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Clinical management of third-generation EGFR inhibitor-resistant patients with advanced non-small cell lung cancer: Current status and future perspectives

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ABSTRACT

Discovery of activating mutations in epidermal growth factor receptor (*EGFR*) as a predictive biomarker for first-generation EGFR tyrosine kinase inhibitors (TKIs) has initiated an era of precision oncology for the treatment of advanced *EGFR*-mutant non-small cell lung cancer (NSCLC). Despite the robust efficacy of first- and second-generation EGFR TKIs, disease relapse is inevitable. *EGFR* T790M mutation is the predominant cause of disease relapse and third-generation, irreversible EGFR inhibitors designed for targeting *EGFR* T790M and activating mutations have demonstrated promising clinical activity and tolerability. Unfortunately, disease progression inevitably occurs and heterogenous resistance mechanisms have been reported with limited subsequent treatment strategies available. Till now, treatment approaches for patients progressed from third-generation EGFR TKIs have not been clearly established. In this review, we summarize the recent findings in resistance mechanisms to third-generation EGFR TKIs and emerging treatment approaches for *EGFR*-mutant patients after resistance to third-generation EGFR TKIs. We further discuss clinical challenges and future perspectives for management of *EGFR*-mutant patients resistant to third-generation EGFR TKIs.

1. Introduction

It has been ten years since epidermal growth factor receptor (*EGFR*) activating mutation was established as a predictive biomarker for first-generation EGFR tyrosine kinase inhibitor (TKI) gefitinib [1]. The milestone Iressa Pan-Asia study (IPASS) has initiated the era of precision oncology in patients with advanced *EGFR*-mutant non-small cell lung cancer (NSCLC) and substantial progress have been made in improving outcomes for this subset of patients. First- and second- generation EGFR TKIs have demonstrated robust efficacy in the first-line treatment of *EGFR* activating mutation-positive patients with advanced non-small cell lung cancer [1–9]. However, resistance to these inhibitors always occurs after a median duration of 9–15 months. The emergence of *EGFR* T790M mutation is the predominant resistance mechanism, occurring in ~50–70% of patients progressed from gefitinib, erlotinib and afatinib [10–13].

Third-generation, irreversible EGFR TKIs, designed for targeting *EGFR* T790M mutation and *EGFR* activating mutations have been developed. To date, osimertinib has gained the FDA, EMA and NMPA approval in the treatment of *EGFR* T790M-positive patients progressed from prior EGFR TKIs, based on objective response rate (ORR) of 61–71% and median progression-free survival (PFS) of ~10 months in *EGFR* T790M-positive patients across AURA studies [12,14,15]. Additionally, osimertinib also demonstrated robust efficacy in the first-line treatment of patients with advanced *EGFR* activating mutation-positive NSCLC with a median PFS of 18.9 months as compared to 10.2 months with standard EGFR TKIs [16]. To date, published data has also demonstrated differences in osimertinib efficacy between different ethnic groups. For pretreated *EGFR* T790M-positive patients, ORR for osimertinib was 72% (95% CI 63-79) among Asian patients as compared to 68% (95% CI 57-79) among Non-Asian patients in AURA 2 study [15]. In AURA 3 study, the hazard ratio (HR) for osimertinib PFS among Asian patients was 0.32 (95% CI 0.24 to 0.44) versus 0.48 (95% CI 0.32 to 0.75) among non-Asian patients [12]. While in untreated *EGFR*-mutated patients, the HR for osimertinib PFS among Asian patients was 0.55 (95% CI 0.42–0.72), as compared to 0.34 (95% CI 0.23–0.48) among non-Asian patients [16]. Several other third-generation EGFR TKIs such as olumitinib, abivertinib (AC0010), rociletinib, ASP8273 and EGF816 are in development [17–22]. Despite the promising response to third-generation EGFR TKIs, resistance inevitably occurs after

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approximately 6–10 months of treatment in *EGFR* T790M-positive patients progressed from prior EGFR TKIs [12,19,20,23].

The resistance mechanisms to third-generation EGFR TKIs are being actively investigated. To date, a growing number of studies have shed light on the heterogeneous resistance landscape to third-generation EGFR TKIs in second-line setting, while limited data have suggested clinical strategies to overcome resistance to this subset of inhibitors. How to use the knowledge of the evolving genomic landscape to guide subsequent treatment upon progression from third-generation EGFR TKIs remains an unmet clinical need. Given the unclearly established framework for third-generation TKIs-resistant setting, this review aims to summarize the emerging evidences on resistance mechanisms to third-generation EGFR TKIs in second-line setting and focus on discussing clinical strategies of treating *EGFR*-mutant patients after acquired resistance to third-generation EGFR TKIs.

2. Resistance to third-generation EGFR TKIs: evolution in diversity under selective pressure

With the use of next-generation sequencing (NGS)-based genomic profiling, emerging data have demonstrated the resistance mechanisms to third-generation EGFR TKIs. Resistance mechanisms to osimertinib and rociletinib have been extensively investigated, and limited studies have also shed light on resistance mechanisms to other inhibitors such as HM61713, AC0010, EGF816 and ASP8273 that are currently under investigation in clinical trials. Emerging data have demonstrated the heterogeneity and drug specificity of resistance mechanisms to third-generation EGFR TKIs (Fig. 1).

2.1. Heterogeneity of resistance landscape to third-generation EGFR TKIs

Resistance to third-generation EGFR TKIs recurrently involves multiples genes such as *EGFR*, *MET*, *HER2*, *PIK3CA*, *KRAS*, *BRAF* and *RET* [23–32]. Regarding EGFR-dependent resistance mechanisms, a diverse set of *EGFR* tertiary mutations have been suggested as resistance-causing mechanisms. Different from first-generation EGFR TKIs in which *EGFR* T790M mutation predominates, multiple *EGFR* tertiary mutations have been observed in patients progressed from third-generation EGFR TKIs. The most common *EGFR* tertiary mutation is *EGFR* C797S, which has been identified in *EGFR* T790M-preserved patients progressed from osimertinib, rociletinib and HM61713 [24,30,32,33]. Other *EGFR* tertiary mutations have also been documented as potential mechanisms of resistance to osimertinib, including *EGFR* C797G and mutations at G796, L792, L718/G719, G724 [26,34–40]. Interestingly, some of these tertiary mutations at G796, G724 and L718 have been documented in *EGFR* T790M-loss cases upon osimertinib progression [36,38,40]. In addition to abovementioned *EGFR* tertiary mutations observed in patients developed resistance to osimertinib, emergent mutations in *EGFR* (E709K, L692V, L798I) have been captured in rociletinib-resistant patients [30]. *EGFR* amplification has also been observed in around 5% and 9–25% of patients who developed resistance to osimertinib and rociletinib, respectively [30–32,41].

Multiple bypass and downstream resistance mechanisms have been reported in patients developed resistance to third-generation EGFR TKIs. Among them, *MET* amplification is the most commonly observed, occurring in ~5–22%, ~8–26% of patients across osimertinib and rociletinib-resistant cohorts (cohorts involving > 15 patients underwent NGS), respectively [25–28,30,32,41,42]. Followed by *PIK3CA* mutations, occurring in ~5–13% and 5–12% of osimertinib and rociletinib-resistant patients, respectively [25–28,30,32,41,42]. Other resistance mechanisms recurrently involve mutations of *KRAS* (G12, G13, Q61, A146), and *BRAF* fusions or mutations, *HER2* amplification, fusions of *FGFR*, *RET* and *NTRK1* and alterations in cell-cycle genes [25,27,32,42]. The diversity of EGFR-independent mechanisms-mediated resistance underscores an emerging clinical need to development of combinational strategies co-targeting *EGFR* and bypass or downstream drivers.

In addition to the genomic evolution upon third-generation EGFR TKIs progression, histologic evolution has also been widely reported. Transformation to small-cell lung cancer have been observed in 2–15% of patients progressed from osimertinib across studies (involving > 15 patients) [25,27,28], and in 17% (2/12) of patients progressed from rociletinib [31]. Transformation from adenocarcinoma to other histology such as squamous cell lung cancer and large cell neuroendocrine lung carcinoma have been observed in patients progressed from osimertinib [29,43]. As expected, these patients maintained the trunk *EGFR* activating mutations, either with the presence or loss of *EGFR* T790M mutation.

2.2. Drug specificity of predominant resistance mechanisms across different third-generation EGFR TKIs

Another feature of resistance landscape to third-generation EGFR TKIs is the drug specificity of predominant resistance mechanisms for different inhibitors. Several studies have observed different patterns of resistance to third-generation EGFR TKIs, differentiating these

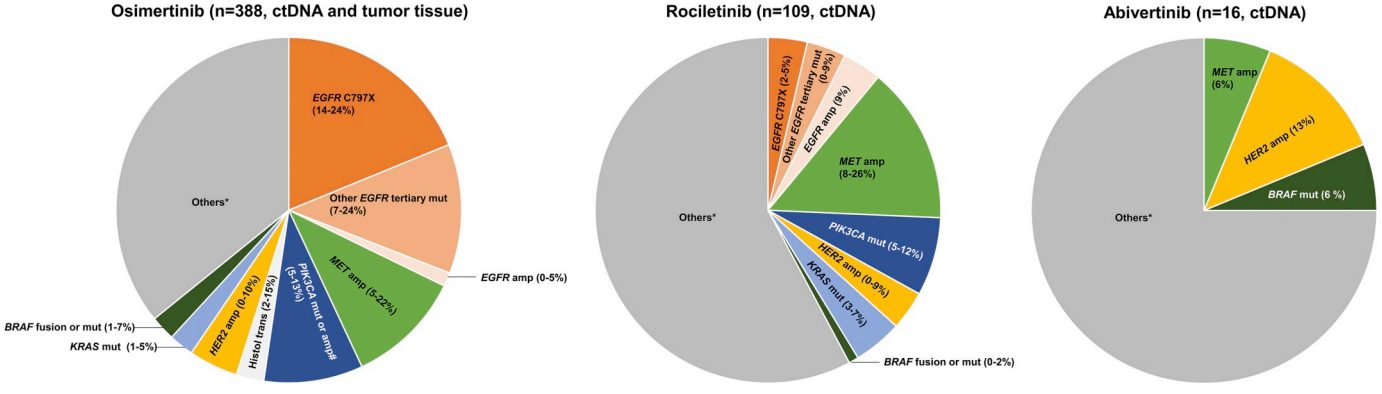

Fig. 1. Heterogeneity and drug specificity of resistance landscape to third-generation EGFR TKIs. These pie-charts summarize data from cohorts with > 15 patients who underwent next-generation sequencing analysis upon progression for each inhibitor. By this approach, 6, 2 and 1 studies on osimertinib, rociletinib and abivertinib resistance are included in the current analysis, respectively. Resistance to osimertinib is the most studied. All data from 5 studies and resistance mechanisms (observed in tissue) from the last study reported by Piotroskwa et al. are included to calculate the frequency of resistance mechanisms to osimertinib. For rociletinib and abivertinib resistance, all studies that are involved in the pie charts performed ctDNA profiling. Thus, these pie-charts for rociletinib and abivertinib are not able to reflect the percentage of histologic transformation. Only frequencies of well-characterized mechanisms of resistance are shown in Fig. 1. Resistance mechanisms may overlap indeed. mut, mutation; amp, amplification; Histol trans, histologic transformation; Others* include but not limit to alterations in *RET*, cell-cycle genes, *RB1*, and those without known resistance mechanisms, due to the criteria for putative resistance mechanisms remains inconsistent among these studies.

inhibitors from first- and second-generation EGFR TKIs, where *EGFR* T790M predominates regardless of which TKIs is used. Vulnerability to develop *EGFR* C797S mutation is the most common observed differences between third-generation EGFR TKIs. Mutations at *EGFR* C797 arise in approximately 14–24% of patients progressed from osimertinib [25–28,41,42]. However, it only occurs in ~2–5% of patients progressed from rociletinib [30,32], and has not been captured in a recent study analyzing resistance mechanisms to abivertinib (AC0010) [23]. These differences in some of the predominant resistance mechanisms may provide rational for sequencing different third-generation EGFR TKIs and deserves further investigation.

2.3. The gap between resistance profiling and identifying the driver of resistance to third-generation EGFR TKIs

Despite a variety of studies have depicted an evolving resistance profile for third-generation EGFR TKIs, limited data have shed light on distinguishing the driver of resistance from "passenger" detected. With the use of NGS-based genomic profiling, multiple putative resistance mechanisms were identified. However, which one is the dominant, for which patient and at which timepoint remains largely unknown [44]. An emerging gap between the observations and driver mechanisms warrants to be bridged, so as to overcome resistance to third-generation EGFR TKIs.

Combining clinical observations with *in* vitro and *in* vivo validation may contribute to identify the real driver of resistance. A recent study has investigated the driver role of putative resistance mechanisms identified by NGS. They evaluated the sensitivity of *PIK3CA* E545K, *BRAF*, *FGFR2b* and *PDGFR* over-expressed HCC4006 cells to osimertinib. This study demonstrated that only *PIK3CA* E545K overexpression confers moderate resistance to osimertinib, while overexpression of the other three alterations which were identified by NGS upon osimertinib progression did not significantly alter osimertinib sensitivity *in* vitro [28]. This study provides the evidences that not all detected alterations could promote resistance to third-generation EGFR TKIs and underscores the importance to carefully interpret resistance mechanisms detected by single NGS assay.

3. Emerging clinical strategies to treat patients with acquired resistance to third-generation EGFR TKIs

With the wide use of osimertinib and implementation of clinical trials of other third-generation EGFR TKIs, treatment approaches after acquired resistance to third-generation EGFR TKIs are exhausted (Fig. 2). On condition of asymptomatic or symptomatic local progression, osimertinib continuation beyond progression and considering local treatments are recommended by NCCN guidelines version 6. 2018 [45]. Platinum-based chemotherapy is the recommended by NCCN for systematic progression upon osimertinib involving multiple lesions [45]. According to the latest Pan-Asian adapted Clinical Practice Guidelines, platinum-based doublet chemotherapy (levels of evidence and grades of recommendation: I,A) or carboplatin/paclitaxel/bevacizumab/atezolizumab (levels of evidence and grades of recommendation: IV, C) represent options for patients who develop systematic progression upon osimertinib [46]. To improve outcome for *EGFR*-mutant patients, a range of novel treatments are being developed. Till now, several studies have demonstrated clinical strategies to treat patients who developed systematic progression to third-generation EGFR TKIs (Table 1).

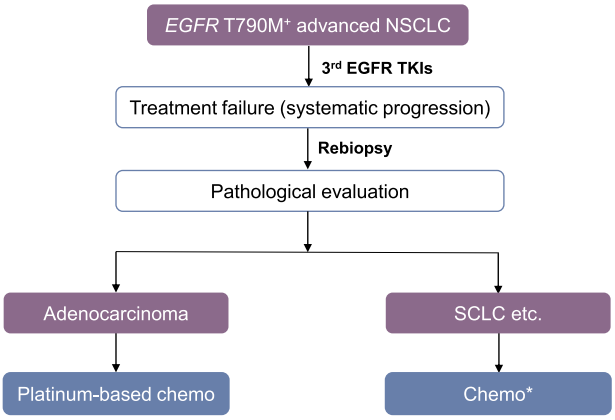

Fig. 2. Present treatment paradigms for *EGFR*-mutant patients developed systematic progression from third-generation EGFR TKIs. *EGFR* T790M$^+$, *EGFR* T790 M mutation-positive; 3rd EGFR TKIs, third-generation EGFR TKIs; SCLC, small-cell lung cancer; chemo, chemotherapy; *,chemotherapy regimen should be selected based on pathology.

3.1. Combination treatment targeting EGFR-dependent resistance mechanisms

Preliminary clinical efficacy of third-generation EGFR TKI osimertinib plus first-generation EGFR TKI have been reported in two patients who developed *EGFR* T790M and C797S mutations, *in trans* allelic context upon osimertinib progression. One patient showed significant symptom improvement after the commencement of combined osimertinib and gefitinib, but experienced disease progression after 1 month of combination treatment [47]. The other patient achieved a brief partial response (PR) response that lasting for 3 months [48]. In addition, a combination of osimertinib, bevacizumab and brigatinib resulted in a PR response in an *EGFR* 21L858R-mutant patient who developed *EGFR* C797S *in cis* with *EGFR* T790M upon osimertinib progression [49].

3.2. Combination treatment targeting EGFR-independent resistance mechanisms

Several studies have reported on clinical strategies to treat patients who developed bypass resistance mechanisms upon osimertinib progression. To our knowledge, *MET* amplification-mediated osimertinib resistance is one of the most studied. Icotinib plus crizotinib was administered in a patient who developed a newly acquired *MET* amplification with *EGFR* T790M loss upon osimertinib progression and achieved a PR response lasting for 3 months [50]. In another two patients who developed *MET* amplification with the presence of *EGFR* T790M mutation upon osimertinib resistance, osimertinib plus crizotinib achieved PR responses in both patients [50,51]. While in a case reported by Ou et al., single agent crizotinib treatment also resulted in a transient symptomatic benefit in a patient who developed acquired *MET* amplification upon osimertinib progression. However, the patient had to hold crizotinib monotherapy due to toxicities and failed to benefit from further combined osimertinib and crizotinib treatment due to rapid symptom deterioration [52].

In addition to *MET* inhibition, clinical evidences in dual pathway suppression of EGFR with RET, ALK and ROS1 have also been demonstrated in individual cases. A recent study has suggested that combined osimertinib and BLU-667 were effective and tolerable in overcoming acquired *RET* fusion-mediated osimertinib resistance, both *in* vitro and in one patient who developed an acquired *CCDC6-RET* fusion upon osimertinib resistance [53]. The efficacy of combined osimertinib with alectinib in overcoming resistance to osimertinib mediated by *PLEKHA7-ALK* fusion has also been reported in an osimertinib-resistant patient [54]. The combination treatment achieved a PR response lasting for 6 months. In another patient who developed golgi-associated PDZ and coiled-coil motif containing gene (GOPC)-ROS1 rearrangement upon osimertinib progression, combined osimertinib and crizotinib was tolerated and resulted in a PR response at 2 months post-combination treatment [55]. Taken together, albeit preliminary,

Table 1
Emerging clinical strategies to treat EGFR-mutant patients with acquired resistance to third-generation EGFR TKIs.

Treatment strategies	Targeted resistance mechanisms	No. of patients	Best response	Duration of treatment (mo)	Toxicities
Treatments for *EGFR*-dependent resistance mechanisms					
Osimertinib + erlotinib [48]	*EGFR* C797S, *in trans**	1	PR	3	Not mentioned
Osimertinib + gefitinib [47]	*EGFR* C797S, *in trans**	1	Clinical improvement	1	No AE
Osimertinib + bevacizumab + brigatinib [49]	*EGFR* C797S, *in cis**	1	PR	2#	No significant AE
Treatments for *EGFR*-independent resistance mechanisms					
Icotinib/osimertinib + crizotinib [50]	*MET* amp	2	PR	3 (n = 1) 1.4# (n = 1)	Not mentioned
Osimertinib + crizotinib [51]	*MET* amp	1	Radiographic response observed	2 (non-PD)	Not mentioned
Crizotinib, followed by osimertinib + crziotinib [52]	*MET* amp	1	crizotinib: SD osimertinib + crizotinib: PD	1.5 (non-PD)	Lower extremity edema & fatigue
Osimertinib + BLU-667 [53]	*CCDC6-RET* fusion	1	PR	4#	Grade 1 fatigue, leukopenia, hypertension, xerostomia & transaminitis
Osimertinib + alectinib [54]	*PLEKHA7-ALK* fusion	1	PR	6	Grade 1 myalgia & grade 2 elevation of CK (resolved by day 50)
Osimertinib + crizotinib [55]	*GOPC-ROS1* rearrangement	1	PR	2#	Grade 2 rash & diarrhea
Treatments for histologic transformation					
EP [56]	SCLC transformation	2	PR	Not mentioned	Not mentioned
EP [57]	SCLC transformation	2	PR (n = 1); PD (n = 1)	Not mentioned	Not mentioned
Sequencing or re-challenging third-generation EGFR TKIs					
Osimertinib (after rociletinib failure) [61]	Unknown	9	PR (n = 3); SD (n = 4); PD (n = 2)	0.6–12.5	Well-tolerated
Osimertinib (after HM61713 failure) [62]	Unknown	1	PR	3#	Not mentioned
Osimertinib (after osimertinib failure) [63]	Unknown	1	PR	2#	Not mentioned

No of patients, number of patients; mo, months *, with T790 M; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event; amp, amplification; SCLC, small-cell lung cancer; CK, creatinine phosphokinase; EP, etoposide and carboplatin; #, not reached till publication; &, and.

emerging clinical evidences have demonstrated the efficacy of dual pathway inhibition to overcome EGFR-independent resistances to osimertinib.

3.3. Subsequent treatments for histologic transformation

Standard SCLC chemotherapy were previously reported to be effective in *EGFR*-mutant patients transformed SCLC transformation upon first-generation EGFR TKIs resistance [11]. In third-generation EGFR TKIs resistant setting, combination treatment of etoposide and carboplatin (EP) resulted in PR responses in two patients transformed to SCLC upon osimertinib progression [56], and in another patient with primary resistance to osimertinib due to the presence of SCLC transformation [57]. While EP regimen resulted in further radiological progression in another case with primary resistance to osimertinib due to pre-existing SCLC transformation [57]. Despite EP regimen remains the current preference for patients underwent SCLC transformation, novel treatments developed for classic SCLC such as the DLL3-directed antibody drug conjugate rovalpituzumab tesirine and immune checkpoint inhibitors should be further investigated in the unique *EGFR*-mutant patients with SCLC transformation [58–60].

3.4. Sequencing or re-challenging third-generation EGFR TKIs

Regarding the drug specificity of pre-dominant resistance mechanisms, sequencing different third-generation EGFR TKIs is anticipate as another treatment approach after progression from the initial third-generation EGFR TKIs. Two studies have demonstrated the efficacy of osimertinib in treating *EGFR*-mutant patients progressed from rociletinib or HM61713 in clinical setting. The first study involved nine *EGFR*-mutant patients with rociletinib and subsequent osimertinib [61]. Among them, seven responded to subsequent osimertinib and two of the seven patients who demonstrated primary resistance to rociletinib due to new lesions in central nervous system showed durable responses to osimertinib. The other two patients who failed to respond to rociletinib demonstrated cross-resistant to osimertinib. In another study, an *EGFR*-mutant patient also responded to osimertinib after HM61713 failure [62]. However, both studies did not demonstrate the resistance profile for aforementioned patients progressed from rociletinib or HM61713. In addition to attributing the success of sequencing third-generation EGFR TKIs to the higher potency and intracranial efficacy of osimertinib as compared to rociletinib and HM61713, future studies warrant to determine which subset of patients may benefit from sequencing third-generation EGFR TKIs from genomic aspect.

In addition to sequence different third-generation EGFR TKIs, successful response to osimertinib re-challenge after intervention chemotherapy was observed in an *EGFR* T790M-positive patient progressed from osimertinib [63]. As osimertinib is the currently only approved third-generation EGFR inhibitor, it remains to be investigated if osimertinib re-challenge will provide additional benefit for a subset of patients pre-treated with osimertinib after intervention systematic treatments.

4. On the horizon: management of *EGFR*-mutant patients in third-generation EGFR TKIs-resistant setting

4.1. Preventing or delaying the emergence of resistance to third-generation EGFR TKIs

Despite osimertinib is actively moving into the first-line setting of advanced *EGFR*-mutant NSCLC, resistance to osimertinib in first-line treatment also eventually occurs and involves multiple genes. The frequent intra- and inter-patient heterogeneity of resistance to third-generation EGFR TKIs has become an emerging clinical challenge. The evolutionary genomic diversity under EGFR TKIs treatment propose a novel shift in treatment strategy from overcoming resistance to preventing or delaying the emergence of resistance to targeted therapies. With the use of NGS-based genomic profiling, this strategy is of particular importance in cases of pre-existing resistance mechanisms detected prior to third-generation EGFR TKIs initiation or the early emergence of resistance mechanisms during the course of treatment. Novel agents with higher potency, broader selectivity and better

intracranial activity are urgently needed. For instance, an EGFR-MET bispecific antibody JNJ-372, targeting both *EGFR* and *MET*, has demonstrated preliminary but clinically significant efficacy and good tolerability in advanced *EGFR*-mutant NSCLC in the phase I clinical trial (NCT02609776) [64], and is currently under investigation in third-generation EGFR TKIs-resistant setting. It is worth to see if this subset of bispecific antibodies will be active to prevent or delay the emergence of resistance mediated by *EGFR* and *MET* aberrations in *EGFR*-mutant NSCLC. A recent preclinical study reported that a novel third-generation EGFR TKI YH25448 not only demonstrated a higher selectivity and potency as compared to osimertinib, but induced profound tumor regression in brain metastasis [65]. This novel inhibitor is currently under investigation in the ongoing phase I/II study (NCT03046992).

Upfront combinational strategies such as osimertinib in combination with gefitinib (NCT03122717), dacomitinib (NCT03810807) or selumetinib (NCT03392246) are being investigated in EGFR inhibitor–naive advanced *EGFR*-mutant lung cancer patients. Osimertinib plus bevacizumab or necitumumab are also currently under investigation in advanced *EGFR*-mutant NSCLC progressed on prior EGFR TKIs (NCT03133546, NCT02496663). Early incorporation of SCLC-directed therapy for patients with lung adenocarcinoma at high-risk for SCLC transformation is another hotspot. Osimertinib, in combination with platinum and etoposide for patients with metastatic *EGFR*-mutant lung cancers with concurrent *RB1* and *TP53* alterations is currently being investigated in a phase I study (NCT03567642). Another third-generation EGFR TKI EGF816 is under investigation in combination with trametinib (NCT03516214) or nivolumab (NCT02323126) in *EGFR* T790M-positive patients progressed from prior EGFR TKIs. Furthermore, a phase I study of EGF816 in combination with selected targeted therapies (ribociclib, trametinib, LXH254, INC 280, gefitinib) is currently under investigation both in EGFR TKI-naïve and *EGFR* T790M-positive patients (NCT02335944).

4.2. Preclinical treatment strategies overcoming resistance to third-generation EGFR TKIs to be investigated in clinical studies

Multiple preclinical studies have proposed strategies to overcome resistance to osimertinib mediated by *EGFR* tertiary mutations. EAI045, a fourth-generation EGFR allosteric inhibitor, has shown encouraging preclinical activities in treating *EGFR* C797S mutation-mediated resistance when combined with cetuximab, but only in mouse models with lung cancer driven by *EGFR* L858R/T790M/C797S mutation [66]. While brigatinib in combination with cetuximab has demonstrated promising preclinical activity in triple mutants *EGFR* C797/T790M/19 deletion [67]. Other *EGFR* tertiary mutations such as *EGFR* L718V, *EGFR* G724S have demonstrated sensitivity to second-generation EGFR TKI afatinib in preclinical studies [38,40]. In addition to these findings in overcoming resistance mediated by EGFR-dependent resistance mechanisms, combination strategies involving third-generation EGFR TKIs and specific bypass inhibitors targeting *AXL*, *BCL-2*, *BRAF* have also demonstrated promising preclinical activities in either preventing intrinsic or overcoming acquired resistance to third-generation EGFR TKIs [68–70]. These data underscore the potential to transform these preclinical findings into clinical investigation. Given the heterogeneity of resistance mechanisms to third-generation EGFR TKIs, clinical trials with novel treatments directed by parallel sequencing of multiple biomarkers such as The MATCH screening trial (NCT02465060) and TRUMP study (NCT03574402) are urgently needed in third-generation TKI resistant setting.

5. Conclusions

The resistance landscape to third-generation EGFR TKIs appear to be heterogeneous involving genomic alterations in EGFR-dependent and EGFR-independent pathways, as well as histologic transformation. In addition, the drug specificity of predominant resistance mechanisms for different inhibitors in this class is another unique characteristic, differentiating it from the resistance landscape for first- or second-generation EGFR TKIs in which *EGFR* T790M mutation predominates regardless of which inhibitors is used. Till now, treatment approaches after acquired resistance to third-generation EGFR TKIs are exhausted, with platinum-based chemotherapy as a treatment option in clinical practice. Given the frequent intra- and inter-patient heterogeneity of resistance mechanisms, emerging case studies have demonstrated a proof-of-concept on combinational strategies to treat patients with *EGFR* C797S, *MET* amplification, *RET* fusion and *ALK* fusion-mediated resistance to osimertinib in clinics. In addition, sequencing or re-challenging different inhibitors in this class has also demonstrated preliminary efficacy to improve outcomes of *EGFR*-mutant patients. These findings warrant to be further explored in larger cohort and treatment approaches post-third-generation EGFR TKIs remain an unmet clinical need. Novel agents with higher potency, broader selectivity and better intracranial activity are urgently needed.

For patients with *EGFR* T790M-positive advanced NSCLC, pre-treatment NGS and Immunohistochemistry (IHC) should be performed to further categorize patients into those with other commitment actionable biomarkers and those without (Fig. 3). For those with other actionable biomarkers prior to third-generation EGFR TKIs initiation, future studies need to investigate if it will be feasible to prevent or delay the emergence of resistance by combination treatments consisting of third-generation EGFR TKIs and targeted therapies designed for other actionable biomarkers such as *MET* amplification and *RET* fusion. For those without other actionable biomarkers before third-generation EGFR TKIs initiation, third-generation EGFR TKIs could be tailored

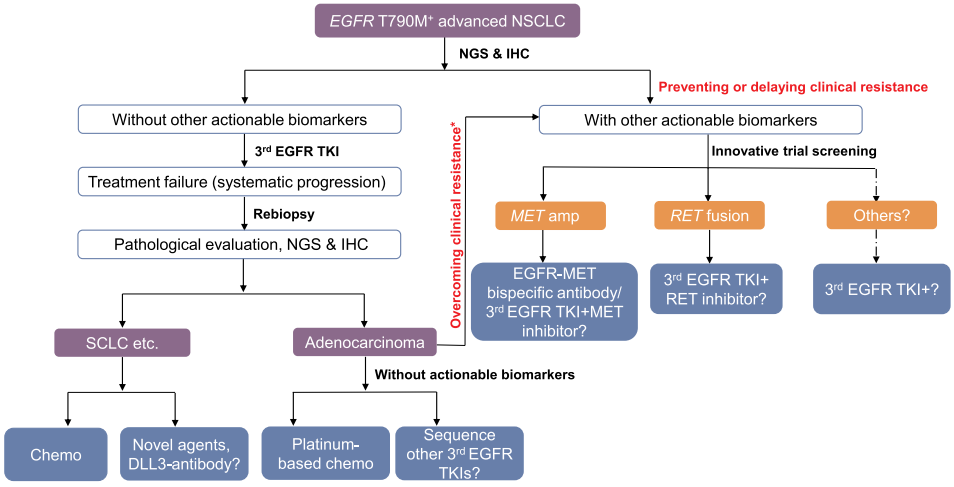

Fig. 3. Treatment paradigms for *EGFR* T790M-positive patients in future. *EGFR* T790M^{+}, *EGFR* T790 M mutation-positive; 3rd EGFR TKIs, third-generation EGFR TKIs; SCLC, small-cell lung cancer; DLL3, delta-like protein 3; Overcoming resistance mechanisms*, whether third-generation EGFR TKIs should be used in case of *EGFR* T790M-negative biopsy post-third-generation EGFR TKIs failure remains unanswered. Considering the selectivity of both *EGFR* activating and T790M mutation, combination regimens involving third-generation EGFR TKIs are suggested here.

until systematic disease progression. Pathological evaluation, NGS and IHC of rebiopsy upon third-generation EGFR TKIs will contribute to the identification of histologic transformation and potential actionable biomarkers to be targeted. Innovative clinical trials directed by NGS will facilitate the clinical investigation of novel combination treatments to overcome resistance to third-generation EGFR TKIs.

Conflicts of interest

QZ declares speaker fees from AstraZeneca and Roche. Y-LW declares speaker fees from AstraZeneca, Eli Lilly, Pfizer, Roche, and Sanofi. Y-CZ has nothing to declare.

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