



Society for Translational Medicine consensus on postoperative management of EGFR-mutant lung cancer (2019 edition)

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Introduction

Non-small cell lung cancer (NSCLC) is the most common and fatal tumor worldwide, with 2.1 million new cases and 1.77 million deaths per year (1). With the wider application of examination approaches and the improvement of health awareness, higher proportions of surgically resectable early and mid-stage lung cancers have been detected. In overall, only 50% of patients have been cured after radical resection. In other cases, however, NSCLC is highly active and recurrence and/or metastasis can easily occur after surgery. In these patients, systemic therapy as a postoperative adjuvant therapy is required to eliminate or reduce residual micro-lesions to lower the risk of recurrence; meanwhile, the patients should be closely monitored to detect early recurrence. EGFR mutation is a major mutation type in lung cancer, and is seen in about 40% of lung cancer cases in Asia (2). Compared with wild types and other mutation types, EGFR-mutant NSCLC has its unique biological properties and drug susceptibilities, and thus requires specific diagnosis and treatment strategies. This expert consensus aims to review the current evidence and provide recommendations on key issues.

A consensus and guideline development panel, with its members including top thoracic surgeons and oncologists all around the world, was established to decide the methodologies, processes, levels of evidence, and related recommendations. The panel members proposed the core

clinical issues in the consensus document and wrote and submitted the outlines to the panel for approval. The panel carried out a problem-oriented literature search for articles published since 1997 in Chinese and foreign databases. The level of evidence was defined using the following criteria: Categories of Evidence and Consensus, Category 1: based upon high-level evidence, there is uniform consensus that the intervention is appropriate; Category 2A: based upon lower-level evidence, there is uniform consensus that the intervention is appropriate; Category 2B: based upon lower-level evidence, there is consensus that the intervention is appropriate; Category 3: based upon any level of evidence, there is major disagreement that the intervention is appropriate. The strength of recommendations was classified as strong or weak according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (3), and the recommendation statement was composed based on the real-world evidence. A “strong” recommendation generally refers to recommendations based on high-level evidence with consistency between clinical behavior and outcome expectancy; in contrast, a “weak” recommendation is typically based on low-level evidence with uncertainty between clinical behavior and outcome expectancy. After the first draft had been completed, all the panel members were involved in revising and finalizing this document.

Consensus 1: detection of EGFR mutations is routinely recommended in surgically resected specimens of non-squamous NSCLC, and other driver mutations may also be detected if the conditions of hospital and patient allow (level of evidence: 2A; strength of recommendation: strong)

Since the use of an EGFR tyrosine kinase inhibitor (EGFR-TKI) mainly depends on the presence of EGFR mutations, the National Comprehensive Cancer Network (NCCN) guidelines require the routine detection of EGFR mutations in patients with advanced non-squamous NSCLC (4). According to the results of several randomized controlled clinical trials including RADIANT, ADJUVANT, and EVAN study (5-7), EGFR-TKI has become one of the optional postoperative adjuvant treatments for patients with EGFR-mutant NSCLC. A clear postoperative EGFR mutation status helps to guide the choice of adjuvant therapy. Moreover, because different types of driver mutations suggest different biological behaviors, EGFR mutation status can predict the risk of postoperative recurrence (8) and the treatment failure patterns (9), which can guide the postoperative recurrence monitoring strategies and the drug selection after relapse. Therefore, for patients with non-squamous NSCLC, routine EGFR mutation testing is recommended after surgery. In addition, a certain proportion of non-smokers with squamous cell carcinoma of the lungs also have EGFR mutations (10), which can be detected according to the actual situations.

With the progress in sequencing technology, multi-genotyping has been widely used, and markers such as TP53 mutation and tumor mutation burden (TMB) have been found to be prognostic (11,12). If the conditions of hospitals and patients allow, other driver mutations (including the main mutations recommended by the NCCN guidelines and other pathway mutations) may also be detected to provide comprehensive genotyping information for predicting prognosis and guiding treatment.

Consensus 2: comprehensive prediction models based on clinical or molecular risk factors can be used to stratify recurrence risk (level of evidence: 2B; strength of recommendation: strong)

The use of adjuvant therapy depends on the risk of recurrence. Currently, adjuvant therapy is recommended

for stage II–IIIA NSCLC patients at a high risk of recurrence, whereas the population more likely to benefit from EGFR-TKI as adjuvant therapy are mainly patients with stage IIIA NSCLC. Although patients with stage I disease are at a low risk of recurrence, relapse still occurs in a notable proportion of patients. There is evidence that patients with high-risk stage I NSCLC may also benefit from adjuvant therapy (13). Many recurrence-related risk factors and comprehensive predictive models have been available for assisting in risk assessment (13-16) and thus informing tailored therapy.

Consensus 3: for patients with EGFR mutations, adjuvant EGFR-TKI can achieve longer disease-free survival (DFS) compared with chemotherapy and thus can be used as one of the postoperative adjuvant treatment options for patients with stage II–IIIA EGFR-mutant NSCLC, especially for those patients at a high risk of recurrence and with poor expected tolerance to chemotherapy. For high-risk stage Ib patients, EGFR-TKI is optionable (level of evidence: 1; strength of recommendation: strong)

In the ADJUVANT study, patients with completely resected stage II–IIIA EGFR-mutant NSCLC were treated with gefitinib for 2 years. Compared with the conventional NP regimen of 4 cycles, the median DFS was significantly prolonged from 18 to 28.7 months and the risk of disease recurrence decreased by 40% (HR 0.60, P=0.005). In addition, patients in stage IIIA were observed to benefit more from the adjuvant gefitinib than those in stage II (6). In the EVAN study, patients with resected stage IIIA–N2 EGFR-mutant NSCLC were treated with erlotinib for 1 year; compared with the conventional NP regimen for 4 cycles, the DFS was significantly prolonged (7). In addition, severe adverse events are less common with EGFR-TKI in comparison to chemotherapy. Based on the above findings and some real-world studies (17), EGFR-TKI can be used as one of the postoperative adjuvant treatment options for patients with stage II–IIIA EGFR-mutant NSCLC, especially in patients at a high risk for relapse and a low expected tolerance to chemotherapy. According to most experts' consensus, for high-risk stage Ib patients, EGFR-TKI is optionable. Notably, overall survival data of the above studies is still awaited, and the positive studies were based on Chinese population so that further confirmation whether these results are translatable across the global community is warranted.

Consensus 4: postoperative adjuvant therapies in patients with EGFR-mutant NSCLC may include the following modes: adjuvant chemotherapy, EGFR-TKI, and adjuvant chemotherapy plus EGFR-TKI (level of evidence: 2A; strength of recommendation: strong)

The main modes of postoperative adjuvant therapy for EGFR-mutant NSCLC include adjuvant chemotherapy, EGFR-TKI, and sequential use of adjuvant chemotherapy and EGFR-TKI (5-7). Due to the lack of strict head-to-head comparisons, all the above models are optional and clinicians may choose the most appropriate mode based on the patient's risk, physical performance, and willingness.

Consensus 5: the postoperative adjuvant EGFR-TKI treatment should last at least 2 years (level of evidence: 2B; strength of recommendation: strong)

The use of EGFR-TKI as adjunctive therapy ranges between 0.5 and 3 years in the currently available studies (5-7,18,19). In the ADJUVANT study, the recurrence-free survival curve showed a significant downward trend after 2 years, which might be explained by the discontinuation of TKI. In the previous adjuvant treatment of breast cancer with endocrine therapy and adjuvant imatinib for gastrointestinal stromal tumors, it was observed that the prolonged medication was associated with a better prognosis (20,21). Furthermore, no evidence has shown that the postoperative use of TKI can induce T790M mutation (22). While the optimal duration of continuous EGFR-TKI use remains unclear, it is agreed that postoperative adjuvant EGFR-TKI should be used continuously for 2 years or more to reduce the risk of recurrence, during which time the drug toxicity should be managed.

Consensus 6: patients with EGFR-mutant NSCLC are at a higher risk of postoperative brain and bone metastases than non EGFR-mutants. Annual brain MRI and bone scans in addition to regular chest CT are recommended for EGFR-mutant NSCLC, and the scan frequencies can be increased in patients at a high risk for recurrence (level of evidence: 2A; strength of recommendation: strong)

Post hoc analysis in the ADJUVANT study and other studies have shown that the main postoperative recurrence patterns in EGFR-mutant NSCLC patients include brain

metastasis, thoracic/pulmonary recurrence and metastasis, and bone metastasis (9). The current NCCN guidelines only recommend regular chest CT examinations, which may lead to delayed diagnosis of recurrence and miss the chance of re-treatment. It is therefore suggested that, based on the biological characteristics of EGFR mutations, annual brain MRI and bone scans on the basis of regular chest CT should be performed in EGFR-mutant NSCLC patients, and the scan frequencies can be increased in patients at a high risk for recurrence.

Consensus 7: in patients with recurrence and metastasis after surgery, the genetic testing results obtained from the surgical specimens could be referred to; alternatively, the surgical specimens stored within the past 2 years, or the re-biopsy specimens, may be used for genetic testing to confirm the gene mutation status to guide therapy. The detection of EGFR mutation by liquid biopsy can be a supplement when tissue samples are not available (level of evidence: 2B; strength of recommendation: strong)

Patients with postoperative recurrence and metastasis should preferably undergo re-biopsy, if conditions allow, to harvest the diseased tissue for genetic testing. If such specimens cannot be collected, the results of genetic testing in the surgical specimens can be used, as there is a high consistency of EGFR mutation between primary and metastatic lesions. Alternatively, the surgical specimens stored within the past 2 years can be used for genetic testing to identify the genetic mutation status. The detection of EGFR mutation by liquid biopsy based on PCR or NGS has high specificity and can be a powerful supplement when tissue samples are not available (22,23).

Consensus 8: in EGFR-mutant NSCLC patients with postoperative recurrence and metastasis, EGFR-TKI (preferably osimertinib) can be a treatment choice for salvage therapy. In patients receiving adjuvant EGFR-TKI therapy after surgery, EGFR-TKI can be re-used if relapse occurs after drug discontinuation. If necessary, re-biopsy can be performed to confirm the T790M status (level of evidence: 1; strength of recommendation: strong)

EGFR-mutant NSCLC patients experiencing postoperative

recurrence and metastasis can be treated with the first-line regimen for advanced disease. EGFR-TKI is recommended as a salvage therapy (24). The study series based on FLAURA found that osimertinib could significantly prolong the PFS and OS when compared with the first-line gefitinib or erlotinib. Therefore, osimertinib is the preferred first-line treatment (4,25,26).

For patients who have used EGFR-TKI as adjuvant therapy, the SELECT study showed that the risk of developing T790M mutations was low (23). Thus, the same EGFR-TKI can still be used as salvage therapy, or the drug may be selected according to the above first-line therapy. If necessary, re-biopsy may be performed to identify the T790M status.

The above consensus was reached among Chinese experts. To gather more extensive views on this issue, we also invited experts outside China to comment on several controversial questions involved in this consensus

Question 1. Do patients with NSCLC who have undergone a radical resection need EGFR mutation profiling?

Expert opinion 1: Dr. Alessandro Brunelli

EGFR mutation profiling should be tested in all patients with NSCLC who have undergone radical resection. EGFR mutated patients may benefit of postoperative adjuvant EGFR-TKI in case of recurrence or locally advanced disease.

Expert opinion 2: Dr. René Horsleben Petersen

All patients with NSCLC who have undergone radical resection should be tested with EGFR mutation profiling in order to provide basis for EGFR-TKI treatment in case of locally advanced disease or recurrence.

Expert opinion 3: Dr. Chia-Chuan Liu

Only when further management is indicated, e.g., some risk—LVI, big tumor, solid or micro papillary type, should patients with NSCLC who have undergone a radical resection need EGFR mutation profiling. Stage I or patients refuse adjuvant TKI treatment do not need the test.

Expert opinion 4: Dr. Tony S. K. Mok

Insufficient evidence for such. You may state that it is optional. For the possibility to have EGFR mutation in non-

smoking squamous cell carcinoma, there is only data of such in stage IV disease and minimal for early resectable SCC.

Expert opinion 5: Dr. Biagio Ricciuti & Dr. Giulio Metro

EGFR testing is recommended in all patients with newly diagnosed advanced NSCLC (4). The superiority of EGFR TKIs over standard cytotoxic chemotherapy in patients with advanced NSCLC harboring EGFR sensitizing mutations has been confirmed in several randomized phase III clinical trials. However, controlled randomized clinical trials with adjuvant EGFR TKIs have shown conflicting results regarding whether adjuvant EGFR-TKIs improves the survival of patients with resected NSCLC. Although a benefit in disease-free survival has been reported in the RADIANT, ADJUVANT and EVAN trials, the overall survival benefit could not be demonstrated. At the present time, in absence of a proven survival benefit with adjuvant EGFR TKIs, routine molecular testing for EGFR mutations in patients should not be recommended outside of clinical trials (4).

Expert opinion 6: Dr. Alessandro Tuzi & Dr. Matteo B. Suter

Speaking for the European setting, the short answer is no. The only instance in which we feel a molecular profile should be carried out, is in a research setting.

Expert opinion 7: Dr. Matthew Evison

Yes. This consensus document recommends adjuvant EGFR-TKI as a potential treatment EGFR mutated NSCLC after surgery, so EGFR testing of resected tumours is essential to guide management decisions.

Expert opinion 8: Dr. Nobuhiko Seki

I agree the statement that “detection of EGFR mutations is routinely recommended in surgically resected specimens of non-squamous NSCLC, and other driver mutations may also be detected if the conditions of hospital and patient allow” and “Moreover, because different types of driver mutations suggest different biological behaviors, EGFR mutation status can predict the risk of postoperative recurrence (8) and the treatment failure patterns (9), which can guide the postoperative recurrence monitoring strategies and the drug selection after relapse. Therefore, for patients with non-squamous NSCLC, routine EGFR mutation testing is recommended after surgery”.

Expert opinion 9: Dr. Shinji Sasada

EGFR mutation profiling is necessary to plan treatment for relapse. The use of EGFR-TKI in postoperative adjuvant chemotherapy is not recommended by Japanese guidelines, so at present, EGFR mutation screening is not essential. However, I think it will be necessary in the future as CTONG data comes out.

Expert opinion 10: Dr. Takhiro Izumo

Yes. Necessary for investigating chemotherapy at the time of recurrence.

Expert opinion 11: Dr. William Chi-Shing Cho

The current data is not strong currently EGFR mutation status has no role to guide adjuvant treatment. However, the detection is attractive and may be more useful in the future.

Question 2. Can EGFR-TKI replace chemotherapy in patients who require adjuvant therapy after resection? If yes, how long should the adjuvant EGFR-TKI last?

Expert opinion 1: Dr. Alessandro Brunelli

There is no head-to-head comparison between adjuvant chemotherapy alone *vs.* EGFR TKI *vs.* chemotherapy+EGFR-TKI. In patients showing mutated EGFR profile EGFR-TKI may replace chemotherapy especially if the patients are considered too high risk for conventional chemotherapy. The compliance rate of adjuvant chemotherapy after surgery is only 60% or less due to the burden of the lung resection. Especially in physiologically high-risk patients EGFR-TKI may replace chemotherapy increasing the compliance rate.

Expert opinion 2: Dr. René Horsleben Petersen

In patients with EGFR mutations and advanced NSCLC, first line treatment with EGFR-TKI provides better progression free survival (23). In the adjuvant setting, data from the ADJUVANT trial and EVAN trial show improvement in progression free survival in favor of EGFR-TKI (6,7). Based on these data adjuvant EGFR-TKI may replace adjuvant chemotherapy, particularly in patients with a low tolerance to chemotherapy. It is unknown how long the adjuvant EGFR-TKI should last, but probably as long as the disease is stable (>2 years).

Expert opinion 3: Dr. Chia-Chuan Liu

Only when TKI is more effective than chemotherapy or patients who cannot receive or refuse chemotherapy, can

EGFR-TKI replace chemotherapy in patients who require adjuvant therapy after resection. Treatment duration depends on the purpose, but the dosage could be modified.

Expert opinion 4: Dr. Tony S. K. Mok

RADIANT study is actually a negative study; ADJUVANT is positive but in the subgroup analysis there is no benefit for stage II; and EVAN is a small size study on only stage IIIA. Data is too weak to give a 2A and strong recommendation for ALL resectable lung cancer. Moreover, in terms of the length of TKI use, please note that less than 50% of patient can take more than 1 year of erlotinib in the RADIANT study.

Expert opinion 5: Dr. Biagio Ricciuti & Dr. Giulio Metro

Adjuvant EGFR TKIs have been compared to standard chemotherapy in large phase III clinical trials with conflicting results. In two early studies, adjuvant gefitinib and erlotinib did not prolong the DFS in patients with early stage NSCLC (5,27). However, both these studies neglected the EGFR mutation status. Differently, the EVAN and the CTONG 1,104 studies showed gefitinib and erlotinib improve the DFS in II-III NSCLC harboring EGFR sensitizing mutations (6,7). A recent pooled analysis showed that adjuvant EGFR-TKI therapy enhances DFS in patients with EGFR-mutant NSCLC but does not improve the OS (28). The lack of OS benefit represents a major concern for the use of adjuvant TKIs. The aim of adjuvant therapies is to eradicate microscopic residual disease and improve the OS. The evidence that EGFR TKIs might delay disease recurrence in high risk NSCLC is clinically relevant, but not enough to replace standard chemotherapy.

Differently, a pooled analysis of individual patient data from the largest 5 randomized largest trial of cisplatin-based chemotherapy in resected NSCLC suggested that adjuvant chemotherapy increases the 5-year overall survival in stage IA to III NSCLC by 5.4%, with a reduction of the risk of death by 17% in stage II-III NSCLC (29). EGFR-mutant NSCLC also seems more sensitive than EGFR-wild type NSCLC to chemotherapy or radiotherapy. Therefore, in absence of a head to head trial showing an overall survival benefit of EGFR TKIs compared with chemotherapy, platinum-based chemotherapy should represent the standard of care for EGFR-mutant NSCLC patients who require adjuvant systemic therapy after resection. Whether an EGFR-TKI with or without chemotherapy would improve clinical outcomes in patients with EGFR-mutant

NSCLC in the adjuvant setting remains to be determined.

Eagerly awaited are also the results of the ADAURA trial, a phase III trial of osimertinib versus placebo in stage IB-IIIa NSCLC following complete tumor resection with or without chemotherapy. (NCT02511106).

Expert opinion 6: Dr. Alessandro Tuzi & Dr. Matteo B. Suter

As stated in the previous answer, limited to Caucasian patients we feel that, despite its toxicity and its small survival benefit, chemotherapy remains the standard adjuvant treatment. TKIs therapy should not be proposed outside of clinical trials. The lack of data is even deeper when talking about therapy duration: although we feel that present evidence points to a longer duration, we think that we are several trials away from having a clear-cut indication.

Expert opinion 7: Dr. Matthew Evison

Yes. I would add that this "...in patients with resected stage III disease or with any N1/N2 involvement". I think the guideline should also say that overall survival data is still awaited. It is also important to state within the document that severe adverse events are less common with EGFR-TKI in comparison to chemotherapy as this is also an important aspect of decision making. It should also make reference that the two studies providing this evidence base (EVAN & ADJUVANT) were both in Chinese populations and consideration should be given as to whether these results are translatable across the global community.

Expert opinion 8: Dr. Nobuhiko Seki

In terms of OS benefit, I do not think that EGFR-TKI replace chemotherapy in patients who require adjuvant therapy after resection. This is because OS benefit was observed only when adjuvant EGFR-TKI was used following chemotherapy (odds ratio 0.50, P=0.003), while OS benefit was not observed when adjuvant EGFR-TKI was used without chemotherapy (P=0.3) (30).

Expert opinion 9: Dr. Shinji Sasada

The CTONG data may be replaced in patients who cannot use cytotoxic anticancer drugs. In addition, regarding the effectiveness of postoperative adjuvant chemotherapy in EGFR mutation-positive patients, there are reports that EGFR inhibitors were better in exon 19 mutation patients than in exon 21 mutation patients (31). It may be beneficial for the patient to do in such case. I think the administration period is 2 years.

Expert opinion 10: Dr. Takhiro Izumo

Yes. We think that a treatment period of EGFR-TKI of about half a year is necessary.

Expert opinion 11: Dr. William Chi-shing Cho

The current available data is not very strong. However, replacing chemotherapy with TKI is a very attractive approach, though it is not yet proven to improve survival. The evidence so far is not conclusive though some data from a single center in China demonstrated the benefit, thus more evidence and studies are needed. For the duration, 2 years of adjuvant EGFR-TKI can be considered to use.

Question 3. Is it necessary to perform regular scanning for bone metastasis as well as brain MRIs for the detection of brain metastasis for EGFR-mutated patients?

Expert opinion 1: Dr. Alessandro Brunelli

EGFR-mutated patients have an increased risk of systemic disease and they should undergo regular ECTs for the detection of bone metastases and brain MRI for the detection of brain metastases.

Expert opinion 2: Dr. René Horsleben Petersen

Patients with EGFR mutations have a high risk of systemic recurrence. Regular brain MRI and bone scans as a supplement to chest CT seems reasonable for early detection.

Expert opinion 3: Dr. Chia-Chuan Liu

Usually brain Mets was symptomatic, it should be concerned all the time if there are any unexplained neurological symptoms, annually brain MRI may also be not efficient and timely for detect brain Mets.

Expert opinion 4: Dr. Biagio Ricciuti & Dr. Giulio Metro

The recommendation to screen for brain metastasis in stage I-III NSCLC varies across international guidelines. While all patients planned for curative stage III NSCLC treatment should receive brain MRI for initial staging, there is no consensus on stage I-II. NCCN guidelines suggest brain MRI in patients with stage IB-IIb who are candidate for curative surgery (\pm adjuvant systemic therapies) while the ACCP guideline restricts it to patients with stage III/IV and symptomatic patients (4,32). Whether regular brain MRI should be considered after curative treatment is unclear.

In the ADJUVANT trial, lung and brain metastases

accounted for major proportion of recurrence, compared to other sites of metastases (9). In addition, the brain represents one of the most common sites of failure of EGFR TKIs in metastatic setting, suggesting a different biology ad EGFR mutant NSCLC compared to non-oncogene addicted NSCLC. Although no data support the use of regular brain MRI after radical treatments, brain MRI can be proposed to patients with high risk stage III NSCLC.

There are no studies supporting the use of regular ECTs for the detection of bone metastases in patients with stage I–IIIA EGFR mutant NSCLC. Accordingly, all guidelines do not recommend regular ECTs in patients with resected NSCLC, regardless of EGFR mutation status. Therefore, ECTs should not be considered in this setting.

In conclusion, at the present time data on the association between EGFR-mutation status and a given pattern of recurrence are too weak in order to suggest a more intensive surveillance including either brain MRI and/or bone scans in EGFR-mutant patients with completely resected stage I–III NSCLC.

Expert opinion 5: Dr. Alessandro Tuzi & Dr. Matteo B. Suter

Current available data do not suggest that an early detection of metastatic relapse can influence overall survival. We recommend, accordingly to European guidelines to perform regular thoracic CT scan, mainly directed to early local intervention (33). As stated for molecular profiling, economic consideration should apply as well.

Expert opinion 6: Dr. Matthew Evison

Yes, given the pattern of disease recurrence described in the published literature and additional factors, such as the prognostic benefit of EGFR +ve status in oligometastatic brain metastases, then it would seem appropriate to recommend a more intensive imaging regime for this patient group.

Expert opinion 7: Dr. Nobuhiko Seki

Annual brain MRI and bone scans in addition to regular chest CT are recommended for EGFR-mutant NSCLC, and the scan frequencies can be increased in patients at a high risk for recurrence. Furthermore, I think the level of evidence “2A” is reasonable. However, I think there is room for reconsidering the strength of recommendation “strong” in terms of OS benefit, I think the strength of recommendation “weak” might be reasonable.

Expert opinion 8: Dr. Shinji Sasada

EGFR mutation-positive lung cancer is likely to be complicated by bone and brain metastases, so we think that regular examination is necessary.

Expert opinion 9: Dr. Takihiro Izumo

Yes. We believe that regular examination is necessary.

Expert opinion 10: Dr. William Chi-Shing Cho

Surveillance by chest computed tomography (CT) has to be used cautiously due to its radiation hazard and lack of survival benefit. The results of the phase III IFCT-0302 trial assessing minimal versus CT-scan-based follow-up for completely resected NSCLC can be referred.

Question 4. For those who relapse, is osimertinib a preferable option for EGFR+ patients?

Expert opinion 1: Dr. Alessandro Brunelli

Osimertinib should be the preferred first-line treatment in patients experiencing postoperative recurrence and metastasis based on the latest evidence showing an improved OS and PFS compared to first line EGFR-TKI (gefitinib or erlotinib).

Expert opinion 2: Dr. René Horsleben Petersen

Osimertinib is a preferable option for EGFR+ patients as it targets both sensitizing EGFR mutation and the resistant exon 20 T790M mutation, especially in patients with CNS metastases.

Expert opinion 3: Dr. Tony S. K. Mok

FLAURA is for mostly patients who presented with stage IV disease but NOT patient who had recurred after resectable lung cancer. This is generalization and cannot be considered level 1 evidence.

Expert opinion 4: Dr. Biagio Ricciuti & Dr. Giulio Metro

Osimertinib mesylate represents the preferred first-line option for patients with EGFR-mutant (del19/L858R) NSCLC who experience postoperative disease relapse. The approval of osimertinib in this setting is based on the results of the FLAURA trial in which the third generation EGFR TKIs osimertinib excelled over first generation EGFR TKIs (gefitinib and erlotinib) in terms of median PFS (18.9 versus 10.2 months, HR: 0.64 (95% CI: 0.37–0.57), P<0.001) and median OS (38.6 versus 31.8 months, HR: 0.79 (95% CI:

0.64–0.99), $P=0.046$) (26,34).

On this basis, osimertinib should be considered as the preferred treatment option at relapse in any case for patients with EGFR-mutant NSCLC (del19/L858R).

Expert opinion 5: Dr. Alessandro Tuzi & Dr. Matteo B. Suter

Osimertinib, when available, should be the preferred option for metastatic, EGFR mutated, NSCLC patients, given its efficacy for progression free and overall survival (34). Also, given its low affinity for wild type EGFR osimertinib is better tolerated than first generation TKIs.

Expert opinion 6: Dr. Matthew Evison

Yes. There is high level evidence from FLAURA and osimertinib should be first line TKI.

Expert opinion 7: Dr. Nobuhiko Seki

On the basis of the FLAURA study, I think Osimertinib can be a preferable treatment choice in terms of multiple positive characteristics, including response rate, activity for brain metastasis, progression free survival, and overall survival.

Expert opinion 8: Dr. Shinji Sasada

Osimertinib has been reported to extend overall survival over first generation EGFR-TKI. I think this is the preferred choice for recurrent cases.

Expert opinion 9: Dr. Takhiro Izumo

Yes. However, at the present time, it is necessary to detect T790M by re-examination with tissue or liquid biopsy at the time of recurrence.

Expert opinion 10: Dr. William Chi-Shing Cho

Yes, osimertinib has demonstrated an overall survival benefit over upfront first- or second-generation EGFR-TKI (e.g., gefitinib, erlotinib or afatinib) (34). The use of osimertinib upfront results in higher objective response rate, longer progression free survival, longer overall survival but lower toxicities. It is preferred all patients with EGFR exon 19 del or L858R mutation in their tumor, but is more expensive than other EGFR-TKI.

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Footnote

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