Osimertinib versus Comparator EGFR-TKI as First-Line Treatment for EGFR-Mutated Advanced NSCLC: FLAURA China, a Randomized Study

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Supplementary material

Supplementary results

Efficacy

*Progression-free survival sensitivity analysis*

The sensitivity analysis of PFS results determined by BICR were consistent with investigator-assessed PFS: HR 0.54, 95% CI 0.36–0.81, with a median PFS of 15.0 months (95% CI 10.8–18.0) in the osimertinib group vs. 11.0 months (95% CI 8.4–12.3) in the comparator EGFR-TKI group. See Supplementary Fig. 2 for Kaplan-Meier curves.

Safety

*Cardiac events*

Among patients with baseline and ≥1 follow-up left ventricular ejection fraction (LVEF) assessment, LVEF decreased from baseline ≥10 percentage points to an absolute LVEF of <50% in 2 of 68 (3%) in the osimertinib group and 0 patients in the comparator EGFR-TKI group. In one patient, the LVEF recovered by the next visit, while still being treated with osimertinib. For the second patient, no further LVEF measurements were taken. LVEF decreased from baseline ≥15 percentage points to an absolute LVEF ≥50% in 0 patients in the osimertinib group and in 2/63 (3%) patients in the comparator EGFR-TKI group.

AEs in the grouped term cardiac effects (cardiac failure), were reported in 3 (4%) patients in the osimertinib group (2 patients with cardiac failure and 1 patient with ejection fraction decreased) and 0 patients in the comparator EGFR-TKI group. The first patient reporting an AE of cardiac failure was a 68-year-old, female non-smoker with bone, locomotor, and lymph node metastases, and metastatic pleural effusion and an ongoing history of left ventricular dysfunction. A grade 1 AE of cardiac failure was reported on Day 86, and considered to be unrelated to treatment by the investigator. Osimertinib treatment was continued and the AE was reported as resolving. The second patient reporting cardiac failure was 71-year-old, female non-smoker with metastatic pleural effusions, had a grade 3 non-serious AE of left ventricular hypertrophy on Day 339, which was considered unrelated to treatment by the investigator. Osimertinib treatment was interrupted from Day 340 to Day 351. On Day 516 a grade 3 SAE of cardiac failure was reported. The patient was hospitalized and treatment of the AE was started, with osimertinib treatment interrupted from Day 521 to 525. The patient was discharged from hospital on Day 535 discontinued treatment on Day 536, and the AE was not resolved at the first DCO. The AE of cardiac failure was considered not related to study treatment by the investigator. The patient reporting ejection fraction decreased was a 56-year-old, female non-smoker, with lung metastases at study entry and a history of hypertension, exertional dyspnea, and thyroid mass, had a grade 1 AE of ejection fraction decreased on Day 85 with no symptoms reported.
The AE was considered as possibly related to treatment by the investigator. Osimertinib dose was not changed and the AE was reported as resolved at Day 253. One AE of cardiac effects (cardiac failure) in the osimertinib group led to a dose interruption; no AEs led to a dose reduction or a discontinuation due to AEs.

The majority of AEs in the grouped term cardiac effects (QT) were ECG QT prolonged, reported in 6 patients (9%) in the osimertinib group and in 3 patients (5%) in the comparator EGFR-TKI group. No AEs of torsades de pointes or arrhythmia were reported in either group. Dose interruptions for AEs of ECG QT prolonged were reported in 3 (4%) patients in the osimertinib group and in 0 patients in the comparator EGFR-TKI group. No dose reductions or discontinuation of treatment due to AEs of ECG QT prolonged were reported in either group.

**Interstitial lung disease**

Time to onset for AEs in the grouped term ILD and pneumonitis in the osimertinib group were 77 days (AE of ILD) and 526 days (AE of pneumonitis). In the comparator EGFR-TKI group, time to onset was 32 days (AE of ILD) and 548 days (AE of pneumonitis).

**Other adverse events of special interest**

Across other AEs identified as of special interest (diarrhea and grouped terms for skin effects, nail effects, ocular effects and upper gastrointestinal inflammatory events), the vast majority of AEs were of grades 1 and 2. Grade 3 AEs were reported in 1 patient in the comparator EGFR-TKI group with skin effects (dermatitis acneiform).

**Dose interruptions and dose reductions due to adverse events**

Dose interruptions due to AEs occurred in 15 patients (21%) in the osimertinib group and 7 patients (11%) in the comparator EGFR-TKI group, most frequently ECG QT prolonged (3 patients; 4%), and neutrophil count decreased (2 patients; 3%) in the osimertinib group and ALT increased (6 patients; 9%) and AST increased (3 patients; 5%) in the comparator EGFR-TKI group. Dose reductions due to AEs were reported in no patients in the osimertinib group and 2 patients (3%) in the comparator EGFR-TKI group (conjunctivitis, paronychia and mouth ulceration in one patient each).
## Supplementary Table 1. Subsequent anticancer therapies (full analysis set).

| Discontinued randomized treatment | Osimertinib (n = 71) | Comparator EGFR-TKI (n = 65) |
|-----------------------------------|----------------------|-----------------------------|
| Any subsequent anticancer therapy | 30 (42)              | 42 (65)                     |
| No subsequent anticancer therapy  | 26 (37)              | 20 (31)                     |
| Ongoing randomized treatment      | 15 (21)              | 3 (5)                       |

### Number of regimens of subsequent anticancer therapy<sup>a</sup>

| Regimen | Osimertinib | Comparator EGFR-TKI |
|---------|-------------|---------------------|
| 1       | 19 (63)     | 27 (64)             |
| 2       | 9 (30)      | 11 (26)             |
| 3       | 1 (3)       | 3 (7)               |
| 4       | 1 (3)       | 0                   |
| ≥5      | 0           | 1 (2)               |

### First subsequent anticancer therapies<sup>a</sup>

| Therapy                      | Osimertinib (n = 71) | Comparator EGFR-TKI (n = 65) |
|------------------------------|----------------------|-----------------------------|
| Cytotoxic chemotherapy       | 30 (42)              | 42 (65)                     |
| EGFR-TKI                     | 17 (57)              | 15 (36)                     |
| Other TKI                    | 10 (33)              | 24 (57)                     |
| VEGF inhibitor               | 4 (13)               | 0                            |
| Other                        | 5 (17)               | 3 (7)                        |

### Second subsequent anticancer therapies<sup>a</sup>

| Therapy                      | Osimertinib (n = 71) | Comparator EGFR-TKI (n = 65) |
|------------------------------|----------------------|-----------------------------|
| Cytotoxic chemotherapy       | 12 (17)              | 16 (25)                     |
| EGFR-TKI                     | 5 (42)               | 9 (56)                      |
| Other TKI                    | 3 (25)               | 5 (31)                      |
| VEGF inhibitor               | 3 (25)               | 2 (13)                      |
| Other                        | 1 (8)                | 1 (6)                       |

<sup>a</sup> Indicates the number of regimens.
The percentage of number of regimens of subsequent anticancer therapies and classes of first and second subsequent therapies received is based on the number of patients receiving the respective subsequent therapy. Patients were counted more than once if they received >1 anticancer therapy or a combination therapy that contained therapies from multiple classifications.

*EGFR-TKI* epidermal growth factor receptor-TKI, *TKI* tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor.
**Supplementary Table 2.** Adverse events considered by the investigator to be possibly causally related to study drug in $\geq 10\%$ of patients (safety analysis set).

| Adverse Event                            | Osimertinib $(n=71)$ | Comparator EGFR-TKI $(n=65)$ |
|------------------------------------------|----------------------|-------------------------------|
| White blood cell count decreased         | 24 (33.8)            | 4 (6.2)                       |
| Platelet count decreased                 | 18 (25.4)            | 1 (1.5)                       |
| Anemia                                   | 12 (16.9)            | 5 (7.7)                       |
| Neutrophil count decreased               | 15 (21.1)            | 2 (3.1)                       |
| Diarrhea                                 | 14 (19.7)            | 11 (16.9)                     |
| Dermatitis acniform                      | 13 (18.3)            | 9 (13.8)                      |
| Leukopenia                               | 12 (16.9)            | 1 (1.5)                       |
| Neutropenia                              | 12 (16.9)            | 1 (1.5)                       |
| Mouth ulceration                         | 11 (15.5)            | 5 (7.7)                       |
| Rash maculo-papular                      | 9 (12.7)             | 12 (18.5)                     |
| AST increased                            | 8 (11.3)             | 27 (41.5)                     |
| Paronychia                               | 8 (11.3)             | 2 (3.1)                       |
| ALT increased                            | 4 (5.6)              | 26 (40.0)                     |
| Dry skin                                 | 4 (5.6)              | 7 (10.8)                      |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase.
**Supplementary Table 3.** Grade 3 or greater adverse events in at least 2 patients in either treatment arm (safety analysis set).

|                          | Osimertinib \(n=71\) | Comparator EGFR-TKI \(n=65\) |
|--------------------------|------------------------|-------------------------------|
| Patients with any grade ≥3 AE | 38 (53.5)              | 18 (27.7)                     |
| Neutrophil count decreased | 4 (5.6)                | 0                             |
| AST increased            | 3 (4.2)                | 1 (1.5)                       |
| Lymphocyte count decreased | 3 (4.2)                | 0                             |
| White blood cell count decreased | 3 (4.2)            | 0                             |
| Back pain                | 2 (2.8)                | 0                             |
| Dyspnea                  | 2 (2.8)                | 0                             |
| ECG QT prolonged         | 2 (2.8)                | 0                             |
| GGT increased            | 2 (2.8)                | 0                             |
| Hyponatremia             | 2 (2.8)                | 0                             |
| Platelet count decreased | 2 (2.8)                | 0                             |
| ALT increased            | 1 (1.4)                | 6 (9.2)                       |
| Lung infection           | 1 (1.4)                | 2 (3.1)                       |

*AE* adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ECG* electrocardiogram, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor, *GGT* gamma-glutamyl transferase.
### Supplementary Table 4. QTcF and QTcF intervals at any time during treatment (safety analysis set).

|                                    | Osimertinib (n=71) | Comparator EGFR-TKI (n=65) |
|------------------------------------|---------------------|-----------------------------|
| QTcF value >500 msec at any time   | 4 (5.6)             | 0                           |
| during treatment                   |                     |                             |
| QTcF increase from baseline        | 29 (40.8)           | 18 (27.7)                   |
| >30 msec at any time during        |                     |                             |
| treatment                         |                     |                             |
| QTcF increase from baseline        | 3 (4.2)             | 2 (3.1)                     |
| >60 msec at any time during        |                     |                             |
| treatment                         |                     |                             |

*EGFR-TKI*, epidermal growth factor receptor tyrosine kinase inhibitor; *QTcF* QT interval corrected for heart rate by Fridericia’s formula.

Note: The number of patients was a cumulative count for each category.
### Supplementary Table 5. Serious adverse events (safety analysis set).

| Event                                      | Osimertinib (n=71) | Comparator EGFR-TKI (n=65) |
|--------------------------------------------|---------------------|---------------------------|
| Patients with any SAE                      | 25 (35.2)           | 12 (18.5)                 |
| Pleural effusion                           | 3 (4.2)             | 1 (1.5)                   |
| Pneumonia                                  | 3 (4.2)             | 1 (1.5)                   |
| Acute kidney injury                        | 1 (1.4)             | 0                         |
| Adenoviral upper respiratory infection     | 1 (1.4)             | 0                         |
| ALT increased                              | 1 (1.4)             | 1 (1.5)                   |
| AST increased                              | 1 (1.4)             | 0                         |
| Atrial fibrillation                        | 1 (1.4)             | 0                         |
| Blood bilirubin increased                  | 1 (1.4)             | 0                         |
| Bone pain                                  | 1 (1.4)             | 1 (1.5)                   |
| Bronchiectasis                             | 1 (1.4)             | 0                         |
| Cardiac arrest                             | 1 (1.4)             | 0                         |
| Cardiac failure                            | 1 (1.4)             | 0                         |
| Cardiac tamponade                          | 1 (1.4)             | 0                         |
| Cerebral infarction                        | 1 (1.4)             | 0                         |
| Death                                      | 1 (1.4)             | 0                         |
| Deep vein thrombosis                       | 1 (1.4)             | 0                         |
| Depression                                 | 1 (1.4)             | 0                         |
| Hepatitis C                                | 1 (1.4)             | 0                         |
| Hyperuricemia                              | 1 (1.4)             | 0                         |
| Hypoglycemia                               | 1 (1.4)             | 0                         |
| Interstitial lung disease                  | 1 (1.4)             | 1 (1.5)                   |
| Lung infection                             | 1 (1.4)             | 0                         |
| Neutropenia                                | 1 (1.4)             | 0                         |
| Pericardial effusion                       | 1 (1.4)             | 0                         |
| Poisoning                                  | 1 (1.4)             | 0                         |
| Respiratory failure                        | 1 (1.4)             | 0                         |
| Tumor lysis syndrome                       | 1 (1.4)             | 0                         |
| Upper gastrointestinal hemorrhage          | 1 (1.4)             | 0                         |
| Condition                  | Count 1 | Count 2 |
|---------------------------|---------|---------|
| Venous thrombosis limb    | 1 (1.4) | 0       |
| White blood cell count decreased | 1 (1.4) | 0       |
| Upper respiratory tract infection | 0       | 1 (1.5) |
| Blood disorder            | 0       | 1 (1.5) |
| Cerebral ventricle dilatation | 0       | 1 (1.5) |
| Cholecystitis              | 0       | 1 (1.5) |
| Duodenal ulcer            | 0       | 1 (1.5) |
| Epilepsy                   | 0       | 1 (1.5) |
| Hemoptysis                 | 0       | 1 (1.5) |
| Rotator cuff syndrome      | 0       | 1 (1.5) |
| Transaminases increased    | 0       | 1 (1.5) |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor, *SAE* serious adverse event.

Note: Patients with multiple events in the same category are counted only once in that category.

Patients with events in more than one category are counted once in each of those categories.
**Supplementary Table 6.** Adverse events leading to permanent discontinuation of study drug (safety analysis set).

|                        | Osimertinib \((n=71)\) | Comparator EGFR-TKI \((n=65)\) |
|------------------------|--------------------------|----------------------------------|
| Patients with any AE leading to permanent discontinuation | 9 (12.7) | 4 (6.2) |
| Pneumonia              | 1 (1.4)                  | 0                                |
| Blood disorder         | 0                        | 1 (1.5)                          |
| Tumor lysis syndrome   | 1 (1.4)                  | 0                                |
| Depression             | 1 (1.4)                  | 0                                |
| Epilepsy               | 0                        | 1 (1.5)                          |
| Atrial fibrillation    | 1 (1.4)                  | 0                                |
| Cardiac tamponade      | 1 (1.4)                  | 0                                |
| Interstitial lung disease | 1 (1.4)              | 1 (1.5)                          |
| Upper gastrointestinal hemorrhage | 1 (1.4) | 0 |
| Hepatitis C            | 1 (1.4)                  | 0                                |
| Death                  | 1 (1.4)                  | 0                                |
| Fatigue                | 0                        | 1 (1.5)                          |
| ALT increased          | 1 (1.4)                  | 0                                |
| AST increased          | 1 (1.4)                  | 0                                |
| Blood bilirubin increased | 1 (1.4)              | 0                                |
| Poisoning              | 1 (1.4)                  | 0                                |

*AE* adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor.

**Note:** Patients with multiple events in the same category are counted only once in that category.

Patients with events in more than one category are counted once in each of those categories.
Supplementary Figure 1. Patient disposition.

PFS DCO, 10 January 2018; OS DCO, 25 June 2019.

*Randomized patients include n=19 patients who were also included in the global FLAURA study.

DCO data cutoff, EGFR-TKI epidermal growth factor receptor-tyrosine kinase inhibitor, PFS progression-free survival, OS overall survival.
Supplementary Figure 2. Kaplan-Meier plot of progression free survival assessed by blinded independent central review (sensitivity analysis; full analysis set).

Censored data are indicated by tick marks. Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date on which the patient was known to be alive.

*BICR* blinded independent central review, *CI* confidence interval, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *PFS* progression-free survival.
Supplementary Figure 3. Kaplan-Meier plot for a time to first subsequent therapy or death and b time to second subsequent therapy or death (full analysis set).

a

b
Censored data are indicated by tick marks. Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date on which the patient was known to be alive.

CI confidence interval, EGFR-TKI epidermal growth factor receptor-tyrosine kinase inhibitor, TFST time to first subsequent therapy, TSST time to second subsequent therapy.