Review Article

Adjuvant therapies in stages I–III epidermal growth factor receptor-mutated lung cancer: current and future perspectives

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Abstract: Surgical resection followed by adjuvant cisplatin-based chemotherapy is the recommended treatment for patients with completely resected stage IB–IIIA non-small cell lung cancer (NSCLC). Even with the best management, recurrence is common and increases with disease stage (stage I: 26–45%; stage II: 42–62%; stage III: 70–77%). For patients with metastatic lung cancer and tumours that harbour epidermal growth factor receptor (EGFR) mutations, EGFR-tyrosine kinase inhibitors (TKIs) have improved survival. Their effectiveness in advanced stages of NSCLC raises the possibility that these agents may improve outcomes for patients with resectable EGFR-mutated lung cancer. In the ADAURA study, adjuvant osimertinib provided a significant improvement in disease-free survival (DFS) and reduced central nervous system (CNS) disease recurrence in patients with resected stage IB–IIIA EGFR-mutated NSCLC, with or without prior adjuvant chemotherapy. To reap the maximum benefits of EGFR-TKIs for patients with lung cancer, the early and rapid identification of EGFR mutations [and other oncogenic drivers, such as programmed cell death-ligand 1 (PD-L1), with matched targeted therapies] in diagnostic pathologic specimens has become essential. To ensure patients receive the most appropriate treatment, routine, comprehensive histological, immunohistochemical, and molecular analyses (with multiplex next generation sequencing) should be undertaken at the time of diagnosis. The potential for personalised treatments to cure more patients with early-stage lung cancer can only be realised if all therapies are considered when the care plan is formulated, by the multi-specialty experts managing patients. In this review, we discuss the progress and prospects for adjuvant treatments as part of a comprehensive plan of care for patients with resected stages I–III EGFR-mutated lung cancer, and explore how the field could go beyond DFS and overall survival to make cure a more frequent outcome of treatment in patients with resected EGFR-mutated lung cancer.

Keywords: Adjuvant therapies; epidermal growth factor receptor (EGFR); epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs); postoperative; non-small cell lung cancer (NSCLC)

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Introduction

Approximately 30–50% of patients with non-small cell lung cancer (NSCLC) present with resectable disease (1-3). For these patients, surgery with curative intent is the recommended treatment (4), undertaken after neoadjuvant chemotherapy in select stage IIIA NSCLC (5), or followed by adjuvant cisplatin-based chemotherapy for patients with completely resected (R0) stage IB–IIIA NSCLC (4,6,7). However, adjuvant chemotherapy provides a 5% absolute increase in survival at five years (8), but with

significant adverse effects (9). Adjuvant radiotherapy is not recommended for patients with completely resected (R0) stage I and II NSCLC, and is not routinely recommended for stage IIIA disease (4). Despite the use of adjuvant chemotherapy and/or radiotherapy, relapse rates remain high; approximately 25–75% of patients with stages I–III resected NSCLC experience recurrent disease within five years with an increasing risk of recurrence with disease stage (stage I: 26–45%; stage II: 42–62%; stage III: 70–77%) (8,10,11). Patterns of disease recurrence after surgery can be distant (44%), locoregional (26%), or both (17%) (10), and can impact patient outcomes, with local recurrence associated with longer post-recurrence survival than distant metastases (12). The most frequently reported sites of distant recurrence in patients with resected NSCLC include the lung (11%), brain (8%), pleura (8%), and bone (6%) (11). In particular, distant recurrence in the central nervous system (CNS) is associated with a poor prognosis and a significant impact on health-related quality of life (13-15). More effective treatments are needed to extend disease-free survival (DFS), overall survival, and reduce the risk of distant recurrence in patients with early-stage resectable lung cancer, and individuals with tumours harbouring epidermal growth factor receptor (EGFR) mutation are no exception. After surgery, these patients generally have no clinically meaningful differences in quality of life compared with the general population (16), highlighting the need for adjuvant treatments which are highly tolerable and maintain quality of life (17).

EGFR exon 19 deletions (ex19del) and L858R point mutations are common oncogenic driver mutations in NSCLC (18) and reported in approximately 40–50% of Asian patients with adenocarcinoma of the lung and around 15–25% of North American and European patients (19-21). EGFR-tyrosine kinase inhibitors (TKIs) are now the standard of care for patients with advanced EGFR-mutated lung cancer (22,23), and have provided significant improvements to patients in the metastatic setting (24-28). Due to their outstanding performance in the metastatic setting, EGFR-TKIs are now being tested to improve outcomes for patients with resectable EGFR-mutated NSCLC.

As shown in *Table 1*, previous studies have investigated early-generation EGFR-TKIs such as gefitinib, erlotinib, and icotinib in the resectable setting (29-38). The phase II EVAN study demonstrated an improvement in DFS with adjuvant erlotinib in patients with resected stage IIIA EGFR-mutated NSCLC compared with chemotherapy [DFS hazard ratio (HR), 0.268; 95% confidence interval (CI): 0.136–0.531; P<0.0001] (29), along with clinically meaningful overall survival improvements (overall survival HR, 0.318; 95% CI: 0.151–0.670) (30). However, these improvements with adjuvant erlotinib have not been duplicated in a phase III study. In the phase III RADIANT study (NCT00373425), an 18-month improvement in DFS was observed in a subset of patients with EGFR-mutated NSCLC who were treated with adjuvant erlotinib compared with placebo, but this difference was not statistically significant (31). In the ADJUVANT/CTONG study (NCT01405079), adjuvant gefitinib led to significantly longer DFS compared with vinorelbine plus cisplatin for patients with stage II–IIIA (N1–N2) EGFR-mutated NSCLC (33), but no overall survival benefit was seen (32). The phase III IMPACT study (UMIN000006252) found no significant improvement in DFS or overall survival with adjuvant gefitinib in this setting (34). Both trials showed a trend towards gefitinib being initially superior to chemotherapy before the crossing of DFS Kaplan-Meier curves to favour chemotherapy after approximately four years (32,34). Despite their targeted mechanisms of action, early-generation EGFR-TKIs are pharmacologically distinct to later generation TKIs; they generally lack ability to cross the blood-brain barrier and penetrate the CNS, demonstrate a lower magnitude of benefit in EGFR-mutated advanced NSCLC, and present specific mechanisms of resistance (39-45). Recently, the phase III EVIDENCE study investigating the first-generation EGFR-TKI icotinib as adjuvant therapy in patients with stage II–IIIA completely resected EGFR-mutated NSCLC demonstrated a DFS benefit compared with chemotherapy (DFS HR, 0.36; 95% CI: 0.24–0.55; P<0.0001) (35), with a shorter median follow-up time of 24.9 months, compared with the ADJUVANT/CTONG (median follow-up: 80 months) and IMPACT studies (median follow-up: 70 months) (32,34). None of these data led to changes in global clinical practice.

Osimertinib is a third-generation EGFR-TKI that inhibits both EGFR-TKI sensitising (ex19del and L858R) and EGFR T790M resistance mutations (26,36,46-50). Recently, osimertinib became the first targeted treatment approved and recommended for use as an adjuvant treatment for patients with stage IB–IIIA EGFR-mutated (ex19del or L858R) resected NSCLC following demonstration of an important DFS benefit with osimertinib compared with placebo in the phase III ADAURA study (NCT02511106; stage II–IIIA DFS HR, 0.23; 95% CI: 0.18–0.30; stage IB–IIIA DFS

Table 1 Results from phase II and III clinical studies investigating EGFR-TKIs in patients with stage I–III resectable EGFR-mutated NSCLC

Adjuvant treatment	Trial identification	Patient population (estimated N)	Study design	Primary end point	Key results
Erlotinib	EVAN NCT01683175	Stage IIIA completely resected EGFR-mutated (N=102)	Phase II, randomised, open-label; erlotinib (n=51) *vs.* CT (n=51)	DFS	Erlotinib *vs.* CT: median DFS: 42.4 *vs.* 21.0 months (HR, 0.268; 95% CI: 0.136–0.531; P<0.0001); 2-year DFS: 81.4% *vs.* 44.6% (RR, 1.823; 95% CI: 1.194–2.784; P=0.0054); 5-year DFS: 48.2% *vs.* 46.2%. Median OS: 84.2 *vs.* 61.1 months (HR, 0.318; 95% CI: 0.151–0.670); 5-year OS: 84.8% *vs.* 51.1% (29,30)
Erlotinib	RADIANT NCT00373425	Stages IB–IIIA completely resected EGFR-mutated subgroup (N=161)	Phase III, randomised, double-blind; erlotinib *vs.* placebo	DFS	Erlotinib *vs.* placebo: median DFS (EGFR-mutated subgroup): 46.4 *vs.* 28.5 months (HR, 0.61; 95% CI: 0.38–0.98; P=0.39); 2-year DFS: 75% *vs.* 54% (31)
Gefitinib	ADJUVANT/ CTONG1104 NCT01405079	Stages II–IIIA completely resected EGFR-mutated (N=222)	Phase III, randomised, open-label; gefitinib (n=111) *vs.* CT (n=111)	DFS	Gefitinib *vs.* CT: median DFS: 30.8 *vs.* 19.8 months (HR, 0.56; 95% CI: 0.40–0.79; P=0.001); 3-year DFS: 39.6% *vs.* 32.5% (P=0.316); 5-year DFS: 22.6% *vs.* 23.3% (P=0.928). Median OS: 75.5 *vs.* 62.8 months (HR, 0.92; 95% CI: 0.62–1.36; P=0.674); 5-year OS: 53.2% *vs.* 51.2% (P=0.784) (32,33)
Gefitinib	IMPACT UMIN000006252	Stages II–IIIA completely resected EGFR-mutated (N=234)	Phase III, randomised, open-label; gefitinib (n=116) *vs.* CT (n=116)	DFS	Gefitinib *vs.* CT: median DFS: 35.9 *vs.* 25.1 months (HR, 0.92; 95% CI: 0.67–1.28; P=0.63); 5-year DFS: 31.8% *vs.* 34.1% (P=0.63). Median OS: NR *vs.* NR (HR, 1.03; 95% CI: 0.65–1.65; P=0.89); 5-year OS: 78.0% *vs.* 74.6% (P=0.89) (34)
Icotinib	EVIDENCE NCT02448797	Stages II–IIIA resected EGFR-mutated (N=320)	Phase III, randomised, open-label; icotinib (n=161) *vs.* CT (n=161)	DFS	Icotinib *vs.* CT: median DFS: 47.0 *vs.* 22.1 months (HR, 0.36; 95% CI: 0.24–0.55; P<0.0001); 3-year DFS: 63.9% *vs.* 32.5%. Median OS: NR *vs.* NR (HR, 0.91; 95% CI: 0.42–1.94) (35)
Osimertinib	ADAURA NCT02511106	Stages IB–IIIA completely resected EGFR-mutated (N=682)	Phase III, randomised, double-blind; osimertinib (n=339) *vs.* placebo (n=343)	DFS	Osimertinib *vs.* placebo: median DFS: 65.8 *vs.* 28.1 months (HR, 0.27; 95% CI: 0.21–0.34); 3-year DFS: 85% *vs.* 44% (36,37)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; CT, chemotherapy; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; RR, relative risk; OS, overall survival; NR, not reached.

HR, 0.27; 95% CI: 0.21–0.34) (36,37,51-53).

Several phase III studies evaluating EGFR-TKIs in the adjuvant setting are currently ongoing and investigating treatments such as aumolertinib, erlotinib, furmonertinib, gefitinib, icotinib and osimertinib (*Table 2*). Other trials in the neoadjuvant setting include the phase II Neoafa study (NCT04470076) investigating neoadjuvant afatinib in combination with chemotherapy in patients with resectable EGFR-mutated NSCLC (54) and the phase II PROGRESS study (NCT02804776) investigating neoadjuvant gefitinib in patients with resectable EGFR-mutated NSCLC (55). Furthermore, neoadjuvant osimertinib is currently being investigated with and without chemotherapy in patients with resectable EGFR-mutated NSCLC in the phase III NeoADAURA study (NCT04351555) (56).

Immune checkpoint inhibitors have also entered the peri-operative space. The anti-programmed cell death-ligand 1 (PD-L1) antibody atezolizumab was approved for use as an adjuvant treatment for patients with stage II–IIIA NSCLC whose tumours have PD-L1 expression on ≥1% of tumour cells (57) based on results from the phase III IMpower010 study (NCT02486718) (DFS HR, 0.66; 95% CI: 0.50–0.88; P=0.0039) (58). Results with the anti-programmed cell death protein-1 (PD-1) antibody

Table 2 Ongoing phase III studies of EGFR-TKIs in stages I–III resectable EGFR-mutated NSCLC

Adjuvant treatment	Trial identification	Patient population (estimated N)	Study design	Primary end point	Estimated primary completion
Aumolertinib	NCT04687241	Stages II–IIIB resected EGFR-mutated (N=192)	Randomised, double-blind, placebo-controlled	DFS	Jan 2026
Aumolertinib	APEX NCT04762459	Stages II–IIIA resected EGFR-mutated (N=606)	Randomised, open-label; aumolertinib ± CT *vs.* CT	DFS	May 2026
Erlotinib	ALCHEMIST NCT02193282	Stages IB–IIIA completely resected EGFR-mutated (N=450)	Randomised, open-label	OS	Oct 2026
Furmonertinib	FORWARD NCT04853342	Stages II–IIIA completely resected EGFR-mutated (N=318)	Randomised, double-blind, placebo-controlled	DFS	Dec 2023
Gefitinib	NCT03381066	Stages IIA–IIIB completely resected EGFR-mutated (N=225)	Randomised, open-label; gefitinib + CT *vs.* CT	DFS	Dec 2022
Icotinib	EVIDENCE NCT02448797	Stages II–IIIA resected EGFR-mutated (N=320)	Randomised, open-label *vs.* CT	DFS	June 2022. Estimated study completion Dec 2022
Icotinib	ICTAN NCT01996098	Stages II–IIIA resected EGFR-mutated (N=318)	Randomised, open-label, CT followed by icotinib *vs.* CT	DFS	Jan 2020. Estimated study completion Jan 2023
Icotinib	ICWIP NCT02125240	Stages II–IIIA resected EGFR-mutated (N=124)	Randomised, double-blind, placebo-controlled	DFS	Dec 2018
Osimertinib	ADAURA NCT02511106	Stages IB–IIIA completely resected EGFR-mutated (N=682)	Randomised, double-blind, placebo-controlled	DFS	Jan 2020. Estimated study completion Jan 2023
Osimertinib	ADAURA2 NCT05120349	Stages IA2–IA3 completely resected EGFR-mutated (N=380)	Randomised, double-blind, placebo-controlled	DFS	Aug 2027

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; CT, chemotherapy; DFS, disease-free survival; OS, overall survival.

pembrolizumab have been reported in patients with stage IB (tumours ≥4 cm), II, or IIIA NSCLC following complete tumour resection and adjuvant chemotherapy (when indicated) in the phase III PEARLS/KEYNOTE-091 study (NCT02504372) (all-comer population DFS HR, 0.76; 95% CI: 0.63–0.91; P=0.0014) (59). Checkpoint inhibitors with and without chemotherapy are also being investigated in the neoadjuvant setting. The anti-PD-1 agent nivolumab was recently approved by the US Food and Drug Administration (FDA) as a neoadjuvant treatment in combination with platinum-doublet chemotherapy for patients with resectable (tumours ≥4 cm or node positive) NSCLC (60) (HR for disease progression, recurrence or death, 0.63; 97.38% CI: 0.43–0.91; P=0.005; pathological complete response odds ratio, 13.94; 99% CI: 3.49–55.75; P<0.001) (61). However, few patients with EGFR-mutated cancer were enrolled in these neoadjuvant studies and some trials specifically excluded them, based on the poorer performance of these agents in patients with metastatic EGFR-mutated lung cancer.

This review discusses the current progress of adjuvant treatments for stages I–III resectable EGFR-mutated lung cancer, and evaluates future prospects based on expert review of the published literature and ongoing studies. We will explore the value of prolonging DFS, the potential for overall survival gains, and the possibility of progress towards cure in this disease setting. In this context, we evaluate how the point of cure could be defined as treatment strategies and disease monitoring methods evolving in this setting.

Adjuvant treatments in stage I–III EGFR-mutated NSCLC and the goal of adjuvant treatment

Across all clinical studies in cancer, overall survival, defined as the length of time from randomisation/treatment until death from any cause, is considered by many the gold standard measure of treatment efficacy (62-64). Overall survival as a primary efficacy endpoint generally requires studies with large patient numbers and extended periods of follow-up, and is confounded by treatment crossover,

subsequent treatments, and non-cancer related death (65). Other endpoints, including DFS and progression-free survival (PFS), provide an additional measure of benefit and can more rapidly assess treatment efficacy (65). The impact of time free from progressive cancer, and the symptoms that accompany cancer growth and spread, is substantial, and considered the most important measure for many in the field of oncology. Additionally, only by maintaining a disease-free state can patients reach the point of cure.

DFS, generally defined as the length of time from randomisation/treatment until disease recurrence, occurrence of secondary cancer, or death from any cause, provides a direct measure of the treatment-effect and is not influenced by subsequent treatments (66). In a retrospective analysis of 104 patients with stage IB–IIIA resected EGFR-mutated NSCLC, HRs for five-year overall survival were found to be similar or slightly reduced compared with those for two-year DFS, supporting DFS as an appropriate surrogate end point for overall survival in the resectable setting (67). Most phase III studies investigating adjuvant treatments in resectable EGFR-mutated NSCLC use DFS as the primary efficacy end point (*Tables 1*,*2*), which illustrates the need to identify adjuvant treatments without waiting for overall survival data. As shown in *Table 2*, phase III clinical studies investigating targeted adjuvant treatments for stages I–III resectable EGFR-mutated NSCLC that are currently underway include the ongoing ADAURA study investigating osimertinib (36,37), the ICWIP, ICTAN, and EVIDENCE studies investigating adjuvant icotinib in stage II–IIIA completely resected EGFR-mutated NSCLC (35,68,69), and two studies investigating aumolertinib in Chinese patients with stage II–IIIA and stage II–IIIB completely resected EGFR-mutated NSCLC (70,71).

In addition to the DFS benefit demonstrated in ADAURA, adjuvant osimertinib also reduced the risk of CNS recurrence in patients with stage II–IIIA disease (CNS DFS HR, 0.24; 95% CI: 0.14–0.42) (36,37,72). Furthermore, a DFS benefit with osimertinib versus placebo has been observed consistently across disease stages IB–IIIA in ADAURA [DFS HR, 0.41 (95% CI: 0.23–0.69) for stage IB, 0.34 (95% CI: 0.23–0.52) for stage II and 0.20 (95% CI: 0.13–0.29) for stage IIIA] (37). These improvements across disease stages were observed in patients that did and did not receive previous adjuvant chemotherapy (73). This substantial DFS benefit across stages, including stage IB (37), supported by data demonstrating maintained health-related quality of life (74), has prompted conversation among patients and physicians on the use of osimertinib more broadly in pathological stage I EGFR-mutated lung cancer. While the ADAURA data reasonably support the use of osimertinib in patients with stage IB NSCLC, these data may also encourage investigation of osimertinib in other stage I NSCLC tumours, where tumours have pathological characteristics that are associated with a higher risk of relapse, including poorly differentiated tumours, vascular invasion, and unknown lymph node status (75). Beyond the ADAURA data in stage IB tumours, there is minimal clinical trial data to guide care specifically for these patients and further research is warranted.

Overall, the magnitude of DFS benefit and evidence of CNS efficacy with adjuvant osimertinib has changed clinical practice in the resectable setting (52,53) and many healthcare professionals recognise the value of prolonging DFS. Whether overall survival benefit will be observed in ADAURA remains an important question. Early-generation EGFR-TKIs have so far failed to provide significant overall survival efficacy benefit for patients with resectable EGFR-mutated NSCLC in phase III trials (32-34). Nevertheless, the magnitude of DFS benefit observed in the ADAURA might lead to a different overall survival outcome. As previously noted, following an initial DFS benefit (29) the EVAN study recently demonstrated clinically meaningful overall survival improvements in resected stage IIIA EGFR-mutated NSCLC with adjuvant erlotinib, despite only being a phase II study (30).

In the adjuvant setting, there is some scepticism about the use of DFS as an alternative end point for overall survival. If the goal of adjuvant treatment is to increase survival while maintaining quality of life, and a clinical trial does not demonstrate evidence of improved overall survival, a patient may benefit from receiving the treatment at the time of disease recurrence when the motivation for treatment and possible acceptance of certain side effects is stronger (76,77). On the other hand, maintaining patients in a 'disease-free' state by prolonging DFS ultimately provides more time living cancer- and cancer symptom-free which can be considered a clinically meaningful goal for patients (66,78,79). Only patients who remain 'on the DFS Kaplan-Meier curve' have the opportunity to be cured. From a physician and patient perspective, it is challenging to question the clinical benefit of preventing or delaying recurrence, irrespective of its ultimate impact on survival. Being alive on therapy is not equivalent to life free of disease; the impact of symptomatic recurrent disease is significant both in terms of patient morbidity and

transferable costs to society. From another perspective, in settings where post-recurrence therapy significantly affects long-term survival, DFS remains an unambiguous measure of a new treatment's impact on the disease process.

While health-related quality of life is seen as an important outcome across all clinical studies in cancer (80), patient-centred outcomes such as pain relief and control of symptoms (e.g., dyspnoea, cough) still do not receive the emphasis they merit in many clinical studies (62). Quality of life considerations are especially important in patients with resectable lung cancer as there is often a need for long-term treatment. With this being the case, a careful assessment of the tolerability profile of adjuvant treatment is required. Regardless, there are arguably no adverse effects considered more serious than the recurrence of lung cancer, which can lead to cancer-related symptoms such as shortness of breath, cough, pain, and ultimately the risk of death. However, EGFR-TKIs such as osimertinib are generally well tolerated, with safety data up to three years from ADAURA indicating that adjuvant osimertinib treatment is well tolerated, with no new safety concerns reported over this treatment duration (81). Furthermore, it is known that side effects such as diarrhoea, which was the most common adverse event leading to treatment interruption in ADAURA (81), can be alleviated with prudent management techniques and dose adjustments, in order to limit the impact on the daily lives of patients. Health-related quality of life data from ADAURA demonstrate that quality of life was maintained during adjuvant osimertinib treatment, compared with placebo (74). As mentioned above, the impact of disease itself on quality of life is also important as there is a high risk of CNS metastases when recurrence does occur (82), which can have a detrimental impact on patient prognosis and quality of life (13). The ability of adjuvant osimertinib to reduce the risk of CNS metastases (37) provides additional data supporting the use of osimertinib as an adjuvant treatment.

As patients who have had their cancer removed by surgery can be considered disease-free, the main focus for adjuvant treatment could be to maintain this disease-free state and allow patients to have a normal/active life (i.e., a quality of life similar or near to before their cancer diagnosis). As patients with completely resected lung cancer have been generally found to have no clinically meaningful differences in quality of life compared with the general population (16), prolonging DFS and CNS DFS supports this objective. Prolonging DFS while maintaining a 'normal life' with an adjuvant treatment associated with manageable side effects is a key consideration for patients, and an important goal of adjuvant treatment.

EGFR-TKIs to extend overall survival benefit

Following the discovery of EGFR mutations in 2004 (83), first-generation EGFR-TKIs such as gefitinib and erlotinib demonstrated significant PFS benefit in patients with EGFR-mutated advanced NSCLC but this did not translate into overall survival benefit (24,25,27,28,84). Significant treatment crossover can occur post disease progression, complicating overall survival estimations. Also a lack of statistically significant CNS efficacy associated with first and second-generation EGFR-TKIs (39,40,44,45) may partly explain why PFS benefit did not translate to overall survival benefit in these studies. Furthermore, tumour heterogeneity, an important factor that can lead to EGFR-TKI resistance (85), has been found to increase with tumour stage (86). Earlier stage EGFR-mutated NSCLC tumours may be more exclusively driven by EGFR mutations, and more sensitive to treatment compared with advanced stage tumours, which are likely to have a greater number of mutations, as well as interactions with stromal and immune cells (87). Consequently, there is the possibility that TKIs may be more effective in earlier lines of treatment and in the resectable setting compared with the advanced setting.

The third-generation EGFR-TKI osimertinib is structurally distinct from earlier-generation EGFR-TKIs, with a pharmacologically differentiated profile that potently and selectively inhibits EGFR-TKI sensitising and EGFR T790M resistance mutations, while sparing wild-type EGFR (46). It was the first EGFR-TKI to demonstrate both PFS and overall survival benefit in patients with previously untreated advanced EGFR-mutated NSCLC in the phase III FLAURA study versus gefitinib/erlotinib (PFS HR, 0.46; 95% CI: 0.37–0.57; P<0.001; overall survival HR, 0.8; 95.05% CI: 0.64–1.00; P=0.046) (26,50). This overall survival benefit was observed despite patient crossover from the comparator EGFR-TKI arm to open-label osimertinib following progression (26,88) and importantly, CNS efficacy was also demonstrated with osimertinib versus gefitinib/erlotinib (CNS PFS HR, 0.48; 95% CI: 0.26–0.86) (48).

Other third-generation EGFR-TKIs with demonstrated PFS and CNS efficacy in advanced EGFR-mutated NSCLC include aumolertinib and furmonertinib. In the ongoing phase III AENAS study, a significant PFS benefit with aumolertinib compared with gefitinib was observed (PFS HR, 0.46; 95% CI: 0.36–0.60) (89). Furthermore,

aumolertinib demonstrated significantly prolonged median CNS PFS compared with gefitinib (CNS PFS HR, 0.30; 95% CI: 0.137–0.657) (90). In the phase III FURLONG study, furmonertinib treatment has also demonstrated significantly longer CNS PFS compared with gefitinib (CNS PFS HR, 0.40; 95% CI: 0.23–0.71) (91). However, overall survival benefit is yet to be demonstrated in these studies.

Progress towards cure in NSCLC

Currently, there is no evidence-based definition of 'cure' in the field of lung cancer, although some experts consider 'remission at five years' (i.e., five years with no disease progression) one definition in early-stage disease (92,93). A definition of 'cure' is certainly challenging to establish, and difficult to measure if defined as the lifelong absence of recurrence. Other definitions of 'cure' include 'statistical cure', where the patient's risk of dying or relapsing becomes equal to the mortality of the general age-matched population (estimated at around ten years after diagnosis), 'personal cure', when a patient dies from a cause other than their cancer, and 'psychological cure', when a patient feels that their chance of the disease returning is sufficiently low enough that they decide to consider themselves 'cured' (93). These definitions of 'cure' are distinctly different to overall survival (64) which may include patients who are still experiencing cancer symptoms (which is more frequently observed, even at five years and with immunotherapy as a treatment option), as well as patients who are strictly disease-free. In general, what most of these definitions of 'cure' have in common is the idea of a complete *absence of cancer* which is more closely linked to a DFS end point (79). Another common theme associated with defining 'cure' is the resolution of symptoms and maintained quality of life. There is a significant amount of literature which aims to define 'cure' by going beyond traditional clinical parameters and focusing more on psychological or everyday quality of life goals (92-94). As techniques to quantify disease status become more precise (95), advancements in molecular testing methods may also help us to better define the point of 'cure' in NSCLC by more accurately determining risk of recurrence from a biological perspective, as well as a statistical perspective. Overall, it is apparent that the goal of 'cure', with its many possible definitions, can encompass several statistical, biological, psychological, and philosophical factors, and extend beyond the clinical parameters of disease-free and overall survival.

The perception that treatment with EGFR-TKIs can only delay disease progression, but not necessarily achieve survival benefit, has been built on experiences from the advanced (incurable) NSCLC setting, where largely only PFS benefit has been achieved (24-28), with the exception of osimertinib. However, improvements in overall survival have been observed in other cancer settings including breast cancer (96,97), melanoma (98), and gastrointestinal stromal tumours (GISTs) (99,100). For example, mitogen-activated protein kinase (MAPK) pathway inhibition via TKI combinations such as dabrafenib plus trametinib, and vemurafenib plus cobimetinib, have led to significantly improved PFS and overall survival in patients with BRAF-mutant melanoma (101-103). Ultimately, achieving cure in lung cancer will require the most appropriate targeted treatments to be used at the most appropriate time, for an optimal duration of time, in the right patients. These treatments are likely to be used as part of existing curative regimens, and multiple treatments may be required depending on the unique molecular profile of the patient and how this may change over time. As more adjuvant treatments become available, it will also be important to evaluate the magnitude of survival benefit required to balance the side effects experienced.

Both osimertinib and atezolizumab are now approved in many countries as targeted adjuvant treatments for resectable NSCLC (53,57), and more regulatory approvals for targeted agents and checkpoint inhibitors in this setting are expected soon. The growing availability of biomarker directed treatments for adjuvant NSCLC highlights the importance of early molecular testing, including for EGFR mutation and PD-L1 expression, in order to personalise treatment for patients and improve patient outcomes. To ensure patients receive the most appropriate treatment, routine, comprehensive histological, immunohistochemical, and molecular analyses (with multiplex next generation sequencing) will be required, which will require molecular testing at diagnosis, ahead of neoadjuvant treatment and surgical resection. In addition to timely diagnosis and improved targeted treatments for resectable disease, early detection and optimal treatment for patients who experience recurrence will also be important to improve long-term patient outcomes in the adjuvant setting.

Conclusions and future perspectives

Treatments for NSCLC can be personalised to target specific oncogenic drivers. Routine early molecular testing for all patients is critical to inform treatment decisions and

enable optimal care. In recent years, we have seen progress in the development and availability of adjuvant treatments for resectable EGFR-mutated NSCLC. While overall survival data from ADAURA are maturing, the magnitude of DFS benefit with osimertinib combined with CNS efficacy and fewer distant recurrences (36,37), provides ample evidence to support its use.

'Cure' has many definitions. Improved diagnostic techniques for NSCLC, as well as screening programmes to identify patients with NSCLC as early as possible, combined with targeted treatments, may enhance the potential for improvement of long-term disease control and cure in resectable NSCLC.

In conclusion, the goal of treatment for stages I–III resectable EGFR-mutated lung cancer is cure. Adjuvant systemic therapies are an important component of treatment which may include surgery, radiotherapy, chemotherapy, or immunotherapy. While cure is the goal, many physicians and patients believe there is significant merit in prolonging cancer-free survival while preserving a normal life for patients, which is not degraded by the symptoms of advanced cancer or side effects of therapy. The improvements in DFS seen with adjuvant osimertinib are significant. Adopting improved diagnostic techniques at diagnosis, regardless of disease stage, and establishing a personalised approach to treatment will extend life and increase the possibility of 'cure' for patients with EGFR-mutated lung cancer.

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