Evolving Landscape of Perioperative Therapy in Locally Advanced NSCLC

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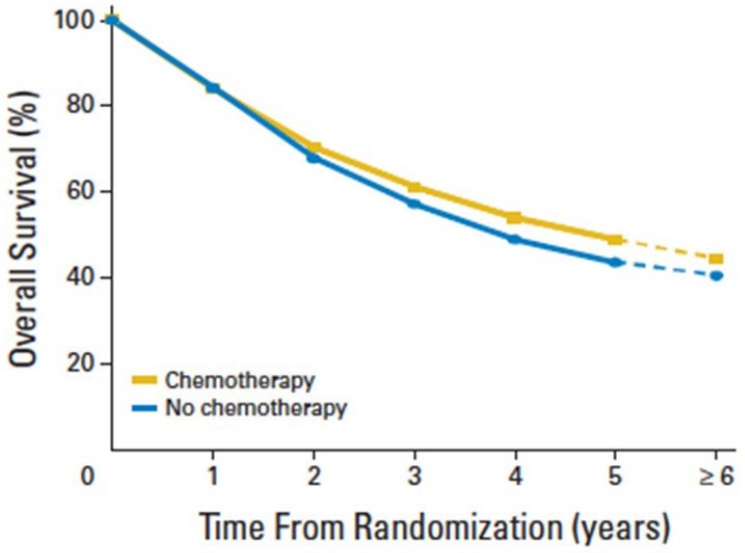
Faculty Disclosure

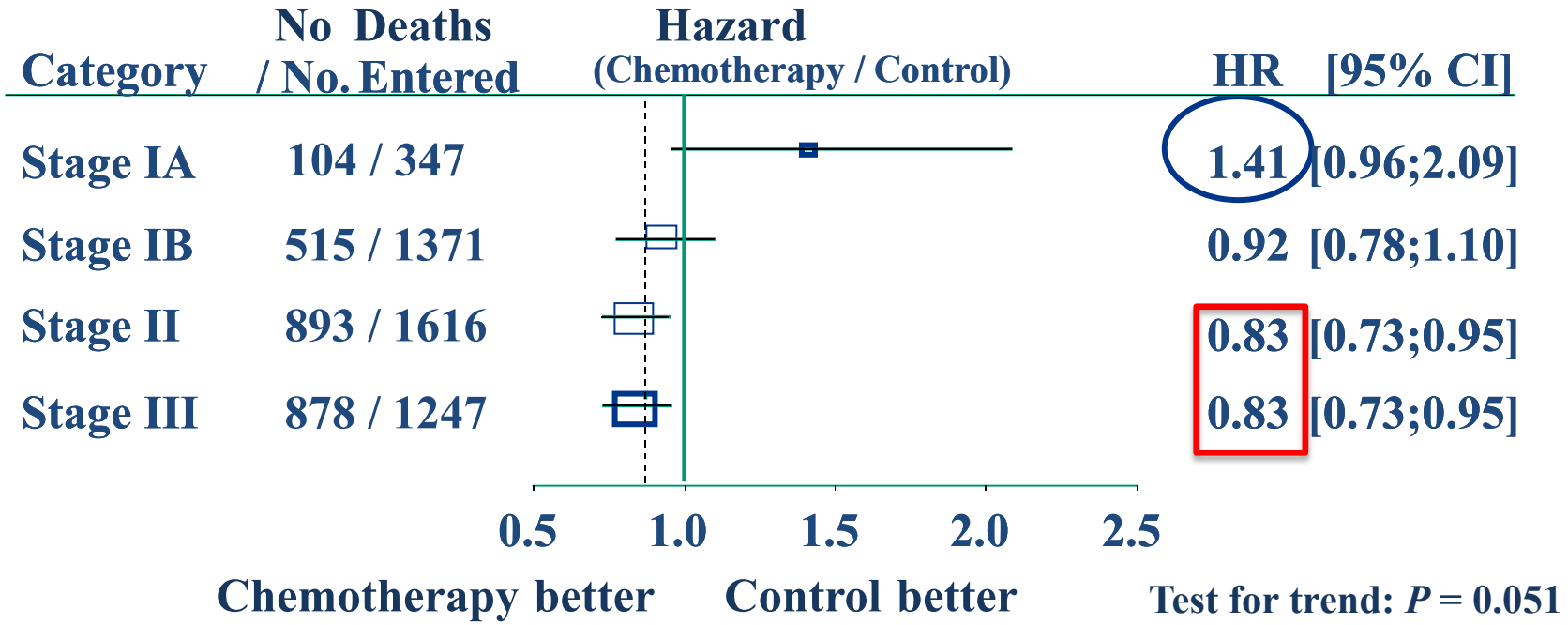
Name of Ineligible Company	Nature of Relevant Financial Relationship
AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, G1 Therapeutics, Johnson & Johnson, Merck, Pfizer, Sanofi, Takeda	• Advisory Board, Consultant
The Arizona Clinical Oncology Society (TACOS), Research to Practice, Scripps MDACC	• Speaker
• None	• Speakers Bureau

An **ineligible company** is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Evolving Landscape of Perioperative Therapy in Locally Advanced NSCLC



LACE Meta-Analysis



Absolute improvement in survival with adjuvant cisplatin-based chemotherapy of 5.4% at 5 years, greatest benefit for stage II and III and may be detrimental for stage IA

Pignon JP, et al. J Clin Oncol. 2008;26:3552-3559.

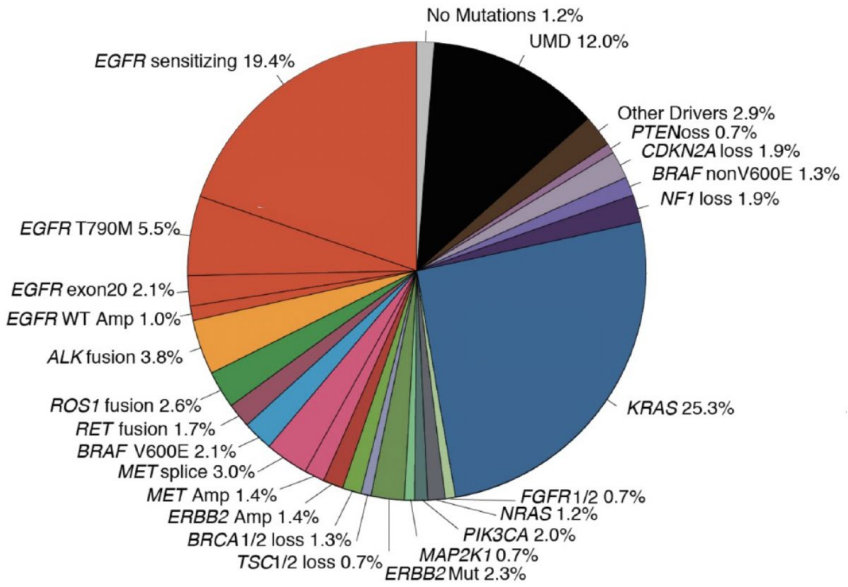
Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

1. Adjuvant Targeted Therapy: EGFRm, ALK

2. Immunotherapy (IO)
   a. Adjuvant IO
   b. Neoadjuvant ChemoIO
   c. Neoadjuvant + Adjuvant IO

Evolving Landscape of Perioperative Therapy in Locally Advanced NSCLC

Adjuvant Anti-EGFR Therapy



EGFR ~ 25%

EGFR Sensitizing 19.4%
EGFR T790M 5.5%
EGFR Exon20 2.1%

1. **Osimertinib is an irreversible TKI**
2. **EGFR T790M mutation in 2017**
3. **1st-Line Advanced EGFRm in 2018**

Jordan EJ et al. Cancer Discovery 2017

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization
1:1
(N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

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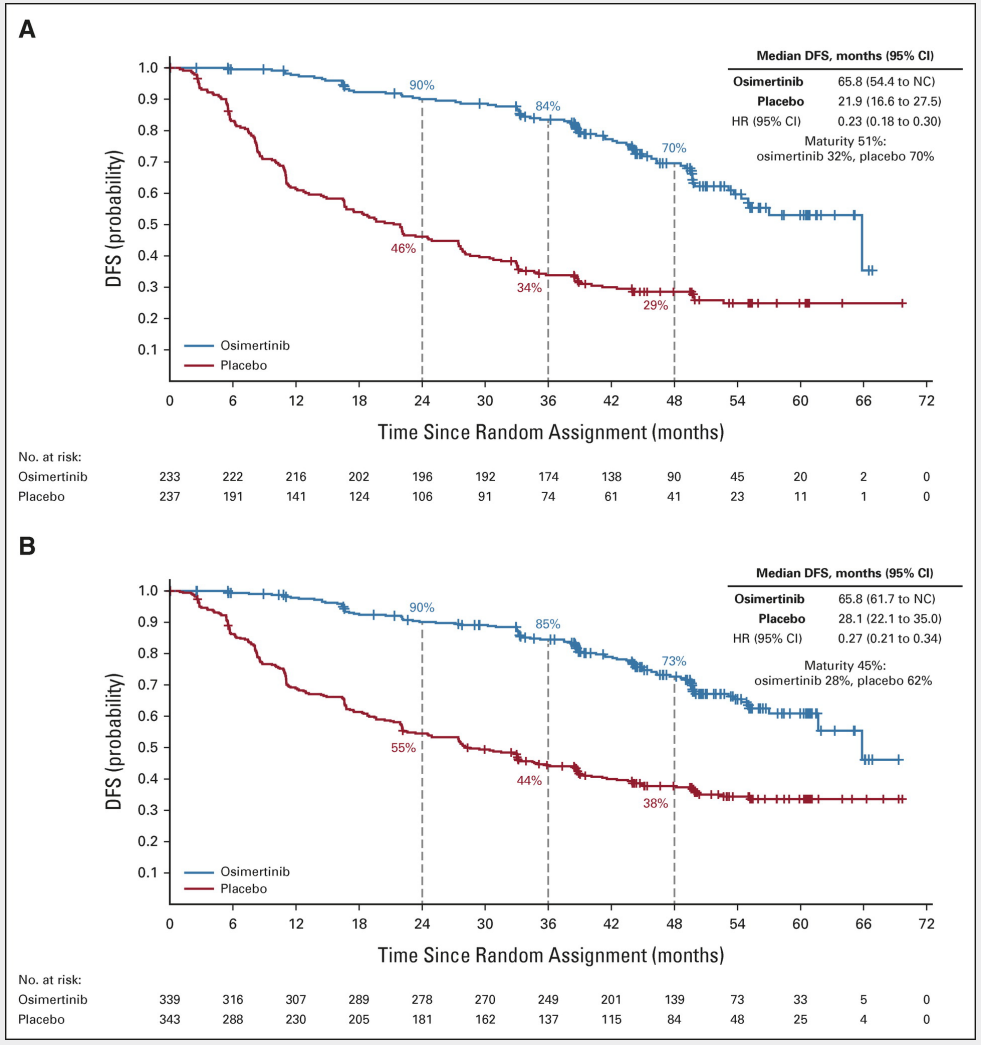
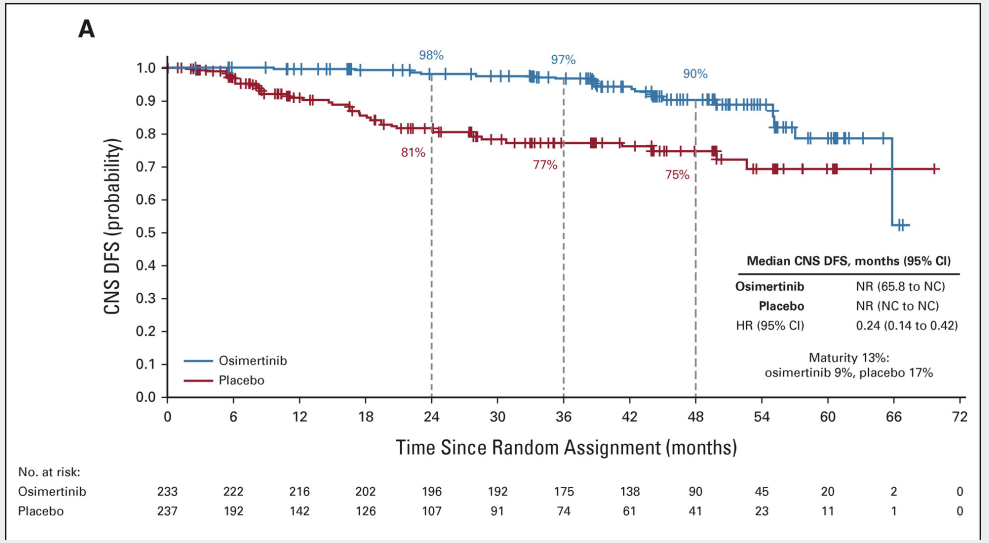
NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

Adjuvant Osimertinib Significantly Improved DFS





	Staging by AJCC/UICC Eighth Edition Staging Manual					
	Stage IB		Stage II		Stage IIIA	
Disease-Free Survival	Osimertinib (n = 101)	Placebo (n = 98)	Osimertinib (n = 113)	Placebo (n = 119)	Osimertinib (n = 110)	Placebo (n = 115)
Months, median (95% CI)	NR (61.7 to NC)	NR (45.0 to NC)	65.8 (54.4 to NC)	33.1 (24.5 to 49.8)	55.1 (49.5 to NC)	14.4 (11.0 to 21.3)
HR (95% CI)[a]	0.44 (0.25 to 0.76)		0.33 (0.21 to 0.50)		0.22 (0.15 to 0.31)	
Patients alive and disease-free, % (95% CI), months						
36	86 (77 to 92)	68 (57 to 76)	85 (76 to 90)	47 (38 to 56)	84 (75 to 89)	24 (17 to 32)
48	80 (69 to 87)	60 (49 to 69)	75 (65 to 83)	43 (34 to 52)	66 (55 to 75)	16 (10 to 24)
60	78 (67 to 86)	55 (43 to 65)	60 (44 to 72)	37 (27 to 47)	47 (33 to 59)	15 (8 to 23)

Abbreviations: AJCC, American Joint Committee on Cancer; FAS, full analysis set; HR, hazard ratio; NC, not calculable; NR, not reached; UICC, Union for International Cancer Control.

[a]The subgroup analysis was performed using a Cox proportional hazards model including treatment, subgroup, and a treatment-by-subgroup interaction term. An HR < 1 favors osimertinib.

Herbst, RS JCO 2023

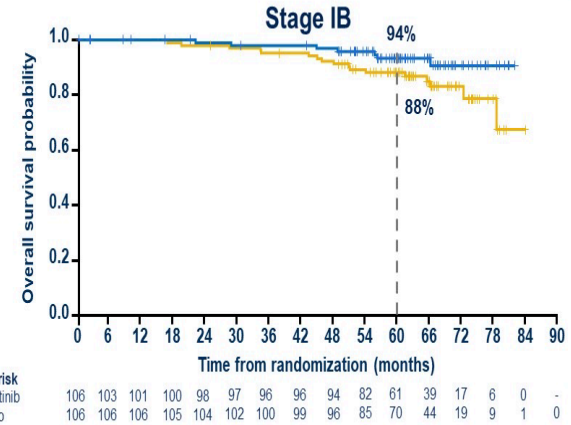
Impact of Osimertinib Approval

- Adjuvant Osimertinib for stage IB/II/IIIA EGFRm NSCLC after complete tumor resection
- EGFR testing (NGS) for all new Non-squamous NSCLC
- Role for adjuvant chemotherapy, in particular, in IB?
  - No definitive answer, personalized approach

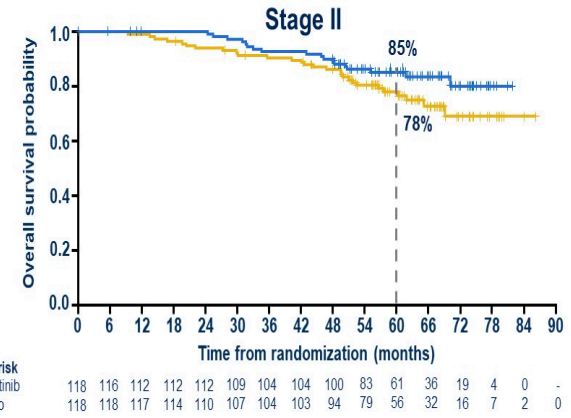
- OS ?

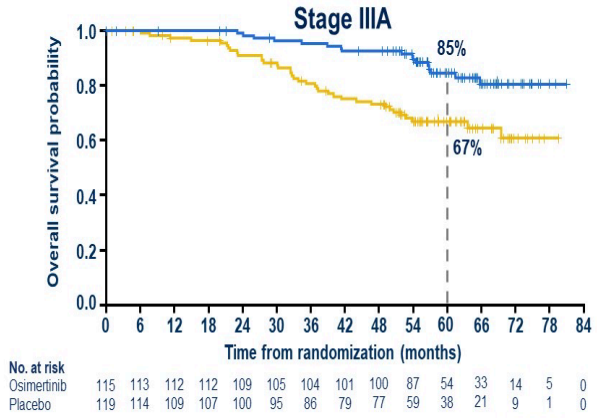
ADAURA trial: Overall Survival

Overall survival by disease stage



	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)

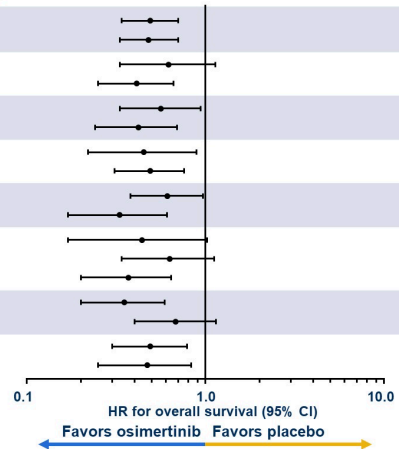


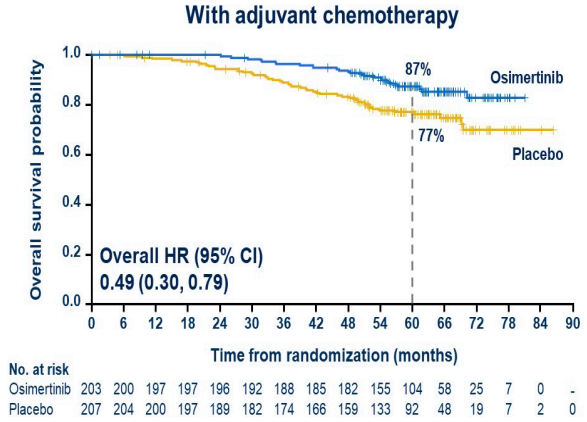


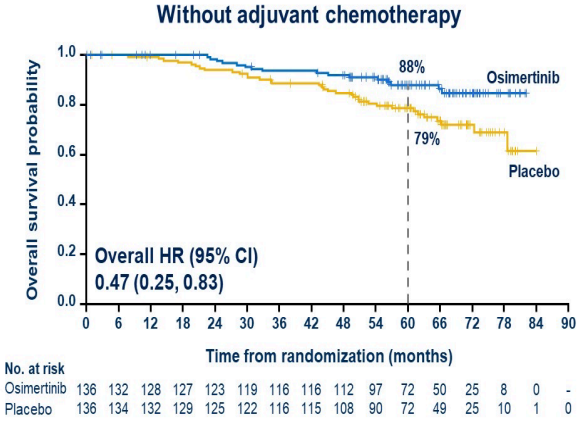
Overall OS HR (95.03% CI)	0.49 (0.34, 0.70) p<0.0001

OS across subgroups: patients with stage IB / II / IIIA disease

Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83

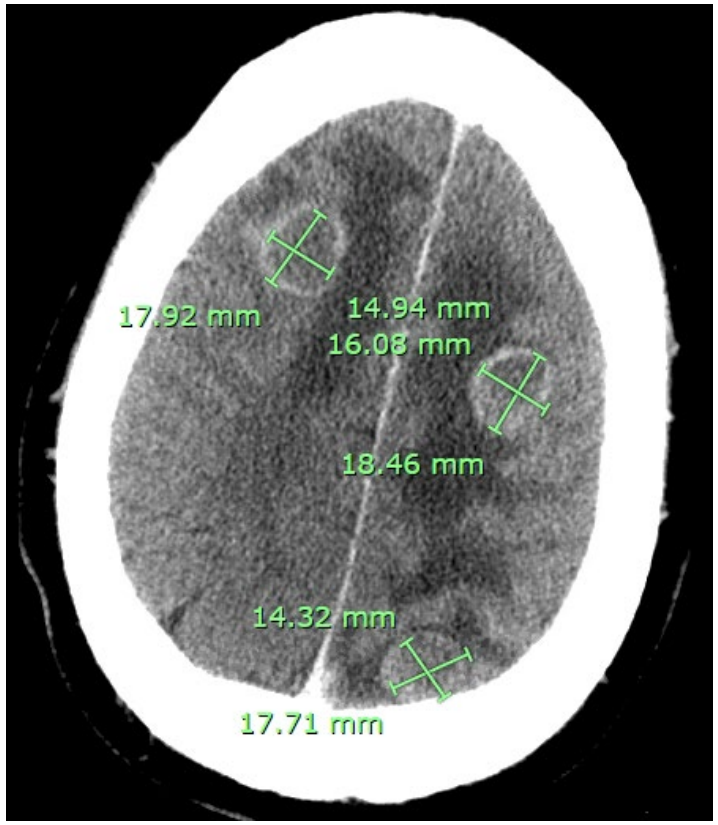






Herbst et al. ESMO 2023

Adjuvant Osimertinib



A 69 y/o man, with 16 PKY smoking history, MVA, s/p neurostimulator placement, preventing MRI
6/30/2020, L lobectomy, pT2aN2M0, IIIB, EGFR L858R S/P ChemoRT and completed 4 cycles of chemotherapy

11/2020, Adjuvant Osimertinib was started
4/2022, Developed multiple brain mets, largest one 3.4 cm, S/P WBXRT
PET/CT negative for mets

6/2022 - Present, Osimertinib 160 mg PO daily was started

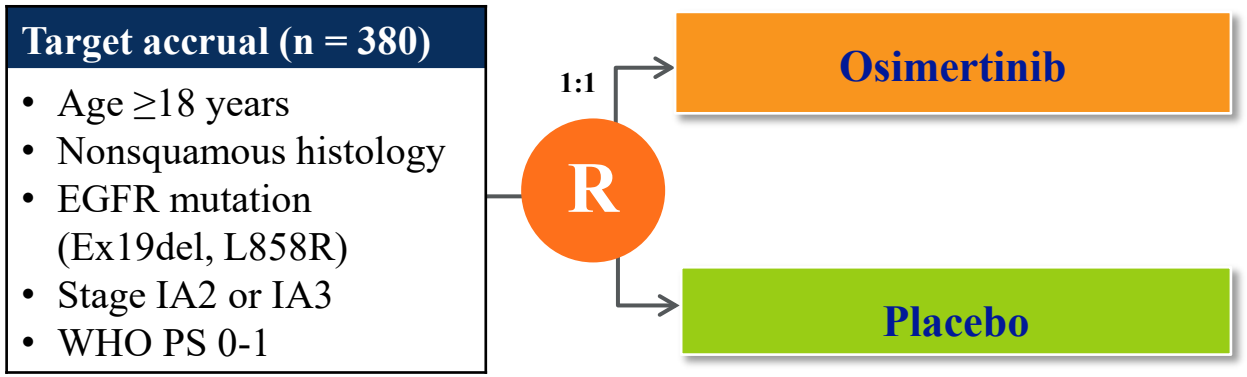
Osimertinib Improves OS in Resected EGFRm NSCLC

Questions Raised

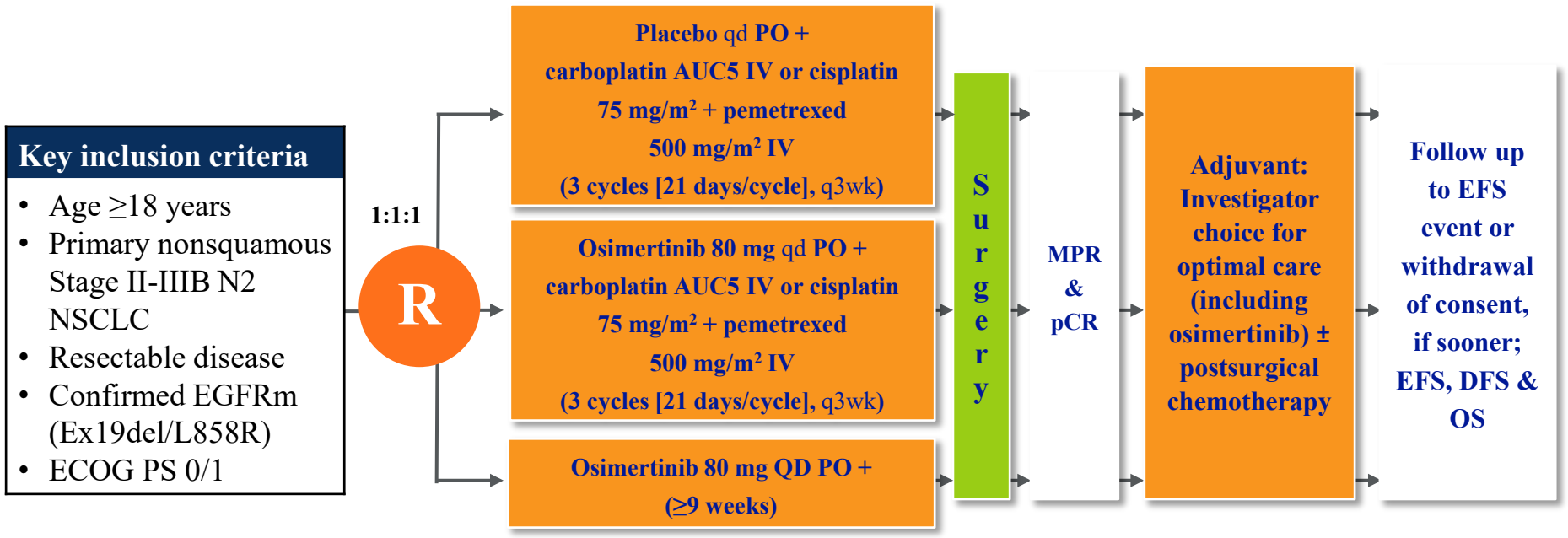
These unprecedented OS results in early-stage NSCLC are practice changing or confirming – Adjuvant treatment is superior to treatment upon recurrence

1. What is optimal duration of Osimertinib?
2. Is chemotherapy necessary for all patients, IB?
3. Can we use ctDNA to choose the right population?
4. What happens after relapse? What is the resistance mechanisms?
5. What about stage IA?
6. What about Neoadjuvant Osimertinib?
7. What about stage II/III treated with definitive chemoRT?
8. What about other mutations, such as ALK, RET fusion?

ADAURA-2: Phase III Trial



NeoADAURA: Phase III Trial



ALINA trial: Adjuvant Alectinib

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → Recurrence

Platinum-based chemotherapy† Q3W; 4 cycles → Recurrence

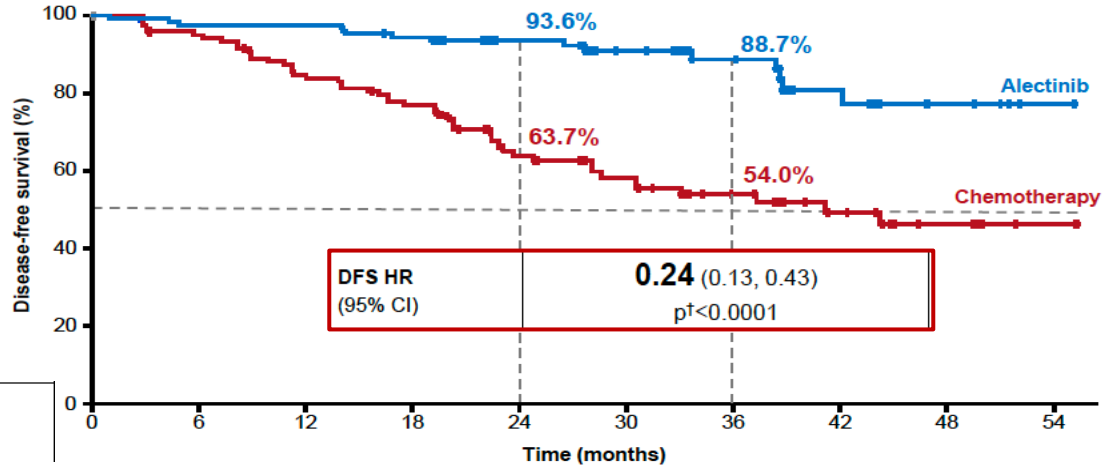
Further treatments at investigator's choice and survival follow-up

CNS-DFS HR* (95% CI) 0.22 (0.08, 0.58)

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

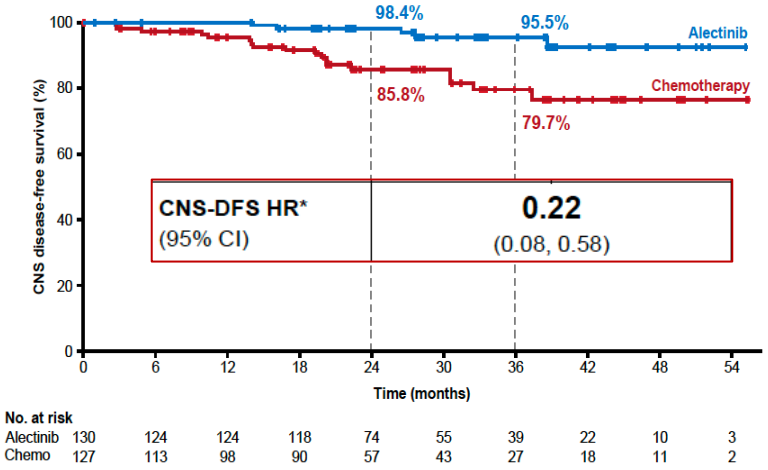
Disease-free survival: stage II–IIIA*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

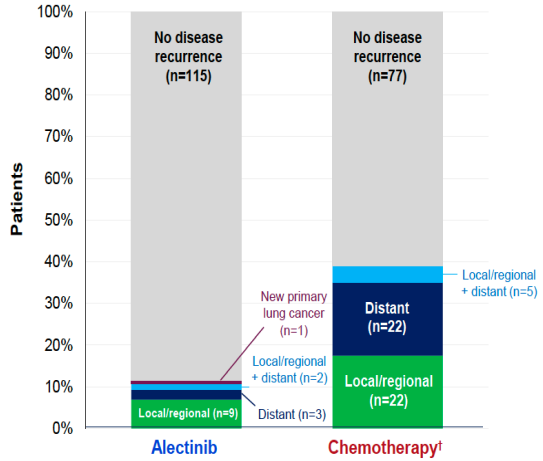
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

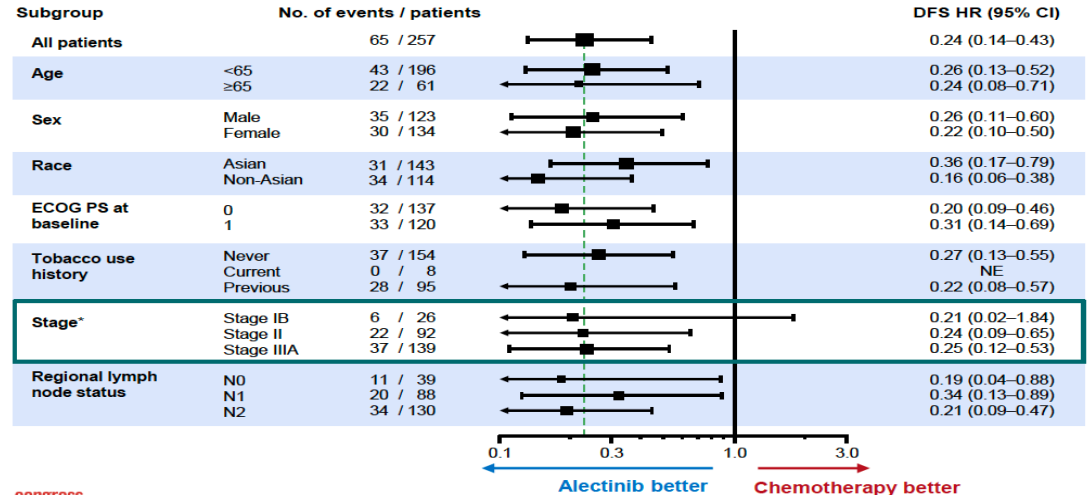


No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

Sites of disease recurrence (ITT)





Solomon et al. ESMO 2023

Evolving Landscape of Perioperative Therapy in Locally Advanced NSCLC

Resected NSCLC

EGFR, ALK mutation (IB, II, IIIA) →

1. Adjuvant Targeted Therapy – Osimertinib
   Alectinib?
2. Immunotherapy (IO)
   a. Adjuvant IO
   b. Neoadjuvant ChemoIO
   c. Perioperative IO

Impower 010: Study design

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

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

N=1280

R 1:1

No crossover

Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

Stratification factors

- Male vs 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:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population

Both arms included observation and regular scans for disease recurrence on the same schedule.

Hierarchical statistical testing

DFS in PD-L1 TC ≥1% stage II-IIIA population[b]

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomized stage IB-IIIA)

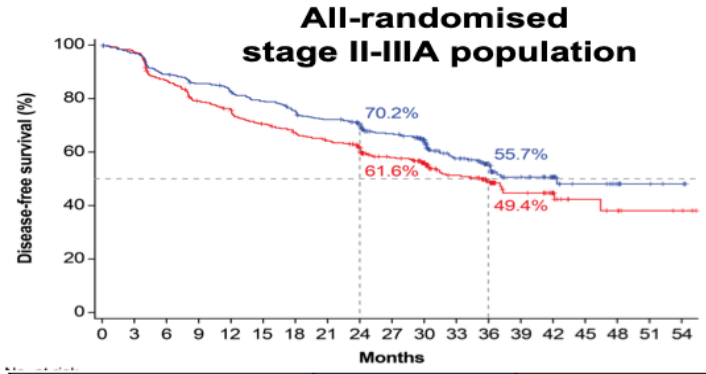
If positive:

OS in ITT population[b] (all-randomized stage IB-IIIA)

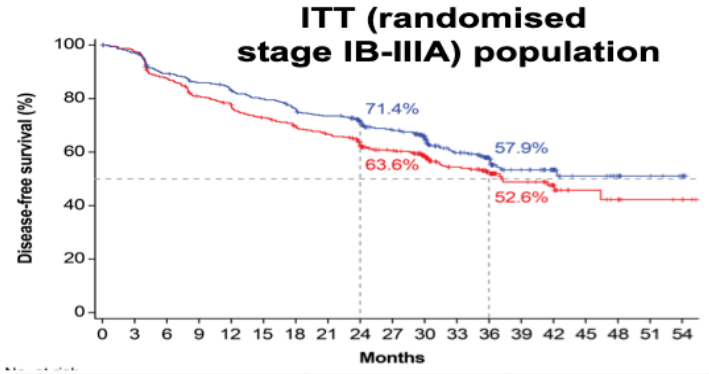
- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Wakelee HA, et al. J Clin Oncol. 2021

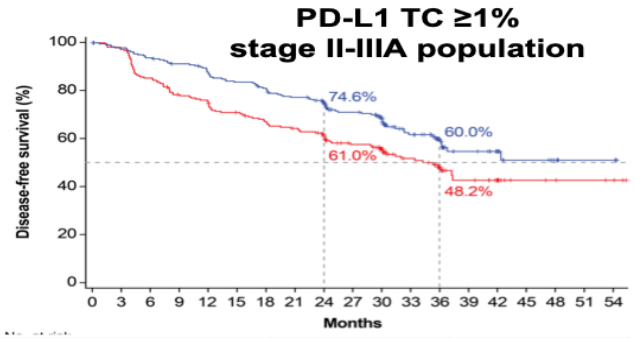
Impower 010: DFS



	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]	

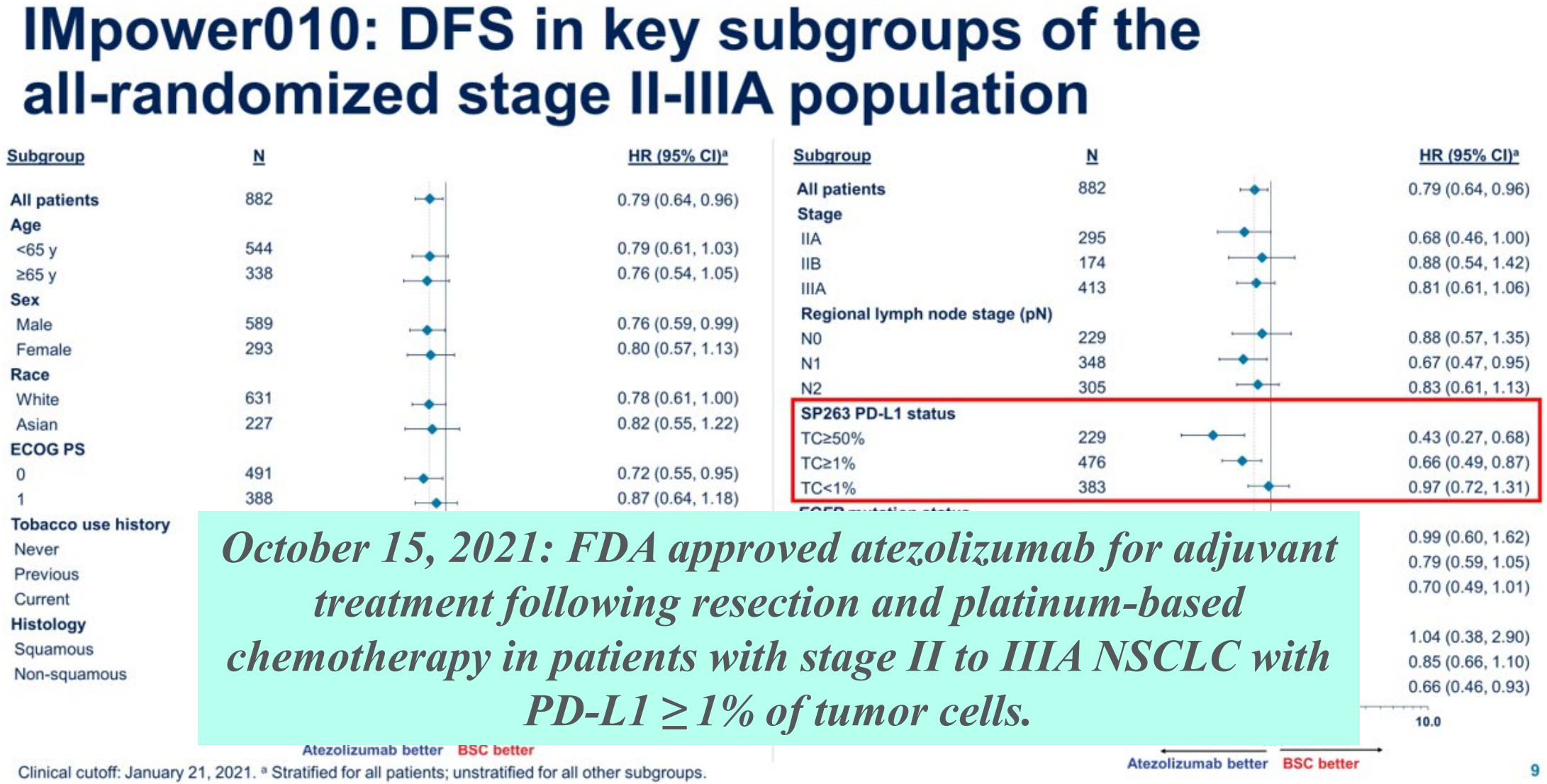


	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	



	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]	

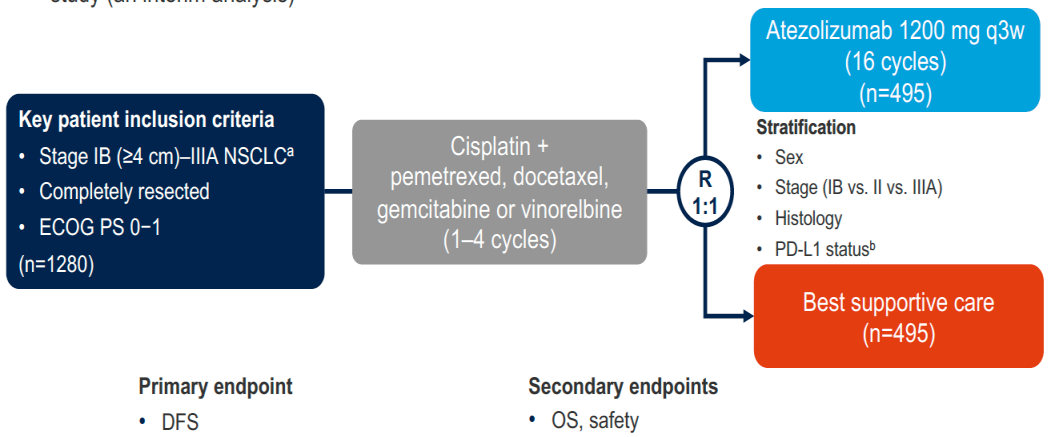
Impower 010: DFS



October 15, 2021: FDA approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC with PD-L1 ≥ 1% of tumor cells.

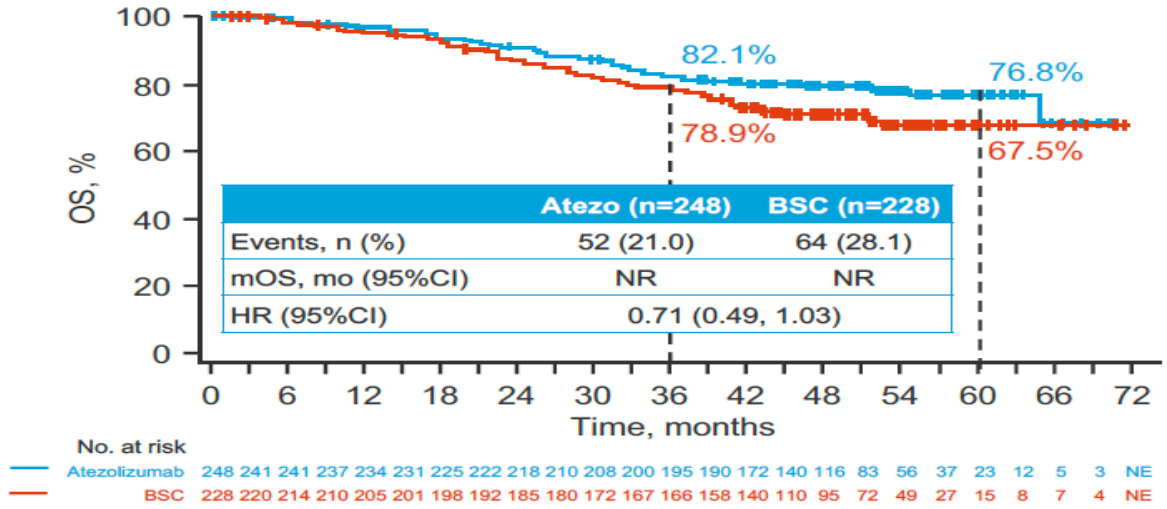
Impower 010 Trial: OS analysis

– To evaluate the efficacy and safety of atezolizumab in patients with resected NSCLC in the IMpower010 study (an interim analysis)



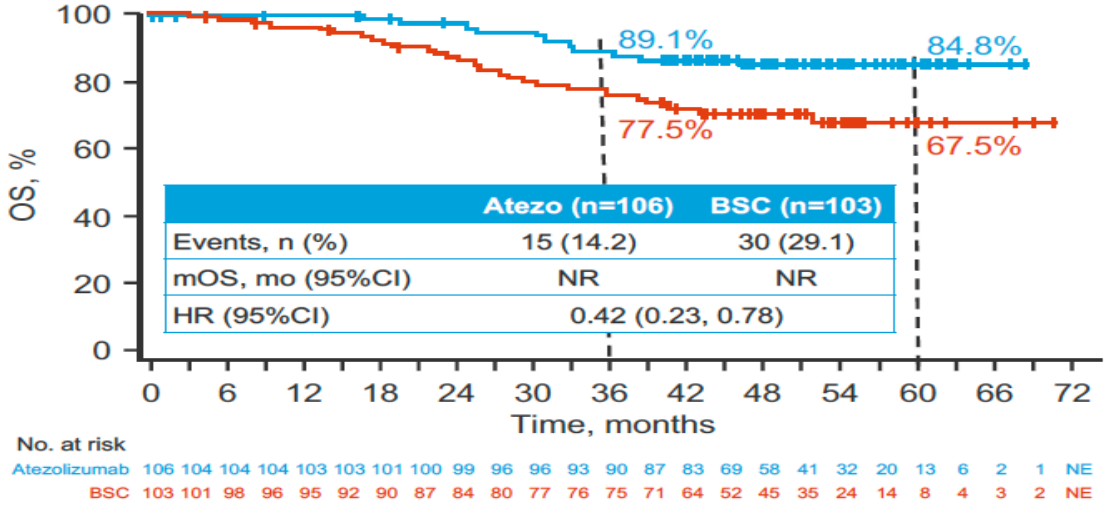
	Atezolizumab	BSC
All randomized (stage II–IIIA), n	442	440
Events, n (%)	115 (26.0)	116 (26.4)
mOS, mo (95%CI)	NR	NR
HR (95%CI)	0.95 (0.74, 1.24)	
ITT (stage IB–IIIA), n	507	498
Events, n (%)	127 (25.0)	124 (24.9)
mOS, mo (95%CI)	NR	NR
HR (95%CI); p-value	0.995 (0.78, 1.28); 0.9661	

PD-L1 TC ≥1% (stage II–IIIA)



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

PD-L1 TC ≥50% (stage II–IIIA) excluding EGFR/ALK+



	Atezo (n=106)	BSC (n=103)
Events, n (%)	15 (14.2)	30 (29.1)
mOS, mo (95%CI)	NR	NR
HR (95%CI)	0.42 (0.23, 0.78)	

Wakelee H et al. WCLC 2022

KEYNOTE-091/PEARLS: Study design

Eligibility for Registration

- Confirmed stage IB (T ≥4 cm), II or IIIA NSCLC (per TNM 7th edition)
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomisation

- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm)
  - Strongly recommended for stage II and IIIA
  - Limited to <4 cycles

R 1:1

- **Pembrolizumab 200 mg Q3W for ≤18 cycles (~1 y)**
- **Placebo 200 mg Q3W for ≤18 cycles (~1 y)**

Stratification factors

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

Dual primary end points

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

Secondary end points

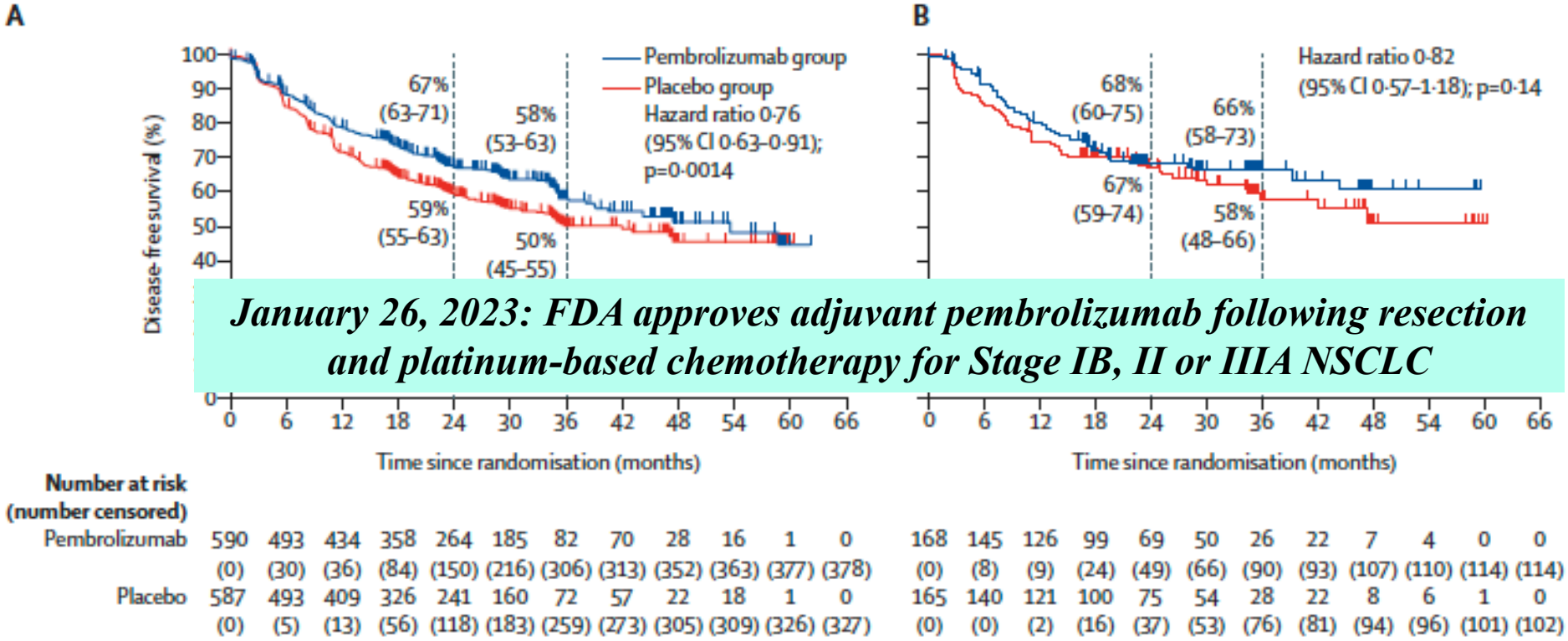
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50% and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Paz-Ares L et al ESMO 2022; O´Brien M et al. Lancet Oncol 2022

PEARLS Trial: DFS in ITT vs PD-L1 ≥50%

Stage IB-IIIA
HR=0.76 (P=.0014,
95% CI 0.63-0.91)

PD-L1>50%
HR=0.82 (P=.14,
95% CI , 0.57-1.18)



January 26, 2023: FDA approves adjuvant pembrolizumab following resection and platinum-based chemotherapy for Stage IB, II or IIIA NSCLC

Paz-Ares L et al ESMO 2022; O´Brien M et al. Lancet Oncol 2022

Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

Resectable NSCLC

EGFR mutation (IB, II, IIIA) →

1. Adjuvant Targeted Therapy - Osimertinib

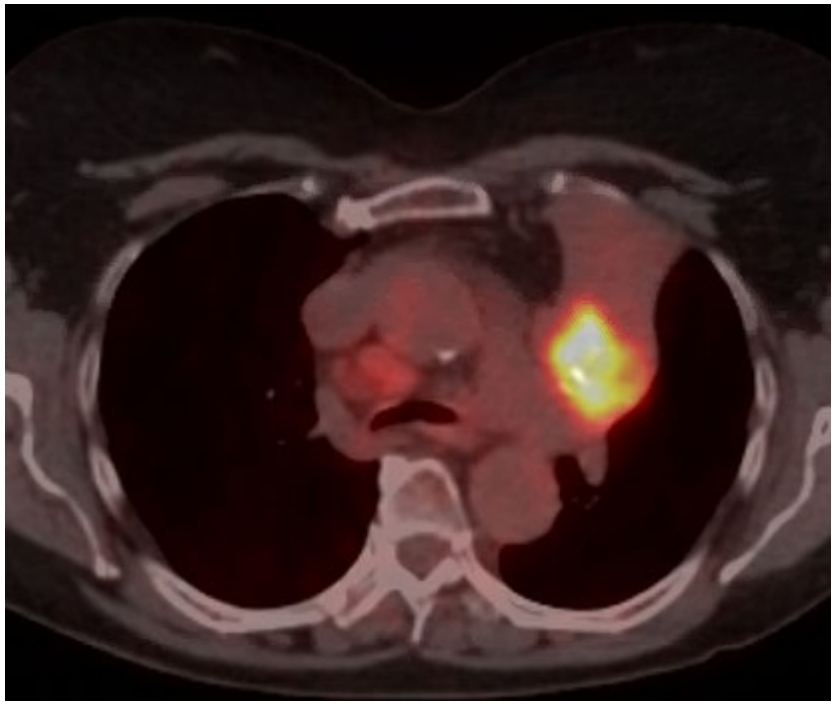
2. Immunotherapy (IO)

a. Adjuvant IO (Atezo, Pembro, Stage1B, PDL1)

b. Neoadjuvant ChemoIO

c. Perioperative IO

Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC



A 79-year-old female, a current heavy smoker with at least 30-pack-year smoking history, presents with LUL squamous cell carcinoma, 3.1 cm 10/14/21, CT demonstrated a left upper lobe collapse was noted as well as some mediastinal lymphadenopathy. MRI brain was negative for mets. 11/2/2021, EBUS biopsy demonstrated 11L node was involved by squamous cell carcinoma. T2aN1M0, stage IIB

ChemoRT vs Surgical Resection vs Neoadjuvant Approach

Possible Left pneumonectomy?

What is next?

CheckMate 816: Study design

Key Eligibility Criteria

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

Stratified by
stage (IB–II vs IIIA), PD-L1 (≥1% vs <1%) and sex

N=358

R 1:1

Primary analysis population

NIVO 360 mg Q3W + chemo Q3W (3 cycles)

Chemo Q3W (3 cycles)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)

Radiologic restaging

Surgery (within 6 weeks post-treatment)

Optional adjuvant chemo ± RT

Primary end points
- pCR by BIPR
- EFS by BICR

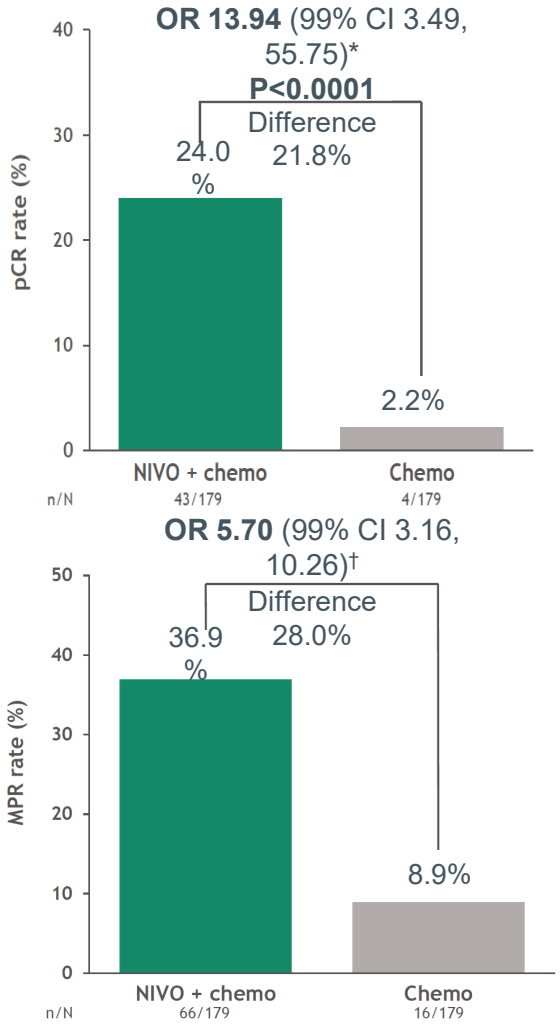
Secondary end points
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory end points
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA)

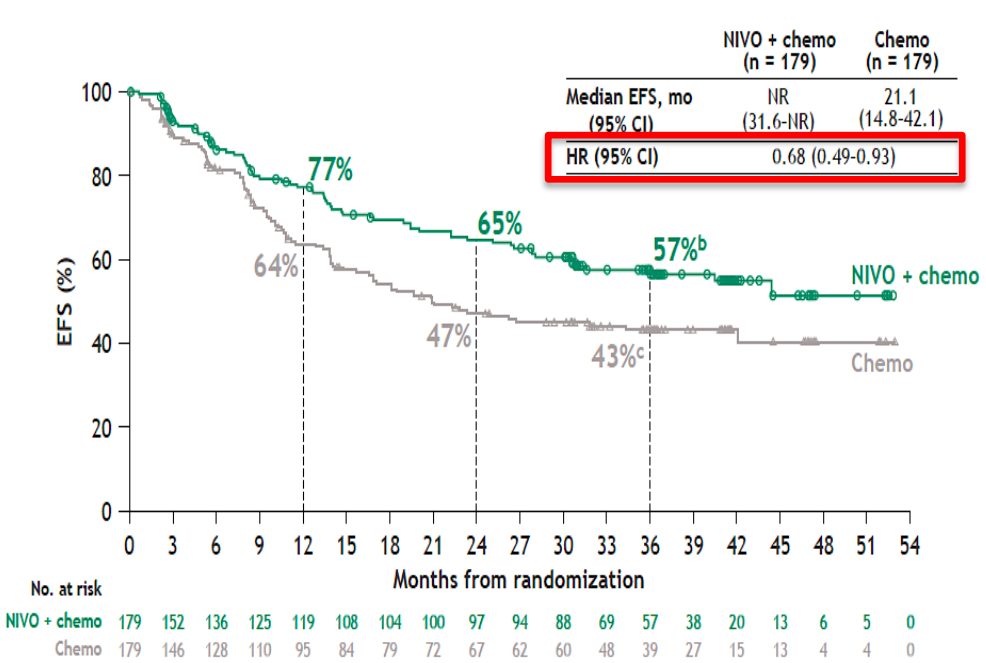
Forde PM, et al. NEJM 2022

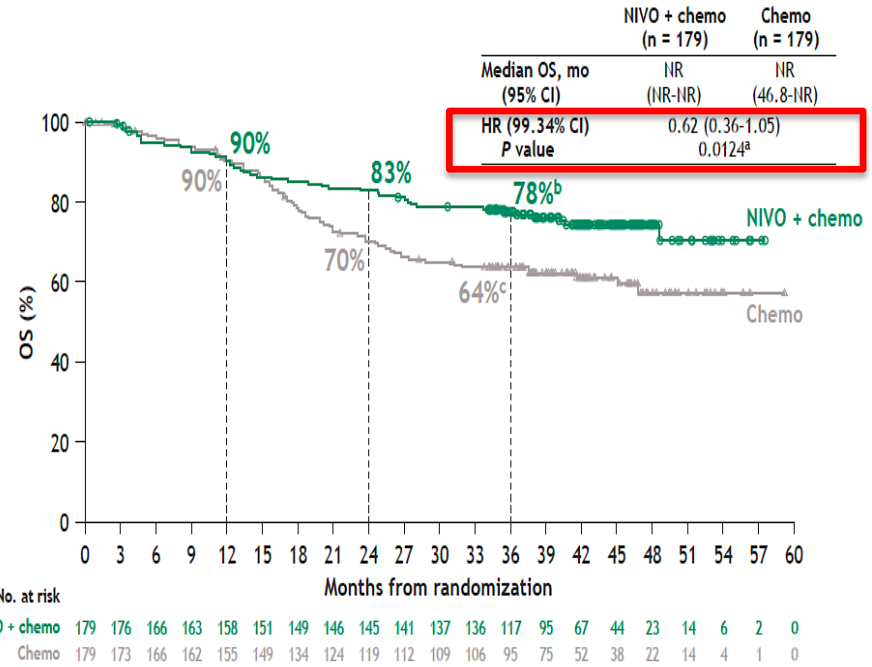
CheckMate 816: 3-year Follow-up

Pathological outcomes



EFS and OS outcomes‡§

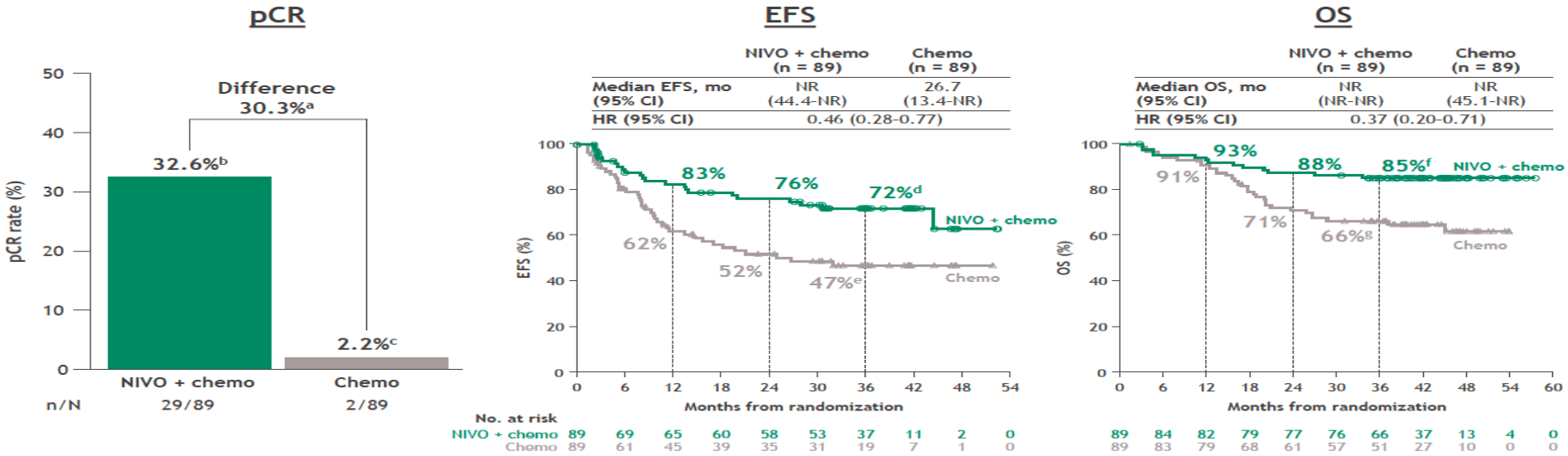




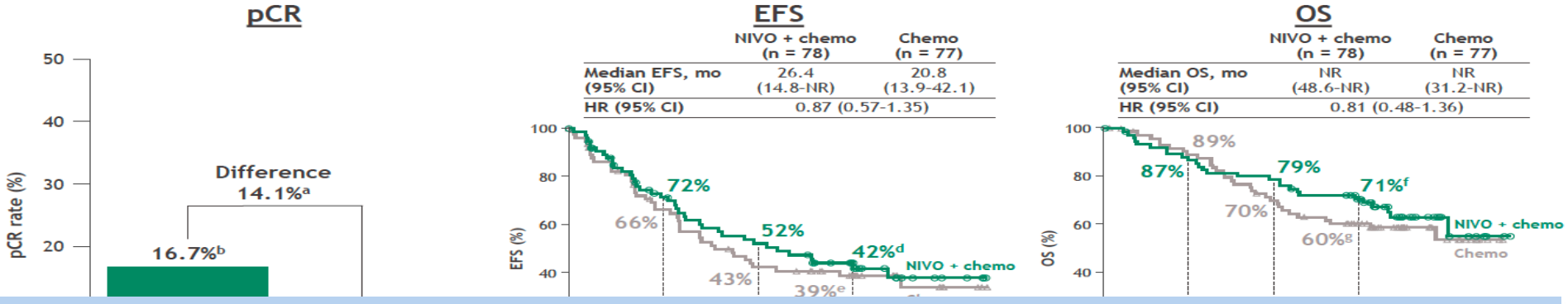
Spicer J, et al. ASCO 2021; Girard N, et al. AACR 2022; Forde PM, et al. N Engl J Med 2022;386:1973–1985

CheckMate 816 trial: PD-L1 Status

PD-L1 +



PD-L1 -



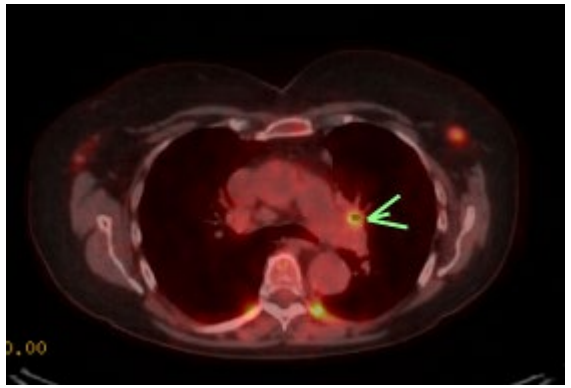
March 4, 2022: FDA approved neoadjuvant Nivo/Chemo for resectable NSCLC

Pulla MP et al. ESMO 2023

Recent Advances in Lung Cancer

Pre

Post



A 79-year-old female, a current heavy smoker with at least 30-pack-year smoking history, presents with LUL squamous cell carcinoma, 3.1 cm. Stage IIB, with collapsed LUL

11/2021, ChemoIO with Carbo/Taxol/Pembrolizumab was started (before Nivo approval)

Developed Immune-related hepatitis after C1, Pembro was held, requiring steroid taper over 6 weeks.

LUL reopened after C2, and responded markedly well after C4

3/8/2022, S/P LUL lobectomy, pT1a (<0.4 cm)N1(1 of lobar LNs)

On clinical surveillance, NED.

Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

Resectable NSCLC

EGFR mutation (IB, II, IIIA) →

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a. Adjuvant IO (Atezo, Pembro, Stage1B, PDL1)

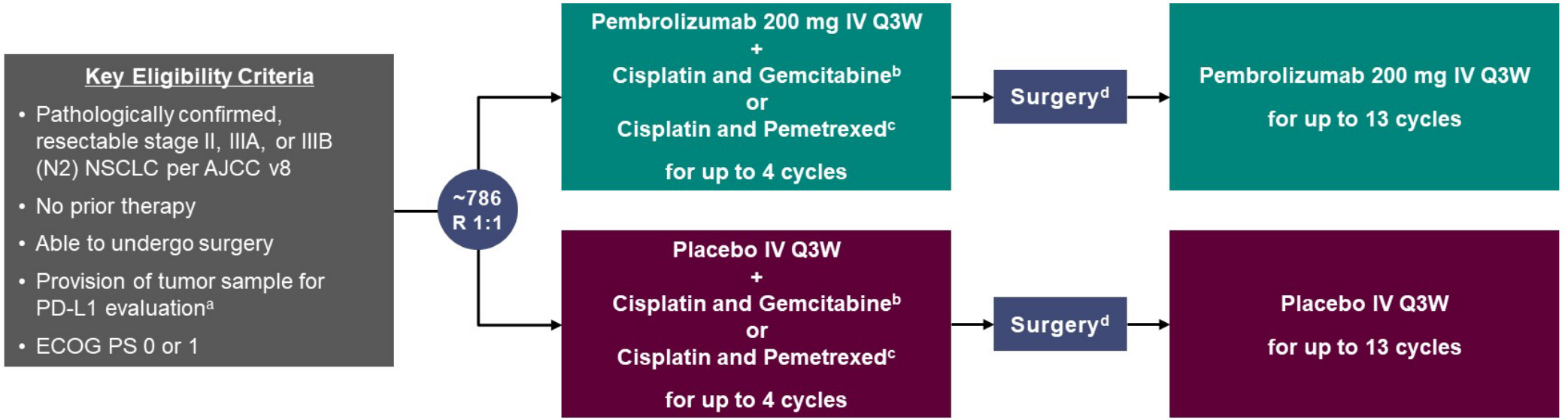
b. Neoadjuvant ChemoIO (Nivo)

c. **Perioperative IO**

- KEYNOTE 671
- CheckMate 77T
- AEGEAN
- NeoTorch

KEYNOTE-671 Study Design

Randomized, Double-Blind, Phase 3 Trial



Stratification Factors

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

Dual primary end points: EFS per investigator review and OS

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

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

Wakelee, H, et al, ASCO 2023

Baseline Characteristics

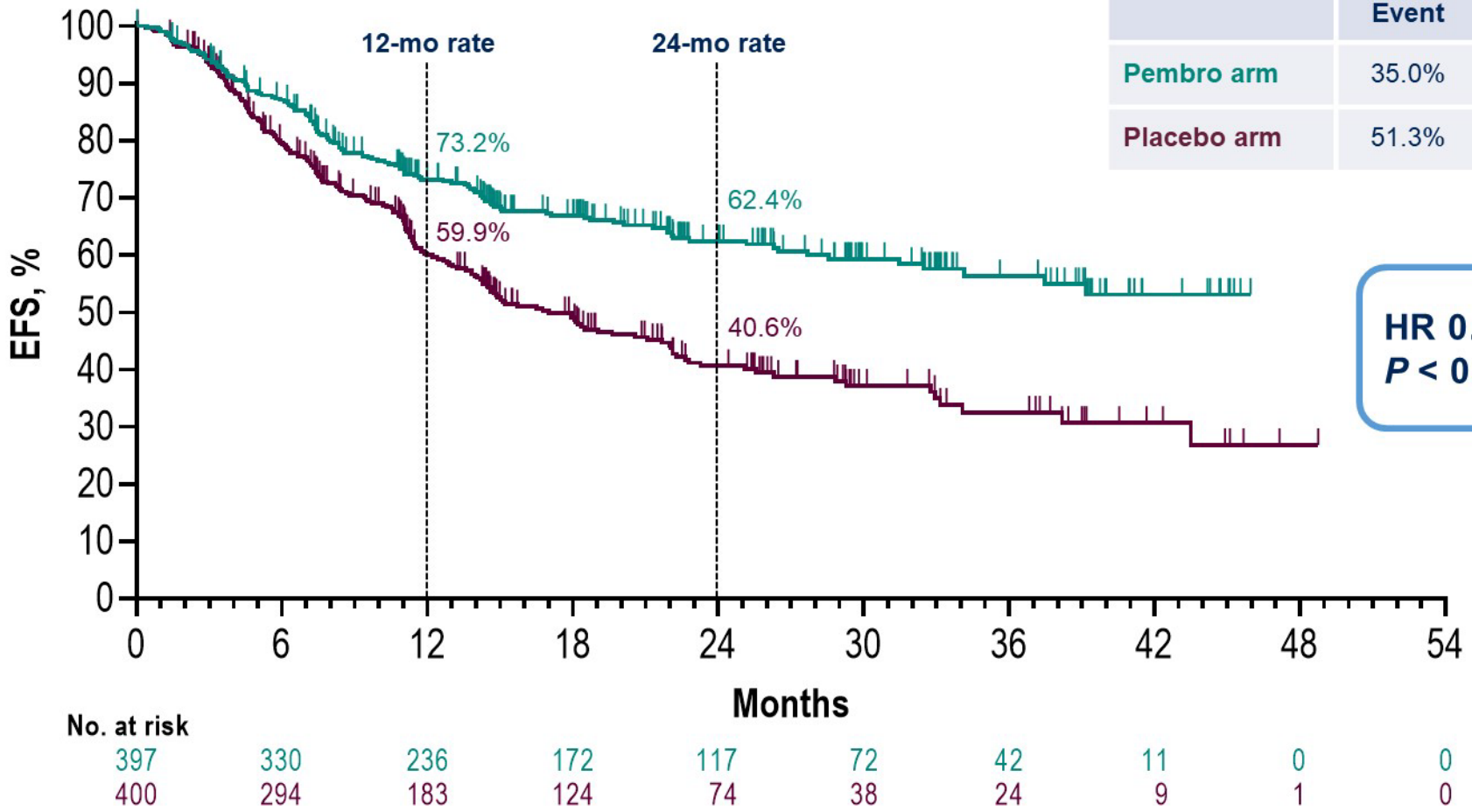
	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Median age (range), years	63 (26-83)	64 (35-81)
Male	279 (70.3%)	284 (71.0%)
Race		
American Indian or Alaska Native	1 (0.3%)	0
Asian	124 (31.2%)	125 (31.3%)
Black or African American	6 (1.5%)	10 (2.5%)
Multiple	3 (0.8%)	10 (2.5%)
White	250 (63.0%)	239 (59.8%)
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%)

[a] *EGFR* mutation and *ALK* translocation status were tested locally per investigator discretion. *EGFR* status was unknown in 272 (68.5%) participants in the pembro arm and 254 (63.5%) in the placebo arm; *ALK* status was unknown in 281 (70.8%) and 258 (64.5%), respectively. Data cutoff date for IA1: July 29, 2022.

Wakelee, H, et al, ASCO 2023

Event-Free Survival



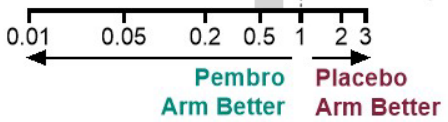
	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

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

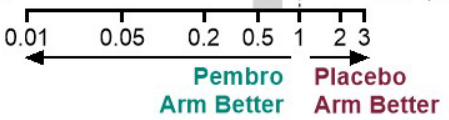
EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Event-Free Survival in Subgroups

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
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)



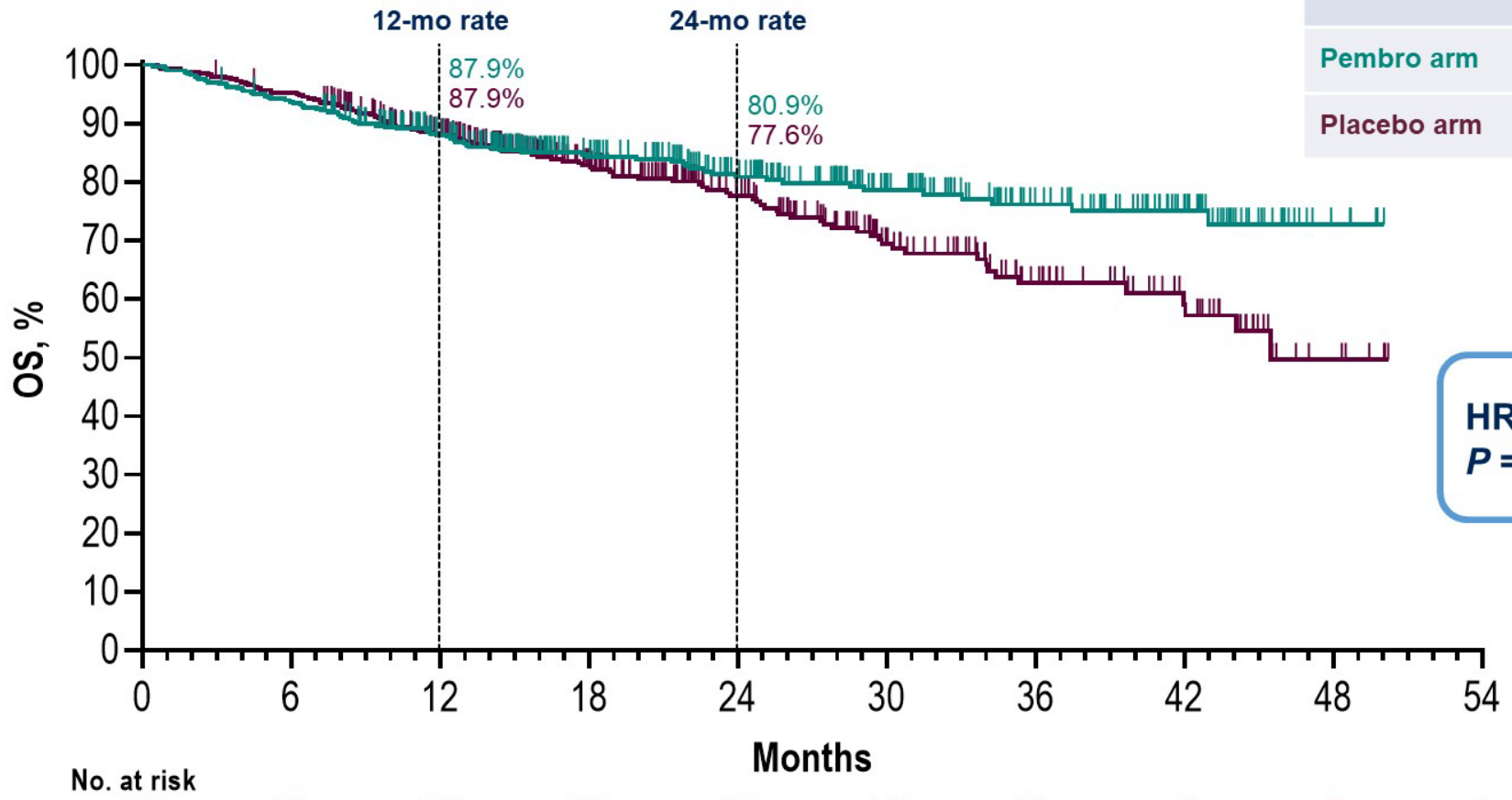
Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	139/397	205/400	0.58 (0.46-0.72)
Pathologic stage			
II	34/118	48/121	0.65 (0.42-1.01)
IIIA	80/217	124/225	0.54 (0.41-0.72)
IIIB	25/62	33/54	0.52 (0.31-0.88)
pN status			
pN0	51/148	70/142	0.57 (0.40-0.82)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



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

Wakelee, H, et al, ASCO 2023

Overall Survival



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

October 16, 2023: FDA approved pembrolizumab with chemotherapy as neoadjuvant treatment, and with continuation of adjuvant for resectable (tumors ≥4 cm or node positive) NSCLC

Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

Resectable NSCLC

EGFR mutation (IB, II, IIIA) → **1. Adjuvant Targeted Therapy - Osimertinib**

2. Immunotherapy (IO)

a. Adjuvant IO (Atezo, Pembro, Stage1B, PDL1)

b. Neoadjuvant ChemoIO (Nivo)

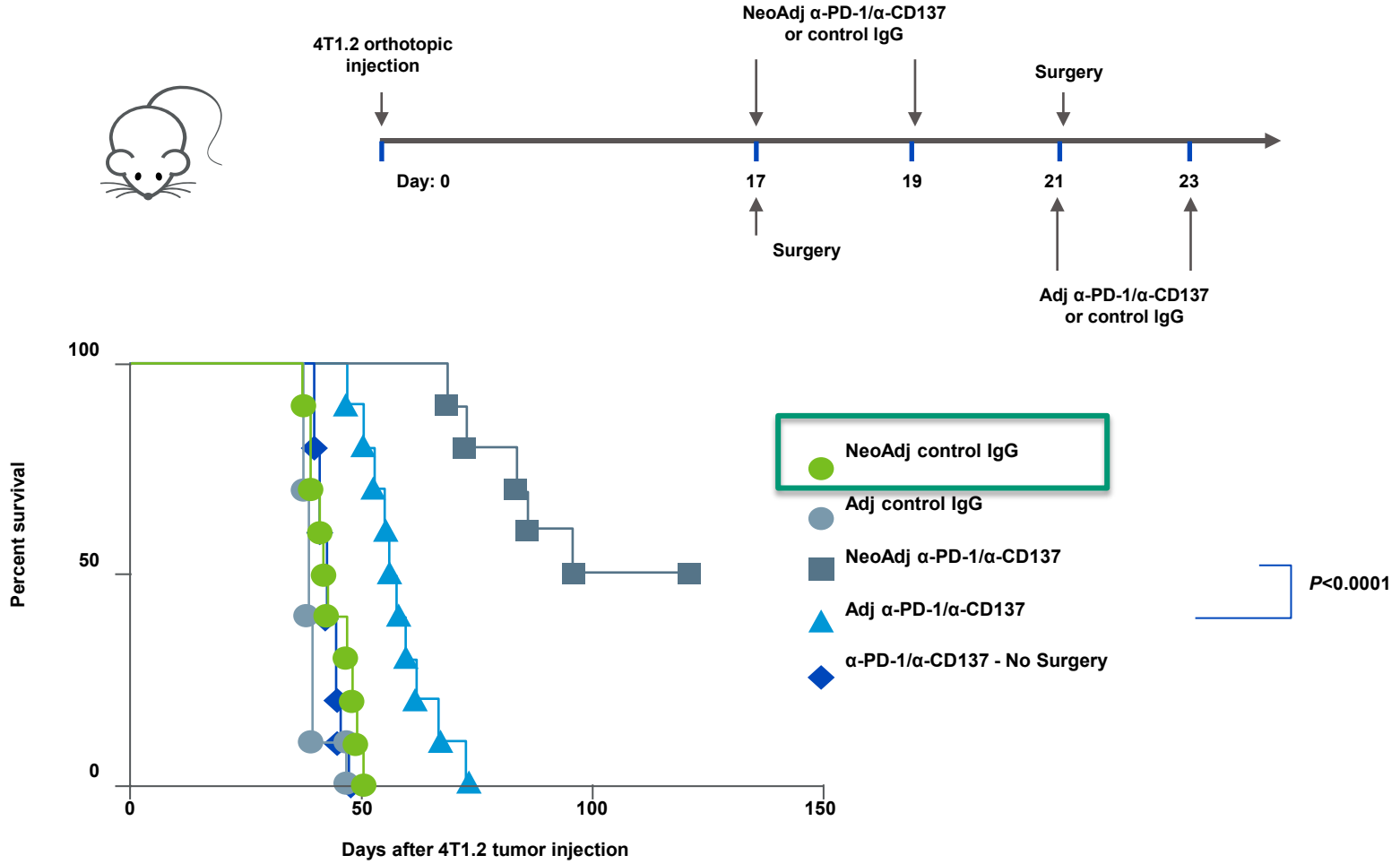
c. Perioperative IO (Pembro, Nivo pending approval)

Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

Neoadjuvant vs Adjuvant Immunotherapy (IO) ?

1. Reduction of tumor volume and stage
2. Assess *in vivo* response to systemic therapy
3. Early treatment of micrometastasis
4. Increase adherence
5. Biomarker analysis
6. Accelerate drug approval
7. Improve efficacy?

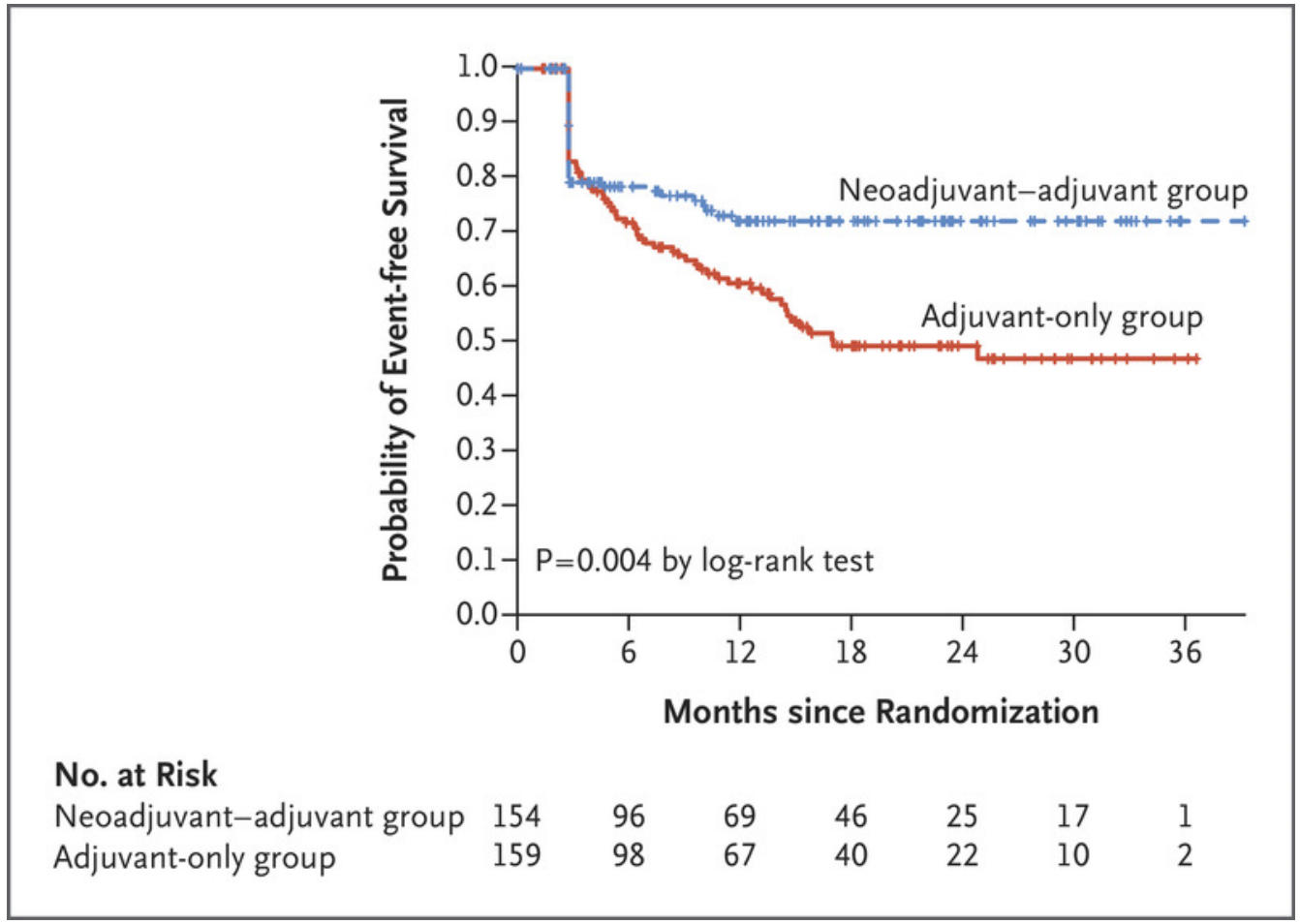
Neoadjuvant Immunotherapy is Superior to Adjuvant in murine model of breast cancer



Gonzalez H et al. *Genes Dev*. 2018. McGranahan N et al. *Science*. 2016. Tohme S et al. *Cancer Res*. 2017. Topalian SL et al. *Science*. 2020. Liu J et al. *Cancer Discov*. 2016.

Neoadjuvant-Adjuvant vs Adjuvant

Pembrolizumab in Resected Melanoma



Patel, SP, et al. NEJM 2023

Neoadjuvant vs Adjuvant IO

Timing is Important

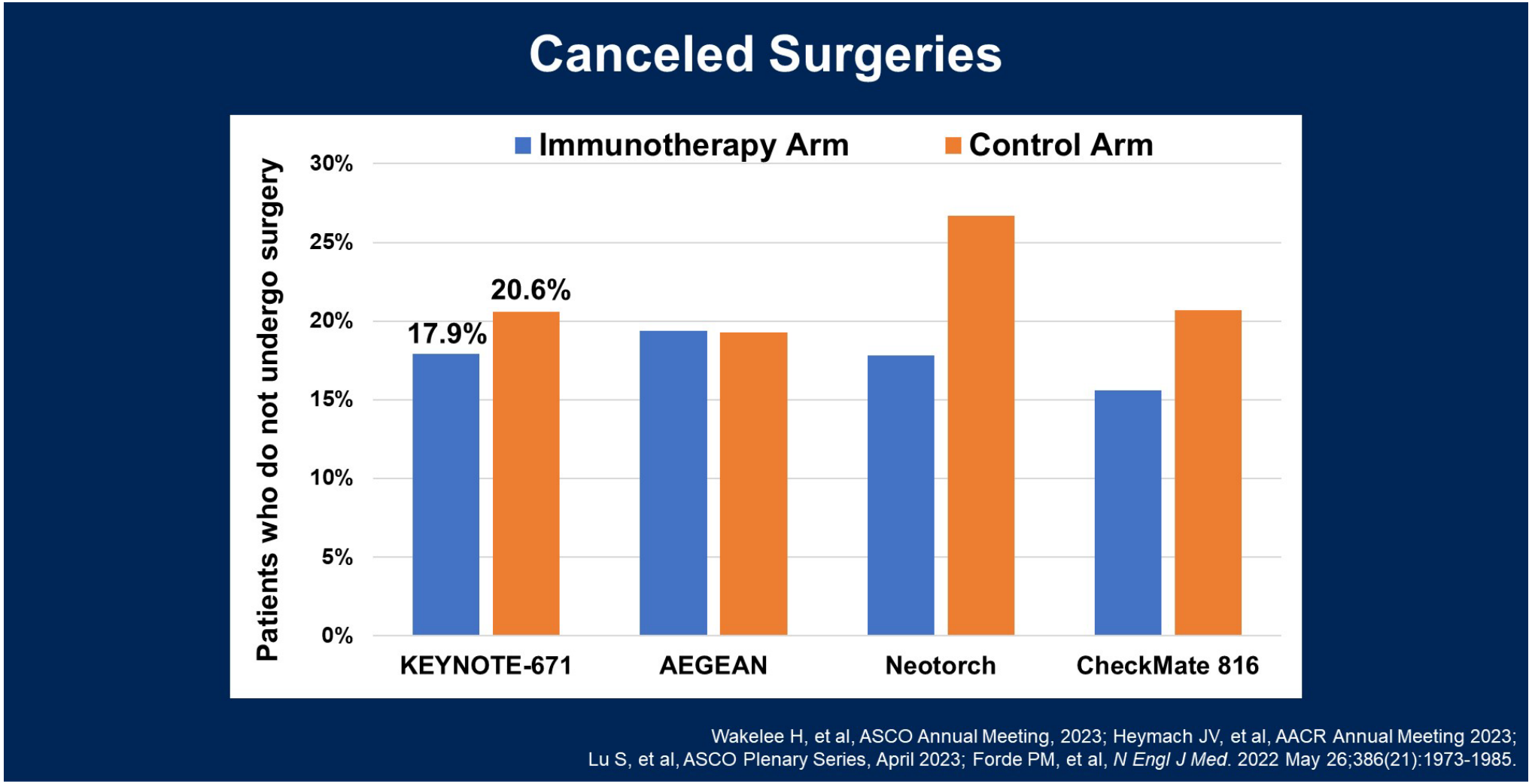
Overall Survival Results Summary (Interim Analyses)

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

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

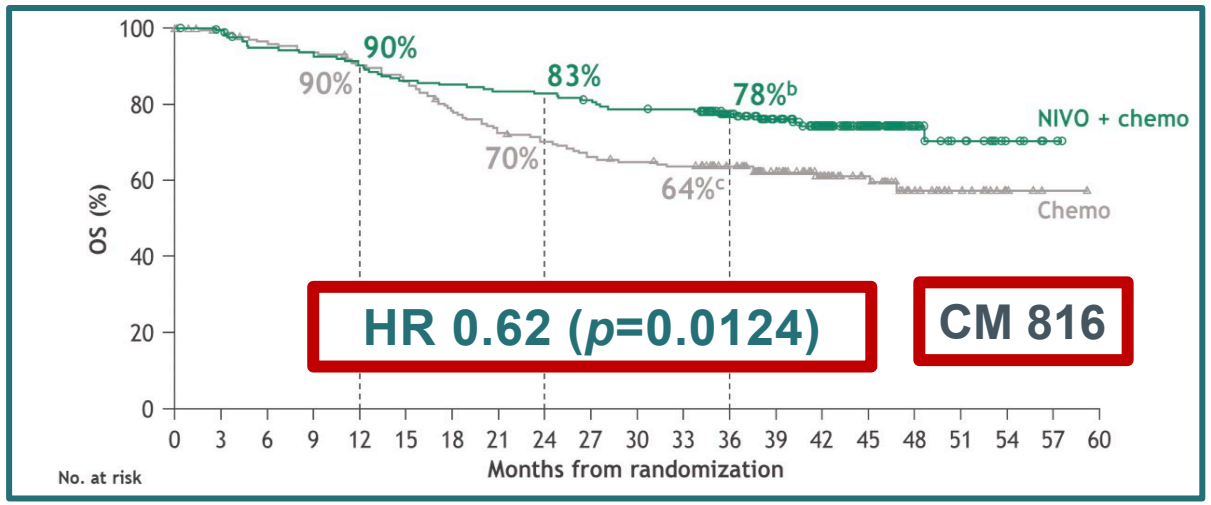
Is Neoadjuvant IO for Everyone?

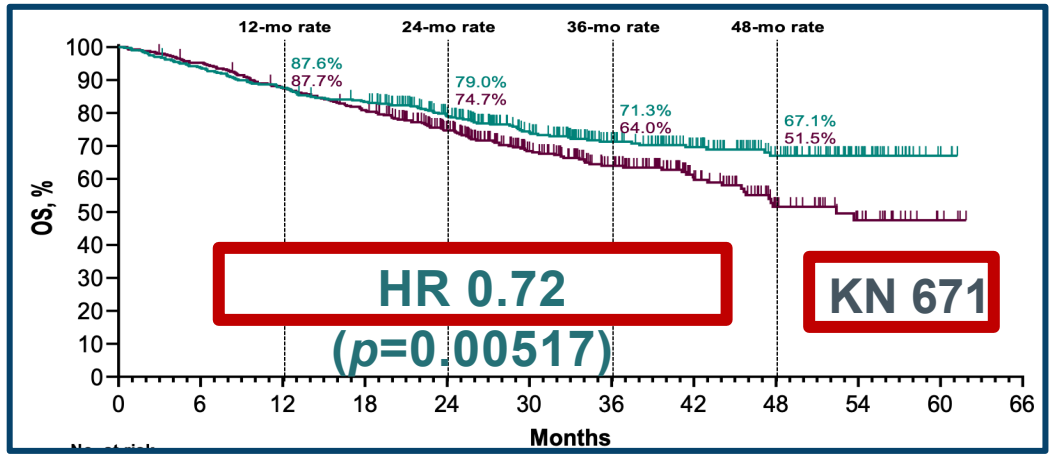
Attrition is ~ 20%

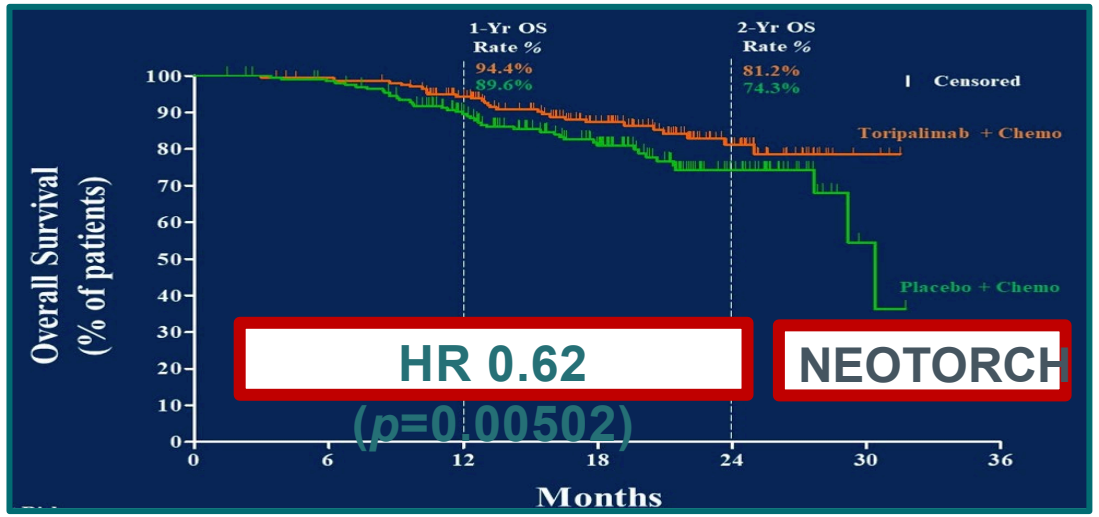


Wakelee H, et al, ASCO Annual Meeting, 2023; Heymach JV, et al, AACR Annual Meeting 2023; Lu S, et al, ASCO Plenary Series, April 2023; Forde PM, et al, *N Engl J Med*. 2022 May 26;386(21):1973-1985.

What does adjuvant IO add after neoadjuvant IO?

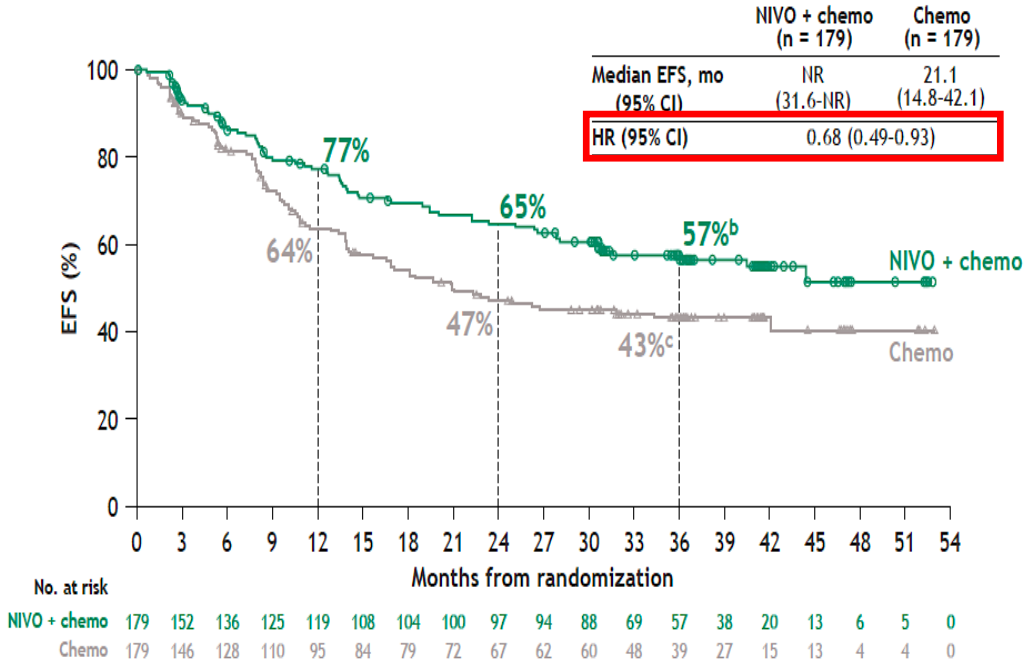


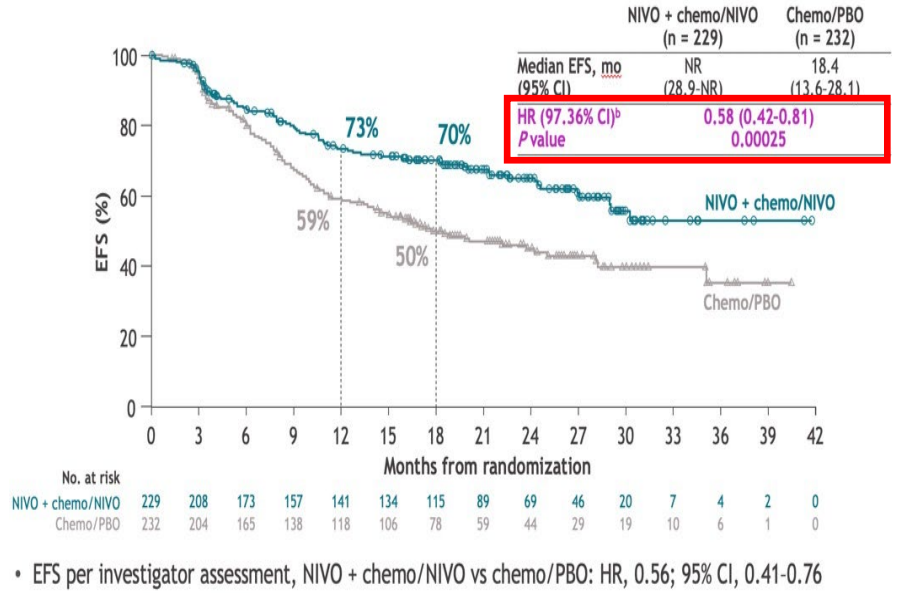




Forde et al NEJM, Spicer et al ESMO 2023; Lu et al ASCO Plenary 2023

What does adjuvant IO add after neoadjuvant IO?





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

CheckMate 816

64% Stage III

50% PD-L1+

CheckMate 77T

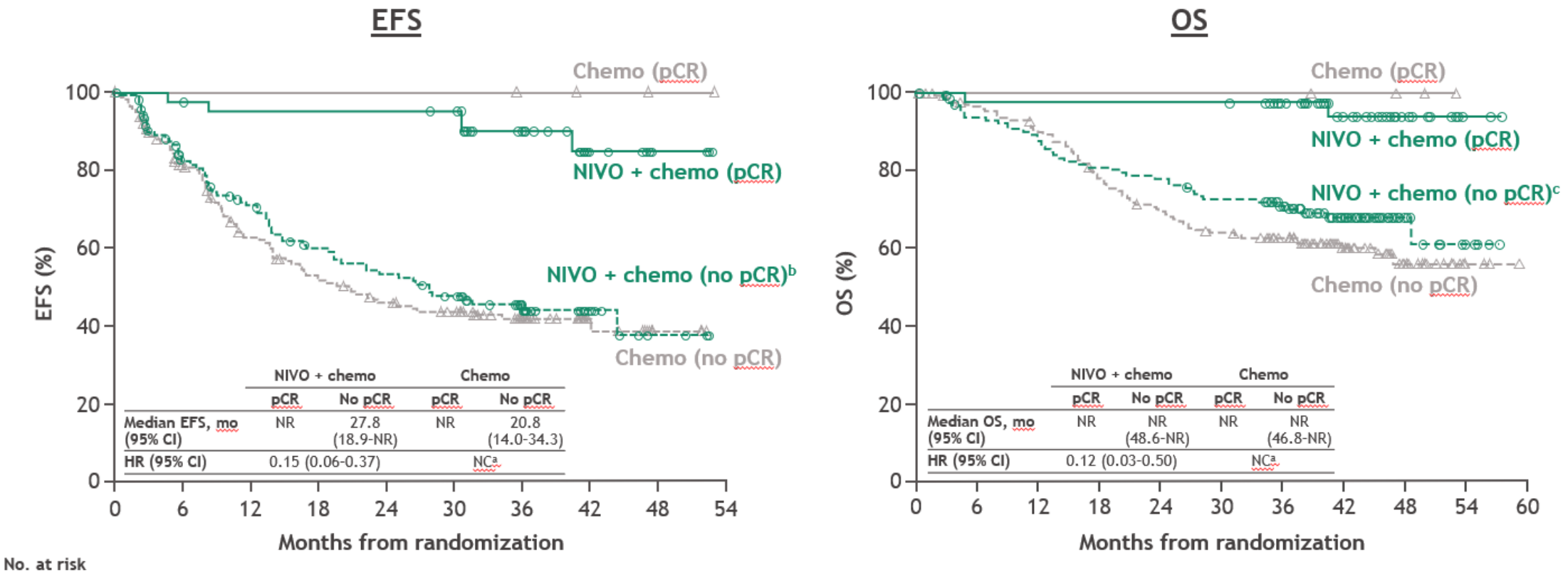
64% Stage III

56% PD-L1+

Forde et al NEJM, Spicer et al ESMO 2023; Lu et al ASCO Plenary 2023; Provencio et al NEJM 2023

What does adjuvant IO add after neoadjuvant IO?

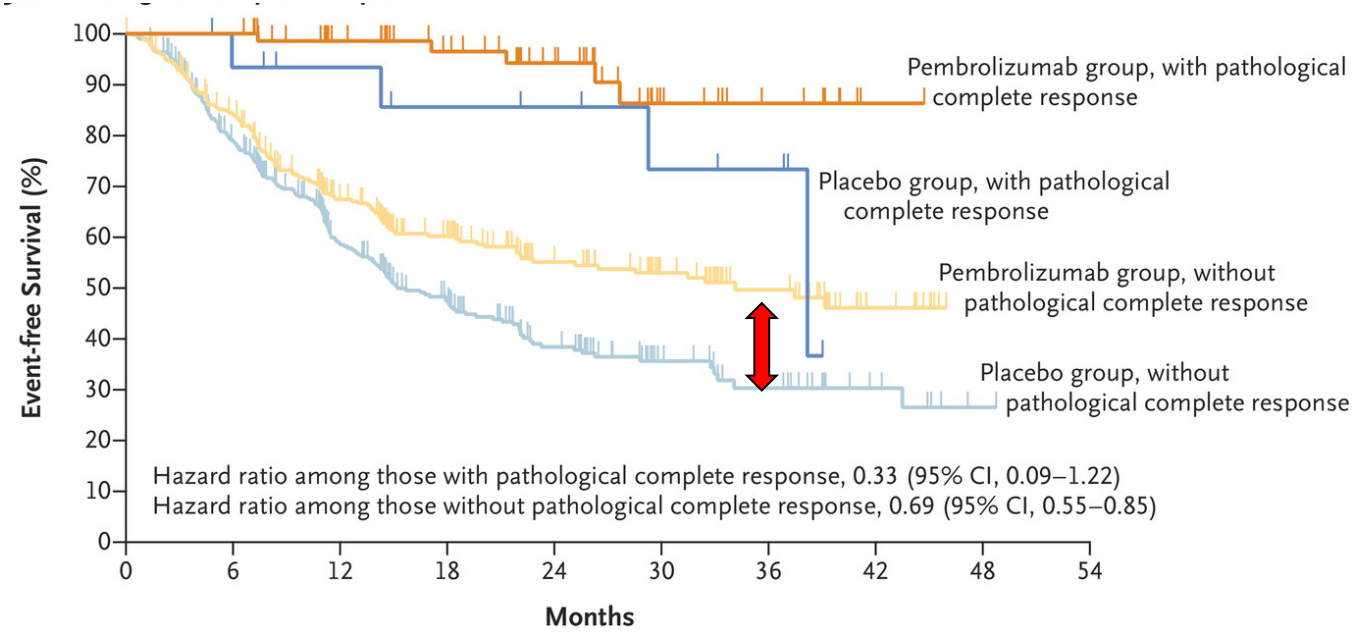
pCR portends a >90% 3 yr EFS and >95% likelihood of being alive at 3 years - *without* adjuvant IO



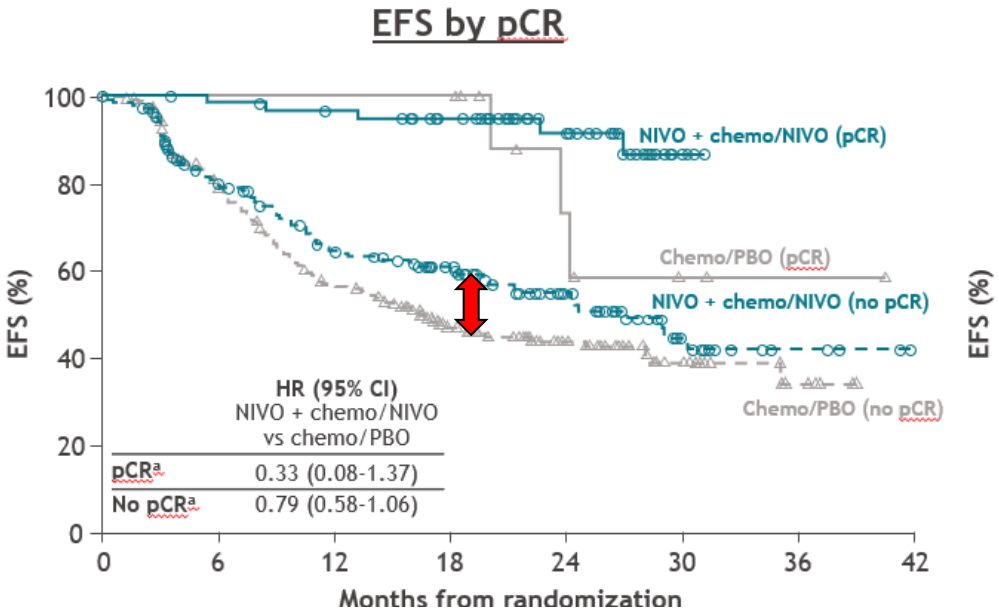
Provencio et al. ASCO 2022

What does adjuvant IO add after neoadjuvant IO?

No pCR/mPR, Outcomes are poor



KN671 - outcomes by pCR status

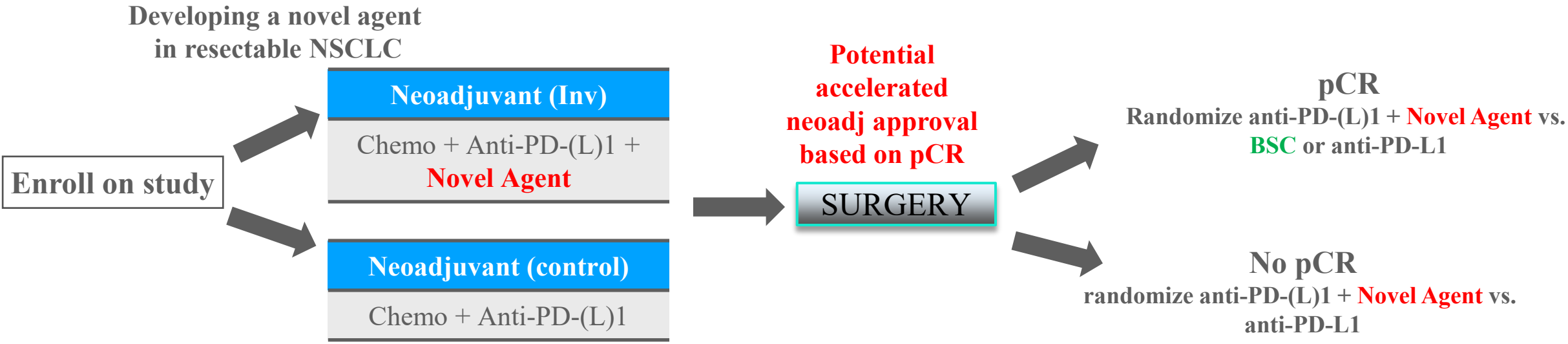


CM77T - outcomes by pCR status

Perioperative Trial	Received at least 1 dose of adj (%ITT)	Completed full course of adj (%ITT)
KN671	73%	48%
AEGEAN	66%	26% (21% still on treatment)
CM77T	62%	41% (6% still on treatment)

Spicer et al ESMO 2023; Heymach et al, AACR 2023; Provencio et al NEJM 2023

Future Directions



Evolving Landscape of Perioperative Therapy in Local Advanced NSCLC

1. Adjuvant Targeted Therapy: EGFRm, ALK+

2. Immunotherapy (IO)
   a. Adjuvant IO
   b. Neoadjuvant ChemoIO
   c. Neoadjuvant + Adjuvant IO

Questions?