Treatments for non-small-cell lung cancer [ID6234]: **Analysis Plan**

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1 Plain English Summary

1.1 Background

NICE, which stands for the National Institute for Health and Care Excellence, helps doctors and healthcare leaders provide the best care to patients. NICE have a process called 'technology appraisal' where they decide if new or existing medicines and treatments should be used in the NHS. They make these decisions with the help of a health economic model. The model includes information that helps them to look at how much of a difference the treatments make to patients and if they are value for money for the NHS.

1.2 What is the problem?

For some illnesses, such as cancer, patients will have a series of treatments. When the first treatment stops working, they can move to a second treatment, and so on. This is known as the treatment pathway, which is like a map that shows all the steps to treat a disease. Nearly half of the technology appraisals at NICE are on just 10 disease areas. Normally, when NICE evaluate a new medicine, they only consider one place in the treatment pathway, such as after the first medicine has stopped working. They don't consider other treatments people might get at different times for the same illness.

Sometimes, when NICE looks at each treatment by itself this can create unclear advice for doctors and patients because it does not take the whole pathway into account. It also means that NICE does the same work again and again every time there is a new medicine they need to consider for the same pathway. Repeating some of the same work is not efficient. It can lead to different treatments for the same illness being judged in slightly different ways and NICE wants to assess them all fairly.

NICE is piloting a new 'pathways approach'. NICE will look at the entire treatment pathway, which will help them to give clear guidance on multiple treatments at once.

1.3 What are we going to do?

We are going to pilot the new 'pathways approach' for lung cancer. Lung cancer is the third most common cancer in the UK, and is responsible for one in five of all cancer deaths. Lung cancer is usually diagnosed based on symptoms, medical history and tests, such as a chest X-ray or CT scan.

There are two main kinds of lung cancer: non-small-cell lung cancer (NSCLC) and small-cell lung cancer. NSCLC is the most common lung cancer. The treatment depends on where the cancer is, how bad it is and if it has spread (stage of cancer). The choice of treatment can also depend on whether the cancer cells have certain genetic changes known as 'mutations'. Choosing the best treatment option for patients with NSCLC can be divided into different 'decision points.' These decision points will reflect how bad the cancer (cancer stage) is and whether the treatment is given as the first treatment option, or after initial treatments.

In this pilot project, we're looking at advanced (stage 4) NSCLC. We will focus on patients who do not have a mutation that can have the first treatment specifically aimed at that mutation. We are developing a new "economic model" that NICE can use to evaluate whether new treatments for these specific patients with lung cancer are good value for money and should be recommended for use in the NHS. To do this we intend to:

- Assess how well each treatment option works at each "decision point" in the treatment pathway for this group of people with NSCLC
- Look at how we can use routinely collected NHS data as well as clinical studies in the model

NICE will be able to use the same model for any future new treatments that are developed for the same advanced (stage 4) NSCLC pathway.

2 Background and decision problem

2.1 Pathways approach

NICE has found that 43% of its HTA guidance covers only 10 disease areas. Single technology appraisals consider a single point in the treatment pathway at a single point in time. However, treatment pathways can change very frequently for some disease areas. This can lead to variation in clinical practice and it creates difficulties for stakeholders, including patients and clinicians, who need to understand and use NICE guidance. A 'pathways approach' to health technology assessment is built around a core model that spans a disease pathway. The core model can be updated and reused to assess multiple technologies across complex decision spaces and at different time points.

NICE has selected two pilot topics to assess the potential of the pathways approach to create efficiencies by incorporating novel technologies into a fully developed disease-specific model, with economic and clinical data updated as required or when it becomes available. The first pilot topic, currently in development is renal cell carcinoma (RCC).[1] Non-Small Cell Lung Cancer (NSCLC) has been selected by NICE as the second pilot topic due to the high number (more than 50) of NICE recommendations with more technologies currently being appraised or scheduled to be appraised in the future.

2.2 Epidemiology of lung cancer

Lung cancer is the third most common cancer in the UK. It accounts for around 13% of all new cancers with almost 50 000 new cases of lung cancer diagnosed each year.[2] It is the most common cause of cancer death, accounting for around one in five of all cancer deaths.[3] UK patients have poorer survival from lung cancer relative to patients in other European countries – estimated 5 year survival was 5-7% lower than Germany, Latvia, Norway, Sweden and Switzerland in 2010-2014.[4]

Lung cancer incidence is strongly related to age. The incidence increases steeply from age 45-59 with highest rates among those aged 75-79 years in women and aged 85-89 years in men.[2] Over the past 10 years lung cancer rates have remained stable overall, but have increased amongst women and decreased amongst men.[2] The main risk factor for lung cancer is smoking status.[5] A number of exposures have been associated with an increased risk of lung cancer: these include genetic susceptibility, diet, occupational exposures and air pollution.[5, 6] In people over the age of 40, the incidence is highest in men. However, in younger people under 40 risk is highest in women.[7]

2.3 Diagnosis of lung cancer

The diagnosis of lung cancer typically integrates a combination of test results in addition to careful assessment of the medical history and symptoms.[8] The initial step in diagnosing lung cancer often involves imaging tests. Some patients will have an initial chest X-rays, followed by a CT scan if the chest x-ray is suggestive of possible lung cancer. If referral for suspected lung cancer is made from a hospital setting or the GP has a high clinical suspicion of lung

cancer, then the patient may proceed straight to a CT scan. Initial tests should be performed within 3 days of referral or presentation to the GP. If the CT scan reports that lung cancer is a possible diagnosis then the patients will be fast tracked to a lung cancer clinic. Additional tests may be requested at this point including a PET-CT scan and diagnostic and staging tests to inform treatment decisions.[8]

As a result of the targeted NHS Lung Health Check programme which is being rolled out in the UK,[9] it is expected that lung cancer will increasingly be diagnosed at an earlier stage when treatment may be more successful. This programme offers an initial appointment to people aged 55 and 75 and have smoked in the past to evaluate their risk of lung cancer. Those considered to be potentially at risk of lung cancer will be referred to their GP who will then follow the standard diagnostic pathway outlined above.

2.4 Classification of lung cancer

Lung cancer can be classified based on histological features, stage of disease, programmed death-ligand 1 (PDL-1) expression, and the presence of oncogenic driver genetic alterations. Each of these affects treatment and prognosis.

2.4.1 Histological classification

Traditionally, lung cancer has been classified into two main histological categories: non-small-cell lung cancers (NSCLC; around 85-90%) and small-cell lung cancers (10-15%).[2] 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] The introduction of molecular and immunohistochemistry testing, added to advances in molecular-targeted therapies has led to a more precise classification. The 2021 World Health Organisation (WHO) Classification of Thoracic Tumours suggests a different approach based on morphology, immunohistochemistry and molecular techniques, and encourages the use of more precise categories instead of the traditional NSCLC (including squamous and non-squamous cell carcinomas) and small cell lung cancer for pathological diagnosis, future research and clinical trials.[10] **Error! Reference source not found.** provides a detailed overview of these two approaches to lung cancer classification, showing the WHO classifications over the background of its corresponding classic categories.[10]

2.4.2 Stage of disease

There are different staging systems for cancer, one of the most commonly used for NSCLC is the number system.[11] This looks at the number and size of lung tumours and comprises the following four 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

2.4.3 PD-L1 status

PD-L1 is a protein found on the surface of some cancer cells, including lung cancer cells. It plays a role in suppressing the body's immune response to cancer. PD-L1 status is important in lung cancer because it helps determine whether a patient is a candidate for immunotherapy treatment, specifically immune checkpoint inhibitors. These drugs work by blocking the interaction between PD-L1 on cancer cells and PD-L1 receptors on immune cells, allowing the immune system to recognize and attack cancer cells more effectively.[12]

The PD-L1 status is assessed through an immunohistochemistry (IHC) biomarker test on a tumour sample.[12] The test results are usually reported as the percentage of tumour cells expressing PD-L1 on their surface. The prevalence of PD-L1 expression in patients with NSCLC ranges from 24 to 60% at a threshold of 5%.[12] Patients with higher PD-L1 expression are more likely to respond to immunotherapy treatment, while those with lower or no PD-L1 expression may not receive as much benefit from these drugs.

2.4.4 Tumour mutations and genetic testing

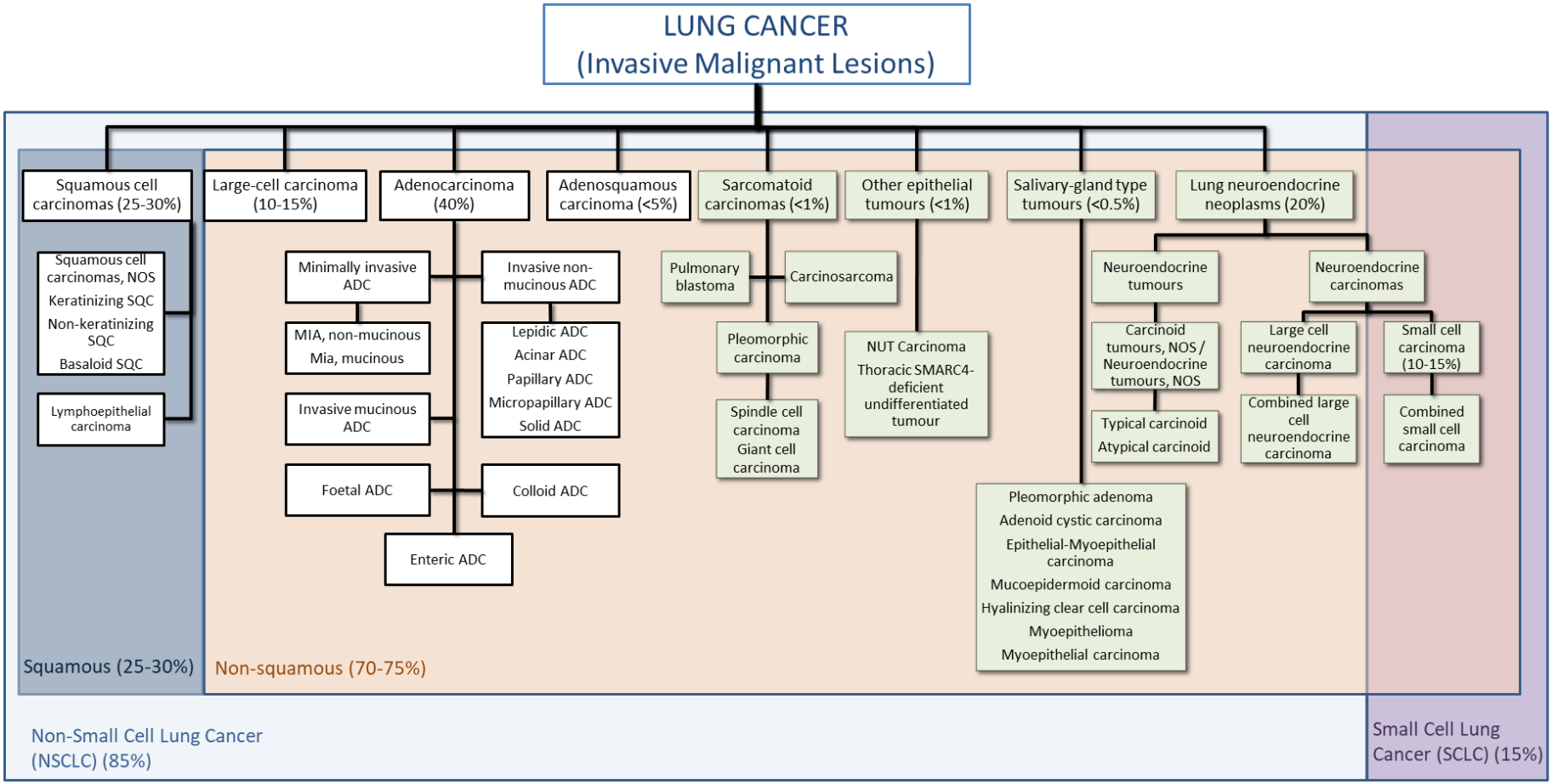
Around 40% of non-squamous NSCLC tumours have an oncogenic driver genetic alteration (targetable tumour mutation), although individual mutations are each only expressed in a small proportion of patients. Table 1 provides an overview of the tumour mutations found in NSCLC tumours with an estimate of their prevalence. These genetic alterations are generally considered to be mutually exclusive although some overlap has been reported between them.[4]

Tumour mutation testing is usually carried out at the point of diagnosis. The National Genomic Test Directory recommends testing for EGFR, ALK, BRAF, KRAS G12C, ROS1, RET, NTRK and MET ex 14 skipping mutations in patients with non-squamous NSCLC, and KRAS-G12C and MET ex 14 skipping in patients with squamous cell cancer, although there may be scenarios where full-panel testing in other subtypes of NSCLC might be considered by clinicians.[13] However, there are regional variations in the availability and timeliness for testing and people may be treated with non-targeted therapies until tested and diagnosed for the presence of specific mutations. There is also a gap between testing and targeted treatment implementation. The Royal College of Physicians conducted a spotlight audit on molecular testing in advanced lung cancer, which showed that 83% of patients with advanced carcinoma were tested for EGFR, ALK and PD-L1, with only 75% of patients with EGFR mutations and 58% of those with ALK translocations receiving targeted treatment.[14]

Table 1 Prevalence of oncogenic genetic alterations in NSCLC[15]

Oncogenic genetic alteration	Estimated Prevalence
Anaplastic lymphoma kinase (ALK)	~5%
Epidermal growth factor receptor (EGFR)	12.5%
ROS proto-oncogene 1 (ROS-1)	1%
KRAS G12C	12%
Mesenchymal-epithelial transition exon 14 skipping (MeTex14)	3-4%
Rearranged during transfection (RET) fusion	1-2%
Neurotrophic tyrosine receptor kinase (NTRK) fusion	0.1-1%
Human epidermal growth factor receptors (HER)2	4% (Non-squamous only)
v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600	1-2%

Figure 1 Overview of lung cancer histologic classification



2.5 Treatment pathway

Treatment depends on the location, stage of cancer and presence of specific tumour mutations. The primary treatment for early-stage (stages 2 to 3) lung cancer is surgical resection with curative intent. The surgery may be preceded by neoadjuvant chemotherapy and is usually followed by adjuvant treatment. The treatment pathway for NSCLC can be divided into interconnected decision points based on the stage of disease and line of therapy. The treatment pathway for NSCLC is outlined in Figure 2 and each decision node is described in more detail in

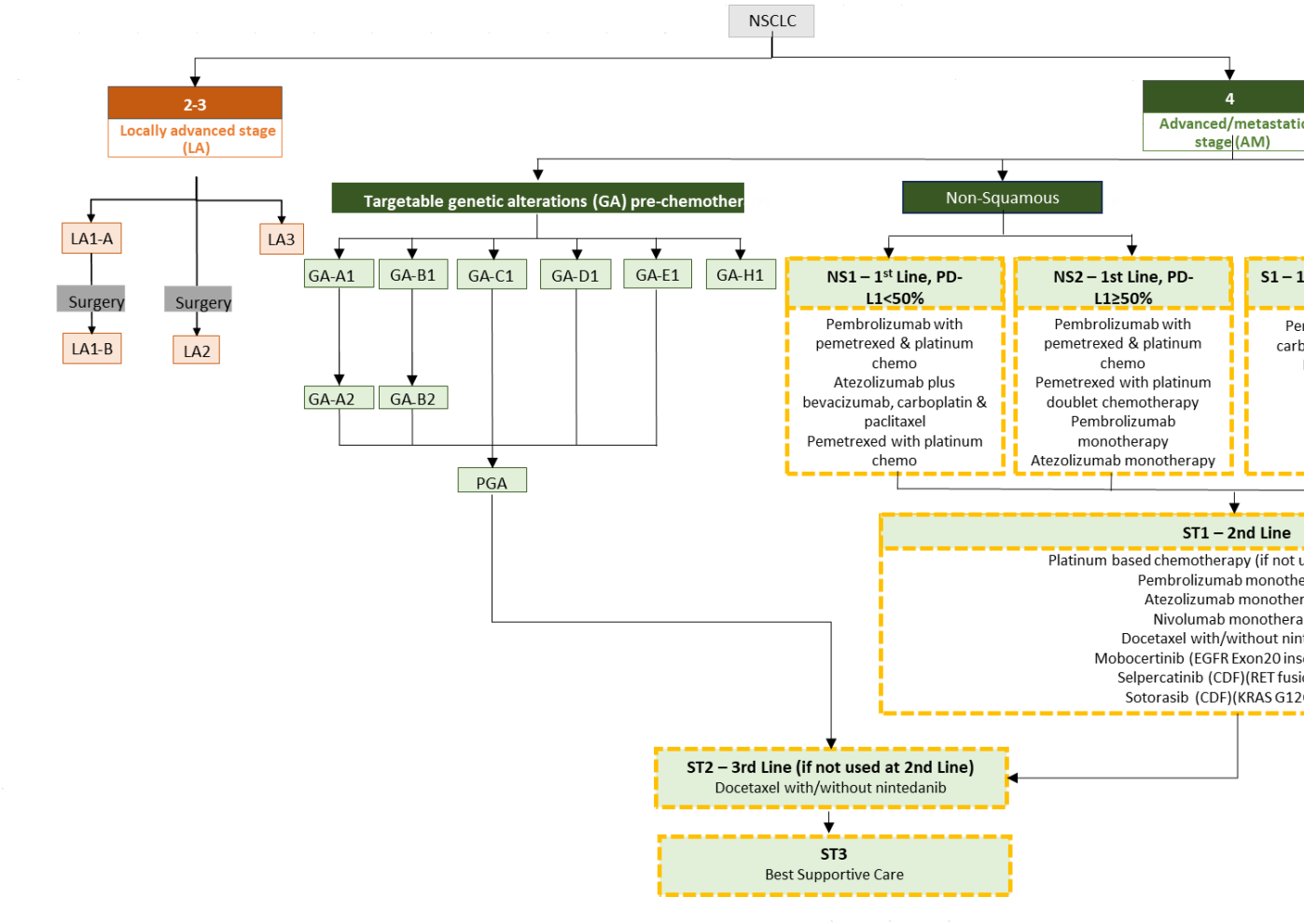


Table 2.

Figure 2 NSCLC pathway made up of decision points. Reproduced in text form in Table 1. Decision points highlighted by orange dotted lines are included in this appraisal.

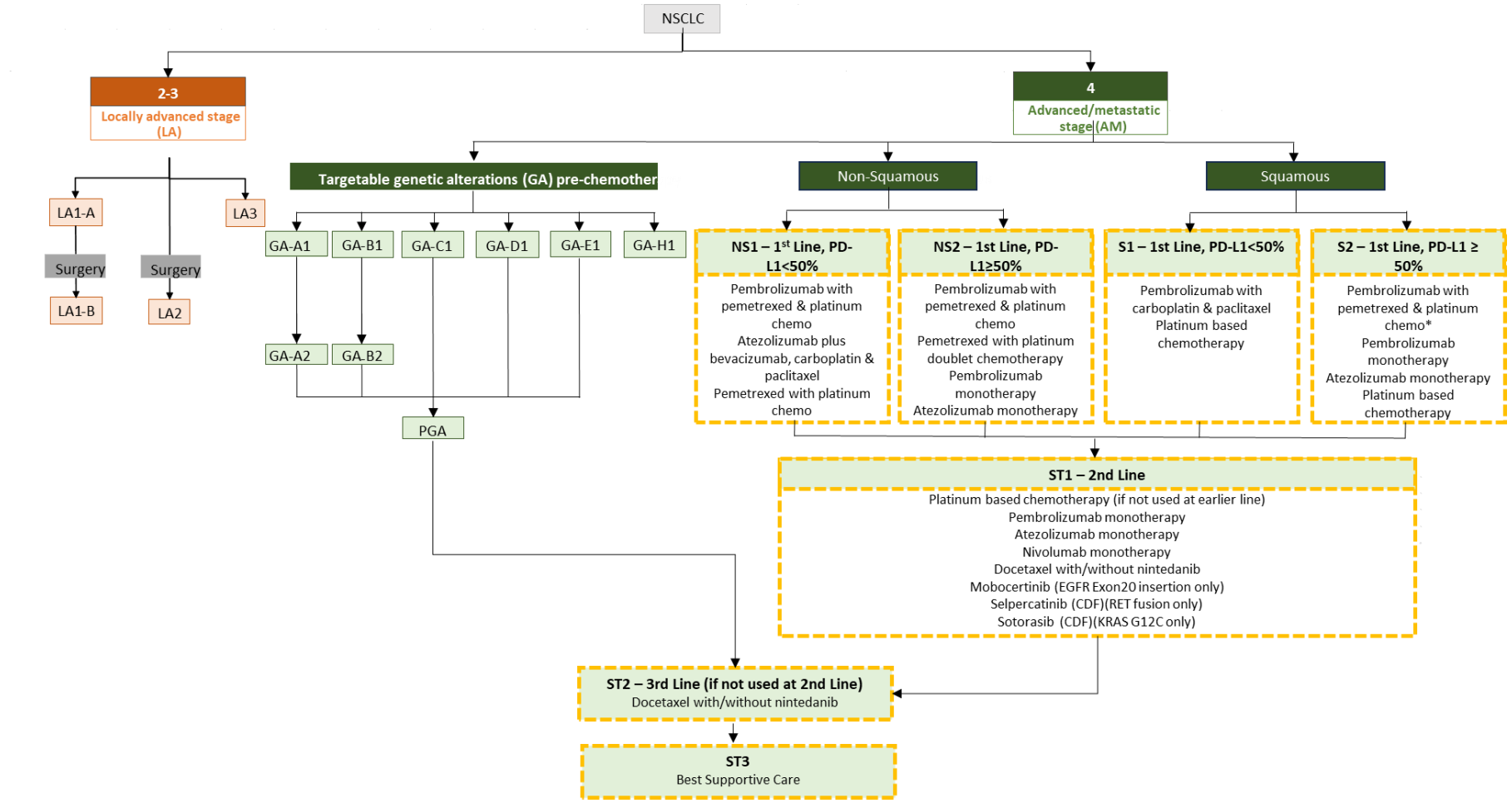


Table 2 Decision points of the NSCLC pathway.[15] Decision points shaded grey are not being modelled in this pilot

Decision Point	Population	Treatment details
Stage 2-3a locally advanced NSCLC (squamous and non-squamous)		
LA1A	Neo-adjuvant therapy	Before surgery, **nivolumab with chemotherapy (TA876)** may be given
LA1B	Adjuvant therapy continuing from neoadjuvant therapy	Where neo-adjuvant therapy is given before surgery, the decision may be taken to continue with the same regimen, or a modification of it, after the surgery has been completed.
LA2	Adjuvant therapy only	Complete resection may potentially be followed by chemotherapy with: • **Osimertinib (TA761)** (Cancer Drugs Fund (CDF)) for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection. • **Atezolizumab (TA823)** (CDF) 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 ≥50%. After incomplete resection radiotherapy alone can be offered.
LA3	Maintenance to chemoradiation	In people who decline surgery or in whom any surgery is contraindicated, treatment options include sequential or concurrent chemoradiotherapy or radiotherapy alone: • **Durvalumab (TA798)** for maintenance treatment of locally advanced unresectable NSCLC in people whose disease has not progressed after concurrent platinum-based chemoradiation and whose tumours express PD-L1 ≥ 1%
Stage 4: Advanced, metastatic NSCLC		
Targeted therapies at first line		
GA-A1 and GA-A2	ALK positive tumours	First line (**GA-A1**) treatment options include **brigatinib (TA670)**, **alectinib (TA536), ceritinib (TA500)** and **crizotinib (TA406)** Second line TKIs can be used after progression on first line options (**GA-A2**): • **Lorlatinib (TA628)** 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 (TA571)** or **ceritinib (TA395)** are recommended in people whose disease has progressed after crizotinib
GA-B1 and GA-B2	EGFR mutation-positive tumours	First line (**GA-A1**) treatment options include **afitinib (TA310), erlotinib (TA595), dacomitinib (TA258), gefitinib (TA192) and Osimertinib (TA654).**

Decision Point	Population	Treatment details
		In people who are EGFR T790M mutation-positive, **Osimertinib (TA653)** can be used after progression on a first-line TKI (GA-B2).
GA-C1	ROS-1 positive tumours	First line treatment options include **entrectinib (TA643)** and **crizotinib (TA529)** (CDF)
GA-D1	METex14 skipping mutation-positive tumours	**Tepotinib (TA789)** is the only targeted treatment recommended. It is usually used at first-line but use at later lines is possible.
GA-E1	BRAF V600E mutation-positive tumours	**Dabrafenib with trametinib (TA898)** for first line use
GA-H1	RET fusion positive tumours	**Selpercatinib (TA5046 in progress)** (CDF) for untreated NSCLC with a RET fusion
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 - **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. **(NG122)**
Non-targeted therapies, first line		
NS1	Non-squamous; PD-L1 <50%	**Pembrolizumab with pemetrexed and platinum chemotherapy (TA683); Atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA584); Pemetrexed with platinum doublet chemotherapy (clinical opinion)**
NS2	Non-squamous; PD-L1 ≥50%	**Pembrolizumab with pemetrexed and platinum chemotherapy (TA683); Pemetrexed with platinum doublet chemotherapy (clinical opinion); Pembrolizumab monotherapy (TA531); Atezolizumab monotherapy (TA705)**
S1	Squamous; PD-L1 <50%	**Pembrolizumab with carboplatin and paclitaxel (TA770); Platinum based chemotherapy**
S2	Squamous; PD-L1 ≥50%	**Pembrolizumab monotherapy (TA531); Atezolizumab monotherapy (TA705); Platinum based chemotherapy**
Targeted therapies at second line		
None	HER2 mutation 2nd line	Currently no NICE recommended treatments.
ST1	EGFR exon 20 fusion positive disease after platinum chemotherapy.	**Mobocertinib (TA855)**
ST1	RET fusion positive disease which is previously treated	**Selpercatinib (CDF) (TA760)**
ST1	KRAS G12C mutation positive disease which is previously treated	**Sotorasib (CDF) (TA781)**
Non-targeted therapies, 2nd line		
ST1	NSCLC with or without targetable genetic alterations that has progressed on previous therapies	If disease has progressed on all previous targeted therapies, immunotherapies and chemotherapies, people may be offered regimens comprising any types of therapy recommended at previous lines, but which had not been used.

Decision Point	Population	Treatment details
ST2	Final chemotherapy line	**Docetaxel**, with or without **nintedanib** can be used after immunotherapy, platinum-based chemotherapy or both **(TA347 and clinical opinion)**
ST3	Mixed histology, subsequent therapies 3	*ST3, all other treatment options exhausted.* **Entrectinib (CDF) (TA644)** and **Larotrectinib (CDF) (TA630)** recommended as options for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive tumours when no satisfactory treatment options exist

3 Aim and Objectives

This project aims to build a cost-effectiveness model to assess multiple technologies across the treatment pathway for advanced/ metastatic non-small-cell lung cancer (NSCLC). We will assess the clinical and cost-effectiveness of treatments at each decision point (node) in the pathway for advanced/metastatic stage 4 NSCLC patients not eligible for targeted therapies at first line.

The decision points to be modelled in the disease pathway are highlighted in Figure 2. Decision node ST3 will be included in the economic model but will not be included in the evidence synthesis. This is because in practice the number of patients receiving these is negligible and so for the purposes of this appraisal, we assume patients receive palliative care after progression on treatment at ST2.

The objectives for this pilot project are to:

1. Conduct evidence syntheses to assess the clinical effectiveness of treatment options at each decision node in the pathway for those advanced/metastatic stage 4 NSCLC patients not eligible for targeted first line therapies.
2. Explore the value in using observational (real world) evidence to characterise the treatment pathway, natural history of the condition, and patient characteristics
3. Develop a cost-effectiveness model encompassing each decision node in the disease pathway, for advanced/metastatic stage 4 NSCLC not eligible for first line targeted therapies

4 Systematic review methods

A systematic review will be conducted to summarise the effectiveness of treatments at each decision point (node) in the pathway for advanced/metastatic stage 4 NSCLC patients not eligible for targeted therapies at first line. The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual[16, 17] and will be reported according to the PRISMA statement.[18]

4.1 Selection criteria

Studies that meet the following criteria will be eligible for inclusion:

4.1.1 Participants

People with advanced/metastatic stage 4 NSCLC. People with both squamous and non-squamous tumours will be considered eligible. People with targetable genetic alterations who receive a targeted treatment as first line therapy will be excluded. Eligible populations for each decision node are outlined in Table 3.

For each decision node, we will restrict inclusion to studies that report data for the specific population defined by that node; where data are not available for this population alone, we will also include studies that report data for a mixed population as long as this includes the population of interest. If data are reported for non-targeted therapies in populations with specific mutations or in mixed populations, these will be eligible for inclusion as treatment effect of these therapies is not expected to be affected by the presence of specific tumour mutations. If data are not available for the treatment line of interest, data from studies conducted at other lines will be considered as the treatment pathway may have evolved over time.

Table 3 Overview of eligible populations and interventions for each population

Node	Eligible population	Eligible interventions
NS1	First line, Non-squamous, PD-L1 <50%	• Pembrolizumab with pemetrexed and platinum chemotherapy (TA683)[19] • Atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA584)[20] • Pemetrexed with platinum doublet chemotherapy (clinical opinion)
NS2	First line, Non-squamous, PD-L1 ≥50%	• Pembrolizumab with pemetrexed and platinum chemotherapy) (TA683)[19] • Pemetrexed with platinum doublet chemotherapy (clinical opinion) • Pembrolizumab monotherapy (TA531)[21] • Atezolizumab monotherapy (TA705)[22]
S1	First line, Squamous, PD-L1 <50%	• Pembrolizumab with carboplatin and paclitaxel (TA770)[23] • Platinum based chemotherapy

Node	Eligible population	Eligible interventions
S2	First line, Squamous, PD-L1 ≥50%	• Pembrolizumab monotherapy (TA531)[21] • Atezolizumab monotherapy (TA705)[21] • Platinum based chemotherapy • Pembrolizumab with pemetrexed and platinum chemotherapy) – only in patients in urgent need of clinical intervention for airway obstruction.
ST1	Second line, Mixed histology, (no previous chemotherapy)	• Platinum based chemotherapy (if not used at earlier line) • Pembrolizumab monotherapy (TA428)[24] • Nivolumab monotherapy [Non squamous only] (TA713)[25] • Nivolumab monotherapy [squamous only] (TA655) [26] • Atezolizumab monotherapy (TA520)[27] • Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347)[28] • Mobocertinib (TA855) *(EGFR Exon20 insertion only)*[29] • Selpercatinib *(CDF)* (TA760) *(RET fusion only)*[30] • Sotorasib *(CDF)* (TA781) *(KRAS G12C only)*[31]
ST2	Third line, Mixed histology, if not used at second line	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347)[28]

4.1.2 Outcomes

Studies that report data on any of the following outcomes will be eligible for inclusion.

- Progression-Free Survival (PFS)
- Time-to-Progression (TTP)
- Overall Survival (OS)
- Time-on-treatment
- Time-to-treatment discontinuation
- Discontinuation due to adverse events
- Any adverse events (AEs) (any and treatment related)
- Serious (grade 3 or 4) adverse events (any and treatment related)
- Health-related quality of life (HRQoL) measured using EQ-5D

4.1.3 Study design

Where comparative evidence is available for all interventions included in a node, the review will be restricted to RCT evidence for that node. For nodes where insufficient randomised evidence is available, we will also consider single arm studies with preference for those with suitable adjustments for bias. Open label extension studies will be eligible to provide data on long term outcomes.

4.1.4 Interventions

Table 4 outlines which treatments will be eligible for each of the decision nodes/populations included in the treatment pathway of interest. Interventions in red text are considered as routine/comparator treatments as they have not been through the NICE appraisal process; studies will only be included for these interventions if they also evaluate one of the other interventions listed in Table 3. If no studies are identified that include these as comparator interventions for any of the populations of interest, then the review will be expanded to include any study that evaluates the intervention in the population of interest. If treatment networks do not connect, then other treatments will be included to create connected networks. We will first start by widening the search to include studies that include comparators of our eligible interventions (Table 4).

Table 4 Overview of eligible interventions and populations for which these are eligible

Eligible interventions	Eligible population	Related TAs	Decision node
Pembrolizumab monotherapy	First line (squamous or non-squamous) PD-L1 ≥50% Second line (no previous chemotherapy)	TA531[21] TA428	NS2 S2 ST1
Pembrolizumab with pemetrexed and platinum chemotherapy	First line, non-squamous, PD-L1 <50% or PD-L1 ≥50%	TA683[19]	NS1 NS2
Pembrolizumab with carboplatin and paclitaxel	First line, Squamous, PD-L1 <50%	TA770[23]	S1
Atezolizumab monotherapy	First line (squamous or non-squamous) PD-L1 ≥50%	TA705[22]	NS1 S2
Atezolizumab plus bevacizumab, carboplatin and paclitaxel	First line, non-squamous, PD-L1 <50%	TA584[20]	NS1
Nivolumab monotherapy	Second line (squamous or non-squamous)(no previous chemotherapy)	TA713[25] TA655[26]	ST1
Docetaxel with nintedanib	Second or third line (non-squamous, adenocarcinoma histology)	TA347[26]	ST1, ST2 ((if not used at second line)
Mobocertinib	Second line, EGFR Exon20 insertion 2nd line	TA855[29]	ST1
Selpercatinib	RET Fusion 2nd line	TA760 (CDF)[30]	ST1
Sotorasib	KRAS G12C 2nd line	TA781 (CDF)[31]	ST1
Pemetrexed with platinum doublet chemotherapy	First line, Non-squamous, PD-L1 <50% or PD-L1 ≥50%	NA	NS1, NS2

Eligible interventions	Eligible population	Related TAs	Decision node
Platinum based chemotherapy	First line, squamous, PD-L1 <50% or PD-L1 ≥50% Second line (if not used earlier)	NA	ST1
Docetaxel	Second or third line	NA	ST1, ST2 (if not used at second line)

4.2 Study identification

4.2.1 Studies included in existing TAs

The first step in identifying studies will be to map existing TAs for each node (Table 3). For each TA in scope, we will extract studies used by companies to make the case for clinical effectiveness and extract associated reports cited in the clinical effectiveness section of the company submission. These will be added to EndNote and exported to Microsoft Access for mapping (see section 4.3.2).

4.2.2 Literature searches

Additional studies/reports of randomised studies or open label extension studies will be identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual.[17]

4.2.2.1 Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid SP)
- EMBASE (Ovid SP)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)

The search strategy will be written by one researcher (CC) and checked by another (CLM). It will take the following form:

1. Terms for Lung Cancer/NSCLC
2. Interventions in scope (see Table 2)
3. The Cochrane Highly Sensitive Search Strategy (HSSS) for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) and the Cooper P3 filter will be used to limit to randomised studies. We have added terminology to identify open label studies.
4. 1 and 2 and 3

The bibliographic search strategy will not be limited by date of publication or by language. A draft search strategy is reported in Appendix 9.1.

4.2.2.2 Non-bibliographic search methods

Completed and ongoing trials will be identified through searches of the following trial registries:

- ClinicalTrials.gov via https://www.clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) via https://www.who.int/clinical-trials-registry-platform

Once eligible studies have been identified, the study's web page on Clinical trials.gov will be re-checked for data (published results) or linked publications.

Whilst systematic reviews are not eligible for inclusion, we will retain any systematic review identified where published in the last three years (2020-current) and which aligns with our scope. We will check the studies included in each review to identify any studies not identified by our searches.

4.2.2.3 Secondary searches

If Single Arm Studies are required, we will utilise the search structure described above for bibliographic databases and substitute Line 3 (study design filters) with this syntax: (single arm*).ti,ab,kw,kf. (Ovid interface) and (single arm*):ti,ab,kw (Wiley interface).

4.2.2.4 Managing the searches

Search results will be exported to EndNote 20. We will use the Bond de-duplication tool to de-duplicate, followed by a manual review of records.[32] We will compare the studies and study reports from the mapping of TAs to our search results. Search results will be exported to Microsoft Access for screening.

4.3 Review strategy

4.3.1 Title and abstract screening

Titles and abstracts from the literature searches will be screened independently by two reviewers. Full copies of all reports considered potentially relevant will be obtained and move to the inclusion mapping stage. Studies included in existing TAs will move straight to the inclusion mapping stage.

4.3.2 Full text inclusion assessment and mapping

Full text studies, including all reports included in existing TAs, will be assessed for inclusion against the criteria specified in section 4.1. We will collect the following additional information to allow us to map the available evidence :

- TA in which the study is included (if applicable)
- NCT ID number – this will be used to link reports of the same study
- Study design
- Decision node
- Population

    - Treatment line
    - Histology
    - PDL-status
    - Tumour mutations
- Intervention
- Comparator
- Outcomes reported
- Follow-up times reported

At this stage, included reports will be linked based on NCT Trial number and Study Name. This stage will be completed by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer. Studies excluded at this stage will be documented, together with reasons for exclusion.

4.3.3 Data decision meeting

For each node, the systematic review and statistics teams will meet to agree on which data will be extracted for each study contributing to that node. It will be necessary for many decisions regarding the source of data for each analysis to be made on a case-by-case basis depending on the robustness and the relevance of the evidence available. We anticipate that data will be prioritised for extraction based on the following characteristics:

- Duration of follow-up available
- Availability of data for specific population of interest for that node
- Availability of Kaplan Meier (KM) curves rather than summary effect estimates (e.g. hazard ratios (HRs).

All decisions taken will be documented and reported for transparency. At this stage, we will review the networks and make decisions regarding whether additional searches are needed to connect the network.

4.3.4 Data extraction

Data will be extracted using standardised data extraction forms developed in Microsoft Access. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

4.3.4.1 Baseline data

Data will be extracted on the following:

- Node
- Study design (RCT, NRSI, open-label or single arm)
- Study phase
- Funding sources (public, industry, mixed)

- Full text or conference abstract
- NCT number
- Study location
- Population
    - Treatment line
    - Histology
    - PDL-status
    - Tumour mutations
    - Previous treatment
- Intervention
    - Treatment name
    - Dose
    - Duration
- Comparator
    - Treatment name
    - Dose
    - Duration
- Number of participants (eligible, randomised and treatment)
- Age
- Sex
- Ethnicity
- ECOG status
- Smoking status

4.3.4.2 Results data

Where possible results data will be extracted for the sub-population of interest and for the longest follow-up period available. This will be determined based on the decision meeting outlined in section 4.3.4. We will explore the impact of these data decisions in sensitivity analyses where we believe they may impact results.

We will extract data on the following outcomes:

Time to event outcomes:

- Progression-Free Survival (PFS)
- Time-to-Progression (TTP)
- Overall Survival (OS)

We will identify where the following outcomes are reported:

- Time-on-treatment (ToT)
- Time-to-treatment discontinuation (TTD)

Ideally, information on ToT / TTD will come from the Systemic Anti-Cancer Therapy (SACT) database (section 5.2.4.3) as any data that is reported in trials is unlikely to be generalisable to UK clinical practice and reflective of UK commissioning rules. However, where these data are not available from real world data but are reported in trials for a particular node, we will extract these data if they are considered useful to inform the economic model.

We will reconstruct IPD from digitized Kaplan-Meier plots where possible using the Guyot method [33], for each decision node and outcome where the validity of a proportional hazards assumption is unlikely to hold based on previous analyses in NICE TAs. Where Kaplan-Meier plots are not available we will extract and synthesise hazard ratios (HR), acknowledging the limitation that this relies on the proportional hazards assumption and highlighting the effect we think this could have on the results.

Dichotomous outcomes:

- Discontinuation due to adverse events
- Any adverse events (AEs)
- Serious (grade 3 or 4) adverse events (any and treatment related)

Where available, treatment related adverse events will be extracted in preference to non-cause-specific adverse events. If these data are not available, non-cause specific adverse events will be extracted.

We will extract data on the number of patients with events and/or number of events and total number of patients in each treatment arm. Summary effect estimates (e.g. odds ratio (OR) or relative risk (RR)) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted.

Continuous outcomes:

- HRQoL measured using EQ-5D-3L

We will extract HRQoL for a single time point. This will be selected to be most consistent across all studies in a node and will be agreed at the data decision meeting (section 4.3.3). Our ideal information is EQ-5D reported for those in a pre-progression health state. However, if this is not available then we will extract data at a time by which the majority of short-term treatment-related adverse events are likely to have occurred, as informed by clinical expertise.

We will extract means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) for the outcome at baseline and at the time-point closest to pre-progression. Summary effect estimates (e.g. mean difference (MD)) together with 95% CIs and p-values for comparisons between groups together with details

on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted.

4.3.4.3 Adjusted analyses

For analyses that incorporate an anchored population adjustment method (e.g., Matched Adjusted Indirect Comparison, Simulated Treatment Comparison), we will only extract results from these if the adjustment is appropriate for the population of interest at that specific node in the pathway. Otherwise, the population adjusted results may be more biased for our target population than the unadjusted analysis. The decision on whether to extract adjusted analyses will be made at the data decision meeting (section 4.3.3).

4.3.4.4 Single arm studies and disconnected networks

For some treatments data may only be available from single-arm trials at a specific decision node in the pathway, or alternatively two treatments within a network may be disconnected ("unanchored"). In these cases, results from unanchored population adjustment analyses may be available in order to estimate the required relative effects. This approach assumes that all prognostic factors and effect modifiers are balanced between the single arm study and data on a comparator.

Where an unanchored population adjustment has been performed and an adjusted Kaplan-Meier plot is available, we will digitise this and extract IPD data using the Guyot method [33]. Where only an adjusted HR is reported then we will extract this and use alternative methods for synthesis (Section 4.5.2.2)

4.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the updated Cochrane Risk of Bias Tool (ROB-2).[34] Non-randomised studies of interventions (NRSI), including single-arm (where some form of comparison is made) and open-label studies, will be assessed using the ROBINS-I tool.[35] Any disagreements will be resolved by consensus or discussion with a third reviewer. Risk of bias assessment will be carried out at the outcome level for all outcomes extracted that will inform the economic model.

4.5 Synthesis methods

We will synthesise evidence separately at each decision node based on line of therapy and subgroup.

4.5.1 Network Meta-Analysis

We will conduct network Meta-Analyses (NMA) at each decision node in the pathway to compare all treatment options simultaneously using the available trial information,. NMA strengthens inference concerning the relative effect of two treatments by including both direct and indirect comparisons while respecting randomisation. Most treatments will not have been compared in head-to-head RCTs, and NMA allows for the use of indirect

information to make that comparison. General details of the method are given in NICE Decision Support Unit Technical Support Document 2 [36], and application with survival data is described in Dias et al.[37]

NMA assumes that all effect modifiers are balanced across studies both within (homogeneity) and between (consistency) treatment comparisons. Many potential effect modifiers (line of therapy, PD-L1, squamous vs non-squamous) are likely to have been accounted for by synthesising evidence at specific decision nodes in the treatment pathway, however there may be other factors (e.g. ECOG score) that could vary across studies. For any networks of evidence with closed loops of direct and indirect evidence we will assess consistency in the final selected model by comparing model fit of the NMA model with the Unrelated Mean Effects (UME) model.[38] Where treatment effects are modelled on multiple parameters, we will assess consistency for each parameter to ensure that inconsistency is detected if present. Dev-dev plots of the residual deviance contribution of individual data points in consistency vs UME models will be used to identify any discrepant data-points.

4.5.2 Synthesis of time-to-event outcomes

The following outcomes will be synthesised to inform the economic model:

- Progression-Free Survival (PFS)
- Time-to-Progression (TTP)
- Overall Survival (OS)

As noted in section 4.3.4.2, we will only synthesis evidence on time-on-treatment / time-to-treatment discontinuation if data is not available from SACT.

Progression-Free Survival (PFS) and Time-to-Progression (TTP) are the primary efficacy outcomes of interest for decision nodes at first and second lines of therapy (NS1, NS2, S1, S2, ST1, GAP-G2, GAP-H2, GAP-I2). This is because in a pathways model, patients are modelled at each node until progression, after which they proceed to a subsequent decision node if further therapy is indicated. Overall Survival (OS) data from first and second lines of therapy will depend on the treatments received at subsequent lines in the trial and will also include patients who do not receive any subsequent lines of therapy. The treatment to which patients are randomised may also affect the choice of treatment received at subsequent lines within that study, which makes use of OS from earlier lines of therapy challenging. Instead, OS can be modelled through progression at each line of therapy in the disease pathway, followed by OS at the last line of therapy. We will only consider synthesis of the OS data at earlier lines of therapy for the purposes of validation of the OS predictions from the model. We will outline possible ways to incorporate OS data in a pathway model in future work (section 4.5.8).

At decision node ST2 (third and last line of therapy) PFS, TTP, and OS are of interest for the model, and we will synthesis evidence for each of these outcomes. This is because whilst there are subsequent treatment options available at decision node ST3, in practise the

number of patients receiving these is negligible and so for the purposes of the evidence synthesis and economic modelling ST2 is the last line of therapy. We assume patients receive best supportive care after progression on treatment at ST2.

4.5.2.1 Within-trial survival analysis

Survival analysis models the effect of treatment on the hazards, the instantaneous rate of experiencing an event at time t conditional on having survived up to time t:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < (t + \Delta t) \mid T > t)}{\Delta t}$$

where T is the time at which an event is experienced. The survival probability is related to the hazards as the exponential of the negative of the cumulative hazard function:

$$S(t) = \exp(-H(t)) = \exp\left(- \int_{u=0}^{t} h(u)du \right)$$

Hazards are often modelled in the treated group as being proportional to that in the control group,[39] and a common assumption is that the hazard ratio (HR) is constant over time (the proportional hazards (PH) assumption). However, in NSCLC there is evidence of non-proportional hazards (e.g. TA531, TA705, TA760, TA770), meaning that proportional hazards models are not recommended.

Alternative approaches for analysing survival data that do not assume proportional hazards include:

- specifying a parametric distribution where the parameters vary between treatment arms
- specifying different parametric distributions for each treatment arm
- specifying flexible models such as splines or fractional polynomials
- pooling time ratios from an Accelerated Failure Time (AFT) model which assumes proportional survival times across treatments
- pooling Restricted Mean Survival Times (RMST).

We plan to use fractional polynomial models as a sufficiently flexible class of models but will explore alternative flexible modelling approaches, and select an approach based on model fit and the plausibility of extrapolations.

Fractional polynomials are well suited to modelling non-linear functions and can capture a wide range of distributions.[40] Fitting fractional polynomials to the log-baseline hazard function and then allowing for the study-specific treatment effects to act on fractional polynomial parameters can allow for a time-varying HR, thereby relaxing the proportional hazards assumption.[41] First and second order models can be fitted, depending on the

complexity of the hazard function, and these have been used in previous technology appraisals for NSCLC (TA584, TA705, TA760).[20, 22, 30]

Many standard parametric survival distributions (Exponential, Weibull, Gompertz) can be expressed as special cases of first order fractional polynomials. We will explore other parametric distributions that are not captured with fractional polynomial models. [39]

We will aim to fit these models using the same likelihood specification so that models can be compared using standard model fit statistics (residual deviance, DIC). The most appropriate approach will be selected based on model fit and interpretability (see section 4.5.6).

4.5.2.2 Synthesis of single arm studies and disconnected networks

For synthesis of single arm studies in which only a population-adjusted HR is reported then we will incorporate this data into the model by applying the HR to the baseline hazard for the comparator, estimated from studies for which the baseline hazard can be estimated (using the methods described in Section 4.5.2.1), acknowledging the limitation that this relies on the proportional hazards assumption.

If only unadjusted Kaplan-Meier data are available, then we will include the single arm trial data by matching to the study with the most similar baseline characteristics and performing a naive indirect comparison.[42] We will explore the impact of this in sensitivity analyses. We will explore the feasibility of using cancer registry data to connect disconnected networks and incorporate single arm studies for future work (section 4.5.8).

4.5.3 Synthesis of Adverse Events (including discontinuation)

We will conduct evidence synthesis of treatment effects for (i) all adverse events (AEs) and (ii) serious (grade 3 or 4) adverse events (SAEs), if sufficient data are available. If clinical advice indicates that AEs occur within a short time-scale, or if events are rare, we will analyse SAEs as binary outcomes summarised with pooled odds ratios. Otherwise, we will analyse SAEs as rate outcomes summarised with pooled hazard ratios.

We will also conduct evidence synthesis of treatment effects for discontinuation due to treatment-related AEs, as this may help to estimate progression from time-on-treatment if registry data (where progression is typically not reported) is used. We will analyse discontinuation due to treatment-related AEs as a rate outcome, summarised with pooled hazard ratios.

4.5.4 Synthesis of Health Related Quality of Life

We will pool evidence on treatment effects for EQ-5D-3L if sufficient data is available, analysed as continuous outcomes summarised as mean differences.

4.5.5 Information Sharing

Data available for synthesis at some nodes in the pathway may be sparse, and sharing of information from other decision nodes in the pathway may improve parameter estimation. For example:

- we might expect that the same distributional assumptions could be used to model the effect of a specific therapy, regardless of the line in the disease pathway
- it may be reasonable to assume that effects seen in a mixed population would apply equally to genetic subgroups, for treatments that are not linked to genetic mutations
- the effect of different histologies may be similar for treatments in the same class.

Note that as the treatment pathway has evolved and new lines of therapy introduced, it may be the case that existing RCT evidence was generated for patients who have not had as many previous lines of therapy as are now currently available. In this situation, where there is a mis-match between the line of therapy for the RCT evidence and current use, we will incorporate the existing RCT evidence by making assumptions on the impact of previous therapies on treatment effects.

A benefit of analysing data at multiple points in the pathway is that sharing information on key parameters from different decision nodes in the pathway is possible. We will explore information sharing in cases where there is limited evidence, and the assumptions are considered clinically plausible in discussion with our expert advisors. Where possible, the effect of information sharing assumptions will be explored in sensitivity analyses.

For some trials, data within a specific subgroup of interest may not be available, in which case we may have to use data from the overall trial population and make assumptions about the relationships across subgroups. For example, we may either assume no effect modification by the subgroup covariate or assume that the impact of effect modifying covariates is shared across drugs of the same class, depending on what our expert advisors consider to be clinically plausible.

4.5.6 Model Implementation

Models will be fitted in a Bayesian framework using WinBUGS, JAGS[43], or multinma.[44] Model selection will be based on the Deviance Information Criterion (DIC), with a difference of 3-5 points being meaningful. For models with similar DIC we will select the simplest model (lowest effective number of parameters) as this supports interpretability.

4.5.7 Predicting survival probabilities from evidence synthesis results

The NMA for survival outcomes will produce relative treatment effect estimates for the parameters of a fractional polynomial model, relative to a reference treatment for each decision node. To obtain estimated survival curves for each treatment, these relative effects can be applied to an assumed fractional polynomial model for the reference treatment. The reference treatment will be chosen based on data availability, completeness of follow-up data, and relevance of the study population to the decision-node in the RCT evidence. We

will work with the health economics team and clinical experts to identify the most appropriate evidence source for the reference treatment in the appropriate population. A fractional polynomial curve will be estimated and then the NMA estimates applied. Uncertainty in the estimates will be captured by simulation from the posterior distribution from the Bayesian analysis.

4.5.8 Areas for further exploratory work

4.5.8.1 Overall Survival data

As explained in section 4.5.2 overall survival (OS) data is challenging to include in a pathway model at all lines of therapy except the last line of therapy. This is because OS data is a complex combination of PFS at subsequent lines of therapy and OS at last line of therapy, averaged over the proportions of patients going on to have each line of therapy and the dependent on subsequent therapies that were received. We will outline potential approaches (and data requirements) that could be used in the future to incorporate OS data with PFS data across multiple lines of therapy in a combined analysis.

4.5.8.2 Registry data to connect networks and incorporate single arm studies

We will explore the feasibility of using the Systemic Anti-Cancer Therapy (SACT) dataset held by the National Cancer Registration and Analysis Service (NCRAS) to connect disconnected networks and incorporate single arm studies for future work. Population adjustment techniques (such as multi-level network meta-regression[45]) can be used to connect evidence networks adjusting for population differences between studies. However, these methods require individual patient data, which is unlikely to be available. One possibility is to use individual patient data from SACT to enable the population adjustment in the evidence network. Barriers to this approach include gaining access to sufficiently detailed data from SACT, and lack of information on progression in SACT. We will outline the analyses that would be necessary to conduct on SACT data and the summary results from those analyses required to enable the population adjustment to be conducted. We will also explore relationships between time to treatment discontinuation (TTD) (which is available in SACT), time to progression (TTP), and progression free survival (PFS) in studies which report two or more of these outcomes. This will help identify whether the TTD data from SACT could be useful to inform analyses on progression outcomes in future.

5 Economic modelling methods

5.1 Aims of the cost-effectiveness modelling

As previously set out in Section 3, a core aim of this pilot project is to:

"Develop a cost-effectiveness model encompassing each decision node in the disease pathway, for advanced/metastatic stage 4 NSCLC not eligible for first line targeted therapies."

Pathway disease models incorporate multiple decision nodes within a treatment pathway that allow technologies to be assessed at various entry points, often corresponding to line of therapy. This approach differs to typical decision analytic models in technology appraisals (TAs), which compare the costs and health-related quality of life benefits for treatment options at a specific point in the pathway, and instead will provide information about treatments within a pathway.

There are many different terms in this domain that are often used interchangeably to communicate different ideas, and so there is value in providing some clarity on the intended meaning of pathway models for the purposes of this pilot project:

- The primary aim is to assess comparators within a given decision node. The pathway model will evaluate the outcomes of each line of treatment explicitly, rather than making simplifications regarding subsequent treatment following the intervention being evaluated.

The following types of pathway models will not be developed for this pilot:

- Pathway models are often referred to as "whole disease models": such a term would be inaccurate for the purposes of this project, as the scope is limited to a subset of treatments for advanced NSCLC and does not model the whole pathway for NSCLC (Figure 2).
- Some pathway models may attempt to explicitly capture conditionality between decision nodes, for example, including the impact of previous treatments on effectiveness, or future decisions about treatments informed by treatment history. Explicit modelling of this is currently outside the scope of this project, but it is expected that committee will consider clinical evidence on relationships between decision nodes.
- A pathway model may also be called a "treatment sequence model" and can also evaluate the optimal point of entry for a drug within a pathway (e.g., whether a drug is more cost-effective when given at first line or second line) or an optimal treatment sequence. This is not the aim of the current pilot pathways project, and the proposed model structure will not be configured to produce these types of results during the pilot phase.

The following sections of this analysis plan set out the approach to model conceptualisation and a preliminary overview of the intended modelling approach. The approaches in this

analysis plan are not final as much of the modelling work is dependent on the availability and nature of the evidence (that is in the process of being identified at the time of writing this analysis plan), from the systematic review (Section 4), from real-world evidence (RWE), and the availability of trial data from previous submissions to NICE TAs. There will also be opportunities for input from the committee lead team and from a stakeholder engagement period on the analysis plan, whereby scenarios may be requested, and additional data provided.

5.2 Economic model conceptualisation

5.2.1 Conventional model structures for advanced NSCLC

Current economic models that evaluate interventions aimed at a single line of therapy for advanced NSCLC largely centre around conducting a partitioned survival analysis,[46] with health states defined by progression status and death. Membership in each of the health states are derived from non-mutually exclusive survival curves for overall survival and progression-free survival.

The partitioned survival analysis is carried out at the line of therapy for which the intervention is intended for, with the impact of subsequent treatments modelled both directly and indirectly. Survival and quality of life on subsequent treatments are modelled indirectly and are typically captured within the overall survival curve of the primary treatment being analysed and the post-progression utility value.

Treatment-related costs of subsequent treatment are modelled directly, albeit using simplifying assumptions, and other disease management-related costs are captured indirectly within the post-progression health state. Because they are not being used for decision making, subsequent treatments are generally not modelled in the same level of detail as interventions at the decision node. A distribution of subsequent treatments, including best supportive care, is estimated from trial data, registry data or clinical expert opinion, and a mean (weighted) cost of further treatment is applied at the point of progression. The partitioned survival method of modelling was used in the majority of company submissions for in-scope TAs (Table 5).[19, 20, 22, 23, 47, 48]

5.2.2 Review of literature on pathways modelling

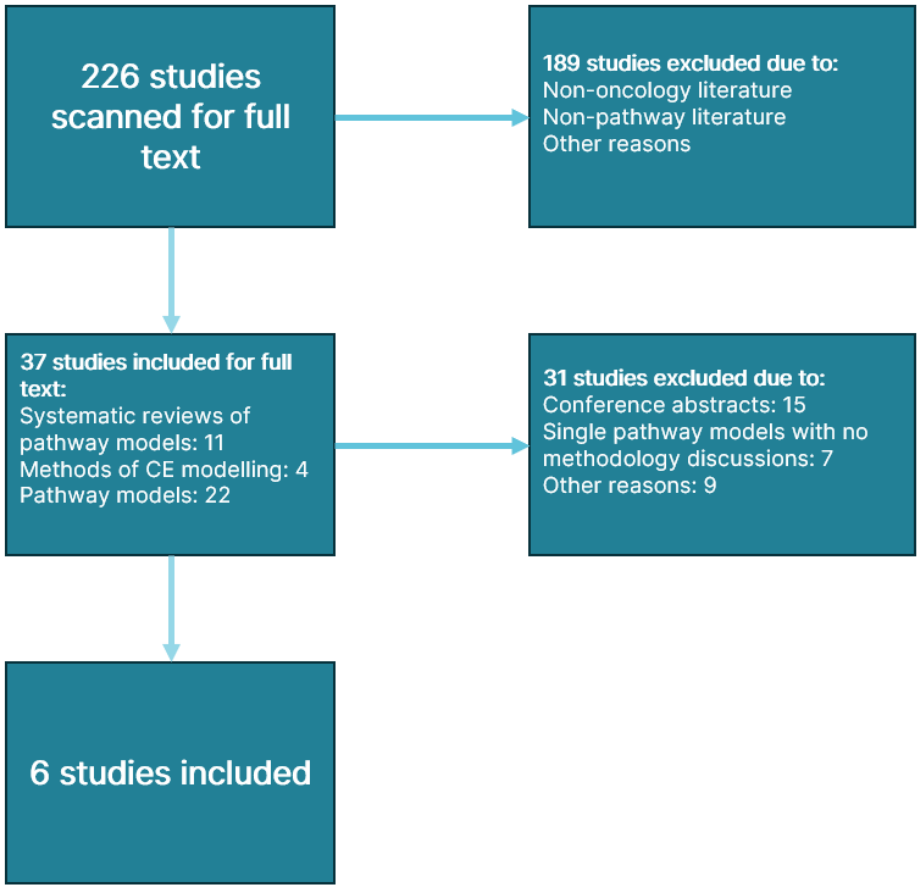
This project is part of a pilot exploring the use of pathways models in NICE TA; there are no previous committee-accepted pathways frameworks available to inform the structure at the point of model conceptualisation. On this basis, a literature review is being conducted to identify methodologies used to evaluate the clinical and cost-effectiveness of interventions in pathways disease modelling within the oncology disease area.

The search aims to identify methodological papers looking at approaches for pathway modelling, methodological papers looking at approaches for evidence synthesis of clinical effectiveness to inform pathways models, and systematic reviews of pathway models critiquing their methodological approaches.

An initial 226 papers were screened for title and abstract by the CfG Economics team with 37 papers moving to the full text review stage. A second sift for titles and abstracts was conducted by Bristol EAG, and concordance established via discussions. The full text screen is currently being undertaken, and from the 37 papers scanned for full text, 6 papers currently satisfy the inclusion criteria (further to second reviewer checks). It should be noted that in the full text review, only papers which explored methodologies to inform pathway models were considered; papers relating to single pathway models, but with no references to the methods were not included.

Details of the review along with reasons for exclusions are outlined in the PRISMA diagram below (Figure 3).

Figure 3: PRISMA diagram for literature review of pathways methodologies



Following full text sift, six studies relating to methodological approaches in pathways modelling were included in the review. Of these, Tappenden et al (2013) was a single model developed based on the methodological framework suggested by Tappenden et al (2012).[49, 50] The relevant principles outlined in the other five papers are listed below, and have been considered when developing the model structure. [51-54] [49]

Huang et al (2022) [54]

Huang et al (2022) carried out a systematic review of treatment sequence related models in oncology, finding that the majority of economic models used either cohort state transitions (74%) or discrete event simulation (20%) models. It should be noted that although Huang et al (2022) indicate that a search of pathways models was conducted, 26 of the 46 included models were from NICE TAs. The current project is a pilot project commissioned by the NICE TA programme exploring the novel use of pathways models in TAs, which suggests that the appraisal models identified by Huang et al. were not pathways models. The likely difference in definitions of what constitutes a pathways model means that conclusions from this paper may have limited applicability. Nonetheless, the Huang et al (2022) paper was assessed to identify methodological approaches relevant to this project.

Methodological issues identified in the paper related to the selection of outcomes for effectiveness, adjusting of treatment efficacy in relation to position in sequence, modelling treatment-free intervals and incorporating indirect treatment comparisons. The paper presents a conceptual model for an oncology pathways model where patients in each line of treatment are in either a progression free or progressed disease health state, and the next line of treatment is initiated if patients experience progression or discontinue the earlier treatment due to tolerability, with a treatment free interval also accounted for. However, it should be noted that the paper does not address the impact of treatments on patients' overall survival that is confounded by their subsequent treatment (see section 5.2.3.1), and is a key issue in pathways model development, and was industry funded.

Tappenden et al (2012)[49]

Tappenden et al (2012) reports a methodological framework for whole disease modelling, primarily developed for cancer but generalizable to other diseases. They propose a generalised process for developing whole disease models based on three principles: model breadth, depth and boundary, decision nodes being conceptually transferable across the model, and structuring in the related costs and consequences of service elements. The paper then outlines a five-stage process for developing and using whole disease models, with recommendations on understanding the decision problem, model conceptualisation, implementation, model checking and engaging with the decision. The whole disease models discussed in the paper are broader than the agreed scope of this pathways model and are designed to enable decision making at much earlier points in the pathways (e.g. diagnosis). The paper highlights that individual-level simulation is likely to be required for whole disease modelling. The framework outlined was later implemented to develop an economic evaluation for colorectal cancer by Tappenden et al (2013). [50]

Zheng et al (2017)[51]

Zheng et al (2017) conducted a review of approaches used to model treatment sequences in health economic models in NICE technology appraisals and provided recommendations to consider when developing models of this nature. The review was not limited to oncology models however 13 out of the 40 treatment sequence models looked at in the review were related to oncology. As with Huang et al (2013), the fact that this project is a pilot

commissioned by the NICE technology appraisals programme suggests the Zheng et al (2017) study may have included models without multiple decisions nodes.
Recommendations made spanned across four topics:

- Model conceptualisation: If the selection, efficacy or costs of treatment are affected by prior treatments the model should account for treatment switching. If the decision problem is about where a new treatment should be positioned in a pathway modelling of different sequences should be considered.
- Type of modelling approach: When deciding on which type of modelling approach to use (eg: between cohort state transitions and DES), consider patient heterogeneity, lines of treatment and types and features of outcome events.
- Consideration of data sources and availability
- Computation: considerations of which software is to be used when developing the model.

Cranmer et al (2023)[52]
Cranmer et al (2023) compared a partition survival analysis and semi- Markov multi-state model with and without attempts to adjust for subsequent therapies on OS for people with relapsed/ refractory multiple myeloma by looking at the impact on ICERs. Results concluded that the advantages gained by the simplicity of the partitioned survival analysis are lost when the OS adjusted for confounding from subsequent therapies. In a complex decision context, the multi-state model structure is considered to be more flexible and adjustments for OS confounding are conceptually simpler than in the partitioned survival analysis. The study notes that data required to estimate MSM transitions are rarely reported and so then methods are likely to require patient-level data.

Lord et al (2013)[53]
Lord et al (2013) developed a model for two published NICE guidelines on prostate cancer and atrial fibrillation, broadly following the framework proposed by Tappenden et al (2012). The exercise highlighted the importance of using DES techniques when modelling questions with more complex care pathways, due to different patient treatment histories and characteristics being captured by a patient-level simulation model. The paper notes however that access to individual-level data on patient characteristics is near essential for DES modelling. Lord et al (2013) proposed a number of good practice recommendations for model development based on key issues that arose in the two case studies. This included:

- The need for clarity about the boundaries of the model
- Establishing whether the model pathway is meant to reflect recommended or current practice
- To develop a model of the disease process rather than just focusing on the service pathway
- To provide a visual representation of the model with textual description where necessary
- To decide on simplifying assumptions made keeping in mind that this may restrict future uses of the model

- To be mindful of potential inconsistencies between bodies of evidence that inform different sections of the model.

5.2.3 Requirements of model structure

5.2.3.1 Requirements

Choice of model structure has been informed by both methodological and operational requirements:

Time-dependency:

Given the pathway nature of the decision problem, with multiple lines of treatments needing to be incorporated, a key requirement of a proposed model structure would be to account for the time-dependent probabilities of progression. Progression-free survival will be modelled as a non-linear function of time, and so the rate at which patients progress and subsequently be modelled to receive subsequent treatment or not will vary over time. Modelling time-dependent probabilities is not a technical challenge for first-line treatments, as patients will enter the model at the same time, and it is straightforward to estimate the time spent in the health state. However, patients will enter the health states reflecting subsequent lines of treatments at different time points, and since outcomes for these patients is also being modelled explicitly and using time-dependent outcomes, it is important to account for the time spent in the health state.

Necessity of modelling line-specific mortality:

In a pathways model, each treatment node needs to be modelled in a way that isolates the effects of the intervention from the effects of subsequent treatments and so survival needs to be modelled separately for each decision node. Isolating the survival benefits of a treatment at a specific decision node requires line-specific survival data. With patients expected to move to a new line of therapy upon progression (see Figure 2), progression-free survival (PFS) data can be considered line-specific. However, overall survival (OS) data collected in trials captures both pre- and post-progression mortality; within this measure there is no differentiation between deaths that occur while a patient is on the intervention of interest and deaths that occur after multiple lines of subsequent treatment. Because of this, OS data does not give a true reflection of line-specific treatment effects on mortality (Section 4.5.2). As all decision nodes will need to capture line-specific mortality, OS data will not be suitable for modelling survival in decision nodes other than the last line of treatment (best supportive care). OS data that has been appropriately adjusted for treatment cross-over may overcome this confounding, but it is unlikely to be widely reported and conducting analyses to adjust for this would require access to individual patient data unlikely to be available to the CfG Economics team.

Data availability:

This project has been commissioned by the NICE TA programme as a pilot for exploring the use of common pathways models that could be used in multiple TAs in a disease area. The model hence needs to be suitable for use in multiple submissions from different

manufacturers. Access to trial data is controlled by various different stakeholders and due to commercial sensitivities, certain data such as individual patient data (IPD) or analyses not commonly reported outside of trial publications may not be available for use in developing or maintaining the model.

Therefore, it is expected that patient level data to estimate outcome probabilities, whether from a trial dataset or simulated, would not be available. Methods do exist to recreate simple pseudo- patient level data from Kaplan Meier curves for the outcome in question; however, co-variance between patient characteristics and different outcomes are unlikely to be widely reported, meaning this data would not represent a plausible patient cohort that captures a patient's history. Simulating patient-level data from trial-reported means would face similar problems. Because of this, a requirement of the model structure is that it is not dependent on patient-level data.

Manageable model run times:

A pathways model is typically complex with multiple detailed decision nodes. Some potential model structures (e.g. patient level simulations, large numbers of tunnel states) are likely to lead to deterministic models with long run times. This could be operationally problematic when working to technology appraisal timelines, as the model would not have the flexibility to output additional scenarios in the time-period preceding a committee meeting. Models with long run times also pose a methodological challenge where conducting probabilistic sensitivity analyses becomes unfeasible in standard timeframes, meaning decisions have to be based on deterministic estimates, whereas 'NICE health technology evaluations: the manual'[17] outlines a preference for probabilistic estimates. Given the broad scope of a project of this nature, a model with a reasonable run time will be beneficial, especially given the different permutations of treatment pathway sequences possible.

Model accessibility:

As outlined above, the model needs to be suitable for use by multiple stakeholders, as it is anticipated that NICE will use the model in future appraisals in this pathway. It therefore needs a high level of transparency that can be understood and operated easily by all involved stakeholders. At present, this leads to a preference for the development of the model in MS Excel given its familiarity amongst stakeholders, and the easily understandable interface. Furthermore, with the pilot model for the RCC pathways project recurrently being developed in R,[55] the development of the NSCLC pathways model in Excel will allow TA to evaluate how an Excel-based model will fare in the context of a project of this nature.

5.2.3.2 Model selection

Due to its reliance on OS data, a conventional partitioned survival model will not be suitable for modelling decision nodes other than the last line of therapy as mortality rates would be confounded by subsequent treatments and so would not be line specific.

Given the multiple lines of therapy involved within the NSCLC pathway structure, a cohort state transition model would either require extensive tunnel states to be incorporated into the model or use a multidimensional matrix approach to account for time dependency. The use of extensive tunnel states can result in a very complex model with a lengthy model run time and increase the possibility of errors when developing the model.

The use of a multidimensional matrix approach (Briggs et al. 2006),[56] whilst being a theoretically robust way to avoid the extensive use of tunnel states, comes with a range of complexities when implementing in commonly used modelling software packages such as MS Excel.

A discrete event simulation (DES) could be flexible enough to address the majority of the complexities involved in the NSCLC pathway structure. However, it will require a plausible patient level dataset (whether from a trial or simulated from trial-reported aggregates) to fully leverage the benefits of this approach and poses the possibility a lengthy run time when running probabilistic versions of the model. Furthermore, the accounting of baseline level heterogeneity, seen as one of the main advantages of a DES model, is unlikely to be a pivotal factor in this disease area, and can be accounted for by selecting appropriate sources of data, e.g. a trial reporting outcomes by histology or PD-L1 status.

Cramner et al (2023) attempted to address the issue of OS data not being line-specific by adjusting for subsequent treatments in a multi-state model.[52] However, multi-state models have the same data requirements as DES models (i.e. either patient-level data or aggregate data that could be used to simulate transitions but which are rarely reported).

Similarly, patient level state transition models could capture the complexities involved in the NSCLC pathway structure but will also require access to patient level data, and have the possibility of a lengthy run time when running the probabilistic version of the model.
None of the existing pathways model structures identified met all model requirements. On this basis, a novel model structure was conceptualised and developed to meet the needs of this project (see Section 5.3.4).

5.2.4 Identifying sources of parameters

5.2.4.1 Clinical parameters

Clinical parameters in the form of both the reference survival curves and relative treatment effects relating to progression-free survival (PFS), time-to-progression (TTP), overall survival (OS) where applicable, and adverse event data (outlined more detail in Sections 5.3.5.1 and 5.3.7) will be sourced from the systematic review (Section 4).

5.2.4.2 Economic parameters

Parameters for quality of life, resource use and cost parameters will be identified via a review of previous TAs of treatments in scope of this project (Table 3). A review of inputs used in previous TAs was deemed sufficient since, in each TA, sources were identified by

undertaking a literature review. As several TAs in the pathway were only published in the last two years,[23, 29-31, 57] it is believed that the sources listed in the TAs are representative of the best available evidence at the time of appraisal and are likely to be the most suitable publicly available sources of data.

5.2.4.3 Real world evidence

This pilot project will explore the use of routinely collected national level data to inform the development of the pathway decision model. If possible, this project will access retrospective UK real-world evidence (RWE) of patients with NSCLC via the Systemic-Anti Cancer Therapies (SACT) database, linked with Office for National Statistics (ONS) data and other datasets through the National Cancer Registration and Analysis Service (NCRAS). This will use existing partnerships with NDRS/NHS England to support this work.

There are challenges to accessing routine data for drugs within the Cancer Drug Fund (CDF). At the time of this pilot, this affects two interventions currently in the CDF: selpercatinib (TA760) and sotorasib (TA781).[30, 31]

Careful consideration will be taken regarding the impact of the COVID pandemic (years 2020 to 2022) on the outcomes in the dataset. Modifications to usual services was made during these years in order to mitigate risk to patients whilst preserving efficacy, and to support the response of the healthcare system to the pandemic to make better use of capacity. Outcomes data and treatment patterns from these years may be less reflective of typical standard practice in the preceding and subsequent years. The impact of the pandemic on the data during these years will be evaluated, and adjustments to the data analysis will be explored with the NICE Data & Analytics team.

The use for this data falls into one of two categories. The results of analyses will either directly inform input parameters in the decision model, or they will be used to justify certain modelling decisions. If the data is not available in the timeframes of this project, alternative approaches to analysis or parameterisation have been outlined in the respective sections.

Model parameters

For each treatment within a line of treatment, key outcomes of interest to be estimated from RWE are:

- Baseline characteristics for each line of therapy: age, gender, body weight
- Overall survival for people receiving best supportive care (i.e. survival from the point of discontinuation of their last therapy),
- Time on treatment, or time to treatment discontinuation,
- The proportion of people moving onto next line of treatment,
- The distribution of treatments those people receive.

All analyses will be specific to the population in the scope and will include people who receive at least one line of systemic therapy for advanced NSCLC. Differences in outcomes

between patient-related characteristics, including squamous and non-squamous tumour histology and PD-L1 expression category, will be explored. If differences are identified, there will be an exploration of whether it is possible to generate these outcomes for each subgroup.

If feasible within the timescales of this project, RWE may be requested on healthcare utilisation, such as on A&E attendance, inpatient stay, critical care, outpatient visits, CT scans and blood transfusions, that can be used to inform health state costs.

Verifying modelling assumptions

The data request will include the number of people receiving each type of treatment at each line of therapy on an annual basis. This data will capture changes in practice over time, and will be used to justify the inclusion of comparators in the model. It can also be used to indicate what represents standard practice for each decision node, for informing the committee as to what could be used as the reference treatment when estimating the severity of the condition (Section 5.4.2)

If possible, data will be used to determine the overall survival for each treatment in scope and will be used to validate the predictions of the model.

Other patient characteristics for each treatment at each line of therapy will also be requested, such as ECOG status, and used to understand the types of people who receive each therapy and how it compares to participants in the clinical trials.

5.2.5 Cost effectiveness literature review

5.2.5.1 Identification of existing evidence

A literature review will be conducted to review all (positive) TAs listed in the scope for this pilot project. The purpose of the review is to provide information at each treatment node to inform the conceptualisation of the pathway model, and to provide outcomes (e.g. lifetime costs, QALYs and life years) that can be used to validate the predictions of the pathway model.

Typically, a systematic review of cost-effectiveness evidence is undertaken for a technology appraisal. For the purposes of informing this pilot project, existing TAs are likely to constitute the most appropriate and applicable sources of evidence for economic evaluations, since they were designed to meet the requirements for a NICE assessment and themselves included a review of the literature. The availability of the information in the committee papers provides more detail on the evaluations and a critique of their application than would be included in a typical journal article. Since the last appraisal for a second-line treatment was published the same year this analysis plan was developed and the last appraisal for a first-line treatment was the year prior, it is unlikely that any other evidence has been published since then.

5.2.5.2 Summary of technology appraisals

Table 5 presents a top-line summary of technology appraisal methods for treatments in the scope of this project. Details included in the table reflect the committee's preferred assumptions. The decision-making cost-effectiveness results are not typically in the public domain as they either contain the submitting company's confidential pricing information, or the topic EAG has applied the comparator companies' confidential pricing information. Where possible, list price results will be extracted, as these results should be replicable using publicly available data.

Table 5 Summary of previous technology appraisal submissions

TA	Population	Intervention	Comparator	Source of effectiveness data	Model type
First-line treatments					
TA683 (update of TA557)[19, 58]	Non-squamous	Pembrolizumab with pemetrexed and platinum chemotherapy	Pemetrexed with carboplatin or cisplatin Pembrolizumab monotherapy (For PD-L1>=50%)	Direct comparison, from KEYNOTE-189 for PD-L1<50% subgroup ITC for comparison with pembrolizumab monotherapy for the PD-L1≥50% subgroup (KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-021)	Partitioned survival model, with health states including progression free, progressed disease, death
TA770 (update of TA600)[23, 59]	Squamous PD-L1 < 50% PD-L1 ≥ 50% and they need urgent clinical intervention	Pembrolizumab with carboplatin and paclitaxel	Chemotherapy (paclitaxel, nab paclitaxel, carboplatin)	Direct comparison, from KEYNOTE-407	Partitioned survival model, with health states including progression free, progressed disease, death
TA531 (update of TA447)[21, 48]	PD-L1 ≥ 50%	Pembrolizumab	Standard of care (gemcitabine/carboplatin, or gemcitabine/cisplatin, paclitaxel/carboplatin, pemetrexed/carboplatin, pemetrexed/cisplatin)	Direct comparison, from KEYNOTE-204	Partitioned survival model, with health states including progression free, progressed disease, death
TA584[20]	Non-squamous PD-L1 < 50%	Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin	Pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance	IMpower150 data for Atezo+Bev+CP Fractional polynomial NMA to model comparators (ERACLE, PRONOUNCE, KEYNOTE-021, KEYNOTE-189)	Partitioned survival model, with health states including progression free, progressed disease, death
TA705[22]	PD-L1 ≥ 50%	Atezolizumab	Pembrolizumab	IMpower110 data for atezolizumab. Fractional polynomial NMA for comparators (KEYNOTE-024 and KEYNOTE-042)	Partitioned survival model, with health states including progression free, progressed disease, death
Subsequent line treatments					
TA855[29]	EGFR exon 20 fusion positive disease after	Mobocertinib	Blended comparator (Atezolizumab (20%), docetaxel (40%),	Study AP32788-15-101 for mobocertinib ITC using inverse probability of treatment weighting for usual care using RWE	Partitioned survival model, with health states including progression free, progressed disease, death

TA	Population	Intervention	Comparator	Source of effectiveness data	Model type
	platinum chemotherapy		docetaxel and nintedanib (40%))		
TA760[30]	RET fusion positive disease	Selpercatinib	Docetaxel monotherapy, docetaxel with nintedanib	LIBRETTO-001 data for selpercatinib REVEL data (docetaxel) to create a pseudo-control, adjusted with Flatiron RWE. NMA for comparator effects	Partitioned survival model, with health states including progression free, progressed disease, death
TA781[31]	KRAS G12C mutation positive disease	Sotorasib	Docetaxel monotherapy, docetaxel with nintedanib	CodeBreak100 data for sotorasib. MAIC for docetaxel comparison (SELECT-1 data), and HR to compare docetaxel vs docetaxel with nintedanib (LUME-Lung trial)	Partitioned survival model, with health states including progression free, progressed disease, death
TA428[24]	PD-L1 positive	Pembrolizumab	Docetaxel monotherapy, nintedanib with docetaxel	Direct comparison with docetaxel using Keynote-010 trial data Indirect comparison for docetaxel and nintedanib with docetaxel (KEYNOTE-010 and LUME-LUNG-1) in adenocarcinoma pop	Partitioned survival model, with health states including progression free, progressed disease, death
TA520[27]	All	Atezolizumab	Docetaxel alone (for PD-L1-negative disease) Pembrolizumab (for PD-L1-positive disease).	Direct comparison with docetaxel using OAK trial data Fractional polynomial NMA for nintedanib plus docetaxel	Partitioned survival model, with health states including on-treatment, off-treatment, death
TA713 (CDF review of TA484)[25]	Non-squamous PD-L1 positive	Nivolumab	Docetaxel monotherapy	Direct comparison with Checkmate 057 data	Partitioned survival model, with health states including progression free, progressed disease, death
TA655 (CDF review of TA483)[26]	Squamous PD-L1 positive	Nivolumab	Docetaxel monotherapy	Direct comparison with CheckMate-017 data	Partitioned survival model, with health states including progression free, progressed disease, death
TA347[28]	All	Nintedanib with docetaxel	Docetaxel monotherapy	Direct comparison with LUME-Lung 1 data	Partitioned survival Markov model containing 3 health states: progression-free (on or off treatment); progressed disease; and death.

5.3 Economic modelling

5.3.1 Population

The model population will align with the decision problem population, which is people with advanced/metastatic stage 4 NSCLC, without targetable genetic alterations who receive a targeted treatment as first line therapy (Section 4.1.1). People with advanced/metastatic NSCLC who receive target treatment at first line therapy are out of the scope of this project.

Patient characteristics in the base case analysis will be estimated from RWE sources if possible, such as the Systemic Anti-Cancer Therapy (SACT) database. If this data is not available within the timeframes of this project, it will be obtained from RCTs in the systematic review of effectiveness evidence. Patient characteristics that are anticipated to be included in the decision model are age and gender at each line of therapy (to estimate general population mortality (Section 0), and quality-adjusted life expectancy (Section 5.4.2), and body weight (to estimate drug doses (Section 5.3.9.1). The analysis may also incorporate prevalence of KRAS G12C and EGFR exon 20 insertion genetic mutations and of RET fusions to determine the proportion of people who receive subsequent therapy with the targeted treatments for these mutations (Section 5.3.6).

Consideration will also be given to:

- Histology (squamous or non-squamous),
- PD-L1 status.

Certain comparators are recommended for specific subpopulations within advanced NSCLC. For example, atezolizumab monotherapy is recommended if the tumours have PD-L1 expression on at least 50% of tumour cells, while atezolizumab in combination is recommended for non-squamous NSCLC with tumours that are PD-L1<50% (Section 4.1.4).[22] Therefore, the model will be configured to generate results for subpopulations based on histology, PD-L1 status and prevalence of genetic mutations, that are specified by the user and will automatically include the appropriate comparators for each population.

An element of complexity is that many of the interventions have overlapping but non-matching indications. For example, pembrolizumab with pemetrexed and platinum chemotherapy (TA683) is recommended for people with non-squamous NSCLC, and atezolizumab monotherapy (TA705) is recommended if PD-L1≥50%.[19, 22] This means that people who are non-squamous and have PD-L1≥50% are eligible to receive either pembrolizumab with pemetrexed and platinum chemotherapy, or atezolizumab monotherapy. However, the clinical evidence for each of these comparators will be broader than this common indication, and so it will be necessary to assess whether evidence from the wider population can used in such comparisons.

Previous TAs (e.g., [26]) and clinical advice note heterogeneity across patient groups by histology and PD-L1 status, and there is evidence to suggest that absolute and relative treatment effects may be different among these patients. The ability to model absolute and

relative treatment effects based on histology and PD-L1 status, and to evaluate whether it is statistically and clinically appropriate to do so, will depend on how data is reported in the trials in the clinical review, and whether any further supplementary data will be provided directly by stakeholders. If data is not available to model these effects for a given intervention, then it will be necessary to make assumptions around how to share information from other decision nodes in the pathway (Section 4.5.5), and may mean that we assume that any treatment effect for the given population is consistent within that population.

Further, clinical advice to the modelling team notes that the prevalence of genetic mutations is greater in those with non-squamous histology, and that these people experience greater symptomatic burden of disease and may have a poorer quality of life than those with squamous histology. If possible, these clinical features will be incorporated into the pathway model.

No further subgroups of interest were included in the scope.

5.3.2 Interventions

The pathway model will include medicines in the NICE scope (Section 4.1.4), which includes those which have received a previous NICE recommendation for treatment in advanced or metastatic stage 4 NSCLC, with the exception of those with a targetable genetic alteration who received a targeted treatment at first line (Figure 2). In addition, the model will include treatments which are recommended in NICE clinical guidelines and include generic treatments which are used routinely in the NHS; the choice of relevant treatments has been based on clinical expert input provided at the scoping workshop held by NICE.

Clinical advice to the CfG Economics team suggests that uptake of immunotherapies at second-line has been low since their introduction at first-line. SACT data will provide further information on their use in current practice, and will be used to justify their inclusion or exclusion as comparators in the pathway model. The pathway model will include the functionality to model all treatments in scope, but decisions regarding the included treatments in future analyses will ultimately lie with the committee.

This iteration of the model will exclude all pipeline treatments which have not yet received a recommendation in a NICE TA. Table 6 outlines the drugs which will be included in the model.

5.3.2.1 CDF treatments

The model will contain some drugs within the cancer drugs fund (CDF) despite them not being routinely commissioned in the NHS. The aim of this is anticipatory of enabling the inclusion of these treatments in the modelling, when they exit the CDF and are re-evaluated for routine commissioning.

The model will include the option to exclude CDF treatments from the analysis. When CDF drugs are excluded, patients will receive relevant comparator treatments available at that node in the pathway. For example, when selpercatinib and sotorasib are removed from the analysis, patients will receive docetaxel with or without nintedanib or platinum base chemotherapy, depending on patient treatment history.

Current NICE methods state that the decision problem is rescoped for CDF exit appraisals. This means that these appraisals are not limited to treatments in the original submission. Therefore, the pathway model will enable a comparison of all relevant treatments.

Table 6: Interventions included at each decision node

Decision nodes	Treatment regimen	Technology appraisals	Mode of administration	Posology	Treatment stopping rule
NS1, NS2	Pembrolizumab with pemetrexed and platinum chemotherapy	TA683[19]	Intravenous infusion	Pembrolizumab 200mg every 3 weeks or 400mg every 6 weeks (See pemetrexed with platinum doublet chemotherapy)	It is stopped at 2 years of uninterrupted treatment, or earlier if the disease progresses
NS1	Atezolizumab plus bevacizumab, carboplatin and paclitaxel	TA584[20]	Intravenous infusion	**Induction** 1,200 mg, followed by bevacizumab (15 mg/kg), paclitaxel (200 mg/m^2), and then carboplatin every 3 weeks for 4 or 6 cycles **Maintenance** Without chemotherapy in which 1,200 mg atezolizumab followed by bevacizumab (15 mg/kg) is administered every 3 weeks	Atezolizumab and bevacizumab are stopped at 2 years of uninterrupted treatment, or earlier if there is loss of clinical benefit (for atezolizumab) or if the disease progresses (for bevacizumab)
NS1, NS2	Pemetrexed with platinum doublet chemotherapy	TA181[60]	Intravenous infusion	The recommended dose of pemetrexed is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin	N/A
NS2, S2	Pembrolizumab monotherapy	TA531[21]	Intravenous infusion	Pembrolizumab 200mg every 3 weeks or 400mg every 6 weeks	Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression or unacceptable toxicity

Decision nodes	Treatment regimen	Technology appraisals	Mode of administration	Posology	Treatment stopping rule
NS2, S2	Atezolizumab monotherapy	TA705[22]	Intravenous infusion	The recommended dose of atezolizumab is either 840 mg administered intravenously every two weeks, or 1200 mg administered intravenously every three weeks, or 1680 mg administered intravenously every four weeks,	Until disease progression or unmanageable toxicity
S1	Pembrolizumab with carboplatin and paclitaxel	TA770[23]	Intravenous infusion	Pembrolizumab 200mg every 3 weeks or 400mg every 6 weeks Carboplatin (AUC 6) and paclitaxel (200mg/m²)	It is stopped at 2 years of uninterrupted treatment or earlier if their disease progresses
ST1	Nivolumab monotherapy	TA655[26]	Intravenous infusion	240 mg every 2 weeks over 30 minutes	Stopped at 2 years of uninterrupted treatment, or earlier if their disease progresses and they have not had a PD-1 or PD-L1 inhibitor before.
ST1	Docetaxel	TA347[28]	Intravenous infusion	In chemotherapy naïve patients treated for non - small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m²as a single agent.	N/A
ST1	Mobocertinib	TA885[29]	Oral administration	The recommended dosage is 160 mg once daily	N/A
ST1	Selpercatinib	TA760[30]	Oral administration	The recommended dose based on body weight is: - Less than 50 kg: 120 mg twice daily. - 50 kg or greater: 160 mg twice daily	N/A
ST1	Sotorasib	TA781[31]	Oral administration	960 mg (eight 120 mg tablets) orally once daily	N/A

Decision nodes	Treatment regimen	Technology appraisals	Mode of administration	Posology	Treatment stopping rule
ST1, ST2	Docetaxel with nintedanib	TA347[28]	Oral administration	75mg/m^2 Docetaxel day 1 Nintedanib 200mg BD days 2-21 per cycle	N/A

5.3.3 Perspective, time horizon, discount rate

The model will use an NHS and Personal Social Services perspective in line with the NICE reference case.

The model will have a lifetime horizon, to reflect all important differences in costs and outcomes between the interventions being compared.

The analysis will discount all costs and QALYs at a rate of 3.5% per year, as specified in the NICE reference case. All costs will be expressed in UK pounds sterling for the 2023/2024 price year.[17]

A weekly cycle length will be applied to account for the difference in dosing regimens across treatments. Half cycle correction will not be applied given the short cycle length.

5.3.4 Model structure

5.3.4.1 Software

As mentioned above (see Section 5.2.3), the proposed model needs to be transparent and easily accessible. MS Excel is commonly used for model development in this disease area, and a substantial number of models in TA submissions use it. So this economic model will be built in MS Excel.The user interface and worksheet-based framework around which MS Excel models operates can allow for greater model transparency when compared to models developed in command-based interfaces such as R or Python, for those who have less experience of these methods. There will be minimal use of VBA-based macros within the MS Excel framework to allow for further model transparency, with the use of these largely being limited to the application of the probabilistic sensitivity analysis (PSA) and for improving model functionality (such as changing between modelling options). Survival analysis for the reference treatment for each node will be carried out in R, with covariates manually copied across to the MS Excel workbook in which the economic model is developed. A similar procedure will be employed for the outcomes of the NMA (Section 4.5) where the NMA outputs are manually copied across to the MS Excel workbook, and the RWE analysis (Section 5.2.4.3).

5.3.4.2 Overview of model structure

As outlined in Section 5.2, the standard partitioned survival analysis structure commonly used in the NSCLC disease area is not suitable to address this pathways decision problem due to its reliance on OS data (which captures the cumulative impact of multiple lines of therapy, and does not isolate the impact of individual lines of treatment). Similarly, standard models addressing pathway decision problems in other areas in oncology such as cohort level state transition, DES, or patient level state transition methodologies are not suitable for this decision problem primarily due to operational restrictions, and to a lesser extent due to methodological limitations (Section 5.2.3).

Hence a novel method of modelling in the form of a ‘nested partitioned survival model’ is proposed, which addresses the complexities of the pathways structure and circumvents operational limitations.

In the proposed model structure, interventions at each line in the pathway structure shall be modelled discretely, with patients moving between lines based on progression status. Costs and QALYs will be calculated within each line of therapy (i.e. pre-progression/ movement to the next line of therapy). Time on treatment data will be used to calculate treatment-related costs and disutility from adverse events at each line of therapy, since some patients may discontinue treatment before progression e.g. due to toxicity and some treatments may have stopping rules. Within this modelling structure there is a simplifying assumption that movement from one line of therapy to another is based upon progression status. Whilst this is a simplification of reality where some patients may discontinue a treatment pre-progression (e.g. due to toxicity or preference) and move onto the next line of therapy before they have progressed, clinical experts have outlined that the simplification is a sufficient approximation of what happens in clinical practice. Clinical experts also advised that people do not generally stay on treatment after progression. The novel structure was informed by two ideas :

1. Data will be available to develop a partitioned survival model at the last treatment line;
2. Conventional partitioned survival models typically used in NSCLC TAs have modelled subsequent treatments in the progressed state using simplifying assumptions about the distribution of subsequent treatments, and have applied a weighted average treatment cost upon progression.

As outlined in Section 5.2.3, OS data includes the combined effects of all treatments a patient receives, and so typically cannot be used to estimate treatment effect on survival for a single line of treatment. This issue is worse for OS estimated at earlier lines of treatment as patients have the potential to receive a higher number of subsequent treatments.

However, this is not a problem for the last line of treatment (in this model, best supportive care) where OS data will reflect the true treatment effect on survival. The last line of treatment can therefore be modelled using conventional partitioned survival methods using OS data from the clinical review. Best supportive care will be modelled in line with the conventions established in previous NSCLC TAs. The results of this analysis will provide average costs and QALYs for each treatment at this node informed by an in-depth analysis with sufficient detail for decision making.

Earlier lines of treatment cannot be modelled this way due to the challenges with OS data. However, as patients are assumed to move to a new line of therapy upon progression, the model for best supportive care captures what happens after progression for the last treatment line. On this premise, the progression-free state will be modelled in detail for the last line of treatment and the average costs and QALYs from the analysis of the best supportive care will be applied at progression. This is similar to the approach used for applying costs and QALYs in the progressed state of conventional partitioned survival models. However, because both pre- and post-progression states will be modelled in sufficient detail for decision making, this approach should yield a more accurate estimate of costs and QALYs accrued from the last line of treatment onwards.

The same principle will apply for all earlier lines of treatment, with the progression-free state explicitly modelled and then aggregated average costs and QALYs for all subsequent treatments applied at progression. The model will hence have a 'nested' structure where the model for each treatment node contains separate models for all subsequent treatment nodes – referred to as a 'nested partitioned survival model'.

The nested model will be developed for relevant treatment sequences in the scope, constrained by their subgroup (defined by histology and PD-L1 expression), commissioning rules (Table 6) and clinical expert input. The costs and QALYs applied at progression in the nested model will be a weighted average of the treatments (including best supportive care) that patients can have at the subsequent treatment node; the distribution of subsequent treatments will be a user input and should be informed by a committee accepted data source (Section 5.3.6).

This approach is consistent with the approach used in other NSCLC TAs where subsequent treatments received after progression are modelled using weighted averages of treatment costs, with the key difference that the treatment costs are based on detailed modelling of subsequent decision nodes rather than simplifying assumptions, and QALYs are modelled directly rather than indirectly (Section 5.2.1).

Model development will start at the end of the pathway, building a partitioned survival model for best supportive care. Treatment nodes will be added moving backwards through the pathway, so that the progressed state in any node with active treatment has already been developed.

5.3.4.3 Modelling active lines of treatment

For each of the active lines of treatment, 3 health states are modelled: progression-free, pre-progression death, and post-progression (which includes both those who are alive and dead). In a given decision node, patients in the progression-free state are assumed to be on treatment and the state will be modelled explicitly in sufficient detail for decision making akin to standard TAs.

The progressed disease state is not modelled explicitly within the decision node. Instead, patients in the progressed disease state are ascribed the mean costs and QALYs estimated via the models for all subsequent lines of treatment after the decision node (i.e. for patients in the post-progression state of decision node 'n', costs and QALYs are estimated from the model of line of treatment 'n+1'). As patients are assumed to move to the next line of treatment on progression, the progressed disease state for the line of treatment 'n' is the progression-free state for the line of treatment 'n+1'. The progression-free state for decision node 'n+1' will be modelled in the same way as for decision node 'n', and the progressed disease will be the aggregate of mean costs and QALYs estimated for all treatments after 'n+2'. The progressed disease state is hence never modelled explicitly, but the costs and

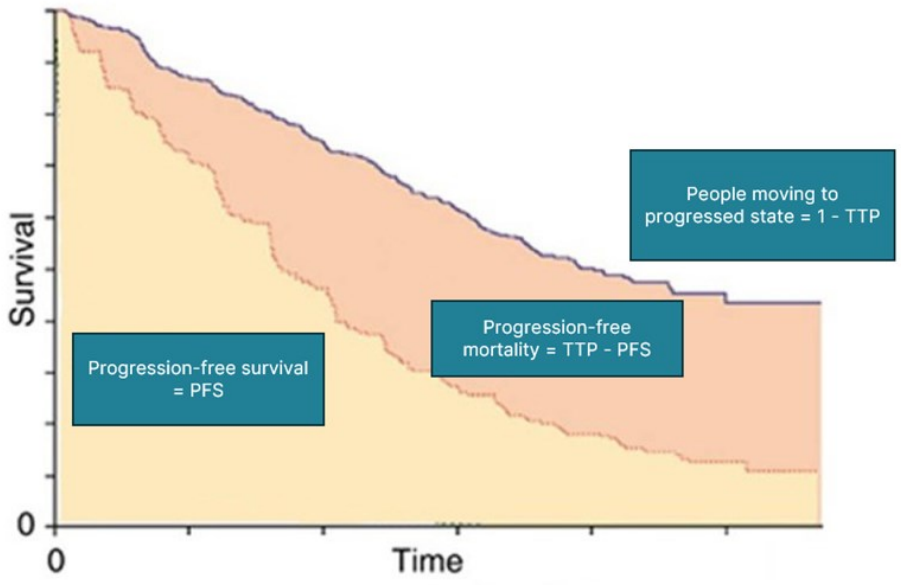
QALYs attributed to the state are estimated from a model with sufficient detail for decision making, and accurately reflects the proportion of people alive over time. This approach is used for all active lines of treatment.

Health state membership will be determined using the principles of conventional partitioned survival analysis but will use different types of survival data to isolate the line-specific treatment effects (Data informing state membership for nested partitioned survival modelFigure 4). The model transitions for patient flow within each cycle for each line-specific treatment model are as follows:

- Progression-free state to progression-free state;
- Progression-free state to progressed state (with progressed state to death captured in the costs and QALYs from the model for the next line of therapy, and hence not explicitly modelled at that line of treatment);
- Progression-free state to death state (otherwise described as progression-free death).

The progression-free state membership will be determined by the PFS curve for the intervention of interest. Movement from the progression-free state to the progressed disease state will be determined by the time-to-progression (TTP) curve for the intervention of interest. PFS is a composite outcome with two events: progression (captured by 1-TTP) and progression-free death (also conceptualised as death before progression). The TTP outcome captures progression events only and censors for death events, and so subtracting the PFS curve from the TTP curve enables the isolation of progression-free death and the progression events. The clinical review will search for evidence on survival curves for PFS and TTP for all treatments at each line (Section 4.1.2). If this data is not available, assumptions around the relationship between the relative treatment effects on TTP and PFS may be explored (Section 0).

Figure 4: Data informing state membership for nested partitioned survival model



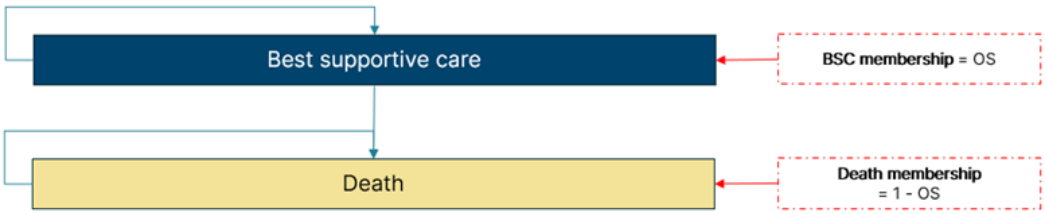
5.3.4.4 Modelling best supportive care

Best supportive care (BSC) can be entered into after any line of treatment but is always considered to be the last line of care (i.e. a patient cannot move from best supportive care to active treatment).

A conventional two-state partitioned survival analysis will be used to model best supportive care, with patients being either alive or dead at this line of therapy. Membership of the best supportive care health state and the death health state is informed by the OS curve. The model will include the same level of detail expected for other decision-making nodes and so should deliver a robust estimation of costs and QALYs gained in the best supportive care state.

Average costs and QALYs will be reported for best supportive care, which will serve as the estimates for the progressed state in the model for the last line of active treatment in whichever treatment sequence is modelled.

Figure 5: Model structure for best supportive care



5.3.4.5 Model diagrams

The resulting model structure is outlined in Figure 6, with progression free survival, time to progression and progression-free death modelled separately for each line of therapy and patients moving on to the next line of therapy when they reach the progressed disease health state. All health states in best supportive care and all progression-free states for active lines of treatment are modelled using partitioned survival analysis. It should be noted that in the model diagram for Figure X there are no arrows directly linking each line of treatment with the subsequent line of treatment. Instead, the black arrows are used to demonstrate how patients who progress at any line of treatment are ascribed the aggregated mean costs and QALYs for all subsequent treatments, depicted in the box on the left-hand side of the diagram. To supplement understanding, Figures 7-9 depict the model structure for each active line of treatment.

Figure 6: Summary model structure

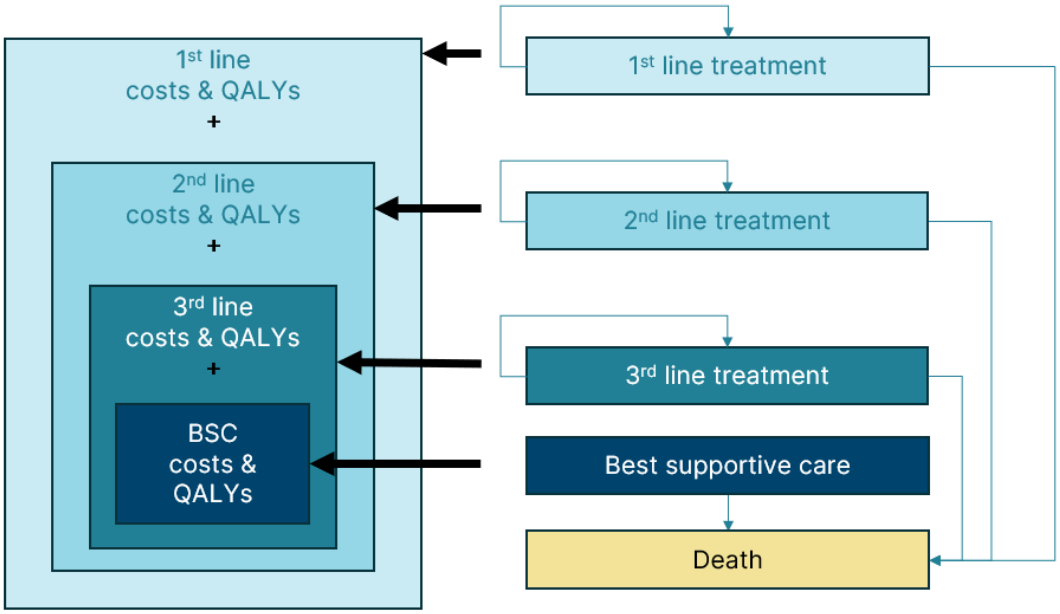


Figure 7: Model structure for the 3rd line of active treatment

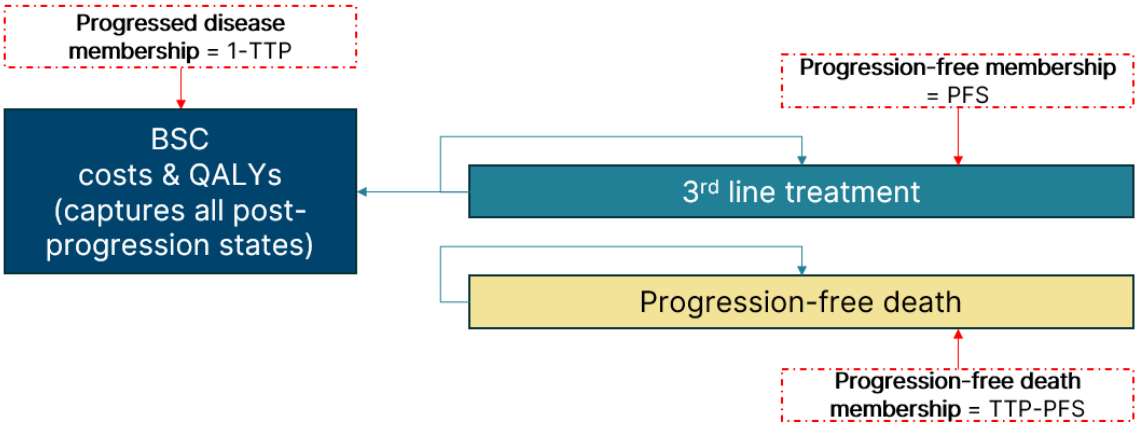


Figure 8: Model structure for 2nd line of active treatment

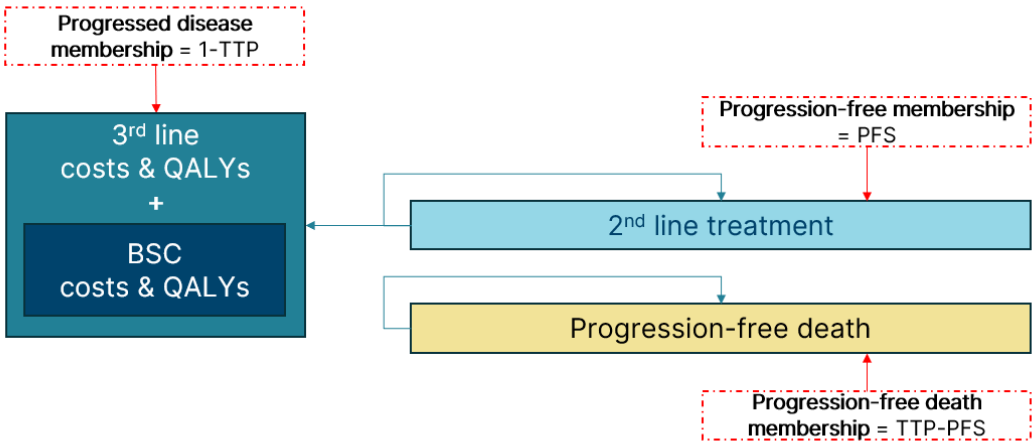
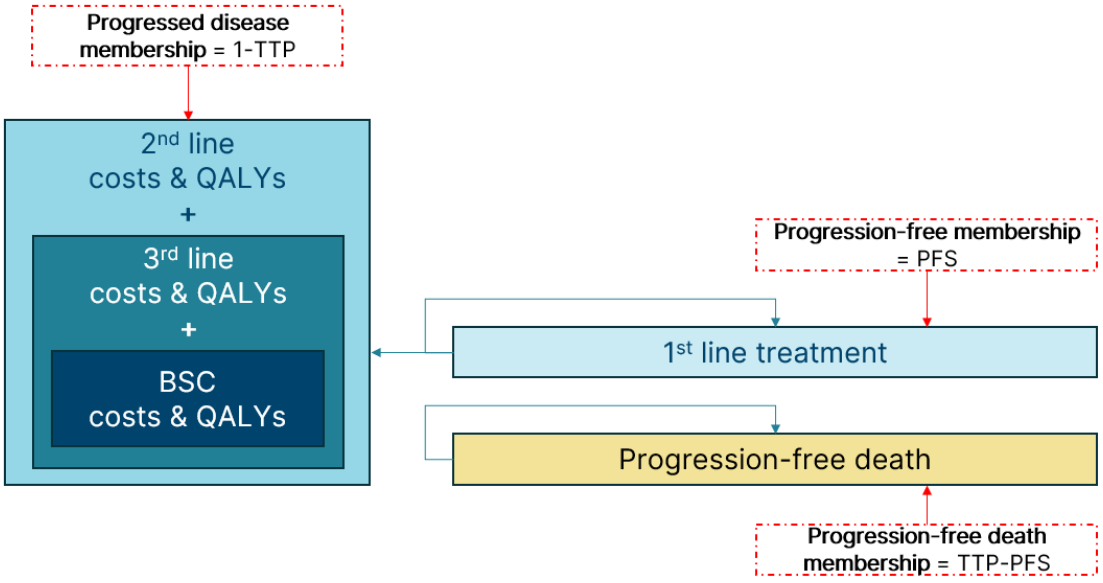


Figure 9: Model structure for first line of treatment



6

5.3.5 Treatment effectiveness and extrapolation

The model structure outlined in Section 5.3.4 relies on a number of model input parameters to inform health state membership. These include:

- **Progression free survival (PFS):** Informed by the clinical review for each treatment node, with the relevant extrapolation techniques and application of treatment effects outlined in Sections 0 and 5.3.5.1.
- **Time to progression (TTP):** Informed by the clinical review for each treatment node, with the relevant extrapolation techniques and application of treatment effects outlined in Sections 0 and 5.3.5.1.

- **Overall survival (OS) for best supportive care:** Informed by RWE (Section 5.2.4.3), with the relevant extrapolation techniques outlined in Section 0.
- **Time on treatment (ToT):** Informed by RWE (Section 5.2.4.3), and modelled as outlined in Section 0.

As outlined in Section 5.3.4, health state membership within each line of therapy will be determined directly from survival curves in line with traditional partitioned survival analysis methods. For all decision nodes other than the final line of treatment, PFS and TTP curves will be used to determine state membership for the progression-free state, pre-progression death state and the progression to the next line of treatment. For best supportive care, OS will be used to determine state membership for the alive and death states.

Time on treatment will not be used to determine health state membership but will be used to model treatment-related costs and adverse events.

5.3.5.1 Relative treatment effects

Progression

Ideally, PFS and TTP curves will be available for all treatments at each decision node. It is expected that the evidence synthesis (see Section 4.5 for further details on the approach to NMA and extrapolation of hazard ratios) will provide outcome curves for one reference treatment at each decision node. The choice of reference treatment at each node will be based on network and data completeness (such as the sample size and follow up). Clinical experts will be also asked to check whether the patient characteristics of the trials used to construct the reference curve are representative of the population at the decision node. Time-varying hazard ratio equations will be output for each other treatment in every node, calculated relative to the reference treatment for that node. By applying the hazard ratio equations to the reference treatment curves PFS and TTP, curves can then be constructed for all treatments at each decision node.

Based on a preliminary review of the literature, it appears unlikely that sufficient trials will report information on TTP to perform an NMA. In such a situation, information from the NMA on PFS will be used to model the relative treatment effects of TTP. If sufficient data on TTP is available for decision nodes (via company data submissions), an NMA for TTP may be conducted.

The lack of information on TTP can also be an issue when choosing a reference treatment for TTP. Whilst in an ideal situation there will be at least one treatment in each decision node reporting TTP, in situations where this is not the case, there are a number of potential options:

- An ideal scenario, where a company having a treatment in that decision node provides data;
- TTP will be constructed as a function of the PFS curve. Available trial data and previous TAs will be reviewed to determine a PFS:TTP ratio for each treatment, with

consideration given to available data for treatments with similar mechanisms of action;
- Leave blank with dummy data, with future submitting companies having the option to supply this. This is also not ideal because it prohibits the model from generating any outcomes in the meantime, which would be required for validation and committee discussion;
- Use TTP from another node – this may lead to an inappropriate relationship between PFS and TTP, as TTP should always be equal or higher to PFS;
- The worst-case scenario of assuming TTP is equal to PFS. This is highly unplausible as it assumes no pre-progression death, and may bias against treatments with a better response rate or lower toxicity as these factors would not be captured.

Time on treatment

ToT will not be used to determine health state membership but will be used to model treatment-related costs and adverse events. The ToT and PFS curves are modelled independently, but as health state membership is progression-based, the model makes an implicit assumption that ToT is sufficiently similar to PFS that discontinuations will not have a big impact on survival estimates for the progression-free state. This assumption has been checked with clinical experts, who advised that only a small number of patients who receive chemotherapy stop early and that patients who discontinue are likely to move straight to the next line of treatment and hence later down the treatment pathway.

Although ToT has been included as an outcome in the clinical review protocol (Section 4.3.4), it is expected that it will not be frequently reported in trials, and any data that is reported is unlikely to be generalisable to UK clinical practice and reflective of UK commissioning rules. As such, it is expected that ToT data will come from RWE via the SACT database (see Section 5.2.4.3). If SACT data is not available within the timeframes of this project, then ToT data will be sought from previous company submissions if publicly available.

Overall survival

OS for people on best supportive care (BSC) will ideally be estimated from RWE (Section 5.2.4.3), if it is available within the timeframes of this pilot project. If RWE is not available, then alternative sources will be explored and RWE may be incorporated into the model at a later stage. BSC is not expected to be a comparator arm in any of the trials in the systematic review (Section 4), and so a targeted review of the literature, including past TAs will be undertaken, with any assumptions validated by clinical expert opinion. The clinical review is expected to extract PFS and OS data on the last line treatment from RCTs, so another potential approach would be to estimate post-progression survival and use this as a proxy for BSC OS if RWE is unavailable.

Clinical advice to Bristol EAG and CfG Economics team is that outcomes for people on BSC are expected to be consistent, regardless of their previous line of therapy or the number of previous lines of therapy. Therefore, OS for BSC will be modelled in this way.

Based on the data available from the clinical review, the model will account for differences in relative treatment effect based on PD-L1 status and histology if appropriate.

Extrapolation of survival curves

As the model will have a lifetime horizon, it is expected that survival curves for PFS and TTP constructed from the effectiveness review (Section 4) will need to be parameterised so that they can be extrapolated beyond the trial follow up periods. ToT data from RWE may also need to be extrapolated.

As described in section 4.5.2.1, survival models that will be explored include standard parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) and flexible models (fractional polynomials or M-splines) following the approach outlined in the NICE decision support unit (DSU) technical support document 14.[39] Extrapolations will be chosen based on goodness-of-fit statistics, visual comparison with Kaplan-Meier curves and clinical expert opinion. Scenario analyses will also be explored with alternative plausible extrapolations relating to scenarios with higher and lower survival estimates.

The preferred models in relevant TAs will also be considered; longer follow-up data may be available for trials since their appraisals and so it is not implausible that alternative models would be more appropriate.

Model calibration

The model will be calibrated to ensure that estimates retain face validity. The probabilistic sensitivity analysis will be constrained to prevent ToT, TTP and PFS from crossing. Mortality rates estimated from OS, PFS and TTP will be constrained to be higher than general population mortality in both the deterministic and probabilistic analyses. Age- and sex-specific mortality estimates for the general population will be taken from ONS life tables.

Some of the previous TAs [19-26, 29, 31] in the NSCLC pathway have modified survival estimates to account for treatment effect waning. In previous TAs, scenarios of treatment effect waning considered include treatment effect waning of 2 years after treatment stopping at 2 years [20, 25], treatment effect waning of 1-3 years after treatment stopping at 2 years [19, 22, 23], and a scenario where the company assumed that the waning of treatment effect was captured by choice of survival curves, whilst the committee preferred a treatment effect waning at 3 or 5 years from the start of treatment [31]. The clinical review will search all study publications to include the longest follow-up time available, which in some cases will be longer than the follow-up available in the TAs, enabling the assumptions from previous TAs to be assessed. The flexible survival models fitted to long-term follow-up data together with

suitable extrapolations is expected to suitably capture any waning of treatment effect. Note also that waning is only typically assumed for OS which will only be modelled at the last line of treatment and for BSC. Treatment waning assumptions from previous TA submissions will be explored as scenario analyses if appropriate. Previous submissions will be reviewed for further detail on how these approaches were implemented (e.g, whether it was applied to OS, PFS or both), and whether it was modelled as a sharp or a gradual decline.

Treatment-related costs and adverse events will be based on ToT data which will be capped to reflect commissioning rules (e.g. a maximum two years on immunotherapy treatment) where appropriate.

5.3.6 Subsequent treatment

5.3.6.1 The proportion receiving further active treatment

The proportion of people receiving further treatment after discontinuation will be an input parameter to the model. This parameter will be modelled specific to each intervention at each line of therapy to fully capture treatment benefits (e.g. capture treatments on which greater proportions of people are fit enough to receive further treatment at the end of their course of treatment). If this is not possible, then class-specific rates of further treatment will be estimated, with the classes (e.g. chemotherapy, immunotherapy monotherapy, immunotherapy with chemotherapy) determined in discussion with clinical experts.

Consideration will also be given to whether these vary by subpopulation (histology and PD-L1 status, prevalence of genetic mutation)

The proportion of people who do not receive any further active therapy after discontinuation and go on to receive best supportive care will be estimated from RWE, such as the SACT database (Section 5.2.4.3), if it is possible to retrieve and analyse these data in the timeframes of this project. The database cut-off will be for the last 5 years; this cut-off should include enough data points to make a robust estimation of these parameters, but is recent enough to reflect modern standards of care. Clinical advice reiterates that the proportion of people able to receive further treatment has been relatively stable over the last 5 years, since the introduction of more options at second-line.

If it is not possible to obtain this information from RWE within the project timescales, the proportion of people receiving further subsequent treatment will be estimated from a review of published TAs as an interim measure, with clinical input to assess their generalisability to current practice in the UK NHS. This information will also be extracted in the systematic review, if it is reported. The model can be subsequently updated with assumptions from RWE should this become available, and data from the TAs and the review may be used as a scenario analysis.

5.3.6.2 Market share of subsequent treatments

The mix of subsequent therapies reflective of actual UK practice will be estimated from the SACT database. Treatment options will be specific to each subpopulation (see Table 3for details), e.g. nintedanib is an option for previously treated people with adenocarcinoma histology, which is a subgroup of non-squamous tumours.[28] This parameter will be modelled using an analytical approach similar to estimating the proportion of people who receive further active treatment: if suitable it will be modelled as specific to each intervention, otherwise class-specific rates of further treatment will be estimated. Estimating class-specific market shares may be a more appropriate approach, as subcategorising the population in this manner may lead to small patient numbers in each category.

As new treatments are added to the pathway over time, the "current" market share of subsequent-line treatments will become outdated. Therefore, these parameters should be re-evaluated over time. The market share should also be re-evaluated with the introduction of a new technology.

5.3.7 Adverse events

The impact of treatment-related toxicity on both costs (Section 5.3.9) and health-related quality of life (Section 5.3.8) will be included within the economic analysis. The patients at risk of adverse events (AEs) will be modelled based on time-on-treatment data.

All incidence data for adverse events will be obtained from the systematic review described in Section 4. The inclusion criterion for AEs in the economic model is Grade 3+ treatment-related AEs with an incidence of ≥ 5% in any trial arm. Rare AEs (i.e., incidence less than 5%) such as febrile neutropenia which have a significant impact on HRQoL and costs will also be considered. Clinical experts will advise whether there are any other AEs at lower grades with a high impact on patient quality of life and NHS resources, such as those that have a cumulative impact over time. The patients at risk of AEs will be modelled based on time-on-treatment data.

5.3.8 Quality of life

Health-related quality of life (HRQoL) in the model is represented by utility values, which is measured on a 0 to 1 scale where 0 is equal to death and 1 is equivalent to perfect health.

5.3.8.1 Approaches to analysis

Progression and time-to-death (TtD) based approaches are commonly used to model health state utility estimates in the NSCLC decision space. The progression-based approach models utility by health states, i.e., progression-free state (PFS) and progressed state (PD), with the implication that progression status is the key driver of quality of life. The TtD approach estimates utility by the time intervals prior to the person's death. A combination-based approach takes into account both progression-related disutility and end-of-life disutility.

Of 14 existing TAs identified across 1st and 2nd lines of therapies in advanced NSCLC, companies used the progression-based approach in 7 TAs, the TtD approach in 4 TAs, and the combination approach in 3 TAs (Table 7). The committees agreed with most TAs regarding the approach to utility estimates except for TA724 where the committee preferred progression-based approach to TtD approach given the substantial data captured after progression.[47] The committee was also inclined to consider both progression-based approach and TtD approach for TA781 due to the uncertainties and plausibility around both approaches.[31]

Given that the proposed model structure for this project is a nested partitioned survival model where patient flow is based on the progression status, the progression-based approach is considered to be the most appropriate for decision making for the pathway model. One limitation of the progression-based approach is the potential utility overestimation in the post-progression state. The utility data for post-progression is typically measured shortly after progression, therefore not capturing the deterioration in HRQoL as patients move towards death. Trial-based post-progression utilities are also implicitly reflective of the distribution of subsequent treatments given in said trial, and do not disentangle impacts due to different types of subsequent management. This will be mitigated by using the pre-progression utility values while patients remain in the pre-progression health state for each line of therapy, and when they progress, either using the pre-progression utility value for the next line of therapy that they move to or the utility value estimated for BSC.

To summarise the application of HRQoL in this proposed economic model, a single progression-based utility value will be applied to all treatments within each decision node, accounting for the difference in HRQoL with respect to patient characteristics, where possible and if appropriate. Any differences between treatments will be captured by applying treatment-related AE disutilities.

5.3.8.2 Estimation of health state utility values

Health state utility values will be attained from previous TAs and any in-confidence data shared by companies. The utilities in the relevant NICE submissions are mostly collected from clinical trials and are measured by the EQ-5D-5L questionnaire, which is consistent with methods outlined in 'NICE health technology evaluations: the manual'.[17]

A summary of publicly available utility values and approaches to utility estimates in the in-scope TAs is presented in Table 7. There is some variation in utility values across different lines of therapies. For example, mobocertinib at second line has a higher utility than publicly reported values for first line. This difference is likely due to treatment regimen and patient characteristics, such as genetic mutations in the clinical trials. In general, HRQoL tends to decrease over time as disease progresses.

To ensure logical consistency in utility values throughout the pathway, the most appropriate utility estimate in the first line and subsequent lines of treatment will be decided dependent

on information identified through this project. Scenario analyses will be also carried out using alternative utility values from previous TAs to explore the uncertainty around quality of life. In TA520,[27] the company applied the utility value from Chouaid (2013)[61] in a scenario analysis; this paper reported utilities according to the line of treatment and progression status, and will be explored as a potential alternative source of utility values if appropriate.

Utilities will not only be assessed for each line of therapy but also be evaluated for each decision node. Feedback from clinical advisers indicates that people with some genetic mutations or tumours with non-squamous histology are more likely to be associated with characteristics, such as smoking status, comorbidities and age, which have an impact on quality of life. HER2, ROS and EGFR mutations are usually identified in younger patients who are non-smokers. Their HRQoL is typically higher than those patients with KRAS mutations who are generally less fit and may not be eligible for targeted therapy. It also implies that patients with squamous NSCLC are more likely to be smokers and have more comorbidities as opposed to patients with non-squamous NSCLC. Thus, people with squamous tumours may have a lower HRQoL than people with non-squamous tumours at the same line of therapy. HRQoL associated with these patient characteristics will be considered in the economic evaluation.

Age-related utility estimates will also be included in the economic model to account for declining utility with age. The utility score for all patients will be adjusted over time using an annual utility decrement, using approaches accepted in previous TAs. For example, in TA520,[27] the EAG applied age-related decrements using the value from Kind et al (1999)[62] (i.e., 0.02 at age 65 years and 0.07 at age 74 years) to reflect the decline in HRQoL as patients get older.

5.3.8.3 Estimating HRQoL for people on BSC

The proposed economic model assumes that all patients who receive BSC will have no further treatment and will have similar outcomes, including HRQoL, regardless of the line of treatment after which they discontinued or the number of previous lines of therapy. This assumption has been supported and validated by clinical advisors.

None of the TAs in scope estimate utility values specifically for BSC, as this is not a relevant comparator in the analyses. Early TAs and TAs for treatments at later lines in the pathway were initially considered for relevance, as it was thought plausible that people who discontinued treatment at progression would have few treatment options available, and so the post-progression utility could be a proxy value for BSC.

Docetaxel with or without nintedanib (TA347) is one of the earlier appraisals for previously treated advanced NSCLC and the post-progression utility value was assessed for relevance to the BSC arm.[28] The utility value estimated for post-progression health state in this appraisal was 0.64; this was considered to be an overestimation within the appraisal itself because it was measured early in the course of the progressed-disease health state, and is

likely to be further overestimated for the purposes of this pathway model. Its eligible population incorporating people with stage IIIB/IV recurrent NSCLC is healthier than the population (i.e., stage IV) in our economic analysis, and may not adequately represent BSC because a proportion of people in the nintedanib trial, from which the utility values were estimated, continued to receive active therapy after discontinuation.

Over the course of the project, approaches to estimating the utility of people on BSC will be explored. This will include evaluating other TAs with relevance to advanced NSCLC that are not in scope (e.g., TA644 and TA630),[63, 64] and adjusting utility values from other TAs, using the multiplicative method outlined in the DSU12 guidance,[65] assuming a constant proportional decrement relative to the baseline, i.e. the percentage reduction in utility from moving from PFS to PD can be estimated from a set of relevant utility values, and applied to the utility for the previous line of therapy. Alternatively, using utility values from the literature that were identified in previous TAs, such as the post-progression utility value from Chouaid et al (2013), will be implemented.[61]

5.3.8.4 HRQoL impact on adverse events

A range of approaches to including the impact of AEs on HRQoL have been taken in previous TAs. Those that do not include it assume that disutility has already been captured through the trial-derived utilities, thus disutility should be excluded to avoid double counting. Those that include it assume that an additional disutility should be incorporated, as average trial-derived utilities underestimate disutilities associated with AEs.

In the economic model, to account for the impact of treatment-related AEs on HRQoL, treatment-specific AE rates will be applied to patients while on treatment (Section 0), and a disutility decrement will be applied. For completeness, a scenario analysis where no AE disutilities applied will be explored in accordance with the first assumption. These disutility values for each type of event will be derived from previous TA submissions. Disutilities associated with the method of administration (intravenous vs oral) will be also considered subject to clinical expert advice and availability of evidence. Quality of life losses due to AEs will be either be captured as a one-off decrement based on the total incidence of AEs for each treatment or estimated over time, depending on how these data are reported and synthesised in the clinical review (Section 4), and the corresponding utility decrements applied.

Table 7 Utility and approaches used in previous technology appraisals

TA	Year	Line	Intervention	Source of utilities	Base case approach	Progression- based utility values (either base case or scenarios)	Methods of treatment-related disutility
TA584[20]	2019	1L	Atezolizumab plus bevacizumab, carboplatin and paclitaxel	Impower150	Time to death	PF: 0.71; PD: 0.69	The committee agreed that the company's revised analyses which included a disutility for treatment-related adverse events that were grade 3 or higher in Impower150 were appropriate for decision making.
TA705[22]	2021	1L	Atezolizumab	Impower110	Progression	Redacted	No disutility from AEs in base-case analysis to avoid double-counting; disutility associated with AEs was assumed to have been captured in the EQ-5D responses in Impower110.
[a]TA724[47]	2021	1L	Nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy	CheckMate-9LA	Time to death	Redacted	Any grade 3 or 4 AEs with ≥ 5% incidence in either treatment arm. Decrements were applied in the model as a one-off decrement based on the incidence of AEs per treatment and corresponding utility decrement. However, the full AE impact on HRQoL was not captured, due to the exclusion of immune-related adverse events and adverse events relating to second-line therapy.
TA531 [21]	2018	1L	Pembrolizumab	KEYNOTE-024	Time to death	PF: 0.778; PD: 0.668	Utility decrements because of grade 3+ AEs were applied during the first cycle in the company model based on AE incidence rates and the

TA	Year	Line	Intervention	Source of utilities	Base case approach	Progression- based utility values (either base case or scenarios)	Methods of treatment-related disutility
							corresponding mean duration across them.
TA683[19]	2021	1L	Pembrolizumab with pemetrexed and platinum chemotherapy	KEYNOTE-189	Combination of time to death and progression	Not available	Time-to-death method with a quality-of-life decrement associated with PD were applied for patients who had progressed as it utilised more health states, potentially offers a better fit to patient data and also took into consideration the progression within each state.
TA770[23]	2022	1L	Pembrolizumab with carboplatin and paclitaxel	PFS based on KEYNOTE-407 and the post-progression was based on TOPICAL with adjustment for the number of people having second-line treatment	Progression	PF: redacted PD: Pem combination therapy: 0.61 SoC: 0.62	QALY losses associated with grade 3-5 AEs were applied to each treatment group in the model; each estimate is applied as a once-only health decrement during the first model cycle.
TA428[24]	2017	2L	Pembrolizumab	KEYNOTE-010	Combination of time to death and progression	[b]PF: 0.753; PD: 0.664	Model included grade 3+ AEs and any grade AEs occurred in at least 5% of patients in either treatment arm. Assumed that AE-related utility decrements have been captured in the EQ-5D score from the trial, no further utility decrements were applied to the model, but considered in the scenario.

TA	Year	Line	Intervention	Source of utilities	Base case approach	Progression- based utility values (either base case or scenarios)	Methods of treatment-related disutility
TA713 [25]	2021	2L	Nivolumab	CheckMate 057	Progression	PF: 0.713; PD: 0.569	AEs of grade 3 or 4 severity, which occurred in ≥ 2% of patients in the trial. In addition to the AE disutility applied in the first cycle, the company applied the disutility of each AE separately.
TA855 [29]	2023	2L	Mobocertinib	EXCLAIM from study AP32788-15-101	Progression	PF: 0.807; PD: 0.763	The utility decrement for ongoing grade ≥3 TEAEs (treatment-emergent adverse events) was combined with AE rates from the relevant studies for each comparator and the mean durations of each grade ≥3 TEAE.
TA781 [31]	2022	2L	Sotorasib	CodeBreaK100	Time to death	PF: 0.734; PD: 0.670	Grade 3+ treatment-related AEs with an incidence of ≥ 5% in any of the comparator arms were included in the model. Treatment- emergent adverse events are presented in a scenario analysis.
TA760 [30]	2022	2L	Selpercatinib	TA484	Proxy data from previous TAs based on progression status	PF: 0.713; PD: 0.628	The impact of AEs on HRQoL was captured as a one-off QALY loss in the first cycle of the model. The durations and disutilities applied to each AE episode were the same for all treatments.

TA	Year	Line	Intervention	Source of utilities	Base case approach	Progression- based utility values (either base case or scenarios)	Methods of treatment-related disutility
TA347[28]	2015	2L/3L	Nintedanib in combination with docetaxel	LUME-Lung 1 trial	Progression	PF: Week 0: 0.710 Week 3: 0.721 Week 6: 0.707 Week 9: 0.699 Week 12: 0.692 Week 15: 0.687 Week 18: 0.682 Week 21: 0.677 Week 24: 0.671 Week 27: 0.666 Week 30: 0.661 PD: 0.638	Utility decrement associated with each AE was applied for a period of one model cycle. The company acknowledged that the model may have double counted disutility as people may have more than one adverse events.
TA520[27]	2018	2L	Atezolizumab	OAK trial	Combination of time to death and progression	Not available	The quality-of-life decrement of all grade 3-5 AEs, which occurred in ≥2% of patients in either treatment arm of the OAK trial was included in the economic model.

TA	Year	Line	Intervention	Source of utilities	Base case approach	Progression- based utility values (either base case or scenarios)	Methods of treatment-related disutility
TA655[26]	2020	2L	Nivolumab	CheckMate 017 trial	Progression	PF: 0.693; PD: 0.509	Grade 3+ AEs which occurred in ≥5% of patients in the CheckMate 017 trial. The expected disutility per patient associated with the incidence of the included AEs was applied in the first cycle.

[a] HRQoL data relating to TA724 is included here given its relevance to the pathway model, although this treatment is not recommended and is out of scope.

[b] Pooled utility values for pembrolizumab 2mg and docetaxel

5.3.9 Cost and healthcare resource use

Throughout the treatment pathway, relevant costs to the NHS and personal social services (PSS) will be included. It is anticipated that the key costs in the pathway will include:

- Treatment-related costs, including drug acquisition costs, administration, and treatment-related monitoring;
- Disease management costs assigned to each model health state;
- Costs associated with diagnostic tests;
- Management of adverse events.

The costs described in this section are not exhaustive and there may be additional miscellaneous costs associated with the patient's pathway which may be identified as the model is developed.

All input costs will be inflated to 2023/2024 prices using the NHS cost inflation index and the PSS pay and prices index. All future costs in the model will be discounted at 3.5% per annum as per the NICE health technology evaluations manual.[17]

5.3.9.1 Treatment costs

Drug costs

Several drugs in the pathway have confidential price agreements, also known as patient access schemes (PAS), associated with them. Where these are included in analyses, they will be treated as confidential (CON) information throughout the model, and results using PAS prices will be marked as confidential information, and where appropriate as comparator PAS (cPAS) status, in all analysis reports. Use of all confidential price data will be fully compliant with our confidential data protocols (Section 0). List prices for these drugs will be obtained from the BNF.

For generic treatments where there is no PAS, drug acquisition costs will be sourced using the drugs and pharmaceutical electronic market information tool (eMIT).[66] For treatments where biosimilar formulations are available e.g. bevacizumab, the cost of biosimilar formulations will also be considered if used in the NHS.

Table 8 outlines the drugs used throughout the pathway, and the available data from TAs on relative dose intensity (RDI) and mode of administration. Staff administration costs will be sourced from the personal social services research unit (PSSRU) unit costs for health and social care and healthcare resource group unit costs from national cost collection for the NHS.[67, 68] Unit costs for each treatment are not described in this analysis plan owing to the large amount of confidential information.

The model will include costs for best supportive care at the end of the pathway. The contents of the BSC health state and its associated costs will be developed using input from clinical experts.

Treatment costs (treatment acquisition costs, administration costs, and treatment-specific monitoring costs) will be applied to patients in the subject to their time on treatment (Section 0).

Treatment doses

To calculate the costs of a course of treatment, treatment doses and dosing schedules for comparators will be obtained from previous TAs and the BNF, and confirmed with clinical advice where appropriate, e.g., for platinum chemotherapy. Where treatments have dosing based on weight or body surface area average patient characteristics will be taken at each line of therapy from SACT data (Section 5.2.4.3).

Relative dose intensity

The RDI reflects the actual total dose given over the course of treatment, relative to the reference standard dose intensity, and captures patients who experience dose interruptions or missed doses, or dose reductions. The model will apply RDI to comparators from the clinical trials, taking clinical advice on where this is appropriate. This will be informed by data reported in previous TAs, and where this data is unavailable, RDI data will be obtained from relevant literature. The model's base case will include treatment costs adjusted for RDI, where appropriate, and a scenario analysis will be run where all RDIs are set to 100%.

There may be some instances where it is not appropriate to apply RDI as it will not impact on the treatment cost and drug wastage will occur: e.g. in TA347,[28] the EAG noted that nintedanib tablets are dispensed to patients at the time of docetaxel administration in blister packs sufficient to self-treat until the date of the next docetaxel dose, and any missed doses are unlikely to alter the dispensing pattern, and thus missed doses will not alter the amount and cost of product dispensed. The decision to apply RDI will be assessed for individual treatments in the model.

Previously, EAGs have suggested it to be reasonable to apply an average relative dose intensity across comparators (TA781).[31] Where RDI data is unavailable for a specific treatment the average RDI of all drugs used at that treatment node will be applied in the base case.

Table 8 outlines the availability of RDI data.

Table 8 Drugs in the treatment pathway and availability of resource use data

Treatments	TAs*	Pathway nodes	Relative dose intensity	Mode of administration
Routine commissioning				
Mobocertinib	TA885[29]	GAP-G2	Adjusted for in TA885	Oral
Nivolumab	TA655, TA713[25, 26]	ST1	Assumed to be the same as atezolizumab in TA885	Oral
Pembrolizumab	TA683, TA531, TA428[19, 21, 24]	NS1, NS2, S1, S2, ST1	Assumed to be the same as atezolizumab in TA885	Intravenous infusion

Treatments	TAs*	Pathway nodes	Relative dose intensity	Mode of administration
Atezolizumab	TA584, TA705, TA520[20, 22, 27]	NS1, NS2, S2, ST1	Available in TA520	Intravenous infusion
Nintedanib	TA347[28]	ST1, ST2	Available in TA347 and TA781	Oral
Cancer drugs fund				
Selpercatinib	TA760[30]	GAP-H2	Not reported	Oral
Sotorasib	TA781[31]	GAP-12	Available in TA781	Oral
Generic				
Pemetrexed	TA181, TA190[60, 69]	NS1, NS2,	Seek from published literature	Intravenous infusion
Docetaxel	N/A	ST1, ST2	Available in TA347 and TA781	Intravenous infusion
Platinum chemotherapy (cisplatin, carboplatin)	N/A	NS1, NS2, S1, S2, ST1	Seek from literature	Intravenous infusion
Bevacizumab	N/A	NS1	Seek from published literature	Intravenous infusion
Paclitaxel	N/A	NS1	Seek from published literature	Intravenous infusion
Other				
Best supportive care	N/A	ST3	Published literature and clinical expert advice	N/A

**Not all of these TAs are listed in the scope and will not be routinely looked at throughout the project, but may be used to source cost data*

Drug administration costs

Drug administration costs will be applied where appropriate for each treatment administration in the model. It is anticipated that all treatments in the pathway will be administered via IV or orally (Table 8). A single cost will be applied to every oral administration and intravenous infusion administration costs will be applied based on the complexity of the infusion. Infusion administration complexity will be informed by previous TAs and the clinical opinion of expert advisers.

The number of drug administrations will depend on the dosing schedules of each therapy regimen. For combination therapies, administration costs will be added each time a drug is administered. For example, if the administration of two intravenous drugs occurs on the same day, it will be assumed that they will be administered simultaneously and a single IV administration cost will be applied.

Additional monitoring costs during and after treatment may be applied if they are not sufficiently accounted for by health state costs. This will be added on a case-by-case basis depending on the characteristics of the health state cost estimates applied at each node.

5.3.9.2 Health state costs

In addition to treatment costs, a cost will be assigned for being in each health state. These will account for costs attributable to all patients at each stage of the pathway modelled,

regardless of treatment regimen. Health state costs will typically include GP visits, inpatient and outpatient hospital visits, biochemistry tests and CT scans. Health state costs will be applied to each patient based on time spent in each health state until they transition to a different state.

In the final 'partitioned survival model' section of the pathway model when patients are on best supportive care, there will be a mean per-cycle cost assigned to people while they remain alive (Table 9). An end-of-life cost will be applied to people in this health state as they transition to the death health state, corresponding to terminal (palliative) care.
In the proceeding decision nodes, a health state cost will be assigned while they are in the 'pre-progression' health state. It will be assumed that if a patient discontinues treatment before progression, they will remain in the pre-progression health state and incur the associated costs until they transition to the next health state.

In addition to the end-of-life costs incurred at the end of the pathway, there will be a separate cost estimate assigned to those patients who are modelled to have a death earlier in the disease pathway. It is anticipated that these patients may die from adverse events or other comorbidities whereby the resource utilisation profile may not be consistent with that of a patient undergoing palliative care.

Health state costs will be obtained from previous NICE TAs of treatments in scope of this project and of relevance to advanced NSCLC (Table 9). When reviewing these health state costs, priority will be given to those which are deemed to best reflect the current UK standard of care. One challenge in modelling these health states is that data from older TAs may not be as relevant as they were during their appraisal due to changes in treatment pathways and changes in UK clinical practice. The date of the cost studies, methodology, and applicability to patients being modelled will all be considered when choosing health state costs for the base case analyses. Furthermore, cost data which uses RWE or registry data are likely to be preferred to those from clinical trials which may not reflect UK clinical practice. Clinical experts will be consulted to ensure the health state costs applied are an accurate reflection of a patient at each stage in the NSCLC pathway.

A pre-progression health state cost for each line of therapy will be selected from previous TAs. Health state costs will be selected so that they have a logical consistency across the pathway, i.e. ensuring that management costs are not lower in subsequent nodes if they should be managed more intensely. Clinical advice suggests that management (outside of managing AEs) is relatively consistent across the pathway, so a scenario will explore a single pre-progression HS cost for all decision nodes.

As part of the evaluation of RWE, healthcare utilisation may be explored (Section 5.2.4.3). If the timelines permit, these data will be analysed and incorporated into the pathways model. Otherwise, this may be incorporated into future phases of this pilot project.

Table 9 Modelled health state costs

Health state	TA sources available	Available costs (uninflated)
NS1 pre-progression	TA584, TA190[20, 69]	TA584 (company) - £61.8 per week (PFS) TA584 (EAG) - £65.53 per week TA190 – Not reported
NS2 pre-progression	TA531, TA705, TA162[21, 22, 70]	TA531- Not reported TA705-£65.71 per week (PFS) TA162-£327 per month (PFS)
S1 pre-progression	TA600, TA770[23, 59]	TA600-£89.53 per week (PFS) TA770 – Not reported
S2 pre-progression	TA531, TA705, TA162 [21, 22, 70]	TA531-£76.75 per week (PFS) TA705-£65.71 per week (PFS) TA162-£327 per month (PFS)
ST1 pre-progression	TA310 [71]	TA310-£220 per month (PFS)
ST2 pre-progression	TA347 [28]	TA347-Unit costs used
BSC pre-progression	TA644, TA630 [63, 64]	TA664-Unit costs used TA630-Redacted
BSC post-progression	TA644, TA630 [63, 64]	TA664-Unit costs used TA630-Redacted
Terminal care costs (end of pathway)	TA724, TA705, TA584, TA531 [20-22, 47]	TA724-£5,377.51 TA705-£4,598.01 TA 584-£4,456.13 TA531- £4,512.04
Health events		
Death in pre-progression health state	Source from available literature	N/A

5.3.9.3 Diagnostic costs

The diagnostic costs for genetic mutations that are not currently routinely tested for, and for which there are targeted treatments in scope, will be included in the model so that they can be included in TAs relating to these comparators. At present, there are three targeted treatments in scope, targeting EGFR exon 20 insertions, RET fusions, and KRAS G12C mutations, and new targeted treatments are anticipated in the future.

Testing costs for a particular mutation will only be applied in analyses of treatments that target that mutation, where it constitutes a change in practice, e.g. if there already exists a treatment with routine recommendation for a targeted mutation, the next one that in that decision space being appraised would not need testing costs associated with it. Testing costs that are already part of standard testing will not be included in the model.

The cost of diagnostic tests will be sourced where possible from published TAs. Previously,[29-31] the company has made the argument that the cost of diagnostic tests for genetic mutations are already part of routine practice within the NHS and no additional costs were needed. However, committee preference in the appraisal of mobocertinib (for EGFR exon 20 insertions) and selpercatinib (for RET fusions) was to include the marginal cost of identifying the mutations. This is either because the gold standard test for the mutations,

next generation sequencing (NGS), has variable availability across the UK at present and would need to be adapted to include the new targets, and other tests are more commonly used (e.g. polymerase chain reaction (PCR) for EGFR exon 20 insertions, or fluorescent in situ hybridation (FISH) tests for RET fusions). Selpercatinib is currently used within the CDF, and clinical advice will be sought regarding current practice for identifying RET fusions in order to support future appraisals.

The incidence of the mutation will be taken into account when estimating the total testing cost per person, which is used to estimate the number needed to treat (NNT) to identify one person with the mutation.

Testing costs will be considered for eligible patients as per the national genomic test directory for cancer.[72] For people with NSCLC, the directory states that generally only non-squamous NSCLC should be routinely analysed for the full gene panel, although there may be scenarios where clinicians wish to test other subtypes of NSCLC, such as squamous NSCLC at later stages of the pathway. Testing costs would be incurred at the start of the pathway, according to advice received at the scoping workshop. The analysis will assume that no further mutations are developed over the course of the pathway.

In this model, where health state costs are said to include diagnostic tests, care will be taken to remove tests for genetic mutations to avoid double counting in the pathway.

Table 10 outlines the cost sources of treatment altering mutations from previous TAs. No evidence gaps were found, however if on further scrutiny of the redacted costs the sources are deemed inappropriate for the model, costs may be instead sourced from the general literature.

Table 10 Sources for the cost of genetic testing in previous TAs

Mutation	TAs included	Cost assumptions
EGFR exon 20 mutations	TA855[29]	£34 marginal cost, £550 total cost per person
RET fusion	TA760 [30]	Cost provided by NHS England, not reported
KRAS G12C	TA781 [31]	No additional costs for KRAS testing

5.3.9.4 Costs of AEs

The costs of adverse events will be included as they occur throughout the pathway. Grade 3 and grade 4 adverse events will be considered. Data on the occurrence of adverse events will be collected in the systematic literature reviews of clinical studies (Section 4).

Where relevant, unit costs for treating these adverse events in the UK will be sought from those used in previous TAs. Costs will be applied based on the modelled likelihood of a patient experiencing each AE on each treatment in the NSCLC pathway.

5.4 Model outputs and analysis

The base-case analysis will be run using both confidential drug prices and list prices so that the model results can be reported without confidential information for validation purposes.

Total lifetime discounted costs and QALYs will be provided for each intervention within the selected decision node. A breakdown of costs and QALYs by health state and line of treatment will also be provided, to aid validation of the analysis and provide additional context regarding the drivers of the model.

The cost effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per life year gained (LYG), net monetary benefit and net health benefit.

The pathway model will include the functionality to report a fully incremental analysis of all treatments at each decision node, and pairwise comparisons of any two selected (appropriate) treatments.

5.4.1 Uncertainty

5.4.1.1 Probabilistic analyses

The pathway model will generate both probabilistic and deterministic results for the base case analyses, which allows for decision making to be made on the basis of a probabilistic analysis in line with the NICE methods manual.[17]

The probabilistic analysis will be estimated from expected costs and QALYs from a number of stochastic iterations of the model, with the number of iterations selected to ensure that model results are stable. The probabilistic analysis quantifies uncertainty in the true values of input parameters and indicate the probability of a comparator being cost-effective relative to other comparators within that decision node. Probability distributions will be specified for all relevant input variables (with the exception of some inputs, e.g., drug acquisition costs). For synthesised outcomes incorporated in the model e.g. PFS (Section 4.5), the CODA sample from the posterior distribution will be used to model uncertainty in these parameters, as it will capture correlations between survival model coefficients. The type of distribution will be chosen with reference to the properties of data of that type (for example, beta distributions for probabilities that are bounded between 0 and 1, and gamma distributions for cost parameters that cannot be negative). Where correlations between certain inputs are not explicitly captured, the model structure will ensure that sensible relationships between parameters are created when the inputs are generated stochastically, e.g. pre-progression and post-progression utilities, TTP and PFS (as per Section 0).

5.4.1.2 Sensitivity analyses

Additional scenario and one-way sensitivity analyses will be conducted where they add value and clarity in decision making. These may be suggested by the committee or relevant

stakeholders during the engagement period of this analysis plan. These analyses will be based on the deterministic results of the model.

Exploration of uncertainty may involve undertaking the following:

- Scenario analyses, where 1 or more parameters are varied by changing assumptions, e.g., adopting a different study as a source of parameters; including or excluding certain costs; etc.
- Structural sensitivity analyses, where the model is configured to include or omit certain events, states, comparators or modes of estimation.

5.4.2 Severity modifiers

The NICE methods manual states that the committee will consider the severity of a condition when making decisions about recommendations, defined as "the future health lost by people living with the condition with standard care in the NHS".[17] QALYs are weighted as to whether criteria are met regarding the severity of condition, as measured by the associated absolute and proportional QALY shortfall (Table 11).

Table 11 QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Estimating the expected quality-adjusted life expectancy (QALE) for the general population has established methods and precedent in the broader NSCLC decision space (TA898).[73] In this appraisal of dabrafenib with trametinib for advanced BRAF V600 mutation-positive NSCLC, the company undertook a QALY shortfall analysis by calculating the expected quality-adjusted life expectancy (QALE) for the general population, in line with methods described by Schneider et al. (2022). Life expectancy for the modelled population was calculated using ONS population mortality data from 2018-2020, and was quality-adjusted using UK population norm values as reported by Hernández Alava et al.[74] (2022). The total QALYs for the general population was 9.871. The QALE will be estimated for each decision node, using the mean age at the start of treatment estimated from RWE (or trial data, if RWE not available within the timeframes of this project).

The reference treatment to which future treatments entering the pathway (or CDF re-appraisals) are compared is unclear in a multi-comparator decision space. As set out in the first pathways pilot for RCC,[75] there are three options:

- Define a common reference treatment to calculate severity modifiers for all other treatments compared to this;
- Estimate a "blended comparator", based on the market share of all the comparators;
- Calculate severity modifiers separately for pairwise comparisons.

Ultimately, the interpretation of the methods to apply severity modifiers in a multi-comparator space and the decision regarding the most appropriate comparator treatment will lie with the committee. The model will estimate the total discounted QALYs for each comparator, to enable QALY shortfall calculations to be made for a range of suitable reference treatment options.

To inform the committee regarding the most suitable reference treatment for each decision node, RWE will be sought on the number of people receiving each type of treatment to indicate which is most frequently used and representative of standard care. Clinical advice will also be sought on the most commonly used comparators in UK clinical practice within each decision node.

5.4.3 Validation

5.4.3.1 Technical validation

Within the CfG Economics team, a process of internal technical validation will be embedded into the model development process. This includes the overseeing of the model development work carried out by analysts (Health Economists), by senior health economists (Health Economic Advisers) who will also carry out a complete technical QA of the model upon completion. Within this particular project, a second Health Economic Adviser and a Senior Health Economic Adviser will also be involved with the technical validation of areas of model development which were overseen by the primary Health Economic Adviser.

Established methods for technical validation of the model will be undertaken, to assess inputs, identify logical, mathematical and computational errors, and review the plausibility of outputs. Principles laid out in the CfG's methods manual for model validation will be followed, as they are suitably rigorous for the purposes of this project.[17] The nature of the technical QA, whilst model specific, will be considered in terms of the appropriate reference case (i.e. the methods NICE considers most appropriate for estimating cost-effectiveness) and be based on a suitable methodology checklist.[76]

Conventions on reporting economic evaluations will be followed (Husereau et al. 2022) [77] to ensure that reporting of methods and results is transparent.

5.4.3.2 External validation

Creating a model capable of looking at the entire treatment pathway adds additional challenges in validation and ensuring the plausibility of predictions of OS. Nonetheless, it is essential that the decision model provides credible results and that these can be transparently verified to create confidence in the model and support its future use. There are a number of options to validate the outcomes predicted by the pathway model:

- Comparing the economic (cost and QALY) results and predicted survival outcomes with previous NICE TAs;
- Comparing the clinical (survival) results with trial data or RWE

These approaches are expected to produce divergent results to the pathways model. The clinical review is expected to return more mature data than the data used in previous TAs, and this data may lead to a different choice of extrapolation which in turn would affect incremental costs and QALYs. Previous TAs have not been based on a pathways model and so subsequent treatments have been modelled using simplified assumptions; it is expected that the detailed modelling of these nodes in the pathways structure may yield different estimates of costs and QALYs. The same argument would apply to any non-pathways model developed for a single decision node, even if it used updated effectiveness data.

As both these approaches are expected to give different estimates of costs and QALYs to pathways model there is a question over the utility in using them for validation of results, as it would be unclear whether differences in results were due to model discrepancies or inherent structural differences in approach.

If possible, model estimates will be compared against OS estimates from SACT data; however, known differences between trial and real-world outcomes may also lead to a divergence of results.

Alternative approaches to validation will also be considered. Model outputs will be compared to the data used as model inputs (for example, visual comparison of survival curve extrapolations to Kaplan Meier data) to ensure the appropriateness of model structure and data derivation. Survival estimates at specific time points will be reviewed by clinical experts when choosing extrapolations.

The decision regarding the approach to external validation of model results will lie with the NICE TA team.

6 Handling information from the companies

Any confidential data 'CON' will be highlighted in blue and underlined. Any data related to company confidential pricing such as patient access schemes 'PAS' will be highlighted in green and underlined and labelled cPAS.

7 Competing interests of authors

Catalina Lopez Manzano has received payment through Clifton Insight from Merck for work in the past 12 months related to Pembrolizumab but in a different indication (colorectal cancer). None of the other authors have any competing interests to declare.

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9 Appendices

9.1 Search strategy

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to July 06, 2023
Date of search: 10 July 2023

#	Search terms	Results
1	*Carcinoma, Non-Small-Cell Lung/	64312
2	((lung* or pulmonar*) adj3 (cancer* or neoplasm* or tumour* or tumor* or carcinom* or malignan*)).ti,ab,kw,kf.	275395
3	(((nonsmall or non-small) adj2 cell*) or NSCLC).ti,ab,kw,kf.	92983
4	1 or 2 or 3 [terms for condition]	281456
5	(atezolizumab* or tecentriq* or tecntriq* or MPDL3280A* or "MPDL 3280A*" or "MPDL-3280A*" or RG7446 or "RG 7446" or "RG-7446" or 52CMI0WC3Y or "1380723-44-3").af.	3063
6	(nintedanib* or cynediv* or intedanib* or ofev* or knin* or vargatef* or "BIBF 1120" or "BIBF-1120" or BIBF1120 or G6HRD2P839 or "656247-17-5").af.	1843
7	(nivolumab* or opdivo* or opdualag* or "BMS 936558" or "BMS-936558" or BMS936558 or "cmab 819" or "cmab-819" or cmab819 or "GTPL 7335" or "GTPL-7335" or GTPL7335 or "MDX 1106" or "MDX-1106" or MDX1106 or "ONO 4538" or "ONO-4538" or ONO4538 or 31YO63LBSN or "946414-94-4").af.	9623
8	(mobocertinib* or exkivity* or "AP 32788" or "AP-32788" or AP32788 or "TAK 788" or "TAK-788" or TAK788 or "WHO 11183" or "WHO-11183" or WHO11183 or 39HBQ4A67L or "1847461-43-1").af.	66
9	(pembrolizumab* or keytruda* or lambrolizumab* or "Merck 3475" or "MK 3475" or "MK-3475" or "MK3475" or "Sch 900475" or Sch900475 or "SCH-900475" or DPT0O3T46P or "1374853-91-4").af.	8960
10	(selpercatinib* or retevmo* or retsevmo* or "LOXO 292" or "LOXO-292" or LOXO292 or "LY 3527723" or "LY-3527723" or LY3527723 or "WHO 10967" or "WHO-10967" or WHO10967 or CEGM9YBNGD or "2152628-33-4").af.	223
11	(sotorasib* or lumakras* or lumykras* or "AMG 510" or "AMG-510" or AMG510 or 2B2VM6UC8G or "2252403-56-6").af.	269
12	or/5-11 [interventions in scope]	19496
13	randomized controlled trial.pt.	596076
14	controlled clinical trial.pt.	95362
15	random*.ti,ab,kw,kf.	1434678
16	placebo.ab.	239739
17	clinical trials as topic.sh.	201068
18	(trial or trail).ti,ab,kw,kf.	788177
19	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	391938
20	((open label or open-label) adj5 (study or studies or trial* or extension*)).ti,ab,hw,kf.	45609
21	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	12167
22	or/13-21 [terms to identify randomised studies: Cochrane HSSS, Cooper P3, and terms for OLE]	2448949
23	4 and 12 and 22	1401
24	("KEYNOTE-189" or NCT02578680).ab,al,kw,kf,rn,ti,cm. [NS1 NS2 TA683]	42

#	Search terms	Results
25	(IMpower150 or NCT02366143).ab,al,kw,kf,rn,ti,cm. [NS1 TA584]	39
26	("KEYNOTE-024" or NCT02142738).ab,al,kw,kf,rn,ti,cm. [NS2 S1 TA531]	63
27	(NCT02409342 or IMpower110 or NCT02031458 or NCT01846416).ab,al,kw,kf,rn,ti,cm. [NS2 S2 TA705, for the last two NCT, it was not possible to search on study name (BIRCH and FIR) as the terms were too sensitive]	13
28	("KEYNOTE-407" or NCT02775435 or "KEYNOTE-799 or NCT03631784").ab,al,kw,kf,rn,ti,cm. [S1 TA770]	25
29	("KEYNOTE-010" or NCT01905657 or "KEYNOTE-001" or NCT01295827).ab,al,kw,kf,rn,ti,cm. [TA428 ST1]	75
30	("CheckMate-057" or NCT01673867 or "CheckMate-057" or NCT01642004).ab,al,kw,kf,rn,ti,cm. [TA 713 ST1]	29
31	(LUME-Lung 1 or NCT00805194 or LUME-Lung 2 or NCT00806819).ab,al,kw,kf,rn,ti,cm. [TA347 ST2 GAP-G2 GAP-I2]	18
32	("AP32788-15-101" or NCT02716116 or NCT03807778).ab,al,kw,kf,rn,ti,cm. [GAP-G2 T855]	10
33	(CodeBreaK100 or NCT03600883).ab,al,kw,kf,rn,ti,cm. [TA781 GAP-I2]	9
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	286
35	23 or 34	1503