National Institute for Health and Care Excellence

Health Technology Evaluation

Treatments for non-small-cell lung cancer ID6234
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
Wording	Merck Sharp & Dohme (MSD) UK	Yes, MSD consider the suggested wording appropriate.	No action required.
	AstraZeneca	The wording of the remit does not entirely reflect the NSCLC treatment pathway being evaluated. AstraZeneca have provided clarifications in the following sections.	Comment noted. The pathway has been updated to reflect comments received during the scoping consultation and scoping workshop.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo agree that the wording of the remit reflects the broad scope of the pathway evaluation.	No action required.
	Roche Products Ltd	It is not clear that NICE are looking to appraise new treatments (and not existing reimbursed treatments). Suggest including the word 'new'.	The remit of this pathways pilot is outlined in the process

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			statement.
	Takeda	No comments. Please see comments on the appropriateness of an evaluation and proposed evaluation route section.	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	It is not clear currently what the remit of the pathway appraisal will be, and what treatments are being appraised. Specifically, it is not clear if all treatments in the pathway are being appraised again, or if just the new treatments listed in the scope are being appraised. The wording of the remit could be more specific in the purpose related to these points.	The remit of this pathways pilot is outlined in the process statement.
	British Thoracic Society	No concerns regarding the wording	No action required.
	British Thoracic Oncology Group (BTOG)	This is satisfactory	No action required.
	LCNUK	Wording is easy to understand and follow. Background information – professionals rarely use stages to describe – however, does simplify grouping.	No action required.

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Additional comments on the draft remit	Merck Sharp & Dohme (MSD) UK	None	No action required.
	AstraZeneca	There are no additional comments on the draft remit.	No action required.
	Daiichi Sankyo UK Ltd	Not applicable	No action required.
	Roche Products Ltd	Do you consider there to be added value to the NHS in a NICE appraisal of subcutaneous atezolizumab? This is not appropriate for NICE appraisal as it is a change in formulation of atezolizumab (as discussed with NICE 15th March 2023). Would having a PD-L1 inhibitor at the adjuvant or neo-adjuvant stage (Nodes A1 to A3) prevent someone from having a PD-L1 inhibitor at a later node (for example Node G)? If so, would you expect these rules to change in the future? As stated in the CDF guidance for first-line NSCLC (https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.255.pdf), "...at least 6 months elapsed between the date of the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease", therefore, re-treatment is possible.	NICE has decided not to assess the cost-effectiveness of subcutaneous atezolizumab in this appraisal. Comment noted.
	Takeda	None	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.

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	Merck Serono	None	No action required.
	British Thoracic Society	There are a lot of technologies currently being appraised. Will the document be out of date before it is even finished given the rate of change in approvals for lung cancer treatments recently?	The interventions will be appraised based on routinely commissioned standard care at the time of the appraisal in line with the NICE manual. As standard care changes, the aim is that the Pathway scope will be updated so that new technologies are appraised against current practice.
	British Thoracic Oncology Group (BTOG)	None	No action required.
	LCNUK	None	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

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Background information	Merck Sharp & Dohme (MSD) UK	• Regarding the treatment pathway in the adjuvant setting (A2) (Appendix B, page 4), the following amendment is suggested (amendment in italics): "~~Surgery~~ *Complete resection* may potentially be followed by chemotherapy *and/*or osimertinib" to capture the option for patients with complete tumour resection to receive osimertinib after adjuvant chemotherapy. Also, details could be included on treatment regimens after incomplete tumour resection, for completeness. • The heading of the treatment pathway section on early stage 2-3, locally advanced NSCLC (Appendix B, page 4) seems to suggest 4 nodes (A1-4) but only three are shown. The remainder of the information is accurate.	Comment noted. The Appendix has been updated to include the treatment options for both complete and incomplete tumour resection. The title for the section on early stage 2-3, locally advanced NSCLC has been updated.
	AstraZeneca	AstraZeneca agree with the information in the background section.	No action required.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo broadly agrees with the wording of the background information. Daiichi Sankyo propose a change to the first sentence of the fourth paragraph because the current wording suggests that the occurrence of any oncogenic driver mutation is rare. As Table 1 (page 1) illustrates, occurrence of some oncogenic driver mutations is common. Daiichi Sankyo suggests the following wording for the first sentence of the fourth paragraph: • *'There are a range of oncogenic driver mutations that, individually, are found in small proportions of non-small-cell lung cancers (see Table 1 for prevalence), but overall they account for approximately 40% of non-squamous non-small-cell lung cancers.'*	Scope has been updated to include the suggested wording.
	Roche Products Ltd	Durvalumab with chemotherapy has the ID6220 in the document, this appears to be a mistake as this does not exist on the NICE website.	ID6220 is the correct topic number for this

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		Table 1 - it is not clear the difference between H1 and H2.	appraisal. The pathway has been updated and differences between the decision points are shown in the treatment pathway and are described in the scope.
	Takeda	No comments	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	No comments	No action required.
	British Thoracic Society	Please see comment below (questions for consultation) about the Targeted Lung Health Check Programme - the stage distribution is very different to symptomatic route- these data are available from NHS England. It also may be helpful to talk about performance status as this influences eligibility for treatment and also survival.	Comment noted. The expected impact of the NHS Lung Health Check Programme has been added to the background section.
	British Thoracic Oncology Group (BTOG)	"Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma" does not adequately inform the reader that the vast majority are adenocarcinomas. Only a tiny proportion are large cell undifferentiated carcinomas, and these are difficult to adequately diagnose: in fact the term is considered obsolete for	Comment noted. The background section has been updated to reflect this.

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		patients diagnosed without surgical resection material to analyse. There are also other equally uncommon types such as pleomorphic carcinomas. In the UK, as NSCLC diagnoses are based on small biopsies or cytological samples, it is sometimes difficult to subcategorize NSCLC and it is called NSCLC (NOS), where NOS is “not otherwise specified.” In the 2020 National Lung Cancer Spotlight Audit on Molecular Testing, for all NSCLCs 66% were adenocarcinoma, 23% squamous cell carcinoma, 2% were large cell neuroendocrine carcinomas, 4% were not otherwise specified, the remainder being others. It is inappropriate to focus on the HER2 gene being abnormal when testing for HER2 is not commissioned in the National Test directory for Cancer and there are no NICE approved (nor MHRA licensed) drugs to target it for NSCLC. The sentence written is accurate. Table 1 is inaccurate in that it uses the term “Oncogenic Driver Mutations”. This should be termed “Oncogenic Driver Genetic Alterations” as the genetical alterations in ALK, ROS, RET, NTRK and gene rearrangements or fusions and can also be mutations. Please also note that NTRK is not 1 gene	Although HER2 mutation is not currently considered an actionable mutation in NSCLC, this will change if T-Dxd becomes licensed and recommended by NICE as a treatment option (as it is being studied in people with a HER2 mutation). The term ‘mutation’ has been replaced with ‘genetic alteration’

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		but 3 separate genes: NTRK1, NTRK2, and NTRK2, collectively termed NTRK1-3 Treatment pathway: yes the treatment decisions are made on staging system and line of therapy, but also on presence or absence of Oncogenic Genetic Alteration or not, which generally occur in non-squamous NSCLC but are rarely seen in other NSCLC types including NSCLC(NOS), NSCLC large cell carcinomas, and NSCLC squamous carcinomas	where appropriate. The treatment pathway includes genetic alteration as a factor which impacts treatment decisions.
	LCNUK	Information is accurate and reads well. Again, TNM staging is used more than 1,2,3,4 staging.	Comment noted. No action required.
The layout of the decision points	Merck Sharp & Dohme (MSD) UK	With regard to decision point A2 (adjuvant treatments) MSD do not anticipate at this stage any groups of people in whom the proposed treatments are expected to be more clinically and cost effective and therefore treatments should be appraised in line with the proposed Marketing Authorisation. Current standard of care (SoC) for NSCLC patients after complete surgical resection with or without adjuvant chemotherapy is the same regardless of stage, histology mutation status and therefore clinical effectiveness and cost effectiveness of the technology in these subgroups would be evaluated in comparison with same SoC.	Comment noted. No action required.
	AstraZeneca	AstraZeneca found two inaccuracies in the 'early stage 2-3, locally advanced NSCLC' part of the treatment pathway: 1. Nivolumab + chemotherapy (TA876) is now recommended by NICE in routine commissioning for neoadjuvant treatment of resectable NSCLC, therefore this treatment option should be added to the neoadjuvant setting (A1). 2. Durvalumab (TA798) is recommended by NICE for maintenance	Comment noted. TA876 has been added to this paragraph. Comment noted. The

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		treatment of locally advanced unresectable NSCLC. The current scope does not clarify that durvalumab is only recommended for patients with stage 3 disease (A3). The comments included in this section focus on the stage 2-3, resectable NSCLC setting. Dividing the stage of NSCLC into two (early-to-locally advanced stage 2-3 and advanced stage 4) is appropriate. Further subdividing the early-to-locally advanced setting based on whether patients are considered resectable (current A1 and A2) or unresectable (A3) is also appropriate. Whilst staging is a key aspect in the treatment decision, other factors are considered by the MDT that define suitability for resectable (A1/A2) versus unresectable (A3). In the scope, the early stages are separated out into two settings: A1 (neoadjuvant) and A2 (adjuvant). However, A1 and A2 should be consolidated to appraise the *perioperative regimen*: neoadjuvant durvalumab + chemotherapy and then adjuvant durvalumab monotherapy following resection. Note that for treatments administered in only neoadjuvant or adjuvant settings, these technologies should be appraised in A1 and A2, respectively. Combining A1 and A2 for perioperative regimens is necessary because the MDT decision requires both neo-adjuvant and adjuvant interventions to be considered upfront, i.e., before surgery. As described in the 'Intervention'	sentence regarding TA798 now specifies that it is recommended for locally advanced cancer. This section of the pathway (previously decision points A1-A3 has been reorganised based on feedback received during the consultation and scoping workshop. Comment noted. No action required. Comment noted. This section of the pathway has been amended to include an 'adjuvant continuation' decision point.

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		section response, it is not appropriate to appraise the adjuvant component of a perioperative regimen separately from the neoadjuvant component, because the option to receive adjuvant treatment is contingent on receipt of the neoadjuvant treatment, and that decision is made prior to surgery. There are no subgroups that should be considered separately within the AEGEAN study, the clinical trial evidence for the durvalumab perioperative regimen. In the AEGEAN study EGFRm/ALK+ patients were excluded. However, in clinical practice EGFR and ALK status are tested across all stages of NSCLC at diagnosis prior to treatment initiation. Therefore, the treatment pathway will differ based on EGFR/ALK status. Patients who are positive for these mutations are routinely treated with targeted therapies (e.g., osimertinib in EGFR positive NSCLC). Patients in the resectable setting with these known mutations will not be treated with durvalumab perioperative regimen.	Comment noted. This section of the pathway has been amended to include an 'adjuvant continuation' decision point. Comment noted. No action required. Comment noted. No action required.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo have focussed their comments to the decision points in the NSCLC treatment pathway that are relevant for trastuzumab deruxtecan (T-DXd). The UK NSCLC pathway is highly complex and recent NICE guidelines recommend treatment choices based on histology (squamous/non-squamous), programmed death ligand-1 (PD-L1) expression (<50%/≥50%) and the presence or absence of an actionable genomic alternation (AGA) (2). Currently, human epidermal growth factor receptor 2 (HER2) mutation is not considered an actionable mutation in NSCLC and hence the treatment of patients harbouring this mutation would be guided by histology and PD-L1 expression. The proposed indication for T-DXd in NSCLC is:	Comment noted. The pathway has been updated to reflect comments received during the scoping consultation and scoping workshop.

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		[redacted] Daiichi Sankyo agrees that the appropriate position for T-DXd is at second- and later-lines for patients consistent with the anticipated licence indication and key clinical evidence from DESTINY-Lung02 (1). DESTINY-Lung02 is a phase II multicentre study assessing T-DXd as a monotherapy (1). Patients in DESTINY-Lung02 were required to have previously received at least one prior systemic treatment which must have included platinum-based therapy. The presence of HER2 mutation is not limited to patients with non-squamous disease. Accordingly, Daiichi Sankyo consider T-DXd to be appropriate at second line or later for patients with squamous or non-squamous disease and harbouring the HER2 mutation. Daiichi Sankyo notes that the majority of patients with HER2 mutation will have non-squamous disease and the available data in patients with squamous disease and HER2 mutation will be limited. Daiichi Sankyo are not aware of any specific subgroups within the anticipated licensed indication that should be considered separately in the analysis.	
	Roche Products Ltd	None	Comment noted. No action required.
	Takeda	We believe Figure 1 broadly represents the treatment pathway for NSCLC. However, there are several specificities relating to stage of disease, subgroups, and positioning we would like to highlight for consideration.	Comment noted. The decision points for post-systemic treatment have been split by

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		NSCLC is a highly heterogeneous disease and comprises of many distinct subpopulations that are defined by specific type of mutation, histological subtypes and stage of disease. Such differences mean that these populations are not directly comparable. Therefore, it is necessary for a pathway economic model to reflect all distinct populations within NSCLC, allowing for the accurate evaluation of new treatments against the comparators that are directly relevant to that specific disease subgroup. This includes the need to consider patients with either EGFR exon20 insertion mutations or ALK-positive NSCLC as distinct populations, ensuring that they are not incorrectly assumed to be comparable or similar to broader or other subtypes of NSCLC. For example, if mobocertinib were to be retained as a comparator for appraisal ID3934, patients with the relevant EGFR exon20 insertion mutations should be considered a distinct subgroup of NSCLC and should not be compared or considered similar to broader EGFR or HER2 mutations. • Patients with EGFR exon20ins mutations are known to differ in characteristics and demographics versus broader NSCLC populations; patients with EGFR exon20ins mutations tend to be younger, with a higher proportion of patients who are female, never smokers, with adenocarcinoma histology, or of Asian ethnicity1,2,3. • As acknowledged in the mobocertinib NICE appraisal (TA855), EGFR exon20ins mutations are also known to be associated with far worse prognosis and treatment outcomes compared to classical EGFR mutations.4,5 Clinical expert opinion suggested that this is due to the worse pathology and more aggressive nature of EGFR exon20ins disease, as well	genetic alteration to make clear that patient subgroups with different genetic alterations would not be directly compared against each other.

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		as the known resistance to most tyrosine kinase inhibitors (TKIs), including the NICE-recommended treatments described in the Draft Scope – afatinib, erlotinib, gefitinib, dacomitinib, and osimertinib. Please see the "Comparators" section below for further detail on our position with respect to mobocertinib as a comparator. Similarly, patients with ALK-positive NSCLC also have distinct characteristics, demographics and outcomes compared to broader NSCLC or other mutations; patients tend to be younger, never smokers with adenocarcinoma histology. Therefore, any comparison of data in these specific subgroups (i.e. patients with EGFR exon20 insertion mutations or ALK-positive NSCLC) against data in classical EGFR or other mutations would be inappropriate. Subgroup analyses should therefore be performed specifically for each population as required. Furthermore, Figure 1 splits NSCLC by stage of disease: early to locally advanced (2–3) and advanced stage (4). However, many treatments for advanced disease, including brigatinib and mobocertinib, are licensed and reimbursed for both locally advanced and metastatic disease. As these patients may therefore be Stage IIIb, we suggest Figure 1 is revised to accurately represent this.	The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this iteration of the

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			Pathways appraisal.However the comment has been noted for future consideration.
	Novartis Pharmaceuticals UK Ltd	Dabrafenib with trametinib is currently being assessed by NICE for the treatment of advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]. The expected publication date is 5th May 2023. Therefore, subject to outcomes from this appraisal, BRAF mutation may need to be included in the decision nodes in the pathway as BRAF is a targetable mutation with a treatment available (pending NICE positive recommendation).	Comment noted. The Pathway has been amended to reflect this.
	Merck Serono	The treatments and subgroups are appropriate for METex14 skipping mutation-positive NSCLC (the relevant population for Merck Serono, as the manufacturer of tepotinib).	Comment noted. No action required.
	British Thoracic Society	None	Comment noted. No action required.
	British Thoracic Oncology Group (BTOG)	In general, Figure 1 is extremely difficult to interpret without having the drug names or clinical settings they represent written next to the boxes. Hence this figure as been difficult to critique. Nevertheless, several inaccuracies and errors have been identified.	Comment noted. The pathway has been updated to reflect comments received during the scoping consultation and scoping workshop.

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		The grouping A1-3 doesn't make clinical sense as this defines pre or post operative therapy for some stage of disease, either are options. Currently we categorize patients by stage, histology, genotype, and PD-L1 status and then work out the best treatment option for the patient. The current categorization addresses stage 2-3 only and misses inclusion of: • T2a(3cm or more)N0= stage 1B EGFR mutant suitable for surgery >> adjuvant Osimertinib • The neoadjuvant approach (chemotherapy-nivolumab) from the recently approved NICE ID3757 indication is completely missing will likely replace what is currently written as A1 (neoadjuvant chemo-radiotherapy) • NICE may wish to consider having an "operable" section for N0, N1, and N2 disease and an "inoperable stage 3" section and then a "stage 4/non-radically treatable stage 3" group instead of the current classifiers • In the near future groups A1 (neoadjuvant) and A2 (adjuvant) will merge as immunotherapy will likely be licensed pre and post surgery, hence the clinical grouping by N0, N1, N2 involvement is more flexible and long lasting • A2 (adjuvant) for clarification, the clinical indication for TA761 (adjuvant osimertinib) is for osimertinib with or without adjuvant chemotherapy, whereas currently the indication is written "Surgery may potentially be followed by chemotherapy or osimertinib" • Groups J specifically pertains to METex14 mutant NSCLC in squamous histology. It is really unclear why NICE have focussed on this as the vast majority of all NSCLC with genetic alterations occurs in adenocarcinomas (not NSCLC NOS) and all genetic alterations (eg EGFR mutation, ALK fusion, ROS1 fusion, etc) can be identified rarely in squamous NSCLC. Hence all the genetic alterations should be groups separately regardless of NSCLC histology, recognizing that 99% of the time these will occur in adenocarcinomas. Thus whilst the text "Tepotinib can be used in both	This section of the pathway (previously decision points A1-A3 has been reorganised based on feedback received during the consultation and scoping workshop. The interventions in this section of the pathway are no longer being appraised in this phase of the Pathways appraisal. However, the comment has been noted for future consideration.

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		squamous (J) and non-squamous NSCLC." Is accurate, it does not reflect that other TKIs eg osimertinib can also be used in squamous (J) and non-squamous NSCLC. • F-G and K-L groups discuss immunotherapy combinations. Such patients may also be treated without immunotherapy if immunotherapy-ineligible for clinical reasons- this is not stated currently. • G: states "These treatments are for people without ALK- or EGFR-positive mutations" indicates that immunotherapy can be used as first-line treatment for ALK or EGFR positive tumours which is factually wrong and clinically harmful. • G: re TA770, the wording is too clinically specific. There is currently clinical choice for squamous cell NSCLC if to use immune monotherapy (TA705, TA531) or chemo-pembrolizumab (TA770). The document cites specific examples which are clinically inaccurate: IE impending major airway obstruction is not necessarily better treated with chemo-immunotherapy that other treatments eg surgery. It is better to avoid specific examples • H1: the concept "induction therapy" does not exist in NSCLC. NICE should use the term TKI therapy or kinase inhibitor therapy as not all kinase inhibitors inhibit a tyrosine residue. • M2 is inaccurately placed. This indication (EGFR ex20insertion NSCLC) should be placed in the "genetically altered" category where the recommended first line treatment is not a TKI but non-immunotherapy based platinum doublet eg carboplatin-pemetrexed followed by maintenance pemetrexed. Mobocertinib would then be used as first subsequent therapy. EGFR ex20insertion NSCLC are typically seen in adenocarcinomas, rather than squamous cell carcinomas • I1: the placement of this box (KRAS G12C) implies that target therapies need to be given then platinum-doublet then sotorasib. This is inaccurate as it can be given in the sequences: immunotherapy>>sotorasib; chemo-immunotherapy>>sotorasib; chemotherapy>>sotorasib. KRAS G12C is	

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		prinripally also identified in adenocarcinomas, hence the box for this in the squamous pathway is redundant	
	LCNUK	None	Comment noted. No action required.
Population at each decision point	Merck Sharp & Dohme (MSD) UK	With regard to decision point A2, MSD suggest that the description of the population be amended as follows (amendment in italics) "*Adults* with NSCLC who have undergone complete surgical resection *with or without adjuvant chemotherapy"*. This amendment is suggested as the interventions of interest in this appraisal were administered to trial patients who had no evidence of disease after completion of a radical treatment plan which includes surgery with or without adjuvant chemotherapy.	The wording of this section has been updated to reflect treatment options for both complete and incomplete resection.
	AstraZeneca	The clinical effectiveness data used for patients treated with durvalumab in combination with chemotherapy as neoadjuvant (A1), and then as adjuvant monotherapy following resection (A2) will be from the AEGEAN trial. Therefore, the population for the appraisal of this perioperative regimen should align with the expected license which is based on the AEGEAN trial (i.e., patients with resectable NSCLC whose tumours have no known EGFR mutations or ALK aberrations). This is consistent with the approach of consolidating A1 and A2 for treatments in the perioperative setting due to the MDT determining treatment strategy upfront i.e., before surgery.	This section of the pathway (previously decision points A1-A3 has been reorganised based on feedback received during the consultation and scoping workshop. The interventions in this section of the pathway are no longer being appraised in this phase of the Pathways appraisal. However the comments has been noted for future

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			consideration.
	Daiichi Sankyo UK Ltd	Yes [defined appropriately]	Comment noted. No action required.
	Roche Products Ltd	None	Comment noted. No action required.
	Takeda	No comments	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	Please see above regarding inclusion of BRAF as a targetable mutation	Comment noted. The Pathway has been amended to reflect this.
	Merck Serono	The populations are defined clearly, including for METex14 skipping mutation-positive tumours. However it is not clear why the following is described for METex14 skipping mutation-positive NSCLC, but not for other driver mutations such as ROS-1. "*METex14 skipping mutation testing is variable across the UK, so people may be treated with non-targeted therapies until diagnosed"* Merck request that this wording is consistent for all treatments which require a positive test from next-generation sequencing (NGS), or that this is removed for tepotinib.	Comment noted. This sentence has been amended to apply more broadly to genetic alterations.
	British Thoracic Society	None	Comment noted. No action required.

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	British Thoracic Oncology Group (BTOG)	No, see above	Comment noted. No action required.
	LCNUK	No concerns with population	Comment noted. No action required.
Intervention at each decision point	Merck Sharp & Dohme (MSD) UK	It is suggested that durvalumab [ID6220] be listed in the decision point A1 only as the population relevant to this indication is patients with resectable non-small-cell lung cancer which is in line with decision point A1 (neoadjuvant setting). The remainder of the interventions were appropriately placed for the adjuvant setting (A2). Pembrolizumab with pemetrexed and platinum chemotherapy is not considered an appropriate comparator for the population specified for the decision point F i.e., “people with unresectable or metastatic *squamous* NSCLC whose disease has progressed after chemotherapy”. Pembrolizumab with pemetrexed and platinum chemo [TA683] is recommended for untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive mutations.	The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. Pembrolizumab with pemetrexed and platinum chemotherapy is only considered a comparator for people with non-squamous NSCLC, in alignment with TA683.

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	AstraZeneca	The intervention included in A1 and A2 (durvalumab with chemotherapy) is not appropriate. The interventions included in the A1 and A2 decision points should be consolidated into one for the appraisal of the durvalumab perioperative regimen. This is because adjuvant treatment is contingent on neoadjuvant treatment as part of the perioperative regimen, and this decision is made prior to surgery. Having neoadjuvant and adjuvant settings appraised together in a resectable population for a perioperative regimen is consistent with previous NICE appraisals (e.g., TA851 (neoadjuvant and adjuvant treatment of pembrolizumab for patients with TNBC)) (1). Within the population described in the section above (i.e., patients with resectable NSCLC whose tumours have no known EGFR mutations or ALK aberrations), the appropriate intervention is durvalumab in combination with chemotherapy as neoadjuvant, and then as adjuvant monotherapy following resection.	This section of the pathway (previously decision points A1-A3 has been reorganised based on feedback received during the consultation and scoping workshop. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo agrees with the position of T-DXd in the pathway at second- and later-lines which is in accordance with the anticipated licensed indication and the clinical trial study population.	Comment noted. No action required.
	Roche Products Ltd	The population listed for subcutaneous atezolizumab is incorrect. However, the new formulation is not appropriate for NICE appraisal as above. We have therefore not provided a suggestion for correction. Subcutaneous atezolizumab is not correctly placed in the pathway. [redacted]	Comment noted. Subcutaneous atezolizumab has been removed from this appraisal.

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	Takeda	No comments	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	Please see above regarding inclusion of BRAF as a targetable mutation	Comment noted. The Pathway has been amended to reflect this.
	Merck Serono	Yes the interventions are appropriately placed in the pathway.	Comment noted. No action required.
	British Thoracic Society	None	Comment noted. No action required.
	British Thoracic Oncology Group (BTOG)	No, see above	Comment noted. No action required.
	LCNUK	Feels they are at correct points where decisions will be made	Comment noted. No action required.
Comparators at each decision point	Merck Sharp & Dohme (MSD) UK	With regard to decision point A2 (adjuvant treatments), MSD believe that active monitoring reflects the current standard of care in the UK for adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy, and therefore it is considered the most appropriate comparator. In the PEARLS/KEYNOTE-091 trial (the pivotal trial supporting the appraisal),	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways

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		randomisation to pembrolizumab or placebo occurred among patients who had no evidence of disease after completion of a radical treatment plan (surgery with or without adjuvant chemotherapy). Patients for whom adjuvant chemotherapy prior to pembrolizumab was not considered to be appropriate would not receive platinum-based chemotherapy as alternative treatment to pembrolizumab, and therefore "platinum-based chemotherapy" is not considered a relevant comparator for this population. Platinum-based chemotherapy was not listed as relevant comparator in the final scope for the appraisal ID3907 (pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer). Both atezolizumab [TA823] and osimertinib [TA761] are recommended in the Cancer Drugs and therefore are not considered relevant comparators at this stage.	appraisal. However the comment has been noted for future consideration.
	AstraZeneca	As specified in the previous sections, in clinical practice only one decision point is required for the perioperative regimen evaluated in the AEGEAN trial (durvalumab in combination with chemotherapy as neoadjuvant, and then as adjuvant monotherapy following resection). Although the treatment landscape is evolving, no other perioperative regimens will be available in clinical practice at the time of this appraisal. Therefore, appropriate comparators include surgery with/ without chemotherapy before/ after surgery. Comments on each comparator included in the scope are presented below. Note that the comparators have been separated out into the A1 and A2 settings to be consistent with the draft scope.	The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration.

Section	Consultee/ Commentator	Comments [sic]	Action
		<u>Neoadjuvant setting (A1)</u> Chemoradiotherapy (CRT) is not a relevant comparator for neoadjuvant durvalumab + chemotherapy. As per the NICE clinical guidelines, neoadjuvant CRT is only recommended for a small subset of stage IIIA patient (stage IIIA-N2 patients), and according to clinical expert opinion cited in TA876, very few stage IIIA-N2 patients in England receive neoadjuvant CRT, at the discretion of the treating clinician (2). CRT is typically reserved for patients who are considered surgically unresectable which differs from the patient population of this appraisal for the durvalumab perioperative regimen. Best supportive care in the neoadjuvant setting needs to be more clearly defined to represent no anti-cancer therapy prior to surgery. Neoadjuvant nivolumab + chemotherapy is not an appropriate comparator for neoadjuvant durvalumab + chemotherapy. The technical appraisal guidance has only recently been published (22nd March 2023) (2) and does not currently represent standard of care in UK clinical practice. <u>Adjuvant setting (A2)</u> Platinum-based combination chemotherapy (PBC) is appropriate as an adjuvant regimen. Osimertinib is recommended in the CDF for patients with adjuvant treatment after complete tumour resection in stage 1B to 3A NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Osimertinib is not a relevant comparator for adjuvant durvalumab monotherapy for the following reasons:	

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		a) As per NICE guidelines, new cancer products under appraisal should not include treatments recommended for use in the CDF as comparators. b) Patients with known EGFR/ALK+ are expected to be ineligible to receive the durvalumab perioperative regimen (based on expected license). Atezolizumab monotherapy is recommended in the CDF for adjuvant treatment after complete tumour resection in adult patients with stage IIB or IIIA or N2 only IIIB NSCLC and with PD-L1 expression on ≥50% of tumour cells and whose disease has not progressed on recently completed adjuvant platinum-based chemotherapy. Atezolizumab should not be considered a relevant comparator for adjuvant durvalumab monotherapy for the following reasons: a) As per NICE guidelines, new cancer products under appraisal should not include treatments recommended for use in the CDF as comparators. To be eligible for atezolizumab patients must not have received prior IO. NHS bluteq forms states 'patients in the adjuvant NSCLC cannot receive atezolizumab if they have received prior treatment with an anti-PD-L1 antibody' (3). To be eligible for atezolizumab in the adjuvant setting, patients may not have received the durvalumab perioperative regimen.	
	Daiichi Sankyo UK Ltd	H1: People with unresectable or metastatic non-squamous NSCLC whose disease has progressed after chemotherapy As discussed in recent appraisals of lung cancer (e.g., TA781 [3]), the treatment pathway in UK clinical practice has evolved significantly in recent years whereby immunotherapy with or without platinum-based chemotherapy is routinely offered as a first-line treatment option in patients without AGA. The inclusion of platinum-doublet chemotherapy with pemetrexed maintenance is not appropriate as a comparator at second line (H1) as	Comment noted. The pathway has been updated to reflect comments received during the scoping consultation and scoping workshop.

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		patients suitable for platinum treatment would be expected to receive this in combination with immunotherapy in first line. Additionally, the eligibility criteria for DESTINY-Lung02 specified at least one prior systemic therapy which must have included a prior platinum-based therapy. The inclusion of atezolizumab with bevacizumab and paclitaxel as a comparator is also not appropriate. Atezolizumab with bevacizumab, carboplatin and paclitaxel is a recommended first-line treatment for patients with non-squamous disease and PD-L1 expression <50%. It is highly unlikely to be used at second line except in patients with an EGFR mutation. The co-occurrence of either of these mutations alongside HER2 is expected to be rare (6). Standard of care treatment at first subsequent therapy is docetaxel monotherapy (in squamous and non-squamous patients), and this should be included as a comparator at decision point H1. Docetaxel with nintedanib is only recommended for patients with advanced NSCLC with non-squamous histology and its use in clinical practice is limited. H2: People with unresectable or metastatic non-squamous NSCLC whose disease has progressed after chemotherapy Patients co-harbouring HER2-mutant and EGFR exon 20 insertion mutation are rare (6) so the inclusion of mobocertinib as a comparator is not appropriate and should be removed. Daiichi Sankyo expect that a small number of patients harbouring the HER2 mutation may have sequential treatment with a platinum-based chemotherapy and an anti-programmed death-1 or anti-PD-L1 delivered at first and second line. For these patients, treatment options at third line would be limited to docetaxel (with or without nintedanib). Hence Daiichi Sankyo believe that	

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		docetaxel should be included as a comparator at second subsequent therapy (H2). I1: People with unresectable or metastatic *non-squamous* NSCLC whose disease has progressed after all standard treatments Docetaxel monotherapy is recommended after standard treatment and is a relevant comparator at this decision point. While the docetaxel plus nintedanib combination is NICE recommended as a treatment option, its uptake in routine NHS practice is limited as discussed in previous technology appraisals (TA713 [4]; TA781 [3]). The relevance of comparators that have limited use in UK clinical practice should be considered given the challenges in identifying appropriate datasets and uncertainty associated with indirect treatment comparisons.	
	Roche Products Ltd	The comparators listed for subcutaneous atezolizumab are incorrect. However, the new formulation is not appropriate for NICE appraisal as above. We have therefore not provided a suggestion for correction.	NICE has decided not to assess the cost-effectiveness of subcutaneous atezolizumab in this appraisal.
	Takeda	We are unclear why mobocertinib has been included as a comparator for the trastuzumab deruxtecan (ID3934) appraisal for HER2-mutated disease. Mobocertinib is licensed and NICE-recommended for treatment of advanced or metastatic NSCLC harbouring *EGFR* exon20 insertion mutations, following platinum-based chemotherapy. Although the Phase 1/2 clinical trial for mobocertinib (NCT02716116) also included two cohorts of patients with	Comment noted. The decision points for post-systemic treatment have been split by genetic alteration to make clear that patient subgroups with different

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		HER2 exon20 insertion or point mutations, the investigation of mobocertinib in *HER2*-mutated disease has since been discontinued. Mobocertinib is therefore not anticipated to be licensed in *HER2*-mutated NSCLC. Furthermore, published literature indicates that *EGFR* exon20ins mutations are mutually exclusive of other oncogenic drivers, and are therefore unlikely to co-occur with *HER2* mutations.[6,7,8] The *EGFR* gene is located on chromosome 7 and *HER2* on chromosome 17; mutations in both genes would be incredibly rare, independent, and therefore likely mutually exclusive of each other. We sought clinical expert opinion on the co-occurrence of *EGFR* exon20 insertion and *HER2* mutations which confirmed that these mutations are mutually exclusive and not seen together in practice. Given the only approved indication for mobocertinib is for patients with *EGFR* exon20ins mutation-positive NSCLC, and with *EGFR* exon20ins representing a distinct population in NSCLC, we believe it is inappropriate to consider mobocertinib as a comparator for a *HER2*-targeted technology. If mobocertinib were to be retained as a relevant comparator in this setting, it would also be relevant to all non-squamous positions in the treatment pathway following platinum-based chemotherapy. This would include H1, H2, and I1 in Table 1 of the Draft Scope. In addition, we would like to query the population for H1 – the wording in Table 1 of the draft scope for the population of H1 matches that of H2 ("disease progressed after chemotherapy"), however the comparators differ. This may need to be amended for clarity.	genetic alterations would not be directly compared against each other.
	Novartis Pharmaceuticals UK Ltd	Please see above regarding inclusion of BRAF as a targetable mutation with a treatment available	Comment noted. The Pathway has been amended to reflect this.

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	Merck Serono	The comparators are appropriate	Comment noted. No action required.
	British Thoracic Society	As part of the modelling do the EAG need to consider stereotactic ablative radiotherapy (SABR) in the treatment for early stage lung cancer? This would not usually be associated with neoadjuvant or adjuvant therapies based on current guidelines but a proportion of patients (depending on patient preference or fitness may be offered this instead of surgery).	The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration.
	British Thoracic Oncology Group (BTOG)	From table 1: For A2: EGFR mutant comparators may be excluded contingent on the trial design and proposed license. For H1: platinum-pemetrexed is not the comparator as this is what patient need to progress on for eligibility. The comparator will be docetaxel-nintedanib, docetaxel, or atezolizumab, nivolumab, pembrolizumab. H1, H2, I1 indications are the same and should be merged For F: the comparator is incorrect for the stated population. Comparators will be nivolumab, pembrolizumab, docetaxel-nintedanib, docetaxel.	The pathway and comparators have been updated to reflect comments received during the scoping consultation and scoping workshop
	LCNUK	To my knowledge [appropriately placed]. But other professionals would comment better.	Comment noted. No action required.
Outcomes at	Merck Sharp &	With regard to decision point A2 (adjuvant treatments), disease-free survival	Comment noted. The

Section	Consultee/ Commentator	Comments [sic]	Action
each decision point	Dohme (MSD) UK	(DFS) is considered a relevant outcome as it captures the most important health-related benefits (and harms) of the technology in the adjuvant setting and is the primary outcome in the KEYNOTE-091 trial. Response rate is not considered an appropriate outcome for the evaluation of an adjuvant treatment (since all patients are thought to be disease free at randomisation) and was not collected in the KEYNOTE-091 trial. The remainder of the outcomes (overall survival, adverse effects of treatment and health-related quality of life) are considered relevant as they capture the most important health-related benefits (and harms) of the technology.	interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. It is acknowledged that there may be different outcomes for different parts of the treatment pathway.
	AstraZeneca	In the neoadjuvant and perioperative setting, EFS (rather than PFS) is the most appropriate endpoint because it considers both progression events before surgery (i.e., whilst the tumour is still present), and recurrence events after surgical resection of the tumour. EFS is the primary endpoint in the AEGEAN trial, the clinical evidence base for the durvalumab perioperative regimen. Rather than response rate, a more specific outcome of pathologic complete response (pCR) is preferred in this setting, which is a primary outcome in the AEGEAN trial, the clinical evidence base for the durvalumab perioperative regimen. Based on the comments above, EFS and pCR should be added to the list of outcomes in place of PFS and response rates, respectively, when considering	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. It is acknowledged that there may be different

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		relevant outcomes in the perioperative settings. DFS, which considers recurrence events after surgical resection of the tumour, measured from the time after surgery, and is a secondary endpoint in the AEGEAN study, could be added as a supportive endpoint to EFS.	outcomes for different parts of the treatment pathway.
	Daiichi Sankyo UK Ltd	The outcomes listed are appropriate and capture the relevant health related benefits of the technology.	Comment noted. No action required.
	Roche Products Ltd	Disease free survival (DFS) and event-free survival (EFS) should be added as an outcome for treatment being assessed under node A1 and A2.	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. It is acknowledged that there may be different outcomes for different parts of the treatment pathway.
	Takeda	Given some therapies in the appraisal can be continued until disease progression or unacceptable toxicity, time to treatment discontinuation should also be included as an outcome.	The outcomes have been updated following feedback received during the consultation and scoping workshop,

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			and to align with the updated remit.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	The outcomes are appropriate	No action required.
	British Thoracic Society	A proportion of people with stage 2 and 3 lung cancer will have recurrence early after initial treatment- there are no boxes after A1-A3 to capture the need for subsequent treatments required. Does this need to be added in?	The feedback from the scoping workshop indicated that these people would then follow the 'advanced' section of the pathway.
	British Thoracic Oncology Group (BTOG)	Yes	No action required.
	LCNUK	Main experience is with quality of life and side effects. This is the priority for most patients considering treatments	No action required.
Appropriateness of an evaluation and proposed evaluation route	Merck Sharp & Dohme (MSD) UK	MSD welcome this evaluation route for this topic. Comments on specific interventions included in the pilot are provided as responses to the questions below	No action required.
	AstraZeneca	AstraZeneca recognises and supports the need for the new Proportionate Approach to Technology Appraisal (PATT) pathways approach to streamline	Comment noted. This appraisal is a pilot

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		and simplify their processes. However, as per the responses provided above, which have highlighted some of the complexities of appraisals within the resectable NSCLC setting alone, the pathway approach may not be appropriate for NSCLC as a whole for the following reasons: a. The heterogeneous nature of NSCLC means one treatment pathway is not relevant for all patients with NSCLC. b. The presence of multiple actionable mutations and the routine testing of these at diagnosis in UK clinical practice makes MDT treatment decision-making more complex than looking at stage of disease only. c. The NSCLC treatment landscape is rapidly evolving; therefore, it is challenging to forecast future treatment decisions. d. The economic modelling approach for early-to-locally advanced stage 2-3 and advanced stage 4 is likely to differ substantially. For example, in previous NICE appraisals in advanced stage 4 NSCLC, partitioned survival models have been used consistently (e.g., TA683, TA705 and TA520). However, state transition models with varying numbers of health states have been used for resectable/ unresectable early-to-locally advanced stage 2-3 (e.g., TA761, TA798 and TA823). Therefore, developing one model for the entire treatment pathway may be inappropriate and unwieldly. Due to there being a lack of experience and limited published information on the PATT pathways approach, AstraZeneca are unable to provide a fully informed response about the appropriateness of an evaluation of the durvalumab perioperative regimen in NSCLC using the pathways appraisal approach.	project for the Pathways approach. As such, the suitability of the approach and the process will be reviewed throughout. For example, to reduce complexity at this stage of the topic, the interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal.
	Daiichi Sankyo	Daiichi Sankyo welcomes the evaluation of T-DXd after at second- and later-	Comment noted. This

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	UK Ltd	lines in patients with advanced NSCLC in accordance with the anticipated licensed indication. Daiichi Sankyo supports NICE as a collaborative partner in efforts to maximise efficiencies in the appraisal process as is proposed in this pilot pathway approach. However, there is limited published information or experience on the Proportionate Approach to Technology Appraisal (PATT) pathways appraisal approach which limits our ability to provide a fully informed response on the appropriateness of this route of evaluation for T-DXd in NSCLC. Daiichi Sankyo considers that the Pathway appraisal approach must be facilitated by pragmatic assumptions given the expected challenges associated with identifying appropriate datasets, and limitations with any pairwise comparisons derived from indirect treatment comparisons. We would request that NICE and academic partners work closely with submitting companies to achieve these objectives. It is important to ensure that the Pathways appraisal process supports the timely production of Guidance to the NHS and subsequent patient access.	appraisal is a pilot project for the Pathways approach. As such, the suitability of the approach and the process will be reviewed throughout. NICE welcomes the opportunity to work closely with submitting companies to achieve the objectives of the initiative.
	Roche Products Ltd	None	No action required.
	Takeda	We believe the appropriateness of evaluating several technologies for NSCLC via a pathways appraisal is unclear at this point, and we would recommend NICE consider the points highlighted below. NSCLC is a highly heterogeneous disease and comprises of many distinct subpopulations that cannot be directly compared, and are defined by: • Different mutations: patients with different mutationally-driven or non-mutationally driven subtypes of NSCLC are known to differ drastically with respect to patient characteristics, (such as age, race, gender, and smoking status), comorbidities, prognosis and outcomes	Comment noted. This appraisal is a pilot project for the Pathways approach. As such, the suitability of the approach and the process will be reviewed throughout. NICE welcomes the opportunity to work closely with submitting

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		• Histological subtypes: patients with non-squamous (including adenocarcinoma) vs squamous disease differ with respect to patient characteristics and prognosis • Stages: treatment objectives and pathways depend on whether the disease is early-stage disease, advanced or metastatic. For example, early-stage disease can be fully resected or can benefit from neoadjuvant or adjuvant therapy, whereas advanced disease is incurable, and treatment has life-extending or palliative intentions. Outcomes are therefore also not comparable across stages of disease. Consequently, it is necessary for any pathway economic model to reflect these distinct populations within NSCLC and allow for the accurate evaluation of treatments against the comparators and associated data that are directly relevant to that specific disease subgroup. It will also be imperative that input parameter values and assumptions used in the pathway model are reflective of the specific subtype or line of therapy being evaluated; applying methodologies and assumptions from one subtype to another could induce bias and uncertainty. In addition, the pathway economic model would need to be future proofed to accommodate emerging innovative technologies that may have specificities or nuances (i.e. in terms of population and outcomes) that require alternative or adapted modelling approaches. We are concerned that the associated complexity and resulting challenges for use and implementation in technology appraisals may outweigh its benefits.	companies to achieve the objectives of the initiative.

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		We therefore believe it is critical that the Committee acknowledges the nuances between the distinct subtypes of NSCLC and the implications this has for the economic model development and appropriateness of a pathway appraisal strategy.	
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	More clarity is needed on the remit and evaluation route of the pathways appraisal before this can be answered	Comment noted. No action required.
	British Thoracic Society	The only concern is whether the appraisal will be out of date before publication given how many new treatment options/ combinations are being approved at the moment.	Comment noted. No action required.
	British Thoracic Oncology Group (BTOG)	This is a worthy topic for evaluation.	No action required.
	LCNUK	None	No action required.
Equality	Merck Sharp & Dohme (MSD) UK	MSD do not consider that the proposed remit, treatment pathway and scope could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments will be licensed or could lead to recommendations that have a different impact on people protected by the equality legislation or could have any adverse impact on people with a particular disability or disabilities.	Comment noted. No action required.

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	AstraZeneca	AstraZeneca is not aware of any equality issues.	No action required.
	Daiichi Sankyo UK Ltd	Daiichi Sankyo is not aware of any specific issues regarding equality raised by the evaluation of T-DXd in the specified NSCLC populations.	No action required.
	Roche Products Ltd	None	No action required.
	Takeda	No comments	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	No comments on equality	No action required.
	British Thoracic Society	The ethnicity of the population can influence the likelihood of having some mutations (eg. EGFR) so some ethnic groups such as East Asian may have more access to the TKIs for example. Also smoking status may affect the likelihood of having a driver mutation, again so never smokers and smokers may be represented differently in the proportions of people eligible for certain treatment options.	Comment noted. Issues related to differences in prevalence or incidence of a disease cannot typically be addressed in a technology appraisal. But the appraisal committee will take into account whether its recommendations could have a different impact on people protected by the equality legislation

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			than on the wider population.
	British Thoracic Oncology Group (BTOG)	No concerns	No action required.
	LCNUK	To my knowledge the decision to treat is one of equality. Treatment decisions are made on fitness which could affect those considered to have disability. Would happily discuss further in the workshop.	Comment noted. No action required.
Other considerations	Merck Sharp & Dohme (MSD) UK	MSD have no additional comments.	No action required.
	AstraZeneca	AstraZeneca have no additional comments.	No action required.
	Daiichi Sankyo UK Ltd	T-DXd is an innovative antibody drug conjugate that is the first HER2-targeted treatment to show efficacy in HER2 mutation advanced NSCLC. DESTINY-Lung02 is a phase II multicentre study assessing the safety and efficacy of Enhertu® at 5.4mg/kg in patients with metastatic HER2 mutated NSCLC who had disease recurrence or progression during/after ≥1 regimen of prior anti-cancer therapy (i.e. second-line or later) that must have contained a platinum-based chemotherapy drug (1). The primary endpoint in DESTINY-Lung02 was confirmed objective response rate (ORR), defined as the proportion of patients with complete response or partial response, as assessed by blinded independent central review (BICR) and based on response evaluation criteria in solid tumours (RECIST) v1.1. Secondary outcomes included: ORR based on investigator's assessment, duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Quality of life data were collected via	Comment noted. No action required.

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		the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and modular supplement to the EORTC core quality of life questionnaire (QLQ-C13) for lung cancer trials scale scores. In the pre-specified early cohort for Enhertu® 5.4 mg/kg arm at the data cut-off of 24 March 2022: • ORR based on BICR was 53.8% (95% CI: 39.5, 67.8) • DCR based on BICR was 90.4% (95% CI: 79.0, 96.8) • Median DoR was not reached • Time to first response was 1.4 months • Median treatment duration was 3.7 (0.7 to 11.8) months In recognition of its innovation, T-DXd was awarded the Innovation Passport designation by the ILAP steering group in May 2022 (ILAP reference number ILAP/IP/22/08265/01)	
	Roche Products Ltd	None	No action required.
	Takeda	No comments	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	No other considerations	No action required.

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	British Thoracic Society	None	No action required.
	British Thoracic Oncology Group (BTOG)	Genotyping implementation: this is poor in the UK leading to poor uptake of MET and RET and ROS1 directed therapies. The algorithm does not adequately capture patients in whom genotyping is unknown or not tested at time to need starting treatment and then later a genetic alteration is identified during 1st line treatment.	Comment noted. A sentence has been added to the scope regarding this issue.
Questions for consultation	Merck Sharp & Dohme (MSD) UK	<u>The pathway</u> Does the pathway described represent current NHS clinical care? Is the pathway split appropriately into clearly defined decision problems? Yes, the pathway described reflects the treatments currently recommended by NICE and used in the standard practice. Treatment options for NSCLC mainly depends on the cancer stage, histology (non-squamous vs squamous), mutation status as well as patient fitness and preferences. Therefore, the pathway described appropriately captures the main subset of patients whose treatment options depend on the factors above. Is the staging system used to define patient populations and decision points the most relevant in NHS clinical practice? Are there other staging systems that have not been considered? The staging system is the most relevant in the clinical practice. TNM classification (8th edition) is also used. When in the diagnostic pathway is genetic testing carried out to determine the presence of targetable mutations? Does the timing of testing vary by mutation type? It is our understanding that the type of testing depends on the actionable mutations that may be found. For example, in early-stage disease it would not	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		be routine to test tumours for ALK, ROS-1, NTRK etc. because there are currently no approved treatments targeting these markers. Routine PD-L1 testing in early-stage lung cancer is understood to be widely available as part of the care pathway following approvals of atezolizumab and durvalumab as PDL1-dependent options after radical treatment. It consists of immunohistochemical (IHC) assay, with the most common being 22C3, SP263, SP142 and 28-8. Would pembrolizumab monotherapy ever be used after adjuvant chemotherapy? Yes. Pembrolizumab is not a “competitor” for adjuvant chemotherapy but is used after successful completion of a radical treatment plan that may or may not include adjuvant chemotherapy. The proportion of patients currently receiving adjuvant chemotherapy varies greatly across centres, ranging from 10% to 80%. In the PEARLS/KEYNOTE-091 trial (the pivotal trial supporting this appraisal), pembrolizumab has been investigated in patients who had no evidence of disease after surgery with or without adjuvant chemotherapy. Therefore, efficacy evidence informing this appraisal will capture this group of patients who have previously received adjuvant chemotherapy. Based on feedback from UK clinical experts, it is our understanding that some of the people with fully resected stage IB (tumour size of 4 cm or greater) to IIIA NSCLC may not be suitable for adjuvant chemotherapy as they are not fit enough due to comorbidities (e.g., cardiovascular diseases). Patient choice is also an important factor alongside ‘suitability’. Are there any other potential technologies that should be included in the pathway that are expected to be available within the UK by early 2024?	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. Comment noted. No

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		Based on current timelines, it is anticipated that pembrolizumab will be available for use in [redacted] in: • the neoadjuvant and adjuvant setting for resectable Stage II, IIIA, and IIIB (T3-4,N2) NSCLC (pivotal RCT KEYNOTE-671; [ID5094]); • in combination with olaparib for the first-line treatment of metastatic squamous NSCLC (pivotal RCT KeyLynk-008; [ID4006]). [redacted]. Have all relevant treatments for NSCLC been included in the scope? Which treatments are established clinical practice in the NHS at each point in the NSCLC pathway? NICE Guideline NG122 also makes several recommendations around radiotherapy (conventional, hyper-fractionated and SABR) with curative intent. Although not explicitly relevant to the technologies under consideration in the scope, it will eventually be important for NICE to capture them as SoC options in decision points A1/A2. Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice? Yes, the positions for the proposed treatment in decision point A2 (adjuvant setting) are appropriate for NHS clinical practice. Please see comment about durvalumab [ID6220] in the section “Intervention at each decision point”.	action required. Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. Comment noted. No action required.

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		What are the key unanswered clinical questions about sequencing of treatments within NSCLC? Are you aware of any trials planned to address these? In all stages of the pathway, the pivotal trials underpinning NICE's recommendations are unlikely to have enrolled heavily pre-treated patients. Outcomes on various downstream treatments are therefore uncertain. The effectiveness of re-treatment with drugs having the same or similar mechanism of action on patients who have failed or had a recurrence on initial therapy is unclear. In the advanced metastatic setting, how many lines of treatment would an average person be expected to have in clinical practice? Does this vary? Are there any biological reasons for any variation? This question is to help inform the pathway model structure. It is our understanding that lines of treatment would depend on individual factors such as performance status, tolerability to treatment and comorbidities. Patient with specific biomarkers (e.g., EGFR /ALK) can be rechallenged multiple times with different generation TKIs. Patients whose tumours do not carry these biomarkers most commonly receive two lines of therapy including chemotherapy and/or immunotherapy and occasionally may receive more than two lines (up to four). SACT data would offer a good understanding of these patterns. <u>Treatment choices and sequences</u> Would having a PD-L1 inhibitor at the adjuvant or neo-adjuvant stage (Nodes A1 to A3) prevent someone from having a PD-L1 inhibitor at a later node (for example Node G)? If so, would you expect these rules to change in the future? The Blueteq form currently restricts treatment with PD-L1 inhibitors in the	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		metastatic setting (nodes F, G and K) to patients that have not received prior treatment with an anti PD-1, anti-PD-L1, anti-PD-L2 antibody. However, based on the discussions occurred in the context of the appraisal of a PD-L1 inhibitor in the adjuvant setting [TA823], current understanding is that retreatment with an immunotherapy would be commissioned in the NHS provided that the disease relapsed after treatment with the PD-L1 inhibitor was stopped, and provided sufficient time had elapsed between end of adjuvant treatment and onset of metastatic disease. <u>Targetable mutations</u> Would having Osimertinib as adjuvant treatment at node A2 prevent someone from having it at either node C1 or C2 later in the treatment pathway? If so, would you expect these rules to change in the future? Would people with targetable mutations always have targeted therapies as first-line therapy in the advanced setting or would immunotherapy be considered in these people? • If yes, what would influence this decision? • If yes, should targeted therapies be included at Node H1 for those whose cancer has a specific mutation but who have immunotherapy at first line. How are treatment decisions made in people whose disease is positive for more than one mutation-type? Is there likely to be co-occurrence of HER2 activating mutations and other targetable mutations? Not applicable to pembrolizumab ID3907. <u>Genetic and biomarker testing</u> How and when would HER2 status be tested for? What treatment would people with HER2 positive cancer have at first-line? Not applicable to decision point A2 of which pembrolizumab ID3907 is part. <u>Other considerations</u>	Comment noted. No action required. No action required.

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		Do you consider there to be added value to the NHS in a NICE appraisal of subcutaneous atezolizumab? No. We do not understand why a full NICE Technology Appraisal is proposed for this topic when this route is not standard for new formulations of products/indications already recommended by NICE. Are the outcomes listed appropriate? Have all core outcomes for NSCLC been considered? Have all relevant patient-reported outcomes been considered? Do outcomes differ across different points in the NSCLC pathway? With regard to decision point A2 (adjuvant setting), disease-free survival (DFS) is considered a relevant outcome as it captures the most important health-related benefits (and harms) of the technology in the adjuvant setting. Progression-free survival (PFS) is most commonly used to evaluate treatments in the advanced/metastatic setting. Response rate is not considered an appropriate outcome for the evaluation of an adjuvant treatment and was not collected in the KEYNOTE-091 trial. The remainder of the outcomes (overall survival, adverse effects of treatment and health-related quality of life) are considered relevant as they capture the most important health-related benefits (and harms) of the technology. Are there any groups of people in whom the proposed treatments are expected to be more clinically and cost effective? Are there other groups of people who should be examined separately? With regard to decision point A2, MSD have not identified at this stage any groups of people in whom the proposed treatments are expected to be more clinically and cost effective and therefore treatments should be appraised in line with the proposed Marketing Authorisation. Current standard of care (SoC) for NSCLC patients after complete surgical resection with or without adjuvant chemotherapy is the same regardless of stage, histology mutation status and therefore clinical effectiveness and cost	Comment noted. Subcutaneous atezolizumab has been removed from this appraisal. Comment noted. The outcomes have been updated following feedback received during the consultation and scoping workshop. It is acknowledged that there may be different outcomes for different parts of the treatment pathway. Comment noted. No action required.

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		effectiveness of the technology in these subgroups would be evaluated in comparison with same SoC. Would neoadjuvant and adjuvant immunotherapies be given differentially based upon PD-L1 status? Atezolizumab [TA823] was appraised and subsequently recommended in the Cancer Drugs Fund for adjuvant treatment of stage 2 to 3a resected NSCLC patients that have PD-L1 biomarker expression on 50% or more of their tumour cells. In the PEARLS/KEYNOTE-091 trial (the pivotal trial supporting this appraisal in the adjuvant setting), the primary endpoint (DFS) has been investigated in the overall trial population regardless of PD-L1 expression. Therefore, pembrolizumab in the adjuvant setting should be appraised in line with the proposed Marketing Authorisation to enable early-stage NSCLC patients to access this innovative treatment regardless of PD-L1 status. Is there any relevant real-world evidence or are there registries collecting data for people with NSCLC? The following registries collect different types of cancer patients' data: • National Cancer Registration and Analysis Service (NCRAS) run by National Disease Registration Service (NDRS)/NHS England, which has updated data from the following data sources: Cancer Outcomes and Services Dataset (COSD), National Radiotherapy Dataset (RTDS) and Systemic Anti-Cancer Therapy Dataset (SACT) • Hospital Episode Statistics (HES) • National Lung Cancer Audit (NCLA) run by Royal College of Surgeons as of 1 February 2022. Information about patients include data from NCRAS and the Welsh Cancer	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. Comment noted. No action required.

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		Would any of the 4 proposed technologies be candidates for managed access? With regard to pembrolizumab in the adjuvant setting, [redacted]. Do you consider that the use of any of the 4 technologies proposed can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. MSD expect that the health-related quality of life benefits of receiving adjuvant pembrolizumab treatment will be captured within the QALY calculation. PEARLS/KEYNOTE-091 trial (NCT02504372), a randomised, triple-blinded phase III trial evaluating pembrolizumab versus placebo in participants with stage IB/II-IIIA NSCLC who have undergone surgical resection with or without adjuvant chemotherapy, will inform the evidence base for this appraisal (decision point A2). NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Let us know if you think that the proposed remit and scope may need changing to meet these aims. In particular, tell us if the proposed remit and scope:	Comment noted. The interventions in the locally advanced pathway (previously decision points A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration. Comment noted for future consideration.

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		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are licensed • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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. MSD do not consider that the proposed remit, treatment pathway and scope could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments will be licensed or could lead to recommendations that have a different impact on people protected by the equality legislation or could have any adverse impact on people with a particular disability or disabilities. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adopting these technologies into practice? If yes, please describe briefly. MSD do not expect any barriers adopting these technologies into practice.	Comment noted. No action required. Comment noted. No action required.
	AstraZeneca	See responses to the 'questions for consultation' not covered in the previous sections: When in the diagnostic pathway is genetic testing carried out to determine the presence of targetable mutations? Does the timing of testing vary by mutation type? Biomarker testing is routine practice at diagnosis in the UK across all stages	Comment noted. No action required.

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		of lung cancer (including early-stage resectable, unresectable, and advanced lung cancer). Targeted therapies which are dependent on the biomarker result are used in the following settings: - Early stage: EGFR (IB-IIIA) and PD-L1 (II-IIIA) - Advanced stage (IV): EGFR, ALK, PD-L1, ROS1, BRAF, MET, RET, NTRK, KRAS In the advanced metastatic setting, how many lines of treatment would an average person be expected to have in clinical practice? Does this vary? Are there any biological reasons for any variation? This question is to help inform the pathway model structure. Multiple treatment lines are expected. Variation is common and is determined by a number of factors. Biomarker expression and genetic mutations are commonly prognostic in NSCLC. Would having a PD-L1 inhibitor at the adjuvant or neo-adjuvant stage (Nodes A1 to A3) prevent someone from having a PD-L1 inhibitor at a later node (for example Node G)? If so, would you expect these rules to change in the future? - NHS bluteq forms states that if there is disease progression during neoadjuvant nivolumab plus chemotherapy, no further anti-PD1 or anti-PDL1 immunotherapy is funded in any indication (3) - If the patient does not have progressive disease during neoadjuvant nivolumab plus chemotherapy and does not have a resection, further anti-PD1 or anti-PDL1 immunotherapy is only potentially possible with a 6-month gap between the date of completion of nivolumab plus chemotherapy and the date of first disease progression subject to all the relevant treatment criteria applying for whichever immunotherapy is requested (3)	Comment noted. No action required. Comment noted. No action required.

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		- The patient can receive atezolizumab and pembrolizumab in the advanced, metastatic setting if the patient has received prior treatment with an anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) antibody and discontinued/completed treatment with checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy without disease progression and at least 6 months elapsed between the date of last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease (3)	
		Would having Osimertinib as adjuvant treatment at node A2 prevent someone from having it at either node C1 or C2 later in the treatment pathway? If so, would you expect these rules to change in the future? Patients can be re-treated with osimertinib provided they did not have disease progression while on osimertinib in the adjuvant setting (3).	Comment noted. No action required.
		Would people with targetable mutations always have targeted therapies as first-line therapy in the advanced setting or would immunotherapy be considered in these people? Yes, patients would receive targeted therapies. Please see comments above.	Comment noted. The updated Pathway reflect this.
		Is there likely to be co-occurrence of HER2 activating mutations and other targetable mutations? It is unlikely that a patient would have > 1 actionable genomic mutation alongside the HER2 mutation (4).	Comment noted. No action required.
		How and when would HER2 status be tested for? What treatment would people with HER2 positive cancer have at first line?	Comment noted. No action required.

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		HER2 testing is available via a next generation sequencing (NGS) panel. These are conducted by the Genomic laboratory hubs (GLHs). Would any of the 4 proposed technologies be candidates for managed access? The durvalumab perioperative regimen is likely to be appropriate for managed access due to the need for longer follow-up data to fully capture benefits and costs of the technology.	Comment noted. No action required.
	Daiichi Sankyo UK Ltd	Is there likely to be co-occurrence of HER2 activating mutations and other targetable mutations? No, it is considered unlikely that a patient would have more than one actionable genomic mutation with the HER2 mutation (6). How and when would HER2 status be tested for? Molecular testing for the HER2 mutation is available on a next generation sequencing (NGS) panel via the Genomic hubs. HER2 mutation is currently not reported alongside other mutations in NSCLC (e.g., EGFR, ALK, ROS, etc. (7)). HER2 mutation would be expected to be tested at time of diagnosis alongside other mutations in NSCLC. What treatment would people with HER2 mutation-positive cancer have at first-line? The majority of patients testing positive for HER2 mutation would be expected to receive a combination of platinum-based therapy and an anti-programmed death 1 or anti-PD-L1 treatment at first line. This combination at first-line is considered standard of care as highlighted in recent NICE appraisals of lung cancer (e.g., TA781 [3]).	Comment noted. No action required. Comment noted. No action required. Comment noted. This is reflected in the updated Pathway.

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	Roche Products Ltd	None	No action required.
	Takeda	When in the diagnostic pathway is genetic testing carried out to determine the presence of targetable mutations? Does the timing of testing vary by mutation type? The genetic tests that are funded by NHS England are outlined in the National Genomic Test Directory.[9] Current funding includes use of next generation sequencing (NGS), which is the gold-standard method to detect all targetable mutations. As NGS testing is already funded for mutations included in the National Genomic Test Directory, testing-related costs should not be incorporated into an economic model evaluating a medicine in populations with these mutations. Costs associated with detection of most targetable mutations by appropriate methods are already accounted for and implemented within the NHS. This aligns with the published view from the Institute of Cancer Research (ICR),[10] which states: "*setting the cost of genetic tests against a drug when those tests are already recommended on the NHS seems to be double counting, and is acting as a penalty to innovation*". Given all patients entering an economic model are assumed to be of the relevant indication (i.e. in this case, the mutation has been confirmed), we believe that the costs of testing should not be incorporated in the economic modelling. Does the pathway described represent current NHS clinical care? Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice? <u>Advanced, metastatic NSCLC: B (ALK-positive tumours)</u>	Comment noted. No action required.

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		We would recommend that the NICE team consider the NHS England Blueteq criteria and NICE Guideline for NSCLC (NG122) to ensure all available treatment options for patients with ALK-positive tumours are reflected. For example: • The NICE recommendation for lorlatinib for previously treated ALK-positive advanced NSCLC (TA628) is for disease that has progressed after alectinib or ceritinib as the first TKI, or crizotinib and at least 1 other ALK TKI. However, the marketing authorisation in Great Britain (GB)[11] and Blueteq criteria[12] for lorlatinib are broader than the NICE recommendation, and this should be reflected in the text to ensure all treatment options are accurately represented. The Blueteq criteria states that patients can be previously treated with alectinib, ceritinib, brigatinib, or crizotinib followed by brigatinib or ceritinib. Therefore, treatment with brigatinib followed by lorlatinib (without the need for prior crizotinib) is commissioned and fully funded, despite not being specifically highlighted in the TA628 NICE recommendation. • The NICE recommendation for first-line brigatinib for ALK-positive advanced NSCLC is for disease not previously treated with an ALK inhibitor. The Blueteq criteria[12] expands on this, and states that patients who received first-line cytotoxic chemotherapy when the ALK status was not known remain eligible for treatment with first-line brigatinib. We propose the wording in this section is updated to reflect that brigatinib in the first-line indication can be used regardless of prior treatment with chemotherapy. Is there likely to be co-occurrence of HER2 activating mutations and other targetable mutations? As discussed above, we are unclear why mobocertinib has been included as	Comment noted. The section has been updated to reflect that lorlatinib can be used directly after brigatinib in NHS practice. Comment noted. The current clinical management and treatment options laid out in the scope reflect the current NICE recommendations” Comment noted. The decision points for post-systemic treatment have been split by genetic alteration to make clear that patient subgroups with different genetic alterations would not be directly

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		a comparator for the trastuzumab deruxtecan (ID3934) appraisal for *HER2*-mutated disease. Mobocertinib is licensed and NICE-recommended for treatment of advanced or metastatic NSCLC harbouring *EGFR* exon20 insertion mutations, following platinum-based chemotherapy. The literature discussed above indicate that *EGFR* exon20ins mutations are generally mutually exclusive of other oncogenic drivers, and are therefore unlikely to co-occur with *HER2* mutations.[6,7,8] This is supported by elicited clinical expert opinion, which stated that *EGFR* exon20 insertion and *HER2* mutations are mutually exclusive and are not seen together in practice. It is therefore inappropriate to consider an *EGFR* exon20ins-targeted technology as a comparator for a *HER2*-targeted technology.	compared against each other
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	Merck request that more information is provided on the remit and process of this NSCLC pathway appraisal.	Comment noted.
	British Thoracic Society	1. Targeted Lung Health Checks are being rolled out across England rapidly at the moment for lung cancer screening. This is increasing the proportion of people who are diagnosed with early stage lung cancer (stage 1 and 2). This might be relevant if the model needs to include the proportions of people diagnosed at each stage of lung cancer as part of the cost effectiveness analysis. The people often also have better performance status than those diagnosed via symptomatic or emergency routes which means that even with advanced disease their prognosis is often better as PS is an important predictor of this. 2. Tests are usually done at the start of the diagnostic pathway. There is a	Comment noted. The expected impact of the NHS Lung Health Check Programme has been added to the background section. Comment noted. The

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		difference in the time it takes for different results to come back (eg. Immunohistochemistry tests such as PDL1 testing will often come back much faster than EGFR testing in many centres). Some centres require tests to be sent away whereas other centres are able to perform all testing in-house. 3. The National Lung Cancer Audit (NLCA) collects data on lung cancer treatments in England and Wales. Also, the Cancer Registry will have data on lung cancer cases. The. Systemic Anti-Cancer Treatment (SACT) and National Radiotherapy Dataset (RTDS) also record treatments given in the UK. 4. NICE recommendation (www.nice.org.uk/guidance/ta876) which is mentioned in Table 1 has now been published (22nd March 2023)- neoadjuvant chemotherapy and nivolumab for resectable (tumours at least 4 cm or node positive) non-small-cell lung cancer (NSCLC) in adults.	variability in testing has been added to the background section. Comment noted. No action required. Comment noted. This has been reflected in the scope.
	British Thoracic Oncology Group (BTOG)	None	No action required.
	LCNUK	None	No action required.
Any additional comments on the draft scope	Merck Sharp & Dohme (MSD) UK	None	No action required.
	AstraZeneca	AstraZeneca have no further comments.	No action required.

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	Daiichi Sankyo UK Ltd	No further comments	No action required.
	Roche Products Ltd	Under A1-4, the treatment regimen listed are neo-adjuvant, adjuvant and and after chemoradiation. If the intervention listed under A1 in Table 1 is referring to durvalumab ID 10304 (https://www.nice.org.uk/guidance/awaiting-development/gid-ta11197), then the definition of the treatment options should include peri-operative as well. The current options are: 1. Neoadjuvant nivolumab + chemotherapy [TA876] 2. Perioperative durvalumab [ID10304] 3. Adjuvant pembrolizumab [ID3907], adjuvant durvalumab [?ID], adjuvant osimertinib [TA761] and adjuvant atezolizumab [TA823] 4. after chemoradiation, durvalumab [TA798]	This section of the pathway (previously decision points A1-A3 has been reorganised based on feedback received during the consultation and scoping workshop. The interventions in the locally advanced pathway (previously nodes A1-3) are no longer being appraised in this phase of the Pathways appraisal. However the comment has been noted for future consideration.
	Takeda	None	No action required.
	Novartis Pharmaceuticals UK Ltd	None	No action required.
	Merck Serono	None	No action required.

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	British Thoracic Society	None	No action required.
	British Thoracic Oncology Group (BTOG)	None	No action required.
	LCNUK	None	No action required.

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

Eli Lilly