NeoADAURA : EGFR 변이 비소세포폐암 치료 패러다임의 재정립

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연세-유일한 폐암 연구소
Yonsei New Il Han Institute for Integrative Lung Cancer Research

CANCER CARE TEAM AWARD from IASLC 2023

Paving an Unprecedented Road for Patients

Disclosures

- Research funding: Yuhan, Johnson and Johnson, MSD
- Consulting role: Amgen, AstraZeneca, Boehringer Ingelheim, Lilly, Takeda, J Ints Bio, BMS, MSD, Oscotec, Merck, Therapex, Yuhan
- Stock ownership: None
- Research support to institution: Amgen, AstraZeneca, Boehringer Ingelheim, BioNTech, GSK, Roche, Hengrui, Daichii-Sankyo, Johnson and Johnson, J Ints Bio, Therapex, Yuhan

Unmet needs

- Neoadjuvant chemoimmunotherapy is an option for resectable NSCLC
- More effective neoadjuvant treatment is required to complete surgery and derive survival benefit in resectable, EGFR-mutant NSCLC
- The Phase 3 NeoADAURA study explored whether neoadjuvant osi +/- chemotherapy can further improve pathological, surgical, and long-term outcomes in resectable, EGFR-mutant stage II-IIIB NSCLC

Adjuvant osimertinib improves DFS and OS

DFS benefit

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Osimertinib is standard-of-care therapy for previously untreated epidermal growth factor receptor (*EGFR*) mutation–positive advanced non–small-cell lung cancer (NSCLC). The efficacy and safety of osimertinib as adjuvant therapy are unknown.

METHODS

In this double-blind, phase 3 trial, we randomly assigned patients with completely resected *EGFR* mutation–positive NSCLC in a 1:1 ratio to receive either osimertinib (80 mg once daily) or placebo for 3 years. The primary end point was disease-free survival among patients with stage II to IIIA disease (according to investigator assessment). The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, and safety.

RESULTS

A total of 682 patients underwent randomization (339 to the osimertinib group and 343 to the placebo group). At 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% confidence interval [CI], 84 to 93) and 44% of those in the placebo group (95% CI, 37 to 51) were alive and disease-free (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001). In the overall population, 89% of the patients in the osimertinib group (95% CI, 85 to 92) and 52% of those in the placebo group (95% CI, 46 to 58) were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001). At 24 months, 98% of the patients in the osimertinib group (95% CI, 95 to 99) and 85% of those in the placebo group (95% CI, 80 to 89) were alive and did not have central nervous system disease (overall hazard ratio for disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Overall survival data were immature; 29 patients died (9 in the osimertinib group and 20 in the placebo group). No new safety concerns were noted.

CONCLUSIONS

In patients with stage IB to IIIA *EGFR* mutation–positive NSCLC, disease-free survival was significantly longer among those who received osimertinib than among those who received placebo. (Funded by AstraZeneca; ADAURA ClinicalTrials.gov number, NCT02511106.)

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*A complete list of the ADAURA investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Wu and Tsuboi contributed equally to this article.

This article was published on September 19, 2020, at NEJM.org.

N Engl J Med 2020;383:1711-23.
DOI: 10.1056/NEJMoa2027071

Wu Y-L et al. *N Engl J Med 2020*; 383:1711-1723.

OS benefit

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC

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ABSTRACT

BACKGROUND

Among patients with resected, epidermal growth factor receptor (*EGFR*)–mutated, stage IB to IIIA non–small-cell lung cancer (NSCLC), adjuvant osimertinib therapy, with or without previous adjuvant chemotherapy, resulted in significantly longer disease-free survival than placebo in the ADAURA trial. We report the results of the planned final analysis of overall survival.

METHODS

In this phase 3, double-blind trial, we randomly assigned eligible patients in a 1:1 ratio to receive osimertinib (80 mg once daily) or placebo until disease recurrence was observed, the trial regimen was completed (3 years), or a discontinuation criterion was met. The primary end point was investigator-assessed disease-free survival among patients with stage II to IIIA disease. Secondary end points included disease-free survival among patients with stage IB to IIIA disease, overall survival, and safety.

RESULTS

Of 682 patients who underwent randomization, 339 received osimertinib and 343 received placebo. Among patients with stage II to IIIA disease, the 5-year overall survival was 85% in the osimertinib group and 73% in the placebo group (overall hazard ratio for death, 0.49; 95.03% confidence interval [CI], 0.33 to 0.73; P<0.001). In the overall population (patients with stage IB to IIIA disease), the 5-year overall survival was 88% in the osimertinib group and 78% in the placebo group (overall hazard ratio for death, 0.49; 95.03% CI, 0.34 to 0.70; P<0.001). One new serious adverse event, pneumonia related to coronavirus disease 2019, was reported after the previously published data-cutoff date (the event was not considered by the investigator to be related to the trial regimen, and the patient fully recovered). Adjuvant osimertinib had a safety profile consistent with that in the primary analysis.

CONCLUSIONS

Adjuvant osimertinib provided a significant overall survival benefit among patients with completely resected, *EGFR*-mutated, stage IB to IIIA NSCLC. (Funded by AstraZeneca; ADAURA ClinicalTrials.gov number, NCT02511106.)

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*A complete list of the ADAURA investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Tsuboi and Herbst contributed equally to this article.

This article was published on June 4, 2023, at NEJM.org.

N Engl J Med 2023;389:137-47.
DOI: 10.1056/NEJMoa2304594

Tsuboi M, Herbst RS et al. N Engl J Med. 2023

Neoadjuvant osimertinib

Neoadjuvant Osimertinib for the Treatment of Stage I-IIIA Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: A Phase II Multicenter Study

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DOI https://doi.org/10.1200/JCO.24.00071

ABSTRACT

PURPOSE To assess the safety and efficacy of the third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor osimertinib as neoadjuvant therapy in patients with surgically resectable stage I-IIIA *EGFR*-mutated non–small cell lung cancer (NSCLC).

PATIENTS AND METHODS This was a multi-institutional phase II trial of neoadjuvant osimertinib for patients with surgically resectable stage I-IIIA (American Joint Committee on Cancer [AJCC] V7) *EGFR*-mutated (L858R or exon 19 deletion) NSCLC (ClinicalTrials.gov identifier: NCT03433469). Patients received osimertinib 80 mg orally once daily for up to two 28-day cycles before surgical resection. The primary end point was major pathological response (MPR) rate. Secondary safety and efficacy end points were also assessed. Exploratory end points included pretreatment and post-treatment tumor mutation profiling.

RESULTS A total of 27 patients were enrolled and treated with neoadjuvant osimertinib for a median 56 days before surgical resection. Twenty-four (89%) patients underwent subsequent surgery; three (11%) patients were converted to definitive chemoradiotherapy. The MPR rate was 14.8% (95% CI, 4.2 to 33.7). No pathological complete responses were observed. The ORR was 52%, and the median DFS was 40.9 months. One treatment-related serious adverse event (AE) occurred (3.7%). No patients were unable to undergo surgical resection or had surgery delayed because of an AE. The most common co-occurring tumor genomic alterations were in *TP53* (42%) and *RBM10* (21%).

CONCLUSION Treatment with neoadjuvant osimertinib in surgically resectable (stage IA-IIIA, AJCC V7) *EGFR*-mutated NSCLC did not meet its primary end point for MPR rate. However, neoadjuvant osimertinib did not lead to unanticipated AEs, surgical delays, nor result in a significant unresectability rate.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

Accepted April 28, 2024
Published July 19, 2024

J Clin Oncol 00:1-10

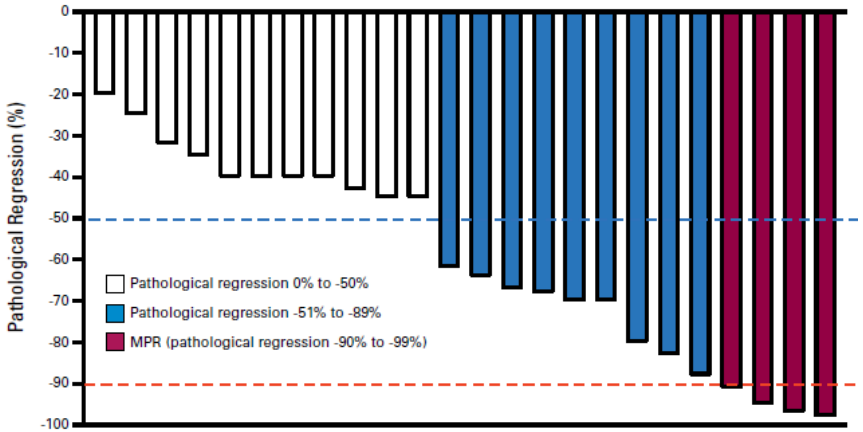
View Online Article

INTRODUCTION

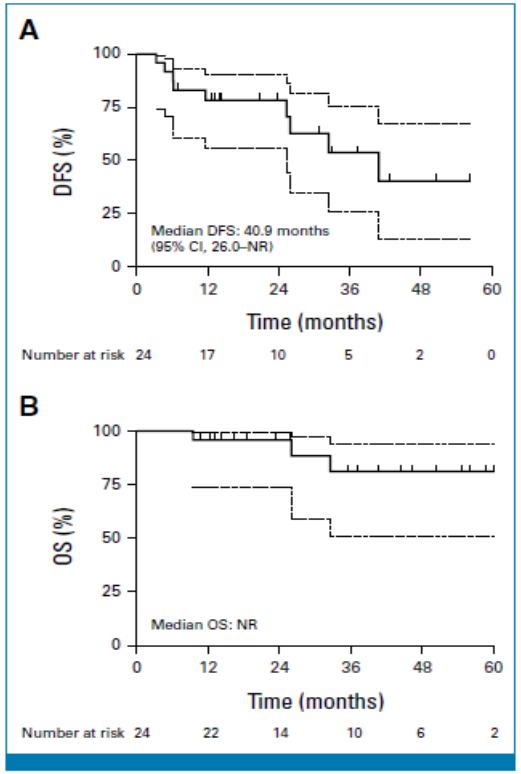
The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is the current standard first-line therapy for patients with metastatic non–small cell lung cancer (NSCLC) harboring an *EGFR* exon 21 p.L858R mutation or exon 19 deletion on the basis of the FLAURA trial showing superiority of osimertinib compared with earlier generation EGFR TKIs both in terms of progression-free survival (PFS) and overall survival (OS).[1,2] More recently, the ADUARA trial demonstrated that adjuvant treatment with osimertinib for up to 3 years after surgical resection improved both disease-free survival (DFS) and OS for patients with stage IB-IIIA EGFR-mutated (p.L858R or exon 19 deletion) NSCLC when compared with placebo.[3] Whether treatment with osimertinib before surgery (neoadjuvant) in patients with early-stage, surgically resectable *EGFR*-mutated NSCLC is safe or effective is unknown.

The potential benefits of neoadjuvant therapy for the treatment of NSCLC are (1) early exposure to systemic therapy to treat micrometastatic disease and (2) potential for shorter duration of treatment compared with adjuvant therapy.[4] Potential risks of neoadjuvant therapy include (1)

- To determine the major pathological response (MPR) for neoadjuvant osimertinib for stage IA-IIIA EGFR-mutated NSCLC

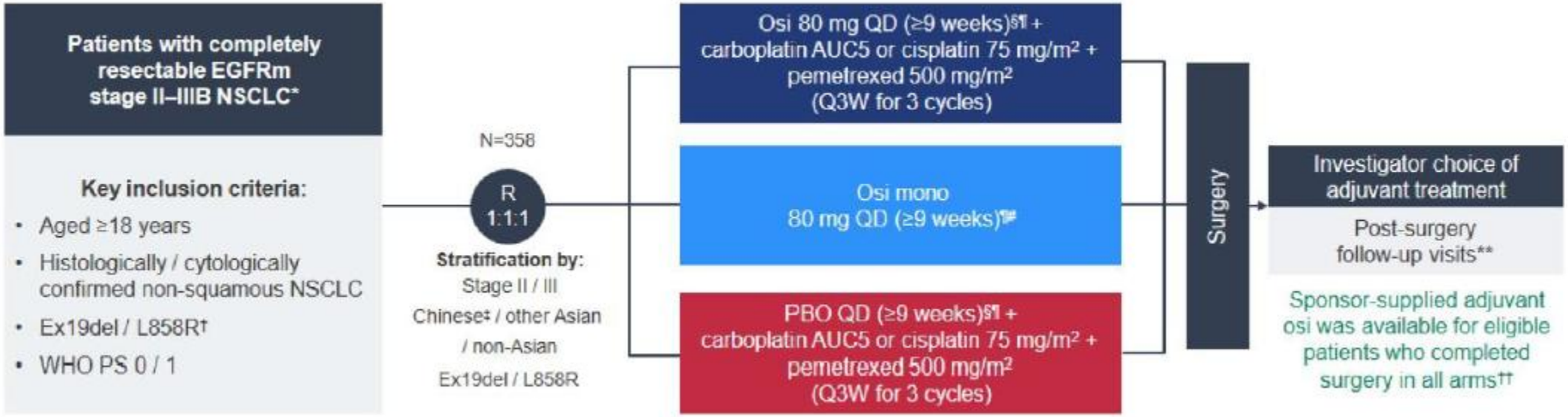


- MPR rate 14.8%
- No PCR
- Neoadjuvant osimertinib did not meet its primary endpoint for MPR rate



Blakely CM, et al. JCO 2024

NeoADAURA: global, randomized, phase 3 controlled study



Endpoints:

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

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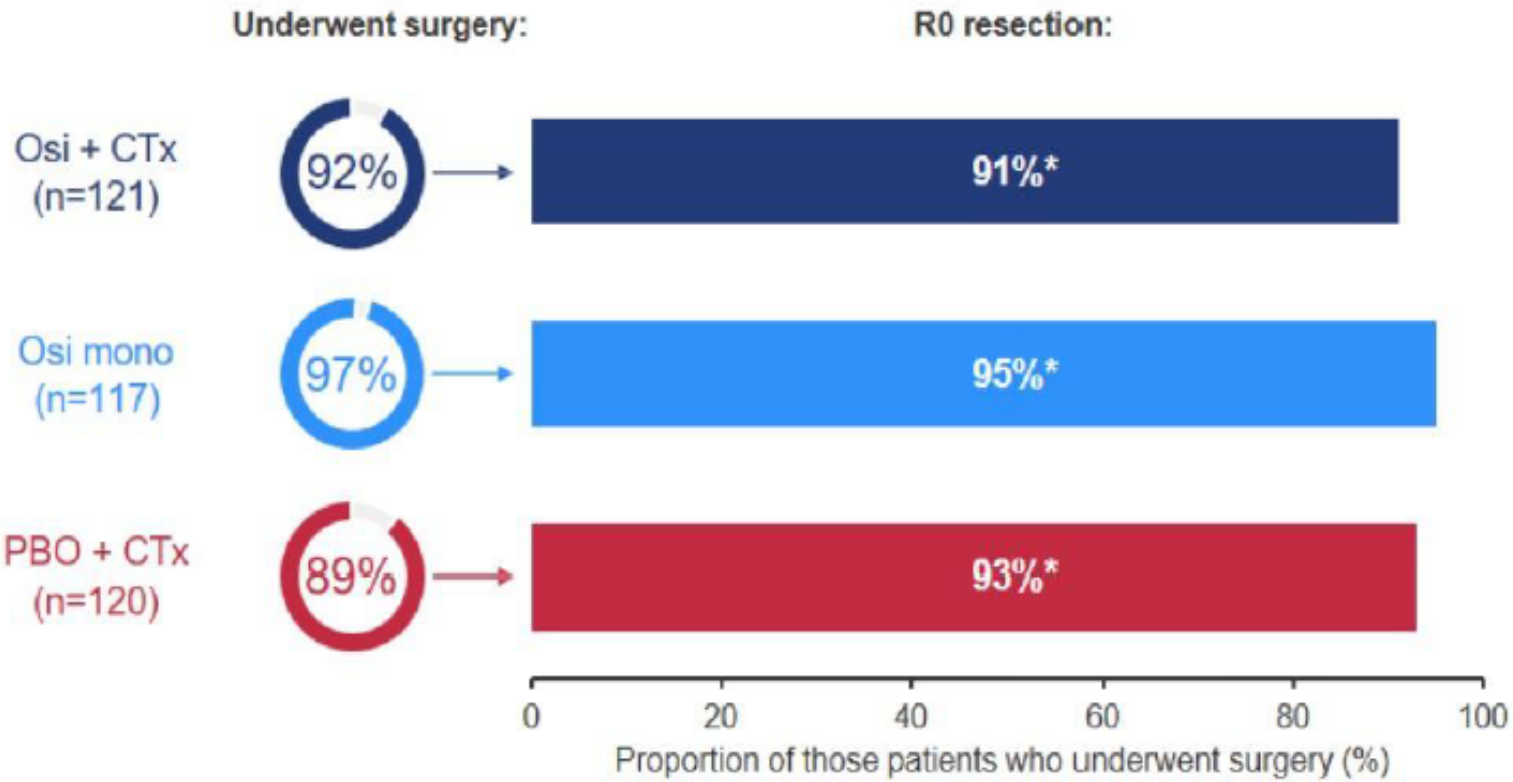
Baseline characteristics

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)

Surgery summary

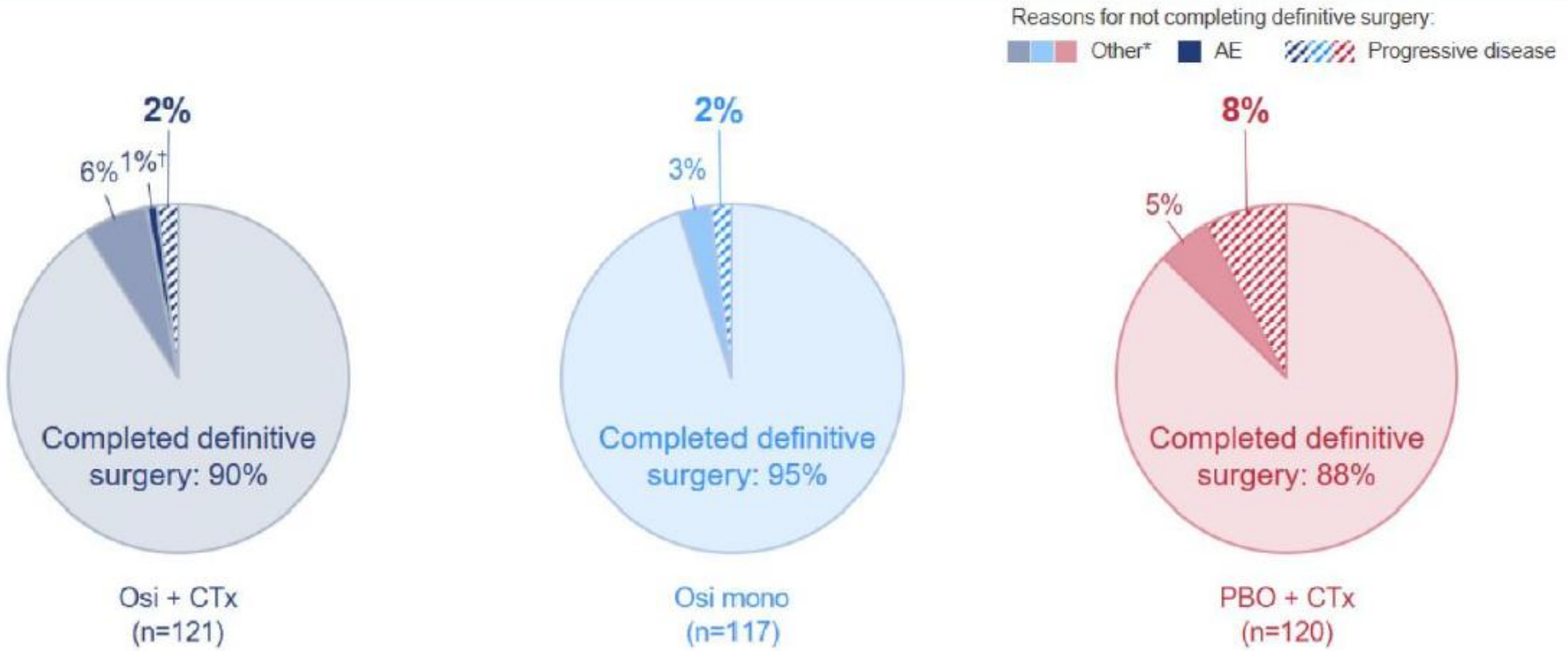


In each arm, **91%** of patients who completed surgery received sponsor-supplied adjuvant osi†

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

Reasons for not undergoing or completing surgery

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



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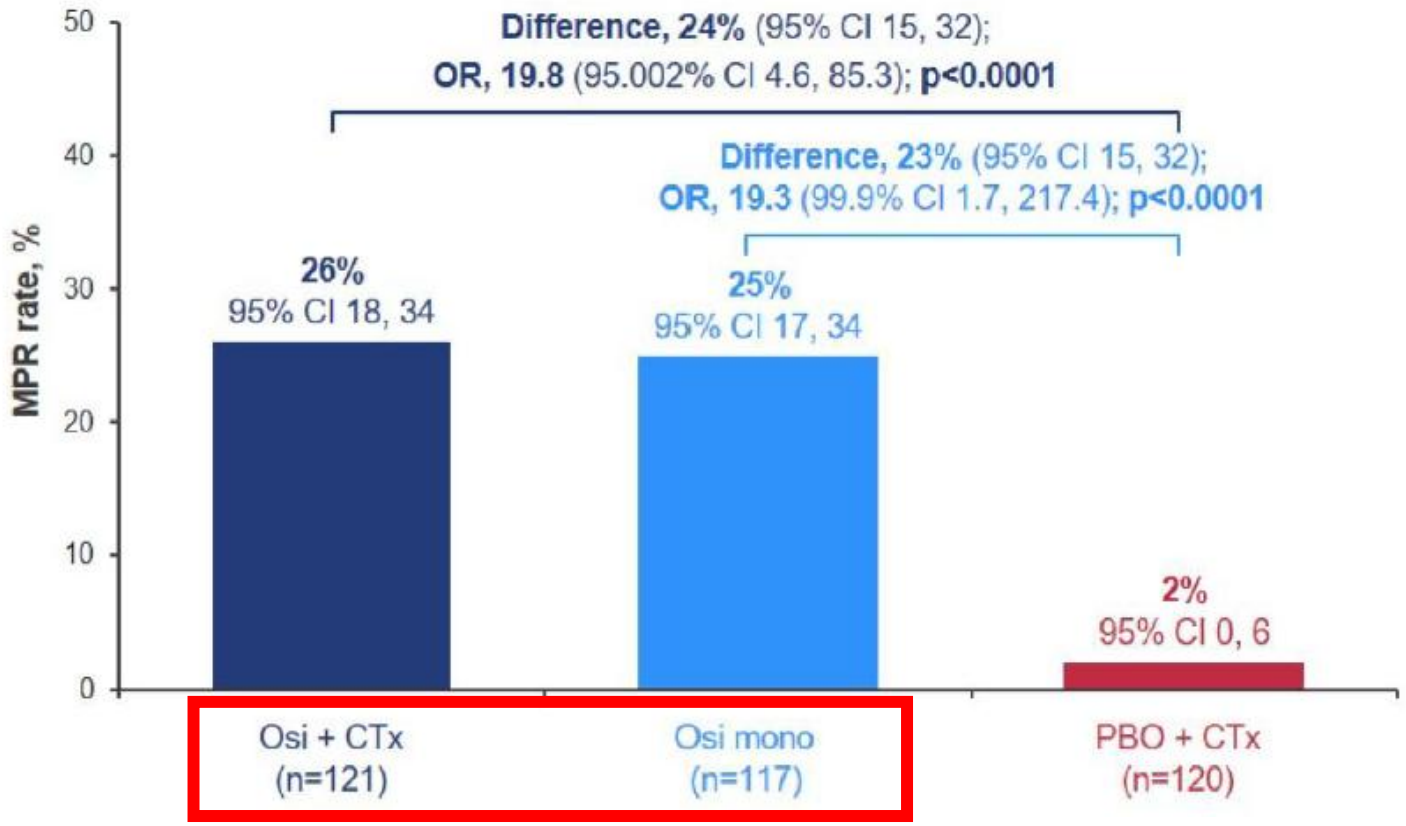
MPR

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



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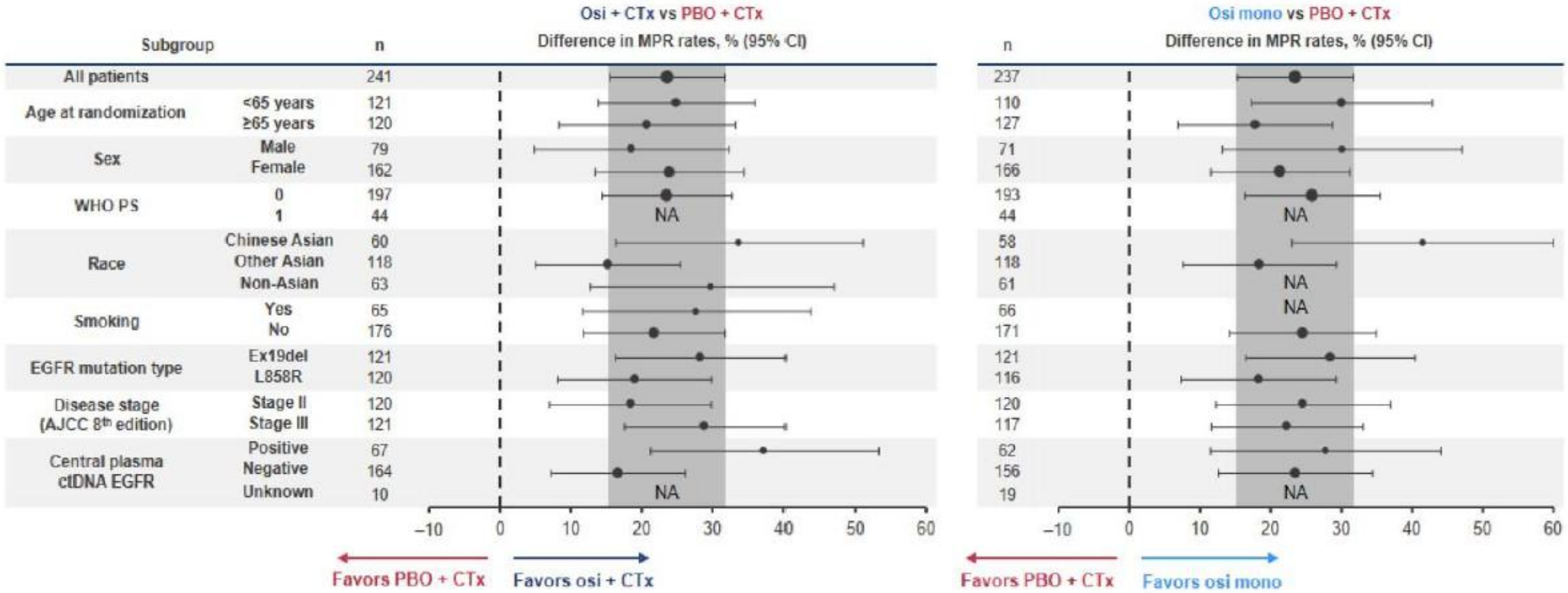
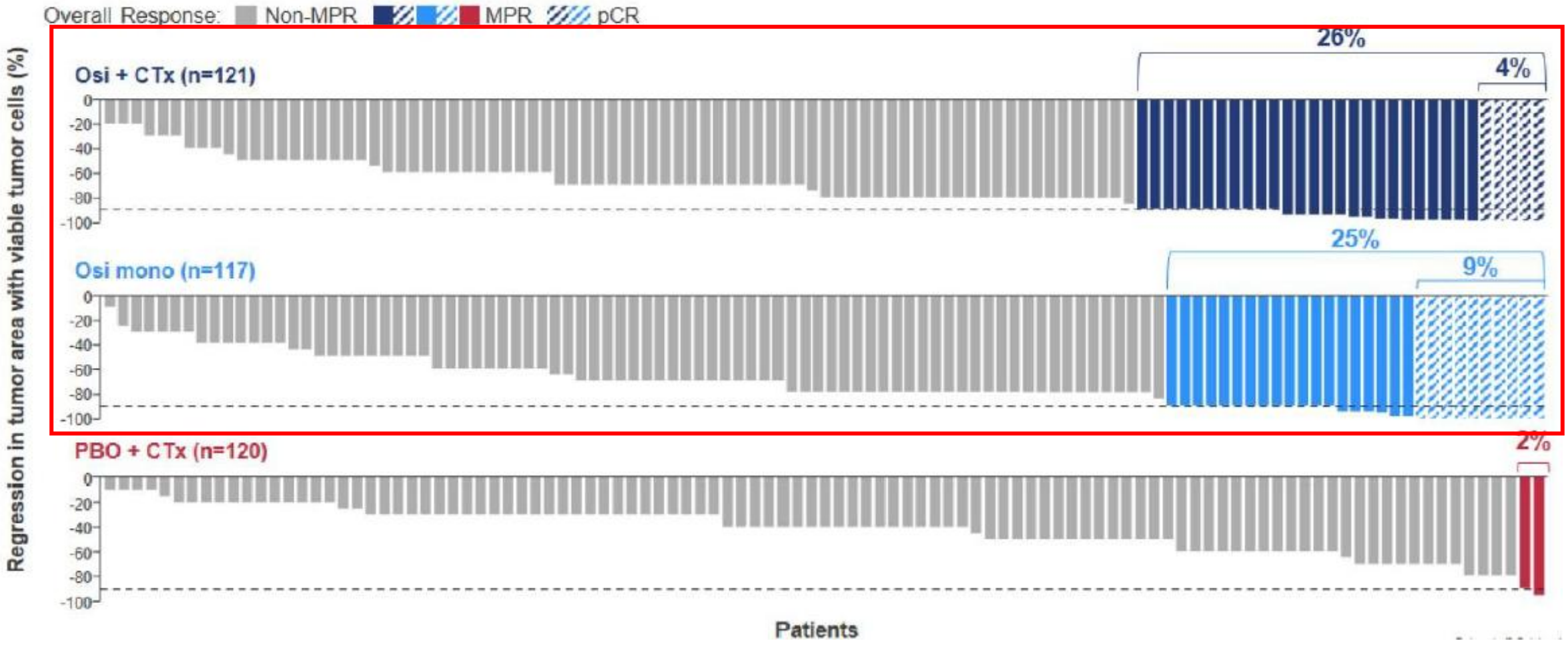
MPR by subgroup

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



Depth of pathological response



Depth of pathological response greater with osi+/- chemotherapy

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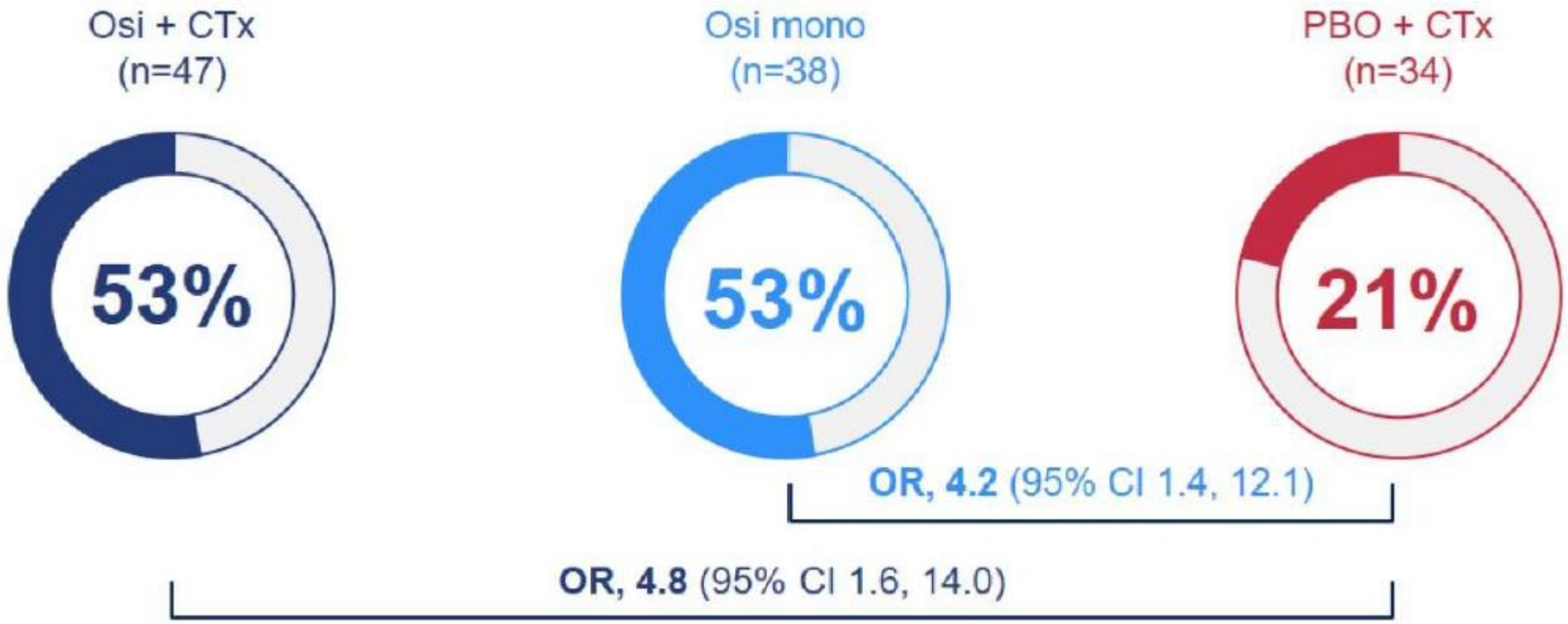
Nodal downstaging



In baseline N2 disease, over 50% of patients were downstaged at surgery with osi +/- chemotherapy

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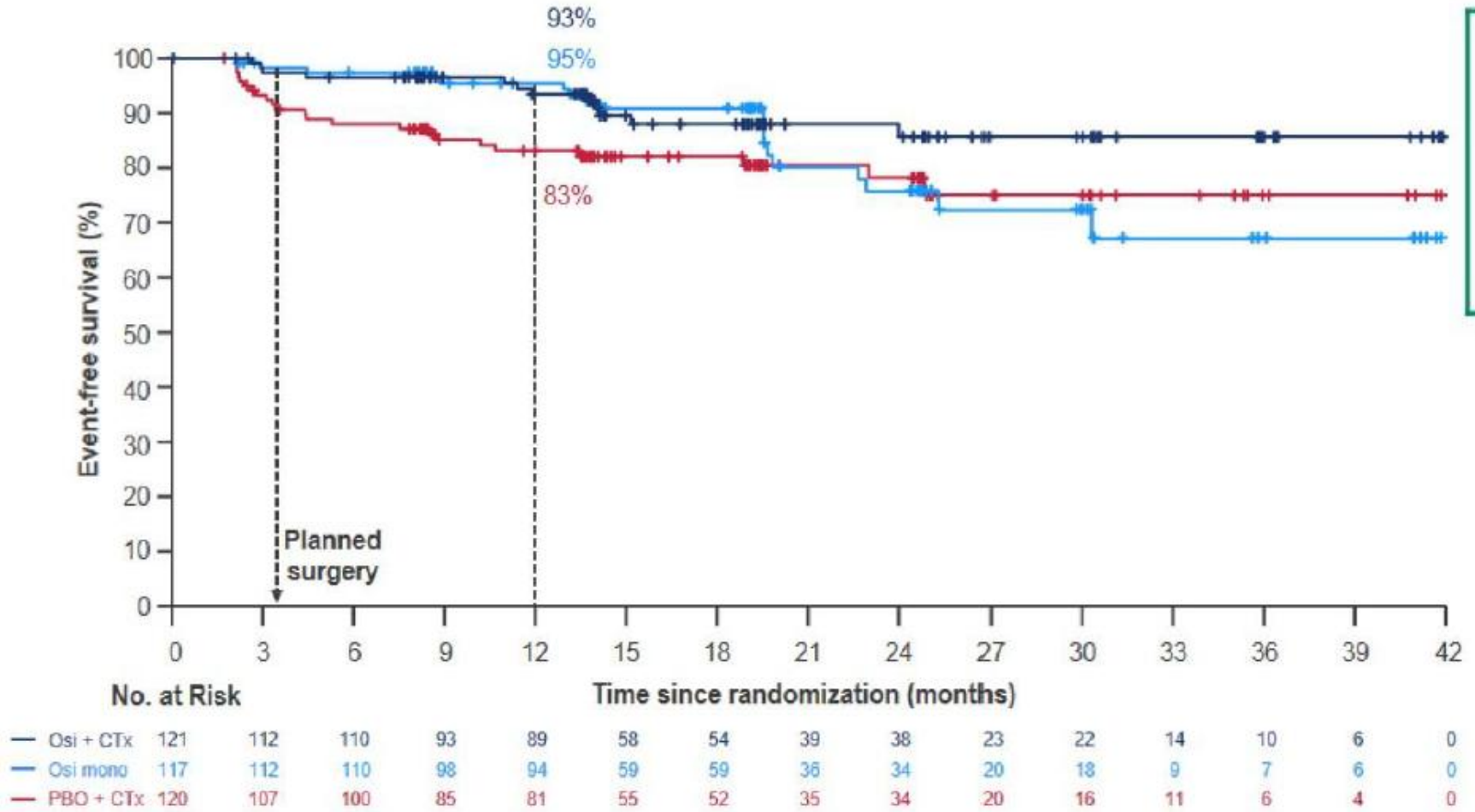
Interim EFS analysis (15% maturity)



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

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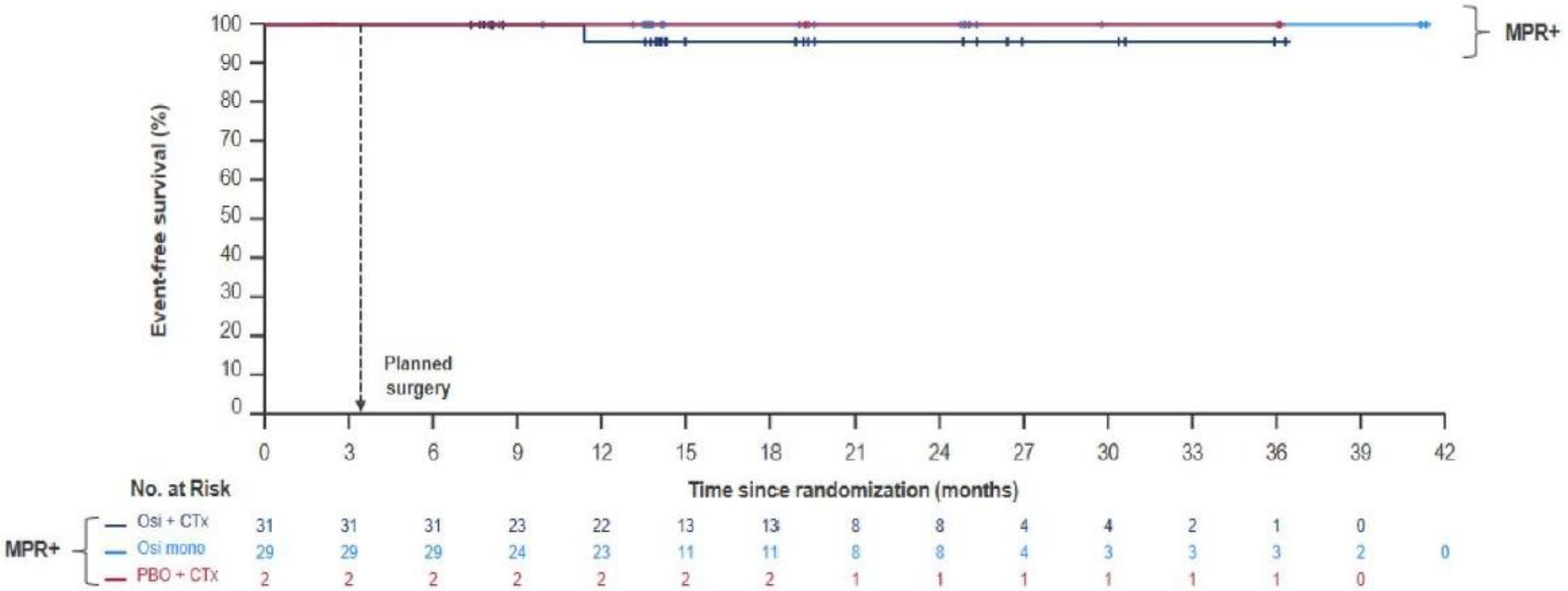
Interim EFS by MPR status



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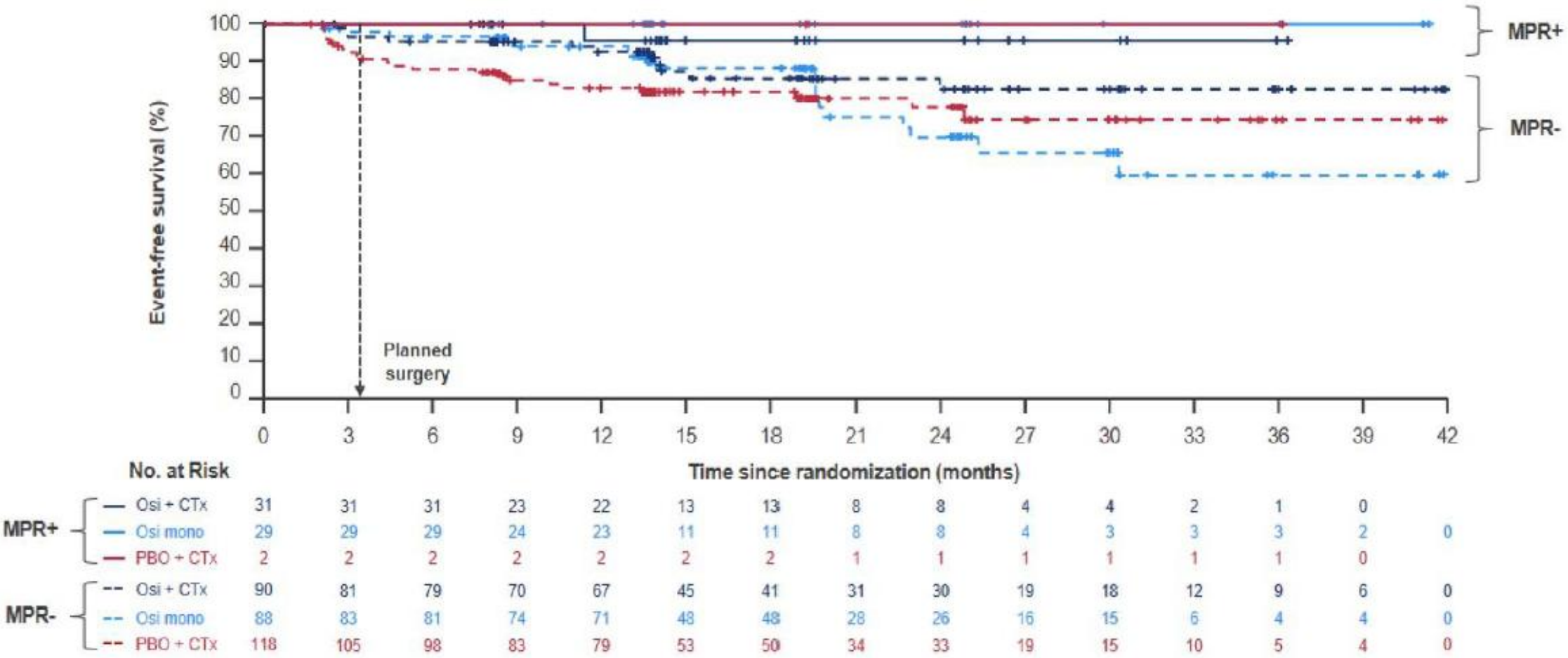
Interim EFS by MPR status



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

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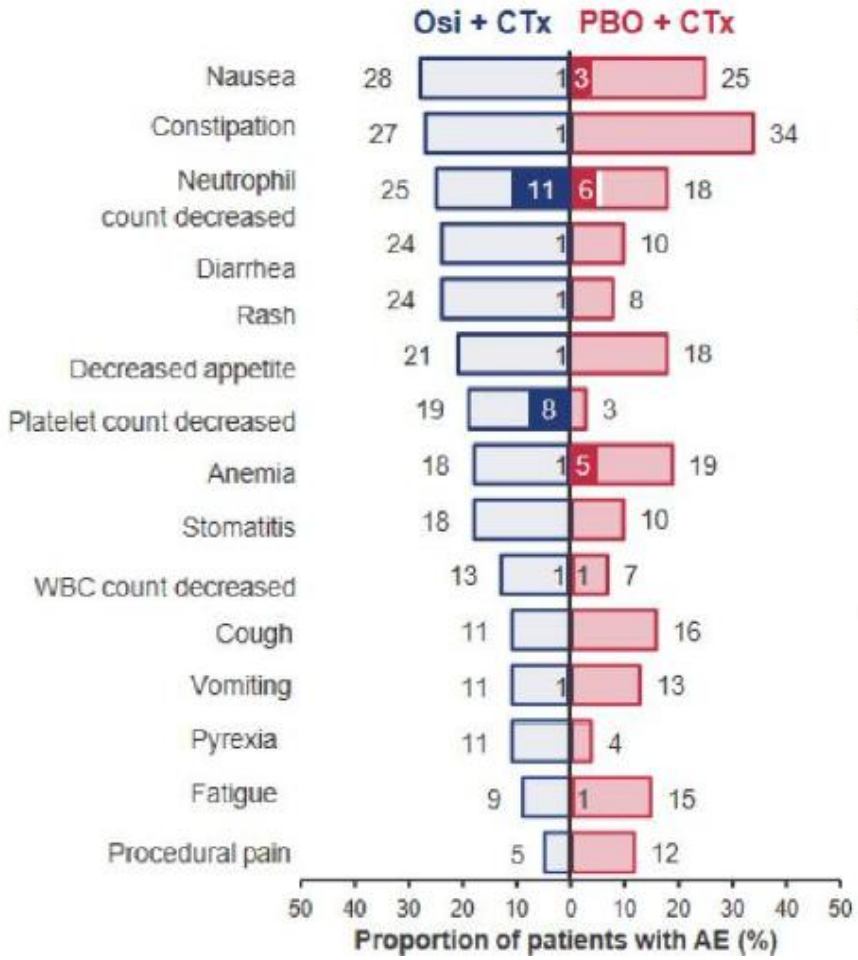
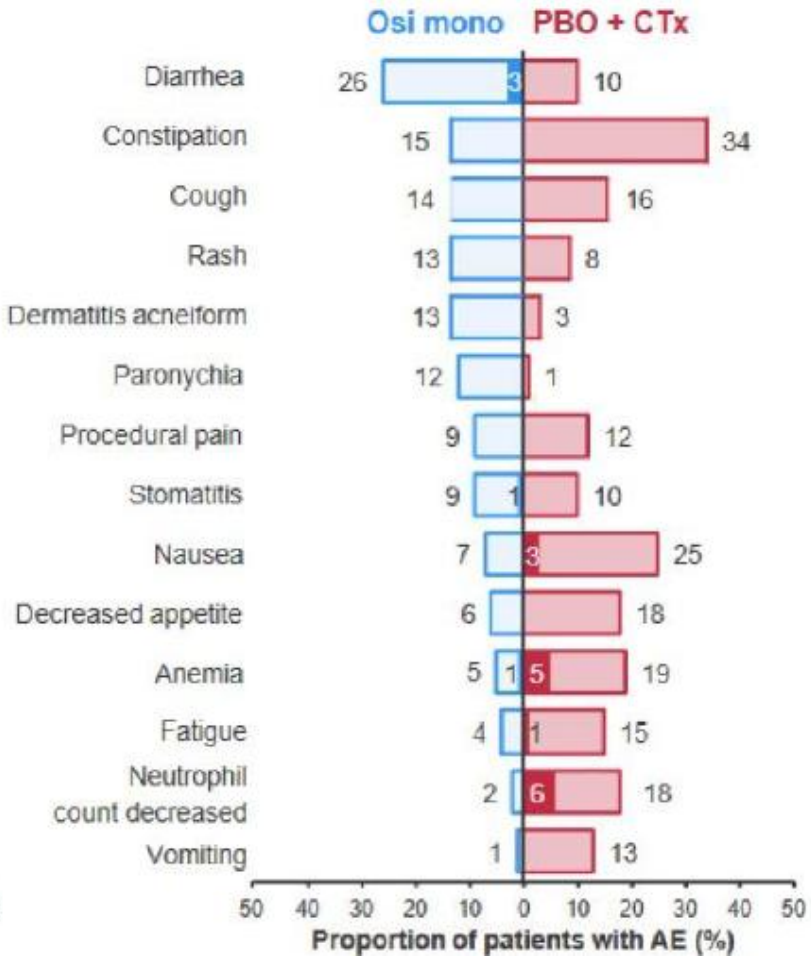
Most common AEs





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

Data cut-off: October 1

Presented by Jamie E Chaft at ASCO 2025

Conclusions

- Neoadjuvant osimertinib, with or without chemotherapy, demonstrated significantly improved MPR rates vs. chemotherapy alone in resectable, EGFRm, stage II-IIIB NSCLC
- Interim EFS favored osi-containing arms
- Over 50% of patients with baseline N2 disease were downstaged at surgery with osi-containing arms
- Safety findings were consistent with the known profiles

Neoadjuvant osimertinib, with or without chemotherapy, should be considered when planning treatment for patients with resectable EGFRm, stage II-IIIB NSCLC

PRINCIPLES OF PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors

Targeted Therapy Options

- **After surgical evaluation, consider osimertinib ± chemotherapy, with the option of single-agent osimertinib as adjuvant therapy after surgery, for patients with stage II–IIIA, IIIB (T2–T3, N2b; T4, N2) NSCLC that is positive for *EGFR* exon 19 deletion or L858R mutation;[5] Other Adjuvant Systemic Therapy**
  - **Chemotherapy options with osimertinib include:**
    - **Cisplatin/Pemetrexed (nonsquamous)**
    - **Carboplatin/Pemetrexed (nonsquamous)**

Chemotherapy Options

- **After surgical evaluation, patients with the following disease stages can be evaluated for the neoadjuvant chemotherapy regimens listed below if ineligible for immunotherapy or targeted therapy and are likely to receive adjuvant chemotherapy:**
  - **Stage IB, IIA (if high-risk features are present)[a]**
  - **Stage IIB, IIIA, IIIB (T2–T3, N2b; T4, N2)**

Preferred (nonsquamous)

- **Cisplatin/Pemetrexed[6]**

Preferred (squamous)

- **Cisplatin/Gemcitabine[7]**
- **Cisplatin/Docetaxel[8]**

Other Recommended

- **Cisplatin/Vinorelbine[9-11]**
- **Cisplatin/Etoposide[10]**

Useful in Certain Circumstances

- **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
  - **Carboplatin/Paclitaxel[12]**
  - **Carboplatin/Gemcitabine[13] (squamous)**
  - **Carboplatin/Pemetrexed[14] (nonsquamous)**

All chemotherapy-only regimens listed above can be used for sequential chemotherapy/RT.

PRINCIPLES OF PERIOPERATIVE SYSTEMIC THERAPY[b]

Other Adjuvant Systemic Therapy

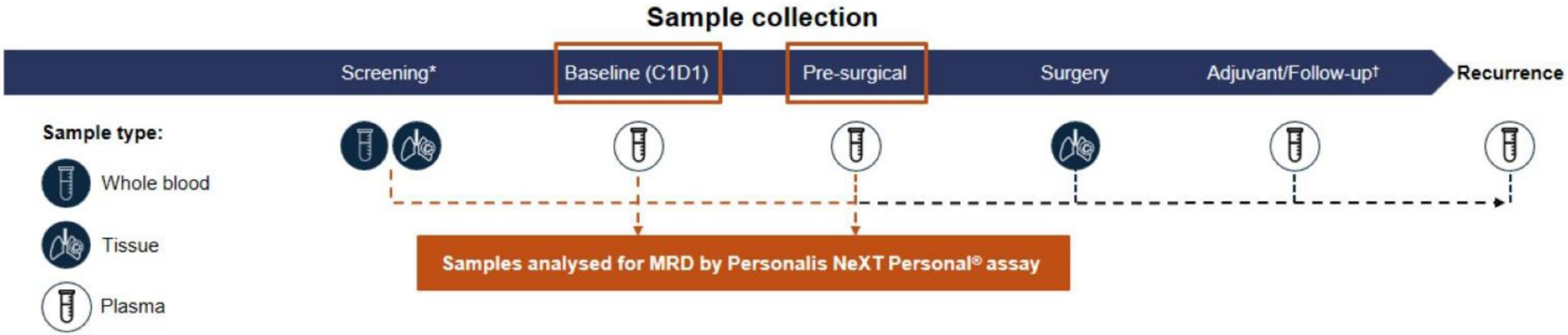
Targeted Therapy Options for Patients with Resected NSCLC

- Alectinib[15] (for patients with ≥4 cm or node-positive NSCLC stages IB–IIIA, IIIB [T2–T3, N2b; T4, N2], and positive for *ALK* gene fusions) (category 1).
- Osimertinib (for patients with NSCLC positive for *EGFR* exon 19 deletion or L858R mutation).
  - For patients with stage IB–IIIA, IIIB (T2–T3, N2b; T4, N2) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (category 1)[16]
  - For patients who received previous neoadjuvant Osimertinib ± chemotherapy[5]

Immune Checkpoint Inhibitor Options for Patients with Resected NSCLC Tumors

- Atezolizumab[17] (for patients with ≥4 cm or node-positive NSCLC stages IB–IIIA, IIIB [T2–T3, N2b; T4, N2] who received previous adjuvant chemotherapy with NSCLC PD-L1 ≥1% and no known *EGFR* mutations or *ALK* gene fusions) (category 1).
- Pembrolizumab
  - For up to a year for patients with ≥4 cm or node-positive NSCLC stages IB–IIIA, IIIB (T2–T3, N2b; T4, N2) who received previous adjuvant chemotherapy and no known *EGFR* mutations or *ALK* gene fusions (category 1).[18] The benefit for patients with PD-L1 <1% is unclear.
  - For up to 39 weeks for patients who received previous neoadjuvant chemotherapy + Pembrolizumab (category 1).[3]
- Durvalumab[4] (for patients who received previous neoadjuvant chemotherapy + Durvalumab and no known *EGFR* mutations or *ALK* gene fusions) (category 1).
- Nivolumab[2] (for patients who received previous neoadjuvant chemotherapy + Nivolumab and no known *EGFR* mutations or *ALK* gene fusions) (category 1).

Molecular Residual Disease (MRD) analysis from NeoADAURA



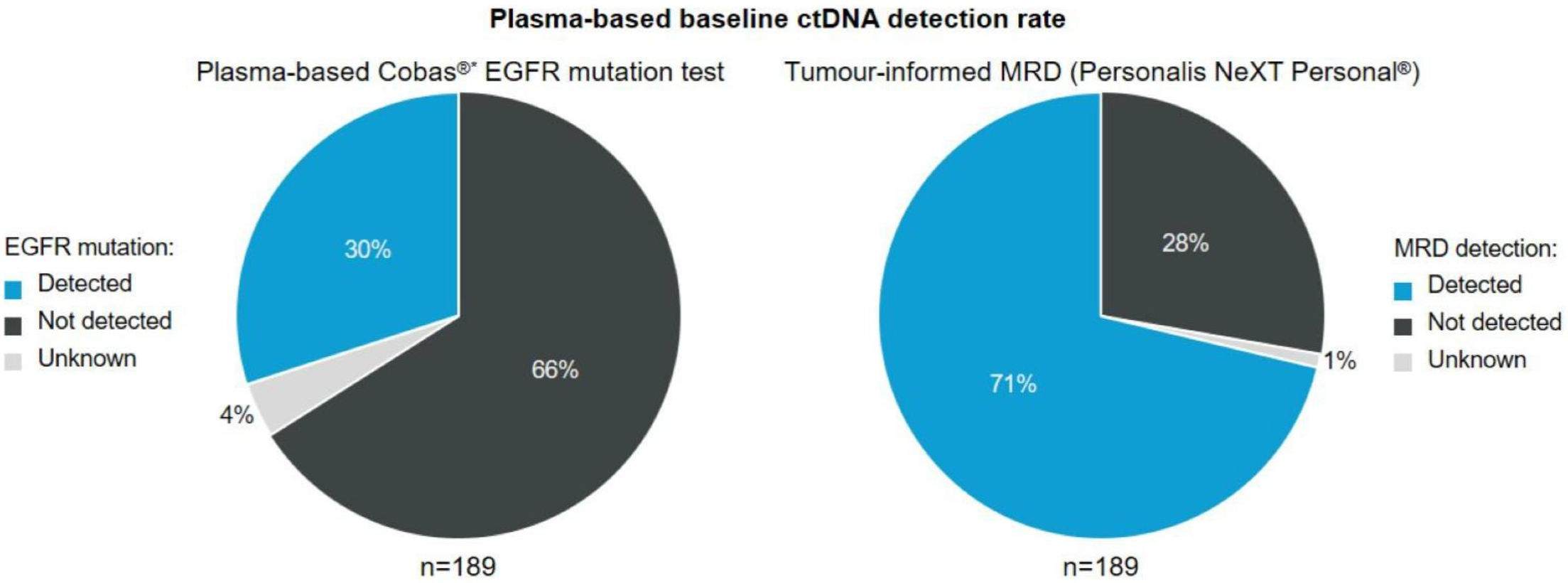
Exploratory analysis: determine the association of ultra-sensitive, tumour-informed MRD ctDNA detection with patient outcomes in NeoADAURA, specifically between:

1. **Baseline MRD status and EFS**
2. **Pre-surgical MRD status and MPR**
3. **Pre-surgical MRD clearance status and MPR**

Personalis NeXT Personal® assay

Presented by Collin M Blakely at WCLC 2025

Molecular Residual Disease (MRD) analysis from NeoADAURA



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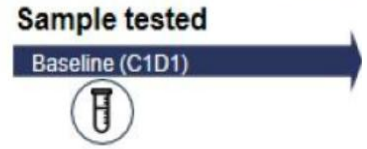
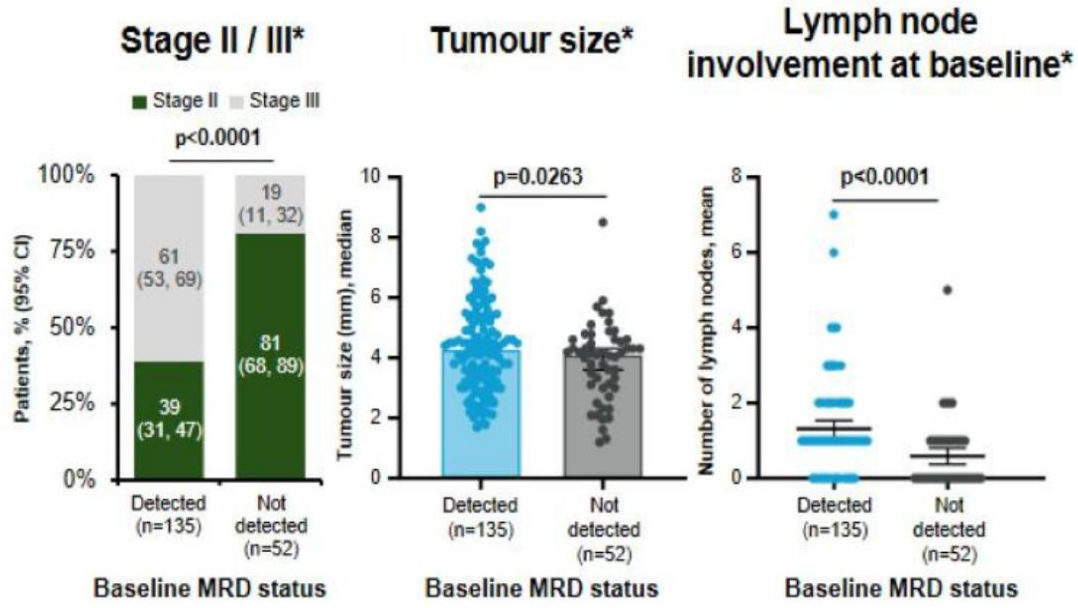
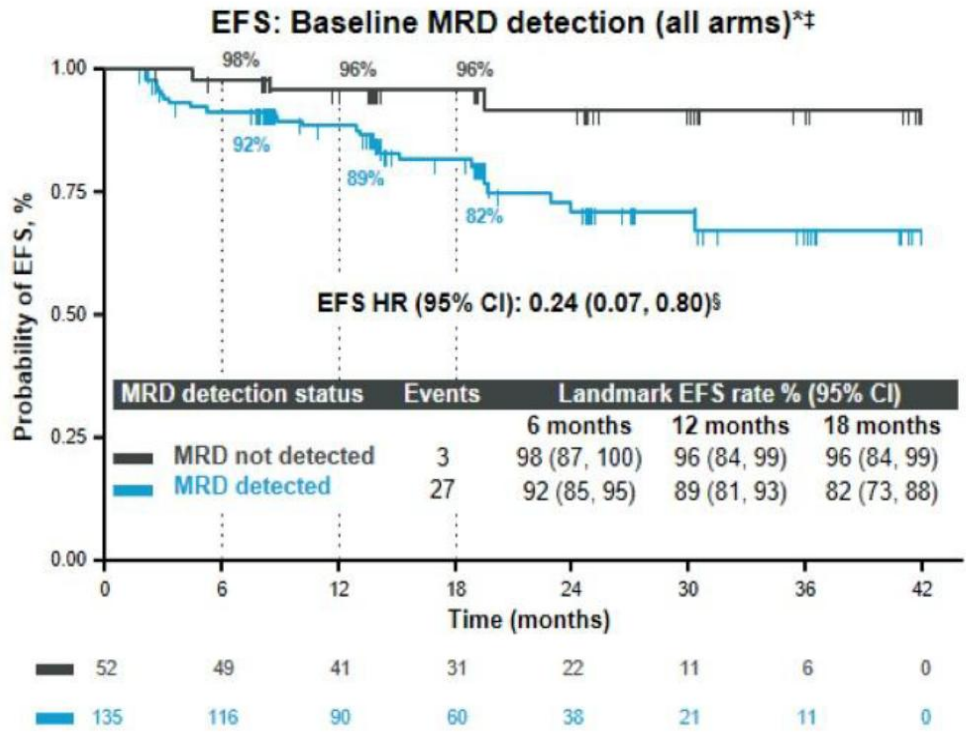
Baseline MRD

Patients with baseline MRD not detected vs MRD detected had less extensive disease and longer EFS





Other patient characteristics (EGFR mutation type, race, age, sex, smoking, WHO PS, surgery) were similar between the baseline MRD detected vs not detected groups†



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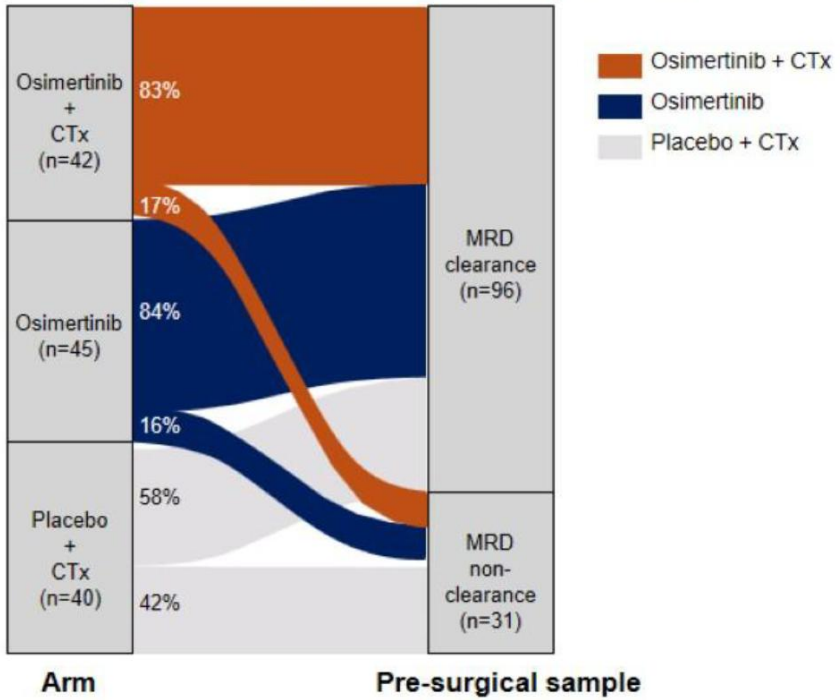
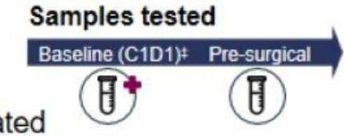
Pre-surgical MRD clearance

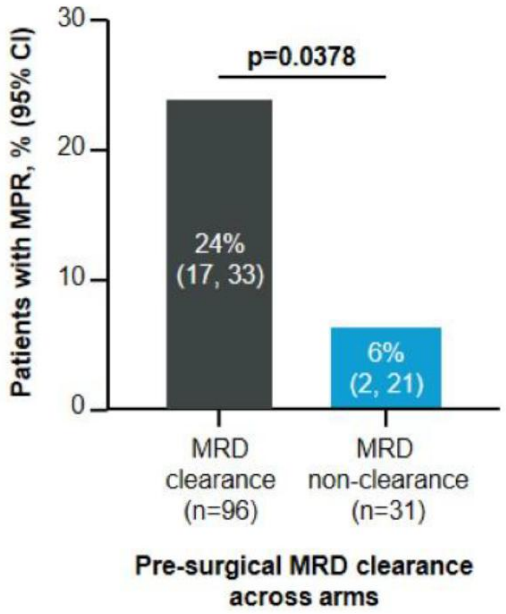
Pre-surgical MRD *clearance* was enriched with osimertinib-containing regimens and in patients with MPR

Treatment with osimertinib-containing regimens led to higher rates of MRD clearance* vs placebo + CTx





MRD clearance was associated with MPR§ across arms



Pre-surgical MRD clearance across arms

MRD clearance: 10-fold decrease in ctDNA or MRD not detected in the presurgical sample after baseline MRD detected

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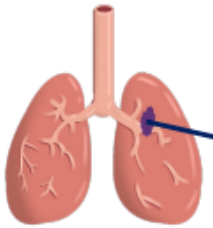
Conclusions

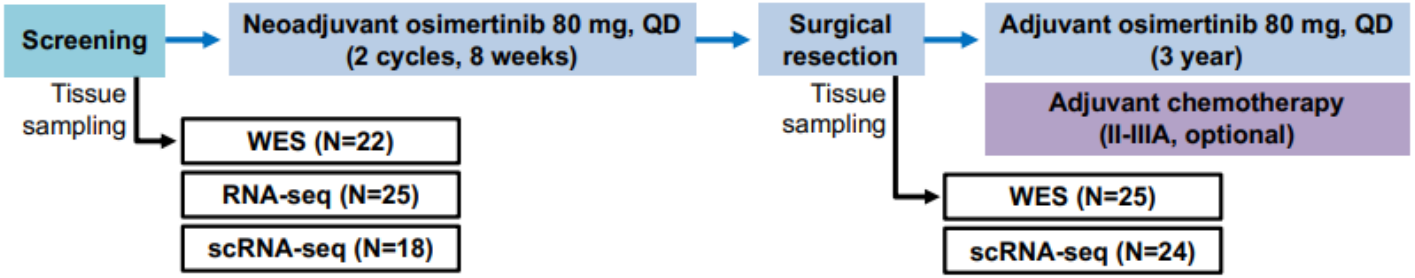
- Baseline MRD status was prognostic for EFS
- Pre-surgical MRD clearance and MRD not detected were associated with MPR
- These findings highlight the utility of MRD to complement MPR

NORA trial (NCT04816838)



Key eligibility criteria

- Surgically resectable NSCLC
- Stage I-IIIA (AJCC 8th)
- *EGFR* mutation (E19del, L858R)
- N=25



ORIGINAL ARTICLE

IASLC

Neoadjuvant and Adjuvant Osimertinib in Stage IA to IIIA, *EGFR*-Mutant NSCLC (NORA)

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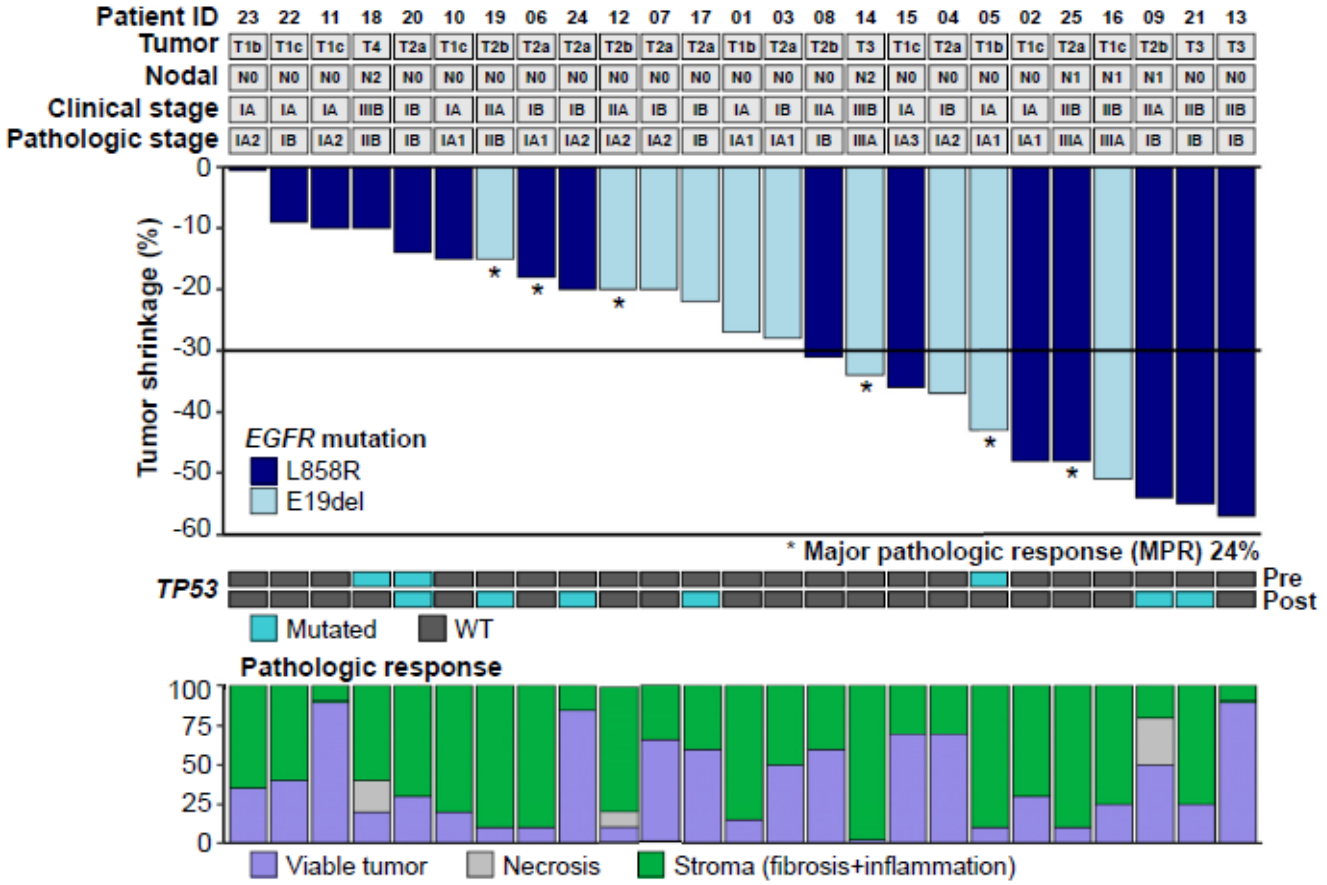
JB Lee, … SM Lim. JTO 2025

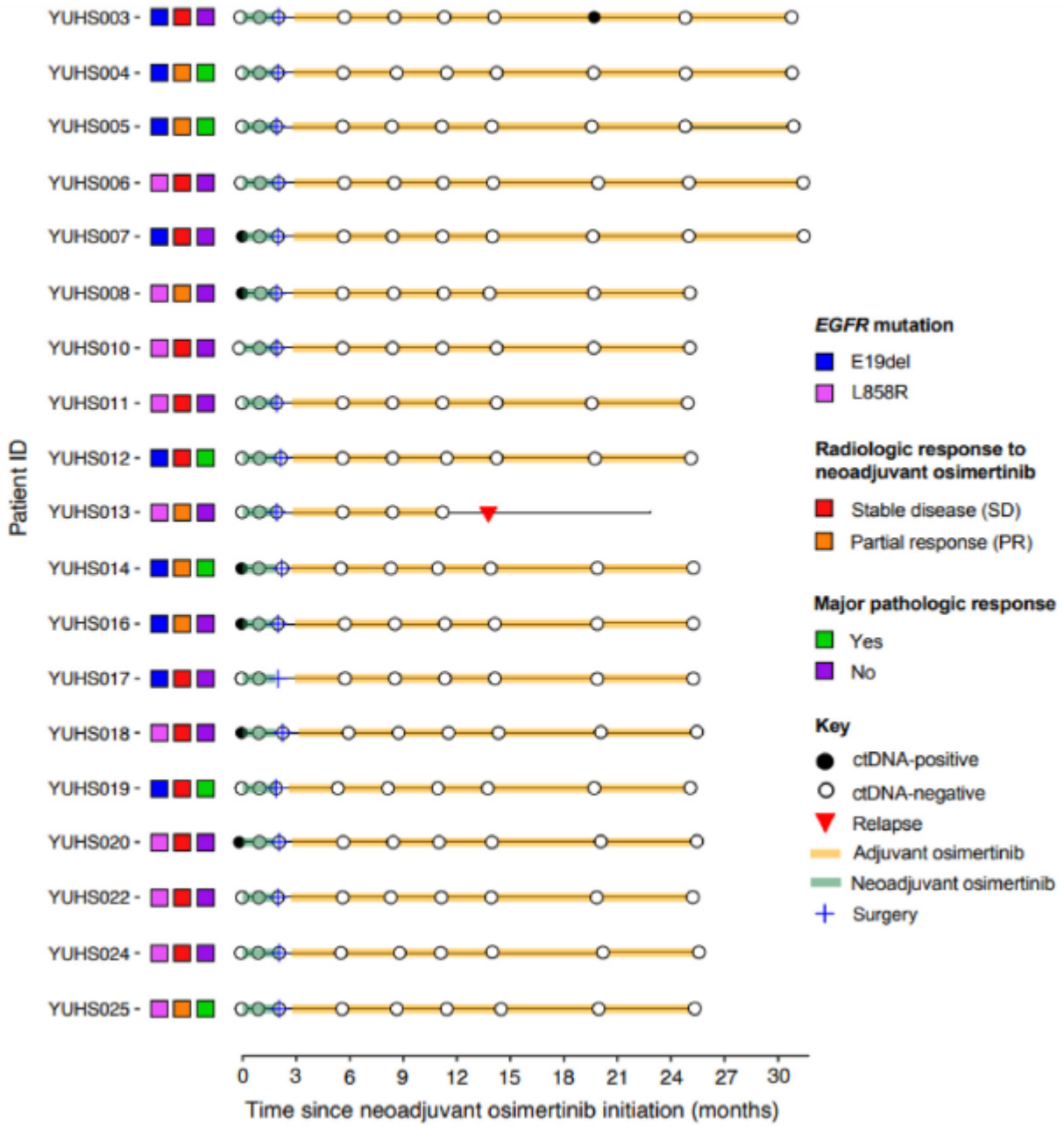
NORA trial

- N=25 patients (IA – IIIA)
- EGFR activating mutations

- ORR 44%
- MPR 24%
- PCR 0%
- DFS: not reached



JB Lee, … SM Lim. JTO 2025



JB Lee, … SM Lim. JTO 2025

Case #1.

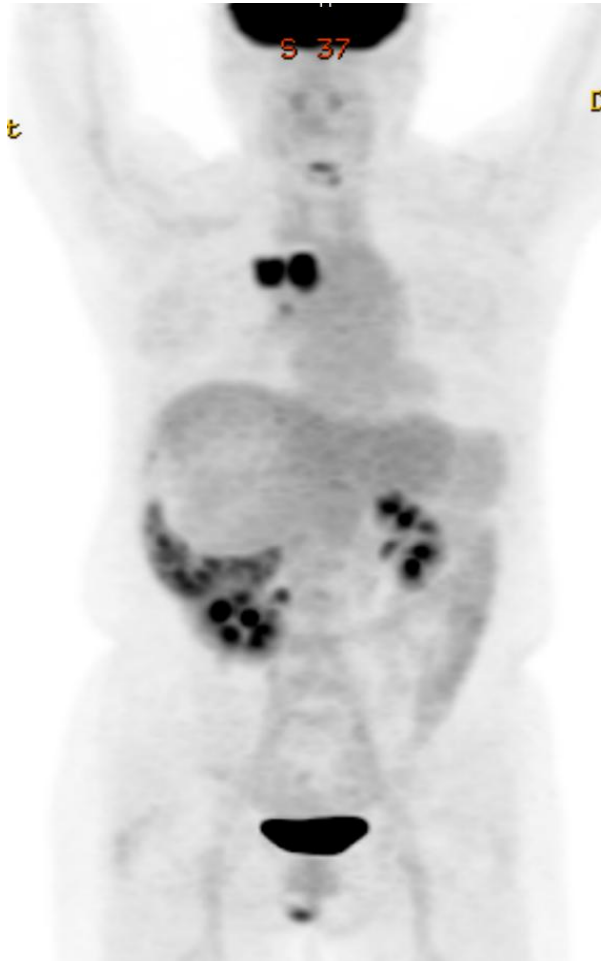
F/60s

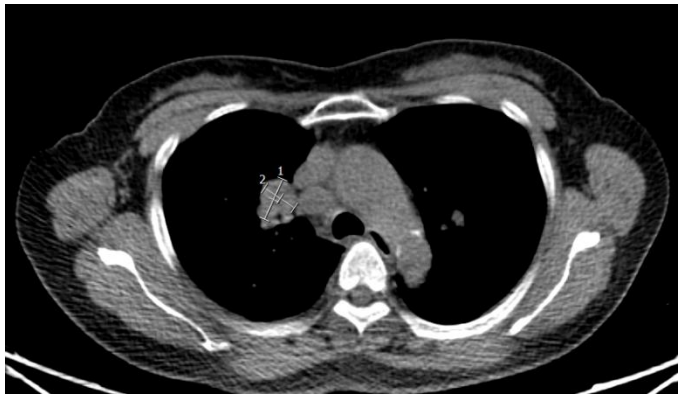
NSCLC, adenocarcinoma, cT2aN2M0, stage IIIA

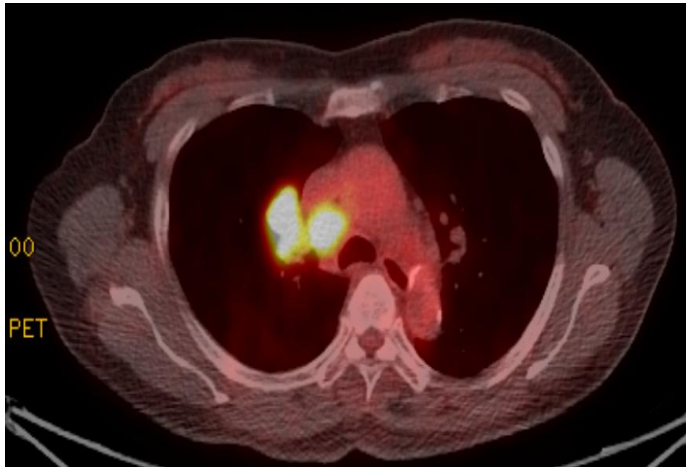
s/p neoadjuvant osimertinib 2 months (2023.7-9)

s/p RUL lobectomy (2023.9)

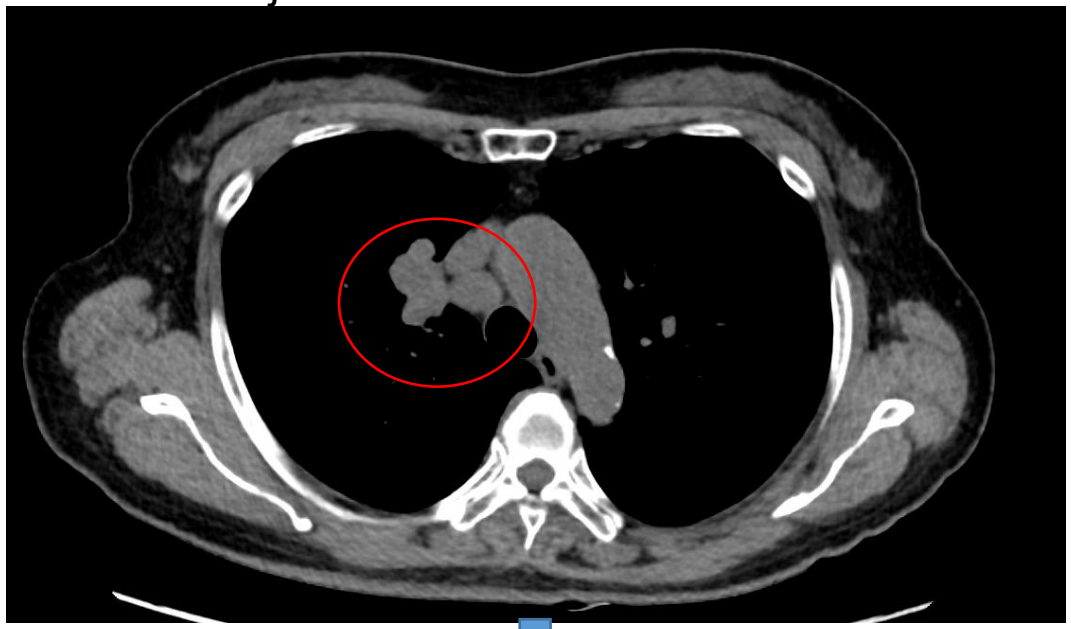
on adjuvant osimertinib (2023.9-)



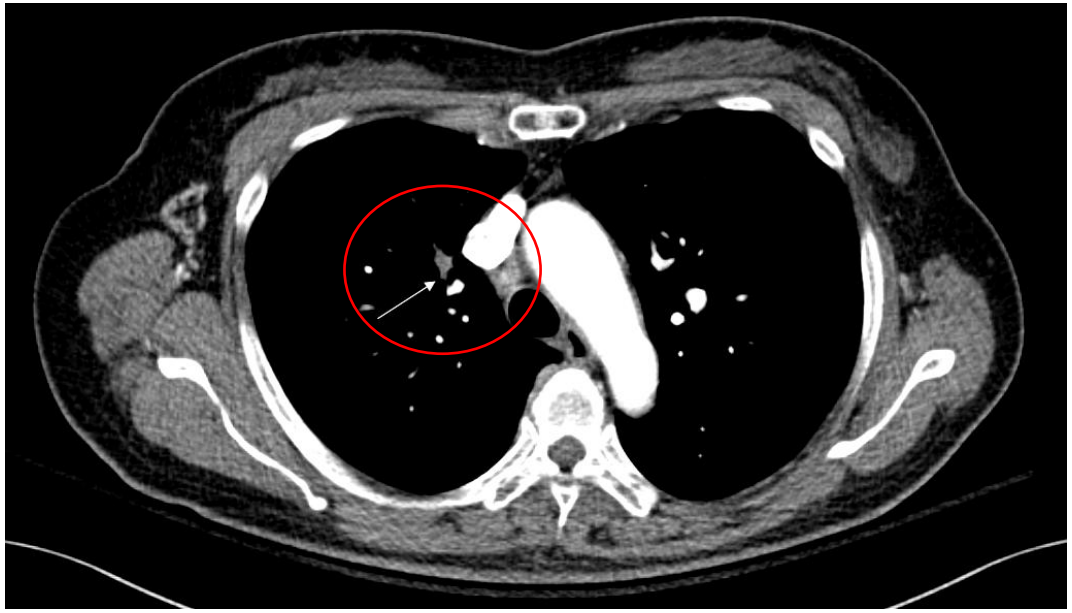




Before neoadjuvant osimertinib



After 2 months of neoadjuvant osimertinib



[Name Of Operation]

Lung, right upper lobe, lobectomy
Lymph nodes, mediastinal lymph node dissection

[Pathological Diagnosis]

[Final report]
Lung, right upper lobe:
1. Status post neoadjuvant therapy (osimertinib)
2. No residual carcinoma in the lung tissue

◇ Total mass size including stroma: 1.2x1.2cm
◇ Viable tumor size: 0cm
◇ Viable tumor volume: 0%
◇ Necrosis: 0%
◇ Stroma (fibrosis and inflammation): 100%
◇ Bronchial involvement: Not involved
◇ Pleura, visceral: Not involved (PL0)
◇ Lymphovascular invasion: Not identified
◇ Perineural invasion: Not identified
◇ Spread through air spaces: Not identified
◇ Non-neoplastic lung: Not remarkable
◇ Resection margins, bronchus and vessel: Free of carcinoma (safety margin: 1.5cm)
◇ Lymph nodes, peribronchial (0/6): Free of carcinoma

◇ Lymph nodes, separately sent: #2 upper paratracheal (0/6), #4 lower paratracheal (1/2), #7 subcarinal (0/7) and #12L lower lobar (0/1); total (1/16): Metastatic carcinoma in 1 out of 16 lymph nodes without perinodal soft tissue extension (size of metastatic carcinoma: 0.5cm)
◇ Representative section: N2
◇ ypT0N2a1 (AJCC 8th ed.)

Case #2.

F/60s

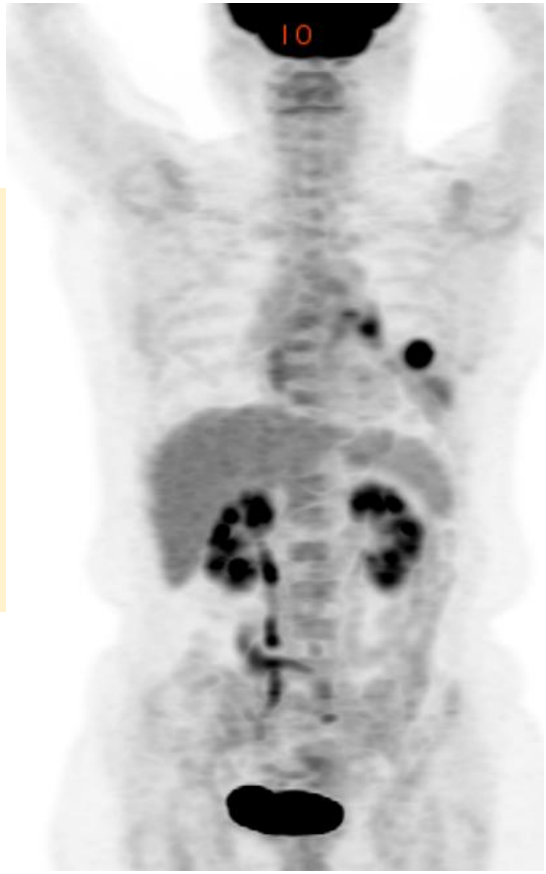
NSCLC, adenocarcinoma, cT1N1M0, stage II

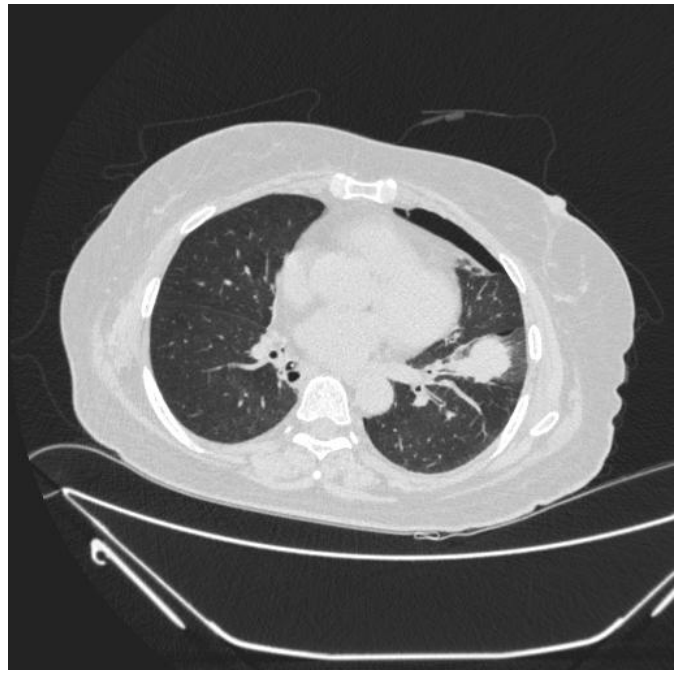
s/p neoadjuvant osimertinib 2 months (2021.2-2021.4)

s/p LLL lobectomy (2021.5), ypT1bN2a2

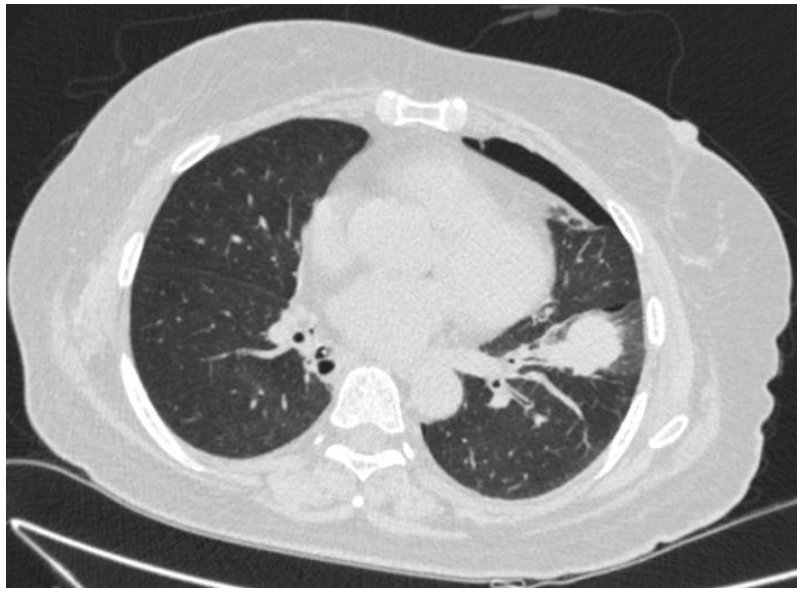
s/p adjuvant osimertinib (2022.5-2025.5)

Recurrence, new fissural nodule in left lingual, left interlobar LN (2026.1)

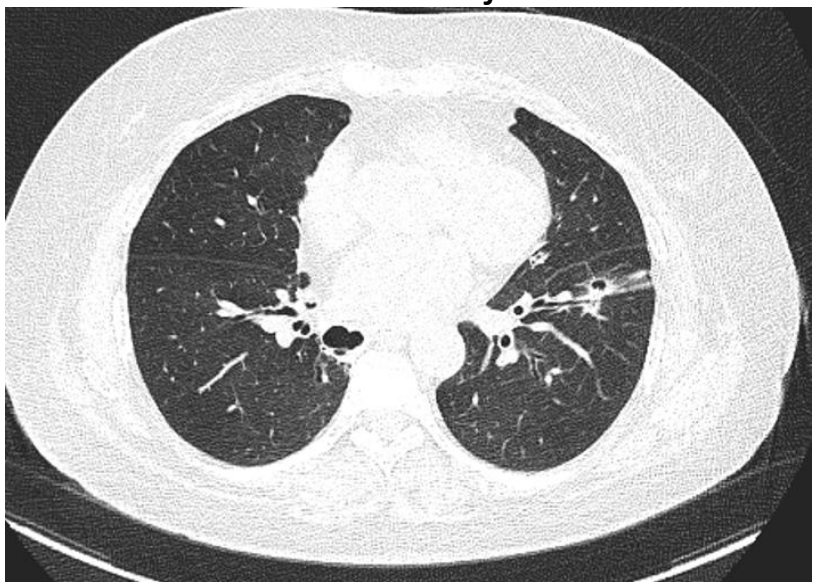




Before neoadjuvant osimertinib



After 2 months of neoadjuvant osimertinib



[Name Of Operation]

Lung, left lower lobe, anterobasal segmentectomy
Lymph nodes, mediastinal lymph node dissection

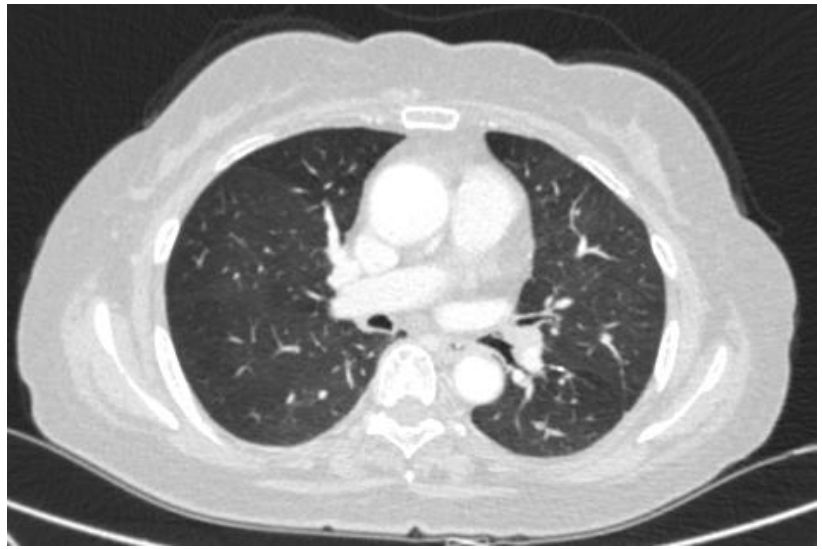
[Pathological Diagnosis]

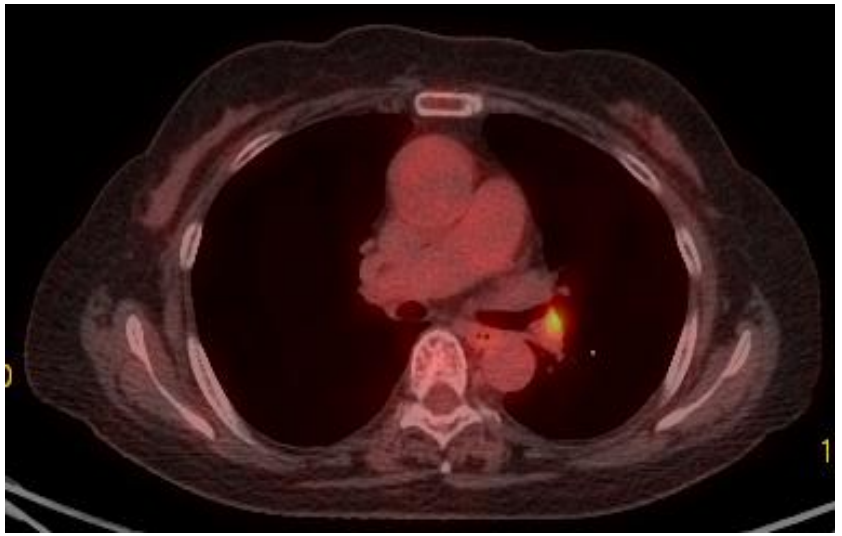
Lung, left lower lobe:
1. Status-post Tagrisso therapy
2. Residual adenocarcinoma, acinar predominant, IASLC Grade 2

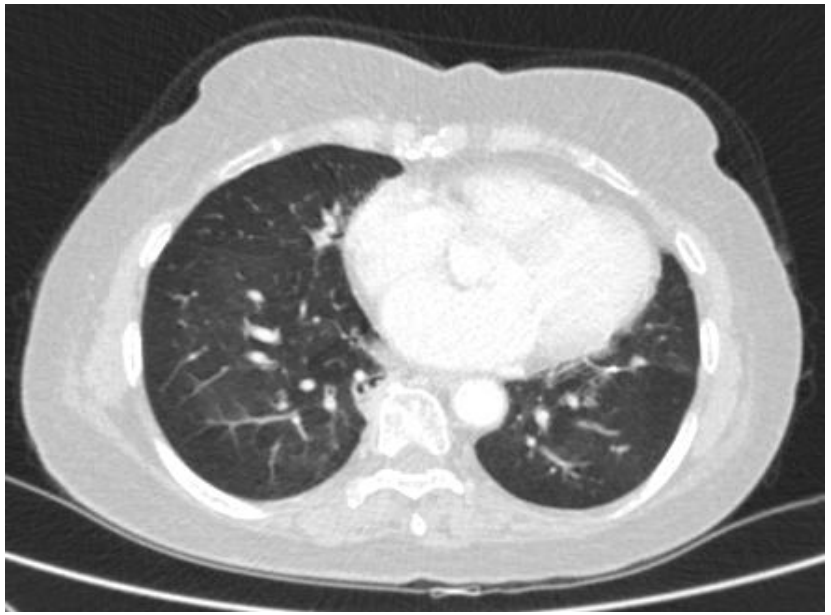
◇ Total mass size including fibrosis: 1.8x1.5cm
◇ Viable tumor size: 1.2cm
◇ Viable tumor volume: 25%
◇ Necrosis: 0%
◇ Stroma (fibrosis and inflammation): 75%
◇ Bronchial involvement: Not involved
◇ Pleura, visceral: Not involved (PL0)
◇ Necrosis: Not identified
◇ Lymphovascular invasion: Not identified
◇ Perineural invasion: Not identified
◇ Spread through air spaces: Not identified
◇ Non-neoplastic lung: Not remarkable
◇ Resection margin, lung parenchymal: Free of carcinoma (safety margin: 0.5cm)
◇ Lymph nodes, peribronchial (1/1): Metastatic carcinoma in 1 out of 1 lymph node without perinodal soft tissue extension (size of metastatic carcinoma: 0.05cm)
◇ Lymph nodes, separately sent: #5 subaortic (0/6), #6 paraaortic (0/3), #7 subcarinal (1/8), #9 IPL (0/5), #10 hilar (0/1), #11 interlobar (0/2) and #12L lower lobar (1/2); total (2/27): Metastatic carcinoma in 2 out of 27 lymph nodes without perinodal soft tissue extension (size of metastatic carcinoma: 0.4cm)
◇ Histologic component: acinar 70%, lepidic 30%
◇ Representative section: A4, A2, A3
◇ ypT1bN2a2 (AJCC 8th ed.), according to invasive size

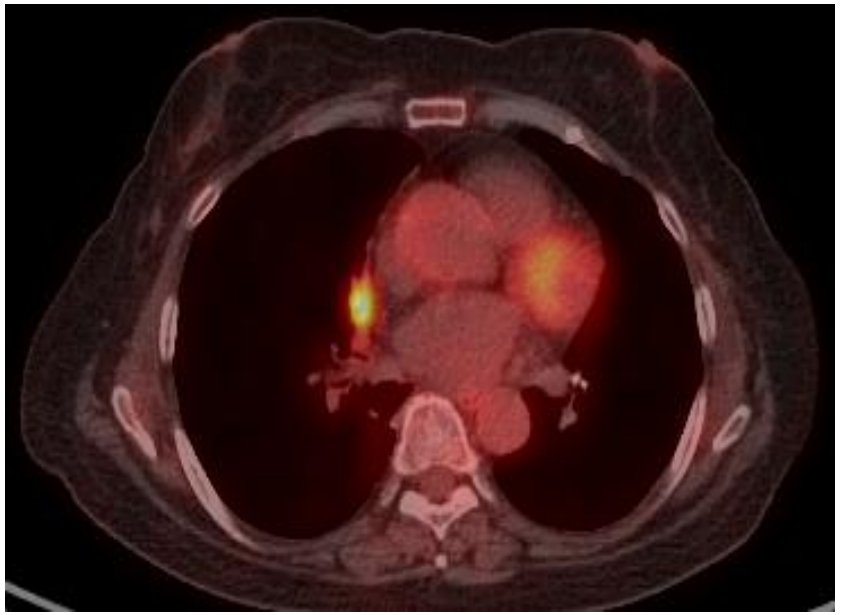
[TNM Stage] y/pT1b/pN2a2

2026 Jan, 8 months after completion of adj osimertinib



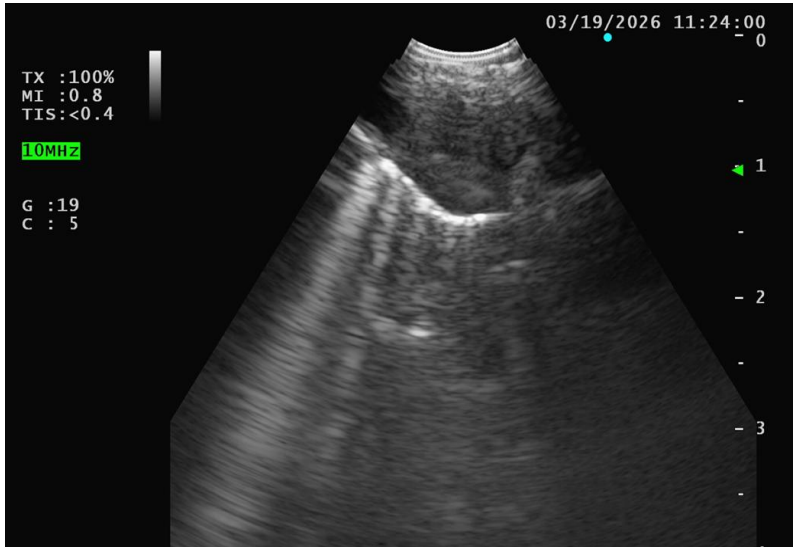






2026 March

EBUS Bx of 11L -> adenoca, EGFR Ex19del



2026 April

Started palliative Lazertinib 240mg

Take Home Message

- Neoadjuvant osimertinib, with or without chemotherapy, should be considered when planning treatment for patients with resectable EGFRm, stage II-IIIB NSCLC
- Duration of adjuvant osimertinib beyond 3 years is under investigation
- Treatment strategies after relapse on adjuvant osimertinib requires further study

Acknowledgements

Yonsei Cancer Center

: Byoung Chul Cho
: Min-Hee Hong
: Jii Bum Lee
: Hye Ryun Kim
: Jin Gu Lee
: Chang Young Lee
: Byoung Jo Park

CANCER CARE TEAM AWARD from IASLC 2023