NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Treatments for non-small-cell lung cancer

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of treatments for non-small-cell lung cancer.

Background

Lung cancer falls into two main histological categories: around 85 – 90% are non-small-cell lung cancers (NSCLC) and the remainder are small-cell lung cancers[1]. NSCLC can be further classified into squamous cell carcinoma and non-squamous cell carcinoma. Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma[2].

Treatment depends on the location and stage of the cancer. There are different staging systems for NSCLC, including the number system[2]. It looks at the number and size of lung tumours. The number system has 4 stages:

- Stage 1 (early stage where tumour is localised to one lobe of the lung)
- Stage 2 (early stage with possible spread to adjacent structures in the chest or lymph nodes in or near the lungs)
- Stage 3 (locally advanced with possible spread to additional lobes of the lung, regional lymph nodes or nearby structures in the chest)
- Stage 4 (advanced, metastatic stage where tumour has spread to the other lung or a distant part of the body)

In 2018 35,239 cases of non-small-cell lung cancer were diagnosed in England and 7%, 21% and 43% of people with lung cancer were diagnosed with stages 2, 3 and stage 4 disease respectively.[3] In the same year, 68%, 63% and 17% of people diagnosed with stage 2, 3 and 4 disease respectively survived for one year or more.[3]

There are a range of oncogenic driver mutations that are generally found in small proportions of non-small-cell lung cancers, see **Table 1** for prevalence. These driver mutations are generally considered to be mutually exclusive although some overlap has been reported between them.[4] HER2 is a gene which produces a protein on the surface of cells that favours cell growth, it can cause cancer by being overexpressed or mutated which results in uncontrolled cell growth.

Oncogenic Driver mutation	Estimated Prevalence ([reference])
ALK	~5%[5]
EGFR	12.5%[6]
ROS-1	1%[7]
KRAS G12C	12%[8]
MeTex14	3-4%[9]
RET fusion	1-2%[10]
NTRK fusion	0.1-3.3%[11]
HER2	4% (Non-squamous only)[12]

Treatment pathway

The treatment pathway for NSCLC can be divided into interconnected decision points based on the number staging system and line of therapy. These represent what treatments are available at each stage of the disease (Figure 1)

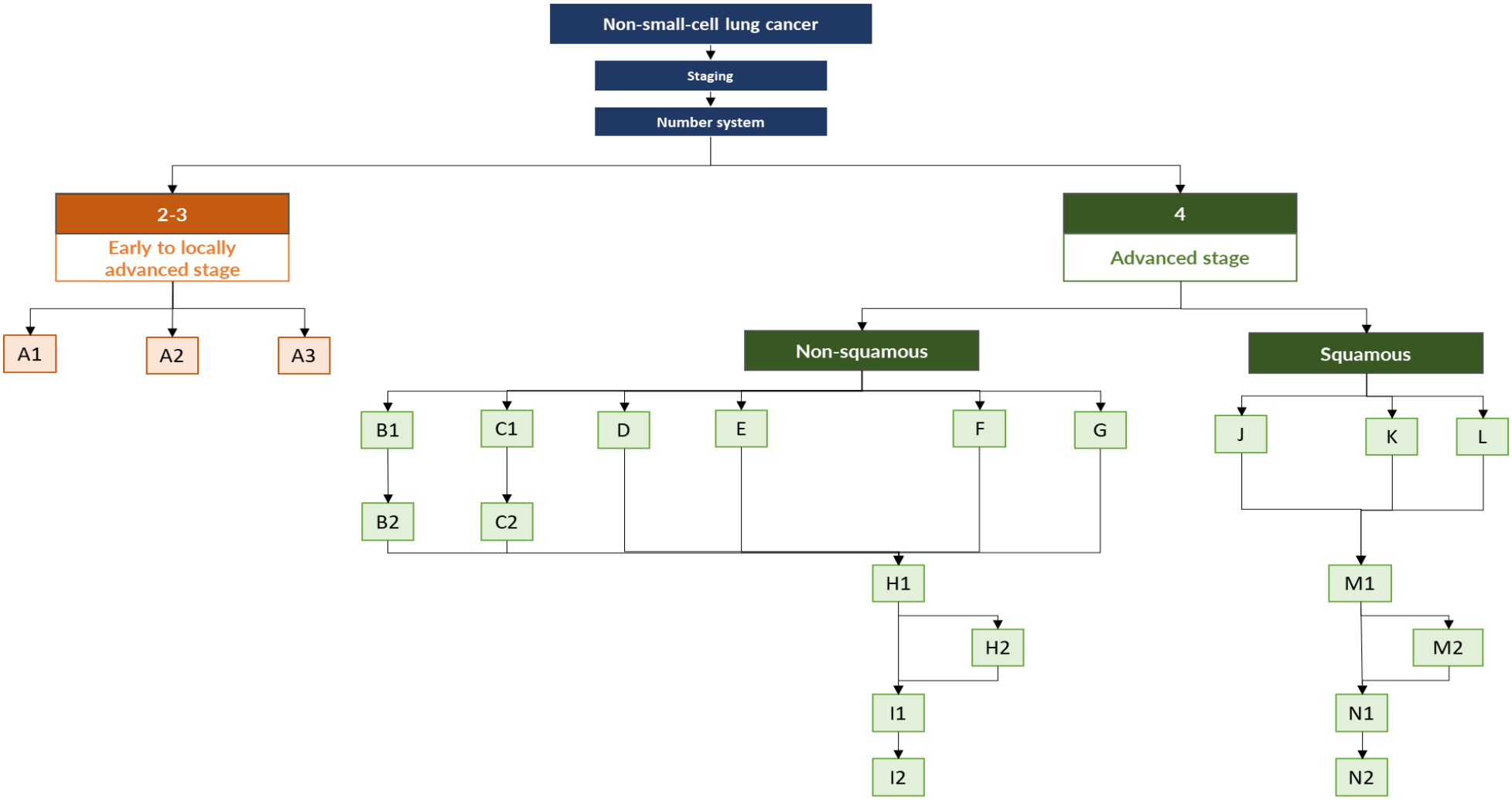

Figure 1 Treatment pathway for NSCLC

The treatment pathway for NSCLC is outlined below (treatmenty appriased in published NICE guidance only):

A1-4: Early stage 2-3, locally advanced NSCLC (squamous and non-squamous)

Treatment options for early-stage NSCLC depend on the cancer stage and the general health and preferences of the person with cancer.

- ***A1, neoadjuvant:*** The primary treatment for early-stage lung cancer is surgical resection with curative intent. Before surgery, chemoradiotherapy may be given (chemotherapy with radiotherapy).

- ***A2, adjuvant*:** Surgery may potentially be followed by chemotherapy or osimertinib, which is recommended in the Cancer Drugs Fund in NICE technology appraisal TA761 for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. NICE technology appraisal TA823 recommends atezolizumab in the Cancer Drugs Fund for adjuvant treatment of stage 2 to 3a resected non-small-cell lung cancer in people whose disease has not progressed after platinum-based adjuvant chemotherapy and have PD-L1 biomarker expression on 50% or more of their tumour cells.

- ***A3, after chemoradiation***: In people who decline surgery or in whom any surgery is contraindicated, treatment options include sequential or concurrent chemoradiotherapy without surgery or radiotherapy alone. NICE technology appraisal TA798 recommends durvalumab for maintenance treatment of unresectable non-small-cell lung cancer in people whose disease has not progressed after platinum-based chemoradiation and whose tumours express PD-L1 on 1% or more of cells.

Advanced, metastatic NSCLC

B-E & J: Tumours with targetable mutations

Current options for untreated advanced NSCLC with targetable mutations include different tyrosine kinase inhibitors (TKIs) based on the mutation type:

- ***B, anaplastic lymphoma kinase (ALK)-positive tumours:*** First line treatment options (**B1**) include brigatinib, alectinib, ceritinib and crizotinib (NICE technology guidance TA670, TA536, TA500 and TA406). Second-line TKIs can be used after progression on first-line options (**B2**). NICE technology appraisal guidance TA628 recommends lorlatinib as an option for ALK-positive advanced NSCLC in adults whose disease has progressed after using alectinib or ceritinib as the first TKI or crizotinib and at least 1 other ALK TKI. Brigatinib or ceritinib are recommended in people whose disease has progressed after crizotinib (NICE technology guidance TA571 and TA395)

- ***C, epidermal growth factor receptor (EGFR)-positive tumours*:** Afitinib, erlotinib, dacomitinib, gefitinib and osimertinib are recommended as first-line treatment options in NICE technology appraisal guidance TA310, TA595, TA258, TA192 and TA654 (**C1**). In people who are EGFR T790M mutation-positive, osimertinib can be used after progression on a first-line TKI (**C2**) NICE technology appraisal guidance TA653.

- ***D, ROS-1-positive tumours***: Treatment options for ROS-1 positive NSCLC include entrectinib and, through the Cancer Drugs Fund, crizotinib (NICE technology appraisal guidance TA643 and TA529)

- ***E & J, METex14 skipping mutation-positive tumours:*** Tepotinib is the only targeted treatment recommended for people with METex14 skipping mutation-positive tumours (NICE technology appraisal guidance TA789). It is usually used at first-line but use at later lines is possible. METex14 skipping mutation testing is variable across the UK, so people may be treated with non-targeted therapies until diagnosed. Tepotinib can be used in both squamous (**J**) and non-squamous (**E**) NSCLC.

F-G and K-L: Tumours without targetable mutations

- ***F & K, PD-L1 expression on less than 50% of tumour cells*****:** For non-squamous NSCLC (**F**), first-line treatment options include pembrolizumab with pemetrexed and platinum chemotherapy (NICE technology appraisal guidance TA683) and atezolizumab plus bevacizumab, carboplatin and paclitaxel (NICE technology appraisal guidance TA584). These treatments are limited to tumours without ALK- or EGFR-positive mutations. For squamous cancer (**K**), NICE technology appraisal guidance TA770 recommends pembrolizumab with carboplatin and paclitaxel at first-line.

- ***G, PD-L1 expression on 50% or more tumour cells*****:** Atezolizumab and pembrolizumab as monotherapies are recommended at first-line for both squamous and non-squamous disease (NICE technology appraisal guidance TA705, TA531). For non-squamous NSCLC only (**G**), NICE technology appraisal guidance TA683 also recommends pembrolizumab with pemetrexed and platinum chemotherapy. These treatments are for people without ALK- or EGFR-positive mutations. For squamous NSCLC (**L**), NICE technology appraisal guidance TA770 recommends pembrolizumab with carboplatin and paclitaxel. This is only in people who require an urgent clinical response to justify the use of combination therapy over pembrolizumab monotherapy (for example, people with impending major airway obstruction).

H: Subsequent systemic therapies

- ***First subsequent systemic therapy*****:**

    - *Non-squamous* (**H1**): Following progression on targeted treatments, NICE clinical guideline NG122 recommends platinum doublet chemotherapy or platinum-based chemotherapy in combination with premetexed in people who have not had platinum based chemotherapy before. If disease has not progressed on induction therapy, premetrexed maintenance treatment is recommended (NICE technology appraisal guidance TA190 and TA402). In people with ALK- or EGFR-positive mutations, atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended after progression on TKIs (NICE technology appraisal guidance TA584).

    - *Squamous* (**M1**): NICE clinical guideline NG122 recommends platinum doublet chemotherapy if not received at first-line.

- ***H2 & M2, second subsequent systemic therapy:*** NICE technology appraisal TA428 recommends pembrolizumab monotherapy after progression

on chemotherapy for people whose tumours express PD-L1 on 1% or more of cells. Atezolizumab and nivolumab monotherapies are recommended after chemotherapy in people with any PD-L1 expression level (NICE technology appraisal guidance TA520 and TA655). Immunotherapies can be used for both squamous (**H2**) and non-squamous (**M2**) NSCLC in people who have not have a PD-L1 inhibitor before. For non-squamous cancer, mobocertinib is recommended for treating EGFR exon 20 insertion mutation-positive NSCLC after platinum-based chemotherapy (NICE technology appraisal guidance TA855).

I & N: Last line therapies, squamous and non-squamous

- ***I1 & N1, after progression on subsequent systemic therapies:*** Docetaxel, with or without nintedanib can be used after immunotherapy, platinum-based chemotherapy or both (NICE technology appraisal guidance TA347). Treatments recommended in the Cancer Drugs Fund include sotorasib for KRAS G12C mutation-positive tumours and selpercatinib for RET fusion-positive disease (NICE technology appraisal guidance TA781 and TA760).

- ***I2 & N2, after all other lines of therapy exhausted*****:** Entrectinib and larotrectinib are recommended for use within the Cancer Drugs Fund as options for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive tumours when no satisfactory treatment options exist (NICE technology appraisal guidance TA644 and TA630).

Table 1: New treatments being appraised

Decision point	A1	A2	H1	H2	I1	F
Interventions	• Durvalumab with chemotherapy [ID6220]	• Pembrolizumab [ID3907] • Durvalumab with chemotherapy [ID6220]	• Trastuzumab deruxtecan [ID3934] (for HER2 mutated disease)	• Trastuzumab deruxtecan [ID3934] (for HER2 mutated disease)	• Trastuzumab deruxtecan [ID3934] (for HER2 mutated disease)	• Subcutaneous atezolizumab [ID6204]
Populations	People with untreated NSCLC which is resectable	People with NSCLC who have undergone complete surgical resection	People with unresectable or metastatic non-squamous NSCLC whose disease has progressed after chemotherapy	People with unresectable or metastatic ***non-squamous*** NSCLC whose disease has progressed after chemotherapy	People with unresectable or metastatic ***non-squamous*** NSCLC whose disease has progressed after all standard treatments	People with unresectable or metastatic ***squamous*** NSCLC whose disease has progressed after chemotherapy
Comparators	• Chemoradiotherapy (Stage 3A-N2) • Best supportive care (Stage 2) • Nivolumab with chemotherapy	• Platinum-based combination chemotherapy For people whose tumours have EGFR exon 19 deletions or exon 21 (L858R)	• Platinum doublet chemotherapy with pemetrexed • Atezolizumab, bevacizumab and paclitaxel	• Atezolizumab • Nivolumab For people whose tumours express PD-L1 with over 1% tumour proportion score	• Docetaxel with or without nintedanib (for adenocarcinoma histology)	• Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Pembrolizumab with pemetrexed and platinum chemo

	(subject to ongoing NICE appraisal)	substitution mutations: • Osimertinib (subject to ongoing NICE appraisal) For people whose tumours express PD-L1 with at least a 50% tumour proportion score: • Atezolizumab after adjuvant cisplatin-based chemotherapy (subject to ongoing NICE appraisal)		• Pembrolizumab For people whose tumours have EGFR exon 20 insertions: • Mobocertinib		

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of trastuzumab deruxtecan is conditional on the presence of the HER2 biomarker. The economic modelling should include the costs associated with diagnostic testing for HER2 in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation). The availability and cost of biosimilar and generic products should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals:** Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (2022). NICE Technology Appraisals guidance 823.

	Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (2022). NICE technology appraisals guidance 761 Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy (2017) NICE technology appraisal guidance 713 Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (2018) NICE technology appraisal guidance 520 Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (2017) NICE technology appraisal guidance 428 Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (2016) NICE technology appraisal guidance 403 Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy. (2015). NICE Technology Appraisal 374. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (2015) NICE technology appraisal guidance 347 **Related appraisals in development:** Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer. NICE Technology Appraisals guidance ID3907. Publication expected August 2024. Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer. NICE technology appraisal guidance ID3757. Publication expected June 2023. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer. NICE Technology Appraisals guidance ID5094. Publication date TBC. **Related Guidelines:** 'Lung cancer: diagnosis and management' (2019). NICE guideline NG122.

	Related Quality Standards: Lung cancer in adults' (2019). NICE quality standard 17
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105: Specialist cancer services (adults).

Questions for consultation

The pathway

Does the pathway described represent current NHS clinical care? Is the pathway split appropriately into clearly defined decision problems?

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?

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?

Would pembrolizumab monotherapy ever be used after adjuvant chemotherapy?

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?

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?

Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice?

What are the key unanswered clinical questions about sequencing of treatments within NSCLC? Are you aware of any trials planned to address these?

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.

Treatment choices and sequences

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?

Targetable mutations

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?

Genetic and biomarker testing

How and when would HER2 status be tested for? What treatment would people with HER2 positive cancer have at first-line?

Other considerations

Do you consider there to be added value to the NHS in a NICE appraisal of subcutaneous atezolizumab?

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?

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?

Would neoadjuvant and adjuvant immunotherapies be given differentially based upon PD-L1 status?

Is there any relevant real-world evidence or are there registries collecting data for people with NSCLC?

Would any of the 4 proposed technologies be candidates for managed access?

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.

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:

- 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.

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.

References

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