UPDATES IN TREATMENT OF EARLY STAGE AND LOCALLY ADVANCED NSCLC

PRESENTED BY:

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Disclosures

- Speaker Bureau fees from Astra Zeneca, Lilly and Merck
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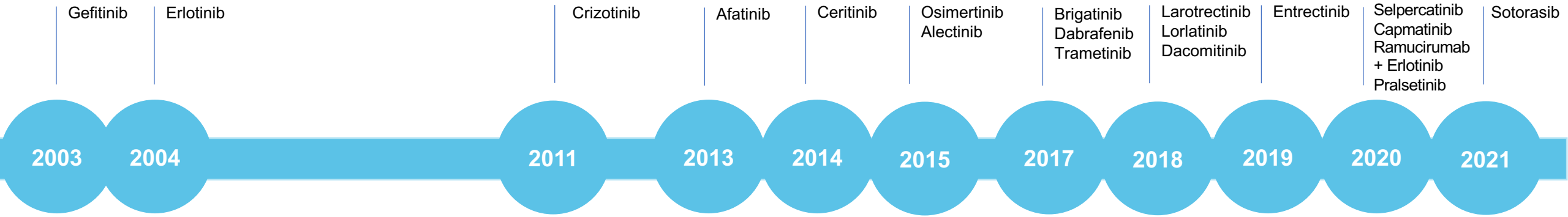
ADVANCES IN NSCLC WITH DRIVER MUTATIONS

Treatment Approvals in Resectable Versus Metastatic NSCLC with Driver Mutations

Resectable Disease

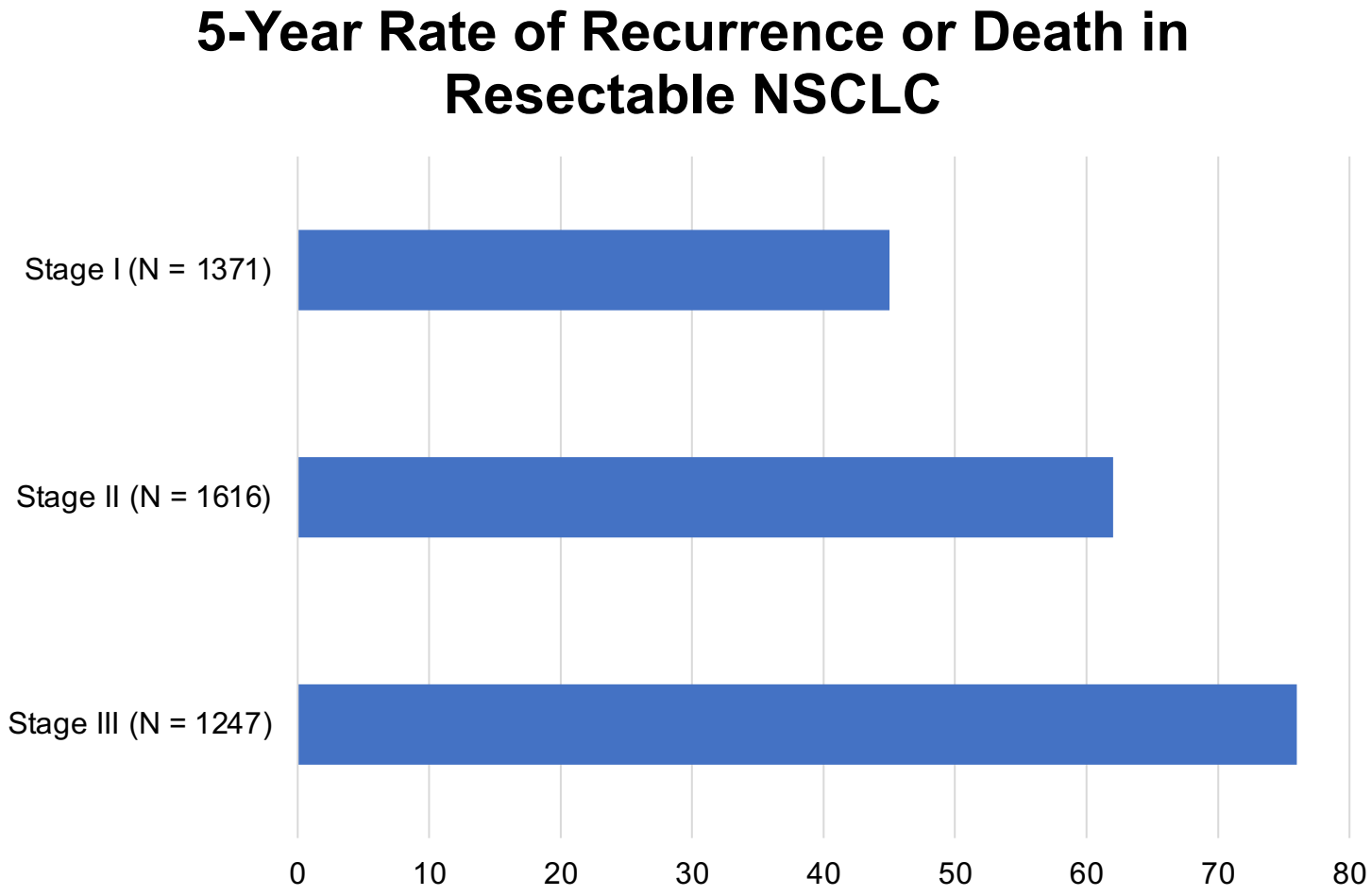
Metastatic Disease



EARLY AND LOCALLY ADVANCED STAGE

Disease Recurrence in Resectable NSCLC

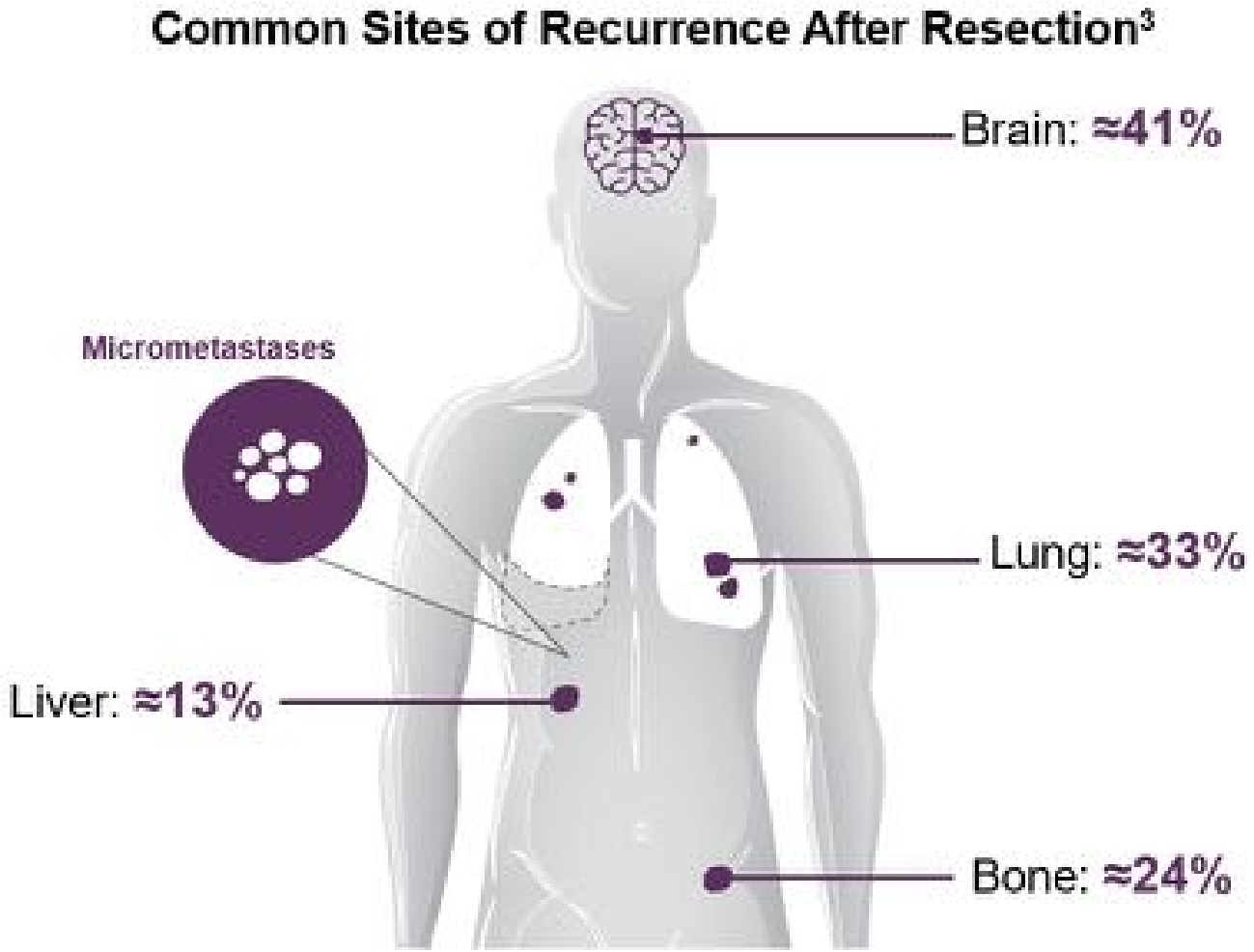
- Majority of resectable Stage IB-III patients will experience disease recurrence or death within 5 years
- Approximately 40% of early stage patients treated with adjuvant chemotherapy recur with metastatic NSCLC
- Multiple ongoing trials are examining neoadjuvant and adjuvant strategies to lower disease recurrence rates in early stage NSCLC



Pignon JP et al. J Clin Oncol 2008
Arriagada R et al. NEJM 2004

Oncogenic Mutational Status and its Impact on Disease Recurrence

- Micrometastases may remain even after successful surgery
- Distinct recurrence patterns are associated with oncogenic mutation status and mutational EGFR subtype
- Approximately 40% of early stage patients will experience metastatic recurrence in multiple sites following surgical resection



Mizuno T et al. Jpn J Clin Oncol. 2016
Chouaid C et al. Lung Cancer 2018

ADUARA: Adjuvant Osimertinib in Resected *EGFR* mutated NSCLC

Key inclusion criteria:

- Confirmed primary nonsquamous Stage IB, II, IIIA NSCLC (AJCC 7th edition)
- Complete tumor resection, with or without prior adjuvant chemotherapy
- EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC
- MRI or CT scan of the brain prior to surgery or randomization
- Maximum interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
- Stage (IB vs II vs IIIA)
- EGFR mutation (exon 19 deletion vs L858R mutation)
- Race (Asian vs non-Asian)

Osimertinib
80 mg once daily
(n=339)

Randomization
1:1
(N=682)

Placebo,
once daily
(n=343)

Treatment duration: 3 years

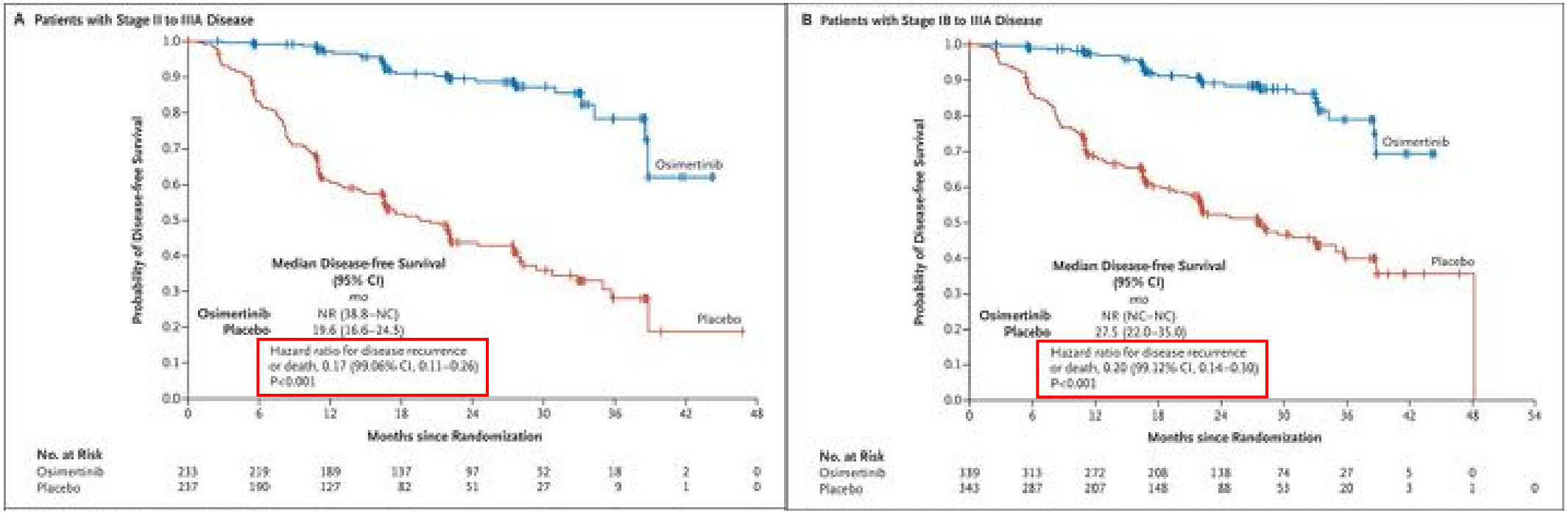
Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow-up:
- Until recurrence: Weeks 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 Stages II-IIIA
- **Secondary**: DFS in the overall population (Stages IB-IIIA), OS, HRQoL, safety

ADAURA: Disease-Free Survival

- 410/682 (60%) patients in the trial received adjuvant CT
- Median duration: 4 cycles
- PFS with or without adjuvant CT was significant IIIA>II>IB

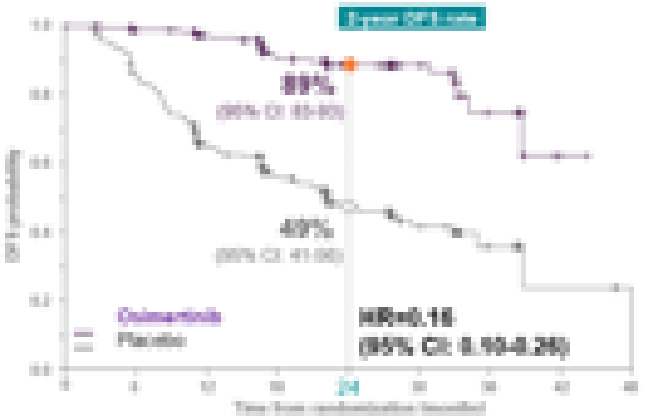


Wu YL et al. NEJM 2020

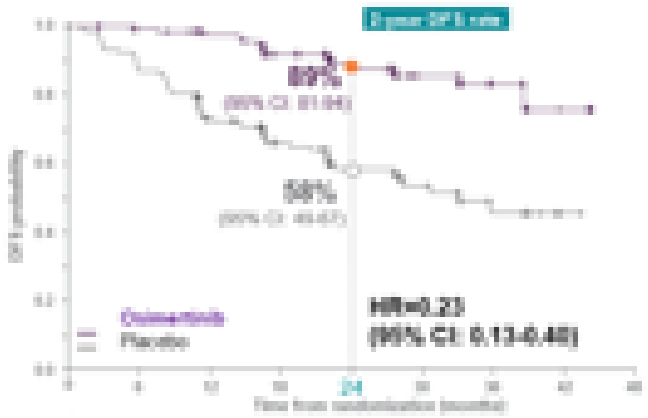
ADAURA: Subgroup Analyses and CNS

DFS in the Overall Population (Stage IB/II/IIIA): HR=0.20 (95% CI: 0.15, 0.27); *P*<0.0001[2,a]

With Prior Adjuvant Chemotherapy[2]

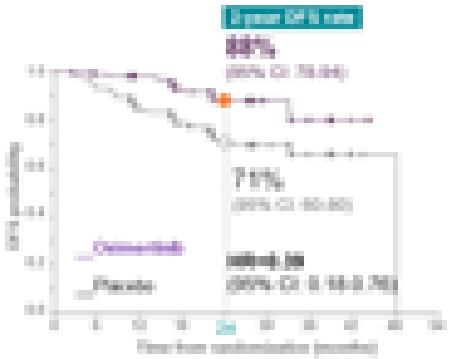


Without Prior Adjuvant Chemotherapy[1]

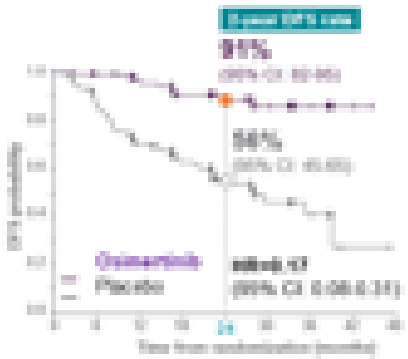


DFS in the Overall Population (Stage IB/II/IIIA): HR=0.20 (95% CI: 0.15, 0.27); *P*<0.0001[2,a]

Stage IB[2]

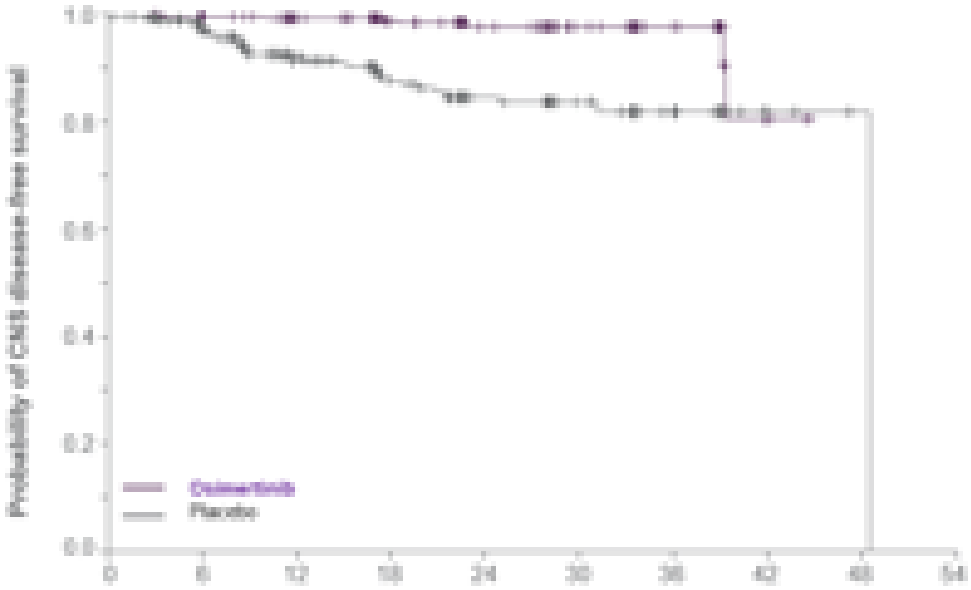


Stage II[2]



Stage IIIA[2]

CNS DFS (Post Hoc Analysis)



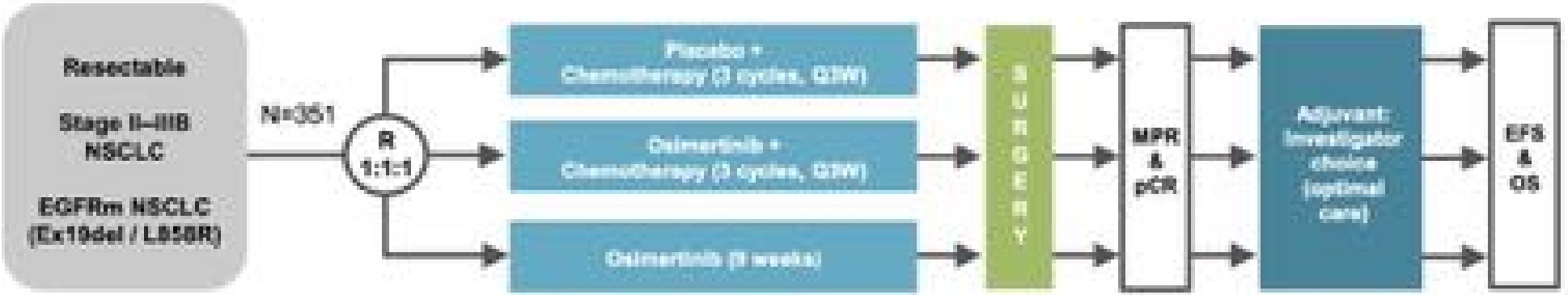
Number at risk									
Time from randomization (months)									
Osimertinib	339	313	272	209	138	74	28	5	0
Placebo	343	288	208	149	88	53	20	3	1	0

Median CNS DFS, months (95% CI)	
Osimertinib	NR (39.0-NC)
Placebo	46.2 (NC-NC)
HR (95% CI)	0.18 (0.10-0.33)

82% reduced risk of CNS recurrence or death with Osimertinib

NEOADAURA: Neoadjuvant Osimertinib in Resectable *EGFR* mutant NSCLC

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



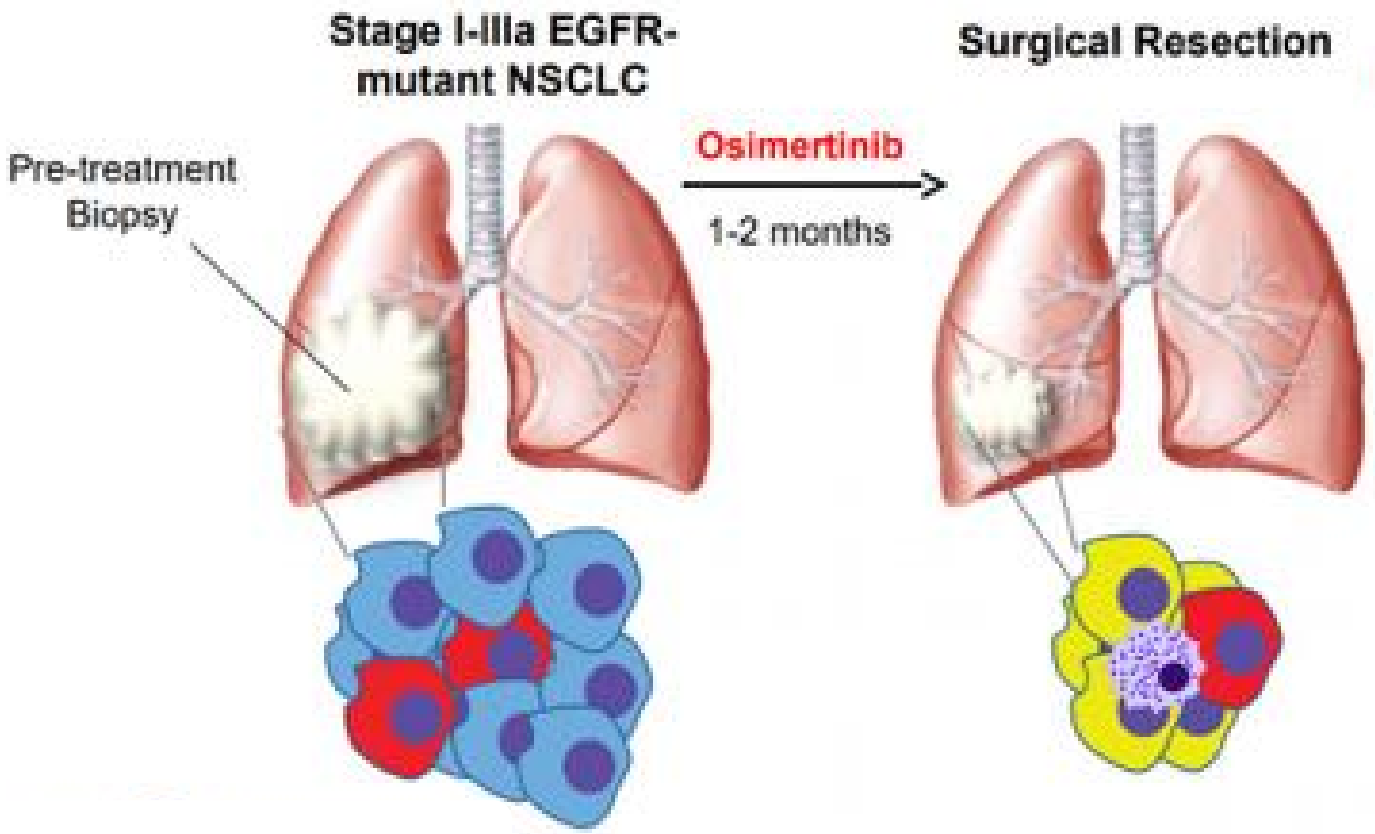
Stratification:
- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:
1. Placebo QD + investigator's choice of pemetrexed 500 mg/m² plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m²
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m² plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m²

Open-label (sponsor-blind) treatment arm:
3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:
- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

NEOS: Neoadjuvant Osimertinib in *EGFR* mutated NSCLC



Primary Endpoint:
Major Pathological Response Rate
(Powered to detect MPR ~ 50%)

Secondary Endpoints:

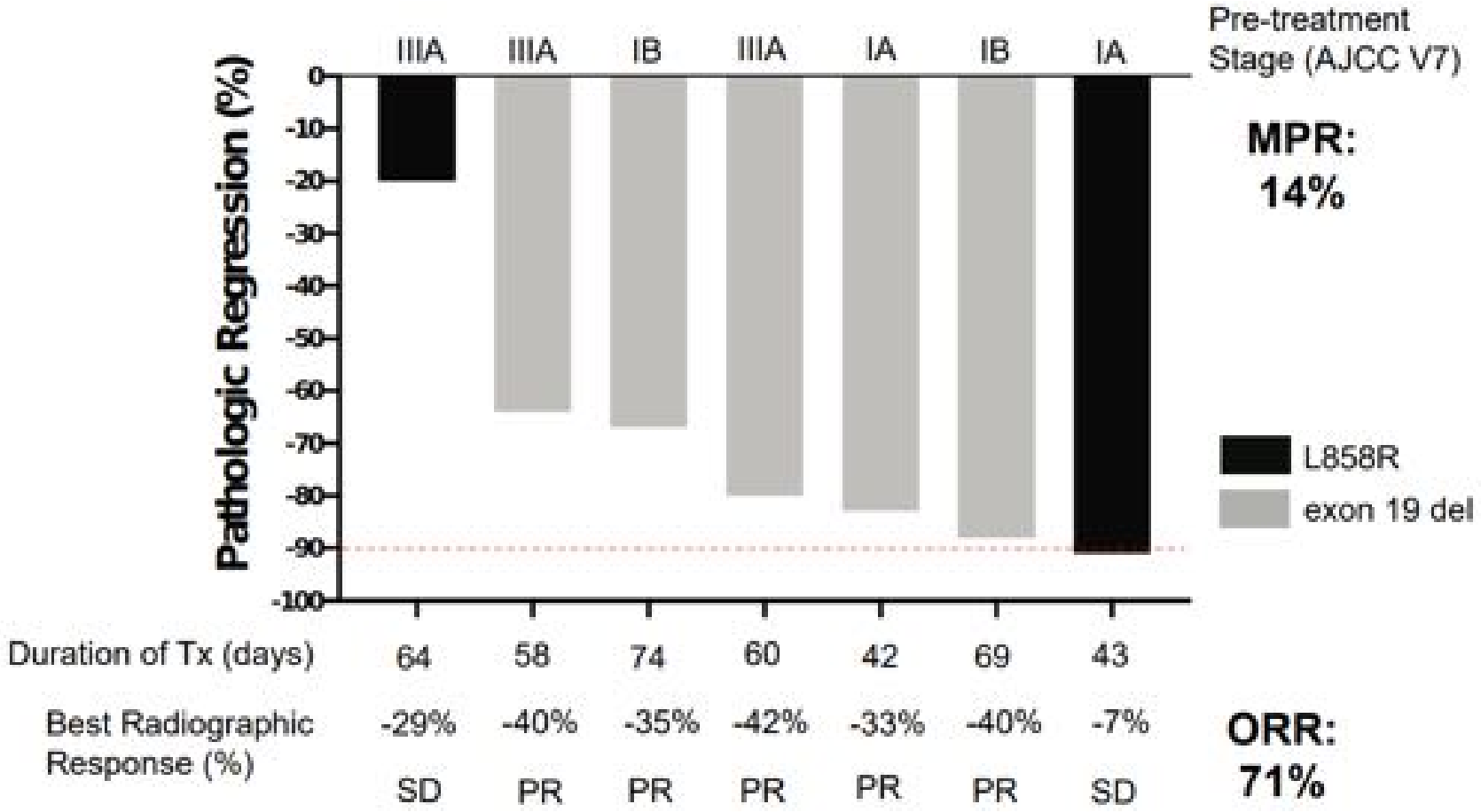
Safety:
Surgical Complications
Unresectability Rate

Efficacy:
Downstaging
ORR
pCR rate
5-year DFS/OS

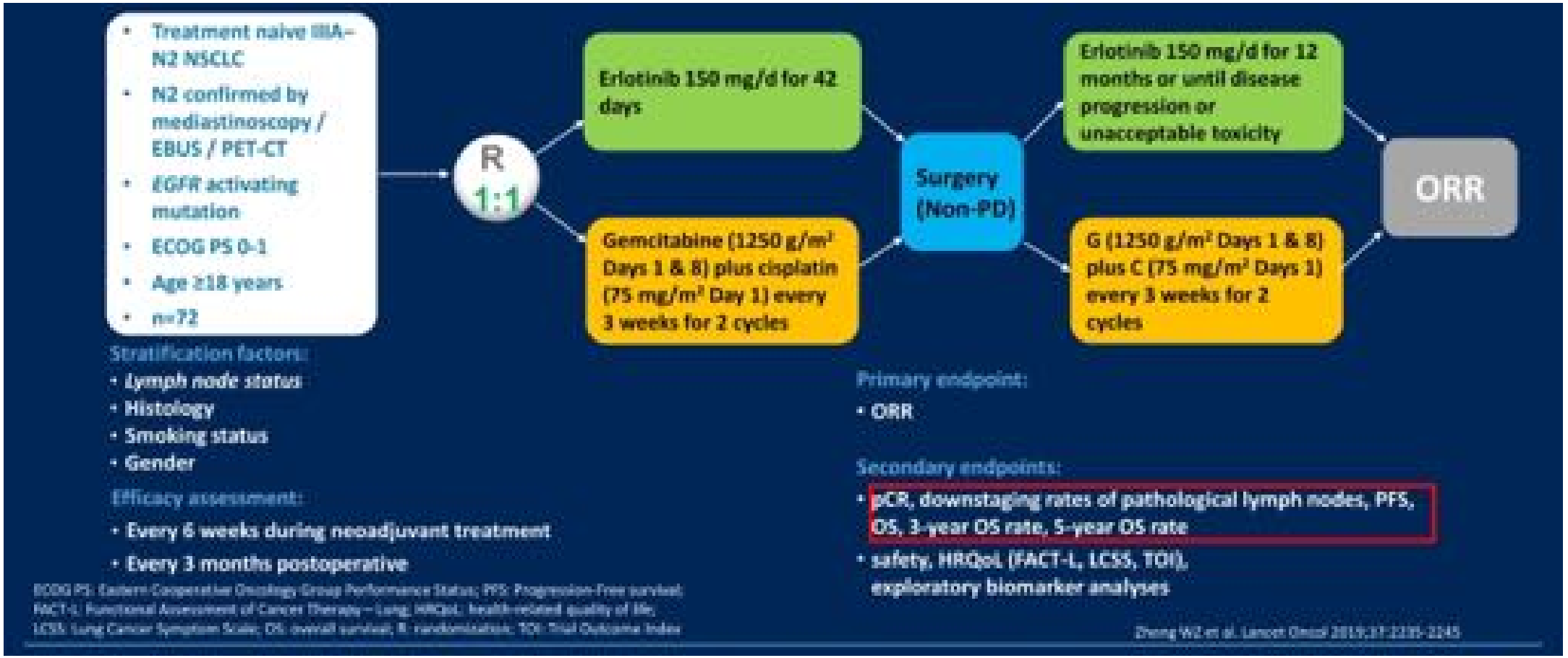
Exploratory:
Single cell RNA-seq
WES
Immune cell changes

NEOS: Tumor Response

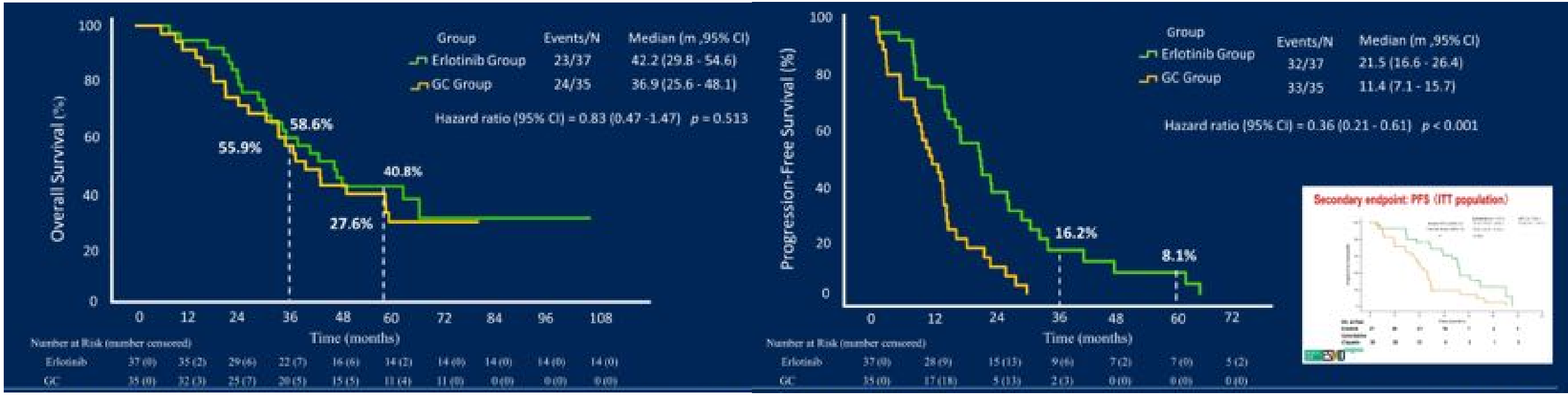
- Neoadjuvant osimertinib is safe
- MPR to osimertinib of 14% is lower than predicted
- High TMB (including RB1 and RBM10 mutations) identified in patient with minimal response to osimertinib



EMERGING-CTONG1103: Neoadjuvant Erlotinib Versus Chemotherapy in Stage IIIA-N2 *EGFR* mutated NSCLC



EMERGING-CTONG1103: Overall Survival and Progression-Free Survival



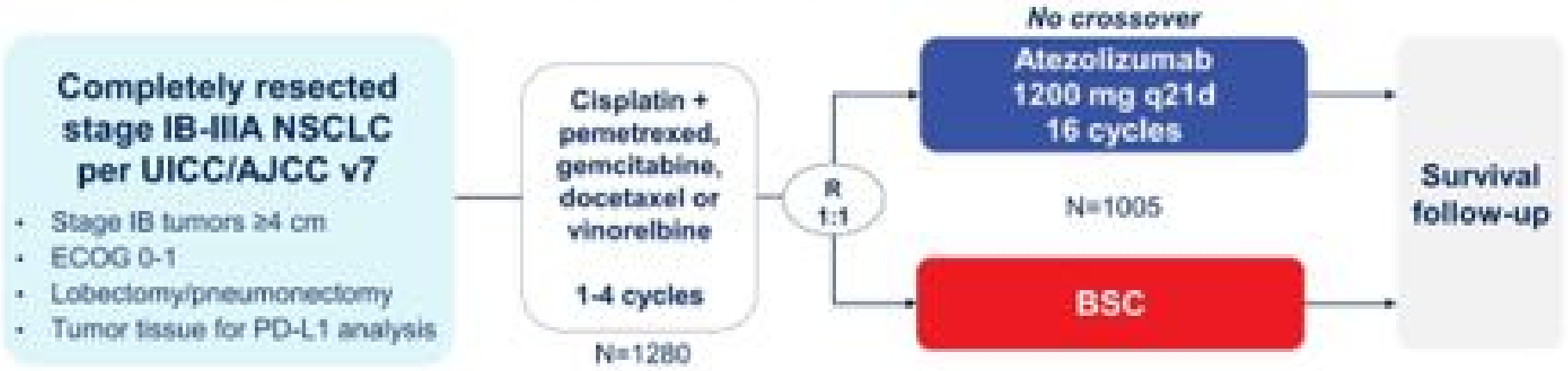
- Median OS was 42.2 months in the erlotinib arm and 36.9 months in the GC arm
- Median PFS was 21.5 months in the erlotinib arm and 11.4 months in the GC arm
- The results demonstrate feasibility of neoadjuvant/adjuvant EGFR TKIs for resected N2 patients

ADVANCES IN NSCLC WITHOUT DRIVER MUTATIONS

Treatment Approvals in Resectable Versus Metastatic NSCLC without Driver Mutations

EARLY STAGE

IMpower010: Adjuvant Atezolizumab in Completely Resected Stage IB-IIIA NSCLC



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

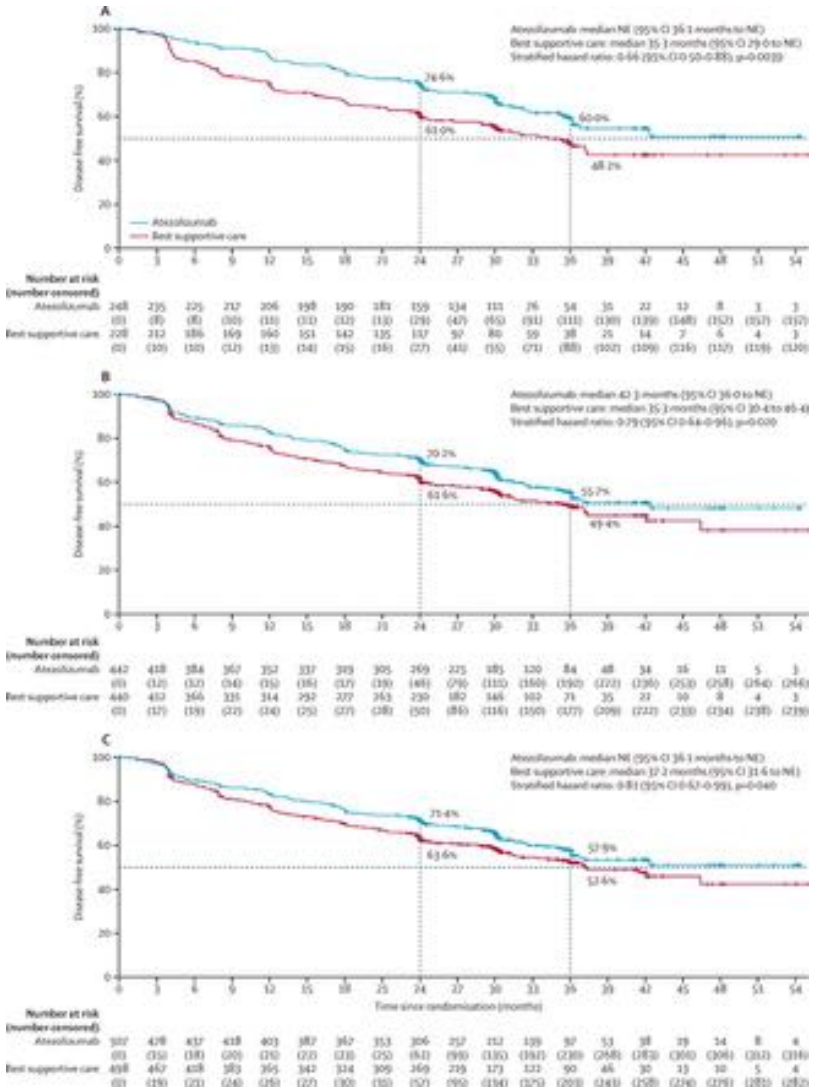
Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

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

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

Adapted from Wakelee, H; ASCO 2021

IMpower010: Disease Free Survival



A: Stage II-IIIA PDL1≥1%

HR=0.66 p=0.0039

B: Stage II-IIIA all population

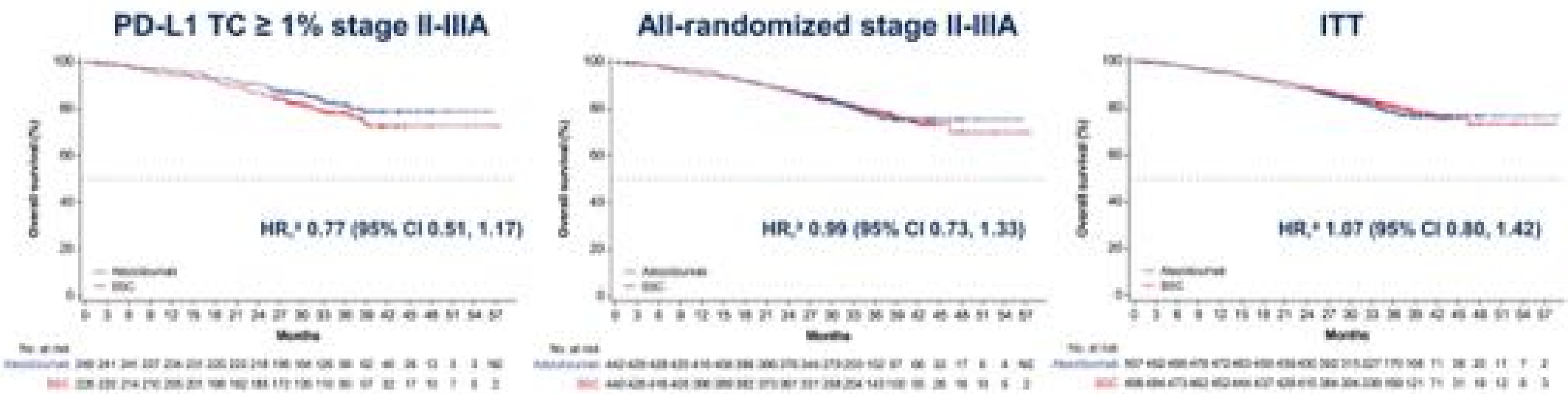
HR=0.79 p=0.020

C: Intention to treat population stage IB-IIIA

HR= 0.81 p=0.040

Adapted from Felip A, Wakelee, H; Lancet 2021

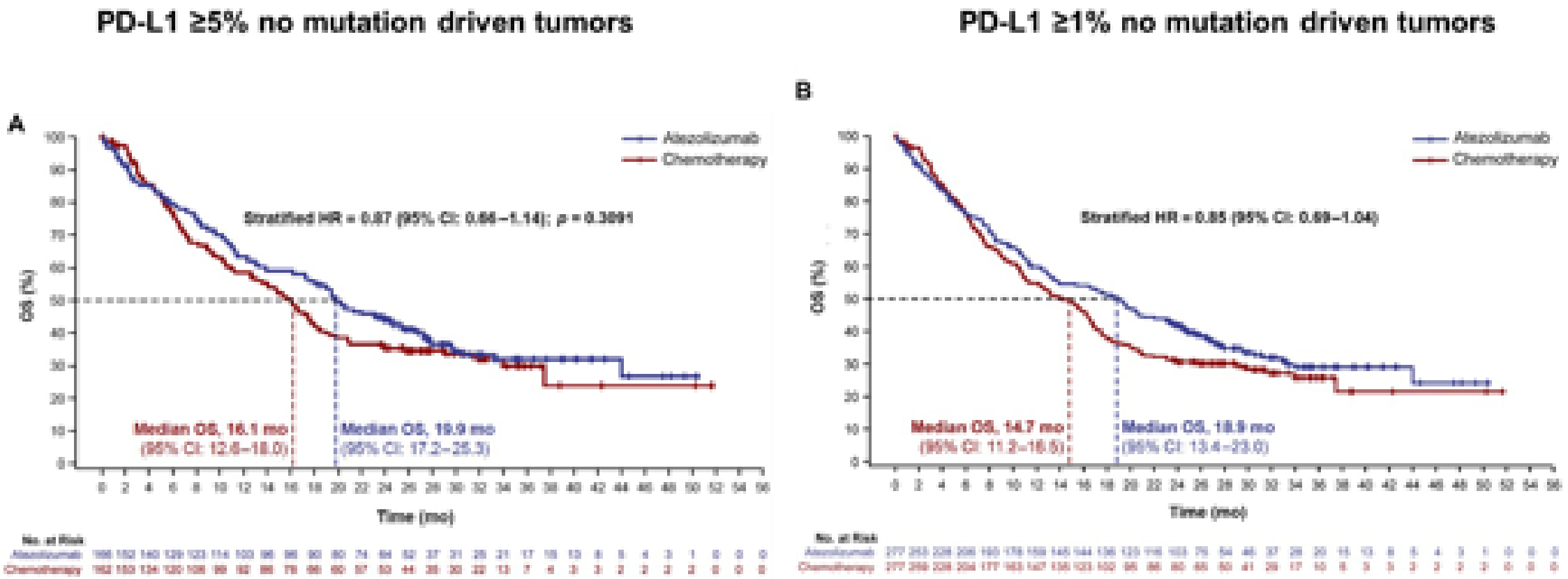
IMpower010: Overall Survival



- OS data were immature at this pre-planned DFS interim analysis
  - OS in the ITT population was not formally tested
  - A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Clinical cutoff: January 21, 2021. [a] Stratified.

Impower010: Updated Overall Survival



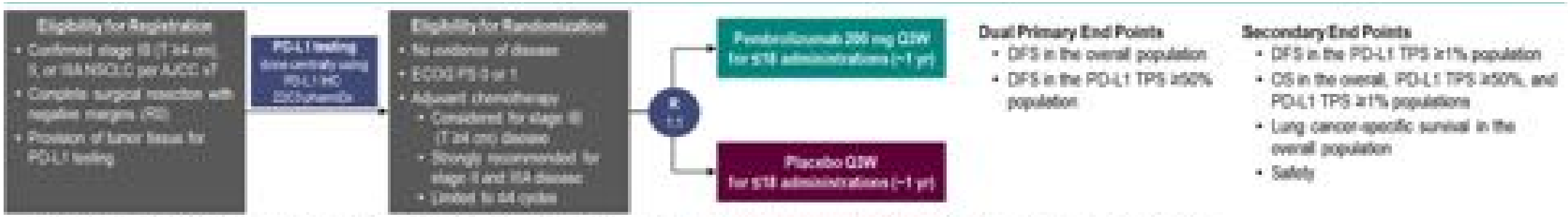
Jassem J et al. JTO 2021

IMpower010: Safety Data

n (%)	Atezolizumab (n=495)	BSC (n=495)
Any-cause AE	459 (92.7)	350 (70.7)
Treatment-related AE	335 (67.7)	–
Grade 3-4 AE	108 (21.8)	57 (11.5)
Treatment-related grade 3-4 AE	53 (10.7)	–
Serious AE	87 (17.6)	42 (8.5)
Treatment-related serious AE	37 (7.5)	–
Grade 5 AE	8 (1.6)*	3 (0.6)*
Treatment-related grade 5 AE	4 (0.8)	–
AE leading to dose interruption of atezolizumab	142 (28.7)	–
AE leading to atezolizumab discontinuation	90 (18.2)	–
Immune-mediated AEs	256 (51.7)	47 (9.5)
Grade 3-4 immune-mediated AEs	39 (7.9)	3 (0.6)
Immune-mediated AEs requiring the use of systemic corticosteroids	60 (12.1)	4 (0.8)

- The safety profile was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy

PEARLS/KEYNOTE-091: Adjuvant Pembrolizumab in Completely Resected Early-Stage NSCLC



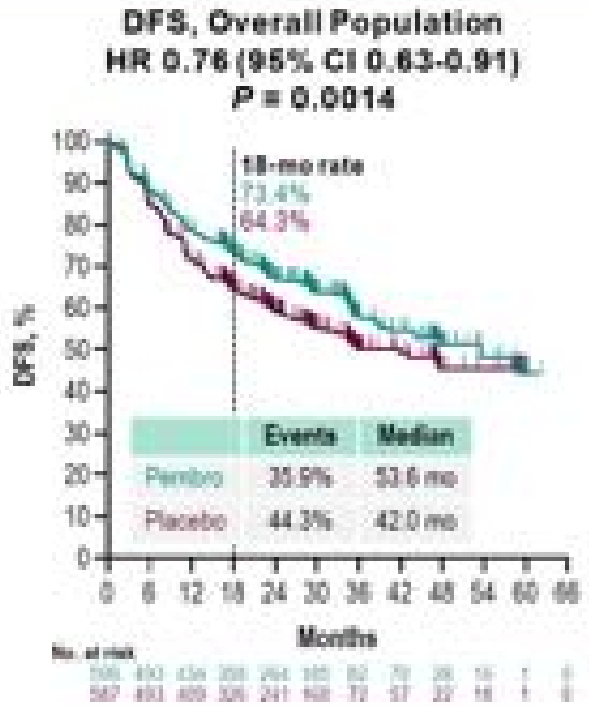
Stratification Factors: disease stage (IB vs II vs IIIA), PD-L1 TPS (<1% vs 1-49% vs ≥50%), adjuvant chemotherapy (yes vs no), geographic region (Asia vs E. Europe vs W. Europe vs ROW)

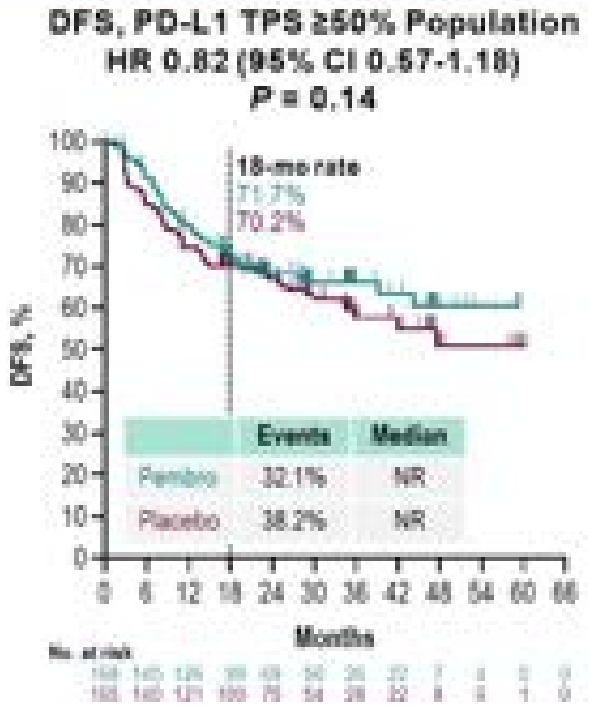
Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range), y	65.0 (31-87)	65.0 (37-85)	64.5 (38-82)	65.0 (37-85)
Male sex	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%

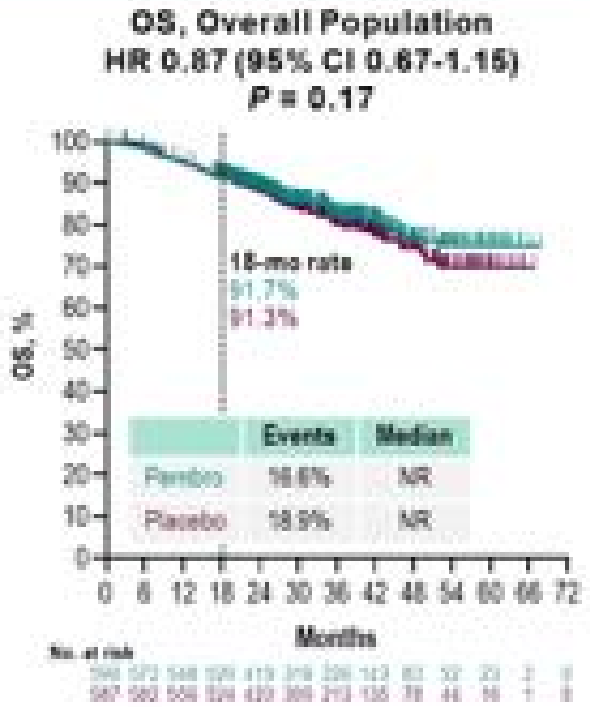
Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Current/former smoker	85.3%	88.8%	91.7%	92.1%
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage[a]				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIA	30.0%	27.6%	31.0%	30.3%
EGFR mutation[b]	6.6%	5.8%	3.6%	3.0%
ALK translocation[c]	1.2%	1.2%	1.8%	0.0%

[a]2 (0.3%) participants in the placebo arm had stage IV disease; neither had TPS ≥50%.
[b]EGFR mutation status was unknown for 56.9% of participants (59.5% with TPS ≥50%).
[c]ALK translocation status was unknown for 83.5% of participants (85.2% with TPS ≥50%).

PEARLS/KEYNOTE-091: Disease free and Overall Survival





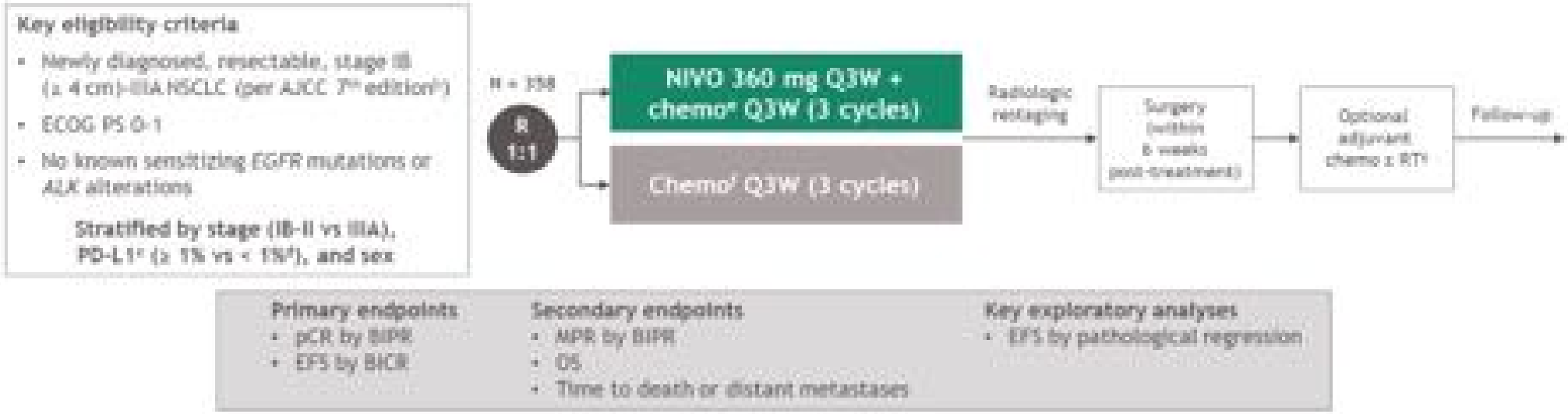


- DFS benefit generally consistent across most protocol-specified subgroups, including PD-L1 TPS <1% (HR 0.78, 95% CI 0.58-1.03) and 1-49% (HR 0.67, 95% CI 0.48-0.92)

- Together with the overall efficacy and safety findings, these data support the benefit of adjuvant pembrolizumab for stage IB (T ≥4 cm) to IIIA NSCLC following complete resection and, if recommended, adjuvant chemotherapy

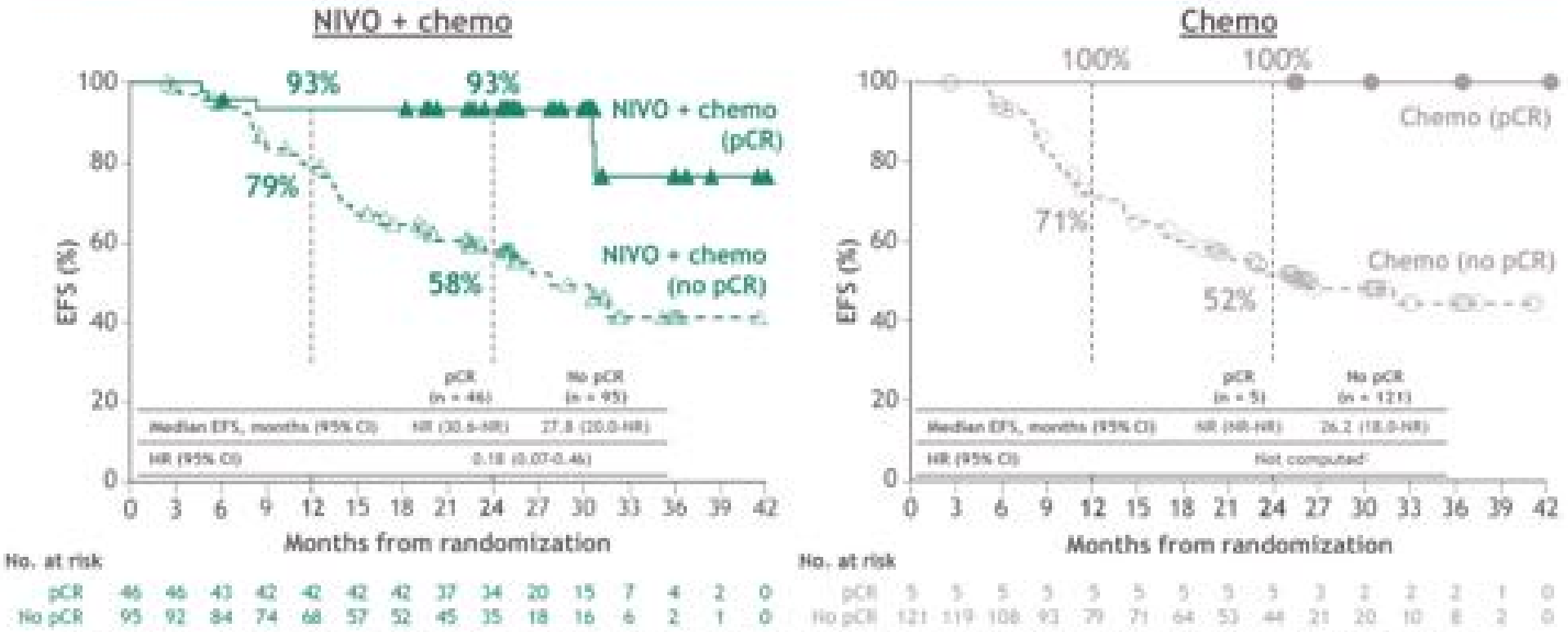
CheckMate 816: Neoadjuvant Nivo + Platinum-Doublet Chemotherapy in Resectable (IB-IIIA) NSCLC

- In CheckMate 816,[a] neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo in patients with resectable NSCLC[1]
  - NIVO + chemo is now indicated in the United States as neoadjuvant treatment for adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC[2]
- Here, we present a post hoc analysis evaluating the association between pathological regression and EFS from CheckMate 816



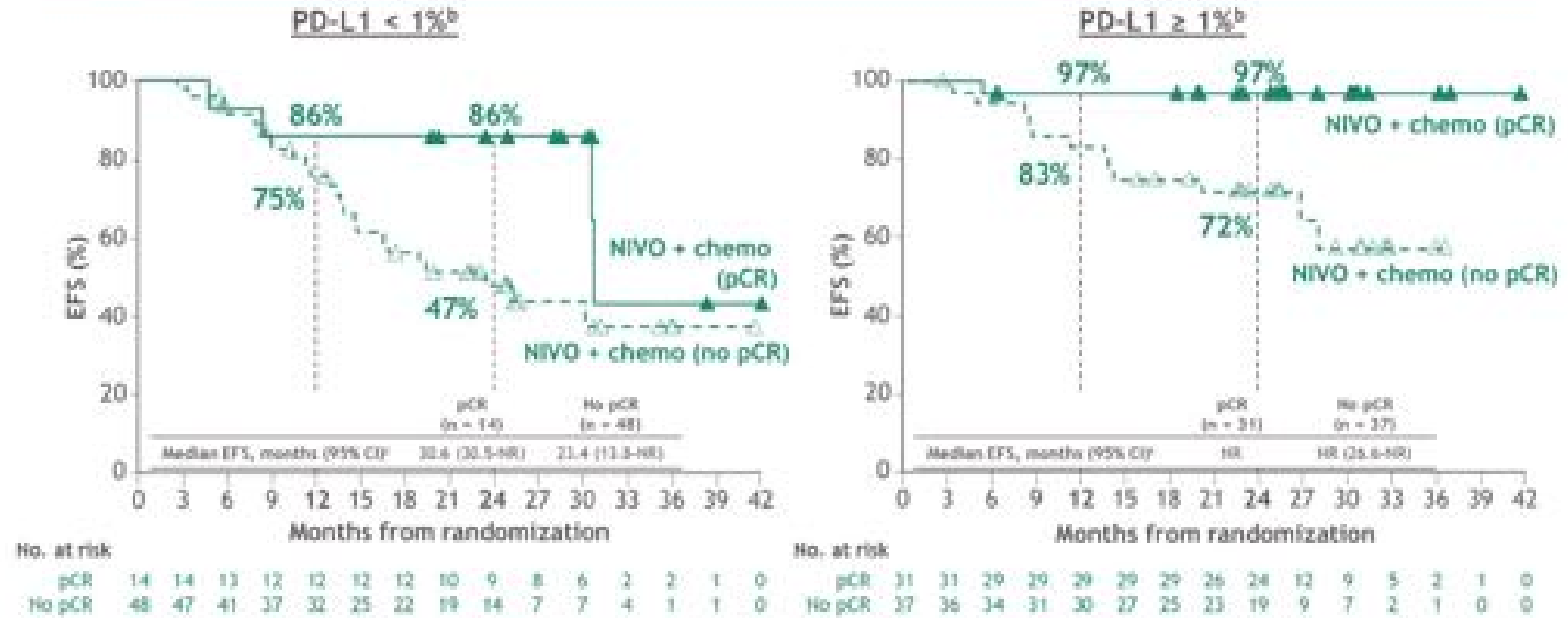
CheckMate 816: Event-Free Survival by pCR Status

EFS by pCR status[a] (primary tumor) in the path-evaluable patient population



- EFS was also improved in patients with MPR[b] in the primary tumor compared with those without; HR (95% CI) was 0.26 (0.14-0.50) for NIVO + chemo and 0.48 (0.22-1.05) for chemo, respectively

CheckMate 816: Event-Free Survival by pCR Status and PD-L1 Expression



- This post hoc analysis from CheckMate 816 provides the first in-depth assessment of pathological regression and EFS in a Phase 3 trial with neoadjuvant immunotherapy
- EFS was improved with neoadjuvant NIVO + chemo and chemo in patients with pCR in the primary tumor relative to those without
  - In the NIVO + chemo arm, EFS improvement in patients who had a pCR was observed regardless of tumor PD-L1 expression

NADIM: Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA NSCLC

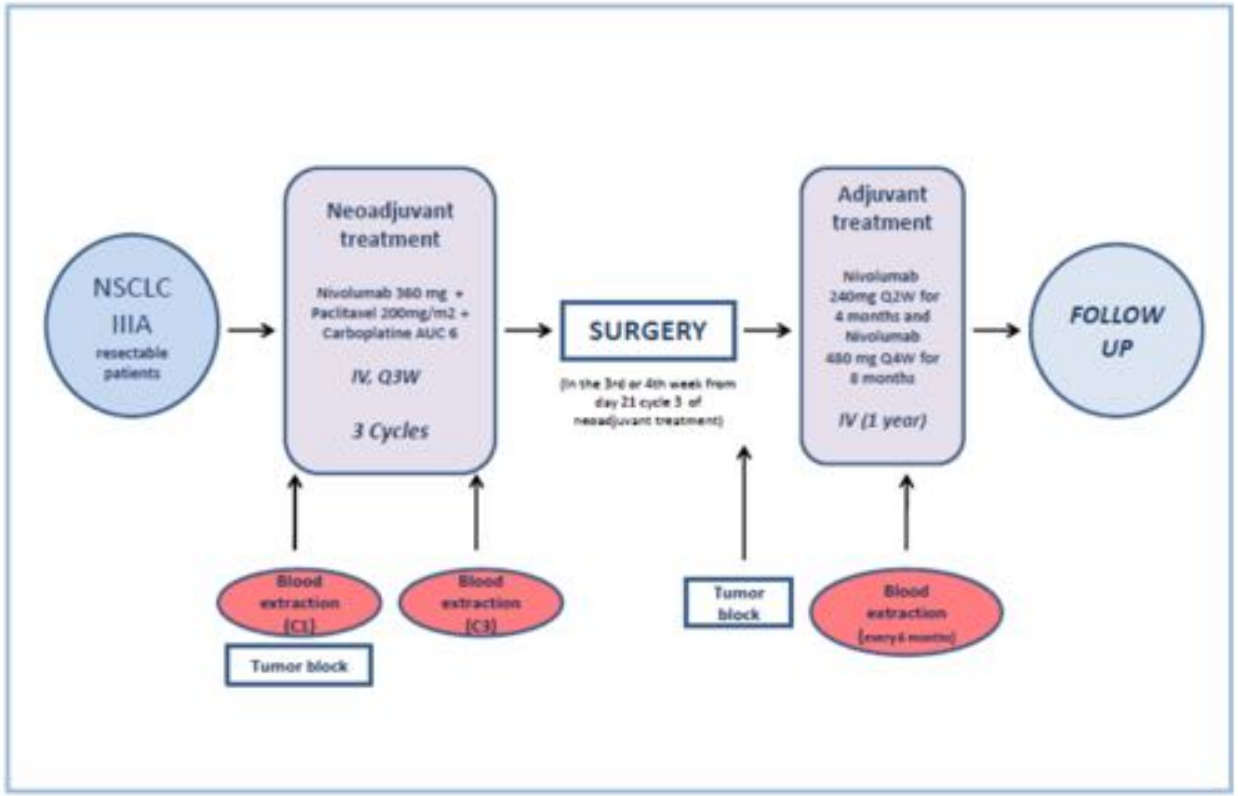
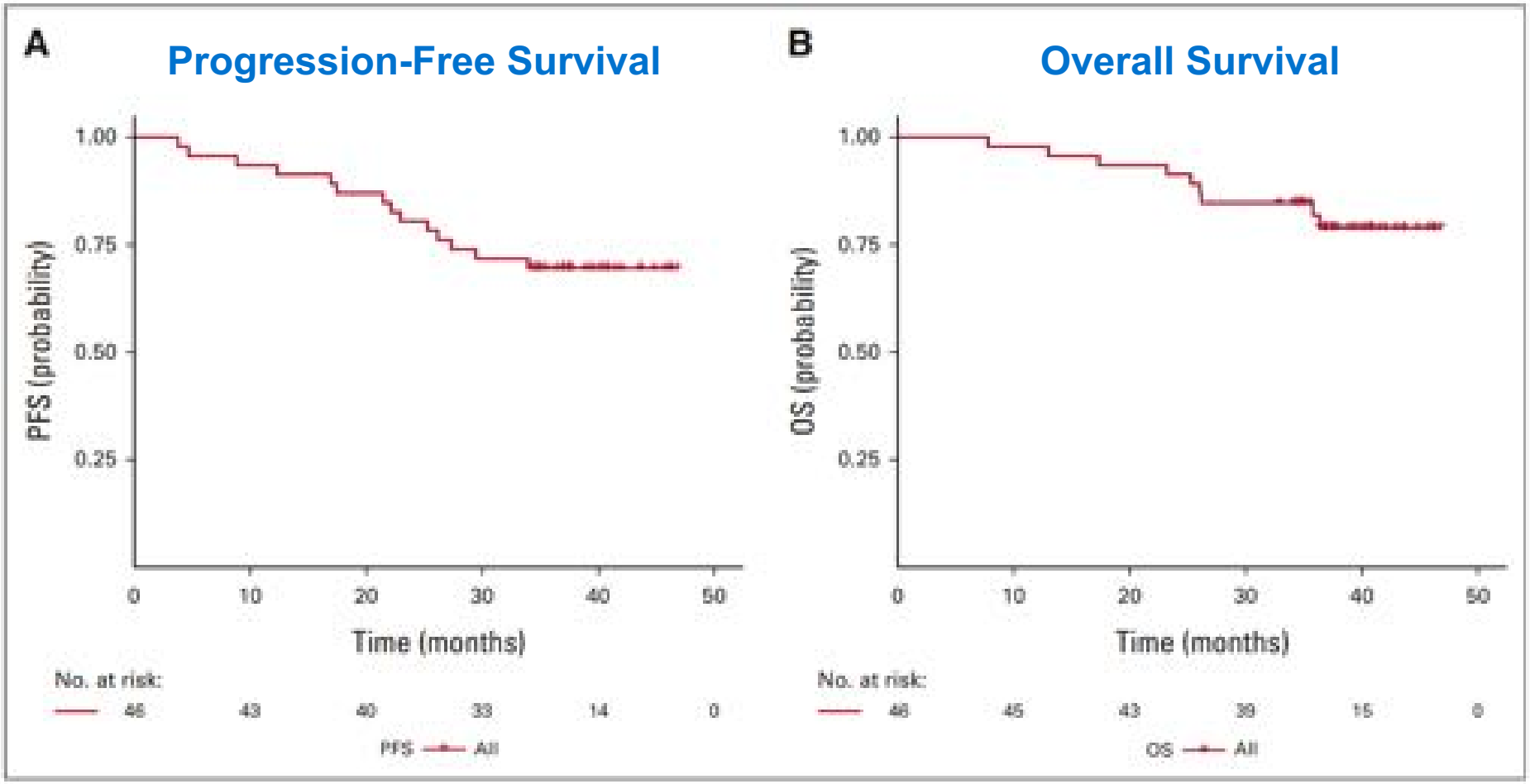


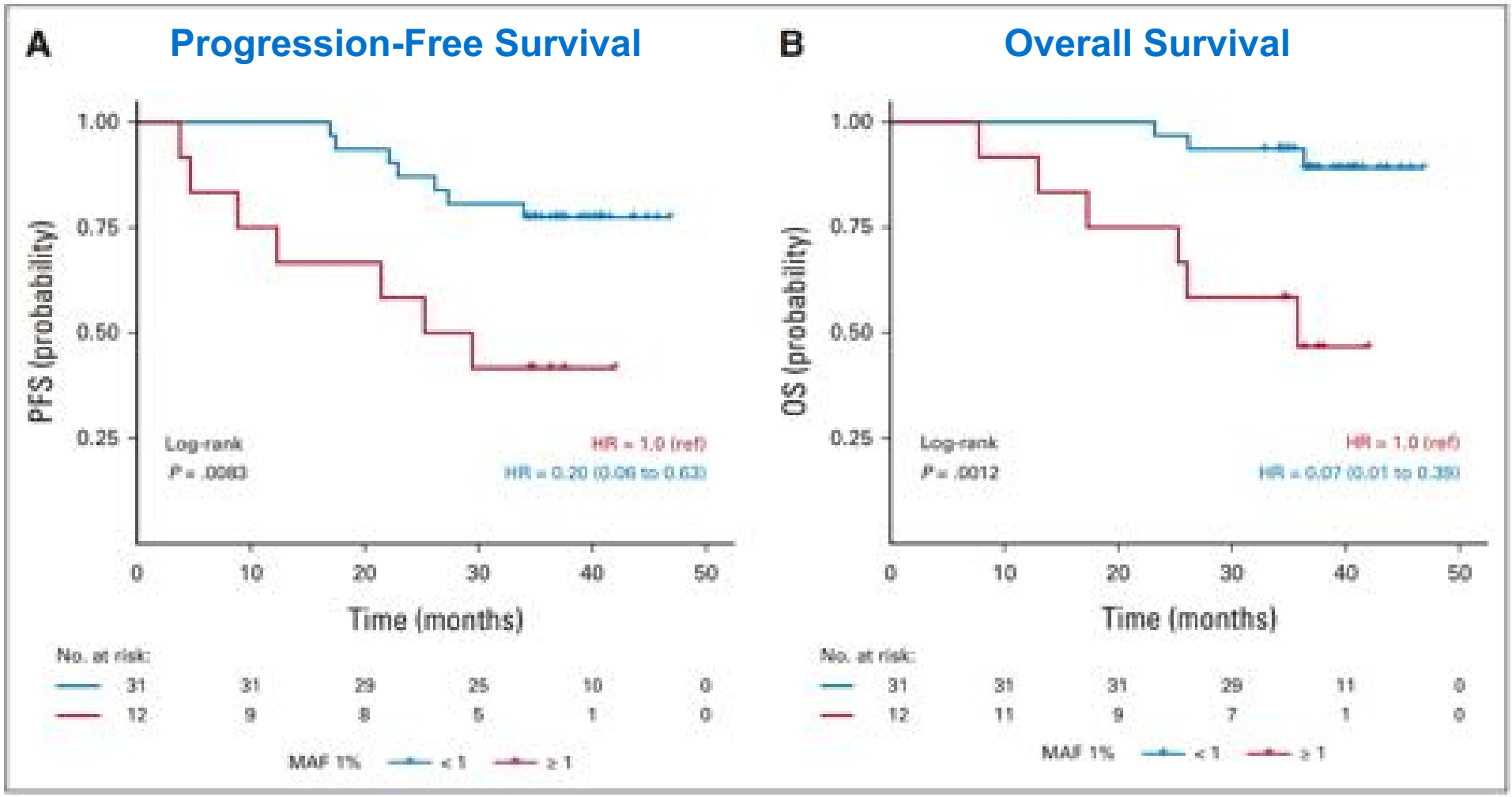
TABLE 1. HR and Corresponding 95% CI According to Each Biomarker (TMB, PD-L1, and ctDNA levels at baseline)

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	*P*[a]	HR (OS)[a]	95% CI[a]	*P*[a]
Basal ctDNA < 1%	43	9	12	0.20	0.06 to 0.63	.006	0.07	0.01 to 0.39	.002
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

NADIM: PFS and OS in the ITT Population



NADIM: PFS and OS by ctDNA Levels at Baseline, Using Cutoff of < 1% MAF



LOCALLY ADVANCED STAGE

PACIFIC TRIAL: Schema

Patients with unresectable Stage III NSCLC

- Completed concurrent platinum-based CRT[a]
  - 92% of patients received a total radiation dose of 54 Gy to 66 Gy
- WHO performance status: 0-1

Patients who had not progressed following ≥2 cycles of CRT (N=713)

Randomized 2:1

Treatment initiated within 6 weeks (42 days) of CRT completion

n=476 — Durvalumab 10 mg/kg Q2W

n=237 — Placebo 10 mg/kg Q2W

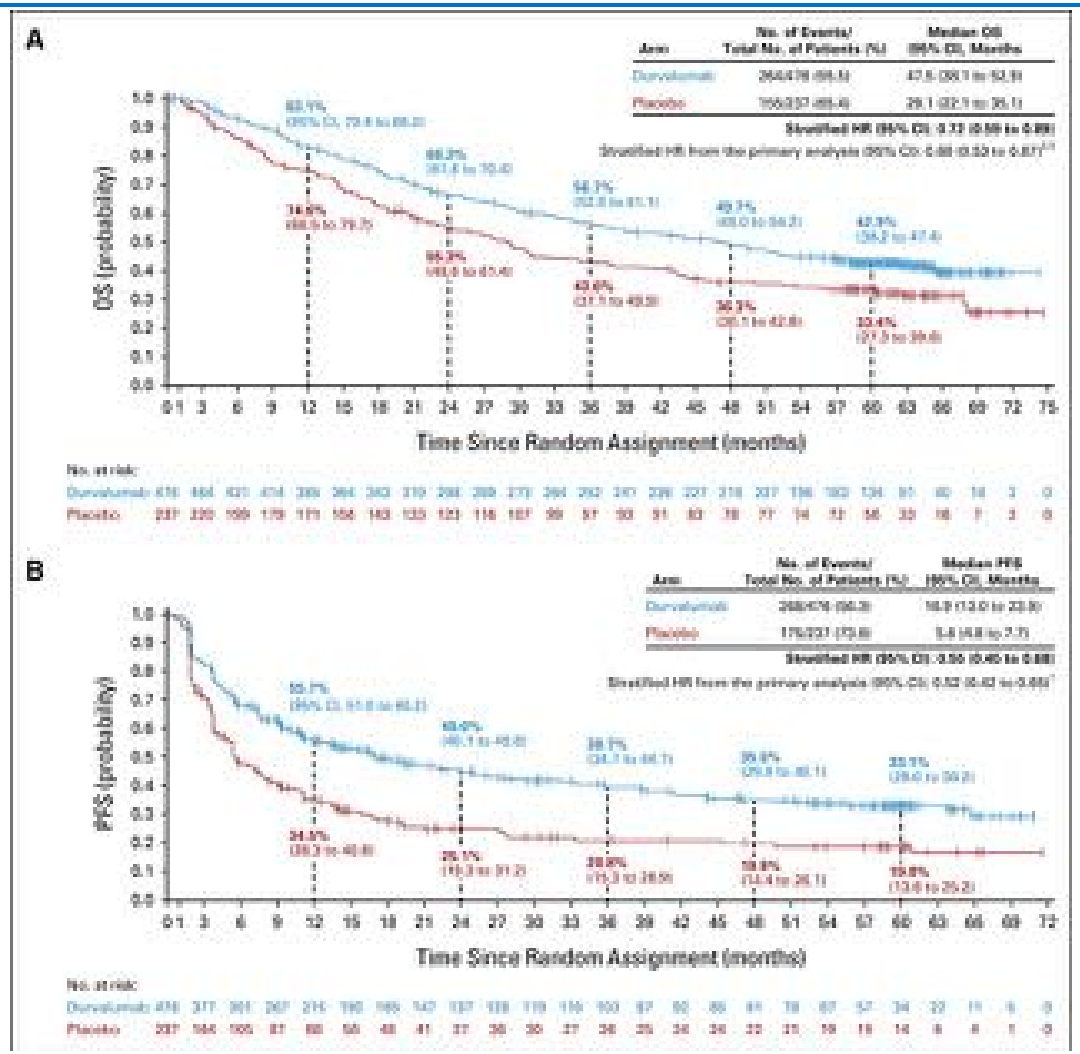
For up to 12 months or until unacceptable toxicity or confirmed disease progression

- Patients were enrolled regardless of PD-L1 expression, EGFR/ALK status, or histology

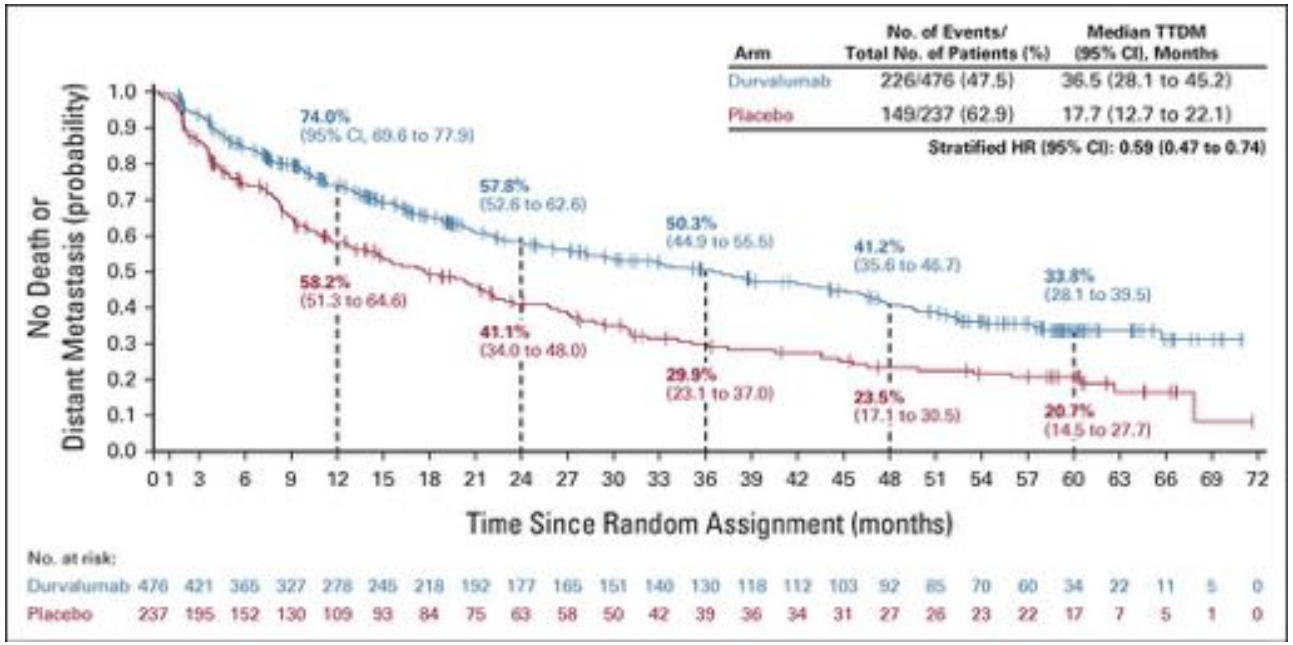
Co-primary endpoints
- PFS
- OS

Select secondary endpoints
- 12-month PFS
- 18-month PFS
- 24-month OS

PACIFIC TRIAL: Updated PFS, OS and Time to Distant Metastases



Time to Distant Metastases by blinded independent central review



KEYNOTE-799: Pembrolizumab Plus Concurrent Chemoradiation Therapy for Unresectable Stage III NSCLC

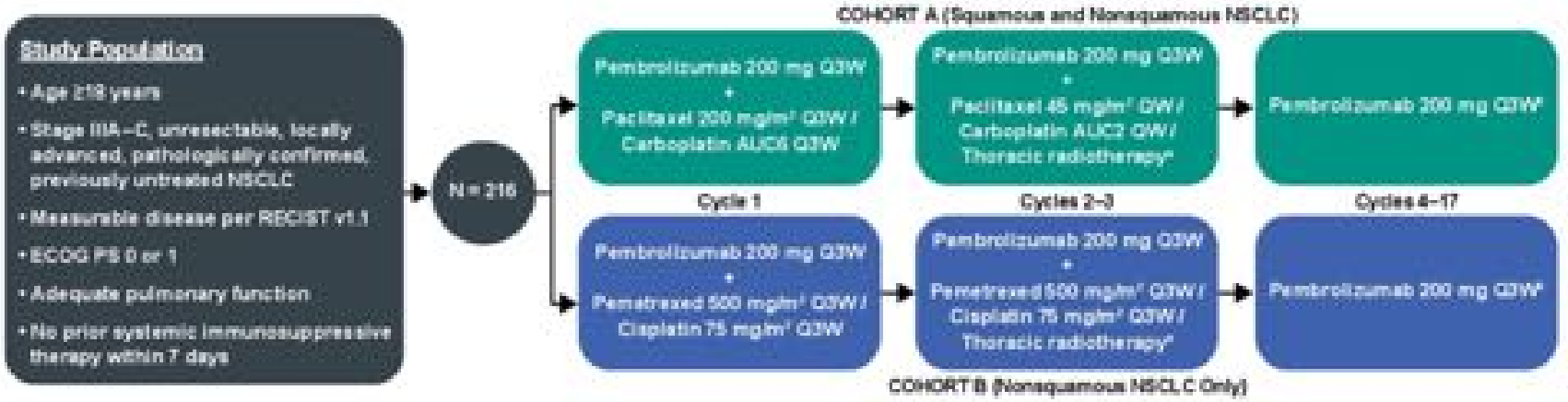


Table 2. Demographics and baseline characteristics

	Cohort A[a] (n = 112)	Cohort B[b] (n = 102)
Age, median (range), y	66.0 (46–90)	64.0 (35–81)
Men	76 (67.9)	62 (60.8)
ECOG PS 1	61 (54.5)	45 (44.1)
Former/current smoker	106 (94.6)	97 (95.1)
Squamous histology	75 (67.0)	NA
Nonsquamous histology	37 (33.0)	102 (100)
PD-L1 status		
TPS <1%	21 (18.8)	28 (27.5)
TPS ≥1%	66 (58.9)	40 (39.2)
Unknown	25 (22.3)	34 (33.3)

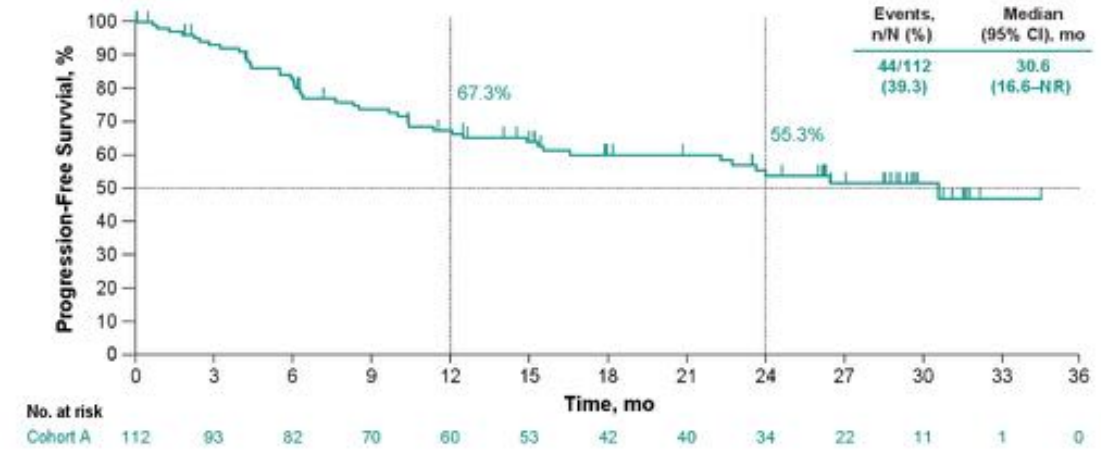
Table 4. Adverse event summary

AE, n (%)	Cohort A[a] (n = 112)	Cohort B[b] (n = 102)
Grade ≥3 pneumonitis[c]	9 (8.0)	7 (6.9)
Treatment-related AEs	105 (93.8)	99 (97.1)
Grade 3–5	72 (64.3)	52 (51.0)
Occurring in >10% of patients in either cohort		
Neutropenia	18 (16.1)	10 (9.8)
Anemia	12 (10.7)	4 (3.9)
Led to death	4 (3.6)[c]	1 (1.0)[b]
Led to discontinuation of any treatment component	38 (33.9)	21 (20.6)
Immune-mediated AEs and infusion reactions[f]	58 (51.8)	46 (45.1)
Grade 3–5	18 (16.1)	9 (8.8)
Occurring in >5% of patients in either cohort		
Pneumonitis	7 (6.3)	6 (5.9)
Led to death	4 (3.6)[c]	1 (1.0)[b]
Led to discontinuation of any treatment component	21 (18.8)	12 (11.8)

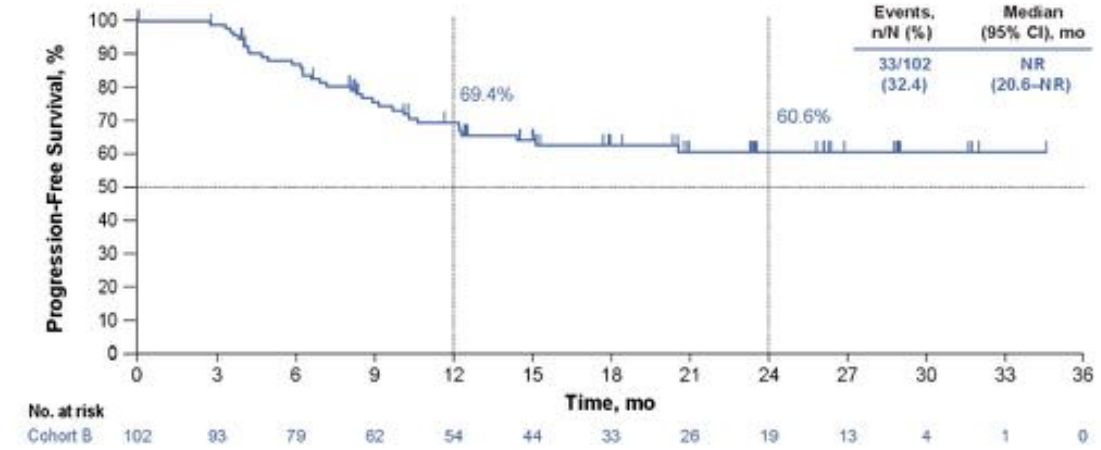
KEYNOTE-799: PFS and OS

Progression-free survival

A. Cohort A (squamous and nonsquamous histology)

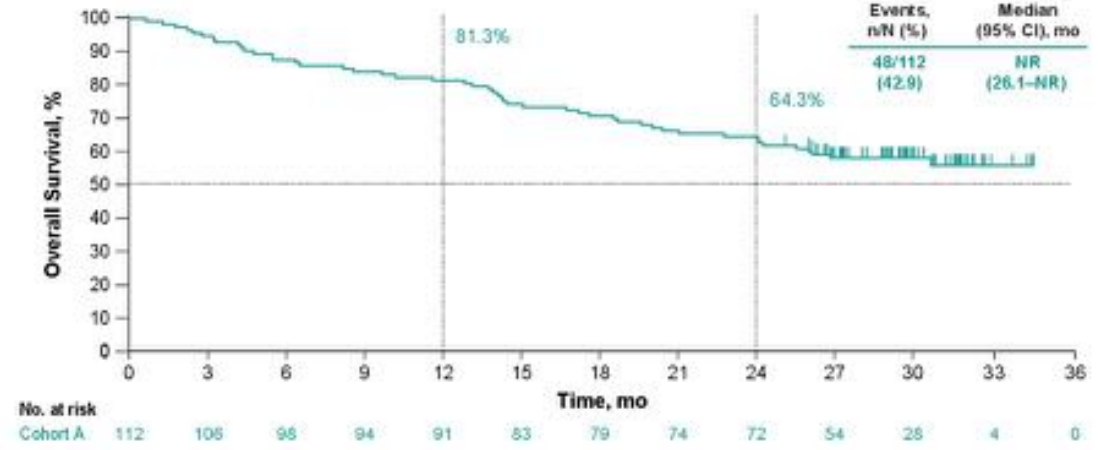


B. Cohort B (nonsquamous histology only)

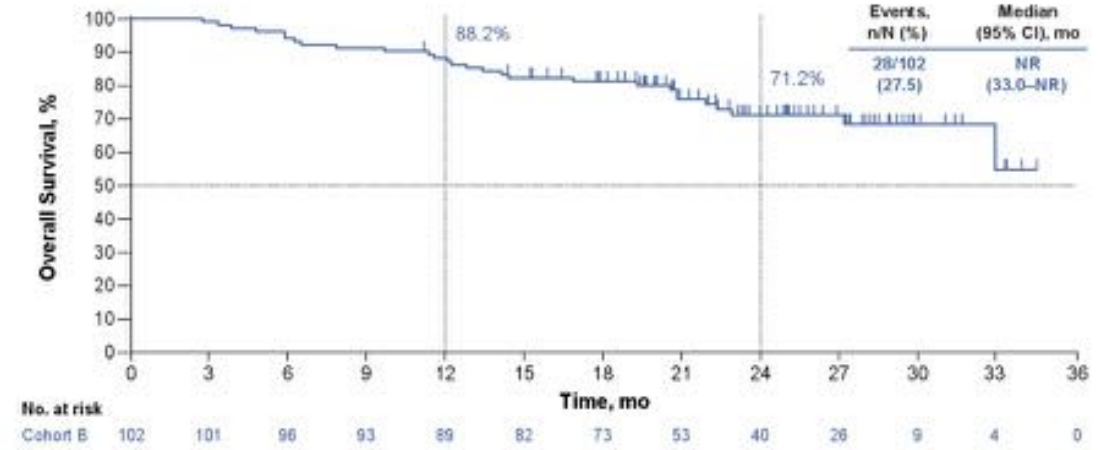


Overall survival

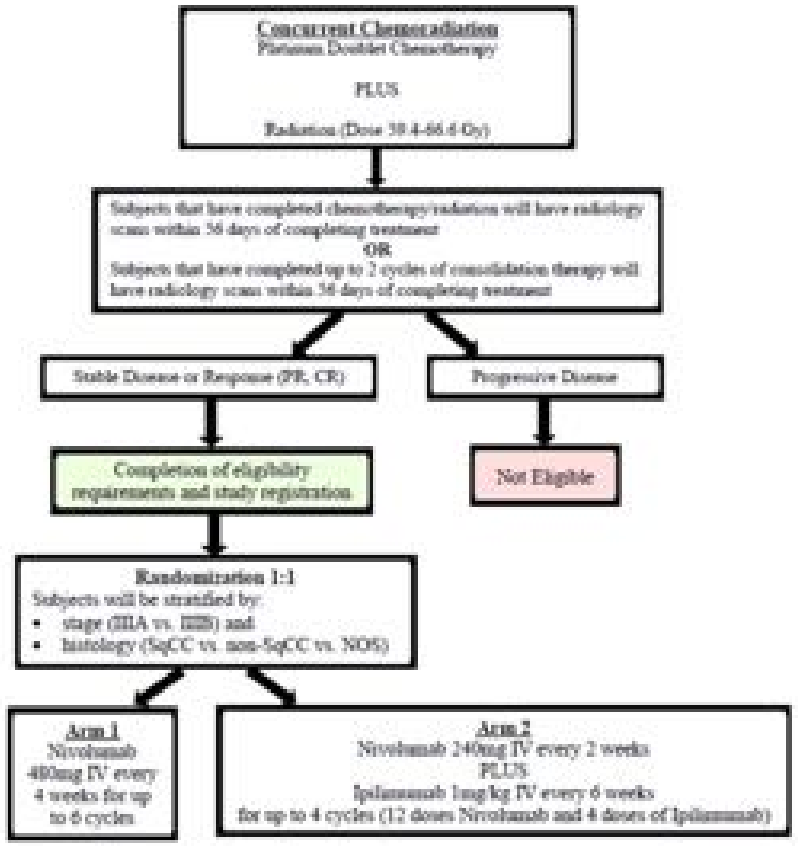
A. Cohort A (squamous and nonsquamous histology)



B. Cohort B (nonsquamous histology only)



BTCRC LUN 16-081: Consolidation Nivo + Ipi or Nivo Alone Following Concurrent Chemoradiation in Unresectable Stage III NSCLC



- This was an open-label, multi-site, randomized phase II trial run through the Big Ten Cancer Research Consortium
- It is an investigator-initiated trial
- Pts all received concurrent chemoradiation prior to enrollment
- If repeat imaging showed SD/PR/CR, they were enrolled and randomized 1:1 to:
  - Nivo alone 480mg IV q4 weeks
  - Nivo 240mg IV q2 weeks and Ipilimumab 1/mg/kg q6 weeks
- Both arms got 6 months of treatment

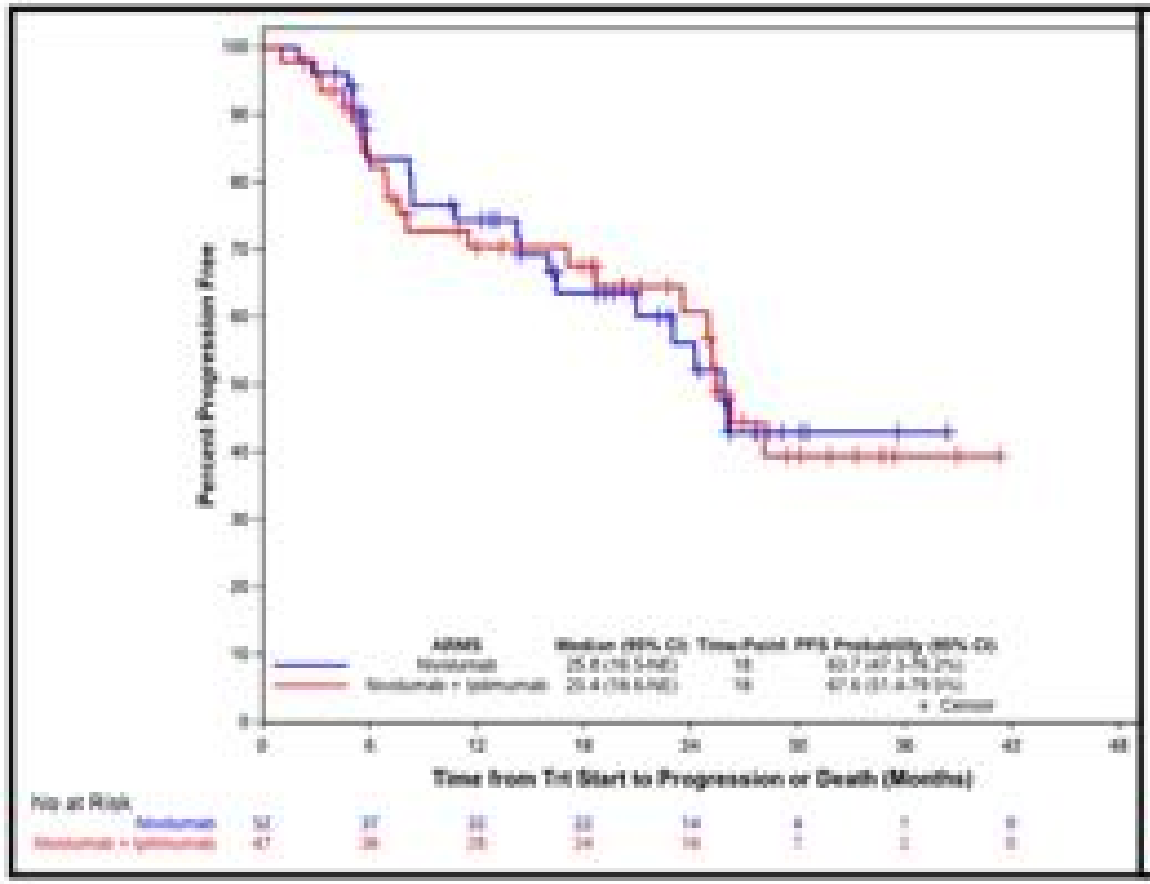
	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	27.7 (2-44.2)	29.2 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	63.7 (47.3-76.2)	67.6 (51.4-79.5)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (16.5-NR)	25.4 (18.6-NR)
Overall Survival		
18- Month (95% CI)	82.7 (69.2-90.6)	85.7 (72.3-92.9)
24- Month (95% CI)	77.7 (63.1-87.1)	80.6 (65.8-89.5)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Primary Endpoint- 18- months PFS

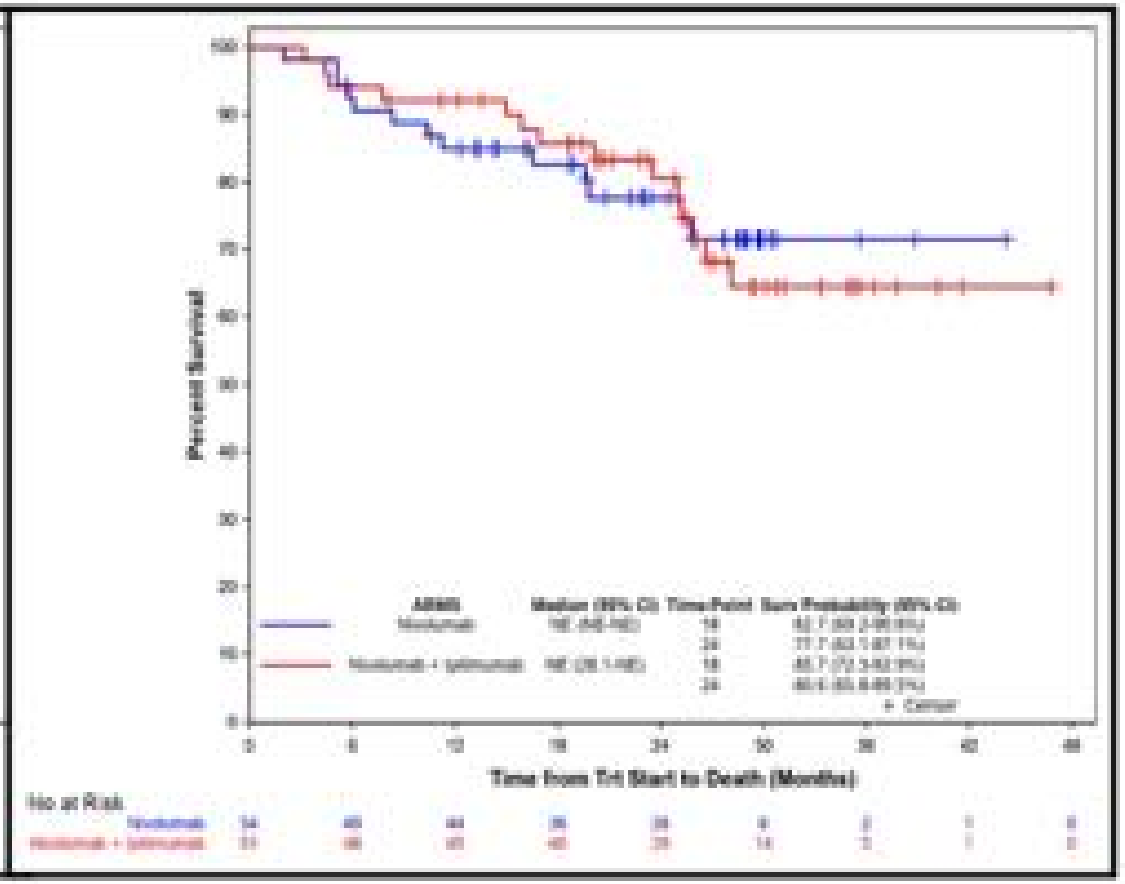
Secondary Endpoints- PFS, OS, time to metastatic disease/death, and toxicity

BTCRC LUN 16-081: PFS and OS

Progression-Free Survival

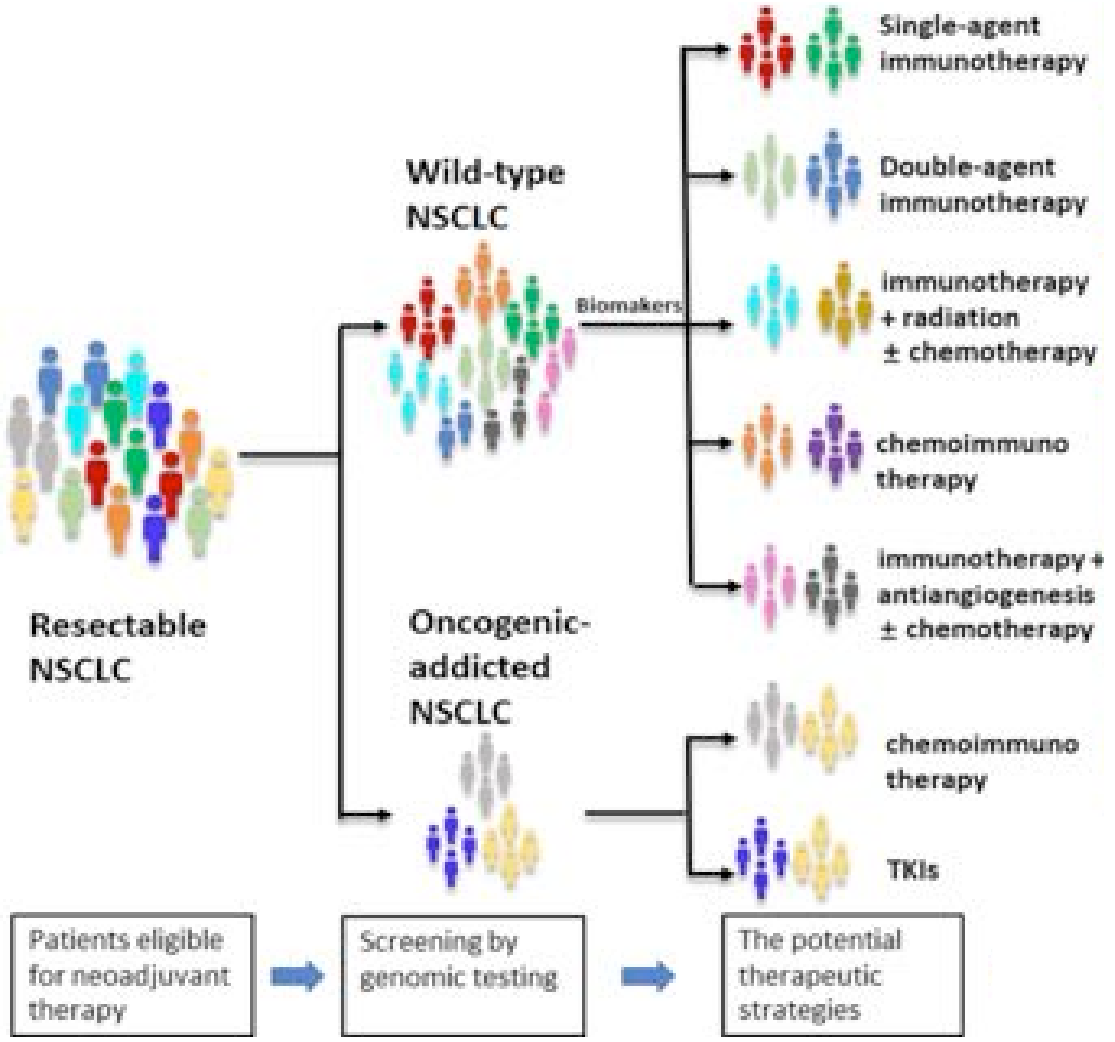


Overall Survival



Conclusions

- Adjuvant therapy with EGFR TKIs have shown efficacy and osimertinib is now approved as adjuvant therapy after surgical resection in stage IB-III EGFR-mutated NSCLC.
- More trials are needed to explore the feasibility of TKIs targeting other driver mutations in early stage NSCLC
- Neoadjuvant and adjuvant therapy with ICIs for NSCLC are FDA approved.
- Further trials are necessary to discover biomarkers of response to select for patients that would benefit from ICI treatment



Adapted from Kang J et al. Cancer Comm 2021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