

# Survival Benefits of local treatment for brain metastases in patients with EGFR-Mutant Non-Small Cell Lung Cancer treated with osimertinib

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## Background

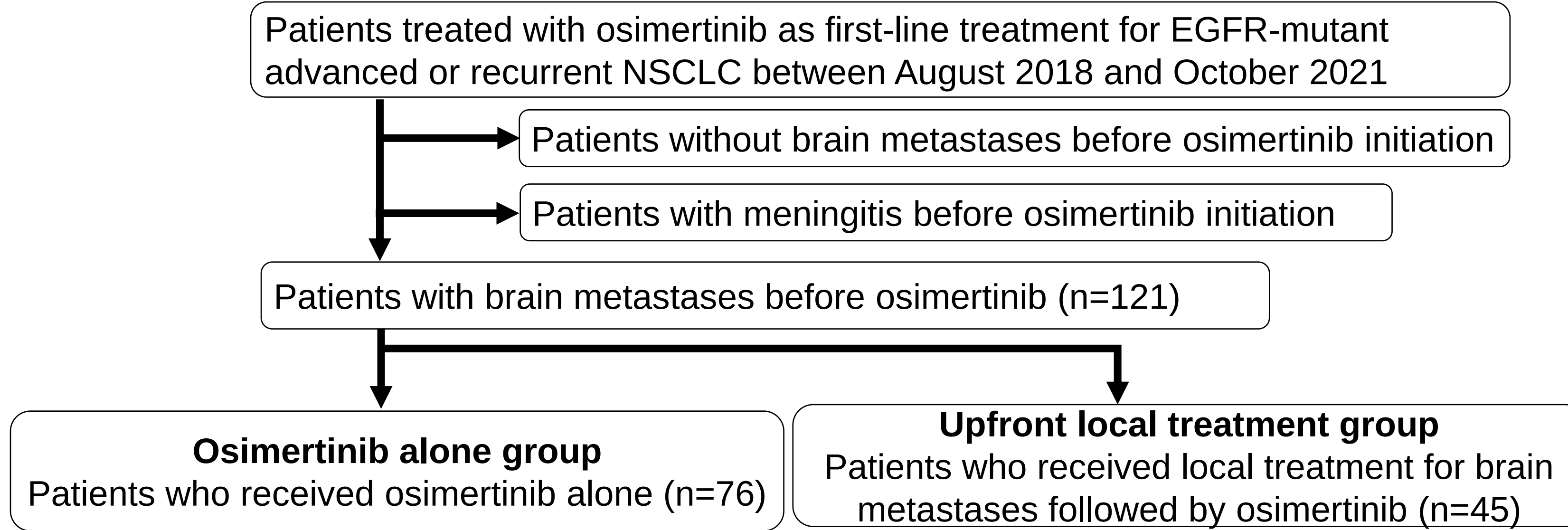
- ✓ Approximately 20–40% of patients with lung cancer have brain metastases (BMs) during their disease course.<sup>1,2</sup> The risk of BMs is higher in epidermal growth factor receptor (EGFR)-mutant NSCLC than in EGFR wild-type NSCLC.<sup>3</sup>
- ✓ Osimertinib showed a higher central nervous system (CNS) penetrability than first generation EGFR-tyrosine kinase inhibitors (TKIs).<sup>4,5</sup>
- ✓ The FLAURA trial showed that CNS-PFS was significantly longer in the osimertinib group than in the gefitinib or erlotinib group.<sup>6</sup> In the phase III ADAURA trial, osimertinib significantly prolonged CNS disease-free survival compared to placebo in patients with EGFR-mutant NSCLC undergoing complete resection.<sup>7</sup>
- ✓ In patients treated with first-generation EGFR-TKIs, upfront local treatment of BMs followed by EGFR-TKIs prolonged OS compared to upfront TKIs.<sup>8</sup>
- ✓ However, local treatment has problems with radiotherapy-related complications such as brain radiation necrosis and leukoencephalopathy, as well as perioperative complications.<sup>9-11</sup>
- ✓ Therefore, it is unclear whether local treatment for BMs should be administered to patients receiving CNS-penetrant TKIs like osimertinib.
- ✓ The present study aimed to investigate the survival benefit of upfront local treatment for BMs in patients with EGFR-mutant NSCLC treated with osimertinib.

## Methods

- ✓ **Design:** Multicenter retrospective cohort study. The data cutoff date was April 30, 2022.
- ✓ **Participants** Consecutive patients with EGFR common mutation (exon 19 deletion [19del] or exon 21 L858R [L858R])-positive NSCLC who received osimertinib at nine institutes of the East Japan Chesters Group in Japan between August 2018 and October 2021 were included. BMs were confirmed on imaging before osimertinib initiation. Patients with meningitis before osimertinib initiation were excluded.
- ✓ **Exposure:** Local treatment for BMs prior to osimertinib initiation
- ✓ **Main Outcomes and Measures:** Overall survival (OS) and central nervous system progression-free survival (CNS-PFS).
- ✓ **Statistical analysis:** Inverse-probability treatment weighting (IPTW) analysis with propensity score matching was performed to adjust for potential confounding factors.

## Results

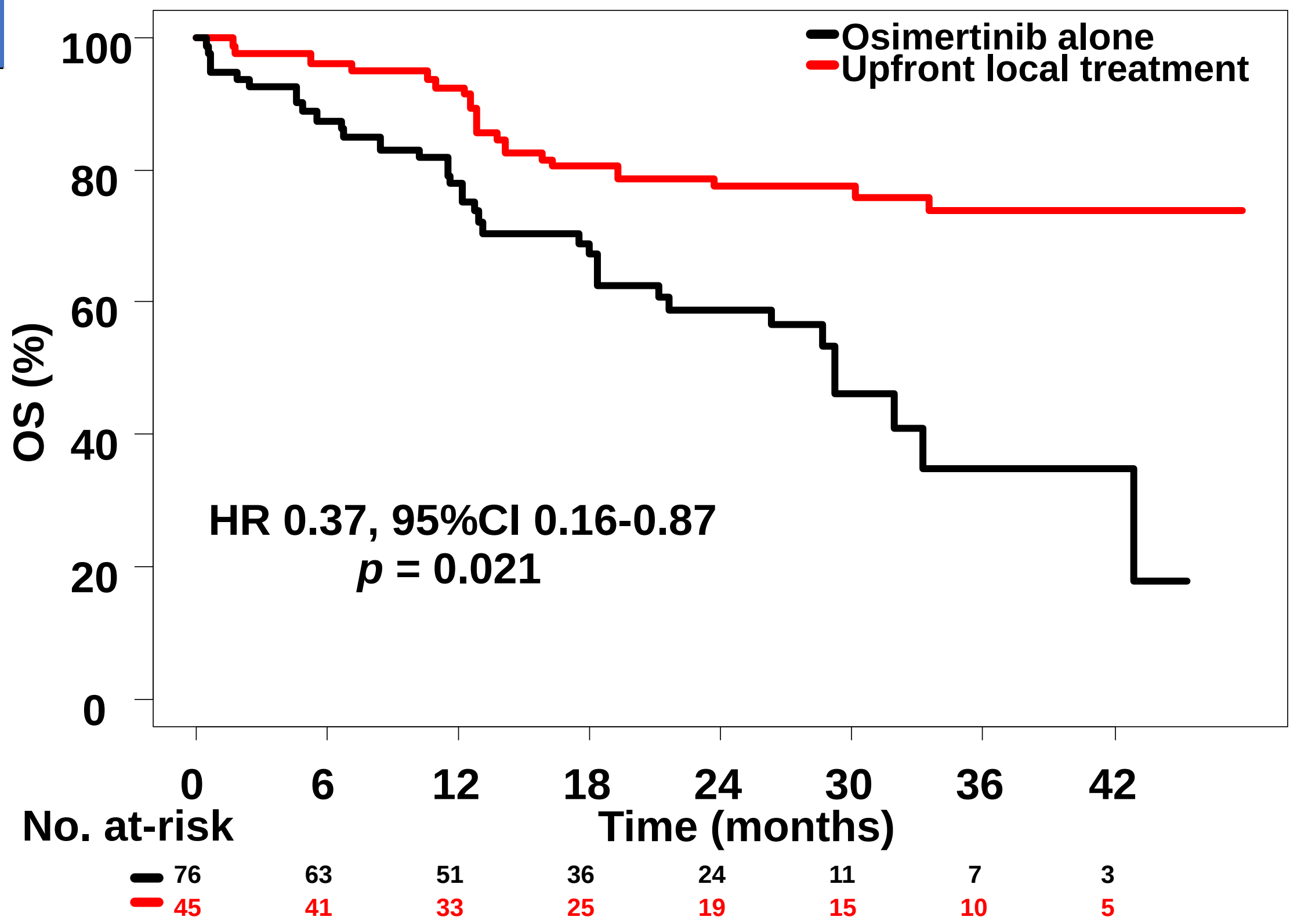
### Patient selection flow



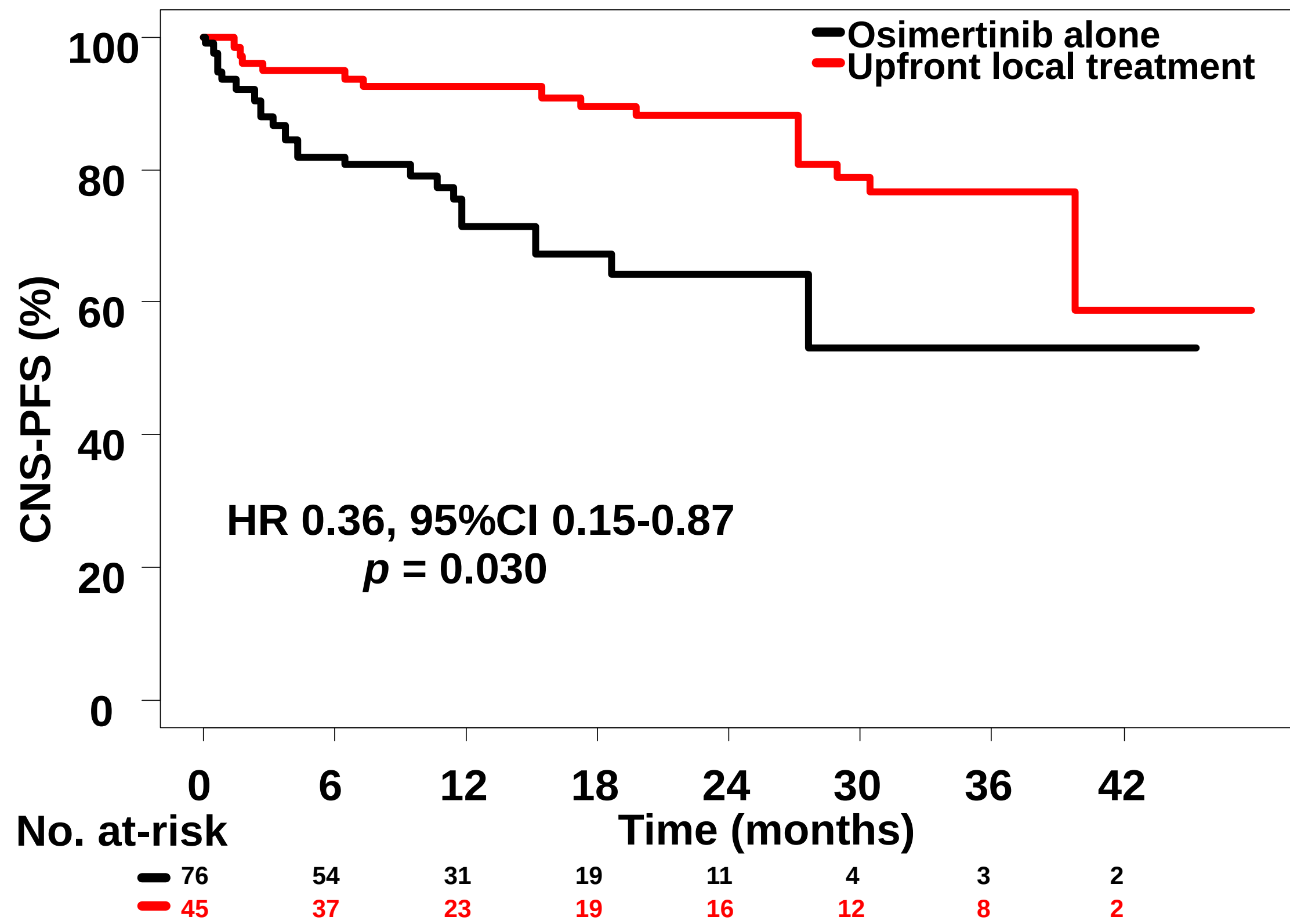
## Patient characteristics

|                                     | Overall (n=121) | Upfront local treatment (n=45) | Osimertinib alone (n=76) | p value |
|-------------------------------------|-----------------|--------------------------------|--------------------------|---------|
| Age (years)                         |                 |                                |                          |         |
| Median (range)                      | 72 (40–89)      | 72 (40–89)                     | 71 (42–86)               | 0.308   |
| Sex, n (%)                          |                 |                                |                          |         |
| Male                                | 38 (31)         | 11 (24)                        | 27 (36)                  | 0.230   |
| Female                              | 83 (69)         | 34 (76)                        | 49 (64)                  |         |
| PS, n (%)                           |                 |                                |                          |         |
| 0-1                                 | 92 (76)         | 36 (80)                        | 56 (74)                  | 0.512   |
| 2-4                                 | 29 (24)         | 9 (20)                         | 20 (26)                  |         |
| Smoking status, n (%)               |                 |                                |                          |         |
| Current/Former                      | 48 (40)         | 18 (40)                        | 30 (39)                  | 1.000   |
| Never                               | 73 (60)         | 27 (60)                        | 46 (61)                  |         |
| Histologic type                     |                 |                                |                          |         |
| Adenocarcinoma                      | 116 (96)        | 43 (96)                        | 73 (96)                  | 1.000   |
| Others                              | 5 (4)           | 2 (4)                          | 3 (4)                    |         |
| Stage, n (%)                        |                 |                                |                          |         |
| IVA                                 | 4 (3)           | 0                              | 4 (5)                    |         |
| IVB                                 | 94 (78)         | 33 (73)                        | 61 (80)                  |         |
| Recurrence                          | 23 (19)         | 12 (27)                        | 11 (15)                  |         |
| EGFR mutation type, n (%)           |                 |                                |                          |         |
| Exon 19 deletion                    | 57 (47)         | 19 (42)                        | 38 (50)                  | 0.454   |
| Exon 21 L858R                       | 64 (53)         | 26 (58)                        | 38 (50)                  |         |
| PD-L1 TPS, n (%)                    |                 |                                |                          |         |
| ≥50%                                | 13 (11)         | 5 (11)                         | 8 (11)                   | 0.317   |
| 1–49%                               | 23 (19)         | 12 (27)                        | 11(14)                   |         |
| <1%                                 | 43 (36)         | 16 (35)                        | 27(36)                   |         |
| Not investigated                    | 42 (34)         | 12 (27)                        | 30(39)                   |         |
| Number of BMs, n (%)                |                 |                                |                          |         |
| 1                                   | 37 (31)         | 10 (22)                        | 27 (36)                  | 0.642   |
| 2-3                                 | 28 (23)         | 12 (27)                        | 16 (21)                  |         |
| 4-5                                 | 10 (8)          | 4 (9)                          | 6 (8)                    |         |
| 6-9                                 | 10 (8)          | 4 (9)                          | 6 (8)                    |         |
| ≥10                                 | 36 (30)         | 15 (33)                        | 21 (28)                  |         |
| Size of largest BMs (mm)            |                 |                                |                          |         |
| Median (range)                      | 10 (1-51)       | 15 (6-51)                      | 8 (1-39)                 | <0.001  |
| Symptoms of BMs, n (%)              |                 |                                |                          |         |
| Symptomatic                         | 26 (21)         | 19 (42)                        | 7 (9)                    | <0.001  |
| Asymptomatic                        | 95 (79)         | 26 (58)                        | 69 (91)                  |         |
| Steroid treatment for BMs, n (%)    |                 |                                |                          |         |
| Yes                                 | 18 (15)         | 12 (27)                        | 6 (8)                    | 0.008   |
| No                                  | 103 (85)        | 33 (73)                        | 70 (92)                  |         |
| Local treatment for BMs, n (%)      |                 |                                |                          |         |
| SRS                                 | 22 (18)         | 22 (49)                        | NA                       |         |
| SRT                                 | 10 (8)          | 10 (22)                        | NA                       |         |
| WBRT                                | 7 (6)           | 7 (16)                         | NA                       |         |
| Surgery                             | 3 (2)           | 3 (7)                          | NA                       |         |
| SRS + Surgery                       | 2 (2)           | 2 (4)                          | NA                       |         |
| WBRT + SRS                          | 1 (1)           | 1 (2)                          | NA                       |         |
| Extracranial disease lesions, n (%) |                 |                                |                          |         |
| Yes                                 | 115 (95)        | 40 (89)                        | 75 (99)                  | 0.026   |
| No                                  | 6 (5)           | 5 (11)                         | 1 (1)                    |         |

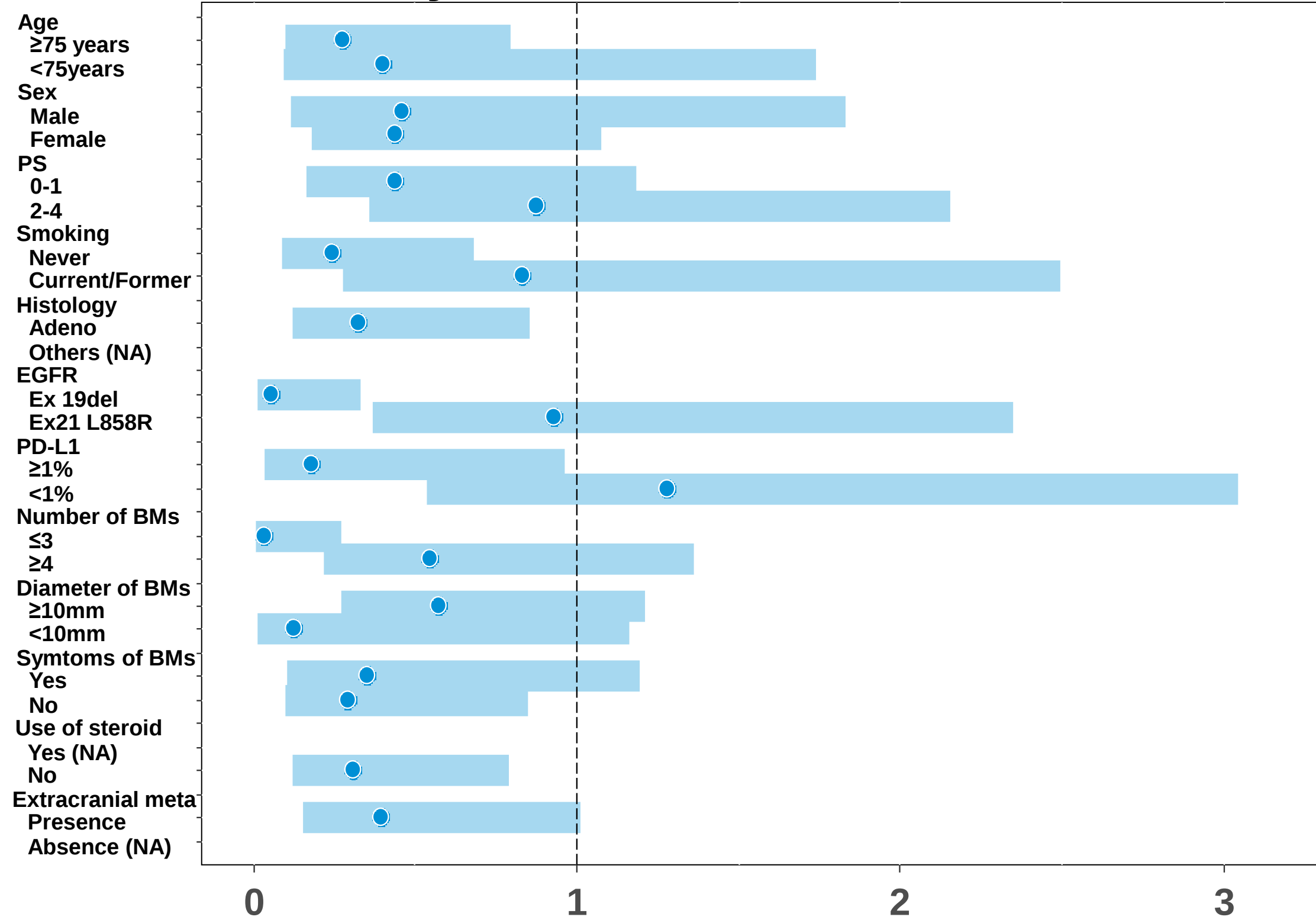
## OS (IPTW analysis)



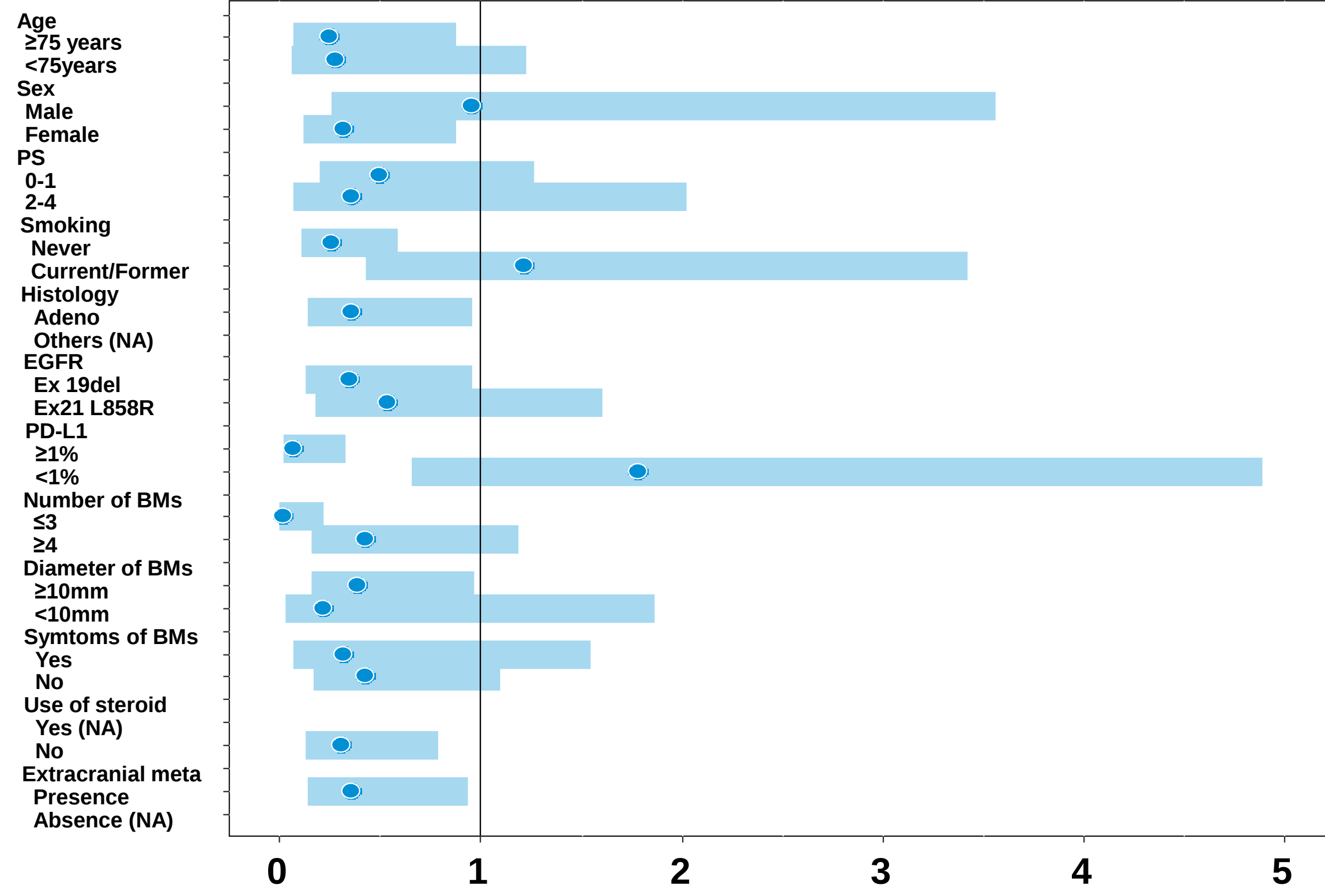
## CNS-PFS (IPTW analysis)



## IPTW-adjusted Hazard ratio for OS



## IPTW-adjusted Hazard ratio for CNS-PFS



## Conclusions

- ✓ Propensity score-weighted analysis showed that the OS and CNS-PFS of patients who received upfront local treatment for BMs were significantly longer than those of patients who received osimertinib alone.
- ✓ Our study supports the benefit of upfront local treatment for BMs in patients with EGFR-mutant NSCLC receiving osimertinib despite the high CNS activity of osimertinib.

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