Peer Review File

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Comments	Response
Reviewer A: This is a well-written and in-depth discussion of the current state of adjuvant therapy for EGFR-positive non-small cell lung cancer. The paper covers a wide topic with an appropriate level of detail, citing the most notable adjuvant studies to-date while also providing expert commentary that looks beyond the raw data. I believe this is an important contribution and have only the following minor comments:	We thank the reviewer for their comment.
1. The authors make a well-founded case for the use of osimertinib in the adjuvant setting based on the DFS data alone that is available from ADAURA. However, do the authors believe that stage I tumors should be approached the same way as stage II-III tumors? A discussion of the subgroup data from ADAURA by stage would be an important nuance to discuss given that survival after surgery alone is higher for stage I NSCLC than stage I-II NSCLC.	DFS benefit was consistently observed across disease stages in ADAURA, as shown by the additional DFS data by disease stage added to the text. Some additional text based on author opinion around the treatment of stage I tumors has now been included. **Text in the 'Adjuvant treatments in stage I−III EGFR-mutated NSCLC and the goal of adjuvant treatment' section (page 8, lines 199−212; tracked copy) has been added, and now reads:** Furthermore, a DFS benefit with osimertinib versus placebo has been observed consistently across disease stages IB–IIIA in ADAURA (HR DFS 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) (53). 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, supported by data demonstrating maintained health-related quality of life (53; 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 tumors, where tumors have pathological characteristics that are associated with a higher risk of relapse, including poorly differentiated tumors, 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.
2. When discussing the importance of quality of life in the setting of being disease-free, it may be helpful to include commentary on the side-effects of adjuvant TKI therapies such as osimertinib. One argument some might use against adjuvant osimertinib before knowing OS data is that, while overall very well-tolerated, there are side-effects with osimertinib that can impact quality of life. A discussion of the balance between maintaining disease-free recurrence and the side-effects of therapy is warranted.	We agree with the reviewer that this is a valuable point so have added that an assessment of the tolerability profile, and it's potential effect on quality of life, is an important aspect when choosing an appropriate adjuvant treatment. **Text in the 'Adjuvant treatments in stage I−III EGFR-mutated NSCLC and the goal of adjuvant treatment' section (page 10, lines 241−264) has been added, and now reads:** While health-related quality of life is seen as an important outcome across all clinical studies in cancer (80), patient-centered outcomes such as pain relief and control of symptoms (e.g. dyspnea, 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, 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 (53) provides additional data supporting the use of osimertinib as an adjuvant treatment.
Reviewer B:	We thank the reviewer for their comment.

Well-summarized review manuscript.	
1. Recently updated OS analysis of Evan trial was published in JCO J Clin Oncol 40:3912-3917. Reference #112 can be replaced with an updated report.	We thank the reviewer for pointing out this literature update. We have added data from this updated EVAN analysis to the manuscript. **Text in the Introduction section (page 4, lines 92−101) has been amended and added and now reads:** As shown in Table 1, previous studies have investigated early generation EGFR TKIs such as gefitinib, erlotinib, and icotinib in the resectable setting (29-33). 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) (34), along with clinically meaningful overall survival improvements (overall survival HR 0.318; 95% CI: 0.151–0.670) (35). 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).
Reviewer C: This paper reviews the literature regarding adjuvant therapy in early stage / locally advanced EGFR-mutated lung cancer. The paper is very informative and well written.	We thank the reviewer for their comment.
1. The paper covers the topic extensively. However, the section on 'EGFR-TKIs to extend overall survival benefit' is pitched around the benefits of EGFR-directed therapy in metastatic disease rather than adjuvant. The authors might consider changing the name of the paper, or else shorten this section.	We have considerably shortened the section on 'EGFR-TKIs to extend overall survival benefit' in line with the reviewer's suggestion to focus on the benefits of adjuvant therapy. **Text in the 'EGFR-TKIs to extend overall survival benefit section' (pages 10–13, lines 284−333) has been edited and now reads:** 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 (37, 38, 42, 43) 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 (44). 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, 28, 48). This overall survival benefit was observed despite patient crossover from the comparator EGFR-TKI arm to open-label osimertinib following progression (26, 85) and importantly, CNS efficacy was also demonstrated with osimertinib versus gefitinib/erlotinib (CNS PFS HR, 0.48; 95% CI: 0.26–0.86) (46). 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.
2. In general, the paper is too long and, in some places, repetitive. In particular, the section ‘Progress towards cure in NSCLC’ could be deleted or summarised in a few sentences.	The text has been streamlined across the manuscript, in particular in the ‘EGFR-TKIs to extend overall survival benefit’ and ‘Progress towards cure in NSCLC’ sections, to remove any repetitious points and to focus more specifically on the key topics and disease setting in question. **Text in the following sections has been deleted:**

	Introduction: page 4, paragraph 1; page 6, paragraph 2 **'Adjuvant treatments in stage I−III EGFR-mutated NSCLC and the goal of adjuvant treatment' section: page 8, paragraph 3** **'EGFR-TKIs to extend overall survival benefit' section: page 10, paragraphs 2 and 3** **'Progress towards cure in NSCLC' section: page 11, paragraphs 3 and 4; page 12, paragraphs 1–3**
3. Introduction. Paragraph 4. Line 125. Deals with DFS benefit for Osimertinib as adjuvant. The HR for stage II-IIA is given as 0.23 and stage IB-IIIA as 0.27. This is not informative for the audience. The stage 1B HR should be given separately.	In response to Reviewer A's comment, we have now added the individual DFS HRs for the separate disease stages, including that for stage IB, to a later section in the manuscript along with a discussion of the implications of these results in terms of treating stage IB disease. **Text in the 'Adjuvant treatments in stage I−III EGFR-mutated NSCLC and the goal of adjuvant treatment' section (page 8, lines 198−203) has been added, and now reads:** Furthermore, a DFS benefit with osimertinib versus placebo has been observed consistently across disease stages IB–IIIA in ADAURA (HR DFS 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) (53). These improvements across disease stages were observed irrespective of whether or not patients received previous adjuvant chemotherapy (73).
4. Table 1. Results from randomised phase 2 and 3 trials using EGFR tki as adjuvant post-surgery. Rather than only showing results for the EGFR tki arm as median DFS and a landmark DFS, the results for the experimental DFS vs standard of care arm DFS should be given. Ideally, OS data should be given also although it is appreciated that there might be insufficient space	Table 1 has been updated with the comparator arm DFS data in addition to available OS data for the respective studies. **Additional data have been added to Table 1.**
5. Minor issue. Introduction, paragraph 1. Line 76. '… is associated with a poor prognosis and can significantly	This sentence has been edited to improve readability. **Edit to the sentence on page 3, lines 71−73 now reads:**

deteriorate patient health related quality of life…' is a clumsy sentence and requires rephrasing	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).
6. Minor issue. Adjuvant treatments in stage I-III EGFR-mutated NSCLC and the goal of adjuvant treatment. Paragraph 5. Line 238. Should be '… still does not …'	We thank the reviewer for pointing out this typo. This section has now been re-phrased. **Edit to 'Adjuvant treatments in stage I−III EGFR-mutated NSCLC and the goal of adjuvant treatment' section (page 10, lines 241−245) which now reads:** While health-related quality of life is seen as an important outcome across all clinical studies in cancer (76), patient-centered outcomes such as pain relief and control of symptoms (e.g. dyspnea, cough) still do not receive the emphasis they merit in many clinical studies (61).