National Institute for Health and Care Excellence

Health Technology Evaluation

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Johnson & Johnson	None	N/A
	AstraZeneca	A single technology appraisal is appropriate for this topic	Thank you for your comment.
	EGFR+ UK	An evaluation of the clinical and cost effectiveness of amivantamab in combination with carboplatin and pemetrexed for EGFR exon 20 patients is not just appropriate, but necessary, as there is a huge unmet need for this patient population.	Thank you for your comment. The committee will take unmet need into account as part of the appraisal process.
	BTOG	Appropriate	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
Wording	Johnson & Johnson	Johnson & Johnson suggests aligning the wording of the draft remit with the wording of the anticipated license from the Medicines and Healthcare products Regulatory Agency (MHRA), as per the following: "*To appraise the clinical and cost effectiveness of amivantamab within its targeted marketing authorisation* [redacted]	Thank you for your comment. The remit wording has been kept in line with the publicly available clinical trial information for transparency and to avoid breaching the confidentiality of the anticipated license.
	AstraZeneca	No comments	N/A
	EGFR+ UK	Yes	Thank you for your comment.
	BTOG	Yes	Thank you for your comment.
Timing issues	Johnson & Johnson	There are no targeted treatments available through routine NHS commissioning for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC and outcomes associated with current treatments used in this population are generally poor. The lack of targeted treatment options has been exacerbated by the withdrawal of the marketing authorisation of mobocertinib in the second-line setting, leaving patients who have EGFR Exon20 insertion mutation-positive advanced NSCLC with no targeted treatments available.	Thank you for your comments. The committee will take unmet need, the natural history of the disease and the clinical evidence into account as part of the appraisal process.

Section	Stakeholder	Comments [sic]	Action
		Outcomes in patients who have advanced NSCLC with EGFR Exon20 insertions mutations are worse compared to patients with common EGFR mutations (Exon19 deletions or L858R point mutations on Exon 21).[(1)] This is attributed to the fact that, unlike common EGFR mutations, EGFR Exon20 insertion mutations exhibit various degrees of primary resistance to conventional EGFR-TKIs due to conformational changes in the kinase binding pocket, leaving patients with very few, unspecific and ineffective treatment options.[(2)] Therefore, there is an urgent need for therapies with novel and targeted mechanisms of action to provide improved outcomes for patients with untreated EGFR Exon20 insertion mutation-positive, advanced NSCLC. Amivantamab is an innovative, bi-specific antibody that has been shown to address this need through data from the registrational Phase 3 PAPILLON trial.[(3)] In the PAPILLON trial, which included patients with locally advanced or metastatic NSCLC with EGFR Exon20 insertion mutations, amivantamab with carboplatin and pemetrexed significantly improved progression free survival (PFS) by blinded independent central review (BICR) compared with carboplatin and pemetrexed: 11.4 months vs 6.7 months, HR, 0.395 (95% CI, 0.30–0.53; P<0.0001). The safety profile of amivantamab plus chemotherapy was consistent with individual agents, with low rates of treatment-related discontinuations associated with amivantamab (7%).[(3)]	
	AstraZeneca	No comments	N/A
	EGFR+ UK	Very urgent. Unlike other EGFR patients, who respond to TKIs, and have a number of different treatment options and drug lines available to them, Exon 20 patients have very few treatment options available. They have significantly	Thank you for your comment. The committee will take

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		poorer outcomes than patients with more common EGFR mutations as a result of this. As such, there is a huge unmet need for this patient groups.	unmet need and outcomes with the current standard of care into account as part of the appraisal process.
	BTOG	There is no currently available targeted therapy for this small cohort of NSCLC patients with a known genomic driver in the NHS and currently available therapies are non-targeted.	Thank you for your comment. The committee will take the current treatment pathway and unmet need into account as part of the appraisal process.
Additional comments on the draft remit	Johnson & Johnson	No additional comments	N/A
	AstraZeneca	No comments.	N/A
	EGFR+ UK	None	N/A
	BTOG	None	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Johnson & Johnson	1. In paragraphs 1 and 2 of the draft scope, prevalence data are reported which are based on Cancer Registration Statistics from 2020. However, more recent data are available from the National Lung Cancer Audit (NLCA) State of the Nation Patient and Public Report 2024.[4] Johnson & Johnson would like to replace the existing wording in paragraphs 1 and 2 of the background section to the following, in order to best capture the most recent epidemiology data for lung cancer in the UK: *"Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 10% of all new cancer cases and 20% of all cancer deaths in 2020.[5] More recent data published in the last two years continues to shed light on the ever-evolving landscape of NSCLC in the UK. Since 2020, lung cancer remains among the top five most common causes of cancer in England[5], with the number of newly diagnosed patients increasing from 31,371 in 2020, to 36,886 in 20223.[4] Most cases of newly diagnosed lung cancer were at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage 3) or to other parts of the body (metastatic disease; stage 4).[4] In 2022, 58.2% (around 21, 500) of people diagnosed with lung cancer in England had NSCLC.* *Around 14% of people with NSCLC in Europe have mutations in the gene coding the EGFR (pooled prevalence data from 62 studies, 95% CI: 12.7% to 15.5%).[6] Exon20 is part of the EGFR gene that can be mutated by an addition to the DNA sequence (an insertion mutation). Mutations in Exon20 occur in 0.7% (around 170) of people diagnosed with any stage NSCLC and in 6.1% of patients with any stage EGFR-positive NSCLC.[7] However, they*	Thank you for your comments. The background section has been updated to use the NLCA 2024 report data where appropriate. The 58.2% value has not been used as this would exclude people who were not tested but who had NSCLC. The proportion of people in the 2024 NLCA who were not tested was assumed to be NSCLC, in line with the footnotes in the NLCA report which stated that people whose lung cancer was not tested were analysed as NSCLC.

Section	Consultee/ Commentator	Comments [sic]	Action
		are associated with poorer outcomes than other EGFR mutations due to the lack of effective targeted treatments.[8]*"* 2. In paragraph 3, the draft scope specifies "*the treatment pathway can be divided into interconnected decision points based on the number staging system and line of therapy*". When articulating the treatment pathway, Johnson & Johnson suggests emphasising there is currently no established treatment pathway following the removal of NICE guidance for patients with EGFR Exon20 insertion mutation-positive NSCLC and there are no NICE recommended therapies for this specific population. Therefore, Johnson & Johnson suggests amending paragraph 3 to: *"There is currently no established treatment pathway for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC and prior NICE guidance for this population has been withdrawn following the withdrawal of mobocertinib by the manufacturer. In addition, there are no treatments that are recommended by NICE specifically within this population. A range of non-targeted therapies are prescribed to patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC, with treatment choice in the first-line setting being influenced by the presence of biological markers (including programmed cell death 1 ligand PD-L1 status), oncogenic driver genetic alterations, and histology (squamous or non-squamous)."*	The background section is intended to give a broad overview of the disease area. Conventional EGFR TKIs have been retained in the scope background although it has been clarified that their limited efficacy may contribute to poor survival in Exon 20 positive disease in line with scope reference 7. Amivantamab as a NICE recommended treatment has been removed from the background.

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		3. In paragraph 4, appraisals of EGFR TKIs that are recommended by NICE in patients with EGFR-positive NSCLC are listed. However, these appraisals do not align with the population within this scoping document. Therefore, Johnson & Johnson suggests amending the wording of paragraph 4 to: "*There is no standard treatment pathway for treating EGFR Exon20 insertion mutation-positive advanced NSCLC. For people with EGFR mutation-positive NSCLC who have not previously had treatment, NICE recommends the following EGFR TKIs (osimertinib [TA 654], dacomitinib [TA 595], afatinib [TA 310], erlotinib [TA 258], and gefitinib [TA 192]). However, these appraisals are focussed on patients with common EGFR mutations (Exon19 deletions or Exon21 L858R point mutations), and do not reflect the population within this scoping document which is specific to patients with EGFR Exon20 insertion mutations. Additionally, EGFR TKIs have been reported as having limited efficacy when EGFR Exon20 insertions are present due to conformational changes in the molecular structure of EGFR which affect the ability of TKI binding to and inhibiting the EGFR receptor. The absence of approved targeted medicines underscores the unmet need for these patients, as there are no targeted medicines available that have demonstrated a significant added benefit."* 4. The draft scope incorrectly states that amivantamab is recommended for EGFR Exon20 insertion mutation-positive NSCLC that has been previously treated with platinum-based chemotherapy (TA850). Please amend to "Although licensed in this setting, a*mivantamab is not recommended by NICE for EGFR Exon20 insertion mutation-positive*	

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		advanced NSCLC that has been previously treated with platinum-based chemotherapy (TA 850)" 5. In paragraphs 4 and 5, the draft scope includes additional treatment options such as platinum doublet chemotherapy, atezolizumab combination, atezolizumab monotherapy, and pembrolizumab monotherapy. However, these have not been specifically investigated in patients with EGFR Exon20 insertion mutation-positive NSCLC. Therefore, Johnson & Johnson suggests amending wording in paragraph 5 to: *"Aside from EGFR TKIs, NICE has recommended platinum-based chemotherapy (NICE guideline 122) and immunotherapy (atezolizumab [TA 705], atezolizumab with bevacizumab plus carboplatin and paclitaxel, pembrolizumab [TA 584], and pembrolizumab with carboplatin and pemetrexed [TA 683]) as treatment options for patients with untreated metastatic NSCLC. However, these have only been investigated within a wild-type population rather than in patients with EGFR Exon20 insertion mutation-positive NSCLC which is the population within this scoping document."*	
	AstraZeneca	No comments.	N/A
	EGFR+ UK	It needs to be made clear that Exon 20 patients have poorer treatment options and outcomes as they don't typically respond to TKIs that are the usual treatment for EGFR mutations. "NICE guidance recommends the TKIs osimertinib, dacomitinib, afatinib, erlotinib, and gefitinib as treatment options (NICE technology appraisal guidance 654, 595, 310, 258, and 192 respectively)." – reads as if this should be a standard treatment pathway for Exon 20 patients. This is misleading and	Thank you for your comments and corrections. The background section has been amended to reflect them. The error

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		not the case. Overwhelmingly, the research literature demonstrates that TKIs (with the possible exception of afatinib) are not appropriate in the patient group, as response rates are really low. The background section incorrectly states: “Amivantamab is recommended for EGFR exon 20 positive NSCLC that has been previously treated with platinum-based chemotherapy (TA850).” However, the actual TA850 recommendation states “Amivantamab is not recommended, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) after platinum-based chemotherapy in adults whose tumours have epidermal growth factor receptor (EGFR) exon 20 insertion mutations.” We know that Ami is approved for use through MHRA, however it does not currently have NICE approval (according to TA850). However, based on the published efficacy evidence and international use of Amivantamab in clinical settings, our charity (EGFR+ UK) believes that this should be available for use with Exon 20 patients, pretreated or otherwise. But this distinction needs to be made clearer in the background information. The background section states “Following disease progression with a TKI, osimertinib is recommended for EGFR T790M mutation-positive disease (NICE technology appraisal 653).” – it is unclear how this is relevant to the treatment of patients with untreated Exon 20 insertion mutations. While T790M occurs on Exon 20, it is not an insertion mutations – it is a mutation that this is responsible for TKI resistance. This isn’t really something we see in our Exon 20 patients, and doesn’t seem relevant to this review.	around amivantamab has been corrected.

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		The background states “Platinum doublet chemotherapy and atezolizumab in combination are also treatment options (NICE guideline 122 and NICE technology appraisal 584). – just to note, 584 is platinum doublet chemotherapy and atezolizumab *and bevacizumab*. – this is missing from the description.	
	BTOG	Only inaccuracy (background, para 4) is that NICE does NOT recommended Amivantamab for treatment post platinum doublet chemotherapy (TA850)	Thank you for this comment. The final scope has been amended to correct the error.
Population	Johnson & Johnson	Johnson & Johnson agrees with the proposed population as per the draft scope issued by NICE. However, Johnson & Johnson would propose a slight change to the wording to align with the anticipated MHRA license: [redacted]	The population wording has been kept in line with publicly available clinical trial information.
	AstraZeneca	No comments	N/A
	EGFR+ UK	Should be made clear that Exon 20 patients represent around 10% of those with EGFR mutations (which is reflected in our membership where we have 9% of patients with Exon 20 mutations).	Thank you for your comments. The first has been clarified in the background section. The second refers to a distinct population and scope is limited to the

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		Only untreated patients are included in the current appraisal, however there is a huge unmet need amongst patients who have previously received chemotherapy.	population specific to the appraisal which is untreated EGFR exon 20 positive NSCLC.
	BTOG	The population is clearly defined, but the correct type of genomic analysis has to be carried out to identify the patients. The test is commissioned but not all centres currently do this test	Thank you for your comment. This has been considered in the section of the final scope titled “Economic analysis”
Subgroups	Johnson & Johnson	The registrational Phase 3 PAPILLON clinical trial has demonstrated consistent efficacy across all pre-specified subgroups.(3) Therefore, subgroup analyses, as proposed in the draft scope, are not considered appropriate.	Efficacy for the subgroups listed in the draft scope was not reported in the Zhou et al publication referenced. The subgroups have been maintained in the final scope to allow committee to consider any available evidence or clinical opinion.
	AstraZeneca	No comments	N/A
	EGFR+ UK	The sub-groups seem appropriate. However, there is a growing body of evidence that suggests the exact location of the Exon 20 insertion mutations may indicate how well (or not) a patient is likely to respond to treatment.	Thank you for your comment. This subgroup has been

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		Considering the different sub-mutations of Exon 20, along with co-mutations and TP53 might also be worth considering (although this may be too granular to get meaningful/powered data).	added to allow committee to consider it should there be any available evidence.
	BTOG	No	Thank you for your comment.
Comparators	Johnson & Johnson	There is no clear treatment pathway or established standard of care (SoC) within EGFR Exon20 insertion mutation-positive advanced NSCLC and a range of treatments are prescribed to patients. This has been validated through advisory boards held by Johnson & Johnson in May 2024 and June 2023 with UK oncologists. The advisory boards highlighted that, on average, the majority of patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC are prescribed a form of platinum-based chemotherapy (carboplatin with pemetrexed) with or without immunotherapy (pembrolizumab) or immunotherapy monotherapy (pembrolizumab). Advisor experts have noted limited use of EGFR TKIs in this population, citing their lack of efficacy. The lack of a clear standard of care and effective treatments for this patient population leads to significant variation in treatments across different regions, hospitals, and clinicians. This treatment variation is supported by RWE data [redacted]	Thank you for your comments. The comparators have been kept inclusive at this stage to allow committee to consider all available evidence. A rationale should be provided for excluding any scoped comparators from the evidence submission, which can then be considered by the appraisal committee.

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		Therefore, Johnson & Johnson have the following comments on the comparators listed within the draft scoping consultation: 1. Chemotherapy Advisory boards held by Johnson & Johnson in May 2024 and June 2023 with UK oncologists have shown that the dominant chemotherapy regimen being used in practice is carboplatin with pemetrexed, with negligible to no use of other chemotherapy regimens such as docetaxel, gemcitabine, paclitaxel or vinorelbine. Additionally, advisor experts have reported limited to no use of cisplatin-based chemotherapy. Therefore, Johnson & Johnson does not consider chemotherapy such as docetaxel, gemcitabine, paclitaxel or vinorelbine, or cis-platin-based chemotherapy regimens to constitute relevant comparators. 2. Atezolizumab Atezolizumab has been recommended by NICE as an option for treating patients with untreated, advanced, NSCLC (TA 705). However, this recommendation does not reflect the population being studied in this draft scope, which is specific to patients with EGFR Exon20 insertion mutation-positive NSCLC. UK RWE data collected by Johnson & Johnson from the NCRAS dataset show [redacted]. This has been supported by advisory boards with UK oncologists.	

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		Therefore, Johnson & Johnson does not consider atezolizumab to constitute a relevant comparator. 3. <u>EGFR TKIs</u> EGFR Exon20 insertion mutations are associated with *de novo* resistance to EGFR TKIs.[2, 9] Additionally, in the appraisal of amivantamab for treating EGFR Exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy, clinical experts explained that EGFR TKIs have limited efficacy when there are EGFR Exon20 insertion mutations and, because of this, are rarely used in this population and are unlikely to represent standard care in the NHS.[10] Due to their very limited efficacy and lack of specific NICE recommendations within patients with untreated EGFR Exon20 insertion mutation-positive NSCLC, Johnson & Johnson does not believe EGFR TKIs are frequently prescribed to patients within this population and should not constitute relevant comparators. If EGFR TKIs are prescribed, this is due to an incomplete testing status, lack of understanding of the genomic testing report, or the need for upskilling in the understanding of genomics and the difference between an EGFR Exon20 insertion mutation versus other EGFR Exon20 mutations (such as T790M). 4. <u>Osimertinib with chemotherapy</u> Johnson & Johnson acknowledge that osimertinib with pemetrexed and platinum-based chemotherapy is currently undergoing a NICE appraisal for untreated EGFR mutation-positive advanced NSCLC. However, Johnson &	

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		Johnson does not believe it should be included as a relevant comparator as it does not currently have an MHRA license, does not currently have a NICE-recommendation, and is not being appraised within patients with EGFR Exon20 insertion mutations; meaning it should not be considered established practice within this population in the UK.	
	AstraZeneca	No comments.	N/A
	EGFR+ UK	The comparators do not seem appropriate in this context. Why have so many been included? We recently ran a survey of our members and found that, of our Exon 20 patients, none of them received immunotherapy (alone, or in combination with chemo). Indeed, the research evidence overwhelmingly suggests that immunotherapy is not usually suitable in this patient group. Instead, the majority of our Exon 20 patients (~70%) received chemotherapy – most commonly carbo/pem, but carbo/vino and carbo/paclitaxel were also cited. Surprisingly (given the lack of research to support it), around ~30% received TKIs (most commonly Osimertinib, but also erlotinib and afatinib). And one of our patients reported receiving Amivantamab (presumably through a trial). Given that none of our patients received immunotherapies, combined with the fact that they are usually PDL1 negative, and that the literature does not support its use in Exon 20 patients, this does not seem like a valid comparator. Additionally, as the literature does not support the use of TKIs with Exon 20 patients, should these be used as comparators? This decision is probably	Thank you for your comments. Inclusion of comparators at the draft scope stage is very inclusive to allow consideration of all potential comparator treatments. The comparators from the draft scope have been retained in the final scope to allow committee to consider the evidence on all potential comparators which may be used in NHS clinical practice. We would encourage EGFR+ UK to submit any evidence and expert opinion on usage

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		more complex, given our survey data suggests that they are being prescribed on the ground…	of potential comparators.
	BTOG	All potential comparators have been included. Platinum and Pemetrexed is the most common and most appropriate comparators although there will likely be some use of immunotherapy either as single agent when PD-L1 is high (atezolizumab or pembrolizumab) or in combination (carboplatin/pemetrexed/pembrolizumab). In addition there may be some inappropriate use of standard EGFR TKIs	Thank you for your comment.
Outcomes	Johnson & Johnson	Johnson & Johnson propose the following outcome measures to be included within the draft scope: • progression-free survival (primary endpoint in the trial) • objective response rate • duration of response • overall survival • time to subsequent therapy • PFS after first subsequent therapy • time to symptomatic progression • incidence and severity of adverse events and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities • serum amivantamab concentrations and anti-amivantamab antibodies • HRQoL (EORTC-QLQ-C30 and PROMIS-PF)	Thank you for your comments. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. The outcomes have been amended where appropriate.

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		• Exploratory:
		  ○ time to treatment discontinuation
		  ○ genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone mechanisms of resistance to amivantamab in combination with chemotherapy
		EQ-5D-5L	

	AstraZeneca	No comments	N/A
	EGFR+ UK	These seem appropriate. However, mental health is really important with this group, and may not be captured by the health-related quality of life measure alone. For example, in our survey of our EGFR members, we found evidence that both anxiety and depression rates are significantly elevated in Exon 20 patients, compared to common EGFR mutations on both anxiety and depression (p<.01 in both cases) - with GAD7 and PHQ9 scores averaging above the clinical cut-offs for clinically significant (likely diagnosable) mental health issues. Our qualitative work with patients suggests this is likely to be due to increased uncertainty around treatments in this group - particularly after the withdrawal from Mobocertinib from the market. It is our belief that increasing the drug lines available for Exon 20 patients is likely to reduce some of this psychological distress – leading to an associated drop in costs of the therapeutic drugs and non-pharmacological interventions that are used in this group.	Thank you for your comment. Health-related quality of life (HRQoL) is included as an outcome on the draft scope and various measures of HRQoL (for example the EQ-5D) do contain an element corresponding to mental health. The committee are also able to consider any benefits not captured in the economic modelling and EGFR+ UK are encouraged to highlight if and why this might be

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			the case in their submission for this appraisal.
	BTOG	Yes.	Thank you for your comment.
Equality	Johnson & Johnson	<u>Ethnicity</u> EGFR Exon20 insertion mutation-positive advanced NSCLC is particularly associated with women, non-smokers and people of Asian heritage. [8, 9] There is evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce treatment delaying behaviour.[11] A recent study assessing differences in screening, diagnosis, and initial care between patients with newly diagnosed with lung cancer of Asian and White ethnicity reported that, compared with patients of White ethnicity, patients of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation.[12] Therefore, Johnson & Johnson believes that ethnicity is an equality consideration that is relevant for the committees to consider. <u>Stigma</u> Lung cancer is associated with substantial stigma owing to the perception that it is 'self-inflicted' due to the public perceiving a link between lung cancer and smoking.[13]	Thank you for your comment. The committee will consider any potential equalities issues during the course of the appraisal.

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		This stigma is compounded when considering patients with EGFR Exon20 insertion mutation-positive NSCLC given EGFR Exon20 insertion mutations are more likely to be associated with never-smokers compared with other mutations.(9) Therefore, Johnson & Johnson believes that stigma is an equality consideration that is relevant for committees to consider.	
	AstraZeneca	No comments	N/A
	EGFR+ UK	I cannot see any issues with equality here	Thank you for your comment.
	BTOG	No specific comments	N/A
Other considerations	Johnson & Johnson	<u>Unmet need:</u> There are no targeted therapies recommended by NICE for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. Additionally, there is no specific NICE guidance for these patients leading to the lack of an established standard of care in this population. Patients with untreated, advanced NSCLC with EGFR Exon20 insertion mutations have poorer treatment outcomes with currently available therapies compared to patients with other types of EGFR mutations.(1) Although platinum-based doublet chemotherapy (carboplatin with pemetrexed) offers some benefit within this population, studies have shown that chemotherapy alone is associated with modest survival improvements.(14) (15)	Thank you for your comments. The committee will take unmet need into account as part of the appraisal process.

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		The above points highlight the urgent unmet need for efficacious, targeted therapies which prolong survival beyond existing therapies in patients with untreated EGFR Exon20 insertion mutation-positive locally advanced or metastatic NSCLC. Amivantamab is a fully human, bispecific antibody that can address this need by simultaneously inhibiting the two key mechanisms of EGFR TKI resistance.(16) As an antibody, amivantamab can bind externally to the EGFR receptor and thereby inhibit the binding of the EGF ligand. Thereby bypassing the TKI binding site resistance against tyrosine kinase inhibitors.(3) Additionally, the ability to address this clinical need has been shown by results from the registrational Phase 3 PAPILLON clinical trial where amivantamab in combination with carboplatin and pemetrexed met its primary endpoint by demonstrating a significant improvement in median PFS (as assessed by BICR) compared with carboplatin and pemetrexed: 11.4 months vs 6.7 (HR, 0.395, 95% CI, 0.30–0.53, P<0.0001).(3)	
	AstraZeneca	No comments	N/A
	EGFR+ UK	No comment	N/A
	BTOG	None	N/A
Questions for consultation	Johnson & Johnson	Below are Johnson & Johnson's responses to the questions for consultation: Where do you consider amivantamab will fit into the existing care pathway for locally advanced or metastatic NSCLC?	Thank you for your comments and responses to questions.

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		Amivantamab in combination with carboplatin and pemetrexed is expected to be used as a first-line treatment for adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. Are immunotherapy containing regimens offered to people with untreated EGFR exon 20 insertion mutation-positive locally advanced or metastatic non-small-cell lung cancer in NHS clinical practice? If so, which regimens and what is considered the standard of care? There is no clear treatment pathway and no established SoC within this setting. RWE that Johnson & Johnson has collected from the NCRAS dataset highlight that [redacted] This is supported by insight gained from advisory boards held by Johnson & Johnson in May 2024 and June 2023 with UK oncologists, where immunotherapy (mainly pembrolizumab in combination with carboplatin) was cited as being used in patients with untreated advanced EGFR Exon20 insertion mutation-positive NSCLC, often being prescribed to those with high burden disease or brain metastasis. Advisor experts have highlighted that, due to its lack of benefit and high toxicity, the use of ABCP in clinical practice has been limited since 2023. Would EGFR inhibitors such as gefitinib, erlotinib, afatinib dacomitinib and osimertinib be used in untreated EGFR exon 20 mutation positive disease in NHS clinical practice?	

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		As highlighted above, there is no clear treatment pathway and no established SoC within this setting. [redacted] Advisory boards held by Johnson & Johnson in May 2024 and June 2023 with UK oncologists have highlighted that EGFR TKIs should not be prescribed to patients with EGFR Exon20 insertion mutations due to their lack of efficacy in this population. However, limited use of these agents is seen within clinical practice; with use often being attributed to an incomplete testing status, lack of understanding of the genomic testing report, or the need for upskilling in the understanding of genomics and the difference between an EGFR Exon20 insertion mutation versus other EGFR Exon20 mutations (e.g., T790m). The lack of efficacy of EGFR TKIs within patients with EGFR Exon20 insertion mutation-positive NSCLC is well-established in literature.[9] [17] [18] RWE indicates that EGFR Exon20 insertion mutations are associated with a ~170% increased risk of disease progression or death after initiating EGFR TKI treatment, compared with patients with common EGFR mutations.[19] Are there any comparator treatments that are not listed that would be used for untreated EGFR exon 20 insertion mutation positive disease in NHS clinical practice? None Are the suggested subgroups appropriate? As described in the above section for ‘subgroups’, Johnson & Johnson are not considering any subgroups separately.	

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		Is testing for EGFR exon 20 insertions mutations done routinely at this point in the treatment pathway (untreated advanced or metastatic disease)? EGFR Exon20 insertion mutations are included in the National Genomic Test Directory. The directory specifies which genomic tests are commissioned by the NHS in England and is available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ EGFR Exon20 insertion mutations are tested routinely in clinical practice as part of a panel of genes, alongside other oncogenic drivers in NSCLC, in a standardised and fully validated approach across the Genomic Laboratory Hubs (GLHs) and different hospitals throughout the UK. Testing for EGFR Exon20 insertion mutations is included in the testing panel as part of the reflex EGFR testing pathway that is conducted at diagnosis for all patients with NSCLC. As such, Johnson & Johnson does not believe that the introduction of amivantamab in patients with EGFR Exon20 insertion mutation-positive locally advanced or metastatic NSCLC will incur additional costs to the NHS that are over and above the current standard of care of EGFR testing requirements for all NSCLC patients. Thus, the costs associated with diagnostic testing for EGFR in people with NSCLC are not anticipated to be included within the base case economic analysis. Would amivantamab be a candidate for managed access?	

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		Amivantamab may be a candidate for managed access. This is to be discussed during the appraisal process. Do you consider that the use of amivantamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Stigma: The effects of stigma associated with lung cancer should be included within the decision-making process and are not inherently captured within the cost per QALY framework. Stigma is included in the NICE social value judgements principles document and as such, should be considered when deciding whether amivantamab is cost-effective in this population. Lung cancer is associated with substantial stigma, largely driven by a perception that it is 'self-inflicted' due to the public recognising the link between lung cancer and smoking.(13) This is particularly pertinent in the case of patients with EGFR Exon20 insertion mutation-positive NSCLC, as this mutation disproportionately affects never-smokers, women and patients of Asian ethnicity.(8) [redacted] The impact of stigma on people living with lung cancer, including patients and caregivers has been well-reported. In one qualitative study, barriers to symptom reporting for lung cancer patients; included blame, stigma and cultural influences.(11) Additionally, an observational, cross-sectional study	

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		has shown that some patients report feeling uncomfortable communicating their symptoms leading to delay in presentation, diagnosis and treatment (or low uptake of treatment).[20] <u>Caregiver burden:</u> Although caregiver costs and disutilities are not included within the QALY framework and have not been included within the *de novo* model that Johnson & Johnson have built, there is evidence to suggest that EGFR Exon20 insertion mutation-positive NSCLC confers a negative impact on caregivers. [redacted]	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. • Literature • Reports from a patient / caregiver study that Johnson & Johnson conducted in 2021 Reports from market research on the impact of EGFR mutated NSCLC on quality of life that Johnson & Johnson conducted in 2023 and 2024	
	AstraZeneca	Where do you consider amivantamab will fit into the existing care pathway for locally advanced or metastatic NSCLC? Amivantamab plus may be considered for treating patients with a confirmed Exon 20 insertion mutation. Would EGFR inhibitors such as gefitinib, erlotinib, afatinib dacomitinib and osimertinib be used in untreated EGFR exon 20 mutation positive disease in NHS clinical practice? Osimertinib is indicated for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.[1] Is testing for EGFR exon 20 insertions done routinely at this point in the treatment pathway (untreated advanced or metastatic disease)? Would amivantamab be a candidate for managed access? Testing for EGFR-TK mutations is well-established in clinical practice and is included in the National Genomic Test Directory.[2,3] The diagnostic guidelines outline that once a contrast-enhanced CT scan suggests lung cancer, a biopsy should be performed which will enable	Thank you for your responses to questions and comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		determination of EGFR-TK mutations.[3] This testing is performed prior to the initiation of treatment, and hence before the point at which a decision is made on which treatment to start. 1. eMC. TAGRISSO 40 mg film-coated tablets. 2024. Available from: . Accessed on 17th June 2024 2. NHSE England. National genomic test directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/(last accessed 10 Nov 2023). 3. National Institute for Health and Care Excellence (NICE). EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer [DG9]. Available at: https://www.nice.org.uk/guidance/dg9/chapter/3-clinical-need-and-practice (last accessed 10 Nov 2023).	
	EGFR+ UK	Testing for EGFR exon 20 insertions is done routinely at this point in the treatment pathway, and therefore should not be factored into the costs for this appraisal. Would amivantamab be a candidate for managed access? – Yes, absolutely! Particular when considering the current context for Exon 20 patients around the lack of suitable drug options (please see comments below for more detail). Do you consider that the use of amivantamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? – Yes, please see my comments about Anxiety and Depression rates above.	Thank you for your comments and responses to questions.

Section	Consultee/ Commentator	Comments [sic]	Action
	BTOG	Where do you consider amivantamab will fit into the existing care pathway for locally advanced or metastatic NSCLC? The trial data is for first line treatment and this is where it would fit.	Thank you for your comment.
Additional comments on the draft scope	Johnson & Johnson	1. The NICE draft scope refers to Janssen-Cilag. Could this be updated to "*Johnson & Johnson*". 2. Johnson & Johnson agrees with the intervention detailed within the draft scope issued by NICE. However, Johnson & Johnson suggests amending the wording to provide more detail over amivantamab and the Phase 3 study: *"Amivantamab (Rybrevant, Johnson & Johnson) does not currently have a marketing authorisation in the UK for* [redacted] ***PAPILLON is the registrational clinical trial for this indication. This is a Phase 3 clinical trial of amivantamab in combination with carboplatin and pemetrexed compared with carboplatin and pemetrexed and includes adult patients with previously untreated EGFR Exon20 insertion mutation-positive locally advanced or metastatic NSCLC".***	Thank you for your additional comments. The company name has been updated. The intervention wording has been amended but NICE is unable to include confidential information in the final scope so the wording has been kept in line with the publicly available clinical trial information.
	AstraZeneca	None	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	EGFR+ UK	This appraisal needs to be considered in the context of the huge unmet need in Exon 20 patients. There is currently no standard pathway for these patients at the moment, and there is a dearth of treatment options available for Exon 20 mutations. The impact of this can be seen in terms of the high levels of anxiety and depression seen in Exon 20 patients compared to EGFR patients with common mutations. One of the appraisal questions asked “Where do you consider amivantamab will fit into the existing care pathway for locally advanced or metastatic NSCLC?” While this appraisal is for untreated patients only, there is also a substantial unmet need in pretreated patients, and we are disappointed to see that only first line is being considered here. In March this year, the UK entered an unprecedented situation where the withdrawal of a drug (Mobocertinib – Takeda) left a treatment gap and an unmet need for Exon 20 patients. Mobocertinib was the only NICE-approved treatment option for this patient group after initial chemotherapy, and its removal has significantly increased the psychological distress experienced by this group, and will certainly increase mortality rates unless access to an alternative treatment option is implemented. While the current appraisal appears to be for untreated patients only, the background information suggests that Amivantamab is recommended for pretreated patients. As far as I am aware, this is not currently the case. However, I want to advocate, in the strongest possible terms, that Amivantamab should be considered for use in subsequent line treatments as well, to fill the gap left by Mobocertinib’s withdrawal. Particularly as we have evidence from members of our charity and the Exon 20 group in the USA that many patients are on this drug for years before seeing progression.	Thank you for your additional comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	BTOG	Are immunotherapy containing regimens offered to people with untreated EGFR exon 20 insertion mutation-positive locally advanced or metastatic non-small-cell lung cancer in NHS clinical practice? If so, which regimens and what is considered the standard of care? As discussed in the comparator section above, Immunotherapy is used in some centres even although the efficacy in patients with EGFR mutations is uncertain. There is limited data in patients with Exon 20 insertions. Would EGFR inhibitors such as gefitinib, erlotinib, afatinib dacomitinib and osimertinib be used in untreated EGFR exon 20 mutation positive disease in NHS clinical practice? The data on activity for standard dose EGFR TKIs is poor (less benefit than chemotherapy). There is some data (van der Wekken, Lung Cancer, August 2022) on 160mg osimertinib in EXON 20 insertions with improved outcomes but this dose is not available on the NHS. Consequently these drugs should not be used, but it is possible that they are used in some centres if the EGFR mutation results have not been understood. Are there any comparator treatments that are not listed that would be used for untreated EGFR exon 20 mutation positive disease in NHS clinical practice? No	Thank you for your comments. The committee will consider issues relating to comparators, subgroups, testing and managed access as part of the appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the suggested subgroups appropriate? No There is no evidence of which I am aware demonstrating that PD-L1 is helpful in this group and there is evidence, in other types of EGFR mutation, that PD-L1 expression does not correlate with benefit from immunotherapy. Is testing for EGFR exon 20 insertions done routinely at this point in the treatment pathway (untreated advanced or metastatic disease)? Yes but some centres carry out limited testing which does NOT necessarily detect EXON 20 insertions Would amivantamab be a candidate for managed access? Potentially yes, but this is a question for the committee to answer	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Merck Sharp & Dohme

References

1. Bazhenova L, Minchom A, Viteri S, Bauml JM, Ou SI, Gadgeel SM, et al. Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. Lung Cancer. 2021;162:154-61.
2. Wang F, Li C, Wu Q, Lu H. EGFR exon 20 insertion mutations in non-small cell lung cancer. Transl Cancer Res. 2020;9(4):2982-91.
3. Zhou C, Tang KJ, Cho BC, Liu B, Paz-Ares L, Cheng S, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med. 2023;389(22):2039-51.

4. National Lung Cancer Audit (NLCA): State of the Nation Patient and Public Report 2024: Results of the National Lung Cancer Audit for patients in England and Wales during 2022 [Available from: https://www.lungcanceraudit.org.uk/wp-content/uploads/2024/04/NLCA-Patient-Public-State-of-the-Nation-Report-2024.pdf.
5. NHS England: Cancer Registration Statistics E. [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2020#.
6. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2016;7(48):78985-93.
7. Van Sanden S, Murton M, Bobrowska A, Rahhali N, Sermon J, Rodrigues B, et al. Prevalence of Epidermal Growth Factor Receptor Exon 20 Insertion Mutations in Non-small-Cell Lung Cancer in Europe: A Pragmatic Literature Review and Meta-analysis. Target Oncol. 2022;17(2):153-66.
8. Oxnard GR, Lo PC, Nishino M, Dahlberg SE, Lindeman NI, Butaney M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. J Thorac Oncol. 2013;8(2):179-84.
9. Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5.
10. National Institute for Health and Care Excellence (NICE): Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non small-cell lung cancer after platinum-based chemotherapy. Technology Appraisal Guidance Published 14 December 2022 [Available from: https://www.nice.org.uk/guidance/ta850/resources/amivantamab-for-treating-egfr-exon-20-insertion-mutationpositive-advanced-nonsmallcell-lung-cancer-after-platinumbased-chemotherapy-pdf-82613545501381.
11. Tod AM, Craven J, Allmark P. Diagnostic delay in lung cancer: a qualitative study. J Adv Nurs. 2008;61(3):336-43.
12. Hu X, Melson JW, Pan SS, Salei YV, Cao Y. Screening, Diagnosis, and Initial Care of Asian and White Patients With Lung Cancer. Oncologist. 2024;29(4):332-41.
13. Lehto RH. Patient views on smoking, lung cancer, and stigma: a focus group perspective. Eur J Oncol Nurs. 2014;18(3):316-22.
14. Dersarkissian M, Bhak R, Lin H. Real-World Treatment Patterns and Survival in Non-Small Cell Lung Cancer Patients with EGFR Exon 20 Insertion Mutations Paper presented at: World Conference on Lung Cancer (WCLC); September 7-10. Barcelona, Spain. 2019. 2019.
15. Wang Y, Yang G, Li J, Xu H, Yang L, Xu F, et al. Real-world treatment outcome of advanced Chinese NSCLC EGFR exon 20 insertion patients. Journal of Clinical Oncology. 2019;37(15_suppl):9043-.
16. . Janssen (Data on File). 2019. CHRYSALIS (protocol amendment 7) A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer.
17. Yasuda H, Park E, Yun CH, Sng NJ, Lucena-Araujo AR, Yeo WL, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med. 2013;5(216):216ra177.
18. Robichaux JP, Elamin YY, Tan Z, Carter BW, Zhang S, Liu S, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. Nat Med. 2018;24(5):638-46.
19. Girard N, Bazhenova L, Minchom A, Ou S, Gadgeel S, Trigo J, et al. MA04.07 Comparative Clinical Outcomes for Patients with NSCLC Harboring EGFR Exon 20 Insertion Mutations and Common EGFR Mutations. Journal of Thoracic Oncology. 2021;16(3):S145-S6.

20. Maguire R, Lewis L, Kotronoulas G, McPhelim J, Milroy R, Cataldo J. Lung cancer stigma: A concept with consequences for patients. Cancer Rep (Hoboken). 2019;2(5):e1201.
21. MHRA: Marketing authorisations granted in November 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040370/Monthly_new_MA_listing_Nov_2021.pdf.
22. EMA/CHMP/174588/2024 Committee for Medicinal Products for Human Use (CHMP): Summary of opinion (post authorisation): Rybrevant amivantamab [Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-summary-positive-opinon-rybrevant-ii-10_en.pdf.