# And Still They Come Over Troubled Waters: Can Asia's Third-Generation EGFR Tyrosine Kinase Inhibitors (Furmonertinib, Aumolertinib, Rezivertinib, Limertinib, Befotertinib, SH-1028, and Lazertinib) Affect Global Treatment of *EGFR*+ NSCLC

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## Introduction

Approximately 50% of patients with NSCLC diagnosed in Asia harbor the two canonical activating *EGFR* mutations (deletion exon 19, L858R) (*EGFR*+).[1] The T790M gatekeeper mutation is the dominant acquired resistance mutation to first-generation (1G) and second-generation (2G) EGFR tyrosine kinase inhibitors (TKIs), which necessitated the development of third-generation (3G) EGFR TKI.[2] Osimertinib is the first 3G EGFR TKI approved on the basis of a significant improvement in median progression-free survival (PFS) than platinum-based chemotherapy (hazard ratio [HR] = 0.30, 95% confidence interval [CI]: 0.23–0.41) in patients with *EGFR* T790M+ NSCLC in the AURA3 trial and an achieved investigator-assessed median PFS (mPFS) of 10.1 months.[3] By late September 2019, osimertinib was approved in 85 countries for the treatment of patients with *EGFR* T790M+ NSCLC.[4]

Contemporaneous development of several other 3G EGFR TKIs that are structurally distinct from osimertinib failed to reach regulatory approval or had their approval rescinded owing to a combination of adverse events, low efficacy, or rapidly changing treatment landscape.[2] Until 2021, osimertinib was the only approved 3G EGFR TKI to treat *EGFR* T790M mutation. The monopoly of a single 3G EGFR TKI to treat 50% of patients with NSCLC in Asia had unintended consequences in cost and accessibility, which led to the recent development of 3G EGFR TKIs by homegrown companies in Asia.[2,5,6] The successful development and approval of the 1G EGFR TKI, icotinib, in the People's Republic of China heralded the regional approach to tackle this major cancer burden.[5] Our editorial discusses recent data published on limertinib, befotertinib, SH-1028, and rezivertinib in patients with previously treated T790M+ NSCLC[7–10] with reference to similar data from osimertinib, aumolertinib, furmonertinib, and lazertinib.[11–15] In addition, we reviewed the phase 3 data of aumolertinib[16] and furmonertinib[17] in patients with treatment-naive NSCLC and their potential effect on the global treatment landscape with benchmark to FLAURA.[18–20]

## 3G EGFR TKIs in Previously Treated *T790M*+ NSCLC

Currently, the seven pyrimidine-based 3G EGFR TKIs developed from Asia share a similar backbone with osimertinib with side-chain modifications (Fig. 1). The pivotal phase 2 trials of four of these compounds against *EGFR* T790M+ NSCLC were published in this issue of the *Journal of Thoracic Oncology*.[7–10] Table 1 summarizes the trial conduct, patient and tumor characteristics, primary end points, clinical efficacies, and adverse events of these four compounds with comparison to previously published data of osimertinib, aumolertinib, furmonertinib and lazertinib.[11–15]

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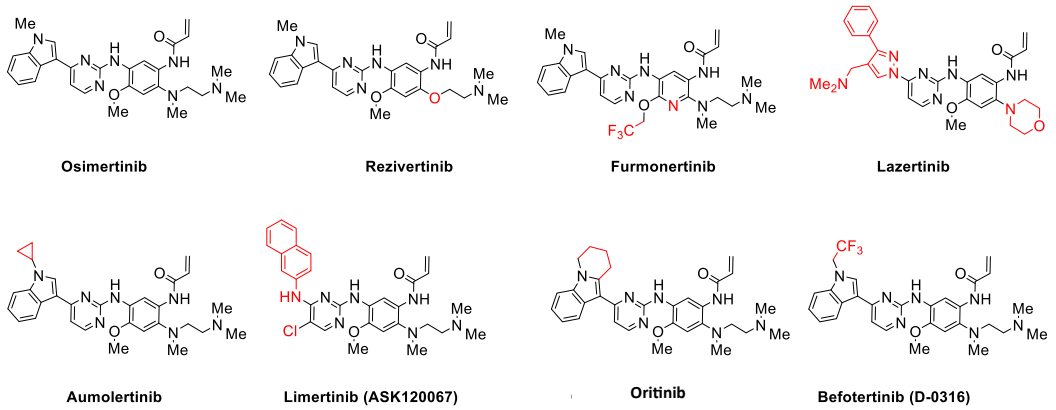


**Figure 1.** Structures of osimertinib, aumolertinib, furmonertinib, lazertinib, rezivertinib, limertinib, befotertinib, and SH-1028. The side chain modifications are highlighted in red.

Limertinib (ASK120067) was dosed at 160 mg twice daily, the only 3G EGFR TKI that is dosed twice daily. The incidence of treatment-related diarrhea from limertinib was unexpectedly high (81.7%), with 13.0% of patients experiencing grade greater than or equal to 3 diarrhea.[7] Indeed, 27.2% of patients required a 50% dose reduction (80 mg twice daily). The independent review committee (IRC)–assessed overall response rates (ORRs) of patients with and without dose adjustment were 76.8% (95% CI: 66.2%–85.4%) and 65.8% (95% CI: 59.1%–72.0%), respectively. The mPFSs of patients with and without dose adjustment were 15.2 (95% CI: 11.0–19.3) months and 11.0 (95% CI: 8.9–12.4) months, respectively.[7] Thus, the optimal dose of limertinib may be between 80 mg and 160 mg twice daily. An ongoing phase 3 trial of limertinib versus gefitinib has completed accrual (Table 2).

Befotertinib (D-0136) used a step-up dosing regimen of 75 mg daily for 3 weeks (one cycle) and then escalated to 100 mg daily. Nevertheless, 26.9% (78 of 290) did not dose escalate to 100 mg, including 19.7% (57 of 290) of the patients who started at 75 mg daily and stayed at 75 mg daily dose owing to thrombocytopenia (59.6%, 34 of 57) or headache (33.3%, 19 of 57). In addition, 4.8% (14 of 290) had to reduce the dose to 50 mg daily owing to thrombocytopenia or investigator decision. Importantly, the ORR and mPFS of patients who started at 75 mg but did not have dose escalation was 57.7% (95% CI: 46.0%–68.8%) and 15.1 (95% CI: 9.8–19.4) months compared with those who have dose escalation to 100 mg with an ORR of 71.2% (95% CI: 64.6%–77.2%) and mPFS of 17.9 (95% CI: 15.0–not evaluable) months.[8] The incidence of greater than or equal to grade 3 thrombocytopenia was 14.5%.[8] Thus, it seems that the therapeutic window of befotertinib is narrow, where dose escalation is necessary for maximum clinical efficacy but toxicity may be dose limiting. The phase 3 trial of befotertinib versus icotinib will likely be presented at the end of 2022 (personal communication, Shun Lu) (Table 2).

SH-1028 (formerly known as oritinib) was dosed at 200 mg once daily. Importantly, only 0.4% of the patient had localized disease, the lowest of all the phase 2 trials (Table 1).[9] The ORR was 60.4% (95% CI: 53.7%–66.8%) and the mPFS was 12.6 (95% CI: 9.7–15.3) months (Table 1). The unique adverse events of SH-1028 are asymptomatic creatinine phosphokinase (CPK) elevation at 28% (Table 1).[9] Nevertheless, SH-1028 was well tolerated at 200 mg once-daily dosing with a mean dose intensity of 100%.

Rezivertinib was dosed at 160 mg once daily on the basis of results from a large-scale phase 1/2a dose-escalation study.[21] A total of 226 patients with *EGFR* T790M+ NSCLC were enrolled in a period of 5 months right before the coronavirus disease 2019 pandemic. The ORR by blinded independent central review was 64.6% (95% CI: 58.0%–70.8%) and mPFS was 12.2 (95% CI: 9.6–13.9) months. Most of the adverse events were myelosuppression and corrected QT interval prolongation at 5.3%.[10]

Overall, unsurprisingly, the results of these four 3G EGFR TKIs were similar given the similarities in their structures. The clinical efficacies of all 3G EGFR TKIs were less against patients with EGFR L858R and those with central nervous system (CNS) metastases. We caution against cross-trial comparisons of PFS owing to differences in the patient composition of each trial (distribution of deletion exon 19/L858R, previous lines of treatment, tumor versus plasma detection of *EGFR* T790M mutation, proportions of CNS metastases, and the proportions of localized NSCLC [e.g., 12.3% in the aumolertinib trial, 4.0% in the furmonertinib trial, 1.3% in the rezivertinib trial, and 0.4% in the SH-1028 trial]) (Table 1). In addition, PFS was numerically higher among localized disease than metastatic disease as evidenced by a numerical difference in the mPFS of localized disease at 17.0 (95% CI: 8.3–19.4) months

**Table 1.** Efficacy and Adverse Events of 3G EGFR TKIs in T790M+ NSCLC From Asia

| | Aumolertinib (Almonertinib, HS-10296) | Furmonertinib (Alflutinib, AST2818) | Lazertinib (YH25448, JNJ-73841937) | Limertinib (ASK120067) | Befotertinib (D-0136)[a] | SH-1028 (Formerly Oritinib)[b] | Rezivertinib (BPI-7711) | Osimertinib (AURA17) | Osimertinib (AURA Extension/ AURA2) Pooled Analysis |
|---|---|---|---|---|---|---|---|---|---|
| Trial specifics | | | | | | | | | |
| n | 244 | 220 | 76 | 301 | 290 | 227 | 226 | 171 | 411 |
| Dose | 110 mg once daily | 80 mg once daily | 240 mg once daily | 160 mg twice daily | 75 mg once daily with dose increase to 100 mg after 3 wk if no grade 2 adverse event[c] | 200 mg once daily | 180 mg once daily | 80 mg once daily | 80 mg once daily |
| Plasma EGFR T790M+alone as enrollment criteria | No | No | No | Allowed | Allowed | No | Allowed | No | No |
| Del19/L858R (%/%) | 63.5/34.8 | 62/38 | 67.9/29.5 | 61.1/33.2 | 65.9/32.8 | 63.4/30.4 | 64.2/35.0 | 64/35 | 68/29 |
| Stage III (%) | 12.3% | 4% | 3.8% | 3.0% | 1.7% | 0.4% | 1.3% | 1% | 4% |
| Second line/ >second line (%/%)[a] | 76.6/23.4 | 77/23 | 64.125.9 | 77.4/21.9 | 87.6/12.4 | 70.9/29.1 | NA | 31/69 | 31.4/68.6 |
| Percentage brain metastasis (%) | 36.1% | 48% | 51.3% | 32.9% | 36.2% | 35.2% | 40.3% | 37% | 39% |
| Asian (%) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 98 | 60 |
| Primary end point | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR | BIRC-assessed ORR |
| Enrollment period (mo) | 5 mo | 6 mo | NA | 20 mo[d] | 7 mo | 29 mo[d] | 6 mo | NA | NA |
| Efficacy results | | | | | | | | | |
| ORR (%) | 68.9% (62.6%-74.6%) | 74% (68%-80%) | 55.3% (44.1%-66.4%) | 68.8% (63.2%-74.0%) | 67.6% (61.9%-71.9%) | 60.4% (53.7%-66.8%) | 64.6% (58%-70.8%) | 62% (54%-69%) | 66% (61%-70%) |
| DOR (mo) (95% CI) | 15.1 (12.5-16.6) | NR (8.4-NR)[a] | 17.7 (9.9-NR) | 11.1 (9.6-13.8) | 12.4 (11.0-14.6) | 12.5 (11.2-NR) | 12.5 (10.0-13.9) | 9.9 (8.3-12.9) | 12.3 (11.1-13.8) |
| mPFS (mo) (95% CI) | 12.4 (9.7-15.0) | 9.6 (8.2-9.7) | 11.1 (5.5-16.4) | 11.0 (9.7-12.4) | 16.6 (15.0-NE) | 12.6 (9.7-15.3) | 12.2 (9.6-13.9) | 9.7 | 9.9 (9.5-12.3) |
| PFS rate (%) | 71.8 (65.6-77.1) | NA | 59.3 (46.9-69.8) | 77.4 (71.6-82.2) | 70.7 (63.8-76.5) | 70.7 (63.8-76.5) | NA | NA | 71 (64-77) |
| (95% CI) | | | | | | | | | |
| -6-mo PFS rate | 51.7 (45.0-57.9) | NA | 48.0 (35.6-59.3) | 47.1 (39.4-54.5) | 52.9 (44.8-60.3) | 52.9 (44.8-60.3) | NA | NA | 44 (37-51 |
| -12-mo PFS rate | | | | | | | | | |
| mPFS (mo) (95% CI) | 10.9 (7.0-13.8) | NA | NA | 9.7 (5.9-11.6) | 12.5 (9.6-NR) | 8.3 (5.6-10.6) | 10.3 (7.0-12.5) | NA | 8.2 (6.9-9.7) |
| -Brain mets present | 16.5 (13.8-18.0) | NA | NA | | 17.9 (15.2-NR) | 13.8 (12.4-NR) | 12.4 (9.7-15.2) | NA | 12.4 (9.8-13.8) |
| -No brain mets | | | | | | | | | |

(continued)

**Table 1.** Continued

| | Aumolertinib (Almonertinib, HS-10296) | Furmonertinib (Alflutinib, AST2818) | Lazertinib (YH25448, JNJ-73841937) | Limertinib (ASK120067) | Befotertinib (D-0136)[a] | SH-1028 (Formerly Oritinib)[b] | Rezivertinib (BPI-7711) | Osimertinib (AURA17) | Osimertinib (AURA Extension/ AURA2) Pooled Analysis |
|---|---|---|---|---|---|---|---|---|---|
| mPFS (mo)<br>-del 19<br>-L858R | 12.4 (9.7–15.0)<br>12.3 (8.3–15.6) | NA<br>NA | NA<br>NA | NA<br>NA | NA<br>NA | 13.8 (12.2-NR)<br>9.7 (5.6-NR) | 12.4 (8.8-15.1)<br>10.3 (8.3-13.9) | NA<br>NA | 11.1 (9.7-13.1)<br>9.5 (7.7-12.3) |
| Adverse events | | | | | | | | | |
| Most common treatment-emergent adverse events (all grades) (%) | CPK increase (20.9)<br>Anemia (15.2)<br>ALT increase (13.1) | QT prolongation (15)<br>AST increase (15)<br>ALT increase (14)<br>WBC decrease (12) | Rash (37.2)<br>Pruritus (34.6)<br>Paresthesia (33.3)<br>Headache (28.2) | Diarrhea (81.7)<br>Anemia (32.9)<br>Rash (29.9)<br>Anorexia (28.2) | Thrombocytopenia (63.1)<br>Headache (28.6)<br>Leukopenia (25.5)<br>Anemia (24.1) | Diarrhea (41.6)<br>CPK increase (28.0)<br>Anemia (18.5)<br>WBC decrease (15.7) | Decrease WBC (27.9)<br>Decrease platelet (23.0)<br>Anemia (22.6) | Diarrhea (35)<br>Rash (30)<br>Cough (25) | Diarrhea (49)<br>Rash (49)<br>Dry skin (36)<br>Paronychia (34) |
| Notable adverse events (%)[e] | CPK increase (20.9) | QT prolongation (15) | Headache (28.2) | Diarrhea (81.7) | Thrombocytopenia (63.1)<br>Headache (28.6) | CPK increase (28)<br>QT prolongation (8) | QT prolongation (5.3) | Back pain (11) | QT prolongation (5) |

[a]Data from 75/100 mg cohort.
[b]From the start of phase 1 dose escalation.
[c]Of the patients, 26.9% did not dose escalate to 100 mg; 19.7% maintained dose at 75 mg.
[d]During COVID-19 pandemic.
[e]Not often associated OR high incidence with EGFR TKIs.
3G, third-generation; ALT, alanine aminotransferase; BIRC, blinded independent review committee; CI, confidence interval; COVID-19, coronavirus disease 2019; CPK, creatinine phosphokinase; del 19, deletion exon 19; DoR, duration of response; mPFS, median progression-free survival; NA, not available; NE, not evaluable; NR, not reached; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

**Table 2.** Design of the Ongoing Pivotal Phase 3 Trials of the 3G EGFR TKIs From Asia

| Compounds | Lazertinib | Rezivertinib | Limertinib | Befotertinib | SH-1028 |
|---|---|---|---|---|---|
| Trial name | LASER301 | NA | NA | NA | NA |
| Principal investigator | Byoung Chul Cho | Yuankai Shi | Yuankai Shi | Shun Lu | Caicun Zhou |
| Double blind | Yes | Yes | Yes | No | Yes |
| Placebo controlled | Yes | Yes | Yes | No | Yes |
| Comparison arm | Gefitinib | Gefitinib | Gefitinib | Icotinib | Gefitinib |
| Stratification factors | Del19 vs. L858R<br>Asian vs. non-Asians | Del19 vs. L858R<br>Brain mets (yes/no) | Del19 vs. L858R<br>Brain mets (yes/no) | Del 19 vs. L858R<br>Brain mets (yes/no) | Del19 vs. L858R<br>Brain mets (yes/no) |
| Randomization | 1:1 | 1:1 | 1:1 | 1:1 | 2:1 |
| Primary end point | Investigator-assessed PFS | IRC-assessed PFS | PFS | IRC-assessed PFS | Investigator-assessed PFS |
| Anticipated accrual number | 393 | 294 | 334 | 362 | 240 |
| Multinational | Yes (Australia, Greece, Hungary, Republic of Korea, Malaysia, Philippines, Russian Federation, Serbia, Singapore, Taiwan, Thailand, Turkey, Ukraine) | No (People's Republic of China only) | No (People's Republic of China only) | No (People's Republic of China only) | No (People's Republic of China only |
| Clinical trial number(s) | NCT04248829 | CTR20190442 | CTR20191523<br>NCT04143607 | CTR20192356<br>NCT04206072 | CTR20192508<br>NCT04239833 |
| Results | October 2022 | 2023 | 2023 | End of 2022 | 2023 |

*Note:* CTR number is for Chinese trial registration.
Data for rezivertinib trial design from http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml. Accessed July 18, 2022.
3G, third-generation; Del19, deletion exon 19; IRC, independent review committee; mets, metastasis; NA, not applicable; PFS, progression-free survival.

compared with 12.0 (95% CI: 9.6–13.8) months for metastatic disease for aumolertinib.[14] Furthermore, some of the trials (limertinib, befotertinib, and rezivertinib) allow patients with plasma-detected *EGFR* T790M+ found only by plasma genotyping to enroll. Patients with detectable *EGFR* T790M circulating tumor DNA generally had higher tumor burden and a poorer outcome from the AURA3 analysis.[22] Indeed, numerically lower ORR and mPFS were achieved by patients with detectable plasma *EGFR* T790M+ NSCLC in the limertinib and rezivertinib trials. The ORR was 75.6% (95% CI: 65.8%–78.3%) and 60.7% (95% CI: 49.1%–70.2%) for patients with tumor- and plasma-detected *EGFR* T790M+ NSCLC treated with limertinib, respectively.[7] The ORR and mPFS for patients on rezivertinib with tumor-detected *EGFR* T790M mutation were 70% (95% CI: 61%–78%) and 13.9 (95% CI: 11.3–17.9) compared to 56.9% (95% CI: 47.4%–66.1%) and 9.6 months (95% CI: 7.0–11.0).[10]

Drug approvals on the basis of less robust study designs are sometimes necessary. Regulatory approval of osimertinib was also accelerated when acquired *EGFR* T790M mutation was identified as an area of great unmet need.[7] In countries and regions where osimertinib is not easily accessible, approvals by local regulatory agencies on the basis of phase 2 data are not unreasonable and avoid delays in access to effective medicines. The fact that these trials enrolled quickly, over 5 to 7 months (before coronavirus disease 2019 pandemic), reflects the challenges patients face in accessing osimertinib, even in countries where it is approved. To date, aumolertinib and furmonertinib are approved in the People's Republic of China and lazertinib is approved in the Republic of Korea for treatment of *EGFR* T790M mutations.[2,23,24] Given the similar clinical efficacy revealed by the four other 3G EGFR TKIs, albeit with different adverse events profile, we anticipated that all of them should be approved by the Chinese National Medical Products Administration for treatment of *EGFR* T790M+ NSCLC. The degree of adoption of any of these new 3G EGFR TKIs in places where approved and available will depend on the cost, first-mover advantage, dosing schedule, side effects profiles, and the first-line phase 3 results.

## 3G *EGFR* TKIs in Treatment-Naive *EGFR*+ NSCLC

The most important utility of 3G EGFR TKI is the upfront treatment of advanced *EGFR*+ NSCLC on the basis

of the statistical improvement in mPFS[18] and overall survival achieved by osimertinib over 1G EGFR TKIs.[19] As such, it is anticipated that the incidence of T790M+ NSCLC will eventually decrease, and the clinical data of these phase 2 trials on "Asian" 3G EGFR TKIs outlined in Table 1 may be of historical rather than clinical significance.

Two of these EGFR TKIs, aumolertinib (AENEAS)[16] and furmonertinib (FURLONG),[17] have completed phase 3 trials (Table 3). Both trials were well-conducted, double-blind, placebo-controlled trials and stratified for known prognostics factors—EGFR subtype and CNS metastasis. The AENEAS study revealed a statistically superior mPFS (HR by IRC = 0.50; 95% CI: 0.39–0.64, $p < 0.0001$) of aumolertinib over gefitinib. All patient subgroups benefited from aumolertinib, including those with known CNS metastases. Toxicities were consistent with what were reported in the phase 2 APOLLO with elevated CPK (34%) being the most common adverse event.[16] Furmonertinib was found to have clinical benefits when compared with gefitinib in previously untreated patients in the phase 3 FURLONG study reference. mPFS was superior with furmonertinib (HR by IRC = 0.44, 95% CI: 0.34–0.58, $p < 0.0001$) with benefit found across all subgroups. The most common toxicities were corrected QT interval prolongation (grades 1–2, 6%, and grade $\geq$ 3, 3%) and diarrhea. Quality of life, assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-L13, although statistically improved, was not clinically significant compared with that in gefitinib.[17]

Both trials compared well to the overall FLAURA population (HR by IRC = 0.45, 95% CI: 0.36–0.51, $p < 0.001$).[18] Among the subgroup of Asian patients enrolled in FLAURA, the statistical benefit of osimertinib remains (HR = 0.54, 95% CI: 0.41–0.72, $p < 0.0001$).[20] Treatment-related QT prolongation occurred in 14% of the osimertinib-treated patients in FLAURA. The safety profile of furmonertinib is most closely similar to that of osimertinib.

## Path for Regulatory Approval of Asia's 3G *EGFR* TKIs in the United States

Two main pillars of drug development are developing novel first-in-class treatments and improving access to effective and affordable therapy but sometimes these two pillars conflict. By strict interpretation, innovation leads to monopoly because any subsequent development of the same class of drugs will carry the "me-too" derogatory label. As the only 3G EGFR TKI available for a long time, the initial price of osimertinib was prohibitively expensive, reflecting the speed in enrolling patients with *EGFR* T790M+ NSCLC into trials, such as 6 months, as recently in late 2019 in the rezivertinib trial.[10]

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency have published guidelines on considerations of foreign data from a regulatory perspective. The ICH-E5 guideline, published in 1998, provides a framework for evaluating a new product's sensitivity to ethnic factors and the need for a bridging study. The goal of the ICH-E5 framework is to avoid repeating clinical trials, which may be costly and delay access to effective medications.[25,26]

Both agencies require validation of compliance to good clinical practices (GCP) and request for GCP inspection on clinical trial sites where a marketing-authorization application has been submitted. The FDA has additional criteria (21 CFR 314.106) for the approval of a drug based only on foreign data, which are as follows: (1) foreign data are applicable to the U.S. population and U.S. medical practice; (2) studies are performed by investigators of recognized competence; and (3) FDA validation of trial data through on-site inspections or other appropriate means.

Some will argue that *EGFR*+ NSCLC is a unifying molecular subtype of NSCLC that responds to EGFR TKIs regardless of ethnicity of the patient. Nevertheless, the process to gain approval is arduous. Take the "re-introduction" of gefitinib into the United States as first-line treatment of patients with *EGFR*+ NSCLC as an example. FDA approval was obtained[27] after a phase 4 single-arm study conducted exclusively in European patients on the efficacy and safety of gefitinib in *EGFR*+ NSCLC (IFUM)[28] in addition to a retrospective, blinded, IRC-assessed PFS of the subgroup of patients with *EGFR*+ NSCLC (retrospectively identified) who received gefitinib versus carboplatin/paclitaxel in the landmark IPASS trial.[29]

The recent decision by the FDA in rejecting the application of sintilimab, studied in the phase 3 ORIENT-11 trial[30,31] in the People's Republic of China, offers insight into the challenges that Asia's 3G EGFR TKIs will face in getting regulatory approval in Western countries.[32,33] Despite vigorous arguments from the supporters of ORIENT-11,[34,35] the rejection reasons highlighted by the FDA were single-country study (does not represent the diversity of the U.S. population, unknown pharmacokinetics of sintilimab in non-Chinese patients), inappropriate control arm (platinum-chemotherapy alone; although KEYNOTE-189 was just approved in the People's Republic of China and carried a huge cost for patients), suboptimal choice of study end points (PFS rather than overall survival for prospective statistical calculation and follow-up), nonadherence to GCP, lack of FDA advance consultation and oversight, and limited clinical inspections due to Covid-19 pandemic.[32,33]

The two most promising 3G EGFR TKIs, aumolertinib and furmonertinib, with their well-conducted AENEAS and FURLONG phase 3 trials, respectively, lack all the criteria set out by the U.S. FDA ORIENT-11 decisions (only conducted in the People's Republic of China,

**Table 3.** List of Trial Characteristics, Clinical Efficacy, and Adverse Events of Randomized Phase 3 Trial of 3G EGFR TKI (Data Applied to the 3G EGFR TKI Arm)

| Trial name | AENEAS (n = 429) | FURLONG (n = 357) | FLAURA Asia Subset (n = 162) | FLAURA Overall (n = 556) |
|---|---|---|---|---|
| Trial characteristics | | | | |
| Investigational 3G EGFR TKI | Aumolertinib 110 mg daily | Furmonertinib 80 mg daily | Osimertinib 80 mg daily | Osimertinib 80 mg daily |
| SOC 1G EGFR TKI | Gefitinib 250 mg daily | Gefitinib 250 mg daily | Gefitinib 250 mg daily OR erlotinib 150 mg daily | Gefitinib 250 mg daily OR erlotinib 150 mg daily |
| Placebo-controlled | Yes | Yes | Yes | Yes |
| Randomization | 1:1 | 1:1 | 1:1 | 1:1 |
| Stratification factors | EGFR del19 vs. L858R<br>CNS mets: yes/no | EGFR del19 vs. L858R<br>CNS mets: yes/no | | EGFR del19 vs. L858R<br>Race: Asian/non-Asian |
| Stage IIIB/C | Allowed | Allowed | Allowed | Allowed |
| CNS metastasis | Asymptomatic (treated/untreated) allowed | Asymptomatic (treated/untreated) allowed | Stable CNS mets allowed | Stable CNS mets allowed |
| Primary end point | Investigator-assessed PFS | IRC-assessed PFS | Investigator-assessed PFS | Investigator-assessed PFS |
| Stage IIIB/C | 6.8% | 4.8% | 4.9% | 5.2% |
| CNS metastasis present | 26.8% | 33.9% | 20.4% | 20.9% |
| EGFR subtype | Del19: 65.5%<br>L858R: 34.4% | Del19: 51.3%<br>L858R: 48.7% | NA | Del19: 62.7%<br>L858R: 37.2% |
| Positive smoking history | 30.1% | 23.8% | 35.8% | 21.2% |
| Asian | 100% | 100% | 100% | 62.4% |
| Median follow-up time | Aumolertinib: 20.5 mo (95% CI: 18.0–20.6)<br>Gefitinib: 20.7 mo (95% CI: 19.3–20.8) | Furmonertinib: 21.0 mo (IQR: 18.0–23.5)<br>Gefitinib: 21.0 mo (IQR: 18.0–23.5) | Osimertinib: 13.8 mo<br>Gefitinib/erlotinib: 10.7 mo | Osimertinib: 15.0 mo (range: 0–25.1)<br>Gefitinib/erlotinib (range: 0–26.1) |
| Results (overall) | | | | |
| Median PFS (investigator-assessed) | Aumolertinib: 19.3 mo (95% CI: 17.8–20.8)<br>Gefitinib: 9.9 mo (95% CI: 8.3–12.6)<br>HR = 0.46 (95% CI: 0.36–0.60); $p < 0.001$ | Furmonertinib: 18.3 mo (95% CI: 15.2–20.8) vs.<br>Gefitinib: 11.0 mo (95% CI: 9.7–12.4)<br>HR = 0.51 (95% CI: 0.39–0.66); $p < 0.0001$ | Osimertinib: 16.5 mo (95% CI: 13.8–20.7)<br>Gefitinib/erlotinib: 11.0 mo (95% CI: 9.5–12.6)<br>HR = 0.54 (95% CI: 0.41–0.72); $p < 0.0001$ | Osimertinib: 18.9 mo (95% CI: 15.2–21.4)<br>Gefitinib/erlotinib: 10.2 mo (95% CI: 9.6–11.1)<br>HR = 0.46 (95% CI: 0.37–0.57); $p < 0.001$ |
| Median PFS (blinded independent review) | Aumolertinib: 17.9 mo (95% CI: 15.1–20.5)<br>Gefitinib: 9.7 mo (95% CI: 9.6–11.2)<br>HR = 0.50 (95% CI: 0.39–0.64); $p < 0.0001$ | Furmonertinib: 20.8 mo (95% CI: 17.8–23.5)<br>Gefitinib: 11.1 mo (95% CI: 9.7–12.5)<br>HR = 0.44 (95% CI: 0.34–0.58); $p < 0.0001$ | NA | Osimertinib: 17.7 mo (95% CI: 15.1–21.4)<br>Gefitinib/erlotinib: 9.7 mo (95% CI: 8.5–11.0)<br>HR = 0.45 (95% CI: 0.36–0.51); $p < 0.001$ |
| ORR | Aumolertinib: 73.8% (95% CI: 67.4–79.6)<br>Gefitinib: 72.1% (95% CI: 65.6–78.0); $p = 0.6939$ | Furmonertinib: 89% (95% CI: 83–93)<br>Gefitinib: 84% (95% CI: 78–89)<br>OR = 1.50 (95% CI: 0.80–2.83; $p = 0.21$ | Osimertinib: 80% (95% CI: 73–86)<br>Gefitinib/erlotinib: 75% (95% CI: 68–82)<br>OR = 1.33 (0.78–2.28); $p = 0.2918$ | Osimertinib: 80% (95% CI: 75–85)<br>Gefitinib/erlotinib: 76% (95% CI: 70–81)<br>OR = 1.27 (95% CI: 0.85–1.90); $p = 0.24$ |

(continued)

**Table 3.** Continued

| Trial name | AENEAS (n = 429) | FURLONG (n = 357) | FLAURA Asia Subset (n = 162) | FLAURA Overall (n = 556) |
|---|---|---|---|---|
| Results (EGFR del19) | | | | |
| Median PFS | Aumolertinib: 20.8 mo (95% CI: 18.1-20.9)<br>Gefitinib: 12.3 mo (95% CI: 9.6-13.8)<br>HR = 0.39 (95% CI: 0.28-0.54); $p < 0.0001$ | HR = 0.35 (95% CI: 0.23-0.53); $p < 0.0001$ | HR = 0.59 (95% CI: 0.41-0.85) | Osimertinib: 21.4 mo (95% CI: 16.5-24.3)<br>Gefitinib/erlotinib: 11.0 mo (95% CI: 9.7-12.6)<br>HR = 0.43 (95% CI: 0.32-0.56); $p < 0.001$ |
| ORR | NA | NA | NA | NA |
| Results (EGFR L858R) | | | | |
| Median PFS | Aumolertinib: 13.4 mo (95% CI: 7.3-18.0)<br>Gefitinib: 8.3 mo (95% CI: 6.8-9.9)<br>HR = 0.60 (95% CI: 0.40-0.89); $p = 0.0102$ | HR = 0.54 (95% CI: 0.37-0.77); $p = 0.0006$ | HR = 0.48 (95% CI: 0.31-0.74) | Osimertinib: 14.4 mo (95% CI: 11.1-18.9)<br>Gefitinib/erlotinib: 9.5 mo (95% CI: 8.1-11.0)<br>HR = 0.51 (95% CI: 0.36-0.71); $p < 0.001$ |
| ORR | NA | NA | NA | NA |
| Results (brain mets present) | | | | |
| Median PFS | Aumolertinib: 15.3 mo (95% CI: 10.8-20.8)<br>Gefitinib: 8.2 mo (6.5-8.3)<br>HR = 0.38 (0.24-0.60); $p < 0.0001$ | Furmonertinib: 18.0 mo (95% CI: 12.4-23.3)<br>Gefitinib: 11.2 mo (95% CI: 8.2-15.1)<br>HR = 0.52 (95% CI: 0.33-0.80); $p = 0.0028$ | HR = 0.68 (95% CI: 0.37-1.22) | Osimertinib: 15.2 mo (95% CI: 12.1-21.4)<br>Gefitinib/erlotinib: 9.6 mo (95% CI: 7.0-12.4)<br>HR = 0.47 (95% CI: 0.30-0.74); $p < 0.001$ |
| ORR | NA | NA | NA | Osimertinib: 76% (95% CI: 62-86)<br>Gefitinib/erlotinib: 86% (95% CI: 75-93)<br>OR = 0.5 (95% CI: 0.2-1.3); $p = 0.16$ |
| Results (brain metastasis absent) | | | | |
| Median PFS | Aumolertinib: 19.3 mo (17.8-NA)<br>Gefitinib: 12.6 mo (9.6-14.0)<br>HR = 0.51 (0.38-0.69); $p < 0.0001$ | Furmonertinib: 20.9 mo (95% CI: 18.0-23.6)<br>Gefitinib: 11.1 mo (95% CI: 9.7-12.5)<br>HR = 0·41 (0.29-0.58); $p < 0.0001$ | HR = 0.52 (95% CI: 0.38-0.72) | Osimertinib: 19.1 mo (95% CI: 15.2-23.5)<br>Gefitinib/erlotinib: 10.9 mo (95% CI: 9.6-12.3)<br>HR = 0.46 (95% CI: 0.36-0.59); $p < 0.0001$ |
| ORR | NA | NA | NA | Osimertinib: 81% (95% CI: 75-86)<br>Gefitinib/erlotinib: 73% (95% CI: 66-79)<br>OR = 1.6 (95% CI: 1.0-2.5); $p = 0.04$ |

(continued)

**Table 3.** Continued

| Trial name | AENEAS (n = 429) | FURLONG (n = 357) | FLAURA Asia Subset (n = 162) | FLAURA Overall (n = 556) |
|---|---|---|---|---|
| Top 5 most common and unique treatment-related adverse events (all grades) | | | | |
| Adverse events | CPK elevation: 34.1% | Elevated AST: 29% | Rash and acne: 57% | Rash and acne: 54% |
| | AST elevation: 28.0% | Diarrhea: 27% | Diarrhea: 47% | Diarrhea: 49% |
| | ALT elevation: 27.6% | Elevated ALT: 26% | Paronychia: 38% | Dry skin: 33% |
| | Decrease WBC count: 20.6% | Rash: 17% | Dry skin: 35% | Paronychia: 33% |
| | Rash: 20.6% | Decrease WBC count: 15% | Stomatitis: 33% | Stomatitis: 25% |
| | | | QT prolongation 14%-unique | QT prolongation (10%)-treatment-emergent |

1G, first generation; 3G, third generation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CNS, central nervous system; CPK, creatinine phosphokinase; Del19, deletion exon 19; HR, hazard ratio; IQR, interquartile range; IRC, independent review committee; mets, metastasis; NA, not available; SOC, standard of care; TKI, tyrosine kinase inhibitor.

inappropriate control arm of 1G EGFR TKI, PFS as primary end point). It remains to be seen whether these two 3G EGFR TKIs will be able to reach the global stage.[36] In addition, the unique side effects of CPK elevation in aumolertinib will likely be needed to be investigated in non-Asian patients minimally ala IFUM single-arm phase 2 design.[28]

Many of the FDA's concerns on study designs on AENEAS and FURLONG also apply to the frontline trials involving Asia's 3G EGFR TKIs. Additionally, befotertinib is compared with icotinib (Table 2), an 1G EGFR TKI that is not approved outside the People's Republic of China, and thus the regulatory path for befotertinib will face additional challenge. Even in the LASER301 study (NCT04248829), which addresses some of the FDA concerns by involving multiregional sites, the lack of participation of U.S. patients likely dims its chance of approval in the United States as monotherapy for frontline treatment of advanced *EGFR*+ NSCLC. Lazertinib alone or in combination with amivantamab is undergoing first-line (MARIPOSA-1, NCT04487080) and second-line (lazertinib + amivantamab + chemotherapy; MARIPOSA-2, NCT04988295) treatment of advanced *EGFR*+ NSCLC, thus having two additional "shots on goal" for regulatory approval albeit at a later date.[37]

## Concluding Remarks

In summary, of the four 3G EGFR TKIs that formed the basis of this editorial, SH-1028 and rezivertinib seem to have both good clinical efficacy and safety and once-daily dosing convenience. The dosing regimens of limertinib and befotertinib will likely need to be optimized in non-Chinese/non-Asian patients if they are going to be developed outside the People's Republic of China given the high incidence of diarrhea (limertinib) and headache and thrombocytopenia (befotertinib). Furthermore, twice-daily dosing (limertinib) or step-up dosing (befotertinib) will limit their adaptability globally in face of first-mover effects of aumolertinib furmonertinib and lazertinib.

Nevertheless, aumolertinib and furmonertinib are the two front-running 3G EGFR TKIs with published clinical efficacy against 1G EGFR TKIs with acceptable adverse events. We eagerly await the disposition of aumolertinib's application to the United Kingdom on the basis of the AEANAS trial,[38] the results of which either set the precedence for approvals of 3G EGFR TKIs outside of the People's Republic of China or remain them a "bridge too far over troubled waters."[39,40]

## CRediT Authorship Contribution Statement

**Sally C. M. Lau, Sai-Hong Ignatius Ou:** Conceptualization, Data curation, Validation, Writing—original draft, Writing—review and editing.

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