The EGFR tyrosine kinase inhibitors (TKIs) have initiated the era of precision medicine in lung cancer. In the past two decades, EGFR TKIs have dramatically extended the overall survival (OS) of patients with advanced NSCLC with EGFR-activating mutations from less than 12 months in the chemotherapy era to 3 years or more in the targeted therapy era. From quinazoline-based reversible inhibitors to irreversible pan-HER inhibitors then to pyrimidine-based irreversible inhibitor, the third-generation (3G) EGFR TKIs target the Thr790Met (T790M) “gatekeeper” mutation, a first-generation (1G)/second-generation (2G) TKI-resistance mutation, by a strong covalent binding to cysteine 797 residue in the adenosine triphosphate binding site of the EGFR kinase domain. So far, more than four 3G TKIs have striking clinical efficacy.

Osimertinib is the first and the only 3G TKI approved by the Food and Drug Administration, European Medicines Agency, and Chinese National Medical Products Administration based on its impressive survival benefit found both in the later-line setting in patients harboring the T790M mutation in treatment-naive patients. Other 3G TKIs including almonertinib (HS-10296) and furmonertinib (alflutinib/AST2818) have been approved by the Chinese National Medical Products Administration recently for previously treated, metastatic EGFR T790M-positive NSCLC. Nevertheless, not all 3G TKIs have been successfully developed. For example, the development of rociletinib (CO-1686), olmutinib (HM61713/BI 1482694), maverlertinib (PF06747775), and naquotinib (ASP8273) has been discontinued owing to off-target toxicity and modest efficacy. Against this backdrop, Cho et al. report a phase 1/2 study of another 3G EGFR TKI lazertinib 240 mg in T790M-mutant advanced NSCLC after previous 1/2G TKI therapy in this issue of Journal of Thoracic Oncology.

Lazertinib (YH25448) is a novel irreversible inhibitor selectively targeting EGFR single (exon 19 deletion [ex19del], L858R, T790M) and double (ex19del/T790M and L858R/T790M) mutations. Preclinical data support the ability of lazertinib to penetrate the blood–brain barrier. In this study, lazertinib 240 mg maintained its promising clinical performance after 2 years of follow-up, exhibiting comparable efficacy with the other 3G TKIs, osimertinib, almonertinib, and alflutinib, in a similar population (Fig. 1 and Supplementary Table 1). In terms of intracranial control, lazertinib had excellent results as well with the objective response rate of 86% (6 of 7) and intracranial progression-free survival (PFS) of 26 months, which is superior to the data currently released by the other 3G TKIs. If these observations can be repeated in larger studies or in the real world in the future, lazertinib may be the drug of choice for patients with brain metastasis. The adverse event spectrum of lazertinib was comparable with that of osimertinib, with the exception that the incidence of cardiac toxicity and interstitial lung disease seemed to be less. Nevertheless, the proportions of treatment adjustments owing to...
Figure 1. Comparison of the efficacy of the current 3G EGFR TKIs in active phase 2 to 3 clinical development. *Subgroup analyses from full-analysis set; #CNS full-analysis set. 3G, three-generation; 19del, exon 19 deletion; CNS, central nervous system; CR, complete response; NA, not available; NR, not reached; OS, overall survival; PD, progression disease; PFS, progression progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
adverse event were higher than that reported for the other 3G TKIs (Table 1).

Several favorable properties of lazertinib ensure its comparable potency and intracranial activity to osimertinib, including lower specific off-target toxicity. First, lazertinib exhibited higher selectivity against various mutant EGFRs, including T790M, and lower activity against wild-type EGFR than did osimertinib.15 The inhibition of downstream EGFR signaling pathways by lazertinib was similarly effective and more pronounced compared with osimertinib in vitro. Second, unlike osimertinib, lazertinib is not a substrate for BCRP and only a weak substrate of MDR1 (P-glycoprotein),15 suggesting lazertinib may be less affected by efflux transporters. Consistent with this hypothesis, lazertinib had superior tumor-shrinking efficacy to osimertinib in a murine brain metastasis model, with a high blood–brain barrier penetration profile. Third, owing to lack of inhibition of HER2 and type 1 insulin-like growth factor receptor,15 lazertinib exhibited less cardiac toxicity and hyperglycemia compared with osimertinib and rociletinib, respectively. This safety profile may allow the conduct of high-dose studies or combinations with agents such as antiangiogenics aimed at specific populations such as those with leptomeningeal metastases and atypical mutations in the future. As a mono-anilino–pyrimidine compound, lazertinib has a similar binding mode to osimertinib, resulting in generally similar acquired resistance mechanisms. Nevertheless, incidence of resistance occurred in different proportions in the current study compared with other 3G TKIs in the second-line setting.16 Of note, the resistance mechanisms of 3G TKIs in the first-line and later-line settings are distinct. We look forward to the results of LASER301 to provide more information.

The development pattern of EGFR TKIs in lung cancer has been the model for tumors with oncogene drivers, changing multiple paradigms in practice.17 Nevertheless, there are many challenges to maximizing the efficacy of 3G TKIs.

First, what is the optimal order to sequence EGFR TKIs with “three” generations under one roof? Osimertinib was found to have superiority in treatment-naive patients with EGFR-sensitizing mutations compared with 1G EGFR TKIs in the FLAURA study. Aumolertinib, another 3G TKI from People’s Republic of China, was found to have prolonged PFS compared with gefitinib in a similar population although the OS data are immature.18 Clinical trials of other 3G TKIs for first-line treatment are currently in progress. Nevertheless, despite this, in the context of less than convincing OS data for osimertinib in specific populations (Asian, L858R mutation) and more complicated resistance mechanisms, the optimal sequencing of
different generations of EGFR TKIs remains controversial. Indeed, in real-world studies of EGFR-mutant advanced NSCLC, initial therapy with 1/2G TKIs followed by osimertinib when there is an acquired T790M mutation achieved a remarkable OS of more than 40 months. Therefore, the value of treatment becomes the key to determine the most suitable treatment strategy. Unlike those from the American Society of Clinical Oncology and the European Society for Medical Oncology, the approach to value the anticancer therapies of the Chinese Thoracic Oncology Group has taken the subsequent treatment into account and distributed different weights to the four aspects, including efficacy (PFS/OS and sequential treatment), safety (treatment-related severe adverse events and dose adjustment), quality of life, and compensation. According to the Chinese Thoracic Oncology Group scoring system, osimertinib is only preferred for untreated patients with EGFR ex19del mutation and brain metastases. Taking into account the differences in ethnicity and affordability, more studies with large sample sizes are needed to delineate optimal treatment patterns.

Second, how can the efficacy of 3G TKIs be better predicted? EGFR-mutant lung cancer has evolved along different trajectories and ended up with the heterogeneity in clinical outcomes in individual patients with different genomic characteristics. EGFR comutations, low-sensitizing variant allele frequency, and specific atypical EGFR-mutant types have been identified as negative predictors of osimertinib efficacy. A structure-based approach was described recently to divide EGFR mutations into four functional groups for a more personalized EGFR TKI choice. Furthermore, although applied in the adjuvant setting and aimed at 1G TKI, the recently proposed MINERVA score on the basis of genomic signatures provided a more precise framework for guiding adjuvant TKI therapy. It may be worth applying this score to 3G TKIs.

Third, how do we overcome the primary and acquired resistance to 3G TKIs? The factors that drive primary resistance to 3G TKIs are poorly understood. EGFR exon 20 insertion and B-cell lymphoma-2–like 11 deletion polymorphism could be potential contributors. Acquired resistance is essentially a tumor clonal evolution under drug pressure, resulting in selective dominance of subclonal cells lacking the original sensitizing mutations, including EGFR-dependent and -independent resistance mechanisms. The resistance patterns for osimertinib are different in different lines of treatment. There are more unknown mechanisms and earlier presence of EGFR-independent mechanisms in the first-line setting, suggesting a complex resistance landscape and altered tumor biology. This difference in resistance mechanisms may extend to the adjuvant setting, given that osimertinib has obtained adjuvant therapy indications from the Food and Drug Administration after the results of the ADAURA study. A variety of strategies are being explored to overcome different types of resistance, including the development of next-generation TKIs, combination of 3G TKIs with other targeted or conventional therapies, combined immunotherapy strategies, and dose escalation in specific populations. Next-generation EGFR inhibitors (EI045, JB-04-125-02, BLU-94535) are still in the early stages of development but found to have great potential. The promising combinations with 3G TKIs include agents targeting distinct alternative bypass pathways, such as MET, HER2, ALK, RET, MEK, and BRAF gene aberrations. Of interest, the combination of lazertinib and an EGFR-MET bispecific antibody amivantamab had promising efficacy with an objective response rate of 36% in osimertinib-relapsed, chemotherapy-naive patients in the phase 1 CHRYS-ALIS study, suggesting switching to another 3G TKI combined with different targeted drugs may overcome the resistance to osimertinib. The combinations of chemotheraphy or antiangiogenic drugs have been broadly investigated with 1G TKIs in the first-line setting, and the survival benefits remain controversial. First, the combination with chemotherapy was at the expense of more adverse effects although OS advantage was considerable, and it is not a typically adopted strategy in clinical practice. Second, the PFS advantage observed in the combination with antiangiogenic therapies failed to translate into an OS benefit. Third, osimertinib plus bevacizumab failed to improve the survival of patients with EGFR T790M mutation compared with osimertinib alone in the second-line setting. Therefore, it is unclear whether the impressive efficacy of the 3G TKIs can be further improved by the combination with antiangiogenic therapy or chemotherapy.

The dominance of osimertinib in the landscape of 3G TKIs has been changing with more and more novel compounds emerging. In the heyday of 3G TKIs, a more precise predictive model for guiding personalized treatment selection and novel combinations based on improved knowledge of resistance mechanisms are the direction of future efforts.

CRediT Authorship Contribution Statement

Fen Wang: Conceptualization, Data curation, Writing - original draft preparation, Visualization.
Qing Zhou: Writing - review & editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of
Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.01.007.

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