Consensus on the lung cancer management after third-generation EGFR-TKI resistance

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Summary

Lung cancer is the most prevalent malignant tumour in the Asia–Pacific region. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Among these, the rate of *EGFR* mutations in Asian patients with lung adenocarcinoma is 40–60%. Third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) have improved the clinical management of NSCLC with *EGFR* mutations, but resistance to these drugs remains a significant challenge. Despite numerous ongoing studies, there is no standardized consensus on managing resistance to third-generation EGFR-TKIs. This consensus integrates international guidelines on EGFR-TKI management, findings from clinical studies, and experiences from the Asia–Pacific region in addressing post-resistance. Detailed recommendations are provided for classification and progression patterns, clinical testing, and post-resistance treatment strategies related to third-generation EGFR-TKI resistance. The aim of these recommendations is to offer reference opinions for the standardized management of patients exhibiting resistance to third-generation EGFR-TKIs in clinical practice.

Keywords: *EGFR* mutation; Non-small cell lung cancer; Third-generation EGFR-TKI; Post-resistance management

Introduction

Non-small cell lung cancer (NSCLC), accounting for approximately 85% of lung cancers, is the most common pathological type and primarily includes adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.[1] The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein with tyrosine kinase activity that is frequently mutated in NSCLC; *EGFR* gene mutations are the most common driver mutations observed.[2] In the Asian NSCLC population, the prevalence of *EGFR* mutation is 30–50%,[3–7] and in lung adenocarcinoma, the prevalence of *EGFR* mutation is as high as 40–60%.[4] The introduction of EGFR tyrosine kinase inhibitors (TKIs) has changed the treatment paradigm for patients with advanced *EGFR*-mutated (*EGFR*m) NSCLC. Compared with traditional platinum-based chemotherapy, first- and second-generation

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Research in context

Evidence before this study

An extensive search was conducted through PubMed and conference abstracts using the MeSH terms "carcinoma, non-small-cell lung" AND "ErbB receptors" AND a combination of terms including "drug resistance" OR "pathology, molecular" OR "disease progression" OR "molecular targeted therapy" OR "immune checkpoint inhibitors" OR "immunoconjugates" OR "antineoplastic agents, immunological" OR "drug therapy, combination" between January 2015 and March 2023. The analysis identified that the resistance mechanisms of third-generation EGFR tyrosine kinase inhibitors, particularly osimertinib, have been thoroughly categorized into three main groups: on-target, off-target, and unknown mechanisms. Developments in novel drugs and strategies have specifically targeted these resistance mechanisms. With the emerging evidence of phase III clinical trials, such as HARMONi-A and MARIPOSA-2, there are more selections for clinicians to manage their patients. The high incidence of *EGFR* mutation in Asian lung cancer population underscores the critical need for standardized clinical management approaches following progression on third-generation EGFR-TKIs.

Added value of this study

To the best of our knowledge, this study constitutes the first expert consensus within the Asia–Pacific region focused on the clinical management of NSCLC post-progression on third-generation TKIs. The consensus comprehensively explores resistance mechanisms, molecular testing strategies, and therapeutic approaches, ultimately resulting in the formulation of numerous recommendations that provide guidance for the standardized management of cases exhibiting resistance to third-generation EGFR-TKIs in a clinical setting.

Implications of all the evidence

Currently, third-generation EGFR-TKIs are the standard of care in the first-line therapy for *EGFRm* NSCLC. The resistance mechanisms to these agents are increasingly understood, with new solutions continuously developing. Studies such as SACHI and SAFFRON are designed for specific demographic groups experiencing distinct genomic resistance alterations, while trials like MARIPOSA2, HARMONi-A, and TROPION-Lung 01 have included a broad range of participants. The landscape is evolving with numerous emerging strategies and therapeutic agents. These advancements necessitate sophisticated clinical management strategies to leverage the growing array of treatment options effectively. Consequently, there is a pressing need to establish standardized diagnostic and treatment protocols to improve outcomes for patients with *EGFRm* NSCLC, which remains a focal point of this consensus.

EGFR-TKIs as first-line treatment for advanced NSCLC with classical *EGFR* mutations (*EGFR* exon 19 deletion mutations or exon 21 L858R point mutations) have significantly improved median progression-free survival (PFS) for patients, although without a benefit in overall survival (OS).[8–10] After progression on first- or second-generation EGFR-TKIs, approximately 50–60% of patients develop resistant T790M mutation.[11] To address this resistance, third-generation EGFR-TKIs targeting activating *EGFR* mutations and T790M have been developed. Compared with first- or second-generation EGFR-TKIs, third-generation EGFR-TKIs have extended the median PFS in patients with *EGFR*-sensitive mutations by approximately 10 months.[12–16] Based on positive data from pivotal phase 3 trials, third-generation EGFR-TKIs have been approved for first-line treatment in patients who have NSCLC with *EGFR*-sensitive mutations worldwide. Among these, osimertinib has multinational approval, while almonertinib, furmonertinib, and befotertinib are approved only in China and lazertinib only in Korea. To extend further therapeutic benefits and improve patient outcomes, the FLAURA2 (osimertinib plus chemotherapy versus osimertinib monotherapy) and MARIPOSA (amivantamab plus lazertinib versus osimertinib monotherapy) trials have initiated a new phase of combinatorial strategies in first-line treatment for NSCLC. However, disease progression following treatment with third-generation EGFR-TKIs remains inevitable, and managing resistance remains a challenge.

With in-depth investigation into resistance mechanisms for third-generation EGFR-TKIs and recent advances in treatment regimens for resistant cases, this consensus carefully addresses key considerations and issues related to resistance to third-generation EGFR-TKIs. We aim to provide clinicians with practical post-resistance management strategies to extend survival further in patients with advanced *EGFR*m NSCLC and enhance their quality of life.

Methods

Timeline and process

This consensus was initiated by the China Thoracic Oncology Group (CTONG) and jointly discussed and formulated by experts from departments of oncology, respiratory medicine, and thoracic surgery across China and the Asia–Pacific region. A leading expert group, comprising 22 experts with prior experience in clinical studies and guideline development, was formed in March 2023. This group took responsibility for drafting, supervising, and reviewing the consensus formation and guiding the overall process (Fig. 1). In April 2023, the leading group conducted an initial questionnaire survey among 91 healthcare professionals and

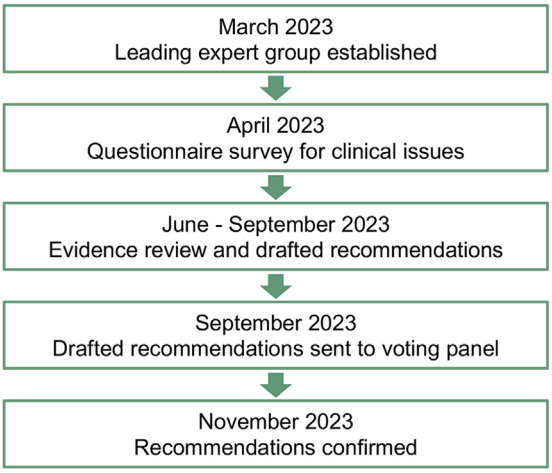

Fig. 1: **Timeline and processes involved in the development of the consensus.**

subsequently selected the key clinical issues to be addressed in this consensus. Following evidence review, the drafted recommendations were reviewed and voted on by a panel of 54 experts from mainland China, Hong Kong, Korea, Japan, and Singapore in September 2023, finalising the recommendations.

Search strategy and selection criteria

References for this review were identified through searches of the PubMed, Embase, and Scopus databases from January 2015 to December 2023, using the MeSH terms "carcinoma, non-small-cell lung" AND "ErbB receptors" AND ("drug resistance" OR "pathology, molecular" OR "disease progression" OR "molecular targeted therapy" OR "immune checkpoint inhibitors" OR "immunoconjugates" OR "antineoplastic agents, immunological" OR "drug therapy, combination"). Only literature published in English was considered. References were also identified through searches of conference abstracts (e.g., American Society of Clinical Oncology annual meeting, European Society for Medical Oncology Congress (ESMO), World Conference on Lung Cancer, European Lung Cancer Congress, ESMO-Asia Congress, and American Association for Cancer Research annual meeting) and relevant files from the authors. All studies meeting the following criteria were included in this review: studies or reviews focused on resistance mechanisms and clinical management of *EGFR*-mutant NSCLC after progression on third-generation EGFR-TKI, and articles published in peer-reviewed journals or conference proceedings. The general exclusion criteria were studies not related to third-generation EGFR-TKI resistance, and unavailable full texts or non-peer-reviewed research articles (except for conference abstracts reporting updated clinical trial results). We also searched ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, and the WHO International Clinical Trials Registry Platform for ongoing studies as of December 2023, using the terms "non-small-cell lung cancer" AND ("*EGFR* mutation" OR "EGFR-TKI" OR "progression" OR "oligo-progression" OR "MET" OR "SCLC transformation" OR "bispecific antibody" OR "ADC" OR "immune checkpoint"). Ongoing trials were included if they provided evidence on clinical-management strategies and novel therapeutic approaches for *EGFR*-mutant NSCLC after progression on third-generation EGFR-TKI. Clinical trials were excluded if their focus was outside the scope of this consensus. The final reference list was generated based on originality and relevance to the comprehensive scope of this consensus. Because the consensus was finalized in June 2024, some data from clinical studies reviewed in this consensus have been updated.

Grading of evidence and recommendations

The leading group discussed and defined the strength of evidence and level of consensus (Table 1), with reference to standards used by other major oncology organizations. For strength of evidence, we referred to the National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC, the guidelines of the Chinese Society of Clinical Oncology (CSCO), and the International Association for the Study of Lung Cancer (IASLC) consensus for neoadjuvant and adjuvant treatment of early-stage resectable NSCLC. A three-tier classification was established. To determine a threshold for recommendation consensus during voting, the expert panel members evaluated consensus and guideline thresholds used by the NCCN, CSCO, and IASLC. The expert group defined a threshold of 85% as indicating consensus, given the importance of these recommendations within a still-emerging field of data.

Limitation

Because only studies published in English were included, there is a slight possibility that relevant research published in other languages may have been overlooked. However, it is unlikely that this information would significantly alter the wording of the recommendations. Additionally, we did not use the Grading of

Strengths of evidence	Levels of consensus
High: evidence from phase III randomized controlled trials (RCTs) or rigorous meta-analysis **Moderate:** evidence from phase II clinical trials **Low:** evidence from retrospective analysis or/and case reports	**Level I:** unanimously recommended by experts (≥85% voting for approval) **Level II:** recommended by most experts, with some controversy (60–85% voting for approval) **Level III:** considerable controversy among the experts (<60% voting for approval)

Table 1: **Definitions of strengths of evidence and levels of consensus.**

Recommendations Assessment, Development, and Evaluation (GRADE) criteria when assessing evidence. This may have introduced bias in evaluating evidence strength.

Resistant types and progression pattern

Consensus I: Resistance to EGFR-TKIs can be classified as intrinsic resistance and acquired resistance. Intrinsic resistance refers to the tumour response evaluation of disease progression (PD) or stable disease (SD) for less than 3 months after initial treatment with EGFR-TKIs; acquired resistance refers to PD occurring after a patient has achieved a complete response (CR), partial response (PR), or stable disease (SD) for 3 months or longer following EGFR-TKI treatment.

(Consensus Level: I; Strength of Evidence: High)

Resistance to EGFR-TKIs can be classified as intrinsic or acquired. Intrinsic resistance refers to a tumour response evaluation of PD or SD for less than 3 months following initial EGFR-TKI treatment, with literature indicating that such patients account for approximately 20–30%.[17,18] Acquired resistance refers to PD occurring after an initial period of clinical response (CR, PR, or SD for 3 months or longer, according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria) following EGFR-TKI treatment.[18,19] This consensus focuses on mechanisms of acquired resistance, testing, and treatment strategies.

Consensus II: The progression patterns after resistance to third-generation EGFR-TKIs are divided into oligoprogression and extensive progression, with oligoprogression defined as PD at ≤3 metastatic lesions that are amenable to local therapies.

(Consensus Level: I; Strength of Evidence: Moderate)

Oligoprogression refers to the occurrence of PD at three or fewer metastatic lesions during treatment with EGFR-TKIs, where the progressing lesions are suitable for local therapies.[20] In cases of oligoprogression, systemic treatment can still control most lesions; therefore, local therapies may be used to control oligoprogressive lesions further, potentially enhancing clinical benefit.[21,22] Evidence implies that in patients who have NSCLC with driver gene mutations, the incidence of oligoprogression is approximately 15–47%. Common sites of oligoprogression include the central nervous system, lungs, lymph nodes, and bones, while the adrenal glands and liver are less commonly affected.[23–25] By contrast, extensive progression refers to progression across multiple systems, which generally cannot be effectively controlled with local therapies such as surgery or radiotherapy.

Mechanisms of resistance

Consensus III: The mechanisms of acquired resistance to third-generation EGFR-TKIs are divided into on-target resistance, off-target resistance, and unknown mechanisms of resistance.

(Consensus Level: I; Strength of Evidence: High)

Currently, resistance mechanisms related to osimertinib are the most frequently reported among all third-generation TKIs, and this consensus uses osimertinib as a representative to elaborate on the mechanisms of resistance to third-generation EGFR-TKIs. Based on different resistance mechanisms and corresponding clinical treatment strategies, this consensus categorizes acquired resistance to third-generation EGFR-TKIs into on-target resistance (EGFR pathway-dependent), off-target resistance (involving the MET pathway, histological transformation, or other oncogene abnormalities), and resistance mechanisms that remain unknown.

On-target resistance

EGFR *mutations*

C797X Mutation. Osimertinib primarily exerts its irreversible inhibitory effect on sensitive *EGFR* mutations and the T790M mutation by targeting the C797 residue in the ATP-binding site through covalent bond formation, making the C797 residue a susceptible site for resistance to osimertinib. The C797X mutation is one of the most significant mechanisms of resistance to osimertinib.[26] In the *EGFR* C797S mutation, cysteine (Cys) at position 797 in the EGFR peptide is replaced by serine (Ser), resulting in loss of the covalent bond between osimertinib and the C797 residue at the ATP-binding site, leading to acquired resistance to osimertinib.[27] Following first- and second-line treatments with osimertinib, the incidence rates of the C797S mutation are approximately 7–15% and 10–26%, respectively.[28,29] Resistant C797S mutations can be categorized into four distinct situations: isolated C797S mutation, cis T790M/C797S mutation (*EGFR* T790M and C797S occurring on the same allele), trans T790M/C797S mutation (*EGFR* T790M and C797S occurring on different alleles), and coexisting cis–trans mutations.[11,30]

Other* EGFR *Mutations. Other *EGFR* resistance mutations, such as L792X, L718Q, and S768I, also occur but are less common. In the FLAURA study, following resistance to first-line osimertinib, the incidence rates of L718Q and S768I mutations were 2% and 1%, respectively.[31] In the AURA3 study, after resistance to second-line osimertinib, the incidence rate of the L792X mutation was 3%, while the incidence rates of G796X, L718Q, and exon 20 insertion mutations were 1%

each.[32] Other rare *EGFR* mutations include L798I, L844V, and L692V, etc.[33]

EGFR *amplification*

EGFR amplification is also a common mechanism of resistance following first- or second-line treatment with osimertinib. In related studies, the incidence rates of *EGFR* amplification after resistance to first- and second-line osimertinib were approximately 4–12% and 6–15%, respectively.[34–36]

Off-target resistance

MET pathway-related resistance

The *MET* gene is a proto-oncogene that encodes the MET protein, a transmembrane receptor. In cancer, aberrant MET oncogenic signalling contributes to tumour invasion, angiogenesis, and metastasis.[37] In NSCLC, *MET* abnormalities mainly encompass *MET* exon 14 skipping, *MET* amplification, *MET* kinase domain mutations, *MET* fusion, and MET protein overexpression.[38]

MET amplification and overexpression are common mechanisms of resistance following treatment with third-generation EGFR-TKIs, with a higher incidence of overexpression.[11] Acquired *MET* amplification acts as a bypass signalling pathway, activating downstream pathways that lead to resistance when the EGFR signalling pathway is inhibited by EGFR-TKIs. Evidence implies that *MET* amplification rates are approximately 7–17% and 5–50% after resistance to first- and second-line osimertinib treatments, respectively.[30,34] MET protein overexpression is also a potential mechanism that may induce resistance to third-generation EGFR-TKIs. Studies have reported incidence rates for MET protein overexpression of 30.4–37.0% in advanced NSCLC cases with *EGFR* mutations treated with EGFR-TKIs.[39,40] In the SAVANNAH study (a phase II study of osimertinib plus savolitinib in patients with concurrent *EGFR*m and *MET* amplification/overexpression NSCLC resistant to osimertinib), 29% of cases resistant to osimertinib exhibited high levels of MET protein overexpression (≥90% tumour cells with IHC 3+).[41]

Histological transformations

Common histological transformations after resistance to third-generation EGFR-TKIs include SCC and SCLC transformations. Evidence implies that after first- and second-line resistance to osimertinib, the incidence of histological transformation is approximately 2–15%.[42] The mechanism of histological transformation has not yet been fully elucidated.

Other oncogene abnormalities

Oncogene abnormalities related to resistance to third-generation EGFR-TKIs include driver gene abnormalities such as *HER2* amplification/mutation, *KRAS* amplification/mutation (e.g., G12D, G12C), *BRAF* mutation (e.g., V600E)/fusion (e.g., *PJA2-BRAF*, *MKRN1-BRAF*), *RET* fusion (e.g., *KIF5B-RET*, *CCDC6-RET*), *ALK* fusion (e.g., *STRN-ALK*, *EML4-ALK*), and *NTRK* fusion (e.g., *MPRIP-NTRK1*, *CD74-NTRK1*), as well as other abnormalities such as *PIK3CA* amplification/mutation (e.g., E545K, E453K), *FGFR* amplification/fusion, and cell cycle gene abnormalities (etc., *CDK4/6* mutation).[29,32] Additionally, AXL overexpression has emerged as resistance mechanism and potential target in recent years.[43] These oncogene abnormalities activate the MAPK and PI3K/AKT pathways, leading to resistance to osimertinib.

Unknown mechanisms of resistance

Despite the increasing exploration of resistance mechanisms, unknown resistance factors remain in 40–50% of cases that progress on first-line and 30–40% of cases on second-line osimertinib treatments, indicating a need for further investigation.[29,32]

The incidence rates of abnormalities related to resistance to third-generation EGFR-TKIs are shown in Fig. 2.

Molecular testing after resistance to third-generation EGFR-TKI

Necessity

> *Consensus IV: Recommend all patients resistant to third-generation EGFR-TKIs to undergo resistance mechanism testing for subsequent clinical treatments*
>
> *(Consensus Level: I; Strength of Evidence: High)*

Performing a biopsy to assess actionable mechanisms of resistance and potential histological transformations after progression on third-generation EGFR-TKIs is highly valuable for guiding subsequent treatments. Therefore, it is recommended that all patients showing resistance to third-generation EGFR-TKIs, particularly those with extensive progression, undergo testing to identify resistance mechanisms to inform further clinical treatment.

Samples

> *Consensus V: Tissue biopsy is recommended as a priority; if tissue samples are not accessible, liquid biopsy can be used as an alternative.*
>
> *(Consensus Level: I; Strength of Evidence: High)*

Histological samples are essential to determine the mechanisms of resistance to third-generation EGFR-TKIs. Tissue biopsies not only facilitate genetic testing to identify post-resistance gene abnormalities but also help confirm the presence of histological transformations. Previous findings indicated that peripheral blood ctDNA samples have limitations in detecting the

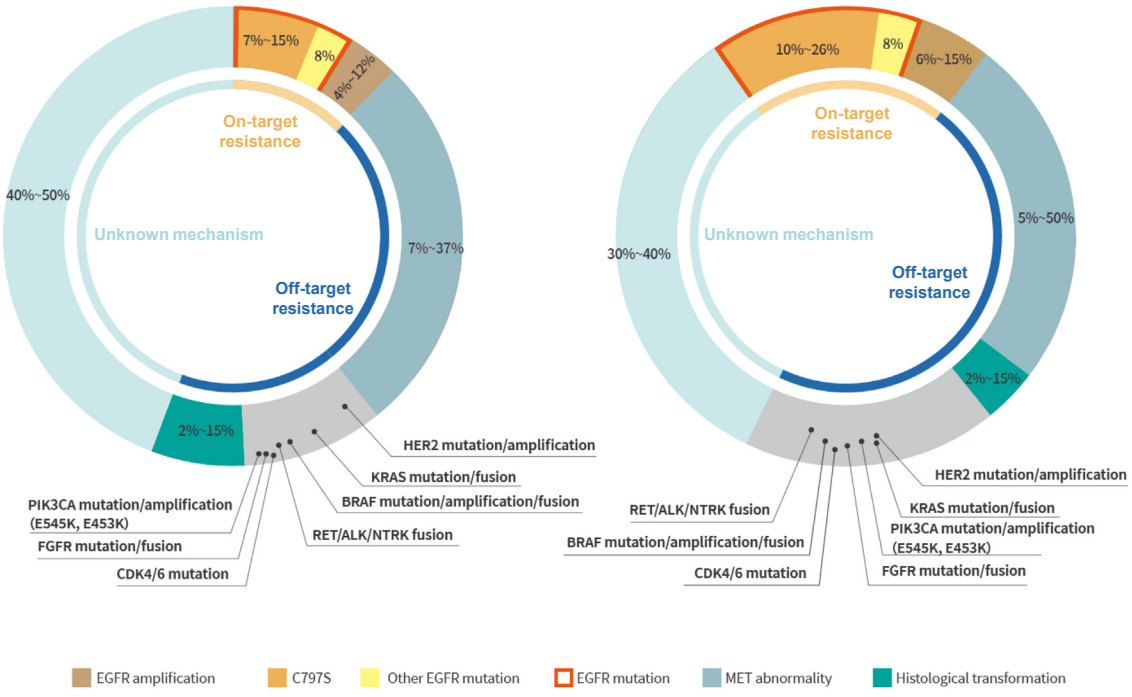

***Fig. 2:* Mechanism of resistance to osimertinib**. Resistance mechanisms emerging after first-line (left) and second-line (right) osimertinib therapy.

types and sensitivity of resistance mechanisms compared to tissue samples, therefore any negative results from ctDNA analysis should be interpreted with caution.[44]

Testing methods and gene coverage

> *Consensus VI: The preferred testing method is next generation sequencing (NGS), which should cover three categories of resistance mechanisms; if NGS testing is not available, the testing should cover EGFR and MET pathway abnormalities at least. MET amplification should be confirmed by fluorescence in situ hybridization (FISH). Histopathological examination should be parallelly conducted to determine the presence of histological transformation and MET protein overexpression.*
>
> *(Consensus Level: I; Strength of Evidence: High)*

NGS technology can comprehensively detect genomic abnormalities at both the DNA and RNA levels, enabling identification of resistance mutation genes across a broad spectrum to guide subsequent treatments. Therefore, it is recommended that all patients resistant to third-generation EGFR-TKIs should preferentially undergo NGS testing. A small panel (30–50 genes) is sufficient to cover known resistance mechanisms and guide subsequent treatment; however, a large panel (≥100 genes) is encouraged to explore unknown resistance mechanisms. If NGS testing is unavailable, given that *MET* amplification and EGFR pathway dependency are the most common resistance mechanisms, it is recommended that patients with resistance undergo at least *MET* amplification and EGFR pathway abnormality testing.

Fluorescence in situ hybridization (FISH) is the gold standard for *MET* amplification testing. In the SAVANNAH study, patients with high *MET* amplification (FISH GCN ≥10) following resistance to osimertinib showed good clinical efficacy with combined treatment of osimertinib and savolitinib. However, FISH can assess only a single gene and lacks a unified standard for evaluation. NGS is also commonly used for *MET* amplification testing, and current data indicate that tissue NGS shows good consistency with FISH for this purpose.[45] Considering that different companies or laboratories may use distinct NGS platforms and bioinformatics analysis strategies with varying cut-off values for *MET* amplification, the presentation of test results may also vary. Therefore, it is recommended that NGS methods for *MET* gene amplification testing should be fully validated for clinical use.

Moreover, considering that MET overexpression may also be a mechanism of resistance to third-generation EGFR-TKIs, and existing studies imply that IHC testing for MET protein overexpression might identify a larger population who could benefit from anti-MET

targeted therapy after resistance to EGFR-TKIs,[46] parallel testing should be considered. However, the cut-off values for MET overexpression vary among clinical trials. The precise cut-off value for MET overexpression to guide clinical treatment still requires further validation through clinical studies. Patients with MET overexpression should be encouraged to participate in clinical studies.

Treatment strategies for patients with resistance to third-generation EGFR-TKIs

Subsequent treatment strategies following resistance to third-generation EGFR-TKIs need to be developed based on a comprehensive assessment of the progression pattern, mechanism of resistance, evidence-based medical data, drug availability, and the patient's performance status and financial situation, with the aim of alleviating symptoms, enhancing quality of life, and maximising survival.

Oligoprogression

Consensus VII: For patients with oligoprogression, it is recommended to combine third-generation EGFR-TKIs with locally aggressive treatments (LATs), such as radiotherapy, surgery, radiofrequency ablation, cryoablation, etc.

(Consensus Level: I; Strength of Evidence: Moderate)

Multiple studies indicate that locally aggressive treatments (LATs) in combination with TKI therapy improve PFS and OS in cases of oligoprogression compared with TKI monotherapy.[47] The main LATs include surgical resection and radiotherapy, and the following factors should be considered when selecting a therapeutic modality for oligoprogressive lesions: radiotherapy may be suitable for patients with limited disease; surgery is preferred when additional biopsy with molecular profiling is required and in these cases, surgery could play a role to eradicate resistant clones.[20] Ongoing studies are evaluating the efficacy and safety of LATs in patients with oligoprogression after third-generation EGFR-TKI treatment, including radiofrequency ablation combined with osimertinib (NCT02759835), LAT combined with osimertinib versus osimertinib monotherapy alone (NCT03410043), SRT combined with almonertinib versus almonertinib monotherapy alone (NCT05800223), furmonertinib combined with radiotherapy (NCT04970693), and cryoablation combined with toripalimab (NCT06127303). The results of these prospective studies will provide stronger evidence for the efficacy and safety of LATs in advanced NSCLC.

Extensive progression

Platinum-based doublet chemotherapy is the regimen recommended by current guidelines for post-line treatment of patients with EGFR-TKI resistance, with a median PFS (mPFS) of approximately 5 months.[48,49] Clinical studies of combinatorial regimens based on chemotherapy in patients with EGFR-TKI resistance are ongoing, examining chemotherapy combined with immune checkpoint inhibitors and anti-angiogenic drugs (the ORIENT-31 and ATTLAS studies) and chemotherapy combined with bispecific antibodies (the MARIPOSA-2 and HARMONi-A studies) (Table 2). Although the aforementioned regimens have shown efficacy in the post-line setting without defining the resistance mechanism, the safety and tolerability of these chemotherapy-based regimens remain issues that need careful consideration. Furthermore, one study suggested that patients may have improved survival when treatment is adapted based on the resistance mechanisms identified at the time of progression.[62]

EGFR pathway-dependent resistance

Consensus VIII: For patients with secondary EGFRm or EGFR amplification after resistance to third-generation EGFR-TKIs, chemotherapy and other regimens approved by local administration are recommended as priorities. Participation in clinical studies can be considered as an option.

(Consensus Level: I, Strength of Evidence: High)

Fourth-generation EGFR-TKIs, represented by BDTX-1535, have also been assessed in patients with C797S mutations following resistance to third-generation EGFR-TKIs. In a phase I trial, BDTX-1535 demonstrated good tolerability and antitumour activity, with an objective response rate (ORR) of 55% and a disease control rate (DCR) of 90.9% in post-osimertinib treatment, with 8 of 11 patients harbouring the C797S mutation.[63] In addition, other fourth-generation TKIs, such as HS-10375 and BPI-361175 are also undergoing clinical trials. Platinum-based doublet chemotherapy remains the standard regimen for patients with EGFR-TKI resistance.

MET *amplification and/or overexpression*

Consensus IX: For patients with MET amplification and/or overexpression after resistance to third-generation EGFR-TKIs, a dual-targeted regimen of MET-TKIs combined with osimertinib is recommended.

(Consensus Level: I; Strength of Evidence: Moderate)

MET-TKIs are potent, highly selective small-molecule inhibitors that target MET tyrosine kinase, with several drugs approved for the treatment of NSCLC cases with *MET* exon 14 skipping mutations, such as savolitinib, capmatinib, glumetinib, bozitinib, and tepotinib. In recent years, multiple studies have

Resistance type	Study	Phase	Acquired resistance	Prior therapy	Treatment arm	Efficacy	Safety
MET amplification and/or overexpression	ORCHARD[50]	II	*MET* amplification	osimertinib	osimertinib + savolitinib	ORR 41%	Grade ≥ 3 AE: 30%; SAE: 30%
	SAVANNAH[41]	II	*MET* amplification/ overexpression[a]	osimertinib	osimertinib + savolitinib	All patients ORR 32%; mDoR 8.3 mo; mPFS 5.3 mo IHC 90+ and/or FISH 10+ group[c] ORR 49%; mDoR 9.3 mo; mPFS 7.1 mo	Grade ≥ 3 AE: 45%; SAE: 29%
	INSIGHT2[51]	II	*MET* amplification[b]	osimertinib	osimertinib + tepotinib	mPFS 5.6 mo; mOS 17.8 mo ORR 50%; mDoR 8.5 mo	Grade ≥ 3 AE: 34.4%; SAE: 29%
RET fusion	Jie et al.[52]	RWE	RET fusion	EGFR/ALK TKI	A: pralsetinib based regimen; B: non-pralsetinib based regimen	mPFS, A: 8.42 mo; B: 6.97 mo ORR, A: 35%; B:18.2% DCR, A: 75%; B: 54.6%	arm A, AE: 64%; SAE: 10%
Histology transformation	Nicolas et al.[53]	retrospective	SCLC transformation	EGFR TKI	chemo	mOS 10.9 mo	(–)
	Léonie Ferrer et al.[54]	retrospective	SCLC transformation	EGFR TKI	chemo	mOS 9 mo	(–)
	Jianghua Ding et al.[55]	retrospective	SCLC transformation	EGFR TKI	Chemo + anlotinib	mPFS 9 mo; mOS 14 mo	(–)
Undefined	ORIENT-31[49]	III	undefined	EGFR TKI	A: sintilimab + IBI305 + chemo; B: sintilimab + chemo; C: chemo	mPFS, A: 7.2 mo; B: 5.5 mo; C: 4.3 mo HR A vs C 0.51 (0.39–0.67) B vs C 0.72 (0.55–0.94)	Grade ≥ 3 TRAE, A: 56%; B: 41%; C: 49%
	ATTLAS[56]	III	undefined	EGFR/ALK TKI	A: atezolizumab + bevacizumab + chemo B: chemo	mPFS, A: 8.48 mo; B: 5.62 mo HR 0.62 (0.45–0.86)	Grade ≥ 3 TRAE, A: 35.1%; B: 14.9%
	HARMONi-A[57]	III	undefined	EGFR TKI	A: ivonescimab + chemo; B: chemo	mPFS, A: 7.1 mo; B: 4.8 mo HR 0.46 (0.34–0.62)	Grade ≥ 3 TRAE, A: 54%; B: 42.9%
	MARIPOSA-2[58]	III	undefined	osimertinib	A: amivantamab + lazertinib + chemo; B: chemo; C: amivantamab + chemo	mPFS, A: 8.3 mo; B: 4.2 mo; C: 6.3 mo HR A vs B 0.44 (0.35–0.56) C vs B 0.48 (0.36–0.64)	Grade ≥3 TEAE, A: 92%; B: 48%; C: 72%
	TROPION-Lung01[59]	III	undefined	one or two prior lines including: targeted therapy according to AGA/chemo/ICI	A: Dato-Dxd; B: Docetaxel	mPFS, A: 4.4 mo; B: 3.7 mo HR 0.75 (0.62–0.91)	Grade ≥ 3 TRAE, A: 25%; B: 41% Serious TRAE, A: 10%; B: 12%
	TROPION-Lung05[60]	II	undefined	at least 1 line of targeted therapy according to AGA + one or two lines of chemo	Dato-Dxd	EGFRm group ORR 43.6%; DCR 82.1% mPFS 5.8 mo	Grade ≥ 3 TEAE: 47%; SAE: 5%
	HERTHENA-Lung01[61]	II	undefined	one line of osimertinib + one or two lines of chemo/ICI	HER3-Dxd	ORR 29.2%; DCR 72.7% mPFS 5.5 mo; mOS 11.9 mo	Grade ≥ 3 TEAE: 64.9%; SAE: 40%

AE, adverse event; DCR, disease control rate; DoR, duration of response; GCN, gene copy number; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SEA, serious adverse event. [a]Amplification defined as FISH: *MET* GCN ≥ 5 and/or *MET*: CEP7 ratio ≥2; overexpression defined as IHC: MET 3+ in ≥50% tumour cells. [b]FISH: *MET* GCN≥5 and/or *MET*: CEP7 ratio ≥2 or NGS: ≥2.3 Archer®. [c]FISH: *MET* GCN10 or IHC: MET 3+ in 90% tumour cells.

***Table 2*: Data summary of clinical trials in *EGFR* mutant metastatic NSCLC cases progressing on 3rd-generation EGFR inhibitors.**

examined the efficacy and safety of combining a MET-TKI with osimertinib in patients with *MET* gene amplification and/or MET protein overexpression after developing resistance to osimertinib, implying that a MET-TKI combined with osimertinib may overcome resistance mediated by MET pathway abnormalities. Related study data are shown in Table 2. Additionally, Bispecific antibodies targeting MET represent an emerging new treatment option and may offer a potential strategy.

Other driver gene abnormalities

Consensus X: For patients with driver gene mutations (HER2/KRAS/BRAF/RET/ALK/NTRK, etc.) that emerge after resistance to third-generation EGFR-TKIs, it

is recommended to receive chemotherapy or participate in clinical studies. Other regimens approved by local administration are also recommended. Corresponding targeted drugs might be considered as options.

(Consensus Level: I; Strength of Evidence: Low)

HER2 *mutation or amplification.* Trastuzumab deruxtecan (T-DXd) is an HER2-targeted antibody–drug conjugate (ADC). The phase II DESTINY-Lung02 study showed that in patients with unresectable or metastatic *HER2*-mutant non-squamous NSCLC who have PD following systemic treatment, the ORR assessed by blinded independent central review was 49.0% in the T-DXd 5.4 mg/kg group versus 56.0% in the 6.4 mg/kg group, with mPFS of 9.9 months and 15.4 months, respectively. The median OS was 19.5 months in the 5.4 mg/kg group and not reached in the 6.4 mg/kg group. Both dose groups demonstrated tolerable and manageable safety profiles, with 5.4 mg/kg having a more favourable safety profile.[64] Based on this phase II study, trastuzumab deruxtecan was approved by the U.S. Food and Drug Administration (FDA) for use in adult patients with *HER2*-mutant unresectable or metastatic NSCLC following prior systemic treatment.

Osimertinib combined with trastuzumab emtansine (T-DM1) is being evaluated in patients with HER2 overexpression or amplification after progression on EGFR-TKI. In a phase II study involving 27 patients, the ORR was 4% and mPFS was 2.8 months.[65] Although the study demonstrated favourable toxicity, its limited efficacy implies that further investigation of this innovative drug in the context of HER2-mediated EGFR-TKI resistance is needed.

KRAS *mutation.* Sotorasib and adagrasib are inhibitors that target *KRAS* G12C. In the CodeBreaK 100 phase I/II clinical study, sotorasib demonstrated an ORR of 40.7%, a DCR of 83.7%, an mPFS of 6.3 months, and an mOS of 12.5 months in NSCLC cases with the *KRAS* G12C mutation previously treated with at least one line of systemic therapy.[66] In the KRYSTAL-1 study, adagrasib had an ORR of 42.9%, a DCR of 79.5%, an mPFS of 6.5 months, and an mOS of 12.6 months.[67] Both sotorasib and adagrasib have been approved by the FDA for post-line treatment of NSCLC patients with the *KRAS* G12C mutation.

BRAF *mutation.* For acquired *BRAF* mutations, combining an EGFR inhibitor with MEK and/or BRAF inhibitors may help to overcome resistance. Recently, a study evaluated a triplet regimen (dabrafenib + trametinib + osimertinib) for the treatment of patients with acquired *BRAF* V600E mutation after progression on EGFR-TKI therapy. The results showed that with this triple–target combination therapy, the ORR and DCR were 58.3% and 83.3%, respectively. The mPFS was 13.5 months, and no patients discontinued treatment due to severe adverse events,[68] implying that patients with *BRAF* V600E mutations may derive greater benefit from this triple regimen.

RET/ALK/NTRK fusion. A multicentre, real-world data analysis in China examined the efficacy of pralsetinib for acquired RET fusion-positive NSCLC resistant to EGFR/ALK TKIs in 32 patients (Table 2). In this study, 83.3% of patients had been treated with third-generation EGFR-TKIs. Patients treated with pralsetinib showed a longer median time to treatment failure (mTTF), ORR, and DCR. For patients with *ALK* fusion following resistance to third-generation EGFR-TKIs, preliminary efficacy was demonstrated in some case reports that assessed combinations of ALK inhibitors.[69] Additionally, some targeted drugs for cases with *NTRK* fusion, including larotrectinib, entrectinib, and Loxo-195, have been approved by the FDA or shown effectiveness in clinical studies.

Overall, most systemic therapeutic strategies without consideration of resistance mechanisms have also been investigated in cases of NSCLC resistant to third-generation EGFR-TKIs (Table 2). Therefore, patients with the aforementioned driver gene abnormalities were included in these studies, even if efficacy data specific to this population were not available.

Histological transformations

Consensus XI: For patients with histological transformations after resistance to third-generation EGFR-TKIs, chemotherapy or participation in clinical studies is recommended.

(Consensus Level: I; Strength of Evidence: Low)

A retrospective study enrolled 67 patients with SCLC transformation following resistance to EGFR-TKI treatment, of whom 33% were treated with osimertinib and 87% received the etoposide + platinum (EP) regimen after SCLC transformation, revealing an ORR of 54% and an mOS of 10.9 months.[53] Another retrospective study enrolled 48 patients, 79% of whom received the EP regimen, and reported a median OS of 9 months.[54] A separate retrospective study reported on 10 patients with SCLC transformation who received the EP plus anlotinib regimen, showing a median PFS of 9 months and OS of 14 months (Table 2).[55] Other trials for SCLC transformation are ongoing (Table 3). For patients with histological transformation to SCC, trial-based evidence is currently lacking, and most related studies are case reports. Based on current evidence, for advanced NSCLC cases with histological transformations after resistance to third-generation EGFR-TKIs, active participation in clinical studies is encouraged and chemotherapy is a treatment option.

Resistance type	Study	Phase	Acquired resistance	Prior therapy	Treatment arm
MET amplification and/or overexpression	SACHI	III	*MET* amplification	EGFR-TKIs (incl. 3rd-generation EGFR-TKI)	osimertinib + savolitinib vs chemo
	SAFFRON	III	*MET* amplification/ overexpression	osimertinib	osimertinib + savolitinib vs chemo
	NCT06110663	III	*MET* amplification	EGFR-TKIs (incl. 3rd-generation EGFR-TKI)	HS-10241 + almonertinib vs chemo
	NCT06093503	III	MET overexpression	osimertinib	telisotuzumab vedotin + osimertinib vs chemo
	NCT05821933	I/II	MET overexpression	EGFR-TKIs (incl. 3rd-generation EGFR-TKI)	RC108 + furmonertinib RC108 + furmonertinib + toripalimab
EGFR C797S	NCT05256290	I/II	C797S	3rd-generation EGFR-TKI	BDTX-1535
Histology transformation	NCT05957510	II	SCLC transformation	EGFR-TKI	serplulimab + chemo
	NCT04538378	II	SCLC transformation	EGFR-TKI	durvalumab + olaparib
Undefined	HERTHENA-Lung02	III	unspecified	3rd-generation EGFR-TKI	HER3-Dxd vs chemo
	NCT05756972	III	unspecified	EGFR-TKIs (incl. 3rd-generation EGFR-TKI)	PM8002 + chemo vs chemo
	NCT05870319	III	unspecified	EGFR-TKIs (incl. 3rd-generation EGFR-TKI)	SKB264 vs chemo
	NCT05132413	III	unspecified	EGFR-TKI	SHR-1701 + chemo + bevacizumab vs SHR-1701 + chemo vs chemo
	NCT03532698	II	unspecified	osimertinib	osimertinib + aspirin vs osimertinib
	NCT05956587	II	unspecified	EGFR-TKI	BL-B01D1 + SI-B003
	NCT03831932	I/II	unspecified	EGFR-TK I (incl. 3rd-generation EGFR-TKI)	osimertinib + telaglenastat vs osimertinib
	CTR20231603	Ib	unspecified	EGFR-TKI	bozitinib + PLB-1004
	NCT06015568	I	unspecified	EGFR-TKI (incl. 3rd-generation EGFR-TKI)	befotertinib + MCLA-129
	NCT04001777	I	unspecified	3rd-generation EGFR-TKI	osimertinib + APG-1252
	NCT04085315	I	unspecified	osimertinib	osimertinib + Alisertib
	NCT02503722	I	unspecified	osimertinib	osimertinib + Sapanisertib

Table 3: **Summary of ongoing clinical trials in *EGFR* mutant metastatic NSCLC progressing on 3rd-generation EGFR inhibitors.**

Other oncogene abnormalities or unknown mechanisms of resistance

> *Consensus XII: For patients with other oncogene abnormalities (PIK3CA/FGFR/cell cycle genes, etc.) related to resistance after third-generation EGFR-TKI treatment, or with unknown mechanisms of resistance, it is recommended to receive chemotherapy or participate in clinical studies. Other regimens approved by local administration are also recommended.*
>
> *(Consensus Level: I; Strength of Evidence: Low)*

There is currently no evidence for precise treatment of NSCLC with *PIK3CA* mutation/amplification, *FGFR* amplification/fusion, cell cycle gene aberrations, other oncogene alterations, or cases with unknown mechanisms of resistance following progression on third-generation EGFR-TKIs. Therefore, we recommend that these patients receive chemotherapy or participate in clinical trials. Based on clinical evidence (e.g., ORIENT-31 and MARIPOSA-2) and local regulations, appropriate regimens may be considered. In addition to combination treatment regimens, some new drugs in development, including ADCs as monotherapies, have shown promising preliminary results, and additional clinical trials are ongoing.

Other therapeutic strategies

In addition to the aforementioned combinatorial and targeted regimens, new drugs in the research and development stage have also shown promising preliminary results, such as Trop-2 and HER-3 ADCs.

Datopotamab deruxtecan (Dato-DXd) is a TROP2-targeted ADC that consists of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a highly potent topoisomerase-I inhibitor payload via a plasma-stable, tumour-selective, tetrapeptide-based cleavable linker. The TROPION-Lung01 study was a global, multicentre, phase III registration clinical study that evaluated the efficacy and safety of Dato-DXd versus docetaxel in patients with locally advanced or metastatic NSCLC, with or without actionable genomic alterations (AGAs), who had received at least one prior treatment (Table 2). The results showed significantly improved PFS in the Dato-DXd group compared with the docetaxel group, particularly in the non-SCC and AGA

populations, with PFS increases of 1.9 and 4.2 months, respectively.[59] TROPION-Lung05 was a phase II single-arm study that evaluated the efficacy and safety of Dato-DXd for advanced metastatic NSCLC with AGAs after progression on previous targeted therapy and platinum-based chemotherapy (Table 2). The results indicated that Dato-DXd demonstrated strong anti-tumour activity in heavily pretreated NSCLC cases with AGAs. In these patients, the confirmed ORR for the *EGFR* mutation subgroup was 43.6%, with a median PFS of 5.8 months,[60] and the benefit for the Asian *EGFR*m population (ORR, 48.9%; PFS, 5.7 months) was consistent with that observed in the global population.[70] These results confirm the efficacy of Dato-DXd in previously treated advanced metastatic NSCLC with AGAs.

Patritumab deruxtecan (HER3-DXd) is an ADC targeting HER3 that was developed using Dxd-ADC technology. HERTHENA-Lung01 was an open-label, pivotal phase II study that evaluated the efficacy and safety of HER3-DXd in *EGFR*-mutated NSCLC cases previously treated with EGFR-TKIs and platinum-based chemotherapy (Table 2). The results showed an ORR of 29.2%, mPFS of 5.5 months, and mOS of 11.9 months.[61] These findings imply potential for HER3-DXd in pretreated *EGFR*m NSCLC cases. A phase III, global multicentre, randomized controlled trial, HERTHENA-Lung02, assessing the efficacy and safety of HER3-DXd versus platinum-based chemotherapy in cases resistant to EGFR-TKIs, is ongoing (Table 3).[71]

The detailed data of clinical trials for *EGFR*-mutant metastatic NSCLC cases progressing on third-generation EGFR-TKIs are summarized in Table 2. Additionally, a summary of ongoing clinical trials for *EGFR*-mutant metastatic NSCLC progressing on third-generation EGFR-TKIs is provided in Table 3.

Conclusion and prospects

In recent years, the landscape of diagnostic and therapeutic approaches for NSCLC has evolved significantly, with the discovery of new targets and the launch of corresponding targeted therapies. The introduction of third-generation EGFR-TKIs has notably improved survival rates for patients with advanced NSCLC harbouring *EGFR* mutations. Additionally, research into resistance mechanisms and the management of resistance post-therapy have become pivotal areas of clinical investigation. This consensus reviewed the resistance mechanisms following treatment with third-generation EGFR-TKIs and provides detailed diagnostic and therapeutic recommendations for patients with oligo-progressive or extensive progression due to different mechanisms of resistance (Fig. 3). However, the mechanisms of resistance to third-generation EGFR-TKIs are complex and diverse, and based on current scientific progress, it is not yet possible to provide specific diagnostic and therapeutic recommendations for all resistance-related mutations. Furthermore, the FLAURA2 and MARIPOSA trials have introduced combination regimens in first-line NSCLC therapy, which are likely to trigger more heterogeneous and complex resistance mechanisms. In the future, as we gain a deeper understanding of the biological mechanisms of resistance to third-generation EGFR-TKIs and more clinical data on post-resistance treatment strategies become available, further and improved therapeutic

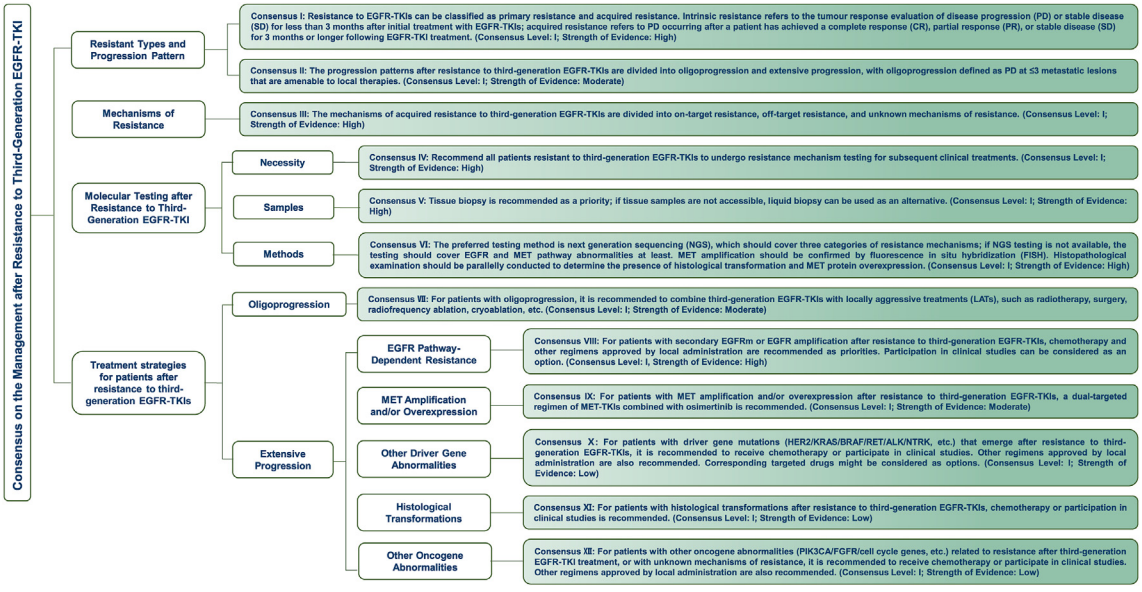

Fig. 3: **Scheme of consensus on the management after resistance to third-generation EGFR-TKI.**

options will be provided for cases resistant to third-generation EGFR-TKIs.

Contributors

Y.W. conceptualized the consensus, initiated the consensus formation and made the final decision to submit for publication. All authors discussed the consensus content, voted for consensus items, and review the manuscript. S. Liu. is responsible for literature search and writing the manuscript. Q.Z. and Y.W. are responsible for verifying the data. Y.W., T.M., M.A., and D.T. supervised and revised the consensus. All authors had access to raw data.

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