Optimizing Sequential Treatment With EGFR Tyrosine Kinase Inhibitor With a Simulation of the T790M Mutation Rate in EGFR-Mutated Lung Cancer

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ABSTRACT

Introduction: The mutation rate of T790M might change the effective therapeutic sequence of EGFR tyrosine kinase inhibitors (TKIs). This simulation estimates the T790M positivity rate required for first-line first- or second-generation EGFR TKI to exceed overall progression-free survival (PFS) of first-line osimertinib.

Methods: The PFS of each treatment with EGFR TKIs as first-line treatment, with osimertinib as second-line treatment among T790M-positive cases, and chemotherapy as second-line treatment among T790M-negative cases was set based on phase 3 trials. Overall PFS A of “upfront osimertinib” and overall PFS B of “first- or second-generation EGFR TKIs followed by osimertinib or chemotherapy” were simulated at different T790M mutation rates, to estimate the T790M mutation rate at which PFS B exceeds PFS A.

Results: Upfront osimertinib: In the setting of PFS of 19 months with first-line osimertinib, the median overall PFS A was 24.8 months (95% confidence interval [CI]: 21.6–28.0 mo). Upfront first- or second-generation EGFR TKI: When the T790M positivity rate was set to 50% and the PFS of second-line osimertinib was 10 months, the total median PFS (PFS B) was 20.2 months (95% CI: 17.5–22.9 mo). Even at a T790M mutation rate of 100%, PFS B (24.7 mo; 95% CI: 21.9–27.9 mo) was shorter than PFS A.

Conclusions: Even with a T790M mutation rate of 100%, upfront osimertinib treatment is associated with better median PFS than the upfront treatment with first- or second-generation EGFR TKIs. Consistent with the results of the FLAURA trial, with regard to EGFR TKI monotherapy in the first-line treatment, upfront osimertinib would contribute to good prognosis.

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Keywords: Non–small cell lung cancer; EGFR; Sequential treatment; Rebiopsy; T790M
**Introduction**

Recent advances in chemotherapy and molecular targeted therapy have led to remarkable improvement in the survival of patients with lung cancer, especially those with NSCLC harboring an activating *EGFR* mutation.

Osimertinib, a third-generation *EGFR* TKI, is active against L858R mutation and ex19del, regardless of the T790M mutation status. In the FLAURA trial, a phase 3 trial that compared osimertinib with first-generation *EGFR* TKIs (gefitinib or erlotinib) in previously untreated patients with *EGFR*-mutated advanced NSCLC, patients who received osimertinib had longer progression-free survival (PFS) than those in the comparator *EGFR* TKI group, and treatment with upfront osimertinib was established as the standard-of-care for *EGFR*-mutated NSCLC.

In contrast, dacomitinib, a new second-generation *EGFR* TKI, had superior efficacy to gefitinib in first-line treatment. In addition, a combination therapy of erlotinib plus an antiangiogenic agent was recently reported to markedly improve PFS over erlotinib alone. Specifically, in the phase 3 RELAY trial, it was reported that patients treated with erlotinib plus ramucirumab had significantly longer PFS than those treated with erlotinib alone (median PFS; 19.4 mo [95% confidence interval [CI]: 15.4–21.6] versus 12.4 months [95% CI: 11.0–13.5], p < 0.0001). In addition, subsequent treatment with osimertinib can be an important therapeutic option as next-line therapy with dacomitinib or a combination therapy of erlotinib plus an antiangiogenic agent because the most common resistance mechanism to first- and second-generation *EGFR* TKIs is the gatekeeper mutation T790M, which is sensitive to osimertinib.

Thus, if the positivity rate of T790M mutation is high, first-line treatment with first- or second-generation *EGFR* TKI monotherapy or erlotinib plus an antiangiogenic agent would achieve better overall PFS in comparison with upfront osimertinib among patients with *EGFR* mutation.

This simulation study investigates whether there is a T790M positivity rate, at which the first-line use of the first- or second-generation *EGFR* TKIs, which would exceed the overall PFS of first-line osimertinib.

**Materials and Methods**

We generated 3000 independent simulation data sets on the basis of the exponential distribution, each with a sample size of 300. Censoring was not considered in this study. All statistical simulations were performed using SAS version 9.4 (The SAS Institute, Cary, NC). The results of the simulations are reported as total median PFS and 95% CI (Fig. 1).

Overall PFS was simulated by changing four factors (PFS of first-line treatment with any *EGFR* TKI, PFS of osimertinib in first- and second-line treatments, and the T790M positivity rate). The T790M mutation rate at which PFS A exceeds PFS B was estimated by comparing overall PFS A (Fig. 2A) of “first- and second-generation *EGFR* TKI followed by osimertinib or chemotherapy” with overall PFS B (Fig. 2B and C) of “upfront osimertinib followed by chemotherapy.”

![Figure 1. The algorithm for the current simulation and the setting of PFS for each treatment. BSC, best supportive care; CI, confidence interval; PFS, progression-free survival.](image-url)
The median PFS of first- and second-generation EGFR TKIs such as gefitinib, erlotinib, and afatinib as first-line treatment was set to 11 months on the basis of their respective phase 3 trials (Table 1, Fig. 1).4,9–16 With regard to dacomitinib in the first-line treatment, the median PFS was set to 15 months.4 On the basis of the three phase 3 trials (NEJ026, CTONG1509, RELAY) comparing erlotinib and erlotinib plus an antiangiogenic agent, the median PFS of erlotinib plus an antiangiogenic agent in the first-line treatment was set to 19 months (Table 1, Fig. 1).6–8

As for osimertinib, its median PFS in the first-line treatment was set to 19 months and that in the second-line treatment was 0 months.2,3,17

In this simulation, the T790M positivity rates, which are the percentages of patients who received osimertinib after first-line treatment with first- or second-generation EGFR TKIs (Fig. 2B and C, c/b + c), of 10% to 100% were generated from the multinomial distribution (interval: 10%). The PFS of cytotoxic chemotherapy after any EGFR TKI treatment was set to 5 months on the basis of the respective phase 3 trials, and the percentage of the patients who transitioned to best supportive care after receiving any treatment was set to 30%.2,11,13–18

For patients who transitioned to chemotherapy, the event was set to the timing of chemotherapy failure. For patients who transitioned to best supportive care, the event was set to the timing of osimertinib failure.

In addition, we analyzed the same simulation for each type of EGFR mutation (e.g., ex19del and L858R). On the basis of the subgroup analysis of each phase 3 trial described previously, each PFS was set as follows: osimertinib (in first-line setting), ex19del: 21 months, L858R: 14 months; gefitinib, erlotinib, or afatinib, ex19del: 12 months, L858R: 10 months; dacomitinib, ex19del: 17 months, L858R: 12 months; erlotinib plus

Figure 2. (A) The overall PFS A with upfront osimertinib treatment followed by chemotherapy is revealed in the red frame. The PFS for first-line osimertinib and chemotherapy is set to 19 months and 5 months, respectively. The percentage of patients who transitioned to BSC after receiving osimertinib was set to 30%. (B) The overall PFS B with first- or second-generation EGFR TKIs followed by osimertinib or chemotherapy is revealed in the blue frame. The PFS for first-line treatment with first- or second-generation EGFR TKIs and dacomitinib was set to 11 months and 15 months, respectively. The PFS for second-line osimertinib and chemotherapy was set to 10 months and 5 months, respectively. The percentage of the patients who received osimertinib (c) among the population receiving second-line treatment (b + c) was set to 10% to 100% (interval: 10%) (c/b + c). The percentage of patients who received osimertinib (c) among the whole first-line treatment population (a + b + c) was set to 7% to 70% (interval: 7%) (c/a + b + c). The percentage of patients who transitioned to BSC after receiving osimertinib was set to 30%. (C) The estimated overall PFS B with first- or second-generation EGFR TKIs plus antiangiogenic agent combination therapy followed by osimertinib or chemotherapy is revealed in the blue frame. The PFS for first-line treatment with erlotinib plus antiangiogenic agent combination therapy was set to 19 months. BSC, best supportive care; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
antiangiogenic agent, ex19del: 18 months, L858R: 19 months; osimertinib (in second-line setting),2,19 ex19del: 11 months, L858R: 10 months (Table 1, Fig. 1). All the PFS data used in this simulation are listed in Table 1.

### Results

#### Upfront Osimertinib

The total PFS, with upfront osimertinib followed by chemotherapy, is given in Table 2. When the PFS with first-line osimertinib was 19 months, the total median PFS was 24.8 months (95% CI: 21.6–28.0 mo; Table 2). With subgroup analysis for the EGFR mutation type, the total median PFS was 26.8 months (95% CI: 23.3–30.4 mo; Table 2). In the population with ex19del, the total median PFS was 24.7 months (95% CI: 21.9–27.9 mo).

#### First-Line Treatment With First- or Second-Generation EGFR TKIs

The total PFS with the first-line treatment with the first- or second-generation EGFR TKIs such as gefitinib, erlotinib, and afatinib, in each setting is found in Table 3. When the T790M-positivity rate was set to 100%, the total median PFS was 24.7 months (95% CI: 21.9–27.9 mo).

| Table 1. The PFS Achieved in the Phase 3 Trials of the Patients With EGFR-Mutated NSCLC Used in the Current Simulation |
|---------------------------------|-------------------------------|-------------------------------|
| EGFR TKI ± Antiangiogenic Agent | Trial                          | Comparatorer                  | Subtypes (n) | PFS (mo) | HR (95% CI) |
|---------------------------------|-------------------------------|-------------------------------|--------------|----------|-------------|
| Osimertinib (first-line)        | FLAURA1                       | Gefitinib or erlotinib        | Common mutation (279) | 17.7     | 0.45 (0.36-0.57) |
|                                 |                               |                               | Del 19 (175)   | 21.4     | 0.43 (0.32-0.56) |
|                                 |                               |                               | L858R (104)    | 14.4     | 0.51 (0.36-0.71) |
| Osimertinib (second-line)       | AURA 3                        | Platinum doublet              | Common mutation | 10.1     | 0.30 (0.23-0.41) |
|                                 |                               |                               | Del 1919       | 11.1     | 0.34 (0.24-0.46) |
|                                 |                               |                               | L858R19        | 9.5      | 0.46 (0.30-0.71) |
| Gefitinib                       | WJTOG34055,10                  | Cisplatin + docetaxel         | Common mutation (86) | 9.2      | 0.49 (0.34-0.71) |
|                                 |                               |                               | Del 19 (56)    | NR       | 0.45 (0.27-0.77) |
|                                 |                               |                               | L858R (30)      | NR       | 0.51 (0.29-0.90) |
|                                 | IPASS11                        | Carboplatin + paclitaxel      | Common mutation (132) | 11.0     | 0.38 (0.26-0.56) |
|                                 |                               |                               | Del 19 (66)    | 9.2      | 0.55 (0.35-0.87) |
|                                 | NEJ00212                       | Carboplatin + paclitaxel      | Common mutation (114) | 10.8     | 0.30 (0.22-0.41) |
|                                 |                               |                               | Del 19 (58)    | 11.5     | NR            |
|                                 |                               |                               | L858R (49)     | 10.8     | NR            |
| Erlotinib                       | OPTIMAL13                      | Platinum doublet              | Common mutation (82) | 13.1     | 0.16 (0.10-0.26) |
|                                 |                               |                               | Del 19 (43)    | 15.3     | 0.13 (0.07-0.25) |
|                                 |                               |                               | L858R (39)     | 12.5     | 0.26 (0.14-0.49) |
|                                 | EURTAC14                       | Platinum doublet              | Common mutation (86) | 9.7      | 0.37 (0.25-0.54) |
|                                 |                               |                               | Del 19 (57)    | 11.0     | 0.30 (0.18-0.50) |
|                                 |                               |                               | L858R (29)     | 8.4      | 0.55 (0.29-1.02) |
|                                 | ENSURE15                       | Gemcitabine + cisplatin       | Common mutation (110) | 11.0     | 0.34 (0.22-0.51) |
|                                 |                               |                               | Del 19 (57)    | 11.1     | 0.20 (0.11-0.37) |
|                                 |                               |                               | L858R (52)     | 8.3      | 0.57 (0.31-1.05) |
| Afatinib                        | LUX-Lung 316                   | Pemetrexed + cisplatin        | Common mutation (204) | 13.6     | 0.47 (0.34-0.65) |
|                                 |                               |                               | Del 19 (113)   | 13.7     | 0.28 (0.18-0.44) |
|                                 |                               |                               | L858R (91)     | 10.8     | 0.73 (0.46-1.17) |
|                                 | LUX-Lung 616                   | Gemcitabine + cisplatin       | Common mutation (216) | 11.0     | 0.25 (0.18-0.35) |
|                                 |                               |                               | Del 19 (124)   | 13.7     | 0.20 (0.13-0.33) |
|                                 |                               |                               | L858R (92)     | 9.6      | 0.32 (0.19-0.52) |
| Erlotinib + bevacizumab         | NEJ0266                       | Erlotinib                     | Common mutation (112) | 16.9     | 0.61 (0.42-0.88) |
|                                 |                               |                               | Del 19 (56)    | 16.6     | 0.69 (0.41-1.16) |
|                                 |                               |                               | L858R (56)     | 17.4     | 0.57 (0.33-0.97) |
| Erlotinib + bevacizumab         | CTONG15097                     | Erlotinib                     | Common mutation (157) | 18.0     | 0.55 (0.41-0.75) |
|                                 |                               |                               | Del 19 (82)    | 17.9     | 0.62 (0.41-0.92) |
|                                 |                               |                               | L858R (75)     | 19.5     | 0.51 (0.33-0.79) |
| Erlotinib + ramucirumab         | RELAY8                        | Erlotinib                     | Common mutation (224) | 19.6     | 0.59 (0.46-0.76) |
|                                 |                               |                               | Del 19 (123)   | 19.6     | 0.65 (0.47-0.90) |
|                                 |                               |                               | L858R (99)     | 19.4     | 0.62 (0.44-0.87) |

*The data are from pooled analysis of two phase 2 trials.19

CI, confidence interval; HR, hazard ratio; NR, not recorded; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Therefore, when the total median PFS is compared with that of first-line osimertinib (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]), the total PFS of this group did not exceed that of the first-line osimertinib group, even if the T790M positivity rate was 100% (hazard ratio = 1.00; Table 3, Fig. 3A, and Supplementary Fig. 1A).

In the subgroup simulation for EGFR mutation with ex19del, when the T790M positivity rate was set to 40%, the total median PFS was 20.7 months (95% CI: 18.1–23.6 mo). In comparison with the total median PFS of osimertinib in ex19del (26.8 mo [95% CI: 23.3–30.4 mo]), gefitinib, erlotinib, or afatinib required 98.7% (95% CI: 98.4%–99.0%) of the T790M positivity rate to exceed that of the first-line osimertinib group (Table 4, Fig. 3B, and Supplementary Fig. 1B). In the subgroup simulation for EGFR mutation with L858R mutation, when the T790M positivity rate was set to 40%, the total median PFS was 18.2 months (95% CI: 15.8–20.7 mo). A T790M positivity rate of 58.6% (95% CI: 58.4%–58.7%) is required for gefitinib, erlotinib, or afatinib to exceed the total median PFS of the first-line osimertinib group (Table 5, Fig. 3C, and Supplementary Fig. 1C).

First-Line Treatment With a New Second-Generation EGFR TKI (Dacomitinib)

The total PFS with the first-line treatment with dacomitinib in each setting is found in Table 3. When the total PFS is compared with that of first-line osimertinib (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]), a T790M positivity rate of 60% is required for the PFS of this group to exceed that of the first-line osimertinib group (Fig. 3A and Supplementary Fig. 1A). When the T790M positivity rate was set to 40%, the total median PFS was 23.8 months (95% CI: 20.8–27.1 mo), which was shorter than that of the first-line osimertinib group (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]).

In the subgroup simulation for EGFR mutation with ex19del, when the T790M positivity rate was set to 40%, the total median PFS was 26.3 months (95% CI: 23.0–30.0 mo). In comparison with the total median PFS of osimertinib in ex19del (26.8 mo [95% CI: 23.3–30.4 mo]), dacomitinib required 44.4% (95% CI: 44.1–44.5%) of T790M positivity rate to exceed that of the first-line osimertinib group (Table 4, Fig. 3B, and Supplementary Fig. 1B). In the subgroup simulation for

| Rate of T790M Positivity of Treated (%) c/(b + c) | Rate of Osimertinib (%) c/(a + b + c) | Gefitinib/Erlotinib/ | Dacomitinib | Erlotinib + Antiangiogenic Agent PFS = 19.0 mo |
|-----------------------------------------------|--------------------------------------|----------------------|-------------|--------------------------------------------|
| 10                                           | 7                                    | 17.2 (15.1–19.5)     | 21.4 (18.7–24.4) | 25.5 (22.3–29.1)                          |
| 20                                           | 14                                   | 17.8 (15.5–20.2)     | 22.2 (19.4–25.24)| 26.4 (22.9–30.0)                          |
| 30                                           | 21                                   | 18.5 (16.2–21.1)     | 22.9 (20.0–26.147)| 27.2 (23.7–31.0)                          |
| 40                                           | 28                                   | 19.3 (16.9–21.9)     | 23.8 (20.8–27.1) | 28.1 (24.7–32.0)                          |
| 50                                           | 35                                   | 20.1 (17.5–22.8)     | 24.7 (21.5–27.9) | 29.1 (25.3–32.9)                          |
| 60                                           | 42                                   | 21.0 (18.3–23.8)     | 25.6 (22.4–28.9) | 30.0 (26.3–34.0)                          |
| 70                                           | 49                                   | 21.9 (19.1–24.7)     | 26.5 (23.2–29.9) | 30.9 (27.1–34.9)                          |
| 80                                           | 56                                   | 22.7 (19.9–25.8)     | 27.4 (24.2–31.0) | 31.9 (28.1–35.9)                          |
| 90                                           | 63                                   | 23.7 (20.8–26.7)     | 28.4 (25.1–32.0) | 32.8 (28.9–36.9)                          |
| 100                                          | 70                                   | 24.7 (21.8–27.8)     | 29.4 (26.1–33.0) | 33.8 (29.9–37.9)                          |

First-line treatment with a new second-generation EGFR TKI (Dacomitinib). The total PFS with the first-line treatment with dacomitinib in each setting is found in Table 3. When the total PFS is compared with that of first-line osimertinib (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]), a T790M positivity rate of 60% is required for the PFS of this group to exceed that of the first-line osimertinib group (Fig. 3A and Supplementary Fig. 1A). When the T790M positivity rate was set to 40%, the total median PFS was 23.8 months (95% CI: 20.8–27.1 mo), which was shorter than that of the first-line osimertinib group (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]).

In the subgroup simulation for EGFR mutation with ex19del, when the T790M positivity rate was set to 40%, the total median PFS was 26.3 months (95% CI: 23.0–30.0 mo). In comparison with the total median PFS of osimertinib in ex19del (26.8 mo [95% CI: 23.3–30.4 mo]), dacomitinib required 44.4% (95% CI: 44.1–44.5%) of T790M positivity rate to exceed that of the first-line osimertinib group (Table 4, Fig. 3B, and Supplementary Fig. 1B). In the subgroup simulation for

| Rate of T790M Positivity of Treated (%) c/(b + c) | Rate of Osimertinib (%) c/(a + b + c) | Gefitinib/Erlotinib/ | Dacomitinib | Erlotinib + Antiangiogenic Agent PFS = 19.0 mo |
|-----------------------------------------------|--------------------------------------|----------------------|-------------|--------------------------------------------|
| 10                                           | 7                                    | 17.2 (15.1–19.5)     | 21.4 (18.7–24.4) | 25.5 (22.3–29.1)                          |
| 20                                           | 14                                   | 17.8 (15.5–20.2)     | 22.2 (19.4–25.24)| 26.4 (22.9–30.0)                          |
| 30                                           | 21                                   | 18.5 (16.2–21.1)     | 22.9 (20.0–26.147)| 27.2 (23.7–31.0)                          |
| 40                                           | 28                                   | 19.3 (16.9–21.9)     | 23.8 (20.8–27.1) | 28.1 (24.7–32.0)                          |
| 50                                           | 35                                   | 20.1 (17.5–22.8)     | 24.7 (21.5–27.9) | 29.1 (25.3–32.9)                          |
| 60                                           | 42                                   | 21.0 (18.3–23.8)     | 25.6 (22.4–28.9) | 30.0 (26.3–34.0)                          |
| 70                                           | 49                                   | 21.9 (19.1–24.7)     | 26.5 (23.2–29.9) | 30.9 (27.1–34.9)                          |
| 80                                           | 56                                   | 22.7 (19.9–25.8)     | 27.4 (24.2–31.0) | 31.9 (28.1–35.9)                          |
| 90                                           | 63                                   | 23.7 (20.8–26.7)     | 28.4 (25.1–32.0) | 32.8 (28.9–36.9)                          |
| 100                                          | 70                                   | 24.7 (21.8–27.8)     | 29.4 (26.1–33.0) | 33.8 (29.9–37.9)                          |

Bold format indicates that the median overall PFS is longer than that of osimertinib in Table 2.

a, b, and c correspond to those in Figure 2B and C, respectively.

c/(a + b + c): the percentage of the patients who received osimertinib among the population receiving second-line treatment. "b" and "c" correspond to those in Figure 2B and C, respectively.
EGFR mutation with L858R mutation, when the T790M positivity rate was set to 40%, the total median PFS was 20.5 months (95% CI: 17.9–23.3 mo). In addition, a T790M positivity rate of T790M of 29.2% (95% CI: 29.0%–29.4%) is required for dacomitinib to exceed the total median PFS of the first-line osimertinib in the

**Figure 3.** The relationship between the HR for disease progression or death and the of T790M positivity rate in each treatment group with EGFR TKIs. (A) The all-common EGFR tyrosine mutation type. (B) The subgroup analysis of the EGFR mutation with ex19del. (C) The subgroup analysis of the EGFR mutation with L858R. HR, hazard ratio; TKI, tyrosine kinase inhibitor.

EGFR mutation with L858R mutation, when the T790M positivity rate was set to 40%, the total median PFS was 20.5 months (95% CI: 17.9–23.3 mo). In addition, a T790M positivity rate of T790M of 29.2% (95% CI: 29.0%–29.4%) is required for dacomitinib to exceed the total median PFS of the first-line osimertinib in the

**Table 4.** The Simulation of Overall PFS With Each First- or Second-Generation EGFR TKI Treatment Followed by Osimertinib or Chemotherapy Among Ex19del

| T790M Positivity Rate of Treated | Rate of Osimertinib c/(b + c) | Gefitinib/Erlotinib/Afatinib PFS = 12.0 mo | Dacomitinib PFS = 15.0 mo | Erlotinib + Antiangiogenic Agent PFS = 18.0 mo |
|----------------------------------|--------------------------------|---------------------------------------------|---------------------------|-----------------------------------------------|
| 10                               | 7                              | 18.3 (16.0–20.8)                            | 23.6 (20.6–26.8)          | 24.6 (21.5–28.1)                              |
| 20                               | 14                             | 19.1 (16.7–21.6)                            | 24.5 (21.3–27.8)          | 25.5 (22.2–29.0)                              |
| 30                               | 21                             | 19.8 (17.3–22.6)                            | 25.3 (22.1–28.9)          | 26.4 (23.0–30.1)                              |
| 40                               | 28                             | 20.7 (18.1–23.6)                            | 26.3 (23.0–30.0)          | 27.4 (24.0–31.2)                              |
| 50                               | 35                             | 21.7 (18.8–24.6)                            | 27.3 (23.7–31.0)          | 28.4 (24.7–32.1)                              |
| 60                               | 42                             | 22.6 (19.7–25.6)                            | 28.3 (24.8–31.1)          | 29.4 (25.7–33.3)                              |
| 70                               | 49                             | 23.6 (20.6–26.6)                            | 29.4 (25.7–33.2)          | 30.5 (26.7–34.5)                              |
| 80                               | 56                             | 24.6 (21.5–27.9)                            | 30.4 (26.8–34.3)          | 31.5 (27.6–35.5)                              |
| 90                               | 63                             | 25.6 (22.6–28.8)                            | 31.5 (27.8–35.5)          | 32.6 (28.8–36.8)                              |
| 100                              | 70                             | 26.7 (23.7–30.2)                            | 32.6 (28.8–36.6)          | 33.7 (30.0–37.8)                              |

Bold format indicates that the median overall PFS is longer than that of osimertinib in Table 2.

\[ \text{c/(b + c): the percentage of the patients who received osimertinib among the population receiving second-line treatment.} \]

\[ \text{“b” and “c” correspond to those in Figure 2B and C.} \]

\[ \text{c/(a + b + c): the percentage of the patients who received osimertinib among the whole of first-line treatment population. “a,” “b,” and “c” correspond to those in Figure 2B and C.} \]

CI, confidence interval; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
The total PFS with first-line treatment with erlotinib plus an antiangiogenic agent in each setting is found in Table 3. When the T790M positivity rate was set to 40%, the total median PFS was 28.1 months (95% CI: 24.7–32.0 mo). When the total PFS was compared with that of first-line osimertinib (PFS: 24.8 mo [95% CI: 21.6–28.0 mo]), a T790M positivity rate of 10% was required for the PFS of this group to exceed that of the first-line osimertinib group (Fig. 3A and Supplementary Fig. 1A).

In the subgroup simulation of ex19del, when the T790M positivity rate was set to 10%, the total median PFS was 24.6 months (95% CI: 21.5–28.1 mo), and when it was set to 100%, the total median PFS was 33.7 months (95% CI: 30.0–37.8 mo). In comparison with the total median PFS of osimertinib among the population with ex19del (26.8 mo; 95% CI: 23.3–30.4 mo), a T790M positivity rate of 33.5% (95% CI: 33.3%–33.7%) is required for the median PFS of this group to exceed that of the first-line osimertinib group in the subgroup analysis of the population with ex19del (Table 4, Fig. 3B, and Supplementary Fig. 1B).

In the subgroup simulation for EGFR mutation with L858R mutation, when the T790M positivity rate was set to 10%, the total median PFS was 25.7 months (95% CI: 22.3–29.1 mo), and when it was set to 100%, the total median PFS was 33.9 months (95% CI: 30.0–38.0 mo). In comparison with the total median PFS of osimertinib in the L858R mutation (19.7 mo [95% CI: 17.3–22.3 mo]), the combination of erlotinib plus an antiangiogenic agent exceeds that of the first-line osimertinib group for any T790M positivity rate in the subgroup analysis of the population with the L858R mutation (Table 5, Fig. 3C, and Supplementary Fig. 1C).

### Discussion

This study revealed that upfront osimertinib followed by chemotherapy was associated with longer overall PFS than sequential treatment with first- or second-generation EGFR TKI monotherapy followed by osimertinib or chemotherapy, regardless of the T790M mutation rate after EGFR TKI monotherapy. This result is generally consistent with the final analysis of overall survival (OS) in the FLAURA trial, which might reveal the accuracy of this simulation. It was reported that upfront osimertinib was associated with significantly longer OS than treatment with comparator EGFR TKIs (hazard ratio = 0.80 [95.05% CI: 0.64–1.00], p = 0.046). Thus, with regard to EGFR TKI monotherapy in the first-line treatment, upfront osimertinib is the optimal treatment to improve the prognosis of patients with EGFR–mutated NSCLC.

In contrast, erlotinib plus antiangiogenic therapy requires a T790M mutation rate of only 10% after first-line treatment to exceed the total PFS of upfront osimertinib treatment. Approximately 50% of the patients whose disease progresses on a first- or second-generation TKI acquire T790M mutation, however, in the clinical setting, the detection rate of T790M mutations seems to be lower owing to the difficulty of accessing certain

| T790M Positivity Rate of Treated (%) | Rate of Osimertinib (%) | Median Overall PFS (mo) (95% CI) |
|-----------------------------------|------------------------|---------------------------------|
| Agent PFS = 10.0 mo               |                        |                                 |
| Gefitinib/Erlotinib/Afatinib       |                        |                                 |
| Erlotinib + Antiangiogenic Agent   |                        |                                 |
| PFS = 12.0 mo                     |                        |                                 |
| PFS = 19.0 mo                     |                        |                                 |
| 10                                | 7                      | 16.1 (14.1–18.3)               | 18.3 (16.0–20.8) | 25.7 (22.3–29.1) |
| 20                                | 14                     | 16.8 (14.6–19.0)               | 19.0 (16.6–21.5) | 26.4 (23.0–30.1) |
| 30                                | 21                     | 17.4 (15.2–19.8)               | 19.7 (17.2–22.4) | 27.2 (23.7–31.1) |
| 40                                | 28                     | 18.2 (15.8–20.7)               | 20.5 (17.9–23.3) | 28.1 (24.7–32.0) |
| 50                                | 35                     | 19.0 (16.5–21.6)               | 21.4 (19.2–26.0) | 29.1 (25.3–32.9) |
| 60                                | 42                     | 19.8 (17.2–22.5)               | 22.2 (19.4–25.1) | 30.0 (26.3–34.0) |
| 70                                | 49                     | 20.7 (18.1–24.5)               | 23.1 (20.2–26.1) | 31.0 (27.3–35.0) |
| 80                                | 56                     | 21.565 (18.9–24.5)             | 24.0 (21.2–27.2) | 31.9 (28.1–36.0) |
| 90                                | 63                     | 22.5 (19.8–25.4)               | 25.0 (21.9–28.2) | 32.9 (28.9–37.0) |
| 100                               | 70                     | 23.5 (20.1–26.8)               | 26.0 (23.0–29.2) | 33.9 (30.0–38.0) |

Bold format indicates that the median overall PFS is longer than that of osimertinib in Table 2.

a) b/(b + c): the percentage of the patients who received osimertinib among the population receiving second-line treatment. “b” and “c” correspond to those in Figure 2B and C.
b) c/(a + b + c): the percentage of the patients who received osimertinib among the whole of first-line treatment population. “a,” “b,” and “c” correspond to those in Figure 2B and C.
c) CI, confidence interval; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
tumor sites and obtaining adequate amounts of tumor cells.²⁰⁻²² Accordingly, in the real-world setting, it was reported that 25% to 39% of the patients received osimertinib as second-line therapy after first-line therapy with first- or second-generation EGFR TKIs.²²⁻²⁵ In contrast, in the RELAY trial, after a relapse during erlotinib plus ramucirumab treatment, the rate of T790M positivity detected with liquid biopsy was approximately 43%.⁹ Taken together, in the real-world setting, at least 30% of the patients received osimertinib after first-line treatment with erlotinib plus ramucirumab. Thus, first-line treatment with erlotinib plus antiangiogenic therapy might also be associated with long total PFS in the real-world setting. In addition, in the RELAY trial, the PFS benefit with erlotinib plus ramucirumab therapy was observed in both patients with ex19del (median PFS = 19.6 mo [95% CI: 15.1–22.2]) and L858R (median PFS = 19.4 mo [95% CI: 14.1–21.9]).⁸ Regarding osimertinib, in the phase 3 FLAURA trial, the median PFS of patients with ex19del was longer than that of patients with L858R (ex19del: 21.4 mo [95% CI: 16.5–24.3] versus L858R: 14.4 mo [95% CI: 11.1–18.9]).¹⁷ Moreover, in a subgroup analysis of OS in the FLAURA study, there was no significant difference between osimertinib and the comparator EGFR TKI group in patients with L858R mutations.¹⁷ In this simulation, if the rate of sequential osimertinib administration was 28%, which is close to the rate of osimertinib administration in real-world data, the total median PFS of erlotinib plus an antiangiogenic would exceed that of upfront osimertinib (osimertinib versus erlotinib plus antiangiogenic: 24.8 mo [95% CI: 21.6–28.0 mo] versus 28.1 mo [95% CI: 24.7–32.0 mo]). Moreover, subgroup analysis of EGFR mutation subtype revealed longer total median PFS of erlotinib plus antiangiogenic therapy than upfront osimertinib in the population with L858R mutation for any positivity rate of T790M mutation (Fig. 3C). Thus, first-line treatment with erlotinib plus an antiangiogenic would be associated with a good prognosis, specifically among patients with L858R mutations, even if biweekly visits to the hospital for infusion and any adverse events that might emerge during treatment are considered. Nevertheless, there have been few phase 3 trials of dacomitinib or erlotinib plus antiangiogenic therapy, and the data are immature. Specifically, regarding erlotinib plus ramucirumab, there has only been one phase 3 trial, and the credibility of the PFS used in this simulation is not high. In contrast, regarding first- or second-generation TKIs, there have been some phase 3 trials with updated OS data, and the PFS of first- or second-generation TKIs used in this simulation has a higher level of credibility. Additional results of ongoing clinical trials and other phase 3 trials are needed to assess these simulations of combination treatment.

This study is associated with some limitations. First, it is a simulation analysis using clinical trial data. In addition, the population of each of the clinical trials used in the current simulation was different, and it is difficult to compare the PFS in each trial directly. Specifically, the trials with osimertinib included patients with brain metastasis whereas those with dacomitinib and erlotinib plus antiangiogenic agents did not, although in the FLAURA trial, the median PFS of a subset of patients without brain metastases was 19.1 months (95% CI: 15.2–23.5), which was not markedly different from that of the overall study population of the trial.¹³ Moreover, patients with a tumor invading or abutting major blood vessels were excluded from the trials with the combination therapy of erlotinib plus antiangiogenic agents.⁵⁻⁶ Additional results of the ongoing clinical trials and a larger prospective study are needed to assess these findings. In addition, results of some ongoing phase 2 trials (WJOG9717, TORG1833, LNCT03909334) comparing osimertinib plus antiangiogenic agents and osimertinib alone are expected.

If new treatments that overcome the mechanisms of EGFR TKI resistance, such as MET amplification and C797S, are established with the development of next-generation sequencing in the near future, the treatment options will be more complicated, and it will be difficult to determine the optimal sequential treatment with randomized clinical trials. It is expected that studies, such as this simulation, with consideration of the combined use of artificial intelligence, will be more important for determining optimal sequential treatments.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100085.

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