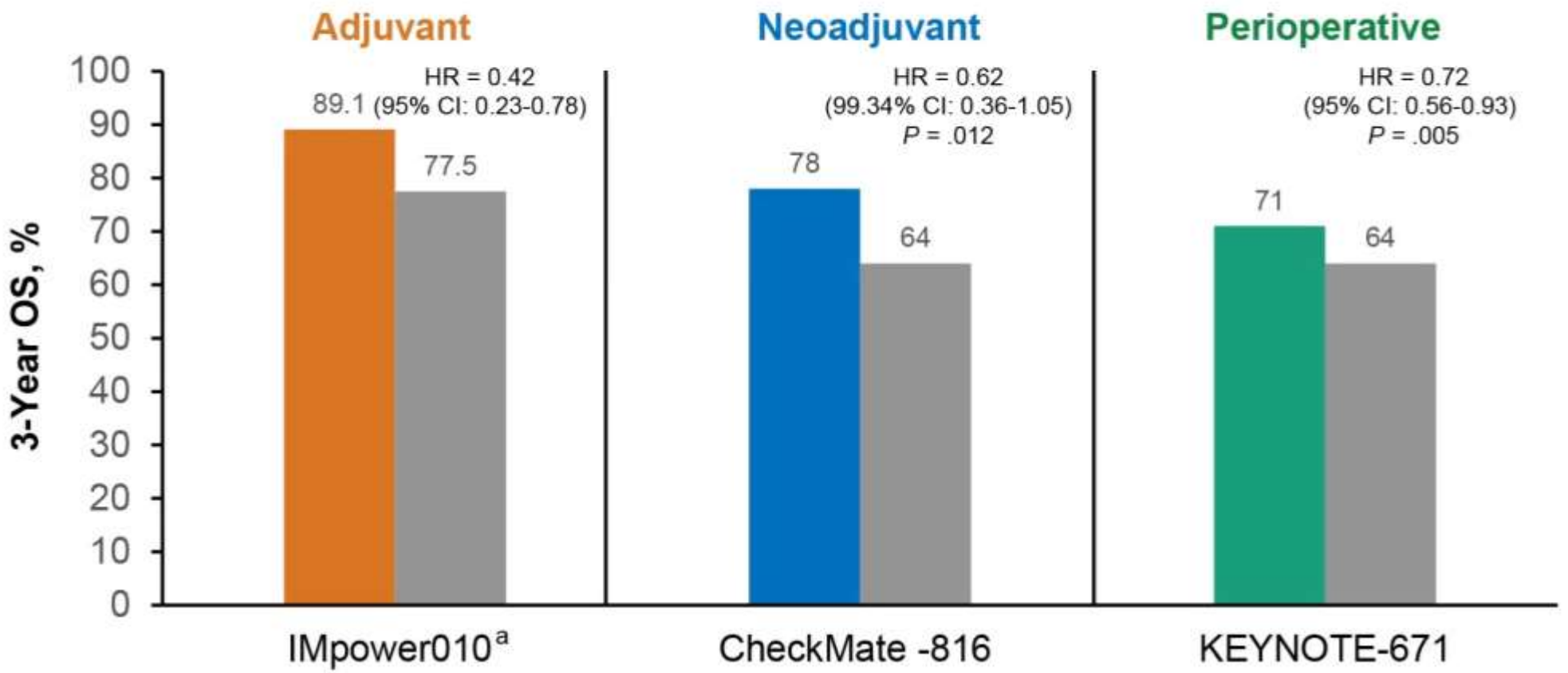
Felipe E et al. Lancet. 2021;398:1344-1357
O'Brian et al. Lancet Onc. 2022,23
Wakelee H et al. NEJM. 2023

Understanding Evidence: 2-Year EFS/DFS Results[1-7]



Felipe E et al. Lancet. 2021;398:1344-1357
O'Brian et al. Lancet Onc. 2022,23
Wakelee H et al. NEJM. 2023

Understanding Evidence: 3-Year OS Results[1-3]



Felipe E et al. Lancet. 2021;398:1344-1357
Wakelee H et al. NEJM. 2023

Adverse events

	KEYNOTE671 – Pembro vs placebo	AEGEAN – Durva vs placebo	NEOTORCH – Toripa vs placebo	CHECKMATE 77T – Nivo vs CT	IMPOWER 010 – Atezo vs BSC	PEARLS – Pembro vs placebo
Any Rx related adverse event	96 vs 95	96.5 vs 94.7	99.5 vs 98.5	96.5 vs 94.7	93 vs 71	96 vs 91
Rx-related adv events leading to discontinuation of Rx	12.6 vs 5.3	12 vs 6	9.4 vs 7.4	12 vs 6	18 vs -	20 vs 6
Immune-mediated adverse events	25.3 vs 10.5	23.7 vs 9.3	42.1 vs 22.8	34.2 vs 8	52 vs 9	39 vs 13
Grade 3-5 adverse events	44.9 vs 37.3	32.4 vs 32.9	63.4 vs 54	32.5 vs 25.2	24 vs 13	34 vs 26

Adverse events

Trial (NCT#)	Adverse events (ICI vs. placebo)				Patients who completed surgery (ICI vs. placebo)
	Total	Neoadjuvant	Adjuvant	ICI mediated	
IMpower010 (NCT02486718)	93% vs. 71%	N/A	93% vs. 71%	52% vs. 9%	100% vs. 100%
KEYNOTE 091/PEARLS (NCT02504372)	96% vs. 91%	N/A	96% vs. 91%	39% vs. 13%	100% vs. 100%
CheckMate 816 (NCT02998528)	92.6% vs. 97.2%	92.6% vs. 97.2%	N/A	20% vs. 1%	83.2% vs. 75.4%
KEYNOTE 671 (NCT03425643)	96.7% vs. 95%	95.7% vs. 93.7% (neoadjuvant + surgery phase)	54.5% vs. 31.8%	25.3% vs. 10.5%	82.1% vs. 79.4%
AEGEAN (NCT03800134)	96.5% vs. 94.7%	91.0% vs. 89.2%	Unknown	23.7% vs. 9.3%	77.6% vs. 76.7%
CheckMate 77T (NCT04025879)	97.4% vs. 97.8%	94.7% vs. 96.1%	87.3% vs. 79.6%	35.2% vs. 7.8%	77.7% vs. 76.7%

Any Rx related adverse event						
Rx-related adv events leading to discontinuation of Rx						
Immune-mediated adverse events	25.3 vs 10.5	23.7 vs 9.3	42.1 vs 22.8	34.2 vs 8	52 vs 9	39 vs 13
Grade 3-5 adverse events	44.9 vs 37.3	32.4 vs 32.9	63.4 vs 54	32.5 vs 25.2	24 vs 13	34 vs 26

CheckMate 816

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)

CheckMate 77T

Outcomes	Nivolumab (N=229)*	Chemotherapy (N=232)
Underwent definitive surgery — no. (%)	178 (77.7)	178 (76.7)
Cancelled definitive surgery — no. (%)	46 (20.1)	50 (21.6)
Disease progression	13 (5.7)	22 (9.5)
Patient refusal	11 (4.8)	8 (3.4)
Surgeon decision	8 (3.5)	6 (2.6)
Adverse event	7 (3.1)	4 (1.7)
Other	7 (3.1)	10 (4.3)
Abandoned definitive surgery — no. (%)	3 (1.3)	4 (1.7)
Delayed definitive surgery — no. (%)	36 (15.7)	33 (14.2)
Logistical issue	8 (3.5)	11 (4.7)
Adverse event	8 (3.5)	7 (3.0)
Patient decision	4 (1.7)	3 (1.3)
Other	12 (5.2)	10 (4.3)

AEGEAN

	Durvalumab arm (N=400)	Placebo arm (N=402)
Patients who underwent surgery†, n (%)	324 (81.0)	327 (81.3)
Patients who did not undergo surgery†, n (%)	76 (19.0)	75 (18.7)
Disease progression	27 (6.8)	30 (7.5)
Unfit for surgery‡	15 (3.8)	10 (2.5)
Patient decision	12 (3.0)	17 (4.2)
Death	9 (2.3)	2 (0.5)
Adverse event	7 (1.8)	5 (1.2)
Surgical resection with curative intent performed outside of the protocol	2 (0.5)	6 (1.5)
Investigator decision	2 (0.5)	2 (0.5)
Other/missing	2 (0.5)	3 (0.7)

Keynote 671

	Pembrolizumab Group (N = 397)	Placebo Group (N = 400)
	no. (%)	
No in-study surgery	71 (17.9)	82 (20.5)
Adverse event	25 (6.3)	17 (4.2)
Clinical progression*	1 (0.3)	1 (0.2)
Local progression preventing surgery	0	6 (1.5)
New non-study anticancer therapy	0	1 (0.2)
Participant refusal	4 (1.0)	3 (0.8)
Physician decision	16 (4.0)	20 (5.0)
Progressive disease†	15 (3.8)	26 (6.5)
Withdrawal of consent	10 (2.5)	8 (2.0)

Neoadjuvant/Perioperative Trials

Phase II

Forde et al.		Nivolumab x 2 doses	SURGERY	
Shu et al.		Atezolizumab + Chemo x 4 cycles		
LCMC3		Atezolizumab x 2 doses		Optional atezolizumab x 1 year
NEOSTAR		Nivolumab + Chemo +/- Ipilimumab x 3 cycles		Optional Chemo
NADIM I		Nivolumab + Chemo x 3 cycles		Nivolumab x 1 year
NADIM II		Nivolumab + Chemo x 3 cycles		Nivolumab x 6 months
SAKK 16/14	Chemo x 3 cycles	Durvalumab x 2 doses		Durvalumab x 1 year
Altorki et al.		SBRT x 3; Durvalumab x 2		

Phase III

CheckMate 816		Nivolumab + Chemo x 3 cycles		Optional chemo or radiation
KEYNOTE-671		Pembrolizumab + Chemo x 4 cycles		Pembrolizumab x 1 year
AEGEAN		Durvalumab + Chemo x 3 cycles		Durvalumab x 1 year
NEOTORCH		Toripalimab + Chemo x 3 cycles		Chemo x 1 cycle / Toripalimab x 1 year
CheckMate 77T		Nivolumab + Chemo x 4 cycles		Nivolumab x 1 year

Adjuvant Trials

IMpower010				SOC Chemo / Atezolizumab x 1 year
PEARLS				SOC Chemo / Pembrolizumab x 1 year

Systematic review and meta-analysis of immune checkpoint inhibitors as single agent or in combination with chemotherapy in early-stage non-small cell lung cancer: Impact of clinicopathological factors and indirect comparison between treatment strategies

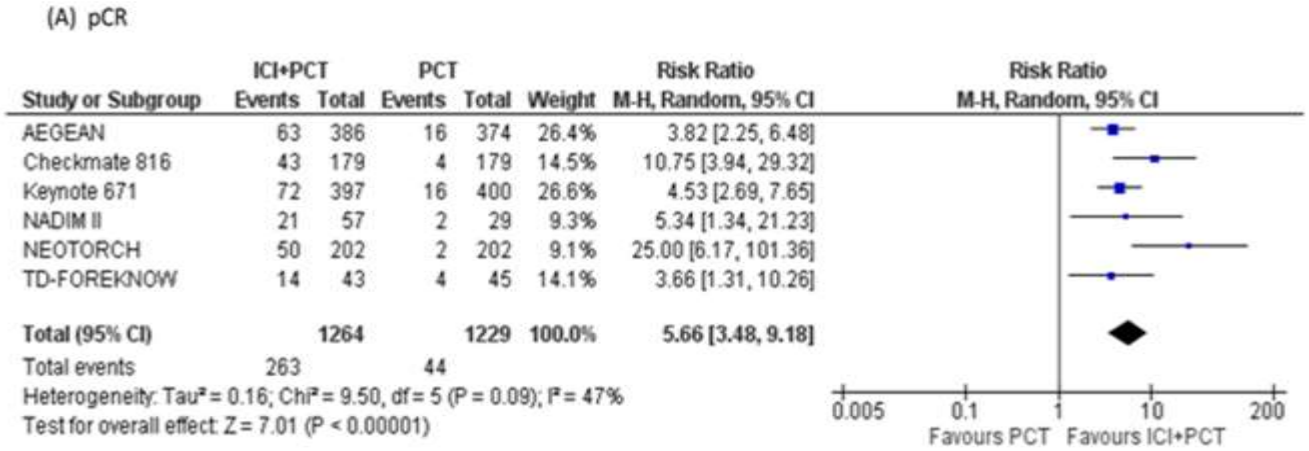
Antonio Nuccio [a,b,1], Giuseppe Viscardi [c,1], Fabio Salomone [d], Alberto Servetto [d],

Antonio Nucio et al. ejcancer 2023

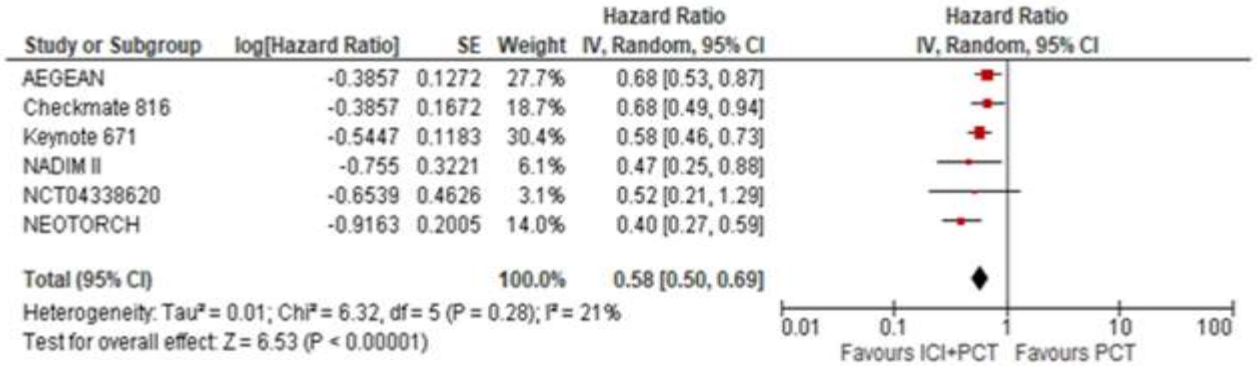
Systematic review and meta-analysis of immune checkpoint inhibitors as single agent or in combination with chemotherapy in early stage non-small cell lu rect comp

Antoni

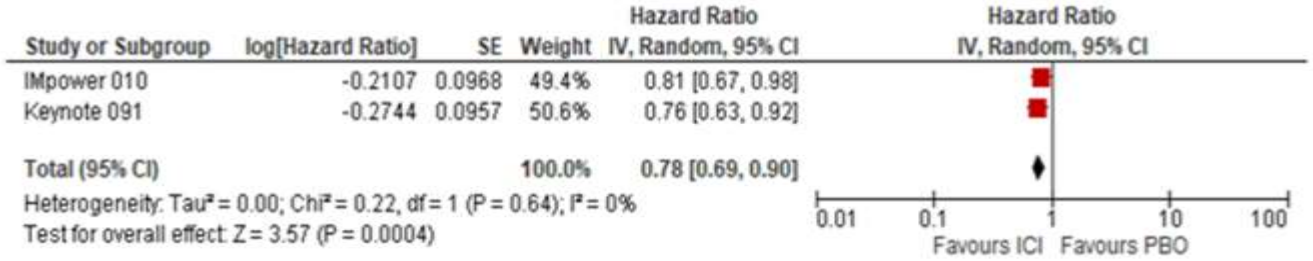
(A) pCR



(B) EFS/PFS



(C) DFS (adjuvant)



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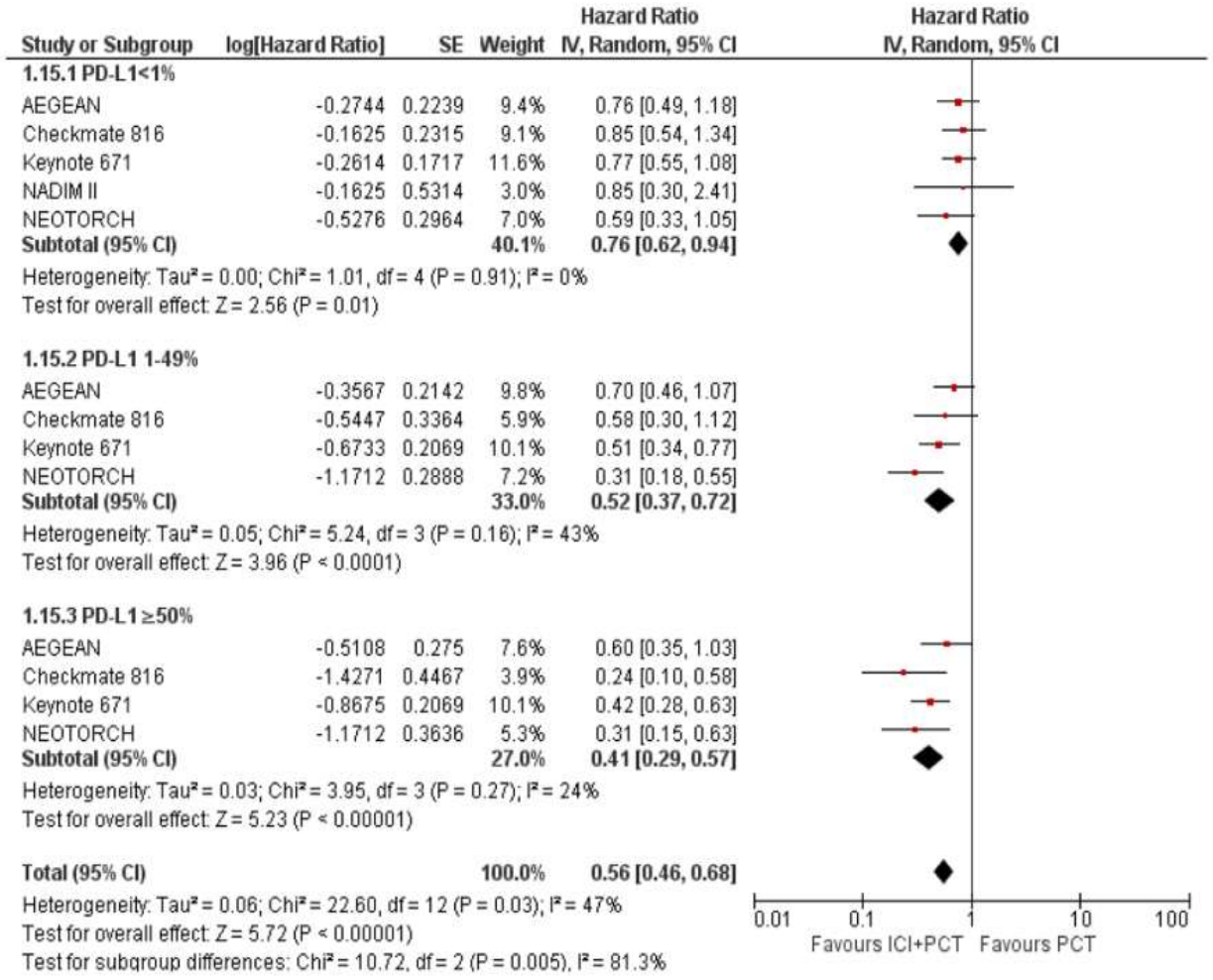
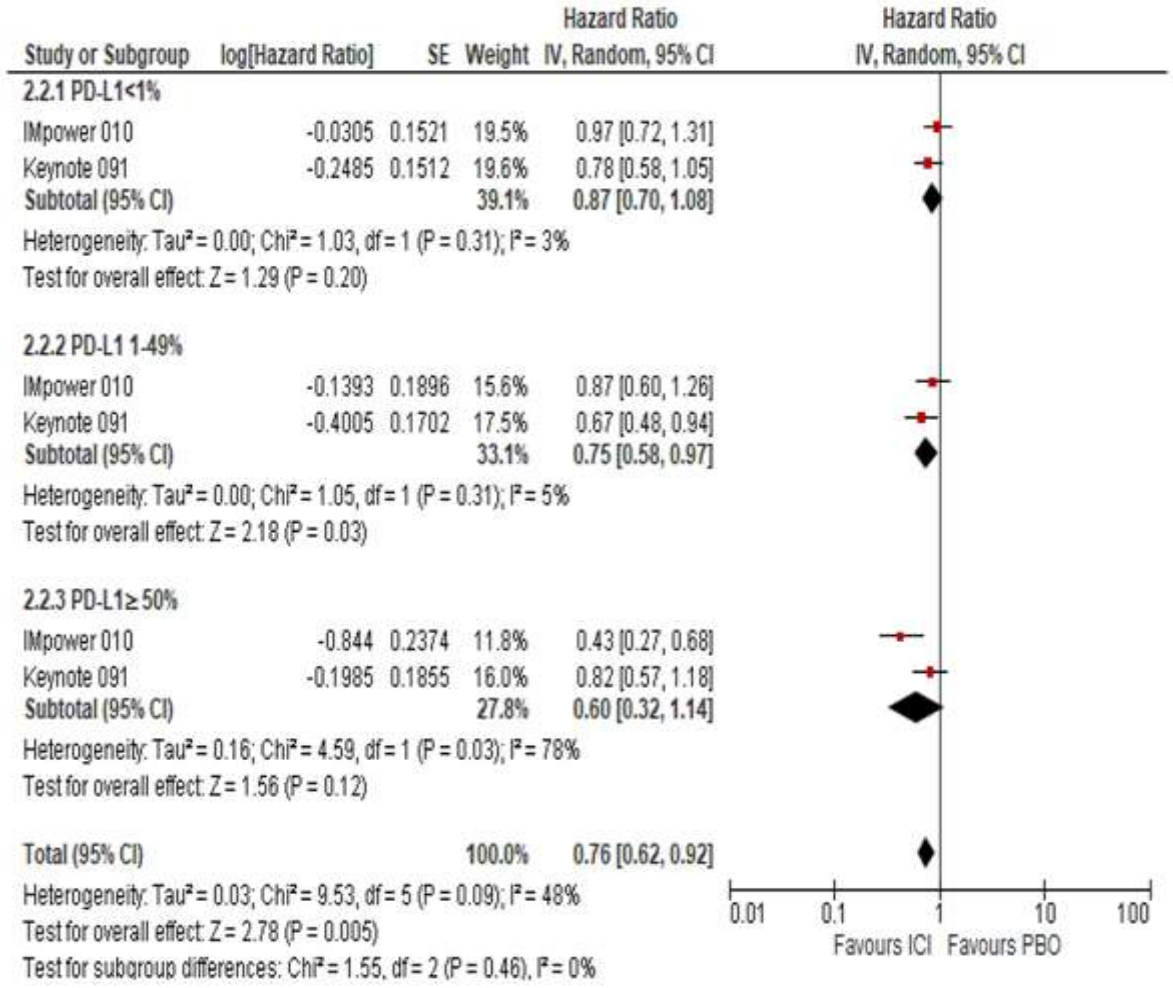
EFS and DFS by PD-L1

(B) EFS by PD-L1 TPS



(C) DFS by PD-L1 TPS



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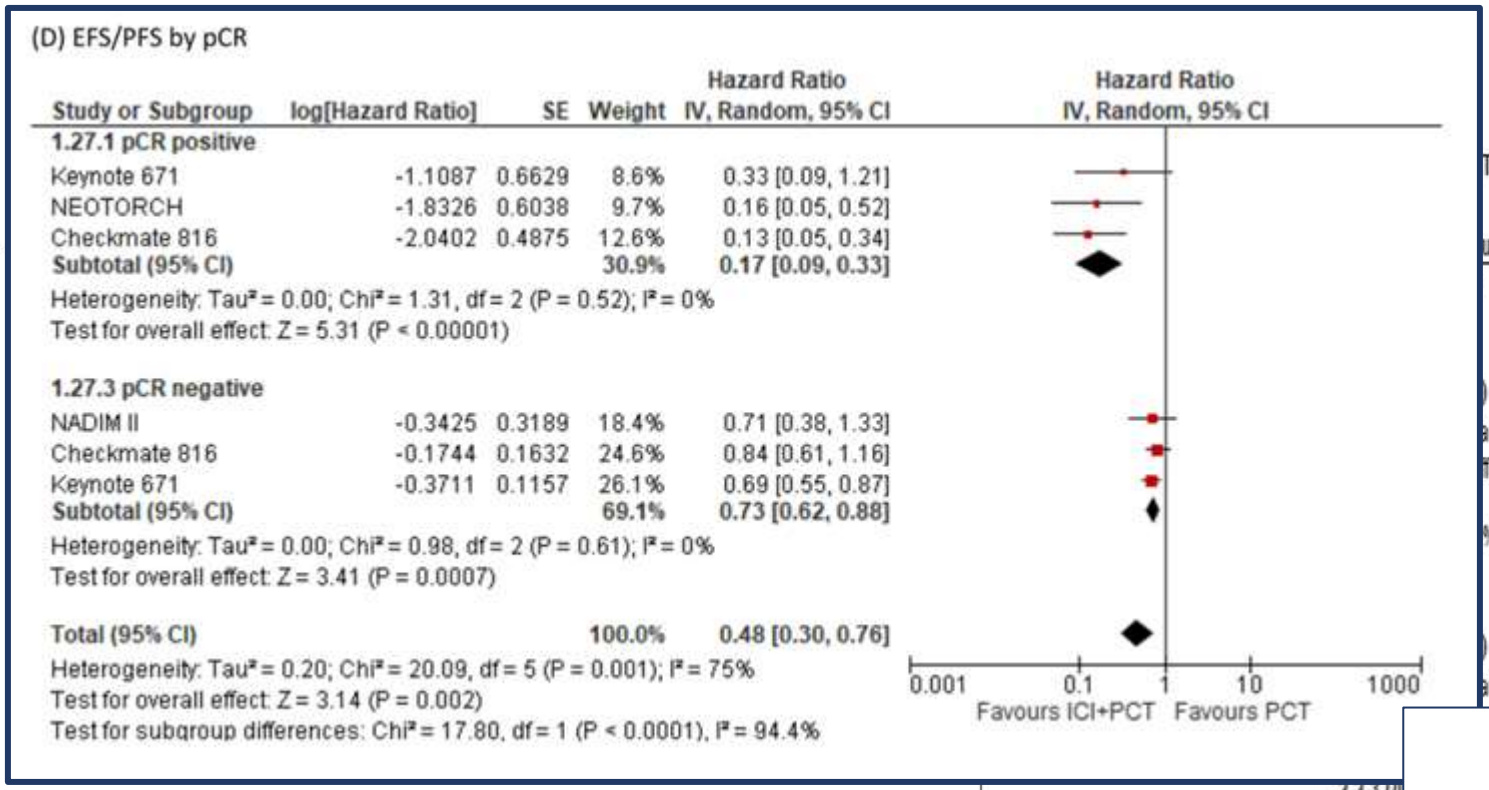
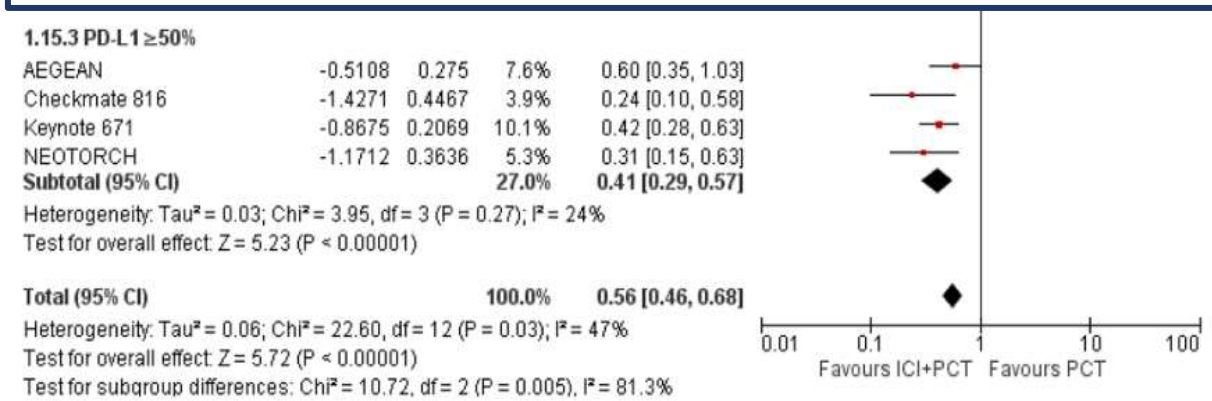
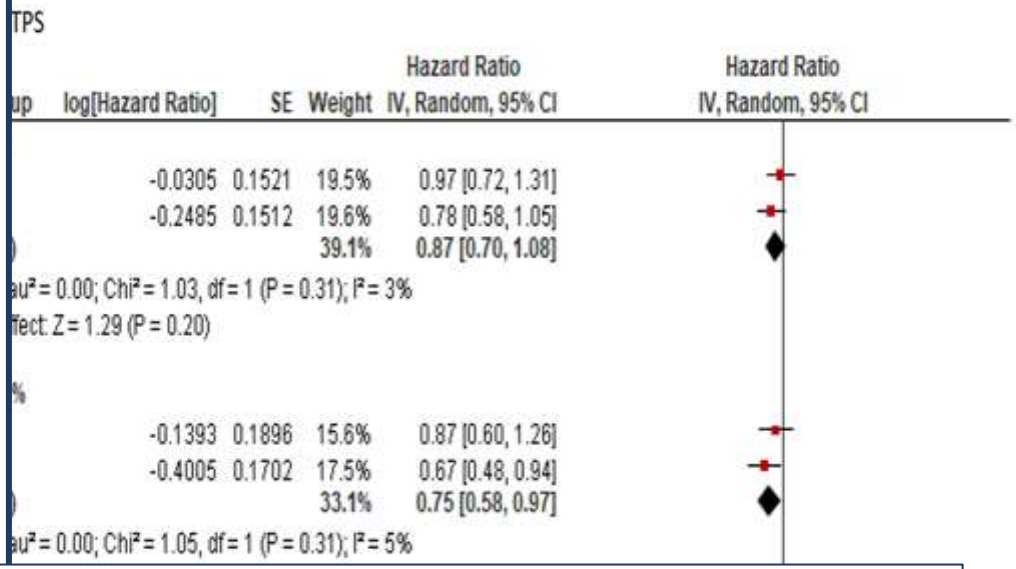
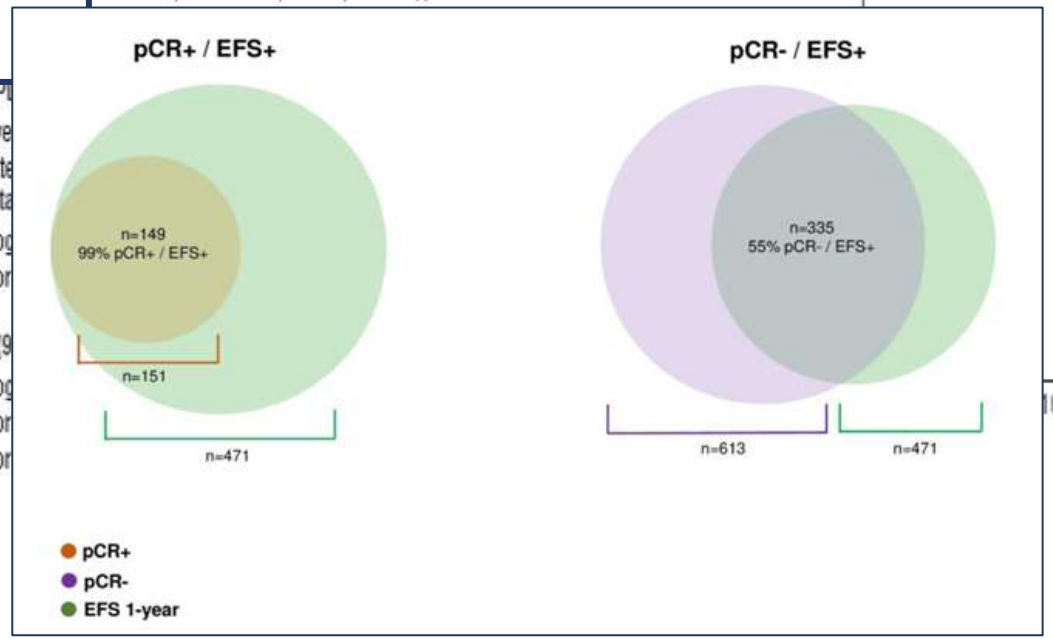
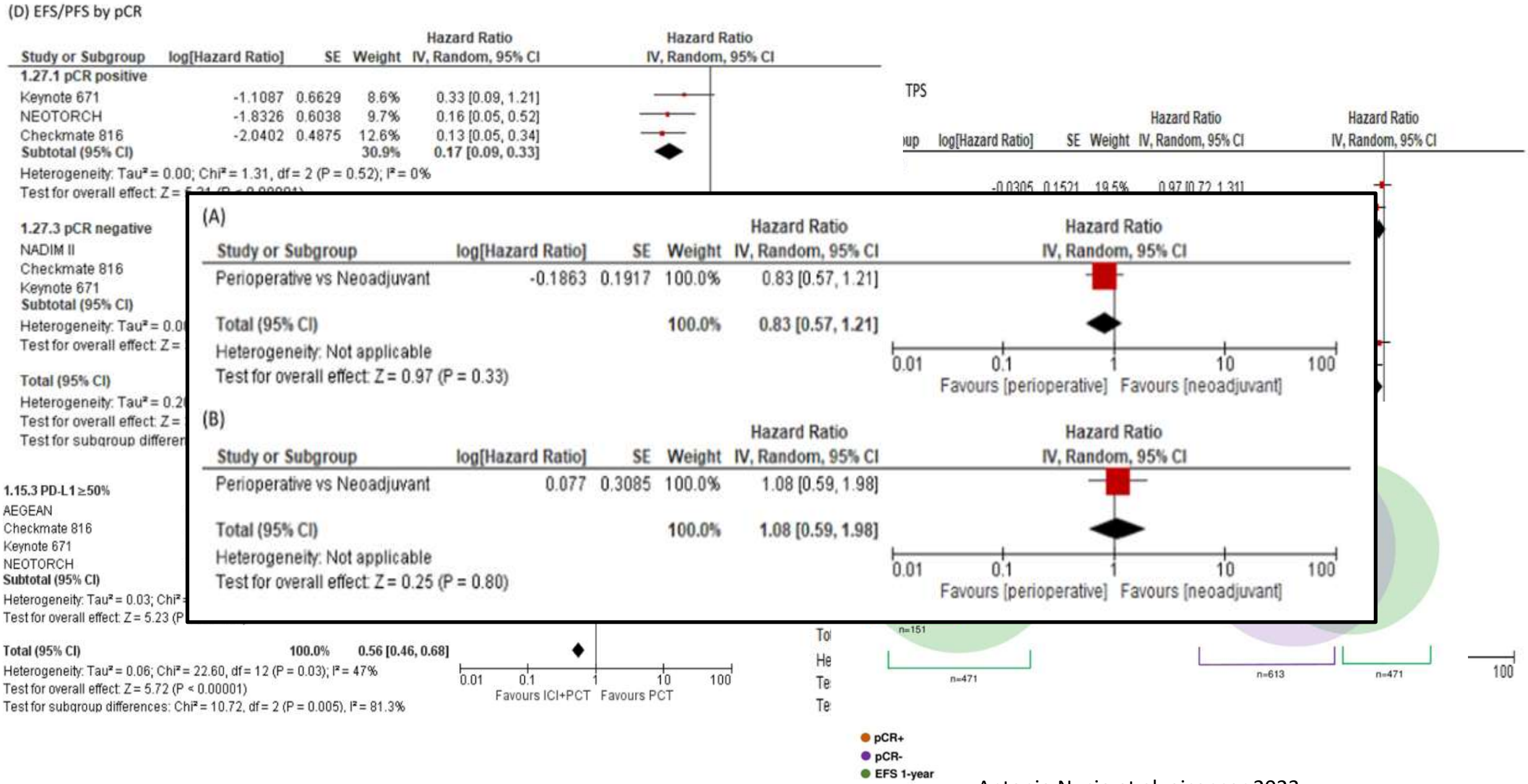
(D) EFS/PFS by pCR











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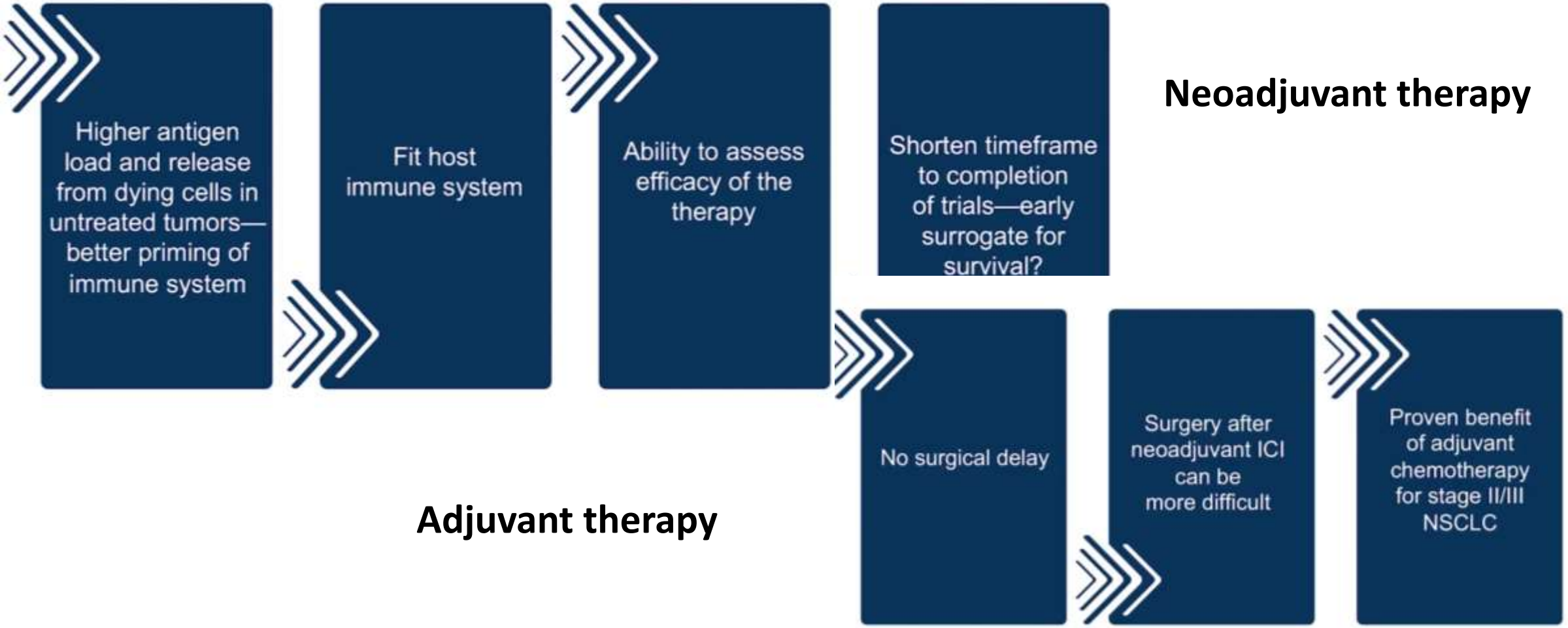
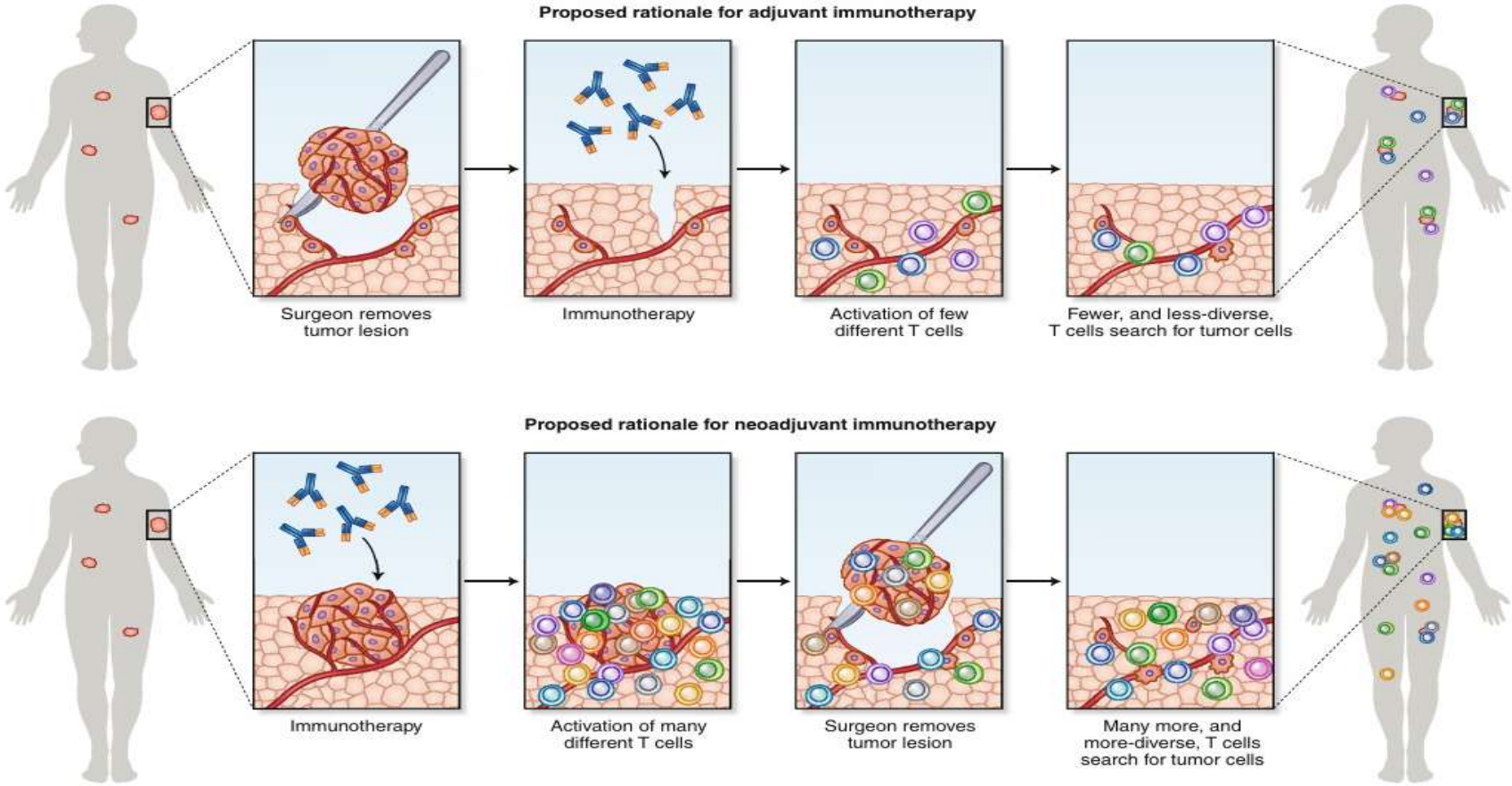
Selection of Strategy

Selection of neoadjuvant vs perioperative vs adjuvant

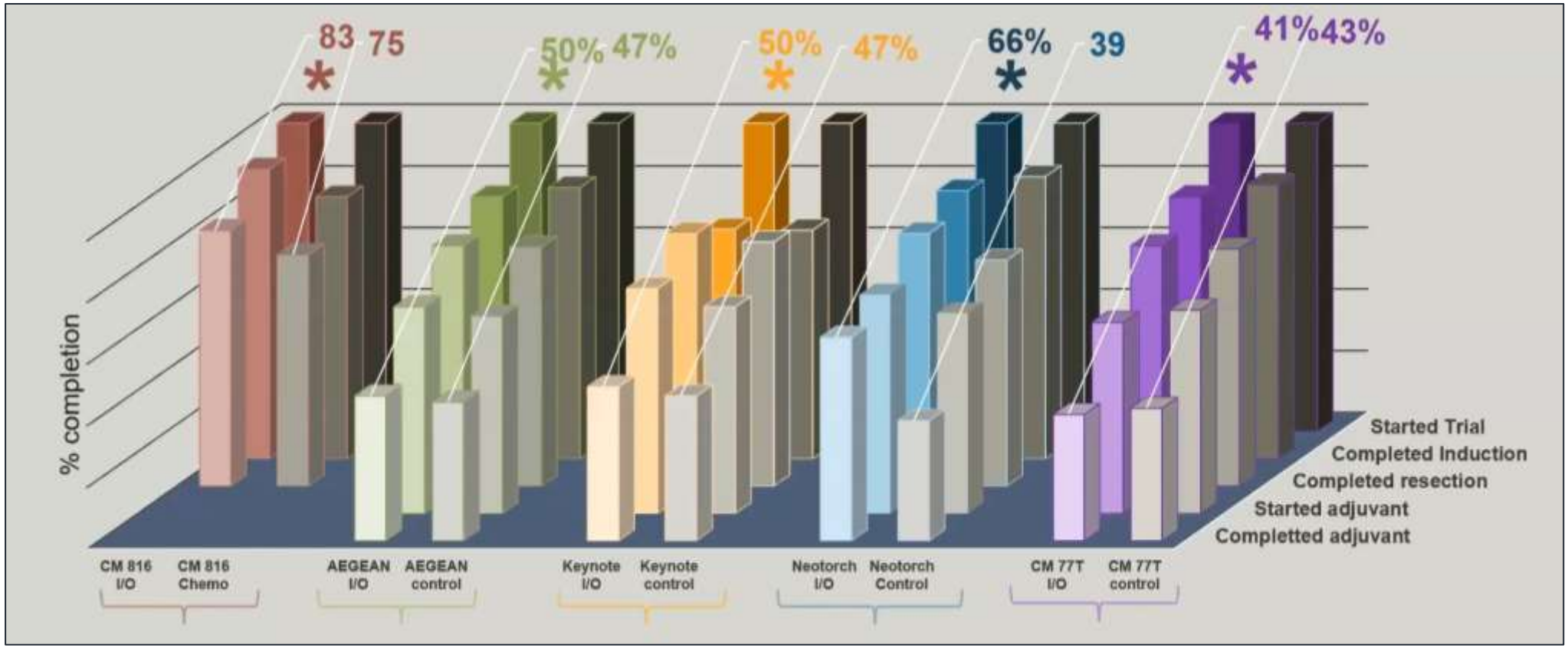


Rationale for neoadjuvant and adjuvant administration of immunotherapy



Versluis JM, Long GV, Blank CU. Learning from clinical trials of neoadjuvant checkpoint blockade. Nat Med. 2020;26:475–84

Completion of Care in Neoadjuvant Perioperative I/O trials



Felipe E et al. Lancet. 2021;398:1344-1357
O'Brian et al. Lancet Onc. 2022,23
Wakelee H et al. NEJM. 2023

- Due to the absence of head-to-head trials, and there is no definitive data to guide treatment selection among these options
- The perioperative pembrolizumab regimen is the only one that has demonstrated significant OS benefit, whereas the significance boundary for OS in the neoadjuvant CheckMate 816 study still has not been met at its most recent 4-year updated analysis, placing the KEYNOTE 671 regimen in a more favorable position when compared with the other options

- The HR for EFS from the KEYNOTE 671, Neotorch, and CheckMate 77T trials were 0.69 (95% CI, 0.55–0.85), 0.53 (95% CI, 0.38–0.74) and 0.70 (95% CI, 0.43–1.13), respectively
- Conversely, in the CheckMate 816, although there was a trend favoring neoadjuvant nivolumab, a higher EFS HR of 0.84 (95% CI, 0.61–1.17) was observed among patients without a pCR, suggesting that three doses of ICI may not be sufficient and a longer exposure to ICI may be required for those who do not achieve pCR

Optimal Duration and Biomarkers

Optimum duration of ICI

- The optimal duration of ICI has not been determined in either the early stage or recurrent/metastatic NSCLC
- The excellent EFS witnessed in those who achieve pCR after surgical resection begs the question as to how to identify which patients can omit adjuvant therapy
- Most of the evidence from perioperative trial which used around 1 year of adjuvant therapy

Biomarker for Immunotherapy

- The perfect biomarker for ICI efficacy would be quick, inexpensive, noninvasive, sensitive, and specific and would be supported by a standardized assay with a standard cutoff to allow reproducibility and comparison between trials
- At present, however, no biomarker for response to ICI therapy fits all of these criteria
- **PD-L1** expression is currently the most widely used biomarker for ICI therapy
- Discrepancy between trials regarding whether ICIs are beneficial in patients with low or negative PD-L1 expression exists

- Tumor mutation burden, the ratio of the number of mutations per megabase, has also been studied as a potential biomarker for ICI therapy
- It has been shown to be associated with ICI response in some advanced-stage NSCLC trials
- CheckMate 816, LCMC3, and NADIM I/II, have not observed an association between tumor mutation burden and response
- STK11 mutation or STK11/KRAS comutation, Loss of Kelch-like ECH-associated protein 1 (KEAP1) was associated with poor response to immunotherapy

- EGFR mutations and ALK fusions are exclusion criteria in most recent ICI trials
- ctDNA is an emerging innovation that has several potential applications in the treatment of patients with resectable NSCLC
- The presence of detectable ctDNA has also been shown to be associated with recurrence
- In CheckMate 816 and NADIM II trials, ctDNA clearance was associated with better results
- ctDNA is an important avenue of investigation to better tailor adjuvant immunotherapy strategies

Ongoing phase III trials evaluating neoadjuvant, perioperative, and adjuvant chemoimmunotherapy in resectable NSCLC

Trial	Patient population	Treatment	Primary endpoint	Study completion
MERMAID-1 (NCT04385368)	Stage II/III NSCLC after resection	Adjuvant durvalumab or placebo plus chemotherapy for 12 weeks followed by durvalumab or placebo for up to week 48	DFS in the MRD+ (measured by whole exome sequencing-based ctDNA test) group	2023-8-31
ANVIL (NCT02595944)	Stage IB (≥ 4 cm) –IIIA NSCLC after resection	Adjuvant nivolumab or observation	OS and DFS	2025-12-31
LungMate-008 (NCT04772287)	Stage II–IIIB (N2) NSCLC after resection	Adjuvant toripalimab or placebo with chemotherapy followed by 4 cycles adjuvant toripalimab or placebo	DFS	2027-12-30
ADOPT-lung (NCT06284317)	Resectable IIB–IIIB (N2)	Adjuvant durvalumab for 12 cycles or observation	DFS	2030-03
NADIM-ADJUVANT (NCT04564157)	Stage IB–IIIA NSCLC after resection	Adjuvant nivolumab with chemotherapy followed by 6-month of nivolumab vs. adjuvant chemotherapy	DFS	2031-04-01
IMpower 030 (NCT03456063)	Resectable stage II, IIIA, or select IIIB	Four cycles of neoadjuvant atezolizumab with chemotherapy and up to 16 cycles of adjuvant atezolizumab or placebo with chemotherapy	EFS	2025-01-19
PROSPECT LUNG (NCT06632327)	Resectable stage IIA to IIIB	Neoadjuvant ICI with 4 cycles of chemotherapy and one year adjuvant ICI vs. adjuvant therapy with 4 cycles chemotherapy and one year ICI	3-year real-world event-free survival (rwEFS) and OS	2030-04-30
CLEAR-INSIGHT (INSIGHT: NCT06498635)	Stage II–IIIB after resection	SOC neoadjuvant platinum-based chemotherapy and anti-PD-(L)1 therapy then surgery pCR: adjuvant durvalumab for 12 cycles vs. observation (INSIGHT) Non-pCR: adjuvant durvalumab and novel inhibitor combination vs. durvalumab for one year	DFS (INSIGHT)	2039-07-15 (INSIGHT)

Kuhlman JJ et al. Curative immunotherapy-based strategies for non metastatic NSCLC. Explor Target Antitumor Ther. 2024

Summary

- ICI therapy has radically revolutionized the treatment of NSCLC
- The addition of immunotherapy has significantly improved outcomes in selected patients with resectable NSCLC
- Multiple trials have shown improved EFS and now OS (in KEYNOTE-671) in patients with surgically resected disease
- Perioperative immunotherapy is safe in surgical patients and does not sacrifice surgical quality and outcomes

- Due to the absence of head-to-head trials, and there is no definitive data to guide treatment selection among these options
- Need for biomarker which can assess efficacy of the treatment accurately
- Studies evaluating the pre- and post-surgical ctDNA and ctDNA monitoring during treatment would be helpful to better guide the most appropriate choice of treatment duration

Thank you!