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Review article

Targeted treatment for unresectable *EGFR* mutation-positive stage III non-small cell lung cancer: Emerging evidence and future perspectives

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ABSTRACT

Epidermal growth factor receptor (*EGFR*) mutations are detected in up to one third of patients with unresectable stage III non-small cell lung cancer (NSCLC). The current standard of care for unresectable stage III NSCLC is consolidation durvalumab for patients who have not progressed following concurrent chemoradiotherapy (the 'PACIFIC regimen'). However, the benefit of immunotherapy, specifically in patients with EGFR mutation-positive (EGFRm) tumors, is not well characterized, and this treatment approach is not recommended in these patients, based on a recent ESMO consensus statement.

EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have demonstrated significant improvements in patient outcomes in EGFRm metastatic NSCLC. The benefits of these agents have also translated to patients with EGFRm early-stage resectable disease as adjuvant therapy. The role of EGFR-TKIs has yet to be prospectively characterized in the unresectable setting. Preliminary efficacy signals for EGFR-TKIs in unresectable EGFRm stage III NSCLC have been reported from a limited number of subgroup and retrospective studies. Several clinical trials are ongoing assessing the safety and efficacy of EGFR-TKIs in this patient population.

Here, we review the current management of unresectable EGFRm stage III NSCLC. We outline the rationale for investigating EGFR-TKI strategies in this setting and discuss ongoing studies. Finally, we discuss the evidence gaps and future challenges for treating patients with unresectable EGFRm stage III NSCLC.

Abbreviations: AE, adverse events; ALT, alanine transaminase; ASCO, American Society of Clinical Oncology; AST, aspartate transaminase; ATORG, Asian Thoracic Oncology Research Group; BBB, blood–brain barrier; CALEB, Cancer and Leukemia Group B; cCRT, concurrent chemoradiotherapy; CI, confidence interval; CNS, central nervous system; CompT, computed tomography; CRT, chemoradiotherapy; CT, chemotherapy; ctDNA, circulating tumor DNA; DFS, disease-free survival; EBUS, endoscopic bronchial ultrasound; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation-positive; EGFRwt, EGFR wild-type; EGFR-TKI, EGFR-tyrosine kinase inhibitor; ERBB2, erythroblastic oncogene B 2; ESMO, European Society for Medical Oncology; EUS, endoscopic ultrasound; Ex19del, exon 19 deletion; FDG, fluorodeoxyglucose; FNAB, fine-needle aspiration biopsy; HR, hazard ratio; ILD, interstitial lung disease; MDT, multidisciplinary team; mo, month; (m)OS, (median) overall survival; mPFS, (median) progression-free survival; MRI, magnetic resonance imaging; NR, not reached; NS, not significant; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PET, positron emission tomography; R0, complete resection; RP, radiation pneumonitis; RT, radiotherapy; SAE, serious adverse event; SBRT, stereotactic body radiotherapy; sCRT, sequential chemoradiotherapy; SoC, standard of care; TTP, time to progression; V20, 20 Gy radiation; wt, wild-type; yr, year.

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1. Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 85% of all cases [1], with 20–30% of patients presenting with stage III disease at diagnosis [2,3], of whom 60–90% have unresectable disease [4–6]. Epidermal growth factor receptor (*EGFR*) mutations, which are observed across all NSCLC stages [7], are common oncogenic mutations in unresectable stage III NSCLC. In Asian countries, 15–30% of patients are reported to have an *EGFR* mutation; a lower frequency (2–10%) is reported in patients from Europe and North/South America [8–18]. In addition to ethnicity, other factors such as smoking, body mass index, and estrogen receptor β expression are potentially associated with the incidence of *EGFR* mutations [19].

While concurrent chemoradiotherapy (cCRT) alone results in a 5-year overall survival (OS) rate of up to 32% in patients with unresectable stage III NSCLC [20], consolidation durvalumab (the 'PACIFIC regimen') has significantly improved outcomes and is standard of care (SoC) for patients who have not progressed following cCRT [21–23]. However, the benefit of immunotherapy specifically in patients with *EGFR* mutation-positive (EGFRm) stage III disease is not well characterized, based on currently available clinical trial results [17,24,25]. Moreover, there are no approved targeted treatments for patients with unresectable EGFRm stage III NSCLC. Given that EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have demonstrated efficacy in EGFRm metastatic NSCLC [26] and EGFRm resectable stage IB–IIIA NSCLC [22], prospective data are needed to assess the role of EGFR-TKIs in unresectable EGFRm stage III NSCLC.

In this review, we summarize the current management of unresectable EGFRm stage III NSCLC, based on efficacy and safety data available in this patient population, and discuss the rationale for ongoing targeted therapy studies in this setting. Finally, we will discuss evidence gaps, challenges, and future perspectives that need to be considered in the treatment of patients with unresectable EGFRm stage III disease.

2. Current management of unresectable EGFRm stage III NSCLC

2.1. Diagnosis

A summary of diagnostic recommendations for unresectable stage III NSCLC from international guidelines is provided in Fig. 1, along with biomarker testing guidelines, which are currently limited in this setting [22,27].

2.2. Current treatment options

Current treatment options for unresectable stage III NSCLC are summarized in Fig. 1. The SoC for these patients is cCRT followed by consolidation durvalumab ('PACIFIC regimen') for up to 12 months in patients without disease progression following CRT [21–23,27]. This is based on results from the PACIFIC study where consolidation durvalumab versus placebo following CRT resulted in a significantly longer progression-free survival (PFS) and OS in all-comer patients with unresectable stage III NSCLC [28,29]. These primary results were further supported by an updated 5-year analysis reporting a PFS hazard

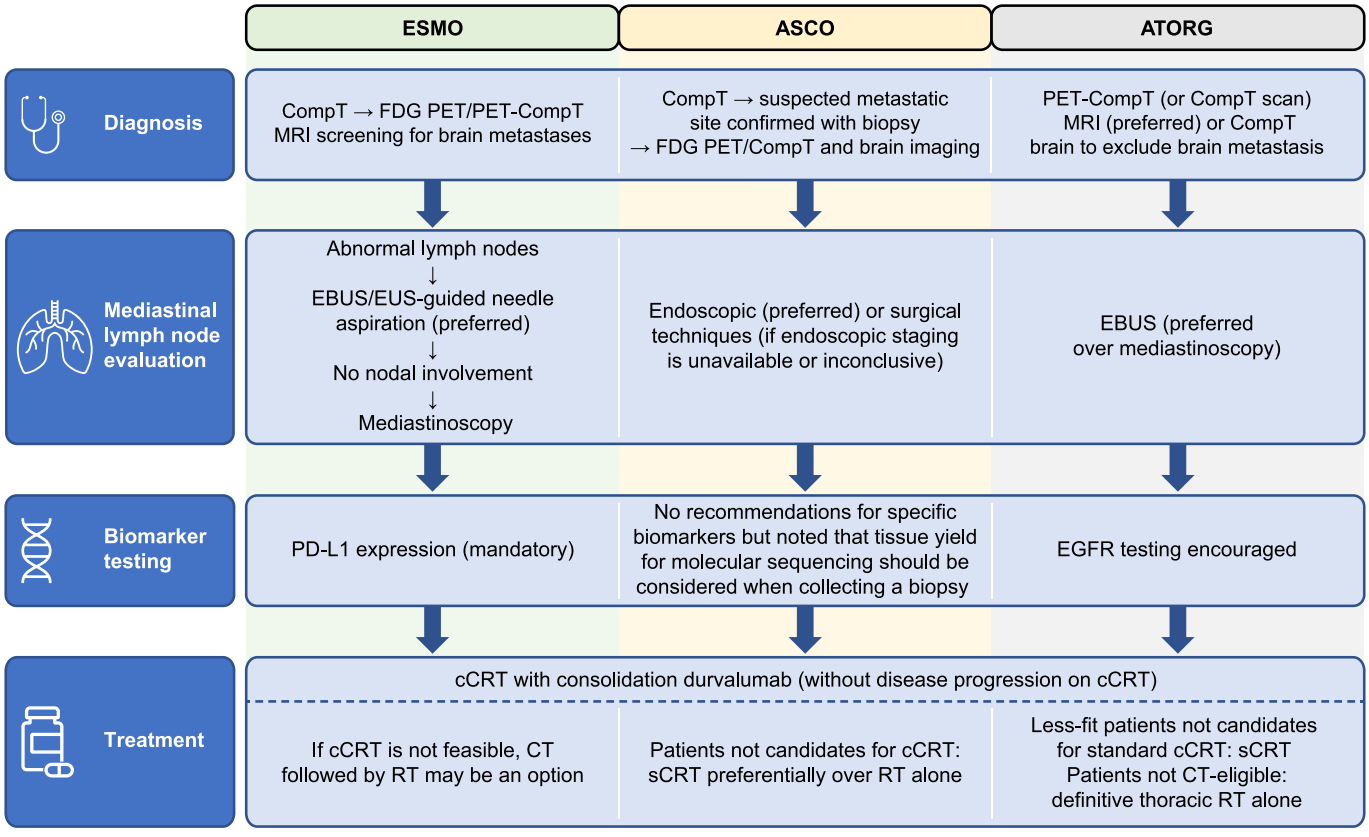

Fig. 1. Guideline recommendations for the management of unresectable stage III NSCLC [21–23,27,33]. ESMO resectable definition: Cases of single station N2 disease where other nodal stations have been biopsied and are benign; T4N0 tumors where nodal disease has been excluded when an R0 resection is feasible; after induction therapy when there has been nodal downstaging and a pneumonectomy can be avoided. ASCO, American Society of Clinical Oncology; ATORG, Asian Thoracic Oncology Research Group; cCRT, concurrent CRT; CompT, computed tomography; CRT, chemoradiotherapy; CT, chemotherapy; EBUS, endoscopic bronchial ultrasound; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PET, positron emission tomography; R0, complete resection; RT, radiotherapy; sCRT, sequential CRT.

ratio (HR) of 0.55 (95% confidence interval [CI]: 0.45, 0.68) and an OS HR of 0.72 (95% CI: 0.59, 0.89) [30].

2.3. Multidisciplinary team (MDT)

Due to disease heterogeneity and the multimodality of potential treatments, the MDT or tumor board, comprising thoracic surgeons, radiation and medical oncologists, pulmonologists, pathologists, and geriatricians (if applicable) plays a crucial role in accurate staging, resectability assessment, tumor biomarker testing, and tailoring treatment for all patients with stage III NSCLC [4,31]. In addition, MDTs can include nurse coordinators, who play a critical role in communicating patient concerns, incorporating patient perspectives in decision–making, and ensuring continuity of care [32]. International guidelines state that disease staging, resectability, and treatment choice should be determined upfront by an MDT [21,23,33]. Indeed, a retrospective study demonstrated that median survival was significantly improved in patients treated after (41.2 months) versus without (25.7 months) MDT discussion [34], highlighting the importance of these upfront multidisciplinary discussions.

2.4. Unmet needs in the management of stage III EGFRm NSCLC

More universally agreed guidelines are needed to define resectability in stage III NSCLC, with regards to both tumor staging and the patient's fitness for surgery. Although the approval of consolidation durvalumab has provided a new SoC for unresectable stage III NSCLC, there are limited data for this treatment for patients with EGFRm tumors, highlighting the need for further research to improve outcomes for these patients. If targeted therapies show clinical benefit in patients with unresectable EGFRm stage III NSCLC, there will also be a need for clearly defined *EGFR* biomarker testing guidance to facilitate this personalized treatment approach.

3. Clinical data for unresectable stage III NSCLC SoC treatment in patients with EGFRm tumors

3.1. CRT studies

Data suggest that cCRT benefits patients with unresectable EGFRm stage III NSCLC, although it is not clear whether outcomes are different in patients with EGFRm versus *EGFR* wild-type (EGFRwt) tumors. Retrospective studies evaluating survival outcomes of patients with unresectable stage III NSCLC receiving initial cCRT or sequential CRT (sCRT) have reported a shorter or similar PFS, but with a trend for longer OS in patients with EGFRm versus EGFRwt tumors [9,12–14,35,36]. This trend for longer OS outcomes might be explained by the use of subsequent targeted treatment in patients with EGFRm tumors [12,14,35,36].

Another important observation from these retrospective studies is that patients with EGFRm tumors had better local control but less favorable distant control than patients with EGFRwt tumors, with distant metastases being more frequently identified as the first recurrence site [9,12–15]. Brain metastases were the most common site of distant metastases in patients with EGFRm tumors, occurring in 25–35% of patients, which was higher than in patients with EGFRwt tumors [9,16,37].

3.2. Immunotherapy studies

The management of unresectable stage III NSCLC was transformed following the approval of consolidation durvalumab in patients without disease progression after cCRT, based on the PACIFIC study results [29]. While patients with EGFRm disease were included in the PACIFIC study, they represented a small subset, and the study was not designed to address efficacy in a biomarker-directed manner [29]. In a *post-hoc* exploratory subgroup analysis of patients with EGFRm tumors from PACIFIC (n = 35), outcomes were similar between durvalumab and placebo, with wide CIs (median PFS [mPFS]: 11.2 versus 10.9 months; HR 0.91; 95% CI: 0.39, 2.13; median OS [mOS]: 46.8 versus 43.0 months; HR 1.02; 95% CI: 0.39, 2.63) [25]. Durvalumab safety data in these patients were consistent with the overall population and known safety profile for durvalumab [25].

A limited number of retrospective studies and exploratory analyses of small subgroups of patients with unresectable EGFRm stage III disease have reported mPFS ranging from 9.0 to 11.2 months with CRT and consolidation durvalumab [12,17,24,25]. A retrospective single-institution US study of 36 patients receiving cCRT plus durvalumab reported that patients with *EGFR/erythroblastic oncogene B 2 (ERBB2)*-mutated tumors had a median disease-free survival (DFS) of 7.5 months, which was shorter than in patients with *EGFR/ERBB2* wild-type tumors (median DFS not reached) [38]. A single-center retrospective study in Singapore (n = 84) reported a higher mPFS (17.5 months) in patients with EGFRm tumors who received cCRT plus durvalumab (n = 5), although PFS was not significantly different to patients with EGFRm tumors who received CRT alone (mPFS of 10.9 months; $p = 0.907$; n = 13) [39]. Differences in immunotherapy efficacy in patients with EGFRm versus EGFRwt tumors are likely due to tumor biology and microenvironment [40,41], and highlight the need for prospective studies to evaluate treatment options for patients with unresectable EGFRm stage III NSCLC. In a recent ESMO consensus meeting on the management of EGFRm NSCLC, the use of consolidation immune checkpoint inhibitors after definitive CRT in this setting was not recommended [42].

4. Targeted treatment strategies in unresectable EGFRm stage III NSCLC

4.1. Role of EGFR-TKIs

The discovery of activating oncogenic mutations in the EGFR kinase domain along with the realization that they conferred sensitivity to the first-generation EGFR-TKIs gefitinib and erlotinib [43–45] was key to revolutionizing treatment for patients with EGFRm advanced disease. In addition to erlotinib and gefitinib, second-generation EGFR-TKIs, afatinib and dacomitinib, and third-generation EGFR-TKIs including osimertinib have been developed, all of which have demonstrated clinical benefits in patients with EGFRm advanced NSCLC [46–49]. Following the FLAURA study results demonstrating significantly longer PFS (HR 0.46; 95% CI: 0.37, 0.57; $p < 0.001$) and OS (HR 0.80; 95.05% CI: 0.64, 1.00; $p = 0.046$) with osimertinib versus comparator EGFR-TKIs in patients with untreated EGFRm advanced NSCLC [48,50], osimertinib is now the preferred first-line treatment in EGFRm metastatic NSCLC and is SoC for second-line treatment of patients with EGFRm T790M-positive advanced NSCLC [26]. The benefits of EGFR-TKIs have also been demonstrated in earlier disease stages with osimertinib now SoC and a recommended adjuvant treatment option for patients with resectable stage IB–IIIA EGFRm NSCLC [22], based on ADAURA study results where osimertinib treatment resulted in prolonged DFS benefit (HR 0.27; 95% CI: 0.21, 0.34) versus placebo [51].

As the development of brain metastases is common in patients with unresectable EGFRm stage III NSCLC, occurring in up to approximately one-third of patients [9,16,37,52], it will be important to assess treatments that can prevent or treat brain metastases. The ability of a drug to cross the blood–brain barrier (BBB) is key to providing a protective effect against central nervous system (CNS) metastases [53]. Osimertinib has demonstrated CNS activity across all disease stages studied [54–57] and can penetrate the BBB more effectively than first-, second- or other third-generation EGFR-TKIs [58–61]. In the ADAURA study, there was a 76% reduction in the risk of CNS disease recurrence or death with adjuvant osimertinib versus placebo among patients with stage II–IIIA NSCLC [51]. The third–generation EGFR-TKIs furmonertinib and

aumolertinib have also demonstrated CNS efficacy in patients with EGFRm advanced NSCLC with CNS metastases [62–64]. Based on data in the resectable and advanced setting, there is a rationale to believe that EGFR-TKIs may improve outcomes in patients with unresectable EGFRm stage III NSCLC, and prospective studies are warranted.

4.2. Efficacy data from EGFR-TKI studies in unresectable EGFRm stage III NSCLC

4.2.1. Prospective clinical studies

Many studies previously evaluated EGFR-TKIs in patients with unresectable stage III NSCLC without selection for *EGFR* mutation status and failed to show benefit in patients with unknown *EGFR* status [65–69]. However, recent EGFR-TKI clinical studies and EGFRm subgroup analyses have provided preliminary efficacy data in these patients (Table 1).

Two studies have examined the strategy of combining EGFR-TKIs with RT. In an open-label, single-arm phase II study (n = 27), the first-generation EGFR-TKI gefitinib plus concurrent RT with consolidation gefitinib did not meet the primary endpoint (2-year PFS rate of 29.6%) [70]. However, erlotinib plus concurrent RT followed by consolidation erlotinib (n = 20) resulted in a significantly longer mPFS versus cCRT alone (n = 20) in the open-label, randomized phase II RECEL study (24.5 versus 9.0 months; HR 0.104; 95% CI: 0.028, 0.389) [71]. Other studies have examined the effects of induction EGFR-TKIs followed by different cCRT and/or EGFR-TKI sequencing combinations. Preliminary efficacy was shown for induction gefitinib followed by cCRT in a single-arm phase II study (n = 20) with a 2-year OS of 90% (95% CI: 65.6, 97.4) [72]. In the open-label, randomized phase II RTOG-1306 study numerical improvements in mPFS (21.1 months; 95% CI: 8.5, not reached [NR]; versus 9.2 months; 95% CI: 8.7, NR) were shown for induction erlotinib followed by cCRT (n = 14) versus cCRT (n = 21) [73], although the study was prematurely terminated due to poor accrual. However, in another very small open-label, randomized, phase II study, no significant differences in mPFS (11.6 months [95% CI: 0.1, 23.2] versus 8.1 months [95% CI: 2.7, 13.6]) or OS (39.3 months [95% CI: 0.7, 83.3] versus 31.2 months [95% CI: 0.1, 90.2]) were observed with induction erlotinib followed by cCRT plus erlotinib followed by consolidation erlotinib (n = 7) versus induction erlotinib followed by cCRT alone (n = 5) [74].

Distant metastases were commonly reported in these studies, with the brain being a common site of progression, occurring in 26–75% of cases [68,70,72,74,75].

It should also be noted that these studies were limited by lack of patient enrollment by mutation status, small patient numbers and low accrual, which impacted the statistical power or resulted in premature termination in some cases [66,68,70–75].

4.2.2. Retrospective studies

Retrospective studies have assessed EGFR-TKI regimens in unresectable EGFRm stage III NSCLC. Data from two retrospective Chinese studies reported preliminary efficacy signals for the concurrent use of EGFR-TKIs and RT +/- CT. mPFS and mOS in one of these studies were 27.9 (95% CI: 18.7, 37.2) and 49.7 (95% CI: 27.7, 71.8) months, respectively, with EGFR-TKI and concurrent RT in patients with EGFRm tumors (n = 20) which were numerically longer than those for patients with EGFRwt or unknown status tumors (n = 25) [76]. In the REFRACT study, combined EGFR-TKI plus RT +/- CT (n = 105) was associated with improved mPFS (26.2 months) versus EGFR-TKI monotherapy (n = 231, mPFS 16.2 months; HR 0.60; 95% CI: 0.46, 0.79; p < 0.001) and CRT alone (n = 104, mPFS 12.4 months; HR 0.40; 95% CI: 0.29, 0.54; p < 0.001) [77]. In REFRACT, combined EGFR-TKI plus RT +/- CT showed mOS improvements (67.4 months) versus CRT alone (mOS 51.0 months; HR 0.61; 95% CI: 0.38, 0.98; p = 0.039) [77].

A comparison of cCRT versus EGFR-TKI monotherapy in the real-world KINDLE study, showed a significantly improved mOS with cCRT (n = 37) compared with EGFR-TKI monotherapy without RT (n = 35) (48 versus 24 months; p < 0.001), whereas no significant differences between treatment groups were observed for median real-world PFS (10.5 versus 14.6 months; p = 0.825) [35]. Conversely, no survival differences were observed between patients receiving EGFR-TKI (n = 177) versus cCRT therapy (n = 22) from a data analysis of the Taiwan Cancer Registry [78].

Two studies have evaluated induction or consolidation EGFR-TKI therapy with (C)RT. In one study, CRT plus EGFR-TKI, as either induction (n = 4) or consolidation (n = 4) therapy, demonstrated a significantly longer mPFS versus CRT plus durvalumab consolidation (n = 13) (26.1 versus 10.3 months) and a reduced risk of recurrence [24]. In another study, patients receiving EGFR-TKI (as either induction or consolidation therapy) plus RT (n = 36) had significantly improved OS and PFS versus EGFR-TKI monotherapy (n = 47) [79].

In summary, preliminary efficacy data for EGFR-TKIs have been reported across several studies in unresectable EGFRm stage III NSCLC. Initial data suggest that the combination of EGFR-TKIs and RT +/- CT may improve outcomes versus CRT alone, or EGFR-TKI monotherapy. Also, additional benefit may potentially be provided with the addition of induction EGFR-TKI to CRT versus CRT alone. However, prospective trials are needed to confirm these results.

4.3. Safety data from EGFR-TKI studies in unresectable EGFRm stage III NSCLC

Combinations of EGFR-TKIs and RT may be associated with an increased risk of overlapping toxicities; radiation pneumonitis/pneumonitis is a toxicity of particular interest. An overview of safety data from key clinical studies is provided in Table 1.

A very high rate of pneumonitis adverse events (AEs; 89%) was reported in an open–label, single-arm, phase II study (n = 27) investigating gefitinib plus concurrent RT, with a median time from treatment initiation to pneumonitis onset of 92 days [70]. While all events of pneumonitis were grade 1 or 2, 8 (30%) patients discontinued treatment due to these events. Of the 8 patients who discontinued due to pneumonitis, 4 resumed gefitinib treatment following recovery. Although most pneumonitis AEs occurred after completion of RT, 2 patients did not complete RT due to pneumonitis [70]. In the RECEL study, radiation pneumonitis was reported in 11% (grade ≥3, 6%) of 18 patients receiving erlotinib + concurrent RT, versus 11% (grade ≥3, 0%) of 19 patients receiving cCRT [71]. After completion of RT, patients in the erlotinib + concurrent RT group received consolidation erlotinib, and 28% (grade ≥3, 17%) reported further radiation pneumonitis events; none of the patients in the cCRT group (without consolidation therapy) reported further radiation pneumonitis events [71]). However, fewer patients (11%) discontinued erlotinib plus RT compared with the cCRT group (32%) in this study. A high rate of radiation pneumonitis/pneumonitis (38%; grade 3, 7%) was also observed in a retrospective study of patients with unresectable stage III NSCLC (with EGFRm [n = 20] and with EGFRwt/unknown status [n = 25] tumors) receiving EGFR-TKI plus concurrent RT. The median time from starting RT to pneumonitis was 74 days, and only 2/17 patients developed pneumonitis after the end of RT (>90 days) [76]. A non-significant association was reported between the duration of EGFR-TKI therapy and the development of grade ≥2 pneumonitis [76], highlighting the need for further investigations to optimize this combination.

For other EGFR-TKI sequencing regimens, induction EGFR-TKI followed by cCRT appears to have a generally tolerable side effect profile based on the limited data available (Table 1). However, a single-arm phase II study (n = 20) reported a high incidence of radiation pneumonitis (82%; all grade 1/2) during the cCRT phase (n = 17) following induction gefitinib, although this improved within 6 months after completion of RT [72].

In a retrospective analysis of patients receiving EGFR-TKI (n = 34 [osimertinib, n = 31; erlotinib, n = 3]) versus durvalumab (n = 34) after

Table 1
Key efficacy and safety clinical study data from patients treated with EGFR-TKIs in unresectable EGFRm stage III NSCLC.

Targeted therapy/Study identifier (country)	Study design	EGFRm/ EGFRwt NSCLC	Key efficacy data	Key safety data
EGFR-TKI + RT/CT/cCRT (→EGFR-TKI/CT consolidation)				
Gefitinib UMIN000008366 WJOG6911L (Japan) [70]	Phase II Gefitinib + RT → consolidation gefitinib (N = 27)	EGFRm	**2-yr PFS: 29.6% (one-sided 95% CI: 17.6%, –)** mPFS 18.6 mo (95% CI: 12.0, 24.5) mOS: 61.1 mo (95% CI: 38.1, NR)	AEs Grade ≥3 AE[a]: ALT elevation (59%), AST elevation (37%), skin reaction (4%), appetite loss (4%) Pneumonitis leading to discontinuation: 30% Pneumonitis AE: 89% (all grade 1/2)
Gefitinib NCT00898924 CALEB 30106 (USA) [66]	Phase II Gefitinib + CT → gefitinib + RT (poor-risk stratum; n = 21) versus gefitinib + cCRT (good-risk stratum; n = 39) → consolidation gefitinib	EGFRm and EGFRwt	**Median OS for EGFRm subgroup:** **Poor-risk stratum (n = 5): 28.4 mo** **Good-risk stratum (n = 6): 7.2 mo**	No reported cases of ILD No additional safety data reported for the EGFRm subgroup
Erlotinib NCT01714908 RECEL (China) [71]	Phase II Erlotinib + RT → consolidation erlotinib (n = 20) versus cCRT (n = 20)	EGFRm	Erlotinib + RT versus cCRT: **mPFS: 24.5 versus 9.0 mo;** **HR: 0.104 (95% CI: 0.028, 0.389); p < 0.001** ORR: 70% versus 61.9%; NS mOS: 33.5 mo versus NR; NS	Erlotinib + RT versus cCRT: Grade ≥3 AEs: 56% versus 53% AE leading to discontinuation: 11% versus 32% Grade ≥3 radiation pneumonitis: 17% versus 0%
Erlotinib NCT00563784 (USA) [68]	Phase II Erlotinib + cCRT → consolidation CT (N = 46)	EGFRm and EGFRwt	EGFRm subgroup (n = 4): **TTP: 10.2 mo** mOS: 41.1 mo 1-, 2-, 5-yr OS: 100%, 100%, 50%	EGFRm subgroup (n = 4): Grade ≥3 toxicities: 25% Pneumonitis: 25% (grade 3 event)
Induction EGFR-TKI → cCRT (+EFGR-TKI) (→EGFR-TKI consolidation)				
Gefitinib[b] UMIN000005086 LOGIK0902/ OLCSG0905 (Japan) [72]	Phase II Gefitinib → cCRT (if without disease progression) (N = 20)	EGFRm	**2-yr OS: 90% (95% CI: 65.6, 97.4)** 1-yr PFS: 58.1% (95% CI: 33.4, 76.4) 2-yr PFS: 36.9% (95% CI: 16.6, 57.6)	Grade ≥3 toxicities Induction (n = 20): AST elevation (25%), ALT elevation (45%), gingival infection (5%) CRT (n = 17): Leucopenia (77%), neutropenia (65%), febrile neutropenia (12%), AST elevation, ALT elevation, hyponatremia, hypokalemia, fatigue, appetite loss, depression, syncope (each 6%) Radiation pneumonitis: 82% (all grade 1/2; during CRT)
Erlotinib[b] NCT00620269 (Republic of Korea) [74]	Phase II Erlotinib → cCRT + erlotinib → consolidation erlotinib (arm A; n = 7) versus erlotinib → cCRT (arm B; n = 5)	EGFRm	Arm A versus arm B **ORR[c]: 71.4% versus 80.0%** **mPFS: 11.6 (95% CI: 0.1, 23.2) mo versus 8.1 (95% CI: 2.7, 13.6) mo; NS** **mOS: 39.3 (95% CI: 0.7, 83.3) mo versus 31.2 (95% CI: 0.1, 90.2) mo; NS** mPFS: 11.6 (95% CI: 0.1, 23.2) mo versus 8.1 (95% CI: 2.7, 13.6) mo; NS	Grade ≥3 hematologic and non-hematologic toxicities (arm A versus B): Induction: skin rash (14% versus 20%) cCRT: anorexia, neutropenia, fatigue/asthenia, radiation esophagitis (0% versus 20% each) Grade ≥3 radiation pneumonitis: 0% versus 0%
Erlotinib[b] NCT01822496 RTOG-1306 (USA) [73]	Phase II Erlotinib → cCRT (n = 14) versus cCRT (n = 21)	EGFRm	Erlotinib → cCRT versus placebo → cCRT **mPFS: 21.1 (95% CI: 8.5, NR) mo versus 9.2 (95% CI: 8.7, NR) mo** ORR: 50.0% (95% CI: 19.0, 81.0; n = 10) versus 26.7% (95% CI: 4.3, 49.1; n = 15)	Erlotinib → cCRT versus placebo → cCRT SAE: 7% versus 35% Pneumonitis AE: 7% versus 15% Pneumonitis SAE: 0% versus 5%
Afatinib[b] NCT01553942 ASCENT (USA) [75]	Phase II Afatinib → cCRT +/- surgery → optional consolidation afatinib (N = 19; unresectable n = 9; potentially resectable n = 10)	EGFRm	**ORR after neoadjuvant afatinib: 58% (95% CI: 33%, 80%)**[d]	Not reported for the unresectable subgroup

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CALEB, Cancer and Leukemia Group B; cCRT, concurrent chemoradiotherapy; CI, confidence interval; CT, chemotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; EGFRm, epidermal growth factor receptor mutation-positive; HR, hazard ratio; ILD, interstitial lung disease; mo, month; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; NS, not significant; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SAE, serious adverse event; TTP, time to progression; wt, wild-type; yr, year. Bolded text indicates the primary efficacy endpoint(s).

[a] Occuring in > 20% of patients or of special interest.

[b] Study terminated early due to slow accrual.

[c] After cCRT.

[d] Includes patients receiving surgery. Other endpoint data (PFS, OS) for the whole population (unresectable and resectable) have not been included.

definitive CRT, incidence of pneumonitis was similar in the two treatment groups, with 21% of patients in each group reporting any-grade pneumonitis (grade ≥3, 3% each) [80].

Of note, from the available data, the highest rates of radiation pneumonitis/pneumonitis AEs reported with EGFR-TKI and (C)RT regimens were observed in Japanese studies (82–89%) [70,72], with lower rates in Chinese studies (28–38%), [71,76] and the lowest rate (7%) in a mixed race population study [73]. These data are in line with observations that higher rates of pneumonitis are reported from Japanese patients with advanced NSCLC receiving EGFR-TKIs compared with non-Japanese patients [81].

In summary, the combination of EGFR-TKI plus (C)RT appears to have a generally manageable safety profile, in line with the known safety profile of EGFR-TKI monotherapy and (C)RT alone. However, it may carry an increased risk of radiation pneumonitis/pneumonitis [70,71,76], which may be higher than with (C)RT alone, as suggested in the RECEL study, where a higher rate of radiation pneumonitis (overall and grade ≥3) was reported in patients receiving erlotinib plus RT followed by consolidation erlotinib, versus those receiving cCRT alone [71]. Of note, available safety data are from limited studies in small numbers of patients, assessing different combinations of first-generation EGFR-TKIs, erlotinib and gefitinib, so it is unclear what the true risk of pneumonitis is with this combination regimen and what the risk will be with second- or third-generation EGFR-TKIs. Overall, when considering all efficacy and safety data, the combination of EGFR-TKIs and (C)RT is a promising treatment approach for this setting, based on the additional efficacy benefit it can provide over (C)RT alone or EGFR-TKI monotherapy; however, further investigations in prospective randomized trials are warranted to better characterize the efficacy and safety profile of this treatment combination.

4.4. Ongoing EGFR-TKI studies

Several ongoing phase II and III studies are prospectively assessing EGFR-TKIs in unresectable EGFRm stage III NSCLC (Table 2). The global, randomized, double-blind, placebo-controlled LAURA study is ongoing and assessing osimertinib as maintenance therapy versus placebo in patients with no disease progression following or during c/sCRT [82,83]; the primary endpoint is PFS. In LAURA, osimertinib will be given until disease progression, unacceptable toxicity, or other discontinuation criteria, as treatment discontinuation could result in tumor flare up and worse prognosis in this setting [82,83]. Careful assessment of known AEs of concern including interstitial lung disease (ILD) or radiation pneumonitis [84,85] will be needed, given the use of c/sCRT followed by osimertinib, although the safety profile of osimertinib has been consistent across EGFRm early-stage and advanced NSCLC settings, with a generally low rate of ILD or pneumonitis with monotherapy [50,56,86].

Two other ongoing studies with a similar design to LAURA are assessing third-generation EGFR-TKIs in Asian patients with unresectable EGFRm stage III NSCLC. A randomized, double-blind, placebo-controlled phase III study is investigating aumolertinib as maintenance therapy versus placebo following c/sCRT in Chinese patients [87]. The open-label, single-arm, phase II PLATINUM study is investigating lazertinib following cCRT in South Korean patients [88]. In both studies, PFS is the primary endpoint and EGFR-TKI treatment is continued until disease progression, unacceptable toxicity or other discontinuation criteria [87,88]; therefore, safety evaluations will be important.

Another strategy of combining EGFR-TKIs with RT or cCRT followed by consolidation EGFR-TKI therapy is being investigated in two open-label phase II Chinese studies [89,90]. One study is assessing aumolertinib plus RT with aumolertinib consolidation in patients with <28% of their total lung volume receiving 20 Gy radiation (V20) versus induction aumolertinib followed by aumolertinib plus RT with aumolertinib consolidation in patients with a V20 ≥28%; the primary endpoint is the incidence of radiation pneumonitis (grade ≥3) within 6 months post-RT [89]. The other single-arm study is evaluating aumolertinib plus cCRT with aumolertinib consolidation and assessing 2-year OS as the primary endpoint [90].

Two further Chinese studies are investigating aumolertinib as induction and consolidation therapy. The randomized, open-label phase III ADVANCE study is assessing induction aumolertinib followed by aumolertinib plus RT versus cCRT for 2 years (primary endpoint: PFS) [91,92] and the randomized, open-label phase II APPROACH study is investigating induction aumolertinib, followed by RT then aumolertinib for 2 years versus circulating tumor DNA-guided aumolertinib treatment (primary endpoint: overall response rate) [93].

5. Future perspectives and next steps in unresectable EGFRm stage III NSCLC

With anticipated data for EGFR-TKIs in unresectable EGFRm stage III NSCLC on the horizon, several questions and challenges will need addressing to understand how EGFR-TKIs should be optimally incorporated into SoC treatment in this setting.

5.1. Biomarker testing

The prevalence of *EGFR* mutations [8–18] and emerging evidence for EGFR-TKI treatment in improving outcomes highlight the importance of *EGFR* testing in unresectable stage III NSCLC. However, biomarker testing in stage III NSCLC is not well defined in treatment guidelines (Fig. 1) and currently not routine in all countries or treatment centers. A key challenge in integrating *EGFR* testing into the treatment pathway is the practicality of obtaining biopsy samples from patients with unresectable disease; it may be difficult to obtain a tissue biopsy, particularly as no sample can be taken during surgery. Using cell blocks obtained via endoscopic bronchial ultrasound (EBUS)-guided fine-needle aspiration biopsy (FNAB) or liquid biopsies are important in cases where it is difficult to obtain tissue samples. While biomarker testing assays performed on liquid biopsies have low sensitivity in early-stage NSCLC, often due to the low level of circulating tumor molecules/cells [94,95], EBUS-guided FNAB performed with a ≥19 gauge needle can provide cell blocks that are suitable for *EGFR* testing [33,96–100]. However, ongoing clinical trials in this patient population employ tissue testing for enrollment [82,101], highlighting the need for trial designs employing EBUS-guided FNAB and liquid biopsy methods for mutation testing and determining their concordance with tissue testing. Additionally, the cost of mutation testing is not usually covered, which could limit access to testing and targeted therapies [102]. To implement *EGFR* testing at the local level, a well-functioning MDT is needed to facilitate collaboration between the clinical team and pathologists [102] and globally, a consistent approach to *EGFR* testing will require standardization in international consensus guidelines. Further studies in defining and optimizing EBUS-guided FNAB and liquid biopsy for *EGFR* testing in this setting as an alternative or complementary method to tissue biopsy will be important to streamline testing.

The evolving treatment landscape in the resectable NSCLC neoadjuvant and adjuvant settings, with new immunotherapy and EGFR-TKI options available, highlights the importance of biomarker testing at diagnosis, to facilitate treatment decision-making. Integration of biomarker testing in resectable disease may help circumvent some challenges relating to biomarker testing in stage III unresectable NSCLC, as testing results may already be available.

5.2. EGFR-TKIs and new agents: Evidence gaps and next steps

Several different EGFR-TKI sequencing strategies may be potential options for improving outcomes for patients with unresectable EGFRm stage III NSCLC, such as sequential or concurrent induction therapy with EGFR-TKI and cCRT or RT followed by consolidation with EGFR-TKI; however, data from prospective clinical trials are needed to determine

Table 2
Ongoing EGFR-TKI studies in unresectable stage III EGFRm NSCLC.

Targeted therapy/Study identifier	Study design/country	Treatment	Duration of treatment	Patient population (estimated N)	Primary endpoint	Estimated primary completion date
cCRT → EGFR-TKI maintenance						
Osimertinib NCT03521154 LAURA [82,83]	Randomized, double-blind, placebo-controlled, multicenter, phase III; global	c/sCRT → osimertinib versus placebo (with no disease progression during or following CRT)	Until disease progression, unacceptable toxicity, or other discontinuation criteria	Unresectable stage III (8th edition staging manual) EGFRm (Ex19del/L858R +/- other mutations) NSCLC N ~216	PFS	Jan-24
Aumolertinib NCT04951635 [87]	Randomized, double-blind, placebo-controlled, multicenter, phase III; China	c/sCRT → aumolertinib versus placebo (with no disease progression following CRT)	Until disease progression, unacceptable toxicity, or other discontinuation criteria	Unresectable stage III (8th edition staging manual) EGFRm (Ex19del/L858R +/- other mutations) NSCLC N ~150	PFS	Jul-24
Lazertinib NCT05338619 PLATINUM [88,101]	Single-arm, open-label, multicenter, phase II; Republic of Korea	cCRT → lazertinib (with no disease progression during or following CRT)	Until disease progression, unacceptable toxicity, or other discontinuation criteria (at least 3 years)	Unresectable stage III EGFRm NSCLC N~77	PFS	Mar-26
EGFR-TKI + cCRT/RT → EGFR-TKI consolidation						
Aumolertinib NCT04636593 [89,117]	Open-label, multicenter, phase II; China	Lung V20 <28%: Aumolertinib + RT → aumolertinib Lung V20 ≥28%: Induction aumolertinib → aumolertinib + RT → aumolertinib	Consolidation aumolertinib for 2 years or until disease progression or intolerable toxicity	Treatment-naïve unresectable stage III (8th edition staging manual) EGFRm (Ex19del/L858R) NSCLC N ~43	RP (grade ≥3)[a]	Dec-21
Aumolertinib NCT04952168 [90]	Open-label, single-arm, phase II; China	Aumolertinib[b] + cCRT → aumolertinib	Until disease progression or intolerable toxicity	Unresectable stage III (8th edition staging manual) EGFRm (sensitizing e.g. Ex19del/L858R) NSCLC N ~26	2-year OS rate	Jun-22
Induction EGFR-TKI → (RT) → EGFR-TKI (+RT) consolidation						
Aumolertinib ChiCTR2000040590 ADVANCE [91,92]	Randomized, open-label, multicenter, phase III; China	Induction aumolertinib → aumolertinib + RT versus cCRT	2 years	Treatment-naïve unresectable stage III (8th edition staging manual) EGFRm (Ex19del/L858R +/- other mutations) NSCLC N ~254	PFS	Dec-24
Aumolertinib NCT04841811 APPROACH [93]	Randomized, open-label, multicenter, phase II; China	Induction aumolertinib → RT → aumolertinib for 2 years versus ctDNA dynamic monitoring-guided treatment[c,d]	2 years	Treatment-naïve stage III (8th edition staging manual) EGFRm (Ex19del/L858R +/- other mutations[e]) NSCLC N ~156	ORR, EFS	Dec-24

CRT, chemoradiotherapy; c/sCRT, concurrent/sequential chemoradiotherapy; ctDNA, circulating tumor DNA; EFS, event-free survival; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation-positive; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RP, radiation pneumonitis; RT, radiotherapy; V20, percentage of total lung volume receiving 20 Gy radiation.

[a] Within 6 months post-RT.

[b] cCRT was only administered to patients who were treated with aumolertinib for 3 months and achieved stable disease, partial response, or complete response.

[c] ctDNA is tested every 3 months; if positive, aumolertinib should be continued, but if negative, aumolertinib treatment should be discontinued, and only restarted if positive ctDNA is subsequently detected.

[d] Only treatment arms for patients judged to be unresectable following RT are shown in the table.

[e] Excluding Exon20 insertion mutations.

the optimal EGFR-TKI-based treatment sequence in this setting. The survival benefits of first-line osimertinib demonstrated in untreated EGFRm advanced NSCLC [48,50] make it a preferred EGFR-TKI. However, there are no clear guidelines for subsequent treatment after acquired resistance to osimertinib.

Preliminary clinical evidence suggests that the addition of EGFR-TKIs to RT, with or without CT, may provide favorable outcomes compared with CRT or EGFR-TKI alone [24,71,79]. Interestingly, *in vitro* studies have suggested that EGFRm NSCLC cells may be more radiosensitive than cells without *EGFR* mutations and that EGFR-TKIs may have a radiosensitizing effect when combined with RT [103,104], supporting the rationale for combining EGFR-TKIs and RT. Erlotinib plus RT versus cCRT alone provided significantly longer mPFS but no OS benefit (HR 1.278) in the RECEL study; however, the OS data were immature [71]. While early evidence from the stage IV setting suggests that RT and EGFR-TKIs can be combined [105,106], additional efficacy and safety assessments in high-quality prospective clinical trials of stage III disease are required.

The role of induction EGFR-TKI in different EGFR-TKI/CRT combinations are also of interest to investigate based on preliminary data [72,73]. One challenge to explore is how patients who respond well to EGFR-TKI induction therapy should be subsequently treated. Further assessment will be needed to investigate options including surgery and adjuvant EGFR-TKI therapy post-induction therapy or cCRT/RT followed by surgery and adjuvant EGFR-TKI therapy. Additionally, whether local CRT treatment is required following induction EGFR-TKI therapy or whether it could be delayed until progression remains to be investigated. Further investigations are needed to determine the optimal treatment strategy for patients with potentially resectable disease, who are eligible for neoadjuvant treatment; careful assessment of toxicity with EGFR-TKI induction versus maintenance treatment will also be required in these patients.

The ongoing global phase III LAURA osimertinib study [82,83], a phase III aumolertinib study [87], and the phase II PLATINUM lazertinib study [88,101] will inform on the benefit of maintenance EGFR-TKIs following CRT in patients with unresectable EGFRm stage III disease (Table 2). These studies will raise the question of whether there is a role of surgery in responding patients, and the subsequent use of adjuvant treatment when surgery has been performed. This question may be addressed through ongoing and future research. In patients who cannot tolerate cCRT, the role of sCRT will be important to consider, and the question of whether CT is an absolute requirement for patients with EGFRm tumors, as part of these treatment regimens, is also deserving of future research. This may be of particular interest for certain patient groups, such as those with poor performance status or comorbidities, where CT may be more challenging to deliver. Furthermore, the optimal duration of EGFR-TKI maintenance/consolidation therapy following CRT is still to be determined as the majority of ongoing trials are evaluating maintenance therapy until progression (Table 2) [82,83,87,88,90,101]. This approach is in line with observations from RECEL and first-generation EGFR-TKI adjuvant studies, in which clinical benefit decreased after treatment was stopped [71,107–109]. Furthermore, in this setting the disease is measurable in most patients, which supports the need to treat in order to prevent disease progression. However, important considerations are the potential for toxicities from long-term treatment, and the consequent impact on patients' quality of life. Therefore, the clinical benefits of treatment need to be weighed against the benefits of living without treatment, and without treatment-related side effects [110,111].

Further assessments will be needed to investigate treatment options for patients who are eligible for RT or stereotactic body radiation therapy (SBRT) only, to determine if they could benefit from maintenance EGFR-TKI treatment following SBRT or CRT.

The issue of overlapping radiation pulmonary toxicities with (C)RT and EGFR-TKI treatment [70,71,76] should be fully evaluated. As previously discussed, patients with unresectable stage III NSCLC with EGFRm tumors may have a higher risk of distant metastases after CRT, which provides a strong rationale for the use of EGFR-TKI after (C)RT. However, the type of EGFR-TKI, as well as the optimal timing and duration of EGFR-TKI treatment may impact on the risk of pneumonitis and therefore, additional data are needed to further assess the safety of the combination of EGFR-TKIs plus (C)RT. While adherence to RT guidelines for radiation dose and field is advised [21,112,113], further data from ongoing studies such as LAURA may be needed, to determine whether adjustments are required for patients with EGFRm disease. Future studies should include strict radiation dose limit criteria for organs at risk such as the lung. EGFR-TKI treatments do also pose the challenge of treatment resistance, so further investigations would be needed to determine which gene alterations are commonly acquired, to evaluate optimal post-progression treatments. Apart from EGFR-TKIs, another interesting option for clinical investigation in the unresectable EGFRm stage III setting would be antibody-drug conjugates, with several clinical studies investigating antibody-drug conjugates in patients with EGFRm advanced NSCLC, including those who have progressed on osimertinib [114]. The emerging radio-immunoconjugate agents [114] may also be of interest to investigate in this patient population, particularly in those with intracranial failure. However, prospective randomized controlled studies, some of which are currently ongoing (Table 2), will be needed to address these questions.

5.3. Study endpoints

Another key question is which endpoints should be used in these studies. For the majority of ongoing studies (Table 2), the primary endpoint is PFS, which is an accepted endpoint for assessing clinical benefit in NSCLC [115]. Although OS is the 'gold standard' endpoint for assessing efficacy, its use can be limited by the need for long follow-up and the potential for confounding by subsequent therapies, treatment crossover, and non-NSCLC-related deaths [116]. PFS is therefore valuable for patients as it provides results earlier than OS and represents a direct measure of a treatment's efficacy without being confounded by the efficacy of subsequent treatments used after disease progression. Moreover, time free of disease progression together with the accompanying symptoms is a clinically meaningful goal [110]. Additionally, long-term landmark PFS rates (ie 5-year rates) could serve as clinically relevant endpoints in this setting, as they can estimate the proportion of patients who maintain a progression-free status and can therefore reach the point of cure [110]. Furthermore, given the high rates of brain metastases that occur in this patient population [9,11,16,37,52,68,72,74], it is important to assess specific CNS activity, such as CNS PFS, which is a secondary endpoint in LAURA as well as the phase II study investigating c/sCRT followed by aumolertinib versus placebo [82,87].

In addition to these efficacy endpoints, the impact of symptoms and side effects from long-term treatment on the patients' quality of life must be taken into consideration. To this end, patient-reported outcomes are important to assess. Quality-adjusted time without symptoms of disease progression or toxicity of treatment would also be another meaningful endpoint for patients, as it provides an integrated measure of clinical benefit, evaluating the tradeoff between toxicities (from treatments and disease symptoms) and survival [111].

6. Conclusions

The SoC in unresectable stage III NSCLC is consolidation durvalumab in patients without progression post-CRT. However, in patients with EGFRm disease, the benefit is not well characterized and there are no approved targeted treatments. Data are emerging showing the potential for EGFR-TKI treatment in patients with unresectable EGFRm stage III NSCLC. New treatment regimens will need to address the high rates of distant recurrences, particularly brain metastases. Ongoing prospective studies may therefore provide new, much needed treatment options for

this patient population.

CRediT authorship contribution statement

Terufumi Kato: Conceptualization, Writing – original draft, Writing – review & editing. **Ignacio Casarini:** Conceptualization, Writing – original draft, Writing – review & editing. **Manuel Cobo:** Conceptualization, Writing – original draft, Writing – review & editing. **Corinne Faivre-Finn:** Conceptualization, Writing – original draft, Writing – review & editing. **Fiona Hegi-Johnson:** Conceptualization, Writing – original draft, Writing – review & editing. **Shun Lu:** . **Mustafa Özgüroğlu:** Conceptualization, Writing – original draft, Writing – review & editing. **Suresh S. Ramalingam:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Terufumi Kato reports consulting/advisory roles: AstraZeneca, BeiGene, Daiichi-Sankyo, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer; honoraria: Amgen Inc., AstraZeneca, BeiGene, Boehringer Ingelheim, Chugai Pharmaceuticals Co., Ltd., Daiichi-Sankyo, Eli Lilly and Company, GlaxoSmithKline, Janssen, Merck KGaA, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical Co., Ltd., Pfizer, Taiho Pharmaceutical, Takeda; employment (spouse): Eli Lilly and company; research support (to institution): AbbVie Inc., Amgen Inc., AstraZeneca, BeiGene, Blueprint Medicines, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo, Eli Lilly and Company, HaiHe Biopharma, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Takeda, Turning Point Therapeutics Inc.

Ignacio Casarini reports local principal investigator role: AstraZeneca, Bristol-Myers Squibb, Exelixis, Lilly, Merck Sharp & Dohme, Novartis, Roche (non-financial and for institution); principal investigator role for multiple clinical studies: AstraZeneca, Bristol-Myers Squibb, Exelixis, Lilly, Merck Sharp & Dohme, Novartis; principal investigator role for one clinical study: Roche.

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