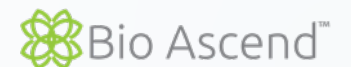




Targeted therapy for Oncogene-Addicted Early-Stage NSCLC

October 25, 2025



Disclosures

Contracted Research support to Institution:

-AstraZeneca, BMS, BioNTech, Genetech/Roche, Lilly, Merck, Taiho

Consultant

-AstraZeneca, Boehringer Ingelheim, Foundation Medicine, Genentech/roche, Lilly, Merck, Natera, NuvationBio, Revolution Biosciences

Early-Stage Lung Cancer Stats with Surgery Alone



Stage IA1: ≤ 1 cm ~92% 5-year survival



Stage IA2: >1-2 cm ~83% 5-year survival



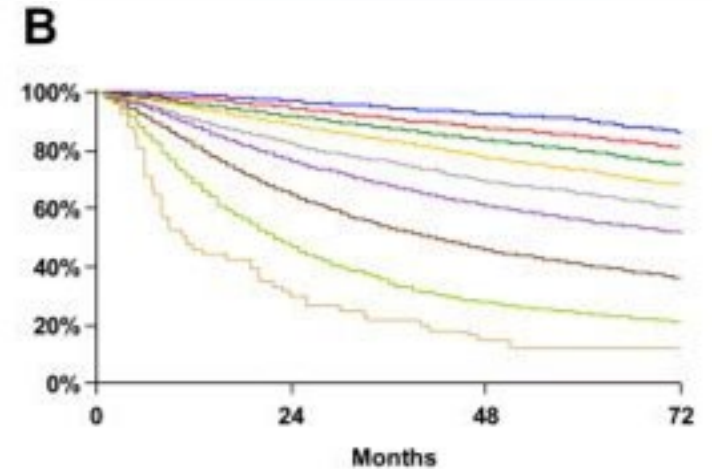
Stage IA3: >2-3 ~77% 5-year survival



Stage IIA: >4 cm ~60% 5-year survival



Once LNs are involved the risk of recurrence and death drastically increases



Survival based on
pathologic stage

Evolution of oncogenic biomarkers in NSCLC

Novel drivers



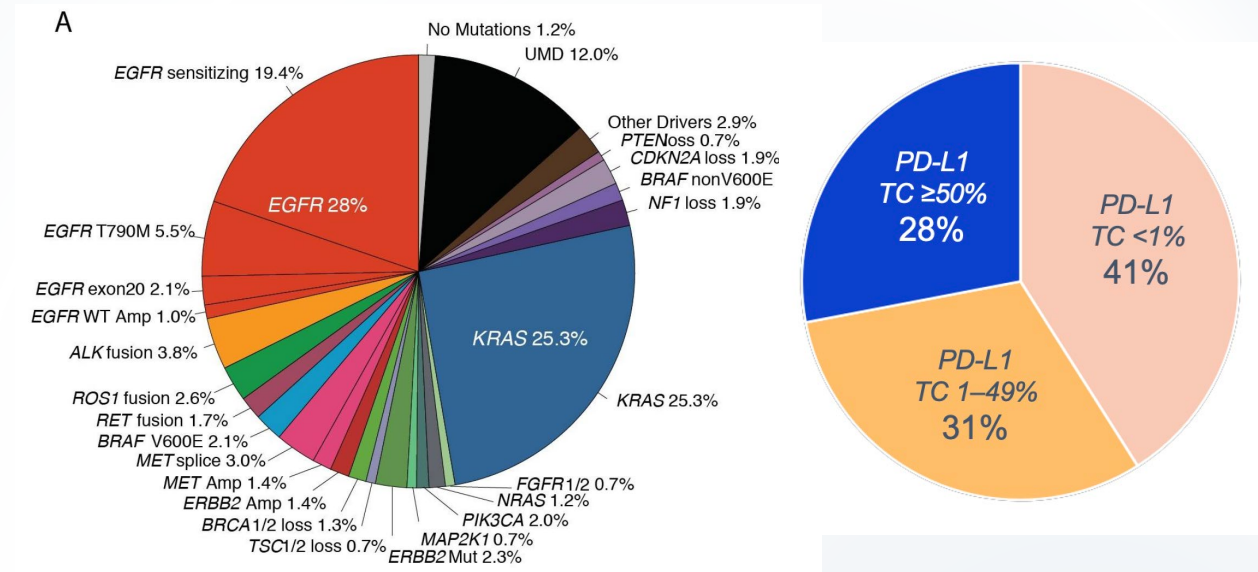
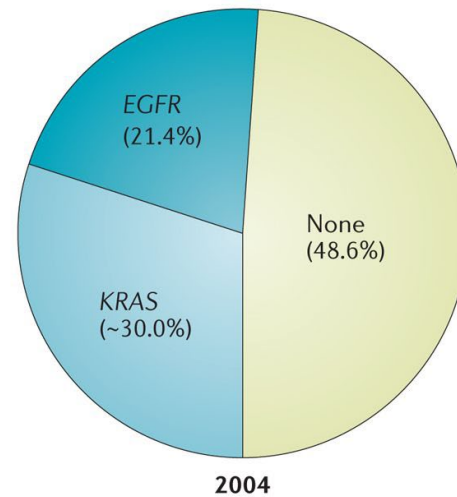
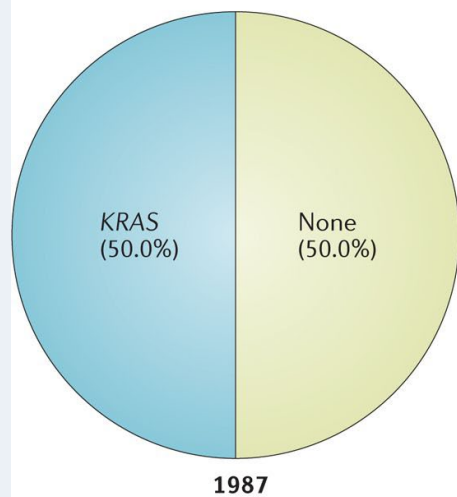
Investigational targets



Clinical-grade predictive biomarkers in 2025

Targeted therapies

Immune checkpoint therapy



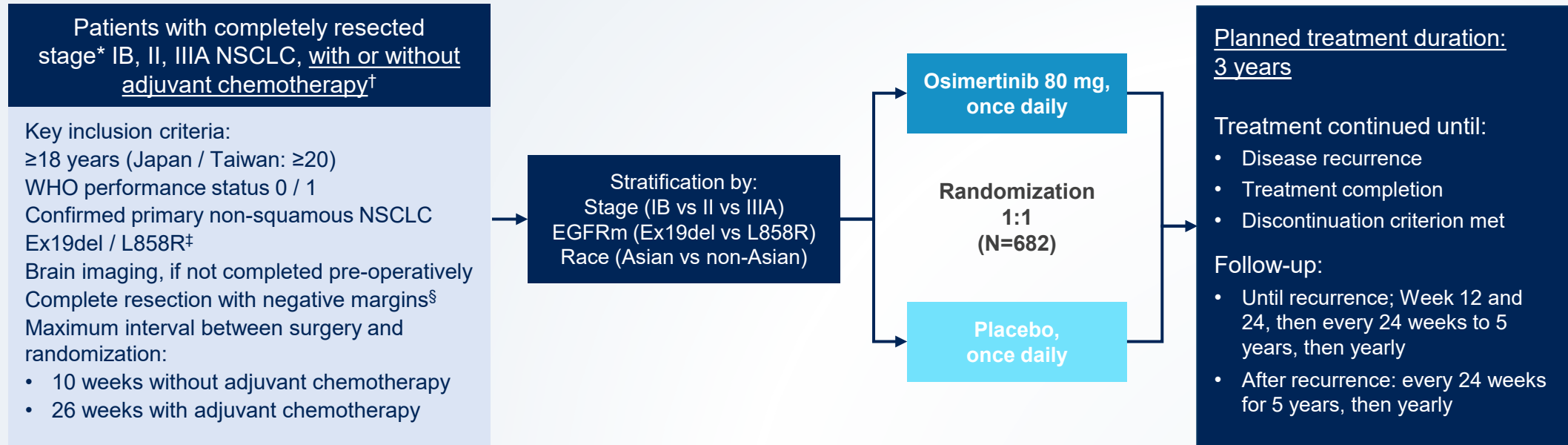
Vargas AJ, Harris CC. Nature Reviews Cancer. 2016 Aug;16(8):525; Jordan EJ et al. Cancer Discovery. 2017 Jun 1;7(6):596-609; Yang SR et al. Seminars in cancer biology 2022 Sep 1; Felip, et al. Lancet 2021; Carbone, et al. WCLC 2020; Forde, et al. N Engl J Med 2022; Kowanetz, et al. AACR 2018; Gandhi, et al. N Engl J Med 2018; Paz-Ares, et al. N Engl J Med 2018; Paz-Ares, et al. Lancet Oncol 2021



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ADAURA



Endpoints

- **Primary endpoint:** DFS by investigator assessment in stage II-IIIa patients
- **Key secondary endpoints:** DFS in the overall population (stage IB-IIIa), landmark DFS rates, OS, safety, health-related quality of life

*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

Herbst RS, et al. Oral presentation at ASCO 2023; June 7 2023; Chicago, IL. Abstract LBA3

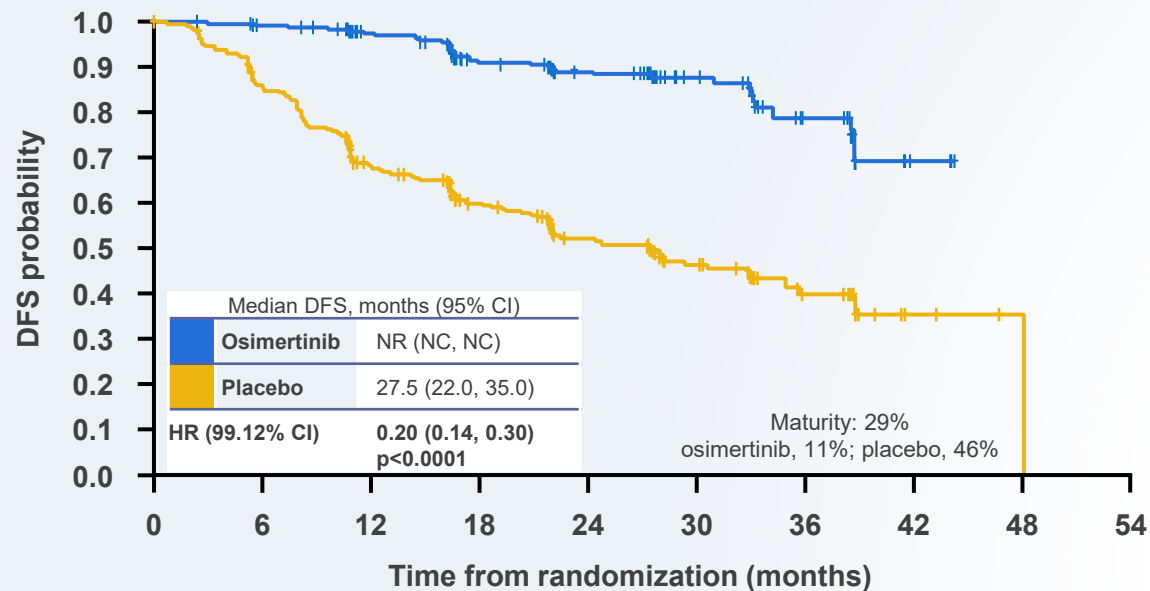


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ADAURA: Adjuvant osimertinib x 3 yr significantly improved DFS vs placebo

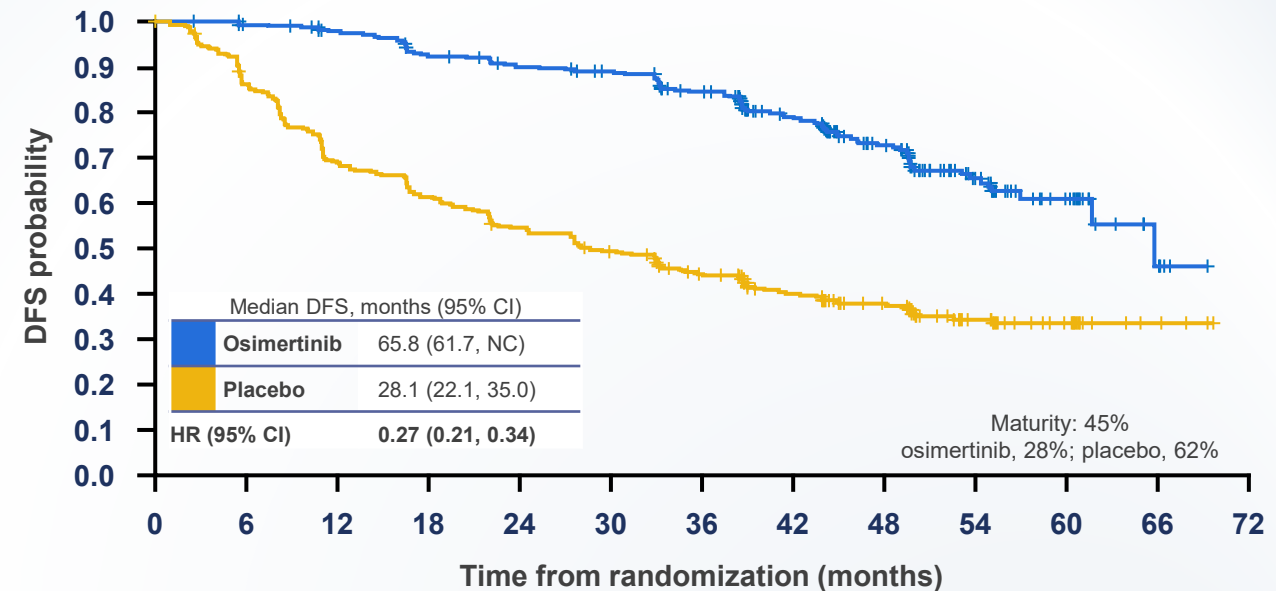
ADAURA primary DFS analysis^{1,2} (stage IB–IIIA)*
NEJM October 2020



No. at risk

Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

ADAURA updated DFS analysis^{3,4} (stage IB–IIIA)[†]
JCO January 2023



No. at risk

Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5
Placebo	343	288	230	205	181	162	137	115	84	48	25	4

CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

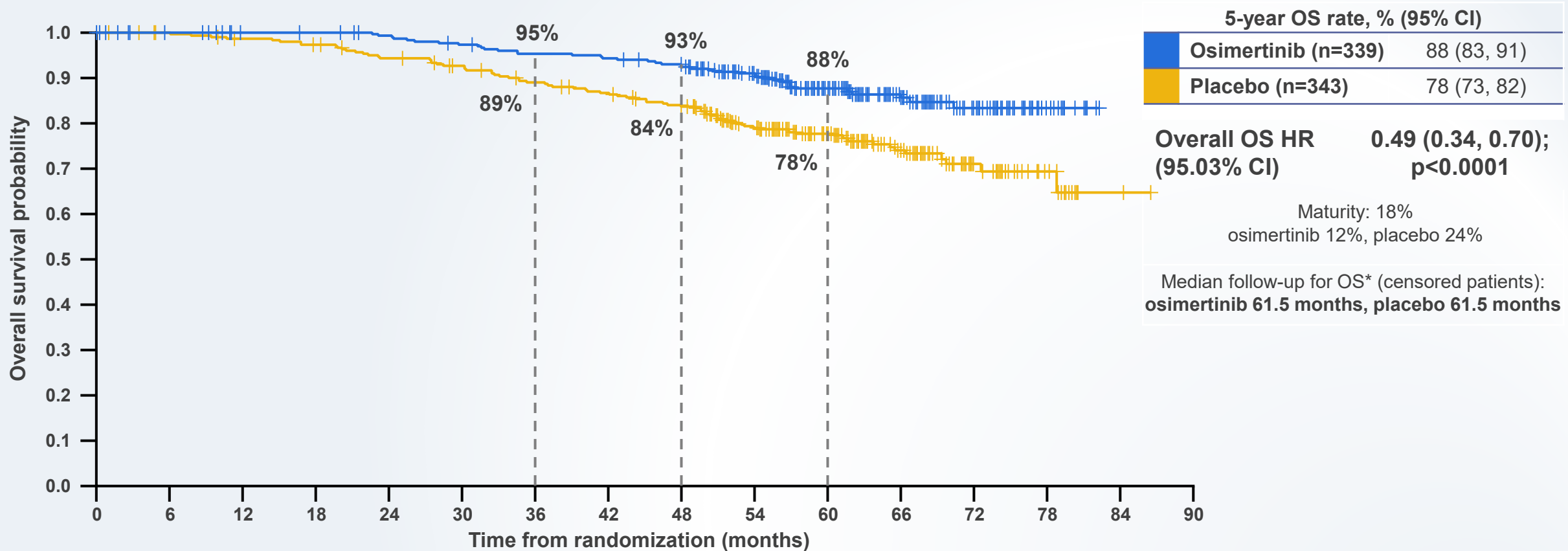
1. Wu et al. N Engl J Med 2020;383:1711-1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830-1840; 4. Tsuboi et al. Ann Oncol. 2022;33(Suppl 7): abstract / oral LBA47.



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ADAURA: Adjuvant osimertinib x 3 yrs—improved overall survival patients with stage IB / II / IIIA disease



No. at risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

CI, confidence interval; HR, hazard ratio; OS, overall survival

Data cut-off: January 27, 2023.

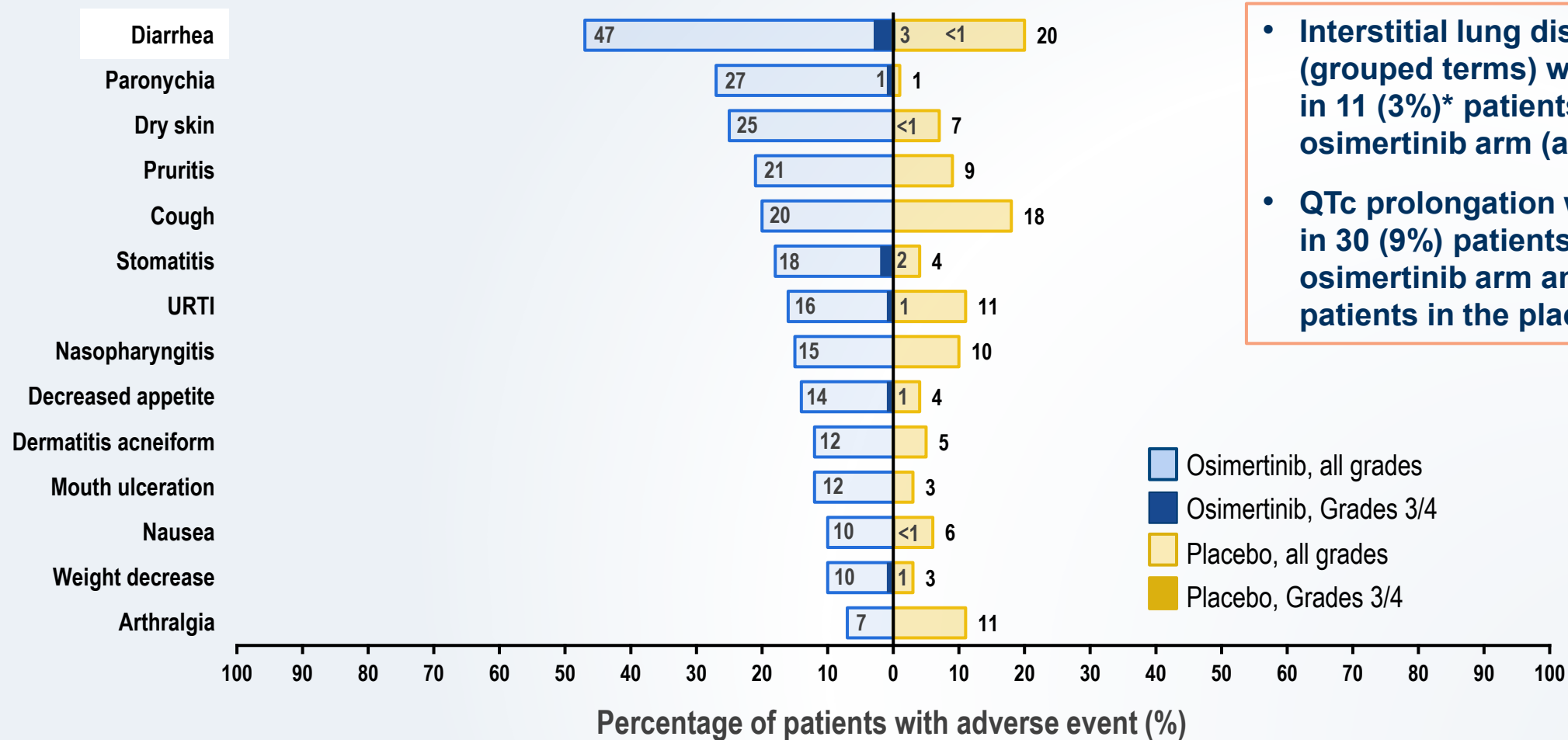
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.



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All Causality Adverse Events (≥10% of Patients)



- Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all Grade 1/2)[†]
- QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm[‡]

*Compared with the January 17, 2020 data cut-off, 1 additional patient reported interstitial lung disease (grouped term): pneumonitis, Grade 2;

[†]Grade 1, n=6; Grade 2, n=5; Grade 3, n=0; [‡]Osimertinib: Grade 1, n=16; Grade 2, n=10; Grade 3, n=4; placebo: Grade 1, n=7; Grade 2, n=0; Grade 3, n=1.

ALINA

Resected Stage IB (≥4cm)-IIIA ALK+ NSCLC

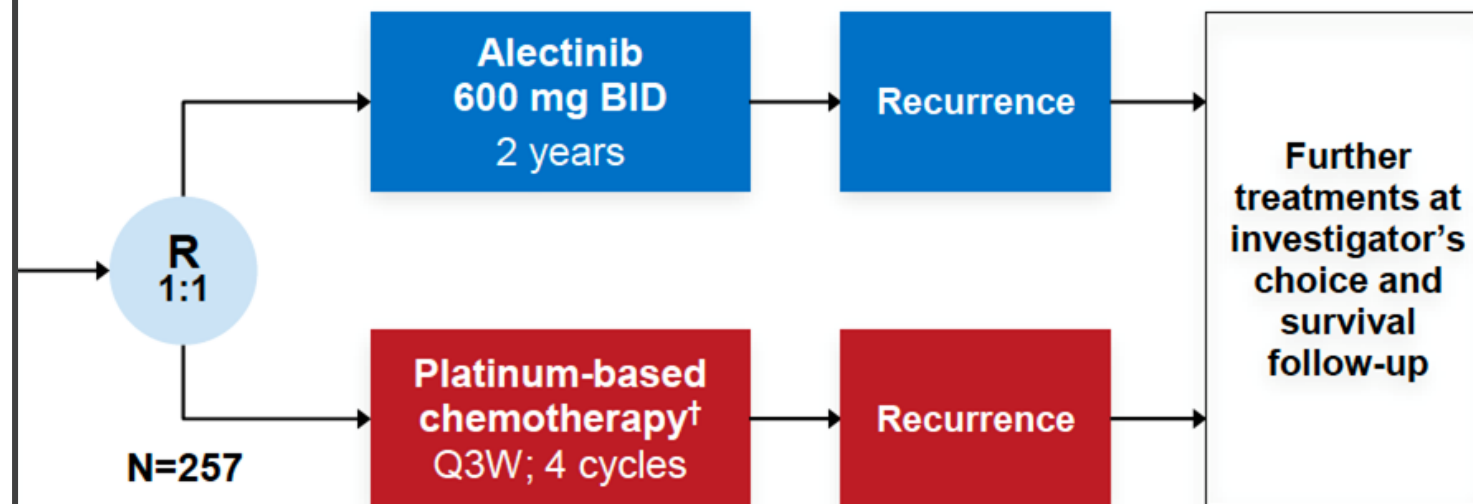
per UICC/AJCC 7th edition

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 (≥4 cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint

- DFS per investigator,[‡] tested hierarchically:
 - Stage II-IIIA → ITT (stage IB-IIIA)

Other endpoints

- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)[§] were conducted: at baseline, every 12 weeks for year 1-2, every 24 weeks for year 3-5, then annually

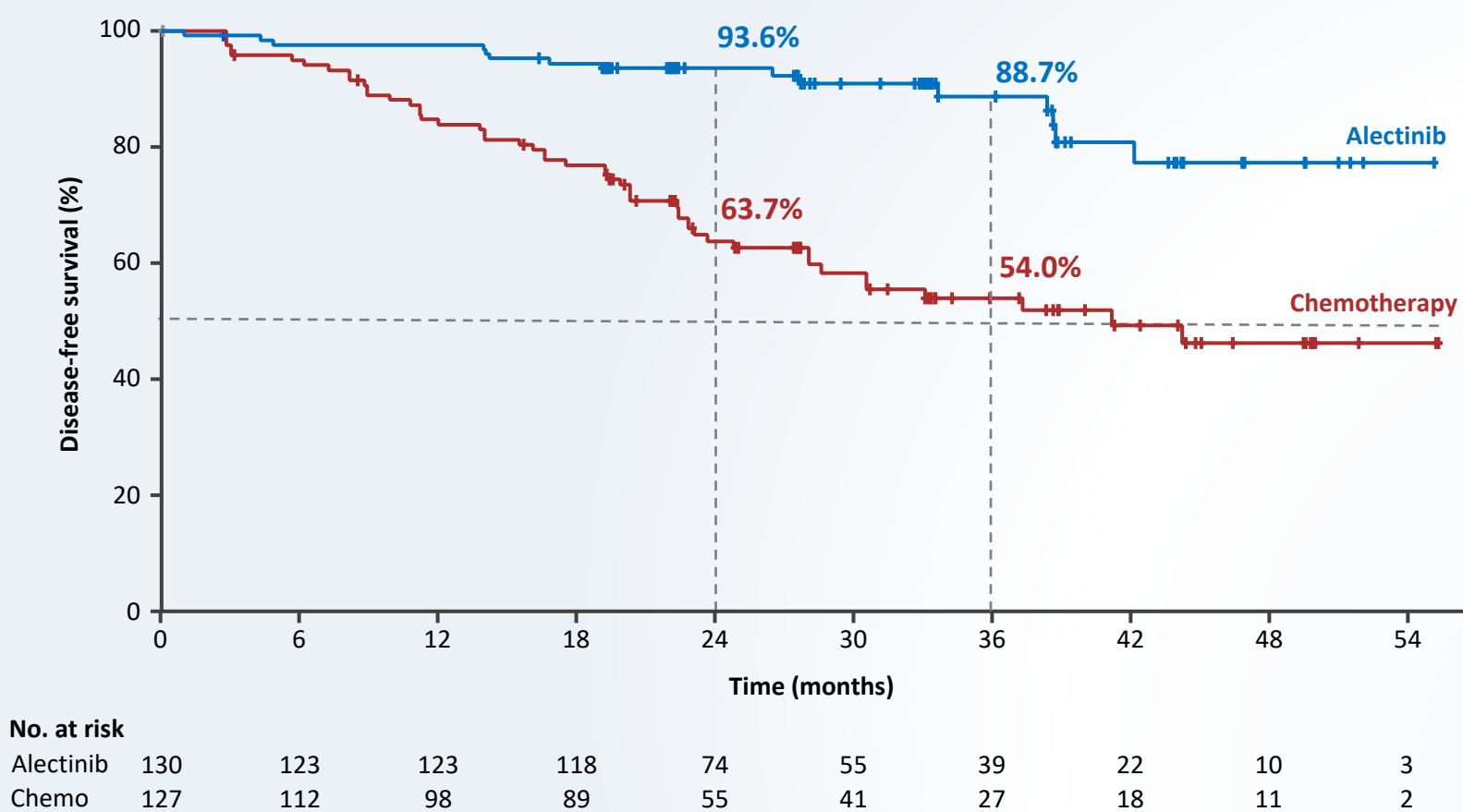
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.



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Disease-free survival: ITT (stage IB-III A)*



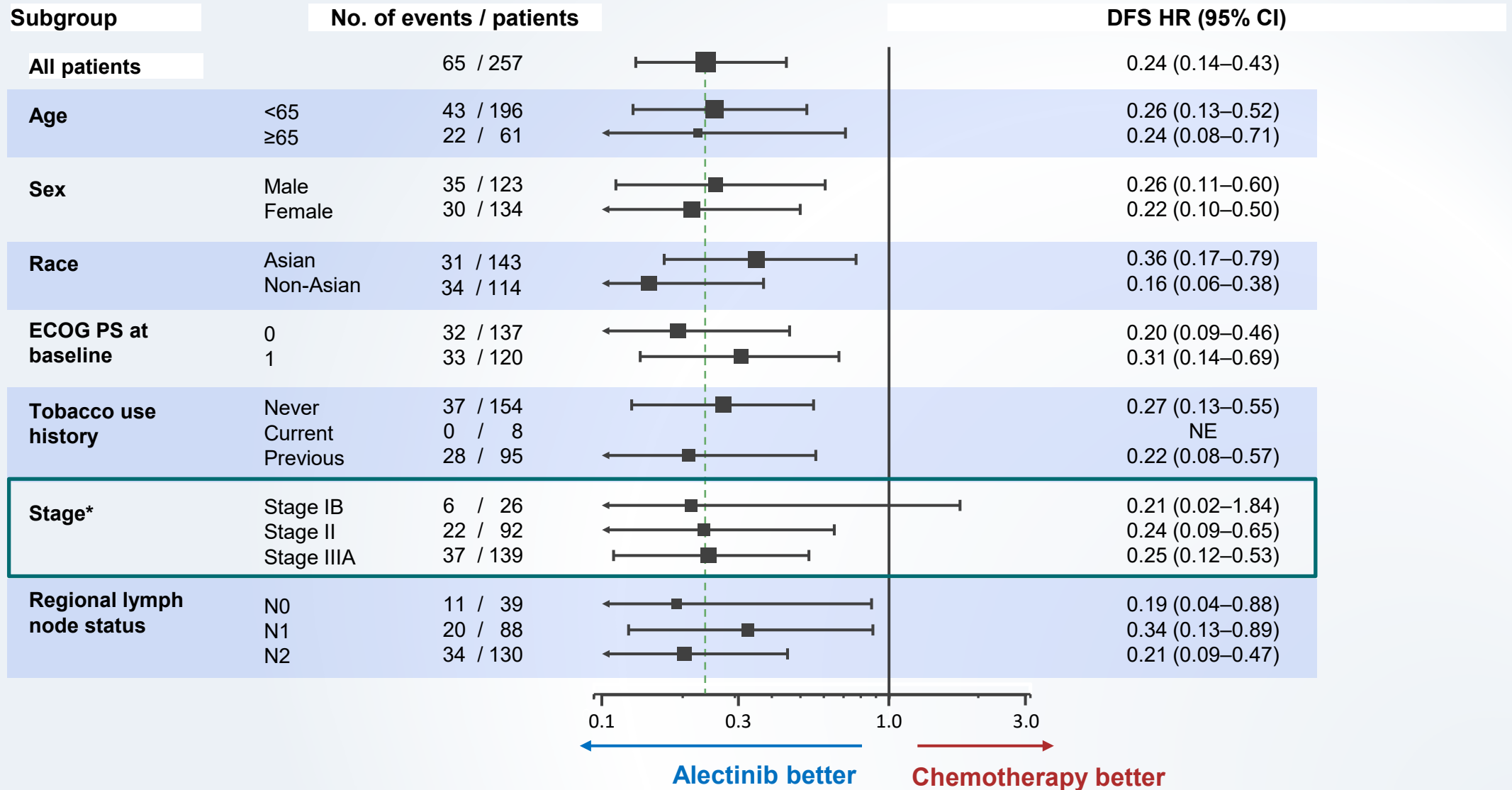
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	15 (12%)	50 (39%)
Death	0	1
Recurrence	15	49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	0.24 (0.13, 0.43) p [†] <0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported[‡]

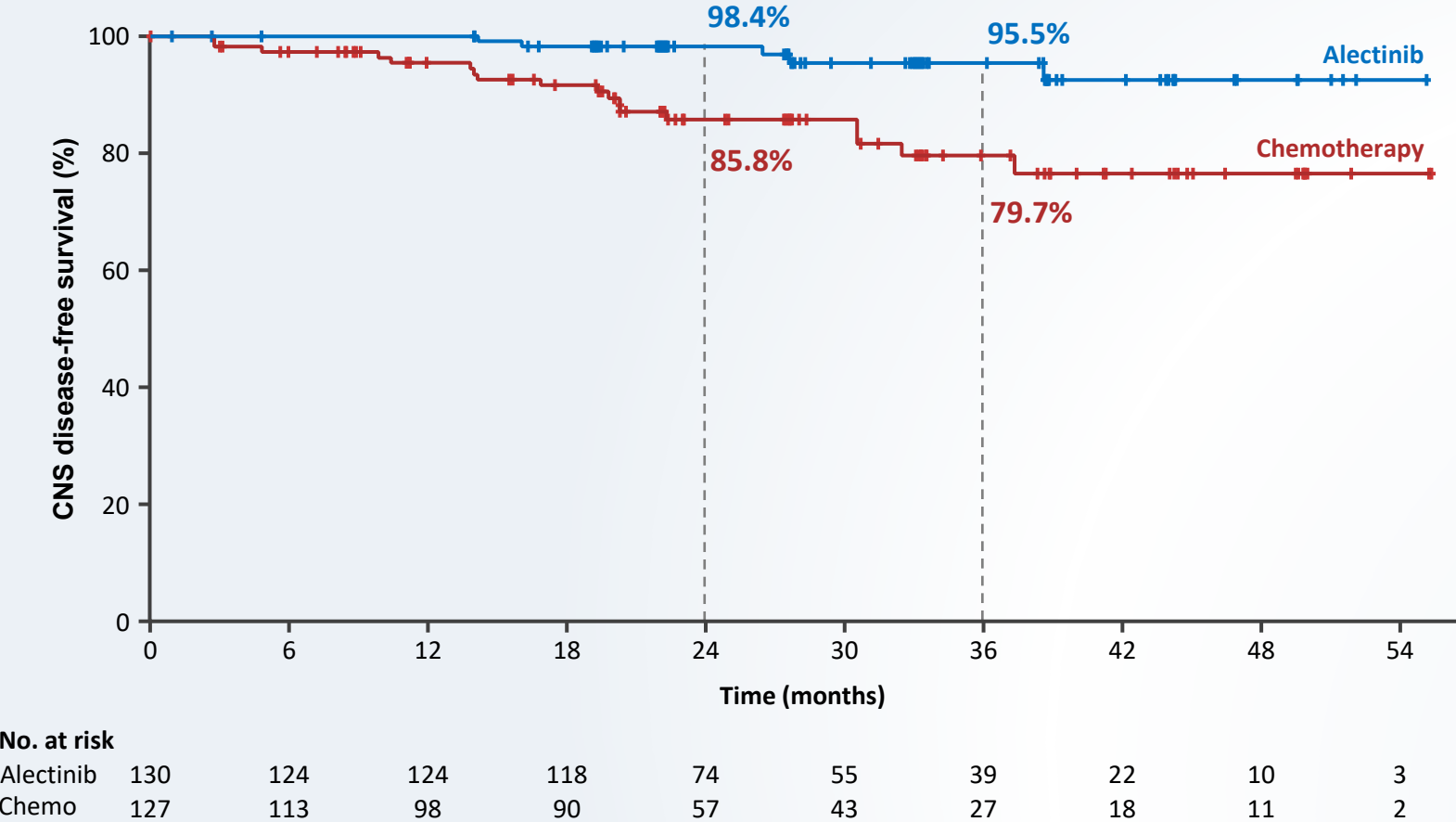
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276, Wu et al. AATS 2024

Disease-free survival subgroup analysis (ITT)



CNS disease-free survival in the ITT population

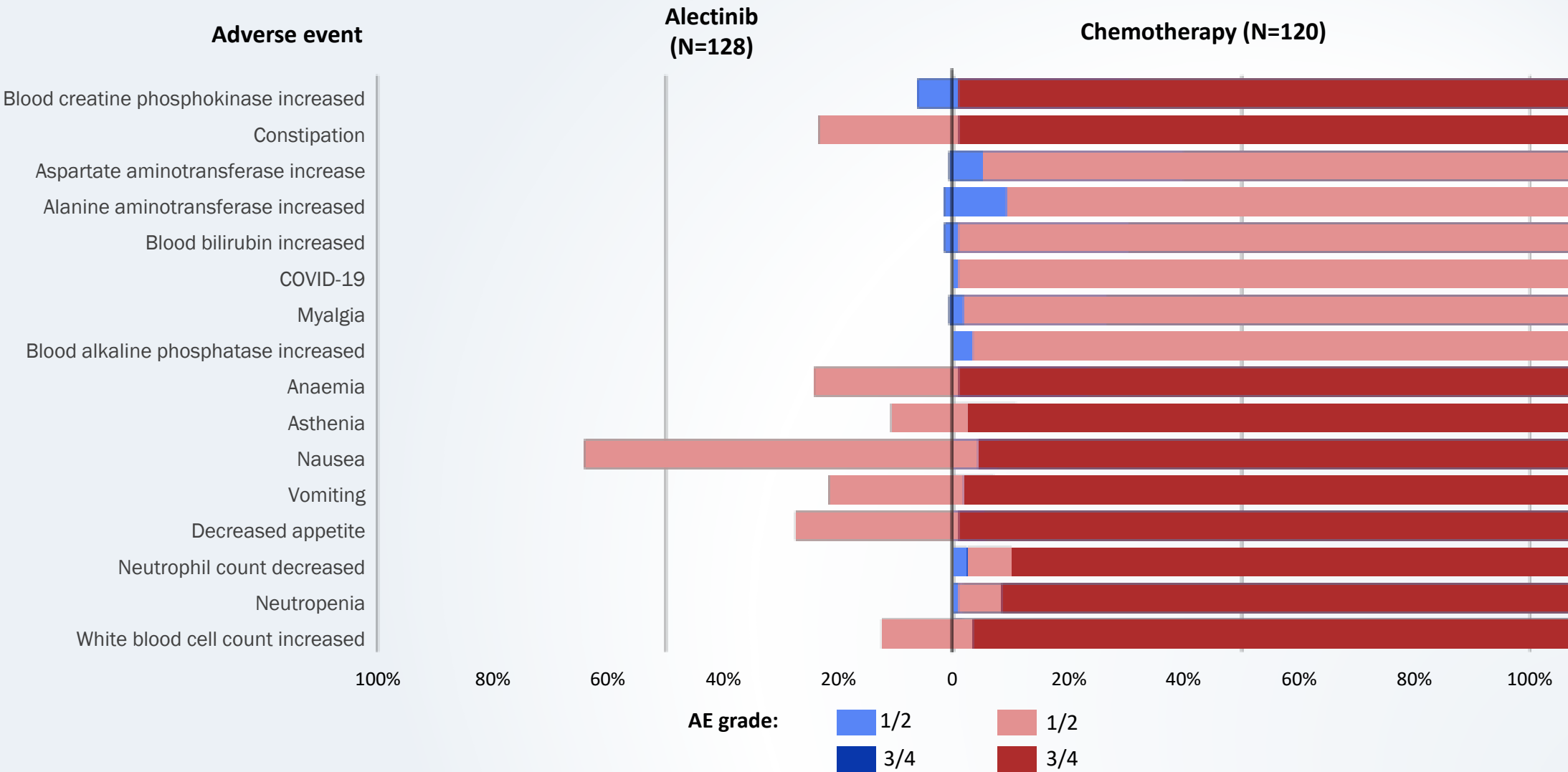


	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	0.22 (0.08, 0.58)	

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

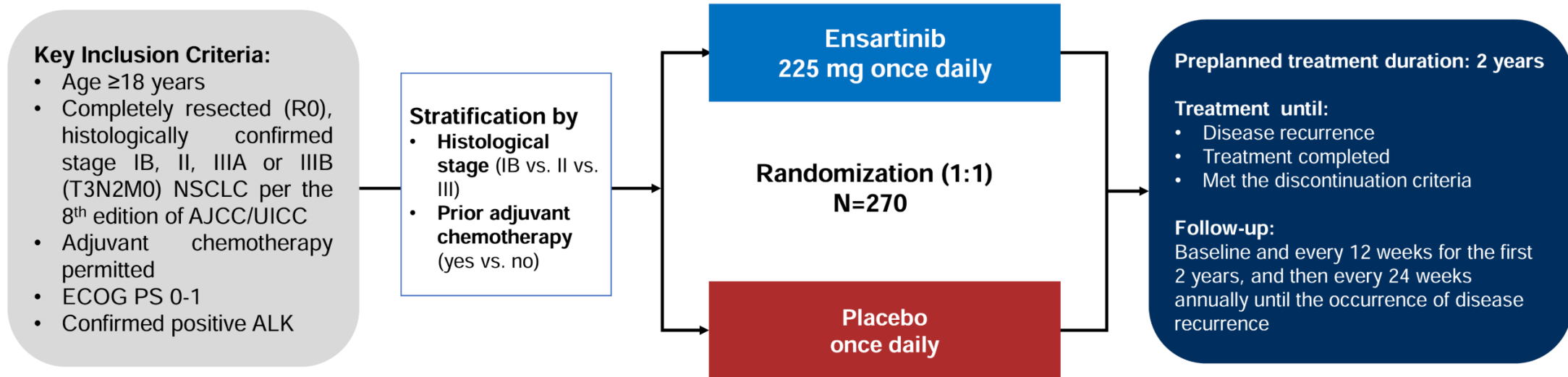
Data cut-off: 26 June 2023
*Stratified analysis with race and stage as stratification factors
CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.

AEs occurred in ≥15% of patients



Data cut-off: 26 June 2023
Median treatment duration was 23.9 months in the alectinib arm and 2.1 months in the chemotherapy arm. No grade 5 events were observed.
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.

Randomized, double-blind phase III trial (data cutoff for interim analysis: 6/26/2025)



Primary endpoint: Investigator-assessed DFS* in patients with stage II to IIIB disease

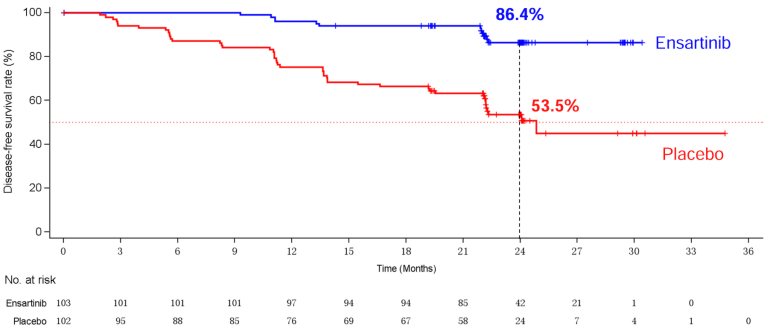
Secondary endpoints: Investigator-assessed DFS in patients with stage IB-IIIB disease (ITT), 3/5-year DFS rate, OS, safety

Statistical analysis:

- This preplanned interim analysis was performed when 70% of events (57 events) were observed in patients with stage II-IIIB disease.

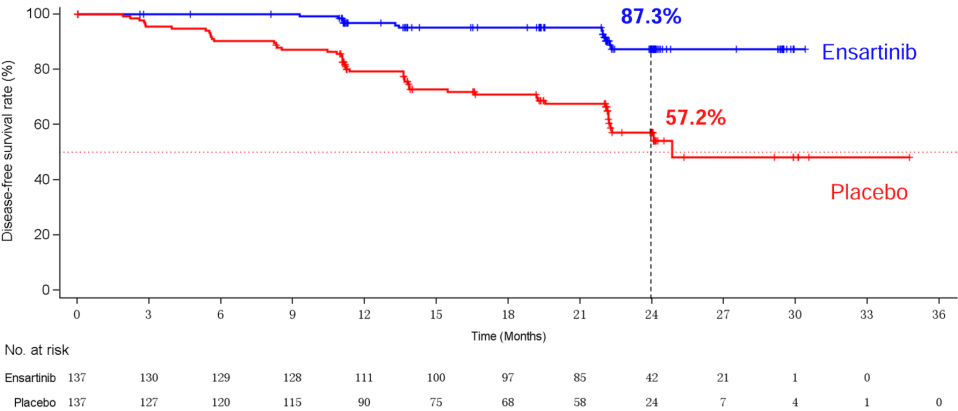
Ensartinib showed an improved DFS in patients with II-IIIB disease

Investigator-assessed DFS



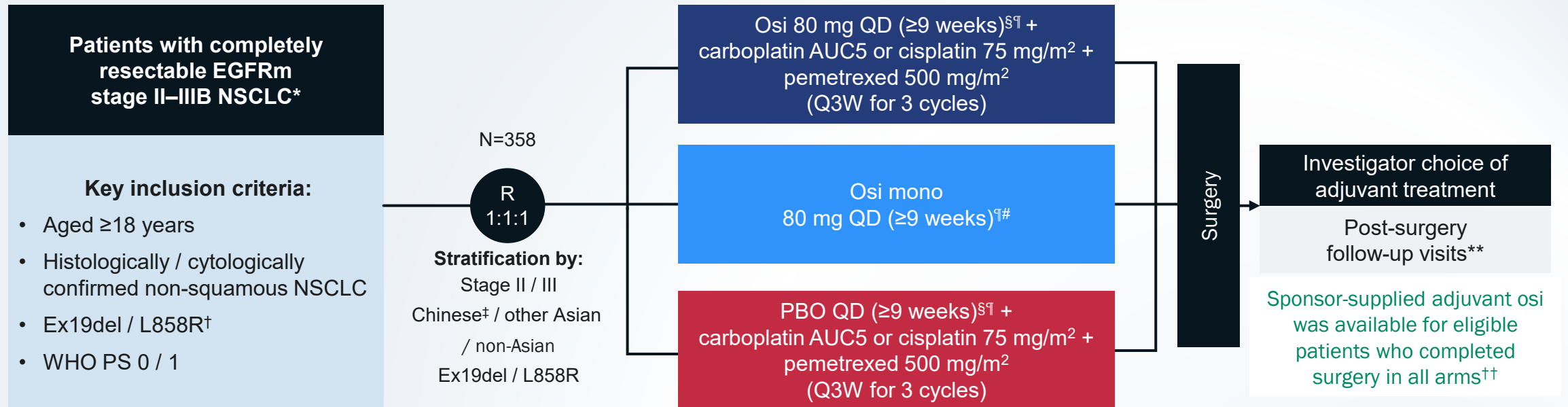
	Ensartinib (n=103)	Placebo (n=102)
Median follow-up	24.0 months	24.0 months
Events	12 (11.7%)	46 (45.1%)
Median DFS, months (95% CI)	NE (NE, NE)	24.8 (22.2, NE)
DFS HR (95% CI)	0.20 (0.11, 0.38), p<0.0001	

Investigator-assessed DFS



	Ensartinib (n=137)	Placebo (n=137)
Median follow-up	22.2 months	22.1 months
Events	12 (8.8%)	48 (35.0%)
Median DFS, months (95% CI)	NE (NE, NE)	24.8 (22.2, NE)
DFS HR (95% CI)	0.20 (0.10, 0.37), p<0.0001	

NEOADAURA: Randomized Phase 3 Study



Endpoints:

- **Primary: major pathological response (MPR; by blinded central pathology review)**
- **Secondary: event-free survival, pathological complete response, nodal downstaging and safety**

NCT04351555. Figure borrowed from "Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA", Tsuboi M et al. Published online July 19, 2021 in *Future Oncology* and reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd, <http://www.tandfonline.com>. The figure was adapted with permission from the authors.

*AJCC Staging Manual 8th edition. [†]Confirmed by sponsor pre-approved local or central tissue testing. [‡]Chinese living in mainland China. [§]Double-blind; [¶]Osi or PBO could be continued up to the date of surgery, at the discretion of the investigator. [#]Open-label, sponsor-blinded. ^{**}At weeks 12 and 24 post-surgery, then every 24 weeks until 5 years, and then every 48 weeks until disease recurrence or other withdrawal criteria were met. ^{††}Adjuvant osi could be given for a maximum 3-year treatment period, or until unacceptable toxicity or disease recurrence.

AJCC, American Joint Committee on Cancer; AUC, area under the curve; CTx, chemotherapy; del, deletion; EGFRm, epidermal growth factor receptor-mutated; Ex19del, Exon 19 deletion; mono, monotherapy; NSCLC, non-small cell lung cancer; osi, osimertinib; PBO, placebo; Q3W, once every 3 weeks; QD, once daily; R, randomization; WHO PS, World Health Organisation performance status

Baseline characteristics

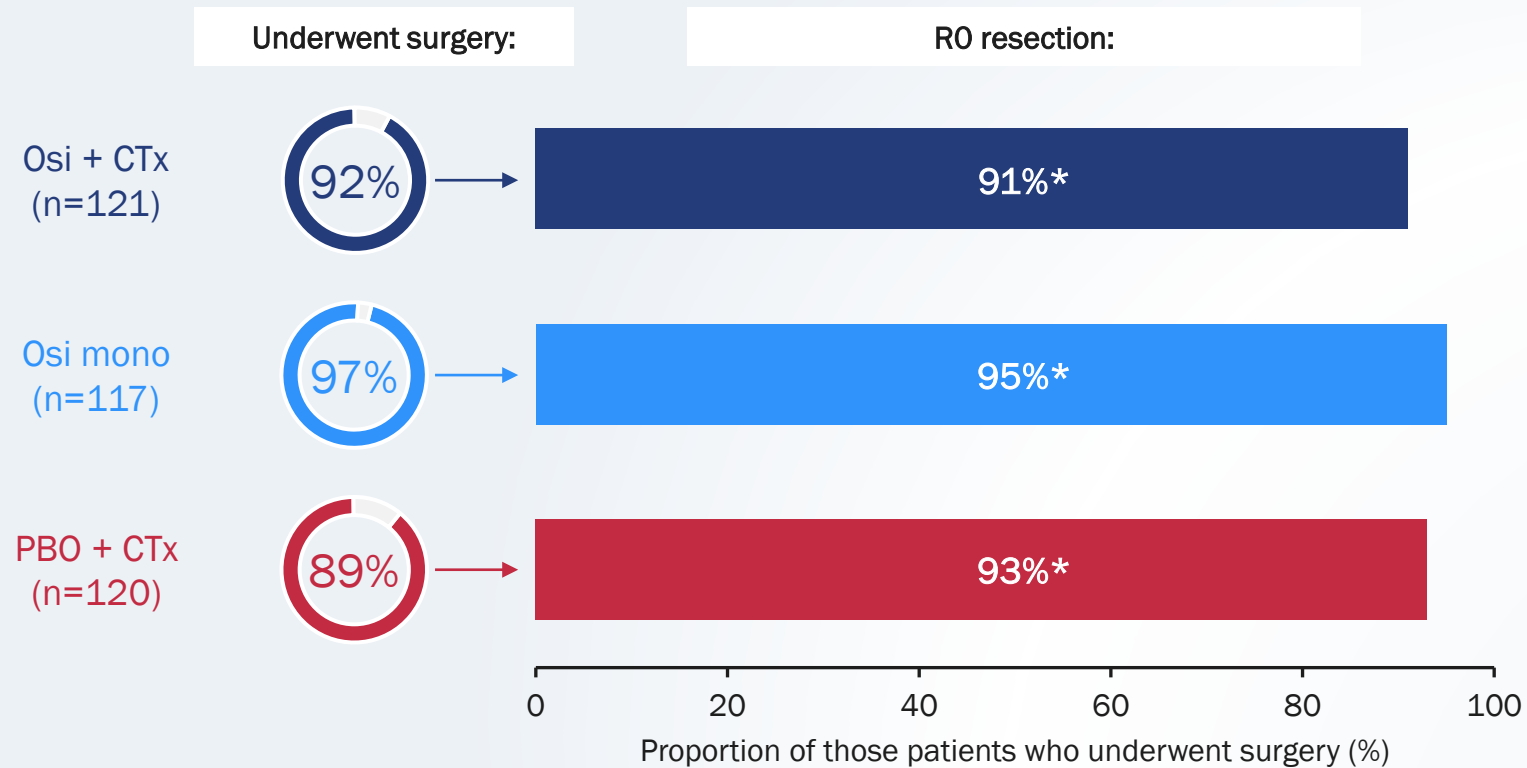
Characteristic, %	Osi + CTx (n=121)	Osi mono (n=117)	PBO + CTx (n=120)
Sex: male / female	40 / 60	35 / 65	25 / 75
Age: median (range), years	63 (31–82)	66 (42–83)	65 (36–86)
Smoking history: former or current / never	32 / 68	34 / 66	22 / 78
Race: * Chinese [†] / other Asian / non-Asian	24 / 49 / 27	23 / 50 / 26	26 / 49 / 25
WHO PS: 0 / 1	80 / 20	79 / 21	83 / 17
Histology: adenocarcinoma / other	98 / 2	100 / 0	100 / 0
EGFR mutation at randomization: * Ex19del / L858R	50 / 50	51 / 49	51 / 49
AJCC staging (8th edition) at diagnosis: * II / III	49 / 51	50 / 50	51 / 49
Regional lymph nodes: N0 / N1 / N2	26 / 35 / 39	26 / 38 / 35	29 / 37 / 34
Baseline tumor size, mean (SD), cm	4.2 (1.4)	4.0 (1.5)	4.3 (1.6)

Data cut-off: October 15, 2024.

*Reported by Investigators using interactive voice response. [†]Chinese living in mainland China.

AJCC, American Joint Committee on Cancer; CTx, chemotherapy; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; mono, monotherapy; osi, osimertinib; PBO, placebo; SD, standard deviation; WHO PS, World Health Organization performance status

Surgery summary



In each arm, **91%** of patients who completed surgery received sponsor-supplied adjuvant osi†

- SAEs causally related to surgery occurred in 10%, 5% and 7% of patients
- No patients died within 30 days post-surgery

*One patient in the osi + CTx arm, two patients in the osi mono arm and one patient in the PBO + CTx arm had missing R status data. One patient in the osi + CTx arm and one patient in the PBO + CTx arm had an R2 resection. †In addition to patients who received sponsor-supplied adjuvant osi, two patients in the osi + CTx arm, one patient in the osi mono arm and two patients in the PBO + CTx arm received commercial supplied osi.

Data cut-off: October 15, 2024.

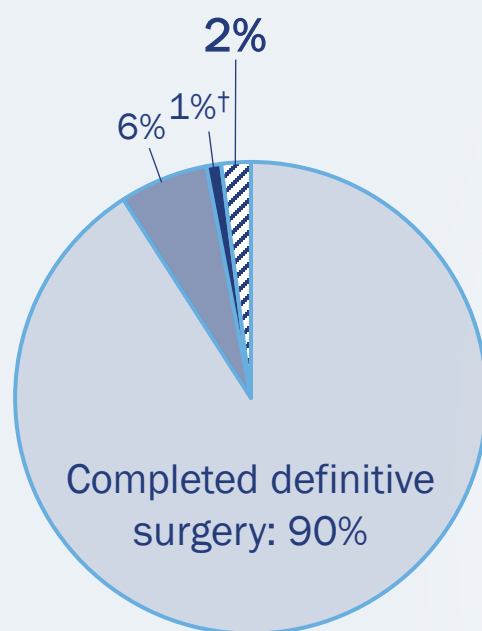
CTx, chemotherapy; mono, monotherapy; osi, osimertinib; PBO, placebo

Reasons for not undergoing or completing surgery

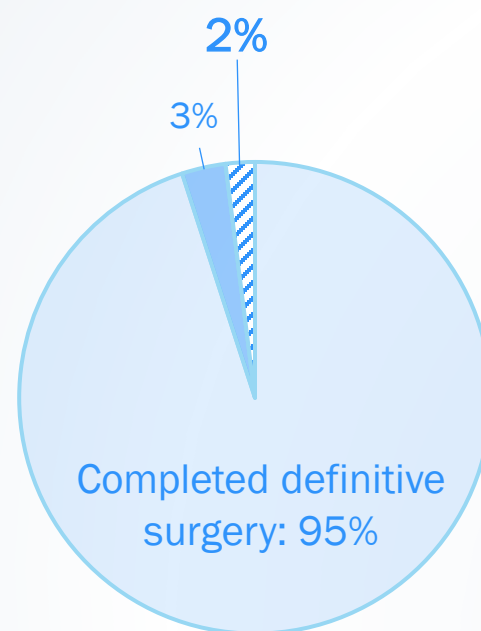
Fewer patients had progressive disease precluding definitive surgery with both osi-containing regimens

Reasons for not completing definitive surgery:

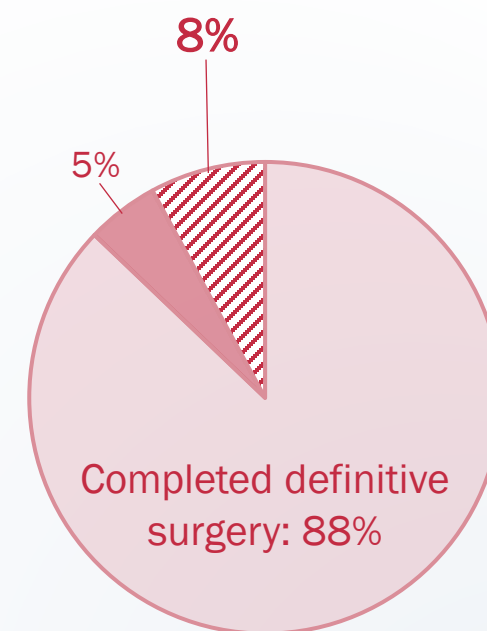
Other* AE Progressive disease



Osi + CTx
(n=121)



Osi mono
(n=117)



PBO + CTx
(n=120)

Data cut-off: October 15, 2024.

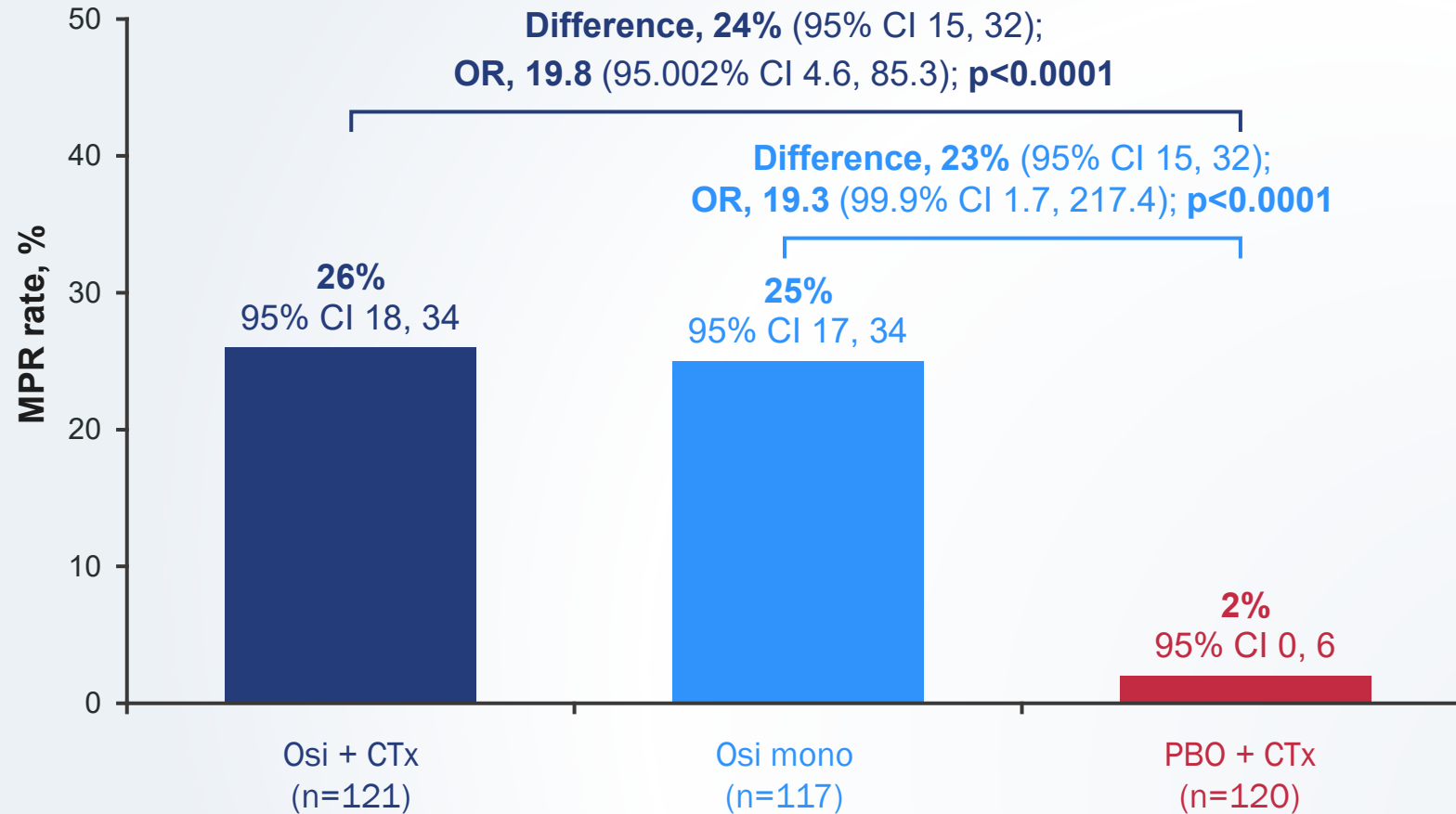
*Other includes patient decision, unfit for surgery, study discontinuation and other reason.

†One patient in Osi + CTx arm did not receive surgery due to Grade 3 thromboembolism causally related to carboplatin and pemetrexed.

MPR



The MPR rate was statistically significantly higher with both osi-containing regimens



MPR defined as $\leq 10\%$ residual viable tumor cells in the lung primary tumor at resection. Patients had to have an R0 result to be classified as responders. MPR assessed using the IASLC method. MPR was analyzed using the Cochran-Mantel-Haenszel test stratified by disease stage (II vs III), race (Chinese vs other Asian vs non-Asian) and EGFR mutation type (Ex19del vs L858R).

Data cut-off: October 15, 2024.



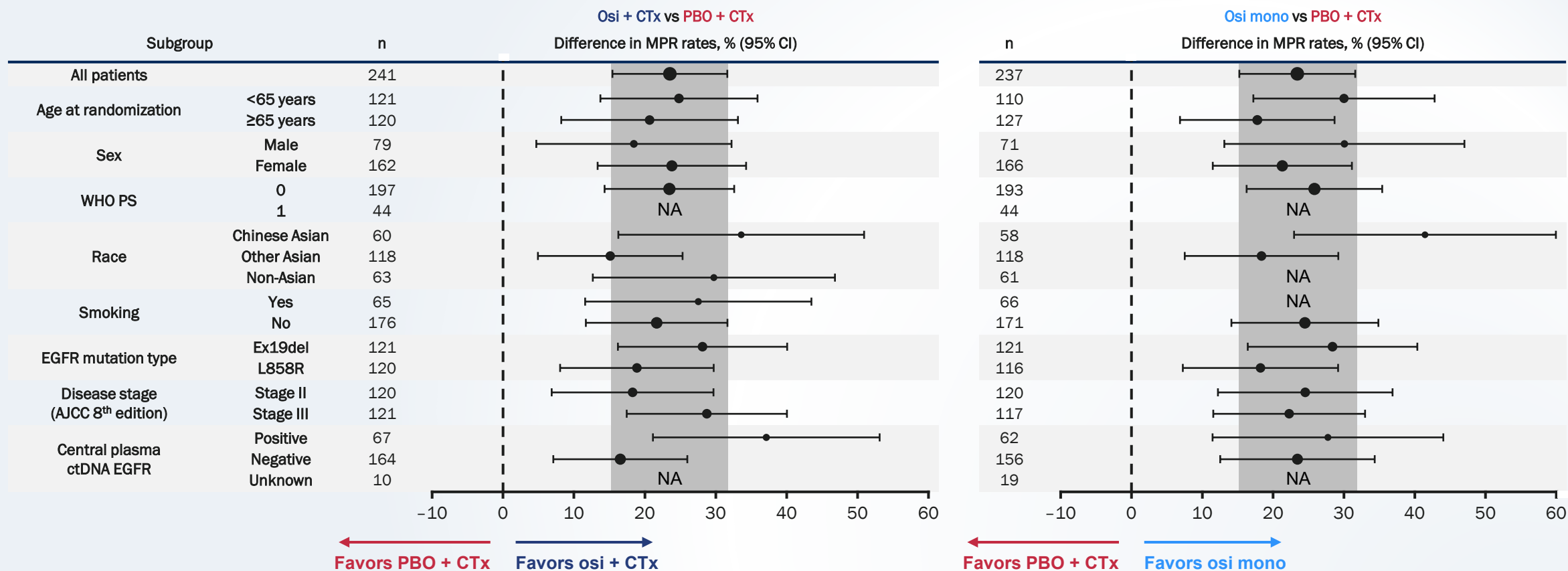
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MPR by subgroup



MPR benefit with the osi-containing regimens was consistent across predefined subgroups



Data cut-off: October 15, 2024.

MPR defined as ≤10% residual viable tumor cells in the lung primary tumor at resection. Patients had to have an R0 result to be classified as responders. MPR assessed using the IASLC method. The treatment difference in MPR rates with 95% CI was analyzed using the Cochran–Mantel–Haenszel test stratified by disease stage (II vs III), race (Chinese vs other Asian vs non-Asian) and EGFR mutation type (Ex19del vs L858R), the size of the data points is proportional to the number of patients in each subgroup, the horizontal bars represent the 95% CIs and shading indicates the difference in MPR rates and 95% CIs for the full analysis set (all randomized patients). Differences in the proportion of patients with an MPR between treatment groups was not calculated for subgroups with <10 responders across the two compared treatment arms.



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Dr. Jamie E. Chaff

AJCC, American Joint Committee on Cancer; CI, confidence interval; ctDNA, circulating tumor DNA; CTx, chemotherapy; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; mono, monotherapy; MPR, major pathological response; NA, not applicable; osi, osimertinib; PBO, placebo; WHO PS, World Health Organization performance status



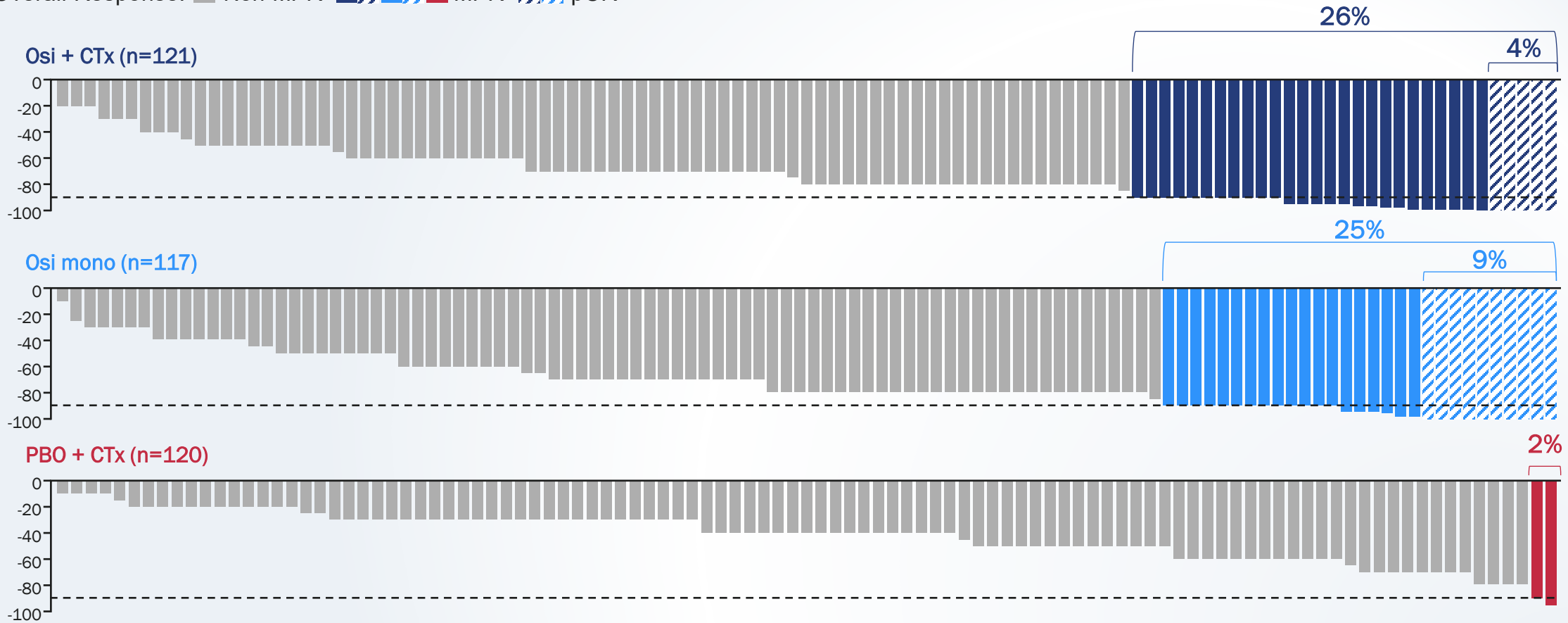
Depth of pathological response



Depth of pathological response was greater with the osi-containing regimens

Overall Response: ■ Non-MPR ■ MPR ■ pCR

Regression in tumor area with viable tumor cells (%)



Patients

Data cut-off: October 15, 2024.



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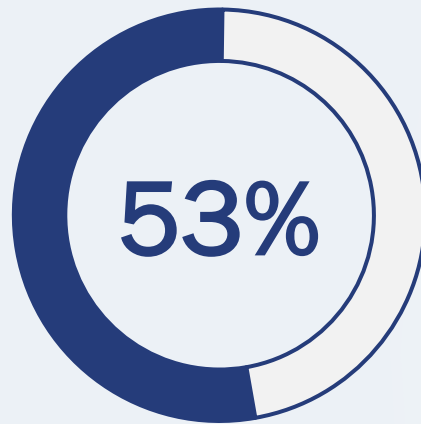
CTx, chemotherapy; mono, monotherapy; IASLC, International Association for the Study of Lung Cancer; MPR, major pathological response; osi, osimertinib; PBO, placebo



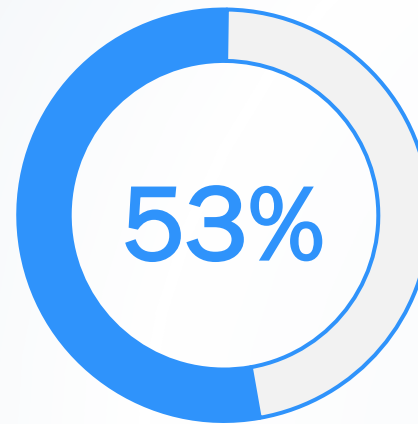
Nodal downstaging

Over 50% of patients with baseline N2 disease were down-staged at surgery with both osi-containing regimens

Osi + CTx
(n=47)



Osi mono
(n=38)



PBO + CTx
(n=34)

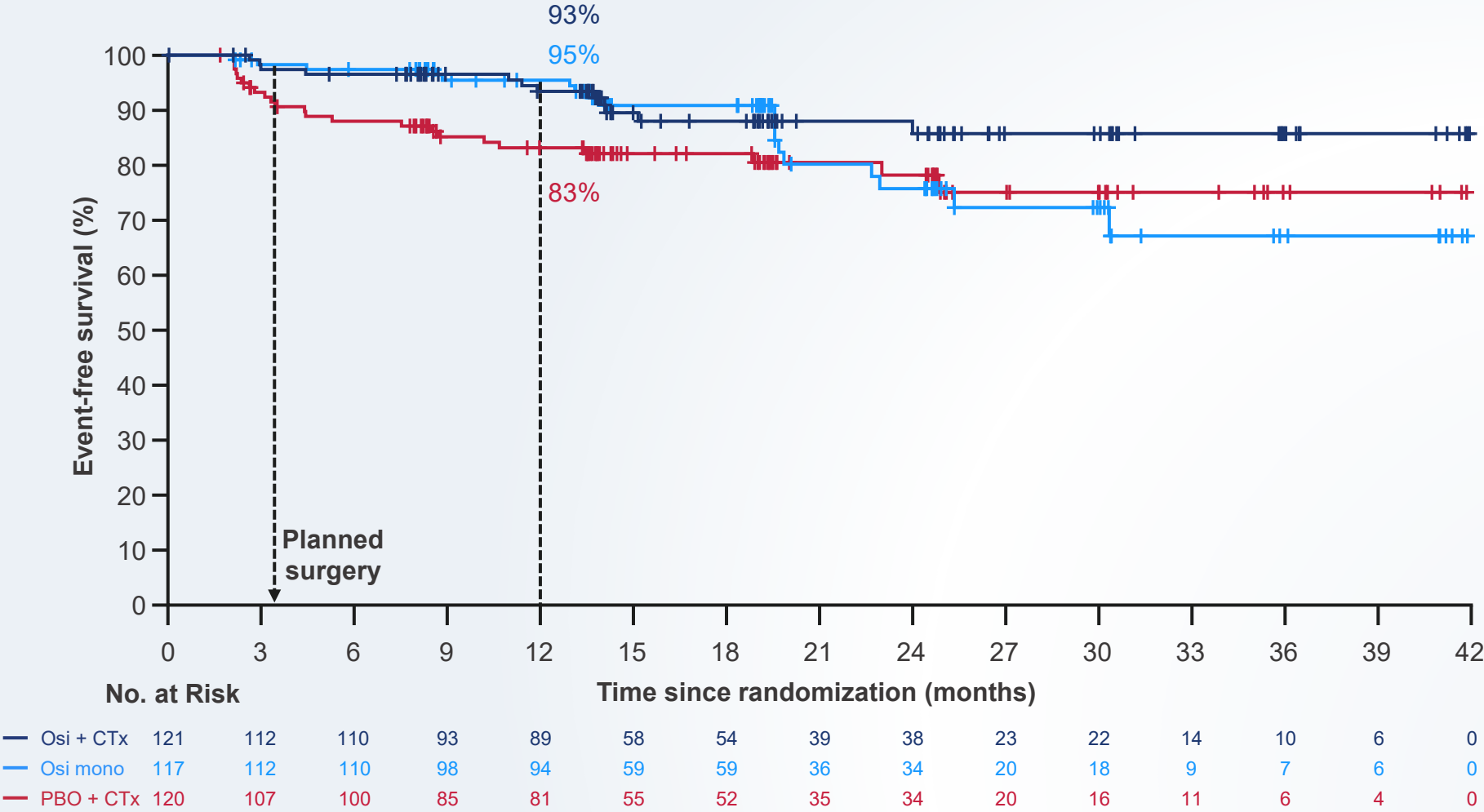


OR, 4.2 (95% CI 1.4, 12.1)

OR, 4.8 (95% CI 1.6, 14.0)

Nodal down-staging is summarized based on patients with N2 at baseline and an assessment at the time of surgery. ORs and CIs were analyzed using the Cochran–Mantel–Haenszel test stratified by disease stage (II vs III), race (Chinese vs other Asian vs non-Asian) and EGFR mutation type (Ex19del vs L858R).

Interim EFS analysis (15% maturity)



EFS HR vs PBO + CTx

Osi + CTx: **0.50**
(99.8% CI 0.17, 1.41); p=0.0382[†]

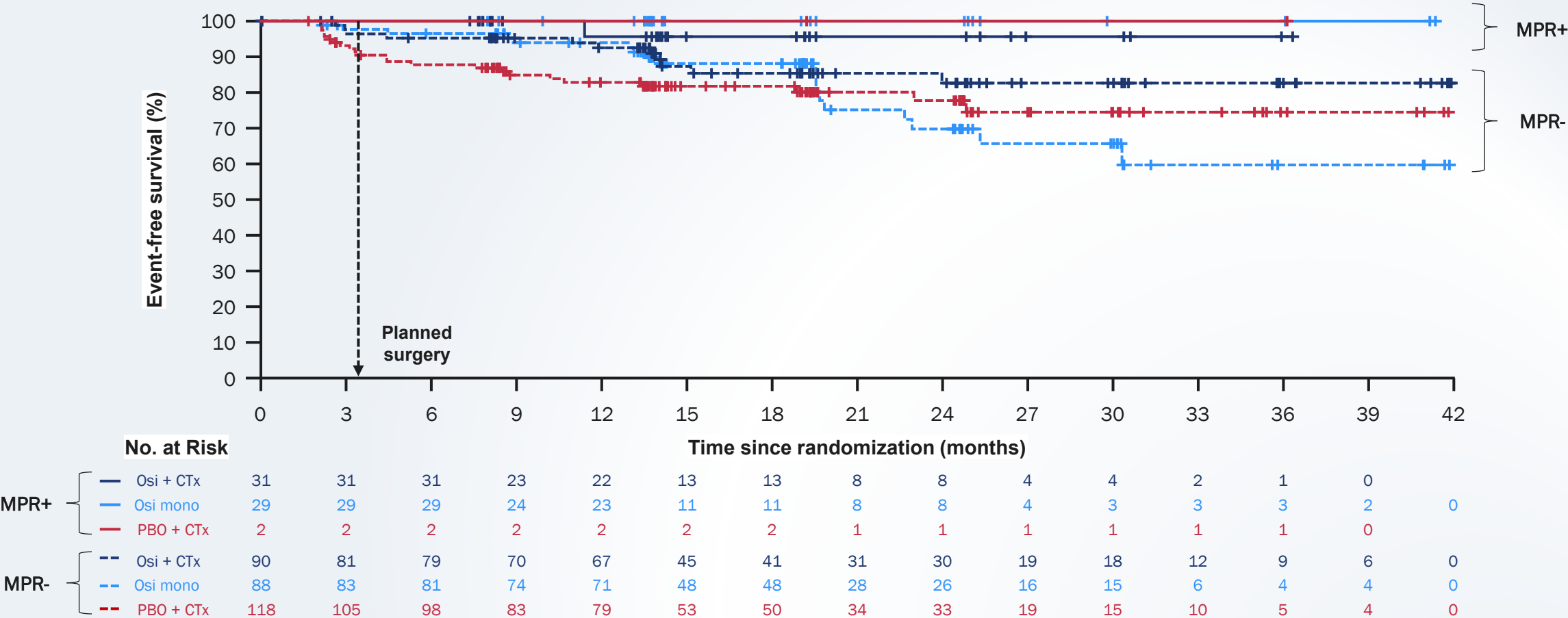
Osi mono: **0.73**
(95% CI 0.40, 1.35)[†]

Median follow-up, months[‡]
osi + CTx 14.3, osi mono 18.3,
PBO + CTx 14.3

Tick marks indicate censored data. EFS was investigator assessed. Median follow-up for EFS (censored patients): osi + CTx 15.9 months, osi mono 18.3 months, PBO + CTx 18.8 months. EFS maturity: osi + CTx 10%, osi mono 15%, PBO + CTx 19%.

[†]EFS analysis performed using a log-rank test stratified by disease stage (II vs III), race (Chinese vs other Asian vs non-Asian) and EGFR mutation type (Ex19del vs L858R). p-value ≤0.002 required for statistical significance at interim analysis. [‡]No p-value calculated. The pre-specified sequential multiple testing procedure required a statistically significant improvement in EFS to be demonstrated for the comparison of osi + CTx vs PBO + CTx before formal testing for the comparison of osi mono vs PBO + CTx could be performed. [§]All patients.

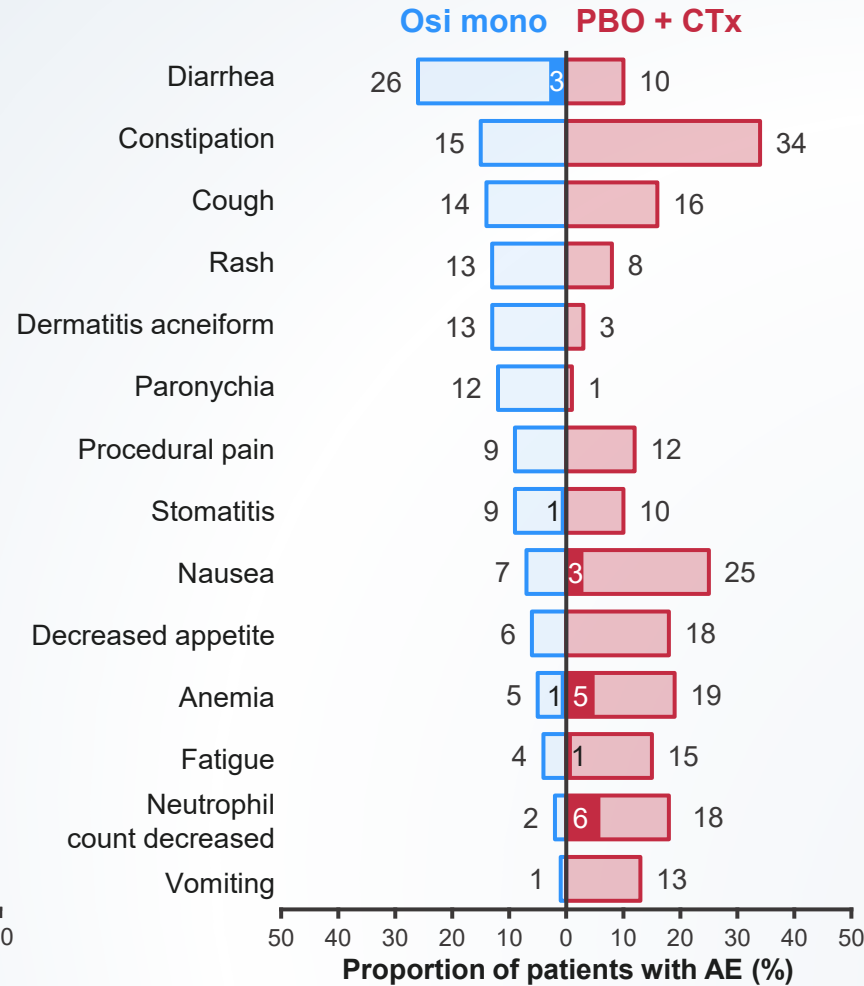
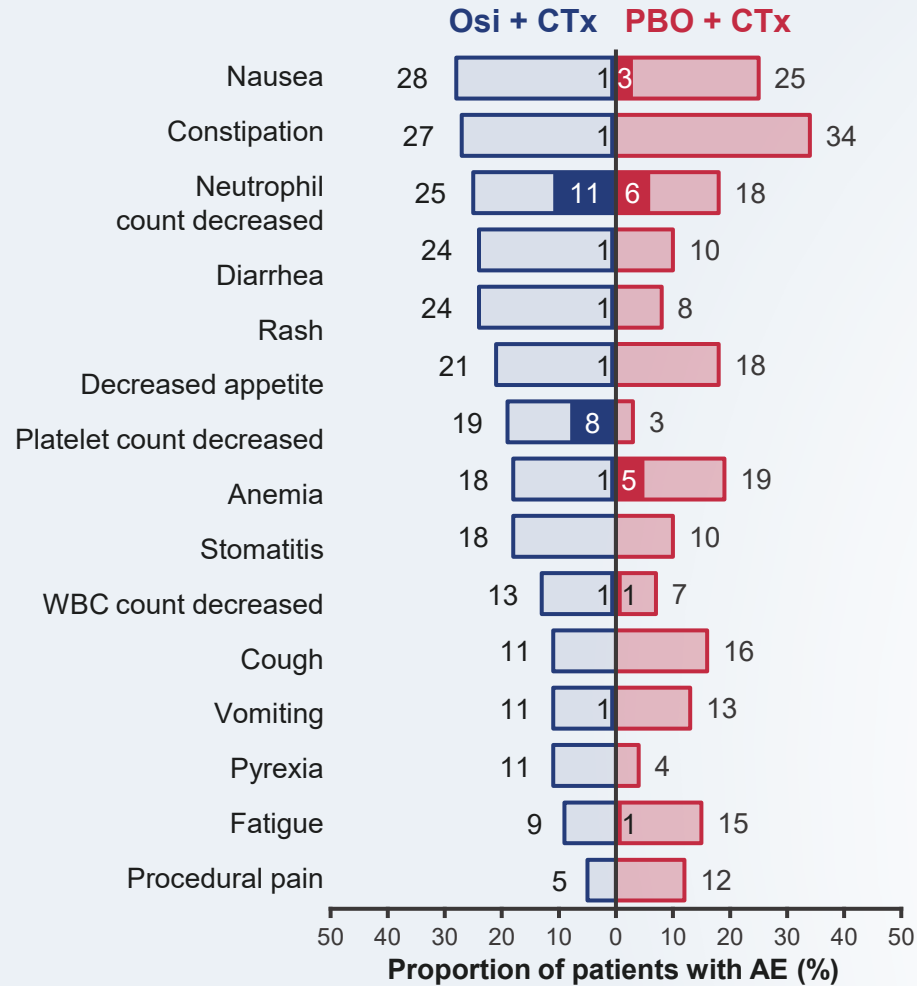
Interim EFS by MPR status



EFS events were reported in 2% (1/62) of patients with an MPR vs 18% (52/296) of patients without an MPR

Most common AEs* (neoadjuvant period)[†]

Safety findings were consistent with the known profiles of the individual agents



AESI, n (%)	Osi + CTx (n=119)	PBO + CTx (n=120)	Osi mono (n=117)
Wound complications	2 (2)	0	1 (1)
Cardiac effects	1 (1)	2 (2)	3 (3)
ILD / pneumonitis	0	0	2 (2)

- Osi + CTx, any grade
- Osi + CTx, max. grade ≥3
- PBO + CTx, any grade
- PBO + CTx, max. grade ≥3
- Osi mono, any grade
- Osi mono, max. grade ≥3

*AEs reported in ≥10% of patients in either treatment arm within the graphs presented. [†]The neoadjuvant analysis period is the time from the first dose to the minimum of: the date of last dose in the neoadjuvant period plus 28 days; the next treatment start date minus 1; the date of withdrawal of consent; or the date of death.

Dr Jamie E. Chaft

AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; CTx, chemotherapy; ILD, interstitial lung disease; osi, osimertinib; PBO, placebo; WBC, white blood cell



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67%

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24%

• osimertinib

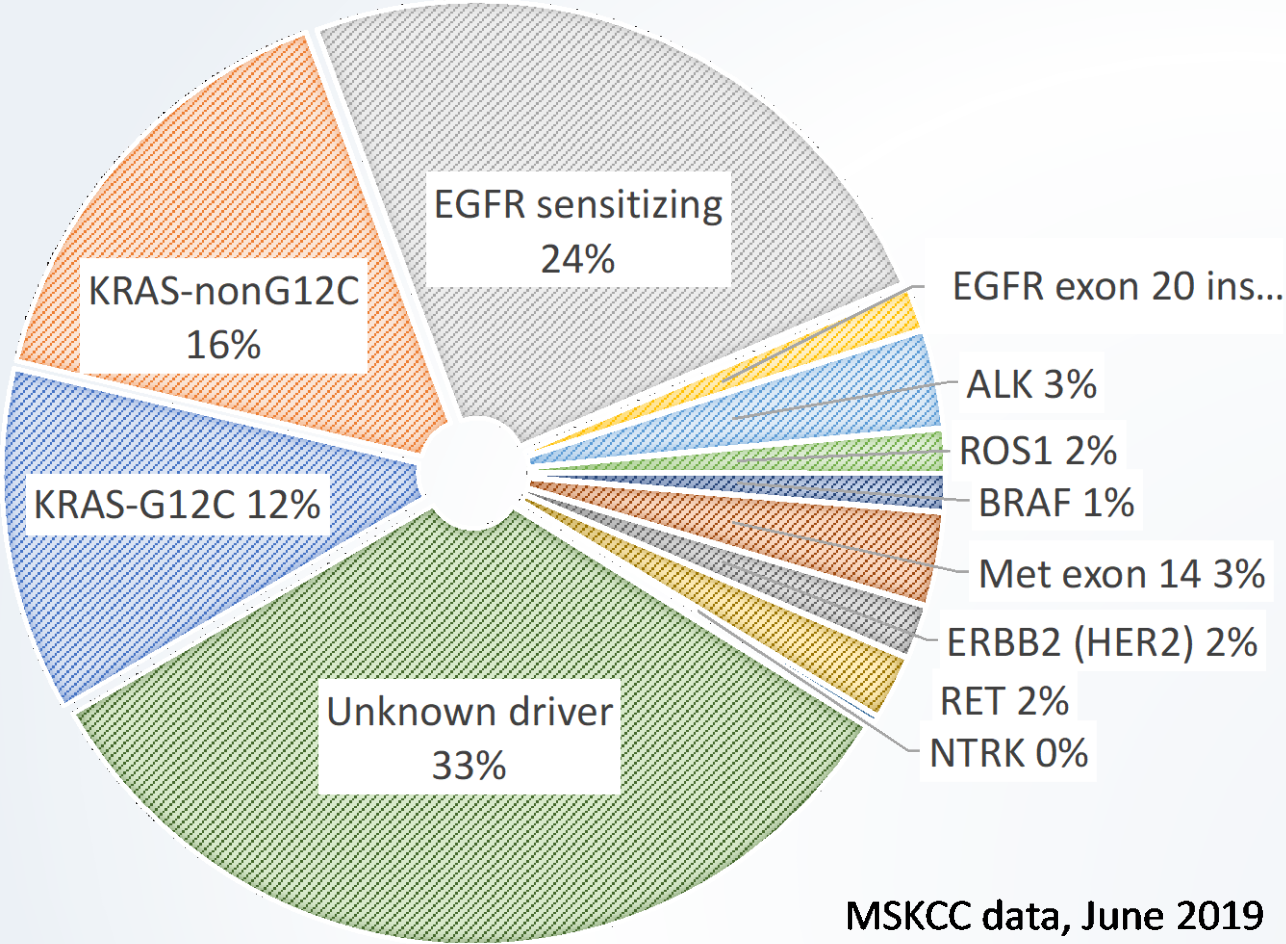
3%

• Alectinib

40%

unmet need

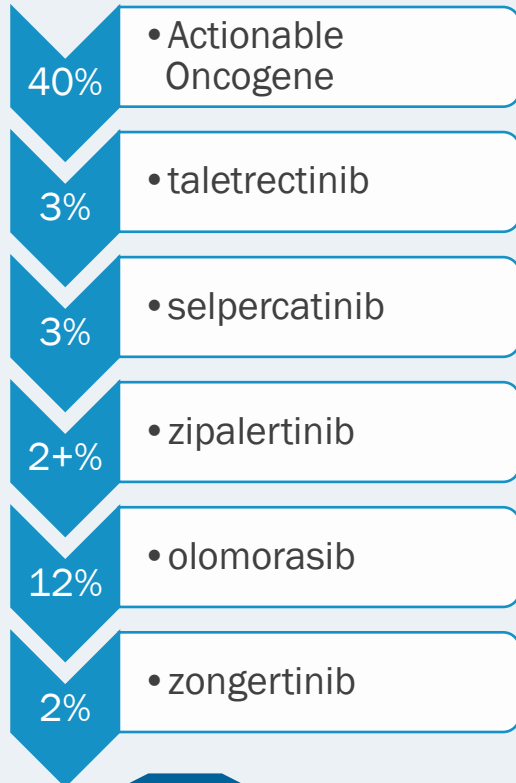
Adjuvant osimertinib



Adjuvant alectinib

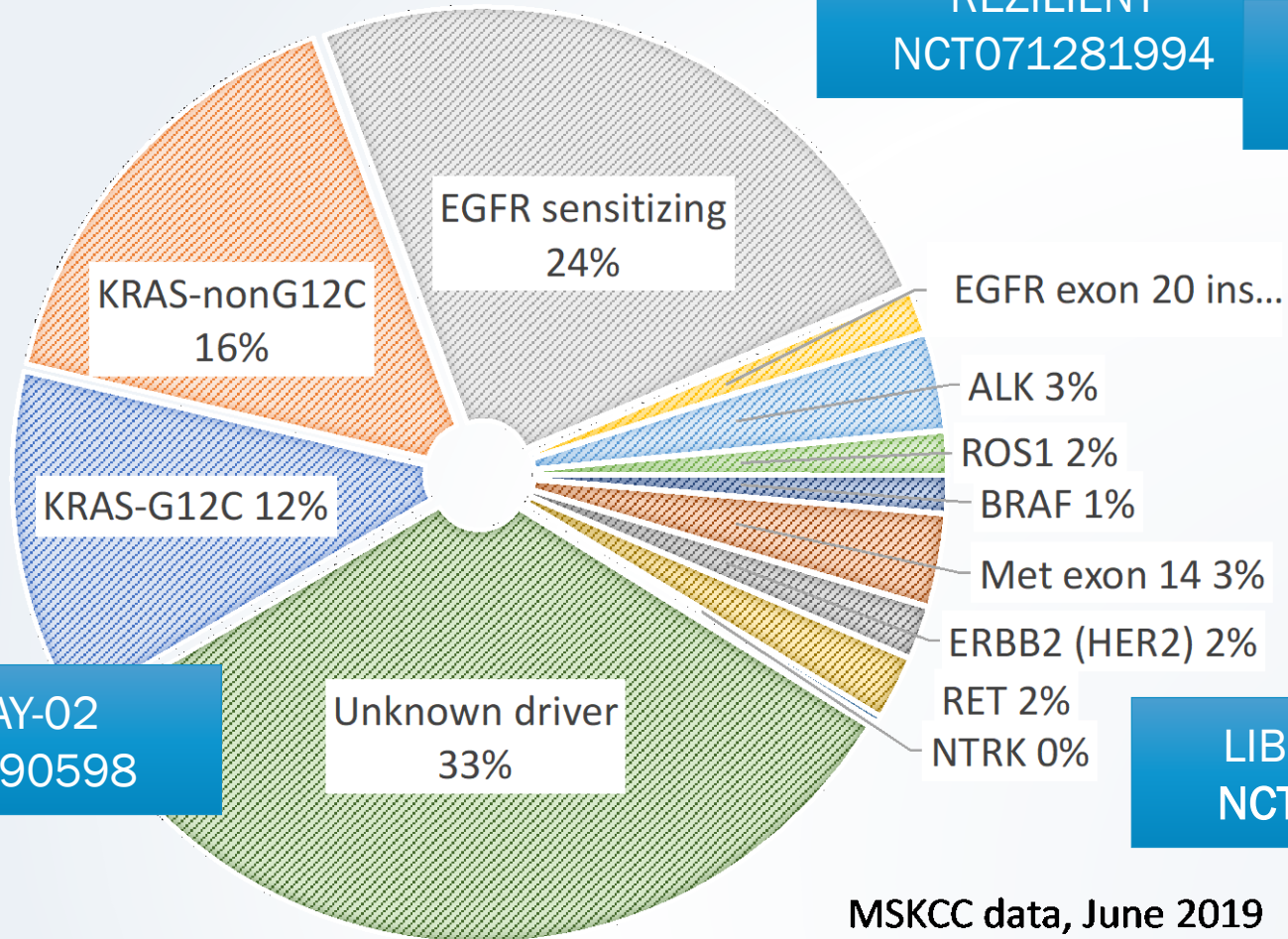
MSKCC data, June 2019

Future looking



18%
unmet
need

SUNRAY-02
NCT06890598



REZILIENT
NCT071281994

WU-KONG16
NCT071282682

ELEVATE

TRUST-IV
NCT07154706

BEAMION-Lung 3
NCT07195695

LIBRETTO-432
NCT04819100

MSKCC data, June 2019

Conclusions

- Targeted Therapy is available for $>1/4$ of patients with resected St II-III adenocarcinoma
 - Osimertinib for classic EGFR+ ≥ 3 cm or LN+
 - Alectinib for ALK+ ≥ 4 cm or LN+
- Neoadjuvant Osimertinib is reasonable for patients with resectable EGFR+ NSCLC appropriate for neoadjuvant therapy
- Many studies are forthcoming to address other populations of patients with resectable oncogene driven lung cancers
 - EGFR Exon 20
 - ROS1+
 - RET+
 - KRAS G12C

