NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Treatments for non-small-cell lung cancer [ID6234]

Final scope

Evaluation objective

To build a cost-effectiveness model to assess multiple technologies across decision spaces in the metastatic non-small-cell lung cancer (NSCLC) pathway. The decision points which are currently being modelled are highlighted in **Figure 1** and detailed in **Table 2**.

Background

Single technology appraisals consider a single point in the treatment pathway at a single point in time. This can lead to variation in clinical practice and difficulties for stakeholders in understanding and using guidance. Using a pathway cost-effectiveness model can better reflect real-world decisions that patients and clinicians need to make and is especially useful in disease areas with complex pathways which contain a high and growing number of technologies. There are over 50 separate NICE recommendations from single technology appraisals for technologies to treat NSCLC with more technologies currently being appraised or scheduled to be appraised in the future. Therefore, this work will focus on the metastatic non-small-cell lung cancers (NSCLC) pathway, with an aim to develop a broader model covering the whole disease area in the future.

Lung cancer falls into two main histological categories: around 85 to 90% are 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 the vast majority of these are 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] As a result of the targeted NHS Lung Health Check programme which is being rolled out in the UK, it is expected that lung cancer will increasingly be diagnosed at an earlier stage when treatment may be more successful.

There are a range of oncogenic driver genetic alterations that individually are found in small proportions of non-small-cell lung cancers. But overall, these account for around 40% of

non-squamous NSCLC, see **Table 1** for prevalence. These genetic alterations 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. There is geographical variability in testing for the various oncogenic driver genetic alterations so people may be treated with non-targeted therapies until diagnosed.

Table 1 – Prevalence of oncogenic genetic alterations in NSCLC

Oncogenic genetic alteration	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	0.1-1%[11,†]
HER2	4% (Non-squamous only)[12]
BRAF V600 mutation	1-2%[13]

† clinical opinion at the Scoping Workshop said UK prevelance of NTRK mutations was maximum of 1%, so this estimate is lower that stated in the reference.

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 (see **Figure 1** and **Table 2**)

Figure 1 – NSCLC pathway made up of decision points. Reproduced in text form in Table 1. Decision points highlighted by dotted lines are being modelled in the first iteration of the NSCLC pathways pilot.

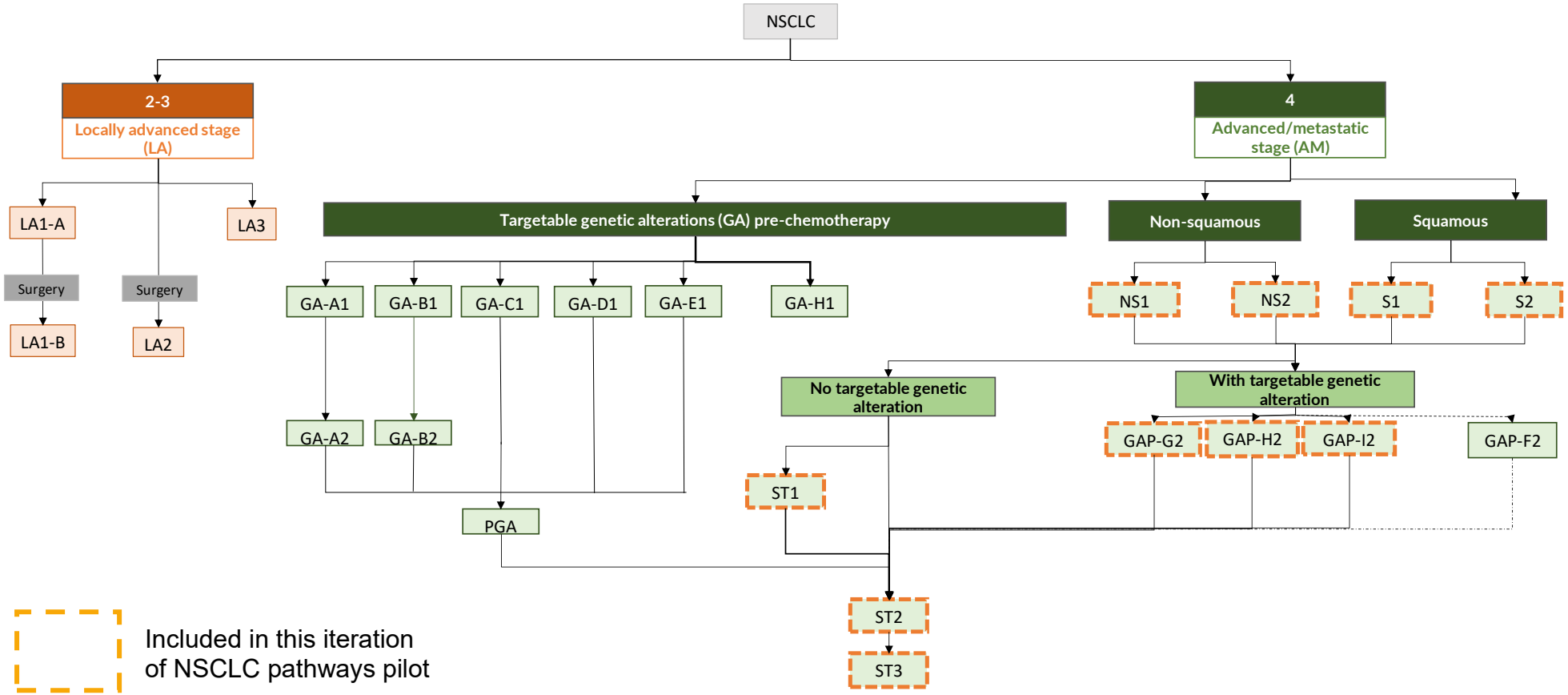

Table 1 – Decision points of the NSCLC pathway. Decision points highlighted in bold are being modelled in the first phase of the NSCLC cost-effectiveness model

Decision Point	Description
LA1A	Neo-adjuvant therapy
LA1B	Adjuvant therapy continuing from neoadjuvant therapy
LA2	Adjuvant therapy only
LA3	Maintenance to chemoradiation
NS1	**Non-squamous, PD-L1 <50%**
NS2	**Non-squamous, PD-L1 50% or more**
S1	**Squamous, PD-L1 <50%**
S2	**Squamous, PD-L1 50% or more**
ST1	**Mixed histology, subsequent therapies (no previous chemotherapy)**
ST2	**Mixed histology, subsequent therapies 2**
ST3	**Mixed histology, subsequent therapies 3**
GA-A1	ALK 1st line
GA-A2	ALK 2nd line
GA-B1	EGFR mutation 1st line
GA-B2	EGFR mutation 2nd line
GA-C1	ROS-1
GA-D1	MetEx Skipping alteration
GA-E1	BRAF V600E
GA-H1	RET fusion 1st line
PGA	Post genetic alteration chemo/immunotherapy
GAP-F2	HER2 mutation 2nd line
GAP-G2	**EGFR Exon20 insertion 2nd line**
GAP-H2	**RET fusion 2nd line**
GAP-I2	**KRAS G12C 2nd line**

The treatment pathway for NSCLC is outlined below (based on NICE guidance and clinical input gathered during the scoping consultation and scoping workshop).

LA1-3: Stage 2-3a locally advanced NSCLC (squamous and non-squamous)

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

- ***LA1A, neoadjuvant:*** The primary treatment for early-stage lung cancer is surgical resection with curative intent. Before surgery, nivolumab with chemotherapy may be given as recommended in TA876.

- ***LA1B, adjuvant continuation:*** Where a neo-adjuvant therapy is given before surgery, the decision may be taken to continue with regimen, or a modification of it, after the surgery has been completed.

- ***LA2, adjuvant*****:** Complete resection may potentially be followed by chemotherapy and where suitable osimertinib, which is recommended in the Cancer Drugs Fund in NICE TA761 for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection. NICE TA823 recommends atezolizumab in the Cancer Drugs Fund for adjuvant treatment of stage 2 to 3a resected NSCLC 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. After incomplete resection radiotherapy alone can be offered.

- ***A3, after chemoradiation***: In people who decline surgery or in whom any surgery is contraindicated, treatment options include sequential or concurrent chemoradiotherapy or radiotherapy alone. NICE technology appraisal TA798 recommends durvalumab for maintenance treatment of locally advanced unresectable non-small-cell lung cancer in people whose disease has not progressed after concurrent platinum-based chemoradiation and whose tumours express PD-L1 on 1% or more of cells.

Advanced, metastatic NSCLC

GA-A to GA-E and PGA: Tumours with targetable genetic alterations

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

- ***GA-A1, anaplastic lymphoma kinase (ALK)-positive tumours:*** First line treatment options (**GA-A1**) include brigatinib, alectinib, ceritinib and crizotinib (NICE guidance TA670, TA536, TA500 and TA406). Second line TKIs can be used after progression on first line options (**GA-A2**). NICE 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 guidance TA571 and TA395)

- ***GA-B1, epidermal growth factor receptor (EGFR) mutation-positive tumours*****:** Afatinib, erlotinib, dacomitinib, gefitinib and osimertinib are

recommended as first-line treatment options in NICE guidance TA310, TA595, TA258, TA192 and TA654 (**GA-B**). In people who are EGFR T790M mutation-positive, osimertinib can be used after progression on a first-line TKI (**GA-B2**) NICE guidance TA653.

- ***GA-C1, ROS-1-positive tumours***: Treatment options for ROS-1 positive NSCLC include entrectinib and, through the Cancer Drugs Fund, crizotinib (NICE guidance TA643 and TA529)

- ***GA-D1 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.

- ***GA-E1, BRAF V600 mutation positive tumours:*** Dabrafenib with trametinib is recommended by NICE guidance TA898 for first line use in NSCLC which is positive for the BRAF V600 mutation.

- ***GA-H1, RET fusion positive tumours:*** Selpercatinib is recommended through the Cancer Drugs Fund for untreated non-small-cell lung cancer with a RET fusion (NICE technology appraisal guidance TA911)

- **PGA, chemoimmunotherapy after progression on 1st or 2nd line targetable therapies:** For those whose disease progresses after using 1st or 1st and 2nd line targeted therapies in decision points GA-A1 to GA-E1, NICE clinical guideline NG122 recommends platinum doublet chemotherapy or platinum-based chemotherapy in combination with pemetrexed in people who have not had platinum based chemotherapy before. Chemoimmunotherapy or immunotherapy alone may also be offered as a subsequent treatment.

NS1 - NS2 and S1 - S2: Tumours without targetable genetic alterations or with targetable genetic alterations which are actionable following chemo-immunotherapy

- ***NS1 and S1, PD-L1 expression on less than 50% of tumour cells*:** For non-squamous NSCLC (**NS1**), first-line treatment options include pembrolizumab with pemetrexed and platinum chemotherapy (NICE technology appraisal guidance TA683) and atezolizumab plus bevacizumab, carboplatin and paclitaxel (NICE guidance TA584).For squamous disease (**S1**), NICE guidance TA770 recommends pembrolizumab with carboplatin and paclitaxel at first-line.

- ***NS2 and S2, 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 guidance TA705, TA531). For non-squamous NSCLC only (**NS2**), NICE guidance TA683 also recommends pembrolizumab with pemetrexed and platinum chemotherapy. For squamous NSCLC (**S2**), NICE guidance TA770 recommends pembrolizumab with carboplatin and paclitaxel.

GAP-F to GAP-I: Targetable mutations after chemoimmunotherapy

- ***GAP-F2, HER2 mutation positive disease after chemotherapy***. For those whose disease progresses after a chemotherapy containing regimen, there are no currently NICE recommended treatments.

- ***GAP-G2, EGFR exon 20 fusion positive disease after platinum chemotherapy***. For those whose disease progresses on any regimen containing platinum chemotherapy, mobocertinib is recommended by NICE guidance TA855.

- ***GAP-H2, RET fusion positive disease which is previously treated.*** For those whose disease has a RET gene fusion and has progressed on a previous treatment, selpercatinib is recommended within the Cancer Drugs Fund by NICE guidance TA760.

- ***GAP-I2, KRAS G12C mutation positive disease which is previously treated.*** For those whose disease has a KRAS G12C mutation and has progressed on a previous treatment, sotorasib is recommended within the Cancer Drugs Fund by TA781.

***Subsequent systemic therapies*:**

- ***ST1, NSCLC with or without targetable genetic alterations that has progressed on previous therapies.*** If the disease has progressed on all previous targeted therapies, immunotherapies and chemotherapies, people may be offered regimens comprising any agents recommended at previous lines, but which had not been used. People may also rechallenge with an immunotherapy if sufficient time has passed between the last immunotherapy and time of progression.

- ***ST2, final chemotherapy line.*** Docetaxel, with or without nintedanib can be used after immunotherapy, platinum-based chemotherapy or both (NICE technology appraisal guidance TA347)

- ***ST3, all other treatment options 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).

The decision points, populations, technologies to be modelled are detailed in Table 2 and Table 3.

Table 2: Decision points, populations and technologies for inclusion in the cost-effectiveness model

Decision point	Populations	Available treatments
NS1	People with advanced or metastatic non-squamous NSCLC that expresses PD-L1 on less than 50% of cells	• Pembrolizumab with pemetrexed and platinum chemotherapy (TA683) • Atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA548) • Pemetrexed with platinum doublet chemotherapy (clinical opinion)
NS2	People with advanced or metastatic non-squamous NSCLC that expresses PD-L1 on 50% or more of cells	• Pembrolizumab with pemetrexed and platinum chemotherapy (TA683) • Pemetrexed with platinum doublet chemotherapy (clinical opinion) • Pembrolizumab monotherapy (TA531) • Atezolizumab monotherapy (TA705)
S1	People with advanced or metastatic squamous NSCLC that expresses PD-L1 on less than 50% of cells	• Pembrolizumab with carboplatin and paclitaxel (TA770) • Platinum based chemotherapy
S2	People with advanced or metastatic squamous NSCLC that expresses PD-L1 on 50% or more of cells	• Pembrolizumab monotherapy (TA531) • Atezolizumab monotherapy (TA705) • Platinum based chemotherapy
ST1	People with advanced or metastatic NSCLC which has progressed after one line of treatment.	• Platinum based chemotherapy (if not used at earlier line) • Pembrolizumab monotherapy (TA428)

		• Nivolumab monotherapy – [Non squamous only] (TA713)
ST2	People with advanced or metastatic NSCLC that has progressed after two lines of treatment	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347)
ST3	People with advanced or metastatic NSCLC where there are no other suitable alternative treatments	• Best supportive care
GAP-G2	People with NSCLC with a EGFR Exon20 insertion that has progressed after one line of treatment	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347) • Mobocertinib (TA855)
GAP-H2	People with NSCLC with a RET fusion that has progressed after one line of treatment	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347) • Selpercatinib (TA760, currently in CDF)
GAP-I2	People with NSCLC with a KRAS G12C mutation that has progressed after one line of treatment	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347) • Sotorasib (TA781, currently in CDF)

Table 3: Outcomes and other details for consideration in the cost-effectiveness model

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response • disease control rate • time to treatment discontinuation • 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).

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