NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Scoping workshop supporting documentation

Key changes made after scoping workshop

1. Key terminology changes
2. Update of pathway after scoping workshop
3. Updates to treatments in the various decision points in the new pathway
4. Specification of decision points to include in current scoping exercise
5. Removal of technologies from this pathways scope
6. Addition of new technologies to this pathways scope

Key terminology changes

- Clinicians considered that the phrase “early disease” was most likely to be interpreted as referring to stage 1 disease. So, the decision point initially titled “Early to locally advanced stage” was renamed “Locally advanced stage”.

- Consensus at the scoping workshop was that clinicians probably would not generally refer to any treatment option as “last line” as it would not be possible to know in advance what the last line of treatment would be. Lines have been renamed with descriptors relating to their place in the pathway (see **Table 1**). For example, subsequent treatment 1 (ST1) or post-genetic alteration treatment (PGA).

- Consultation comments noted that the draft scope had referred to “genetic mutations” when discussing all of the targeted therapies and that many of these targeted fusions or insertions. They advised that the term “genetic alteration” was more accurate. This has been amended throughout the scoping documents.

Figure 1 – Provisional NSCLC treatment pathway as it appeared in the draft scope

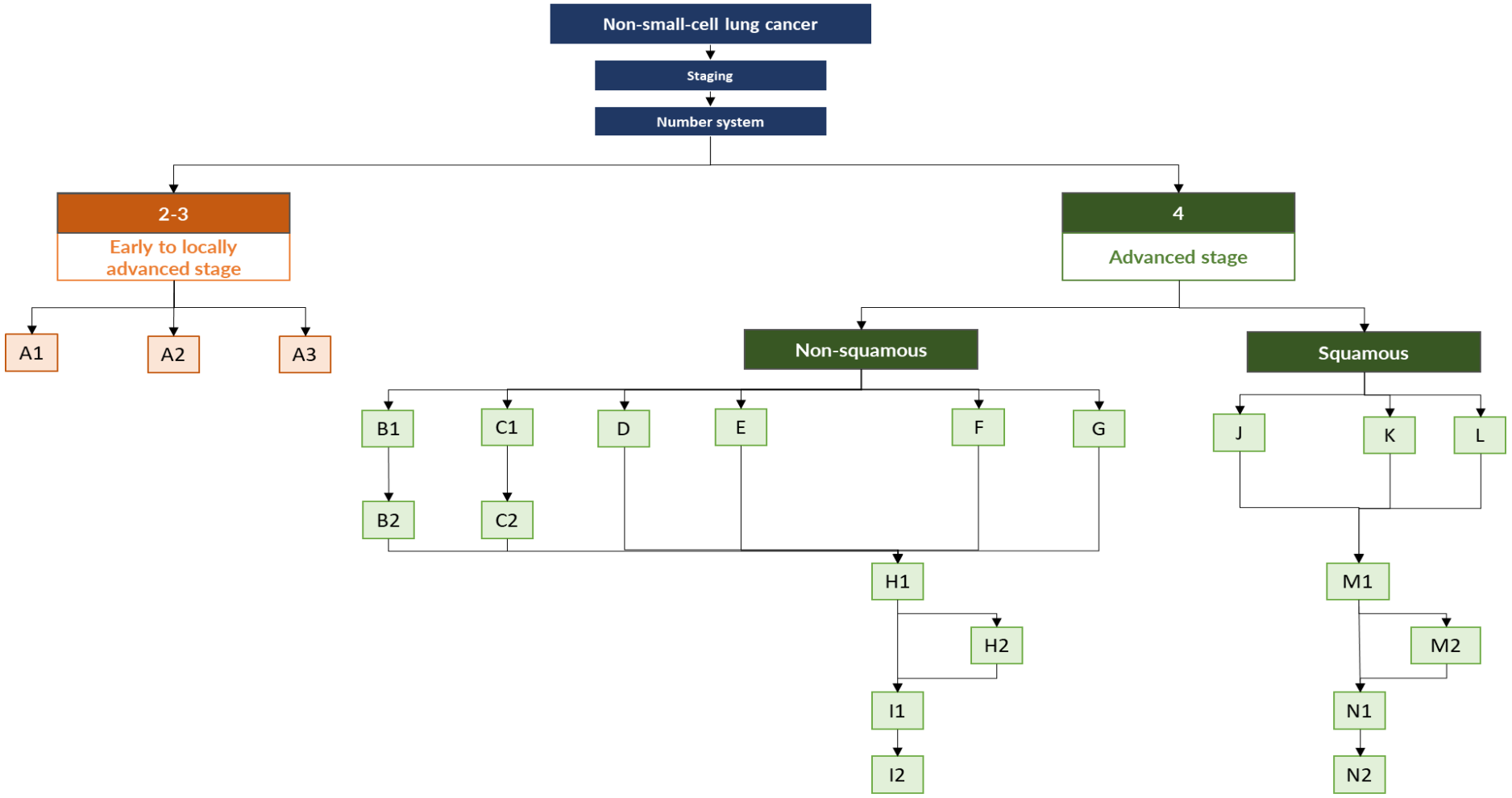

Figure 2 – NSCLC pathway made up of decision points. Reproduced in text form in Table 1. Decision points highlighted by dotted lines are being modelled in the first iteration of the NSCLC pathways pilot.

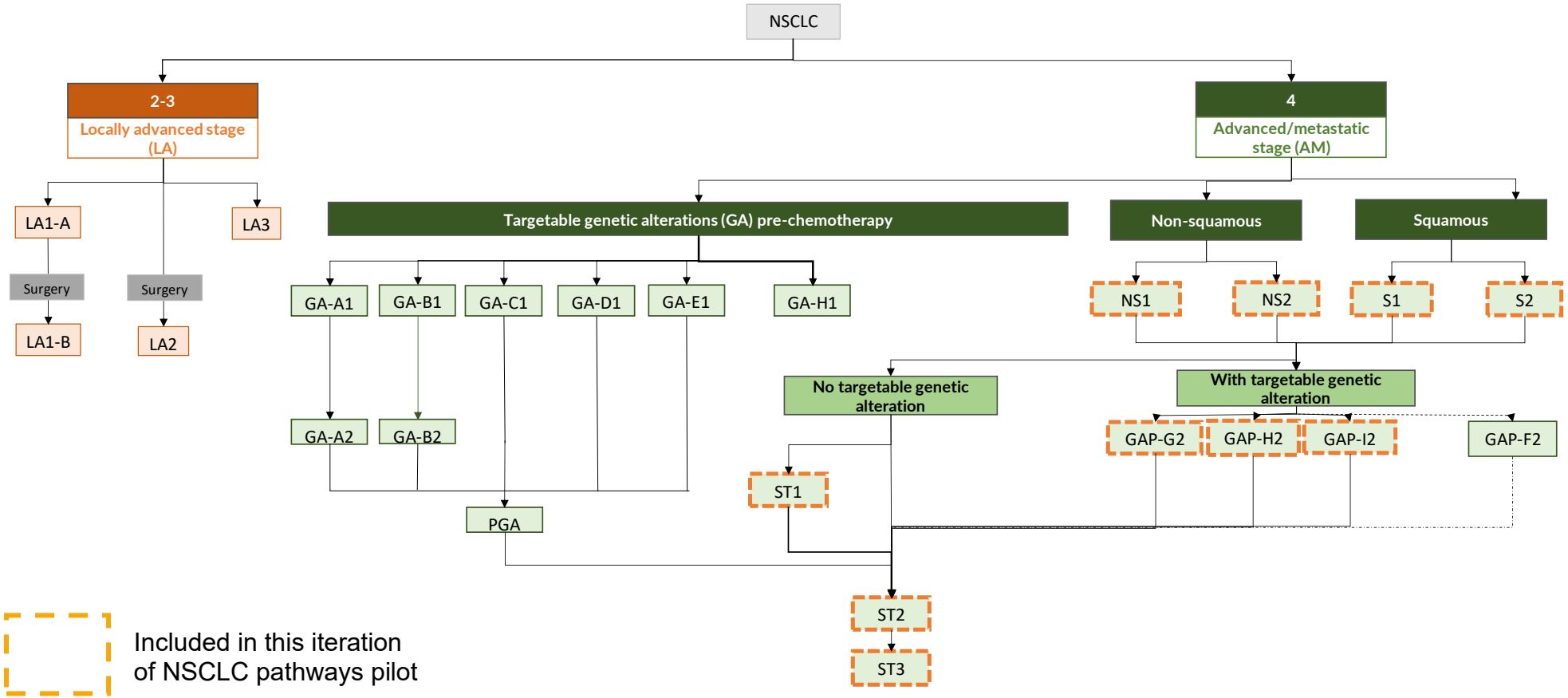

Table 1 – Decision points of the NSCLC pathway. Decision points highlighted in bold are being modelled in the first phase of the NSCLC pathways pilot

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

Update of pathway after clinical feedback

The non-small-cell lung cancer (NSCLC) treatment pathway was updated to that seen in **Figure 2** after clinician and stakeholder feedback on the draft treatment pathway that was included in the draft scope (see **Figure 1**). The key changes are summarised below.

Locally advanced stage (LA)

Consultation responses and clinical feedback generally considered the locally advanced decision points to be appropriate. One consultation response and clinician feedback considered that splitting the decision points differently into operable and inoperable, with inoperable being further split into radically treatable or not, was a more appropriate way to plot the pathway. Several consultation comments and discussion at the scoping workshop covered the fact that chemoimmunotherapy was likely to become the mainstay of treating locally advanced resectable disease alongside surgery. It was considered that some people might have neo-adjuvant chemoimmunotherapy followed by surgery, which may or may not be followed by continuation adjuvant immunotherapy. Some stakeholders considered that this would be a single decision point whilst others noted that there would likely be a separate decision, taken after surgery, on whether to continue with an adjuvant treatment. Clinicians noted that they would not likely change the immunotherapeutic agent used from the neo-adjuvant to the adjuvant setting. Therefore, two new decision points were created, LA-1A (see **Figure 2**) to represent neo-adjuvant therapy, which is followed by LA-1B which represents the decision space of whether or not to continue with the immunotherapeutic agent after surgery. The decision point LA2 represents the decision space of what adjuvant agent to use when no neo-adjuvant treatment was given prior to surgery. The decision point LA3 (maintenance after concurrent chemoradiation) was maintained in the pathway.

Advanced stage disease with a genetic alteration

Consultation comments and clinician feedback considered that, whilst the majority of targetable genetic alterations were found in the non-squamous histology (mostly in adenocarcinomas), anyone whose disease was identified as having a targetable genetic alteration would be offered similar treatment options. It was therefore

considered more appropriate to house all of the genetic alteration specific decision points in a separate branch of the pathway. This resulted in the decision points which were previously titled A to E being moved to a separate “genetic alterations” branch and renamed GA-A1 to GA-E1 with second line targeted decision points named GA-A2 for example. GA-E1 was created after feedback that dabrafenib with trametinib was recently recommended by NICE and occupies a new decision space for BRAF V600 mutation positive disease. For those whose disease had progressed after first or first and second line targeted treatments a common decision point named PGA was added to represent post genetic alteration specific treatments which may include immunotherapy, chemotherapy or chemoimmunotherapy.

Advanced stage disease with no genetic alteration or no recommended first line targeted treatments.

Decision points F, G and K and L were renamed NS1 and NS2 and S1 and S2 respectively. NS1 and S1 refer to disease which has a PD-L1 score of less than 50% and is either of the non-squamous or squamous histology respectively. NS2 and S2 refer to disease which has a PD-L1 score of 50% or more and is of a non-squamous or squamous histology respectively. For those whose disease progresses on any of the treatment options in NS1/2 or S1/2 there are two sub-branches. One contains decision spaces for disease which has no currently targetable genetic alterations and another for disease which has a targetable genetic alteration (currently EGFR exon20 insertion, RET fusion, KRAS G12C mutation or a HER2 mutation although as this appraisal has not yet completed the HER2 node will not be included in this iteration of the NSCLC pathways pilot. The decision points GAP-F2 to GAP-I2 represent these alterations and were created from the previous decision points M1 and H1. They were combined after the consideration by clinicians that disease with targetable mutations was likely to be considered independent of histology. Decision point ST1 represents a subsequent treatment option where those who did not have either chemotherapy or immunotherapy at an earlier line may opt to have it, however people who previously had chemoimmunotherapy would skip this decision point. Points ST2 and ST3 represent subsequent treatment lines after previous treatment options have been exhausted.

Subsequent treatment options

It was discussed in the scoping workshop that there may be a smaller number of people who get to decision point ST1 in the pathway. These points were created to cover the decision space of which chemotherapeutic agents (or immunotherapies if eligible) to use once previous chemoimmunotherapy or targeted treatments have been exhausted. The final decision point ST3 was created to cover recommendations for drugs which optimise for situations where there are “no suitable alternatives”.

Specification of decision points to be included in this scoping exercise

In the consultation responses and during the scoping workshop the complexity of the NSCLC pathway was discussed. It was decided that given that this was a pilot to for a wider pathways approach it would be appropriate to only model a section of the pathway in the first instance. It was decided not to model the locally advanced branch and the first- and second-line targetable mutation branches at this time. This was to allow the teams working on this pilot to concentrate on a smaller, less complex area of the pathway and additional information on the excluded sections is provided below.

Locally advanced branch

There was consensus at the scoping workshop that the locally advanced and particularly the neo-adjuvant and adjuvant decision points represented a fast moving area with numerous developments and treatments in the pipeline. There were also consultation comments which noted that the NHS targeted lung health check programme may result in an increase in diagnoses at this stage of disease. Furthermore, clinical feedback at the scoping workshop confirmed that the clinically significant outcomes for neo-adjuvant and adjuvant decision points were distinct from those for advanced and metastatic disease. Disease free survival was a key outcome of interest for adjuvant treatment and event free survival and pathological complete response (pCR) were key outcomes for neo-adjuvant treatment. This

would require a different modelling approach to the other decision points in the pathway. For these reasons it was decided to exclude the locally advanced branch from this iteration of the NSCLC pathways approach. This means that the technologies which were included in the draft scope and housed in these decision points will now be routed as single technology appraisals (STA).

Pre-chemotherapy targetable genetic alterations decision points

Discussion at the scoping workshop around genetic testing results confirmed that certain tests are done routinely and efficiently with results returned relatively quickly whereas others may be less routine. There was also reported variation with some sites reportedly using the genomic laboratory hubs' (GLH) next generation sequencing approaches more extensively than others which relied on local testing capacity using PCR testing. It was also reported that PCR testing was unable to detect certain genetic alterations. Clinicians reported that in theory, the results of all tests conducted at GLHs should come back at the same time but in reality there were differences in reporting time. It was also reported that in practice, if there was a delay in a genetic test then clinicians would likely start treatment using a non-targeted treatment (likely chemoimmunotherapy as per the non-squamous branch of the pathway). It was considered that over time, delays in genetic testing results should fall. Therefore, attempts to model the pre-chemotherapy targetable genetic alterations decision points at present would either have to model a future treatment landscape which would not represent current NHS clinical practice, or could model current practice but may soon become obsolete (as less and less people have non-targeted treatments due to delays in genetic testing results). The decision was taken that these decision points would not be included in the current pathways pilot. No treatments were included at these decision points in the draft scope so no alterations to the appraised technologies will result from this decision.

No first line targetable genetic alteration branch

The remaining decision points are set to be included in the first wave of the NSCLC pathways pilot. These decision points cover the branch of the pathway where non-targeted therapies, chemoimmunotherapy, immunotherapy or chemotherapy are used first line. This covers decision points NS1, NS2, S1 and S2, GAP-F2 to GAP-I2

for those whose disease has a genetic alteration for which a targeted therapy is licenced at second line or afterwards and decision points ST1 to ST3 which cover any subsequent therapies. It was noted that decision points ST1 to ST3 may contain people who have progressed via the targetable genetic alteration route (via decision point PGA) but that, as this branch is not included in the current pilot the populations at the ST decision points will be restricted to those who have progressed through the "non-squamous" and "squamous" branches of the pathway.

Removal of technologies from the current pathways scope

As noted in previous sections, the removal of certain branches and decision points from this iteration has resulted in the following technologies being removed from the NSCLC pathways approach:

- Durvalumab with chemotherapy (ID6220)
- Pembrolizumab (ID3907)

These technologies will now be appraised through the STA route.

Subcutaneous atezolizumab (ID6204) was removed as a technology to be appraised after discussion with stakeholders where it was decided that, as a reformulation it was not currently appropriate for this to be appraised.

Trastuzumab deruxtecan (ID3934) will not be appraised in the NSCLC pathway approach, as the timelines have been revised and this appraisal is not anticipated to have begun at the time this invitation to participate is sent out. The appraisal timings will ensure the company is able to make a suitably comprehensive and robust submission.

Technologies at decision points in the NSCLC pathway which are currently being modelled

Decision point	Populations	Technologies
NS1	People with advanced or metastatic non-squamous NSCLC that expresses PD-L1 on less than 50% of cells	• Pembrolizumab with pemetrexed and platinum chemotherapy (TA683) • Atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA548) • Pemetrexed with platinum doublet chemotherapy (clinical opinion)
NS2	People with advanced or metastatic non-squamous NSCLC that expresses PD-L1 on 50% or more of cells	• Pembrolizumab with pemetrexed and platinum chemotherapy (TA683) • Pemetrexed with platinum doublet chemotherapy (clinical opinion) • Pembrolizumab monotherapy (TA531) • Atezolizumab monotherapy (TA705)
S1	People with advanced or metastatic squamous NSCLC that expresses PD-L1 on less than 50% of cells	• Pembrolizumab with carboplatin and paclitaxel (TA770) • Platinum based chemotherapy
S2	People with advanced or metastatic squamous NSCLC that expresses PD-L1 on 50% or more of cells	• Pembrolizumab monotherapy (TA531) • Atezolizumab monotherapy (TA705) • Platinum based chemotherapy
ST1	People with advanced or metastatic NSCLC which has progressed after one line of treatment.	• Platinum based chemotherapy (if not used at earlier line) • Pembrolizumab monotherapy (TA428) • Nivolumab monotherapy – [Non squamous only] (TA713)

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

Technologies at decision points in the NSCLC pathway which are not yet being modelled

Decision point	Populations	Technologies
LA1A	People with NSCLC who are eligible for neo-adjuvant therapy	• Nivolumab with chemotherapy (TA876), • Platinum based chemotherapy (clinical opinion)
LA1B	People with NSCLC who are eligible for adjuvant therapy continuing on from neoadjuvant therapy	• Platinum based combination therapy (clinical opinion)
LA2	People with NSCLC who would have adjuvant therapy but who did not have neo-adjuvant therapy	• Platinum based combination chemotherapy (clinical opinion) • Atezolizumab (TA823, currently in CDF) • Osimertinib (for EGFR mutation positive disease only, TA761, currently in CDF)
LA3	People with NSCLC who have had chemoradiation therapy without progression	• Durvalumab monotherapy (TA798)
GA-A1	People with untreated advanced NSCLC with an ALK mutation	• Brigatinib (TA670) • Alectinib (TA536) • Ceritinib (TA500) • Crizotinib (TA405)
GA-A2	People with advanced NSCLC with an ALK mutation that has progressed after one line of therapy	• Lorlatinib (TA628) • Brigatinib (TA571) • Ceritinib (TA595)

GA-B1	People with advanced untreated NSCLC with an EGFR mutation	• Afatinib (TA310) • Erlotinib (TA258) • Dacomitinib (TA595) • Gefitinib (TA192) • Osimertinib (TA654)
GA-B2	People with advanced NSCLC with an EGFR mutation that has progressed after one line of therapy	• Osimertinib (TA653)
GA-C1	People with advanced untreated advanced NSCLC with a ROS-1 fusion	• Entrectinib (TA643)
GA-D1	People with advanced untreated NSCLC with a MetEx skipping alteration	• Tepotinib (TA789)
GA-E1	People with advanced untreated NSCLC with a BRAF V600 mutation	• Dabrafenib with trametinib (TA898)
GA-H1	People with advanced untreated NSCLC with a RET fusion	• Selpercatinib (TA911, currently in CDF)
PGA	People with advanced NSCLC that has progressed following treatment with a first or a first and second line targeted therapy	• Platinum doublet chemotherapy
GAP-F2	People with NSCLC with a HER2 mutation that has progressed after one line of treatment	• Docetaxel (clinical opinion) • Docetaxel with nintedanib (TA347) • Trastuzumab deruxtecan (subject to NICE appraisal)