NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from AstraZeneca**

3. **Comments on the Appraisal Consultation Document from experts:**
   a. Dr Gary Doherty – Clinical Expert, nominated by AstraZeneca
   b. Professor Eric Lim – Clinical Expert, nominated by AstraZeneca

4. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	AstraZeneca	**<u>Uncertainty about the extent a benefit in DFS translates into a benefit in OS</u>** There is strong clinical rationale to suggest that osimertinib's unprecedented clinically meaningful and statistically significant DFS benefit will translate into OS. Even in the absence of OS, by significantly extending the disease-free period (and the time to subsequent treatments) in patients with resected EGFRm positive NSCLC, adjuvant osimertinib will provide patients with invaluable long-term benefits compared to existing active monitoring. The improvement in DFS is expected to drive the cost-effectiveness of osimertinib in the adjuvant setting. **a) The DFS benefit demonstrated in ADAURA is likely to be maintained** After the ADAURA trial demonstrated overwhelming and unprecedented clinical benefit of adjuvant osimertinib, the IDMC recommended that the trial was unblinded 2 years early to allow for early analysis of data[1,2]. The study was only unblinded to the Company and after all patients had follow up of at least one year. In the primary analysis, the majority (63%) of the DFS events expected in the planned final analysis in patients with stage II-IIIA had already occurred[3]. **This suggests that the substantial DFS benefit in osimertinib arm will not significantly change with more mature data and is expected to be maintained.** A recent publication initiated and performed by the FDA and Project Orbis partners provides rationale for the regulatory approval decision-making for ADAURA, it is noted that ***"it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFR-mutated NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS"***[3]. At the time of analysis in the overall ADAURA population, 46.4% of patients in the placebo arm and 10.9% of patients in the osimertinib arm had disease recurrence or died[2,4]. While the early unplanned analysis may result in data maturity which is lower than originally planned, it does support the relatively low number of recurrence or death events in the osimertinib arm relative to placebo, reflecting the benefit of treating with osimertinib in the adjuvant setting.	Thank you for your comment. The committee considered your comment at the second meeting, however uncertainty remains on the extent to which a benefit in DFS translates into a benefit in OS. The committee was also concerned that that there is currently no evidence to show that after stopping treatment with osimertinib the hazards, and therefore the hazard ratios, for disease-free survival does not increase (as with the other TKIs). Section 3.5 of the FAD has been updated.

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			b) However, if the DFS benefit significantly reduces over time, osimertinib will still remain a cost-effective treatment for the NHS in favour of placebo even in the worse-case scenario [redacted] **Even in the most extreme case** where the HR for the placebo arm of the ADAURA trial outperforms the osimertinib treatment arm at the final analysis ([redacted]), the median HR across both data readouts (primary analysis plus final analysis) is [redacted]. Despite this worst possible case, adjuvant osimertinib remains a cost effective use of resources with an ICER of £17,662. Furthermore, the economic model used by the Company and the ERG assumes that over time, the clinical magnitude of DFS benefit decreases (HRs increase) to reflect the natural progression of the disease. See Table 1 below. **Table 1: Changes in the modelled DFS in the Company's economic over time** [redacted] Abbreviations: DFS, disease free survival; HR, hazard ratio. **c) By significantly extending the disease-free period (and the time to subsequent treatments) in patients with resected EGFRm positive NSCLC, adjuvant osimertinib will provide patients with**	

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			invaluable long-term benefits compared to existing active monitoring, even in the absence of long term OS Fear of cancer recurrence is cited as one of the most distressing concerns for resectable NSCLC patients, making the extension of living cancer-free a primary goal. Many cancer survivors experience emotional and psychological issues (including distress, anxiety, depression, cognitive changes and fear of cancer recurrence) at the end of treatment, with fear of cancer recurrence as one of the most distressing concerns of patients[6-9]. Adjuvant osimertinib will transform the EGFRm NSCLC patient journey by delaying/preventing recurrence and keeping patients in the curative intent setting for longer. As a result the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis. Additionally, a clinically meaningful decrease in central nervous system (CNS) recurrence or death was observed with osimertinib, and a reduction in distant metastases vs placebo (ADAURA trial). This highlights the clinical potential of osimertinib for improving post-surgical outcomes including OS. The low proportion of patients experiencing CNS recurrence with osimertinib contrasts with trials of earlier-generation EGFR-TKIs, gefitinib and erlotinib, in the adjuvant setting, in which brain metastases drove disease recurrence. Brain metastases are the most common type of recurrence in NSCLC, impose a heavy burden on patients quality of life, and mark a transition to incurable disease. Thus, by preventing brain recurrences in the resectable EGFRm population, osimertinib also meets a substantial unmet need. **d) By keeping patients disease-free for longer, the upfront investment with osimertinib will delay and avoid costs of progression to advanced disease – regardless of whether osimertinib is preventing or delaying recurrence as patients are remaining in the curative intent setting for longer** CNS metastases (specifically brain metastases) is the most common form of distant recurrence in NSCLC patients and causes patients to suffer a significantly higher disease burden, such a seizures, fatigue, speech problems and mobility issues vs patients with non-brain metastases[10,11]. As a result, NSCLC patients with brain metastases have a significantly higher economic burden compared to those patients without CNS metastases. Using osimertinib in the adjuvant setting will offset costs associated with progression to advanced disease stages (annual per-patient costs are higher in the advanced/metastatic setting)[12] including:[13,14] • Treatment related costs (including osimertinib in 1L metastatic setting) • Hospitalisation days • Emergency room visits • Home nursing • Hospice care	

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			As a result the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis. Therefore the Company's cost effectiveness analysis and ICERs may be conservative. **e) There is strong clinical rationale to suggest that osimertinib's unprecedented clinically meaningful and statistically significant DFS benefit will translate into OS** Collecting mature OS data in the adjuvant NSCLC setting from event driven trials is challenging due to the effectiveness of treatment (particularly with osimertinib), however, a numerical benefit was observed in the overall population for osimertinib vs placebo (in total, 9 patients in the osimertinib arm and 20 patients in the placebo arm had died (2.7% and 5.8%, respectively)[2,4]. Despite the OS data being less mature than expected due to the early unblinding, UK clinicians interviewed by the Company[15,16] and [redacted][17] stated and agreed that adjuvant osimertinib is undoubtedly expected to translate into long-term survival benefits. This was also confirmed by the clinical experts at the NICE appraisal committee meeting on 14th July 2021. This is based on the following evidence: • **The unprecedented magnitude of DFS benefit observed with osimertinib in ADAURA** – Osimertinib demonstrated an 80% reduction in the risk of recurrence or death vs. placebo across stages IB-IIIA of resected EGFRm NSCLC (HR 0.20, p<0.001; secondary endpoint). It is the first EGFR-TKI to demonstrate this magnitude of benefit in DFS (see Table 2). This unprecedented benefit was consistent across all patient subgroups[2]. • **The reduced rate of recurrence with distant/CNS metastases observed with osimertinib vs placebo** – Brain metastases are the most common type of recurrence in NSCLC, impose a heavy burden on patients quality of life, and mark a transition to incurable disease. Osimertinib had fewer local, regional and distant relapses than those who received placebo, with an **82% reduction in the risk of CNS disease recurrence or death.** Reducing CNS metastases is likely to reduce disease burden associated with distant recurrence and improve prognosis. Osimertinib is also the first EGFR-TKI in the adjuvant setting to demonstrate a significant improvement in CNS outcomes. The reduction in CNS metastases with adjuvant osimertinib is expected to provide an OS benefit. This further supports that osimertinib in the adjuvant setting is keeping patients in the curative intent setting (disease free) for longer. • **Osimertinib has demonstrated superior OS benefit vs first generation EGFR-TKIs in the faster progressing metastatic setting supported by a significant and sustained progression-free survival (PFS) extension and reduction in risk of CNS metastases vs EGFR-TKIs**	

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			– The metastatic setting is generally considered by clinicians as more difficult to treat and patients typically progress faster[18]. Despite this, osimertinib has already demonstrated a superior OS benefit vs first-generation TKIs (HR 0.80; 95.05% CI, 0.64–1.00, p=0.046)[19] supported by a significant and sustained extension in PFS and a significant reduction in the risk of CNS metastases[20,21]. – The ACD states that the committee was also aware of recent publications by Gyawali (2021) and Uprety (2021), which noted that other adjuvant tyrosine kinase inhibitors demonstrated DFS benefits that have not translated to an overall survival benefit. ○ The publications by Gyawali 2021[22] and Uprety 2021[23] are standalone editorial comment articles that are the opinion of one or two authors. The editorial articles are not robust, peer reviewed nor reflective of the clinical community across the UK. Comparing osimertinib to older generation EGFR-TKI data in the adjuvant setting is not appropriate as outlined throughout this document (Comment 2). Therefore, these two editorial articles are an inappropriate source to use to question the link between DFS and OS with osimertinib. ○ A recent independent, peer-reviewed publication initiated and performed by the FDA and Project Orbis partners provides an unbiased summary of the DFS benefits relating to EGFR-TKIs. This publication has received regulatory and government approval and would be more fit as a source for decision making over the editorials cited in the ACD[3]. **References** 1. AstraZeneca. Tagrisso Phase III ADAURA trial will be unblinded early after overwhelming efficacy in the adjuvant treatment of patients with EGFR-mutated lung cancer. *Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/tagrisso-phase-iii-adaura-trial-will-be-unblinded-early-after-overwhelming-efficacy-in-the-adjuvant-treatment-of-patients-with-egfr-mutated-lung-cancer.html [last accessed: 07/01/2021].* 2020. 2. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. *New England Journal of Medicine.* 2020;383(18):1711-1723. 3. Koch AL, Vellanki PJ, Drezner N, et al. FDA Approval Summary: Osimertinib for adjuvant treatment of surgically resected non-small cell lung cancer, a collaborative Project Orbis review. 2021:clincanres.1034.2021. 4. AstraZeneca. Clinical Study Report: A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA). *Data on file.* 2020. 5. AstraZeneca. Value of DFS. *Data on file.* 2021.	

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			6. Simard et al. Journal of Cancer Survivorship 4.4 (2010): 361-371. 7. Thewes et al. Supportive Care in Cancer 20.11 (2012): 2651-2659. 8. Cancer Council Australia Optimal care pathway for people with lung cancer (2020).; Assessed December 2020. 9. Lee et al. Journal of the Formosan Medical Association 119.6 (2020): 1101-1108. 10. Nadler E, Espirito JL, Pavilack M, Baidoo B, Fernandes A. Real-world disease burden and outcomes of brain metastases in EGFR mutation-positive non-small-cell lung cancer. *Future Oncology.* 2020;16(22):1575-1584. 11. Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung Cancer.* 2018;124:310-316. 12. Andreas S, Chouaid C, Danson S, et al. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: A retrospective observational study (LuCaBIS). *Lung Cancer.* 2018;124:298-309. 13. Fernandes et al. J Med Econ. 2017;20:1136-1147. 14. Chooback et al. J Oncol Pract 2018 Oct;14(10):e612-e620. 15. AstraZeneca. UK ADAURA key external expert interviews. *Data on file.* 2020. 16. AstraZeneca. Additional UK KEE insights. *Data on file.* 2021. 17. AstraZeneca. Global Delphi Panel. *Data on file.* 2021. 18. AstraZeneca Lung Cancer National Advisory B. Early Stage Resectable Non-Small Cell Lung Cancer Advisory Board (EGFR/IO). 22nd July 2020, virtual meeting. 2020. 19. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. New England Journal of Medicine. 2019;382(1):41-50. 20. AstraZeneca. Clinical study report, second interim data cut: a Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation-positive, Locally-advanced or Metastatic Non-small-cell Lung Cancer (FLAURA). Data on file. 2019. 21. AstraZeneca. Clinical study report: A Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation-positive, Locally-advanced or Metastatic Non-small-cell Lung Cancer (FLAURA). Data on file. 2017. 22. Gyawali B, West HJ. Lessons From ADAURA on adjuvant cancer drug trials: Evidence, ethics, and economics. J Clin Oncol 2021;39:175-7. 23. Uprety D. Osimertinib Should Not Yet Be Considered the Standard of Care for EGFR-Mutant NSCLC in the Adjuvant Setting. J Thorac Oncol. 2021;16(3):371-374.	

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>2</td><td>Consultee (company)</td><td>AstraZeneca</td><td>

<u>Uncertainty around how osimertinib, as a third generation EGFR-TKI, mode of action and clinical benefit differs from previous first and second generation EFGR TKIs</u>

a) Comparison to earlier EGFR-TKI data in the adjuvant setting is not appropriate. Osimertinib is a third generation, differentiated EGFR-TKI designed to provide targeted, irreversible inhibition of both EGFRm and EGFR T790M, with demonstrated CNS penetration

Alongside the shared feature of inhibiting EGFR with the most common TKI-sensitising mutations (exon 19 deletion and L858R), osimertinib differs from earlier EGFR-TKIs by:

Inhibiting EGFR T790M
Showing lower activity for wild-type EGFR[1,2]
Possessing lower activity for IR and IGFR
Good penetration of the blood brain barrier ($K_{puu,brain}$ 0.39)[3].

b) In comparison to other EGFR-TKIs, osimertinib has a higher blood brain barrier penetration resulting in a clinically meaningful reduction in the risk of CNS progression in early stage NSCLC vs placebo. In the adjuvant setting, osimertinib is the first EGFR-TKI to provide a significant DFS benefit vs placebo, across stages IB-IIIA EGFRm NSCLC[4]

ADAURA is the first global, randomised study of adjuvant EGFR-TKI prospectively designed and fully carried out in the completely resected EGFRm NSCLC patient population[4].
Other EGFR-TKIs are not indicated in the adjuvant setting[5] and their studies were single country, or single arm, without an appropriate genotype-specific population, or did not require negative surgical margins[6-10].
The magnitude of DFS benefit observed with osimertinib is unlike earlier generation EGFR-TKIs previously trialed in the adjuvant setting. A comparison of DFS observed with previous Phase III randomised controlled trials (RCTs) of first-generation EGFR-TKIs in the adjuvant setting is provided in Table 2.
Osimertinib has demonstrated superior OS benefit vs first generation EGFR-TKIs in the faster progressing metastatic setting (HR 0.80; 95.05% CI, 0.64–1.00, p=0.046)[11].

Table 2: DFS results in Phase III RCTs on adjuvant first-generation EGFR-TKIs in NSCLC

<table>
<tr><th>Study</th><th>NSCLC population</th><th>Treatment arms</th><th>DFS HR (95% CI)</th></tr>
<tr><td>ADAURA[4]</td><td>Completely resected stage IB-IIIA EGFRm*</td><td>Osimertinib following complete resection with or without chemotherapy vs placebo</td><td>0.20
[0.14, 0.30]</td></tr>
</table>

</td><td>Thank you for your comment.
At the second committee meeting the committee heard that the benefits of osimertinib, particularly around reducing CNS metastases, were greater than the earlier TKIs. However, the committee noted there is currently no evidence to show that after stopping treatment with osimertinib the hazards, and therefore the hazard ratios, for disease-free survival does not increase (as with the other TKIs). This is addressed in section 3.5 of the FAD.</td></tr>
</table>

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ADJUVANT/ CTONG 1104[12,13]	Resected stage II–IIIA EGFRm	Gefitinib vs vinorelbine plus cisplatin	**0.60** [0.42, 0.87]
RADIANT[8]	Resected stage IB–IIIA (EGFR-expressing/ amplified)	Erlotinib vs placebo	**0.61** [0.38, 0.98]

*with negative margins only

Abbreviations: CI, confidence interval; DFS, disease free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials; TKI, tyrosine kinase inhibitors. RRR, relative risk reduction

- Despite reported intracranial responses, first generation EGFR-TKIs are generally thought to have poor CNS penetration[3,14]. The unique ability of osimertinib to penetrate the intact blood brain barrier is a likely contributor to the substantially fewer CNS recurrences vs placebo[4]. A comparison of CNS recurrence observed with previous Phase III randomised controlled trials (RCTs) of first generation EGFR-TKIs in the adjuvant setting is provided in Table 3.

Table 3: Incidence of CNS recurrence in Phase III RCTs on adjuvant first-generation EGFR-TKIs in NSCLC

Study	NSCLC population	Treatment arms	Incidence of CNS recurrence %
ADAURA[5]	Resected stage IB-IIIA EGFRm	Osimertinib following complete resection with or without chemotherapy vs placebo	1% osimertinib vs 10% placebo
ADJUVANT/ CTONG 1104[12,13]	Resected stage II–IIIA EGFRm	Gefitinib vs vinorelbine plus cisplatin	27.4% gefitinib vs 24.1% vinorelbine plus cisplatin
RADIANT[8]	Resected stage IB–IIIA (EGFR-expressing/ amplified)	Erlotinib vs placebo	40.0% erlotinib vs 12.9% placebo

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RRR, relative risk reduction; TKI, tyrosine kinase inhibitor.

- In other adjuvant EGFR-TKI studies, the duration of therapy was up to 2 years[8,9]. The maximum treatment duration in ADAURA is 3 years based on the following considerations:
  - The highest rate of recurrence is seen within the first 2-3 years after complete tumour resection[4].

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			– Osimertinib has demonstrated a favourable safety profile with adverse events of grade 3 or higher being reported in fewer patients than in the standard EGFR-TKI group[4,11,15]. **References** 1. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer discovery. 2014;4(9):1046-1061. 2. FDA TAGRISSO™ PI 2020. 3. Ballard P, Yates JW, Yang Z, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. Clin Cancer Res. 2016;22(20):5130-5140 4. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. *New England Journal of Medicine.* 2020;383(18):1711-1723. 5. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw. 2021;19(3):254-266. 6. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol. 2018;19(1):139-148. 7. Wu Y-L, Zhong W, Wang Q, et al. CTONG1104: Adjuvant gefitinib versus chemotherapy for resected N1-N2 NSCLC with EGFR mutation—Final overall survival analysis of the randomized phase III trial 1 analysis of the randomized phase III trial. Journal of Clinical Oncology. 2020;38(15_suppl):9005-9005. 8. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. 2015;33(34):4007-4014. 9. Pennell NA, Neal JW, Chaft JE, et al. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. J Clin Oncol. 2019;37(2):97-104. 10. Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med. 2018;6(11):863-873. 11. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine.* 2019;382(1):41-50. 12. Suda K. For a better adjuvant strategy for resected lung cancer-lessons from treatment failure patterns of the ADJUVANT trial (CTONG 1104). Transl Lung Cancer Res. 2019;8(Suppl 4):S395-s399. 13. Xu ST, Xi JJ, Zhong WZ, et al. The Unique Spatial-Temporal Treatment Failure Patterns of Adjuvant Gefitinib Therapy: A Post Hoc Analysis of the ADJUVANT Trial (CTONG 1104). J Thorac Oncol. 2019;14(3):503-512.	

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			14. Heon S, Yeap BY, Lindeman NI, et al. The Impact of Initial Gefitinib or Erlotinib versus Chemotherapy on Central Nervous System Progression in Advanced Non–Small Cell Lung Cancer with EGFRMutations. 2012;18(16):4406-4414. 15. Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;378(2):113-125.	
3	Consultee (company)	AstraZeneca	**<u>Uncertainty about the company's OS predictions- Modelling survival</u>** **a) The Company disagree with the committees' conclusion that the company's choice of extrapolations was driven by the company's cure assumption rather than the goodness of fit** • The Company followed standard, well established approaches to determine the most appropriate extrapolations which is in no way influenced by the cure assumption consideration. • Alongside visual inspection, the goodness of fit was also evaluated based on the mean squared error (MSE) of the predicted model vs the Kaplan-Meier (KM). Therefore, the resultant model was selected based upon a visual inspection of the combined DF and OS curves, that achieved a good fit to the observed KM data (evaluated by the MSE diagnostic test) and were deemed clinically plausible, as evaluated by an independent UK advisory board. To achieve a clinically realistic and good fit of the data to the combined DF and OS curves, survival curves applied for individual transitions were assessed primarily visually (as recommended by Williams et al, 2017)[1] for clinical plausibility. However, where several curves were deemed viable in terms of clinical plausibility and visual fit to the data, statistical fit (using fit based on Akaike Information Criterion [AIC]/Bayesian Information Criterion [BIC] values and MSE) was also taken into account for the purpose of curve selection. **b) The cure assumption is an independent function and separate from the extrapolated curves** • The cure assumption is an independent function within the economic model. The model includes the functionality to vary the time point considered for cure, and the proportion of patients who achieve it. After the defined cure timepoint, survival for the proportion of patients who are assumed to be cured is adjusted to follow that of the age and sex matched general population. • The cure function is independent from the extrapolation survival curves. Survival curves were selected based upon clinically plausibility, visual fit and goodness of fit statistics. Following selection of appropriate survival, the cure function within the model adjusted the survival of patients (as predicted by the selected curve) to assume that a proportion of patients will be cured at defined time point. The choice of curve therefore is not impacted by the cure assumption.	Thank you for your comment. The committee noted that, for the transition from disease free to distant metastases, the generalised gamma chosen by the company had the best statistical fit for the placebo arm. However, the log-normal had the best fit for the osimertinib arm. The ERG explained that because of the cure assumption, the choice of extrapolation has little effect beyond the cure timepoint. So in this situation it is appropriate to give more weight to the statistical fit to the observed data. At the second meeting, the committee also considered the company's comments on the ERG's additional sensitivity analysis (ASA4a and ASA4b). The ERG explained that, when the cure assumption is factored in, the DFS curves do not cross. This is detailed in Section 3.8 of the FAD. The committee considered that the log-normal

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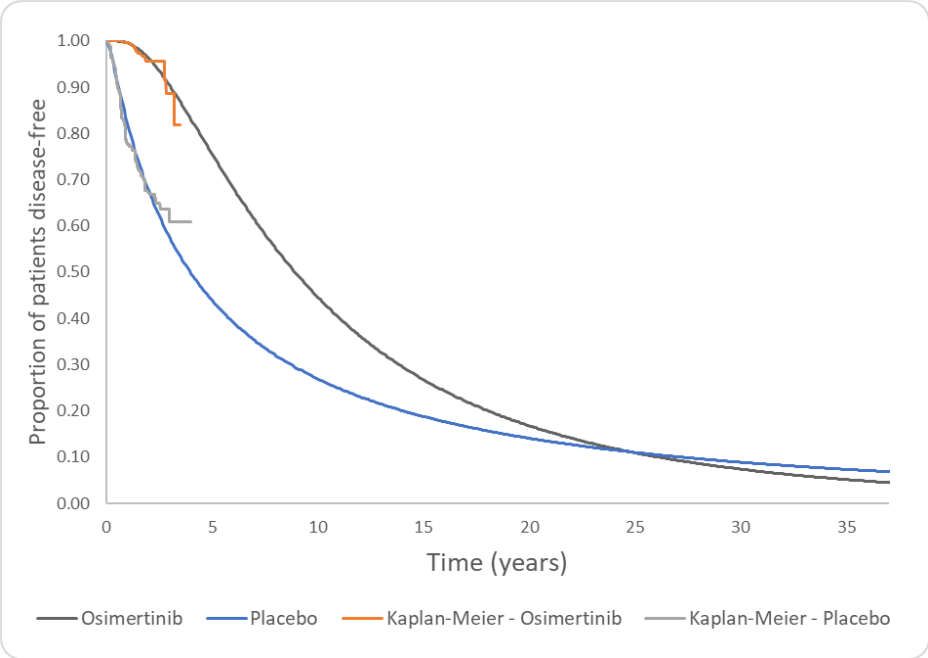
			• In order to alleviate concerns surrounding the cure assumption, the Company have provided a number of scenarios exploring the impact of changing the cure year and assuming no cure across treatment arms. **c) The Company disagree that the survival predictions may be optimistic** Although published data on longer-term survival outcomes in this setting are limited – particularly in stage IB–IIIA EGFRm-positive NSCLC – several studies were identified in patients with completely resected stage IB–IIIA NSCLC. These studies indicate that the underlying risk of disease recurrence in the earlier follow-up period (noted as before 36–48 months) is not representative of the risk of recurrence at later time periods. Generally, patients who are disease-free following complete tumour resection appear to be exposed to a far higher risk of recurrence early in the follow-up period, with the risk of recurrence decreasing over time. It is important to note that the extrapolation of DF data from the ADAURA trial to derive the transition probabilities applied in the cost-effectiveness model are based on a period (up to 48 months) that appears to correspond with an increased risk of recurrence rate. Therefore, it is reasonable to assume that the extrapolated disease recurrence is being overestimated and the Company are being conservative. **d) The Company agree that alternative parametric distributions can be used to assess the range of uncertainty. It is necessary, however, that alternative parametric distributions selected produce clinically plausible long-term estimates that are aligned with expert clinical opinion** **The ERG's ASA4a and 4b are clinically implausible.** Both of the additional sensitivity analyses produce non credible and overly pessimistic estimates of adjuvant osimertinib's long-term survival that are in direct contradiction with data from the ADAURA clinical trial and expert clinical opinion. Neither of these scenarios were discussed at the open part of the Committee Meeting and therefore no clinical expert opinion was sought on their clinical plausibility during the meeting. Clinical experts consulted by the Company stated that both of these additional sensitivity analyses were not considered clinically plausible and had no logical scientific explanation as they assume that the risk of transition from DF to DM1 is greater in the osimertinib arm and the curves for osimertinib and placebo cross (at approximately 22 years for ASA4a and at approximately 11 years for ASA4b)[2]. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which is not clinically plausible. The clinical experts stated that given that osimertinib is a three year treatment option there is no conceivable scientific or biological rationale to explain why a patient would	distribution was as plausible as the generalised gamma. Usually it is appropriate to use the same distribution for both arms. However, given the cure assumption and stopping of treatment with osimertinib, the committee considered that it was possible that there might be a different profile of hazards between the two arms. The committee concluded that other approaches to modelling overall survival may be plausible and it would consider these in its decision making. Section 3.8 of the FAD has been updated.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			suddenly recur 10 or 25 years after stopping osimertinib treatment. If a patient is to recur following adjuvant osimertinib, it would be soon after stopping treatment and most certainly within 2 years[2,3]. • **ASA4a - the log-normal model, when applied to both treatment arms, produces more pessimistic long-term estimates (Figure 1)** – The estimates of mean and median OS and DFS produced when the log-normal model is selected for transition probability (TP) 2 have not been validated by clinicians. – Clinicians validated that the base case (TP2: generalised gamma) aggregated OS and DFS, with cure at Year 5 for both arms, produced the most clinically plausible long-term survival estimates for osimertinib and the comparator arm. – When the log-normal model is selected for TP2 in both arms, the curves for osimertinib and placebo cross at approximately 22 years into the model time horizon. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which is clinically implausible based on the observed benefit of osimertinib in ADAURA trial and osimertinib efficacy profile in the metastatic setting. – The assumption that the risk of transition from DF to DM1 is eventually greater in the osimertinib arm directly undermines data from the ADAURA trial (assumes a HR that shows DFS progression is lower in the osimertinib arm).	

Figure 1: Extrapolations for DF to DM1 (TP2) – both arms: log-normal



Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability

- The pattern of disease recurrence produced in this analysis directly contradicts the overwhelming efficacy exhibited by adjuvant osimertinib in the ADAURA trial.
  - The primary analysis demonstrated that patients in the osimertinib arm had fewer locoregional and distant recurrences than placebo. When recurrence did occur, this was more frequently at locoregional sites in the osimertinib group, and by contrast, more frequently distant metastases in the placebo group.
  - Furthermore, clinical feedback received from UK clinicians provides further support to the expected long-term survival benefit of osimertinib in this setting as loco-regional recurrence may offer clinicians another opportunity to effectively 'cure' a patient.
- Therefore this scenario should not be used to inform decision making. However, if the committee firmly believes that the log-normal should be selected for TP2, the hazards for this transition should be amended so that after ~22 years, the risk of recurrence for both arms is set to be equal. Although this is a more plausible scenario than that presented by

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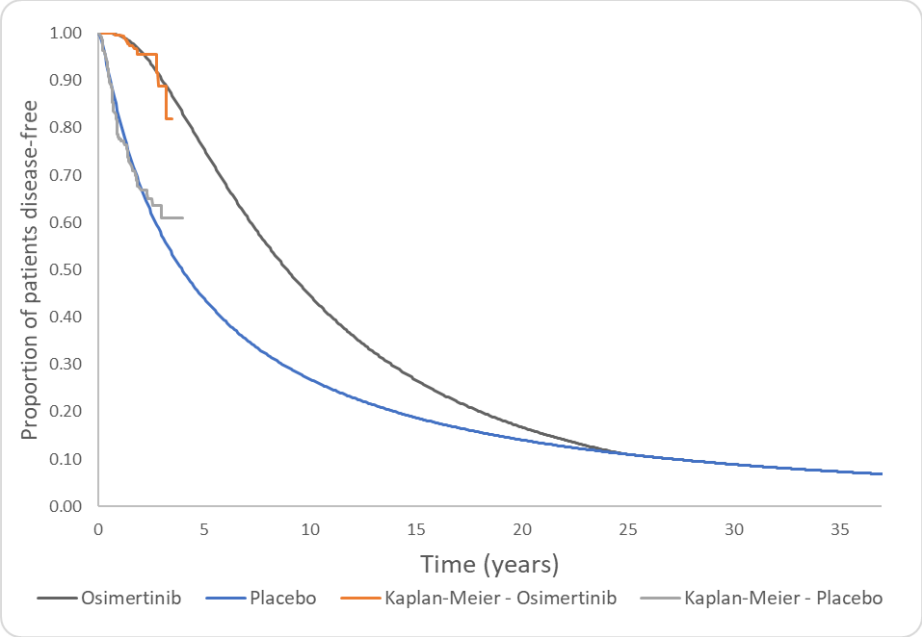
the ERG the weight of evidence and clinical opinion suggests this remains highly conservative (Table 4).

Figure 2: Extrapolations for DF to DM1 (TP2) – both arms: log-normal, adjusted hazards



Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability

Table 4: ASA4a (adapted to prevent curves crossing) - scenario analysis results

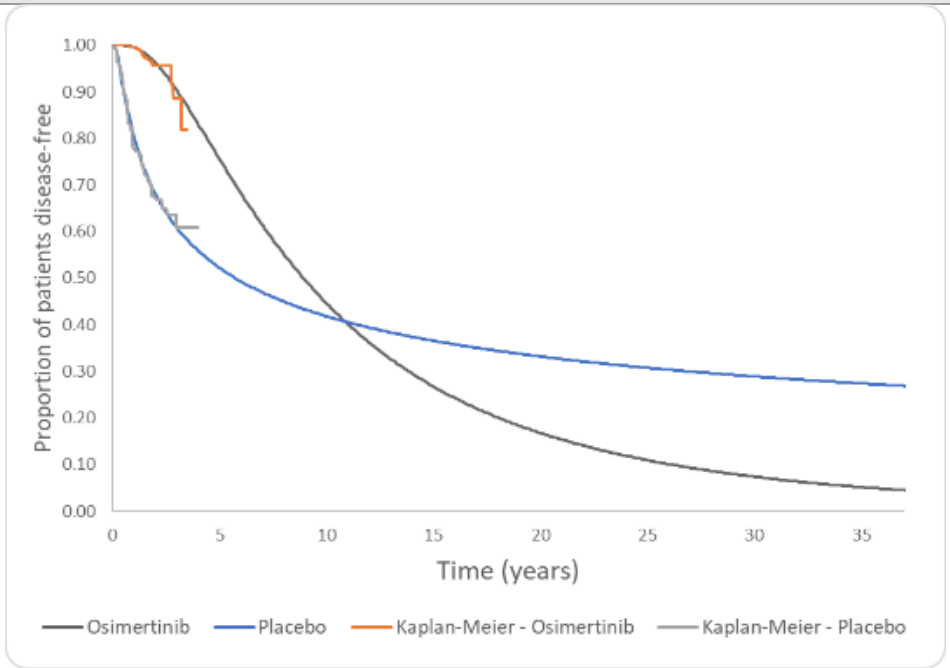
Scenario	ICER (deterministic)			
	Optimistic: 5-year cure	Pessimistic: 8-year cure in osimertinib	Pessimistic: 8-year cure in both arms	No cure

	arm, 5-year cure in placebo arm		
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
Adapted ASA4a: Use log-normal for TP2 (DF to DM1) in both arms but adjust so lines don't cross	£9,326	£25,544	£13,046	£23,012

Abbreviations: ASA, additional sensitivity analyses; DF, disease free; DM, distant metastases; ERG, Evidence Review Group; TP, transition probability

- **ASA4b: This analysis is clinically implausible as it assumes that patients progress faster following treatment with osimertinib than receiving placebo**
  - The NICE Decision Support Unit (DSU) technical support document (TSD) 14 states that the same parametric function should be used across both treatment arms where feasible, as this ensures consistency and limits potential problems such as the extrapolated curves crossing over one another[4]. Fitting different types of parametric model (for example generalised gamma for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification and that fitting the same distribution is likely to be "most sensible"[4].
  - However no substantial justification has been provided as to why different models have been selected in this scenario. The following statement on Page 112 *"In the current context where a new drug has a marked effect on disease relapse compared to standard of care, it is likely that the hazards may take quite different forms in the two treatment arms and this possibility should be investigated"* lacks clinical rationale. Osimertinib is expected to significantly reduce long-term disease recurrence, however there is no clinical evidence to suggest that the hazards of the two arms will take quite different forms.
  - When the log-normal model is selected for only osimertinib in TP2, the curves produced are highly clinically implausible. In this scenario the osimertinib and placebo curves cross at approximately 11 years into the model time horizon. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm. This is even more pessimistic than the analysis presented in ASA4a and once again contradicts the pattern of disease recurrence observed with adjuvant osimertinib in the ADAURA trial. As previously discussed, disease recurrence in the osimertinib arm was more frequently at locoregional sites, and by contrast, more frequently distant metastases in the placebo group.

Figure 3: Extrapolations for DF to DM1 (TP2) – osimertinib: log-normal, placebo: generalised gamma

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability Scenario ASA4b results in clinically implausible modelled survival outcomes. It predicts that up to approximately 11 years, treatment with osimertinib results in a reduced risk of progression to the DM1 health state compared to standard of care (SoC). However, from 11 years onwards the risk of progression is modelled to dramatically reverse such that a patient who has remained progress-free up to 11 years following treatment with osimertinib would have a higher risk of transitioning in the DM1 health state compared to a patients in the SoC arm, with the risk of transition plateauing out in the SoC arm. This strongly contradicts the clinical evidence from ADAURA and the feedback obtained from clinical experts. **As such this scenario is clinically implausible, lacks credibility and therefore is in no way appropriate to inform decision making.** **References** 1. Williams C, Lewsey JD, Mackay DF, Briggs AH. Estimation of Survival Probabilities for Use in Cost-effectiveness Analyses: A Comparison of a Multi-state Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling. Med Decis Making. 2017;37(4):427-439. 2. AstraZeneca. Additional UK KEE insights. Data on file. 2021.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			3. AstraZeneca. UK ADAURA key external expert interviews. Data on file. 2020. 4. National Institute for Health and Care Excellence. NICE DSU Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data. *Available at: http://nicedsu.org.uk/technical-support-documents/technical-support-documents/ [Accessed: January 2021].* 2013.	
4	Consultee (company)	AstraZeneca	**Uncertainty about the Company's cure assumptions and timing of cure** **a) A significant proportion of patients already achieve a functional "cure" with current standard of care** • Clinical evidence validates the curative potential of treatment for resected EGFRm NSCLC. As described in the Company submission, clinical trial evidence in patients with resected NSCLC receiving placebo demonstrates a plateauing effect in DFS at approximately 48-60 months following surgical resection, indicating that the majority of patients are no longer at risk of disease recurrence, and thus providing support for the assumption of functional cure in this patient population. **b) The 5-year functional cure in both arms is supported by published clinical evidence and expert clinical opinion** • The model is largely based on data from the primary analysis of the ADAURA trial, therefore extrapolations of survival outcomes were necessary. However, when the extrapolated OS and DFS curves (aggregated from the multi-state model) were presented to clinical experts,[1] they found the long-term estimates were extremely pessimistic for this patient population compared to the outcomes observed in clinical practice, stating them to be more reflective of outcomes in the metastatic setting. • In addition, the clinicians felt the extrapolations were unrealistic given the unprecedented efficacy of osimertinib demonstrated in the ADAURA trial and the expectation of a functional cure after 5 years DFS[1]. To reflect the clinicians' expected clinical outcomes using trial data, parametric distributions were selected and a 5-year cure timepoint was applied, taking into account their expectation of a plateau towards the 5-year mark (disease-free patients are typically discharged and not followed by clinicians after 5 years, and therefore are considered to be functionally cured). – The 5-year cure assumption as confirmed by 13 key clinical experts in a recent [redacted][2]. This was further validated through discussions with UK clinical experts that agreed with the Global Panel outputs[3] - [redacted]	Thank you for your comments. The committee considered these comments during the second meeting. The committee noted that there was significant uncertainty about the company's cure assumptions. The committee concluded that due to this uncertainty, it considered both of the ERG's approaches in its decision making. The committee also noted that more formal statistical modelling of cure may address some uncertainty. Section 3.6 and section 3.9 of the FAD have been updated to reflect these considerations.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			– UK clinicians agreed that patients who are disease-free at 5 years would have a very low risk of recurrence, their survival would be similar to that of the general population and these patients are considered functionally cured[1,3]. **c) The ERG preferred pessimistic scenario (cure at 8 years for the osimertinib arm vs 5 years for placebo) is overly pessimistic and clinical experts agreed that timing of the cure assumption should be consistent across arms, regardless of timepoint** • Clinical experts consulted by the Company felt that, regardless of the timepoint being used, the cure assumption should be applied at the same timepoint for both arms as **there was no rationale for why cure on the osimertinib arm would be later than placebo**.[18] Even if we were to assume that osimertinib delays rather than prevents recurrence then there is no reason to suggest that patients would recur faster on osimertinib than placebo, particularly when clinical trial and real-world evidence supports that there is a plateauing effect in DFS at approximately 48–60 months following surgical resection. For this reason, the Company have provided an alternative pessimistic and conservative scenario which assumes cure being applied at 8 years in both arms (please see Table 5 below for associated ICERs). **d) Without the structural cure assumption, osimertinib remains a cost-effective use of NHSE resources** • Despite the overwhelming efficacy of osimertinib observed in the ADAURA trial, the Company recognise there is uncertainty regarding the long-term outcomes of patients treated with adjuvant osimertinib due to the immaturity of the data in ADAURA. • To further evaluate the clinical uncertainty, we have also presented a scenario analysis in which the structural cure assumption is removed altogether. Although this scenario is deemed clinically unrealistic (as the extrapolated ADAURA DFS curves likely overestimate the long-term rate of disease recurrence and are therefore overly pessimistic for an early-stage resected population) we have provided this scenario to demonstrate that even in the extreme case of an absence of a cure assumption, osimertinib remains a cost-effective use of NHSE resources with an incremental cost-effectiveness ratio of £17,219 versus placebo (Table 5). Removing the cure assumption does not interfere with the model extrapolations as it is an independent function that can be switched on and off. **Table 5: Scenario analyses on model cure assumption** **Scenario** | **ICER (deterministic)**	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
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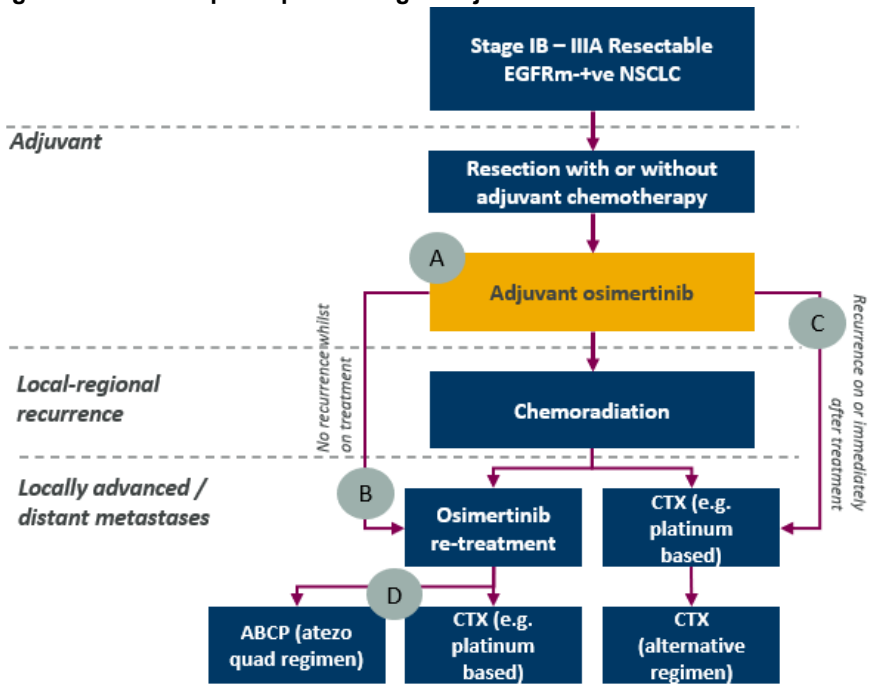
<tr><th></th><th>Optimistic: 5-year cure</th><th>Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm</th><th>Pessimistic: 8-year cure in both arms</th><th>No cure</th></tr>
<tr><td>ERG preferred analysis</td><td>£9,979</td><td>£20,417</td><td>£11,557</td><td>£17,219</td></tr>
</table>
Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio

References
1. AstraZeneca. UK ADAURA key external expert interviews. Data on file. 2020.
2. AstraZeneca. Global Delphi Panel. Data on file. 2021.
3. AstraZeneca. Additional UK KEE insights. Data on file. 2021.
</td><td></td></tr>
<tr><td>5</td><td>Consultee (company)</td><td>AstraZeneca</td><td><u>Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib)</u>

The Company agree that there is some uncertainty associated with later treatments with or without adjuvant osimertinib and as a result have further engaged with clinical experts to inform the assumptions used in the economic modelling</td><td>Thank you for your comments
The committee considered these comments during the second meeting.
For the percentage of people in the active monitoring arm that have treatment with osimertinib for metastatic disease, the committee concluded that it was appropriate to base its decision making on the latest available prescribing data. Therefore, 80% was appropriate to use in the analyses. This is detailed in Section 3.10 of the FAD.

The committee noted that the proportion of people having retreatment with osimertinib remained uncertain. The committee concluded that retreatment with osimertinib would be offered to some people whose disease had progressed after having osimertinib as an adjuvant</td></tr>
</table>

Figure 4: The anticipated positioning of adjuvant osimertinib in the current treatment pathway



A: In the absence of adjuvant osimertinib (placebo arm). B: Patients that recur within 2 years of completing 3 years of adjuvant osimertinib - osimertinib re-treatment. C: Patients that recur whilst on adjuvant osimertinib. D:Patients that progress to 2L mNSCLC following treatment with osimertinib.
Abbreviations: ABCP, atezolizumab plus bevacizumab, carboplatin and paclitaxel; CTX, chemotherapy; EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer.

a) In the absence of adjuvant osimertinib (placebo arm):

- Osimertinib is considered the mainstay treatment option and represents the current standard of care in 1L EGFRm NSCLC. All clinicians (n=20) consulted agreed that osimertinib is a more potent, efficacious and the best tolerated EGFR-TKI vs other TKIs and therefore unless there is a clear reason not to, they would prescribe osimertinib **to all newly diagnosed patients** (100% of patients) with metastatic EGFR NSCLC[1].

treatment. This is detailed in Section 3.3 of the FAD.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
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– Clinicians unanimously agreed that if a patient is not fit for osimertinib then they would not be fit for any other EGFR-TKI therefore osimertinib in the first line metastatic setting is the treatment of choice.

• Osimertinib was routinely recommended as a treatment option for use in the first line metastatic setting in October 2020 and since then its market share has risen sharply. The 64% assumption is based on complete market share data which includes patients who started on first and second generation EGFR-TKIs prior to osimertinib becoming established standard of care. It is therefore imperative to use the market share assumption relating to the newly diagnosed patients and not the entire cohort of patients.
• [redacted]Therefore focusing on only newly diagnosed patients would per definition lead to a market share between 80% and 100%.
• The Company therefore conducted two exploratory analyses that conservatively assume 80% and 90% of patients in the active monitoring arm receive treatment with osimertinib in DM1 (Table 6). The remaining proportion of patients in DM1 are assumed to receive other EGFR-TKIs (erlotinib, gefitinib, afatinib or dacomitinib) and relative proportions were informed by the IQVIA national prescribing data provided in the clarification question responses.
• In both exploratory analyses osimertinib remains a cost-effective use of resources for all cure assumption scenarios (optimistic and pessimistic, Table 6).

Table 6. Company’s revised ASA3 – scenario analysis results
<table>
<tr><th rowspan="2">Scenario</th><th colspan="4">ICER (deterministic)</th></tr>
<tr><th>Optimistic: 5-year cure</th><th>Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm</th><th>Pessimistic: 8-year cure in both arms</th><th>No cure</th></tr>
<tr><td>ERG preferred analysis</td><td>£9,979</td><td>£20,417</td><td>£11,557</td><td>£17,219</td></tr>
<tr><td>ASA3a: Different mix of TKIs (80% osimertinib market share in 1L mNSCLC)</td><td>£16,846</td><td>£29,970</td><td>£20,267</td><td>£28,626</td></tr>
</table>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

ASA3a: Different mix of TKIs (90% osimertinib market share in 1L mNSCLC)	£13,706	£25,631	£16,296	£23,454

Abbreviations: ASA, additional sensitivity analyses; ERG, Evidence Review Group; mNSCLC, metastatic non-small cell lung cancer; TKI, Tyrosine kinase inhibitors

b) Following successful treatment of adjuvant osimertinib (Figure 4):

- **Patients that recur within 2 years of completing 3 years of adjuvant osimertinib - osimertinib re-treatment**
  - The impact of introducing osimertinib in resected stage IB-IIIA EGFRm NSCLC on subsequent treatments (i.e. the rest of the treatment pathway) is unknown as the use of osimertinib in the adjuvant setting represents a step change in clinical practice.
  - UK clinicians consulted in interviews agreed that they would consider re-treatment with osimertinib for patients who successfully completed 3 years of adjuvant treatment with osimertinib and who did not relapse within a year of treatment completion. Clinical experts advised that re-treatment with other EGFR-TKIs would not be considered as these are generally considered to be less potent and less efficacious versus osimertinib.
  - As noted in the Committee meeting slides, the clinical experts stated that “Patients who progress after treatment with osimertinib, should be treated like other patients newly presenting with metastatic disease and would be offered osimertinib if they meet the criteria. It would be unethical not to offer rechallenge of osimertinib to these patients.”
  - It is not possible to accurately predict what proportion of patients will be prescribed osimertinib for metastatic NSCLC following successful adjuvant treatment in future clinical practice. Therefore, a conservative approach was applied in the model where 50% patients in the DM1 state were retreated at 5 years, and 50% were not. The Company has also provided a sensitivity analysis exploring differing levels of osimertinib re-treatment in the metastatic NSCLC setting (40% and 60%) and in all scenarios osimertinib remains a cost-effective use of resources (Table 7).

Table 7: Retreatment with osimertinib - scenario analyses results

Scenario	ICER (deterministic)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	Optimistic: 5-year cure	Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm	Pessimistic: 8-year cure in both arms	No cure
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
40% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,644	£22,491	£13,480	£20,977
50% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,808	£22,989	£13,945	£21,854
60% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,972	£23,478	£14,404	£22,709

Abbreviations: ICER, incremental cost-effectiveness ratio; ERG, Evidence Review Group

c) Patients that recur whilst on adjuvant osimertinib (Figure 4):

- For patients that recur whilst on treatment with adjuvant osimertinib, The Company has assumed that 100% of patients would be treated with pemetrexed and cisplatin as per the current treatment paradigm.

d) Patients that progress to 2L mNSCLC following treatment with osimertinib (Figure 4):

- Whilst atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) is recommended as an option for patients with EGFRm-positive NSCLC who have previously received targeted treatment, clinical advisors to the Company stated that the relative proportion of patients receiving treatment with this regimen is small.
- Clinicians advised that the 4-drug regimen is associated with considerable toxicities and contraindications, resulting in intensive monitoring requirements. In general, clinical advisors stated that a relatively low number of patients are likely to be fit enough to tolerate treatment with the 4-drug regimen, and therefore it does not represent the mainstay treatment in the 2L metastatic NSCLC (mNSCLC) disease setting.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• In addition, IQVIA prescribing data reported that just 16% of patients received the 4-drug regimen for the 2L treatment of EGFRm-positive mNSCLC in Q4 2020. • The limitations of this regimen are also noted in the NICE final appraisal determination (FAD) document for TA584, within which the patient expert highlighted the importance of careful selection of people who would be offered atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice. In addition, the CDF lead stated that this regimen should only be considered appropriate for patients with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 because of the intensive dosing regimen as atezolizumab and bevacizumab were being added to chemotherapy and the dose of carboplatin would be higher than typically used in clinical practice. As a result, it was concluded that the number of EGFRm-positive patients requiring treatment for 2L mNSCLC with an ECOG performance status of 0 or 1 and considered well enough to tolerate the 4-drug regimen would be considered small. • For patients that progress in the mNSCLC setting we have assumed that a proportion of patients would receive the 4-drug regimen in line with current standard of care. • It would be inappropriate to include ABCP as a treatment option in 1L mNSCLC for patients completing adjuvant osimertinib as this is currently only reimbursed in the 2L EGFRm population. **References** 1. AstraZeneca. UK ADAURA key external expert interviews. Data on file. 2020.	
6	Consultee (company)	AstraZeneca	**<u>Innovation status</u>** **The Company disagrees with the committee's conclusion that all additional benefits associated with osimertinib have been captured in the economic analysis and as a result it can be assumed that the cost-effectiveness analyses undertaken are highly conservative** • Fear of cancer recurrence is cited as one of the most distressing concerns for resectable NSCLC patients, making the extension of living cancer-free a primary goal. Many cancer survivors experience emotional and psychological issues (including distress, anxiety, depression, cognitive changes, and fear of cancer recurrence) at the end of treatment. • Adjuvant osimertinib will transform the EGFRm NSCLC patient journey by delaying/preventing recurrence and keeping patients in the curative intent setting for longer. As a result, the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis.	Thank you for your comments. The committee considered your comments during the second meeting. It recognised osimertinib as an innovative therapy in the adjuvant setting but concluded that it did not consider there were any additional benefits associated that had not been captured in the economic analysis. See Section 3.15 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• The economic model only captures the downstream costs associated with drug treatment and not the additional indirect costs associated with the impact of recurrence/metastases– including CNS recurrence which have been to incur significant economic burden compared to patients without CNS metastases due to higher monitoring costs and resources, increased number of hospitalisation days/emergency room visits and increased home nursing/hospice care requirements. • CNS metastases are also associated with vast decrements in health-related quality of life. Health economic analyses in previous NICE appraisals in NSCLC have explicitly accounted for the impact of CNS metastases on health-related quality of life. In NICE TA536, the economic model included a separate health state for patients who progressed with CNS metastases. Patients in this health state were assumed to have a significantly lowered quality of life (0.52) compared to patients who had non-CNS disease progression. The CNS progression health state was not incorporated in this appraisal due to data limitations, however, as osimertinib is associated with a significant reduction in CNS metastases it is highly likely utility benefits of treatment have not been captured. • There are several other benefits of osimertinib in the proposed setting that could not be adequately captured in the economic analysis, including the impact of living disease-free on the patient's social life, ability to work, mental health and emotional well-being and the positive impact for family members and carers. • As numerous benefits associated with osimertinib in the adjuvant setting have not been accounted for in the health economic analysis, it can be assumed that the cost-effectiveness results produced are highly conservative.	
7	Consultee	AstraZeneca	**Appropriateness of CDF** **The Company believe that NICE is in a position to make a positive recommendation for routine commissioning at this time and do not believe that reimbursement via the CDF is the most appropriate route for access for the following reasons:** • **Osimertinib has been demonstrated to be cost effective at the PAS price** – All the clinically plausible ICER scenarios presented in our Company Submission and the ERG Report, are below the NICE willingness to pay threshold. – The scenarios being proposed (ASA4a/b) by NICE were not discussed in open part of the Committee meeting and both of these scenarios were considered 'very pessimistic' by the ERG in their report. Additionally, these scenarios were considered clinically implausible by clinical experts as they assume that adjuvant osimertinib performs worse than placebo which is not consistent with the DFS and CNS recurrence presented in the ADAURA data[1].	Thank you for your comments. The committee considered your comments during the second meeting. The committee was aware that, although a period of time in the Cancer Drugs Fund may not produce enough mature overall survival data for a robust mixture-cure model, there would still be benefits such as producing more mature disease-free survival, a better understanding of the effect of the 3-year stopping rule and more data will be

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			– Additional ICER scenarios including a no-cure analysis are within the NICE willingness to pay thresholds (Table 5). • **Further data collection in the CDF would not serve to reduce uncertainty in a reasonable time frame** – While the ADAURA primary analysis data is less mature than anticipated, the majority (63%) of the DFS events expected in the planned final analysis in patients with II-IIIA had already occurred. This suggests that the DFS benefit in osimertinib arm will not significantly change with more mature data and is expected to be maintained. – The only remaining efficacy analyses for the study are an exploratory analysis of DFS in the primary efficacy population (patients with Stage II–IIIA disease) when the number of prespecified DFS events (247) are observed and the analysis of OS when the pre-specified 94 deaths have occurred. – As noted by the Project Orbis team, "it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFRm NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS"[2]. – The committee has acknowledged that it won't be possible to collect OS data in the CDF. The ADAURA OS data is event driven and in [redacted]. Once all the clinically implausible scenarios have been removed from analyses, the Company firmly believe that osimertinib remains a cost effective use of NHS resources under all scenarios, despite any residual uncertainty. As a result, the Company feels that the CDF should only be considered if the Committee still perceive there to be substantial, justifiable and clinically plausible uncertainties that would result in ICERs above acceptable cost effective thresholds. **References** 1. AstraZeneca. Additional UK KEE insights. *Data on file*. 2021. 2. Koch AL, Vellanki PJ, Drezner N, et al. FDA Approval Summary: Osimertinib for adjuvant treatment of surgically resected non-small cell lung cancer, a collaborative Project Orbis review. 2021:clincanres.1034.2021	available to estimate the extent of the cure proportion. Section 3.14 has been updated to reflect these considerations.
8	Clinical expert		I am concerned that this recommendation may imply that there is not clearly significant enough clinical benefit from the technology. This clear significant clinical benefit is outlined in the document and in my prior evidence	Thank you for your comment. At the second

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			(written and verbal) and that of others. Reliance on future overall survival outcomes will be hampered by (a) the early unblinding of the trial owing to overwhelming efficacy seen; and (b) timescales. Although I agree that there is uncertainty regarding overall survival prolongation extent, it seems very unlikely that DFS outcomes will change significantly with further follow up in the first three years for patients receiving the technology. I would argue that DFS, alongside the very important CNS DFS, are in themselves the clinically meaningful and patient-centric endpoints on which to focus. Given the caveats above regarding overall survival given unblinding, it seems that there is overreliance on overall survival in the ACD. Further, this is not the same technology as previous generation TKIs in similar populations, and it seems to me to be unfair to make this comparison (as I have also brought up verbally in the committee meeting).	committee meeting the committee noted the importance of DFS, however, there is currently no evidence to show that after stopping treatment with osimertinib the hazards, and therefore the hazard ratios, for disease-free survival does not increase (as with the other TKIs). Therefore, the committee reiterated its concern over the immaturity of the disease-free survival and overall survival data as well as the uncertainty regarding the extent to which disease-free survival can accurately predict overall survival, as detailed in Section 3.5 of the FAD.
9	Clinical expert		It seems important to me in modelling that patients receiving the technology versus those observed should be subjected to the same outcome measures and timings – i.e. that cure or progression assumptions are dealt with in the same manner from the outset for both groups.	Thank you for your comment. This point was discussed at the second committee meeting. The committee noted that there was significant uncertainty about the company's cure assumptions. The committee also noted that more formal statistical modelling of cure may address some uncertainty. Section 3.6 and section 3.9 of the FAD have been updated to reflect these considerations.
10	Clinical expert		The emphasis on cure seems to underestimate the significant clinical impact of delaying progression. While it is clear that there is significant uncertainty about the proportion of patients cured by the technology, there is no doubt to me that there will a significant survival impact from either cure or delaying progression. To me, a most	Thank you for your comment. At the second committee meeting the committee recognised that

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			conservative scenario that delays progression only in this disease with very high metastatic propensity still would result in substantial clinical efficacy. It seems implausible that treating these patients earlier, many of whom simply have subclinical stage IV disease, will not have very significant overall survival benefits.	osimertinib may delay rather than prevent recurrence. This discussion is detailed in Section 3.5 Taking into account that there were no data on people who have stopped osimertinib treatment, and the evidence from other tyrosine kinase inhibitors used as adjuvant treatment the committee considered that the ERG's optimistic and pessimistic analyses may be plausible.
11	Clinical expert		Some of the ERG modelling referred to (e.g. log normal where lines cross) appears clinically implausible to me (i.e. that patients receiving the technology do worse in the long term).	Thank you for your comment. At the second meeting, the committee considered the ERG's additional sensitivity analysis (ASA4a and ASA4b). The ERG explained that, when the cure assumption is factored in, the DFS curves do not cross. This is detailed in Section 3.8 of the FAD.
12	Clinical expert		Downstream treatment pathway uncertainty is an issue that relates to, and is dependent upon, the availability of osimertinib upon progression for a population receiving the technology in the adjuvant setting– as per my previous written submission, in my opinion there should be full flexibility for clinicians in this regard as retreatment with osimertinib as a first line must surely be the right thing to do for patients who progress while not receiving Osimertinib at that time.	Thank you for your comment. Retreatment with osimertinib was discussed at the second committee meeting. The committee noted that the proportion of having retreatment with osimertinib remained uncertain. The committee concluded that retreatment with osimertinib would be offered to some people whose disease had progressed after having osimertinib as an adjuvant

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				treatment. This is detailed in Section 3.3 of the FAD.
13	Clinical expert		Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Answer: I feel that the extrapolations using a family of parametric models is somewhat arbitrary (BIC and AIC criteria), and the methodology needs to be re-assessed when longer term data is released to determine if the assumptions made are appropriate.	Thank you for your comment. The committee recommended osimertinib for use within the Cancer Drugs Fund. The committee also noted that when the guidance is next reviewed the company should consider using formal statistical modelling of cure (for example a mixture-cure model) if the data allows. See Section 3.14 of the FAD.
14	Clinical expert		Question: Are the recommendations sound and a suitable basis for guidance to the NHS? Answer: I believe that osimertinib should be recommended based on existing evidence that (in my opinion) is sufficiently strong.	Thank you for your comment. The committee recommended osimertinib for use within the Cancer Drugs Fund. Section 1.1 of the FAD has been updated.
15	Clinical expert		Section 3: "Cure" assumptions seems arbitrary and archaic. Currently defined in this consultation as alive and disease free at 5 years. However "cure" varies with a) how hard you look for recurrence and b) the time frame. In my opinion, decisions should be made at face value in that death and recurrence at reduced by 80% during the trial interval as presented.	Comment noted. Consideration around the company's cure assumption is addressed in Section 3.9 of the FAD.
16	Clinical expert		Section 3.3 - Retreatment with osimertinib would be offered to some people whose disease has progressed In the case of recurrent (metastatic) disease, the decision to exclude treatment based on receipt of adjuvant osimertinib seems overtly restrictive, especially in the presence of EFGRm.	Retreatment with osimertinib was discussed at the second committee meeting. The committee noted that, although the proportion of people having retreatment with osimertinib remained uncertain, it made no significant difference to the cost effectiveness estimates. The committee concluded that retreatment with osimertinib would be

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				offered to some people whose disease had progressed after having osimertinib as an adjuvant treatment. This is detailed in Section 3.3 of the FAD.
17	Clinical expert		Section 3.9 - There is uncertainty about the company's cure assumptions Given cure itself is a function of method of detection of disease and timeframe, the difference between "delay" and "cure" itself is arbitrary. Ultimately, it could be stated that all cancer is cured given sufficient delay in presentation.	Comment noted.
18	Clinical expert		Section 3.13 - Osimertinib is not recommended for routine use in the NHS It is quite a hard and punitive stance when the trial was stopped early (from an ethical point of view) because the data is overwhelmingly in favour of osimertinib. It seems that the recommendation is suggesting that trials should continue accruing death and recurrence in the non-treatment arm in order to satisfy a higher level of certainty for the purposes of commissioning.	Thank you for your comment. The committee recommended osimertinib for use within the Cancer Drugs Fund. Section 1.1 of the FAD has been updated.

NICE National Institute for Health and Care Excellence

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 26 August 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
-	**Summary of the Company's Position** The Company appreciate that the Committee recognises that there are currently no targeted adjuvant treatments available in England for non-small cell lung cancer (NSCLC) after complete tumour resection. The Company also agree with the Committee that osimertinib is an innovative and promising new treatment option for the adjuvant treatment of stage IB to IIIA NSCLC after complete tumour resection in adults whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. The Company is convinced that osimertinib represents an efficacious, tolerable and cost-effective treatment option that can be recommended for routine commissioning and appreciate the opportunity to respond to the Appraisal Consultation Document (ACD). Please find enclosed the Company's response to the key areas of uncertainty raised in the ACD. 1) Uncertainty about the extent a benefit in disease-free survival (DFS) translates into a benefit in overall survival (OS) 2) Uncertainty around how osimertinib, as a third generation EGFR tyrosine kinase inhibitor (TKI), mode of action and clinical benefit differs from previous first and second generation EFGR TKIs 3) Uncertainty about the Company's OS predictions 4) Uncertainty about the Company's cure assumptions and timing of cure 5) Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib) **The Company disagree that the most plausible incremental cost-effectiveness ratios (ICERs) for osimertinib are highly uncertain.** The most clinically plausible ICERs remain within the NICE willingness to pay threshold. Both of the additional sensitivity analyses (ASA4a/4b) referenced produce highly clinically implausible and overly pessimistic estimates of adjuvant osimertinib's long-term survival. This contradicts the data from the ADAURA clinical trial and are inconsistent with the demonstrated safety and efficacy profile of osimertinib in metastatic lung cancer.[1,2] Clinical experts consulted by the Company agreed that both of these additional sensitivity analyses are not clinically plausible as they assume that the risk of transition from disease free (DF) to distant metastases 1 (DM1) is greater in the osimertinib arm and the curves for osimertinib and placebo cross (at approximately 22 years for ASA4a and at approximately 11 years for ASA4b). After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which contradicts the clinical evidence base. Since there is a consensus amongst clinical experts that

these scenarios are not clinically possible, we have suggested alternative scenarios for consideration in Table 1 below.

Table 1: Summary of the cost effective analysis for osimertinib in the adjuvant setting

Scenario	ICER (deterministic)			
	Optimistic: 5-year cure	Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm	Pessimistic: 8-year cure in both arms	No cure
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
ASA3a: Different mix of TKIs (80% osimertinib market share in 1L mNSCLC)	£16,846	£29,970	£20,267	£28,626
Adapted ASA4a: Use log-normal for TP2 (DF to DM1) in both arms but adjust so lines don't cross	£9,326	£25,544	£13,046	£23,012
ASA7: Allow re-treatment with osimertinib (50%)	£10,808	£22,989	£13,945	£21,854

Abbreviations: ASA, additional sensitivity analyses; DF, disease free; DM, distant metastases; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; mNSCLC, metastatic non-small cell lung cancer; TP, transition probability; TKIs, tyrosine kinase inhibitors.

The Company believe that NICE is in a position to make a positive recommendation for routine commissioning at this time and do not believe that osimertinib in the adjuvant setting is an appropriate candidate for the Cancer Drugs Fund (CDF) for the following reasons:

- Osimertinib has been demonstrated to be cost effective at the Patient Access Scheme (PAS) price in all clinically plausible scenarios.
- Further data collection in the CDF would not serve to reduce uncertainty in a reasonable time frame.
  - While the ADAURA primary analysis was conducted earlier than planned at the recommendation by the Independent Data Monitoring Committee (IDMC) due to overwhelming efficacy, the majority (63%) of the DFS events expected in the planned final analysis in patients with II-IIIA had already occurred. This suggests that the DFS benefit in osimertinib arm will not significantly change with more mature data and is expected to be maintained.
  - The only remaining efficacy analyses for the study are an exploratory analysis of DFS in the primary efficacy population (patients with stage II–IIIA disease) when the number of prespecified DFS events (247) are observed and the analysis of OS when the pre-specified 94 deaths have occurred.

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	○ The committee has acknowledged that it won't be possible to collect OS data in the CDF. The ADAURA OS data is event driven and in [redacted] – As noted by the Project Orbis team, "it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFR-mutated (EGFRm) NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS".[3]
1	**<u>Uncertainty about the extent a benefit in DFS translates into a benefit in OS</u>** There is strong clinical rationale to suggest that osimertinib's unprecedented clinically meaningful and statistically significant DFS benefit will translate into OS. Even in the absence of OS, by significantly extending the disease-free period (and the time to subsequent treatments) in patients with resected EGFRm positive NSCLC, adjuvant osimertinib will provide patients with invaluable long-term benefits compared to existing active monitoring. The improvement in DFS is expected to drive the cost-effectiveness of osimertinib in the adjuvant setting. **a) The DFS benefit demonstrated in ADAURA is likely to be maintained** After the ADAURA trial demonstrated overwhelming and unprecedented clinical benefit of adjuvant osimertinib, the IDMC recommended that the trial was unblinded 2 years early to allow for early analysis of data.[4,5] The study was only unblinded to the Company and after all patients had follow up of at least one year. In the primary analysis, the majority (63%) of the DFS events expected in the planned final analysis in patients with stage II-IIIA had already occurred.[3] **This suggests that the substantial DFS benefit in osimertinib arm will not significantly change with more mature data and is expected to be maintained.** A recent publication initiated and performed by the FDA and Project Orbis partners provides rationale for the regulatory approval decision-making for ADAURA, it is noted that ***"it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFR-mutated NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS"***.[3] At the time of analysis in the overall ADAURA population, 46.4% of patients in the placebo arm and 10.9% of patients in the osimertinib arm had disease recurrence or died.[5,6] While the early unplanned analysis may result in data maturity which is lower than originally planned, it does support the relatively low number of recurrence or death events in the osimertinib arm relative to placebo, reflecting the benefit of treating with osimertinib in the adjuvant setting. **b) However, if the DFS benefit significantly reduces over time, osimertinib will still remain a cost-effective treatment for the NHS in favour of placebo even in the worse-case scenario** [redacted]

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[redacted]

Even in the most extreme case where the HR for the placebo arm of the ADAURA trial outperforms the osimertinib treatment arm at the final analysis ([redacted]), the median HR across both data readouts (primary analysis plus final analysis) is [redacted]. Despite this worst possible case, adjuvant osimertinib remains a cost effective use of resources with an ICER of £17,662.

Furthermore, the economic model used by the Company and the ERG assumes that over time, the clinical magnitude of DFS benefit decreases (HRs increase) to reflect the natural progression of the disease. See Table 2 below.

Table 2: Changes in the modelled DFS in the Company's economic over time

Time (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DFS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DFS, disease free survival; HR, hazard ratio.

c) By significantly extending the disease-free period (and the time to subsequent treatments) in patients with resected EGFRm positive NSCLC, adjuvant osimertinib will provide patients with invaluable long-term benefits compared to existing active monitoring, even in the absence of long term OS

Fear of cancer recurrence is cited as one of the most distressing concerns for resectable NSCLC patients, making the extension of living cancer-free a primary goal. Many cancer survivors experience emotional and psychological issues (including distress, anxiety, depression, cognitive changes and fear of cancer recurrence) at the end of treatment, with fear of cancer recurrence as one of the most distressing concerns of patients.[8-11] Adjuvant osimertinib will transform the EGFRm NSCLC patient journey by delaying/preventing recurrence and keeping patients in the curative intent setting for longer. As a result the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis.

Additionally, a clinically meaningful decrease in central nervous system (CNS) recurrence or death was observed with osimertinib, and a reduction in distant metastases vs placebo (ADAURA trial). This highlights the clinical potential of osimertinib for improving post-surgical outcomes including

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OS. The low proportion of patients experiencing CNS recurrence with osimertinib contrasts with trials of earlier-generation EGFR-TKIs, gefitinib and erlotinib, in the adjuvant setting, in which brain metastases drove disease recurrence. Brain metastases are the most common type of recurrence in NSCLC, impose a heavy burden on patients quality of life, and mark a transition to incurable disease. Thus, by preventing brain recurrences in the resectable EGFRm population, osimertinib also meets a substantial unmet need.

d) By keeping patients disease-free for longer, the upfront investment with osimertinib will delay and avoid costs of progression to advanced disease – regardless of whether osimertinib is preventing or delaying recurrence as patients are remaining in the curative intent setting for longer

CNS metastases (specifically brain metastases) is the most common form of distant recurrence in NSCLC patients and causes patients to suffer a significantly higher disease burden, such a seizures, fatigue, speech problems and mobility issues vs patients with non-brain metastases.[12,13] As a result, NSCLC patients with brain metastases have a significantly higher economic burden compared to those patients without CNS metastases. Using osimertinib in the adjuvant setting will offset costs associated with progression to advanced disease stages (annual per-patient costs are higher in the advanced/metastatic setting)[14] including:[15,16]

- Treatment related costs (including osimertinib in 1L metastatic setting)
- Hospitalisation days
- Emergency room visits
- Home nursing
- Hospice care

As a result the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis. Therefore the Company's cost effectiveness analysis and ICERs may be conservative.

e) There is strong clinical rationale to suggest that osimertinib's unprecedented clinically meaningful and statistically significant DFS benefit will translate into OS

Collecting mature OS data in the adjuvant NSCLC setting from event driven trials is challenging due to the effectiveness of treatment (particularly with osimertinib), however, a numerical benefit was observed in the overall population for osimertinib vs placebo (in total, 9 patients in the osimertinib arm and 20 patients in the placebo arm had died (2.7% and 5.8%, respectively).[5,6]

Despite the OS data being less mature than expected due to the early unblinding, UK clinicians interviewed by the Company[17,18] and [redacted][19] stated and agreed that adjuvant osimertinib is undoubtedly expected to translate into long-term survival benefits. This was also confirmed by the clinical experts at the NICE appraisal committee meeting on 14th July 2021. This is based on the following evidence:

- **The unprecedented magnitude of DFS benefit observed with osimertinib in ADAURA**
  - Osimertinib demonstrated an 80% reduction in the risk of recurrence or death vs. placebo across stages IB-IIIA of resected EGFRm NSCLC (HR 0.20, p<0.001; secondary endpoint). It is the first EGFR-TKI to demonstrate this magnitude of benefit in DFS (see Table 3). This unprecedented benefit was consistent across all patient subgroups.[5]

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- **The reduced rate of recurrence with distant/CNS metastases observed with osimertinib vs placebo**
  - Brain metastases are the most common type of recurrence in NSCLC, impose a heavy burden on patients quality of life, and mark a transition to incurable disease. Osimertinib had fewer local, regional and distant relapses than those who received placebo, with an **82% reduction in the risk of CNS disease recurrence or death.** Reducing CNS metastases is likely to reduce disease burden associated with distant recurrence and improve prognosis. Osimertinib is also the first EGFR-TKI in the adjuvant setting to demonstrate a significant improvement in CNS outcomes. The reduction in CNS metastases with adjuvant osimertinib is expected to provide an OS benefit. This further supports that osimertinib in the adjuvant setting is keeping patients in the curative intent setting (disease free) for longer.
- **Osimertinib has demonstrated superior OS benefit vs first generation EGFR-TKIs in the faster progressing metastatic setting supported by a significant and sustained progression-free survival (PFS) extension and reduction in risk of CNS metastases vs EGFR-TKIs**
  - The metastatic setting is generally considered by clinicians as more difficult to treat and patients typically progress faster.[20] Despite this, osimertinib has already demonstrated a superior OS benefit vs first-generation TKIs (HR 0.80; 95.05% CI, 0.64–1.00, p=0.046)[21] supported by a significant and sustained extension in PFS and a significant reduction in the risk of CNS metastases.[1,2]
  - The ACD states that the committee was also aware of recent publications by Gyawali (2021) and Uprety (2021), which noted that other adjuvant tyrosine kinase inhibitors demonstrated DFS benefits that have not translated to an overall survival benefit.
    - The publications by Gyawali 2021[22] and Uprety 2021[23] are standalone editorial comment articles that are the opinion of one or two authors. The editorial articles are not robust, peer reviewed nor reflective of the clinical community across the UK. Comparing osimertinib to older generation EGFR-TKI data in the adjuvant setting is not appropriate as outlined throughout this document (Comment 2). Therefore, these two editorial articles are an inappropriate source to use to question the link between DFS and OS with osimertinib.
    - A recent independent, peer-reviewed publication initiated and performed by the FDA and Project Orbis partners provides an unbiased summary of the DFS benefits relating to EGFR-TKIs. This publication has received regulatory and government approval and would be more fit as a source for decision making over the editorials cited in the ACD.[3]

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2

Uncertainty around how osimertinib, as a third generation EGFR-TKI, mode of action and clinical benefit differs from previous first and second generation EFGR TKIs

a) Comparison to earlier EGFR-TKI data in the adjuvant setting is not appropriate. Osimertinib is a third generation, differentiated EGFR-TKI designed to provide targeted, irreversible inhibition of both EGFRm and EGFR T790M, with demonstrated CNS penetration

Alongside the shared feature of inhibiting EGFR with the most common TKI-sensitising mutations (exon 19 deletion and L858R), osimertinib differs from earlier EGFR-TKIs by:

- Inhibiting EGFR T790M
- Showing lower activity for wild-type EGFR[24,25]
- Possessing lower activity for IR and IGFR
- Good penetration of the blood brain barrier ($K_{puu,brain}$ 0.39).[26]

b) In comparison to other EGFR-TKIs, osimertinib has a higher blood brain barrier penetration resulting in a clinically meaningful reduction in the risk of CNS progression in early stage NSCLC vs placebo. In the adjuvant setting, osimertinib is the first EGFR-TKI to provide a significant DFS benefit vs placebo, across stages IB-IIIA EGFRm NSCLC[5]

- ADAURA is the first global, randomised study of adjuvant EGFR-TKI prospectively designed and fully carried out in the completely resected EGFRm NSCLC patient population.[5]
- Other EGFR-TKIs are not indicated in the adjuvant setting[27] and their studies were single country, or single arm, without an appropriate genotype-specific population, or did not require negative surgical margins.[28-32]
- The magnitude of DFS benefit observed with osimertinib is unlike earlier generation EGFR-TKIs previously trialed in the adjuvant setting. A comparison of DFS observed with previous Phase III randomised controlled trials (RCTs) of first-generation EGFR-TKIs in the adjuvant setting is provided in Table 3.
- Osimertinib has demonstrated superior OS benefit vs first generation EGFR-TKIs in the faster progressing metastatic setting (HR 0.80; 95.05% CI, 0.64–1.00, p=0.046).[21]

Table 3: DFS results in Phase III RCTs on adjuvant first-generation EGFR-TKIs in NSCLC

Study	NSCLC population	Treatment arms	DFS HR (95% CI)
ADAURA[5]	Completely resected stage IB-IIIA EGFRm*	Osimertinib following complete resection with or without chemotherapy vs placebo	**0.20 [0.14, 0.30]**
ADJUVANT/ CTONG 1104[33,34]	Resected stage II–IIIA EGFRm	Gefitinib vs vinorelbine plus cisplatin	**0.60** [0.42, 0.87]
RADIANT[30]	Resected stage IB–IIIA (EGFR-expressing/ amplified)	Erlotinib vs placebo	**0.61** [0.38, 0.98]

*with negative margins only

Abbreviations: CI, confidence interval; DFS, disease free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials; TKI, tyrosine kinase inhibitors. RRR, relative risk reduction

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- Despite reported intracranial responses, first generation EGFR-TKIs are generally thought to have poor CNS penetration.[26,35] The unique ability of osimertinib to penetrate the intact blood brain barrier is a likely contributor to the substantially fewer CNS recurrences vs placebo.[5] A comparison of CNS recurrence observed with previous Phase III randomised controlled trials (RCTs) of first generation EGFR-TKIs in the adjuvant setting is provided in Table 4.

Table 4: Incidence of CNS recurrence in Phase III RCTs on adjuvant first-generation EGFR-TKIs in NSCLC

Study	NSCLC population	Treatment arms	Incidence of CNS recurrence %
ADAURA[5]	Resected stage IB-IIIA EGFRm	Osimertinib following complete resection with or without chemotherapy vs placebo	1% osimertinib vs 10% placebo
ADJUVANT/ CTONG 1104[33,34]	Resected stage II–IIIA EGFRm	Gefitinib vs vinorelbine plus cisplatin	27.4% gefitinib vs 24.1% vinorelbine plus cisplatin
RADIANT[30]	Resected stage IB–IIIA (EGFR-expressing/ amplified)	Erlotinib vs placebo	40.0% erlotinib vs 12.9% placebo

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RRR, relative risk reduction; TKI, tyrosine kinase inhibitor.

- In other adjuvant EGFR-TKI studies, the duration of therapy was up to 2 years.[30,31] The maximum treatment duration in ADAURA is 3 years based on the following considerations:
  - The highest rate of recurrence is seen within the first 2-3 years after complete tumour resection.[5]
  - Osimertinib has demonstrated a favourable safety profile with adverse events of grade 3 or higher being reported in fewer patients than in the standard EGFR-TKI group.[5,21,36]

3

<u>Uncertainty about the company's OS predictions- Modelling survival</u>

a) The Company disagree with the committees' conclusion that the company's choice of extrapolations was driven by the company's cure assumption rather than the goodness of fit

- The Company followed standard, well established approaches to determine the most appropriate extrapolations which is in no way influenced by the cure assumption consideration.
- Alongside visual inspection, the goodness of fit was also evaluated based on the mean squared error (MSE) of the predicted model vs the Kaplan-Meier (KM). Therefore, the resultant model was selected based upon a visual inspection of the combined DF and OS curves, that achieved a good fit to the observed KM data (evaluated by the MSE diagnostic test) and were deemed clinically plausible, as evaluated by an independent

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	UK advisory board. To achieve a clinically realistic and good fit of the data to the combined DF and OS curves, survival curves applied for individual transitions were assessed primarily visually (as recommended by Williams et al, 2017)[37] for clinical plausibility. However, where several curves were deemed viable in terms of clinical plausibility and visual fit to the data, statistical fit (using fit based on Akaike Information Criterion [AIC]/Bayesian Information Criterion [BIC] values and MSE) was also taken into account for the purpose of curve selection. **b) The cure assumption is an independent function and separate from the extrapolated curves** • The cure assumption is an independent function within the economic model. The model includes the functionality to vary the time point considered for cure, and the proportion of patients who achieve it. After the defined cure timepoint, survival for the proportion of patients who are assumed to be cured is adjusted to follow that of the age and sex matched general population. • The cure function is independent from the extrapolation survival curves. Survival curves were selected based upon clinically plausibility, visual fit and goodness of fit statistics. Following selection of appropriate survival, the cure function within the model adjusted the survival of patients (as predicted by the selected curve) to assume that a proportion of patients will be cured at defined time point. The choice of curve therefore is not impacted by the cure assumption. • In order to alleviate concerns surrounding the cure assumption, the Company have provided a number of scenarios exploring the impact of changing the cure year and assuming no cure across treatment arms. **c) The Company disagree that the survival predictions may be optimistic** Although published data on longer-term survival outcomes in this setting are limited – particularly in stage IB–IIIA EGFRm-positive NSCLC – several studies were identified in patients with completely resected stage IB–IIIA NSCLC. These studies indicate that the underlying risk of disease recurrence in the earlier follow-up period (noted as before 36–48 months) is not representative of the risk of recurrence at later time periods. Generally, patients who are disease-free following complete tumour resection appear to be exposed to a far higher risk of recurrence early in the follow-up period, with the risk of recurrence decreasing over time. It is important to note that the extrapolation of DF data from the ADAURA trial to derive the transition probabilities applied in the cost-effectiveness model are based on a period (up to 48 months) that appears to correspond with an increased risk of recurrence rate. Therefore, it is reasonable to assume that the extrapolated disease recurrence is being overestimated and the Company are being conservative. **d) The Company agree that alternative parametric distributions can be used to assess the range of uncertainty. It is necessary, however, that alternative parametric distributions selected produce clinically plausible long-term estimates that are aligned with expert clinical opinion** **The ERG's ASA4a and 4b are clinically implausible.** Both of the additional sensitivity analyses produce non credible and overly pessimistic estimates of adjuvant osimertinib's long-term survival that are in direct contradiction with data from the ADAURA clinical trial and expert clinical opinion.

	Neither of these scenarios were discussed at the open part of the Committee Meeting and therefore no clinical expert opinion was sought on their clinical plausibility during the meeting. Clinical experts consulted by the Company stated that both of these additional sensitivity analyses were not considered clinically plausible and had no logical scientific explanation as they assume that the risk of transition from DF to DM1 is greater in the osimertinib arm and the curves for osimertinib and placebo cross (at approximately 22 years for ASA4a and at approximately 11 years for ASA4b).[18] After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which is not clinically plausible. The clinical experts stated that given that osimertinib is a three year treatment option there is no conceivable scientific or biological rationale to explain why a patient would suddenly recur 10 or 25 years after stopping osimertinib treatment. If a patient is to recur following adjuvant osimertinib, it would be soon after stopping treatment and most certainly within 2 years.[17,18] • **ASA4a - the log-normal model, when applied to both treatment arms, produces more pessimistic long-term estimates (Figure 1)** – The estimates of mean and median OS and DFS produced when the log-normal model is selected for transition probability (TP) 2 have not been validated by clinicians. – Clinicians validated that the base case (TP2: generalised gamma) aggregated OS and DFS, with cure at Year 5 for both arms, produced the most clinically plausible long-term survival estimates for osimertinib and the comparator arm. – When the log-normal model is selected for TP2 in both arms, the curves for osimertinib and placebo cross at approximately 22 years into the model time horizon. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which is clinically implausible based on the observed benefit of osimertinib in ADAURA trial and osimertinib efficacy profile in the metastatic setting. – The assumption that the risk of transition from DF to DM1 is eventually greater in the osimertinib arm directly undermines data from the ADAURA trial (assumes a HR that shows DFS progression is lower in the osimertinib arm).

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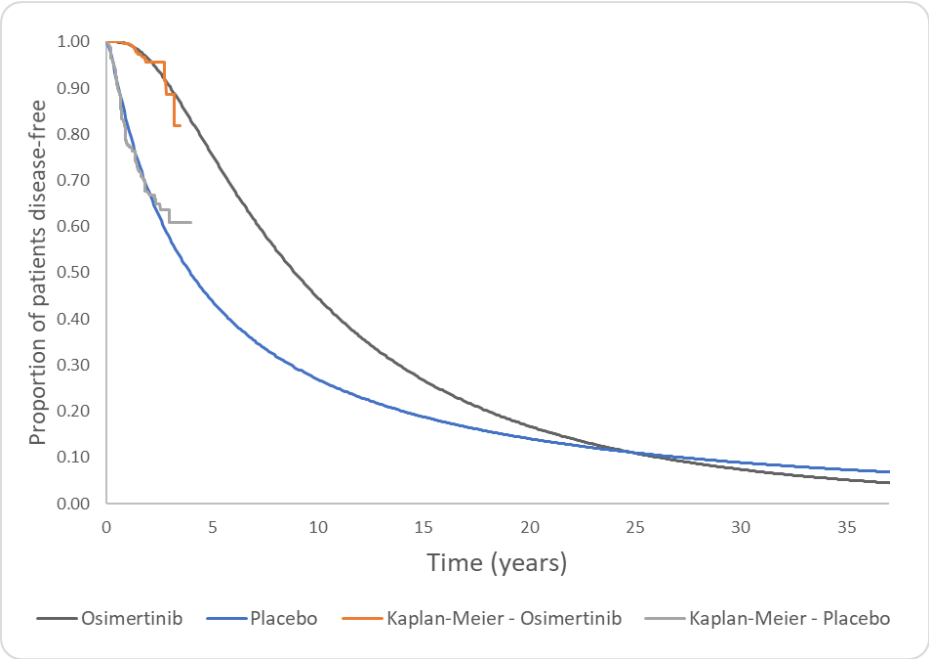
Figure 1: Extrapolations for DF to DM1 (TP2) – both arms: log-normal



Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability

- The pattern of disease recurrence produced in this analysis directly contradicts the overwhelming efficacy exhibited by adjuvant osimertinib in the ADAURA trial.
    - The primary analysis demonstrated that patients in the osimertinib arm had fewer locoregional and distant recurrences than placebo. When recurrence did occur, this was more frequently at locoregional sites in the osimertinib group, and by contrast, more frequently distant metastases in the placebo group.
    - Furthermore, clinical feedback received from UK clinicians provides further support to the expected long-term survival benefit of osimertinib in this setting as loco-regional recurrence may offer clinicians another opportunity to effectively 'cure' a patient.
- Therefore this scenario should not be used to inform decision making. However, if the committee firmly believes that the log-normal should be selected for TP2, the hazards for this transition should be amended so that after ~22 years, the risk of recurrence for both arms is set to be equal. Although this is a more plausible scenario than that presented by the ERG the weight of evidence and clinical opinion suggests this remains highly conservative (Table 5).

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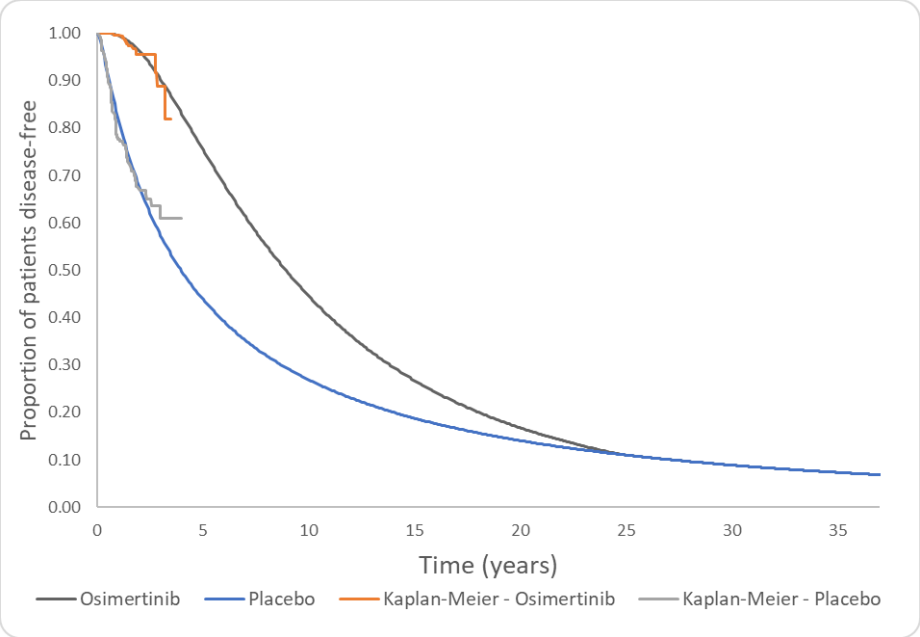
Figure 2: Extrapolations for DF to DM1 (TP2) – both arms: log-normal, adjusted hazards



Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability

Table 5: ASA4a (adapted to prevent curves crossing) - scenario analysis results

Scenario	ICER (deterministic)			
	Optimistic: 5-year cure	Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm	Pessimistic: 8-year cure in both arms	No cure
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
Adapted ASA4a: Use log-normal for TP2 (DF to DM1) in both arms but adjust so lines don't cross	£9,326	£25,544	£13,046	£23,012

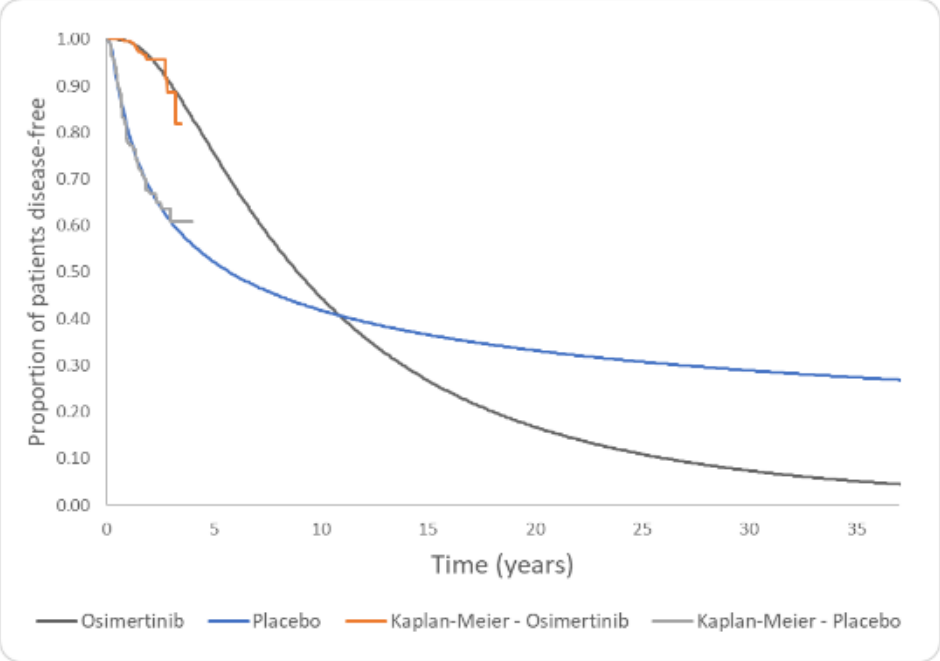
Abbreviations: ASA, additional sensitivity analyses; DF, disease free; DM, distant metastases; ERG, Evidence Review Group; TP, transition probability

- **ASA4b: This analysis is clinically implausible as it assumes that patients progress faster following treatment with osimertinib than receiving placebo**
  - The NICE Decision Support Unit (DSU) technical support document (TSD) 14 states that the same parametric function should be used across both treatment arms where feasible, as this ensures consistency and limits potential problems such as the extrapolated curves crossing over one another.[38] Fitting different types of parametric model (for example generalised gamma for one treatment arm and a log normal for the other) to different treatment arms would require

substantial justification and that fitting the same distribution is likely to be "most sensible".[38]

- However no substantial justification has been provided as to why different models have been selected in this scenario. The following statement on Page 112 *"In the current context where a new drug has a marked effect on disease relapse compared to standard of care, it is likely that the hazards may take quite different forms in the two treatment arms and this possibility should be investigated"* lacks clinical rationale. Osimertinib is expected to significantly reduce long-term disease recurrence, however there is no clinical evidence to suggest that the hazards of the two arms will take quite different forms.
- When the log-normal model is selected for only osimertinib in TP2, the curves produced are highly clinically implausible. In this scenario the osimertinib and placebo curves cross at approximately 11 years into the model time horizon. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm. This is even more pessimistic than the analysis presented in ASA4a and once again contradicts the pattern of disease recurrence observed with adjuvant osimertinib in the ADAURA trial. As previously discussed, disease recurrence in the osimertinib arm was more frequently at locoregional sites, and by contrast, more frequently distant metastases in the placebo group.

Figure 3: Extrapolations for DF to DM1 (TP2) – osimertinib: log-normal, placebo: generalised gamma



Abbreviations: DF, disease free; DM, distant metastases; TP, transition probability

Scenario ASA4b results in clinically implausible modelled survival outcomes. It predicts that up to approximately 11 years, treatment with osimertinib results in a reduced risk of progression to the DM1 health state compared to standard of care (SoC). However, from 11 years onwards the risk of

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	progression is modelled to dramatically reverse such that a patient who has remained progress-free up to 11 years following treatment with osimertinib would have a higher risk of transitioning in the DM1 health state compared to a patients in the SoC arm, with the risk of transition plateauing out in the SoC arm. This strongly contradicts the clinical evidence from ADAURA and the feedback obtained from clinical experts. **As such this scenario is clinically implausible, lacks credibility and therefore is in no way appropriate to inform decision making.**
4	**<u>Uncertainty about the Company's cure assumptions and timing of cure</u>** **a) A significant proportion of patients already achieve a functional "cure" with current standard of care** • Clinical evidence validates the curative potential of treatment for resected EGFRm NSCLC. As described in the Company submission, clinical trial evidence in patients with resected NSCLC receiving placebo demonstrates a plateauing effect in DFS at approximately 48-60 months following surgical resection, indicating that the majority of patients are no longer at risk of disease recurrence, and thus providing support for the assumption of functional cure in this patient population. **b) The 5-year functional cure in both arms is supported by published clinical evidence and expert clinical opinion** • The model is largely based on data from the primary analysis of the ADAURA trial, therefore extrapolations of survival outcomes were necessary. However, when the extrapolated OS and DFS curves (aggregated from the multi-state model) were presented to clinical experts,[17] they found the long-term estimates were extremely pessimistic for this patient population compared to the outcomes observed in clinical practice, stating them to be more reflective of outcomes in the metastatic setting. • In addition, the clinicians felt the extrapolations were unrealistic given the unprecedented efficacy of osimertinib demonstrated in the ADAURA trial and the expectation of a functional cure after 5 years DFS.[17] To reflect the clinicians' expected clinical outcomes using trial data, parametric distributions were selected and a 5-year cure timepoint was applied, taking into account their expectation of a plateau towards the 5-year mark (disease-free patients are typically discharged and not followed by clinicians after 5 years, and therefore are considered to be functionally cured). – The 5-year cure assumption as confirmed by 13 key clinical experts in a recent [redacted].[19] This was further validated through discussions with UK clinical experts that agreed with the Global Panel outputs[18] [redacted] – UK clinicians agreed that patients who are disease-free at 5 years would have a very low risk of recurrence, their survival would be similar to that of the general population and these patients are considered functionally cured.[17,18]

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c) The ERG preferred pessimistic scenario (cure at 8 years for the osimertinib arm vs 5 years for placebo) is overly pessimistic and clinical experts agreed that timing of the cure assumption should be consistent across arms, regardless of timepoint

- Clinical experts consulted by the Company felt that, regardless of the timepoint being used, the cure assumption should be applied at the same timepoint for both arms as **there was no rationale for why cure on the osimertinib arm would be later than placebo**.[18] Even if we were to assume that osimertinib delays rather than prevents recurrence then there is no reason to suggest that patients would recur faster on osimertinib than placebo, particularly when clinical trial and real-world evidence supports that there is a plateauing effect in DFS at approximately 48–60 months following surgical resection. For this reason, the Company have provided an alternative pessimistic and conversative scenario which assumes cure being applied at 8 years in both arms (please see Table 6 below for associated ICERs).

d) Without the structural cure assumption, osimertinib remains a cost-effective use of NHSE resources

- Despite the overwhelming efficacy of osimertinib observed in the ADAURA trial, the Company recognise there is uncertainty regarding the long-term outcomes of patients treated with adjuvant osimertinib due to the immaturity of the data in ADAURA.

- To further evaluate the clinical uncertainty, we have also presented a scenario analysis in which the structural cure assumption is removed altogether. Although this scenario is deemed clinically unrealistic (as the extrapolated ADAURA DFS curves likely overestimate the long-term rate of disease recurrence and are therefore overly pessimistic for an early-stage resected population) we have provided this scenario to demonstrate that even in the extreme case of an absence of a cure assumption, osimertinib remains a cost-effective use of NHSE resources with an incremental cost-effectiveness ratio of £17,219 versus placebo (Table 6). Removing the cure assumption does not interfere with the model extrapolations as it is an independent function that can be switched on and off.

Table 6: Scenario analyses on model cure assumption

Scenario	ICER (deterministic)			
	Optimistic: 5-year cure	Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm	Pessimistic: 8-year cure in both arms	No cure
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio

5

<u>Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib)</u>

The Company agree that there is some uncertainty associated with later treatments with or without adjuvant osimertinib and as a result have further engaged with clinical experts to inform the assumptions used in the economic modelling

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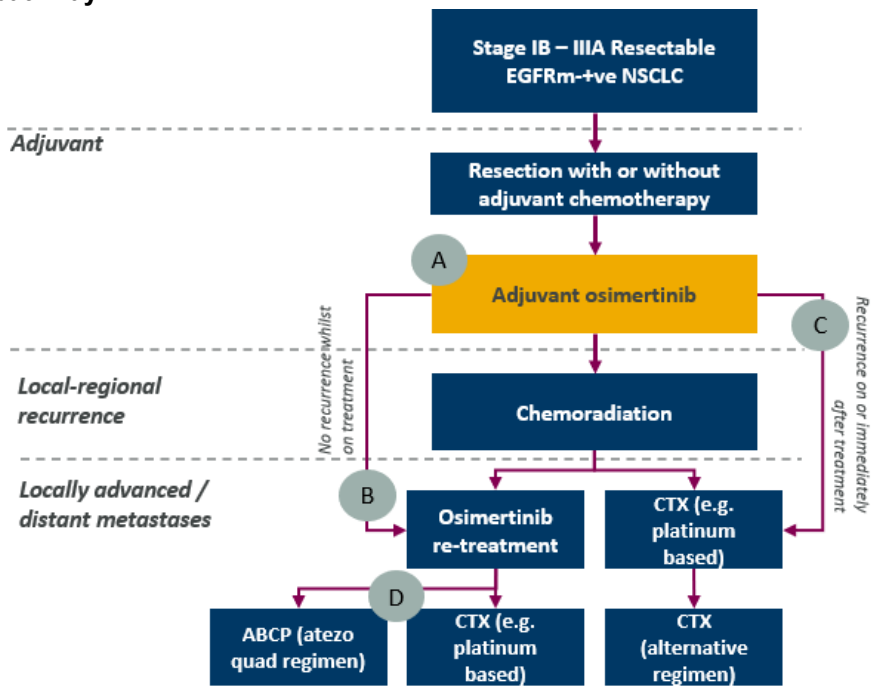
Figure 4: The anticipated positioning of adjuvant osimertinib in the current treatment pathway



A: In the absence of adjuvant osimertinib (placebo arm). B: Patients that recur within 2 years of completing 3 years of adjuvant osimertinib - osimertinib re-treatment. C: Patients that recur whilst on adjuvant osimertinib. D:Patients that progress to 2L mNSCLC following treatment with osimertinib.
Abbreviations: ABCP, atezolizumab plus bevacizumab, carboplatin and paclitaxel; CTX, chemotherapy; EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer.

a) In the absence of adjuvant osimertinib (placebo arm):

- Osimertinib is considered the mainstay treatment option and represents the current standard of care in 1L EGFRm NSCLC. All clinicians (n=20) consulted agreed that osimertinib is a more potent, efficacious and the best tolerated EGFR-TKI vs other TKIs and therefore unless there is a clear reason not to, they would prescribe osimertinib **to all newly diagnosed patients** (100% of patients) with metastatic EGFR NSCLC.[17]
  - Clinicians unanimously agreed that if a patient is not fit for osimertinib then they would not be fit for any other EGFR-TKI therefore osimertinib in the first line metastatic setting is the treatment of choice.
- Osimertinib was routinely recommended as a treatment option for use in the first line metastatic setting in October 2020 and since then its market share has risen sharply. The 64% assumption is based on complete market share data which includes patients who started on first and second generation EGFR-TKIs prior to osimertinib becoming established standard of care. **It is therefore imperative to use the market share assumption relating to the newly diagnosed patients and not the entire cohort of patients.**
- [redacted]

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[redacted] Therefore focusing on only newly diagnosed patients would per definition lead to a market share between 80% and 100%.

- The Company therefore conducted two exploratory analyses that conservatively assume 80% and 90% of patients in the active monitoring arm receive treatment with osimertinib in DM1 (Table 7). The remaining proportion of patients in DM1 are assumed to receive other EGFR-TKIs (erlotinib, gefitinib, afatinib or dacomitinib) and relative proportions were informed by the IQVIA national prescribing data provided in the clarification question responses.
- In both exploratory analyses osimertinib remains a cost-effective use of resources for all cure assumption scenarios (optimistic and pessimistic, Table 7).

Table 7. Company's revised ASA3 – scenario analysis results

Scenario	ICER (deterministic)			
	Optimistic: 5-year cure	**Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm**	**Pessimistic: 8-year cure in both arms**	**No cure**
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
ASA3a: Different mix of TKIs (80% osimertinib market share in 1L mNSCLC)	£16,846	£29,970	£20,267	£28,626
ASA3a: Different mix of TKIs (90% osimertinib market share in 1L mNSCLC)	£13,706	£25,631	£16,296	£23,454

Abbreviations: ASA, additional sensitivity analyses; ERG, Evidence Review Group; mNSCLC, metastatic non-small cell lung cancer; TKI, Tyrosine kinase inhibitors

b) Following successful treatment of adjuvant osimertinib (Figure 4):

- **Patients that recur within 2 years of completing 3 years of adjuvant osimertinib - osimertinib re-treatment**
  - The impact of introducing osimertinib in resected stage IB-IIIA EGFRm NSCLC on subsequent treatments (i.e. the rest of the treatment pathway) is unknown as the use of osimertinib in the adjuvant setting represents a step change in clinical practice.
  - UK clinicians consulted in interviews agreed that they would consider re-treatment with osimertinib for patients who successfully completed 3 years of adjuvant treatment with osimertinib and who did not relapse within a year of treatment completion. Clinical experts advised that re-treatment with other EGFR-TKIs would not be considered as these are generally considered to be less potent and less efficacious versus osimertinib.

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- As noted in the Committee meeting slides, the clinical experts stated that "Patients who progress after treatment with osimertinib, should be treated like other patients newly presenting with metastatic disease and would be offered osimertinib if they meet the criteria. It would be unethical not to offer rechallenge of osimertinib to these patients."
- It is not possible to accurately predict what proportion of patients will be prescribed osimertinib for metastatic NSCLC following successful adjuvant treatment in future clinical practice. Therefore, a conservative approach was applied in the model where 50% patients in the DM1 state were retreated at 5 years, and 50% were not. The Company has also provided a sensitivity analysis exploring differing levels of osimertinib re-treatment in the metastatic NSCLC setting (40% and 60%) and in all scenarios osimertinib remains a cost-effective use of resources (Table 8).

Table 8: Retreatment with osimertinib - scenario analyses results

Scenario	**ICER (deterministic)**			
	Optimistic: 5-year cure	**Pessimistic: 8-year cure in osimertinib arm, 5-year cure in placebo arm**	**Pessimistic: 8-year cure in both arms**	**No cure**
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
40% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,644	£22,491	£13,480	£20,977
50% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,808	£22,989	£13,945	£21,854
60% of patients in adjuvant osimertinib arm receive retreatment with osimertinib	£10,972	£23,478	£14,404	£22,709

Abbreviations: ICER, incremental cost-effectiveness ratio; ERG, Evidence Review Group

c) Patients that recur whilst on adjuvant osimertinib (Figure 4):

- For patients that recur whilst on treatment with adjuvant osimertinib, The Company has assumed that 100% of patients would be treated with pemetrexed and cisplatin as per the current treatment paradigm.

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	d) Patients that progress to 2L mNSCLC following treatment with osimertinib (Figure 4): • Whilst atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) is recommended as an option for patients with EGFRm-positive NSCLC who have previously received targeted treatment, clinical advisors to the Company stated that the relative proportion of patients receiving treatment with this regimen is small. • Clinicians advised that the 4-drug regimen is associated with considerable toxicities and contraindications, resulting in intensive monitoring requirements. In general, clinical advisors stated that a relatively low number of patients are likely to be fit enough to tolerate treatment with the 4-drug regimen, and therefore it does not represent the mainstay treatment in the 2L metastatic NSCLC (mNSCLC) disease setting. • In addition, IQVIA prescribing data reported that just 16% of patients received the 4-drug regimen for the 2L treatment of EGFRm-positive mNSCLC in Q4 2020. • The limitations of this regimen are also noted in the NICE final appraisal determination (FAD) document for TA584, within which the patient expert highlighted the importance of careful selection of people who would be offered atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice. In addition, the CDF lead stated that this regimen should only be considered appropriate for patients with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 because of the intensive dosing regimen as atezolizumab and bevacizumab were being added to chemotherapy and the dose of carboplatin would be higher than typically used in clinical practice. As a result, it was concluded that the number of EGFRm-positive patients requiring treatment for 2L mNSCLC with an ECOG performance status of 0 or 1 and considered well enough to tolerate the 4-drug regimen would be considered small. • For patients that progress in the mNSCLC setting we have assumed that a proportion of patients would receive the 4-drug regimen in line with current standard of care. • It would be inappropriate to include ABCP as a treatment option in 1L mNSCLC for patients completing adjuvant osimertinib as this is currently only reimbursed in the 2L EGFRm population.
7	**<u>Innovation status</u>** **The Company disagrees with the committee's conclusion that all additional benefits associated with osimertinib have been captured in the economic analysis and as a result it can be assumed that the cost-effectiveness analyses undertaken are highly conservative** • Fear of cancer recurrence is cited as one of the most distressing concerns for resectable NSCLC patients, making the extension of living cancer-free a primary goal. Many cancer survivors experience emotional and psychological issues (including distress, anxiety, depression, cognitive changes, and fear of cancer recurrence) at the end of treatment. • Adjuvant osimertinib will transform the EGFRm NSCLC patient journey by delaying/preventing recurrence and keeping patients in the curative intent setting for

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	longer. As a result, the true value of osimertinib in the adjuvant setting may not be fully captured in conventional clinical and health economic analysis. • The economic model only captures the downstream costs associated with drug treatment and not the additional indirect costs associated with the impact of recurrence/metastases– including CNS recurrence which have been to incur significant economic burden compared to patients without CNS metastases due to higher monitoring costs and resources, increased number of hospitalisation days/emergency room visits and increased home nursing/hospice care requirements. • CNS metastases are also associated with vast decrements in health-related quality of life. Health economic analyses in previous NICE appraisals in NSCLC have explicitly accounted for the impact of CNS metastases on health-related quality of life. In NICE TA536, the economic model included a separate health state for patients who progressed with CNS metastases. Patients in this health state were assumed to have a significantly lowered quality of life (0.52) compared to patients who had non-CNS disease progression. The CNS progression health state was not incorporated in this appraisal due to data limitations, however, as osimertinib is associated with a significant reduction in CNS metastases it is highly likely utility benefits of treatment have not been captured. • There are several other benefits of osimertinib in the proposed setting that could not be adequately captured in the economic analysis, including the impact of living disease-free on the patient's social life, ability to work, mental health and emotional well-being and the positive impact for family members and carers. • As numerous benefits associated with osimertinib in the adjuvant setting have not been accounted for in the health economic analysis, it can be assumed that the cost-effectiveness results produced are highly conservative.
8	**<u>Appropriateness of CDF</u>** **The Company believe that NICE is in a position to make a positive recommendation for routine commissioning at this time and do not believe that reimbursement via the CDF is the most appropriate route for access for the following reasons:** • **Osimertinib has been demonstrated to be cost effective at the PAS price** – All the clinically plausible ICER scenarios presented in our Company Submission and the ERG Report, are below the NICE willingness to pay threshold. – The scenarios being proposed (ASA4a/b) by NICE were not discussed in open part of the Committee meeting and both of these scenarios were considered 'very pessimistic' by the ERG in their report. Additionally, these scenarios were considered clinically implausible by clinical experts as they assume that adjuvant osimertinib performs worse than placebo which is not consistent with the DFS and CNS recurrence presented in the ADAURA data.[18] – Additional ICER scenarios including a no-cure analysis are within the NICE willingness to pay thresholds (Table 6).

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	• **Further data collection in the CDF would not serve to reduce uncertainty in a reasonable time frame** – While the ADAURA primary analysis data is less mature than anticipated, the majority (63%) of the DFS events expected in the planned final analysis in patients with II-IIIA had already occurred. This suggests that the DFS benefit in osimertinib arm will not significantly change with more mature data and is expected to be maintained. – The only remaining efficacy analyses for the study are an exploratory analysis of DFS in the primary efficacy population (patients with Stage II–IIIA disease) when the number of prespecified DFS events (247) are observed and the analysis of OS when the pre-specified 94 deaths have occurred. – As noted by the Project Orbis team, "it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFRm NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS".[3] – The committee has acknowledged that it won't be possible to collect OS data in the CDF. The ADAURA OS data is event driven and in [redacted] Once all the clinically implausible scenarios have been removed from analyses, the Company firmly believe that osimertinib remains a cost effective use of NHS resources under all scenarios, despite any residual uncertainty. As a result, the Company feels that the CDF should only be considered if the Committee still perceive there to be substantial, justifiable and clinically plausible uncertainties that would result in ICERs above acceptable cost effective thresholds.

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9

Factual inaccuracies

Factual inaccuracy	Description of inaccuracy
Section 4.3, Page 8: This is a phase 3 randomised, double-blind, placebo-controlled, multicentre trial in adults with completely resected stage 1b to 3a NSCLC (stratified by EGFR mutation).	This statement is factually inaccurate. Stratification factors at randomisation in the ADAURA trial included tumour stage, race (Asian versus non-Asian) and EGFR (ex19del versus L858R) status. Please amend accordingly.
Section 3.9, Page 12: The ERG's optimistic analysis retained the company's original approach, whereas the pessimistic analysis applied a later timepoint for cure in the adjuvant osimertinib group of 8 years (5-year cure timepoint in the active monitoring group plus the 3-year osimertinib treatment period). The company explained that it considered the ERG's pessimistic analysis was overly pessimistic and clinically implausible because of the suggested change in survival probabilities being equal at the relative cure points.	This statement is factually inaccurate. This statement made by the Company on the ERG's highly pessimistic analysis that sets the survival probabilities for adjuvant osimertinib and active monitoring to be approximately equal at their relative cure timepoints was describing the ERG's Additional Sensitivity Analysis (ASA) 5, not the ERG's preferred pessimistic analysis. A detailed explanation of this ASA can be found in Section 5.4.1 of the ERG report and Pages 20-27 of the Company's initial factual accuracy response to the ERG report. Please kindly consider removing this statement from the ACD as it is potentially misleading.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**N/A**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Dr Gary Doherty**

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that this recommendation may imply that there is not clearly significant enough clinical benefit from the technology. This clear significant clinical benefit is outlined in the document and in my prior evidence (written and verbal) and that of others. Reliance on future overall survival outcomes will be hampered by (a) the early unblinding of the trial owing to overwhelming efficacy seen; and (b) timescales.
2	Although I agree that there is uncertainty regarding overall survival prolongation extent, it seems very unlikely that DFS outcomes will change significantly with further follow up in the first three years for patients receiving the technology. I would argue that DFS, alongside the very important CNS DFS, are in themselves the clinically meaningful and patient-centric endpoints on which to focus. Given the caveats above regarding overall survival given unblinding, it seems that there is overreliance on overall survival in the ACD. Further, this is not the same technology as previous generation TKIs in similar populations, and it seems to me to be unfair to make this comparison (as I have also brought up verbally in the committee meeting).
3	It seems important to me in modelling that patients receiving the technology versus those observed should be subjected to the same outcome measures and timings – i.e. that cure or progression assumptions are dealt with in the same manner from the outset for both groups.
4	The emphasis on cure seems to underestimate the significant clinical impact of delaying progression. While it is clear that there is significant uncertainty about the proportion of patients cured by the technology, there is no doubt to me that there will a significant survival impact from either cure or delaying progression. To me, a most conservative scenario that delays progression only in this disease with very high metastatic propensity still would result in substantial clinical efficacy. It seems implausible that treating these patients earlier, many of whom simply have subclinical stage IV disease, will not have very significant overall survival benefits.
5	Some of the ERG modelling referred to (e.g. log normal where lines cross) appears clinically implausible to me (i.e. that patients receiving the technology do worse in the long term).
6	Downstream treatment pathway uncertainty is an issue that relates to, and is dependent upon, the availability of osimertinib upon progression for a population receiving the technology in the adjuvant setting– as per my previous written submission, in my opinion there should be full flexibility for clinicians in this regard as retreatment with osimertinib as a first line must surely be the right thing to do for patients who progress while not receiving Osimertinib at that time.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	Eric Lim
Comment number	**Comments**

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1	Has all of the relevant evidence been taken into account? Yes.
2	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I feel that the extrapolations using a family of parametric models is somewhat arbitrary (BIC and AIC criteria), and the methodology needs to be re-assessed when longer term data is released to determine if the assumptions made are appropriate.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? I believe that osimertinib should be recommended based on existing evidence that (in my opinion) is sufficiently strong.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.
5	• Section 3 "Cure" assumptions seems arbitrary and archaic. Currently defined in this consultation as alive and disease free at 5 years. However "cure" varies with a) how hard you look for recurrence and b) the time frame. In my opinion, decisions should be made at face value in that death and recurrence at reduced by 80% during the trial interval as presented.
6	• Section 3.3 - Retreatment with osimertinib would be offered to some people whose disease has progressed In the case of recurrent (metastatic) disease, the decision to exclude treatment based on receipt of adjuvant osimertinib seems overtly restrictive, especially in the presence of EFGRm.
7	• Section 3.9 - There is uncertainty about the company's cure assumptions Given cure itself is a function of method of detection of disease and timeframe, the difference between "delay" and "cure" itself is arbitrary. Ultimately, it could be stated that all cancer is cured given sufficient delay in presentation.

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8	• Section 3.13 - Osimertinib is not recommended for routine use in the NHS It is quite a hard and punitive stance when the the trial was stopped early (from an ethical point of view) because the data is overwhelmingly in favour of osimertinib. It seems that the recommendation is suggesting that trials should continue accruing death and recurrence in the non-treatment arm in order to satisfy a higher level of certainty for the purposes of commissioning.

Insert extra rows as needed

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Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection: A Single Technology Appraisal

Addendum: ERG's commentary on the company's ACD response

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	1st September 2021

1. Introduction

In July 2021, the National Institute for Health and Care Excellence (NICE) issued its Appraisal Consultation Document (ACD) for osimertinib for the adjuvant treatment of epidermal growth factor reception (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after complete tumour resection.[1] Section 1.1 of the ACD states: *"The committee recognised that osimertinib is promising, but was not persuaded that there is sufficient evidence of clinical and cost effectiveness to recommend it for routine commissioning for the adjuvant treatment of stage 1b to 3a non-small-cell lung cancer (NSCLC) after complete tumour resection in adults whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations."* Sections 1.2 and 1.3 of the ACD indicate that the Appraisal Committee believed that osimertinib might be suitable for use in the Cancer Drugs Fund (CDF) and describe the requirements of a proposal for its inclusion in the CDF in this indication.

In August 2021, the company submitted a written response to the NICE ACD.[2] The company's ACD response states that the company does not believe that osimertinib is an appropriate candidate for the CDF. The company's response includes discussion around five areas of uncertainty raised in the NICE ACD:

1. Uncertainty about the extent to which a benefit in disease-free survival (DFS) translates into a benefit in overall survival (OS)
2. Uncertainty around how osimertinib's mode of action and clinical benefit differs from previous first and second generation EFGR tyrosine kinase inhibitors (TKIs)
3. Uncertainty about the company's OS predictions
4. Uncertainty about the company's cure assumptions and timing of cure
5. Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib).

The company's ACD response[2] also includes further discussion regarding why osimertinib is not considered to be an appropriate candidate for the CDF and additional discussion relating to innovation. Whilst the Evidence Review Group (ERG) was anticipating that the company would provide additional data on DFS from a later data-cut of ADAURA,[3] this has not been presented as part of the company's ACD response. Similarly, no further data on OS from ADAURA have been presented.

This ERG addendum provides a commentary on the key issues discussed in the company's ACD response.[2]

2. Commentary on key issues discussed in the company's ACD response

Issue 1: Uncertainty about the extent to which a benefit in DFS translates into a benefit in OS

The NICE ACD[1] states that *"The committee concluded that it was not certain to what extent a benefit in disease-free survival translates into a benefit in overall survival."* The company's ACD response[2] provides a detailed discussion to support the argument that the DFS benefit observed in ADAURA[3] will translate into an OS benefit. In particular, the company argues that:

- The DFS benefit observed in the trial is likely to be maintained
- If the DFS benefit significantly reduces over time, osimertinib will remain cost-effective. This discussion includes details of a tipping-point analysis in which different hazard ratios (HRs) for DFS were assumed in Stage II/IIIA patients in the future data-cuts of ADAURA,[3] which resulted in a worst-case [redacted] for osimertinib versus placebo and an incremental cost-effectiveness ratio (ICER) for osimertinib versus active monitoring of £17,662 per quality-adjusted life year (QALY) gained.
- Even if there is no OS advantage, extending DFS will provide patients with invaluable long-term benefits compared with active monitoring
- Preventing/delaying recurrence will delay or avoid costs of progression to advanced disease
- There is a strong clinical rationale to suggest that osimertinib's DFS benefit will translate into OS gains, including the unprecedented magnitude of DFS benefit observed in ADAURA,[3] the reduced rate of recurrence with distant/central nervous system (CNS) metastases and superior OS benefit observed in the metastatic setting compared with first generation TKIs.

The ERG's view regarding the uncertainty around DFS and the magnitude of any resulting OS gain for adjuvant osimertinib is described in the ERG report[4] (Sections 4.2.3 and 5.3.4). The ERG's view on this issue remains unchanged. The ERG agrees that there is value in extending DFS in patients with resected EGFRm NSCLC. The company's model predicts a substantial OS gain of [redacted] years as a consequence of improved DFS. As discussed in the ERG's technical engagement (TE) response,[5] the ERG agrees that the reasons provided as to why adjuvant osimertinib is expected to result in a significant OS benefit are all plausible. However, due to the immaturity of OS data from ADAURA[3] (9 deaths [2.7%] in the osimertinib arm and 20 deaths [5.8%] in the placebo arm), the magnitude of any OS benefit is very uncertain. The impact of this uncertainty has been explored within the ERG's exploratory analyses (see ERG report, Section 5.4). The ERG believes that the Appraisal Committee's conclusion in the ACD regarding the uncertainty around OS gains is reasonable. The ERG notes the following additional observations:

- The company has not provided the economic model used for the tipping-point analysis and it is unclear how this scenario has been implemented. In addition, the description provided in the company's ACD response[2] indicates that it relates to the Stage II/IIIA population rather than

the overall population. The company's ICER for this subgroup was lower than that for the overall population used in the company's base case analysis (company's subgroup ICER = £5,292 per QALY gained; company's base case ICER for overall population [post-clarification model] = £11,136 per QALY gained).

- The company's ACD response[2] argues that the avoidance of fear of relapse is important to patients and may not be fully captured in the company's clinical and economic analyses. The ERG notes that the company's updated model provided after the clarification round was amended to assume general population utility values in the disease-free (DF) health state, with patients experiencing comparatively lower utility after distant relapse. The ERG does not believe that an additional utility gain should be applied over and above the utility value already assumed in the DF state of the company's economic model.
- The company argues that CNS metastases are associated with an increased economic burden, that the true value of osimertinib in the adjuvant setting may not be fully captured in the economic analysis and that the company's ICERs may be conservative. The ERG notes that costs associated with managing CNS metastases are already included in the company's economic model; as such, it is unclear what the company believes is missing from the analysis.

Issue 2: Uncertainty around how osimertinib's mode of action and clinical benefit differs from previous first and second generation EFGR TKIs

The NICE ACD[1] states that *"The committee was concerned that the experience with earlier generation TKIs such as erlotinib suggested that disease often recurred after stopping treatment. However, a clinical expert cautioned against placing too much weight on this because erlotinib does not have the same brain penetration as osimertinib."* The company's ACD response[2] argues that making comparisons against other trials of adjuvant TKIs is not appropriate and highlights that in comparison to other EGFR-TKIs, osimertinib has a higher blood-brain barrier penetration, resulting in a clinically meaningful reduction in the risk of CNS progression in early stage NSCLC versus placebo. The company's response also highlights that the magnitude of DFS benefit with osimertinib appears to be greater than that for earlier generation EGFR-TKIs in the adjuvant setting. The company's response further argues that it is not appropriate to cite the editorials by Gyawali *et al.*[6] and Uprety *et al.*[7] in the NICE ACD as these *"are not robust, peer reviewed nor reflective of the clinical community across the UK."*[2]

The ERG notes that the company's submission (CS)[8] also highlights that previous trials of EGFR-TKIs erlotinib and gefitinib as adjuvant therapies have demonstrated initially promising DFS rates, but few long-term benefits. The ERG considers that, given the limited OS data available, it is reasonable to consider this aspect of benefit to be highly uncertain. The ERG also notes that the NICE ACD[1] already

refers to the clinical expert's view that osimertinib has greater blood-brain penetration than earlier generation TKIs.

Issue 3: Uncertainty about the company's OS predictions

The NICE ACD[1] includes a discussion of the Appraisal Committee's view regarding the company's survival modelling approach, cure assumptions and model predictions of OS. The company's ACD response[2] states that:

- The company disagrees with the Appraisal Committee's conclusion that the company's choices of extrapolations were driven by the cure assumption rather than goodness-of-fit
- The cure assumption is an independent function and is separate from the extrapolated curves
- The company disagrees that the survival predictions may be optimistic
- It is reasonable to consider alternative survival models, but only if they are clinically plausible.

The ERG's views regarding the company's survival modelling can be found in the ERG report[4] (Section 5.3.4). The ERG's view remains unchanged and is not repeated here. With respect to the points raised in the company's ACD response,[2] the ERG notes the following:

- The company's ACD response[2] does not present any new evidence which reduces uncertainty around the modelled OS benefits for adjuvant osimertinib.
- The company's ACD response[2] states that the selection of parametric survival models was *"in no way influenced by the cure assumption consideration."* The ERG believes that this statement is inaccurate and notes that page 87 of the CS[8] states that *"the exponential, Weibull, Gompertz and loglogistic distributions can be excluded as they produce pessimistic long-term survival estimates incompatible with the underlying functional cure assumption."*
- The company's ACD response[2] states that *"After the defined cure timepoint, survival for the proportion of patients who are assumed to be cured is adjusted to follow that of the age and sex matched general population."* This is an inaccurate description of the company's implemented cure assumption. In the company's economic model, patients in the DF state are assumed to have general population mortality risks at all timepoints. The cure assumption reduces the probability of relapse predicted by the parametric survival models by 95% after the cure timepoint (5 years in company's base case analysis).
- The company's ACD response[2] argues that extrapolated disease recurrence may be overestimated and that company is being conservative because the risk of recurrence is expected to be lower beyond the maximum follow-up timepoint in ADAURA.[3] The ERG believes that the parametric survival models fitted by the company reflect the trend in the underlying hazard of relapse over time in the trial and that the structural cure assumption results

in low relapse probabilities beyond the cure timepoint, irrespective of which parametric survival model is selected.

- The company's ACD response[2] argues that ERG additional sensitivity analyses (ASAs) 4a and 4b are not clinically plausible because the curves for the transition from DF to first-line treatment for distant metastases (DM1) cross after around 22 years in ASA4a and at 11 years for ASA4b. Figures 1 and 3 of the company's ACD response show scenarios in which the extrapolated functions cross. However, these plots do not include the structural cure assumption and therefore they do not reflect the scenarios presented in the ERG report. When the cure assumption is included, the overall DFS curves do not cross (see Figure 1 and Figure *2*)
- With respect to ASA4b and ASA5, the company's ACD response[2] argues that *"no substantial justification has been provided as to why different models have been selected in this scenario."* The ERG believes that it is reasonable to consider relaxing the requirement for using the same model form in both treatment groups, as has been done in ASA4b and ASA5, because the intervention group relates to an active treatment, whilst the comparator group does not. However, the ERG notes that these scenarios were presented only as sensitivity analyses and do not reflect the ERG's preferred analyses. As described in the ERG report,[4] ASA5 reflects a highly pessimistic analysis.

Figure 1: DFS plot for ERG ASA4a (pessimistic)

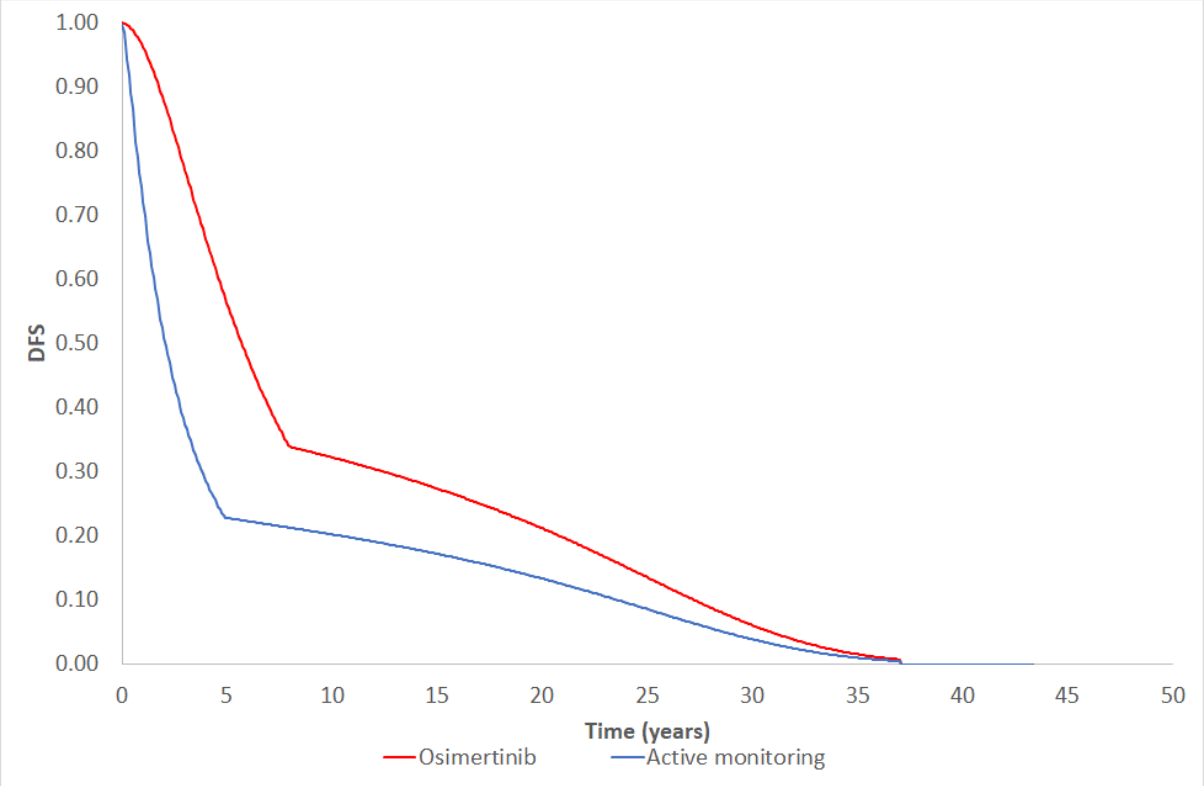
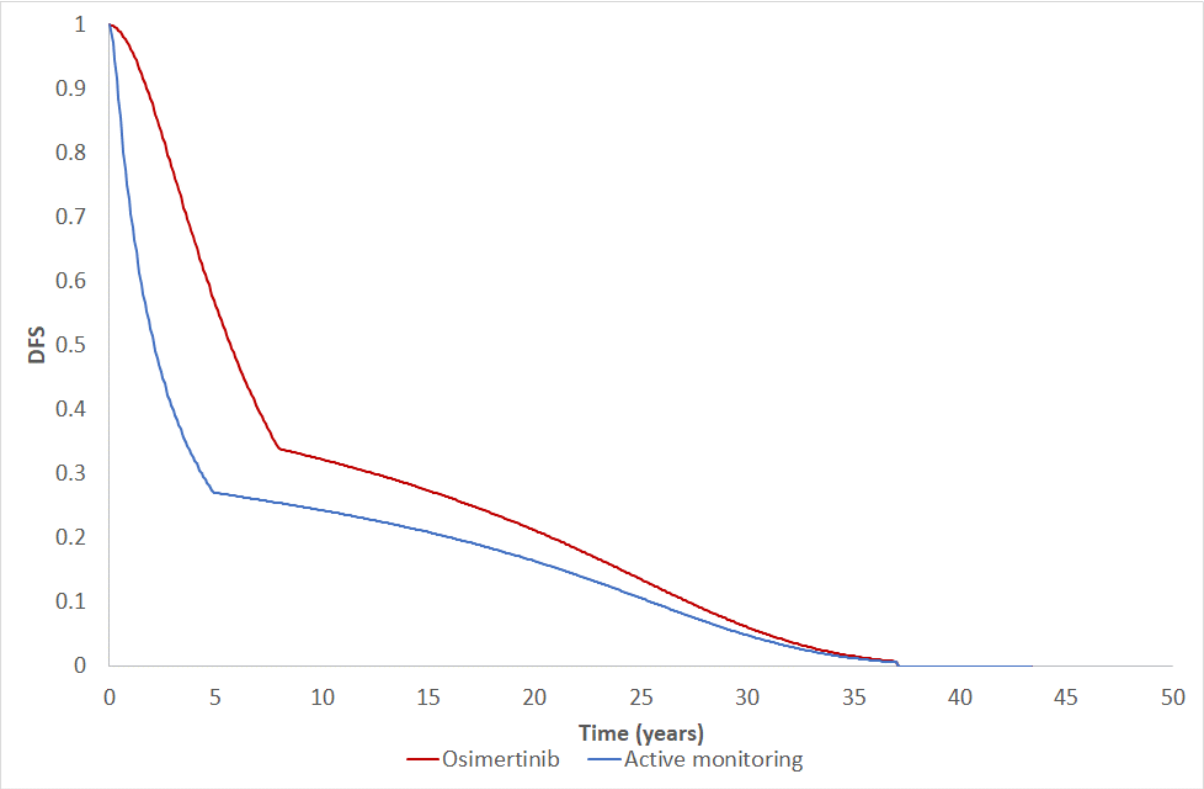


Figure 2: DFS plots for ERG ASA4b (pessimistic)



Issue 4: Uncertainty about the company's cure assumptions and timing of cure

The NICE ACD[1] states that *"the Appraisal Committee concluded that there was significant uncertainty about the company's cure assumptions."* The company's ACD response[2] states that:

- A significant proportion of patients already achieve a functional "cure" with current standard of care
- The 5-year functional cure in both arms is supported by published clinical evidence and expert clinical opinion
- The ERG's preferred pessimistic scenario (cure at 8 years for the osimertinib arm versus 5 years for active monitoring) is overly pessimistic and clinical experts agreed that timing of the cure assumption should be consistent across arms, regardless of timepoint
- Without the structural cure assumption, osimertinib remains a cost-effective use of NHS resources.

The ERG's view regarding the company's cure assumptions can be found in the ERG report[4] (Section 5.3.4). The ERG's view remains unchanged. With respect to the issues raised in the company's ACD response,[2] the ERG notes the following:

- The company's approach to modelling cure is somewhat unconventional. The company's ACD response emphasises that *"the majority of patients are no longer at risk of disease recurrence and thus providing support for the assumption of functional cure in this patient population."*

However, the company's survival modelling characterises the risk of relapse in a single homogenous group of patients and the implemented cure assumption includes an indefinite residual risk of relapse beyond the cure timepoint. The ERG would have preferred to see formal statistical modelling of cure (e.g. using a mixture-cure model), but accepts that the limited OS data from ADAURA[3] may have precluded such an analysis. Such an analysis may have been possible for the transitions which inform DFS.

- The ERG's clinical advisors broadly agreed with the company's 5-year cure assumption for patients who undergo active monitoring. However, as discussed in the ERG report[4] (Section 5.3.4) the clinical advisors suggested that it was feasible that adjuvant osimertinib may delay disease relapse, rather than prevent it. This is the reason why the ERG presented their preferred pessimistic scenarios as well as the additional sensitivity analysis ASA5.
- The company's ACD response[2] includes an additional analysis which assumes an 8-year cure point in both treatment groups (see Table 1). This analysis resulted in an ICER for osimertinib versus active monitoring of £11,557 per QALY gained. However, this analysis is not consistent with the company's experts' views on cure for the active monitoring group, and it ignores the ERG's advisors' concerns that osimertinib may only delay relapse, which represents the rationale for the ERG's preferred pessimistic analysis.
- The company's ACD response[2] includes a scenario which excludes the cure assumption from both treatment groups (see Table 1). This analysis resulted in an ICER for osimertinib versus active monitoring of £17,219 per QALY gained. However, the ERG does not consider this analysis to be meaningful because it applies parametric survival models which do not explicitly allow for the potential of cure to a population in whom cure is expected for a proportion of patients.

Issue 5: Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib)

The NICE ACD[1] discusses the Appraisal Committee's concerns that the company's economic analysis does not fully reflect the NSCLC treatment pathway. The company's ACD response[2] states that the company has further engaged with clinical experts to inform the assumptions regarding the NSCLC treatment pathway with and without adjuvant osimertinib. In summary, the company's ACD response states the following:

- Currently, osimertinib represents standard care for the first-line treatment of metastatic EGFRm NSCLC. The estimated proportion of patients who receive first-line osimertinib in DM1 in ERG scenario ASA3 (proportion = [redacted]) includes patients who started on first and second generation EGFR-TKIs prior to osimertinib becoming established standard care. The company believes that this estimate should not be used and instead the model should reflect only the proportion of newly diagnosed/relapsed patients receiving osimertinib. The company believes

that this would result in a higher proportion of 80% to 100% receiving osimertinib in DM1. The company's ACD response[2] reports the results of ASA3 with alternative assumptions that 80% and 90% of patients receive first-line osimertinib for distant metastases. These scenarios result in ICERs which are lower than ASA3 for both the ERG's preferred optimistic and pessimistic scenarios (see Table 1).

- The impact of introducing adjuvant osimertinib on the downstream treatment pathway is unknown. Clinicians consulted by the company agreed that they would consider re-treatment with osimertinib for patients who completed 3 years of adjuvant treatment with osimertinib if they relapsed >12 months after treatment completion. Other TKIs would not be used. The company highlights that the slides presented at the Appraisal Committee Meeting stated that clinical experts suggested that *"patients who progress after treatment with osimertinib, should be treated like other patients newly presenting with metastatic disease and would be offered osimertinib if they meet the criteria."* The proportion of patients who will be re-treated with osimertinib is uncertain. The company's ACD response[2] presents additional scenarios assuming re-treatment proportions of 40%, 50% and 60%. These analyses result in ICERs which are higher than the ERG's preferred analyses (no re-treatment), but which remain below £30,000 per QALY gained (see Table 1).
- The company's ACD response[2] highlights that the economic model assumes that all patients who progress whilst on adjuvant osimertinib receive pemetrexed plus cisplatin (PDC).
- For patients who progress to second-line treatment, the company's ACD response[2] states that atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) is not commonly used. The company also states that it would be inappropriate to include this regimen as a first-line treatment option as it is only reimbursed in the second-line setting.

Table 1: Summary of ICERs generated from company's additional analyses

Scenario	ERG optimistic: 5-year cure in both groups	ERG pessimistic: 8-year cure in osimertinib group	Company scenario: 8-year cure in both groups	Company scenario: No cure
ERG preferred analysis	£9,979	£20,417	£11,557	£17,219
ASA3a: Different mix of TKIs (80% osimertinib in DM1)	£16,846	£29,970	£20,267	£28,626
ASA3a: Different mix of TKIs (90% osimertinib in DM1)	£13,706	£25,631	£16,296	£23,454
40% patients re-treated with osimertinib	£10,644	£22,491	£13,480	£20,977
50% patients re-treated with osimertinib	£10,808	£22,989	£13,945	£21,854
60% patients re-treated with osimertinib	£10,972	£23,478	£14,404	£22,709

ERG - Evidence Review Group; ASA - additional sensitivity analysis; TKI - tyrosine kinase inhibitor; DM1 - first-line treatment for distant metastases

The ERG notes the following points relating to this aspect of the company's ACD response:[2]

- The ERG's preferred optimistic and pessimistic analyses assume that all patients in the active monitoring group receive first-line osimertinib following distant recurrence, rather than other EGFR-TKIs.
- The estimated proportion of patients receiving first-line osimertinib (proportion = [redacted]) was provided by the company as part of the factual accuracy check of the ERG report and was based on national prescribing data from Q1 2021.[9] Whilst the company's assumption that the market share for osimertinib is likely to increase may be reasonable, the estimates of 80%-100% appear to be based on speculation and do not reflect current usage. The NICE ACD[1] states that the Appraisal Committee concluded that *"it was appropriate to base its decision making on the latest available prescribing data."* The company may wish to present additional analyses using up-to-date prescribing data which reflect the current usage of osimertinib in the metastatic setting. The ERG does not have access to these data and cannot present these analyses.
- The NICE ACD[1] states that the Appraisal Committee concluded that *"retreatment with osimertinib would be offered to some people whose disease had progressed after having osimertinib as an adjuvant treatment."* The ERG's preferred analyses assume no re-treatment with osimertinib. This assumption was based on personal communication received from NHS England. As discussed in the ERG report[4] (Section 4.2.3), the proportion of patients who would be re-treated with osimertinib is unknown and there are no clinical studies of osimertinib in patients with metastatic disease who have previously received adjuvant osimertinib. The ERG's clinical advisors commented that re-treatment with osimertinib would likely not be as effective as first-time use in the metastatic setting.
- The ERG agrees that currently the use of first-line ABCP in the metastatic setting is low and that most patients currently receive first-line osimertinib or other TKIs. The ERG's clinical advisors stated that if TKIs are not appropriate, first-line treatment would include ABCP as an option. For patients who are not fit or who have contraindications to some of the components of the ABCP regimen, platinum doublet chemotherapy may be used. The NICE ACD[1] states that *"The Cancer Drugs Fund clinical lead also said that atezolizumab, bevacizumab, carboplatin and paclitaxel would be offered first line if treatment with tyrosine kinase inhibitors is inappropriate."* The ERG's clinical advisors also commented that ABCP is currently commonly used in the second-line setting.

Additional issue: Innovation

The company's ACD response[2] argues that the company's ICERs are highly conservative because several aspects of value are not included in their economic analyses: (i) the avoidance of fear of relapse; (ii) indirect costs associated with disease recurrence/metastases; (iii) separate impacts of CNS

metastases on patients' health-related quality of life (HRQoL); (iv) the impact of living disease-free on a patient's social life, ability to work, mental health and emotional wellbeing and (v) impacts on family members and carers.

The ERG believes that the company's economic analysis is in line with the NICE Reference Case.[10] As such, it is not appropriate to include indirect costs. Whilst carer effects can be included within an economic analysis, the company has not presented any evidence to quantify these impacts, nor have they provided any justification that such effects would be greater than technologies displaced by the use of adjuvant osimertinib. As discussed above, the company's model includes general population utility values for patients in the DF state and already includes additional costs associated with the treatment of CNS metastases. The ERG does not believe that any relevant aspects of the value of adjuvant osimertinib have clearly been omitted from the company's economic analyses.

Additional issue: Appropriateness for the CDF

The company's ACD response[2] argues that adjuvant osimertinib is not an appropriate candidate for the CDF because it is cost-effective at the Patient Access Scheme (PAS) price and because further data collection would not reduce uncertainty in a reasonable time frame.

The ERG believes that demonstrating plausible potential for cost-effectiveness is a requisite for entry into the CDF, rather than a reason why a technology should not be considered as a candidate for the CDF. The ERG also believes that collecting further data from ADAURA[3] would inevitably reduce uncertainty, particularly around DFS, including the impact of stopping treatment at 3 years. Despite the uncertainty around the long-term effectiveness of osimertinib, the ERG notes that their preferred optimistic and pessimistic ICERs remain below £30,000 per QALY gained and that the ICER for adjuvant osimertinib is higher only under pessimistic assumptions. The ERG believes that if available, the Appraisal Committee may find the following analyses useful:

(i) Updated analyses which incorporate updated clinical data from later data-cuts of ADAURA
(ii) Updated estimates of current prescribing rates for osimertinib in the metastatic setting.

3. References

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