Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Mirati Therapeutics**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. Association of Respiratory Nurses

4. **Expert personal perspectives** from:
   a. Jason Adhikaree, Consultant Medical Oncologist, clinical expert nominated by British Thoracic Oncology Group
   b. Shobhit Baijal, Consultant Medical Oncologist, clinical expert nominated by Bristol Myers Squibb

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

6. **External Assessment Report – factual accuracy check**

7. **External Assessment Report – supplementary appendix**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Adagrasib for previously treated *KRAS* G12C mutation-positive advanced non-small cell lung cancer [ID6339]

Document B

Company evidence submission

November 2024

File name	Version	Contains confidential information	Date
ID6339_Adagrasib-KRAS-NSCLC_Doc-B_[redacted]	1.0	No	08 November 2024

Contents

Tables and Figures

List of Tables

List of Figures

Abbreviations

2L+	Second line and later
3-IGI	3-item global index
AE	Adverse event
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASBI	Average symptom burden index
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BRAF	V-raf murine sarcoma viral oncogene homologue B
BSA	Body surface area
CDF	Cancer Drugs Fund
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrI	Credible interval
CSR	Clinical study report
CT	Computed tomography
DIC	Deviance information criteria
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOL	End of life
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimension
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FE	Fixed-effects
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
ic	Intracranial
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IPD	Individual patient data
IV	Intravenous
KRAS	Kirsten rat sarcoma viral oncogene homologue
LCSS	Lung Cancer Symptom Scale
LY	Life year
MET	Mesenchymal-to-epithelial transition
MID	Minimally important difference
MMRM	Mixed model for repeated measures
NE	Not estimable
NHS	National Health Service
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ-C30	Quality of life Questionnaire Core 30
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random-effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
ROS1	Proto-oncogene 1 receptor tyrosine kinase
SACT	Systemic anti-cancer therapy
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTI	Time to first improvement
TTP	Time to progression
VAS	Visual analogue scale

WPAI	Work Productivity and Activity Impairment

B.1 Decision problem, description of the technology and clinical care pathway

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, representing 13% of new cancer cases and 21% of cancer deaths.[1] Non-small cell lung cancer (NSCLC) accounted for 87% of lung cancers in England in 2022.[2]

Mutations in certain genes can cause aberrant cell signalling and proliferation.[3] These mutated genes are referred to as oncogenic driver mutations, and they are present in up to 50% of NSCLC cases and 64% of adenocarcinomas.[4]

- In NSCLC, oncogenic driver mutations can occur in genes such as *ALK*, *BRAF*, *EGFR*, *MET*, *NTRK*, *RET*, *ROS1*, and *KRAS*.
- Mutations in the Kirsten rat sarcoma viral oncogene homologue (*KRAS*) gene result in a structural defect in the KRAS protein. The defect resulting from the G12C mutation disrupts cellular signalling, leading to cell growth and disruption of apoptosis.[5–8]

KRAS is the most prevalent driver mutation in NSCLC, representing 25–35% of adenocarcinomas. G12C is the most frequent *KRAS* variant, comprising 41% of *KRAS*-mutant cases of NSCLC.[9] Overall, *KRAS* G12C mutations occur in 13.8% of cases of NSCLC.[10]

- Based on epidemiology data and the frequency of *KRAS* G12C mutations,[2, 10] it can be estimated that the annual incidence of *KRAS* G12C mutation-positive advanced or metastatic NSCLC in England and Wales is approximately 2,535.

KRAS mutations are a negative prognostic biomarker vs wild-type NSCLC for progression-free survival[11–13] and for overall survival.[12–19] Some studies suggest that *KRAS* G12C may even be a negative prognostic biomarker relative to other *KRAS* mutations.[17, 20]

In advanced NSCLC, treatment is not curative and is intended to extend survival and improve quality of life.[4]

- After disease progression on initial therapy (most patients receive immunotherapy alone or in combination with platinum-based chemotherapy), patients face second-line treatment options that are associated with poor outcomes and significant toxicity.
- The non-targeted treatment options, docetaxel as monotherapy or in combination with nintedanib, can cause potentially life-threatening myelosuppression.[21–24]

Despite the prevalence of *KRAS* G12C mutations and the associated poor prognosis, patients with this mutation are underserved compared to those with other driver mutations. Sotorasib is the only available therapy targeted to *KRAS* G12C-mutated NSCLC, is not routinely commissioned by the National Health Service (NHS) and is only available via the Cancer Drugs Fund (CDF).[25]

Adagrasib is a selective, irreversible KRAS G12C inhibitor that demonstrates near maximal inhibition of KRAS G12C protein throughout the dosing interval with minimal off-target activity[26] and has molecular properties that suggest the potential for central nervous system activity in patients with brain metastases,[27] who account for 23–42% of patients with advanced NSCLC.[28–31]

B.1.1 Decision problem

Adagrasib as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

The appraisal submission covers the technology's full marketing authorisation for this indication.

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal. Any differences between the decision problem and the NICE final scope are outlined in Table 1.

Table 1: The decision problem

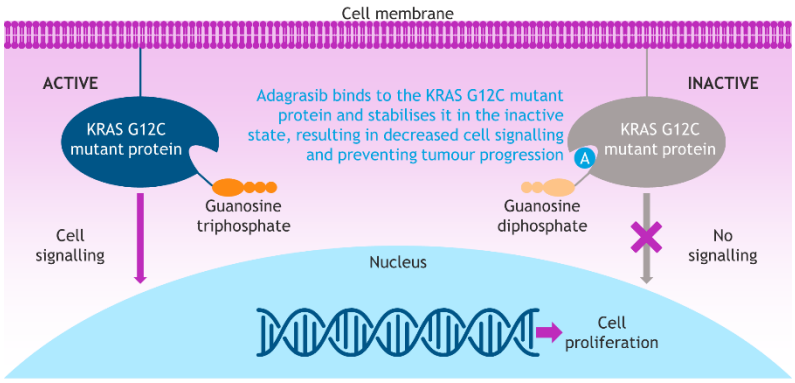
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced NSCLC that is positive for a *KRAS* G12C mutation and is not suitable for, or has progressed after treatment with, platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy	As per scope	Not applicable
Intervention	Adagrasib	As per scope	Not applicable
Comparator(s)	• Docetaxel • Docetaxel + nintedanib • Sotorasib (subject to managed access review)	• Docetaxel • Docetaxel + nintedanib	Sotorasib is recommended within the CDF and is not routinely commissioned in the NHS. According to NICE's Position Statement on CDF therapies, it is therefore not a comparator.[32] Given the US FDA's feedback[33, 34] on potential bias in the pivotal sotorasib trial, there is ongoing uncertainty regarding the availability of data that would support sotorasib's transition from the CDF to routine commissioning. For this reason, routine commissioning of sotorasib is not expected within the timeframe of this appraisal of adagrasib.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope, with addition of: • Duration of response • Intracranial efficacy	Not applicable
Subgroups to be considered	If the evidence allows, the following subgroups will be considered:	The company is not aware of any subgroups in which adagrasib would be more clinically or cost	KRYSTAL-12 was not powered to detect differences in the subgroups specified by NICE.

	• Disease stage • Histology • Previous treatment • Newly diagnosed or recurrent distant metastatic disease	effective; subgroup analysis is therefore not presented.	Trial participants with brain metastases represent a prespecified/stratified subgroup with high unmet need. For that reason, this submission presents intracranial efficacy data in patients with treated and untreated brain metastases.

Abbreviations: CDF, Cancer Drugs Fund; FDA, Food and Drug Administration; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; US, United States.

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Adagrasib (KRAZATI®)
Mechanism of action	Mutations in the *KRAS* gene result in a structural defect in the KRAS protein, which plays an important role in cellular signalling. The defect resulting from the G12C mutation disrupts cellular signalling by preventing the KRAS protein from hydrolysing GTP to GDP, thereby promoting cell growth and survival and disrupting apoptosis.[5–8] Adagrasib is a selective, irreversible KRAS G12C inhibitor that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive, GDP-bound conformation, which prevents KRAS-dependent downstream signalling without affecting wild-type KRAS protein. Adagrasib demonstrates near maximal inhibition of KRAS G12C protein throughout the entire dosing interval, resulting in durable inhibition of KRAS-dependent signal transduction. Adagrasib inhibits tumour cell growth and viability in cells harbouring the *KRAS* G12C mutation and results in regression in *KRAS* G12C-positive nonclinical tumour models with minimal off-target activity.[26] **Figure 1: KRAS G12C inhibitor mechanism of action[8]** 
Marketing authorisation/CE mark status	The MHRA granted adagrasib conditional marketing authorisation on 3 November 2023 and renewed the authorisation on 4 November 2024.[26] Full marketing authorisation is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Adagrasib as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.[26]
Method of administration and dosage	The recommended dose of adagrasib is 600 mg (three 200-mg tablets) orally twice daily, with or without food. The tablets should be swallowed whole with water.[26]
Additional tests or investigations	The presence of a *KRAS* G12C mutation must be confirmed using a validated test prior to initiation of therapy with adagrasib.[26] This test is routinely commissioned by NHS England.[35] Therefore, no additional tests are required beyond those used in the routine diagnostic work and management of patients.
List price and average cost of a course of treatment	Adagrasib proposed NHS list price: ▪ Cost per 180-pack of 200-mg tablets: [redacted]

	▪ Adagrasib does not have a specified course duration.
Patient access scheme	This submission includes the confidential simple patient access scheme for adagrasib. • Cost per 180-pack of 200-mg tablets: [redacted]

Abbreviations: CE, conformité européenne (European conformity); CEM, cost-effectiveness model; GDP, guanosine diphosphate; GTP, guanosine triphosphate; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NSCLC, non-small cell lung cancer; PAS, patient access scheme; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; SmPC, summary of product characteristics; UK, United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Lung cancer is the third most common cancer in the UK, representing 13% of all new cancer cases.[1] Despite being the third most common cancer, lung cancer is the most common cause of cancer death, accounting for 21% of all cancer deaths each year.[1] Risk factors for developing lung cancer include smoking tobacco, older age, exposure to certain substances (e.g. asbestos, radon gas, air pollution), previous radiotherapy to the chest, having lowered immunity, and family risk (could be genetic or due to shared risk factors).[36]

Lung cancer can be classified into histologic subtypes; NSCLC accounted for 87% of lung cancers in England and Wales in 2022.[2] NSCLC can be further classified into histological subtypes, including the two most common types of adenocarcinoma (66% of advanced NSCLC cases) and squamous cell carcinoma (23%).[37]

In non-advanced NSCLC, patients may undergo treatment with curative intent. The standard of care for non-advanced NSCLC is neoadjuvant nivolumab followed by surgery, although other treatment options such as surgery alone, radiotherapy, chemotherapy, or a combination are available.[38] In advanced NSCLC, the goal of systemic anti-cancer therapy is to extend survival and improve quality of life.[4]

B.1.3.1.1 Diagnosis and staging

Diagnosis typically starts with patients presenting with symptoms that are consistent with lung cancer (Section B.1.3.2.1). People with known or suspected lung cancer are assessed with a contrast-enhanced chest computed tomography (CT) scan.[38, 39] Inclusion of the liver, adrenal glands, and lower neck in the scan supports staging.[38] Beyond contrast-enhanced CT, techniques such as positron emission tomography CT, ultrasound, magnetic resonance imaging (MRI), and biopsy may be used for staging of lung cancer.[38]

Using tissue samples from biopsies, tumour histology is determined by microscopy and driver mutations are identified by molecular testing.[37] Molecular testing is routinely used at the time of NSCLC diagnosis to identify any driver mutation that could be a therapeutic target (Section B.1.3.1.2).[4, 40]

B.1.3.1.2 *KRAS* G12C mutation and other oncogenic driver mutations in NSCLC

Mutations in certain genes can effect molecular alterations in cells, potentially leading to the initiation and maintenance of tumour growth and invasiveness.[3] These oncogenic driver mutations are present in up to 50% of NSCLC cases and 64% of adenocarcinomas.[4]

Mutations in the *KRAS* gene result in a structural defect in the KRAS protein, which plays an important role in cellular signalling. The G12C mutation disrupts cellular signalling by preventing the KRAS protein from hydrolysing guanosine triphosphate to guanosine diphosphate, thereby promoting cell growth and survival and disrupting apoptosis.[5–8]

Understanding of the specific molecular alterations associated with driver mutation allows treatment to be tailored – or targeted – to that oncogenic driver.[41] In NSCLC, targeted therapies have been developed against anaplastic lymphoma kinase (*ALK*), V-raf murine sarcoma viral oncogene homologue B (*BRAF*), epidermal growth factor receptor (*EGFR*), mesenchymal-to-epithelial transition (*MET*), neurotrophic tyrosine kinase (*NTRK*), rearranged during transfection (*RET*), and proto-oncogene 1 receptor tyrosine kinase (*ROS*1) mutations,[40] and most recently for the *KRAS* G12C mutation.[42] Genetic testing is routinely used at the time of NSCLC diagnosis to identify any driver mutation that could be a therapeutic target,[4, 40] and this routine testing includes tests for variants in *KRAS*.[24]

KRAS is the most prevalent driver mutation in NSCLC, representing 25–35% of adenocarcinomas.[9, 43] G12C is the most frequent *KRAS* variant, comprising 41% of *KRAS*-mutant cases of NSCLC.[9, 44] Overall, *KRAS* G12C mutations occur in 13.8% of cases of NSCLC.[10] Further information on the epidemiology of *KRAS* G12C mutation-positive advanced or metastatic NSCLC is presented in Section B.1.3.1.3.

KRAS mutations, as a group, are a negative prognostic biomarker vs wild-type NSCLC for progression-free survival (PFS)[11–13] and for overall survival (OS).[12–19] Some studies suggest that *KRAS* G12C may even be a negative prognostic biomarker relative to other *KRAS* mutations (Section B.1.3.2.1.2).[17, 20]

Despite *KRAS* being the most prevalent driver mutation in NSCLC and G12C being the most frequent *KRAS* variant, patients with the *KRAS* G12C mutation are underserved relative to those with other driver mutations, for which a broader range of therapies are available (Table 3). Sotorasib, currently only available via the CDF and not routinely commissioned by the NHS,[25] is the only available therapy targeted to *KRAS* G12C mutation-positive NSCLC, leaving patients with limited treatment options.

Table 3: Targeted therapies by driver mutation

Driver mutation	Recommended therapy or therapies (NICE TA)
ALK	Alectinib (TA536[45]); Brigatinib (TA571,[46] TA670[47]); Ceritinib (TA395,[48] TA500[49]); Crizotinib (TA406,[50] TA422[51]); Lorlatinib (TA628[52])
BRAF V600	Dabrafenib + trametinib (TA898[53])
EGFR-TK	Afatinib (TA310[54]); Dacomitinib (TA595[55]); Erlotinib (TA258[56]); Gefitinib (TA192[57]); Osimertinib (TA653,[58] TA654[59])
***KRAS* G12C**	**Sotorasib (TA781*;[25] currently under managed access review)**
MET exon 14 skipping	Tepotinib (TA789[60])
NTRK fusion	Entrectinib (TA644*[61]); Larotrectinib (TA630*[62])
RET fusion	Selpercatinib (TA760*,[63] TA911[64])
ROS1	Crizotinib (TA529*[65]); Entrectinib (TA643[66])

*Recommended within the Cancer Drugs Fund.
Abbreviations: *ALK*, anaplastic lymphoma kinase; *BRAF*, V-raf murine sarcoma viral oncogene homologue B; *EGFR*-TK, epidermal growth factor receptor tyrosine kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; *MET*, mesenchymal-to-epithelial transition, NICE, National Institute for Health and Care Excellence; *NTRK*, neurotrophic tyrosine kinase; *RET*, rearranged during transfection; *ROS1*, proto-oncogene 1 receptor tyrosine kinase; TA, technology appraisal.

B.1.3.1.3 Epidemiology

In 2022, per the National Lung Cancer Audit, 36,886 patients in England and 2,211 patients in Wales were diagnosed with lung cancer. Patients with NSCLC accounted for approximately 87% of cases with known histology, and about 54% of all patients diagnosed with lung cancer in 2022 with known stage had advanced (Stage IIIB or IIIC) or metastatic (Stage IV) disease at the time of diagnosis.[2] Given the 13.8% frequency of *KRAS* G12C mutations in NSCLC,[10] the estimated annual incidence of *KRAS* G12C mutation-positive advanced or metastatic NSCLC in England and Wales is 2,535.

B.1.3.2 Burden of NSCLC

B.1.3.2.1 Clinical burden of disease

B.1.3.2.1.1 Disease symptoms

Lung cancer symptoms can include cough and/or change in cough, coughing up blood, persistent or repeated chest infection, shortness of breath, persistent chest or shoulder pain, hoarse voice, loss of appetite, unexplained weight loss, and fatigue.[67] Cross-sectional studies show that some of the most common symptoms in advanced NSCLC are significant negative predictors of quality of life (QoL), including fatigue (experienced by 98% of patients with advanced NSCLC), loss of appetite (98%), shortness of breath (94%), cough (93%), and pain (90%).[68, 69]

B.1.3.2.1.2 Mortality and prognosis

Lung cancer is the most common cause of cancer death in the UK, accounting for approximately 34,800 deaths (21% of all cancer deaths) each year.[1] Prognosis worsens with increasing stage of disease.[70–72]

Presence of a *KRAS* mutation is a negative prognostic biomarker vs wild-type NSCLC for PFS[11–13] and for OS.[12–19] In a retrospective real-world study combining current (n=4,240

treated after the introduction of immunotherapy) and historical (n=2,357 treated in the pre-immunotherapy era) cohorts of patients with advanced or metastatic NSCLC, mortality was significantly lower for patients with no *KRAS* mutation vs those with *KRAS*-mutated disease, with a hazard ratio (HR) for death of 0.80 (95% confidence interval [CI], 0.70 to 0.91; p=0.0009).[14]

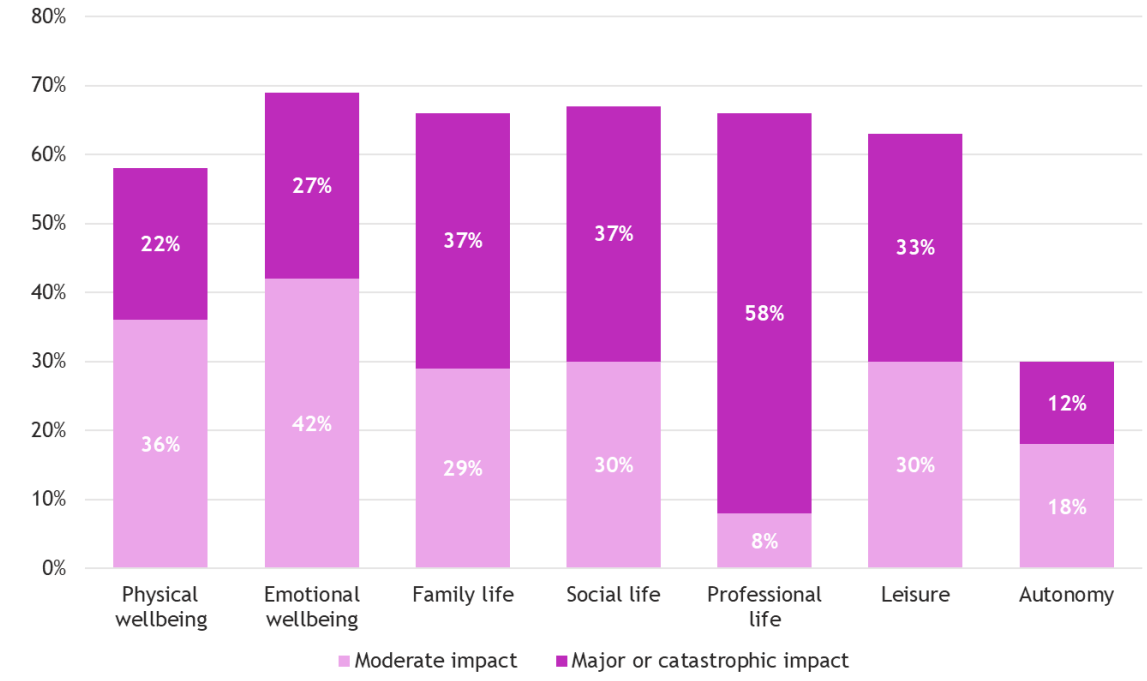
Some studies suggest that *KRAS* G12C may confer even worse outcomes than other *KRAS* mutations.

- In a retrospective chart review of patients with *KRAS*-mutated advanced or metastatic adenocarcinoma (n=37), 12-month OS was numerically lower for patients with *KRAS* G12C mutations (25.0%) than for patients with other *KRAS* mutations (47.6%).[20]
- Similarly, a retrospective study of patients with advanced or metastatic NSCLC (n=127) demonstrated median OS of 6.4 months for patients with *KRAS* G12C mutations and 10.3 months for patients with other *KRAS* mutations (p=0.011).[17]

B.1.3.2.2 Burden of disease on patients' quality of life

A European survey of patients with Stage IV NSCLC (n=73) showed that the disease impacts many aspects of patients' lives, including both physical and emotional wellbeing, patients' roles in family, social, and professional life, and aspects of leisure and autonomy (Figure 2).[73]

Figure 2: Patient-reported impact of Stage IV NSCLC on various aspects of life



Abbreviations: NSCLC, non-small cell lung cancer.
Source: Adapted from Tufman 2022[73]

The burden of lung cancer begins with the emotional impact of diagnosis, which may leave patients feeling shocked, numb, fearful, angry, guilty, or sad.[73, 74] Survey responses highlighted the emotional turmoil patients experience.

"I was panicking, afraid to die and not to have my wife with me at my death. I was concerned not knowing how she would cope alone."
Male patient, aged 61[73]

"My wife, as well as my daughter, suffers for me."
Male patient, aged 54[73]

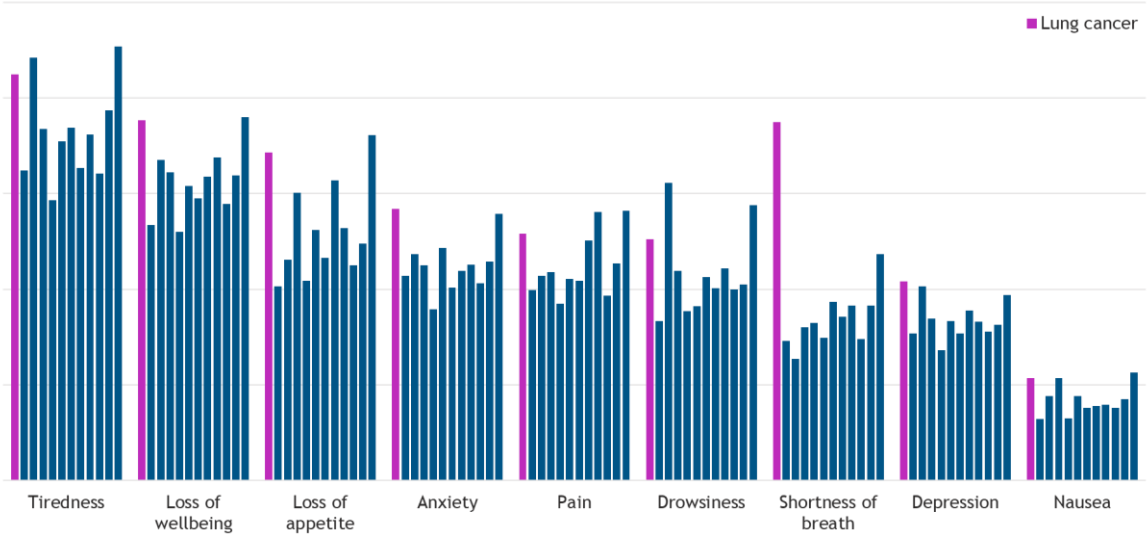
Further impacts on patients' QoL are the result of high symptom burden, a decline in functioning, progression of disease, and fears surrounding their own prognosis as well as the impact on loved ones. Indeed, patients with NSCLC have significantly lower global QoL than the age- and sex-standardised general population (mean difference on the European Organisation for the Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-C30], -10.3, $p<0.001$).[75]

"I felt like I was falling into an abyss, it was frightening and dark and very lonely."
Female patient, aged 51[73]

Cross-sectional studies show that Lung Cancer Symptom Scale (LCSS) scores for some of the most common symptoms in advanced NSCLC are significant negative predictors of QoL as measured by the Functional Assessment of Cancer Therapy – Lung, including fatigue (experienced by 98% of patients with advanced NSCLC),[69] loss of appetite (98%),[68, 69] shortness of breath (94%),[68, 69] cough (93%),[68] and pain (90%).[68, 69] Other factors associated with reduced QoL in advanced NSCLC include mental distress,[75] disease progression,[76] brain metastasis (vs other metastases),[77] and declining Eastern Cooperative Oncology Group (ECOG) performance status.[78]

A cross-sectional study of >45,000 ambulatory patients with various cancers demonstrated that patients with lung cancer had the worst burden of symptoms according to the Edmonton Symptom Assessment System.[79] Of the nine symptoms measured by the assessment, patients with lung cancer had among the highest scores for six symptoms and the highest score for three symptoms (shortness of breath, anxiety, and depression) relative to patients with other types of cancer (Figure 3).[79]

Figure 3: Mean symptom scores on the Edmonton Symptom Assessment System by cancer type



Higher scores indicate worse symptom burden. Scores for patients with lung cancer are shown in purple. From left to right within each symptom cluster, the blue bars show the scores of patients with the following cancers: breast, central nervous system, gastrointestinal, genitourinary, gynaecologic, haematology, head/neck, sarcoma, skin, other, and primary unknown.
Source: Barbera 2010[79]

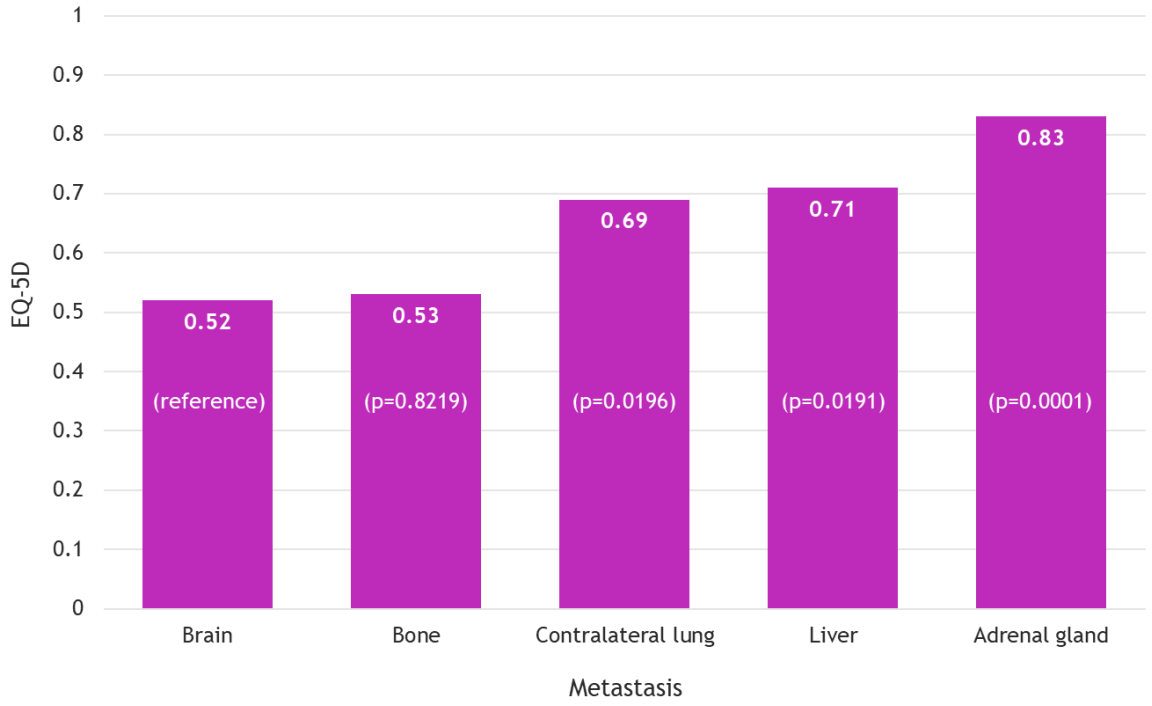
B.1.3.2.3 Burden of disease in patients with brain metastasis

Studies suggest that patients with *KRAS* G12C mutations have a higher frequency of brain metastases (ranging from 23% to 42%) than patients with other *KRAS* mutations or wild-type *KRAS*.[28–31] Patients with *KRAS* G12C mutations are significantly more likely to develop brain metastasis (42%) than patients with oncogenic fusion events (*RET*, *ALK*, or *ROS1*, 22%; p=0.005).[30] For patients with NSCLC who also have brain metastases, symptom burden is higher and QoL is lower than for those without brain metastasis.

A retrospective study in patients with *EGFR* mutation-positive NSCLC (n=402) demonstrated significantly higher rates of common symptoms such as fatigue (p<0.0001), nausea (p<0.0001), anxiety (p=0.0221), depression (p=0.0031), and vomiting (p<0.0001) for patients with brain metastases relative to those without brain metastases.[80] Patients with brain metastases also had significantly higher rates of less common symptoms (occurring in ≥10% with and <10% without brain metastases) such as focal neurologic deficits (p<0.0001), problems with memory (p<0.0001), drowsiness (p=0.0003), speech problems (p<0.0001), seizures (p<0.0001), and altered mental status (p=0.0246).[80]

In a cross-sectional survey of patients with NSCLC (n=498), QoL according to the EuroQol 5-Dimension (EQ-5D) was significantly lower for patients with brain metastases compared with contralateral lung, adrenal gland, and liver metastases. EQ-5D was similar between patients with bone and brain metastases (Figure 4).[77]

Figure 4: QoL in patients with advanced NSCLC and metastasis at various sites



Abbreviations: EQ-5D, EuroQol 5-Dimension; NSCLC, non-small cell lung cancer; QoL, quality of life.
Source: Roughley 2014[77]

B.1.3.2.4 Treatment burden

For patients with *KRAS* G12C mutation-positive NSCLC, initial treatment options include platinum-based chemotherapy (typically carboplatin in combination with pemetrexed), immunotherapy (pembrolizumab or atezolizumab) or a combination of platinum-based chemotherapy and immunotherapy.[38] For patients whose disease progresses following initial therapy, further treatment options include docetaxel-based regimens (as monotherapy or in combination with nintedanib), or the KRAS G12C-targeted agent sotorasib, which is currently only available through the CDF and is not routinely commissioned by the NHS.[38] For more information on the treatment pathway, see Section B.1.3.3.

B.1.3.2.4.1 Current non-targeted treatments are associated with poor outcomes

Docetaxel-based regimens are associated with low response rates, short duration of response for the few patients who respond to treatment, and poor survival (Table 4). There is a lack of data for docetaxel + nintedanib in a *KRAS*-mutated NSCLC population, but treatment with regimens of docetaxel + nintedanib and docetaxel monotherapy gave similarly poor results in the Stage IIIB/IV NSCLC population of LUME-Lung 1.[81] Similar efficacy was shown for docetaxel monotherapy in a *KRAS*-mutated NSCLC population in SELECT-1.[82] Duration of response was longer and progression-free and overall survival were marginally longer for patients with *KRAS* G12C-mutated NSCLC in CodeBreaK 200,[83] but these improvements were not observed in real-world data collected in the United States.[84]

Table 4: Efficacy of docetaxel-based regimens

Study (intervention) *Population*	ORR, % (95% CI)	DOR, months (95% CI)	PFS, months (95% CI)	OS, months (95% CI)
LUME-Lung 1[81] (docetaxel + nintedanib) *Stage IIIB/IV NSCLC at 2L after Pt-based ChT (n=655)*	4.4 (NR, NR)	NR	3.4 (2.9, 3.9)	10.1 (8.8, 11.2)
LUME-Lung 1[81] (docetaxel) *Stage IIIB/IV NSCLC at 2L after Pt-based ChT (n=659)*	3.3 (NR, NR)	NR	2.7 (2.6, 2.8)	9.1 (8.4, 10.4)
SELECT-1[82] (docetaxel) *KRAS-mutated aNSCLC at 2L (n=254)*	13.7 (NR, NR)	4.5 (2.8, 5.6)	2.8 (IQR: 1.4, 5.5)	7.9 (IQR: 3.8, 20.1)
CodeBreaK 200[83] (docetaxel) *KRAS G12C-mutated aNSCLC after Pt-based ChT and IO (n=174)*	13.2 (8.6, 19.2)	6.8 (4.3, 8.3)	4.5 (3.0, 5.7)	11.3 (9.0, 14.9)
US real-world data[84] (docetaxel) *KRAS G12C-mutated aNSCLC at 2L (n=295)*	NR	NR	3.4 (2.7, 4.2)	6.0 (4.9, 7.1)

Abbreviations: 2L, second line; aNSCLC, advanced non-small cell lung cancer; ChT, chemotherapy; CI, confidence interval; DOR, duration of response; IO, immuno-oncology; IQR, interquartile range; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NR, not reported; NSCLC, non-small cell lung cancer; ORR, objective/overall response rate; OS, overall survival; PFS, progression-free survival; Pt, platinum; US, United States.

B.1.3.2.4.2 Current non-targeted treatments are associated with life-threatening toxicities and unfavourable route of administration

A series of interviews with five UK clinicians highlighted myelosuppression as a safety concern for docetaxel-based regimens,[24] consistent with the summary of product characteristics (SmPC).[21] Myelosuppression may result in anaemia, thrombocytopenia, and/or neutropenia.[21] Chemotherapy-induced neutropenia suppresses the haematopoietic system, which increases risk of infections. Neutropenia, which can be life-threatening, may limit the dose of chemotherapy and thus potentially compromise treatment outcomes.[23] Neutropenia associated with docetaxel may be exacerbated by nintedanib; the SmPC for nintedanib reports a higher frequency of Grade ≥3 neutropenia events with docetaxel + nintedanib vs docetaxel alone.[22]

The impact of chemotherapy toxicity burden has been clearly demonstrated in a European social media listening study. Analysis of 1,360 social media conversations generated by patients, caregivers, and healthcare professionals about lung cancer demonstrated that conversations expressed negative sentiment towards chemotherapy over twice as frequently as positive sentiment (28% vs 12%; n=318 conversations). Discussion of the physical challenges of lung cancer (38% of the conversations) were mainly associated with the adverse effects of treatment (primarily chemotherapy).[85]

Docetaxel-based regimens require intravenous (IV) infusion,[21, 86, 87] which is not aligned with the patient preference for an oral route of administration. In a review of 13 studies on the preferences of patients undergoing cancer treatment, 11 studies reported a patient preference for oral administration of treatment over IV administration. Reasons for preferring

oral medications included convenience and the ability to receive treatment at home, a perception of fewer side effects, and the pain of IV administration.[88] Among patients with NSCLC specifically, 58% of patients prefer an oral cancer treatment over an injected one, according to a European survey (n=292).[73]

B.1.3.2.4.3 The only available KRAS G12C-targeted therapy offers limited efficacy at the cost of significant toxicity

Sotorasib, currently only available via the CDF and not routinely commissioned by the NHS,[25] is the only available therapy that targets KRAS G12C. This leaves patients with limited treatment options compared with patients with other driver mutations who have broader treatment options (Section B.1.3.1.2). In the pivotal CodeBreaK 200 study, median PFS was 5.6 months (95% CI, 4.3 to 7.8) in the sotorasib arm and 4.5 months (95% CI, 3.0 to 5.7) in the docetaxel arm.[83] However, there is limited evidence that this translates into an OS benefit for patients with KRAS G12C mutation-positive NSCLC, and the Food and Drug Administration (FDA) has since questioned the integrity of the PFS results based on multiple signals of potential systemic bias and study conduct issues,[33] with the Oncologic Drugs Advisory Committee voting 10 to 2 that PFS cannot be reliably interpreted in CodeBreaK 200.[34] As a result, the FDA has issued a new post marketing requirement for a confirmatory trial to support full approval of sotorasib.[89]

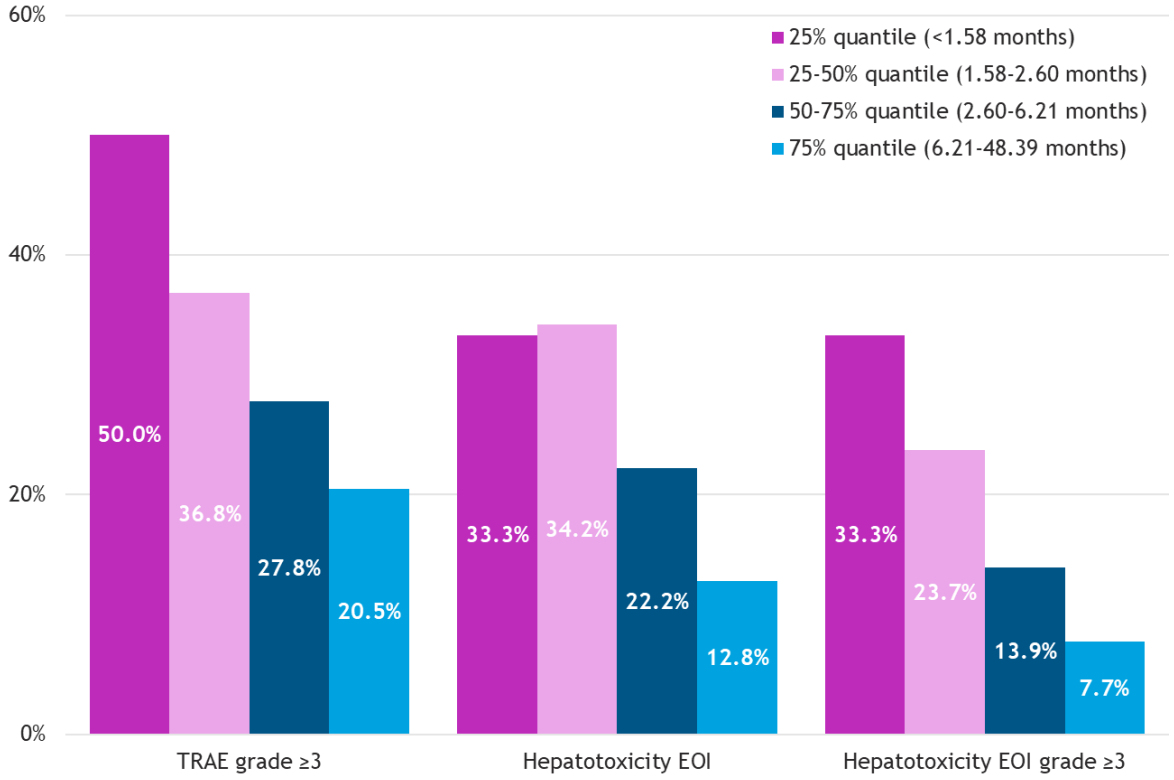
The intracranial efficacy of sotorasib was assessed in a *post hoc* analysis of CodeBreaK 200 among 40 patients in the sotorasib arm and 29 patients in the docetaxel arm who presented with treated, stable (non-progressing) central nervous system (CNS) metastases at baseline. Within the subgroup of patients with CNS metastases, among those with measurable CNS lesions, intracranial objective response rate (icORR) was 33% (n=6/18) in the sotorasib group and 15% (n=2/13) in the docetaxel group.[90] In CodeBreaK 100, the phase 2 trial of sotorasib, icORR was 19% (n=3/16) among all patients with treated, stable brain metastases.[91]

To confirm the CNS-specific activity of a targeted systemic anti-cancer therapy (SACT), ideally, there would be prospective efficacy data in patients with *untreated* CNS metastasis. The only available data on sotorasib's efficacy in *untreated* brain metastases come from case reports[92–96] and one retrospective case series[97] that reports intracranial PFS (median 3 months) and OS (median 4 months) for patients (n=5) with active brain metastasis who did not receive local therapy within 1 month of initiating sotorasib. Based on the available data, the National Comprehensive Cancer Network includes adagrasib in its recommendations (Category 2A) for patients with brain metastases,[98] whereas sotorasib is included as a category 2B recommendation (a recommendation based on lower-level evidence[99]).[98]

A *post hoc* analysis of CodeBreaK 200 data showed a higher incidence of treatment-related Grade ≥3 adverse events and hepatotoxicity events (overall and Grade ≥3) among patients with a shorter time gap between treatment with immunotherapy and subsequent treatment with sotorasib vs those with a longer time gap (Figure 5).[83] This finding was despite an eligibility criterion requiring 28 days to elapse between previous treatment with SACT and initiation of study treatment (i.e. a "washout" period).[83] A retrospective study produced similar results, demonstrating an incidence of sotorasib-related Grade ≥3 hepatotoxicity (defined as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase, or bilirubin elevated per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 cutoffs) that was threefold greater (33% vs 11%, p=0.006) among patients who had immunotherapy as their last line of therapy vs those who did not

(87% of whom received another treatment regimen between immunotherapy and sotorasib and 13% of whom never received immunotherapy).[100]

Figure 5: Adverse events observed in all patients who received prior immunotherapy, presented by the quantiles of time gap from latest prior immunotherapy to initiation of sotorasib



Abbreviations: EOI, event of interest; TRAE, treatment-related adverse event.
Source: de Langen 2023[83]

Clinicians consulted by the company report taking into consideration a patient's prior treatment with immunotherapy when prescribing sotorasib in their clinical practice. To minimise toxicity, it is common practice to either pause treatment temporarily (approximately 6 weeks) to allow immunotherapy "wash out" or to treat with a docetaxel- or platinum-based regimen before introducing sotorasib.[24] Clinical experts confirmed that they may also start patients on a reduced dose of sotorasib to minimise risk of hepatotoxicity.[24]

B.1.3.2.5 Societal and economic burden of NSCLC

Although the available economic data are not specific to NSCLC, a study of preventable cancers in the UK makes it clear that the economic burden of lung cancer more broadly is high, totalling £39.5 billion in 2023 alone (Table 5). The strongest cost drivers were productivity loss, loss of QoL, and healthcare costs.

Table 5: Costs of lung cancer in the UK in 2023

Cost	Cost for all cases	Cost per case
Total costs	**£39,500,000,000**	**£920,000**
Individual costs		

Quality of life lost	£22,400,000,000	£521,600
Out-of-pocket expenditure	£26,100,000	£600
Healthcare costs		
Primary care	£29,900,000	£700
Secondary care	£668,200,000	£15,500
Community care	£800,000	-
Social care costs		
Ongoing social care (public)	£107,000,000	£2,500
Ongoing social care (private)	£50,000,000	£1,200
End-of-life social care	£76,400,000	£1,800
Opportunity cost of care		
Opportunity cost	£652,300,000	£15,200
Economic costs		
Paid productivity lost	£1,730,000,000	£40,200
Unpaid productivity lost	£13,771,800,000	£320,300

Abbreviations: UK, United Kingdom.
Source: Frontier Economics 2023,[101] Frontier Economics 2023 correction[102]

The productivity loss associated with advanced NSCLC is well illustrated by patient-reported outcomes (PROs). A retrospective chart review (n=1,030) in Europe showed that as a patient's functionality (according to ECOG performance status) deteriorates, impairment on the Work Productivity and Activity Impairment (WPAI) questionnaire worsens, affecting all four domains: work time missed (p=0.0255), impairment while working (p=0.0026), overall work impairment (p=0.0005), and activity impairment (p<0.0001).[78] In a European survey, patients with Stage IV NSCLC (n=73) reported a heavy professional burden, with 8% of patients experiencing a 'moderate' impact on their professional life and 58% of patients experiencing a 'major or catastrophic' impact. Household finances were impacted 'moderately' and 'severely' for 19% and 23% of patients, respectively, and 39% of patients retired before age 65 due to NSCLC.[73]

One source of healthcare resource utilisation (HCRU) and costs in advanced NSCLC is neutropenic sepsis in patients treated with docetaxel. A retrospective study in the UK showed mean hospital stays of 9.2 and 4.7 days for patients with confirmed (n=11) and suspected (n=10) neutropenic sepsis, respectively, with associated mean costs of neutropenic sepsis totalling £3,163 and £1,790 per patient.[103]

Two retrospective studies of US-based patients with *ALK*-positive NSCLC demonstrated that the presence of brain metastasis increases HCRU and healthcare costs relative to the absence of brain metastasis.[104, 105] Brain metastasis is also associated with increased economic burden compared with other metastases, according to a retrospective study in France that showed a greater number of hospitalisations, higher rates of palliative care, and greater costs for patients with brain metastases (n=971) than for those with other metastases (n=1,529) in non-squamous NSCLC.[106]

B.1.3.2.6 Caregiver burden

Family members and friends acting as caregivers for patients with NSCLC also experience stress, reduced QoL, and economic impact as a result of the disease.

In a longitudinal study of caregivers (n=163) of patients with NSCLC, responses on the Caregiver Burden Scale revealed consistently high subjective stress burden, which is defined as the perceived emotional response to caregiving responsibilities. Other measures demonstrated a worsening state for caregivers over time, including moderate and numerically rising psychological distress as measured by the Psychological Distress Thermometer and moderate and significantly decreasing overall QoL as assessed by the City of Hope-QoL Scale – Family Version.[107]

The increase in caregiver burden over time may be related to the deterioration of the loved one with NSCLC. A European survey of caregivers (n=427) showed that caregivers of patients receiving later lines of therapy (i.e. patients whose disease has progressed on, or not responded to, earlier lines of therapy) rate their own health status as significantly lower compared with caregivers of patients receiving first-line therapy (p=0.0039).[108] Declining ECOG performance status of a patient with advanced NSCLC is associated with worsening caregiver anxiety/depression domain of the EQ-5D (p=0.0150) and with increased caregiver burden (p<0.0001) and increased risk of depression (p=0.0011) on the Zarit Burden Interview.[78]

The caregiver activity impairment domain of the WPAI also worsens with declining patient ECOG performance status (p<0.0001) in advanced NSCLC, highlighting the economic burden faced by caregivers.[78] The opportunity cost of care provided to patients with lung cancer totalled £652 million in the UK in 2023, with an opportunity cost of £15,200 per case of lung cancer.[101]

B.1.3.3 Current treatment pathway and proposed adagrasib positioning

B.1.3.3.1 Treatment goals

In the non-advanced disease setting, patients may undergo treatment with curative intent, such as surgery, radiotherapy, chemotherapy, or a combination.[38] For patients with advanced NSCLC, which is not amenable to curative therapies, treatment comprises SACT,[38] with a goal of delaying disease progression, extending survival, and improving QoL.[4]

B.1.3.3.2 Treatment guidelines

Clinicians in England and Wales typically follow NICE NG122. This guideline provides SACT treatment pathways for advanced NSCLC that are specific to tumour histology, level of programmed death ligand 1 (PD-L1) expression, and targetable mutations, including the *KRAS* G12C mutation.[38]

The European Society for Medical Oncology (ESMO) provides a guideline for oncogene-addicted metastatic NSCLC, which includes adagrasib as a second-line treatment option.[41] The ESMO guidelines are summarised in Appendix M.

A summary of the UK treatment pathway, based on NICE NG122 and clinical expert opinion, is summarised in Section B.1.3.3.4.

B.1.3.3.3 Relevant NICE TAs

Table 6 summarises the relevant NICE technology appraisals (TAs) from previously reimbursed therapies,[25, 109–118] which are referenced in the NICE treatment pathway for advanced NSCLC with a *KRAS* G12C mutation.[38]

Table 6: Summary of NICE technology appraisals referenced in the NICE treatment pathway for advanced NSCLC with a *KRAS* G12C mutation

TA	Year	Intervention	Population/indication
***KRAS* G12C mutation-specific technology appraisals**			
781[25]	2022	Sotorasib	*KRAS* G12C mutation-positive locally advanced or metastatic NSCLC in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-(L)1 immunotherapy
Technology appraisals for advanced NSCLC			
770[109]	2022	Pembrolizumab + carboplatin + paclitaxel	Untreated metastatic squamous NSCLC in adults whose tumours express PD-L1 with a tumour proportion score of <50% or whose tumours express PD-L1 with a tumour proportion score of ≥50% and are in need of urgent clinical intervention
713[110]	2021	Nivolumab	Locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy if their tumours are PD-L1 positive and they have not had a PD-(L)1 inhibitor before
705[111]	2021	Atezolizumab	Untreated metastatic NSCLC in adults if their tumours have PD-L1 expression on ≥50% of tumour cells or 10% of tumour-infiltrating immune cells and their tumours do not have EGFR or ALK mutations
683[112]	2021	Pembrolizumab + pemetrexed + platinum chemotherapy	Untreated, metastatic, non-squamous NSCLC in adults whose tumours have no EGFR or ALK mutations
655[113]	2020	Nivolumab	Locally advanced or metastatic squamous NSCLC in adults after chemotherapy if they have not had a PD-(L)1 inhibitor before
584[114]	2019	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Metastatic non-squamous NSCLC in adults who have not had treatment for their metastatic NSCLC before and whose PD-L1 proportion score is <50% or when targeted therapy for EGFR- or ALK-positive NSCLC has failed
531[115]	2018	Pembrolizumab	Untreated PD-L1-positive metastatic NSCLC in adults whose tumours express PD-L1 with ≥50% tumour proportion score and have no EGFR or ALK mutations
520[116]	2018	Atezolizumab	Locally advanced or metastatic NSCLC in adults who have had chemotherapy
428[117]	2017	Pembrolizumab	Locally advanced or metastatic PD-L1-positive NSCLC in adults who have had at least one chemotherapy
347[118]	2015	Docetaxel + nintedanib	Locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy

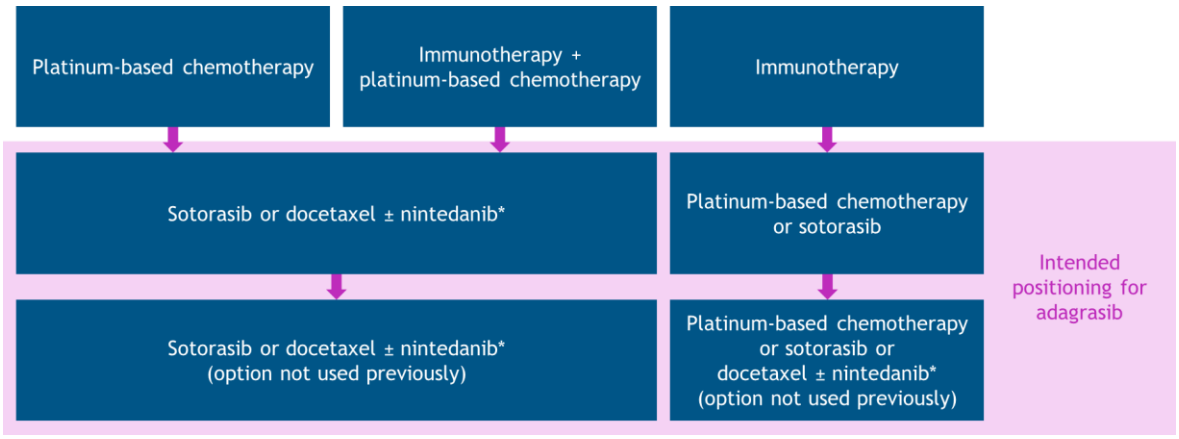
Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; TA, technology appraisal; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1.
Source: NICE NG122[38]

B.1.3.3.4 Current clinical practice

Figure 6 provides an overview of the treatment pathway for patients with advanced NSCLC and *KRAS* G12C mutations in England and Wales; it is derived from NG122, currently reimbursed therapies, and clinical expert opinion elicited from leading UK key opinion

leaders in 2024.[24, 38] This overview represents the pathway typically followed in clinical practice[24] and does not show all funded options.

Figure 6: Summary of the typical treatment pathway used in UK clinical practice for advanced NSCLC with a *KRAS* G12C mutation and proposed adagrasib positioning



*Nintedanib is reimbursed only in patients with adenocarcinoma histology; patients with other histologies receive docetaxel as monotherapy.
Abbreviations: *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; UK, United Kingdom.
Sources: NICE NG122,[38] clinical expert opinion[24]

Options for initial treatment are platinum-based chemotherapy, immunotherapy, or a combination of the two.[24, 38] The treatment most commonly received by patients (about three-quarters, based on clinical expert advice and the proportions of PD-L1 expression in advanced NSCLC) in clinical practice is immunotherapy in combination with platinum-based chemotherapy.[24, 119] For patients whose disease progresses following initial therapy, further treatment options include sotorasib, docetaxel, and (for people with adenocarcinoma) docetaxel + nintedanib.[24, 38] After receiving combination therapy initially, most patients receive sotorasib (85%) in preference to a docetaxel-based regimen due to the targeted nature of sotorasib treatment and toxicity concerns associated with docetaxel.[24] Most patients who receive a docetaxel-based regimen receive docetaxel in combination with nintedanib (60–80%).[24] The phase 3 trial LUME-Lung 1 demonstrated that docetaxel in combination with nintedanib was more effective than docetaxel alone in delaying progression of NSCLC.[81]

B.1.3.3.5 Proposed place of adagrasib in therapy

The licensed indication for adagrasib is treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and progressive disease after prior therapy with (or intolerance to) platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.[26] The proposed positioning for adagrasib, in line with its licensed indication, is as a second- and later-line therapy following prior treatment with (1) immunotherapy as monotherapy, (2) platinum-based chemotherapy alone, or (3) both immunotherapy and platinum-based chemotherapy, either concurrently or sequentially (Figure 6).

Sotorasib is currently only available through the CDF and awaiting NICE appraisal in its managed access review.[120] Sotorasib is not an appropriate comparator for adagrasib based on NICE's position statement that therapies only available via the CDF are not relevant comparators.[32] Given the US FDA's feedback[33, 34] on potential bias in the pivotal sotorasib

trial, there is ongoing uncertainty regarding the availability of data that would support sotorasib's transition from the CDF to routine commissioning. For this reason, routine commissioning of sotorasib is not expected within the timeframe of this appraisal of adagrasib.

Therefore, the relevant comparators for adagrasib in this appraisal are:

(1) docetaxel monotherapy

(2) docetaxel in combination with nintedanib.

B.1.3.4 Unmet need

Patients with advanced *KRAS* G12C mutation-positive NSCLC whose disease has progressed on first-line therapy face high disease burden and poor prognosis.

Among the current second-line therapies, the non-targeted platinum- and docetaxel-based regimens are associated with limited efficacy outcomes in NSCLC, particularly for patients with *KRAS* G12C mutations (Section B.1.3.2.4.1). These treatment options are administered intravenously, which is burdensome for patients and costly in terms of NHS resource, and they are associated with potentially life-threatening myelosuppression that can limit tolerability and compromise treatment outcomes (Section B.1.3.2.4.2).

Sotorasib, a therapy that targets KRAS G12C but that is currently only available via the CDF and is not routinely commissioned by the NHS, is associated with hepatotoxicity. Clinical trials and real-world data demonstrate that the incidence of Grade ≥3 hepatotoxicity events increases the sooner the initiation of sotorasib after immunotherapy (Section B.1.3.2.4.3). Clinical experts confirm that sotorasib's hepatotoxicity is often exacerbated by prior immunotherapy, which most patients with *KRAS* G12C mutation-positive NSCLC receive as initial treatment in routine UK practice.[24] Clinicians report that patients may initiate a reduced dose of sotorasib to lower the risk of toxicity. Alternative approaches are either temporarily pausing treatment between immunotherapy and sotorasib (Section B.1.3.2.4.3) or bridging the patient with docetaxel or platinum-based chemotherapy while waiting for the immunotherapy to "wash out".

There remains a significant unmet need for a targeted treatment for patients with *KRAS* G12C mutation-positive NSCLC that provides a survival benefit and is associated with an improved safety profile and maintenance of QoL. Oral therapies offer patients the convenience of having to travel less for their treatment and a reduction in the number of burdensome infusions and injection-site reactions associated with parenteral therapy.

Burden of disease is particularly high for patients with brain metastases (Section B.1.3.2.3) and efficacy of current therapies is limited in this population (Section B.1.3.2.4.3). Treatments that address this unmet need would be valuable for patients and their families as well as their treating clinicians.[24]

B.1.4 Equality considerations

No equality considerations relating to the use of adagrasib have been identified.

B.2 Clinical effectiveness

KRYSTAL-12 is an ongoing international, open-label, randomised phase 3 trial of adagrasib compared with docetaxel in patients with previously treated advanced NSCLC with *KRAS* G12C mutation.[121]

At the 31 December 2023 data cutoff, treatment with adagrasib led to a clinically meaningful and statistically significant difference in the primary endpoint of PFS compared with docetaxel in the intent-to-treat (ITT) population.[121]

- Median PFS was 5.49 months in the adagrasib arm vs 3.84 months in the docetaxel arm.[121]
- Adagrasib was associated with a 42% reduction in the risk of progression or death: HR, 0.58; 95% CI, 0.45 to 0.76; p<0.0001.[121]
- The majority of subgroups also showed a significant treatment benefit, and in the few remaining subgroups (all with HRs numerically favouring adagrasib), the number of patients comprise a small fraction of the ITT population.[121]

KRYSTAL-12 PFS results are supported by OS data from KRYSTAL-1, a completed single-arm phase 1/2 trial.[122, 123]

- The results of the KRYSTAL-12 interim OS analysis are currently considered to be highly immature and inconclusive due to several factors. Consequently, the interim OS results remain restricted. The study will continue as planned until the prespecified final OS analysis.[121, 124]
- After a median follow-up of 15.6 months, median OS in KRYSTAL-1 phase 2 Cohort A was 12.6 months (95% CI, 9.2 to 19.2).[122, 123] In the combined dataset (phase 1/1b and phase 2), median OS was 14.1 months (95% CI, 9.2 to 18.7) after a median follow-up of 26.9 months.[125]
- Given that surrogacy analyses in NSCLC show a moderate to high correlation between progression and survival both at study and individual levels,[126, 127] and PFS is consistent and similar between KRYSTAL-1 and KRYSTAL-12, an OS benefit for adagrasib over docetaxel is anticipated for the KRYSTAL-12 OS data.

PROs demonstrate that patient wellbeing is maintained over time while taking adagrasib.[121]

- EQ-5D results demonstrate that according to both the health utility index and visual analogue scale, patient QoL is maintained with only marginal changes over time.[121]
- LCSS scores show greater improvement with adagrasib than with docetaxel. Adagrasib demonstrated clinically significant ≥10-point advantage over docetaxel in fatigue, pain, dyspnoea, and cough.[128]

NMA results suggest that adagrasib demonstrates improved efficacy in treating patients with *KRAS* G12C mutation-positive NSCLC, compared with existing treatment options.

- In the proportional hazards NMA, adagrasib was associated with a reduction in the risk of progression or death vs docetaxel ([redacted]) and vs docetaxel + nintedanib ([redacted]). These findings were broadly consistent in the time-varying NMA.

The low-grade nature of key treatment-emergent adverse events (TEAEs) along with PROs indicate that adagrasib is generally tolerable with a manageable safety profile.[121]

- Although gastrointestinal events and hepatotoxicity were observed with adagrasib, most of these TEAEs were Grade 1–2 and did not interfere with patient wellbeing.[121]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant published evidence on the clinical efficacy, safety, and tolerability of second-line therapies for treatment of *KRAS* G12C mutation-positive advanced NSCLC. Searches were conducted on 2 July 2024. Full details of the methodology and results of the SLR are provided in Appendix D.

Two relevant trials were identified relating to the efficacy of adagrasib in patients with *KRAS* G12C mutation-positive advanced NSCLC whose disease progressed after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

- KRYSTAL-12, a phase 3 randomised controlled trial (RCT) that enrolled a total of 453 patients, of whom 301 were assigned to treatment with adagrasib and 152 were assigned to treatment with docetaxel monotherapy: 1 publication (congress abstract) and unpublished data sourced from the clinical study report (CSR).[121, 129]
- KRYSTAL-1[a], a phase 1/2 single-arm trial that enrolled 116 patients in phase 2 Cohort A, all of whom were treated with adagrasib: 1 publication (journal article) and unpublished data sourced from the CSR for the phase 2 Cohort A portion of the trial.[122, 123, 130]

The SLR identified 128 publications relating to appraisal comparators[b].

- Docetaxel monotherapy: 127 publications (95 unique RCTs and 7 unique non-RCTs)
- Docetaxel + nintedanib: 4[c] publications (1 unique RCT and 1 unique non-RCT)

Among these results, one trial was identified as relevant to the UK for network meta-analysis (Section B.2.9).

- LUME-Lung 1, a phase 3 RCT that enrolled a total of 1,314 patients, of whom 655 were assigned to treatment with docetaxel + nintedanib and 659 were assigned to treatment with docetaxel + placebo: 3 publications (journal articles).[81, 131, 132]

B.2.2 List of relevant clinical effectiveness evidence

Table 7: Clinical effectiveness evidence

Study	KRYSTAL-12 (NCT04685135)	KRYSTAL-1 (NCT03785249)
Study design	International, multicentre, open-label, randomised, two-arm, phase 3 trial	Multicentre, open-label, single-arm, dose-escalation and multiple expansion cohort, phase 1/2 trial

[a] KRYSTAL-1 is relevant to this submission for two reasons. (1) The KRYSTAL-12 interim OS results remain restricted, so the KRYSTAL-1 phase 2 Cohort A OS data are used to supplement the KRYSTAL-12 PFS data. (2) KRYSTAL-12 evaluated intracranial efficacy in patients with treated CNS metastases (n=78 in the adagrasib arm and n=36 in the docetaxel arm), but not in patients with *untreated* CNS metastases. The phase 1b portion of KRYSTAL-1 evaluated intracranial efficacy in a cohort of patients with untreated CNS metastases (n=25). These data are presented to demonstrate the intracranial efficacy of adagrasib in patients whose response cannot be confounded with localised therapy (Section B.1.3.2.4.3).

[b] Sotorasib was included in the SLR as it was a suggested comparator in the final scope issued by NICE. The SLR identified five publications relating to sotorasib, including two publications (one journal article and one conference abstract) reporting results from CodeBreaK 200. However, sotorasib's inclusion in the scope was subject to managed access review. At the time of submission, timelines for this review of TA781 (ID6287) are not publicly available, and sotorasib is not considered a relevant comparator for this appraisal as it has not exited the CDF.

[c] Three of these four publications are also included in the count for docetaxel monotherapy, as LUME-Lung 1 compared docetaxel + nintedanib vs docetaxel monotherapy.

Population	Patients with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation and disease progression on or after treatment with a platinum-based regimen and an immune checkpoint inhibitor.	Phase 2 Cohort A*: Patients with advanced NSCLC with *KRAS* G12C detected in tumour tissue and measurable disease after treatment with a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy.
Intervention(s)	Adagrasib (MRTX849)	Adagrasib (MRTX849)
Comparator(s)	Docetaxel	Not applicable
Indicate if study supports application for marketing authorisation	No; application for marketing authorisation was supported by KRYSTAL-1	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale for use/non-use in the model	KRYSTAL-12 is the pivotal phase 3 study of adagrasib vs docetaxel in the relevant patient population and provides the primary evidence base for this submission.	As the KRYSTAL-12 interim OS results remain restricted, data from KRYSTAL-1 are used to estimate survival outcomes in the economic model.
Reported outcomes specified in the decision problem†	• **Progression-free survival** • **Overall survival** • Response rates • **Adverse effects of treatment** • **Health-related quality of life**	• **Progression-free survival** • **Overall survival** • Response rates • Adverse effects of treatment
All other reported outcomes	• Duration of response • Intracranial efficacy	• Duration of response • Intracranial efficacy

*Cohort B comprised patients with NSCLC with *KRAS* G12C mutation detected in blood (i.e. circulating tumour DNA) and Cohort E comprised patients with NSCLC with *KRAS* G12C and STK11 mutations in the first-line systemic treatment setting. Cohorts C, D, F, and G included patients with other cancers. The KRYSTAL-1 phase 2 data presented in this dossier are for Cohort A only.
†Outcomes in bold font are those used in the economic model.
Abbreviations: DNA, deoxyribonucleic acid; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; OS, overall survival.
Sources: KRYSTAL-12 CSR,[121] KRYSTAL-1 phase 2 Cohort A CSR[122]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

B.2.3.1.1 KRYSTAL-12

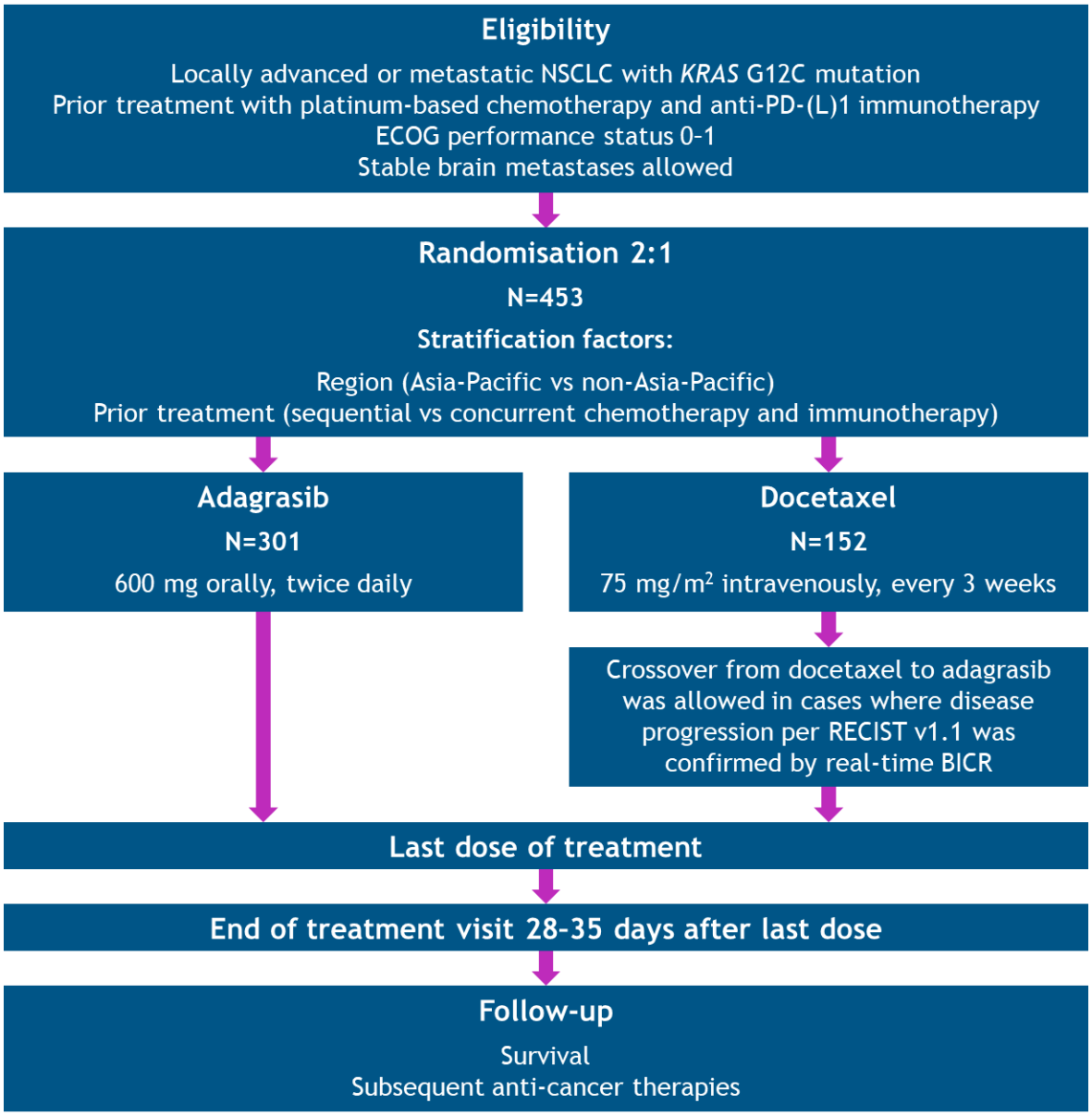
KRYSTAL-12 (NCT04685135) is an international, multicentre, open-label, randomised, two-arm phase 3 trial (Figure 7). The study enrolled patients from 173 of 304 activated sites, with 186 activated sites across 17 countries in Europe (including the UK), 63 activated sites across 4 countries in Asia, 48 activated sites in the US, and 7 activated sites in Australia.[121]

Eligible patients were adults with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation and disease progression on or after prior treatment with a platinum-containing regimen (cisplatin or carboplatin) and an immune checkpoint inhibitor (i.e. anti-PD-1/PD-L1 inhibitor), either concurrently or sequentially. The presence of active brain metastases was an exclusion criterion, although patients were eligible if brain metastases

were treated and neurologically stable for ≥2 weeks prior to randomisation. Eligible patients were randomised 2:1 to adagrasib (n=301) and docetaxel monotherapy (n=152) using a centralised Interactive Web Response System, with randomisation stratified by region (Asia-Pacific vs non-Asia-Pacific) and prior treatment (sequential vs concurrent platinum-based chemotherapy and immunotherapy).[121, 124]

The primary efficacy endpoint was PFS assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary endpoints included ORR assessed by BICR according to RECIST v1.1, duration of response (DOR), OS, safety, and PROs. The primary analysis of PFS was performed when 257 PFS events had occurred. The data cutoff for this analysis was 31 December 2023, with a median trial follow-up of 9.43 (95% CI, 8.02 to 10.38) months. For OS, a group sequential design was utilised with an interim analysis for OS conducted at the time of final PFS analysis. For the reasons outlined in Section B.2.6.1.2, the interim OS results remain restricted. The study will continue as planned until the prespecified final OS analysis. The final OS analysis is planned when approximately [redacted] OS events have occurred, which is projected to occur approximately in [redacted] with outputs/reports availability in [redacted].

Figure 7: KRYSTAL-12 | Study design



Abbreviations: BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours.
Sources: KRYSTAL-12 protocol,[124] KRYSTAL-12 CSR[121]

B.2.3.1.2 KRYSTAL-1

KRYSTAL-1 (NCT03785249) was a multicentre, open-label, single-arm dose-escalation and multiple expansion cohort, phase 1/2 trial conducted across 29 sites in the United States (Figure 8). In phase 2, Cohort A enrolled 116 patients.[122]

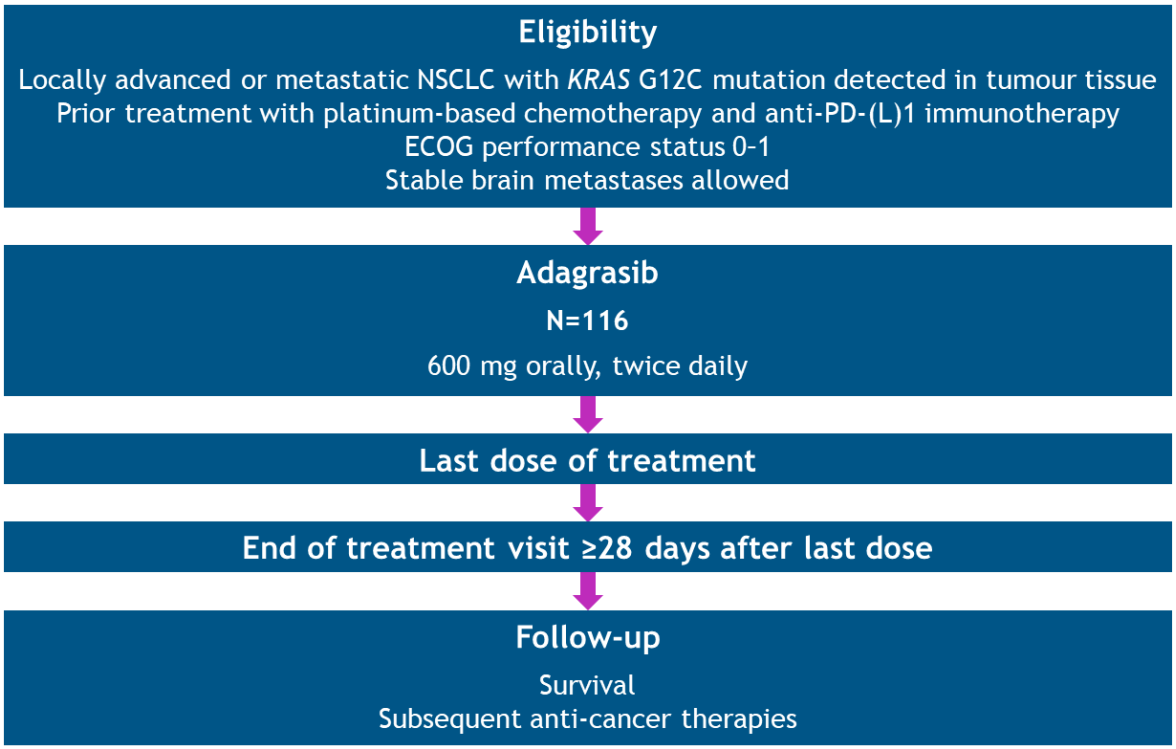
Patients eligible for Cohort A were patients with NSCLC with *KRAS* G12C detected in tumour tissue and measurable disease after treatment with a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy. Cohort B comprised patients with NSCLC with *KRAS* G12C mutation detected in blood and Cohort E comprised patients with

NSCLC with *KRAS* G12C and STK11 mutations in the first-line systemic treatment setting. Cohorts C, D, F, and G included patients with other cancers.[122, 133] The KRYSTAL-1 phase 2 data presented in this dossier are for Cohort A only[d].

The primary efficacy endpoint was ORR assessed by BICR according to RECIST v1.1. Additional endpoints included DOR, PFS, OS, safety, and pharmacokinetics. The primary data cutoff for efficacy analyses was 15 June 2021, with a median follow-up in the enrolled population of 9.0 months. At the time of this primary data cutoff, 40 patients remained on treatment. Further efficacy and safety analyses followed a second data cutoff date of 15 October 2021, and an additional OS analysis was conducted following a data cutoff date of 15 January 2022.[122, 123, 133]

KRYSTAL-1 also included a phase 1b cohort that enrolled patients with neurologically stable, asymptomatic, untreated CNS metastases (n=25).[133, 134] Intracranial efficacy in this cohort is discussed in Section B.2.7.2 along with KRYSTAL-12 data for the subgroup of patients with brain metastases.

Figure 8: KRYSTAL-1 phase 2 Cohort A | Study design



Abbreviations: ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1.
Sources: KRYSTAL-1 protocol,[133] KRYSTAL-1 phase 2 Cohort A CSR[122]

B.2.3.2 Trial methodology

Table 8 provides a summary of KRYSTAL-12 and KRYSTAL-1 trial methodologies.

[d] Cohort A was the cohort of focus as it had a larger sample size, whereas the largely hypothesis-generating Cohort B, with its smaller sample size, was intended to support the results observed in Cohort A.

Table 8: Comparative summary of KRYSTAL-12 and KRYSTAL-1 methodology

Trial name	KRYSTAL-12 (NCT04685135, phase 3)	KRYSTAL-1 (NCT03785249)
Study objective	To compare the efficacy of adagrasib vs docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior treatment with a platinum-based regimen and immune checkpoint inhibitor therapy.	To evaluate the clinical activity/efficacy of adagrasib in cohorts of patients having selected solid tumour malignancies with *KRAS* G12C mutation.
Location	International study: 304 study sites in 23 countries across 4 continents (United Kingdom, Australia, Austria, Belgium, China, Czechia, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russia, Singapore, South Korea, Spain, Switzerland, United States); 5 sites were located in the UK.	29 study sites in the United States
Method of randomisation	Patients were randomised in a 2:1 ratio using a centralised Interactive Web Response System to receive treatment assignment to either adagrasib or docetaxel.	Not applicable. KRYSTAL-1 was a single-arm, open-label trial.
Method of blinding	KRYSTAL-12 is an open-label trial. However, central radiology reviewers were blinded to treatment assignment.	Not applicable. KRYSTAL-1 was a single-arm, open-label trial.
Participant eligibility criteria	**Key inclusion criteria** • Age ≥18 years • Histologically or cytologically confirmed diagnosis of NSCLC with *KRAS* G12C mutation • Unresectable, locally advanced or metastatic disease • Presence of evaluable or measurable disease per RECIST v1.1 • Receipt of prior treatment with a platinum-containing regimen (cisplatin or carboplatin) and an immune checkpoint inhibitor (i.e. anti-PD-[L]1 inhibitor) concurrently or sequentially for advanced or	**Key inclusion criteria (Cohort A)** • Age ≥18 years • Histologically confirmed diagnosis of squamous or non-squamous NSCLC with *KRAS* G12C mutation • Unresectable or metastatic disease • Presence of measurable disease per RECIST v1.1 • No available treatment with curative intent • Receipt of prior treatment with at least a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy • ECOG performance status of 0 or 1

	metastatic disease with the outcome of objective disease progression on or after treatment • ECOG performance status of 0 or 1	
	Key exclusion criteria • Active brain metastases. Patients are eligible if brain metastases are treated and patients are neurologically stable for at least 2 weeks prior to randomisation. If patients require the use of corticosteroids, patients must be on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) prior to randomisation • Prior treatment with an agent targeting KRAS G12C (e.g. AMG 510, sotorasib) • Prior treatment with docetaxel	**Key exclusion criteria (Cohort A)** • Active brain metastases. Patients are eligible if brain metastases are adequately treated and patients are neurologically stable for at least 2 weeks prior to enrolment without the use of corticosteroids or are on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) • Prior treatment with a therapy targeting KRAS G12C
Duration of study	Median follow-up: 9.43 months	Median OS follow-up: 15.6 months Median follow-up for other endpoints: 12.9 months
Trial drugs	**Intervention (n=301)** Adagrasib 600 mg administered orally twice daily until disease progression, unacceptable adverse events, investigator decision, patient refusal, or death	**Intervention (Cohort A, n=116)** Adagrasib 600 mg administered orally twice daily until disease progression, unacceptable adverse events, patient refusal, or death
	Comparator (n=152) Docetaxel 75 mg/m^2 administered by intravenous infusion over 1 hour every 3 weeks until disease progression, unacceptable adverse events, investigator decision, patient refusal, or death	
Permitted and disallowed concomitant medications	**Permitted concomitant medication** • Prophylactic anti-emetics that do not cause QT prolongation • Bisphosphonates and RANKL inhibitors (provided patients have been on stable oral doses for ≥2 weeks prior to study entry or stable with ≥2 parenteral injections prior to study entry; this stable dose should be maintained during the treatment period)	**Permitted concomitant medication** • Prophylactic anti-emetics that do not cause QT prolongation • P-gp substrates and cytochrome P450 substrates should be used with caution • Growth factors • Vaccines made from inactivated micro-organisms or from agents derived from or similar to pathogenic micro-organisms or toxins

	• Strong inhibitors of CYP2C8 should be used with caution with adagrasib • Growth factors • Vaccines made from inactivated micro-organisms, from agents derived from or similar to pathogenic micro-organisms or toxins, or developed using RNA technology	
	Prohibited concomitant medication • Other anti-cancer or experimental therapy • Proton pump inhibitors, loperamide, substrates of cytochrome P450, BCRP inhibitors, substrates of P-gp, and medications with QTc-prolonging activity should be avoided with adagrasib • Strong inhibitors of CYP3A4 should be avoided with docetaxel, and should be avoided with adagrasib until adagrasib has reached steady state approximately 8 days after continuous dosing • Strong inducers of CYP3A4 should be avoided during the study • Herbal medications/preparations • Vaccines consisting of live, attenuated micro-organisms	**Prohibited concomitant medication** • Other anti-cancer systemic therapy (approved or investigational) • Proton pump inhibitors and medications with QTc-prolonging activity should be avoided • Herbal medications/preparations • Vaccines consisting of live, attenuated micro-organisms to be reviewed with the Medical Monitor
Primary outcomes	PFS assessed by BICR, defined as the time from randomisation to the date of PD per RECIST v1.1 or death due to any cause, whichever occurs first	ORR assessed by BICR, defined as the percentage of patients achieving a confirmed CR or PR per RECIST v1.1
Other outcomes used in the model/specified in scope	• Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Response rates • Adverse effects of treatment
Pre-planned subgroups	PFS was determined for prespecified subgroup analysis defined by: • Gender: female vs male • Age: <65 vs ≥65 years old; <65, 65–75 vs ≥75 years old	ORR and DOR were determined for prespecified subgroup analysis defined by: • Sex • Age group: <65 vs ≥65 years of age

	• Race: white vs non-white • ECOG performance status: 0 vs 1 • Smoking history: lifetime non-smoker, past smoker, vs current smoker • Region: non-Asia-Pacific vs Asia-Pacific • Administration of the last prior platinum-based chemotherapy and anti-PD-(L)1 antibody treatment: sequential vs concurrent • Number of prior lines of therapy in advanced/metastatic setting: 1, 2, vs >2 • Brain metastasis at baseline: yes vs no • Liver metastasis at baseline: yes vs no • Bone metastasis at baseline: yes vs no • Tumour proportion score (PD-L1 protein expression): <1%, 1–49%, vs ≥50% • Best overall response of the last prior therapy in advanced/metastatic setting: CR, PR, SD, vs PD	• Number of prior systemic treatment regimens: 1 vs >1 regimen • Concurrent vs sequential prior platinum therapy and checkpoint inhibitor therapy • Smoking history: never smoked vs current smoker vs past smoker • Baseline ECOG performance status: 0 vs 1 • Liver metastases at baseline: yes vs no • Brain metastases at baseline: yes vs no • Bone metastases at baseline: yes vs no • Adrenal metastases at baseline: yes vs no

Abbreviations: BCRP, breast cancer resistance protein; BICR, blinded independent central review; CR, complete response; CYP, cytochrome P450; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1; PFS, progression-free survival; P-gp, P-glycoprotein; PR, partial response, QTc, QT corrected for heart rate; RANKL, receptor activator of nuclear factor kappa beta; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; SD, stable disease.
Sources: KRYSTAL-12 protocol,[124] KRYSTAL-12 CSR,[121] KRYSTAL-1 protocol,[133] KRYSTAL-1 phase 2 Cohort A CSR.[122]

B.2.3.2.1 Trial outcomes

KRYSTAL-12 endpoints, their definitions, and simplified censoring rules are shown in Table 9. Full details of the censoring rules can be found in the KRYSTAL-12 CSR.[121] Key KRYSTAL-1 endpoints are presented in Table 10 and additional endpoints are detailed in Appendix N.

Table 9: KRYSTAL-12 | Summary of key endpoints

Endpoint/assessment	Definition	Censoring rules
Primary endpoint		
PFS assessed by BICR	Time from randomisation to date of disease progression per RECIST v1.1 or death due to any cause, whichever occurs first	Censored on the date of the last evaluable disease assessment when: • PD or death occur after ≥2 consecutive missed or NE tumour assessments • patient administered alternative cancer treatment prior to documented PD • patient lost to follow-up • patient withdrawal of consent for follow-up • patient continues on study treatment without PD at the time of DCO or EoS • patient with lesion affected by concomitant procedure before PD or death
Key secondary endpoint		
OS	Time from randomisation to date of death due to any cause	Patients alive: censored on date last known to be alive. Patients with no on-study data: censored on date of randomisation (Day 1).
Secondary endpoints		
ORR assessed by BICR	Percentage of patients achieving a confirmed CR or PR per RECIST v1.1	Not applicable
DOR assessed by BICR	Time from first documentation of CR/PR per RECIST v1.1 to first documentation of PD or death due to any cause	As above for PFS
PRO endpoints	Assessed using LCSS and EQ-5D-5L	Not applicable
Exploratory endpoints		
icORR by BICR	Percentage of patients in the CNS population achieving a confirmed icCR or icPR per RECIST v1.1	Not applicable

icDOR assessed by BICR	Time from first documentation of icCR/icPR per RECIST v1.1 to first documentation of icPD or death due to any cause	As above for PFS
icTTP assessed by BICR	Time from randomisation to first documentation of icPD, based on either new brain metastases or progression of existing brain metastases	Not reported
Safety endpoints		
Safety and tolerability	Extent of study drug exposure AEs: any reaction, side effect, or medical event that occurs during trial participation TEAEs: first occur or increase in severity on/after first dose of study treatment and ≤28 days after last dose of study treatment and prior to initiating subsequent SACT SAEs: result in death, are life-threatening, require hospitalisation, result in disability, or require medical or surgical intervention to prevent one of the outcomes above Laboratory data Vital signs Physical examinations, ECGs, and other safety-related observations	Not applicable

Abbreviations: AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCO, data cutoff; DOR, duration of response; ECG, electrocardiogram; EoS, end of study; EQ-5D-5L, EuroQol 5-Dimension 5-Level; ic, intracranial; LCSS, Lung Cancer Symptom Scale; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease, PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumours; SACT, systemic anti-cancer therapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TTP, time to progression.
Sources: KRYSTAL-12 protocol,[124] KRYSTAL-12 SAP,[135] KRYSTAL-12 CSR[121]

Table 10: KRYSTAL-1 | Summary of key endpoints

Endpoint/assessment	Details	Censoring rules
Primary endpoint		
ORR assessed by BICR	Percentage of patients achieving a confirmed CR or PR per RECIST v1.1	Not applicable
Additional endpoints		
PFS assessed by BICR and investigator	Time from date of first study treatment to date of disease progression per RECIST v1.1 or death due to any cause in the absence of documented PD, whichever occurs first	Censored on the date of the last evaluable disease assessment when: • PD or death occur after ≥2 consecutive missed or NE tumour assessments • patient administered alternative cancer treatment prior to documented PD • patient lost to follow-up • patient withdrawal of consent for follow-up • patient continues on study treatment without PD at the time of DCO or EoS
OS	Time from date of first study treatment to date of death due to any cause	Patients continuing study at the time of DCO, lost to follow-up, or withdrew consent: censored on date last known to be alive. Patients not receiving study treatment: censored on informed consent date. Patients with no follow-up after first dose of study drug: censored at date of first dose.

Abbreviations: BICR, blinded independent central review; CR, complete response; DCO, data cutoff; EoS, end of study; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
Sources: KRYSTAL-1 protocol,[133] KRYSTAL-1 phase 2 Cohort A SAP,[136] KRYSTAL-1 phase 2 Cohort A CSR,[122] KRYSTAL-1 phase 2 Cohort A CSR addendum[123]

B.2.3.3 Baseline demographic and disease characteristics

Baseline characteristics for patients in KRYSTAL-12 and KRYSTAL-1 are presented in Table 11. Baseline characteristics were well-balanced between the KRYSTAL-12 treatment arms, and similar to those of the KRYSTAL-1 population. Mean age was 64 years (range, 34–83) and 65 years (range, 45–80) in the adagrasib and docetaxel arms of KRYSTAL-12, respectively, and 64 years (range, 25–89) in KRYSTAL-1. There were 64% and 72% males in the adagrasib and docetaxel arms of KRYSTAL-12, respectively, which differed from the 44% in KRYSTAL-1.[121, 122, 130]

Disease characteristics were also similar in the KRYSTAL-12 treatment arms and the KRYSTAL-1 population, including tumour histology and disease stage. The KRYSTAL-12 population included a greater proportion of patients with an ECOG performance status of 0 (32% and 31% in the two treatment arms) relative to KRYSTAL-1 (15.5%).[121, 122, 130]

The proportion of patients who received prior therapy with both platinum-based chemotherapy and immunotherapy is comparable across populations (100% in both KRYSTAL-12 treatment arms and 98.3% in KRYSTAL-1), as is the proportion of concurrent vs sequential prior treatment (73% concurrent in both KRYSTAL-12 treatment arms and 70.7% in KRYSTAL-1).[121, 122, 130] These aspects of prior treatment and treatment sequencing are also consistent with the patient populations described by clinical experts.[24]

Table 11: Patient baseline demographic and disease characteristics

Baseline characteristic	KRYSTAL-12		KRYSTAL-1
	Adagrasib (n=301)	Docetaxel (n=152)	Adagrasib (n=116)
Age, years			
Mean (SD)	63.6 (8.66)	63.9 (7.81)	64.4 (9.64)
Median (range)	64 (34–83)	65 (45–80)	64.0 (25–89)
Age group, n (%)			
<65 years	160 (53.2)	74 (48.7)	59 (50.9)
≥65 years	141 (46.8)	78 (51.3)	57 (49.1)
≥65 to <75 years	111 (36.9)	67 (44.1)	NR
≥75 to <85 years	30 (10.0)	11 (7.2)	NR
≥85 years	0	0	NR
Sex, n (%)			
Male	193 (64.1)	110 (72.4)	51 (44.0)
Female	108 (35.9)	42 (27.6)	65 (56.0)
Childbearing potential	8 (7.4)	4 (9.5)	3 (2.6)
Post-menopausal	89 (82.4)	34 (81.0)	49 (42.2)
Surgically sterile	11 (10.2)	4 (9.5)	13 (11.2)
Race, n (%)			
White	135 (44.9)	81 (53.3)	97 (83.6)
Black or African American	0	0	9 (7.8)
Asian	72 (23.9)	37 (24.3)	5 (4.3)
American Indian or Alaska Native	0	0	1 (0.9)
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (0.7)	1 (0.7)	4 (3.4)

Not reported	81 (26.9)	30 (19.7)	NA
Missing	11 (3.7)	3 (2.0)	NA
Region			
Asia-Pacific	78 (25.9)	40 (26.3)	NA
Non-Asia-Pacific	223 (74.1)	112 (73.7)	NA
ECOG PS, n (%)			
0	96 (31.9)	47 (30.9)	18 (15.5)
1	205 (68.1)	104 (68.4)	97 (83.6)
2	0	0	0
3	0	0	0
4	0	0	0
Missing	0	1 (0.7)	1 (0.9)
Tumour histology, n (%)			
Adenocarcinoma	283 (94.0)	147 (96.7)	113 (97.4)
Large cell carcinoma	4 (1.3)	1 (0.7)	0
Unclassified/undifferentiated carcinoma	6 (2.0)	1 (0.7)	0
Squamous	6 (2.0)	0	3 (2.6)
Other	2 (0.7)	3 (2.0)	0
Tumour PD-L1 expression, n (%)			
<1%	61 (20.3)	34 (22.4)	47 (40.5)
1–49%	126 (41.9)	69 (45.4)	27 (23.3)
≥50%	71 (23.6)	29 (19.1)	12 (10.3)
Not evaluated	43 (14.3)	20 (13.2)	30 (25.9)
Disease stage, n (%)			
Locally advanced	18 (6.0)	8 (5.3)	13 (11.2)
Metastatic	283 (94.0)	144 (94.7)	103 (88.8)
Metastasis by BICR / INV, n (%) / n (%)			
Adrenal	68 (22.6) / 70 (23.3)	24 (15.8) / 26 (17.1)	22 (19.0)*
Bone	68 (22.6) / 132 (43.9)	39 (25.7) / 61 (40.1)	46 (39.7)*
Brain	52 (17.3) / 75 (24.9)	28 (18.4) / 27 (17.8)	NR
CNS	NR	NR	24 (20.7)*
Liver	46 (15.3) / 47 (15.6)	18 (11.8) / 17 (11.2)	19 (16.4)*
Lung	255 (84.7) / 269 (89.4)	123 (80.9) / 129 (84.9)	NR
Lymph node	187 (62.1) / 194 (64.5)	93 (61.2) / 96 (63.2)	NR
Other	110 (36.5) / 109 (36.2)	58 (38.2) / 48 (31.6)	NR
Smoking history, n (%)			
Lifetime non-smoker	17 (5.6)	9 (5.9)	5 (4.3)
Current smoker	56 (18.6)	30 (19.7)	11 (9.5)
Former smoker	228 (75.7)	112 (73.7)	100 (86.2)
Missing	0	1 (0.7)	NA
Number of prior systemic regimens, n (%)			
1	185 (61.5)	100 (65.8)	50 (43.1)
2	89 (29.6)	40 (26.3)	40 (34.5)
3	19 (6.3)	10 (6.6)	12 (10.3)
4+	8 (2.7)	2 (1.3)	14 (12.1)
Mean (SD)	1.5 (0.77)	1.4 (0.68)	2.0 (NR)
Median (range)	1.0 (1–5)	1.0 (1–4)	2.0 (1–7)

Prior systemic therapy, n (%)			
Platinum agent only	0	0	2 (1.7)
Checkpoint inhibitor only	0	0	0
Both platinum and CIT	301 (100)	152 (100)	114 (98.3)
Concurrent	221 (73.4)	111 (73.0)	82 (70.7)
Sequential	80 (26.6)	41 (27.0)	32 (27.6)

*Source of diagnosis (i.e. BICR or investigator) is not reported.
Abbreviations: BICR, blinded independent central review; CIT, checkpoint inhibitor therapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; NA, not applicable; NR, not reported; PD-L1, programmed death ligand 1; SD, standard deviation.
Sources: KRYSTAL-12 CSR,[121] KRYSTAL-1 phase 2 Cohort A CSR,[122] Jänne 2022[130]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

Table 12 describes the populations included in KRYSTAL-12 and KRYSTAL-1.

Table 12: Analysis sets in KRYSTAL-12 and KRYSTAL-1

Analysis set	Definition	KRYSTAL-12		KRYSTAL-1
		Adagrasib n (%)	Docetaxel n (%)	Adagrasib n (%)
ITT	All randomised patients	301 (100)	152 (100)	NA
CNS ITT	All patients who were identified as having non-measurable and/or measurable brain disease at baseline per RECIST v1.1	78 (25.9)	36 (23.7)	NA
FAS – BICR	All patients with measurable disease (assessed by BICR per RECIST v1.1) at baseline who received ≥1 dose of adagrasib	NA	NA	112 (96.6)
FAS – investigator	All patients with measurable disease (assessed by investigator per RECIST v1.1) at baseline who received ≥1 dose of adagrasib	NA	NA	116 (100)
Safety	All patients who received any part of a dose of study medication	298 (99.0)	140 (92.1)	116 (100)
PK evaluable	All patients who received adagrasib and have adequate and reliable data for the evaluation of adagrasib PK	289 (96.0)	43 (28.3)	111 (95.7)

Abbreviations: BICR, blinded independent central review; CNS, central nervous system; FAS, full analysis set; ITT, intent-to-treat; NA, not applicable; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours.
Sources: KRYSTAL-12 CSR,[121] KRYSTAL-1 phase 2 Cohort A CSR[122]

B.2.4.2 Statistical analyses

Statistical analysis methods for KRYSTAL-12 are summarised in Table 13. Analyses for the key endpoints are described in the table, while the methods for additional endpoints can be found in the CSR.[121]

Table 13: KRYSTAL-12 | Summary of statistical analyses

Hypothesis objective	Fixed-sequence testing procedure: • Primary hypothesis: PFS tested at α=0.05 (2-sided) • Key secondary hypothesis: ORR tested at α=0.05 (2-sided) • Key secondary hypothesis: OS tested at α=0.05 (2-sided)
Statistical analysis	**Randomisation** Patients were randomised 2:1 to adagrasib or docetaxel and stratified based on region (non-Asia-Pacific vs Asia-Pacific) and administration of prior platinum-based chemotherapy and anti-PD-L1 antibody (sequential vs concurrent). **Primary endpoint: PFS** The distributions of PFS were estimated using the KM method. The stratified log-rank test was used to compare the PFS between the two treatment arms. The stratification factors used for randomisation were used in the stratified analyses. The KM method was used to estimate the median, Q1 and Q3 along with 95% CI, as well as the estimated PFS rate at 3, 6, 9, and 12 months. The CIs were calculated based on Brookmeyer and Crowley method using log-log transformation. The estimate of the standard error was calculated using Greenwood's formula. A stratified Cox proportional hazard model with stratification factors used for randomisation was used to assess the magnitude of the treatment difference (i.e. HR). Each stratum defines a separate baseline hazard function. Efron's method was used to handle ties. The HR and its 95% CI from the stratified Cox proportional hazard model with a single treatment covariate is reported. The fixed-sequence testing procedure to control the familywise error rate was used for testing of PFS and the secondary efficacy endpoints. Initially, the PFS hypothesis was tested at α=0.05 (2-sided). Because the PFS test was statistically significant, the ORR hypothesis was tested at α=0.05 (2-sided). A sensitivity analysis using the investigator's assessment of PFS were performed. All other sensitivity analyses were performed for PFS by BICR. **OS** OS was analysed using methods similar to those for PFS. One interim analysis was planned for after approximately 50% of the expected death events had occurred. At the time of PFS analysis (after 257 PFS events had occurred, 164 [54.5%] in the adagrasib arm and 93 [61.2%] in the docetaxel arm), 60 death events had occurred. Because the ORR test was statistically significant, the OS hypothesis was tested at α=0.05 (2-sided). A group sequential design was used with the O'Brien–Fleming boundary as implemented by the Lan–DeMets alpha spending method. Final analysis is planned for [redacted]. **EQ-5D-5L** Changes in EQ-5D scores were examined via MMRM, which summarises the individual change over time and systematic differences in changes between groups. An unstructured correlation structure was assumed for

	measurements collected across visits. In case the estimation procedure did not converge, other covariance structures, namely, autoregressive 1 and compound symmetry were executed. The fit of the model to the data was assessed via Akaike's information criterion and Bayesian information criterion. Each EQ-5D profile was converted into a utility value by using the UK value set. **LCSS** LCSS is a nine-item disease-specific measure of QoL that evaluates HRQoL in terms of the following domains: symptoms, total symptomatic distress, impact on activities, and overall QoL. Six of the nine items assess lung cancer symptoms across appetite loss (anorexia), fatigue, cough, shortness of breath (dyspnoea), blood in sputum (haemoptysis), and pain, which comprise the average symptom burden index (ASBI) score. The remaining three items are the global impression of lung cancer symptoms, impact of lung cancer on activities, and overall QoL, which comprise the 3-item global index (3-IGI). Changes in LCSS scores were examined via MMRM as described above for EQ-5D. **Exploratory endpoints** *icORR* The analysis method was per the primary analysis of ORR but used Fisher's Exact Test, rather than the Cochran–Mantel–Haenszel chi-square test to compare the response rate between the treatment arms. *icDOR* The icDOR was summarised and analysed similar to DOR in the subset of the CNS ITT population with an icBOR of CR or PR.
Sample size, power calculation	The sample size of 450 is primarily estimated from the secondary endpoint of OS. For the PFS endpoint, the study was planned to have 90% power to detect an HR of 0.645 (under the assumption of median PFS for docetaxel arm of approximately 4 months compared to 6.2 months for the adagrasib arm) at a 2-sided level of significance of 0.05 based on 246 disease progression or death events. For the secondary endpoint, OS, the study was planned to have 80% power to detect an HR of 0.72 (under the assumption of median OS for docetaxel arm of approximately 10 months compared to 13.9 months in the adagrasib arm) at a 2-sided level of significance of 0.05 based on 334 death events.
Data management, patient withdrawals	Imputation of missing data was performed for missing start and stop dates for AEs and prior/concomitant medications, for start dates of alternative cancer treatment, and for diagnosis and prior disease history. Data from patients who were lost to follow-up or had missing observations before reaching an endpoint in any of the time-to-event analyses were treated as censored as described in Table 9. No other replacement or imputation of missing data was performed for dropouts.
Statistical analysis timepoints	The final analysis of PFS was performed when 257 PFS events had occurred. The data cutoff for this analysis was 31 December 2023. For the reasons outlined in Section B.2.6.2.2, the interim OS results remain restricted. The study will continue as planned until the prespecified final OS analysis. The final OS analysis is planned when approximately [redacted] OS events have occurred, which is projected to occur approximately in [redacted] with outputs/reports availability in [redacted].

Abbreviations: 3-IGI, 3-item global index; AE, adverse event; ASBI, average symptom burden index; BOR, best overall response; CI, confidence interval; CNS, central nervous system; CR, complete response; CSR, clinical study report; DOR, duration of response; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HR, hazard ratio; ic, intracranial; ITT, intent-to-treat; KM, Kaplan–Meier; MMRM, mixed model for repeated measures; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; Q1, first quartile; Q3, third quartile; VAS, visual analogue scale.
Sources: KRYSTAL-12 SAP,[135] KRYSTAL-12 CSR,[121] KRYSTAL-12 PRO supplemental SAP[137]

Statistical analysis methods for KRYSTAL-1 are summarised in Table 14. Analyses for the key endpoints are described in the table, while the methods for additional endpoints can be found in the phase 2 Cohort A CSR.[122]

Table 14: KRYSTAL-1 | Summary of statistical analyses

Statistical analysis	**Primary endpoint: ORR** Descriptive statistics (frequency and percentage) for ORR, and of best overall response (CR, PR, SD, PD) based on the response assessments by the BICR and investigator, and the exact 95% Clopper–Pearson CI for the ORR, were presented. Patients who could not be assessed for response were counted as not evaluable. **Time-to-event variables** Time-to-event variables were summarised, descriptively, using the KM estimate. The median and Q1 and Q3 and their 2-sided 95% CIs were calculated. In addition, the range was also displayed, as well as the rates at 3, 6, 9, and 12 months using KM estimation (Greenwood's formula).
Sample size, power calculation	The primary endpoint for evaluation of efficacy for Cohort A was ORR. The standard of care for patients treated in this setting is docetaxel with or without ramucirumab*, which is associated with ORR of up to 23%. The design for Cohort A utilised a 95% CI to exclude an ORR of 23%. Assuming adagrasib would result in an ORR of at least 35% in this treatment setting, a sample size of approximately 105 evaluable patients would be sufficient for the lower bound of a 2-sided 95% CI (Clopper–Pearson method) to exclude an ORR of 23%.
Data management, patient withdrawals	CRF data were captured via data entry in Medidata Rave. Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. Imputation of missing data was performed for missing start and stop dates for AEs and prior/concomitant medications and for diagnosis and prior disease history.
Statistical analysis timepoints	The design for Cohort A included a non-binding stopping rule for futility derived using East® software v6.5 to control the Type 2 error rate of 0.2. The Type 2 error spending function was based on the Rho family with parameter 2.0. The futility analysis was to be conducted when approximately 32 evaluable patients (approximately 30% of the total number of patients) were available for the response assessment. The futility bound was ≤6 observed responses among the first 32 patients.

*Ramucirumab is not a reimbursed treatment option in the UK, but is the standard of care in the US, where KRYSTAL-1 was conducted.
Abbreviations: AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CR, complete response; CRF, case report form; KM, Kaplan–Meier; ORR, objective response rate; PD, progressive disease; PR, partial response; Q1, first quartile; Q3, third quartile; SD, stable disease;
Sources: KRYSTAL-1 phase 2 Cohort A SAP,[136] KRYSTAL-1 phase 2 Cohort A CSR[122]

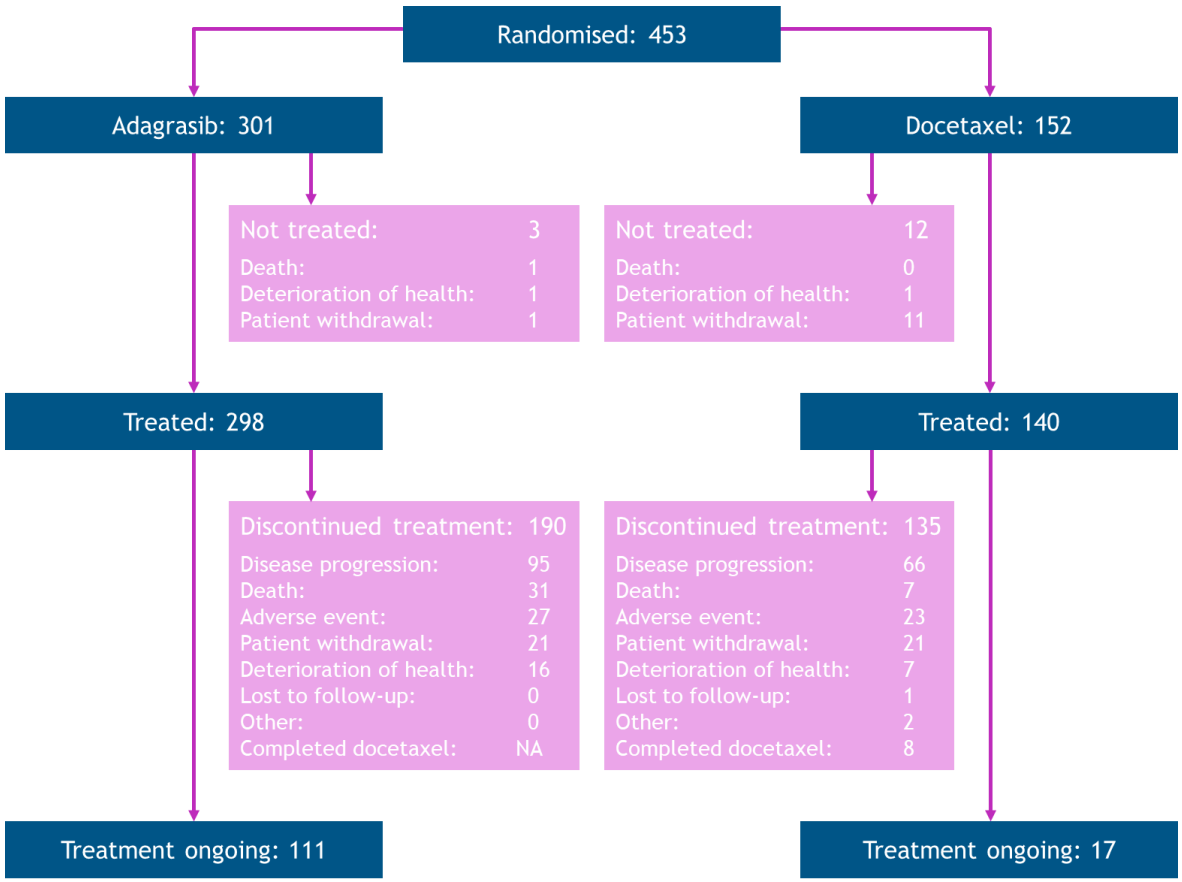
B.2.4.3 Patient flow

Patient flow in KRYSTAL-12 is shown in Figure 9. Of the 1,021 patients who were screened, a total of 568 patients were excluded at pre-screening (assessment of tumour *KRAS* G12C status only, n=423) and screening (for the whole study, n=145). Reasons for exclusion in pre-screening were ineligibility (389, 38.1%), withdrawal of consent (14, 1.4%), death (2, 0.2%), and other (18, 1.8%). Further exclusions at screening were due to ineligibility (133, 13.0%), withdrawal of consent (5, 0.5%), death (2, 0.2%), and other (4, 0.4%), and missing (1, 0.1%). The remaining 453 patients were randomised to either adagrasib (n=301, 66.4%) or docetaxel (n=152, 33.6%). Three (1.0%) patients assigned to the adagrasib arm and 12 (7.9%) patients in the docetaxel arm did not receive treatment, leaving 298 patients (99.0%) who received at least one dose of adagrasib and 140 patients (92.1%) who received at least one dose of docetaxel.[121]

At the time of data cutoff (31 December 2023), 190 patients (63.1%) in the adagrasib arm and 135 patients (88.8%) in the docetaxel arm had discontinued their assigned treatment, leaving 111 patients still receiving adagrasib and 17 patients still receiving docetaxel. The most frequent reason for treatment discontinuation was disease progression (95 patients [31.6%] in the adagrasib group and 66 [43.4%] in the docetaxel group); 44 patients (28.9%) crossed over from docetaxel to adagrasib after BICR-confirmed disease progression.[121]

Patient flow in KRYSTAL-1 phase 2 Cohort A is presented in Appendix D.

Figure 9: KRYSTAL-12 | Patient disposition | DCO 31 December 2023



Abbreviations: DCO, data cutoff.
Source: KRYSTAL-12 CSR[121]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Limitations of the evidence base

Critical appraisal of KRYSTAL-12 was conducted according to the NICE checklist,[138] which is adapted from Systematic Reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[139] This assessment concluded that KRYSTAL-12 was methodologically robust and had low risk of bias overall, with an appropriate randomisation scheme, well-balanced patient characteristics between the treatment arms, no unexpected imbalances in drop-outs between groups, and good quality assurance for the trial (Table 15). Critical appraisal of KRYSTAL-1, LUME-Lung 1, and CodeBreaK 200 is presented in Appendix D.

A discussion of the strengths and limitations of the KRYSTAL-12 and KRYSTAL-1 studies is provided in Section B.2.12.2.

Table 15: KRYSTAL-12 | Critical appraisal

Question	KRYSTAL-12
Was the randomisation method adequate?	Yes. Investigators randomised eligible patients by centralised Interactive Web Response System. Random assignment was stratified by region (Asia-Pacific vs non-Asia-Pacific) and prior treatment (sequential vs concurrent platinum-based chemotherapy and immunotherapy).
Was the allocation adequately concealed?	No. KRYSTAL-12 was an open-label study; thus, patients and investigators were not blinded to treatment assignment.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Random assignment was stratified by region and prior treatment.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	KRYSTAL-12 was an open-label study; thus, patients and investigators were not blinded to treatment assignment. However, outcomes were assessed by blinded independent central review.
Were there any unexpected imbalances in drop-outs between groups?	No. 99% of patients assigned to adagrasib and 92% of patients assigned to docetaxel received at least one dose of study treatment. After initiation of treatment, discontinuation due to patient withdrawal was 7.0% for adagrasib and 13.8% for docetaxel.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The ITT population was used in analyses of the efficacy endpoints. Imputation of missing data was performed as described in Table 13.

Was there good quality assurance for this trial?	Yes. The trial was conducted in accordance with ICH GCP guidelines and regulatory requirements. Quality assurance audits were conducted.

Abbreviations: GCP, ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ITT, intent-to-treat; PRO, patient-reported outcome.
Sources: KRYSTAL-12 protocol,[124] KRYSTAL-12 SAP,[135] KRYSTAL-12 CSR[121]

B.2.6 Clinical effectiveness results of the relevant trials

The following data are from KRYSTAL-12 and KRYSTAL-1 phase 2 Cohort A. All KRYSTAL-12 efficacy results were analysed at a data cutoff of 31 December 2023 after a median trial follow-up of 9.43 months when 257 PFS events (164 [54.5%] in the adagrasib arm and 93 [61.2%] in the docetaxel arm) had occurred.[121] For the reasons outlined in Section B.2.6.2.2 below, the KRYSTAL-12 interim OS results remain restricted. For this reason, KRYSTAL-1 OS data are used to supplement the KRYSTAL-12 PFS data.

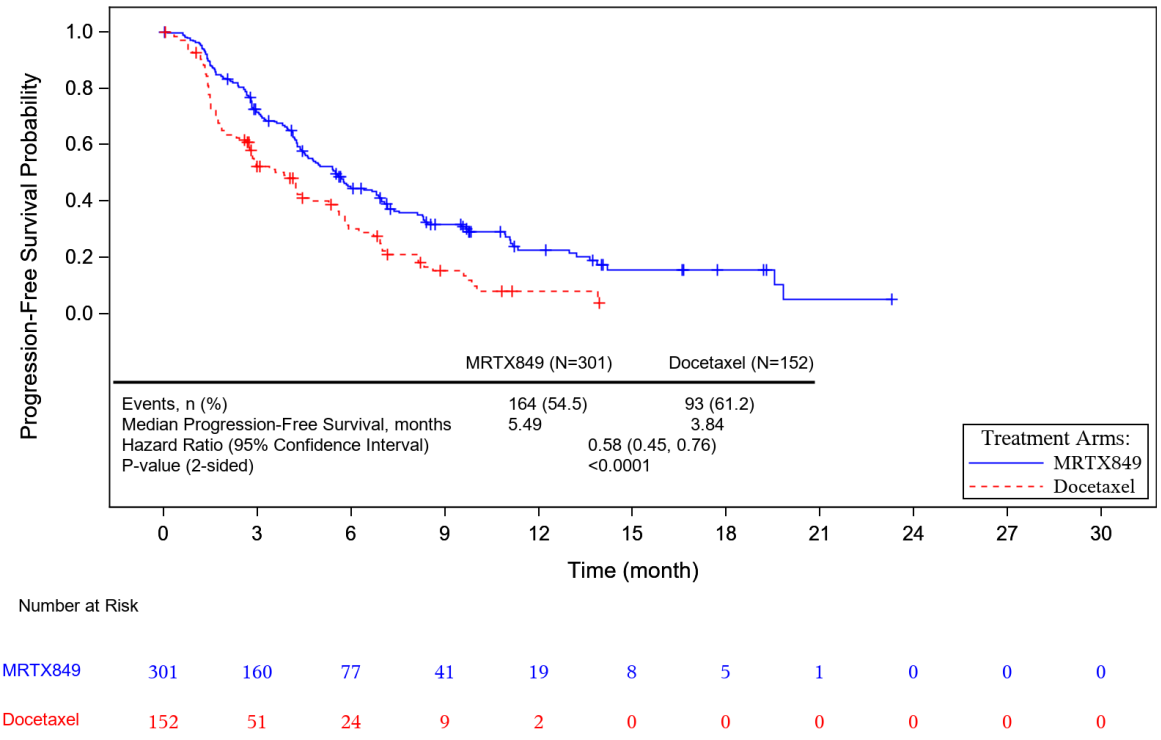
In addition to OS data, KRYSTAL-1 results for PFS, ORR, and safety are discussed briefly below in the context of consistency with KRYSTAL-12 results. Additional KRYSTAL-1 data are reported in Appendix N.

B.2.6.1 KRYSTAL-12

B.2.6.1.1 Progression-free survival

The primary endpoint in KRYSTAL-12 was PFS as assessed by BICR, defined as the time from randomisation to date of disease progression per RECIST v1.1 or death due to any cause. At the time of data cutoff, 164 (54.5%) PFS per BICR events were observed in the adagrasib arm vs 93 (61.2%) events in the docetaxel arm. Median PFS was 5.49 months (95% CI, 4.53 to 6.67) in the adagrasib group and 3.84 months (95% CI, 2.73 to 4.73) in the docetaxel group, with a HR for progression or death of 0.58 (95% CI, 0.45 to 0.76) corresponding to a 42% risk reduction for adagrasib relative to docetaxel ($p<0.0001$; Figure 10).[121] PFS rates were higher in the adagrasib arm across all time points evaluated, and the differences emerged rapidly, beginning at 3 months post-randomisation (Table 16).[121]

Figure 10: KRYSTAL-12 | Kaplan–Meier plot of PFS per BICR | DCO 31 December 2023



Number at Risk

MRTX849	301	160	77	41	19	8	5	1	0	0	0
Docetaxel	152	51	24	9	2	0	0	0	0	0	0

Abbreviations: BICR, blinded independent central review; DCO, data cutoff; PFS, progression-free survival.
Source: KRYSTAL-12 CSR[121]

Table 16: KRYSTAL-12 | PFS rate (95% CI) by time post-randomisation

	Adagrasib (n=301)	Docetaxel (n=152)
3 months	71.71% (65.74%, 76.83%)	52.20% (42.77%, 60.80%)
6 months	44.58% (37.80%, 51.11%)	30.13% (21.23%, 39.51%)
9 months	31.75% (25.14%, 38.55%)	15.20% (8.36%, 23.92%)
12 months	22.70% (16.10%, 30.01%)	7.88% (2.90%, 16.15%)

Abbreviations: CI, confidence interval; PFS, progression-free survival.
Source: KRYSTAL-12 CSR[121]

PFS by the investigator was consistent with the results from PFS by BICR, indicating a clinically meaningful increase in PFS with adagrasib vs docetaxel. Median PFS was 5.42 months (95% CI, 4.60 to 6.87) in the adagrasib group and 2.89 months (95% CI, 2.50 to 4.17) in the docetaxel group, with a HR for progression or death of 0.57 (95% CI, 0.45 to 0.74; p<0.0001).[121] As with the PFS by BICR results, PFS by investigator demonstrated higher rates for adagrasib vs docetaxel at 3 months (70.75% vs 49.38%), 6 months (44.34% vs 30.07%), 9 months (32.14% vs 17.61%), and 12 months (25.55% vs 8.05%).[121]

B.2.6.1.2 Overall survival

In line with the clinical study protocol and statistical analysis plan (SAP), an interim analysis for OS was conducted for KRYSTAL-12 at the time of final PFS analysis.[124, 135] The interim OS analysis HR did not cross the prespecified boundary for efficacy. In addition, these results are currently considered to be highly immature and inconclusive due to several factors including:

- The information fraction of OS at interim analysis was only [redacted]
- [redacted]
- [redacted]
    - [redacted]

Additionally, it should also be noted that due to the allowance of patients within the docetaxel arm to cross over and potentially receive adagrasib, upon BICR-confirmed progression, this may further potentially affect any meaningful interpretation of this analysis specially on an immature OS interim analysis data. The prespecified crossover-adjusted/ treatment switching analysis are described within the clinical SAP, which will be conducted at the point of final OS analysis.

Consequently, the interim OS results remain restricted. The study will continue as planned until the prespecified final OS analysis. The final OS analysis is planned when approximately [redacted] OS events have occurred, which is projected to occur in approximately [redacted] with outputs/reports availability in [redacted].

B.2.6.1.3 Response to treatment

ORR as assessed by BICR, defined as the percentage of patients achieving a confirmed complete response (CR) or partial response (PR) per RECIST v1.1, was a secondary endpoint in KRYSTAL-12. ORR by BICR was more than threefold greater for adagrasib (31.9%; 95% CI, 26.7% to 37.5%) than for docetaxel (9.2%; 95% CI, 5.1% to 15.0%) with an odds ratio (OR) of 4.68 (95% CI, 2.56 to 8.56) in favour of adagrasib (p<0.0001). Three (1.0%) patients in the adagrasib group had complete responses, while docetaxel produced no complete responses.[121] Response to treatment as assessed by BICR is summarised in Table 17.

Table 17: KRYSTAL-12 | Response to treatment as assessed by BICR

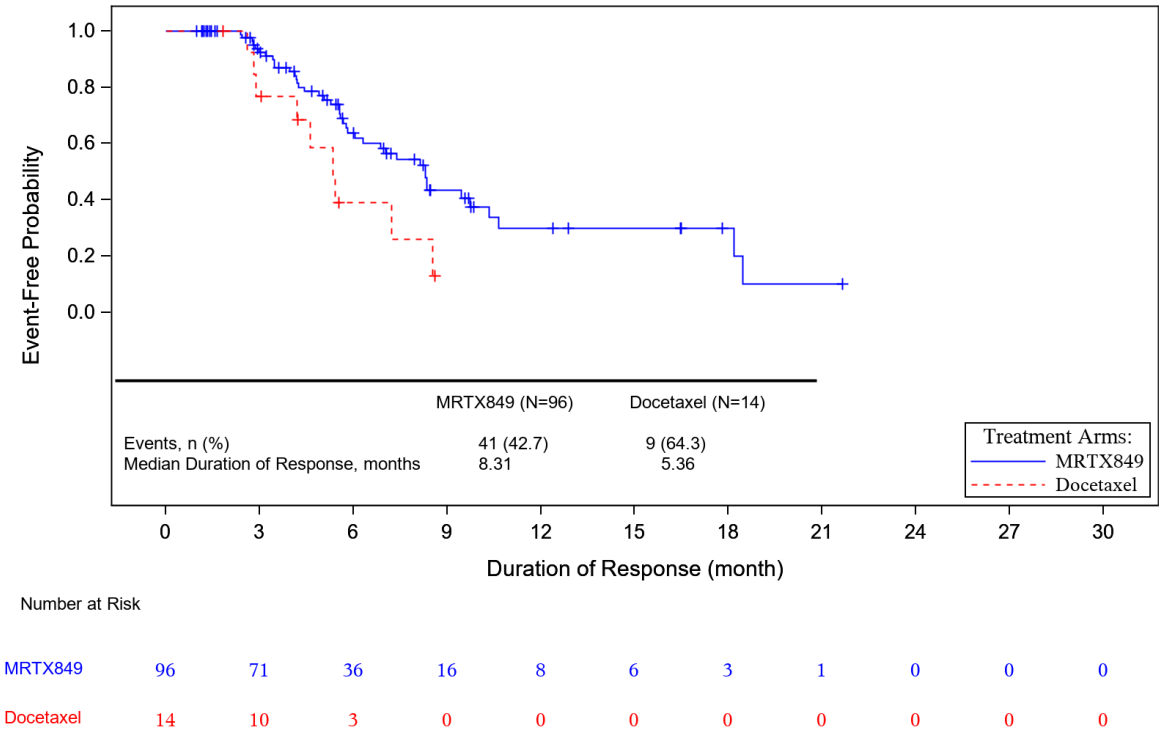
	Adagrasib (n=301)	Docetaxel (n=152)
Best OR, n (%)		
Complete response	3 (1.0)	0
Partial response	93 (30.9)	14 (9.2)
Stable disease	140 (46.5)	75 (49.3)
Progressive disease	28 (9.3)	34 (22.4)
Not evaluable	37 (12.3)	29 (19.1)
ORR, n (%) [95% CI]	96 (31.9) [26.7, 37.5]	14 (9.2) [5.1, 15.0]

Abbreviations: CI, confidence interval; OR, objective response; ORR, objective response rate.
Source: KRYSTAL-12 CSR[121]

The investigator ORR was consistent with the BICR analysis, indicating a clinically meaningful increase in ORR with adagrasib vs docetaxel. ORR by the investigator's assessment was 34.9% (95% CI, 29.5% to 40.6%) for adagrasib and 8.6% (95% CI, 4.6% to 14.2%) for docetaxel, resulting in an OR of 5.56 (95% CI, 3.02 to 10.24) in favour of adagrasib (p<0.0001).[121]

DOR as assessed by BICR was also a secondary endpoint in KRYSTAL-12 and was defined as the time from first documentation of objective response per RECIST v1.1 to first documentation of progressive disease or death due to any cause. For patients achieving a response, DOR by BICR was 8.31 months (95% CI, 6.05 to 10.35) in the adagrasib arm and 5.36 months (95% CI, 2.86 to 8.54) in the docetaxel arm (Figure 11).[121] DOR by BICR rates were higher in the adagrasib arm across evaluable time points, beginning at 3 months post-randomisation (Table 18).[121] DOR by BICR was ≥6 months for 36 (37.5%) responders in the adagrasib group and 3 (21.4%) responders in the docetaxel group.[121]

Figure 11: KRYSTAL-12 | Kaplan–Meier plot of DOR per BICR | DCO 31 December 2023



Abbreviations: BICR, blinded independent central review; DCO, data cutoff; DOR, duration of response.
Source: KRYSTAL-12 CSR[121]

Table 18: KRYSTAL-12 | DOR rate (95% CI) by time post-randomisation

	Adagrasib (n=301)	Docetaxel (n=152)
3 months	92.47% (84.00%, 96.55%)	76.92% (44.21%, 91.91%)
6 months	63.72% (50.92%, 74.01%)	39.07% (12.57%, 65.33%)
9 months	43.35% (30.05%, 55.93%)	Not estimable*
12 months	30.01% (16.68%, 44.55%)	Not estimable*

*No patients had DOR ≥9 months at the time of data cutoff.
Abbreviations: CI, confidence interval; DOR, duration of response.
Source: KRYSTAL-12 CSR[121]

The investigator-assessed DOR was consistent with the BICR analysis, indicating a clinically meaningful increase in DOR with adagrasib vs docetaxel. Median DOR by investigator was 9.69 months (95% CI, 6.74 to 12.42) in the adagrasib group vs 6.93 months (95% CI, 4.21 to not estimable [NE]) vs the docetaxel group.[121]

At the time of analysis, the follow-up time for patients who were more recently allocated to treatment may have been insufficiently long to accurately estimate DOR. At this time, responses (by BICR) were ongoing in 53.1% of patients in the adagrasib arm and in 35.7% of patients in the docetaxel arm.[121]

B.2.6.1.4 Patient-reported outcomes

PROs comprised the EQ-5D-5L and the LCSS. Both assessments were collected on Day 1 and Day 15 of treatment Cycles 1–4 and on Day 1 of every treatment cycle thereafter, as well as at the end-of-treatment visit.[121]

The PRO analysis population included 254 patients in the adagrasib arm and 112 patients in the docetaxel arm who had EQ-5D or LCSS data at baseline and ≥1 post-baseline visit within 6 months. The PRO analysis set therefore included 84.4% (254/301) of patients in the adagrasib arm of the ITT population and 73.7% (112/152) in the docetaxel arm of the ITT poulation.[140]

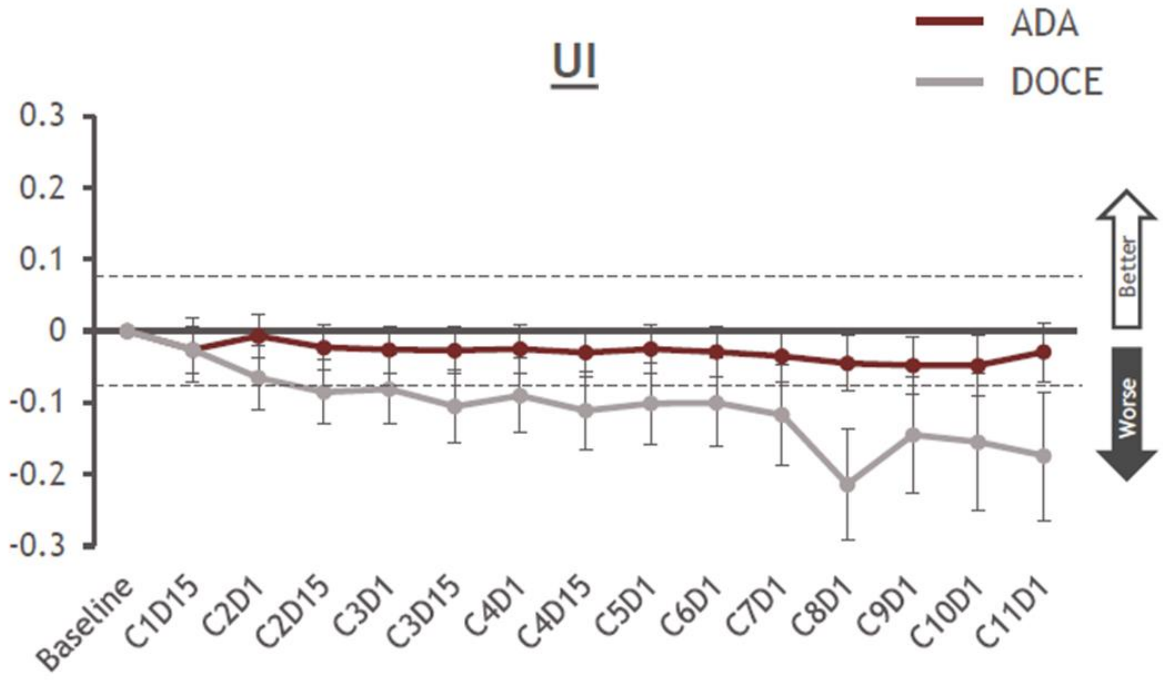
Completion rates among the expected population (i.e. patients who were alive and had not dropped out of the study) were >85% at most visits in both arms through Cycle 11, when there were ≥10 patients per arm with available data.[140]

B.2.6.1.4.1 EQ-5D-5L

The EQ-5D-5L included data from both the index and the visual analogue scale (VAS) scores. The minimally important difference (MID) was defined as a score difference of 0.078 points for the EQ-5D health utility index and 7 points for the VAS.[135]

Change from Baseline was analysed for both the index score and the VAS using a mixed effects model for repeated measurements. The overall LS mean change from Baseline in the index score (using UK utility scores) was −0.030 (95% CI, −0.056 to −0.005) for adagrasib and −0.112 (95% CI, −0.152 to −0.072) for docetaxel, with a mean difference of 0.082 (95% CI, 0.037 to 0.126; Figure 12).[128, 140] The overall LS mean change from Baseline in VAS was −0.7 (95% CI, −2.7 to 1.3) vs −6.1 (95% CI, −9.2 to −3.1) for adagrasib vs docetaxel, respectively, with a mean difference of 5.4 (95% CI, 2.0 to 8.9; Figure 13).[128, 140] For patients receiving docetaxel, the changes in index score and the VAS both surpass their respective MIDs, indicating a worsening of QoL. In contrast, the MID is not reached for patients receiving adagrasib, suggesting maintained QoL during treatment with adagrasib.

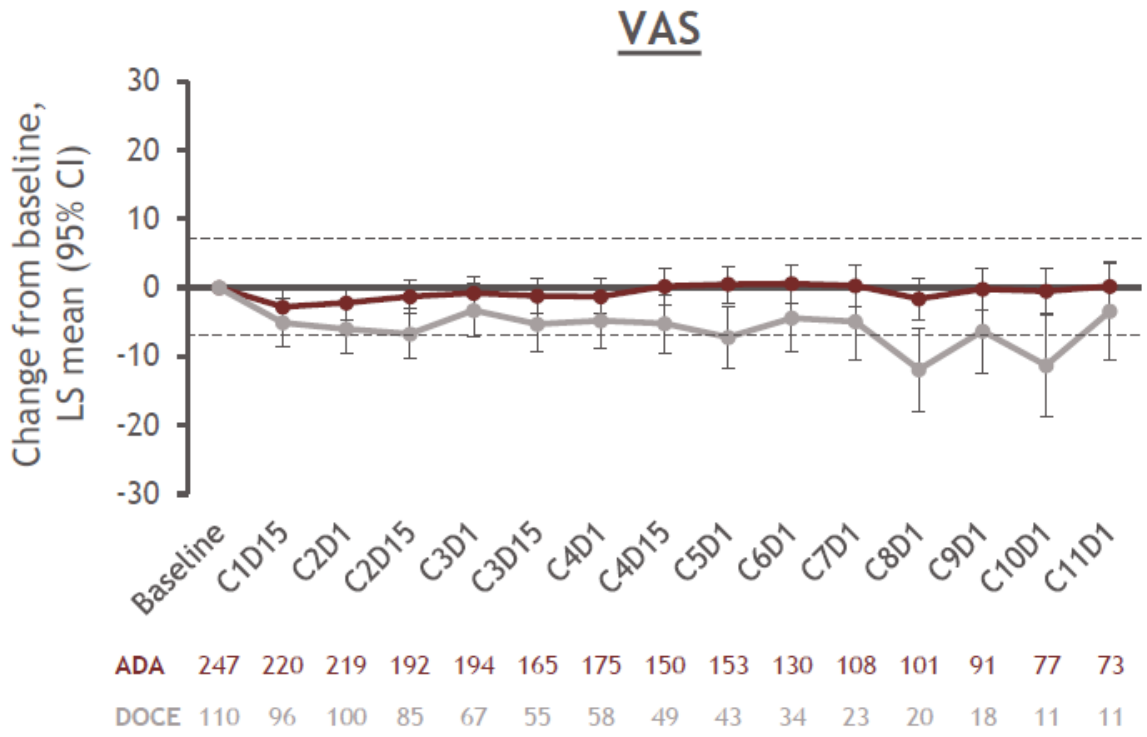
Figure 12: KRYSTAL-12 | EQ-5D-5L index score* change from Baseline over time



	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.030 (-0.056 to -0.005)	-0.112 (-0.152 to -0.072)
Mean difference (95% CI)	0.082 (0.037 to 0.126)	

*UK utility scores (Sheffield Decision Support Unit algorithm).
Abbreviations: ADA, adagrasib; C, cycle; CI, confidence interval; D, day; DOCE, docetaxel; EQ-5D-5L, EuroQol 5-Dimension 5-Level; LS, least squares; UI, utility index.
Sources: Felip 2024[140]

Figure 13: KRYSTAL-12 | EQ-5D VAS score change from Baseline over time



	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.7 (-2.7 to 1.3)	-6.1 (-9.2 to -3.1)
Mean difference (95% CI)	5.4 (2.0 to 8.9)	

Abbreviations: ADA, adagrasib; C, cycle; CI, confidence interval; D, day; DOCE, docetaxel; EQ-5D, EuroQol 5-Dimension; LS, least squares; VAS, visual analogue scale.
Sources: Felip 2024[140]

B.2.6.1.4.2 LCSS

The LCSS is a disease-specific measure of QoL. Patients rated each of the six lung cancer symptoms (appetite loss, fatigue, cough, dyspnoea, haemoptysis, and pain) and three summary global items (distress/severity of lung cancer symptoms, impact on activities, and quality of life) on the degree of impairment from 0 (no impairment) to 100 (maximal impairment) using a VAS. The average symptom burden index (ASBI) score is the sum of the six symptom scores, the 3-item global index (3-IGI) is the sum of the three global scores, and the average total score is the sum of all nine scores.[121]

The MID was defined as 10 points for the individual items of the LCSS, the overall LCSS, and LCSS ASBI scores. A MID of 30 points (10% of the maximum possible score; based on the sum of the 10-point MIDs for the three global items) was selected for the LCSS 3-IGI.[135]

The change from Baseline in ASBI, 3-IGI, and average total score were analysed using a mixed effects model for repeated measurements. Adagrasib demonstrated significant improvement vs docetaxel (Table 19).[128]

Table 19: KRYSTAL-12 | LS mean (95% CI) change from Baseline in LCSS scores

	Adagrasib (n=301)	Docetaxel (n=152)
ASBI	–4.8 (–6.3, –3.3)	4.9 (2.5, 7.2)
	Mean difference –9.7 (–12.3, –7.0) nominal p<0.0001	
3-IGI	–9.3 (–16.4, –2.2)	20.3 (9.5, 31.1)
	Mean difference –29.6 (–41.7, –17.6) nominal p<0.0001	
Average total score	–4.4 (–6.0, –2.7)	5.5 (2.9, 8.0)
	Mean difference –9.8 (–12.7, –7.0) nominal p<0.0001	

Abbreviations: 3-IGI, 3-item global index; ASBI, average symptom burden index; CI, confidence interval; LCSS, Lung Cancer Symptom Scale.
Source: KRYSTAL-12 PRO Analysis Initial Report[128]

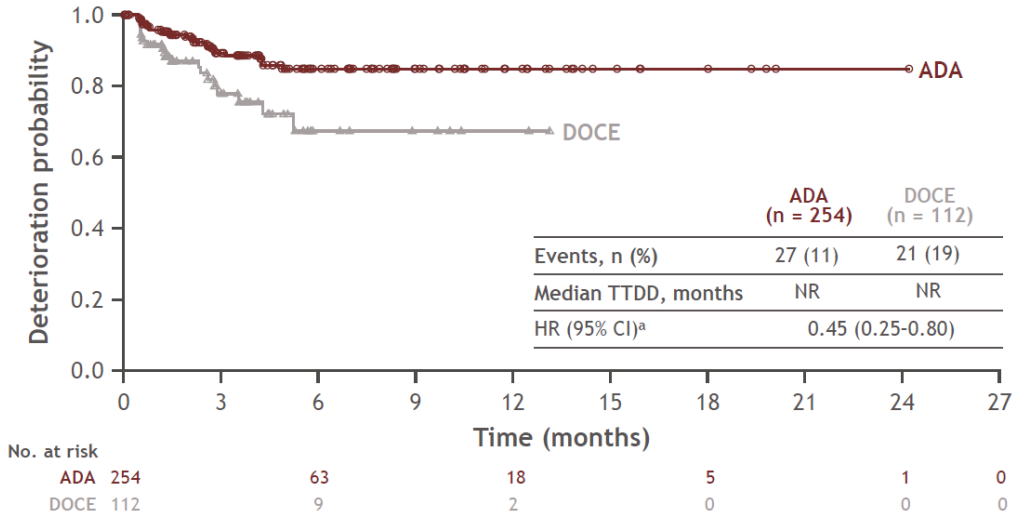
Time to first improvement (TTI) in LCSS ASBI was defined as the time to first improvement from Baseline ASBI score of ≥MID. The cumulative incidence curves showing TTI in ASBI score are shown in Figure 14. Improvement events occurred in [redacted] ([redacted]) patients in the adagrasib arm and [redacted] ([redacted]) patients in the docetaxel arm. Median TTI in LCSS ASBI score was [redacted] months (95% CI, [redacted] to [redacted]) in the adagrasib arm and was not met in the docetaxel arm.[141]

Figure 14: KRYSTAL-12 | Cumulative incidence plot of time to improvement in LCSS ASBI score

Abbreviations: ASBI, average symptom burden index; LCSS, Lung Cancer Symptom Scale.
Source: KRYSTAL-12 PRO analysis data on file[141]

Time to definitive deterioration was also assessed as determined by a ≥10-point decrease in an LCSS item, disease progression, or death. A Kaplan–Meier plot of time to deterioration demonstrates an advantage for adagrasib over docetaxel (Figure 15).[140]

Figure 15: KRYSTAL-12 | Kaplan–Meier plot of time to definitive deterioration of LCSS | DCO 31 December 2023



Abbreviations: DCO, data cutoff; LCSS, Lung Cancer Symptom Scale.
Source: Felip 2024[140]

Mean change from Baseline through Cycle 11 for LCSS symptoms prespecified in the statistical analysis plan are shown in Table 20. Adagrasib demonstrated clinically significant ≥10-point improvement from Baseline in cough ([redacted]) and dyspnoea ([redacted]), as well as a clinically significant ≥10-point advantage over docetaxel in fatigue ([redacted]), pain ([redacted]), dyspnoea ([redacted]), and cough ([redacted]).[128]

Table 20: KRYSTAL-12 | Mean (95% CI) change in LCSS scores for individual symptoms from Baseline to Cycle 11 Day 1

Mean (SD) change [n]	Adagrasib (n=301)	Docetaxel (n=152)
Appetite loss	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Haemoptysis	*	*
Pain	[redacted]	[redacted]

*Not analysed, as this was not a prespecified symptom in the patient-reported outcome statistical analysis plan.
Abbreviations: LCSS, Lung Cancer Symptom Scale; SD, standard deviation.
Source: KRYSTAL-12 PRO Analysis Initial Report[128]

B.2.6.2 KRYSTAL-1

B.2.6.2.1 Progression-free survival

PFS as assessed by BICR was defined as the time from date of first study treatment to date of disease progression per RECIST v1.1 or death due to any cause. After a median follow-up of 12.9 months, 66 (58.9%) PFS by BICR events were observed. Similar to KRYSTAL-12 results, median PFS was 6.5 months (95% CI, 4.7 to 8.4).[123] Additional data are reported in Appendix N.

B.2.6.2.2 Overall survival

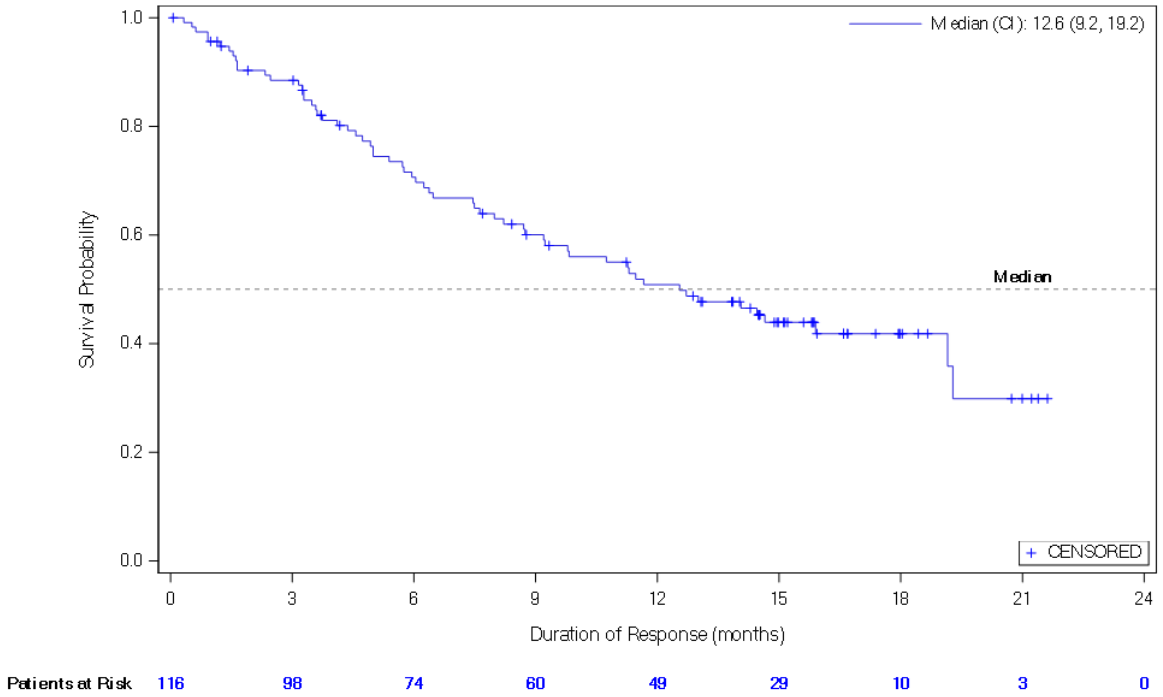
OS was defined as the time from date of first study treatment to date of death due to any cause. OS was first analysed after a median follow-up of 9.0 months (data cutoff 15 June 2021) with additional analyses after median follow-up durations of 12.9 months (data cutoff 15 October 2021) and 15.6 months (data cutoff 15 January 2022; Table 21).[122, 123] After a median follow-up of 15.6 months, 61 (52.6%) death events were observed. Median OS was 12.6 months (95% CI, 9.2 to 19.2; Figure 16).[123]

Table 21: KRYSTAL-1 | Analyses of OS

Median follow-up	Data cutoff	Median OS, months (95% CI)
9.0 months	15 June 2021	11.3 (8.7, NE)
12.9 months	15 October 2021	11.7 (9.2, NE)
15.6 months	15 January 2022	12.6 (9.2, 19.2)

Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: KRYSTAL-1 phase 2 Cohort A addendum[123]

Figure 16: KRYSTAL-1 | Kaplan–Meier plot of OS | DCO 15 January 2022 (median follow-up 15.6 months)



Abbreviations: CI, confidence interval; DCO, data cutoff; OS, overall survival.
Source: KRYSTAL-1 phase 2 Cohort A addendum[123]

B.2.6.2.3 Response to treatment

ORR as assessed by BICR, defined as the percentage of patients achieving a confirmed CR or PR per RECIST v1.1, was the primary endpoint in KRYSTAL-1. ORR was 42.9% (95% CI, 33.5 to 52.6), with one patient achieving a CR and 47 patients achieving a PR.[122] Additional data are reported in Appendix N.

B.2.6.3 Efficacy conclusions

KRYSTAL-12 is an RCT that enrolled 453 patients and was powered for PFS, with a median trial follow-up of 9.43 months.[121] KRYSTAL-1 was a single-arm trial that enrolled 116 patients and had a median OS follow-up of 15.6 months.[123] KRYSTAL-1 is a source of valuable supporting evidence for KRYSTAL-12.

Survival outcomes in KRYSTAL-12 consistently favoured adagrasib compared with docetaxel. For the primary endpoint of PFS by BICR, adagrasib was associated with a clinically meaningful and statistically significant 42% reduction in the risk of progression or death (HR, 0.58; 95% CI, 0.45 to 0.76; p<0.0001) relative to docetaxel.[121] Median PFS was 5.49 months vs 3.84 months for adagrasib vs docetaxel, respectively. PFS rates were higher in the adagrasib arm across all time points evaluated (3, 6, 9, and 12 months post-randomisation). The PFS by BICR result was supported by sensitivity analyses of PFS based on investigator assessment (HR, 0.57; 95% CI, 0.45 to 0.74; p<0.0001; median PFS 5.42 months vs 2.89 months).[121]

As described in Section B.2.6.2.2, KRYSTAL-12 interim OS results remain restricted. The study will continue as planned until the prespecified final OS analysis.[121, 124] For this reason, KRYSTAL-1 data are used to predict KRYSTAL-12 OS for adagrasib and docetaxel. After a median follow-up of 15.6 months, median OS in KRYSTAL-1 was 12.6 months (95% CI, 9.2 to 19.2).[123] Given that surrogacy analyses in NSCLC show a moderate to high correlation between progression and survival both at study and individual levels,[126, 127] and PFS is consistent and similar between KRYSTAL-1 and KRYSTAL-12, an OS benefit for adagrasib vs docetaxel is anticipated for the KRYSTAL-12 OS data. This surrogate relationship is presented in detail in Section B.3.3.2 and Appendix P, and supports the prediction of OS in KRYSTAL-12.

KRYSTAL-12 ORR for adagrasib was more than three times that of docetaxel (31.9% vs 9.2%), representing both a clinically meaningful and statistically significant improvement (OR, 4.68; 95% CI, 2.56 to 8.56; p<0.0001). Likewise, the duration of response (8.31 months vs 5.36 months for docetaxel) is a convincing demonstration of improved efficacy vs docetaxel.[121]

PROs suggest that adagrasib does not have a negative impact on patient wellbeing. EQ-5D results showed that QoL was maintained over time according to both the index score and the VAS.[121] Adagrasib demonstrated clinically significant ≥10-point improvement from Baseline in cough and dyspnoea, as well as a clinically significant ≥10-point advantage over docetaxel in fatigue, pain, dyspnoea, and cough.[128] These results suggest an improvement in symptom burden and HRQoL for patients receiving adagrasib vs docetaxel.

The KRYSTAL-12 trial comparator, docetaxel, is appropriate for evaluating comparative efficacy, as it is used in UK clinical practice from second line onward in patients with *KRAS* G12C mutation-positive advanced NSCLC[24] and was included by NICE as a suggested comparator in the final scope for this appraisal. Patient baseline demographic and disease characteristics were consistent between KRYSTAL-12 treatment arms and KRYSTAL-1 Cohort A. Together, KRYSTAL-12 and KRYSTAL-1 provide a strong evidence base for demonstrating the comparative efficacy of adagrasib.

In conclusion, KRYSTAL-12 and KRYSTAL-1 demonstrate a clinically meaningful and statistically significant survival advantage for adagrasib compared with docetaxel, as well as improved response to treatment and maintained baseline QoL.[121, 123] These clinical data provide a strong indication of efficacy in a population with an urgent need for effective targeted therapy.

B.2.7 Subgroup analysis

B.2.7.1 All prespecified subgroups

Subgroups prespecified for PFS and ORR in KRYSTAL-12 comprised gender, age, race, ECOG performance status, smoking history, region, administration of prior treatment, number of prior lines of therapy, metastases at baseline, PD-L1 expression, and best overall response to last prior therapy. The definitions of these subgroups are presented in Table 22.

Table 22: KRYSTAL-12 | Subgroup definitions

Subgroup	Definition
Gender	Female vs male
Age	<65 vs ≥65 years old; <65, 65–75 vs ≥75 years old
Race	White vs non-white
ECOG performance status	0 vs 1
Smoking history	Lifetime non-smoker, past smoker, vs current smoker
Region	Non-Asia-Pacific vs Asia-Pacific
Administration of prior therapy	Sequential vs concurrent administration of platinum-based chemotherapy and anti-PD-(L)1 immunotherapy
Number of prior lines of therapy	1, 2, vs >2
Brain metastasis at baseline	Yes vs no
Liver metastasis at baseline	Yes vs no
Bone metastasis at baseline	Yes vs no
Tumour proportion score (PD-L1 protein expression)	<1%, 1–49%, vs ≥50%
BOR of the last prior therapy in the advanced/metastatic setting	Complete response, partial response, stable disease, vs progressive disease

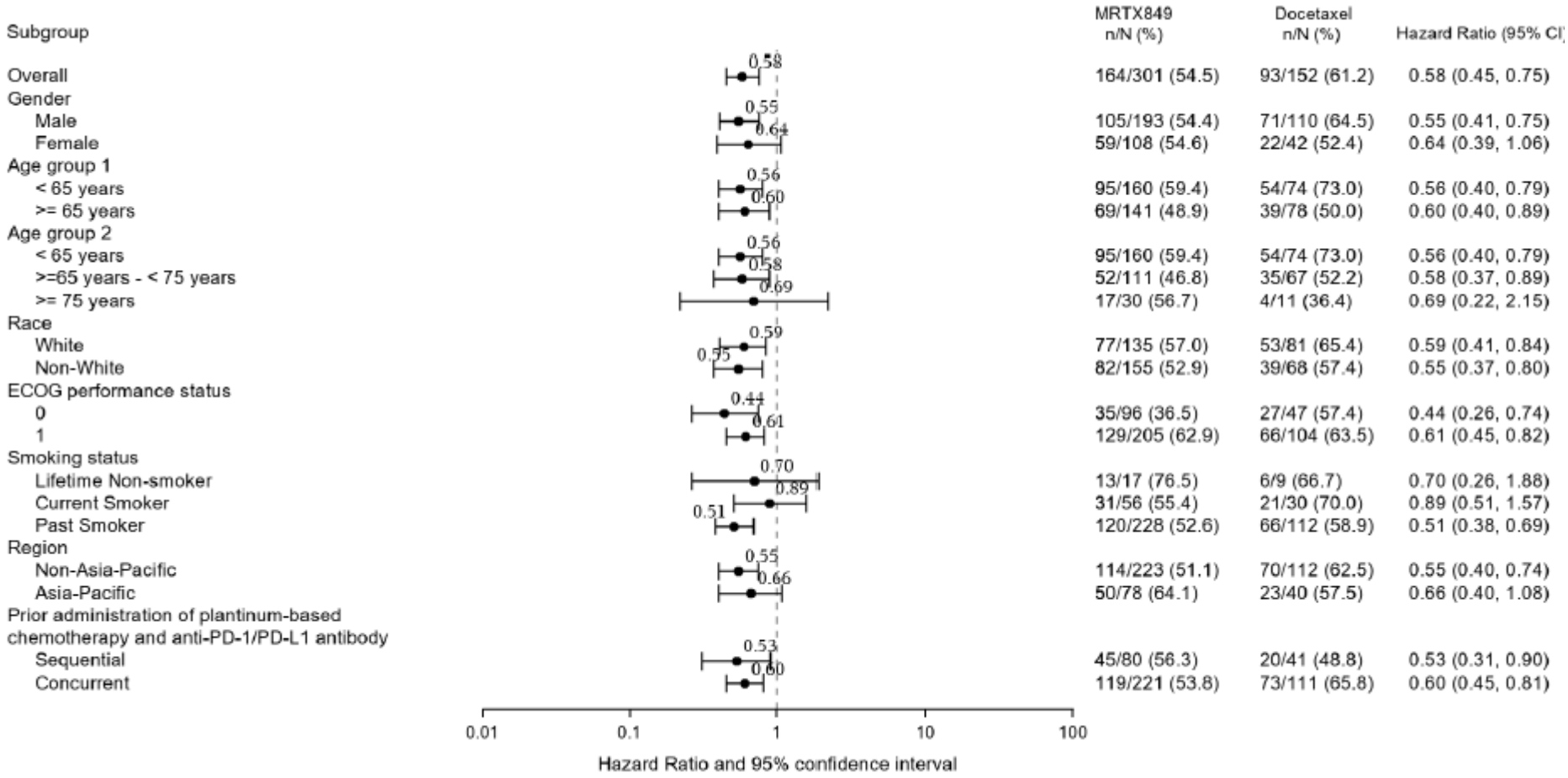
Abbreviations: BOR, best overall response; ECOG, Eastern Cooperative Oncology Group; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1.
Source: KRYSTAL-12 protocol,[124] KRYSTAL-12 CSR[121]

PFS results across subgroups were consistent with the ITT population (HR, 0.58; 95% CI, 0.45 to 0.76; p<0.0001), with the majority of subgroups showing a significant treatment benefit with adagrasib vs docetaxel (Figure 17 and Figure 18).[121] In the few remaining subgroups in which the HRs numerically favoured adagrasib over docetaxel (no HR favoured

docetaxel in any subgroup), the number of patients was a small fraction of the number of patients in the ITT population.[121]

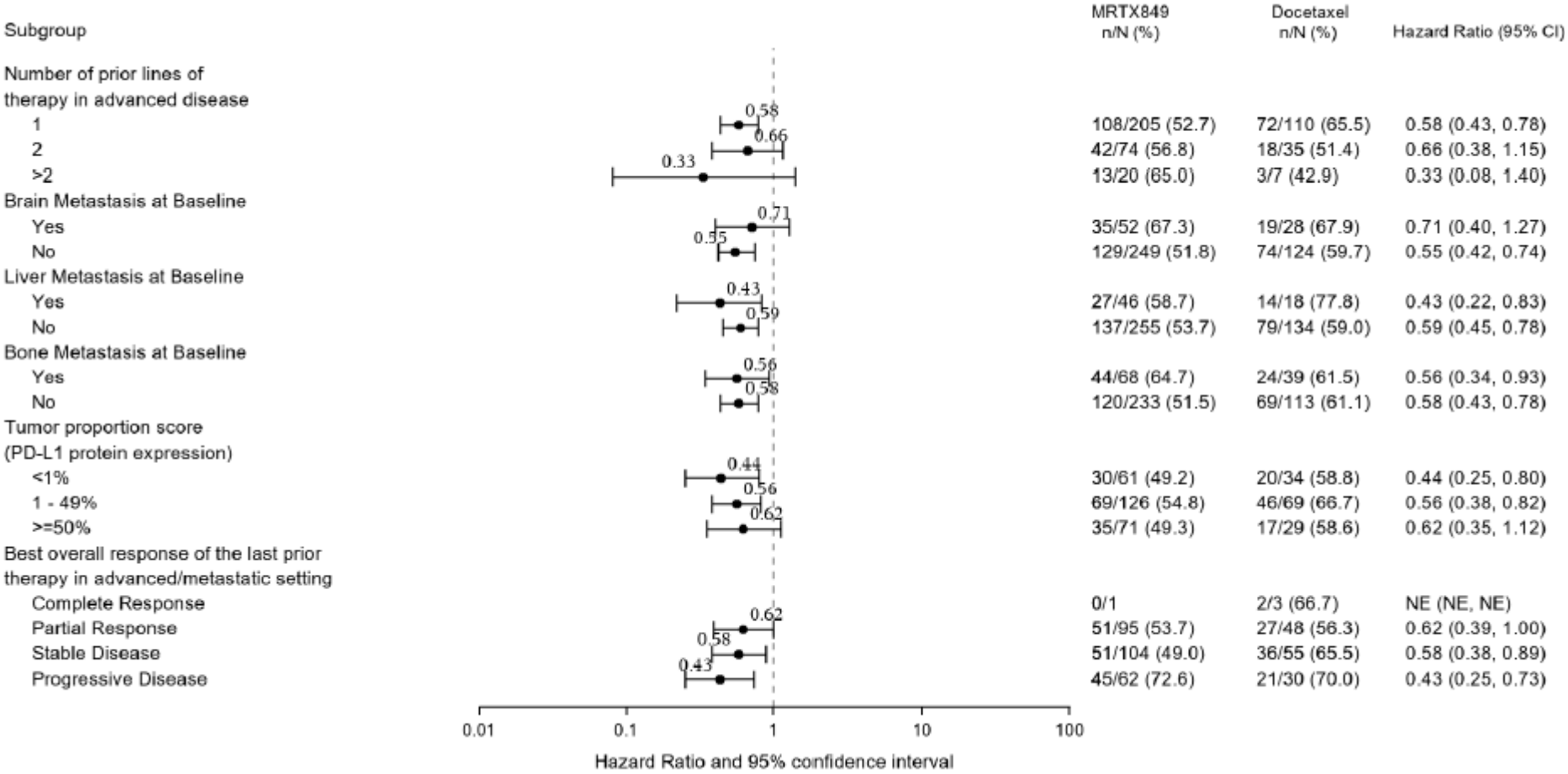
ORR results across subgroups were also consistent with the ITT population (OR, 4.68; 95% CI, 2.56 to 8.56; p<0.0001), with the majority of subgroups showing a significant treatment benefit with adagrasib vs docetaxel (Figure 19 and Figure 20).[121] In subgroups in which numerical ORR difference favoured adagrasib over docetaxel but for which the 95% CI lower bound of the unweighted difference crossed 0, the number of patients was a small fraction of the number of patients in the ITT population. Docetaxel was favoured by only one subgroup (patients with complete response to last prior therapy in the advanced or metastatic setting) with a very wide confidence interval due to the small size of the subgroup (n=4).[121]

Figure 17: KRYSTAL-12 | Forest plot of PFS per BICR for prespecified subgroups (1/2)



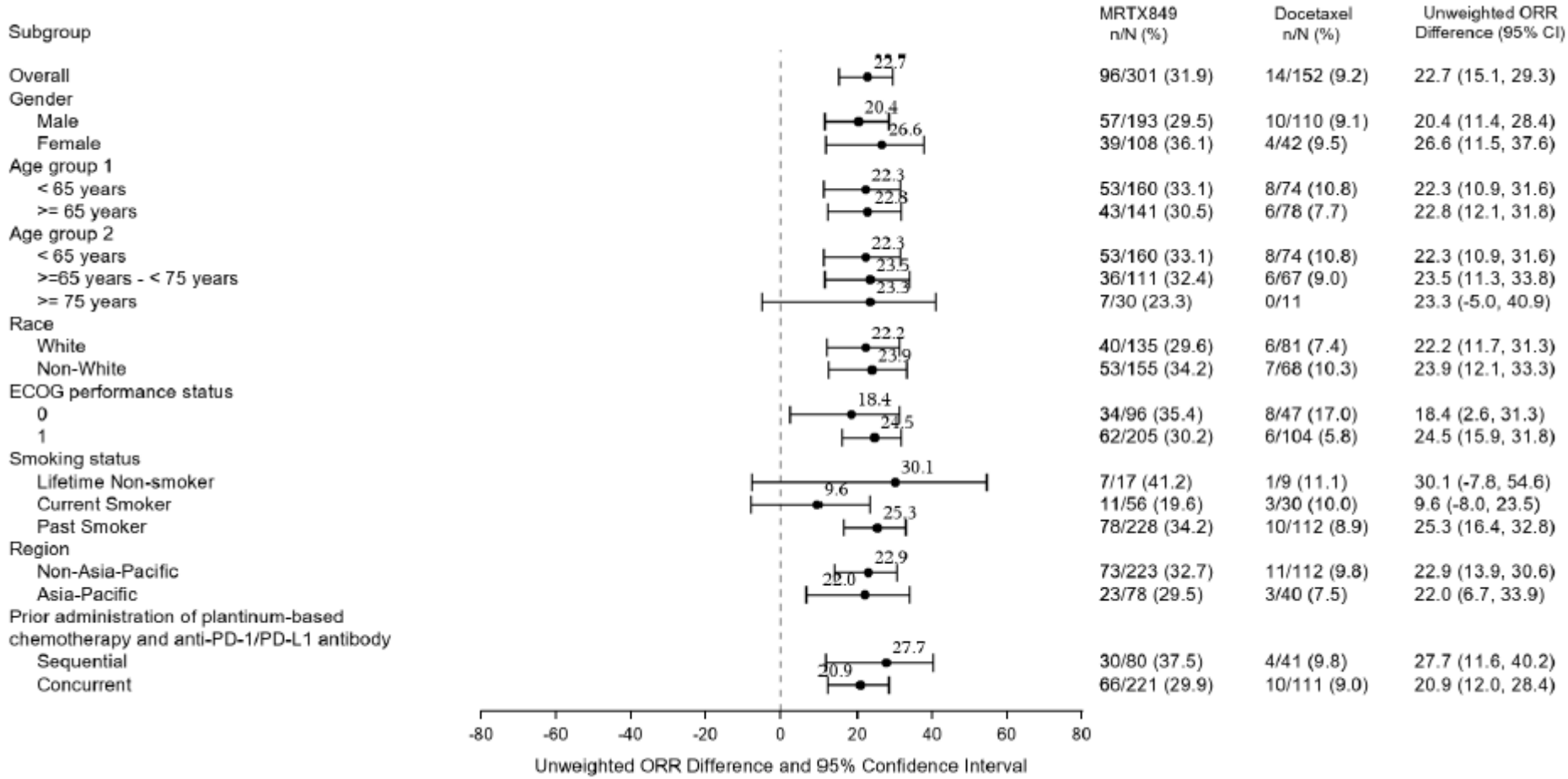
Abbreviations: BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1; PFS, progression-free survival.
Sources: KRYSTAL-12 CSR[121]

Figure 18: KRYSTAL-12 | Forest plot of PFS per BICR for prespecified subgroups (2/2)



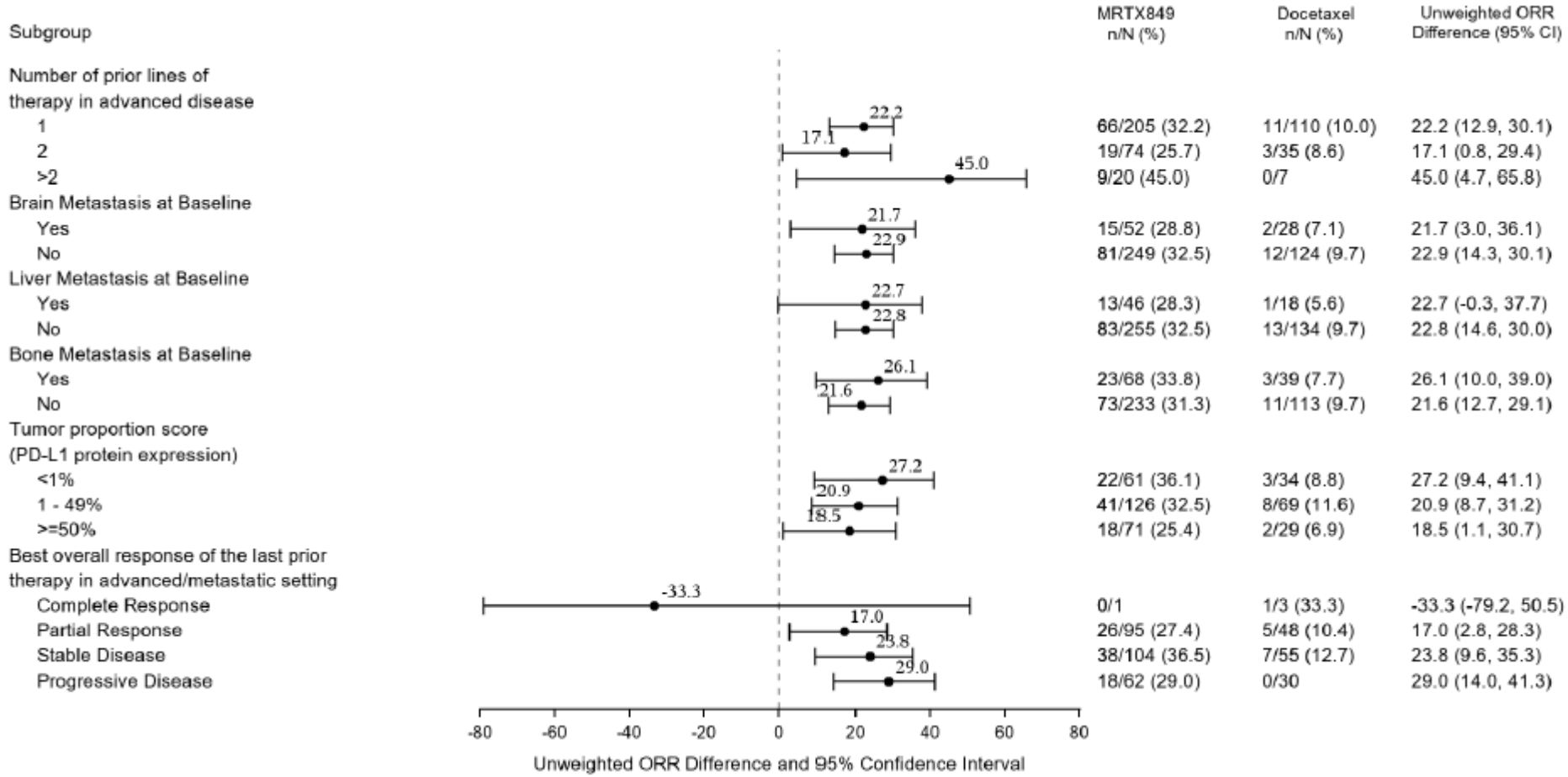
Abbreviations: BICR, blinded independent central review; CI, confidence interval; NE, not estimable; PD-L1, programmed death ligand 1; PFS, progression-free survival.
Sources: KRYSTAL-12 CSR[121]

Figure 19: KRYSTAL-12 | Forest plot of ORR per BICR for prespecified subgroups (1/2)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PD-(L)1, programmed cell death protein 1 or programmed death ligand 1.
Sources: KRYSTAL-12 CSR[121]

Figure 20: KRYSTAL-12 | Forest plot of ORR per BICR for prespecified subgroups (2/2)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate; PD-L1, programmed death ligand 1.
Sources: KRYSTAL-12 CSR[121]

B.2.7.2 Patients with CNS metastasis

One of the prespecified subgroups in KRYSTAL-12 was patients with brain metastasis. As discussed in Section B.1.3.4, UK clinical experts have confirmed that this is a population with high residual unmet medical need.[24] KRYSTAL-12 included intracranial activity endpoints as exploratory endpoints and included patients with *treated*, neurologically stable brain metastases.[121, 124] In addition, KRYSTAL-1 included a phase 1b cohort that enrolled 25 patients with *untreated*, neurologically stable, asymptomatic CNS metastases, 19 of whom were radiographically evaluable for intracranial activity.[133, 134] Adagrasib has demonstrated intracranial efficacy in both populations.

Evaluating the true intracranial efficacy of a systemic therapy can be challenging in patients with treated CNS metastases, as it may not be possible to discern whether treatment effects are due to systemic therapy or to localised treatment aimed at the metastases (e.g. radiotherapy). For this reason, KRYSTAL-1 intracranial activity data for *untreated* CNS metastases are presented below, in addition to the KRYSTAL-12 data for *treated* CNS metastases.

B.2.7.2.1 Baseline characteristics

Table 23 presents the patient baseline demographic and disease characteristics for the KRYSTAL-12 ITT population, the KRYSTAL-12 subgroup of patients with treated brain metastases (n=78 in the adagrasib arm and n=36 in the docetaxel arm), and the KRYSTAL-1 phase 1b cohort of patients with untreated, neurologically stable, asymptomatic CNS metastases (n=25). Within the KRYSTAL-12 subgroup, baseline characteristics were well-balanced between treatment arms.

Table 23: Patient baseline demographic and disease characteristics for the KRYSTAL-12 ITT population, KRYSTAL-12 subgroup of patients with treated CNS metastases, and KRYSTAL-1 phase 1b cohort with untreated CNS metastases

Baseline characteristic	KRYSTAL-12 | ITT population		KRYSTAL-12 | Patients with CNS metastases		KRYSTAL-1 | Phase 1b
	Adagrasib (n=301)	Docetaxel (n=152)	Adagrasib (n=78)	Docetaxel (n=36)	Adagrasib (n=25)
Age, years					
Mean (SD)	63.6 (8.66)	63.9 (7.81)	NR	NR	NR
Median (range)	64 (34–83)	65 (45–80)	64.0 (45–81)	62.5 (45–79)	66 (47–89)
Age group, n (%)					
<65 years	160 (53.2)	74 (48.7)	(56)	(56)	NR
≥65 years	141 (46.8)	78 (51.3)	(44)	(44)	NR
Sex, n (%)					
Male	193 (64.1)	110 (72.4)	(60)	(64)	NR
Female	108 (35.9)	42 (27.6)	NR	NR	13 (52)
Childbearing potential	8 (7.4)	4 (9.5)	NR	NR	NR
Post-menopausal	89 (82.4)	34 (81.0)	NR	NR	NR
Surgically sterile	11 (10.2)	4 (9.5)	NR	NR	NR
Race, n (%)					
White	135 (44.9)	81 (53.3)	NR	NR	21 (84)
Black or African American	0	0	NR	NR	1 (4)
Asian	72 (23.9)	37 (24.3)	NR	NR	1 (4)
American Indian or Alaska Native	0	0	NR	NR	NR
Native Hawaiian or other Pacific Islander	0	0	NR	NR	NR
Other	2 (0.7)	1 (0.7)	NR	NR	2 (8)
Not reported	81 (26.9)	30 (19.7)	NR	NR	NA
Missing	11 (3.7)	3 (2.0)	NR	NR	NA
ECOG PS, n (%)					
0	96 (31.9)	47 (30.9)	(27)	(19)	7 (28)
1	205 (68.1)	104 (68.4)	(73)	(81)	18 (72)
2	0	0	NA	NA	NA

3	0	0	NA	NA	NA
4	0	0	NA	NA	NA
Missing	0	1 (0.7)	NA	NA	NA
Tumour histology, n (%)					
Adenocarcinoma	283 (94.0)	147 (96.7)	(95)	(94)	NR
Large cell carcinoma	4 (1.3)	1 (0.7)	NR	NR	NR
Unclassified/undifferentiated carcinoma	6 (2.0)	1 (0.7)	NR	NR	NR
Squamous	6 (2.0)	0	NR	NR	NR
Other	2 (0.7)	3 (2.0)	(5)	(6)	NR
Smoking history, n (%)					
Lifetime non-smoker	17 (5.6)	9 (5.9)	(5)	(6)	1 (4)
Current smoker	56 (18.6)	30 (19.7)	NR	NR	7 (28)
Former smoker	228 (75.7)	112 (73.7)	NR	NR	17 (68)
Current or former smoker	NA	NA	(95)	(94)	NA
Missing	0	1 (0.7)	NA	NA	NA
Number of prior systemic regimens, n (%)					
0	0	0	NR	NR	4 (16)
1	185 (61.5)	100 (65.8)	NR	NR	15 (60)
2	89 (29.6)	40 (26.3)	NR	NR	3 (12)
3	19 (6.3)	10 (6.6)	NR	NR	3 (12)*
4+	8 (2.7)	2 (1.3)	NR	NR	NR
Prior systemic therapy, n (%)					
Platinum agent	301 (100)	152 (100)	(100)	(100)	17 (68)
Checkpoint inhibitor	301 (100)	152 (100)	(100)	(100)	20 (80)
Both platinum and CIT	301 (100)	152 (100)	(100)	(100)	NR
Concurrent	221 (73.4)	111 (73.0)	(67)	(83)	NR
Sequential	80 (26.6)	41 (27.0)	(33)	(17)	NR

Abbreviations: CIT, checkpoint inhibitor therapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; PD-L1, programmed death ligand 1; SD, standard deviation.
Sources: KRYSTAL-12 CSR,[121] Barlesi 2024,[142] Negrao 2023[134]

B.2.7.2.2 KRYSTAL-12 subgroup | Efficacy in treated CNS metastases

Exploratory analysis of systemic efficacy indicated a treatment benefit for adagrasib vs docetaxel in the subgroup of patients with CNS metastases and also specifically showed intracranial activity in this subgroup.

B.2.7.2.2.1 Systemic efficacy in patients with CNS metastases at Baseline

Exploratory analysis in the KRYSTAL-12 subgroup of patients with CNS metastases showed a systemic ORR of 26.9% in the adagrasib arm and 2.8% in the docetaxel arm.[142] For patients with CNS metastases who had a systemic response, median DOR was 7.4 months in the adagrasib arm and 5.4 months in the docetaxel arm.[142] Median PFS was 4.4 months (95% CI, 3.1 to 5.8) in the adagrasib arm and 2.9 months (95% CI, 2.0 to 6.2 months) in the docetaxel arm, with a HR of 0.70 (95% CI, 0.43 to 1.20).[142]

B.2.7.2.2.2 Intracranial efficacy

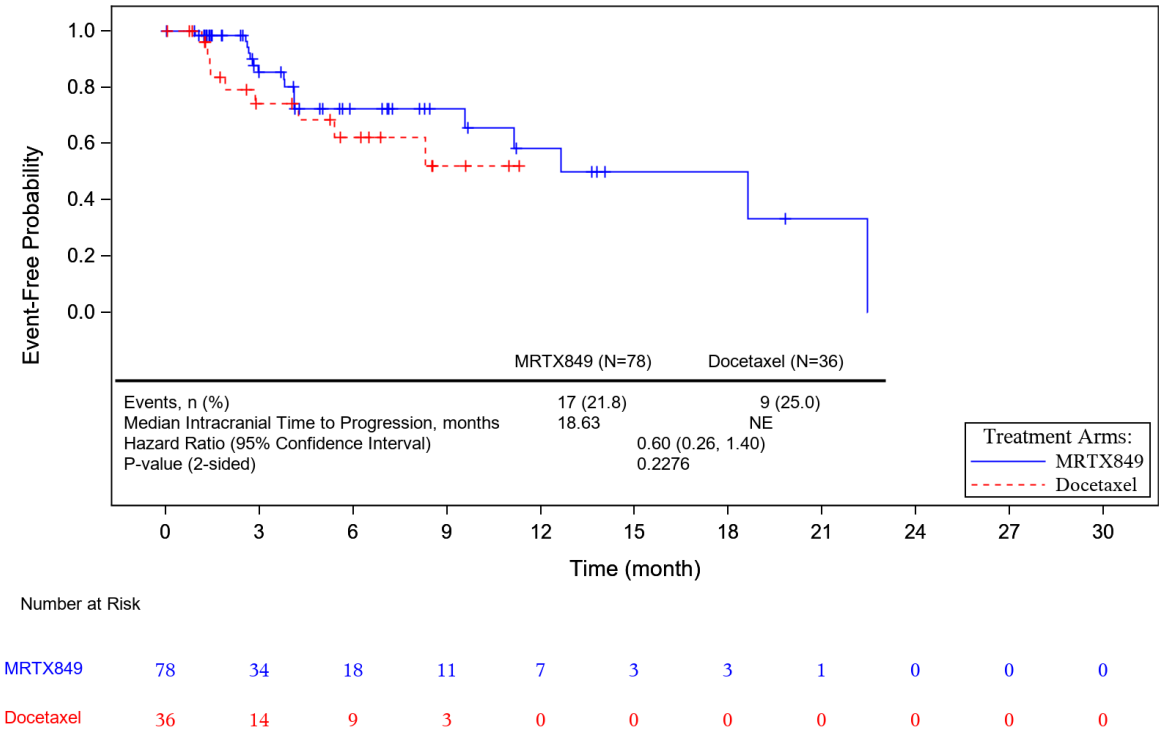
icORR as assessed by BICR was defined as the percentage of patients in the CNS metastasis population achieving a confirmed intracranial CR (icCR) or intracranial PR (icPR) per RECIST v1.1. Exploratory analysis among all patients with baseline CNS metastases (n=78 in the adagrasib arm and n=36 in the docetaxel arm) showed that icORR was 24.4% for adagrasib (n=19/78; 95% CI, 15.3% to 35.4%), including an icCR rate of 14.1% (n=11/78), which was more than double that of docetaxel at 11.1% (n=4/36; 95% CI, 3.1% to 26.1%), producing an OR of 2.58 (95% CI, 0.81 to 8.23).[121] In the subset of patients with ≥1 target lesion[5] and ≥1 post-baseline assessment (CNS evaluable population), icORR was even higher in the adagrasib arm (40%; n=10/25) and remained unchanged in the docetaxel arm (11%; n=1/9).[129]

Intracranial DOR (icDOR) as assessed by BICR was defined as the time from first documentation of icCR or icPR per RECIST v1.1 to first documentation of intracranial progressive disease or death due to any cause. Median icDOR was 19.91 months (95% CI, 9.43 to NE) among the 19 patients achieving a response in the adagrasib arm, with 5 patients having events. Median icDOR could not be estimated in the docetaxel arm because there were no events among the four patients achieving a response.[121]

Intracranial time to progression (icTTP) was assessed by BICR according to RECIST v1.1. Median icTTP was 18.63 months (95% CI, 9.56 to NE) vs NE in the adagrasib vs docetaxel arms, respectively, with events occurring in 17 (21.8%) patients and 9 (25.0%) patients, respectively (Figure 21). The resulting HR of 0.60 (95% CI, 0.26 to 1.40) was not statistically significant (p=0.2276), but numerically favoured adagrasib over docetaxel.[121] Similarly, The HR for intracranial PFS (icPFS) of 0.93 (95% CI, 0.50 to 1.73) favoured adagrasib over docetaxel but was not statistically significant.[142] For both HRs, the wide confidence intervals reflect the small number of patients in the subgroup.

[5] For a lesion to be considered a target lesion, it must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

Figure 21: KRYSTAL-12 | Kaplan–Meier plot of icTTP per BICR | DCO 31 December 2023

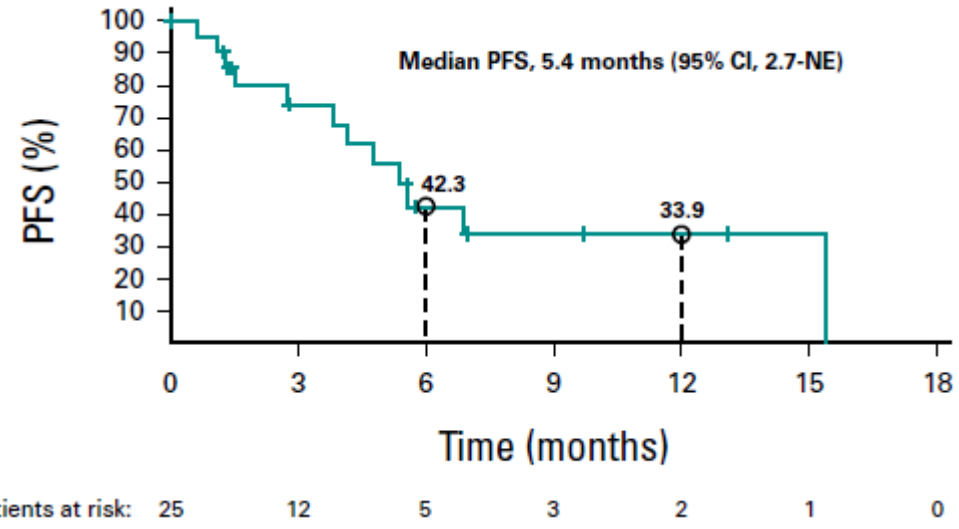


Abbreviations: BICR, blinded independent central review; DCO, data cutoff; icTTP, intracranial time to progression; NE, not estimable.
Source: KRYSTAL-12 CSR[121]

B.2.7.2.3 KRYSTAL-1 phase 1b cohort | Efficacy in untreated CNS metastases

In the KRYSTAL-1 phase 1b cohort of 25 patients with untreated, neurologically stable, asymptomatic CNS metastases, 19 patients were radiographically evaluable for intracranial activity (Appendix O). In this cohort, icORR was 42.1% (n=8/19; 95% CI, 20.3% to 66.5%), with three complete and five partial intracranial responses. For patients achieving a response, icDOR was 12.7 months (95% CI, 3.9 to NE).[134] Median icPFS was 5.4 months (95% CI, 2.7 to NE; Figure 22).[134]

Figure 22: KRYSTAL-1 | Kaplan–Meier plot of icPFS (median follow-up 13.7 months)



Abbreviations: CI, confidence interval; icPFS, intracranial progression-free survival; NE, not estimable.
Source: Negrao 2023[134]

B.2.8 Meta-analysis

The methods and results of the indirect comparison are described and presented in Section B.2.9.

B.2.9 Indirect and mixed treatment comparisons

Head-to-head trial data were only available for the comparison of adagrasib with docetaxel. Therefore, an indirect comparison was required to compare the relative efficacy of adagrasib with the remainder of the comparators of relevance to the decision problem.

As it is possible to form a connected network of RCTs (discussed in Section B.2.9.2 below) including key trials for the relevant comparators and KRYSTAL-12 for adagrasib, a network meta-analysis (NMA) was conducted. Potential effect modifiers were identified, and an assessment of heterogeneity between trials was performed (discussed in Section B.2.9.3). For some studies in the network (namely, KRYSTAL-12 and CodeBreaK 200), no major differences in potential effect modifiers were identified. However, when compared with other studies in the network, some differences in patient characteristics were observed. For example, differences to LUME-Lung 1 were observed in requirements for prior therapy (specifically, patients in LUME-Lung 1 were not exposed to prior immunotherapy). However, population adjustment methods such as multilevel network meta-regression or matching adjusted indirect comparisons were not considered feasible, as it is not be possible to adjust for key differences in patient characteristics between KRYSTAL-12/CodeBreaK 200 and some of the other studies in the network. More specifically, in KRYSTAL-12 and CodeBreaK 200, all patients had *KRAS* G12C mutation-positive NSCLC and were previously exposed to immunotherapy, meaning there is no variability in the KRYSTAL-12 individual patient data (IPD) required for covariate adjustments to patients in LUME-Lung 1 (who were not immunotherapy-exposed and had unknown KRAS status) for example. In effect, if attempts to match the *KRAS* G12C mutation-positive and previously immunotherapy-exposed patients to patients in the other comparator trials, the effective sample size would be zero. Therefore,

taking the above into consideration, the NMA was conducted to compare the relative efficacy of adagrasib and relevant comparators, using the connected network of RCTs. The outcomes considered in the NMA were based on the outcomes specified in the final scope issued by NICE, as well as the availability of data reported in the literature. The outcomes used to inform the cost-effectiveness analysis (OS and PFS) are presented in the following sub-sections; objective response rate results are presented in Appendix D.

B.2.9.1 Identification and selection of relevant studies from the clinical SLR

An SLR was conducted to identify evidence on the efficacy and safety of second line and later (2L+) therapies in patients with advanced/metastatic (Stage III or IV) NSCLC (including description and characterisation of the treatment landscape for *KRAS* mutation, *KRAS* G12C mutation, and advanced/metastatic NSCLC 2L+ therapies). Full details of the SLR are provided in Appendix D.

B.2.9.2 Comparators of interest and overview of selected studies

Table 24 presents the identified evidence of relevance to this appraisal.

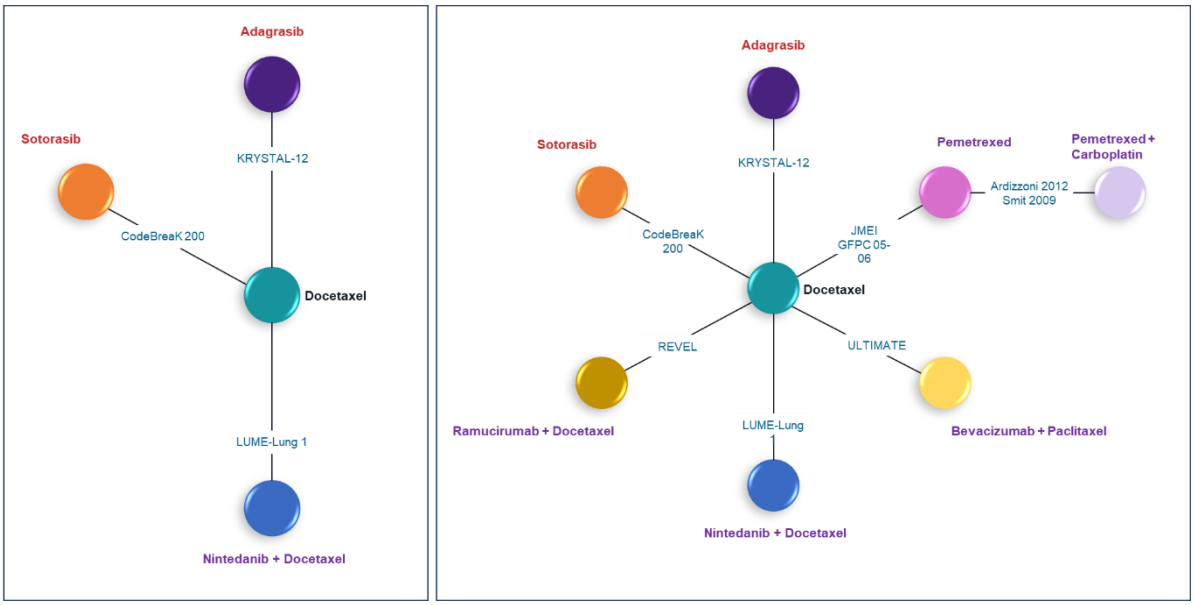
In line with the final scope issued by NICE, the comparators of interest in NHS practice are docetaxel and nintedanib + docetaxel. It was also necessary to include sotorasib in the indirect comparison as it was included in the final scope issued by NICE as subject to managed access review. However, at the time of submission, the timelines for the managed access review of TA781 (ID6287) are not publicly available, and sotorasib is therefore not considered a relevant comparator for this appraisal as it has not exited the CDF.[120]

Table 24: Trials for inclusion in the network meta-analysis relevant to the UK

Trial name	Treatment
KRYSTAL-12	Adagrasib Docetaxel
CodeBreaK 200	Sotorasib Docetaxel
LUME-Lung 1	Docetaxel + nintedanib Docetaxel

Figure 23 compares the 'UK-based' network diagram (left) to a 'global' network of evidence (right), which includes a broader range of treatment options than those relevant to the scope of this appraisal, as the analysis was conducted for several jurisdictions. As the global network is 'star-shaped', the NMA results from the global and UK networks would be consistent. Therefore, results from the broader global network are utilised in this submission and to inform the cost-effectiveness analysis reported in Section B.3. In Section B.2.9.6, NMA results from the global network are presented for the treatments included in the final scope issued by NICE (adagrasib, sotorasib [subject to NICE appraisal], docetaxel, and docetaxel + nintedanib).

Figure 23: NMA, UK-based network (left) and global network (right)



Note: As NMA results would be consistent between the UK-based and global analysis due to the 'star-shaped' network, the global NMA is used to inform the cost-effectiveness analysis for the relevant treatments. It was necessary to include sotorasib in the NMA, as it was included in the final scope issued by NICE as subject to managed access review.
Abbreviations: NMA, network meta-analysis.

B.2.9.3 Heterogeneity assessment of included trials

Study similarity was assessed for heterogeneity according to the patient characteristics at baseline, outcome definitions, and study design. This was done by assessing the distribution of (potential) treatment effect modifiers within and across trials in terms of: a) treatment or outcome definitions, b) patient characteristics, c) baseline risk, and d) reported outcomes (including evaluation of the proportional hazards assumption for time-to-event outcomes).

The study characteristics and eligibility criteria were similar between KRYSTAL-12 and CodeBreaK 200, which are both phase 3 studies actively controlled with docetaxel, including patients with previously treated (including prior immunotherapy) metastatic NSCLC with a *KRAS* G12C mutation. However, there were some differences between KRYSTAL-12 and CodeBreaK 200, and other studies included in the network. Notably, LUME-Lung 1 (which compared docetaxel with nintedanib + docetaxel) included NSCLC patients i) irrespective of their *KRAS* status, ii) with only platinum-based exposure in prior lines but no anti-PD-(L)1 therapy exposure (with possible differences in lines of therapy).

A summary of the RCTs included in the NMA that are relevant to the decision problem addressed in this appraisal are presented in Table 25.

Table 25: Overview of RCTs included in the global network meta-analysis that are relevant to the decision problem

Trial	Phase & masking	Study location	*KRAS* status	Prior treatment	Histology	Sample size
KRYSTAL-12, NCT04685135	Phase 3, open label	Multicentre, multinational (incl. Asia)	*KRAS* G12C	Receipt of prior treatment with a platinum-containing regimen and an immune checkpoint inhibitor	All*	Adagrasib 301 Docetaxel 152
CodeBreaK 200, NCT04303780	Phase 3, open label	Multicentre, multinational (incl. Asia)	*KRAS* G12C	Disease progression after previous PBC and a PD-1 or PD-L1 inhibitor	All*	Sotorasib 171 Docetaxel 174
LUME-Lung 1, NCT00805194	Phase 3, double blind	Multicentre, multinational (incl. Asia)	NR	Recurrent NSCLC with one previous chemotherapy regimen	All	Docetaxel + nintedanib 655 Docetaxel 659

*Derived based on patient characteristics.
Abbreviations: *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, Non-small cell lung cancer; NR, not required; PBC, platinum-based chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RCT, randomised controlled trial.

With regards to patient characteristics, median age was similar across trials. KRYSTAL-12 included more Asian patients (24%) than LUME-Lung 1 (18.2%) and CodeBreaK 200 (12.5%). LUME-Lung 1 included more 'never' smokers than KRYSTAL-12 and CodeBreaK 200 (4%-6%). KRYSTAL-12 and CodeBreaK 200 included a high proportion of non-squamous patients (95%-97%), due to selecting *KRAS* G12C mutation-positive patients. All trials included patients with ECOG PS 0 and ECOG PS 1, with similar distributions across KRYSTAL-12, CodeBreaK 200, and LUME-Lung 1 (Appendix D.3.1). The highest proportion of patients with CNS involvement was seen in CodeBreaK 200 (34%), while LUME-Lung 1 reported only 6% of patients with brain metastases at baseline. Variation was observed across the included studies for the number of prior lines of therapy; KRYSTAL-12 (8%) and CodeBreaK 200 (16%) included patients with >2 prior therapies, whereas LUME-Lung 1 included patients with one prior line of therapy.

With regards to outcome definitions between studies, the assessment of progression was conducted by BICR in KRYSTAL-12 and CodeBreaK 200, and by central independent review in LUME-Lung 1. The assessment schedule for response and progression status was every 6 weeks in KRYSTAL-12 and LUME-Lung 1, or similarly, 5–7 weeks in CodeBreaK 200.

Although the proportional hazards assumption could not be rejected for the PFS endpoint in KRYSTAL-12, it was determined that the proportional hazard assumption was violated for the OS endpoint in CodeBreaK 200, and for PFS in LUME-Lung 1 (Table 26). As such, both proportional-hazards and time-varying NMAs for OS and PFS were evaluated.

Table 26: Proportional hazards assumption for studies in the network that are relevant to the decision problem

Trial ID	Intervention	PFS		OS	
		Grambsch-Therneau p-value	Wald test p-value	Grambsch-Therneau p-value	Wald test p-value
KRYSTAL-12	Adagrasib Docetaxel	0.508	0.424	NA	NA
CodeBreaK 200	Sotorasib Docetaxel	0.315	0.204	0.051	0.022
CodeBreaK 200 (crossover adjusted)*	Sotorasib	NA	NA	0.098	0.042
LUME-Lung 1	Docetaxel + Nintedanib Docetaxel	0.036	0.030	0.988	0.897

Notes: Red text indicates p<0.05, and violation of the proportional hazard assumption. Orange text indicates no violation of the proportional hazard assumption, but a low p-value (<0.2). *Based on the two-stage method, results provided in the sotorasib G-BA submission.
Abbreviations: OS, overall survival; PFS, progression-free survival.

B.2.9.4 KRYSTAL-12 OS (patient-level surrogacy analysis)

As described in Section B.2.9.2, KRYSTAL-12 is the primary source of clinical effectiveness data for adagrasib and docetaxel, and it is used to inform the NMA and subsequently the cost-effectiveness analysis presented in Section B.3.

As described in Section B.2.6.1.2, in line with the clinical study protocol and SAP, an interim analysis for OS was conducted for KRYSTAL-12 at the time of final PFS analysis. The interim OS analysis HR did not cross the prespecified boundary for efficacy. In addition, these results are currently considered to be highly immature and inconclusive due to several factors (see Section B.2.6.1.2 for further details). Consequently, the interim OS results remain restricted.

Therefore, data from KRYSTAL-1 (a phase 1/2 single-arm trial described in Section B.2.3) are used to inform a patient-level surrogacy analysis, with the following analysis objectives:

- To assess the relationship between progression and survival at the individual-level for patients with *KRAS* G12C mutation-positive NSCLC
- To predict OS for KRYSTAL-12 (for adagrasib and docetaxel) using the individual-level surrogacy relationship derived from KRYSTAL-1, given the observed TTP from KRYSTAL-12

Simulated KRYSTAL-12 OS data from the surrogacy analysis is used to inform the NMA and cost-effectiveness analysis. The surrogacy relationship is described in detail in Section B.3.3.2, with the technical specification of the analysis provided in Appendix P.

B.2.9.5 NMA methodology

As the network of evidence was fully connected, NMAs were conducted in a Bayesian framework using Monte Carlo Markov Chain methods. NMAs were implemented in the JAGS software package, with a first series of iterations from the JAGS sampler discarded as 'burn-

in', and inferences based on additional iterations using two chains. All analyses were performed using R version 4.3.3 (http://www.r-project.org/) and JAGS version 4.3.1.

Both fixed-effects (FE) and random-effects (RE) models were fitted and were compared based on the deviance information criteria (DIC) to determine which was the better fitting model (with lower DIC values indicating a better fit to the data). When DIC differences are small (i.e. less than 3 to 5 points) across different fitted models, common practice is to choose the simplest model because the additional complexity does not result in better model fit.[143] For the random-effects models, one parameter for the between-study heterogeneity is used, assuming that the between-study heterogeneity was the same for each intervention relative to the overall reference treatment of choice. If the number of trials to estimate between-study heterogeneity is limited, random-effects models with non-informative priors for the between-study heterogeneity parameter may not be feasible and informative prior for the between-study heterogeneity parameter can be used according to Turner et al., 2015.[144]

For dichotomous outcomes (such as objective response rate, presented in Appendix D), a generalised linear model was applied, with treatment effects synthesised using the proportion of patients experiencing the event of interest in the respective treatment arms. A logistic regression model with a logit link function and a binomial likelihood was used to model the log odds of the outcome on a given treatment, in a given trial via either a fixed or random effect. A non-informative prior was assigned for the treatment effect, in both fixed and random-effects models, $N(0, 100^2)$.

Proportional-hazards NMAs were modelled using constant HRs reported for OS and PFS from individual trials (and using the predicted OS HR for KRYSTAL-12, as described in Section B.2.9.4 and Section B.3.3.2). In NMAs, the HR is typically preferred to survival at specific time points (or median survival), as these measures only capture the cumulative effect of the treatment at that point in time, while ignoring any variation in treatment effects over time, up to, and beyond that time point. However, HRs are typically estimated using a Cox model, thus requiring that the ratio of hazards is constant over time (i.e. relying on the proportional hazards assumption).

Time-varying NMAs were performed using a two-step approach, proposed by Cope *et al.* (2020).[145] Firstly, parametric survival distributions were fitted to IPD for each arm of each trial in the evidence network, with pseudo-IPD obtained through digitisation where needed.[146] An exact likelihood distribution was used for survival times to estimate the trial-specific parameters based on (pseudo) IPD. One- and two-parameter survival distributions were explored for six distributions (i.e. exponential, Weibull, gamma, Gompertz, log-normal and log-logistic). For KRYSTAL-12, the parametric distributions were fit to each OS sample from the surrogacy analysis; the distributional parameters were calculated as the average across the predicted samples (adjusting the associated variance using Rubin's rules as described in the technical specification of the surrogacy analysis in Appendix P). Arm-level plots of survival and hazards were generated for each trial, and the most appropriate survival distribution across all arms of all trials was identified based on goodness-of-fit measures such as Akaike information criterion (AIC) and clinical expert opinion on the long-term plausibility of the extrapolated curves.

Secondly, the parameters were synthesised with a multivariate NMA framework using models proposed by Achana *et al.* (2014).[147] Of note, the NMA model in this second step was based on one specific parametric distribution that was assumed to apply to all arms of all trials within the network of evidence. Alternative parametric distributions were considered

as sensitivity analyses, but different distributions could not be combined within one network of evidence as this would have violated the transitivity assumption.

The estimates from the two-step model included multivariate relative treatment effect parameters regarding scale and shape of the survival distribution/function, which were used to describe time-varying treatment effects.

B.2.9.6 NMA results

B.2.9.6.1 Proportional-hazards NMA

B.2.9.6.1.1 Progression-free survival

Results of the proportional-hazards NMA are presented in Table 27 for PFS. Results were consistent between the fixed-effects and random-effects models, with no meaningful difference in model fit between the two (fixed-effects DIC = 19.54; random-effects DIC = 16.31; difference of <5). The fixed-effects model was therefore selected in the base case; the results of the random-effects model are presented in Appendix D.

The findings of the proportional-hazards NMA for the PFS endpoint indicate that the hazard of progression or death is most favourable for the comparison of adagrasib vs docetaxel ([redacted]). Furthermore, the credible interval for the comparison of adagrasib and docetaxel does not contain one. This is consistent with the within-trial comparison of KRYSTAL-12 PFS described in Section B.2.6.1.1. Adagrasib also showed an improvement in PFS compared to nintedanib + docetaxel ([redacted]). The point estimate PFS HR was also in favour of adagrasib vs sotorasib ([redacted].

Table 27: Estimated constant HRs (95% CrI) from the fixed-effects NMA for PFS

Docetaxel	[redacted]	[redacted]	[redacted]
[redacted]	**Nintedanib + docetaxel**	[redacted]	[redacted]
[redacted]	[redacted]	**Sotorasib**	[redacted]
[redacted]	[redacted]	[redacted]	**Adagrasib**

Notes: Each cell represents the comparison (HR and 95% CrI) of the row treatment vs the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 19.54; Deviance: 12.54.
Abbreviations: CrI, credible internal; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

B.2.9.6.1.2 Overall survival

Results of the proportional-hazards NMA are presented in Table 28 for OS. Results were consistent between the fixed-effects and random-effects models, with no meaningful difference in model fit between the two (fixed-effects DIC = 14.25; random-effects DIC = 15.19; difference of <1). The fixed-effects model is presented in Table 28; the results of the random-effects model are presented in Appendix D.

As introduced in Section B.2.9.4 and further detailed in Section B.3.3.2, the NMA uses simulated KRYSTAL-12 OS from the patient-level surrogacy analysis, as the interim OS results from KRYSTAL-12 remain restricted. For sotorasib, crossover-adjusted CodeBreaK 200 OS data were used in the NMA.

For OS, as with PFS, the point estimate is most favourable for the comparison of adagrasib vs docetaxel (HR = [redacted]). This is consistent with the patient-level surrogacy analysis for simulated KRYSTAL-12 OS reported in Section B.3.3.2.2.1. The point estimate HRs are in favour of adagrasib vs nintedanib + docetaxel (HR = [redacted]) and vs sotorasib (HR = [redacted]). [redacted]

Table 28: Estimated constant HRs (95% CrI) from the fixed-effects NMA for OS

Docetaxel	[redacted]	[redacted]	[redacted]
[redacted]	**Nintedanib + docetaxel**	[redacted]	[redacted]
[redacted]	[redacted]	**Sotorasib****	[redacted]
[redacted]	[redacted]	[redacted]	**Adagrasib***

Note: Each cell represents the comparison (HR and 95% CrI) of the row treatment vs the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 14.25; Deviance: 7.25.
*Based on the simulated OS from KRYSTAL-12 PFS, using the KRYSTAL-1 patient-level surrogacy model.
**Crossover-adjusted CodeBreaK 200 results were used in the network meta-analysis.
Abbreviations: CrI, credible internal; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival

B.2.9.6.2 Time-varying NMA

As described in Section B.2.9.3, it was determined that the proportional hazard assumption was violated for the OS endpoint in CodeBreaK 200, and for PFS in LUME-Lung 1. Therefore, time-varying NMAs were modelled, and are used to inform the base case in the cost-effectiveness analysis described in Section B.3.

As described in Section B.2.9.5, the time-varying NMA uses a two-stage approach with multivariate relative treatment effect parameters regarding the scale and shape of survival distributions. Results of the time-varying NMA are presented as time-varying HRs below (for selected parametric distributions).

B.2.9.6.2.1 Progression-free survival

The gamma distribution from the time-varying NMA is used to inform the base case in the cost-effectiveness analysis described in Section B.3, based on a combination of factors including goodness-of-fit statistics (Section B.3.3, Table 41) and clinical plausibility of the long-term extrapolations. Time-varying HRs for this model are presented in Table 29.

The findings of the time-varying NMA are broadly consistent with the proportional-hazards NMA. In the base-case analysis, the point estimate PFS HR for adagrasib vs docetaxel ranged from [redacted] at 3 months to [redacted] at 24 months, indicating a lower hazard of progression or death for patients receiving adagrasib vs docetaxel (credible intervals do not contain one).The point estimate HRs indicated a numerical improvement in relative PFS for adagrasib vs nintedanib + docetaxel (ranging from [redacted] to [redacted], [redacted]. The point estimate HRs favour adagrasib vs sotorasib across timepoints ([redacted] to [redacted]), [redacted].

Table 29: Estimated time-varying HRs (95% CrI) from the fixed-effects NMA (gamma model) for PFS

Adagrasib vs	Time-varying HR (95% CrI)					
	3 months	6 months	9 months	12 months	18 months	24 months
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: All bolded values are statistically significant at the 0.05 significance level.
Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

B.2.9.6.2.2 Overall survival

Based on a combination of goodness-of-fit ranking (Section B.3.3, Table 43) and the clinical appropriateness of the long-term extrapolation (described in Section B.3.3), the gamma distribution is selected as the base-case model for the OS NMA (Table 30).

In the base case, the time-varying HRs for OS were broadly consistent over time, the point estimate HR vs docetaxel at 3 months is [redacted], and at 24 months is [redacted], indicating a numerically lower hazard of death in the adagrasib arm. OS results were similar in the base-case comparison of adagrasib vs nintedanib + docetaxel (with estimated time-varying HRs ranging from [redacted]). For the comparison of adagrasib versus sotorasib, the point estimate HRs were in favour of adagrasib, and reduced over time from [redacted].

Table 30: Estimated time-varying HRs (95% CrI) from the fixed-effects NMA (gamma model) for OS

Adagrasib* vs	Time-varying HR (95% CrI)					
	3 months	6 months	9 months	12 months	18 months	24 months
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotorasib**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Based on the simulated OS from KRYSTAL-12 PFS, using the KRYSTAL-1 patient-level surrogacy model.
**Crossover-adjusted CodeBreaK 200 results were used in the network meta-analysis.
Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

Some variability in study and patient characteristics of the included trials was evident, suggesting between-study differences could impact the indirect comparisons. Although KRYSTAL-12 and CodeBreaK 200 were similar with regards to study characteristics and eligibility criteria, differences to LUME-Lung 1 were observed in requirements for prior

therapy (with KRYSTAL-12 and CodeBreaK 200 both specifying that patients must have received prior checkpoint inhibitor treatment) and other potential effect modifiers (see Appendix D.3.1). Furthermore, KRYSTAL-12 and CodeBreaK 200 limited inclusion to those with *KRAS* G12C mutation-positive NSCLC, while LUME-Lung 1 did not specify requirements for mutations or biomarkers. It is uncertain whether these patient characteristics should be considered effect modifiers for the NMA, and it was not feasible to conduct subgroup analyses or stratify by prior immunotherapy or *KRAS* mutation status due to data availability. However, given the mechanism of action of alternative treatments, it may be assumed that *KRAS* mutation status only impacts outcomes of KRAS inhibitors.

Both fixed-effect and random-effects models were conducted. For the random-effects models, an informative prior for the between-study heterogeneity parameter was required because the number of studies was too limited to estimate this parameter from the data.[144] DICs showed a similar fit of fixed-effects (Section B.2.9.6) and random-effects models, and the random-effects models generally showed greater uncertainty of estimated treatment effects (Appendix D).

The validity of the NMA findings further depends on the quality of the RCTs. For the reasons outlines in Section B.2.6.1.2, interim OS results from KRYSTAL-12 remain restricted; as such, simulated KRYSTAL-12 OS is incorporated into the NMA based on a surrogacy relationship between progression and survival, derived from patient-level data from KRYSTAL-1. LUME-Lung 1 was considered to have a low risk of bias. For CodeBreaK 200, limitations of OS and PFS data were recently discussed in the literature.[148, 149] The introduction of a protocol amendment towards the end of patient recruitment in the CodeBreaK 200 trial limited sample size of the trial and permitted crossover. The lower than anticipated sample size likely reduced study power to evaluate OS, and allowing crossover resulted in many patients receiving sotorasib upon disease progression, further reducing the ability to establish or exclude survival gain.[148, 149] Alharbi (2024) indicated that investigators may have triggered early crossover to sotorasib in the docetaxel arm, indicating bias in (investigator-assessed) PFS.[150] Furthermore, an imbalance in censoring rates was observed between treatment arms in the trial, with higher rates reported earlier in the docetaxel treatment arm.

B.2.9.8 Conclusions of the NMA

Overall, the NMA results suggest that adagrasib demonstrates improved efficacy in treating patients with *KRAS* G12C mutation-positive NSCLC, compared with existing treatment options. In the proportional-hazards NMA for PFS and OS, the point estimates were consistently more favourable for adagrasib vs docetaxel, docetaxel + nintedanib and sotorasib. Furthermore, in the comparison of PFS for adagrasib vs docetaxel and adagrasib vs docetaxel + nintedanib, the credible intervals did not contain one. Findings were consistent in the time-varying NMA, where adagrasib was associated with an improved PFS vs docetaxel across most timepoints (and favourable point estimate HRs across timepoints for adagrasib vs docetaxel for PFS and OS). In the time-varying NMAs, a numerical improvement in PFS and OS based on the point estimate HRs was also observed for adagrasib across time points for the comparisons of adagrasib vs docetaxel + nintedanib and adagrasib vs sotorasib.

B.2.10 Adverse reactions

The following data are from the safety population of KRYSTAL-12, defined as all patients who received any part of a dose of study medication. The safety population consisted of 298 patients in the adagrasib arm and 140 patients in the docetaxel arm. TEAEs were collected from the 31 December 2023 data cutoff.[121]

TEAEs were defined as adverse events that first occurred or increased in severity on or after the first dose of study treatment and ≤28 days after the last dose of study treatment and prior to the initiation of subsequent SACT. The adverse events reported below are further categorised as treatment-related TEAEs, serious TEAEs, and severity level (Grade 1–5).

Additional KRYSTAL-12 safety data, along with KRYSTAL-1 safety data, are presented in Appendix F.

B.2.10.1 Treatment exposure and compliance

Exposure and compliance to treatment is summarised in Table 31. The mean duration of exposure at the time of the data cutoff was 5.56 months (standard deviation [SD], 4.982) vs 3.17 months (SD, 2.563) for adagrasib vs docetaxel, respectively, and the median duration of exposure was 3.91 months (range, 0.1 to 24.6) vs 2.71 months (range, 0.2 to 13.3). The median number of cycles started was 6 (range, 1 to 31) vs 4 (range, 1 to 19) and 207 (69.5%) vs 71 (50.7%) patients started ≥4 cycles of treatment.[121]

For adagrasib, median compliance was 100% (range, 46.6% to 103.3%), and most patients (294, 98.7%) were >80% compliant. Median overall relative dose intensity was 80.33% (range, 20.7% to 103.3%) vs 100% (range, 52.6% to 100%) for adagrasib vs docetaxel, respectively. Note that relative dose intensity was calculated based on the planned dose at study start (i.e. 600 mg twice daily), so planned dose decreases result in lower intensity but not lower compliance.[121]

Of the patients in the adagrasib group, 4 (1.3%) received adagrasib capsules and 298 (100%) received tablets.[121]

Table 31: KRYSTAL-12 | Exposure and compliance to study treatment

	Adagrasib (n=298)	Docetaxel (n=140)	Crossover adagrasib (n=44)
Treatment duration (months)			
Mean (SD)	5.56 (4.982)	3.17 (2.563)	4.79 (3.818)
Median (min, max)	3.91 (0.1, 24.6)	2.71 (0.2, 13.3)	3.99 (0.1, 16.3)
Cycles started			
Mean (SD)	8.0 (6.68)	4.1 (3.22)	7.2 (5.54)
Median (min, max)	6.0 (1, 31)	4.0 (1, 19)	6.0 (1, 25)
Cycles started, n (%)			
1	24 (8.1)	21 (15.0)	5 (11.4)
2	39 (13.1)	40 (28.6)	5 (11.4)
3	28 (9.4)	8 (5.7)	5 (11.4)
4	26 (8.7)	25 (17.9)	0
5	29 (9.7)	8 (5.7)	6 (13.6)
6	21 (7.0)	18 (12.9)	5 (11.4)
7+	131 (44.0)	20 (14.3)	18 (40.9)
Cumulative dose received (mg)		Not applicable	
Capsules	n=4		n=0
Mean (SD)	184,400.0 (72,053.87)		
Median (min, max)	214200.0 (78,000, 231,200)		
Tablets	n=298		n=44
Mean (SD)	149,670.5 (139,618.11)		144,213.6 (111,456.82)
Median (min, max)	101,600.0 (600, 879,600)		116,500.0 (2,400, 427,200)
RDI (%)			
Mean (SD)	77.71 (20.490)	92.00 (11.956)	86.14 (16.902)
Median (min, max)	80.33 (20.7, 103.3)	100.00 (52.6, 100.0)	98.08 (69.44, 100.00)
Compliance		Not applicable	
Mean (SD)	98.26 (5.047)		98.67 (3.767)
Median (min, max)	100.00 (46.6, 103.3)		100.00 (80.5, 100.0)
Compliance, n (%)		Not applicable	
≤70%	3 (1.0)		0
>70–80%	1 (0.3)		0
>80–90%	8 (2.7)		2 (4.5)
>90%	286 (96.0)		42 (95.5)

Abbreviations: RDI, relative dose intensity; SD, standard deviation.
Sources: KRYSTAL-12 CSR[121]

B.2.10.2 TEAEs

Table 32 provides an overall summary of TEAEs. In the safety population, 298 (100%) patients in the adagrasib group and 138 (98.6%) patients in the docetaxel group experienced TEAEs. Treatment-related TEAEs were experienced by 280 (94.0%) vs 121 (86.4%) patients, respectively. Grade ≥3 TEAEs occurred in 213 (71.5%) vs 93 (66.4%) patients, and treatment-related Grade ≥ 3 TEAEs occurred in 140 (47.0%) vs 64 (45.7%)

patients. TEAEs led to dose reductions for 154 (51.7%) and 36 (25.7%) patients, with treatment-related TEAEs accounting for the reductions in 143 (48.0%) and 33 (23.6%) patients. Among 226 (75.8%) and 47 (33.6%) patients with dose interruptions because of TEAEs, 177 (59.4%) and 26 (18.6%) had interruptions due to treatment-related TEAEs.[121]

Serious TEAEs were experienced by 149 (50.0%) vs 50 (35.7%) patients on adagrasib vs docetaxel, respectively, and 62 (20.8%) vs 23 (16.4%) patients experienced treatment-related serious TEAEs. Fatal TEAEs occurred in 48 (16.1%) vs 10 (7.1%) patients within 28 days of their last dose of study treatment, and 4 (1.3%) vs 1 (0.7%) patients experienced treatment-related fatal TEAEs within 28 days of their last dose.[121]

TEAEs led to discontinuation of treatment for 40 (13.4%) vs 25 (17.9%) patients on adagrasib vs docetaxel, respectively, and 23 (7.7%) vs 20 (14.3%) patients discontinued treatment because of treatment-related TEAEs.[121]

Table 32: KRYSTAL-12 | Overall summary of TEAEs

TEAE type, n (%)	Adagrasib (n=298)	Docetaxel (n=140)	Crossover adagrasib (n=44)
TEAE			
Any	298 (100)	138 (98.6)	44 (100)
Related	280 (94.0)	121 (86.4)	41 (93.2)
Grade ≥3 TEAE			
Any	213 (71.5)	93 (66.4)	26 (59.1)
Related	140 (47.0)	64 (45.7)	19 (43.2)
Serious TEAE			
Any	149 (50.0)	50 (35.7)	20 (45.5)
Related	62 (20.8)	23 (16.4)	7 (15.9)
Fatal events			
Any	48 (16.1)	10 (7.1)	11 (25.0)
Related	4 (1.3)	1 (0.7)	0
TEAE leading to dose reduction			
Any	154 (51.7)	36 (25.7)	18 (40.9)
Related	143 (48.0)	33 (23.6)	17 (38.6)
TEAE leading to dose interruption			
Any	226 (75.8)	47 (33.6)	25 (56.8)
Related	177 (59.4)	26 (18.6)	18 (40.9)
TEAE leading to dose reduction or interruption			
Any	237 (79.5)	67 (47.9)	28 (63.6)
Related	192 (64.4)	47 (33.6)	23 (52.3)
TEAE leading to discontinuation			
Any	40 (13.4)	25 (17.9)	2 (4.5)
Related	23 (7.7)	20 (14.3)	0

Abbreviations: TEAE, treatment-emergent adverse event.
Sources: KRYSTAL-12 CSR[121]

B.2.10.2.1 Most common TEAEs

All 298 patients (100%) in the adagrasib group and 138 (98.6%) patients in the docetaxel group experienced TEAEs, while 280 (94.0%) vs 121 (86.4%) patients, respectively, experienced treatment-related TEAEs.[121] The most common TEAEs (≥5% of patients on either treatment arm) and treatment-related TEAEs (≥10% of patients on either treatment arm) are summarised in Table 33.

TEAEs experienced by ≥20% of patients in either treatment arm were diarrhoea (56.7% vs 31.4% of patients on adagrasib vs docetaxel, respectively), vomiting (41.3% vs 8.6%), nausea (38.3% vs 22.1%), ALT increased (33.2% vs 2.9%), AST increased (33.2% vs 1.4%), decreased appetite (31.5% vs 25.7%), anaemia (30.5% vs 35.0%), blood creatinine increased (27.5% vs 2.9%), asthenia (27.2% vs 32.9%), fatigue (23.2% vs 19.3%), and dyspnoea (20.5% vs 17.9%). The most common treatment-related TEAEs were diarrhoea (53.0% vs 30.7% of patients on adagrasib vs docetaxel, respectively), nausea (33.9% vs 19.3%), vomiting (34.6% vs 6.4%), decreased appetite (23.5% vs 21.4%), anaemia (19.1% vs 30.0%), alanine ALT increased (30.2% vs 2.9%), asthenia (18.8% vs 27.1%), and AST increased (30.9% vs 0).[121]

All patients who crossed over from docetaxel to adagrasib experienced TEAEs. The most common (≥10%) TEAEs were diarrhoea (68.2%), vomiting (38.6%), nausea (36.4%), blood creatinine increased (31.8%), decreased appetite (27.3%), anaemia (25.0%), asthenia (22.7%), dyspnoea (15.9%), oedema peripheral (15.9%), hypoalbuminaemia (15.9%), AST increased (11.4%), blood alkaline phosphatase increased (11.4%), constipation (11.4%), pyrexia (11.4%), and hyponatraemia (11.4%). The most common (≥10%) treatment-related TEAEs were diarrhoea (65.9%), vomiting (31.8%), nausea (31.8%), decreased appetite (22.7%), blood creatinine increased (20.5%), anaemia (15.9%), and asthenia (15.9%).[121]

Table 33: KRYSTAL-12 | TEAEs occurring in ≥5% of patients in any group and treatment-related TEAEs occurring in ≥10% of patients in either treatment arm

TEAE, n (%)	Adagrasib (n=298)		Docetaxel (n=140)		Crossover adagrasib (n=44)	
	Any	Related	Any	Related	Any	Related
Diarrhoea	169 (56.7)	158 (53.0)	44 (31.4)	43 (30.7)	30 (68.2)	29 (65.9)
Vomiting	123 (41.3)	103 (34.6)	12 (8.6)	9 (6.4)	17 (38.6)	14 (31.8)
Nausea	114 (38.3)	101 (33.9)	31 (22.1)	27 (19.3)	16 (36.4)	14 (31.8)
Alanine aminotransferase increased	99 (33.2)	90 (30.2)	4 (2.9)	4 (2.9)	4 (9.1)	3 (6.8)
Aspartate aminotransferase increased	99 (33.2)	92 (30.9)	2 (1.4)	0	5 (11.4)	4 (9.1)
Decreased appetite	94 (31.5)	70 (23.5)	36 (25.7)	30 (21.4)	12 (27.3)	10 (22.7)
Anaemia	91 (30.5)	57 (19.1)	49 (35.0)	42 (30.0)	11 (25.0)	7 (15.9)
Blood creatinine increased	82 (27.5)	59 (19.8)	4 (2.9)	2 (1.4)	14 (31.8)	9 (20.5)
Asthenia	81 (27.2)	56 (18.8)	46 (32.9)	38 (27.1)	10 (22.7)	7 (15.9)
Fatigue	69 (23.2)	47 (15.8)	27 (19.3)	20 (14.3)	2 (4.5)	1 (2.3)
Dyspnoea	61 (20.5)	*	25 (17.9)	*	7 (15.9)	*
Constipation	49 (16.4)	*	20 (14.3)	*	5 (11.4)	*
Blood alkaline phosphatase increased	49 (16.4)	44 (14.8)	4 (2.9)	1 (0.7)	5 (11.4)	3 (6.8)
Pyrexia	48 (16.1)	*	13 (9.3)	*	5 (11.4)	*
Gamma-glutamyltransferase increased	44 (14.8)	38 (12.8)	6 (4.3)	3 (2.1)	2 (4.5)	2 (4.5)
Weight decreased	43 (14.4)	*	8 (5.7)	*	2 (4.5)	*
Oedema peripheral	40 (13.4)	*	16 (11.4)	*	7 (15.9)	*
Lipase increased	40 (13.4)	35 (11.7)	3 (2.1)	2 (1.4)	4 (9.1)	4 (9.1)
Hypoalbuminaemia	39 (13.1)	*	9 (6.4)	*	7 (15.9)	*
Cough	37 (12.4)	*	26 (18.6)	*	3 (6.8)	*
Hyponatraemia	32 (10.7)	*	6 (4.3)	*	5 (11.4)	*
Abdominal pain upper	30 (10.1)	*	4 (2.9)	*	3 (6.8)	*
Amylase increased	30 (10.1)	*	2 (1.4)	*	1 (2.3)	*

Rash	29 (9.7)	*	9 (6.4)	*	2 (4.5)	*
COVID-19	28 (9.4)	*	13 (9.3)	*	2 (4.5)	*
Pneumonia	27 (9.1)	*	13 (9.3)	*	6 (13.6)	*
Arthralgia	27 (9.1)	*	12 (8.6)	*	0	*
Abdominal pain	24 (8.1)	*	6 (4.3)	*	3 (6.8)	*
Platelet count decreased	24 (8.1)	*	5 (3.6)	*	1 (2.3)	*
Hypokalaemia	23 (7.7)	*	11 (7.9)	*	2 (4.5)	*
Pain in extremity	23 (7.7)	*	8 (5.7)	*	2 (4.5)	*
Malignant neoplasm progression	23 (7.7)	*	5 (3.6)	*	5 (11.4)	*
Dizziness	23 (7.7)	*	4 (2.9)	*	2 (4.5)	*
Back pain	22 (7.4)	*	9 (6.4)	*	2 (4.5)	*
Headache	22 (7.4)	*	6 (4.3)	*	2 (4.5)	*
Pruritus	21 (7.0)	*	3 (2.1)	*	0	*
Electrocardiogram QT prolonged	20 (6.7)	*	0	*	1 (2.3)	*
Blood creatine phosphokinase increased	19 (6.4)	*	0	*	2 (4.5)	*
Insomnia	18 (6.0)	*	8 (5.7)	*	1 (2.3)	*
Hypomagnesaemia	18 (6.0)	*	7 (5.0)	*	1 (2.3)	*
Lymphocyte count decreased	17 (5.7)	*	7 (5.0)	*	4 (9.1)	*
Stomatitis	16 (5.4)	*	14 (10.0)	*	1 (2.3)	*
Non-cardiac chest pain	16 (5.4)	*	7 (5.0)	*	3 (6.8)	*
Hypotension	16 (5.4)	*	6 (4.3)	*	1 (2.3)	*
Thrombocytopenia	16 (5.4)	*	5 (3.6)	*	1 (2.3)	*
General physical health deterioration	15 (5.0)	*	4 (2.9)	*	1 (2.3)	*
Hyperkalaemia	15 (5.0)	*	3 (2.1)	*	1 (2.3)	*
Hypocalcaemia	15 (5.0)	*	3 (2.1)	*	3 (6.8)	*
Productive cough	14 (4.7)	*	8 (5.7)	*	3 (6.8)	*
Hypophosphataemia	14 (4.7)	*	7 (5.0)	*	1 (2.3)	*
White blood cell count decreased	13 (4.4)	*	15 (10.7)	*	0	*

Myalgia	13 (4.4)	*	9 (6.4)	*	2 (4.5)	*
Hyperglycaemia	12 (4.0)	*	11 (7.9)	*	3 (6.8)	*
Dysgeusia	12 (4.0)	*	9 (6.4)	*	0	*
Neutrophil count decreased	10 (3.4)	9 (3.0)	23 (16.4)	23 (16.4)	0	0
Neutropenia	9 (3.0)	8 (2.7)	17 (12.1)	17 (12.1)	2 (4.5)	1 (2.3)
Haemoptysis	8 (2.7)	*	10 (7.1)	*	1 (2.3)	*
Musculoskeletal pain	4 (1.3)	*	7 (5.0)	*	1 (2.3)	*
Alopecia	3 (1.0)	2 (0.7)	35 (25.0)	34 (24.3)	0	0
Neuropathy peripheral	3 (1.0)	*	11 (7.9)	*	0	*
Hypoproteinaemia	3 (1.0)	*	3 (2.1)	*	3 (6.8)	*
Musculoskeletal chest pain	3 (1.0)	*	1 (0.7)	*	3 (6.8)	*
Urinary retention	0	*	0	*	3 (6.8)	*

*Treatment related in <10% of patients in all arms and therefore not reported here.
Abbreviations: TEAE, treatment-emergent adverse event.
Sources: KRYSTAL-12 CSR[121]

B.2.10.2.2 Grade ≥3 TEAEs

Grade ≥3 TEAEs occurred in 213 patients (71.5%) in the adagrasib arm vs 93 patients (66.4%) in the docetaxel arm, and treatment-related Grade ≥3 TEAEs occurred in 140 (47.0%) vs 64 (45.7%) patients, respectively.[121] Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs occurring in ≥2% of patients in either treatment arm are summarised in Table 34.

The most common (≥5% on either arm) Grade ≥3 TEAEs were ALT increased (9.1% of patients on adagrasib vs 0 patients on docetaxel), malignant neoplasm progression (7.7% vs 3.6%), AST increased (6.7% vs 0), gamma-glutamyltransferase increased (6.4% vs 1.4%), diarrhoea (5.7% vs 4.3%), asthenia (5.4% vs 11.4%), fatigue (5.0% vs 2.1%), anaemia (4.7% vs 5.7%), pneumonia (4.4% vs 7.1%), neutropenia (2.0% vs 10.0%), neutrophil count decreased (1.3% vs 11.4%), and white blood cell count decreased (0.7% vs 5.7%).[121]

The most common (≥5% on either arm) treatment-related Grade ≥3 TEAEs were ALT increased (7.7% vs 0), AST increased (6.4% vs 0), diarrhoea (5.4% vs 4.3%), gamma-glutamyltransferase increased (5.0% vs 0), asthenia (4.4% vs 10.0%), neutropenia (1.7% vs 10.0%), neutrophil count decreased (1.3% vs 11.4%), and white blood cell count decreased (0.7% vs 5.0%).[121]

Table 34: KRYSTAL-12 | Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs occurring in ≥2% of patients in either treatment arm

TEAE, n (%)	Adagrasib (n=298)		Docetaxel (n=140)	
	Any	Related	Any	Related
Any TEAE	213 (71.5)	140 (47.0)	93 (66.4)	64 (45.7)
Alanine aminotransferase increased	27 (9.1)	23 (7.7)	0	0
Malignant neoplasm progression	23 (7.7)	*	5 (3.6)	*
Aspartate aminotransferase increased	20 (6.7)	19 (6.4)	0	0
Gamma-glutamyltransferase increased	19 (6.4)	15 (5.0)	2 (1.4)	0
Diarrhoea	17 (5.7)	16 (5.4)	6 (4.3)	6 (4.3)
Asthenia	16 (5.4)	13 (4.4)	16 (11.4)	14 (10.0)
Fatigue	15 (5.0)	10 (3.4)	3 (2.1)	3 (2.1)
Anaemia	14 (4.7)	10 (3.4)	8 (5.7)	6 (4.3)
Lipase increased	14 (4.7)	12 (4.0)	0	0
Pneumonia	13 (4.4)	*	10 (7.1)	*
General physical health deterioration	13 (4.4)	*	3 (2.1)	*
Dyspnoea	12 (4.0)	0	5 (3.6)	3 (2.1)
Decreased appetite	12 (4.0)	*	3 (2.1)	*
Nausea	9 (3.0)	9 (3.0)	1 (0.7)	1 (0.7)
Amylase increased	8 (2.7)	6 (2.0)	0	0
Vomiting	7 (2.3)	*	2 (1.4)	*
Blood alkaline phosphatase increased	7 (2.3)	*	1 (0.7)	*
Neutropenia	6 (2.0)	5 (1.7)	14 (10.0)	14 (10.0)
Pulmonary embolism	6 (2.0)	*	3 (2.1)	*
Acute kidney injury	6 (2.0)	*	1 (0.7)	*
Electrocardiogram QT prolonged	6 (2.0)	*	0	*
Hyperkalaemia	6 (2.0)	*	0	*
Hyponatraemia	6 (2.0)	*	0	*
Hypokalaemia	5 (1.7)	*	3 (2.1)	*
Neutrophil count decreased	4 (1.3)	4 (1.3)	16 (11.4)	16 (11.4)
White blood cell count decreased	2 (0.7)	2 (0.7)	8 (5.7)	7 (5.0)
Arthralgia	1 (0.3)	*	4 (2.9)	*
Leukopenia	1 (0.3)	1 (0.3)	3 (2.1)	3 (2.1)
Pleural effusion	1 (0.3)	*	3 (2.1)	*
Febrile neutropenia	0	0	5 (3.6)	4 (2.9)

*Treatment related in <2% of patients in all arms and therefore not reported here.
Abbreviations: TEAE, treatment-emergent adverse event.
Sources: KRYSTAL-12 CSR[121]

B.2.10.3 Deaths and serious TEAEs

B.2.10.3.1 On-study deaths

Fatal (Grade 5) TEAEs occurred in 48 (16.1%) patients in the adagrasib arm and 10 (7.1%) patients in the docetaxel arm. Fatal TEAEs of >1 patient on the adagrasib arm were malignant neoplasm progression (22 [7.4%] patients), death (5 [1.7%]), dyspnoea (2 [0.7%]), respiratory failure (2 [0.7%]), and septic shock (2 [0.7%]). Fatal TEAEs of >1 patient on the docetaxel arm were malignant neoplasm progression (5 [3.6%]) and cardio-respiratory arrest (2 [1.4%]).[121]

Fatal treatment-related TEAEs occurred in 4 (1.3%) vs 1 (0.7%) patients in the adagrasib and docetaxel arms, respectively. These events were hepatic failure, hepatic ischaemia, death (unknown cause), and epilepsy in the adagrasib arm and sepsis in the docetaxel arm.[121]

B.2.10.3.2 Serious TEAEs

Serious TEAEs occurred in 149 (50.0%) vs 50 (35.7%) patients on adagrasib vs docetaxel, respectively. Serious TEAEs experienced by ≥1% patients are summarised in Table 35. The most common serious TEAEs (≥2% on either arm) were pneumonia (3.7% vs 5.0%), COVID-19 (1.3% vs 2.1%), dyspnoea (2.0% vs 1.4%), pulmonary embolism (1.3% vs 2.1%), malignant neoplasm progression (7.4% vs 3.6%), vomiting (3.0% vs 1.4%), pyrexia (2.3% vs 0.7%), general physical health deterioration (2.0% vs 0.7%), febrile neutropenia (0 vs 2.9%), ALT increased (2.0% vs 0), and acute kidney injury (2.0% vs 0).[121]

Treatment-related serious TEAEs occurred in 62 (20.8%) vs 23 (16.4%) patients on adagrasib vs docetaxel, respectively. The most common treatment-related serious TEAEs (≥2% on either arm) were vomiting (2.3% vs 1.4%), ALT increased (2.0% vs 0), diarrhoea (0.7% vs 2.1%), and febrile neutropenia (0 vs 2.9%).[121]

Of the patients who crossed over from docetaxel to adagrasib, 20 (45.5%) patients experienced serious TEAEs and treatment-related serious TEAEs occurred in 7 (15.9%) patients. The most common serious TEAEs (≥2 patients) were pneumonia (6 [13.6%]), malignant neoplasm progression (5 [11.4%]), and diarrhoea (2 [4.5%]). The treatment-related serious TEAEs, each occurring in one patient, were diarrhoea, myelosuppression, general physical health deterioration, transaminases increased, interstitial lung disease, pneumonia, dizziness, vision blurred, and pericardial effusion.[121]

Table 35: KRYSTAL-12 | Serious TEAEs occurring in ≥1% of patients

TEAE, n (%)	Adagrasib (n=298)	Docetaxel (n=140)	Crossover adagrasib (n=44)
Any TEAE	**149 (50.0)**	**50 (35.7)**	**20 (45.5)**
Infections and infestations	**38 (12.8)**	**15 (10.7)**	**10 (22.7)**
Pneumonia	11 (3.7)	7 (5.0)	6 (13.6)
COVID-19	4 (1.3)	3 (2.1)	0
Sepsis	4 (1.3)	2 (1.4)	1 (2.3)
COVID-19 pneumonia	3 (1.0)	2 (1.4)	0
Infection	0	2 (1.4)	0

Respiratory, thoracic and mediastinal disorders	**26 (8.7)**	**12 (8.6)**	**3 (6.8)**
Dyspnoea	6 (2.0)	2 (1.4)	1 (2.3)
Pulmonary embolism	4 (1.3)	3 (2.1)	0
Pleural effusion	3 (1.0)	2 (1.4)	1 (2.3)
Pneumonitis	3 (1.0)	2 (1.4)	0
Respiratory failure	4 (1.3)	1 (0.7)	0
Chronic obstructive pulmonary disease	0	2 (1.4)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**26 (8.7)**	**6 (4.3)**	**5 (11.4)**
Malignant neoplasm progression	22 (7.4)	5 (3.6)	5 (11.4)
Gastrointestinal disorders	**22 (7.4)**	**9 (6.4)**	**3 (6.8)**
Vomiting	9 (3.0)	2 (1.4)	1 (2.3)
Diarrhoea	4 (1.3)	3 (2.1)	2 (4.5)
Nausea	3 (1.3)	0	0
Stomatitis	0	2 (1.4)	0
General disorders and administration site conditions	**25 (8.4)**	**6 (4.3)**	**2 (4.5)**
Pyrexia	7 (2.3)	1 (0.7)	0
General physical health deterioration	6 (2.0)	1 (0.7)	1 (2.3)
Death*	5 (1.7)	0	0
Blood and lymphatic system disorders	**7 (2.3)**	**10 (7.1)**	**1 (2.3)**
Anaemia	2 (0.7)	2 (1.4)	0
Febrile neutropenia	0	4 (2.9)	0
Neutropenia	2 (0.7)	2 (1.4)	0
Myelosuppression	0	2 (1.4)	1 (2.3)
Investigations	**16 (5.4)**	**0**	**1 (2.3)**
Alanine aminotransferase increased	6 (2.0)	0	0
Aspartate aminotransferase increased	5 (1.7)	0	0
Renal and urinary disorders	**10 (3.6)**	**2 (1.4)**	**1 (2.3)**
Acute kidney injury	6 (2.0)	0	0

*Unknown cause of death
Abbreviations: TEAE, treatment-emergent adverse event.
Source: KRYSTAL-12 CSR[121]

B.2.10.4 Safety events of clinical interest: hepatotoxicity

Clinical experts consulted by the company indicated that hepatotoxicity was a concern when prescribing sotorasib, another KRAS G12C inhibitor.[24] Hepatic TEAEs observed in KRYSTAL-12 are therefore summarised in Table 36. Although one-third of patients experienced hepatic TEAEs, most events (73–80%) and most treatment-related events (74–79%) were Grade 1–2, and only 2% of all patients experienced serious increase in ALT or AST.[121] This distribution of adverse events suggests that the safety profile of adagrasib is manageable for the vast majority of patients.

Table 36: KRYSTAL-12 | Hepatic TEAEs

	Adagrasib (n=298)	
	Any	**Related**
Alanine aminotransferase increased		
TEAE, n (%)	99 (33.2)	90 (30.2)
Grade ≥3 TEAE, n (%)	27 (9.1)	23 (7.7)
Serious TEAE, n (%)	6 (2.0)	6 (2.0)
Aspartate aminotransferase increased		
TEAE, n (%)	99 (33.2)	92 (30.9)
Grade ≥3 TEAE, n (%)	20 (6.7)	19 (6.4)
Serious TEAE, n (%)	5 (1.7)	5 (1.7)

Abbreviations: TEAE, treatment-emergent adverse event.
Sources: KRYSTAL-12 CSR[121]

As demonstrated in Section B.1.3.2.4.3, sotorasib shows a higher incidence of treatment-related Grade ≥3 adverse events and hepatotoxicity events (overall and Grade ≥3) among patients with a shorter time gap between treatment with immunotherapy and treatment with sotorasib vs those with a longer time gap.[83, 100] In contrast, KRYSTAL-1 showed that among the 12 patients who received immunotherapy less than 30 days before adagrasib, none had Grade ≥3 treatment-related hepatotoxicity events (defined as increased ALT or AST, increased liver function test, and mixed liver injury).[125] As a result, the KRYSTAL-12 protocol did not require a washout period between prior immunotherapy and initiation of study treatment.[124] Additionally, an ongoing phase 2/3 trial, begun in 2020 and estimated to complete in 2029, is evaluating the efficacy and safety of adagrasib in combination with pembrolizumab.[151]

B.2.10.5 Safety conclusions

Data from the KRYSTAL-12 safety population, consisting of all patients treated with adagrasib (n=298) or docetaxel (n=140), showed differentiated safety profiles for the two treatments, with higher rates of gastrointestinal TEAEs and hepatotoxicity for patients receiving adagrasib, and higher rates of alopecia, cough, Grade 3/4 neutropenia, febrile neutropenia, and peripheral neuropathy for patients taking docetaxel. These differences were observed despite a longer mean exposure for adagrasib (5.56 months vs 3.17 months for docetaxel) and consequent longer TEAE reporting period for adagrasib. The safety profile of adagrasib was generally similar to that described in KRYSTAL-1 (Appendix F), with no new safety signals observed.

Although gastrointestinal events and hepatotoxicity were observed with adagrasib, most of these TEAEs were Grade 1–2, and PROs suggest that these effects did not interfere with patient wellbeing. EQ-5D results, when compared to the MID, showed that QoL was maintained over time according to both the index score and the VAS (Section B.2.6.1.4.1). Adagrasib demonstrated clinically significant ≥10-point advantage over docetaxel in fatigue, pain, dyspnoea, and cough (Section B.2.6.1.4.2). The low-grade nature of key TEAEs along with PROs indicate that adagrasib is generally tolerable with a manageable safety profile.

Results from KRYSTAL-1 suggest that prior treatment with immunotherapy does not lead to Grade ≥3 hepatotoxicity events after initiating adagrasib (Section B.2.10.4), as is the case

for sotorasib (Section B.1.3.2.4.3). Given that the majority of patients receive immunotherapy (either alone or in combination with platinum-based chemotherapy) as their initial treatment in UK clinical practice (Section B.1.3.3.4), this improvement in the incidence of hepatotoxicity events could be crucial for patients needing to initiate adagrasib rapidly and without interruption.

B.2.11 Ongoing studies

The pivotal phase 3 trial, KRYSTAL-12, is ongoing with final OS analysis expected in [redacted].

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

KRYSTAL-12, a phase 3, open-label, randomised study that enrolled 453 patients with *KRAS* G12C mutation-positive advanced NSCLC (301 randomised to adagrasib and 152 to docetaxel), demonstrates superiority of adagrasib for PFS in patients who had disease progression on or after treatment with a platinum-based regimen and an immune checkpoint inhibitor.[121] Treatment with adagrasib significantly reduced the risk of progression or death by 42% relative to docetaxel, (HR, 0.58; 95% CI, 0.45 to 0.76; p<0.0001).[121] The significant treatment benefit for adagrasib was maintained across the majority of subgroups.[121]

While KRYSTAL-12 interim OS results remain restricted, the PFS findings are reinforced by the KRYSTAL-1 phase 2 Cohort A data that demonstrates a median OS of 12.6 months (95% CI, 9.2 to 19.2).[123] Given that surrogacy analyses in NSCLC show a moderate to high correlation between progression and survival both at study and individual levels,[126, 127] and PFS is consistent and similar between KRYSTAL-1 and KRYSTAL-12 (Section B.2.6.1), an OS benefit for adagrasib over docetaxel is anticipated for the KRYSTAL-12 OS data. This surrogate relationship is presented in detail in Section B.3.3.2 and Appendix P and supports the inclusion of OS estimates from KRYSTAL-1 in the economic model.

Adagrasib also demonstrated intracranial efficacy in patients with *treated* brain metastases. In the KRYSTAL-12 subgroup of patients with baseline CNS metastasis, icORR was 24.4% (n=19/78; 95% CI, 15.3% to 35.4%) for adagrasib and 11.1% (n=4/36; 95% CI, 3.1% to 26.1%) for docetaxel (OR, 2.58; 95% CI, 0.81 to 8.23).[121] In the CNS evaluable population, icORR was even higher in the adagrasib arm (40%; n=10/25) and remained unchanged in the docetaxel arm (11%; n=1/9).[129] For patients achieving a response, icDOR was 19.91 months (95% CI, 9.43 to NE) in the adagrasib arm.[121] Median icTTP was 18.63 months (95% CI, 9.56 to NE).[121]

Importantly, KRYSTAL-1 phase 1b data show that adagrasib is also efficacious in patients with *untreated* brain metastases. In this cohort, icORR was 42.1% (95% CI, 20.3% to 66.5%) with an icDOR of 12.7 months (95% CI, 3.9 to NE).[134] The resulting icPFS was 5.4 months (95% CI, 2.7 to NE).[134]

Although gastrointestinal events and hepatotoxicity were observed with adagrasib, most of these TEAEs were Grade 1–2, and PROs suggest that these effects did not negatively impact patient wellbeing. Indeed, EQ-5D index and VAS scores in the adagrasib group were maintained over time in KRYSTAL-12, and LCSS scores demonstrated clinically significant ≥10-point advantage over docetaxel in fatigue, pain, dyspnoea, and cough.[128] The low-grade

nature of key TEAEs along with PROs indicate that adagrasib is generally tolerable with a manageable safety profile.

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the evidence base

KRYSTAL-12 is a phase 3 RCT that enrolled 453 patients across 23 countries (including the UK) with *KRAS* G12C mutation-positive advanced NSCLC. The study was powered for the primary endpoint of PFS as well as 80% power to detect an HR of 0.72 in the secondary endpoint of OS (although the interim OS results remain restricted as described in Section B.2.6.1.2). Patient baseline demographic and disease characteristics were well-balanced between treatment arms.[121] KRYSTAL-1 (phase 2, Cohort A) was a single-arm trial that enrolled 116 patients.[123] Patient baseline demographic and disease characteristics were consistent with those reported in KRYSTAL-12.

KRYSTAL-12 and KRYSTAL-1 demonstrated internal consistency of outcomes as well as agreement of results between the two trials. PFS was similar for KRYSTAL-12 and KRYSTAL-1, and both trials showed the treatment benefit of adagrasib in terms of response rates and duration of response. The positive PFS findings were reinforced by a KRYSTAL-1 OS of 12.6 months.[121–123]

The patient populations and prior treatment histories included in KRYSTAL-12 and KRYSTAL-1 are generalisable to UK clinical practice.

- Clinical experts confirmed that the KRYSTAL-12 trial comparator, docetaxel, may be used from second line onward in UK clinical practice in patients with *KRAS* G12C mutation-positive advanced NSCLC.[24]
- With the exception of two patients enrolled in KRYSTAL-1 in whom immunotherapy was contraindicated, patients in both trials had received both platinum-based chemotherapy and anti-PD-(L)1 immunotherapy, either concurrently (73% in KRYSTAL-12 and 71% in KRYSTAL-1) or sequentially (27% in KRYSTAL-12 and 28% in KRYSTAL-1), prior to trial enrolment.[121, 122] This reflects the treatment pathway in clinical practice, in which the majority of patients receive concurrent platinum-based chemotherapy and immunotherapy as initial treatment.[24]
- In KRYSTAL-12, randomisation was stratified by concurrent vs sequential treatment with platinum-based chemotherapy and immunotherapy.[121]

KRYSTAL-12 efficacy results are similar regardless of concurrent vs sequential treatment with platinum-based chemotherapy and immunotherapy (Section B.2.7.1).

B.2.12.2.2 Potential limitations of the evidence base

Although KRYSTAL-12 was an open-label study, the lack of blinding is unlikely to have substantially affected interpretation of response or progression because these endpoints were assessed in accordance with RECIST v1.1 by BICR.[121, 124]

KRYSTAL-12 employed docetaxel as the control treatment, allowing a direct comparison between adagrasib and a relevant appraisal comparator. The lack of direct comparison with other comparators from the final scope resulted in a need for indirect treatment comparisons. It was possible to form a connected network of RCTs including key trials for the relevant

comparators, and KRYSTAL-12 for adagrasib. As such, an NMA was performed. Some variability was observed in study and patient characteristics between some trials in the network. For example, differences with LUME-Lung 1 were observed in requirements for prior therapy and *KRAS* mutation status. However, as it is not be possible to adjust for these difference, population adjustment methods were not considered feasible for the indirect comparison. It is uncertain whether these patient characteristics should be considered effect modifiers for the NMA; however, given the mechanism of action of alternative treatments, it may be assumed that *KRAS* mutation status only impacts outcomes of KRAS inhibitors.

Because the KRYSTAL-12 interim OS results remain restricted at the time of this appraisal, it was necessary to extrapolate survival estimates from an alternative data source. Using a patient-level surrogacy analysis to predict OS (described in Section B.3.3.2 and Appendix P) allows progression and survival data from KRYSTAL-1, and progression data from KRYSTAL-12 to be leveraged, and is therefore determined to be the most robust approach for estimating OS. A range of alternative scenarios, including using external OS data for adagrasib and docetaxel from KRYSTAL-1 and SELECT-1, respectively, are tested in the cost-effectiveness analysis in Section B.3, to explore uncertainty in the OS estimates.

B.2.12.3 Summary and conclusions

KRAS is the most prevalent driver mutation in NSCLC, and G12C is the most frequent *KRAS* variant, with *KRAS* G12C mutations occurring in approximately 13% of all NSCLC cases (Section B.1.3.1.3). *KRAS* mutations, as a group, are a negative prognostic biomarker vs wild-type NSCLC for PFS and OS. Some studies suggest that *KRAS* G12C can confer even worse outcomes than other *KRAS* mutations. A high frequency of brain metastases at diagnosis may also contribute to the poor prognosis of patients with *KRAS* G12C mutation-positive NSCLC (Section B.1.3.2.1.2).

Patients with the *KRAS* G12C mutation are underserved compared to those with other driver mutations, for which a broader range of therapies are available (Section B.1.3.2.1.2). Sotorasib, currently only available through the CDF and not routinely commissioned by the NHS, is the only therapy available to patients that targets *KRAS* G12C mutation-positive NSCLC, leaving patients with limited treatment options. The non-targeted docetaxel-based regimens are associated with limited efficacy outcomes (Section B.1.3.2.4.1), as well as potentially life-threatening myelosuppression that can negatively impact tolerability and compromise treatment outcomes (Section B.1.3.2.4.2)

Adagrasib is a novel, oral, KRAS G12C-targeted treatment option that offers a clinically meaningful and statistically significant PFS benefit (42% reduction in the risk of progression or death vs docetaxel; Section B.2.6.1.1). This treatment benefit is demonstrated consistently across the majority of the prespecified subgroups (Section B.2.7.1). Given that surrogacy analyses in NSCLC show a moderate to high correlation between progression and survival both at study and individual levels,[126, 127] and PFS is consistent and similar between KRYSTAL-1 and KRYSTAL-12 (Section B.2.6), an OS benefit for adagrasib over docetaxel is anticipated for the KRYSTAL-12 analysis expected in [redacted] (estimate; event-driven).This surrogate relationship is presented in detail in Section B.3.3.2 and Appendix P, and supports the inclusion of OS estimates from KRYSTAL-1 in the economic model.

The results of the NMA suggest that adagrasib demonstrates improved efficacy in treating patients with *KRAS* G12C mutation-positive NSCLC, compared with existing treatment options. Across the proportional-hazards and time-varying NMAs, for PFS and OS

(estimated using a surrogate relationship), point estimate HRs were consistently in favour of adagrasib vs comparators (Section B.2.9).

Evidence shows that for patients with NSCLC who also have brain metastases, symptom burden is higher, survival is shorter, and QoL is lower than for those without brain metastasis (Section B.1.3.2.3). Clinical experts confirmed that patients with brain metastases represent a population with high unmet need.[24] In addition to demonstrating intracranial activity in patients with *treated* brain metastases, adagrasib is also intracranially active in patients with *untreated* brain metastases (Section B.2.7.2). Thus, adagrasib may fulfil a need that is unmet by current therapies, including sotorasib (Section B.1.3.2.4.3).

Adagrasib's toxicity profile is manageable (Section B.2.10), and patient responses on the EQ-5D and LCSS demonstrate that any observed toxicity has little impact on patient wellbeing (Section B.2.6.1.4).

Overall, these data support the use of adagrasib as an efficacious alternative treatment option with a manageable safety profile that, if reimbursed, would fulfil a significant unmet need for patients who have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-(L)1 immunotherapy.[121–123, 130, 134]

B.3 Cost effectiveness

The cost-effectiveness analysis considers adults with advanced NSCLC with *KRAS* G12C mutation, whose disease has progressed after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. The modelled population aligns with adagrasib trial evidence (KRYSTAL-1 and KRYSTAL-12) and marketing authorisation.

In line with the final scope issued by NICE for this appraisal, the comparators included in the economic analysis are docetaxel and docetaxel + nintedanib.

The model uses a three-state partitioned survival analysis framework (with health states for pre-progression, progressed disease, and death). The model structure reflects the progressive nature of the disease, allows for the incorporation of relevant clinical trial endpoints (namely, OS and PFS), and is consistent with the only prior NICE appraisal in advanced *KRAS* G12C mutation-positive NSCLC (as well as many other prior economic evaluations and NICE submissions in NSCLC and other solid tumours).

Model settings are aligned with the NICE reference case:

- Lifetime horizon (20 years)
- 3.50% discount rates for costs and QALYs
- NHS and PSS perspective on costs, and direct health effects for patients
- 1-week cycle length

Clinical effectiveness data for adagrasib and docetaxel are primarily sourced from KRYSTAL-12:

- For the reasons outlined in Section B.2.6.1.2, KRYSTAL-12 interim OS results remain restricted. In the base case, a patient-level surrogacy analysis for OS was estimated based on TTP, using IPD from KRYSTAL-1 to simulate KRYSTAL-12 OS for adagrasib and docetaxel.
- In scenario analysis, OS data from KRYSTAL-1 (adagrasib) and SELECT-1 (docetaxel) are used as a proxy for OS data from KRYSTAL-12.

In the absence of head-to-head data for adagrasib vs docetaxel + nintedanib, an NMA was performed. As proportional hazards were violated for PFS in the LUME-Lung 1 study (docetaxel + nintedanib), the time-varying NMA was used in the base case.

For the time-varying NMA, the gamma curve is selected in the base case for PFS and OS. The time-varying NMA methods specify that the same distribution is applied across treatment arms; the gamma curves provide a good statistical fit to the observed data, and were noted to produce clinically plausible long-term extrapolations in KOL validation.

Health state utility values were estimated from KRYSTAL-12 data (EQ-5D-5L mapped to 3L in line with the NICE reference case). Treatment-specific health state utility values are used in the base case, to account for the HRQoL impact of differences between adagrasib (an orally administered targeted therapy) and docetaxel (an intravenously administered chemotherapy).

The model captures drug acquisition, administration, subsequent treatment, healthcare resource use, adverse event management, and end-of-life care costs.

Unit costs were taken from standard UK sources including the BNF, eMIT, National Cost Collection, and Unit Costs of Health and Social Care.

In the base-case analysis, pairwise ICERs for adagrasib are £413 vs docetaxel + nintedanib and £29,107 vs docetaxel. Incremental analysis indicates docetaxel + nintedanib is extendedly dominated by adagrasib. OWSA, PSA, and scenario analyses

demonstrated the robustness of base-case findings to parametric and methodological uncertainties.

Results of the analysis demonstrate that adagrasib represents a cost-effective use of NHS resources for treating patients with previously treated *KRAS* G12C mutation-positive NSCLC.

Abbreviations: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PSS, Personal Social Services; QALYs, quality-adjusted life years; TTP, time to progression.

B.3.1 Published cost-effectiveness studies

A systematic review of the literature was conducted to identify published economic evaluations, cost-effectiveness studies, and healthcare resource use studies relevant to the decision problem addressed within the appraisal.

Full details of the methods, results (including PRISMA diagram), and outcomes of the economic SLR are provided in Appendix G. In summary, searches were conducted on 2 July 2024, and the electronic databases searched were Embase, MEDLINE®, NHS economic evaluation database (NHS EED), and EconLit.

The SLR included economic evaluations and cost-effectiveness studies for treatments in 2L+ advanced/metastatic NSCLC. As searches were not limited to *KRAS* G12C mutation-positive NSCLC, the scope of the SLR was broader than the population considered within this appraisal. Of the 57 economic evaluations identified in the SLR, one was a UK-based cost-effectiveness analysis comparing treatment options for people with advanced *KRAS* G12C mutation-positive NSCLC that have been previously treated with platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy. This single prior NICE appraisal (TA781, sotorasib) in previously treated *KRAS* G12C mutation-positive NSCLC is therefore one of the most relevant sources of information for informing this submission, due to the consistency between the decision problems addressed.[25]

In TA781, sotorasib was recommended for use within the CDF.[25] At the time of submission, the timelines for the managed access review of TA781 (ID6287) are not publicly available.[120]

B.3.2 Economic analysis

As no previous published economic evaluations have assessed the cost-effectiveness of adagrasib for people with previously treated *KRAS* G12C mutation-positive NSCLC, it was necessary to develop a de novo cost-effectiveness model.

The cost-effectiveness model (developed in Microsoft Excel) compares adagrasib with existing treatment options for the patient population relevant to this appraisal in an NHS England setting. These treatment options are docetaxel and docetaxel + nintedanib. Key features of the economic analysis are described in the sub-sections that follow.

The only prior NICE appraisal in previously treated *KRAS* G12C-mutated advanced NSCLC was reviewed to inform the development of the de novo model. In TA781, a three-state partitioned survival analysis with health states comprising progression free, progressed disease, and death was developed to compare sotorasib with docetaxel and docetaxel + nintedanib. Features of this prior economic analysis are described in further detail, and compared with this submission, in Table 37.

B.3.2.1 Patient population

The patient population considered within the economic analysis is adults with advanced NSCLC with *KRAS* G12C mutation, whose disease has progressed after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. Testing for the *KRAS* G12C mutation in patients with NSCLC is routine practice in NHS England, per the National genomic test directory,[35] and as reported in the prior NICE appraisal in *KRAS* G12C-mutated NSCLC.[25]

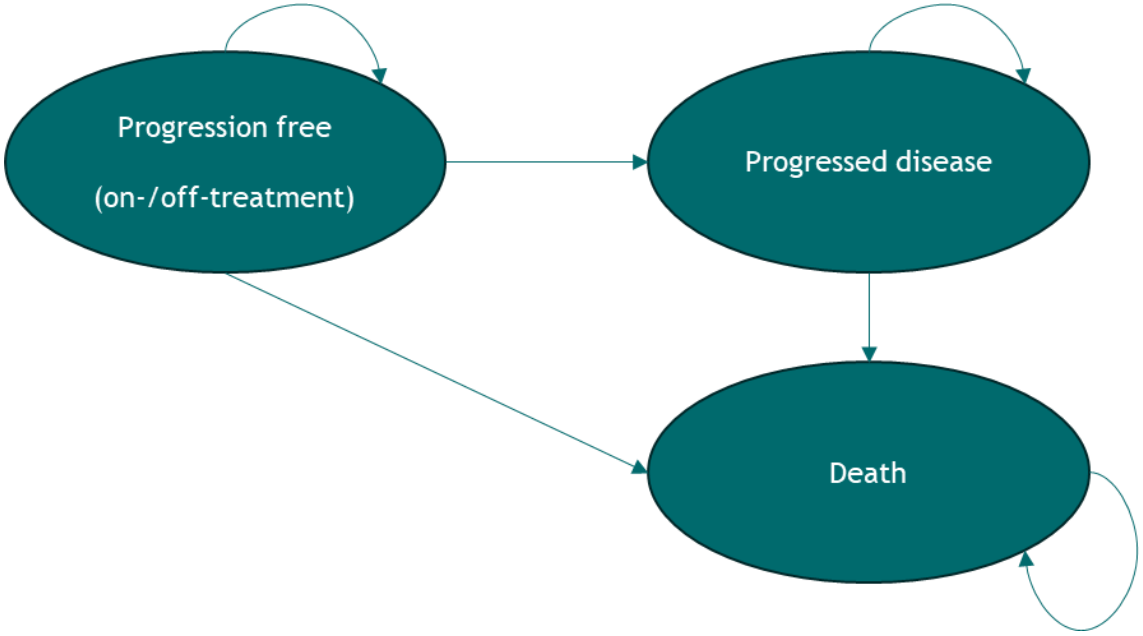
The modelled population is consistent with the final scope issued by NICE (Section 0), and the MHRA granted conditional marketing authorisation for adagrasib (Section B.1.2).[26] Furthermore, the modelled population corresponds with patients from the available clinical trial programme for adagrasib (KRYSTAL-1 and KRYSTAL-12). As described in Section B.2.1, KRYSTAL-12 is an ongoing, international, multicentre, open-label, phase 3 RCT comparing adagrasib with docetaxel, while KRYSTAL-1 was a multicentre, open-label, single-arm phase 1/2 trial. Patients who participated in the KRYSTAL-12 and KRYSTAL-1 trials are considered generalisable to NHS England clinical practice.

B.3.2.2 Model structure

The selected model structure (Figure 24) comprises three health states that are of clinical relevance to the patient population considered in this appraisal. A partitioned survival analysis (PartSA) framework was used to determine health state occupancy; that is, the proportion of patients residing in each health state each model cycle. The modelled health states are:

- Progression free (also commonly referred to as 'pre-progression')
- Progressed disease (also commonly referred to as 'post-progression')
- Death

Figure 24: Model structure diagram



Note: Health state occupancy determined using a PartSA approach (see Figure 25).
Abbreviations: PartSA, partitioned survival analysis.

The rationale for the selected model structure and framework is multifaceted. Firstly, the three-state model is reflective of the progressive nature of advanced/metastatic NSCLC, as patients can remain in their current state, progress, or die, but cannot regress to a health state they previously resided in. This in turns allows costs and health outcomes to be accurately captured within the model.

Secondly, the PartSA framework is well aligned with commonly reported clinical trial endpoints (particularly in the context of time-to-event data), and therefore allows relevant clinical effectiveness data (namely, OS and PFS) to be incorporated with relative ease and transparency.

Furthermore, PartSA models allow time-dependency in the risk of transitioning between health states to be captured (through various parametric survival models, which are described in Section B.3.3.2). This is not the case for conventional Markov models which are 'memoryless', and therefore rely on an exponential assumption for extrapolations.

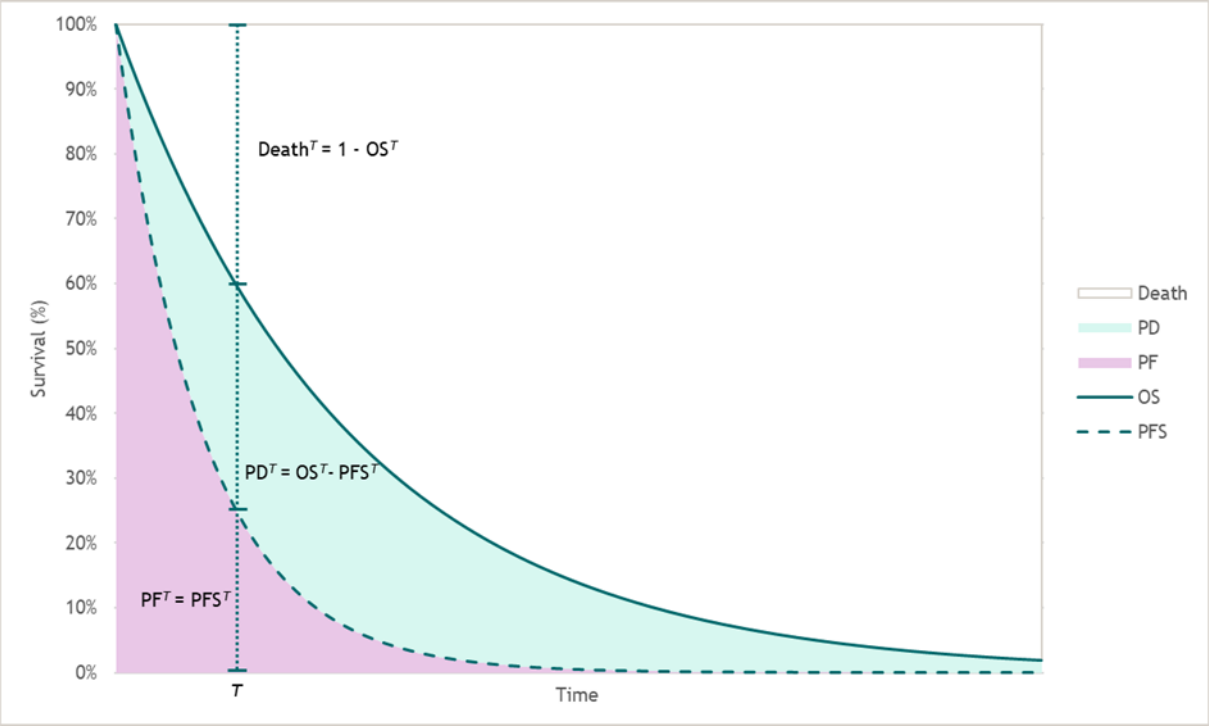
Finally, the chosen model structure is commonly used, and consistent with, several economic evaluations in oncology (across a range of appraisals in an advanced/metastatic NSCLC setting, and many other solid tumours).[152] This includes the model used for decision making in the prior NICE appraisal in *KRAS* G12C mutation-positive NSCLC (TA781).[25]

All patients enter the model in the progression-free state, where they can remain, experience disease progression, or die. Once in the progressed disease health state, patients can remain in their current state or die. Death is an absorbing health state.

Figure 25 presents an illustrative PartSA model, describing how health state occupancy is determined. Rather than explicitly modelling transitions between health states, the proportion of patients in each health state is determined using independently modelled OS and PFS curves. The proportion of patients in the progression-free state is determined by the area under the PFS curve. The proportion of patients in the progressed disease health state is calculated as the difference between the OS and PFS curves. Finally, the proportion of patients who are in the death state is calculated as 1 minus the OS curve. In the model, time to treatment discontinuation curves can be used to further partition the progression-free state into on- and off-treatment periods, to reflect treatment acquisition and administration costs.

As OS and PFS are modelled independently in a PartSA framework, but are non-mutually exclusive endpoints, a cap is used to ensure that the OS and PFS projections do not cross (that is, PFS is set to be less than or equal to OS each cycle). Furthermore, it is assumed that the risk of death for the modelled patient population would not be lower than that of the age-matched general population; this is implemented in the model by a capping of the hazards.

Figure 25: Health state occupancy, illustrative PartSA model



Abbreviations: OS, overall survival, PartSA, partitioned survival analysis; PD, progressed disease; PF, progression free; PFS, progression-free survival.

B.3.2.2.1 Model settings

Table 37 summarises the features of the economic analysis, compared with the previous appraisal in *KRAS* G12C-mutated advanced NSCLC.

In line with the NICE reference case, the perspective of the analysis is that of the NHS and Personal Social Services (PSS) in England for costs, and direct health effects for patients.

As such, the following cost categories are considered: drug, administration, subsequent treatment, health care resource use, AE management, and end-of-life care costs (described further in Section B.3.5). Health outcomes include life years (LYs) and quality-adjusted life years (QALYs), which are derived using the EQ-5D-3L mapping function developed by the Decision Support Unit (DSU) as recommended in the NICE manual (described further in Section B.3.4). Costs and QALYs are discounted at 3.50% in line with the NICE reference case.[153]

The model considers a lifetime horizon of 20 years in the base case, as the NICE reference case stipulates that all important differences in costs or outcomes between technologies should be captured.[153] The time horizon was determined using the age at baseline in KRYSTAL-12 (63.7 years, SD 8.38),[121] and the proportion of patients modelled to have died at 20 years across treatment arms (>99%).

A cycle length of 1 week was selected, which was considered short enough to adequately reflect changes in health status for patients. Furthermore, the 1-week cycle length facilitates drug and administration cost calculations across several treatments with different formulations, dosing regimens, and pack sizes.

Table 37: Features of the economic analysis

Factor	TA781[25]	Chosen values	Justification
Population	Adults with previously treated *KRAS* G12C-mutated, locally advanced or metastatic NSCLC	Adult patients with advanced NSCLC with *KRAS* G12C mutation detected in tumour tissue previously treated with systemic therapy	Consistent with the final scope issued by NICE
Model structure and framework	Three-state PartSA (progression free, progressed, death)	Three-state PartSA (progression free, progressed, death)	To reflect the progressive nature of disease To incorporate relevant clinical trial data For consistency with prior appraisals in NSCLC and other solid tumours
Perspective	NHS and PSS	NHS and PSS	Consistent with the NICE reference case
Annual discount rate	3.50% for costs and QALYs	3.50% for costs and QALYs	Consistent with the NICE reference case
Time horizon	20 years (lifetime)	20 years (lifetime)	Capture the relevant differences in costs and outcomes between treatment arms 20 years is sufficient based on the baseline age (63.7 years), as >99% experience death by this time in the model
Cycle length	1 week	1 week	To capture changes in health outcomes for patients To facilitate accurate drug and administration costing calculations
Measure of health effects	QALYs	QALYs	Consistent with NICE reference case
Source of utility values	CodeBreaK 100 and published literature	KRYSTAL-12 (base case) and published literature (scenario analysis)	In line with NICE reference case (EQ-5D-5L mapped to EQ-5D-3L value set)
Source of costs	UK standard costs sources: NHS Reference costs and eMIT/MIMs	eMIT (generic treatment) BNF (branded treatment) NHS National Cost Collection (administration, AE management, and resource use) PSSRU unit costs (resource use)	Standard sources for informing UK-based economic evaluations, and in line with the NICE reference case

Abbreviations: AE, adverse event; eMIT, electronic drugs and pharmaceutical electronic market information tool; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PartSA, partitioned survival analysis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

As described in Section B.2.1, the intervention is adagrasib (KRAZATI®), a novel *KRAS G12C*-targeted treatment. Adagrasib is administered twice daily at a dose of 600 mg (three 200-mg tablets).

The MHRA granted conditional marketing authorisation for adagrasib in November 2023 and renewed authorisation in November 2024, for the treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.[26] Treatment with adagrasib is recommended until disease progression or unacceptable toxicity. Full marketing authorisation is expected in [redacted].

B.3.2.3.2 Comparators

The current treatment pathway for advanced NSCLC with a *KRAS* G12C mutation in NHS practice is described in Section B.1.3.3. In line with the previous appraisal in advanced *KRAS* G12C-mutated NSCLC, and the final scope issued by NICE for this appraisal, the relevant comparators considered within the economic analyses are:

- Docetaxel
- Docetaxel + nintedanib

The recommended dose of docetaxel is 75 mg/m^2 on Day 1 of every 21-day cycle.[21] In combination therapy, the recommended dose is docetaxel (as above) plus nintedanib 200 mg orally twice daily on days 2–21, every 3 weeks until unacceptable adverse events or disease progression.[81]

As reported in the Final Appraisal Determination for TA781, the NICE committee considered that docetaxel and docetaxel + nintedanib were the relevant comparators when sotorasib was recommended for use within the CDF as an option for treating *KRAS* G12C mutation-positive locally advanced or metastatic NSCLC in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy.[25] Adagrasib would be positioned in the same place as sotorasib in the treatment pathway.

It should be noted that sotorasib is only included in the final scope as 'subject to NICE appraisal'. Although clinical guidance (NG122 and clinical expert opinion) indicates that most patients would receive sotorasib after platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy; NICE guidance stipulates that "technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators".[153] At the time of submission, the current status of the managed access review of TA781 (ID6287) is unclear.[120] On this basis, sotorasib has been excluded from the analysis.

B.3.3 Clinical parameters and variables

Table 38 provides a topline summary of the clinical data sources informing the model, including the base-case approach and various scenarios considered.

Patient baseline characteristics are sourced from KRYSTAL-12 and apply to the full modelled cohort.

As described in Section B.2.9, to compare the clinical efficacy of adagrasib against external comparators, NMA methods (proportional-hazards and time-varying) were explored. As described in Section B.2.6.1.2, the KRYSTAL-12 interim OS results remain restricted. Therefore, in the base case, KRYSTAL-12 OS data are predicted based on the observed progression, and a patient-level surrogacy relationship between TTP and OS estimated using KRYSTAL-1 trial data (see Section B.3.3.2 and Appendix P). Simulated OS data from the surrogacy analysis are used to inform the NMA and subsequently the cost-effectiveness analysis.

Safety data used to inform the model are sourced from KRYSTAL-12 for adagrasib and docetaxel, and LUME-Lung 1 for nintedanib + docetaxel.

Table 38: Summary of clinical data sources informing the model

Clinical data	Application within the model	Source(s) for adagrasib	Source(s) for docetaxel	Source(s) for docetaxel + nintedanib
Baseline characteristics	General population mortality Age-adjusted utility values	KRYSTAL-12 (applied for the cohort, independent of treatment arm)		
OS	Parametric survival curves to estimate lifetime outcomes and determine health state occupancy	Base case Time-varying NMA* Scenario(s) KRYSTAL-12 (independent curves)* KRYSTAL-1 (independent curves)	Base case Time-varying NMA* Scenario(s) KRYSTAL-12 (independent curves)* SELECT-1 (independent curves)	Base case Time-varying NMA Scenario(s) Proportional-hazards NMA
PFS	Parametric survival curves to estimate lifetime outcomes and determine health state occupancy	Base case Time-varying NMA Scenario(s) KRYSTAL-12 (independent curves)	Base case Time-varying NMA Scenario(s) KRYSTAL-12 (independent curves)	Base case Time-varying NMA Scenario(s) Proportional-hazards NMA
AEs	AE management costs AE utility decrements	KRYSTAL-12	KRYSTAL-12	LUME-Lung 1

*Simulated adagrasib and docetaxel OS from patient-level surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS (described further in Section B.3.3.2 and Appendix P).
Abbreviations AE, adverse event; IPD, individual patient data; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

B.3.3.1 Baseline patient characteristics

Baseline patient characteristics informing the model (age, sex, and body surface area [BSA]) were sourced from KRYSTAL-12.

Age and sex were used in the model to estimate background mortality rates, which are applied to survival projections to ensure the hazard of death is not lower than that of the general population. Furthermore, these characteristics were required to estimate age- and sex-matched general population utility values, which are subsequently used to calculate an age-adjustment multiplier, to reflect a natural decline in health-related quality of life (HRQoL) associated with age.

BSA was calculated using height and weight data from KRYSTAL-12 in the Mosteller formula,[154] and is used to calculate treatment costs for docetaxel.

KRYSTAL-12 baseline patient characteristics (Table 39) are considered generalisable to the patient population who would be eligible for treatment with adagrasib in NHS England clinical practice.

Table 39: Baseline patient characteristics

Patient characteristic	Value	Source
Age – years, mean (SD)	63.7 (8.38)	KRYSTAL-12 CSR (Table 16), ITT population[121]
Sex – female, n (%)	150 (33.1%)	
Weight – kg, mean (SD)	70.53 (15.651)	KRYSTAL-12 CSR (Table 14.1.7), ITT population[121]
Height – cm, mean (SD)	168.29 (9.018)	
BSA – m^2	1.82	Calculation (Mosteller formula)[154]

Abbreviations: CSR, clinical study report; BSA, body surface area; ITT, intent-to-treat; SD, standard deviation.

B.3.3.2 Efficacy

B.3.3.2.1 Overview

To inform the economic model, estimates of clinical effectiveness for adagrasib and docetaxel are primarily based on data from the KRYSTAL-12 trial. For PFS, survival analysis was conducted for the ITT population using the primary endpoint definition (PFS as assessed by BICR); data cutoff 31 December 2023. As detailed in Section B.2.6.1.1, the PFS HR for adagrasib vs docetaxel was 0.58 (95% CI, 0.45 to 0.76), indicating a clinically meaningful and statistically significant reduction in the risk of progression or death for patients receiving adagrasib. Kaplan–Meier plots are presented in Figure 10.

As noted in Section B.2.6.1.2, KRYSTAL-12 interim OS results remain restricted. It was therefore necessary to utilise external data sources to inform the cost-effectiveness analysis. Notably, OS was an endpoint in the single-arm phase 2 KRYSTAL-1 study (see Section B.2.6.2.2). Median OS for patients receiving adagrasib in KRYSTAL-1 was 12.6 months (95% CI, 9.2 to 19.2; Figure 16).

To mitigate uncertainty in the absence of OS data from KRYSTAL-12, several approaches for modelling OS were considered, which are described in the following sub-sections.

B.3.3.2.2 Approaches for estimating OS

B.3.3.2.2.1 Approach 1: surrogacy analysis

One approach to predicting the KRYSTAL-12 OS is to apply an established relationship between progression and survival, derived from similar studies, to the available progression data from KRYSTAL-12.

The use of surrogacy relationships is increasingly common in health technology assessment, as they may provide an earlier measurement of treatment performance in settings where a long follow-up time is required before an accurate measurement of the final clinical outcome is feasible.[155] A recent surrogacy analysis of immunotherapies and/or targeted therapies (not including KRAS inhibitors) in NSCLC conducted by Hua *et al.* (2022) found that, at a trial-level, PFS HR had a 'modest' association with OS HR in first- (R= 0.768; 95% CI 0.621, 0.863) and second- (R=0.550; 95% CI 0.377, 0.686) line therapy.[126] Another recent surrogacy analysis conducted by Horita *et al.* (2022), evaluating surrogacy of progression and survival in trials of immune checkpoint inhibitors, showed an association between PFS and OS both at study and individual levels, pointing to a 'high' or 'moderate' correlation between progression and survival at the patient level in first (R=0.71) and second or later (R=0.59) lines.[127]

These findings suggest that there is a moderate association between progression and survival in NSCLC. Importantly, none of the surrogacy analyses in NSCLC focused on the relationship of progression and survival in *KRAS*-mutated disease or included KRAS inhibitors. Given the limited number of trials in this target population, evaluating trial-level surrogacy between progression and survival was not feasible. Therefore, to inform the cost-effectiveness analysis, it was necessary to explore patient-level surrogacy between progression and survival for adagrasib and docetaxel, to estimate KRYSTAL-12 OS.

KRYSTAL-1, the completed single-arm phase 1/2 trial, was identified as appropriate for informing a patient-level surrogacy analysis for several reasons. Firstly, progression (TTP/PFS) and survival (OS) data are mature from KRYSTAL-1. Secondly, BMS have access to IPD from the KRYSTAL-1 study, and it would not be sufficient to use pseudo-IPD reconstructed from published KMs for this analysis, since both outcomes need to be modelled at the same time to fit the individual-level surrogacy model. Furthermore, KRYSTAL-1 was conducted in the patient population considered within the decision problem of this appraisal, and therefore provides *KRAS* G12C mutation-specific data.

In the surrogacy analysis, IPD were used to estimate a relationship between TTP and OS, for patients with previously treated advanced *KRAS* G12C mutation-positive NSCLC (referred to as the 'KRYSTAL-1 model'). This model was then applied to observed TTP data from both arms of KRYSTAL-12, to 'simulate' KRYSTAL-12 OS data (for both adagrasib and docetaxel). It is acknowledged that the data informing the KRYSTAL-1 surrogacy model only includes patients receiving adagrasib; as such, applying the surrogacy model to TTP data from both arms of KRYSTAL-12 assumes that the relationship between TTP and OS for a KRAS-targeted therapy (i.e., adagrasib) applies equally to a non-targeted therapy (i.e., docetaxel). However, a key benefit of this patient-level surrogacy approach is allowing both KRYSTAL-1 and KRYSTAL-12 to be leveraged, whilst maintaining consistency in the target population across the progression and OS endpoints.

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Furthermore, this patient-level surrogacy approach allows covariates of importance to be accounted for when predicting OS. The base-case model included ECOG performance status (PS) 0 or 1 as a covariate. Including additional covariates in the surrogacy analysis (namely, age ≥65 years, and gender) produced very similar results to the base-case model, while increasing the leverage of patient subgroups with very low event numbers. Other covariates such as disease stage, histology (squamous vs non-squamous), and smoking status were not included due to the small proportions of patients presenting these characteristics in KRYSTAL-1.

The patient-level surrogacy analysis was conducted by adapting a joint frailty-copula model proposed by Emura *et al*. (2017) and Emura *et al.* (2022).[156, 157] The technical specification of the patient-level surrogacy analysis, including details of the methods and validation, are presented in Appendix P.

The output of the patient-level surrogacy analysis is simulated KRYSTAL-12 OS data, which are presented as Kaplan–Meier curves in Figure 26. The simulated KRYSTAL-12 OS curves can be extrapolated using standard parametric models (described further below), to inform the cost-effectiveness model. Furthermore, the simulated OS data are applied in the NMA similar to the way that observed survival data would be applied (described in Section B.2.9).

Results of the patient-level surrogacy analysis are provided in Figure 26 and Table 40 below. The predicted KRYSTAL-12 OS for adagrasib and docetaxel resulted in a median survival of [redacted] and [redacted], respectively. Adagrasib was favourable versus docetaxel (point estimate HR=[redacted].

Figure 26: KRYSTAL-12 OS (simulated using KRYSTAL-1 model)

[redacted]

Abbreviations: OS, overall survival.

Table 40: KRYSTAL-12 OS simulated using KRYSTAL-1

Treatment arm	Predicted median OS (95% CI)	HR (95% CI) of adagrasib vs docetaxel
Adagrasib	[redacted]	[redacted]
Docetaxel	[redacted]	Reference

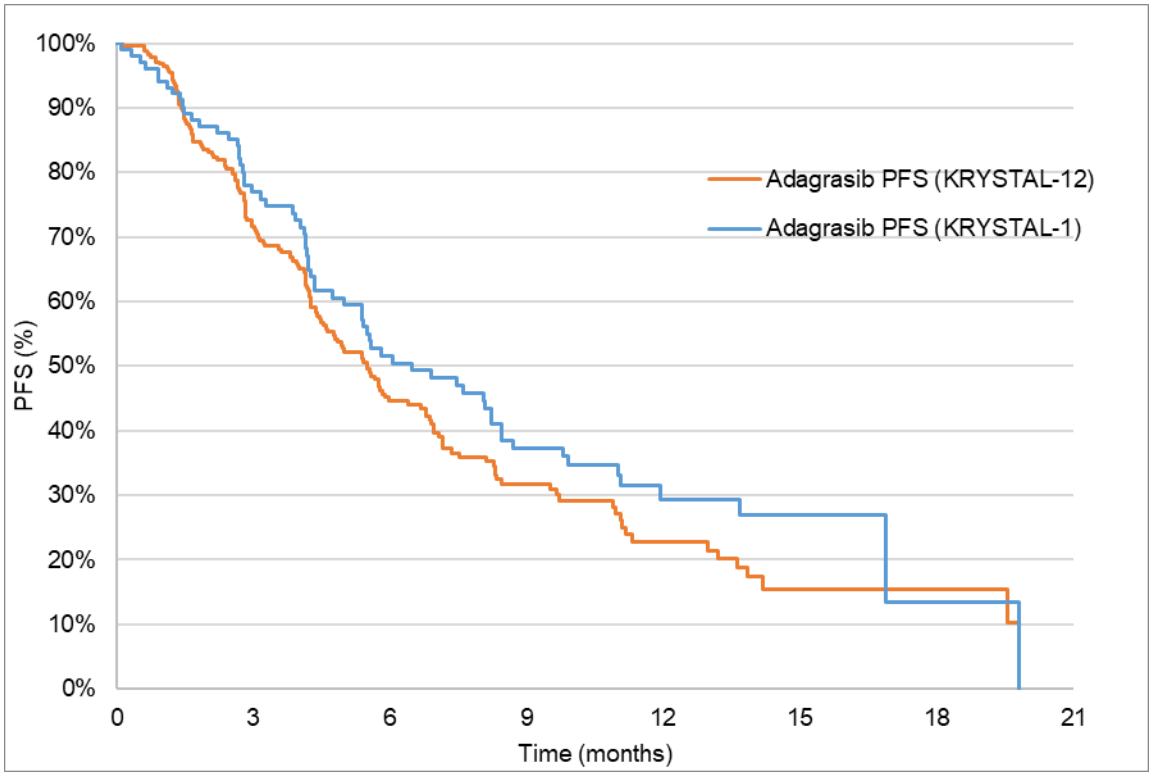
Abbreviations: CI, confidence internal; HR, hazard ratio; OS, overall survival; NE, not evaluable.

B.3.3.2.2.2 Approach 2: external OS data

An alternative method to generate OS for adagrasib is to use unadjusted external OS data as a proxy for KRYSTAL-12 OS data. For adagrasib, KRYSTAL-1 OS data can be applied directly within the cost-effectiveness model. Although KRYSTAL-1 is a single-arm, phase 2 study, this approach provides an appropriate alternative to the surrogacy analysis described above in the absence of KRYSTAL-12 OS data, due to general alignment between the study populations. As described in Section B.2.3.3 (Table 11), overall baseline characteristics were well-balanced between the KRYSTAL-12 treatment arms and the KRYSTAL-1 population.

Figure 27 presents overlayed KM data for the PFS endpoint from the two studies. The figure demonstrates similarity between the curves (median PFS 6.5 months vs 5.49 months), although KRYSTAL-12 PFS falls marginally below KRYSTAL-1 PFS between months 3 and 17. Figure 28 presents the simulated KRYSTAL-12 OS (using the KRYSTAL-1 surrogacy model in the base case) compared with KRYSTAL-1 OS data (used as a proxy in scenario analysis).

Figure 27: KRYSTAL-1 and KRYSTAL-12 PFS



Abbreviations: PFS, progression-free survival.

Figure 28: KRYSTAL-12 OS* (simulated using KRYSTAL-1 surrogacy analysis) vs KRYSTAL-1 OS

Abbreviations: OS, overall survival.
* Simulated adagrasib OS from patient-level surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS (Appendix P)

For the docetaxel arm, the model considers external OS data directly from SELECT-1. SELECT-1 was a multinational RCT including a docetaxel arm in patients with *KRAS* G12C-mutated advanced NSCLC, which was identified in the clinical SLR described in Appendix D.

Figure 29 presents the simulated KRYSTAL-12 OS (using the surrogacy model in the base case) compared with SELECT-1 OS (used in scenario analyses).

Figure 29: KRYSTAL-12 OS* (simulated using the surrogacy analysis) vs SELECT-1 OS

*Simulated docetaxel OS from patient-level surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS.
Abbreviations: OS, overall survival.

B.3.3.2.3 Indirect treatment comparison

As there are no head-to-head trial data available comparing adagrasib with docetaxel + nintedanib, it was necessary to conduct an indirect comparison to inform the model for this comparison. The methods and results are described in detail in Section B.2.9. As described, a Bayesian NMA was performed to compare OS and PFS between the treatments of interest (i.e. adagrasib, docetaxel, and docetaxel + nintedanib).

As described in B.2.9.5, both proportional-hazards NMAs (using reported HRs) and time-varying NMAs (using Kaplan–Meier data) were conducted, as the proportional hazards assumption was violated for PFS in the LUME-Lung 1 study (Table 26).

The time-varying NMA described in Section B.2.9 was considered appropriate for informing the base-case analysis. The proportional-hazards NMA (based on constant HRs) is explored in scenario analyses, combined with parametric curve fits for the within-trial comparison of adagrasib and docetaxel. Regardless of the NMA approach considered, to form a network including KRYSTAL-12, simulated OS based on the patient-level surrogacy analysis are used in the NMA.

NMA results are presented in Section B.2.9.6.

B.3.3.2.4 Extrapolation methods

As Kaplan–Meier data from KRYSTAL-12 or external studies are not complete, it is necessary to extrapolate beyond the trial period to estimate outcomes over a lifetime horizon.

As already noted, two overarching approaches were considered for modelling OS and PFS within the cost-effectiveness analysis:

1. Time-varying NMA (adagrasib, docetaxel and docetaxel + nintedanib) – **base case**
2. Independent curve fits (adagrasib, docetaxel) and proportional-hazards NMA (docetaxel + nintedanib) – **scenario analysis**

B.3.3.2.4.1 Time-varying NMA (base case)

As described in Section B.2.9.5, the time-varying NMA was conducted using a two-step approach; the second step of which is based on one specific parametric distribution that is assumed to apply to all arms of all trials within a network of evidence. One- and two-parameter survival distributions were explored for six distributions (i.e. exponential, Weibull, gamma, Gompertz, log-normal and log-logistic) in the time-varying NMA. While it is possible to explore alternative parametric distributions as sensitivity analysis, different distributions cannot be combined across treatments within one network of evidence as this would violate the transitivity assumption. The parametric models from the time-varying NMA that are used in the base case cost-effectiveness analysis are presented in Section B.3.3.3.

This approach differs from a proportional-hazards NMA, which applies a HR to the modelled comparators relative to a baseline curve.

B.3.3.2.4.2 Independent curve fits + proportional-hazards NMA (scenario analysis)

For the within-trial comparison of adagrasib and docetaxel, a range of standard parametric models were fitted to the data in line with NICE DSU Technical Support Document (TSD) 14,[158] including: exponential, generalised gamma, Gompertz, log-logistic, log-normal, Weibull, and gamma.

To inform the various scenario analyses that were explored, parametric survival models were fitted to the following time-to-event data:

- KRYSTAL-12 PFS data for adagrasib and docetaxel
- Simulated KRYSTAL-12 OS for adagrasib and docetaxel (obtained using the surrogacy model and KRYSTAL-12 progression data)
- KRYSTAL-1 OS data for adagrasib
- SELECT-1 OS data for docetaxel

In the case of SELECT-1, in the absence of IPD, published Kaplan–Meier curves were digitised and pseudo-individual-level patient data generated using the algorithm published by Guyot *et al.* (2012).[146]

NICE DSU TSD 14 reports that it is generally considered unnecessary to rely on the proportional hazards assumption where patient-level data are available, as is the case for adagrasib and docetaxel.[152] Furthermore, in TSD 21, it is noted that assuming proportional

treatment effects is restrictive and may result in poorly fitting (and implausible) survival models and extrapolations.[159] Additionally, adagrasib is a KRAS G12C-targeted therapy whereas docetaxel is a chemotherapy, and due to these differing mechanisms of action, it may not be reasonable to assume that the hazard profiles are proportional over time.

Therefore, in the scenario analyses where the within-trial comparison is combined with the proportional-hazards NMA, independent curves fits are used for OS and PFS extrapolations.

The following steps were performed to determine the most appropriate curves fits:

- Assessed visual and statistical goodness of fit of the curves to the data (AIC and Bayesian information criterion [BIC])
- Assessed the clinical plausibility of the long-term extrapolations with UK clinical experts (consultant oncologists who treat patients with NSCLC in treatment centres in England), and with external data sources

The independent curve fits used in scenario analysis are presented in Appendix Q.

B.3.3.3 Parametric survival curves

B.3.3.3.1 Progression-free survival

Parametric survival curves from the time-varying NMA (see Section B.2.9.6), which are used to inform PFS outcomes in the base-case cost-effectiveness analysis, are presented in Figure 30, for adagrasib, docetaxel, and docetaxel + nintedanib.

The sum of AICs across all studies in the NMA was used to determine the statistical goodness of fit of the models to the PFS data. These are presented collectively in Table 41 along with each model's respective ranks.

Table 41: Statistical goodness-of-fit scores, time-varying NMA, PFS

Model	Sum of AICs	Rank
Weibull	18297.88	4
Gompertz	18527.25	5
Log-logistic	18071.26	2
Log-normal	18026.24	1
Gamma	**18183.04**	**3**
Exponential	18612.76	6

Note: Bold text indicates base case selected model.
Abbreviations: AIC, Akaike information criterion; NMA, network meta-analysis; PFS, progression-free survival.

As previously noted, different distributions cannot be used across treatments within one network of evidence when using the time-varying NMA approach. The gamma model is selected in the base case for PFS, based on the statistical goodness of fit to the observed data (third ranked model), and the long-term plausibility of the extrapolations based on clinical expert opinion. In interviews with clinical experts, the log-logistic and log-normal curves were consistently ruled out as overly optimistic (despite having the best statistical fit to the data), and the gamma model was consistently described as producing plausible PFS estimates (although it was often noted that all curves except for the log-logistic and log-normal were similar). As such, the gamma model is used in the base case and the log-normal model is explored in a scenario analysis. Table 42 presents the survival landmarks

for adagrasib, docetaxel, and docetaxel + nintedanib PFS at 1 year, 2 years, 3 years, 5 years, and 10 years, predicted when using gamma curves. Median survival is also presented.

Table 42: Landmark PFS estimates, time-varying NMA, gamma

Model	Landmark PFS estimates					Median PFS (months)
	1 year	2 years	3 years	5 years	10 years	
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMA, network meta-analysis; PFS, progression-free survival.

Figure 30: Base-case PFS extrapolations, time-varying NMA, gamma

[redacted]

Abbreviations: NMA, network meta-analysis; PFS, progression-free survival.

B.3.3.3.2 Overall survival

As described in Section B.2.9 and B.3.3.2, simulated KRYSTAL-12 data are used to inform the NMA and cost-effectiveness analysis, based on the patient-level surrogacy analysis derived from KRYSTAL-1.

Parametric curves from the time-varying NMA were used to inform OS outcomes in the base case. The sum of AIC scores across all studies was used to determine the statistical goodness of fit (Table 43), along with each model's respective ranks, where the lowest sum of AICs represents the best fit to the data.

Table 43: Statistical goodness-of-fit scores, time-varying NMA, OS

Model	Sum of AICs	Rank
Weibull	24399.82	3
Gompertz	24477.12	5
Log-logistic	24340.01	1
Log-normal	24441.11	4
Gamma	**24369.56**	**2**
Exponential	24518.26	6

Abbreviations: AIC, Akaike information criterion; NMA, network meta-analysis; OS, overall survival
Note: Bold text indicates base case selected model

Although the log-logistic model indicates the best statistical goodness of fit, the second-best fitting gamma model is selected in the base case due to the plausibility of the long-term extrapolations. Clinical expert opinion consistently reported that gamma and Weibull curves were broadly aligned, fit the data well, and provided sensible long-term extrapolations. As such, the gamma model is used in the base case (consistent with PFS), with the Weibull model explored in scenario analysis. Table 44 presents the survival landmarks for adagrasib, docetaxel, and docetaxel + nintedanib OS at 1 year, 2 years, 3 years, 5 years, and 10 years, predicted when using gamma model. Median survival is also presented.

Table 44: Landmark OS estimates, time-varying NMA, gamma

Model	Landmark OS estimates					Median OS (months)
	1 year	2 years	3 years	5 years	10 years	
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMA, network meta-analysis; OS, overall survival.

Figure 31: Base-case OS extrapolations, time-varying NMA, gamma

Abbreviations: NMA, network meta-analysis; OS, overall survival.

B.3.3.4 Adverse events

The HRQoL and cost implications of patients experiencing adverse events (AEs) are captured in the economic model. Health effects are detailed in Section B.3.4.4, and AE management costs in Section B.3.5.3.

AE frequencies in the adagrasib and docetaxel arms are based on data from the KRYSTAL-12 study.[121] For docetaxel + nintedanib, AEs are sourced from the LUME-Lung 1 trial, in line with TA781.[25, 81]

Grade 3+ treatment-related AEs (TRAEs) with an incidence of ≥5% (i.e. occurring in more than 5% of patients in any treatment arm) were considered in the economic analysis, in line with the approach used in TA781.[25] AE frequencies that are not reported in comparator trial publications or literature are assumed to be 0%. As TRAEs were not reported in the LUME-Lung 1 publication [81], treatment-emergent AEs were used to inform the safety profile of docetaxel + nintedanib, in line with the prior NICE submission for sotorasib (TA781).[25]

AEs are applied as a one-off cost and disutility in the first model cycle. The disutility is calculated as a single, aggregated QALY loss per treatment, with further details in Section B.3.4.4. Similarly, the management and resolution cost associated with modelled AEs is calculated as a single, aggregated cost per treatment, with further details in Section B.3.5.3.

Table 45 presents the AE frequencies, by treatment arm, that are included in the cost-effectiveness analysis.

Table 45: Grade 3+ (≥5%) adverse events included in the cost-effectiveness model

Adverse event	Adagrasib (KRYSTAL-12)	Docetaxel (KRYSTAL-12)	Docetaxel + nintedanib (LUME-Lung 1)
Asthenia	0.00%	10.00%	0.00%
Diarrhoea	5.37%	0.00%	6.60%
Fatigue	0.00%	0.00%	5.67%
Febrile neutropenia	0.00%	0.00%	7.06%
Increased ALT	7.72%	0.00%	7.82%
Increased AST	6.38%	0.00%	0.00%
Neutrophil count decreased	0.00%	11.43%	0.00%
Neutropenia	0.00%	10.00%	44.17%
White blood cell decreased	0.00%	5.00%	16.41%
γ-Glutamyl transferase increased	5.03%	0.00%	0.00%

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

In the KRYSTAL-12, HRQoL outcomes were assessed using multiple disease-specific and generic instruments, including the EQ-5D and the LCSS. Both questionnaires were completed on Days 1 and 15 of Cycles 1 to 4 and on Day 1 of subsequent cycles. EQ-5D-5L questionnaires were always to be completed before LCSS.

Patients in the docetaxel arm of KRYSTAL-12 were permitted to 'cross over' to the adagrasib arm upon evidence of RECIST 1.1 defined disease progression per BICR. Thus, to avoid generating biased results in the HRQoL analysis, patients who crossed over to receive adagrasib after progression in the docetaxel arm are censored at the time they progressed.

Utility scores were included in the HRQoL analysis if they met the following criteria:

- They were derived from the ITT population
- The date of the EQ-5D questionnaire is known
- They were derived before the data cutoff date
- They were not derived before randomisation
- They were derived before crossover to adagrasib

A maximum of one score per visit window is included. If more than one assessment is carried out in the same cycle, the assessment completed at the closest timepoint to the visit is selected. All EQ-5D assessments, even if they fall outside of the ±2 days' time window, are considered for the analysis.

B.3.4.2 Mapping

To align with the NICE reference case, EQ-5D-5L responses from the KRYSTAL-12 trial were 'cross-walked' to the EQ-5D-3L. This mapping was conducted using the approach developed by Hernández-Alava *et al*.[160]

Descriptive measures to explore EQ-5D utility scores for individuals with and without disease progression, as well as EQ-5D utility scores by treatment arm, are presented in Table 46 and Table 47. Furthermore, to evaluate the distribution of EQ-5D utilities, histograms are presented for both the progression-free and progressed disease health states (Figure 32), and for the adagrasib and docetaxel arms (Figure 33).

Table 46: Descriptive EQ-5D scores by health state

EQ-5D utility score	Progression-free	Progression
Number of participants	[redacted]	[redacted]
Number of questionnaires	[redacted]	[redacted]
Questionnaires per participant**	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

*[redacted].
**Rounded to the nearest integer.
Abbreviations: EQ-5D, EuroQol Group 5-Dimensional; SD, standard deviation.

Table 47: Descriptive EQ-5D scores by treatment arm

EQ-5D utility score	Adagrasib N = 293	Docetaxel N = 138	Total N = 431
Number of participants	[redacted]	[redacted]	[redacted]
Number of questionnaires	[redacted]	[redacted]	[redacted]
Questionnaires per participant	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol Group 5-Dimensional; SD, standard deviation.

Figure 32: KRYSTAL-12, histogram of utility values; progression free (left) and progressed disease (right)

[redacted]

Figure 33: KRYSTAL-12, histogram of utility values; adagrasib (left) and docetaxel (right)

[redacted]

EQ-5D observations from 431 participants were included in the analysis. For these participants, a total of 4,019 EQ-5D questionnaires were considered. The following variables were considered for inclusion in the analysis:

- Unique subject identifier
- Utility score
- Disease progression
- Treatment arm
- Age at baseline
- Sex

A mixed model for repeated measures (MMRM) was used to analyse mapped EQ-5D-3L utility values. This model allows for the consideration of repeated EQ-5D measurements at the patient level, given that individuals may provide several assessments during the study follow-up period.

In the base case, all variables were included in the model (i.e. progression status, treatment arm, age, and sex), including interaction effects. In scenario analysis, a model without the treatment arm variable was explored.

The base-case model estimates an intercept, a coefficient for progression, a coefficient for intervention arm, a coefficient for the interaction effects, and two coefficients for age and sex; results are presented in Table 48. The coefficient for progression status is [redacted], with post-progression status as the reference category. The coefficient for the adagrasib arm ([redacted]) is positive, suggesting that patients in the intervention group (adagrasib=1) have higher utility than docetaxel, whilst controlling for progression status and holding all other aspects constant. The coefficient for the interaction effects is [redacted].

In the model explored in scenario analysis (Table 49), the coefficient for progression status is [redacted], with post-progression status as the reference category. This indicates that patients who are progression-free have a greater utility value, holding all other aspects constant.

Table 48: MMRM model, base case (progression status and treatment arm)

Variable name	Estimate	SE	p-value	95% CI lower bound	95% CI upper bound
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (PFS=1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intervention arm (Adagrasib=1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interaction (progression status [PFS=1] * intervention arm [adagrasib=1])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (Male = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

Table 49: MMRM model, scenario analysis (progression status)

Variable name	Estimate	SE	p-value	95% CI lower bound	95% CI upper bound
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (PFS=1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (Male = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

The model in Table 48 is considered appropriate for informing the base-case analysis for several reasons. Firstly, adagrasib is an oral treatment that is administered at home, unlike docetaxel which must be administered intravenously as hospital-based chemotherapy, which may be more burdensome for patients. In TA781, the company reported that UK clinical experts verified that a treatment-specific disutility for both docetaxel and nintedanib plus docetaxel would be appropriate to capture in the base-case analysis. However, rather than deriving the treatment-specific HRQoL implications through the EQ-5D analysis, the company applied a utility decrement associated with IV vs oral administration from a previous study in NSCLC to the derived health state utility values. In TA781, the EAG agreed that the use of treatment-specific utilities may be justified but raised concerns around the source of the utility decrement used by the company (which was derived by using a VAS instrument in a general population).

As such, the selected base-case model presented in this appraisal allows for treatment-specific utility values to be captured, while utilising the pivotal trial data, aligning with the data and approach for deriving health state utilities, and directly overcoming critique raised of the external data source to inform the decrements in the prior appraisal in this indication.

Furthermore, in KRYSTAL-12, quality of life as assessed by the LCSS showed greater improvement with adagrasib than with docetaxel. Adagrasib demonstrated clinically significant ≥10-point improvement from Baseline in cough ([redacted]) and dyspnoea ([redacted]), as well as a clinically significant ≥10-point advantage over docetaxel in fatigue ([redacted]), pain ([redacted]), dyspnoea ([redacted]), and cough ([redacted]) (Section B.2.6.1.4.2).

Finally, more broadly, an observational study has demonstrated that stage IV NSCLC patients with a targetable driver mutation have favourable HRQoL over time compared to stage IV NSCLC patients without a targetable driver mutation,[161] which may support the application of treatment-specific utility values further.

The treatment-specific health state utility values used in the cost-effectiveness analysis base case are summarised in Table 50.

Table 50: Health state utility values used in the base case

Health state	Treatment arm	Utility value
Pre-progression	Adagrasib	[redacted]
	Docetaxel*	[redacted]
Progressed disease	Adagrasib	[redacted]
	Docetaxel*	[redacted]

*A class effect is assumed, and the same utility values applied, for the docetaxel monotherapy and docetaxel + nintedanib arms.

B.3.4.3 Health-related quality-of-life studies

A systematic review of the literature was conducted to identify relevant published HRQoL data for previously treated patients with NSCLC with *KRAS* G12C mutation. Searches were conducted on 2 July 2024. Details of the HRQoL SLR are provided in Appendix H.

The health utility values reported in the prior NICE appraisal in this disease area (TA781) were considered suitable for inclusion within the economic model in scenario analysis.

In the prior NICE appraisal in previously treated NSCLC with *KRAS* G12C mutation (TA781, sotorasib),[25] utility values were derived from EQ-5D-5L data from the CodeBreaK 100 trial, mapped to EQ-5D-3L to align with the NICE reference case. This was done using the NICE recommended crosswalk algorithm (at the time of the previous submission) using the UK tariff, published by van Hout (2012).[162] A summary of the utility values identified in TA781 using this method is presented in Table 51.

Table 51: Health state utility values from TA781 (CodeBreaK 100)[25], scenario analysis

Health state	Mean (95% CI)
Pre-progression	0.739 (0.704, 0.774)
Disutility in progressed disease	0.084 (0.044, 0.123)
Progressed disease	0.655

B.3.4.4 Adverse reactions

In the base case, the cost-effectiveness analysis considers the impact on HRQoL of experiencing Grade 3+ AEs (occurring in ≥5% patients). In scenario analysis, the effect of excluding AE disutility values on cost-effectiveness outcomes is tested.

AE-specific QALY decrements (Table 52) were sourced from a targeted review of the literature, including the NICE appraisal of sotorasib in *KRAS* G12C-mutated NSCLC (TA781).[25]

The HRQoL impact for each treatment arm is captured as a one-off QALY decrement in the first model cycle. QALY decrements are calculated by multiplying the proportion of patients experiencing the AE from the relevant clinical trials (Table 45) with the AE disutility values presented in Table 52.

The resulting one-off QALY decrements applied in the model are -0.006 (adagrasib), -0.007 (docetaxel), and -0.018 (docetaxel + nintedanib).

Table 52: Adverse event QALY decrements

Adverse event	AE QALY decrement	Source
Asthenia	-0.073	Nafees *et al.* (2008)[163]
Diarrhoea	-0.047	Nafees *et al.* (2008)[163]
Fatigue	-0.073	Nafees *et al.* (2008)[163]
Febrile neutropenia	-0.090	Nafees *et al.* (2008)[163]
Increased ALT	-0.050	NICE TA781[25]
Increased AST	0.000	NICE TA781[25]
Neutrophil count decreased	0.000	Assumed same as neutropenia
Neutropenia	0.000	Nafees *et al.* (2008)[163]
White cell blood decrease	0.000	Assumption
γ-Glutamyl transferase increase	0.000	Assumption

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; QALY, quality-adjusted life year.

B.3.4.5 Age-related utility decrement

Age-related utility decrements are included in the model base case to account for a natural decline in HRQoL associated with age. Utility values from the general population at each age were calculated using the approach of Hernandez *et al*., 2022, following recommendation in the DSU report for age and sex adjustment of utilities in the UK.[164] This analysis was based on updated Health Survey for England data from 2014 (n=7,085) and employed adjusted limited dependent variable mixture models to estimate EQ-5D-3L utility values separately for males and females according to age. The age-related utility decrement is applied in the model as a multiplier each cycle.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

In addition to the economic SLR reported in Section B.3.1 and Appendix G, relevant previous NICE appraisals were searched to find cases where costs and resource use implications for patients in this indication were reported. The single, most relevant, appraisal for patients with previously treated *KRAS* G12C mutation-positive NSCLC was NICE TA781 (sotorasib, within the same indication).[25] In light of this, resource use assumptions used by the committee for decision making in this previous appraisal are used to inform the cost-effectiveness analysis.

Cost inputs, which are described in further detail throughout this section, were obtained from sources typical for informing UK-based economic evaluations, and in line with the NICE reference case.[153] The following sources were used to identify costs:

- The drugs and pharmaceuticals electronic market information tool (eMIT) for generic drug costs
- The British National Formulary (BNF) for branded drug costs
- The NHS National Cost Collection (also known as NHS reference costs) for administration, resource use costs, and adverse event management costs

- Published literature and prior NICE appraisals for end-of-life care costs
- Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care for staff costs and inflation indices

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment acquisition costs

Drug unit costs for each treatment included within the cost-effectiveness model are presented in Table 53. The proposed NHS list price for adagrasib is £[redacted] (200 mg x 180 tablets). A simple patient access scheme for adagrasib is proposed, which results in a pack price of £[redacted]. The adagrasib PAS price is reflected throughout the cost-effectiveness analysis results (Section B.3.9). For comparators, drug costs are sourced from eMIT where possible, or the BNF (for branded treatments where no generic option is available), in line with the NICE reference case.[153, 165]

Table 53: Drug unit costs

Treatment	Pack size	Unit	Cost	Source
Adagrasib	180 tablets	200 mg	£[redacted]	BMS (PAS price)
Docetaxel	1 vial	20 mg / 1 ml	£4.49	eMIT[165]
Nintedanib	120 capsules	100 mg	£2,151.10	BNF[166]

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool.

B.3.5.1.1.1 Dosing

The adagrasib daily dose (600 mg twice daily) used in the model is consistent with the anticipated license and the dosing regimen used in the KRYSTAL-1 and KRYSTAL-12 studies. The adagrasib dose is comprised of three 200-mg tablets (600 mg) which are taken orally, twice daily.

Dosing information for docetaxel is taken directly from the license and KRYSTAL-12 trial, where patients receive 75 mg/m^2 docetaxel intravenously, once every 3 weeks, in line with UK clinical practice.[21] Dosing for docetaxel plus nintedanib aligns with the standard docetaxel treatment cycle, with the addition of 200 mg nintedanib taken orally, twice daily, on days 2 to 21 of the cycle.[22]

B.3.5.1.1.2 Relative dose intensity

The relative dose intensity (RDI) represents the ratio of the actual dose intensity divided by the intended dose intensity. If there is no upfront healthcare payer cost associated with a reduction in dose (i.e. planned treatments not received), then it is appropriate to adjust the intervention and comparator dosage for RDI in the economic analysis. In KRYSTAL-12, RDI was calculated based on the planned dose at study start (i.e. 600 mg twice daily for adagrasib), so planned dose decreases result in lower intensity but not lower compliance. The resulting dose in the economic model therefore includes an RDI adjustment.

The mean RDI for adagrasib ([redacted]%) and docetaxel ([redacted]%) are sourced directly from the KRYSTAL-12 CSR.[121] The mean RDI for nintedanib (92.10%) is sourced from the prior NICE appraisals for sotorasib (TA781).[25]

B.3.5.1.1.3 Wastage

Adagrasib and nintedanib are orally administered treatments. Oral treatments are costed in the model by assuming the full cost of a new pack is incurred in any model cycle in which there would not otherwise be enough tablets remaining to complete treatment, based on the required dose and cycle length.

For treatments administered intravenously (docetaxel), vial wastage is considered in the model. As docetaxel requires a BSA-based dosing regimen, the required dose (75 mg/m^2) was multiplied by the cohort-level BSA (sourced from KRYSTAL-12) to determine the average number of vials required per dose. For docetaxel, this resulted in an average required dose of 75 mg/m^2 × 1.82 m^2 = 136.18 mg, which equates to 7 vials when accounting for the cost of the wasted dose.

B.3.5.1.2 Treatment administration costs

Costs associated with treatment administration are presented in Table 54. In line with NICE TA781,[25] docetaxel is assumed to be associated with the cost of delivering simple parenteral chemotherapy (SB12Z), taken from the latest available National Cost Collection database (2022/23).[167] It is assumed that additional administration costs of adagrasib and nintedanib are zero (£0), as these treatments are administered orally.

Table 54: Administration costs

Administration method	Cost	Source
Oral	£0.00	Assumption
IV	£449.26	National Cost Collection (2022/23); SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance. Day Case.[167]

Abbreviations: IV, intravenous.

B.3.5.1.3 Time to treatment discontinuation

Time to treatment discontinuation (TTD) curves are used to capture treatment acquisition and administration costs in the model. Kaplan–Meier data observed in the KRYSTAL-12 trial for TTD and PFS are presented in Figure 34. The curves did not differ notably for adagrasib, however in the docetaxel arm, TTD declined faster than PFS.

In the model, the relative difference between TTD and PFS was summarised using a HR by treatment arm. The TTD and PFS curves were almost overlapped for adagrasib, which resulting in an estimated HR of 1 for TTD vs the modelled PFS curve. For docetaxel, the estimated HR for TTD vs PFS was [redacted]. In the absence of reported TTD Kaplan–Meier data for docetaxel plus nintedanib from external studies, a class effect was assumed for the relationship between TTD and PFS (i.e. the docetaxel monotherapy HR of 1.46 was also applied in the nintedanib plus docetaxel arm to generate TTD from the modelled PFS curve).

Figure 34: TTD vs PFS, KRYSTAL-12

Abbreviations: PFS, progression-free survival; TTD, time to (treatment) discontinuation.

B.3.5.2 Health state unit costs and resource use

The cost-effectiveness analysis captures resource utilisation costs specific to each health state, including regular healthcare resource usage in the pre-progression and progressed disease health states, and one-off resource usage associated with treatment initiation and disease progression.

Published literature reporting healthcare resource usage for patients with previously treated *KRAS* G12C mutation-positive NSCLC in NHS practice is limited, therefore resource use estimates are consistent with those used for decision making in TA781 (Table 55 and Table 56), and several prior appraisals in advanced/metastatic NSCLC.[25] Unit costs were sourced from the NHS reference costs 2022/23 and PSSRU 2023.[167, 168]

Resulting per-cycle and one-off resource use costs are presented in Table 57.

Table 55: One-off resource use frequency and unit costs

Resource	Treatment initiation	Upon progression	Unit cost (£)	Source
Oncology visit	2.92	0.00	188.56	Non-Admitted Face-to-Face Attendance, Follow-up; WF01A
CT scan (thorax/abdominal)	1.00	1.40	216.63	Computerised Tomography Scan of One Area, without Contrast, 19 years and over; RD20A
Complete blood count	1.20	0.00	1.86	Chemical Pathology Service; DAPS03
GP outpatient visit	0.08	0.00	42.00	Per surgery consultation lasting 10 minutes; Including direct care staff costs, without qualification costs
Radiotherapist	0.14	0.00	145.96	Non-Admitted Face-to-Face Attendance, Follow-up; WF01A
Palliative care	0.01	0.00	243.00	PSSRU 2023; Outpatient, medical specialist palliative care attendance (19 years and over)
Psychologist	0.01	0.00	63.00	PSSRU 2023; Band 7 per hour
Complete metabolic panel	1.20	0.00	2.06	Chemical Pathology Service; DAPS04
Lactate dehydrogenase test	1.20	0.00	2.06	Chemical Pathology Service; DAPS04
99Tc bone scintigraphy scan	0.17	0.00	362.11	Diagnostic Imaging Service; RN16A
X-ray	0.18	0.00	40.81	Direct Access Plain Film; DAPF
Echography	0.05	0.00	79.07	Ultrasound Scan with duration of less than 20 minutes, without Contrast; RD40Z
MRI brain	0.15	0.00	228.06	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over; RD01A
PET scan	0.05	0.00	692.06	Positron Emission Tomography (PET), 19 years and over; RN07A
Oncology/general ward per day	0.17	0.00	750.00	Total HRGs - Respiratory Neoplasms without Interventions, with CC Score 0-3; DZ17V
Renal function test	0.00	0.00	2.06	Chemical Pathology Service
Hepatic function test	0.00	0.00	2.06	Chemical Pathology Service
Electrolytes	0.00	0.00	2.06	Chemical Pathology Service

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 56: Per-cycle health state resource use frequency and unit costs

Resource	Progression free (per cycle)	Progressed disease (per cycle)	Unit cost (£)	Source

Oncology visit	0.33	0.15	188.56	Non-Admitted Face-to-Face Attendance, Follow-up; WF01A
CT scan (thorax/abdominal)	0.09	0.09	216.63	Computerised Tomography Scan of One Area, without Contrast, 19 years and over; RD20A
Complete blood count	0.33	0.33	1.86	Chemical Pathology Service; DAPS03
Renal function test	0.33	0.15	2.06	Chemical Pathology Service; DAPS04
Hepatic function test	0.33	0.15	2.06	Chemical Pathology Service; DAPS04
Electrolytes	0.33	0.15	2.06	Chemical Pathology Service; DAPS04

Abbreviations: CT, computed tomography.

Table 57: Healthcare resource use costs

Health state	Cost
Pre-progression (per model cycle)	£84.37
Progressed disease (per model cycle)	£49.32
Treatment initiation (one-off)	£1,070.43
Upon progression (one-off)	£303.28

B.3.5.3 Adverse reaction unit costs and resource use

Section B.3.4.4 describes the inclusion criteria for AEs in the economic model. Unit costs associated with the management or resolution of AEs were sourced from the latest NHS National Cost Collection (2022/23).[167] Where there were multiple treatment codes based on CC score, a weighted average was taken based on the reported unit costs and frequency. AE unit costs are presented in Table 58.

Table 58: AE unit costs

Adverse event	Unit cost	Source
Asthenia	£627.09	Total HRGs - Non-elective short stay SA09G-L
Diarrhoea	£552.31	Total HRGs - Non-elective short stay FD01A-J
Fatigue	£738.43	Total HRGs - Non-elective short stay SA03G-H
Febrile neutropenia	£1,229.90	Total HRGs - Non-elective short stay PM45A-D
Increased ALT	£738.55	Total HRGs - Non-elective short stay GC01C-F
Increased AST	£738.55	Total HRGs - Non-elective short stay GC01C-F
Neutrophil count decreased	£1,229.90	Total HRGs - Non-elective short stay PM45A-D
Neutropenia	£1,229.90	Total HRGs - Non-elective short stay PM45A-D
White blood cell decreased	£527.46	Total HRGs - Non-elective short stay SA08G-J
γ-Glutamyltransferase increase	£738.55	Total HRGs - Non-elective short stay GC01C-F

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HRG, healthcare resource group.

The unit costs associated with managing AEs (Table 58) are combined with the AE frequencies (Table 45) in the model. This produces a one-off AE cost per treatment arm, which is applied as an upfront cost in the first model cycle. Resulting AE management costs were £170.94 (adagrasib), £352.65 (docetaxel), and £852.71 (docetaxel + nintedanib).

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatment costs

Subsequent treatments were included in the economic model as a basket of therapies, which is used to estimate a weighted average subsequent treatment cost by treatment arm. Treatments included within the basket of subsequent therapies are best supportive care, platinum chemotherapy and docetaxel. Best supportive care is assumed to be associated with zero acquisition or administration costs, while cisplatin (100 mg/ml) is representative of platinum chemotherapy (£37.34 per vial).[165]

The proportion of patients receiving each subsequent treatment is aligned with values used for decision making in TA781, as presented in Table 59. The subsequent treatment duration is also aligned with TA781, at 14 weeks.[25]

Table 59: Subsequent treatment distributions

Treatment	Subsequent treatment			Source
	Best supportive care	Platinum chemotherapy	Docetaxel	
Adagrasib*	50%	10%	40%	TA781 (sotorasib)
Docetaxel	70%	30%	0%	TA781
Nintedanib + docetaxel	70%	30%	0%	TA781

*Adagrasib is assumed to have equal subsequent treatment distributions to sotorasib in TA781.

It is not possible to explicitly track newly progressed patients in a PartSA model framework, as health state occupancy in the progressed disease health state is estimated as the difference between the OS and PFS curves in each cycle. However, the number of newly progressed patients for subsequent treatment cost application can be estimated using the proportion of patients leaving the PFS state each cycle.

The resulting subsequent treatment acquisition and administration costs are shown in Table 60.

Table 60: Subsequent treatment costs by treatment

Treatment	Acquisition costs	Administration costs
Adagrasib	£53.86	£1,020.69
Docetaxel	£18.13	£483.49
Docetaxel + nintedanib	£18.13	£483.49

B.3.5.4.2 End-of-life costs

End-of-life (EOL) care costs were applied as a one-off cost to patients upon entering the death health state in the cost-effectiveness model. These costs were sourced from the literature and uplifted to the latest cost year (2022/23), using inflation indices reported in the PSSRU Unit Costs of Health and Social Care 2023.[168]

In the base case, EOL care costs are sourced from Round *et al.* (2015).[169] In this study, the mean estimated cost for lung cancer patients was reported (Table 61). Alternative EOL care cost sources from the literature were tested in scenario analyses, including the average end-of-life cost across several cancer types (i.e. non-lung cancer specific) from Round *et al.* (2015) (Table 62), and the EOL care costs from TA781 (Table 63).[25, 169]

Table 61: EOL costs – Round *et al.*[169] (lung cancer), base case

Category	Cost (lung cancer); mean (95% CrI)	
	2013/14	**2022/23 (uplifted)**
Health care	£3,157 (£332 to £8,944)	£3,883
Social care	£1,358 (£39 to £4,838)	£1,670
Total EOL cost	£4,515	**£5,554**

Abbreviations: CrI, credible interval; EOL, end of life.

Table 62: EOL costs – Round *et al.*[169] (all cancer types), scenario analysis

Category	Cost (mean across cancer types)	
	2013/14	**2022/23 (uplifted)**
Health care	£4,254	£5,233
Social care	£1,829	£2,250
Total EOL cost	£6,083	**£7,483**

Abbreviations: EOL, end of life.

Table 63: EOL costs – TA781,[25] scenario analysis

Category	Cost	
	2018/19	**2022/23 (uplifted)**
Total EOL cost	£3,759.73	**£4,321**

Abbreviations: EOL, end of life.

B.3.5.4.3 Testing costs

Testing costs are excluded from the economic model since testing for *KRAS* G12C mutation is routine in NHS England practice.[35] Therefore, the availability of adagrasib as a treatment option would incur no additional testing cost to those already routinely commissioned by the NHS in NSCLC. This approach is consistent with the prior appraisal in *KRAS* G12C-mutated advanced NSCLC (TA781).[25]

B.3.6 Severity

NSCLC is a severe form of cancer and is associated with poor prognosis (Section B.1.3.2). Approximately 13.8% of patients are diagnosed with *KRAS* G12C mutation-positive advanced/metastatic disease,[10] and studies suggest, for non-targeted therapies, OS estimates are <10 months with second-line treatment and <7 months with third-line treatment.[25] Within the context of the patient population considered in this appraisal – patients with advanced NSCLC with *KRAS* G12C mutation who have progressive disease after prior therapy – median OS in the docetaxel arm of the economic model is approximately [redacted].

In TA781, which was conducted prior to the introduction of the severity modifier by NICE, sotorasib was recommended for use within the CDF, and the committee determined that sotorasib met the short life expectancy criterion for end of life.

There is a clear unmet need for safe and efficacious targeted treatments for patients with advanced NSCLC with *KRAS* G12C mutation in NHS practice. As such, a severity modifier is included within the model (per the NICE health technology evaluations manual and NICE DSU TSD 23: '*A guide to calculating severity shortfall for NICE evaluations*').[170,171] To estimate the QALY shortfall, baseline characteristics in the economic model (sourced from

KRYSTAL-12) were used to estimate expected lifetime QALYs for an equivalent population without the disease. Summary features of the shortfall analysis are presented in Table 64.

Table 64: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Age – years, mean (SD)	63.7 (8.38)	B.3.3.1
Sex – female, n (%)	150 (33.1%)	B.3.3.1

Abbreviations: QALY, quality-adjusted life years; SD, standard deviation.

A summary of the health state utility values and base-case analysis undiscounted life years for patients receiving docetaxel is presented in Table 65.

Table 65: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value	Docetaxel undiscounted life years
Pre-progression	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life years.

The relevant severity modifier has been applied to the results presented within this document, as calculated within the executable model. QALY shortfall calculations were estimated using ONS-reported general population mortality rates and general population utility values (Section B.3.4.5).

A summary of the results from the QALY shortfall analysis is presented in Table 66, where adagrasib is shown to meet the criteria for applying a severity modifier / QALY weight of x1.7 (based on proportional shortfall).

Table 66: Summary of QALY shortfall analysis

Treatment	Absolute shortfall	Proportion shortfall	QALY weighting
Docetaxel	10.76	95.37%	1.70

Abbreviations: QALY, quality-adjusted life years

B.3.7 Managed access proposal

The available clinical data (KRYSTAL-1 and KRYSTAL-12) and indirect treatment comparisons (time-varying and proportional-hazards NMAs) support the use of adagrasib as a safe and effective treatment option for patients with previously treated *KRAS* G12C-mutated advanced NSCLC. Furthermore, the results of the cost-effectiveness analysis (Section B.3.9) demonstrate that adagrasib provides a cost-effective use of resources in NHS England practice.

The methods described throughout this submission have been carefully considered and justified and are believed to be the most appropriate available to support decision making. Therefore, BMS anticipate that the evidence presented will enable the NICE committee to recommend adagrasib via routine commissioning for the patient population considered within this appraisal.

Although this is the case, if the NICE committee feels unable to make a positive recommendation for routine NHS funding based on the currently available data from the ongoing phase 3 KRYSTAL-12 trial (PFS only) and the completed phase 1/2 KRYSTAL-1 trial, then BMS would be open to discussions with NICE and NHS England around potential inclusion in the CDF.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of key base-case analysis inputs

A summary of the key base-case model inputs is provided in Appendix R.

B.3.8.2 Assumptions

Table 67 presents a summary of key modelling assumptions.

Table 67: Summary of key assumptions in the economic model

Assumption	Description	Justification
Time horizon	20 years constitutes a lifetime horizon	>99% of the modelled cohort reside in the death health state by 20 years, across treatment arms.
Cycle length	Weekly cycle length	A short cycle length is required to reflect changes in health status due to the poor prognosis of patients with advanced *KRAS* G12C mutation-positive NSCLC.
Patient-level surrogacy analysis	As the KRYSTAL-12 interim OS results remain restricted, KRYSTAL-12 OS data are simulated based on a patient-level surrogacy relationship	The approach leverages available individual-level patient data in a KRAS G12C mutation-positive setting from the adagrasib trial program, while maintaining a structural relationship between progression and survival, based on covariates of importance.

	between TTP and OS, using data from KRYSTAL-1	In the absence of OS data from KRYSTAL-12, KRYSTAL-1 (adagrasib) and SELECT-1 (docetaxel) data are used as a proxy in scenario analysis.
Indirect comparison	Time-varying NMA	As the proportional hazards assumption is violated in the LUME-Lung 1 study for PFS, a time-varying NMA is used in the base case, with the proportional-hazards NMA testing in scenario analysis.
Parametric curve selection	Gamma for OS and PFS (time-varying NMA)	Curve selection was based on clinical plausibility of the long-term extrapolation based on KOL interviews, and visual and statistical goodness of fit to the data. Alternative sources and parametric models are tested in scenario analysis.
HRQoL	HRQoL data are captured using a health state utility approach	In TA781, the EAG preferred a health state approach to utility values, compared with a time-to-death utility approach.
	Treatment-specific health state utility values are applied	In TA781, the EAG agreed that the use of treatment-specific utilities may be justified but raised concerns around the source of the utility decrement used by the company. In this analysis, utility values are based on data from KRYSTAL-12. Patient-reported outcome data using EQ-5D demonstrate that HRQoL is maintained among patients using adagrasib, whereas HRQoL of patients using docetaxel is meaningfully (beyond the MID) reduced. Further, numerical improvement in LCSS score was seen for the adagrasib arm vs a worsening for the docetaxel arm. While adagrasib is an oral treatment that is administered at home, docetaxel must be administered intravenously as hospital-based chemotherapy, which may be more burdensome for patients.
Relative dose intensity	Relative dose intensity is sources from KRYSTAL-12 for adagrasib and docetaxel, and the literature for docetaxel + nintedanib	Aligns with clinical effectiveness data informing the model. For adagrasib, relative dose intensity in KRYSTAL-12 was calculated based on the planned dose at study start (i.e. 600 mg BID), so planned dose decreases result in lower intensity but not lower compliance.

Abbreviations: LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

Base-case cost-effectiveness results are presented in Table 70 to Table 70. Pairwise results tables are presented for adagrasib vs docetaxel and adagrasib vs docetaxel plus nintedanib. Furthermore, results are presented using full incremental analysis, in line with the NICE reference case, as more than two treatments are compared.

When considering a x1.7 QALY weighting (Section B.3.6), the ICER for adagrasib vs nintedanib plus docetaxel, which is the primary comparator based on real-world usage estimate of 60-80% informed by KOL opinion, is £413. The ICER for adagrasib vs docetaxel plus nintedanib is considerably below the lower limit of the NICE willingness-to-pay threshold per QALY gained. Furthermore, adagrasib is associated with an ICER of £29,107 vs docetaxel, which falls below the upper limit of the NICE decision-making threshold.

The incremental analysis results demonstrate that nintedanib plus docetaxel is extendedly dominated by adagrasib (as adagrasib generates more QALYs at a lower cost per QALY).

The results of the cost-effectiveness analysis indicate that adagrasib provides a cost-effective use of NHS resources for people with previously treated advanced NSCLC with *KRAS* G12C mutation.

Table 68: Base-case results (pairwise), deterministic, adagrasib vs docetaxel

Technologies	Total costs (£)	Total LYG	Total QALYs (x1.7)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	[redacted]				
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,107

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 69: Base-case results (pairwise), deterministic, adagrasib vs docetaxel + nintedanib

Technologies	Total costs (£)	Total LYG	Total QALYs (x1.7)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]				
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	413

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 70: Base-case results (full incremental analysis), deterministic

Technologies	Total costs (£)	Total LYG	Total QALYs (x1.7)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental analysis (£/QALY)
Docetaxel	[redacted]	[redacted]	[redacted]				
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,107

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). In PSA, all parameters (exhibiting uncertainty) are simultaneously varied from an assigned probability distribution. The list of selected distributions for the parameters included in PSA are shown in Appendix R. PSA results were recorded over 1,000 iterations within the economic model.

Mean probabilistic results are presented in fully incremental analysis in Table 71. In comparison with the deterministic results (Table 70), probabilistic results (average costs and LYs, and QALYs across 1,000 iterations) are consistent.

The cost-effectiveness acceptability curve for adagrasib versus docetaxel and docetaxel + nintedanib is presented in Figure 35. The probability of adagrasib being the cost-effectiveness treatment option at a WTP threshold of £30,000 is [redacted]%.

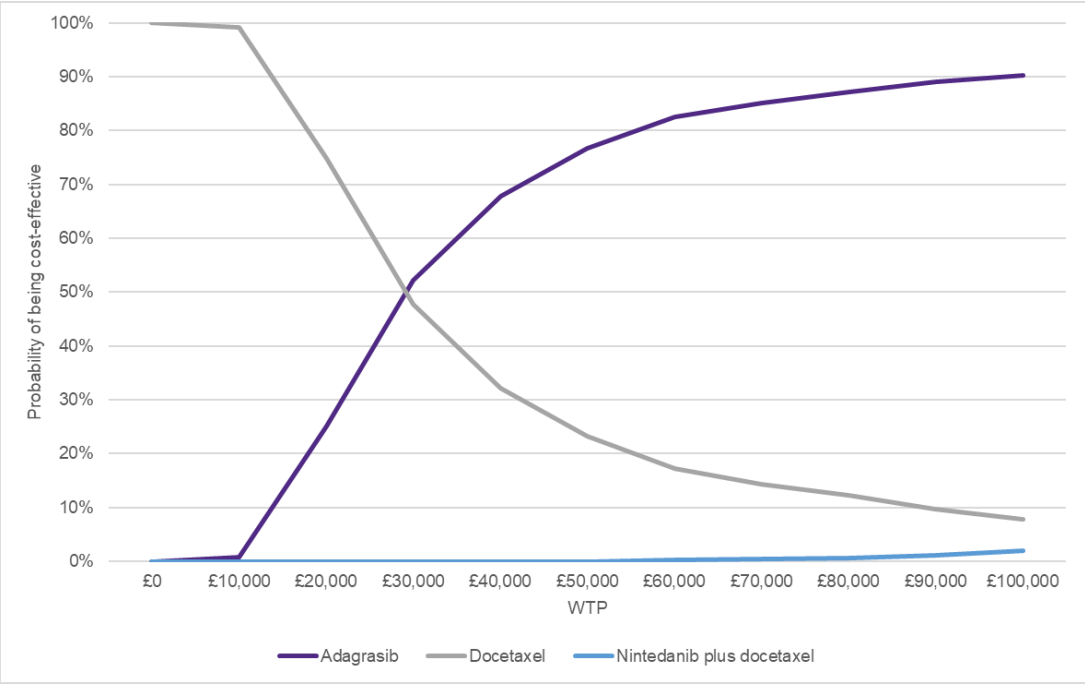
Figure 36 and Figure 37 present pairwise cost-effectiveness planes of the incremental costs and QALYs for adagrasib versus docetaxel and docetaxel + nintedanib, respectively. Out of the 1,000 PSA iterations, [redacted]% and [redacted]% indicate that adagrasib provides greater benefit (QALYs) than docetaxel and docetaxel + nintedanib, respectively. Furthermore, [redacted]% of the 1,000 PSA iterations indicate that adagrasib dominates docetaxel + nintedanib; providing additional benefit for less cost.

Table 71: Base-case results (full incremental analysis), probabilistic

Technologies	Total costs (£)	Total LYG	Total QALYs (x1.7)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental analysis (£/QALY)
Docetaxel	[redacted]	[redacted]	[redacted]				
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,902

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 35: Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay.

Figure 36: Cost-effectiveness plane showing 1,000 PSA iterations of incremental results for adagrasib vs docetaxel

Abbreviations: QALYs, quality-adjusted life years; PSA, probabilistic sensitivity analysis.

Figure 37: Cost-effectiveness plane showing 1,000 PSA iterations of incremental results for adagrasib vs docetaxel + nintedanib

Abbreviations: QALYs, quality-adjusted life years; PSA, probabilistic sensitivity analysis.

B.3.10.2 Deterministic sensitivity analysis

Individual parameter uncertainty was explored in the model through one-way sensitivity analysis (OWSA). During OWSA, parameters are varied (in turn) at their lower and upper bound, while all else throughout the economic model remains constant. This in turn highlights the impact that each parameter has on the ICER or INMB. When assessing the upper and lower bounds, if the variance of a parameter was not available, an assumption that the standard error was 10% of the mean value was applied. Correlated inputs with joint uncertainty (e.g. survival model parameters) are excluded from OWSA.

Pairwise OWSA results (using the INMB as the outcome measure) are presented in turn below for docetaxel and docetaxel + nintedanib in Figure 38 and Figure 39.

Figure 38 and Figure 39 show that the parameters with the largest impact on cost-effectiveness results are the health state utility values (which are a driver of QALYs), and the HRs for TTD versus PFS (which are drivers of treatment acquisition costs).

Figure 38: Tornado diagram showing OWSA results for adagrasib versus docetaxel (INMB)

Abbreviations: INMB, incremental net monetary benefit; OWSA, one-way sensitivity analysis.
Note: Results are presented for a WTP threshold of £30,000. QALYs include a x1.7 severity modifier throughout these results. Parameters with joint uncertainty are excluded from analysis.

Figure 39: Tornado diagram showing OWSA results for adagrasib versus docetaxel + nintedanib (INMB)

Abbreviations: INMB, incremental net monetary benefit; OWSA, one-way sensitivity analysis.
Note: Results are presented for a WTP threshold of £30,000. QALYs include a x1.7 severity modifier throughout these results. Parameters with joint uncertainty are excluded from analysis.

B.3.10.3 Scenario analysis

A range of scenarios were also explored to test key methodological uncertainties present in the cost-effectiveness model. Scenarios were explored in turn, with the full list provided in Table 72. As scenarios were run, the severity modifier for each scenario was outputted, depending on the corresponding model settings (see Table 73). Scenarios included exploring the time horizon, discount rates, parametric curve fits and approaches, different data sources for adagrasib and docetaxel OS, and alternate cost settings.

Results of the scenario analysis (Table 73) demonstrated the robustness of the cost-effectiveness findings. In the comparison with docetaxel + nintedanib, adagrasib remain cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained in all 15 scenarios explored. When compared with docetaxel, adagrasib remained cost-effective at the upper limit of the NICE threshold in 10/15 scenarios (including when exploring alternative curve fits and data sources for OS). Applying non-treatment-specific utility values had the largest impact of cost-effectiveness results.

Table 72: List of scenario analyses

Scenario #	Parameter / setting	Base case	Scenario
1	Time horizon	20 years	10 years
2			5 years
3	Discount rates	3.5%	1.5%
4			6.0%
5	PFS parametric distribution (time-varying NMA)	Gamma	Log-normal
6	OS parametric distribution (time-varying NMA)	Gamma	Weibull
7	PFS & OS parametric distributions (time-varying NMA)	Gamma PFS & Gamma OS	Log-normal PFS & Weibull OS
8	Efficacy approach	Time-varying NMA	Independent curves (within-trial) + proportional-hazards NMA: Gamma PFS (adagrasib & docetaxel), Generalised gamma OS (adagrasib), Weibull OS (docetaxel)
9			Independent curves (within-trial) + proportional-hazards NMA: Gamma OS (adagrasib & docetaxel)
10	KRYSTAL-1 adagrasib OS & SELECT-1 docetaxel OS	KRYSTAL-12 OS	Exponential (adagrasib) Gamma (docetaxel)
11	Disutility values	Include	Exclude
12	Health state utility values	Treatment-specific health state (KRYSTAL-12)	Non-treatment-specific utility (KRYSTAL-12)
13			Non-treatment-specific utility (TA781)
14	EOL cost source	Round et al. (lung cancer specific)	Round (all cancer types)
15			TA781

Abbreviations: EOL, end-of-life, NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Table 73: Deterministic scenario analysis results

Scenario #	Incremental versus docetaxel			Incremental versus docetaxel + nintedanib			Severity modifier
	Costs (£)	QALYs	ICER (£/QALY)	Costs (£)	QALYs	ICER (£/QALY)	
1	£11,316	[redacted]	£29,108	£24,575	[redacted]	£413	[redacted]
2	£11,281	[redacted]	£29,334	£24,547	[redacted]	£355	[redacted]
3	£11,397	[redacted]	£28,811	£24,667	[redacted]	£592	[redacted]
4	£11,221	[redacted]	£41,738	£24,466	[redacted]	£277	[redacted]
5	£13,311	[redacted]	£33,194	£25,394	[redacted]	£4,229	[redacted]
6	£11,336	[redacted]	£28,748	£24,475	[redacted]	£502	[redacted]
7	£13,209	[redacted]	£32,569	£25,267	[redacted]	£3,893	[redacted]
8	£11,810	[redacted]	£20,289	£24,383	[redacted]	£1,357	[redacted]
9	£11,320	[redacted]	£29,007	£24,541	[redacted]	£501	[redacted]
10	£13,456	[redacted]	£15,084	£24,754	[redacted]	£2,668	[redacted]
11	£11,316	[redacted]	£29,231	£24,575	[redacted]	£438	[redacted]
12	£11,316	[redacted]	£59,830	£24,575	[redacted]	£951	[redacted]
13	£11,316	[redacted]	£55,601	£24,575	[redacted]	£885	[redacted]
14	£11,304	[redacted]	£29,077	£26,458	[redacted]	£397	[redacted]
15	£11,323	[redacted]	£29,126	£23,371	[redacted]	£423	[redacted]

B.3.11 Subgroup analysis

Not applicable.

B.3.12 Benefits not captured in the QALY calculation

A *post hoc* analysis of CodeBreaK 200 data showed a higher incidence of treatment-related Grade ≥3 adverse events and hepatotoxicity events (overall and Grade ≥3) among patients with a shorter time gap between treatment with immunotherapy and subsequent treatment with sotorasib vs those with a longer time gap.[83]

Clinicians consulted by the company report taking into consideration a patient's prior treatment with immunotherapy when prescribing sotorasib in their clinical practice. To minimise toxicity, it is common practice to either pause treatment temporarily (approximately 6 weeks) to allow immunotherapy "wash out" or to treat with a docetaxel- or platinum-based regimen before introducing sotorasib.[24] This delay in treatment can be detrimental for patient outcomes because it allows time for their disease to progress and for their fitness for further treatment to decline.

In contrast, KRYSTAL-1 showed that among the 12 patients who received immunotherapy less than 30 days before adagrasib, none had Grade ≥3 treatment-related hepatotoxicity events.[125] As a result, the KRYSTAL-12 protocol did not require a washout period between prior immunotherapy and initiation of study treatment.[124] Additionally, an ongoing phase 2/3 trial, begun in 2020 and estimated to complete in 2029, is evaluating the efficacy and safety of adagrasib in combination with pembrolizumab, indicating that adagrasib has the potential benefit of being used concurrently with immunotherapy.[151]

These results suggest that adagrasib may allow patients with *KRAS* G12C mutation-positive NSCLC, a population with high unmet need, to circumvent delays in treatment and thus benefit from improved therapeutic outcomes.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

Base-case cost-effectiveness results (Section B.3.9) suggest mean PFS estimates (undiscounted progression-free LYs) of [redacted] years (adagrasib), [redacted] years (docetaxel), and [redacted] (docetaxel + nintedanib). Mean modelled life expectancy is [redacted] years in the adagrasib arm), [redacted] years for docetaxel, and [redacted] for docetaxel + nintedanib. As described in Section B.2.6.1.2, the KRYSTAL-12 interim OS results remain restricted, and the study will continue as planned until the prespecified final OS analysis. It is therefore challenging to validate absolute and relative survival estimates associated with adagrasib in the anticipated patient group. However, median PFS estimates in the model base case are close to the observed KRYSTAL-12 data for adagrasib (5.98 vs 5.49 months) and docetaxel (3.68 vs 3.84 months). Median modelled PFS in the docetaxel + nintedanib arm (from the time-varying NMA in the base case) is marginally higher than that observed in LUME-Lung 1 (4.4 vs 3.4 months). For OS in the docetaxel + nintedanib arm, median survival from the time-varying NMA in the model was marginally below that observed in LUME-Lung 1 ([redacted] vs 10.1 months).

As described in Appendix P, the patient-level surrogacy analysis which was used to predict KRYSTAL-12 OS in the model was validated prior to being applied to KRYSTAL-12, by comparing simulated KRYSTAL-1 OS (using the modelled surrogacy relationship) and

observed KRYSTAL-1 OS (visually and using restricted mean survival times). The findings of the validation, and specifically how well the simulations capture the trends in the OS curve, support the use of the individual-level surrogacy model for simulating the OS based on KRYSTAL-12 progression data.

Finally, expert opinion was sought to validate the survival extrapolations informing OS and PFS in the economic analysis. Three one-on-one interviews with UK clinical experts were conducted to determine the parametric models that provide clinically plausible long-term estimates.

Prior to submission, the executable cost-effectiveness model (Microsoft Excel) was quality assured as part of the internal processes of the external analysts who developed the model. As part of this process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g. how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g. if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g. is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

B.3.14 Interpretation and conclusions of economic evidence

The current prognosis for people with previously treated advanced NSCLC with a *KRAS* G12C mutation is poor. *KRAS* is the most prevalent driver mutation in NSCLC, and G12C is the most frequent *KRAS* variant; however, there remains a clear unmet need for tolerable and effective treatment options. Although sotorasib targets *KRAS* G12C mutation-positive NSCLC, it is currently only available through the CDF and not routinely commissioned by the NHS, leaving patients with limited treatment options.

Adagrasib is a novel, oral, KRAS G12C-targeted treatment option that offers a statistically significant PFS benefit vs docetaxel, which is clinically meaningful to the patient group that would receive adagrasib in NHS practice.

Results of the patient-level surrogacy analysis (detailed in Section B.3.3.2 and Appendix P) and NMA (described in Section B.2.9) also suggest that adagrasib may improve survival for the population considered in this appraisal, when compared with existing treatment options.

The results of the cost-effectiveness analysis support the expectation that adagrasib provides a cost-effectiveness treatment option for patients with previously treated advanced NSCLC with a *KRAS* G12C mutation, at the willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.

It is acknowledged that, as the KRYSTAL-12 interim OS results remain restricted as the study is ongoing, there is uncertainty around the magnitude of the relevant benefit that

adagrasib may offer patients, which can translate to challenges in the accurate estimation of cost-effectiveness. However, the methods and data used to inform the cost-effectiveness analysis of adagrasib have been carefully considered and justified and are believed to be the most appropriate available to support decision making. The model includes a comprehensive range of sensitivity and scenario analyses, to explore the impact of parametric and methodological uncertainties on cost-effectiveness outcomes. For example, the patient-level surrogacy analysis uses data from both the KRYSTAL-1 and KRYSTAL-12 studies in the relevant population in the base case, with external data sources also explored in scenario analysis. Furthermore, both time-varying and proportional-hazards NMAs were explored, and a range of parametric survival models tested, following validation with clinical experts.

Despite docetaxel being the clinical trial comparator, docetaxel in combination with nintedanib is used in 60-80% of the eligible population. The predicted cost-effectiveness of adagrasib versus this clinical standard of care in England is well below the £20,000 to £30,000 threshold, costing only £413 per patient to generate an additional QALY.

The key strengths of the analysis lie in the flexible and transparent modelling framework, alignment with the NICE reference case, and consistency with many of the assumptions used for decision making in the prior NICE appraisal in previously treated, advanced, *KRAS* G12C mutation-positive NSCLC.

Overall, the cost-effectiveness evidence presents a case for adagrasib to be recommended via routine commissioning for the patient population considered within this appraisal, in NHS practice.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Adagrasib for previously treated *KRAS* G12C mutation-positive advanced non-small cell lung cancer [ID6339]

Summary of Information for Patients (SIP)

November 2024

File name	Version	Contains confidential information	Date
ID6339_Adagrasib-KRAS-NSCLC_SIP	1.0	No	08 November 2024

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from National Institute for Health and Care Excellence (NICE) for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Adagrasib Brand name: KRAZATI®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adagrasib is intended to be used as monotherapy (not in combination with any other therapy) to treat adult patients with advanced non-small cell lung cancer (NSCLC) with Kristen rat sarcoma viral oncogene homologue (*KRAS*) G12C mutation who have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or immunotherapy.[1]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The MHRA granted adagrasib conditional marketing authorisation on 3 November 2023 and renewed the authorisation on 4 November 2024: 'KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy'. See link here for full document.[1] PD-1 and PD-L1 are programmed cell death protein 1 and programmed death ligand 1, respectively, which are the proteins targeted by the immunotherapy.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Bristol Myers Squibb is not involved in any collaborations that could be considered a potential conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Advanced *KRAS* G12C mutation-positive NSCLC

Lung cancer is the third most common cancer in the UK, representing 13% of all new cancer cases.[2] NSCLC is one type of lung cancer, and it accounted for 87% of lung cancers in England and Wales in 2022.[3] NSCLC can be further classified by cell type, including the two most common types of adenocarcinoma (66% of advanced NSCLC cases) and squamous cell carcinoma (23%).[4]

Changes called mutations in certain genes can drive molecular changes in cells that lead to tumour growth.[5] These driver mutations occur in up to 50% of NSCLC cases overall, and 64% of people with the adenocarcinoma NSCLC subtype.[6] Understanding the specific molecular changes associated with a driver mutation allows treatment to be tailored – or targeted – to those molecular changes (Section 3a).[7]

Mutations in the *KRAS* gene result in a structural defect in the KRAS protein, which plays an important role in cell signalling. The defect resulting from the G12C mutation disrupts cell signalling, leading to cell growth and disruption of cell death, which promotes tumour growth.[8–11] *KRAS* mutations, as a group, are associated with worse survival (earlier death) in NSCLC,[12–20] and some studies suggest that *KRAS* G12C may be linked to even worse survival relative to other *KRAS* mutations.[18,21]

Lung cancer symptoms can include cough (including coughing up blood), persistent or repeated chest infection, shortness of breath, persistent chest or shoulder pain, hoarse voice, loss of appetite, unexplained weight loss, and fatigue.[22] Some of the most common symptoms in advanced NSCLC negatively impact quality of life.[23,24] Indeed, patients with NSCLC have significantly lower quality of life than people of the same age and sex in the general population.[25] A European survey of patients with Stage IV NSCLC showed that the disease impacts many aspects of their lives, including both physical and emotional wellbeing, their roles in family, social, and professional life, and aspects of leisure and independence.[26]

Adding to the burden of disease, current therapies are associated with potentially life-threatening toxicities, including neutropenia.[27,28] Neutropenia results when chemotherapy suppresses bone marrow so that it does not make enough neutrophils, a type of white blood cell. This increases the risk of infections, which may limit patients' dose of chemotherapy and threaten treatment outcomes.[29] These treatments also require intravenous infusion,[27,28,30] whereas patients tend to prefer oral treatment.[26,31]

Number of patients with advanced *KRAS* G12C mutation-positive NSCLC

KRAS is the most common driver mutation in NSCLC, representing 25–35% of adenocarcinomas.[32,33] G12C is the most frequent type of *KRAS* mutation, accounting for 41% of *KRAS*-mutant cases of NSCLC.[33,34] Overall, *KRAS* G12C mutations occur in 13.8% of cases of NSCLC.[35]

In 2022, 36,886 patients in England and 2,211 patients in Wales were diagnosed with lung cancer. Patients with NSCLC accounted for approximately 87% of cases, and an estimated 54% of all patients diagnosed with lung cancer in 2022 had advanced (Stage IIIB or IIIC) or metastatic (Stage IV) disease at the time of diagnosis.[3] Assuming a 13% frequency of *KRAS* G12C mutations in NSCLC,[33] the estimated annual incidence of *KRAS* G12C mutation-positive advanced or metastatic NSCLC in England and Wales is 2,535.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People with known or suspected lung cancer are assessed using various imaging techniques (e.g. computed tomography [CT] scan, magnetic resonance imaging [MRI], ultrasound).[36,37] Inclusion of the liver, adrenal glands, and lower neck in the scan helps to assign a stage (Stage I to Stage IV) to the tumour(s).[37]

Using tissue samples from biopsies, tumour cell type is determined by microscopy. Driver mutations are identified by genetic testing of tissue samples.[4] Genetic testing is funded by the NHS and routinely used at the time of NSCLC diagnosis (before starting any treatment) to identify any driver mutation that could be treated with a targeted therapy.[6,38] This routine testing includes tests for many mutations, including mutations in the *KRAS* gene.[39]

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
    - Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

In advanced NSCLC, systemic (distributed throughout the body) anti-cancer therapy is used[37] with the goal of extending survival and improving quality of life.[6]

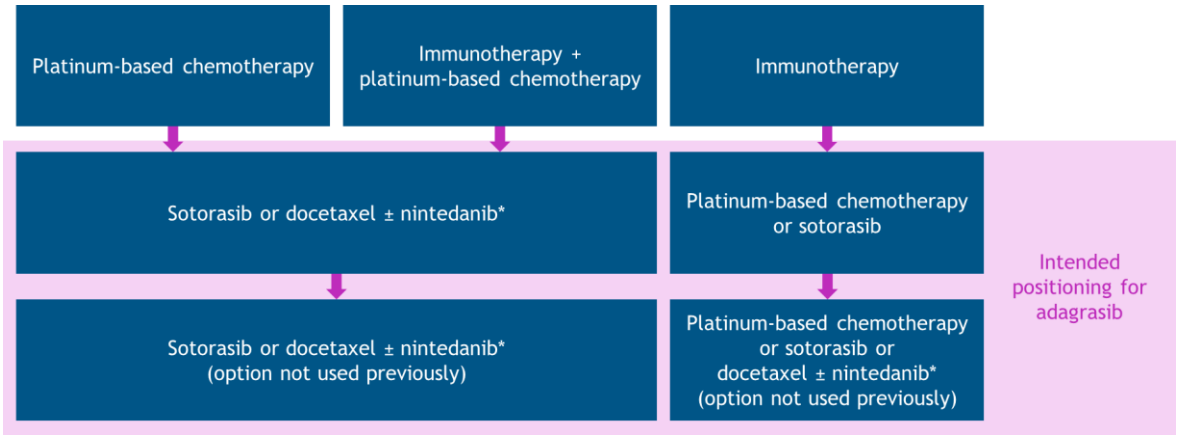
Clinicians in England and Wales typically follow NICE Guideline NG122.[37] This guideline provides systemic anti-cancer treatment pathways for advanced NSCLC that are specific to tumour cell type and targetable mutations, including the *KRAS* G12C mutation.

Figure 1 provides an overview of the treatment pathway for patients with advanced NSCLC and *KRAS* G12C mutations in England and Wales. It is derived from a combination of NICE Guideline (NG122), currently reimbursed therapies, and expert opinion from five UK clinicians in 2024.[37,39] This overview represents routine clinical practice in England and Wales,[39] although there are additional funded options that are not part of established management and are not shown here.

Options for initial treatment are platinum-based chemotherapy, immunotherapy, or a combination of the two.[37,39] In clinical practice, most patients (about three in every four) receive immunotherapy in combination with platinum-based chemotherapy (based on clinical expert advice and the proportions of PD-L1 expression in advanced NSCLC).[39]

For patients whose disease progresses following initial therapy, treatment options include sotorasib (a targeted therapy), docetaxel (a chemotherapy), or (for people with adenocarcinoma) docetaxel + nintedanib (a chemotherapy-based regimen).[37,39] After receiving combination therapy initially, most patients receive sotorasib (85–90%) in preference to a docetaxel-based regimen (docetaxel alone or in combination with nintedanib) due to the targeted nature of sotorasib treatment and toxicity concerns associated with docetaxel-based regimens.[39] Most patients who receive a docetaxel-based regimen receive docetaxel in combination with nintedanib (60–80%).[39] Sotorasib is currently only available via the Cancer Drugs Fund and not reimbursed through routine funding by the NHS.[40] If it does not achieve routine funding in the current managed access review, it will no longer be a treatment option for patients.

Figure 1: Summary of the typical treatment pathway used in UK clinical practice for advanced NSCLC with *KRAS* G12C mutation and proposed adagrasib positioning



*Nintedanib is reimbursed only in patients with adenocarcinoma. Patients with other tumour cell types receive docetaxel as monotherapy.
Abbreviations: *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; UK, United Kingdom.

The proposed positioning for adagrasib, in line with its licensed indication, is following prior treatment with (1) immunotherapy as monotherapy, (2) platinum-based chemotherapy alone, or (3) both immunotherapy and platinum-based chemotherapy, either in combination or in sequence. Adagrasib is expected to displace a proportion of sotorasib and docetaxel-based regimen use in the treatment pathway.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patient burden

A European survey of patients with Stage IV NSCLC showed that the disease impacts many aspects of their lives, including both physical and emotional wellbeing, their roles in family, social, and professional life, and aspects of leisure and autonomy.[26]

The burden of lung cancer begins with the emotional impact of diagnosis, which may leave patients feeling shocked, numb, fearful, angry, guilty, or sad.[26,41] Survey responses highlight the emotional turmoil patients experience.

"I was panicking, afraid to die and not to have my wife with me at my death. I was concerned not knowing how she would cope alone."
Male patient, aged 61[26]

"My wife, as well as my daughter, suffers for me."
Male patient, aged 54[26]

Further impacts on patients' quality of life are the result of high symptom burden, a decline in functioning, progression of disease, and fears surrounding their own prognosis as well as the impact on loved ones. Indeed, patients with NSCLC have significantly lower quality of life than people of the same age and sex in the general population.[25]

"I felt like I was falling into an abyss, it was frightening and dark and very lonely."
Female patient, aged 51[26]

Some of the most common symptoms in advanced NSCLC predict worse quality of life, including fatigue (experienced by 98% of patients with advanced NSCLC),[24] loss of appetite (98%),[23,24] shortness of breath (94%),[23,24] cough (93%),[23] and pain (90%).[23,24] Among these symptoms, loss of appetite and fatigue were rated as the most severe.[24] Quality of life deteriorates as the disease progresses,[24] making it even more important to address the substantial disease burden for patients who have already received initial therapy. Other factors associated with reduced quality of life include mental distress,[25] disease progression,[42] brain metastasis (vs other metastases),[43] and declining functioning status.[44]

A symptom severity assessment completed by >45,000 patients with various cancers (lung cancer as well as breast, central nervous system, gastrointestinal, genitourinary, gynaecologic, haematology, head/neck, sarcoma, and skin cancers) demonstrated that patients with lung cancer experienced the worst burden due to their symptoms.[45] Of the nine symptoms measured by the assessment, patients with lung cancer had among the highest (i.e. worst) scores for six symptoms (tiredness, drowsiness, loss of wellbeing, loss of appetite, nausea, and pain) and the highest score for the remaining three symptoms (shortness of breath, anxiety, and depression) relative to patients with other types of cancer.[45]

Caregiver burden

Family members and friends acting as caregivers for patients with NSCLC also experience stress, reduced quality of life, and economic impact because of the disease.

In a study of caregivers of patients with NSCLC, survey results revealed consistently high subjective stress burden, which is defined as the perceived emotional response to caregiving responsibilities. Other measures demonstrated a worsening state for caregivers over time, including rising psychological distress and decreasing overall quality of life.[46]

The increase in caregiver burden over time may be related to the deterioration of the loved one with NSCLC. A European survey showed that caregivers of patients receiving later lines of therapy (i.e. patients whose disease has progressed on, or not responded to, previous therapy) rate their own health status as significantly lower compared with caregivers of patients receiving initial therapy.[47] Declining functioning status of a patient with advanced NSCLC is associated with worsening caregiver anxiety/depression, increased risk of depression, and increased caregiver burden.[44]

Caregivers' activity impairment at work also worsens with declining patient functioning status in advanced NSCLC, highlighting the economic burden faced by caregivers.[44] In the UK in 2023, the value of the time spent caring for patients with lung cancer (instead of performing paid work) totalled £652 million, with a value of £15,200 per case of lung cancer.[48]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

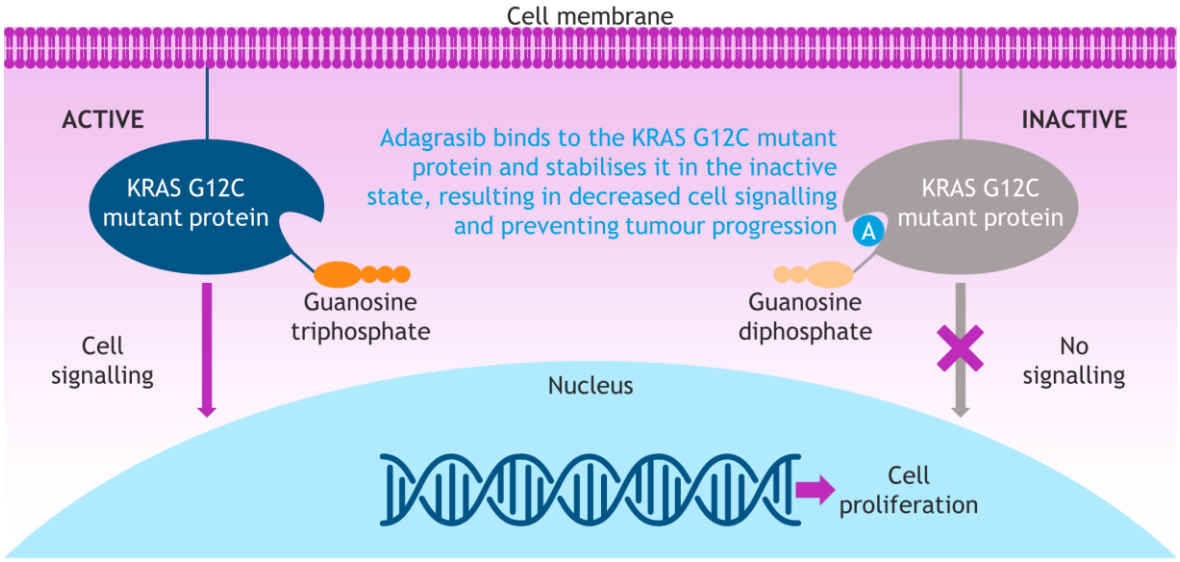
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How does adagrasib work?

Mutations in the *KRAS* gene result in a structural defect in the KRAS protein, which plays an important role in cell signalling. The defect resulting from the G12C mutation disrupts cell signalling, leading to cell growth and a disruption of cell death, promoting tumour growth.[8–11]

Adagrasib is a KRAS G12C inhibitor that binds to the KRAS G12C mutant protein and locks it in its inactive state. This prevents KRAS-dependent cell signalling and therefore inhibits tumour cell growth without affecting non-mutant KRAS protein (Figure 2).[1]

Figure 2: KRAS G12C inhibitor mechanism of action



Source: Adapted from Kwan 2022[11]

How is adagrasib innovative?

Adagrasib is a new treatment that targets KRAS G12C. Sotorasib, currently only available via the Cancer Drugs Fund and not reimbursed through routine funding by the NHS,[40] is the only available therapy targeted to this mutation, leaving patients with limited treatment options. Adagrasib will provide another option for this disadvantaged population.

Sotorasib shows a higher rate of treatment-related Grade ≥3 (higher severity rating) liver toxicity events among patients with a shorter time gap between treatment with immunotherapy and subsequent treatment with sotorasib vs those with a longer time gap.[49] In contrast, trial data for adagrasib showed that among 12 patients who received immunotherapy less than 30 days before adagrasib, none had Grade ≥3 treatment-related liver toxicity events (Section 3k).[50]

Adagrasib[51] and sotorasib[52,53] both demonstrate intracranial efficacy (i.e. can treat brain metastases) in patients whose brain metastases have been previously treated with local therapy such as radiotherapy. Adagrasib also demonstrates intracranial efficacy in patients with *untreated* brain metastases,[54] while the evidence for sotorasib is limited.[55–60] Adagrasib is unique in having prospective (pre-planned) trial evidence for intracranial efficacy in patients who have *KRAS* G12C mutation-positive NSCLC and *untreated* brain metastases, thus making progress towards addressing the high unmet need in this population (Section 3k).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Adagrasib is to be taken on its own and not in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of adagrasib is 600 mg (three 200-mg tablets) orally twice daily, with or without food. The tablets should be swallowed whole with water. Treatment with adagrasib is recommended until disease progression or unacceptable toxicity. Doses can be reduced or modified depending on side effects as per the summary of product characteristics.[1]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Evidence for adagrasib for the treatment of patients with *KRAS* G12C mutation-positive advanced NSCLC who have disease progression following prior treatment with platinum-based chemotherapy and immunotherapy come from the phase 3 KRYSTAL-12 trial and the phase 1/2 KRYSTAL-1 trial.

KRYSTAL-12

KRYSTAL-12 is an ongoing phase 3 trial conducted across 304 sites in 23 countries, including the UK. A total of 453 patients were enrolled and randomly assigned to treatment with either adagrasib (301 patients) or docetaxel (152 patients). The study has an open-label design, meaning that each patient and their physician know which treatment the patient is receiving. However, response to treatment and disease progression are assessed by independent reviewers who do not know which treatment each patient is receiving.[51]

The primary outcome in KRYSTAL-12 is progression-free survival (PFS, assessed by independent reviewer), defined as the length of time from randomisation in the trial to the date of disease progression or death due to any cause. Overall survival (OS) was defined as the length of time from randomisation to the date of death due to any cause. Additional outcomes included objective response rate and duration of response (both assessed by independent review) and patient-reported outcomes measuring health-related quality of life and the severity of lung cancer symptoms.[51]

The first KRYSTAL-12 data cutoff (date on which subsequently collected data were not included in analysis) of 31 December 2023 was for the analysis of the primary outcome of PFS as well as the additional outcomes. Because the results of the OS analysis were considered to be highly immature and inconclusive at the time of the data cutoff, the OS results currently remain restricted.[51,61] For this reason, OS results from KRYSTAL-1 are used to inform the economic evaluation of adagrasib; these data are presented below.

KRYSTAL-1

KRYSTAL-1 was an open-label phase 1/2 trial conducted across 29 sites in the United States. A total of 116 patients were enrolled and received adagrasib. The primary outcome was objective response rate (assessed by independent review). Additional

outcomes included duration of response and PFS (both assessed by independent review), and OS.[62]

Data cutoff dates for KRYSTAL-1 were 15 June 2021 (median follow-up 9.0 months) and 15 October 2021 (12.9 months), with an additional OS analysis following a cutoff date of 15 January 2022 (15.6 months).[62,63]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Progression-free survival

(See company submission, Document B, Section B.2.6.1.1)

In KRYSTAL-12, adagrasib showed improvements in how long patients lived before their disease progressed, with a 42% reduction in the risk of disease progression or death compared with docetaxel.[51] The benefit in PFS was sustained across all timepoints, with higher PFS rates in the adagrasib group than in the docetaxel group at 3, 6, 9, and 12 months after randomisation.[51] PFS results across subgroups (patients grouped by gender, age, geography, level of functioning, etc.) were consistent with the full trial population, with the majority of subgroups showing significant treatment benefit with adagrasib vs docetaxel.[51]

Overall survival

(See company submission, Document B, Section B.2.6.2.2)

KRYSTAL-12 OS data are currently highly immature and remain restricted, and it was therefore necessary to use external data (data from outside of KRYSTAL-12) to estimate OS for adagrasib and docetaxel in the company submission. KRYSTAL-1 was identified as a relevant study for informing efficacy. After a median follow-up of 15.6 months (data cutoff of 15 January 2022) in KRYSTAL-1, median OS was 12.6 months for adagrasib.[63]

Using statistical methods (referred to as 'surrogacy analysis'), progression and survival data from KRYSTAL-1, alongside progression data from KRYSTAL-12, were used to predict OS from the KRYSTAL-12 study. Predicting KRYSTAL-12 OS for adagrasib and docetaxel allows the treatments to be compared with each other, and with docetaxel + nintedanib. Results of the surrogacy analysis (predicted KRYSTAL-12 OS) are presented in Section B.3.3.2 of the company submission.

Response to treatment

(See company submission, Document B, Section B.2.6.1.3)

The KRYSTAL-12 objective response rate, defined as the percentage of patients achieving a complete or partial response to treatment, was more than three times greater for adagrasib than for docetaxel.[51] The majority of subgroups also showed a significant treatment benefit with adagrasib vs docetaxel.[51] For those patients whose disease responded to treatment, the duration of response was longer with adagrasib relative to docetaxel. This benefit was evident at all timepoints (3, 6, 9, and 12 months after randomisation).[51]

Intracranial efficacy

(See company submission, Document B, Section B.2.7.2)

KRYSTAL-12 | Intracranial efficacy in patients with *treated* brain metastases

The intracranial objective response rate with adagrasib, defined as the percentage of patients with brain metastases achieving a complete or partial intracranial response, was more than double the rate with docetaxel.[51]

KRYSTAL-1 | Intracranial efficacy in patients with *untreated* brain metastases

Intracranial objective response rate with adagrasib was 42.1% (8 of 19 patients).[54] For patients achieving a response, intracranial duration of response was 12.7 months.[54] This finding cannot be directly compared to any other medicine because KRYSTAL-1 was a single-arm trial. However, it is important to note that this is the first prospective (pre-planned) trial evidence of intracranial efficacy of a KRAS G12C inhibitor in a population with *untreated* brain metastases (Section 3k).

Indirect treatment comparison to docetaxel + nintedanib

(See company submission, Document B, Section B.2.9)

The two-arm trial design of KRYSTAL-12 allows a direct comparison of PFS and response to treatment between adagrasib and docetaxel. The previously mentioned 'predicted KRYSTAL-12 OS' (simulated using progression and survival data from KRYSTAL-1 and progression data from KRYSTAL-12) allows a comparison of OS between adagrasib and docetaxel.

Because the combination of docetaxel + nintedanib is the treatment option that most patients (60–80%) receive in clinical practice, a comparison to this regimen is also needed. This comparison is achieved using indirect (non-trial-based) methods. A statistical approach referred to as 'network meta-analysis (NMA)' was used to indirectly compare to docetaxel + nintedanib. This was possible because the trial assessing docetaxel + nintedanib (LUME-Lung 1) also included a docetaxel arm, so there was a common comparator between KRYSTAL-12 and LUME-Lung 1 that enabled an indirect comparison of adagrasib and docetaxel + nintedanib.

The results of the NMA are presented in Section B.2.9.6 of the company submission. Overall, the NMA results suggest that adagrasib demonstrates improved efficacy in treating patients with *KRAS* G12C mutation-positive NSCLC, compared with existing treatment options.

3f) Quality-of-life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

(See company submission, Document B, Section B.2.6.1.4)

Patient quality of life was measured in KRYSTAL-12 using the following patient-reported questionnaires:

- The EuroQol 5-Dimension, 5-Level (EQ-5D-5L) is a non-disease-specific measure of quality of life (also known as health utility). Patients completed the descriptive assessment of five dimensions or categories (mobility, self-care, usual function status, pain/discomfort, and anxiety/depression) with five response levels (no problems, slight problems, moderate problems, severe problems, or unable to/ extreme problems), which are valued to give a health utility index score, as well as the visual analogue scale (VAS) for self-rated overall health from 0 (worst imaginable) to 100 (best imaginable).[51]
- The Lung Cancer Symptom Scale (LCSS) is a disease-specific measure of quality of life. Patients rated six lung cancer symptoms (appetite loss, fatigue, cough, shortness

of breath, coughing up blood, and pain) and three summary global items (distress/severity of symptoms, impact on activities, and quality of life) on the degree of impairment from 0 (no impairment) to 100 (maximal impairment) using a VAS.[51]

EQ-5D-5L and LCSS were assessed at Baseline, regularly during treatment, and at the end-of-treatment visit. For each item in these two measures, the change from Baseline was compared to the minimally important difference, which is the smallest change in a score that patients would perceive as meaningful.[51]

In the adagrasib group, the change from Baseline in EQ-5D-5L was less than the minimally important difference for both the index score and the VAS, showing that quality of life was maintained (i.e. did not worsen) over time. In the docetaxel group, the same was true for the VAS but not for the index score, which showed clinically significant worsening of quality of life.[51] These data suggest that patient quality of life does not significantly decrease while taking adagrasib, whereas the same may not be true for patients taking docetaxel.

Adagrasib also demonstrated a clinically significant advantage over docetaxel in improvement from Baseline through Cycle 11 in fatigue, pain, shortness of breath, and cough.[64] These patient responses show some improvement in lung cancer symptom burden after patients began taking adagrasib and also suggest a lower symptom burden when taking adagrasib vs taking docetaxel.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In KRYSTAL-12, treatment-related adverse events were experienced by 94.0% of patients in the adagrasib group and 86.4% of patients in the docetaxel group. Grade ≥3 (higher severity rating) treatment-related events occurred in 47.0% and 45.7% of patients in the two groups, respectively.

Patients receiving adagrasib experienced higher rates of gastrointestinal events (diarrhoea, 53.0% vs 30.7%; vomiting, 34.6% vs 6.4%; nausea, 33.9% vs 19.3%) and liver toxicity (increased alanine aminotransferase, 30.2% vs 2.9%; increased aspartate aminotransferase, 30.9% vs 0%) relative to docetaxel.[51] Most of the gastrointestinal events were Grade 1–2 (lower severity rating). The safety profile of adagrasib was generally similar to that described in KRYSTAL-1, with no new safety signals.[51]

Although some gastrointestinal events and liver toxicity were observed with adagrasib, most of these events were Grade 1–2 (lower severity rating), and could be addressed with dose modification.[51] Notably, patient-reported outcomes suggest that the observed effects did not interfere with patient wellbeing (Section 3f).[51] The low-grade nature of key safety events along with patient-reported outcomes indicate that adagrasib is generally tolerable with a manageable safety profile.

Patients receiving adagrasib had lower rates of experiencing Grade 3–4 (higher severity rating) neutropenia (low number of white blood cells called neutrophils; 1.7% vs 10.0%) and neutropenia with fever (0% vs 2.9%).[51]

Patients receiving adagrasib had more treatment-related safety events leading to dose reduction (48.0% vs 23.6%) and dose interruption (temporarily stopping treatment; 59.4% vs 18.6%) than patients receiving docetaxel. However, patients receiving adagrasib were

less likely to have a treatment-related safety event leading to permanent discontinuation of treatment relative to patients receiving docetaxel (7.7% vs 14.3%).[51]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Improvement in progression-free survival

In KRYSTAL-12, adagrasib demonstrated a 42% reduction in the risk of disease progression or death compared with docetaxel. This benefit was sustained across all timepoints and the majority of subgroups.[51]

Improvement in response to treatment

The objective response rate was more than three times greater for adagrasib than for docetaxel. For those patients whose disease responded to treatment, the duration of response was longer with adagrasib relative to docetaxel.[51]

Maintains quality of life and is convenient for patients

For patients taking adagrasib, quality of life was maintained over time according to the EQ-5D-5L index score and VAS.[51] LCSS scores demonstrated clinically significant improvement from Baseline through Cycle 11 for adagrasib vs docetaxel in fatigue, pain, shortness of breath, and cough.[64]

Adagrasib's oral route of administration aligns with patient preference[26,31] for the convenience of oral treatment and the ability to receive it at home.[31] Patients also associate intravenous administration with pain and more side effects relative to oral treatments.[31]

Manageable safety profile

Although some gastrointestinal events and liver toxicity were observed with adagrasib, most of these events had low severity ratings, and patient-reported outcomes suggest that the effects did not interfere with patient wellbeing.[51] These results suggest that adagrasib is generally tolerable with a manageable safety profile.

A targeted treatment option for patients with *KRAS* G12C mutation-positive NSCLC

Despite *KRAS* being the most common driver mutation in NSCLC[32,33] and G12C being the most frequent type of *KRAS* mutation,[33,34] patients with the *KRAS* G12C mutation have fewer treatment options relative to those with other driver mutations. Sotorasib, currently only available via the Cancer Drugs Fund and not reimbursed through routine funding by the NHS,[40] is the only available therapy targeted to this mutation, leaving patients with limited treatment options. Adagrasib will provide another option for this disadvantaged population.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with most cancer therapies, treatment with adagrasib is associated with side effects (Section 3g).

In KRYSTAL-12, patients receiving adagrasib experienced higher rates of gastrointestinal events and liver toxicity relative to docetaxel. Patients receiving adagrasib also had more safety events leading to dose reduction and interruption than patients receiving docetaxel, although they were less likely to discontinue treatment relative to patients receiving docetaxel.[51]

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model

No economic models currently exist which assess the cost effectiveness of adagrasib for treating adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. Therefore, a new cost-effectiveness model was developed for this submission.

The model was structured using three 'health states', where both the costs to the NHS and the impact on length and quality of life for the average patient with advanced NSCLC with *KRAS* G12C mutation were captured. The 'health states' were defined as 'progression-free', 'progressed disease', and 'death'.

Costs included in the model are treatment costs, the costs for administering treatments, the costs of managing adverse events (related to each treatment), the costs for disease management (monitoring), subsequent treatment costs (i.e. the cost for treatments used after this line of therapy), and finally the costs of care at the end of life.

The health effects captured within the analysis are a combination of quantity of life and quality of life (known in economic modelling as quality-adjusted life years [QALYs]). A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

Docetaxel and nintedanib + docetaxel were the comparators included in the economic model. NICE require that cost effectiveness is estimated based on a 'lifetime' horizon for the average patient, which is often longer than the duration of clinical trials. Therefore, trial data were extrapolated over a lifetime using statistical methods, to predict how long patients would remain progression-free and alive when treated with adagrasib, docetaxel, or docetaxel + nintedanib.

Data from the KRYSTAL-12 trial were primarily used to inform the effectiveness of adagrasib and docetaxel in the model. As KRYSTAL-12 OS data are currently highly immature, it was necessary to use external data (data from outside of KRYSTAL-12) to estimate OS in the cost-effectiveness model. To estimate adagrasib and docetaxel OS, statistical methods were implemented using progression and survival data from the KRYSTAL-1 study, applied to KRYSTAL-12 progression data, to obtain predicted KRYSTAL-12 OS. As nintedanib + docetaxel was not included in the KRYSTAL studies,

data from another trial were obtained and compared to inform the effectiveness of this comparator.

Cost-effectiveness analysis for the patient population

Adagrasib increases the amount of time spent progression-free in comparison to both docetaxel and nintedanib + docetaxel, and is predicted to increase the overall amount of time spent alive by ultimately delaying disease progression.

Additional value of adagrasib is shown in the economic model by reducing the cost and quality-of-life burden of drug administration, as adagrasib is administered orally, compared to docetaxel which is a chemotherapy administered through the veins (intravenously) every 3 weeks in a hospital setting. This means that, although the total treatment cost associated with adagrasib is greater than that of the comparators, the length of life and quality of life benefit (i.e. total QALYs) are also greater, and administration costs are reduced.

The measure of cost effectiveness used by NICE is the incremental cost-effectiveness ratio (ICER), which is calculated by dividing incremental costs between treatment options by the incremental QALYs (i.e. the ratio of additional costs to additional QALYs for a new drug). The willingness to pay threshold used by NICE is £20,000-£30,000 per QALY gained. The company base-case results show that the ICER for adagrasib vs docetaxel + nintedanib is £413, and the ICER for adagrasib vs docetaxel is £29,107. This includes a x1.7 QALY weighting (or severity modifier), where the severity and poor prognosis of advanced NSCLC with *KRAS* G12C mutation is taken into consideration.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Treatment option for the *KRAS* G12C mutation-positive NSCLC population

Adagrasib is a novel treatment that targets KRAS G12C. Despite *KRAS* being the most common driver mutation in NSCLC[32,33] and G12C being the most frequent type of *KRAS* mutation,[33,34] patients with the *KRAS* G12C mutation have fewer treatment options relative to those with other driver mutations. Sotorasib, currently only available via the Cancer Drugs Fund and not reimbursed through routine funding by the NHS,[40] is the only available therapy targeted to this mutation, leaving patients with limited treatment options. Adagrasib will provide another option for this disadvantaged population.

Improved safety profile for patients receiving prior immunotherapy

Data from a trial of sotorasib showed a higher rate of treatment-related Grade ≥3 (higher severity rating) adverse events and liver toxicity events (overall and Grade ≥3) among patients with a shorter time gap between treatment with immunotherapy and subsequent treatment with sotorasib vs those with a longer time gap.[49] In contrast, KRYSTAL-1 showed that among the 12 patients who received immunotherapy less than 30 days before adagrasib, none had Grade ≥3 treatment-related liver toxicity events.[50] As a result, the KRYSTAL-12 trial did not require patients to pause treatment between prior immunotherapy and initiation of study treatment.[61]

Intracranial efficacy

Studies suggest that patients with *KRAS* G12C mutations are more likely to have brain metastases than patients with other *KRAS* mutations or non-mutant *KRAS*.[65–68] Patients with *KRAS* G12C mutations are significantly more likely to develop brain metastasis (42%) than patients with oncogenic fusion events (another type of driver mutation, 22%).[67] For patients with NSCLC who also have brain metastases, symptom burden is higher[69] and quality of life is lower[43] than for those without brain metastasis. Clinical experts have

confirmed that patients with brain metastases represent a population with high residual unmet need.[39]

Adagrasib[51] and sotorasib[52,53] both demonstrate intracranial efficacy (i.e. can treat brain metastases) in patients whose brain metastases have been previously treated with local therapy such as radiotherapy. However, when patients have received local therapy for their brain metastases, the intracranial benefit of subsequent systemic therapy such as adagrasib or sotorasib may be difficult to quantify. For this reason, efficacy data in patients with *untreated* brain metastases are needed to confirm that a systemic therapy has intracranial efficacy. The only available data on sotorasib's efficacy in *untreated* brain metastases come from case reports[55–59] and one case series of five patients.[60] In contrast, an intracranial response to treatment with adagrasib occurred in 42.1% of patients (8 of 19) in a subgroup of patients with *untreated* brain metastases.[54]

Adagrasib is therefore unique in having evidence from a prospective (pre-planned) trial for intracranial efficacy in patients who have *KRAS* G12C mutation-positive NSCLC and *untreated* brain metastases, thus making notable progress towards addressing the high unmet need in this population.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality considerations relating to the use of adagrasib have been identified.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Information related to NSCLC and/or lung cancer more broadly:

- Cancer Research UK
- Macmillan Cancer Support
- NHS
- UK Lung Cancer Coalition
- Roy Castle Lung Cancer Foundation
- Oncogene-Driven Lung Cancer Patient Alliance UK

Published KRYSTAL-1 clinical trial data (KRYSTAL-12 data are not yet published):

- Jänne et al. Adagrasib in Non–Small-Cell Lung Cancer Harboring a KRASG12C Mutation. N Engl J Med. 2022 Jul 14;387(2):120–31. https://doi.org/10.1056/nejmoa2204619[70]
- Negrao et al. Intracranial Efficacy of Adagrasib in Patients From the KRYSTAL-1 Trial With KRASG12C-Mutated Non-Small-Cell Lung Cancer Who Have Untreated CNS Metastases. J Clin Oncol Off J Am Soc Clin Oncol. 2023 Oct 1;41(28):4472–7. https://doi.org/10.1200/jco.23.00046[54]

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

KRAS – Kirsten rat sarcoma viral oncogene homologue is a gene that codes for the KRAS protein. Mutations in the *KRAS* gene lead to structural defects in the KRAS protein that can cause lung, colorectal, and pancreatic cancers.

Locally directed anti-cancer therapy – These are treatments that are directed to a specific organ or area of the body. Examples include, but are not limited to, surgery and radiation therapy.

Marketing authorisation – Permission to sell a medicine after the evidence (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

Metastasis/metastatic – Metastasis is the spread of cancer from the initial site (e.g. lung) to other parts of the body (e.g. brain). Cancer is described as metastatic (Stage IV) when metastasis has occurred.

Mutation – A change or mistake in the DNA sequence of a gene. This change can alter how the gene works, sometimes causing it to function differently or not at all.

PD-L1 expression – The programmed death ligand 1 protein is normally found on certain healthy cells, and it functions to stop T cells (a type of cell in the immune system) from attacking the healthy cells. If cancer cells have high amounts of PD-L1 protein, they can also stop T cells from attacking them. PD-L1 expression refers to the percentage of cells in a tumour that express the PD-L1 protein. Tumours that express high amounts of PD-L1 (≥50%) may respond well to anti-PD-L1 immunotherapy. For this reason, the PD-L1 expression of a patient's tumour may guide a clinician's treatment recommendations.

Single-arm trial – A trial in which all participants are given the same experimental therapy.

Systemic anti-cancer therapy – Systemic therapies are medicines that work throughout the whole body. Examples are chemotherapy, immunotherapy, targeted therapy (such as adagrasib), and hormonal therapy.

Targeted therapy – A type of systemic therapy that is targeted to the specific molecular changes in cancer cells (caused by a specific driver mutation) that help them grow and spread.

Visual analogue scale (VAS) – A straight line used as by patients to rate the intensity of an experience on a spectrum. For example, a patient could point to any point along the VAS line to rate their health between 0 (worst imaginable) and 100 (best imaginable).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Response to clarification questions

December 2024

File name	Version	Contains confidential information	Date
ID6339 adagrasib response to CQs 241212 [CON]	1.0	Yes	12/12/2024

Section A: Clarification on effectiveness data

Overall survival

A1. PRIORITY: A planned interim analysis for overall survival (OS) was conducted for KRYSTAL-12. Although the interim OS analysis was not statistically significant at the time of primary progression-free survival (PFS) analysis, please provide the restricted interim OS analysis in confidence (marked commercial in confidence [CIC]). If this is not possible, please justify why the interim OS analysis cannot be provided in confidence.

a. Please provide the Kaplan-Meier (KM) plot of interim OS, including numbers of participants at risk.

Response: [redacted]

[redacted]

Figure 1: Kaplan–Meier plot of overall survival (ITT population)

Table 1: Summary of overall survival censoring reasons

	Adagrasib (N=301)	Docetaxel (N=152)
Status, n (%)		
Death	[redacted]	[redacted]
Censored		
Lost to Follow-up		
Withdrawal by Patient		
Ongoing Without an Event		
Randomisation after Sep 30 2023[a]		
Randomisation after Jun 30 2023[b]		

[redacted]

Table 2: Subsequent cancer therapy

Variable [n (%)]	Adagrasib (N=301)	Docetaxel (N=152)
Patients with any Follow-up Anti-Cancer Therapies, including crossover to adagrasib	[redacted]	[redacted]
KRAS G12C Inhibitor	[redacted]	[redacted]
Adagrasib cross over		
Sotorasib		
Other		
Taxane		
Docetaxel		
Paclitaxel		
Platinum		
Bevacizumab		
Gemcitabine		
PD-(L)1 Inhibitor		
Other		

[redacted]

b. Please indicate what proportion of participants within the docetaxel arm crossed over to receive (i) adagrasib and (ii) to any other Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C targeted treatment in the interim OS analysis.

Response: 38.8% (59 of 152) of patients within the docetaxel arm crossed over to receive (KRAS) G12C targeted treatment: 28.9% (44 of 152) adagrasib and 9.9% (15 of 152) other (KRAS) G12C targeted treatment [redacted].

c. Please provide subgroup analyses of OS for prespecified subgroups as per Figures 17 and 18 in the company submission.

Response: Per the clinical study SAP version 4.0, subgroup analyses of OS for prespecified subgroups are planned only at Final OS analysis. Note that in the company evidence submission BMS state final OS is expected in [redacted]. Based on the most recent events sweeps, final OS is expected in [redacted].

A2. PRIORITY: The Clinical Study Report (CSR) for adagrasib reports [redacted] of deaths in the adagrasib arm compared to the

docetaxel arm in KRYSTAL-12 (Table 14, p93) and [redacted] fatal treatment-emergent adverse events (Table 31, p132).

a. Please comment on the [redacted] mortality rates reported in Tables 14 and 31 of the CSR.

Response: CSR Table 14.3.3.1 (Table 3 below) summarises the primary cause of death for all patients. The table also breaks down cause of death based on the time since last dose of study drug. [redacted]. Deaths due to disease progression >28 days since last dose of study drug [redacted]

Per CSR Table 31, any fatal treatment-related TEAEs are [redacted]. Fatal TEAEs (irrespective of relationship) are higher in the [redacted] arm, potentially due to [redacted], respectively).

b. Please provide a summary of causes of death in each arm.

Response: Please see table with summary of all deaths (Table 3).

Table 3: KRYSTAL-12 summary of all deaths

[redacted]

c. Please justify the assumption of an OS benefit for adagrasib vs. docetaxel based on the interim OS analysis, the [redacted] mortality rates reported in Tables 14 and 31, and the [redacted] PFS-2 from KRYSTAL-12 (Figure 10 of CSR).

Response: [redacted]

Table 4: Conditional probability of observing a positive OS trend at final OS analysis given observed interim OS HR

Positive trend with different HR cutoff	Probability of observing the trend (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

PFS2 includes a high proportion ([redacted]) of patients randomised to receive docetaxel who went on to receive adagrasib and should not be used to make any direct inference to OS, especially considering the immaturity of OS data and [redacted]. Further, external key opinion leaders considered that PFS2 data are too immature at this time to be reliably interpreted, based on the median follow up of [redacted]. With short follow up time, treatment crossover, and censored information, PFS2 should not be used to infer potential of OS benefit.

A3. PRIORITY: The CodeBreaK 200 trial, which also evaluated a KRAS GC12C inhibitor, did not show a relationship between PFS and OS (crossover adjusted analysis) and very limited survival benefit for sotorasib vs. docetaxel.

a. Please justify the use of a surrogacy relationship to inform OS data for KRYSTAL-12 considering the lack of evidence supporting significant OS benefits for sotorasib despite an observed PFS benefit.

Response: Analyses of surrogacy between PFS and OS in NSCLC demonstrated moderate levels of associations at a trial level between PFS and OS HRs. A recent study by Hua et al. (2022)[1] found that, at a trial-level, PFS HR had a 'modest' association with OS HR in first- (R=0.768; 95% CI 0.621, 0.863) and second- (R=0.550; 95% CI 0.377, 0.686) line of therapy. At an arm-level, the association

between median PFS and median OS was stronger in first-line (R=0.832; 95% CI 0.763, 0.882) than second-line of therapy (R=0.599; 95% CI 0.495, 0.686), and was more pronounced among targeted agents (R=0.756; 95% CI 0.672, 0.821) as compared to immunotherapies (R=0.656; 95% CI 0.506, 0.768), but more similar compared to chemotherapies (R=0.786; 95% CI 0.687, 0.857). Another recent surrogacy analysis by Horita et al. (2022),[2] evaluating surrogacy of PFS and OS in trials of immune checkpoint inhibitors, showed an association between PFS and OS both at study- and individual-level, pointing to a 'high' or 'moderate' correlation between PFS and OS at the patient level in first-line (R=0.71) and second- or later lines (R=0.59). Overall, this previous research has established the biological plausibility of a relationship between PFS and OS in NSCLC, which supports a moderate association between PFS and OS. The strength of that association may vary in first- versus second-line setting, with the potential for a stronger effect when investigating targeted therapies.

It is not feasible to assess trial-level surrogacy based on an individual trial, such as CodeBreaK 200. A meta-analysis of several RCTs is required for an estimation of a relative effect in terms of an OS HR. Nonetheless, in Table 5, we compare the HRs from CodeBreaK 200 in terms of PFS and two-stage crossover adjusted OS, which illustrates that the OS HR for adagrasib versus docetaxel predicted in KRYSTAL-12 using the individual-level predictive surrogacy model is consistent with the crossover-adjusted OS HR estimated in CodeBreaK 200, both of which suggest a non-significant benefit in OS for KRAS inhibitor versus chemotherapy.

Table 5: Comparison between PFS and (predicted) OS HRs

Trial	PFS HR	OS HR
CodeBreaK 200[3]	Primary analysis: 0.66 (95%CI: 0.51-0.86)	*Crossover adjusted*:* 0.89 (95%CI: 0.17-1.328)
KRYSTAL-12[4]	Primary analysis: 0.58 (95%CI: 0.45-0.76)	*Predicted individual-level surrogacy:* [redacted]

Notes: *Two-stage method as reported in the sotorasib G-BA submission (refer to https://www.g-ba.de/downloads/92-975-6366/2023_02_01_Modul_4A_Sotorasib.pdf, Section 4.3.1.3.1.1). Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

However, we do not consider CodeBreaK 200 to provide sufficient evidence of presence or absence of a surrogacy relationship between PFS and OS:

- There were issues with the conduct and results of the trial as highlighted by the FDA ODAC (https://www.fda.gov/media/172756/download), as well as others (Olivier et al. 2023,[5] Brazel et al. 2023,[6] Alharbi et al. 2024,[7] Zhang et al. 2023[8])
- Sotorasib and adagrasib, while belonging to the same class of treatments, are not the same molecule and as such one cannot be used to make direct inference on the characteristics or efficacy profile of the other (see *Response A3.b*)

b. Please comment on how the specific targeting of KRAS G12C mutation-positive advanced NSCLC and pharmacology of adagrasib provides a plausible and different mechanism of action for survival gains than for sotorasib.

Response: Enhanced understanding of the biologic characteristics of KRASG12C mutations, including resynthesis half-life (approximately 24 hours), suggests that inhibition of KRASG12C may require sustained inhibition over the entire dosing period.[9]

At 600 mg BID dosing, the steady-state concentration exceeds the modelled exposure associated with maximal efficacy in the least- and most sensitive animal models across the dosing period.[10] Sustained exposure above a target threshold inhibits KRAS throughout the dosing interval theoretically maximising the depth and duration of antitumour activity.

By comparison, sotorasib has a shorter half-life than adagrasib (5 hours vs. 23 hours), with plasma concentration dipping below the concentration of the inhibitor needed to achieve 90% inhibition of pERK activity, potentially allowing reactivation of the KRAS pathway.[11]

A4. PRIORITY: Median PFS-2 was [redacted] between the two treatment arms of KRYSTAL-12 (Figure 10 of CSR, p133), which [redacted] for adagrasib.

a. Please provide an analysis of PFS-2 with adjustment for crossover to adagrasib or to any other *KRAS* G12C targeted treatment. Specifically, the equivalent to Figure 10 of the CSR but with treatment crossover adjustment. Please provide justification for selecting the most

appropriate crossover approach Nand present sensitivity analysis results using alternative methods.

Response: Crossover adjustment of PFS-2 is not considered in our statistical analysis plan. BMS are unaware of precedent for PFS-2 crossover-adjustment and given the immaturity of PFS-2 it is not considered informative to use PFS-2, even if crossover-adjusted, to infer an OS benefit.

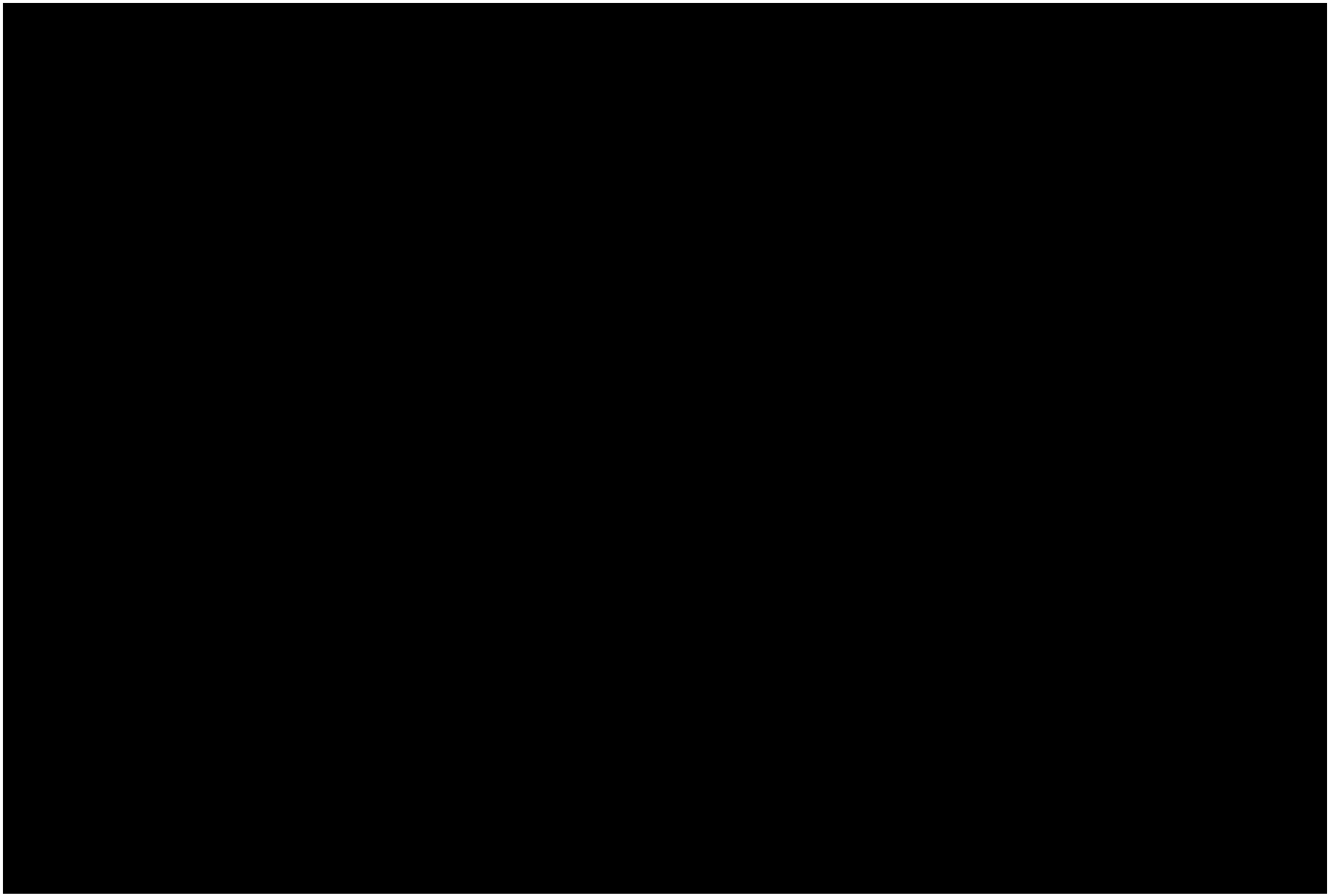
b. **Please use the adjusted PFS-2 analysis to support a mortality benefit for adagrasib vs. docetaxel, or comment on the absence of one.**

As above.

KRYSTAL-12

A5. PRIORITY: Please present a breakdown of censoring events for PFS (blinded independent central review [BICR]) at the December 2023 data cut with reasons in both arms of KRYSTAL-12 (e.g. every 6 weeks from baseline where available). Please assess whether any informative censoring may have occurred (e.g. due to unequal attrition rates between treatment arms), using additional analyses as appropriate.

Response: A breakdown of events for adagrasib and docetaxel are provided below. A tipping point analysis to address the question concerning informative censoring is presented in the response to A7C.



A6. The schedule of assessments in KRYSTAL-12 CSR indicates that disease evaluation was conducted every 6 weeks (+/- 10 days) until Week 49, then every 12 weeks. Disease progression events could have occurred any time within intervals between assessments. Please discuss whether any bias may have been introduced to PFS estimates due to the schedule of assessments, supported by additional analyses as appropriate e.g. using an interval-censoring analysis.

Response: A supplemental ad-hoc analysis was performed to assess whether any differences in the scan intervals were observed. Table 6 demonstrates that for both adagrasib and docetaxel, actual scan intervals were consistent with the scheduled scan intervals.

Table 6: Relative timing of radiologic scans descriptive statistics

[redacted]

[redacted]

A7. Table 14 of the CSR (p93) shows that [redacted] of participants in KRYSTAL-12 crossed over from docetaxel to adagrasib.

a. Please report separately the baseline characteristics of participants who crossed over from docetaxel to (i) adagrasib and (ii) to any other KRAS G12C targeted treatment.

Response: Please see Table 7 and Table 8 with demographics and disease characteristics, respectively.

Table 7: Demographic and baseline characteristics

Table 8: Primary disease history

[redacted]

b. Please discuss whether there were any significant differences in baseline characteristics between participants who crossed over and were censored from the analysis and those who did not.

Response: There is no censoring in the docetaxel arm at crossover to adagrasib (BICR confirmed progression).

c. Please provide a sensitivity analysis for PFS to explore the potential impact of early drop out of participants in the docetaxel arm.

Response: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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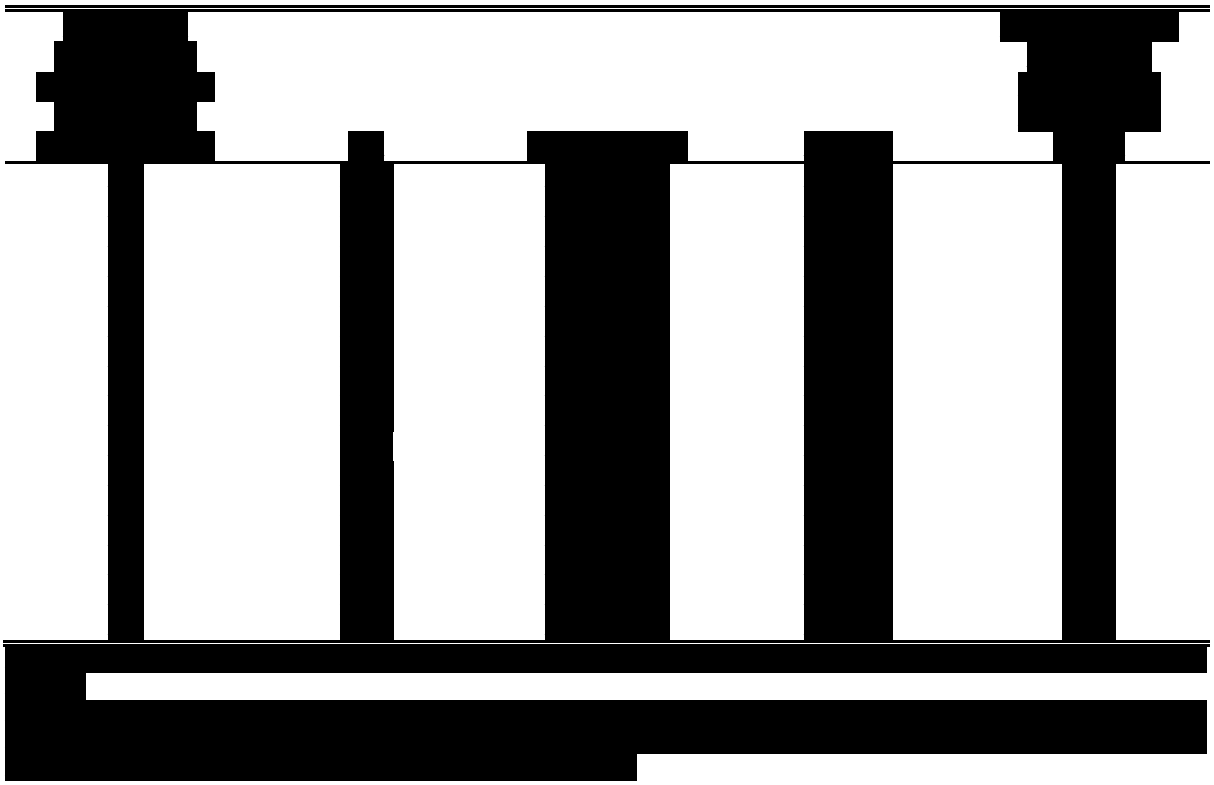
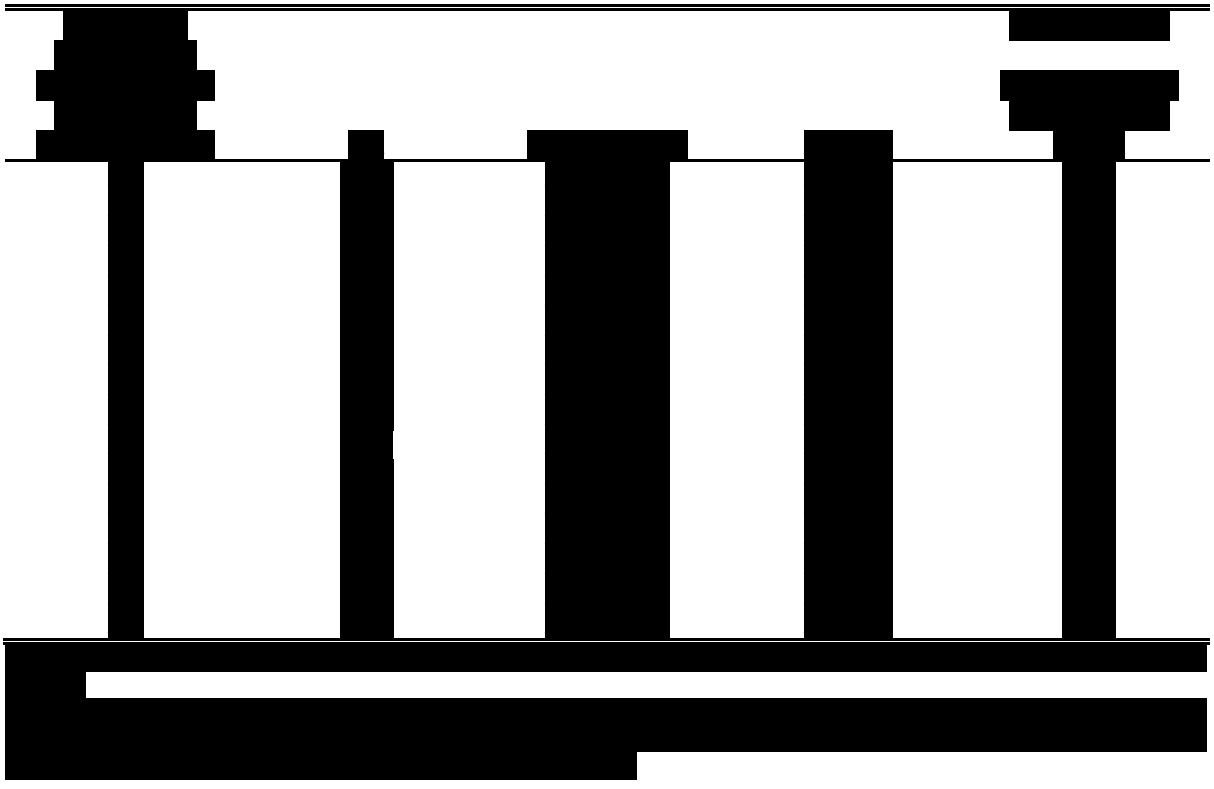
[redacted]

[redacted]



[redacted]

[redacted]



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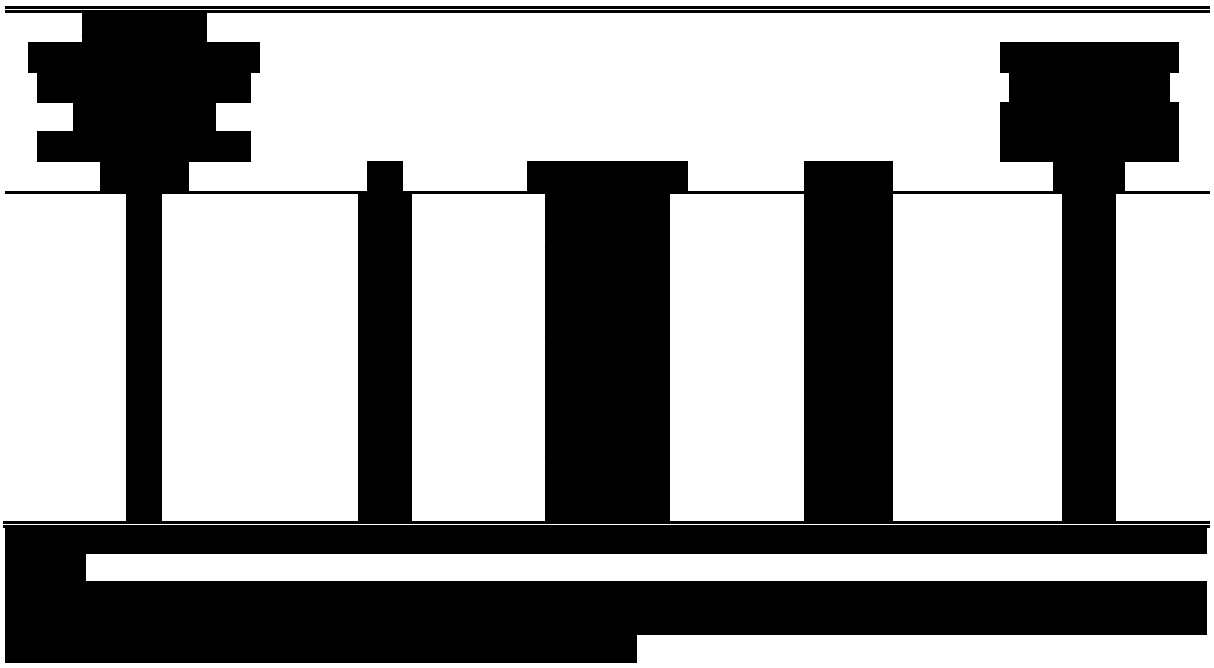


[redacted]

[redacted]

[redacted]

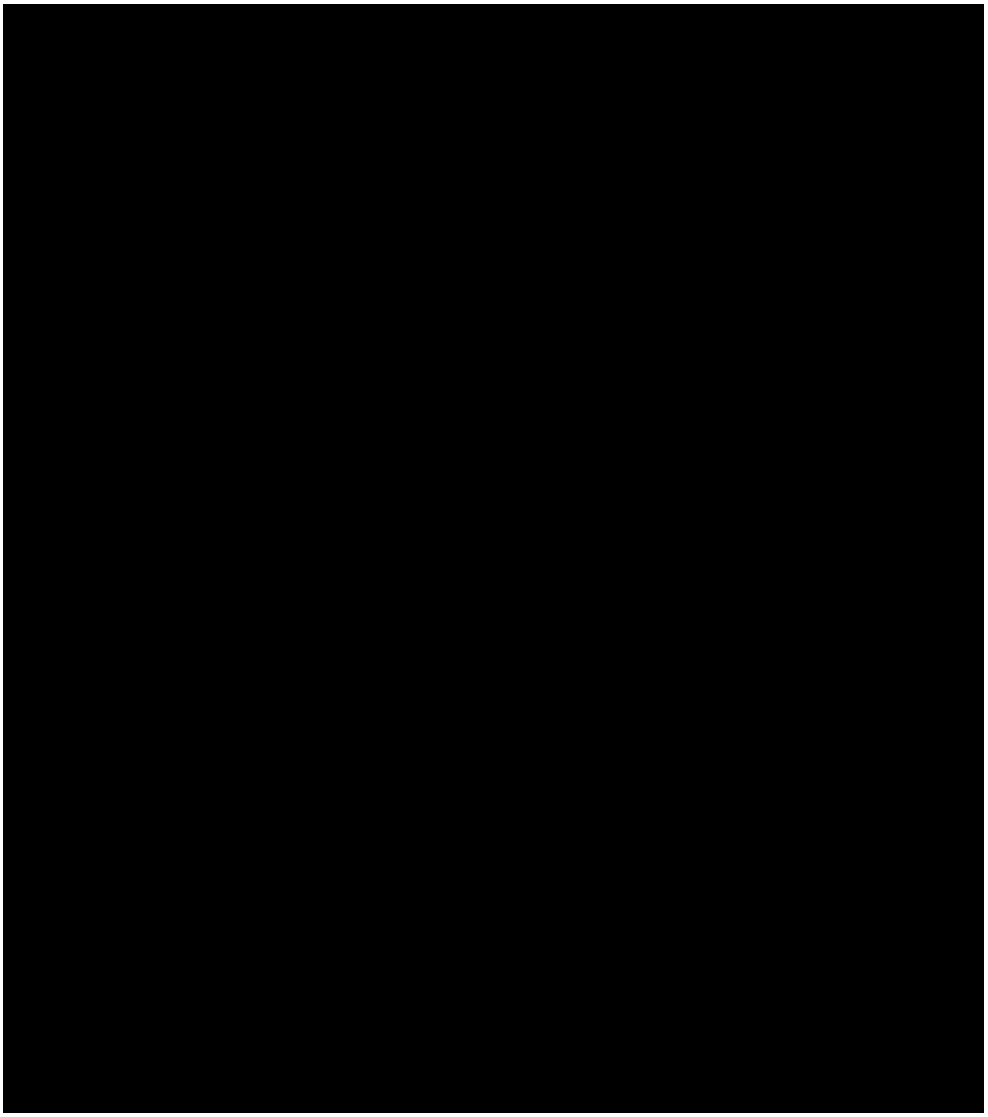
[redacted]

[redacted]

A8. Please provide a waterfall plot of the percentage of tumour shrinkage by levels of confirmed best overall response (complete response, partial response, stable disease and progressed disease) for each treatment arm of KRYSTAL-12.

Response: Figure 5 shows objective response rate, disease control rate, and duration of response among all patients, and maximum tumour change from baseline among patients who had at least one target lesion at baseline and at least one post-baseline tumour assessment. Tumour response was assessed by blinded independent central review according to RECIST v1.1. Objective response rate was defined as the percent of patients documented to have a confirmed complete or partial response by blinded independent central review. Disease control rate was defined as the percent of patients documented to have a confirmed complete or partial response or stable disease by blinded independent central review. Duration of response was defined as the time from the date of first documentation of complete or partial response to the first documentation of progressive disease or death due to any cause in the absence of documented progressive disease. Duration of response was only calculated for patients with confirmed complete or partial response.

Figure 5: Tumour shrinkage by best overall response



KRYSTAL-1

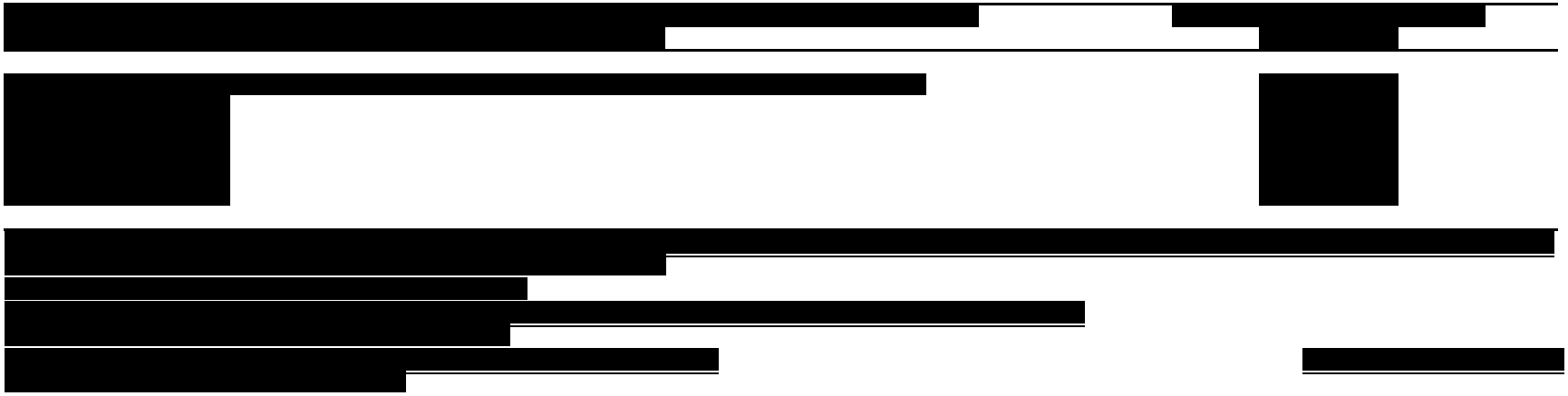
A9. Please provide the following additional information:

a. PRIORITY: The number of participants who received an alternative systemic anticancer therapy following documented disease progression and which therapies were administered.

Table 12: Subsequent Cancer Therapy Summary following documented PD per BICR

b. PRIORITY: The number of participants who received an alternative systemic anticancer therapy before documented disease progression and which therapies were administered.

Table 13: Subsequent Cancer Therapy Summary before documented Progression



c. PRIORITY: KRYSTAL-1 CSR Addendum reports that the censoring rate for OS was [redacted] at the January 2022 data cut. The censoring rate for PFS (BICR) was [redacted] at the October 2021 data cut. Please provide a breakdown by reason for censoring for both outcomes at these data cuts (or at a later data cut if available).

Table 14: Status of Censored Subjects, Overall Survival

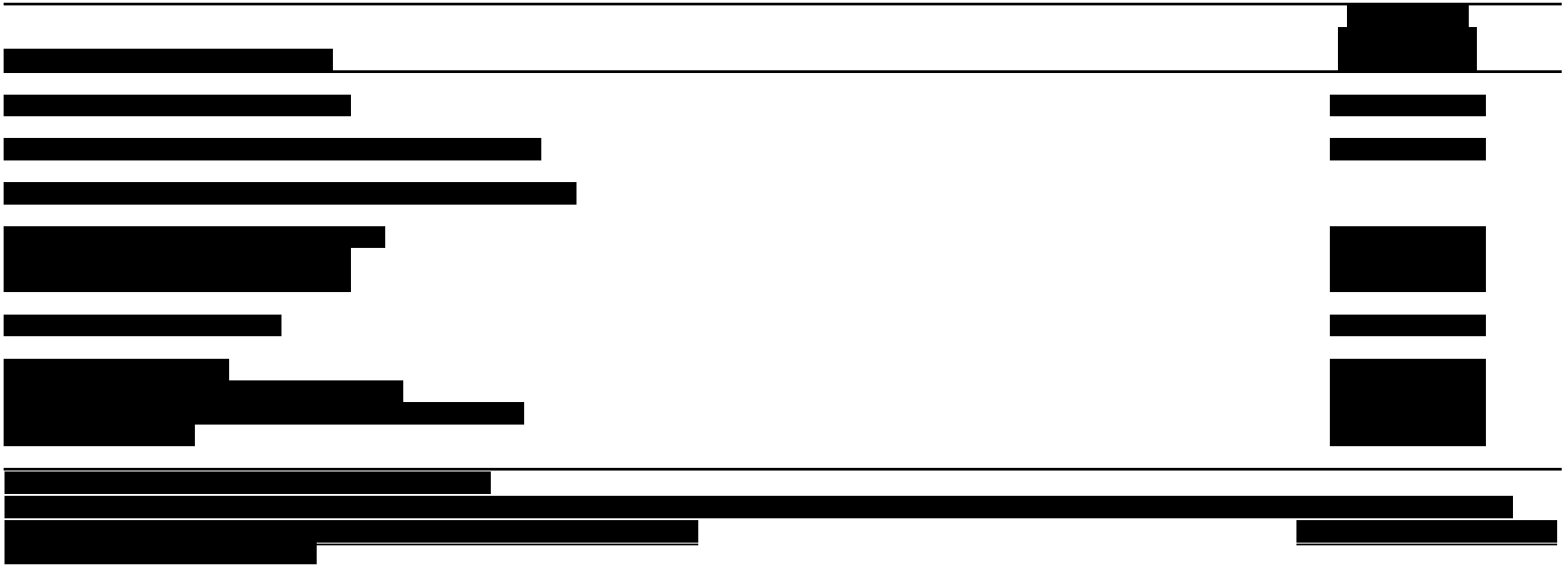
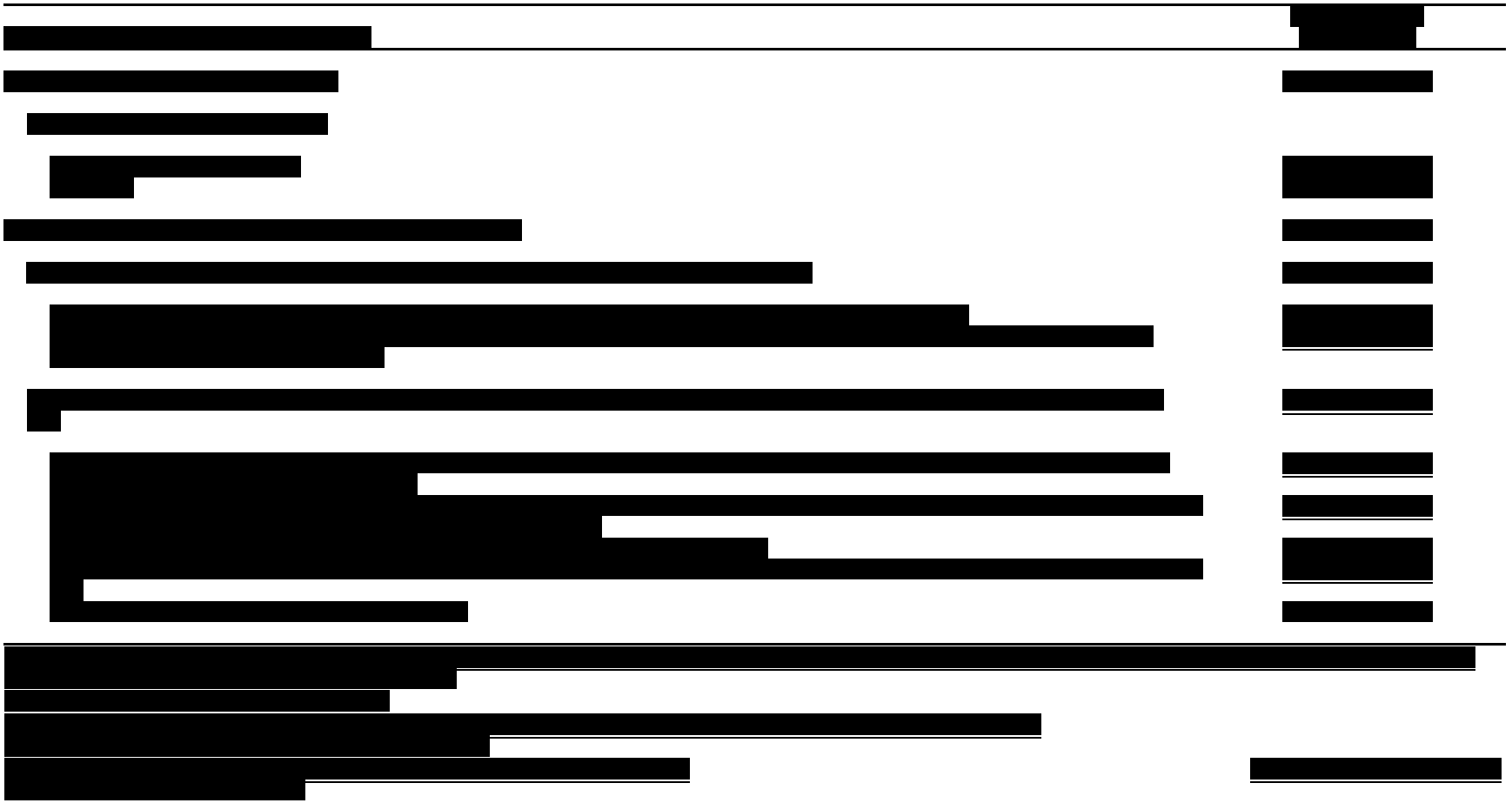


Table 15: Reason for Censoring, PFS



d. **PRIORITY: Censoring rules for KRYSTAL-1 presented in CS Table 10 state that participants were censored on the date of the last evaluable disease assessment when patient administered alternative cancer treatment *prior* to documented progressive disease. Please clarify whether censoring occurred in patients who had progressive disease and subsequently received systemic anticancer therapy.**

Response: Per the SAP, the PFS and DOR endpoints were censored for patients with progressive disease.

e. PFS-2 analyses with KM curves for adagrasib (as per KRYSTAL-12, CSR, pp.132-133), where possible.

PFS-2 was not an outcome planned for within KRYSTAL-1 (single arm Ph I/II study) and, thus, the relevant data to support this analysis was not collected during the trial. To enable PFS-2 analysis, data would need to be proactively planned for to enable it to be collected routinely and appropriately.

Protocol amendments and deviations

A10. Please provide complete lists of major protocol amendments and protocol deviations for KRYSTAL-12 and KRYSTAL-1, with justifications as appropriate.

a. The Clinicaltrials.gov record for KRYSTAL-12 indicates that OS was a primary outcome (along with PFS) when the study was first registered (12/2020) and at reported time of study start (04/2021), and subsequently became a secondary outcome (10/2021). In a subsequent protocol amendment (04/2023), the timeframe of all specified outcomes was prolonged, including OS (from 30 months to 49 months). Please provide a justification for these protocol amendments, supported by results of analyses that informed these decisions as appropriate.

Response: During the course of the K12 confirmatory study, the study design was impacted by the evolving treatment and regulatory landscape, with the first KRAS G12C (Sotorasib) receiving US accelerated approval in May 2021. Further, during the original adagrasib regulatory review leading to an accelerated approval in December 2022, the FDA advised the sponsor to make some design changes (endpoints, treatment crossover, sample size, monitoring, etc.) in light of the competitive

landscape and the potential for earlier study readouts while maintaining a comprehensive understanding of adagrasib treatment effects.

Key amendments related to primary/secondary endpoints of PFS and OS, and inclusion on treatment crossover were made based on discussions and recommendations from regulatory bodies, more specifically the FDA.

- Due to FDA accelerated approval of sotorasib, Amendment 3, protocol version 4 (17 Nov 2021) which allowed for treatment crossover from the docetaxel arm, which necessitated the revision of the primary endpoint to be solely PFS by BICR and OS as secondary endpoint, and re-sizing of the sample size and statistical considerations respectively.

- Amendment 5, version 6 (19 DEC 2022) revised the primary endpoint to be dual PFS and OS and increased sample size and respective statistical considerations. However, it should be noted that no patients were enrolled during this late protocol amendment.

- Amendment 6, version 7 (24 MAR 2023) following discussions with the FDA the primary endpoint was revised to be solely PFS and OS as secondary endpoint with sample size reduced and statistical considerations updated accordingly.

KRYSTAL-12 Protocol: Summarised history of key amendments

- **Version 1 (original protocol): 24 AUG 2020**

- **Amendment 1, version 2: 16 NOV 2020**

    - In alignment with US FDA during the original protocol review, adaptation to EU local regulations, and minor clarifications and consistency across the adagrasib program

- **Amendment 2, version 3: 09 MAR 2021**

    - Updated the study population to include patients with unresectable, locally advanced disease in addition to patients with metastatic disease. Minor updates from nonclinical, clinical and PK data.

- **Amendment 3, version 4: 17 NOV 2021**
    - Adaptations were prompted by the evolving NSCLC treatment landscape, and inclusion of option for crossover for participants in the docetaxel arm, which necessitated a change in the primary endpoint to Progression-Free Survival (PFS), with Overall Survival (OS) as a secondary endpoint.
- **Amendment 4, version 5: 31 MAY 2022**
    - Further clarifications were implemented based on updated background information and site inquiries during patient enrolment. Overall Response Rate (ORR) was added as a well-recognised 2nd endpoint in NSCLC studies.
- **Amendment 5, version 6: 19 DEC 2022**
    - The primary endpoint was changed to include both PFS and OS meant to provide a more comprehensive understanding of treatment effects (increased sample size).
    - No patients were enrolled under this amendment.
- **Amendment 6, version 7: 24 MAR 2023**
    - During the US accelerated approval review, FDA advised to revert to PFS as a sole primary endpoint in light of the competitive landscape and the potential for earlier study readouts (decreased sample size).

Network meta-analysis

A11. PRIORITY: Please provide sufficient information to allow the replication and critique of the network meta-analysis (NMA) presented in the company submission, including for time-varying analyses. This includes:

a. All codes (R-code and JAGS), data (synthetic data where real data is not possible), initial values, number of iterations used for burn-in and inference, details on the prior distributions used for the heterogeneity for the time-varying and proportional hazards (PH) NMAs, residual deviance for

each model (fixed effect and random effect), and full set of graphs and diagnostics used for the assessment of the PH assumption.

Response: All analyses were performed in a Bayesian framework and involved a model with parameters, data, and a likelihood distribution, and prior distributions. Data for all analyses has been provided in the zip file of supplementary materials (refer to NMA - Data folder). The parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo method as implemented in the JAGS software package. JAGS code of the NMA models is provided in the zip file of supplementary material (refer to NMA – Code folder). The code for the constant HR NMA was consistent with the methods and code outlined by Dias et al., 2011.[12] The JAGS code can be called using the rjags R package, with example code below:

jags.model(file = “Normal differences FE bad NMA 2arm.txt”, data = bugsdata, n.chains = 2, n.adapt = 1000, inits = list(list(.RNG.name = "base::Wichmann-Hill", .RNG.seed = 1), list(.RNG.name = "base::Wichmann-Hill", .RNG.seed = 2)))

The example code is also defining initial values as available in the r2jags package.

The methods and code used to run the time-varying HR NMA were sourced from Cope et al., 2020.[13] In step one of this two-step NMA, the following competing six parametric survival distributions are fitted to (pseudo) individual patient level data (IPD) for each arm of each trial in the evidence network: Weibull, Gompertz, log-normal, log-logistic, exponential and gamma. Models were fit using the flexsurv R package, with example code provided below:

flexsurvreg(Surv(time, event) ~ 1, dist=’lnorm’, data = datause)

Note that estimates of the parametric models for OS in KRYSTAL-12 were directly obtained from the surrogacy analyses (refer to NMA – Data folder). Step two of the method synthesised the parameters estimated in step one, leveraging methods and code from Achana et al., 2014 (refer to the NMA – Code folder in zip file with supplementary materials).[14] A first series of 20,000 iterations (for constant HR NMAs) or 50,000 iterations (for time-varying HR NMAs) from the JAGS sampler was discarded as ‘burn-in’ and the inferences were based on additional iterations using two chains of 80,000 iterations (for constant HR NMAs) or 20,000 iterations (for time-varying HR NMAs).

Table 16 provides an overview of the models, likelihood and priors used for each outcome; both fixed and random-effects models were explored (except for the two-step NMA which was restricted to fixed-effects). Given that the number of trials to estimate between-study heterogeneity based on random-effects models was limited, an informative prior for the between-study heterogeneity parameter was used according to Turner et al., 2015.[15] Residual deviance and DIC for both fixed and random-effects model is summarised in Table 17.

The PH assumption was assessed for the time-to-event outcomes in each individual trial using the Grambsch-Therneau test and visual inspection of the log-cumulative hazards plot, Schoenfeld residual plot, and smoothed hazards plot. There were violations in the PH assumption for OS in CodeBreaK 200 and for PFS in LUME-Lung 1.

Table 16: Overview of analyses by outcome

Outcome	Outcome type	Trial population	NMA regression link	Likelihood	Relative effects normal prior	Between-study heterogeneity log-normal prior	Relative effect
OS	TTE	ITT	2-step NMA	Multivariate Normal	Mean=0; var= 10^3	NA (fixed effects only)	Time-varying HR
PFS	TTE	ITT	2-step NMA	Multivariate Normal	Mean=0; var= 10^3	NA (fixed effects only)	Time-varying HR
OS	TTE	ITT	Identity link	Normal	Mean=0; var=10^4	Meanlog=-4.18 Sdlog=1.41[a]	Constant HR
PFS	TTE	ITT	Identity link	Normal	Mean=0; var=10^4	Meanlog=−3.95 Sdlog=1.79[b]	Constant HR

Notes: a) OS used “All-cause mortality” prior distributions as described by Turner (2015). b) PFS analysis used “cause-specific mortality/major morbidity event/composite mortality or morbidity” prior distributions as described by Turner (2015).

Table 17: Summary of DIC and residual deviance across constant HR network meta-analyses

Outcome	Trial population	Fixed-effects		Random-effects	
		DIC	Residual deviance	DIC	Residual deviance
OS	ITT	[redacted]	[redacted]	[redacted]	[redacted]
PFS	ITT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

b. Summary statistics for the posterior distribution of the heterogeneity, along with plots of the priors and posterior distributions of the heterogeneity parameter for all random effect models fitted.

Response: The heterogeneity parameter (posterior) is summarised in Table 18 for the random-effects models fitted, and density plots are provided in the zip file of supplemental materials (refer to NMA – Output – constant HR folder).

Table 18: Summary of heterogeneity from random-effects models

Outcome	Analysis type	Trial population	Heterogeneity (95% CrI)
OS	Constant HR NMA	ITT	[redacted]
PFS	Constant HR NMA	ITT	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; ITT, intention-to-treat; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

c. If available, please provide a full NMA report with further details on methods and more complete results (including on convergence).

Response: A full report of the NMA is not available for the UK analysis, however, we have covered all relevant information of methods and results in our responses to the NMA questions (A11-A14; B5). Convergence was confirmed via visual inspection of density plots and the Gelman-Rubin statistic. Diagnostics from the constant HR NMA (refer to *NMA – Output – constant HR* folder) and the time-varying HR NMA (refer to *NMA – Output – time varying HR* folder) are provided in the zip file of supplemental materials.

A12. PRIORITY: The NMA does not include safety results. Please provide additional safety results including all cause Grade 3-5 adverse events, serious adverse events, and hepatoxicity, accounting for treatment crossover where possible and appropriate.

Response: It was assumed that CodeBreaK 200 accounted for crossover from docetaxel to sotorasib in the analysis of safety outcomes (refer to legend of Table S16 in De Langen 2023: "TEAE in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients crossed over from docetaxel to sotorasib, whichever occurred earlier."). KRYSTAL-12 safety data were adjusted for crossover as well (i.e. adverse events after initiation of crossover adagrasib treatment in the docetaxel arm were excluded). It was assumed that LUME-Lung 1 safety data was not influenced by crossover as it was not reported in the study design. Input data of the NMA is provided in the zip file with supplementary materials (refer to NMA – Data folder).

Results from the fixed and random-effects NMAs are presented in Table 19 and Table 20 for all cause grade 3-5 TEAEs, in Table 21 and Table 22 for serious TEAEs, Table 23 and Table 24 for serious TRAEs, and grade 3-5 hepatotoxicity in Table 25 and Table 26. Note that the low rates of grade 3-5 hepatotoxicity observed in the docetaxel arm of both CodeBreaK 200 and KRYSTAL-12 introduced uncertainty and resulted in wide credible intervals. Additionally, the NMA was conducted for both serious TEAEs and serious TRAEs, because LUME-Lung 1 only reported serious TEAEs (is our interpretation) and CodeBreaK 200 only reported serious TRAEs.

Adagrasib demonstrated a comparable risk of cause grade 3-5 TEAEs versus nintedanib + docetaxel ([redacted]); however, a trend of an [redacted] risk of serious TRAEs ([redacted]). Adagrasib demonstrated a trend of [redacted] grade 3-5 TEAEs versus sotorasib ([redacted]) and a trend of [redacted] hepatotoxicity ([redacted]). However, adagrasib was associated with [redacted] risk of serious TRAE versus sotorasib ([redacted]).

Table 19: Estimated odds ratios (95% credible intervals) from the fixed-effects NMA for any cause grade≥3 TEAEs

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 11.36; Deviance: 5.36. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TEAEs, treatment emergent adverse events.

Table 20: Estimated odds ratios (95% credible intervals) from the random-effects[a] NMA for any cause grade≥3 TEAEs

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

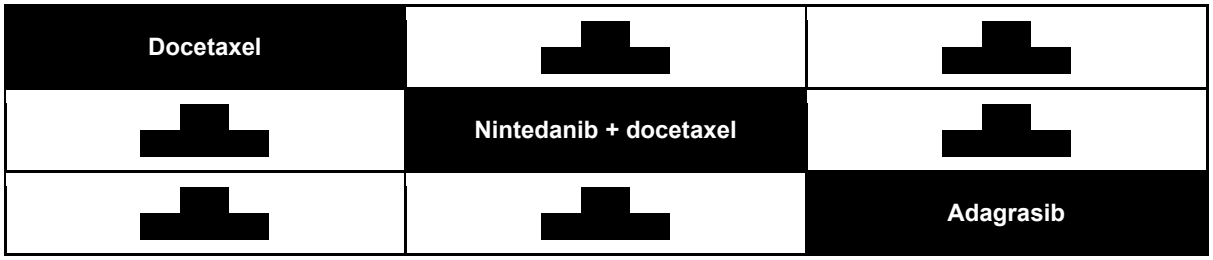
Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 11.35; Deviance: 5.35. a) Random-effects models used an informative prior for the between-study heterogeneity parameter according to Turner (2015), specifically the “adverse events” prior distribution. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TEAEs, treatment emergent adverse events.

Table 21: Estimated odds ratios (95% credible intervals) from the fixed-effect NMA for serious TEAEs; safety population

Docetaxel		
	Nintedanib + docetaxel	
		Adagrasib

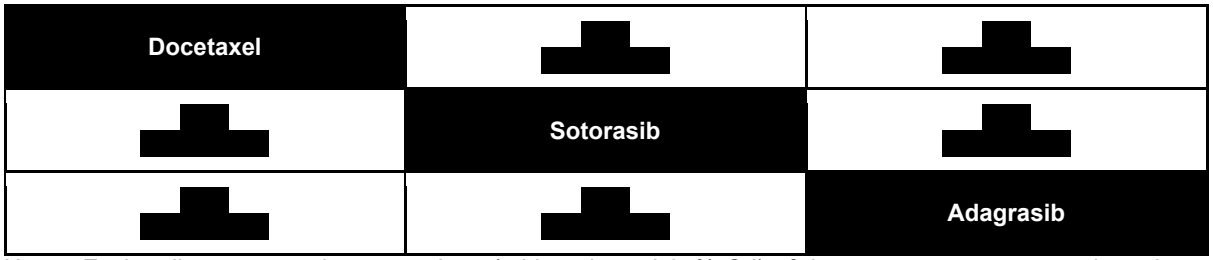
Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.38; Deviance: 3.37. a) Random-effects models used an informative prior for the between-study heterogeneity parameter according to Turner (2015), specifically the “adverse events” prior distribution. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TEAEs, treatment emergent adverse events.

Table 22: Estimated odds ratios (95% credible intervals) from the random-effects[a] NMA for serious TEAEs; safety population



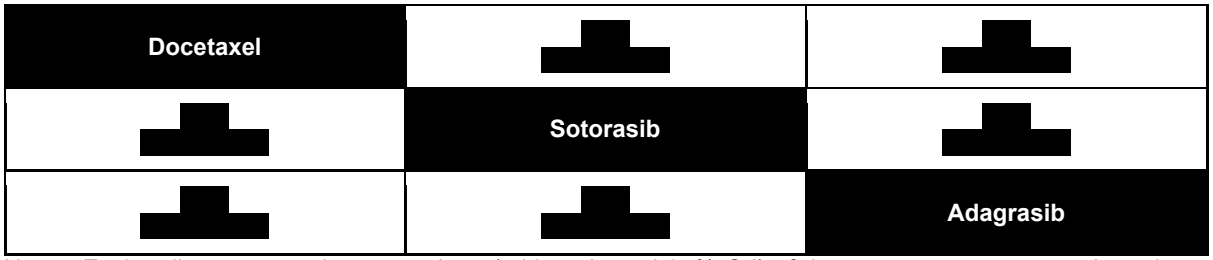
Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.38; Deviance: 3.37. a) Random-effects models used an informative prior for the between-study heterogeneity parameter according to Turner (2015), specifically the "adverse events" prior distribution. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TEAEs, treatment emergent adverse events

Table 23: Estimated odds ratios (95% credible intervals) from the fixed-effect NMA for serious TRAEs; safety population



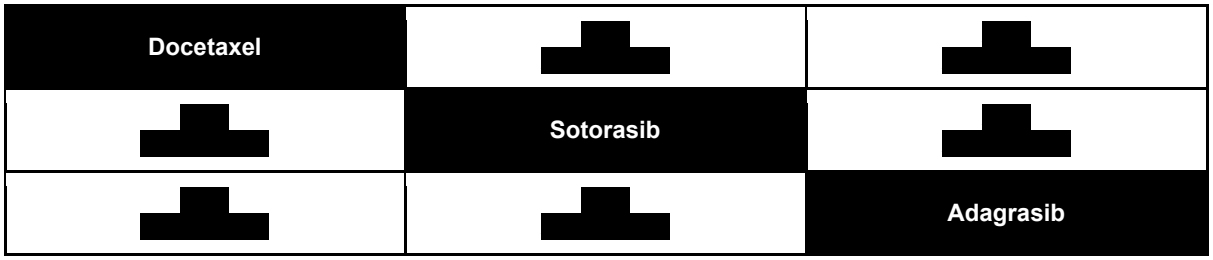
Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.37; Deviance: 3.37. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TRAEs, treatment related adverse events.

Table 24: Estimated odds ratios (95% credible intervals) from the random-effects[a] NMA for serious TRAEs; safety population



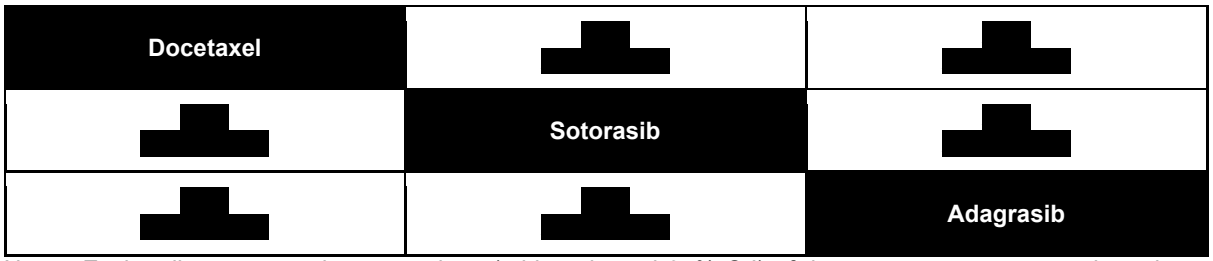
Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.38; Deviance: 3.38. a) Random-effects models used an informative prior for the between-study heterogeneity parameter according to Turner (2015), specifically the "adverse events" prior distribution. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis; TRAEs, treatment related adverse events.

Table 25: Estimated odds ratios (95% credible intervals) from the fixed-effect NMA for grade≥3 hepatotoxicity; safety population



Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.42; Deviance: 3.45. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis.

Table 26: Estimated odds ratios (95% credible intervals) from the random-effects[a] NMA for grade≥3 hepatotoxicity; safety population



Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 7.38; Deviance: 3.38. a) Random-effects models used an informative prior for the between-study heterogeneity parameter according to Turner (2015), specifically the "adverse events" prior distribution. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis.

A13. CS Appendix D3. shows that the population from LUME-Lung 1 differs significantly from the populations in KRYSTAL-12 and CodeBreaK 200 (for instance, lack of prior immunotherapy, lack of KRAS GC-12 specific data, younger age, high proportion of non-adenocarcinoma tumour histology, etc.).

a. Please assess the extent to which the evidence from LUME-Lung 1 is applicable to the population defined in the NICE scope, using additional evidence as appropriate.

Response: The population defined in the NICE scope was "adults with advanced NSCLC that are positive for a KRAS G12C mutation and are not suitable for, or have progressed after treatment with, platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy." In the absence of data for nintedanib + docetaxel specifically for this target population, LUME-Lung 1 is the only relevant RCT evaluating nintedanib + docetaxel in previously treated NSCLC; this was also discussed in the sotorasib NICE submission and the corresponding committee papers (TA781), which took a consistent approach.[16] Most patients in LUME-Lung 1 were pre-treated with platinum

chemotherapy (>95%), however, the trial was conducted before immunotherapy was approved as first line therapy in NSCLC and as such patients were not previously exposed to checkpoint inhibitors. Further, LUME-Lung 1 was conducted when targeted therapy for KRAS mutated NSCLC was not available and KRAS status was not reported. It is likely that LUME-Lung 1 included patients with mutated and wild-type KRAS.

It is uncertain whether previous exposure to immunotherapy and KRAS status impact the relative treatment effect of nintedanib + docetaxel vs docetaxel (refer also to our response to question A13b). As such, between-study differences in the target population might not be relevant.

Real-world studies investigated nintedanib + docetaxel in immunotherapy pretreated NSCLC (e.g. VARGADO, also mentioned in CS, Table 6 in Appendix D). An indirect treatment comparison based on KRYSTAL-12 and real-world data would be unanchored and thus requires adjustment for all prognostic factors and effect modifiers; additionally, differences in study design would need to be addressed (trial versus real-world). Consequently, our NMA, which preserves randomisation and was based on phase III RCTs, relies on fewer assumptions (see further explanation in our response to A13b).

b. Please discuss to what extent these population differences may impact the NMA results.

Response: The LUME trial recruited patients between December 23, 2008, and February 9, 2011, over a decade ago. Since then, the treatment landscape for NSCLC has evolved significantly, particularly with the advent of immuno-oncology (IO) therapies. In contrast, most patients in the KRYSTAL-12 or CodeBreaK 200 trials received IO therapy prior to KRAS G12C-targeted treatment. As a result, the patient populations in the LUME trial and K12 differ substantially, reflecting the advancements in NSCLC treatment over the past decade.

The exchangeability (similarity) assumption of NMA requires that the distribution of patient characteristics that predict the relative treatment effects (i.e. treatment effect modifiers) is similar across trials (more specifically, across treatment comparisons in the network). Although various patient characteristics differ between KRYSTAL-12 and LUME-Lung 1, it is uncertain whether these variables are predictive factors. For

instance, subgroup analyses stratifying patients by prior immunotherapy exposure were not conducted (not feasible) in LUME-Lung 1.

A summary of the other patient characteristics is provided in Table 27. Beyond differences in prior immunotherapy exposure and KRAS status, as indicated by the EAG, differences were observed in the distribution of age, histology, smoking status, brain metastasis and the number of prior therapies. We discuss the implications of between-study differences for each of these characteristics individually.

Prior immunotherapy: There is limited evidence regarding prior treatment with immunotherapy as a treatment effect modifier. Prior treatment with immunotherapy did have an impact on the docetaxel versus pemetrexed treatment effect in J-AXEL.[17] No significant difference in OS was observed between docetaxel and pemetrexed in patients without prior immunotherapy (HR 0.91; 95% CI 0.72-1.14), whereas strong treatment effect was observed in patients with prior immunotherapy (HR 0.43; 95% CI 0.24-0.79). Also, the ESMO clinical guideline recommended docetaxel + nintedanib as a treatment option specifically for patients with contraindications for use of immunotherapy. As such, prior immunotherapy might predict outcomes of nintedanib + docetaxel; however, it is challenging to make any reliable inference on the effect of between study differences on NMA results.

KRAS status: Similarly, LUME-Lung 1 did not report on subgroup analyses by KRAS status. However, considering the mechanism of action of nintedanib + docetaxel, KRAS G12C status is not expected to impact the treatment effect of nintedanib + docetaxel.

Age: Age did not show a subgroup effect in KRYSTAL-12 (refer to CSR) and LUME-Lung 1; as such, age was not considered a predictive factor and between study differences should not impact NMA results.

Histology: The impact of histology was investigated in an analysis including adenocarcinoma patients of LUME-Lung 1 and corresponding NMA results are provided as response to question A13C.

Smoking status: In terms of smoking status, Table 28 provides the results of a sensitivity analysis for PFS in current and former smokers (sample size for never smokers is limited in KRYSTAL-12; [redacted]), which suggests that adagrasib still has a

beneficial treatment effect compared to nintedanib + docetaxel ([redacted]). Note that an NMA stratifying current vs former smokers was not feasible, because the corresponding data were not reported in LUME-Lung 1.

Brain metastasis: The proportion of patients with brain metastasis differed between trials ([redacted] in KRYSTAL-12, 6% in LUME-Lung 1), and subgroup data were reported for patients with and without brain metastases. However, only 67 patients with brain metastasis were included in the PFS subgroup analysis in LUME-Lung 1, resulting in uncertainty in the HR for PFS for nintedanib + docetaxel (refer to Figure 4a and Figure S1, Reck et al [2014][18]). Therefore, subgroup analyses stratifying the NMA by brain metastasis were not considered informative. It was assumed that a higher proportion of patients with brain metastasis in KRYSTAL-12 was likely to provide conservative adagrasib estimates in the NMA. This is supported by subgroup analyses reported in the KRYSTAL-12 CSR, which showed a stronger adagrasib treatment effect in patients without baseline brain metastasis (HR PFS= [redacted]) versus patients with baseline brain metastasis (HR PFS= [redacted]).

Prior treatment lines: The number of prior treatment lines did not show a subgroup effect in KRYSTAL-12 (refer to CSR); as such, the number of prior treatment lines is not considered a predictive factor and between study differences should not impact NMA results.

Table 27: Patient characteristics in KRYSTAL-12, CodeBreaK 200 and LUME-Lung 1

Characteristic	KRYSTAL-12		CodeBreaK 200		LUME Lung	
	Adagrasib (n=301)	Docetaxel (n=152)	Sotorasib (n=171)	Docetaxel (n=174)	Nintedanib + Docetaxel (n=655)	Docetaxel (n=659)
Age, median (range) Age ≥ 65 years, n (%)	[redacted]	[redacted]	64 (32 – 88) 80 (46.8%)	64 (35 – 87) 79 (45.4%)	60 (53–67) 200 (30.5%)	60 (54–66) 214 (32.5%)
Male, n (%)	[redacted]	[redacted]	109 (63.7%)	95 (54.6%)	476 (72.7%)	479 (72.7%)
Region Europe, n (%) North America, n (%) Asia, n (%) Rest of the world, n (%)	[redacted]	[redacted]	 126 (73.7%) 20 (11.7%) - 25 (14.6%)	 126 (72.4%) 22 (12.6%) - 26 (14.9%)		
Race/ethnicity Caucasian, n (%) Black, n (%) Asian, n (%) Missing/Unknown, n (%) Other, n (%)	[redacted]	[redacted]	 142 (83.0%) 2 (1.2%) 21 (12.3%) 1 (0.6%) 5 (2.9%)[a]	 144 (82.8%) 0 (0%) 22 (12.6%) 1 (0.6%) 7 (4.0%)[a]	 533 (81.4%) 4 (0.6%) 116 (17.7%) - 2 (0.3%)	 530 (80.4%) 5 (0.8%) 123 (18.7%) - 1 (0.2%)
ECOG PS ECOG 0, n (%) ECOG 1, n (%) ECOG 2, n (%) Missing/Unknown, n (%)	[redacted]	[redacted]	 59 (34.5%) 112 (65.5%) - -	 59 (33.9%) 115 (66.1%) - -	 187 (28.5%) 467 (71.3%) 1 (0.1%) -	 189 (28.7%) 470 (71.3%) - -
Smoking status Current/Former smoker, n (%) Never smoker, n (%)	[redacted]	[redacted]	 166 (97.1%) 5 (2.9%)	 166 (95.4%) 8 (4.6%)	 490 (74.8%) 165 (25.2%)	 498 (75.6%) 161 (24.4%)
Histology Adenocarcinoma, n (%)[c] Other, n (%)	[redacted]	[redacted]	 169 (98.8%) 2 (1.2%)	 165 (94.8%) 9 (5.1%)	 322 (49.2%) 333 (50.8%)	 336 (51.0%) 323 (49.0%)
Disease stage Locally advanced, n (%) Metastatic, n (%)	[redacted]	[redacted]	 9 (5.3%) 162 (94.7%)	 8 (4.6%) 166 (95.4%)	 NR	 NR
Bone metastases, n (%)	[redacted]	[redacted]	81 (47.4%)	69 (39.7%)	NR	NR
Liver metastases, n (%)	[redacted]	[redacted]	30 (17.5%)	35 (20.1%)	NR	NR
CNS involvement[d], n (%)	[redacted]	[redacted]	History CNS invol.: 58 (33.9%)	History CNS invol.: 60 (34.5%)	38 (5.8%)	38 (5.8%)
$KRAS^{G12C}$ mutated	[redacted]	[redacted]	171 (100%)[e]	174 (100%)[e]	0 (0%)[e]	0 (0%)[e]
Number of previous LOT	[redacted]	[redacted]	1: 77 (45.0%) 2: 65 (38.0%) >2: 29 (17.0)	1: 78 (44.8%) 2: 69 (39.7%) >2: 27 (15.5%)	1: 655 (100.0%)	1: 659 (100.0%)
≥ 2 previous LOT, n (%)	[redacted]	[redacted]	94 (55.0%)	96 (55.2%)	0 (0%)	0 (0%)
Prior IO (%)	[redacted]	[redacted]	171 (100%)[e]	174 (100%)[e]	0 (0%)[e]	0 (0%)[e]

Characteristic	KRYSTAL-12		CodeBreaK 200		LUME Lung	
	Adagrasib (n=301)	Docetaxel (n=152)	Sotorasib (n=171)	Docetaxel (n=174)	Nintedanib + Docetaxel (n=655)	Docetaxel (n=659)
Best response to prior therapy						
OR, n (%)	[redacted]	[redacted]	35 (20.5%)	47 (27.0%)	227 (35.1%)	196 (30.1%)
SD, n (%)			50 (29.2%)	53 (30.5%)	249 (38.5%)	249 (38.2%)
PD, n (%)			67 (39.2%)	57 (32.8%)	127 (19.7%)	139 (21.4%)
Missing, n (%)			-	-	43 (6.7%)	67 (10.3%)

Notes: a) Other and multiple race; b) One patient with missing data; c) Non-squamous for CodeBreaK 200; d) n, % patients with brain metastases in KRYSTAL-12: adagrasib: [redacted]; docetaxel: [redacted]; e) derived based on patient eligibility criteria. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CNS: central nervous system; invol, involvement; IO, immunotherapy; LOT, line of treatment; NR, not reported; PD, progressive disease; OR, objective response; SD, stable disease.

Table 28: Estimated constant hazard ratios (95% credible intervals) from the fixed-effects NMA for progression-free survival; current/former smokers

Docetaxel	[redacted]	[redacted]
[redacted]	**Nintedanib + docetaxel**	[redacted]
[redacted]	[redacted]	**Adagrasib**

Notes: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Abbreviations: CrI, credible interval; DIC, deviance information criterion; NMA, network meta-analysis.

c. Please present the results of a NMA sensitivity analysis of OS and PFS including the subgroup with adenocarcinoma only from LUME-Lung 1 (rather than from the whole LUME-Lung 1 population).

Response: Please find the results of the sensitivity analysis below, with results from the ITT NMA as benchmark. The sensitivity analyses of patients with non-squamous disease included the ITT population of KRYSTAL-12 and CodeBreaK 200, where most patients were non-squamous ([redacted]). OS in KRYSTAL-12 was predicted based on surrogacy analyses. For CodeBreaK 200, treatment effects from the crossover-adjusted analysis were used in the NMA for OS (two-stage adjustment as reported in the sotorasib G-BA submission; refer to question A14 and corresponding answer). Adagrasib continued to show a longer PFS compared to nintedanib + docetaxel in adenocarcinoma NSCLC, with slightly increased uncertainty which may be explained by the lower sample size of patients with adenocarcinoma in LUME-Lung 1 (HR 0.75; 95% CrI 0.54, 1.06). The treatment effect for OS was consistent with the analysis of the ITT population; with the HR increasing from [redacted].

Table 29: Estimated constant hazard ratios (95% credible intervals) from the fixed-effects NMA for progression-free survival; ITT population

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

Notes: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Abbreviations: CrI, credible interval; ITT, intention to treat; NMA, network meta-analysis.

Table 30: Estimated constant hazard ratios (95% credible intervals) from the fixed-effects NMA for progression-free survival; non-squamous patients

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

Notes: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Abbreviations: CrI, credible interval; NMA, network meta-analysis.

Table 31: Estimated constant hazard ratios (95% credible intervals) from the fixed-effects NMA for overall survival; ITT population

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

Notes: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Abbreviations: CrI, credible interval; ITT, intention to treat; NMA, network meta-analysis

Table 32: Estimated constant hazard ratios (95% credible intervals) from the fixed-effects NMA for overall survival; non-squamous patients

Docetaxel			
	Nintedanib + docetaxel		
		Sotorasib	
			Adagrasib

Notes: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Abbreviations: CrI, credible interval; NMA, network meta-analysis

A14. For sotorasib, crossover-adjusted CodeBreaK 200 OS data were used in the NMA based on the two-stage method provided in the sotorasib G-BA submission.

a. Please justify the choice of the two-stage method over the other methods used, i.e. the Rank Preserving Structural Failure Time (RPSFT) and Inverse Probability of Censoring Weighting (IPCW) methods, which have been reported in the FDA 2023 ODAC Minutes - Sotorasib file in the CS reference pack (p37).

Response: The proportional hazard assumption was violated for OS; therefore, time-varying hazard ratios were estimated using the two-step NMA approach described by Cope et al. (2020).[13] OS of sotorasib vs docetaxel (CodeBreaK 200) was informed by the crossover adjusted analyses, specifically the two-stage method, as reported in the *sotorasib G-BA submission* (refer to https://www.g-ba.de/downloads/92-975-6366/2023_02_01_Modul_4A_Sotorasib.pdf, Section 4.3.1.3.1.1), because this submission provided Kaplan-Meier curves required to estimate time-varying hazard ratios. Crossover adjusted Kaplan-Meier curves were not provided in the FDA ODAC minutes (refer to https://www.fda.gov/media/172756/download; note, erratum available providing HRs similar to HRs in sotorasib G-BA submission: https://www.fda.gov/media/172699/download [Table 33]).

The two-stage adjusted OS provided the most conservative estimate from an adagrasib NMA perspective (HR sotorasib vs docetaxel in G-BA submission: 0.88 [95%CI: 0.172-1.328]) compared to the other crossover adjustment analyses (e.g. HR RPSFT G-BA submission: 1.01 [95%CI: 0.66-1.49]) and the ITT analysis (HR 1.01 [95%CI 0·77-1·33]).

Table 33: Results of crossover adjusted OS in CodeBreaK 200; analyses results available from sotorasib G-BA submission and ODAC FDA meeting (erratum)

	G-BA	FDA (erratum)
RPSFTM	1.010 (0.660, 1.492)	1.010 (0.660, 1.492)
IPCW	0.990 (0.733, 1.337)	0.990 (0.733, 1.337)
Two-stage	0.885 (0.172, 1.328)	0.889 (0.350, 1.294)

Abbreviations: IPCW, inverse-probability-of-censoring weighting; RPSFTM, rank preserving structural failure time model.

b. Please comment on the differences in the estimates of survival benefit for sotorasib based on the three alternative methods (i.e. two-stage, RPSFT and IPCW methods) and the implications for the NMA results.

Response: See response to question A14A.

c. Following the crossover-adjusted OS results reported on page 37 of the FDA 2023 ODAC Minutes - Sotorasib file in the CS reference pack, the 2-stage adjusted OS hazard ratio (HR) for sotorasib vs. docetaxel does not match the corresponding estimate in Table 18 (Appendix D). Furthermore, in the G-BA document cited in the g footnote reported OS for ITT on the mortality table (see below). Please clarify the source from which the crossover-adjusted OS HR estimates were extracted and provide the corresponding document.

Mortality

Endpoint	Sotorasib		Docetaxel		Sotorasib vs docetaxel
	N	**Median time to event in months [95% CI]** *Patients with event n (%)*	N	**Median time to event in months [95% CI]** *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	171	10.64 [8.94; 13.96] *109 (63.7)*	174	11.30 [9.00; 14.85] *94 (54.0)*	1.010 [0.77; 1.33] 0.94

Response: See response to A14A. An erratum was available for the numbers presented during the ODAC FDA meeting.

A15. The systematic review reported in Appendix D included a total of 374 publications, including 196 unique randomised controlled trials (RCTs). Only three RCTs were included in the NMA. Please provide a justification for the exclusion from the NMA of most studies included in the systematic review, including a list of excluded with reasons where available.

Response: The SLR was conducted with a broad (global) scope and identified 196 unique RCTs. Only nintedanib + docetaxel, docetaxel monotherapy and sotorasib were considered relevant comparators according to the scope of the submission (Table 34). LUME-Lung 1 and CodeBreaK 200 were the only RCTs that provided comparative efficacy data of these treatments and form an interlinked network with KRYSTAL-12 (required for the conduct of the NMA). All other 193 RCTs identified by the SLR either investigated therapies that fall outside the scope of the submission or

did not connect to the network diagram with KRYSTAL-12, LUME-Lung 1 and CodeBreaK 200 (i.e. did not have a common comparator).

Table 34: Selection criteria for the NMA

PICOS item	Selection criteria for the NMA
Population	Adult, 2L+ patients with advanced or metastatic NSCLC, who have been treated with at least one prior systemic therapy Subgroups of interest: CNS involvement
Interventions	$KRAS^{G12C}$ inhibitors: sotorasib monotherapy Angiogenesis inhibitors (nintedanib plus docetaxel) Chemotherapy (docetaxel monotherapy)
Comparators	Any of the above interventions Docetaxel
Outcomes	PFS, ORR, DOR, OS, any grade TRAEs/TEAEs, grade 3-4 TRAEs/TEAEs, and discontinuations due to TRAEs/TEAEs
Study design	Randomised controlled trials

Section B: Clarification on cost-effectiveness data

Surrogacy relationship

B1. PRIORITY: Simulated OS data for both treatment arms of KRYSTAL-12 was derived based on an individual-level surrogacy relationship between time to progression (TTP) and OS data from KRYSTAL-1 (a phase 1/2 single-arm trial).

The NICE methods guideline (sections 4.6.7 - 4.6.8)[19] requires good evidence that the relative effect of a technology on the surrogate end point is predictive of its relative effect on the final outcome (i.e., using the hazard ratio of treatment on PFS to predict the corresponding HR on OS). This should preferably come from a meta-analysis of level 1 evidence (that is, RCTs) that reported both the surrogate and the final outcomes, using bivariate meta-analytic methods. Furthermore, the biological plausibility of the surrogacy relationship should be established, and its validity should be demonstrated for both the specific population and the technology.

a. **Please justify why a within-trial approach using a single phase 1/2 study was selected to model the surrogacy relationship, given it deviates from the NICE recommended approach, (a meta-analytic approach which would have been more robust) and that the method applied was developed for validation of surrogate outcomes rather than prediction.**
    i. **Please justify the need to predict absolute OS based on individual-level data rather than estimate a relative effect in terms of OS hazard ratio.**

Response: A meta-analysis of several RCTs is required for an estimation of a relative effect in terms of an OS hazard ratio.[20] As outlined in response to question A3A, recent trial-level surrogacy analyses of PFS-OS HRs in NSCLC include multiple RCTs (N=38 in Horita et al. [2022],[2] and N=138 in Hua et al. [2022][1]), which suggest a moderate association between PFS and OS HRs in NSCLC; however, this association varies by treatment class, treatment line, trial phase, and masking. Furthermore, none of the included RCTs have evaluated $KRAS^{G12C}$ inhibitors nor have they included patients corresponding to the target population from KRYSTAL 12. Therefore, existing trial-level evidence cannot be used to reliably predict an OS HR in KRYSTAL-12, which

compares a $KRAS^{G12C}$ inhibitor (adagrasib) to chemotherapy (docetaxel) in pretreated patients with $KRAS^{G12C}$ mutation.

RCT evidence in patients with a $KRAS^{G12C}$ mutation is limited to one trial (i.e. CodeBreaK 200). As multiple RCTs are required for a robust meta-analysis,[20] CodeBreaK 200 alone cannot be used to inform an analysis of trial-level surrogacy. However, our response to *question A3.a* outlines that predicted OS HR for KRYSTAL-12 based on patient-level surrogacy is not inconsistent with evidence from CodeBreaK 200, which should be interpreted with caution given concerns regarding study conduct.

Based on the limitations outlined above, OS in KRYSTAL-12 cannot be simulated using the existing surrogacy evidence of TTP/PFS-OS in NSCLC. Consequently, a de novo patient-level surrogacy analysis predicting absolute OS data must be conducted. The method used for the de novo patient-level surrogacy analysis was adapted from the joint-frailty copula model developed by Emura et al. (2017),[21] who developed it to predict death for individual patients given progression status. Joint-frailty copula model developed by Emura et al. (2017)[21] and adaptations made for the purposes of the predictions of OS in KRYSTAL-12 are outlined in Appendix P of the CS.

ii. **If alternative approaches were explored but not reported in the CS, please provide estimates of the predicted OS hazard ratio, with details of the approaches used.**

Response: Alternative approaches to surrogacy of TTP-OS or PFS-OS for predicting OS in KRYSTAL-12 were not explored due to a lack of trial-level evidence of surrogacy of TTP-OS or PFS-OS in patients with NSCLC with $KRAS^{G12C}$. See above response to question B1Ai.

b. **Please present evidence to support the validity and the biological plausibility of a surrogacy relationship between OS and TTP (and PFS if relevant) for adagrasib and for this specific population (NSCLC with KRAS G12C mutation). Also discuss if the survival data available for sotorasib (e.g., from CodeBreaK 200) is supportive of the surrogacy relationship between OS and TTP/PFS in the NSCLC with KRAS G12C population.**

Response: Please see response to question A3A, where we provide an overview of the evidence from the literature regarding trial- and individual-level surrogacy in

NSCLC, which has established the biological plausibility of a relationship between PFS and OS and supports a moderate association between PFS and OS in NSCLC overall.

Mechanism of Action and Targeted Population: For KRAS inhibitors specifically, targeting $KRAS^{G12C}$ mutations with adagrasib directly inhibits the mutated protein, disrupting the downstream pathways required for tumor growth and delaying disease progression, which aligns with improvements in TTP and PFS. Consequently, this mechanism delays tumor progression, reduces tumor-associated complications, thus, has a plausible relationship with extending OS. Therefore, the KRAS-specific activity of adagrasib may provide an even stronger argument for the biological plausibility regarding surrogacy as compared to non-targeted agents. For example, another targeted agent, amivantamab (in combination with chemotherapy) for advanced NSCLC harbouring EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, EMA accepted PFS as a surrogacy endpoint for OS. Existing evidence from NSCLC combined with the mechanism of action of $KRAS^{G12C}$ inhibitors support the biological plausibility of surrogacy between TTP and OS for $KRAS^{G12C}$ inhibitors.

Clinical Evidence: Despite the need for additional evidence to support validity of surrogacy between TTP and OS for $KRAS^{G12C}$ inhibitors, our response to question A3A also outlines the consistency between the predicted HR for adagrasib versus docetaxel for KRYSTAL-12 using individual-level surrogacy model and the crossover-adjusted OS HRs for CodeBreaK 200, both of which suggest an OS benefit for KRAS inhibitors versus chemotherapy. This further reinforces the biological plausibility of the surrogacy for $KRAS^{G12C}$ inhibitors. However, it is important to consider critiques regarding the conduct and results of CodeBreaK 200, as well as how adagrasib provides a unique profile despite belonging to the same class as sotorasib (see response to question A3A).

Finally, it was not feasible to validate the TTP-OS surrogacy model developed based on KRYSTAL-1 in the absence of individual patient data from CodeBreaK 200 or CodeBreaK 100. However, it is important to note that the surrogacy model internal validation and external validation (based on SAPPHIRE evaluating docetaxel), performed well,[22] reinforcing validity of the proposed model. Lastly, it is important to highlight that our OS prediction algorithm also leveraged the events from KRYSTAL-12 where available and propagated the uncertainty regarding the surrogacy

relationship in our predictions, which was also incorporated into the cost-effectiveness model.

c. Please provide examples of the use of the joint frailty-copula model in other HTA submissions.

Response: We are not aware of previous examples of HTA submissions that used the joint frailty-copula model for prediction of OS. However, Eura et al. (2017)[21] is cited by 119 references in Google Scholar and the principles of the proposed model align with broader guidelines regarding surrogacy in the NICE DSU guidelines.[20] Finally, this method has an R package available, which allows for reproducibility and may increase uptake of these methods for future HTA submissions: *Joint frailty-copula models for tumour progression and death in meta-analysis*. 2022. https://CRAN.R-project.org/package=joint.Cox

B2. PRIORITY: The surrogacy analysis was conducted by adapting a joint frailty-copula model proposed by Emura et al. (2017)[21] and Emura et al. (2022).[23,24]

a. Please provide a clear and detailed intuitive explanation of how the OS predictions are estimated from observed TTP data from KRYSTAL-12, over and above the technical specification provided in Appendix P of CS.

Response: An intuitive explanation is provided below. Consider three patients, each in one of the disease states (i.e. stable, progressed, or dead) defined in the following figure:

Figure 6: Disease states considered for OS predictions

1. In the simplest case, the patient falls into the right box of the figure (i.e. death). Their TTP is censored due to death (i.e. an OS event has occurred); for this patient, prediction of OS is not necessary, and the OS event is recorded at the observed TTP censor time.

2. Next consider a patient that falls into the bottom box of the figure (i.e., progressed). They have already experienced a progression (i.e. a TTP event is observed); prediction of OS for this patient is necessary and there is only one other state that the patient can transition to – the transition from the progressed state to the death state.

3. The last patient to consider falls into the left box of the figure (i.e. stable). They are alive but have yet to experience a progression (i.e. their TTP is censored for a reason other than death); prediction for this patient is necessary and there are two possible states that they can transition to – the transition directly into the death state or a transition into the progressed state followed by a transition into the death state.

Given the possible transitions above, OS is predicted for each of the patients in KRYSTAL-12 that fall into cases 2 or 3, with the transitions between states being informed by a single set of parameters from the joint-frailty copula model based on Emura et al. (2017)[21] and the dynamic prediction formula outlined in Emura et al. (2018),[25] estimated using KRYSTAL-1. Note, all transition probabilities are conditional on a patient's covariates values, and further, the probability of transitioning into the death state is conditional on whether a patient has progressed or not.

For each patient for which OS needs to be predicted, we start at their last known time alive (i.e. their TTP event/censor time) and proceed to sample possible transitions in small, discrete increments of time until either the patient is predicted to die, or a predefined stopping time is reached. This is what the algorithm defined in Appendix P of CS outlines.

Now, consider a patient in KRYSTAL-12 that has experienced a progression, and thus falls into case 2 above. This patient's OS starts as a censor at their last known time alive and the algorithm proceeds as follows:

- We increase time by some amount (e.g. one week) and calculate the probability of that patient transitioning to the death state in that week.

- We take a random sample from a Bernoulli distribution with that probability.

- If the sample is 1, the patient has a predicted transition into the death state and an OS event is recorded in that week.
- If the sample is 0, the patient remains in the progressed state and their OS censor time is changed to their last known time alive plus one week.

- The above two steps are repeated until either the patient transitions into the death state or the predefined simulation stopping time is reached.

Finally, consider a patient in KRYSTAL-12 that is alive and has yet to experience a progression, thus falling into case 3 defined above. At the start of the OS prediction, this patient can transition into either the progressed state or the death state.

The same mechanism of prediction described above is used for death and progression events, i.e. increasing time at discrete intervals and sampling from Bernoulli distributions. If the predicted transition is to the death state, the end of the simulation for that patient is reached. If the predicted transition is to the progression state, this patient falls into case 2 from this point onwards, and we proceed until the patient transitions into the death state, or the predefined stopping time is reached.

Once the above has been conducted for all patients in KRYSTAL-12 we have a single complete OS dataset up to the prespecified simulation end time. However, a single prediction set would not capture the uncertainty in the model parameters estimated using KRYSTAL-1. Therefore, the prediction algorithm is run many times (500), each with a different set of parameters sampled from their joint multivariate-normal distribution, to propagate the parametric uncertainty. The result is 500 predicted OS datasets that can be averaged over to obtain estimates for quantities of interest in place of the KRYSTAL-12 OS trial data.

b. Please justify the specific choice of copula (Clayton) and clarify whether any alternative copulas were considered (and if not, the rationale for not examining alternatives e.g. Hougaard and Frank copula functions). If feasible, please undertake additional comparisons using these alternative copula's to further support the use of Clayton copula.

Response: The Clayton copula was chosen to be consistent with the model developed by Emura et al. (2017).[21] Further, a simulation done by Weber and Titman (2019)[26] to evaluate different copula-based models (in addition to other models) for

estimating the PFS-OS association in oncology trials, showed that the Clayton copula provided the least biased estimate of Kendall's τ among the mentioned copulas in realistic scenarios.

c. Please provide the interpretation of the Kendal's τ estimate reported in Table 52 (appendix P, p108) and discuss any conclusions from this value.

Response: In the context of time-to-event data, Kendall's τ measures the agreement (or disagreement) in endpoints between patients – that is, consistency in short (or long) progression times leading to short (or long) death times. Kendall's τ can take values between -1 and 1, where positive values represent agreement and negative values represent disagreement.

To provide an intuitive explanation, consider a pair of patients where for patient 1 we observe TTP and OS times from the random variables (X_1, Y_1) and similarly for patient 2 we observe TTP and OS times from (X_2, Y_2). Mathematically, Kendall's τ can be written as:

$$\tau = P\{(X_1 - X_2)(Y_1 - Y_2) > 0\} - P\{(X_1 - X_2)(Y_1 - Y_2) < 0\}$$

Here the first term is the probability of concordance, e.g. if we observe a shorter (or longer) TTP in patient 1 than patient 2, then we will also observe a shorter (or longer) OS time for patient 1 when compared to patient 2. The second term is the probability of discordance, or the probability that the order of TTP times and the order of OS times between the two patients are different. Thus, for τ to be positive the probability of concordance must be larger than the probability of discordance, i.e. there must be consistency in the difference between TTP and OS across patients.

Literature providing guidance on the interpretation of Kendall's τ in the context of a surrogacy relationship is limited. Surrogacy studies in oncology typically output correlation terms (R) and correlation coefficients (R^2) for analyses conducted in a frequentist framework. These outputs are then generally interpreted in the context of the guidance provided by the Institute for Quality and Efficiency in Health Care (IQWIG)[27] (i.e. 'high correlation' when the lower limit of the 95% CI of R is ≥0.85, 'medium correlation' when R is >0.70 to <0.85, and 'low correlation' when the upper limit of the 95% CI of R is ≤0.70) or the Biomarker-Surrogacy Evaluation Schema (BSES).[28] Similar guidelines do not exist for the interpretation of τ, which makes it

challenging to assess the strength of association between TTP/PFS and OS; however, guidance on the interpretation of correlation coefficients more broadly,[29] suggests that a τ of [redacted] with a confidence interval of ([redacted]) for the TTP-OS model can be considered to be a moderate correlation.

We assessed the surrogacy between TTP and OS (τ of [redacted] with a confidence interval of [redacted]), as well as the between PFS and OS (τ [redacted]). The strength of the association for PFS and OS (τ) was higher than the association between TTP and OS. Although this τ can also be considered moderate in line with previous surrogacy analyses of PFS-OS in other oncology indications,[8,30] the stronger association was likely driven by inclusion of deaths in the PFS definition and should therefore be interpreted with caution.

Finally, our aim was to predict KRYSTAL-12 OS, rather than to measure the strength of the association between TTP/PFS-OS. Therefore, we selected the TTP-OS model for the KRYSTAL-12 predictions, which outperformed the PFS-OS model in terms of the OS predictions based on the KRYSTAL-1 internal validation, as well as the SAPPHIRE external validation.[22] As a final note, it is also important to highlight that a frailty term was included in the TTP-OS surrogacy model from KRYSTAL-1, which also induces correlation between outcomes within patients, and may affect the interpretation of Kendall's τ. However, this frailty term adds uncertainty and can be considered a conservative approach.

d. Please explain why the joint frailty-copula model was chosen for the surrogacy analysis, and whether regression based predictive models, such as those proposed by Wang et al.(2016)[31] could have been used as an alternative approach to predict OS from surrogate outcomes.

Response: Thank you for sharing the Wang et al. (2016)[31] reference. Although it is conceptually similar to the current surrogacy approach (i.e. using a single trial to define the relationship between the surrogate and final endpoint, the structure of the prediction algorithm, the imputation/prediction of many OS datasets, and the use of observed deaths in the data imputation step, there are several differences worth considering. First, the research question in Wang et al. (2016)[31] does not align with our objectives, as it centres around using surrogate information to predict *analysis time* for final OS, by way of imputing OS data in the same trial. Our research question differs

in that it focuses on predicting OS data in a new trial, which we don't believe can be done with the method. Importantly, Wang et al. (2016)[31] do not include covariates in their model, thereby limiting population adjustment to account for differences between KRSTYAL-1 and KRSTYAL-12. Further, the method outlined by Wang et al. (2016)[31] deviates from those typically used in the surrogacy literature, which involve the use of copulas in IPD-based analyses. Lastly, Wang et al. (2016)[31] also use the exponential distribution in their analysis, rather than splines, which may limit the fit of the OS predictions to observed data.

We chose the joint frailty-copula model developed by Emura et al. (2017)[21] as it aligns well with our research question and the individual-level surrogacy literature in that it uses a copula based approach, implemented using flexible models (i.e. splines), provides a measure of correlation through Kendall's τ, and allows for population adjustment. The approach outlined by Emura et al. (2017)[21] is also more frequently cited than Wang et al. (2016),[31] with 119 citations in Google Scholar for the former vs 1 citation for the latter, at the time of writing, which further supports the precedent for using the Emura et al. (2017)[21] in the current analysis.

e. **Please provide details on how TTP is defined in KRYSTAL-1. More specifically, please indicate whether deaths were censored from the TTP. Please also report separately the number of deaths and progressed disease in the TTP curve.**

Response: In the context of the surrogacy analyses, TTP was derived based on PFS, censoring patients at time of death, rather than considering deaths as events like in the PFS definition. Due to OS data restrictions, deaths over time were not analysed.

f. **Please explain why TTP is used rather than PFS, which is the primary endpoint of the trials.**

Response: TTP was preferred over PFS to align better with the structure of the joint frailty-copula model by Emura et al. (2017),[21] where the final endpoint can censor the surrogate endpoint (e.g. OS events censor TTP but not PFS). Whilst it is possible to include PFS in common copula-based methods, doing so (by the definition of PFS) increases the dependency between outcomes in the data when compared to TTP. For typical individual-level surrogacy applications interested in measuring the correlation between endpoints this is not an issue. However, when we move to predicting OS using the surrogate endpoint, the increased dependency in PFS has the unfavourable

effect of artificially increasing the probability of transitioning from the progression state to death state that is derived in the conditional failure function of Emura et al. (2018).[25]

Furthermore, copula-based models do not allow for events in the surrogate and final endpoints to coincide (i.e. values coincide with probability 0) and thus are theoretically mis-specified for PFS and OS. An analysis by Dejardin et al. found a small bias in estimating Kendall's tau under this scenario.[32] Using TTP instead of PFS avoids this issue. Please see also see response to question B1C, which outlines that although the strength of the association between TTP-OS was less than for PFS-OS, the TTP-OS model outperformed in terms of OS predictions based on the KRYSTAL-1 internal validation, as well as the SAPPHIRE external validation, which was the primary objective.[22]

g. **Please also confirm that the prediction model for OS only predicts death events (and their timing) for patients who are right-censored in KRYSTAL-12. That is, death events (and their timing) for individual participants in KRYSTAL-12, either prior to progression or after progression, are used directly in the OS analysis where available.**

Response: All observed deaths are included in the simulated OS datasets for KRYSTAL-12 (see Response B2.a). This is done by recording all patients in KRYSTAL-12 PFS whose event description includes death. Thus, the simulation of OS events and their timing is only for patients in KRYSTAL-12 who have been censored due to reasons other than death.

h. **Please justify the use of the IPD from the KRYSTAL-1 October 2021 data cutoff instead of the corresponding IPD for 15th January 2022 to inform the surrogacy model and clarify what is the most recent OS data cut available for KRYSTAL-1. If OS data subsequent to the 15th January 2022 data cut-off is available, please provide the Kaplan-Meier OS data for KRYSTAL-1 with numbers of patients at risk (as per Figure 16, p62, CS) for the most recent data cutoff.**

Response: The most recent data cut off (DCO) of KRYSTAL-1 is January 2022, and this DCO has updated OS but not updated PFS. Given that the purpose of the surrogacy model was to evaluate the relationship between disease progression and OS, it was preferable to use of same DCO for both endpoints. Therefore, the latest DCO for KRSTYAL-1 reporting both PFS and OS was used for the surrogacy analysis

to maintain the relationship between outcomes, which reflected the October 2021 DCO.

Figure 7 illustrates the KRYSTAL-1 OS from the October 2021 and January 2022, respectively, which highlights that OS is relatively consistent, and if anything might provide a more conservative estimate based on the October 2021 DCO, given the slight flattening of the tail in the January 2022 DCO beyond 15 months. Please note that analyses in response to question B4 further explores the impact of adjusting for differences in patient characteristics between KRYSTAL-1 and KRYSTAL-12 using both DCOs.

Figure 7: Overall survival in KRYSTAL-1, October 2021 and January 2022 DCOs

i. **Please clarify if the Kaplan-Meier OS data for KRYSTAL-1 shown in Figure 28, p114, CS) corresponds to the data reported in Figure 16 (p62, CS). If not, please clarify the source used and present an equivalent figure with numbers of patients at risk also included (as per Figure 16, p62, CS).**

Response: The data in Figure 28, p114, CS corresponds to the January 2022 DCO OS data for KRYSTAL-1 which is presented in Figure 16 (p62, CS), which reports numbers of patients at risk.

The figure below reports OS at the October 2021 DCO, based on a median follow-up of [redacted]. The median survival was [redacted].

Figure 8: Overall survival in KRYSTAL-1, October 2021 DCO

[redacted]

Baseline overall survival

B3. Please justify your choice of baseline OS curve in the economic model (i.e. informed by the simulated OS KRYSTAL-12 data for the docetaxel arm) and comment on why this was considered more appropriated than alternative data sources.

Response: OS in the docetaxel arm of the model was informed using the simulated KRYSTAL-12 data for several reasons. Firstly, the base case facilitates a consistent modelling approach for the within-trial comparison of adagrasib and docetaxel, with OS in both arms being informed by the simulated KRYSTAL-12 data. Secondly, these simulated data are predicted using the KRYSTAL-1 study (described in Section B.2.9.4 of the submission), meaning that the OS predictions are informed by patient-level data specific to the population relevant to the scope of this appraisal (i.e. a KRAS G12C mutation-specific population). As noted in our response to question B4, KRYSTAL-1 and KRYSTAL-12 are very similar in terms of including advanced NSCLC

patients with KRAS G12C mutations (non-squamous histology), pre-treated with immunotherapy and chemotherapy. Furthermore, the surrogacy approach leverages observed progression data from the docetaxel arm of KRYSTAL-12, and therefore maintains as much consistency as is feasible between the modelling of PFS and OS.

The plausibility of the long-term parametric survival curve projections based on the simulated docetaxel OS data in the model was validated with UK clinical experts, and methodological uncertainty around the base case approach was tested by exploring alternative sources of docetaxel OS (i.e. SELECT-1 pseudo-individual-level data, as presented in Table 72 of Document B and Section 3.2 of Appendix Q).

External overall survival data

B4. PRIORITY: Please provide an analysis whereby the KRYSTAL-1 OS observed data (most up to date data cut-off) is adjusted to match the KRYSTAL-12 population, using formal statistical methods (e.g., propensity score matching) and update the model to allow using the standard parametric curves fitted to the adjusted KRYSTAL-1 KM curve (equivalent to what is implemented in the original version of the model for the unadjusted KRYSTAL-1 OS).

Response: Overall, KRYSTAL-1 (N=116) and KRYSTAL-12 (N=301) are very similar in terms of including advanced NSCLC patients with KRAS G12C mutations (non-squamous histology) pretreated with immunotherapy and chemotherapy, who were treated with adagrasib and assessed in terms of PFS and OS (using consistent definitions). Patient characteristics were generally similar, with some differences identified in terms of country (US in KRYSTAL-1 and multinational in KRYSTAL-12) as well as the following patient characteristics: % male, ECOG PS, prior lines of therapy, race (Asian versus non-Asian).

As requested, an analysis has been conducted whereby the KRYSTAL-1 OS observed data (most up to date data cut-off) is adjusted to match the KRYSTAL-12 population using propensity score matching methods (inverse probability treatment weighting).

Weighted OS estimates for KRYSTAL-1, adjusting for age, gender, ECOG, and prior line of therapy given the KRYSTAL-12 target population, were similar to the unweighted OS KRYSTAL-1 estimates, with only a minor shift in the weighted

estimates (effective sample size [ESS]=[redacted]). A sensitivity analysis including race did not change the interpretation of results, although effective sample size was further reduced (ESS=[redacted]) due to more extreme weights for the small proportion of Asian patients in KRYSTAL-1 (4%) and this introduced an imbalance in age (Table 35).

Table 35: Key baseline characteristics before and after weighting

Patient characteristic		KRYSTAL-1	KRYSTAL-12	IPTW KRYSTAL-1	
ESS reduction (% of original size)		Adagrasib (N=116)	Adagrasib (N=301)	Base, ESS=[redacted]	Sensitivity, ESS=[redacted]
Age	≥65 years	49.1%	46.8%	[redacted]	[redacted]
Sex	Males	44.0%	64.1%	[redacted]	[redacted]
ECOG PS	1	84.5%[a]	68.1%	[redacted]	[redacted]
Number of prior LoTs	≥2	56.9%	38.5%	[redacted]	[redacted]
Race	Asian	4.3%	23.9%[b]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; LoT, lines of therapy.
Note: a) Data for one patient with missing ECOG data were imputed as ECOG PS 1; b) Data from 125 patients with missing race from Europe were imputed as non-Asian.

Weighted OS estimates for KRYSTAL-1 were consistent with the predicted OS in KRYSTAL-12 based on the individual-level surrogate analysis adjusted for ECOG status. Weighted OS estimates were similar between the KRYSTAL-1 DCOs. The additional follow-up available from KRYSTAL-1 January 2022 DCO suggests that OS estimates using the KRYSTAL-1 October 2021 DCO may be conservative, as the tail flattens out slightly beyond 12 months.

Kaplan-Meier curves are presented for the following IPTW scenarios (compared with unadjusted KRYSTAL-1 data and the simulated KRYSTAL-12 data from the surrogacy analysis):

- 4 covariates, K-1 Jan22 DCO (Figure 9) – *included in updated model*
- 5 covariates, K-1 Jan22 DCO (Figure 10)
- 4 covariates, K-1 Oct21 DCO (Figure 11)
- 5 covariates, K-1 Oct21 DCO (Figure 12)

Figure 9: OS – IPTW (4 covariates), KRYSTAL-1 Jan22 DCO – *included in updated model*

Abbreviations: DCO, data cut-off; IPTW, inverse probability treatment weighting; OS, overall survival

Figure 10: OS – IPTW (5 covariates), K-1 Jan22 DCO

Abbreviations: DCO, data cut-off; IPTW, inverse probability treatment weighting; OS, overall survival

Figure 11: OS – IPTW (4 covariates), K-1 Oct21 DCO

Abbreviations: DCO, data cut-off; IPTW, inverse probability treatment weighting; OS, overall survival

Figure 12: OS – IPTW (5 covariates), K-1 Oct21 DCO

Abbreviations: DCO, data cut-off; IPTW, inverse probability treatment weighting; OS, overall survival

It is believed that leveraging the relationship between TTP (or PFS) and OS from KRYSTAL-1 to inform OS KRYSTAL-12 predictions provides a more nuanced approach to integrate evidence from KRYSTAL-1, while relying on KRYSTAL-12 PFS to inform predictions. However, the standard parametric curves fitted to the weighted KRYSTAL-1 OS (latest data cut, adjusting for age, gender, ECOG, and prior line of therapy) have been incorporated into an updated version of the economic model. The impact on results is minimal, compared with using unadjusted KRYSTAL-1 data. These parametric curves can be explored using the following settings in the updated model:

- Worksheet 'CQ', Cell 'B4' – "Yes"
- Worksheet 'Clinical_data', Cell 'OSmodelling' – "Independent (within trial comparators)"
- Worksheet 'Clinical_data', Cell source_adagrasib_OS – "KRYSTAL-1"

B5. Please justify why the docetaxel arm of SELECT-1 was selected as the external data source to inform the OS of this treatment in scenario analyses and comment on why this was considered more appropriated than alternative data sources.

Response: SELECT-1 was selected as the external data source to inform scenario analysis for several reasons. Firstly, SELECT-1 was conducted in the target population relevant to this appraisal (in patients with previously treated advanced KRAS-mutant NSCLC) and was identified systematically, as reported in Appendix D of the CS. Secondly, SELECT-1 reported outcomes for the comparator and endpoint of interest for informing the model (docetaxel OS). Additionally, OS data from SELECT-1 are mature, with the Kaplan-Meier curve reaching the x-axis as seen in Appendix Q of the CS. Furthermore, SELECT-1 was also used to inform the prior NICE appraisal for sotorasib in previously treated KRAS G12C-mutated NSCLC (TA781). Although it is acknowledged that other clinical trials are available which assess docetaxel in previously treated KRAS G12C-mutated NSCLC (i.e. CodeBreaK200), as reported in response to clarification question A3, there were issues reported with the conduct and results of this trial.

Parametric models statistical goodness-of-fit scores

B5. Please report the sum of Akaike information criteria (AIC) by treatment arm for each parametric model fitted in the time-varying NMAs for PFS and OS (Tables 41 and 43 of CS.

Response: The AIC by treatment arm for each parametric model fitted to the PFS and OS data are provided in Table 36 and Table 37. The tables below include the treatments relevant to the UK, the full list of AIC values for the broader range of treatments in the global network can be seen in the 'TVNMADataStore' worksheet of the model.

Table 36: Goodness of fit measures for progression-free survival (AIC)

Trial and treatment arm	Weibull	Log-logistic	Gompertz	Log-normal	Gamma	Exponential
KRYSTAL-12 BMS 2023 PFS Adagrasib ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KRYSTAL-12 BMS 2023 PFS Docetaxel ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUME-Lung1 Reck 2014 PFS Docetaxel (ITT)	1,738.66	1,677.90	1,795.03	1,659.15	1,709.31	1,816.22
LUME-Lung1 Reck 2014 PFS Nintedanib + docetaxel (ITT)	1,711.15	1,699.07	1,757.87	1,694.51	1,697.70	1,796.00

Abbreviations: AIC, Akaike information criterion; ITT, intention-to-treat; PFS, progression-free survival.

Table 37: Goodness of fit measures for overall survival (AIC)

Trial and treatment arm	Weibull	Log-logistic	Gompertz	Log-normal	Gamma	Exponential
KRYSTAL-12 BMS 2023 OS Adagrasib ITT (simulated from KRYSTAL-1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KRYSTAL-12 BMS 2023 OS Docetaxel ITT (simulated from KRYSTAL-1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUME-Lung1 Reck 2014 OS Docetaxel (ITT)	4,015.72	3,975.38	4,034.01	3,984.61	4,004.65	4,032.30
LUME-Lung1 Reck 2014 OS Nintedanib + docetaxel (ITT)	4,153.44	4,140.29	4,164.93	4,173.88	4,148.10	4,163.61

Abbreviations: AIC, Akaike information criterion; ITT, intention to treat; OS, overall survival.

Health-related quality of life utility values

B6. PRIORITY: Health-related quality of life data from KRYSTAL-12.

a. Please provide details on numbers of participants providing EQ-5D scores by treatment arm for progression-free (PF) and progressed disease (PD), i.e., update Table 46, p121 of CS, to separate the numbers in the PF and PD health states by treatment arm.

Response: Details on the number of participants providing EQ-5D scores by treatment arm and progression status are presented in Table 38.

Table 38: Descriptive EQ-5D scores by health state and by intervention

	Study: KRYSTAL-12					
EQ-5D utility score	**Progression-free**			**Progression**		
	Adagrasib	**Docetaxel**	**Total**	**Adagrasib**	**Docetaxel**	**Total**
Number of participants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of questionnaires	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Questionnaires per participant**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

** Rounded to the nearest integer
Abbreviations: EQ-5D: EuroQol Group 5-Dimensional, SD: Standard Deviation.

b. Please provide histograms of utility values in KRYSTAL-12 by progression status and treatment arm (i.e., for PF on docetaxel, PF on adagrasib, PD on docetaxel and PD on adagrasib).

Figure 13: Histogram EQ-5D scores for adagrasib arm when health state is progression-free

[redacted]

Figure 14: Histogram EQ-5D scores for docetaxel arm when health state is progression-free

Figure 15: Histogram EQ-5D scores for adagrasib arm when health state is progressed disease

Figure 16: Histogram EQ-5D scores for docetaxel arm when health state is progressed disease

c. Please clarify how the number of participants providing PD utility scores was derived in Table 46 if only [redacted] (footnote to Table 46, p121).

Response: Table 38 shows the number of participants that have observations in progression-free and in progression during the trial. A total of [redacted] patients transitioned from progression-free to progression. For [redacted] patients, data for the progression-free state are missing, and only observations in the progression state are available. In total, [redacted] patients reported observations in the progression state.

d. Please clarify whether missing EQ-5D-5L data were imputed and, if appropriate, please provide details on the methods used.

Response: No imputation was performed. EQ-5D-5L index scores cannot be calculated if any of the 5 items on the EQ-5D-5L instrument are missing.

e. Please justify the use of a differential utility value in the PD health state for adagrasib vs. docetaxel considering the PFS-2 data, which was similar between the two treatment arms (Figure 10 of CSR, p133), and the lack of a

statistically significant interaction term for progression status and treatment arm in the model (Table 48 of CS, p123).

Response: Using treatment-specific utilities captures the HRQoL associated with each treatment. In contrast, pooling or averaging these values across treatments may mask the variation in HRQoL, leading to potential underestimation of the benefits associated with adagrasib. While the interaction term for progression status and treatment arm (progression status * treatment arm) is not statistically significant (P = [redacted]), this does not undermine the significance of the treatment arm's main effect. The non-significance of the interaction term suggests that the relative benefit of adagrasib over docetaxel does not vary substantially between progression-free and progressed health states. In other words, the treatment effect, as captured by the main effect, remains consistent and robust across different progression states.

Therefore, the main effect of treatment arm alongside the utility differences observed between arms justifies the use of different utilities for each treatment arm in the PD and PFS health states.

f. Please update the mixed model for repeated measures (MMRM) by removing the non-statistically significant interaction term for progression status and treatment arm and provide the corresponding estimates for the coefficients in Table 48.

Response: Please find the requested estimates in Table 39, and the corresponding variance-covariance matrix in Table 40.

Table 39: MMRM model (progression status and treatment arm, no interaction term)

Variable name	Estimate	Std. Error	P value	95% CI lower bound	95% CI upper bound
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (PFS=1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm (Adagrasib=1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error

Table 40: Variance-Covariance matrix (progression status and treatment arm, no interaction term)

	Intercept	Progression status	Treatment arm	Age	Gender

Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm					
Age					
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

g. Please provide a revised version of the electronic model incorporating the updated estimates of utility without the non-statistically significant interaction term, with sufficient flexibility to switch between alternative estimates of PD utility values. Please signpost the changes made to the model.

Response: A revised version of the electronic model has been provided, which incorporates the utility model without the non-statistically significant interaction term presented in Table 39. The user can choose between the utility model from the CS base case (Model 1) and the utility model without the interaction term (Model 2) using the switch in Sheet 'CQ', Cell M6. The impact of cost-effectiveness results is relatively small. The regression models and variance-covariance matrices for the CS base case (Model 1) and scenario with interaction term (Model 2) have also been included in the model on the 'CQ_utility' sheet. Furthermore, alternative estimates of PD utility values can be tested directly on the 'Utility' sheet, Cells H15:H18.

h. Please clarify how uncertainty was captured in the estimates of utility values used in the model. If not already included, please incorporate uncertainty in the regression outputs through the variance-covariance matrices.

Response: In the original CS, uncertainty around state health utility values was captured using an assumed standard error. In response to this question, a revised version of the model has been submitted incorporating the regression outputs and variance-covariance matrices, allowing uncertainty to be captured in probabilistic sensitivity analysis using a multivariate normal distribution (see Sheet 'CQ_utility'). The regression models and variance-covariance matrices for the CS base case (Model 1) and scenario with interaction term (Model 2) have been included in the model on the 'CQ_utility' sheet. The probabilistic sensitivity analysis around the company base case has been re-run in response to this question (see Appendix). Furthermore, as parameters with joint uncertainty are not included in the OWSA (i.e., utility models in

the revised cost-effectiveness model), the OWSA has also been re-run (see Appendix).

i. **Please justify the use of treatment-specific utility values by health state, based on limited comparative data from one trial. Please discuss the reasons for the higher utility value for adagrasib compared to docetaxel for the same PF health state.**

Response: Given that the data are derived from a single randomised controlled trial, we estimate treatment-specific utilities to capture the nuances of the patient experience with each treatment whilst controlling for numerous patient characteristics. Pooling or averaging these values across treatments may mask important differences in HRQoL.

Therefore, utilities account for the distinct effects treatments may have on patient's quality of life. The higher utility values observed for adagrasib compared to docetaxel in both progression-free (PF) and progression (PD) health states (difference of [redacted] in each) likely reflect differences in patients' HRQoL. This uncertainty is captured within the probabilistic analysis within the cost-effectiveness model.

j. **Please comment on how the magnitude of the decrement in utility for PD relative to PF for adagrasib from KRYSTAL-12 ([redacted]) compares to the corresponding decrement associated with the PD health state from different external sources (e.g., that used in previous NICE TAs, including TA781), and explain the reasons for the difference.**

Response: In KRYSTAL-12, the decrement in utility for progression (PD) relative to progression-free (PF) for adagrasib is [redacted] ([redacted] − [redacted]). By contrast, the decrement associated with progression in TA781/CodeBreaK100 is 0.084 (0.739 − 0.655). This indicates that the decline in HRQoL when patients move from progression-free to progression is [redacted] in KRYSTAL-12 compared to TA781/CodeBreaK100. Various factors may explain this difference:

- Different value set: TA781/CodeBreaK100 utilised the Van Hout value set, whereas KRYSTAL-12 applied the Hernandez-Alava value set. Differences in the utility weights can lead to variations in the observed decrements.

- Different trial design: TA781/CodeBreaK100 is a single-arm trial. Therefore, there is no direct comparative data available on the health quality of life associated with sotorasib versus relevant comparators. However, we present the comparative analysis reported in KRYSTAL-12, an open-label, randomised (2:1) clinical trial. The presence of a comparator arm shows that differences in health state utilities may be partially driven by the treatment received.

- Different HRQoL at baseline. Patients in K-12 and CodeBreak100 may have different HRQoL at baseline or different disease progression leading to differences in the overall utility decrement estimates. This is evidenced by the number of people reporting “no problems” or “slight problems” at baseline in any of the EQ-5D dimensions in our study (85.15% and 71.22%, respectively) in comparison with the CodeBreak 100 trial (68% and 94%).

k. Please comment on whether the EQ-5D data from KRYSTAL-12 was sufficient to capture the impact of treatment-related adverse events of Grade 3+ with an incidence of less than 5% and Grade 2 and below.

Response: It is acknowledged that the recall period of the EQ-5D refers to “today”, however treatment-related AEs, such as nausea or diarrhoea, may be acute or temporary. Since the EQ-5D is administered at set intervals these may miss short-term fluctuations, particularly if assessments occur between AE episodes. The limitations above may hinder the EQ-5D’s ability to capture mild and acute events in particular. However, it is expected that these would have a low impact on cost-effectiveness outcomes, given the components of the QALY model (i.e., quality of life and duration of life) and model drivers.

B7. PRIORITY: Please comment on the appropriateness of the assumption of the same utility values for docetaxel plus nintedanib and docetaxel monotherapy (footnote to Table 50 of CS, p125) considering the different response rates for combination therapy of docetaxel plus nintedanib.

Response: In the absence of nintedanib-specific health-related quality of life data, it was necessary to make an assumption regarding the approach to modelling health state utility values in the nintedanib plus docetaxel arm of the cost-effectiveness analysis. It is considered that KRYSTAL-12 data used in the model provides the best understanding of HRQoL for the population considered within this appraisal. Assuming

equivalent utility values to docetaxel monotherapy was considered the most suitable approach for several reasons. Firstly, whether as combination or monotherapy, patients must still receive the docetaxel component and therefore receive a non-targeted intravenously administered chemotherapy in a hospital setting, which may be more burdensome for patients compared with solely receiving an oral therapy at home. Furthermore, in TA781, the company reported that UK clinical experts verified that a treatment-specific disutility for both docetaxel and nintedanib plus docetaxel would be appropriate to capture in the base-case analysis (rather than solely applying a decrement in the docetaxel monotherapy arm).

Time to treatment discontinuation

B8. Please comment on [redacted] (Figure 34 of CS, p129) and report the area under the curve between the TTD and PFS KM for adagrasib.

It should be noted that Figure 34 of CS compares TTD with PFS as assessed by BICR. However, the observed difference between TTD and PFS is negligible in the adagrasib arm if the investigator PFS endpoint is used (rather than BICR per the CS), as shown in Figure 17 below. Therefore, it is anticipated that [redacted] is largely an artefact of differences in assessment or timing between PFS-INV and PFS-BICR, and these are the likely cause of the slight difference between the TTD and PFS curves. When using the PFS-INV outcome, the two curves associated with adagrasib are effectively overlapping after the initial separation and convergence at 5 months, and the estimated HRs between them are [redacted] and [redacted] for adagrasib and docetaxel, respectively.

Figure 17: TTD vs PFS-INV, KRYSTAL-12

Abbreviations: PFS, progression-free survival; TTD, time-to-treatment discontinuation

B9. Please revise the model to allow the performance of a scenario analysis whereby TTD for adagrasib and docetaxel in the model is informed directly by TTD in KRYSTAL-12 and clarify whether the company is proposing to restrict the use of adagrasib to patients who have not undergone radiographic progression free disease.

As described in response to clarification question B8, treatment beyond progression with adagrasib would not occur in NHS clinical practice. This is consistent with duration of treatment in the summary of product characteristics, which states that treatment is recommended until disease progression or unacceptable toxicity.

Therefore, the model has been revised to include the functionality to model TTD using parametric curves fitted to KRYSTAL-12 data (see Worksheets 'CQ' and 'CQ_TTD'); however, TTD is capped at PFS in this scenario. This is to reflect anticipated use of adagrasib in NHS England practice.

Adverse events

B10: Please comment on whether a washout period from prior immunotherapy for patients who initiate adagrasib is required to manage the risk of hepatotoxicity. If so, please provide details.

Response: A washout period following prior immunotherapy is not specified in the summary of product characteristics for adagrasib. Aligned to this, in the KRYSTAL-12 protocol, no washout period was required between prior anti-PD-(L)1 therapy and study treatment.

In a post-hoc analysis of KRYSTAL-1 data, [redacted] ([redacted]) patients who received immunotherapy within 30 days of adagrasib had Grade ≥3 hepatotoxicity.[33]

Further, adagrasib is being combined with immunotherapy (pembrolizumab) in the KRYSTAL-7 and KRYSTAL-17 trials which are currently underway, which demonstrates that it is feasible to combine these therapies (i.e., demonstrating a washout period is not required). Note that KRYSTAL-7 and KRYSTAL-17 are trials investigating the use of adagrasib in advanced NSCLC.

B11. Please comment on whether additional monitoring is required for adagrasib for hepatoxicity and whether this is required in the model. If this is not reflected in the model, please justify and provide a revised version of the model which includes any additional monitoring costs for hepatotoxicity with adagrasib, and signpost the changes made to the model.

Response: For completeness, a revised version of the model including treatment-specific monitoring costs has been provided. Unit costs and treatment-specific monitoring frequencies are presented on a new 'CQ_mon' worksheet in the model.

The treatment monitoring requirements are based on the corresponding summary of product characteristics for intervention and comparators treatments (Table 41). The unit costs for liver function test and proteinuria test (£2.06) and complete blood count (£1.86) are sourced from the NHS National Cost Collection 2022/24 (Code DAPS04 and DAPS03). It should be noted that the impact of including treatment-specific monitoring on cost-effectiveness results is relatively small (Table 42).

Table 41: Treatment specific monitoring (summary of product characteristics)

Treatment	Monitoring resource use	Total weekly cost
Adagrasib	Liver test prior to the start of treatment and monthly for 3 months or as clinically indicated	£0.64 (up to 3 months) £0.00 (after 3 months)
Docetaxel	Complete blood count test prior to each dose (every 3 weeks)	£0.62
Nintedanib plus docetaxel	Complete blood count, liver test, renal test prior to each dose (every 3 weeks)	£1.99

Table 42: Cost-effectiveness results including treatment-specific monitoring

Adagrasib versus	ICER (original CS base case)	ICER (treatment monitoring scenario)	Change from base case
Docetaxel	£29,107	£29,102	-£5
Docetaxel plus nintedanib	£413	£323	-£90

B12. Please comment on whether additional monitoring costs for adagrasib are required to monitor other adverse events not included in the model such as an increased risk of arrhythmias, risk of interstitial lung disease or pneumonitis, severe gastrointestinal (including diarrhoea, nausea, and vomiting) and cutaneous adverse reactions (including Steven-Johnson syndrome and toxic epidermal necrolysis). If considered relevant, please provide a revised version of the model to include additional monitoring costs for adagrasib, and signpost the changes made to the model.

Response: Additional monitoring costs for adagrasib are not expected.

Cost-effectiveness results

B13. Please update the cost-effectiveness model so that it simultaneously outputs the fully incremental and pairwise cost-effectiveness results for the treatments under comparison.

Response: As discussed in NICE clarification call (2 December 2024), and agreed with EAG, we have not updated the core results sheet in the CEM, however the fully incremental and pairwise cost-effectiveness results are both available in the QALY shortfall sheet. Note that we have updated the model to also include probabilistic fully incremental results on the PSA sheet.

Section C: Textual clarification and additional points

Literature searches

C1. Several search strategies were missing. For the clinical evidence searches in Appendix D, search strategies were not provided for conference proceedings or clinical trial registries. For the cost-effectiveness studies in Appendix G, search strategies were not provided for conference proceedings or health technology assessment agency websites. For the health-related quality of life studies in Appendix H, search strategies were not provided for conference proceedings or health technology assessment agency websites. Please provide these strategies.

Response: For each of the clinical, cost-effectiveness, and HRQoL components, conference proceedings were searched during the main electronic database searches as Embase indexed the conferences of interest, and thus no separate search was required.

For the clinical evidence, search strategies for clinical trial registries are provided in Table 43.

Table 43: Search strategy for clinical trials registry databases | Clinical SLR

Search executed: 2 July 2024			
Website	**Search String**	**Hits**	**Included**
http://clinicaltrials.gov	Non-small cell lung cancer and second-line	686	0
https://www.clinicaltrialsregister.eu/	Non-small cell lung cancer and second-line	104	0
https://www.who.int/clinical-trials-registry-platform	Non-small cell lung cancer and second-line	326	0

Abbreviations: SLR, systematic literature review.

For the cost-effectiveness evidence, search strategies for HTA agency websites are provided in Table 44.

Table 44: Search strategy for HTA websites | Economic evaluations SLR

Search executed: 2 July 2024			
Website	**Search String**	**Hits**	**Included**
NICE	Non-small cell lung cancer and second-line	59	1
AWMSG	Non-small cell lung cancer and second-line	306	0
CDA	Non-small cell lung cancer	69	0
ICER	Non-small cell lung cancer	1	0
PBAC	Non-small cell lung cancer	35	0
SMC	Non-small cell lung cancer	85	0
IQWiG	Non-small cell lung cancer	81	0
TLV	Lung cancer	13	0
HAS	Non-small cell lung cancer	69	0

Abbreviations: AWSMG, All Wales Medicines Strategy Group; CDA, Canada's Drug Agency; HTA, health technology assessment; ICER, US Institute for Clinical and Economic Review; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Health for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium; TLV, Dental and Pharmaceutical Benefits Agency of Sweden.

For the health-related quality of life evidence, search strategies for HTA agency websites are provided in Table 45.

Table 45: Search strategy for HTA websites | HRQoL SLR

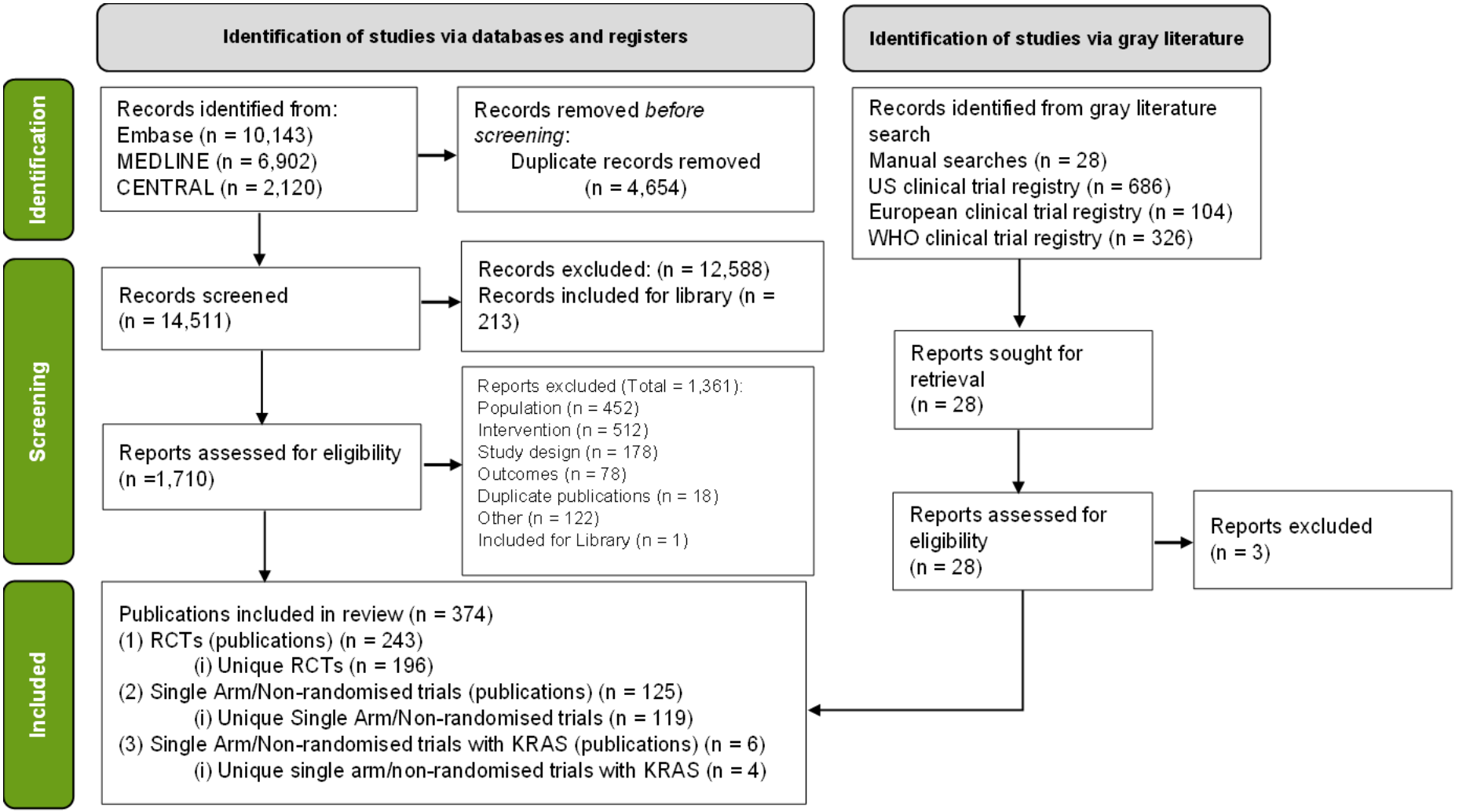
Search executed: 2 July 2024			
Website	**Search String**	**Hits**	**Included**
NICE	Non-small cell lung cancer and second-line	59	0
CDA	Non-small cell lung cancer	69	0
ICER	Non-small cell lung cancer	1	0
PBAC	Non-small cell lung cancer	35	0
SMC	Non-small cell lung cancer	85	0
IQWiG	Non-small cell lung cancer	81	0
TLV	Lung cancer	13	0
HAS	Non-small cell lung cancer	69	0

Abbreviations: CDA, Canada's Drug Agency; HRQoL, health-related quality of life; HTA, health technology assessment; ICER, US Institute for Clinical and Economic Review; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Health for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium; TLV, Dental and Pharmaceutical Benefits Agency of Sweden.

C2. In the Company Submission, Appendix D, clinical evidence searches, the grey literature searches do not show the hits per source in the PRISMA diagram. Please provide an updated PRISMA diagram.

Response: The updated PRISMA diagram is provided below with number of hits for each clinical trial registry searched (Figure 18).

Figure 18: PRISMA flow diagram | Clinical SLR



Abbreviations: KRAS, Kirsten rat sarcoma viral oncogene homologue; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review; US, United States; WHO, World Health Organization.

C3. In the Company Submission, Appendix D, clinical evidence searches, no dedicated health technology assessment or systematic review databases were searched. Please discuss whether any relevant evidence may have been missed as a result.

Response: For the clinical evidence, search strategies were only conducted for the main electronic databases (MEDLINE®, Embase, and Cochrane Controlled Register of Trials) and for the clinical trial registries in Table 43.

Systematic literature reviews identified by the main electronic databases or hand-searching were included and checked for any missed studies by performing bibliography checks.

There were no dedicated searches specifically for HTA as at the time of the literature searches only one other therapy (sotorasib) was approved by NICE for treating *KRAS* G12C mutation-positive locally advanced or metastatic NSCLC in adults whose disease has progressed on, or who could not tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy.

C4. Please provide the full list of all relevant interventions and comparators included in the clinical evidence searches.

Response: Interventions included in the clinical evidence searches are as follows:

1. Adagrasib
2. Afatinib
3. Aflibercept
4. Alectinib
5. Amivantamab
6. Atezolizumab
7. Bevacizumab
8. Brigatinib
9. Ceritinib
10. Cisplatin
11. Carboplatin
12. Crizotinib
13. Dabrafenib
14. Dacomitinib
15. Docetaxel
16. Durvalumab
17. Erlotinib
18. Etoposide
19. Gefitinib
20. Gemcitabine
21. Ipilimumab

22. Lorlatinib
23. Luminespib
24. Mobocertinib
25. Nintedanib
26. Nivolumab
27. Osimertinib
28. Paclitaxel
29. Pembrolizumab
30. Pemetrexed
31. Poziotinib
32. Pralsetinib
33. Ramucirumab
34. Selpercatinib
35. Sotorasib
36. Tarloxotinib
37. Tepotinib
38. Trametinib
39. Trastuzumab
40. Taxanes
41. Vinorelbine

C5. For the clinical evidence searches in Appendix D; the cost-effectiveness studies in Appendix G; and the health-related quality of life studies in Appendix H, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For the population terms, there was no hyphenation of 'non-small-cell' or 'non-small cell' and the terms for cancer could have been more sensitive (e.g., including tumor* and tumour*). There are also several types of non-small cell lung cancer which were not searched for: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma, adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, salivary gland carcinoma, carcinoid tumour, and unclassified carcinoma. Moreover, the concept of metastasis could have been expanded to include terms for mutation, progressive disease, or previously treated, etc. Please clarify if any relevant evidence may have been missed as a result.

Response: Since the target therapeutic area of interest was NSCLC as a disease group, it was decided that including search terms for specific forms of NSCLC would not be required in order to identify all relevant evidence. In addition, the search strategies were aimed to be sensitive and did include search terms for stage 3, stage 4, advanced, and metastatic disease and hence did not restrict the evidence based on mutation or previous treatment; thus, the inclusion of these types of search terms was not deemed necessary.

On 5 December 2024, clinical evidence searches were repeated using the additional population terms 'non-small-cell', 'non-small cell', tumor*, and tumour* with date limiters to exclude studies published after the original searches conducted on 2 July 2024. The expanded searches resulted in 280 additional records across the three databases (Table 46). The 280 records were screened according to the PICOS inclusion criteria, and no additional records were found to be relevant for inclusion.

Table 46: Population terms | Clinical search results

Database	Original search (2 July 2024) - Hits	Expanded search terms (2 July 2024)* - Hits	Number of additional studies
Embase	10,143	10,340	197
Ovid MEDLINE® ALL	6,902	6,916	14
EBM Reviews - Cochrane Central Register of Controlled Trials	2,120	2,189	69

*Searches conducted on 5 December 2024 with date limiters to exclude studies published after the original searches conducted on 2 July 2024.
Abbreviations: EBM, evidence-based medicine.

Economic evidence searches were repeated using the same additional population terms and the same date limiters as described for the clinical searches. The expanded searches resulted in 743 additional records across the four databases (Table 47). The 743 records were screened according to the PICOS inclusion criteria, and no additional records were found to be relevant for inclusion.

Table 47: Population terms | Economic and HCRU search results

Database	Original search (2 July 2024) - Hits	Expanded search terms (2 July 2024)* - Hits	Number of additional studies
Embase	7,587	8,325	738
Ovid MEDLINE® ALL	2,334	2,339	5
EconLit	23	23	-
NHS EED	122	122	-

*Searches conducted on 5 December 2024 with date limiters to exclude studies published after the original searches conducted on 2 July 2024.
Abbreviations: HCRU, healthcare resource utilisation; NHS EED, National Health Service Economic Evaluation Database.

Quality of life evidence searches were also repeated using the same additional population terms and the same date limiters. The expanded searches resulted in 531 additional records across the three databases (Table 48). The 531 records were screened according to the PICOS inclusion criteria, and no additional records were found to be relevant for inclusion.

Table 48: Population terms | HRQoL search results

Database	Original search (2 July 2024) - Hits	Expanded search terms (2 July 2024)* - Hits	Number of additional studies
Embase	11,559	11,977	418
Ovid MEDLINE® ALL	2,363	2,366	3
EBM Reviews - Cochrane Central Register of Controlled Trials	3,005	3,115	110

*Searches conducted on 5 December 2024 with date limiters to exclude studies published after the original searches conducted on 2 July 2024.
Abbreviations: EBM, evidence-based medicine; HRQoL, health-related quality of life.

C6. For the clinical evidence searches in Appendix D, reviews were removed as a publication type. Please clarify why and whether any relevant evidence was missed as a result.

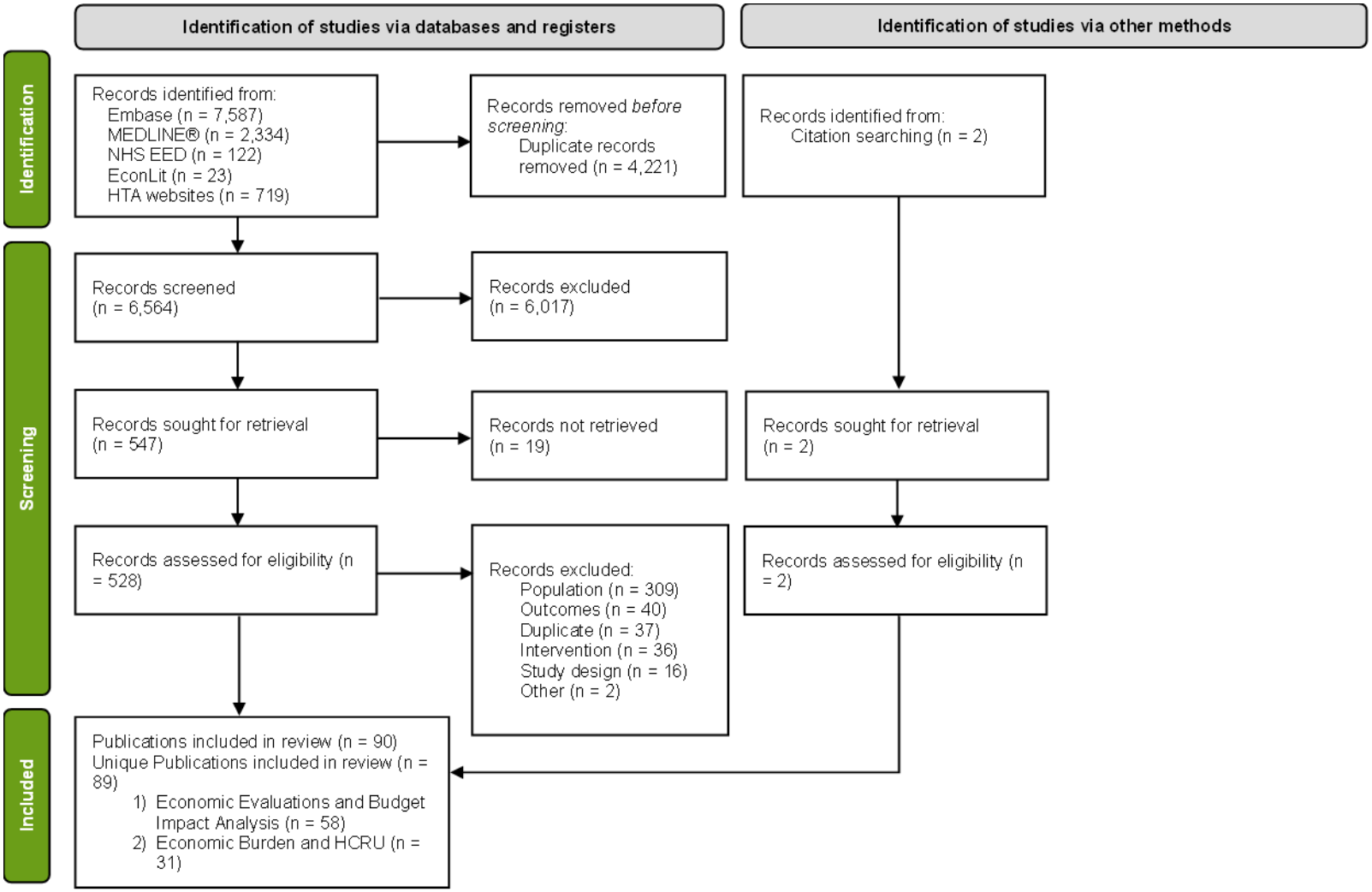
Response: For the clinical evidence, only narrative reviews were excluded based on study design; however, systematic literature reviews were included and checked for any missed studies by performing bibliography checks. We do not anticipate that any relevant information would have been excluded based on exclusion of narrative reviews.

C7. For the cost-effectiveness studies in Appendix G, HTA websites is included in multiple places in the PRISMA diagram with different numbers of results (under both 'databases and registers' and 'other methods'). Moreover, conference abstracts are not shown in the PRISMA diagram. Please provide a clearer and more detailed PRISMA diagram.

Response: The updated PRISMA diagram is provided below with number of hits for HTA websites consolidated (Figure 19).

For the cost-effectiveness evidence, conference proceedings were searched during the main electronic database searches as Embase indexed the conferences of interest, and thus no separate search was required.

Figure 19: PRISMA flow diagram | Economic SLR



Abbreviations: HCRU, healthcare resource utilisation; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Appendix

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) was re-run in response to Question B6h, where the utility regression variance-covariance matrix is included in the cost-effectiveness model and the utility model parameters were jointly varied during PSA using a multinormal distribution. Mean probabilistic results are presented in Table 49. PSA results are recorded over 1,000 iterations within the economic model, in line with results presented in Document B.

An updated cost-effectiveness acceptability curve for adagrasib versus docetaxel and docetaxel + nintedanib is presented in Figure 20. Figure 21 and Figure 22 show the updated pairwise cost-effectiveness planes of the incremental costs and QALYs for both adagrasib versus docetaxel and docetaxel + nintedanib, respectively.

Table 49: Re-run base-case results (full incremental analysis), probabilistic

Technologies	Total costs (£)	Total LYG	Total QALYs (x1.7)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental analysis (£/QALY)
Docetaxel	[redacted]	[redacted]	[redacted]				
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,590

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 20: Cost-effectiveness acceptability curve using re-run probabilistic results

Abbreviations: WTP, willingness-to-pay

Figure 21: Cost-effectiveness plane showing 1,000 re-run PSA iterations of incremental results for adagrasib vs docetaxel

Abbreviations: QALYs, quality-adjusted life years; PSA, probabilistic sensitivity analysis

Figure 22: Cost-effectiveness plane showing 1,000 re-run PSA iterations of incremental results for adagrasib vs docetaxel + nintedanib

Abbreviations: QALYs, quality-adjusted life years; PSA, probabilistic sensitivity analysis

One-way sensitivity analysis

The OWSA was re-run in response to Question B6h. Correlated inputs with joint uncertainty are excluded from OWSA. Since the regression model is now included directly in the cost-effectiveness model, these values exhibit joint uncertainty and are therefore excluded from the OWSA.

The re-run pairwise OWSA results (using the INMB as the outcome measure) are presented in turn below for docetaxel and docetaxel + nintedanib in Figure 23 and Figure 24, respectively.

Figure 23: Tornado diagram showing re-run OWSA results for adagrasib versus docetaxel (INMB)

Abbreviations: INMB, incremental net monetary benefit; OWSA, one-way sensitivity analysis.
Note: Results are presented for a WTP threshold of £30,000. QALYs include a x1.7 severity modifier throughout these results. Parameters with joint uncertainty are excluded from analysis.

Figure 24: Tornado diagram showing re-run OWSA results for adagrasib versus docetaxel + nintedanib (INMB)

Abbreviations: INMB, incremental net monetary benefit; OWSA, one-way sensitivity analysis.

Note: Results are presented for a WTP threshold of £30,000. QALYs include a x1.7 severity modifier throughout these results. Parameters with joint uncertainty are excluded from analysis.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1820 Advisory board Honoraria) - Roche (1 year funding of GLCC project; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Novocure (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £500 for Meeting Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)

If so, please state the name of the company, amount, and purpose of funding.	- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker honorarium) - Regeneron (£30,000 for 1 year funding of GLCC project) - Gilead (£30,000 for 1 year funding of GLCC project; £460 speaker honorarium) - Merck (£30,000 for 1 year funding of GLCC project) - J &J (£20,000 for Lung Cancer Awareness Month initiative)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	none
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lung cancer symptoms, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. Around 13% of patients with non small cell lung cancer (nsclc) have the KRAS G12C mutation. This mutation, historically, has been indicative of poor prognosis.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	We note that in March 2022, Sotorasib was approved by NICE for people with previously treated KRAS G12 mutation positive advanced nsclc [TA781]. Such patients would have progressed on platinum based chemotherapy and/or immunotherapy. There are no studies directly comparing Sotorasib and Adagrasib in this setting. Both drugs are taken orally.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publicly available. We note, however, the updated results of the KRYSTAL-1 study, published in the Journal of Thoracic Oncology in September 2023. In the two year pooled analysis, median progression free survival was 6.9 months and the median overall survival was 14.1 months. Notably, 52.8% of patients were still alive at one year and 31.3% at two years. Adagrasib has been found to penetrate the central nervous system and as such, could slow down the growth of cancer cells in the brain.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Side effects of the treatment. We note that in the KRYSTAL-1 study, treatment related adverse events were noted in 97.4% of patients – Grade 1 and 2 in 52.6%; Grade 3 or higher in 55.8% (including two treatment related deaths) and resulting in drug discontinuation in 6.9% of patients. The most common side effects associated with Adagrasib include diarrhea, nausea, fatigue, vomiting, anaemia, dyspnoea, increased blood creatinine levels, loss of appetite. Abnormal liver function tests and cardiac toxicity (QT prolongation) are also associated with this treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• KRAS G12 mutated lung cancer is associated with poor prognosis • Adagrasib has been shown to have activity in this patient group and provides an additional treatment option for KRAS G12C mutation positive nsclc. • Adagrasib has been shown to have intracranial activity in patients with KRAS G12C mutated nsclc and untreated brain metastasis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Professional Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	Lung Cancer Specialist Nurse
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stop further progression of disease, improve functional status, improve quality of life, improve symptoms
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of disease burden, no further progression of disease following commencement of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, lung cancer remains difficult to treat. All avenues of second line treatments should be explored to improve patient survival.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Sotorasib for second line treatment.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance 781

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, in my experience pathway is well defined and oncologists follow the pathway.
9c. What impact would the technology have on the current pathway of care?	Additional form of second line treatment available to give wider treatment options to patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, I believe it will.
10a. How does healthcare resource use differ between the technology and current care?	Could be incorporated into current care
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary care, specialist oncology clinic.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients.
11. Do you expect the technology to provide clinically meaningful	Yes/

benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This may depend on performance status and comorbidities and then interactions of Adagrasib with other medications being taken.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Should be equivalent to current care. Side effect profile will need to be considered – GI adverse interactions – dose interruption or dose reduction in approx. 30% of patients Prolonged QTC interval – need to consider regular ECG monitoring and clinical history Liver monitoring due to hepatotoxicity Pneumonitis – consider need for treatment and how this can impact patient / local services.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Will need biopsy to be KRAS G12C tested and positive.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, hopefully will give further treatment options to patients.
16a. Is the technology a 'step-change' in the management of the condition?	It is alongside current second line treatment but provides an alternative.
16b. Does the use of the technology address any particular unmet need of the patient population?	Ensure alternative for the treatment of KRAS mutation positive lung cancer

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Potential for GI side effects which would affect quality of life and will need monitoring and treatment. Liver monitoring, cardiac monitoring, pneumonitis. May all impact quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Quality of life and life expectancy Progression free survival measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA781]?	no
21. How do data on real-world experience compare with the trial data?	Unable to find data from real world experience

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Good data to support use of Adagrasib in the defined population • Side effect profile significant • Infrastructure to support additional monitoring must be considered • Patients quality of life should be measured / recorded •

Thank you for your time.

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Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Clinical expert statement

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The deadline for your response is **5pm** on **24 February 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating KRAS G12C mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jason Adhikaree
2. Name of organisation	British Thoracic Oncology Society / University of Nottingham
3. Job title or position	Clinical Associate Professor and Honorary Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for KRAS G12C mutation-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for KRAS G12C mutation-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prevent progression of cancer and reduce or prevent symptom deterioration from cancer.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A progression free survival advantage of over 1 month can be clinically significant particularly in context of objective response and symptom improvement.
10. In your view, is there an unmet need for patients and healthcare professionals in KRAS G12C mutation-positive advanced non-small-cell lung cancer?	Yes, there are no NICE approved drugs targeting this mutation. There is a competitor (Sotorasib) available on CDF. For most patients there only exist 2 lines of treatment (Platinum chemotherapy with immunotherapy) and Doectaxel. Therefore additional treatment options are a high unmet need.
11. How is KRAS G12C mutation-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients will either receive 1st line Platinum-based chemotherapy with immunotherapy, or immunotherapy single agent as per NICE guidelines based mainly on PDL1 expression, performance status and co-morbidities. Those with poor performance status may receive chemotherapy doublet only. On progression of 1st line agents KRAS G12C inhibitor therapy can be considered. If a patient has 1st line single agent anti-PD1/PDL1, then platinum doublet may be used prior to KRAS G12C. The KRAS inhibitor comparison agent is Docetaxel+/-Nintedanib. This would be the first KRAS G12C specific inhibitor NICE approved and second in class available to clinicians. This is a vital step forward for personalised medicine.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The use will mainly compete with Sotorasib which is the main competitor for KRAS G12C mutations. This should be a specialist prescription only. Routine testing of KRAS G12C should be occurring in every hospital. Continued investment in timely roll out into next generation sequence at genomic hubs is required to ensure these treatments are available to all patients.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes published phase II single arm data showed objective response rates of 43% and duration of response over 8 months. The randomised phase III trial, primary analysis shows a statistically increased progression free survival advantage over docetaxel. The overall survival data is not published. Data of symptoms deterioration and health related quality of life suggested presented at World Conference of Lung Cancer 2024 that Adagrasib was superior to Docetaxel
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is only effective for those patients whom have KRAS G12C mutation. There is trial biomarker research suggesting patients with co-existing KEAP1 mutation perform less well, but this is not tested in routine practice. Whether the later group respond better to alternate treatments is unknown currently.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This technology will be easier to manage compared to intravenous chemotherapy since the patient will be taking the treatment at home therefore freeing up chemotherapy unit capacity. Most adverse events occur is first 3 months hence close monitoring in outpatient clinics will be required initially comparable to most small molecular inhibitors in routine clinical practice for cancer.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are no additional rules outside the licencing indication to be considered

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This treatment is more easy to administer for both healthcare systems and patients with it being an oral treatment compared to intravenous chemotherapy. There is also an unmet need in patients whom only have 2 lines of treatment for a terminal diagnosis.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a step-change technology alongside Sotorasib on the CDF. The KRAS mutations were seen as undruggable and this novel approach of targeting KRAS has reinvigorated drug development in this area. There is a high unmet need since there are no NICE approved KRAS inhibitors and limited treatment options with SACT for lung cancer.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are deemed manageable to Oncological practice and include diarrhoea, fatigue, changes in liver function and less commonly inflammation on the lung. These are manageable to sustain a patient's quality of life. Some of the side effects are residual effects of prior immunotherapy treatment and therefore toxicity algorithms in clinical trials are recognising this.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, the clinical trials include post immunotherapy and platinum chemotherapy patients as would be the UK practice. KRAS G12C mutations is prevalent in the UK population matching worldwide prevalence. The significant outcomes are objective response, progression free survival and maintenance in quality of life, being measure in the phase 3 trial. There are no adverse events not captured in the published data, but management guidelines for adverse events are reflecting prior immunotherapy exposure and use of steroids where appropriate.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The latest trial data from Krystal-12, a randomised, phase 3 trial was presented at ASCO2024 and WCLC2024 and published in supplementary oral presentations in the conference associated journals. Prior phase 2 single arm data is published.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 781 [TA781]?	No other comparators than Docetaxel+/-Nintedanib and CDF Sotorasib
23. How do data on real-world experience compare with the trial data?	Real-world published data suggest similar experience to published data. The UK experience is restricted to clinical trials since this drug is not available on CDF.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	There are no populations disadvantaged by this technology and KRAS mutations are seen in all treatment groups. It is the most prevalent targetable mutation in a UK cohort.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Step-change in treatment option by targeting first generation of KRAS G12C

Improvement in progression free survival compared to Docetaxel

Improves Quality of life compared to Docetaxel

Objective response rates seen in approximately 40% of patients

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Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Clinical expert statement

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Part 1: Treating KRAS G12C mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Shobhit Baijal
2. Name of organisation	University Hospitals Birmingham NHS Trust
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for KRAS G12C mutation-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a

8. What is the main aim of treatment for KRAS G12C mutation-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Improve overall survival of patients
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement or equivalent PFS than SOC, but more convenient and favourable side effect profile
10. In your view, is there an unmet need for patients and healthcare professionals in KRAS G12C mutation-positive advanced non-small-cell lung cancer?	yes
11. How is KRAS G12C mutation-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently there is availability of Sotorasib The current technology would replace it
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	No difference in terms of administration compared with current SOC It would be used in cancer units

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No further investment
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with KRAS G12C mutation
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Compared with Docetaxel (comparator in the trial) this is more convenient (oral versus IV) and better tolerated. Compared with Sotorasib it does have more favourable aspect – no washout needed post immunotherapy
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment till loss of clinical benefit

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes There remains high unmet need for this patient subgroup for more effective and more tolerable treatments
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicities are manageable with appropriate dose modification and supportive medication
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes PFS TEAE's

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 781 [TA781]?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	n/a

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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External Assessment Group Report

Adagrasib for previously treated *KRAS* G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Alexis Llewellyn, Research Fellow, CRD, University of York Rojé Layne, Research Fellow, CHE, University of York Chinyereugo Umemneku-Chikere, Research Fellow, CRD, University of York Carlos Chivardi, Research Fellow, CHE, University of York Helen Fulbright, Information Specialist, CRD, University of York Sofia Dias, Professor, CRD, University of York Claire Rothery, Professor, CHE, University of York Kerry Dwan, Senior Research Fellow, CRD, University of York Ana Duarte, Senior Research Fellow, CHE, University of York
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Date completed	27/01/2025

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Alexis Llewellyn performed the critical review of the clinical effectiveness evidence, drafted Section 1 (clinical issues) and parts of Section 3 and contributed to drafting Section 2.

Rojé Layne performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 6 of the report.

Chinyereugo Umemneku-Chikere performed the critical review of the clinical effectiveness evidence, and drafted Section 2 and parts of Section 3.

Carlos Chivardi performed the critical review of the economic analyses, validated the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.

Helen Fulbright reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support.

Sofia Dias provided methodological advice, commented on drafts of the report and reviewed the whole report.

Claire Rothery performed the critical review of the economic analyses, wrote the critique of the surrogacy analysis, contributed to drafting Sections 4-7 of the report and provided advice on the report as a whole.

Kerry Dwan provided methodological advice, commented on drafts of the report and reviewed the whole report, and takes joint responsibility for the report as a whole.

Ana Duarte performed the critical review of the economic analyses evidence, contributed to drafting Sections 4, 5 and 7 of the report, led the economic analyses, reviewed the report, and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted].

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
AE	Adverse event
AEDC	Discontinuation due to adverse events
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASBI	Average symptom burden index
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BRAF	V-raf murine sarcoma viral oncogene homologue B
BSA	Body surface area
BSC	Best supportive care
CASP	Critical appraisal skills programme
CDA	Canada Drug Agency
CDF	Cancer Drugs Fund
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrI	Credible interval
CS	Company submission (Document B)
CSR	Clinical study report
CT	Computed tomography
DIC	Deviance information criterion
DOR	Duration of response
DSU	Decision Support Unit
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EoL	End of life
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimension
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FE	Fixed effects
HCRU	Healthcare resources Utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
IC	Intracranial
ICER	Incremental cost effectiveness ratio
IGI	Item global index

INV	Investigator
ITT	Intent – to – treat
IPD	Individual patient data
IPCW	Inverse probability of censoring weighting
IRT	Interactive response technology
IV	Intravenous
KRAS	Kirsten rat sarcoma viral oncogene homologue
LCSS	Lung Cancer Symptom Scale
LS	Least square
LY	Life years
MET	Mesenchymal-to-epithelial transition
MHRA	Medicine and Healthcare products regulatory agency
MID	Minimally important difference
MMRM	Mixed model for repeated measures
NHS	National Health Service
NICE	National Institute for health and care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase
ODAC	Oncologic Drugs Advisory Committee
OR	Odd ratios
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PAS	Patient Access Scheme
PD	Progressed disease
PD-L1	Programmed death ligand 1
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services research Unit
QALY	Quality adjusted life year
QLQ-C30	Quality of life Questionnaire Core 30
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumour
RET	Rearranged during transfection
ROS1	Proto-oncogene 1 receptor tyrosine kinase
RPSFTM	Rank preserving structural failure time model

SACT	Systemic anti-cancer therapy
SAP	Statistical analysis plan
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
sNDA	Supplemental new drug application
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TRAE	Treatment related adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
TTI	Time to first improvement
TTP	Time to progression
UK	United Kingdom
VAS	Visual analogue scale
WPAI	Work Productivity and Activity Impairment

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID6339	Summary of issue	Report sections
1	The effect of adagrasib relative to docetaxel +/- nintedanib on overall survival (OS) is unknown.	3.2.1, 4.2.6
2	The surrogacy analysis used to predict absolute OS for KRYSTAL-12 is subject to several important limitations.	3.2.3
3	The lack of blinding may have introduced systematic bias in KRYSTAL-12.	3.2.1.1
4	There is no evidence to suggest that the overall safety profile of adagrasib is superior to docetaxel +/- nintedanib.	3.2.1.2
5	Limitations in the evidence used to inform the NMA.	3.3.2, 3.4
6	Use of treatment-specific utility value for the progressed disease (PD) health state in the model	4.2.9

There are two key differences between the EAG's preferred assumptions and the company's preferred assumptions:

(i) The effect of adagrasib relative to docetaxel +/- nintedanib on OS is lower than the company's surrogacy analysis.

(ii) The use of a treatment-independent utility value for the PD health state, rather than an increment applied to adagrasib compared to docetaxel +/- nintedanib in the company's base case.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who are alive and progression-free over time relative to the comparators, which is associated with improved HRQoL.
- Assuming a higher utility value for patients treated with adagrasib compared to docetaxel +/- nintedanib in the progression-free (PF) and PD health states.
- A small difference in QALYs associated with adverse events.

Overall, the technology is modelled to affect costs by:

- Increasing the time on treatment compared to the comparators and the proportion of the cohort who remain progression-free for longer, with associated drug acquisition costs.
- Decreasing the proportion with progressive disease and associated costs of subsequent therapies upon progression.
- A small difference in costs associated with adverse events.

The two critical parameters in the partitioned survival analysis impacting the cost-effectiveness of adagrasib relative to the comparators are: (i) the unknown effect of adagrasib vs. docetaxel on OS; and (ii) the treatment-specific health state utility values. The effect of adagrasib relative to docetaxel +/- nintedanib on OS being unknown is a critical issue for both the clinical and cost-effectiveness of adagrasib.

The modelling assumptions that have the greatest effect on the ICER are:

- The OS predictions for adagrasib relative to docetaxel +/- nintedanib.
- The utility values for PF and PD health states.

1.3 The decision problem: summary of the EAG's key issues

The EAG does not have any key issues relating to the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 The effect of adagrasib relative to docetaxel +/- nintedanib on overall survival is unknown

Report section	3.2.1, 4.2.6
Description of issue and why the EAG has identified it as important	There is an absence of mature OS data from KRYSTAL-12 to inform the treatment effect of adagrasib relative to docetaxel on OS. In the interim OS analysis, the median OS was [redacted] in the adagrasib arm and [redacted] in the docetaxel arm, resulting in a HR of [redacted] the EAG notes that [redacted] Therefore, the effect of adagrasib relative to docetaxel +/- nintedanib OS is unknown.
What alternative approach has the EAG suggested?	In the absence of conclusive OS evidence for adagrasib, and uncertainties concerning the validity of the company's proposed surrogacy approach (Issue 2), the EAG explores the impact of alternative estimates for the OS HR of adagrasib vs. docetaxel on the cost-effectiveness of adagrasib: • [redacted] the primary ITT analysis from CodeBreaK 200 for sotorasib (the only other KRAS inhibitor with data in the relevant population), i.e., HR = 1.0. • Same effect of adagrasib on OS from the two-step crossover adjusted analysis for sotorasib vs. docetaxel from CodeBreaK 200, i.e., HR = 0.89. • Effect of adagrasib on OS based on evidence from KRYSTAL-1 for adagrasib and assuming that there is no class effect for KRAS G12C inhibitors (i.e. excluding evidence relating to sotorasib), i.e., HR = [redacted].
What is the expected effect on the cost-effectiveness estimates?	The ICER for adagrasib vs. docetaxel ranges from £30,853 /QALY (optimistic HR of [redacted], in favour of adagrasib), £44,575/QALY (mid-range HR of 0.89 for adagrasib) and £67,571/QALY (less-optimistic HR of 1.0, i.e., no effect), including a severity weight of 1.7 and holding all other parameters the same as base case. Docetaxel + nintedanib is dominated by adagrasib under the three scenarios.
What additional evidence or analyses might help to resolve this key issue?	Mature OS evidence from KRYSTAL-12 is required to address this uncertainty. The company stated that the final OS analysis is projected to occur in approximately [redacted], and outputs/reports availability are planned for [redacted] or [redacted]. However, the EAG is concerned that, in view of [redacted]

Abbreviations: HR: hazard ratio; ICER, incremental cost-effectiveness ratio; OS: overall survival

Issue 2 Validity of the surrogacy analysis between progression and survival

Report section	3.2.3
Description of issue and why the EAG has identified it as important	Given the immaturity of KRYSTAL-12 OS data, the company conducted a surrogacy analysis to assess the relationship between time to progression (TTP) and survival using individual participant-data from a single-arm phase 1/2 trial of adagrasib (KRYSTAL-1) and used it to predict OS for KRYSTAL-12 in censored patients, for both adagrasib and docetaxel, based on progression data from KRYSTAL-12. The surrogacy analysis has several important limitations: • There is no evidence to suggest that improvements in progression-free survival (PFS) observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC. • It cannot be demonstrated whether the relative effect of adagrasib on progression is predictive of relative OS based on a single-arm study. Predictions of OS from the *de-novo* analysis based on adapting the joint frailty-copula model of Emura et al. (2017) have not been assessed relative to other bivariate survival models and different copulas. • The surrogacy analysis has not been externally validated in the target population. • The surrogacy relationship is unlikely to be exchangeable between *KRAS*-targeted and non-targeted therapies because evidence from previous trials in the broader NSCLC population (Hua et al., 2022 and Horita et al., 2022) suggests that the strength of the association varies by treatment class and line of treatment. The results of the surrogacy analysis are incorporated in the company's network meta-analysis and cost-effectiveness analysis, which introduces significant uncertainty for the assessment of cost-effectiveness of adagrasib relative to its comparators.
What alternative approach has the EAG suggested?	Robust evidence is required to show that improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC. Without this evidence, it cannot be assumed that a surrogacy relationship holds in the target population. The EAG explores the impact of alternative estimates for the relative effect of adagrasib on OS – see Issue 1.
What is the expected effect on the cost-effectiveness estimates?	See Issue 1.
What additional evidence or analyses might help to resolve this key issue?	See Issue 1.

Abbreviations: TTP: time to progression; PFS: progression-free survival; HR: hazard ratio; OS: overall survival; *KRAS*: Kirsten rat sarcoma viral oncogene homologue

Issue 3 Lack of blinding and risk of bias in KRYSTAL-12

Report section	3.2.1.1
Description of issue and why the EAG has identified it as important	The EAG is concerned that the lack of blinding may have introduced systematic bias favouring adagrasib in KRYSTAL-12.
What alternative approach has the EAG suggested?	In KRYSTAL-12, the proportion of early withdrawals prior to receiving treatment was lower in the adagrasib arm (n=3, 1.0%) than in the docetaxel arm (n=12, 7.9%). The EAG requested that the company perform additional sensitivity analyses to explore the potential impact of early asymmetric dropout and informative censoring on PFS. These analyses [redacted] but it is unclear whether the prognosis of patients who remained in the control group was balanced with those remaining in the adagrasib group. It is also uncertain whether withdrawal may have biased estimates of OS, objective response rates (ORR), and safety outcomes. KRYSTAL-12 found that adagrasib led to statistically and clinically meaningful improvement in symptom burden and HRQoL for patients receiving adagrasib compared with docetaxel. However, the subjective nature of patient-reported outcomes (PROs), lack of blinding mean that HRQoL outcomes in KRYSTAL-12 may have been overestimated.
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	A separate trial with blinding of participants and study personnel would help to resolve this uncertainty, although this is highly unlikely to be conducted.

Abbreviations: EAG: external assessment group; PFS: progression-free survival; BICR: blinded independent central review; OS: overall survival; ORR: objective response rate; PRO: patient-reported outcome

Issue 4 Safety of adagrasib compared with docetaxel with or without nintedanib

Report section	3.2.1.2
Description of issue and why the EAG has identified it as important	There is currently no evidence to show that the safety profile of adagrasib is superior overall to that of docetaxel. In KRYSTAL-12, fatal treatment emergent adverse events (TEAES), Grade ≥ 3 TEAEs and serious TEAEs were all more frequent in the adagrasib arm than the docetaxel arm. The company's network meta-analysis (NMA) showed a similar trend, and did not show evidence to suggest that adagrasib was safer than docetaxel+nintedanib overall.
What alternative approach has the EAG suggested?	None based on the evidence currently available.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of adagrasib may be impacted if there are differences in the safety profile of adagrasib relative to docetaxel +/- nintedanib. The extent of this impact is dependent on the frequency of events over time and the distribution of events across treatments.

What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up from KRYSTAL-12 and surveillance data will provide further information on the safety profile of adagrasib, although this is not expected within the timeline of this appraisal.

Abbreviations: TEAEs: treatment emergent adverse events; NMA: network meta-analysis

Issue 5 Validity of the network meta-analysis due to the quality of the evidence

Report section	3.3.2, 3.4
Description of issue and why the EAG has identified it as important	Due to the absence of direct comparison between adagrasib and docetaxel+nintedanib or sotorasib, the company conducted a NMA. The NMA included KRYSTAL-12 (and for OS, a surrogacy analysis including data from KRYSTAL-1 and SELECT-1 trials), LUME-Lung 1 (docetaxel+nintedanib vs. docetaxel+placebo) and CodeBreaK 200 (sotorasib vs. docetaxel). The EAG is concerned about the validity of the NMA results due to limitations of the evidence, including: a. The validity of the OS data for adagrasib (see Issues 1 and 2); b. risk of bias in KRYSTAL-12 (see Issue 3); c. the population from LUME-Lung 1, which has limited comparability with KRYSTAL-12; d. the lack of loops in the evidence and limited number of studies, preventing any assessment of consistency and heterogeneity.
What alternative approach has the EAG suggested?	Incorporating results from the subgroup of patients with adenocarcinoma from LUME-Lung 1 may partially address concern about the comparability of this trial.
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	Mature OS evidence from KRYSTAL-12 is required, although it is uncertain whether the final KRYSTAL-12 results will be conclusive (see Issue 1).

Abbreviations: NMA: network meta-analysis; EAG: external assessment group; OS: overall survival

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

One of the key issues affecting the cost-effectiveness evidence pertains to the treatment effect of adagrasib relative to docetaxel +/- nintedanib on OS being unknown. The EAG has discussed this issue in full in Section 1.4 (Issue 1) including its implications for the cost-effectiveness of adagrasib, and, therefore, the issue is not reiterated in the current Section to avoid repetition.

Issue 6 Use of treatment-specific utility value for the progressed disease health state in the model

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The company applied an increment in utility for adagrasib relative to docetaxel+/-nintedanib in the PF and PD health states based on an analysis of EQ-5D responses from KRYSTAL-12. The company justified the increment in utility for adagrasib on the basis that it is an oral treatment that is administered at home, whereas docetaxel is administered intravenously as hospital-based chemotherapy. The EAG is reasonably satisfied that adagrasib may be associated with an increment in utility in the PF health state due to its oral administration at home, but the EAG is not satisfied with a treatment-specific uplift in utility for adagrasib in the PD health state because patients have discontinued their initial treatment of adagrasib upon progression and have moved to subsequent treatments. Furthermore, patients in the docetaxel arm of KRYSTAL-12 that crossed over to adagrasib were censored from the company's utility analysis resulting in potential selection bias in the post-progression analysis of KRYSTAL-12 data.
What alternative approach has the EAG suggested?	The use of a single treatment-independent utility value for the PD health state for adagrasib, docetaxel monotherapy and docetaxel + nintedanib.
What is the expected effect on the cost-effectiveness estimates?	The ICER increases by approximately £5,500 when holding all other parameters the same as the company's base case.
What additional evidence or analyses might help to resolve this key issue?	HRQoL data for patients post-progression by treatment.

Abbreviations: EAG: external assessment group; HRQoL: health-related quality of life; PD: progressed disease; PF, progression-free.

1.6 Other key issues: summary of the EAG's view

Evidence for docetaxel+nintedanib is limited to one RCT, LUME-Lung 1, which did not restrict patient inclusion by NSCLC histology or *KRAS* mutation. None of the LUME-Lung 1 participants had prior exposure to PD(L)-1 inhibitors. Docetaxel+nintedanib is only recommended by NICE for patients with adenocarcinoma (TA347),[1] and most *KRAS* G12C positive patients have adenocarcinoma. Therefore, subgroup data from LUME-Lung 1 that includes only patients with adenocarcinoma may be more applicable to the decision problem. However, the lack of *KRAS* G12C specific data and prior PD(L)-1 inhibitors means that evidence from LUME-Lung 1 still has limited applicability to the NICE scope population.

Although the CS presented evidence for a number of subgroups (including sequential vs. concurrent prior combination therapy; number of prior lines of therapy; presence of brain, liver and bone

metastases), there is no separate relevant evidence to inform outcomes for any of the subgroups as defined in the NICE scope, including: disease stage, histology, previous treatment, and newly diagnosed vs. recurrent distant metastatic disease. This further limits the applicability of the CS evidence to the decision problem.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 and Table 3 summarises the EAG's preferred assumptions and resulting ICER for the comparison of adagrasib with docetaxel monotherapy and docetaxel + nintedanib for deterministic and probabilistic analysis, respectively. Note that the QALYs are adjusted by applying a 1.7 severity weight. Results without the severity weight are reported in Appendix 2.

Table 2 Cost-effectiveness results for the EAG's preferred assumptions – fully incremental deterministic analysis

Name	**Option**	**Total costs**	**Total QALYs***	**Inc. Costs**	**Inc. QALYs**	**ICER (/QALY)**
Company's base-case results	Docetaxel	[redacted]	[redacted]			
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£29,107
EAG base case 1: No effect of adagrasib on OS (HR = 1.0 for adagrasib vs. docetaxel) and same PD utility value for all treatments	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£108,086†
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2: Same effect of adagrasib on OS as observed for sotorasib (HR = 0.89 for adagrasib vs. docetaxel) and same PD utility value for all treatments	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£58,794
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

*Adjusted by applying a 1.7 severity weight

† Note that the value of the ICER is sensitive to the [redacted]

Table 3 Cost-effectiveness results for the EAG's preferred assumptions – fully incremental probabilistic analysis

Name	Option	Total costs	Total QALYs*	Inc. Costs	Inc. QALYs	ICER (/QALY)
Company's base-case results	Docetaxel	[redacted]	[redacted]			
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£27,590
EAG base case 1: No effect of adagrasib on OS (HR = 1.0 for adagrasib vs. docetaxel) and same PD utility value for all treatments	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£66,744
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2: Same effect of adagrasib on OS as observed for sotorasib (HR = 0.89 for adagrasib vs. docetaxel) and same PD utility value for all treatments	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£43,554
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

*Adjusted by applying a 1.7 severity weight

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report reviews the clinical and cost effectiveness evidence submitted by the company to the National Institute for Health and Care Excellence (NICE) in support of adagrasib as a monotherapy for the treatment of adults with advanced non-small cell lung cancer with Kirsten rat sarcoma viral oncogene homologue (*KRAS*) G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

Adagrasib (KRAZATI®) is a selective, irreversible *KRAS* G12C inhibitor that covalently binds to the mutant cysteine in *KRAS* G12C and locks the mutant *KRAS* protein in its inactive, GDP- bound conformation, which prevents *KRAS*-dependent downstream signalling without affecting wild-type *KRAS* protein.[2]

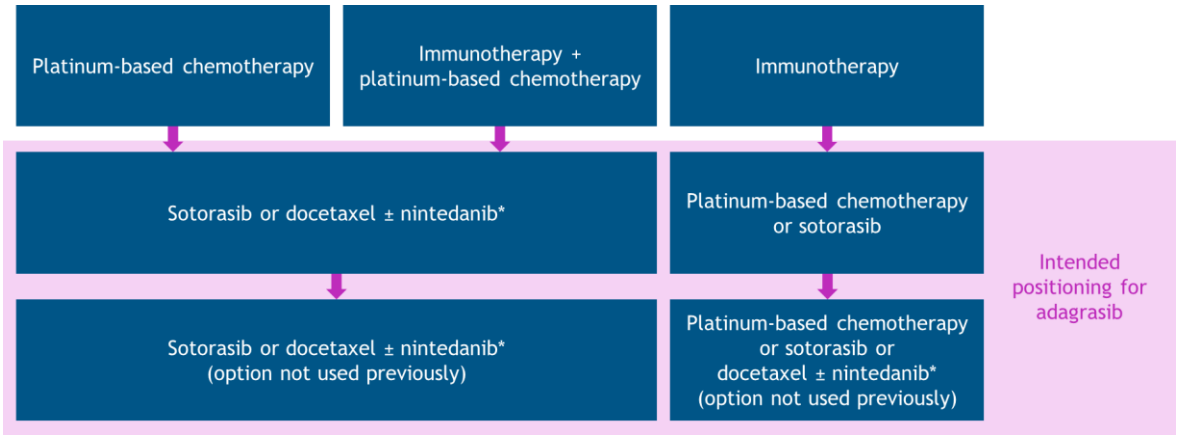
The MHRA granted a conditional marketing authorisation for adagrasib on 3 November 2023, which was renewed on the 4 November 2024 under the 'conditional approval' scheme, pending further evidence[2, 3].

2.2 Background

The EAG considers the company's description of the health condition (Company submission [CS] Section B.1.3) to be appropriate and relevant to the decision problem. The description of the diagnosis, staging, burden, and management of advanced *KRAS* G12C mutation-positive NSCLC in adults reflects current UK practice. The company's description of the unmet need for *KRAS* G12C patients with progressive disease following prior therapy is generally appropriate. The EAG agrees with the company's description of the limited efficacy and significant toxicity of targeted and non-targeted therapies in this population and the need for effective targeted therapy with less toxicity than standard of care.

The proposed position of adagrasib in the NHS clinical pathway, if approved by NICE, is presented in CS Figure 6 and reproduced below in Figure 1.

Figure 1: Summary of the typical treatment pathway used in UK clinical practice for advanced NSCLC with a *KRAS* G12C mutation and proposed adagrasib positioning



*Nintedanib is reimbursed only in patients with adenocarcinoma histology; patients with other histology receive docetaxel as monotherapy.
Abbreviations: *KRAS*, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; UK, United Kingdom.
Sources: CS Figure 6, NICE NG122,[38] clinical expert opinion[24]

The EAG clinical adviser noted that Figure 1 was generally an accurate summary of the treatment pathway for *KRAS* G12C mutated advanced NSCLC in UK practice. The choice of first line (1L) therapy is dependent on tumour histology and level of programmed death ligand 1 (PD-L1) expression, as well as patient fitness. The clinical adviser to the EAG agrees with the company that the treatment received by approximately three-quarters of patients is immunotherapy in combination with platinum-based chemotherapy (combination therapy). Other 1L treatment options include either platinum-based chemotherapy or immunotherapy as single-agents. For patients whose disease progresses following initial therapy and who are sufficiently fit, further treatment options include sotorasib (under the Cancer Drugs Fund [CDF]), docetaxel, and (for people with adenocarcinoma) docetaxel + nintedanib.[1, 4, 5] The EAG's clinical adviser agrees with the CS that following 1L combination therapy, most patients (approximately 85%) receive sotorasib in preference to a docetaxel-based treatment due to the targeted nature of sotorasib therapy and toxicity concerns associated with docetaxel. Most patients who receive a docetaxel-based regimen receive docetaxel in combination with nintedanib (60–80%). The clinical adviser to the EAG noted that about 90% of patients whose disease progresses following docetaxel +/- nintedanib will receive best supportive care (BSC) without any systemic anti-cancer therapies (SACT), because they would be unfit to proceed to another therapy.

Given that sotorasib is the only licenced alternative *KRAS* G12C therapy, the EAG's clinical adviser anticipates that, if approved, adagrasib would be positioned in the same place as sotorasib in the current treatment pathway.

2.2.1 Sotorasib

Sotorasib (Lumykras) is a targeted monotherapy for adults previously treated *KRAS* G12C mutation – positive locally advanced or metastatic NSCLC. The half-life of sotorasib is 5 hours (compared with 24 hours for adagrasib).[6, 7] It is recommended for use within the CDF Managed Access Scheme since March 2022 as an option for treating *KRAS* G12C mutation-positive locally advanced or metastatic NSCLC in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy.[4]

As sotorasib is currently only recommended for use within the CDF, it is not available for routine commissioning and is therefore not a relevant comparator within the context of this appraisal. The timelines for the managed access review of TA781[8] (ID6287) are not publicly available at the time of this report. Sotorasib is the only MHRA licenced therapy that targets *KRAS* G12C mutation-positive NSCLC aside from adagrasib. In TA781[4], the clinical evidence for sotorasib was primarily sourced from a phase 2 single arm trial, CodeBreaK 100[9, 10]. Since the NICE appraisal, the company has completed the then on-going phase 3 randomised controlled trial, CodeBreaK 200 (NCT04303780),[11] that evaluates the efficacy and safety of sotorasib versus docetaxel. CodeBreaK 200 primary analyses showed a statistically significant treatment effect for sotorasib vs. docetaxel on PFS (HR=0.66, 95% CI 0.51 to 0.86)), similarly to what was observed in KRYSTAL-12 for adagrasib vs. docetaxel (HR=0.58, 95% CI 0.45 to 0.76). However, the treatment effect for sotorasib vs. docetaxel on OS was not statistically significant (HR 1.01, 95% CI 0.77 to 1.33).

In May 2021, the FDA granted accelerated approval to sotorasib for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC with at least one prior systemic therapy based on the results of CodeBreaK 100, and pending the results of CodeBreaK 200.[12] In October 2023, following the review of CodeBreaK 200 results, the FDA's Oncologic Drugs Advisory Committee (ODAC) rejected the submitting company's supplemental new drug application (sNDA) requesting a full approval for sotorasib.[13, 14] The ODAC raised several concerns about the results of CodeBreaK 200. They notably questioned whether the study results could be reliably interpreted due to asymmetric early dropout and early crossover of patients on the control arm prior to confirmation of disease progression by blinded independent central review (BICR). Many committee members also noted that the PFS results did not translate to an OS benefit.[13] Hence, the FDA required a new post-marketing study by February 2028.

The European Medicines Agency (EMA) granted sotorasib its first marketing authorisation on 6, January 2022, and renewed it on 20 November 2023. Sotorasib has a conditional marketing authorisation pending further evidence.[15] The MHRA granted conditional marketing authorisation for adagrasib on 3 November 2023.[2]

2.3 Critique of company's definition of decision problem

Table 4 presents a description of the NICE final scope, the decision problem addressed within the CS and EAG comments on any differences between the two.

2.3.1 Population

The population addressed in the company decision problem is reflective of the population in the KRYSTAL-12 trial, which is narrower than the population in the NICE scope. The NICE scope includes people with a *KRAS* G12C mutation who have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. The KRYSTAL-12 study includes patients with *KRAS* G12C mutation and disease progression on or after prior treatment with a platinum-containing regimen (cisplatin or carboplatin) *and* an immune checkpoint inhibitor (i.e. anti-PD-1/PD-L1 inhibitor), either concurrently or sequentially. Therefore, the company decision problem excludes patients who did not receive both an immune checkpoint inhibitor and a platinum-containing regimen, or patients who do not have disease progression but are intolerant to either therapy. The EAG's clinical adviser considered that although narrower than the NICE scope, the population in the company decision problem is largely reflective of the population that would receive adagrasib on the NHS, should it be approved.

2.3.2 Comparators

The comparators (docetaxel +/- nintedanib) included in the CS are in line with the NICE final scope. Due to its licence, docetaxel+nintedanib is restricted to patients with adenocarcinoma histology. Therefore docetaxel + nintedanib is only a relevant comparator for the subpopulation with adenocarcinoma within the NICE scope. The exclusion of sotorasib is justified because sotorasib is only available within the CDF at the time of writing the EAR.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with advanced NSCLC that is positive for a *KRAS* G12C mutation and is not suitable for, or has progressed after treatment with, platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy	As per scope	n/a	The population addressed in the CS decision problem was narrower than NICE's final scope and in line with the population in the KRYSTAL-12 study which includes patients with *KRAS* G12C mutation and disease progression on or after prior treatment with a platinum-containing regimen (cisplatin or carboplatin) and an immune checkpoint inhibitor (i.e. anti-PD-1/PD-L1 inhibitor), either concurrently or sequentially. The EAG's clinical adviser considered that the trial population is broadly reflective of patients who would receive adagrasib in practice if it were approved.
Intervention	Adagrasib	As per scope	n/a	The intervention, adagrasib (600mg – 3x 200mg tablets – orally twice daily), is in line with the NICE final scope.
Comparator(s)	• Docetaxel • Docetaxel + nintedanib • Sotorasib (subject to managed access review)	• Docetaxel • Docetaxel + nintedanib	Sotorasib is recommended within the CDF and is not routinely commissioned in the NHS. According to NICE's Position Statement on CDF therapies, it is therefore not a comparator.[32] Given the US FDA's feedback[33, 34] on potential bias in the pivotal sotorasib trial, there is ongoing uncertainty regarding the availability of data that would support sotorasib's transition from the CDF to routine commissioning. For this reason, routine commissioning of sotorasib is not expected within the timeframe of this appraisal of adagrasib.	The comparators evaluated in the CS, docetaxel +/- nintedanib, are in line with NICE's final scope. At the time of the CS and of writing this EAR, sotorasib is only recommended in the CDF. Therefore the company's decision to exclude sotorasib from the decision problem is appropriate.
Outcomes	The outcome measures to be considered include: • PFS	As per scope, with addition of: • Duration of response	Not applicable	The outcomes reported in the CS covered all the outcomes required in NICE's final scope. Duration of response and intracranial efficacy are appropriate to the decision problem.

	• OS • Response rates • Adverse effects of treatment • Health-related quality of life	• Intracranial efficacy		Evidence from KRYSTAL-12 was provided for PFS, ORR, DOR and IC-TTP by blinded independent central review (BICR) and adverse events. Following a request for clarification from the EAG, the company presented the results of an interim OS analysis from KRYSTAL-12.
Economic analysis	As per NICE reference case.		n/a	As per the NICE scope, except for the population, as noted above.
Subgroups	If the evidence allows, the following subgroups will be considered: • Disease stage • Histology • Previous treatment • Newly diagnosed or recurrent distant metastatic disease	The company is not aware of any subgroups in which adagrasib would be more clinically or cost effective; subgroup analysis is therefore not presented.	KRYSTAL-12 was not powered to detect differences in the subgroups specified by NICE. Trial participants with brain metastases represent a prespecified/stratified subgroup with high unmet need. For that reason, this submission presents intracranial efficacy data in patients with treated and untreated brain metastases.	Subgroup analyses were not presented for any of the subgroups specified in the NICE scope. Subgroup analyses for PFS and ORR were presented in the CS (B.2.7.1) and included: presence of metastases at baseline (three separate subgroups for brain, liver and bone metastases); PD-L1 protein expression; number of prior lines of therapy; sequential vs. concurent use of prior combination therapy (platinum-based and anti-PD-1/PD-L1). The EAG agrees that the additional intracranial efficacy is relevant to the decision problem.
Source: NICE [ID6434], CS, Document B, Table 1 **Abbreviations:** n/a, not applicable; CS: company submission; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; DOR, duration of response; IC-TTP: intracranial time to progression.				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant evidence regarding the clinical efficacy and safety of ≥2L treatments for adults with advanced *KRAS* G12 mutation-positive NSCLC. Details of the review are reported in CS, Appendix D. This section presents a critique of the SLR methods including bibliographic searches, study selection, data extraction and quality assessment.

Searches

The search strategies to identify studies of adagrasib and comparator drugs for the treatment of advanced *KRAS* G12 mutation NSCLC were reported in CS, Appendix D, and additional information was provided in the company's response to EAG points for clarification, Section C. The literature search was conducted on 2 July 2024 and the CS followed the PRISMA guideline in identifying the articles included and excluded in the SLR (Appendix D of CS and section C of the company's response on point for clarification). The PRISMA flow diagram is presented in the CS Appendix D, Figure 1 with further details added in clarification response to question C1, Figure 18. A critique of the clinical evidence searches is presented in Table 5.

Table 5 EAG appraisal of company clinical evidence searches

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	In the original CS search strategies were not provided for conference proceedings or clinical trial registries. This was raised with the company, who responded with the strategies for the clinical trials registries. The company clarified that conference proceedings were searched as part of the database strategies, although the section on 'congress searches' in Appendix D, section D.1.1.1, suggested otherwise. The original CS grey literature searches did not show the hits per source in the PRISMA diagram. The company responded with a clearer and more detailed diagram.
Were appropriate sources searched?	PARTLY	A limited range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched. No dedicated health technology assessment or systematic review databases were searched. This was raised with the company, who explained that supplementary searches were performed to find any studies potentially missed by the strategies.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.

Topic	EAG response	Note
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	The searches combined the condition with intervention and the study type. In the original company submission, it was unclear whether it was appropriate to include interventions (and not to include terms for comparators) within the strategies. Although it was clear that the population should have been previously treated it was unclear which interventions the condition should have been previously treated with.
Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. In the population terms, there was no hyphenation of 'non-small-cell' or 'non-small cell' and the terms for cancer could have been more sensitive (e.g., including tumor* and tumour*). There are also several types of non-small cell lung cancer which were not searched for: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma, adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, salivary gland carcinoma, carcinoid tumour, and unclassified carcinoma. Moreover, the concept of metastasis could have been expanded to include terms for mutation, progressive disease, or previously treated, etc. This was raised with the company, who performed additional searches which found no new relevant records.
Were any search restrictions applied appropriate?	PARTLY	Animal studies and irrelevant paper and publication types were removed in some of the search strategies. It is unclear why reviews were removed as a publication type, which was raised with the company. The company explained that this was unlikely to have removed any relevant studies.
Were any search filters used validated and referenced?	UNCLEAR	Search filters were used but not referenced. Therefore, it was unclear if the filters used were validated.
EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE		

Inclusion criteria

The study eligibility criteria for the clinical effectiveness SLR are presented in CS Appendix D. Two sets of PICOS were presented; it appears that Appendix D, Table 5 criteria, which are aligned with the NICE scope, were used (rather than the much broader set of eligibility criteria presented in Appendix D, Table 4). The company's inclusion criteria were appropriate to inform the decision problem, and appropriate processes were reported to select studies and resolve disagreements. The EAG and EAG clinical adviser believe that all relevant trials were identified, and it is unlikely that any relevant evidence was excluded. The company's network meta-analyses (NMAs) included RCT evidence, as well as data from the single-arm KRYSTAL-1 trial. This is further discussed in Sections 3.3 and 0.

Data extraction

The data extraction process was generally appropriate. Data extraction was performed by two reviewers independently and discrepancies were reconciled by the two reviewers.

Quality assessment

The quality of the RCTs included in the SLR was assessed using NICE's quality assessment checklist (CS Appendix D, Table 7). The CS did not report whether the quality assessment was performed in duplicate and how disagreements (if any) in quality assessments were resolved.

Evidence synthesis

In the absence of direct evidence comparing adagrasib with nintedanib or sotorasib, an NMA was conducted (CS, Section B.2.9). A critique of the company NMAs is presented in Section 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The CS evidence for adagrasib included one phase 3 RCT, KRYSTAL-12 (NCT04685135),[16] and the results for a subset of participants from a single-arm, phase 1/2 trial, KRYSTAL-1 (NCT03785249).[17] The company presented the results of an interim OS analysis, for which data are immature and results inconclusive. Therefore, the company used IPD from KRYSTAL-1[17] to derive a surrogacy relationship between TTP and OS which is used to predict absolute OS for KRYSTAL-12[18] in *KRAS* G12C mutation-positive NSCLC, even though no evidence exists to support the use of a surrogacy relationship to inform OS in this target population. Sections 3.2.1 and 3.2.2 provide a critique of KRYSTAL-12[18] and KRYSTAL-1.[17] Section 3.2.3 provides a critique of the surrogacy relationship assumed by the company.

3.2.1 KRYSTAL-12

3.2.1.1 Study design

KRYSTAL-12[18] is an ongoing phase 3, international, multicentre, open-label trial. The design and characteristics of the trial are described in CS Section B.2.3. A total of 453 patients were randomised in a 2:1 ratio to adagrasib (n=301) and docetaxel (n=152). Study treatment was administered in three-week cycles. Adagrasib was administered at a starting dose of 600 mg twice daily orally. Docetaxel was administered intravenously every three weeks at 75 mg/m^2 over 1 hour or according to institutional practices. Patients in the docetaxel arm were permitted to cross over to adagrasib after blinded independent central review (BICR)-confirmed disease progression.

Eligible participants were adults with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation-positive and disease progression on or following prior treatment with a platinum-based therapy (cisplatin or carboplatin) and an immune checkpoint inhibitor (i.e. anti-PD-1/PD-L1 inhibitor), received either concurrently or sequentially. Patients with brain metastases were eligible if brain metastases were treated and neurologically stable for ≥ 2 weeks before randomisation. Randomisation was stratified by region (Asia-Pacific vs non-Asia-Pacific) and prior treatment (sequential vs. concurrent platinum-based chemotherapy and immunotherapy). The primary outcome was PFS assessed by BICR, defined as the time from randomisation to date of disease progression per

RECIST v1.1 or death due to any cause. Disease evaluation was conducted at screening (with a 28-day window allowed) and every 6 weeks from randomisation (+/- 10 days) until Week 49, then every 12 weeks. Secondary outcomes included OS , ORR by BICR, duration of response (DOR) by BICR, and patient-reported outcomes (PRO) of health-related quality of life (HRQoL) measured by EQ-5D-5L and the Lung Cancer Symptoms Scale (LCSS). Safety and tolerability, and exploratory intra-cranial response and progression outcomes, were also assessed.

The statistical analysis plan (SAP) specified one analysis for the PFS endpoint and one interim analysis (~50% of the expected death events) for OS.[19] An adaptive, group sequential design was planned for OS. The interim OS analysis plan also allowed for a non-binding futility boundary (allowing the study to continue even if the futility boundary is reached).

For the PFS (BICR) endpoint, the study has 90% power to detect a HR of 0.645 (assuming a median PFS of 6.2 months for the adagrasib arm and 4 months for docetaxel arm) at a 2-sided level of significance of 0.05 based on 246 PFS events. For OS, the study has 80% power to detect a HR of 0.72 (under an assumed median OS for adagrasib of approximately 13.9 months, compared with 10 months for docetaxel) at a 2-sided level of significance of 0.05 based on 334 death events.

Baseline characteristics

Baseline characteristics of patients included in KRYSTAL-12 are presented in CS Table 11. Baseline demographic and disease characteristics were broadly comparable between the adagrasib and docetaxel arms. Clinical advice to the EAG indicated that the patients included in KRYSTAL-12 are broadly comparable with an NHS population, except for ethnicity. The proportion of white patients (47.7% across arms) and black patients (0) is lower than in NHS practice, and the proportion of Asian patients (24.1%) is higher. However, the EAG's clinical adviser stated that the ethnicity distribution of KRYSTAL-12 participants is unlikely to affect the applicability of the trial to the decision problem.

Risk of bias

The company's quality assessment of the KRYSTAL-12 trial is presented in CS Document B, Section 2.5.1. The company concluded that KRYSTAL-12 was at low risk of bias. The EAG has concerns with the design of KRYSTAL-12, including the impact of crossover and subsequent *KRAS* G12C therapies in the control arm, and the potential implications of the open-label design.

Cross-over and subsequent KRAS G12C therapies in the docetaxel arm

A protocol amendment in KRYSTAL-12 requested by the FDA, in line with CodeBreaK 200, permitted crossover to adagrasib in patients assigned to the docetaxel arm (see response to clarification question A10). In response to a clarification request from the EAG, the company reported that [redacted] proportion of participants ([redacted]) in the docetaxel arm received a *KRAS* G12C inhibitor as subsequent therapy: [redacted] of participants crossed over from docetaxel to adagrasib, and an additional [redacted] received another *KRAS* G12C inhibitor following docetaxel

(see response to clarification question A7). The subset of patients in the docetaxel arm who crossed over to adagrasib or received another *KRAS* G12C inhibitor had shorter mean time since metastatic diagnosis (11.5 months vs. 15.0 months). The EAG did not identify any other notable differences in baseline characteristics. It is unclear how many patients in the docetaxel arm crossed over to adagrasib or received another subsequent *KRAS* G12C inhibitor prior to confirmed progression by .

Since crossover was permitted, it is possible that patients in both groups may have benefited from adagrasib, and a subset of patients in the docetaxel arm may also have benefited from subsequent sotorasib therapy (or a non-licenced *KRAS* G12C inhibitor). However, based on the results of the KRYSTAL-12 interim OS analyses and of the CodeBreaK 200 trial,[11] it is also possible that subsequent *KRAS* G12C therapies did not result in any improvement in survival or were detrimental. In the absence of mature OS data with crossover-adjusted analyses, the potential impact of crossover and of subsequent *KRAS* G12C inhibitors in the docetaxel arm on OS is uncertain.

Open-label design, asymmetric drop out and informative censoring

The EAG is concerned that knowledge of the intervention received (and a possible expectation of higher benefit favouring adagrasib, a new-generation targeted therapy, over docetaxel chemotherapy), may have affected patient retention in the docetaxel arm. The proportion of early withdrawals prior to receiving treatment was significantly lower in the adagrasib arm (n=3, 1.0%) than in the docetaxel arm (n=12, 7.9%), and the difference between groups was statistically significant (p=0.0001, EAG calculated). The reason for not receiving treatment in the docetaxel arm was 'withdrawal by subject' in 11 out of 12 participants. Following treatment initiation, the percentage of 'withdrawal by patient' was approximately twice as high in the docetaxel arm compared with adagrasib (21 [7.0%] in the adagrasib arm vs. 21 [13.8%] in the docetaxel arm [p=0.018, EAG calculated]). To address these concerns, the EAG requested that the company perform additional sensitivity analyses to explore the potential impact of early asymmetric dropout and informative censoring on PFS. In response to clarification question A7c, the company presented tipping point analyses [redacted] The company concluded that [redacted] The EAG agrees with the company that the tipping point analyses [redacted]. However, it is unclear whether the characteristics and health of patients who remained in the control group were balanced with those remaining in the adagrasib group following dropout. Due to lack of access to IPD, the EAG was not able to replicate these analyses. It is uncertain whether informative censoring or imbalances in dropout may have affected estimates of OS, ORR, HRQoL and safety outcomes.

The EAG agrees with the company that the fact that response outcomes were assessed by BICR limits the risk of performance bias due to lack of blinding of participants and study personnel. However, the subjective nature of PROs means that HRQoL outcomes in KRYSTAL-12 are at high risk of bias.

Disease evaluation schedule

Disease evaluation was conducted every 6 weeks (+/- 10 days) until Week 49, then every 12 weeks. Following a request for clarification from the EAG, the company presented a post-hoc analysis showing that actual scan intervals were consistent with the scheduled scan intervals and showed no systematic differences in timing of assessment between study arms (see response to clarification question A6), alleviating concerns that the schedule of assessment may have introduced bias in the analyses of outcomes that are based on disease evaluation (PFS, ORR, DOR).

Applicability to NHS practice

Docetaxel is the relevant comparator in this appraisal. However, as discussed in Section 2.2, currently most adult patients (approximately 85%) with *KRAS* G12C advanced NSCLC who progress on initial combination therapy in the NHS receive sotorasib via the CDF. In patients who receive docetaxel-based regimens, most (60-80%) will receive it in combination with nintedanib, which is only recommended for patients with adenocarcinoma.

Five of the 173 trial sites were based in the UK; the countries with the most sites were the USA (48), China (37), Spain (28), Italy (25), France (21), South Korea (18), Germany (15), Portugal (14), Romania (12), Greece (11) and Russia (11).

As discussed in Section 2.3, KRYSTAL-12 includes a narrower population than its MHRA license and the corresponding NICE scope. Although the EAG clinical adviser considers that the population KRYSTAL-12 is largely reflective of UK clinical practice, the applicability of KRYSTAL-12 results to patients who are intolerant to platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy, or to patients with no prior chemotherapy, is uncertain. Unlike the MHRA license, KRYSTAL-12 only included patients with an ECOG performance status of 0 or 1, which may limit the applicability of the trial results to less fit patients.

3.2.1.2 Results

Clinical effectiveness results of KRYSTAL-12 are presented in CS Section B.2.6.1. All KRYSTAL-12 efficacy results were analysed at a data cut of 31 December 2023 after a median trial follow-up of 9.43 months. The final OS analysis is projected to occur approximately in [redacted].

Progression-free survival

At the time of the data cut, 164 (54.5%) PFS per BICR events were observed in the adagrasib arm and 93 (61.2%) events in the docetaxel arm. Median PFS was 5.49 months (95% CI, 4.53 to 6.67) in the adagrasib arm and 3.84 months (95% CI, 2.73 to 4.73) in the docetaxel arm. The HR for PFS (BICR)

was 0.58 (95% CI, 0.45 to 0.76). The Kaplan-Meier curve for PFS is presented in CS Figure 10 and shows a separation of the survival curves from approximately 2 to 3 months post-randomisation. PFS results by investigator assessment were also reported and generally similar to BICR assessments. CS Figures 17 and 18 suggested no significant differences in PFS by BICR across pre-specified subgroups.

As discussed in Section 3.2.1.1, asymmetric drop out was observed between study arms, and although sensitivity analyses conducted by the company showed no significant impact on PFS estimates, it is unclear whether the characteristics and health of patients who remained in the control group were balanced with those remaining in the adagrasib group following dropout.

Progression-free survival 2

PFS2 was reported as an exploratory endpoint in the KRYSTAL-12 CSR and was defined as the time from randomization to the earliest disease progression assessed by investigator on next line of therapy, or death from any cause, whichever occurred first. PFS2 may provide potential information where analysis of OS could be confounded by subsequent therapies, notably subsequent *KRAS* inhibitors in patients randomised to the docetaxel arm.

Figure 2 presents the Kaplan-Meier curve for PFS2. In the adagrasib arm, [redacted] patients received at least 1 subsequent treatment, including [redacted] and [redacted] In the docetaxel arm, [redacted] patients received a [redacted] as subsequent therapy, of which [redacted] crossed over to adagrasib and [redacted] patients received [redacted] of which [redacted] Median PFS2 was [redacted] in the adagrasib arm and [redacted] arm. There was [redacted] between the study arms [redacted] These results show [redacted] following subsequent treatment.

Figure 2 Kaplan-Meier Plot of PFS2 (KRYSTAL-12, December 2023 data cut-off)

Source: CSR, Figure 10. Abbreviations: MRTX849, adagrasib

Overall survival

The company conducted an interim analysis for OS as per the study protocol and statistical analysis plan (SAP).[19, 20] However, the CS did not present the results of this analysis because the data were highly immature and results inconclusive, and due to the potential confounding effect of crossover which was not adjusted for in the interim analyses. Following a request from the EAG the company provided the results of the interim analyses for OS conducted at the time of the primary PFS analysis (31 December 2023; see response to clarification question A1).

Figure 3 presents the Kaplan-Meier curve for OS. The overall median follow-up for OS was [redacted] with a minimum follow-up (duration from last subject randomised to the data cut) of [redacted] of the events for the final analysis [redacted] were observed.

The median OS was [redacted] in the adagrasib arm and [redacted] in the docetaxel arm; HR of [redacted] The p-value for OS was [redacted] and [redacted]

Figure 3 Kaplan-Meier plot of overall survival (ITT population) Interim analysis, December 2023 data cut

The Kaplan-Meier curve shows significant censoring throughout the follow-up period. A total of [redacted] patients were censored within the first 6 months across both treatment arms. Across the available follow-up period, the most common reason for censoring was [redacted] treatment arms [redacted] means that no conclusions regarding the relative efficacy of adagrasib and docetaxel can be drawn from these results. As discussed above, the PFS2 results [redacted]

As [redacted]. The company stated that the final OS analysis is planned when approximately [redacted] OS events have occurred, which is projected to occur in approximately [redacted]. Outputs/reports availability are planned for [redacted].

A [redacted] deaths were reported at the 31 December 2023 data cut in the adagrasib arm compared with the docetaxel arm. In response to a request for clarification (question A1), the company provided further details including a summary of causes of death. This is further discussed in the safety section below.

Given the interim OS analysis results, [redacted] mortality rates and PFS2 results from KRYSTAL-12, the EAG requested from the company that they justify the assumption of an OS benefit for adagrasib vs. docetaxel (see clarification question A2c). In response, the company estimated the conditional probability of observing a positive OS trend at final OS analysis (i.e., at HR thresholds ranging between <0.85-1.00) given the observed interim OS HR estimated (Table 4, response to clarification question A2.c); the analysis suggests that the probability of the OS HR for adagrasib vs. docetaxel favouring adagrasib is [redacted]. The methodology and assumptions underlying the company's analysis were not provided, so the EAG cannot comment on the validity of the results. The company also considered that the KRYSTAL-12 PFS2 data could not be used to infer the potential of OS benefit given interim OS results due to its immaturity, short follow up ([redacted]) and the proportion of cross-over to adagrasib in the docetaxel arm [redacted]. The company did not provide an analysis of crossover adjusted PFS2 as requested by the EAG, which might have been helpful to explore the extent to which crossover may be driving the similarity of PFS2 outcomes between treatment arms.

In light of the evidence presented by the company, the EAG considers that the existing head-to-head OS and PFS-2 evidence for adagrasib vs. docetaxel from KRYSTAL-12 does not support the existence of [redacted]

Given the limitations of the OS data in the interim OS analyses from KYRSTAL-12, the relative treatment effectiveness of adagrasib vs. docetaxel on OS is unknown.

Response rates

ORR was defined as the percentage of patients with a documented confirmed complete response or partial response by BICR. ORR was 31.9% for adagrasib (95% CI, 26.7% to 37.5%) and 9.2% for docetaxel (9.2%; 95% CI, 5.1% to 15.0%); the odds ratio (OR) for the difference between arms favoured adagrasib and was statistically significant (OR 4.68; 95% CI, 2.56 to 8.56). All responses were partial responses, except for three complete responses (1.0%) in the adagrasib arm. Although the rate of non-evaluable participants was higher in the docetaxel arm than the adagrasib arm (19.1% and 12.3% respectively), the EAG clinical adviser agrees with the company that the difference in ORR between study arms may be clinically significant, although these results need to be interpreted alongside other relevant outcomes including PFS and OS. Median DOR (BICR) was 8.31 months (95% CI: 6.05 to 10.35 months) on the adagrasib arm and 5.36 months (95% CI: 2.86 to 8.54 months) on the docetaxel arm.

Health-related quality of life

HRQoL was assessed with EuroQol 5-Dimension (EQ-5D-5L) and the Lung Cancer Symptom Scale (LCSS) using a mixed model for repeated measures (MMRM). Data was collected on Day 1 and Day 15 of treatment Cycles 1–4 and on Day 1 of every subsequent treatment cycle and at the end-of-

treatment visit. The PRO analysis population included 84.4% (254/301) of randomised patients in the adagrasib arm and 73.7% (112/152) of patients in the docetaxel arm who had EQ-5D or LCSS data at baseline and at least one post-baseline visit within 6 months.

The LCSS is a disease-specific measure of QoL, which includes six lung cancer symptoms (appetite loss, fatigue, cough, dyspnoea, haemoptysis, and pain) and three summary global items (distress/severity of lung cancer symptoms, impact on activities, and quality of life). The degree of impairment from 0 (no impairment) to 100 (maximal impairment) is recorded using a visual analogue scale (VAS). The average symptom burden index (ASBI) score is the sum of the six lung cancer symptom scores, the 3-item global index (3-IGI) is the sum of the three global scores, and the average total score is the sum of all nine scores.

Results for the EQ-5D-5L and LCSS are reported in CS Section B.2.6.1.4.1. Completion rates were above 85% for most assessments in both arms. The least square (LS) mean change from baseline in average EQ-5D-5L total score over time was -0.7 (95% CI -2.7 to 1.3) in the adagrasib arm, and -6.1 (95% CI -9.2 to -3.1) in the docetaxel arm. The mean difference in LS mean change in EQ-5D-5L index scores from baseline between adagrasib and docetaxel was 0.082 (95% CI 0.037 to 0.126) and favoured adagrasib. The difference was statistically significant; however, the minimally important difference specified in the SAP (7 points score difference on the VAS scale) was not met.[19]

The LS mean change from baseline in average total score in LCSS was -4.4 (95% CI -6.0 to -2.7) in the adagrasib arm (indicating reduced impairment), and 5.5 (95% CI 2.9 to 8.0) (indicating increased impairment) in the docetaxel arm. The mean difference in LCSS in average total score between adagrasib and docetaxel was -9.8 (95% CI -12.7 to -7.0) and favoured adagrasib. The difference was statistically significant and the average difference in total score was just below the company's prespecified MID threshold (10 points).[19] A comparable effect was reported for ASBI and 3-IGI scores (CS Table 19). Further results including time to first improvement and time to deterioration are reported in CS Section B.2.6.1.4.2.

Overall, the EAG agrees with the company that KRYSTAL-12 suggests an improvement in symptom burden and HRQoL for patients receiving adagrasib compared with docetaxel. However, the lack of blinding means that PROs are at high risk of bias. Therefore, the relative magnitude of HRQoL and symptoms benefits from adagrasib may have been overestimated. The PRO analysis population included a subset of the ITT population, and a lower percentage of patients randomised in the docetaxel arm (73.7%) compared with the adagrasib arm (84.4%). It is uncertain whether this imbalance in completed responses introduced bias in relative estimates of HRQoL change from baseline. Due to dropout (most notably in the docetaxel arm), effect estimates in later follow-up evaluations are imprecise. As most patients were evaluated in non-UK sites, the applicability of the PROs to the NHS context is uncertain.

Safety

Safety data for KRYSTAL-12 were presented in CS Section B.2.10 and Appendix F. The safety population of KRYSTAL-12 was defined as all patients who received any part of a dose of study medication and consisted of 298 patients in the adagrasib arm and 140 patients in the docetaxel arm. Separate results were reported for the 44 patients who crossed over from docetaxel to adagrasib. Treatment emergent adverse events (TEAEs) were adverse events that first occurred or increased in severity on or after the first dose of study treatment and ≤ 28 days after the last dose of study treatment and prior to the initiation of subsequent systemic anticancer therapy. TEAEs were collected from the December 2023 data cut.

Treatment exposure and compliance is summarised in CS Section B.2.10.1. The mean duration of exposure was 5.56 months (SD 4.98) for adagrasib and 3.17 months (SD 2.56) for docetaxel. Compliance with adagrasib was high (mean 98.3%, SD 5.1). Mean overall dose intensity was 77.7% (SD 20.5) of the 600mg dose for adagrasib and 92.0% (SD 12.0) for docetaxel.

TEAEs are summarised in CS Section B.2.10.2. All 298 (100%) patients in the adagrasib group and 138 (98.6%) patients in the docetaxel group experienced TEAEs.

Fatal TEAEs occurred in 48 (16.1%) patients in the adagrasib arm and 10 (7.1%) patients with docetaxel; the most common cause of fatal TEAE was malignant neoplasm progression (22 [7.4%] in the adagrasib arm, and 5 [3.6%] in the docetaxel arm). Fatal TEAEs classed as treatment-related by the investigator occurred in 4 (1.3%) and 1 (0.7%) participants in the adagrasib and docetaxel arms, respectively. These fatal events were hepatic failure, hepatic ischaemia, death (unknown cause), and epilepsy in the adagrasib group and sepsis in the docetaxel group. In response to clarification point A2a, the company noted that the [redacted] of fatal TEAEs in the adagrasib arm may be explained by the [redacted] However, no additional analyses were provided to support this statement, therefore the EAG is unable to comment on its validity. Grade ≥ 3 TEAEs occurred in 213 (71.5%) with adagrasib and 93 (66.4%) with docetaxel. Serious TEAEs were experienced by 149 (50%) with adagrasib compared to 50 (35.7%) with docetaxel. TEAEs led to treatment discontinuation for 40 (13.4%) patients on adagrasib and 25 (17.9%) on docetaxel. TEAEs that led to dose reductions or interruption were reported in 237 (79.5%) with adagrasib and 67 (47.9%) with .

The most common Grade ≥ 3 TEAEs were ALT increased (9.1% of patients on adagrasib vs 0 patients on docetaxel), malignant neoplasm progression (7.7% vs 3.6%), AST increased (6.7% vs 0), gamma-glutamyltransferase increased (6.4% vs 1.4%), diarrhoea (5.7% vs 4.3%), asthenia (5.4% vs 11.4%), fatigue (5.0% vs 2.1%), anaemia (4.7% vs 5.7%), pneumonia (4.4% vs 7.1%), neutropenia (2.0% vs 10.0%), neutrophil count decreased (1.3% vs 11.4%), and white blood cell count decreased (0.7% vs 5.7%). Hepatoxicity is summarised in CS Section B.2.10.4.

Overall, the company concluded that adagrasib and docetaxel had different safety profiles, and that the low-grade nature of key TEAEs along with PROs indicate that adagrasib is generally tolerable with a manageable safety profile (CS Section B.2.10.5). The EAG believes that these conclusions fail to recognise that, despite the fact adagrasib is a targeted therapy and given the known toxicity of docetaxel, there is insufficient evidence to show that the safety and tolerability profile of adagrasib is superior to that of docetaxel. The higher incidence of fatal TEAEs in the adagrasib arm is of particular concern. The incidence of Grade ≥ 3 TEAEs, and TEAEs leading to dose reduction or interruption was also numerically higher in the adagrasib arm compared with the docetaxel arm.

Adagrasib is associated with a higher incidence of hepatic adverse events (including fatal events) compared with docetaxel (see CS B.2.10.4); based on the results of KRYSTAL-1 the trial did not include a washout period and was not designed to evaluate whether prior exposure to immunotherapy and the time gap between immunotherapy discontinuation and initiation of adagrasib affected the incidence or severity of hepatic TEAEs. The EAG clinical adviser commented that hepatoxicity after immunotherapy is thought to be less of a concern with adagrasib than with sotorasib. Although cross-over from docetaxel to adagrasib was only permitted for patients whose disease progressed, as discussed in Section 3.2.1.1, knowledge of the safety profiles of the two drugs and lack of blinding may have affected the rates of discontinuation and switching to newer generation therapies in the docetaxel arm.

3.2.2 KRYSTAL-1

3.2.2.1 Methods

KRYSTAL-1 (NCT03785249) is a US-based, multicentre, open-label, single-arm dose-escalation and multiple expansion cohort, phase 1/2 trial. The CS presented the results of the phase 2, Cohort A which enrolled 116 patients with NSCLC previously treated with platinum-based chemotherapy and anti-PD-1/L1 therapy, and who received adagrasib at a starting dose of 600 mg twice daily orally.

The primary outcome was ORR assessed by BICR. Secondary outcomes included OS, PFS, DOR rates and adverse effects of treatment. Disease evaluation was conducted at screening (with a 28-day window allowed) and every 6 weeks from randomisation (+/- 10 days) until Week 49, then every 12 weeks.

Eligibility criteria are reported in CS Table 8. Overall, these were comparable with KRYSTAL-12, although only KRYSTAL-1 permitted patients with prior docetaxel therapy.

Baseline characteristics

Baseline characteristics are presented in CS Table 11. Although the study was conducted in the US exclusively, the EAG's clinical adviser considered these to be broadly representative of UK clinical practice. The company stated that the baseline characteristics of KRYSTAL-12 were similar to those

of KRYSTAL-1. Whilst the EAG agrees this is true for most of the baseline characteristics, KRYSTAL-1 included a lower percentage of male participants (44.0%, vs. 64.1% and 72.4% in the adagrasib and docetaxel arms of KYRSTAL-12, respectively), a higher percentage of white ethnicity (83.6% vs. 44.9% and 53.3%), a higher percentage of ECOG 1 (83.6% vs. 68.1% and 68.4%). Whilst nearly all (98.3%) KRYSTAL-1 patients had received both platinum and checkpoint inhibitor therapy, they were also more likely to have received more than one prior systemic regimen, and had a higher median number of prior systemic regimens compared with KRYSTAL-12 (median 2.0 [range 1-7] in KRYSTAL-1, vs. 1.0 [range 1-5] and 1.0 [range 1-4] in the adagrasib and docetaxel arms of KYRSTAL-12, respectively); 22.4% had received three or more systemic therapies A total of 17 (14.7%) patients in cohort A had prior docetaxel therapy versus none in KRYSTAL-12.

Risk of bias

The quality assessment was performed using a modified version of the CASP checklist, with results presented in CS Appendix Table 8. The EAG generally agrees with the company's assessment.

The main limitation of KRYSTAL-1 is its lack of control arm, which prevents any direct comparison of the relative effectiveness and safety of adagrasib against standard of care. This significantly limits the relevance of KRYSTAL-1 to the decision problem.

Although all 116 patients (100%) received at least 1 dose of study medication and were included in the safety population and full analysis set evaluated by investigator, four out of 116 participants did not have measurable disease at baseline by BICR, and 112 (96.6%) were included in the full analysis set (FAS) BICR assessment. Given the small percentage of missing patients, the impact on BICR assessed outcomes is likely to be minimal.

Applicability to NHS practice

The EAG has some concerns regarding the applicability of KRYSTAL-1 to UK clinical practice. Similarly to KRYSTAL-12, the KRYSTAL-1 trial includes a narrower population than its MHRA license and the corresponding NICE scope. The applicability of KRYSTAL-1 results to patients who are intolerant to platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy, or to patients with no prior chemotherapy, is uncertain.

All patients included in KRYSTAL-1 were from US centres and were more heavily pre-treated on average than in UK clinical practice. Unlike KRYSTAL-12, KRYSTAL-1 included a subset of patients (14.7%) with prior docetaxel therapy, which is higher than in UK practice. KRYSTAL-1 only included patients with an ECOG performance status of 0 or 1, which may limit the applicability of the trial to less fit patients.

3.2.2.2 Results

Clinical effectiveness results of KRYSTAL-1 are presented in CS Section B.2.6.2, with further details in CS Appendix N. Results were presented at a data cut of 15 October 2021, except for OS for which results were presented up to a data cut of 15 January 2022, at a median follow-up of 15.6 months.

Results of the phase 1/1B that preceded the phase 2 are not presented in the CS but are reported in a separate publication as they included non-NSCLC patients, except for a subset of NSCLC patients with neurologically stable, asymptomatic, untreated CNS metastases (n=25).[21, 22] Intracranial efficacy in this cohort is discussed in CS Section B.2.7.2 along with KRYSTAL-12 data for the subset of patients with brain metastases.

Progression-free survival

After a median follow-up of 12.9 months, 66 (58.9%) PFS by BICR events were reported. Median PFS was 6.5 months (95% CI 4.7 to 8.4). Censoring rate PFS (BICR) was [redacted] at the October 2021 data cut. Reasons for censoring were presented in response to an EAG clarification request (clarification question A9c) and did not raise significant concerns; [redacted], censored patients were continuing on study treatment without progressive disease.

Time to progression

TTP, which corresponded to PFS censoring for death events, was reported in CS Appendix Figure 25. Although TTP was not a protocol-specified outcome in KRYSTAL-1, IPD from this outcome was used to estimate a surrogacy relationship between TTP and OS. This is further discussed in Section 3.2.3.

Overall survival

After a median follow-up of 15.6 months, 61 (52.6%) death events were reported. Median OS was 12.6 months (95% CI 9.2 to 19.2). CS Figure 16 presents a Kaplan-Meier curve for OS at the January 2022 data cut. Compared with the KRYSTAL-12 interim analyses, the KRYSTAL-1 KM curve shows a similar pattern for adagrasib, although with less early censoring.

The censoring rate for OS was [redacted] at the January 2022 data cut. Reasons for censoring were presented in response to an EAG clarification request (clarification question A9c) and did not raise significant concerns; [redacted], censored patients were continuing on study treatment without progressive disease; a [redacted] were still on treatment following progression.

In response to a request for clarification (question A9b), the company reported that a total of [redacted] of out of [redacted] FAS patients who were in PD (by BICR) received subsequent anticancer therapies, and [redacted] received a subsequent therapy before progressive disease. This means that [redacted] of the FAS received a subsequent anticancer therapy. Given the relatively limited

number of patients concerned and limited efficacy of subsequent therapies in this setting, the potential impact from subsequent anticancer therapies is likely to be small.

Response rates

ORR was 42.9% (95% CI, 33.5 to 52.6), with one patient achieving a CR and 47 patients achieving a PR. Median DOR in responders was 7.3 months (95% CI 5.1 to NE).

Health-related quality of life

HRQoL was not an endpoint in KRYSTAL-1.

Safety

Safety results for the safety population of KRYSTAL-1 are presented in CS Appendix F2. The safety population included all 116 patients who had received at least one dose of adagrasib.

The mean duration of exposure to adagrasib was 5.8 months (SD 4.02). Mean compliance with adagrasib was 85.9% (SD 16.7), lower than in KRYSTAL-12 (mean 98.3%, SD 5.1). Mean overall relative dose intensity was 75.5% (SD 22.2) of the 600mg dose for adagrasib and similar to KRYSTAL-12 (77.7%, [SD 20.5]).

All 116 (100%) patients experienced TEAEs. Twenty (17.2%) patients died; the most common cause of death was malignant neoplasm progression (8 [6.9%]). Fatal TEAEs classed as treatment-related by the investigator occurred in 2 (1.7%) patients (cardiac failure and pulmonary haemorrhage). Grade ≥3 TEAEs occurred in 94 (81.0%). Ninety-five patients (81.9%) had dose reductions or interruptions because of TEAEs and 17 patients (14.7%) discontinued adagrasib because of TEAEs. Serious TEAEs were experienced by 70 (60.3%).

3.2.3 Surrogacy analysis using KRYSTAL-1 to inform OS in KRYSTAL-12

In the absence of a conclusive interim OS analysis from KRYSTAL-12, data from the single-arm phase 1/2 KRYSTAL-1 study was used to inform a patient-level surrogacy analysis in order to (i) assess the relationship between progression and survival at the individual-level for patients with *KRAS* G12C mutation-positive NSCLC, and to (ii) predict OS for KRYSTAL-12 in censored patients for both adagrasib and docetaxel using the individual-level surrogacy relationship derived from KRYSTAL-1 and applied to progression data from KRYSTAL-12. The predicted KRYSTAL-12 OS from the surrogacy analysis is used to inform the company's NMA and cost-effectiveness analysis.

Methods

IPD from KRYSTAL-1 were used to estimate a relationship between TTP and OS for patients with previously treated advanced *KRAS* G12C mutation-positive NSCLC. The estimated relationship was then applied to separate TTP data from each arm of KRYSTAL-12 to generate 'simulated' KRYSTAL-12 OS data in censored patients for both adagrasib and docetaxel. The company states

that the key benefit of this patient-level surrogacy approach is that it allows information in KRYSTAL-1 and KRYSTAL-12 to be used, whilst maintaining consistency in the target population for patients with *KRAS* G12C mutation-positive NSCLC across the progression and OS endpoints. The approach also allows covariates to be accounted for when predicting OS. In the company's base case analysis, ECOG performance status (PS) 0 or 1 is the only covariate included; the company states that the covariates of age ≥65 years and gender produced similar results to the base case, while other covariates such as disease stage, histology (squamous vs non-squamous), and smoking status were not included due to the small proportions of patients presenting with these characteristics in KRYSTAL-1.

The patient-level surrogacy analysis was based on adapting the joint frailty-copula model proposed by Emura et al. (2017)[23] and developed as a tutorial paper for application by Emura et al. (2022).[24] Details of the technical specification are presented in Appendix P of the CS. The joint frailty-copula model focuses on the association between TTP and OS in the form of a bivariate model and leverages the model first described by Rondeau et al., (2015),[25] where the hazards for TTP and OS are specified within a meta-analytic framework that takes into account the study-specific random effects in a meta-analysis. In this approach, the baseline hazards are approximated using cubic M-splines, adjusted for covariates, which capture the dynamic behaviour of the two hazards for TTP and OS. Inference under the cubic spline approximation is implemented with a penalised maximum likelihood estimator and the statistical computation implemented in the software R using the *joint.Cox* package.

Emura et al. (2017)[23] generalises the joint frailty model of Rondeau et al., (2015)[25] by accounting for the intra-subject dependence between TTP and OS using IPD from studies, in addition to the study-specific random effects from a meta-analysis. The method is used for validating the surrogate relationship between TTP and OS in the meta-analytic framework, where the Clayton copula is used to describe the dependency between TTP and OS and the strength of the association between endpoints related to Kendall's tau statistic.[23] The proposed model also allows for predictions of OS from the validated surrogate endpoint using dynamic simulation given progression status and death events.

The company adapted the proposed model by Emura et al. (2017)[23] and application in Emura et al. (2022) [24, 26] in the following ways:

- The meta-analytic approach was modified to use a single data source (i.e., the KRYSTAL-1 study only), such that the meaning of the unobserved cluster-level study frailties (i.e., study-level random effects) were used to represent individual-level random effects instead.
- The dynamic simulation was used to simulate OS event times for a cohort of alive individuals rather than a single alive individual.

- Simulation was run for a set time period, which was set to be the maximum observed event time. However, the survival curves from KRYSTAL-1 showed flat tails with few events due to few participants at risk at later times. To avoid over-reliance of the simulated events on the tails, the data from KRYSTAL-1 were censored when 5% or less of participants were still at risk of a progression event.

The model was fit using IPD for adagrasib from KRYSTAL-1 (data cutoff: October 2021, n=116). Participants with missing PFS data (n=4) were removed prior to model fitting. Goodness of fit to determine the internal validity of the predicted model was evaluated by comparing the simulated OS for KRYSTAL-1 based on the surrogacy model with the observed OS from KRYSTAL-1 (see Appendix P Figure 25) and relative differences in restricted mean survival time (RMST). The visual fit was good and the relative difference in RMST was [redacted], which suggests good internal validity of the surrogacy model with KRYSTAL-1. However, the company did not assess external validity of the predicted model to the target population with *KRAS* G12C mutation-positive NSCLC. The surrogacy relationship between TTP and OS from KRYSTAL-1 was applied to separate TTP data from each arm of KRYSTAL-12 to generate 'simulated' KRYSTAL-12 OS data for both adagrasib and docetaxel.

Results

The predicted KRYSTAL-12 OS curves for adagrasib and docetaxel are presented in CS Figure 26. These resulted in a median survival of [redacted] for adagrasib and [redacted] for docetaxel, with [redacted].

Points for critique

The use of a surrogacy relationship to infer OS requires good evidence that the relative effect of the treatment on the surrogate end point is predictive of its relative effect on the final outcome (i.e., the HR of adagrasib vs. comparators on progression is predictive of the corresponding HR on OS).[27] The NICE manual (Sections 4.6.7 - 4.6.8)[27] states that the evidence to support a consistent association between the surrogate endpoint and final outcome should preferably come from a meta-analysis of level 1 evidence (i.e., RCTs) reporting both the surrogate and the final outcomes, using bivariate meta-analytic methods. Furthermore, the biological plausibility of the surrogacy relationship should be established, and its validity demonstrated for both the target population and the treatments considered. The EAG considers that the company have not followed the recommendations set out in the NICE manual and the evidence supporting the surrogacy relationship based on a single-arm phase 1/2 study is weak and has not been sufficiently validated.

The EAG considers the following critique points in relation to the company's surrogacy analysis:

1. Evidence to support trial-level relative effect associations and the biological plausibility of a surrogacy relationship between progression and OS for *KRAS* G12C inhibitors and for docetaxel in a *KRAS* population.
2. Choice of model used to inform the surrogacy analysis.
3. Association between progression and OS in external studies to support the validity of the surrogacy analysis.

Evidence to support trial-level relative effect associations

The approach used by the company represents the first surrogacy analysis of targeted therapies for *KRAS* inhibitors in NSCLC. The company have highlighted two previous studies that examined the strength of surrogacy between PFS and OS at trial-level and arm-level from phase 2 and 3 studies in NSCLC, but these do not include *KRAS* inhibitors. In the analysis by Hua et al. (2022),[28] trial-level associations of PFS HR for targeted therapy and immunotherapy was considered at most a modest surrogacy for OS HR, with better association for treatments at 1L (Spearman's rank correlation coefficient, R=0.768 [95% CI 0.621, 0.863]) compared to second-line (R=0.550 [95% CI 0.377, 0.686]). A similar association at 1L- and 2L was also derived in Horita et al. (2022)[29] from a surrogacy analysis evaluating progression and survival at patient-level in trials of immune checkpoint inhibitors (R=0.71 at 1L and R=0.59 at 2L+). In response to EAG clarifications (question A3), the company states that this previous research has established the biological plausibility of a relationship between PFS and OS in NSCLC, which supports a moderate association between the two endpoints. However, the EAG notes that the strength of the association varies between 1L and 2L, treatment class and trial phase. Therefore, previous evidence to support trial-level associations between the relative effect of targeted therapies on progression that are commensurate of the effect on OS in NSCLC is largely dependent on the treatments received and the setting, and cannot be used to reliably predict OS for KRYSTAL-12 with a *KRAS* G12C inhibitor (adagrasib). Furthermore, the company have not assessed whether a trial-level surrogacy for the broader NSCLC population might be applicable to the target population, over and above reporting the findings from the two previous studies by Hua et al. (2022)[28] and Horita et al. (2022).[29]

Importantly, the EAG notes that none of the surrogacy analyses in NSCLC have examined the relationship between progression and survival in *KRAS*-mutations or included *KRAS* inhibitors. However, the limited number of trials in the target population with *KRAS* G12C mutation means that evaluating a trial-level surrogacy between progression and survival for *KRAS* G12C mutation-positive NSCLC would be limited to examining the relationship in CodeBreaK 200, the only RCT with mature OS data that evaluated a *KRAS* G12C inhibitor in *KRAS* G12C mutated patients with advanced NSCLC with prior platinum chemotherapy and anti PD-(L) immunotherapy. CodeBreaK 200 found a statistically significant improvement in PFS for sotorasib compared with docetaxel monotherapy, but no statistically significant improvement in OS. There was no evidence that crossover from the docetaxel arm to sotorasib had a significant impact on OS. A critique of CodeBreaK 200 is provided

in Section 3.3. Therefore, there is currently no evidence that improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC.

In response to clarifications (question A3) the company do not consider CodeBreaK 200 to provide sufficient evidence of presence or absence of a surrogacy relationship between PFS and OS for two main reasons: (i) concerns regarding the conduct and results of the CodeBreaK 200 trial as highlighted by the FDA[13] and (ii) while adagrasib and sotorasib belong to the same class of treatments they are not the same molecule, sotorasib has a shorter half-life than adagrasib, which the company states has the potential for allowing reactivation of the *KRAS* pathway.

One further key assumption underlying the company's approach is that the surrogacy relationship between progression and survival for a *KRAS* G12C mutation-targeted therapy (adagrasib) from the single arm KRYSTAL-1 trial can be applied equally to a non-*KRAS* targeted therapy (docetaxel), i.e., the same relationship between TTP and OS for a *KRAS*-targeted therapy holds for a non-targeted therapy. With the limited number of trials in the target population with *KRAS* G12C mutation it is not possible for the EAG to assess whether the surrogacy relationship is exchangeable between *KRAS*-targeted and non-targeted therapies, although the evidence from the previous trials for the broader NSCLC population suggests that this is not the case because the strength of the association varies by treatment class and line of treatment.[28, 29]

Joint frailty-copula model used to inform the surrogacy analysis

The surrogacy analysis used in the CS represents a *de-novo* analysis based on adapting the joint frailty-copula model proposed by Emura et al. (2017).[23] This appears to be the first application of the use of the joint frailty-copula model in an HTA submission (note that the EAG does not have access to the data used in the CS to reproduce the surrogacy analysis used to predict OS for KRYSTAL-12). The joint frailty-copula model by Emura et al. (2017)[23] focuses on the association between TTP and OS. In the context of the surrogacy analysis, TTP was derived based on PFS, where patients were censored at time of death, rather than considering deaths as events within the definition of PFS (i.e., a PFS event may be progression or death). This means that any deaths from other causes or toxicities are effectively censored out of the surrogacy analysis. In response to EAG clarifications (question B1f) the company justified the choice of TTP over the primary endpoint of the trials of PFS to align with the structure of the joint frailty-copula model in Emura et al. (2017),[23] where the final endpoint can censor the surrogate endpoint (i.e., OS events censor TTP but not PFS). Furthermore, since the company was interested in predicting absolute OS using the surrogate endpoint rather than examine or validate the association between TTP/PFS and OS, the use of TTP was preferred over PFS because it removed the dependency between endpoints where both OS and PFS contain death events. The EAG considers the company's choice of TTP as the surrogate endpoint to be reasonable in light of the additional uncertainties introduced by using PFS.

In Emura et al. (2017)[23] the surrogate relationship between TTP and OS is derived within a meta-analytic framework. The company modified the meta-analytic approach to use a single data source with individual-level data such that the meaning of study-level random effects was changed to represent individual-level random effects instead. The EAG is not aware of any other applications of the methods that have changed the interpretation of the study-level effects. Importantly, the joint frailty-copula method was specifically developed to address the limitations of standard bivariate survival models in the literature that were not tailored for meta-analysis. Therefore, the EAG is unclear why a joint frailty-copula model is required when the company are only using a single study to derive the surrogacy relationship between progression and survival. Other regression-based predictive models, such as those proposed by Wang et al (2016),[30] could be considered as alternative approaches to predict OS from surrogate outcomes.

The EAG believes that the company should have undertaken a systematic literature review to identify all alternative approaches and assessed the advantages of using the joint frailty-copula method over other alternative approaches in the literature. Given that the company was only using a single study and had access to IPD from this study, the EAG considers it appropriate to assess alternative models to see whether they lead to similar predictions of OS; however, the EAG acknowledges that since the company have used a single arm study, the choice of alternative approaches may be limited because alternative bivariate survival models are used to predict a relative effect for OS, such as a HR, rather than predict absolute OS. It is unclear whether the model properties still hold in this single study scenario.

In the joint frailty-copula method, the Clayton copula is used to describe the dependency between TTP and OS. In EAG clarifications (question B2b), the EAG requested justification for the specific choice of copula (Clayton) because different copula functions generate a different dependence structure between outcomes, and to clarify whether any alternative copulas were considered, such as the Hougaard and Frank copula functions. The company indicated that the Clayton copula was chosen for consistency with the methods outlined in Emura et al. (2017).[23] The literature on copulas suggests that the theoretical properties of different copula functions should be considered alongside the best fitting copula when selecting the most appropriate copula to describe the dependency between outcomes.

The strength of the association between TTP and OS in the surrogacy analysis is related to Kendall's tau statistic, but the literature providing guidance on the interpretation of Kendall's tau in the context of a surrogacy relationship is limited. The company acknowledged in its response to EAG clarifications (question B2c) that this makes it challenging to assess the strength of association between TTP/PFS and OS from the surrogacy analysis. Kendall's tau was [redacted] for the association between TTP and OS in the company's surrogacy analysis, which the EAG judge to be low to moderate. In a separate poster

presentation, the company also examined the surrogacy relationship between PFS and OS using the same joint frailty-copula method;[31] this analysis showed a higher strength of association between PFS and OS with a Kendall's tau of [redacted], but the company argues that this stronger association should be interpreted with caution because it is likely to have been driven by the inclusion of deaths in the definition of PFS, which are excluded from TTP. Nonetheless, the EAG notes that the internal validity of the surrogacy analysis was very good as demonstrated by the goodness of fit of the simulated OS for KRYSTAL-1 based on the surrogacy model with the observed OS from KRYSTAL-1 (Appendix P Figure 25). Therefore, the EAG is reasonably satisfied that the surrogacy relationship generated from the KRYSTAL-1 single arm study is a good reflection of the observed KRYSTAL-1 OS.

External validity of the surrogacy analysis

The true test of the strength of the surrogacy relationship for predicting OS in the target population is with application to *KRAS* G12C mutation-positive NSCLC, i.e., an assessment of the external validity of the surrogacy analysis for *KRAS* inhibitors. The CS does not report an assessment of external validity, but in response to EAG clarifications (question B1b) the company refers to a poster presentation with external validation to the docetaxel arm of the SAPPHIRE trial.[31] SAPPHIRE is a phase 3 RCT that compared sitravatinib plus nivolumab against docetaxel in patients with advanced non-squamous NSCLC previously treated with platinum-based chemotherapy and a checkpoint inhibitor. Eligibility was not restricted by *KRAS* mutation status. The simulated OS predictions for the docetaxel arm of SAPPHIRE performed well for the TTP-OS model and less well for the PFS-OS model.[31] The company do not provide justification for the choice of the SAPPHIRE trial for external validation, which did not include *KRAS* inhibitors or restrict eligibility by presence of a *KRAS* mutation. The EAG notes that the only trials available in the target population to assess the validity of the surrogacy analysis are the CodeBreaK 200[11] or CodeBreaK 100[9, 10] (single arm trial of sotorasib). While the company may not have access to IPD from these trials, pseudo-IPD could be generated from the Kaplan-Meier PFS from these trials and used to assess the external validity of the surrogacy analysis for predicting OS in the population of interest. In the absence of this, there is no external validation of the predicted model to *KRAS* G12C mutation-positive NSCLC.

OS prediction

The EAG also notes that the company is predicting OS for the same length of follow-up time as KRYSTAL-1, but with data from KRYSTAL-1 censored when 5% or less of participants are still at risk of a progression event. Consequently, the EAG is concerned that the predicted OS estimates are overly precise in the company's surrogacy analysis because uncertainty arising from the long flat tails with few events due to few participants at risk at later time points is not reflected in the precision of the estimates. The resulting 'simulated' KRYSTAL-12 OS data for both the adagrasib and docetaxel arms based on the surrogacy analysis is likely to be underestimating the true uncertainty.

Summary of EAG's key points

The company used a within-study relationship based on analysis of the KRYSTAL-1 single-arm phase 1/2 trial to predict absolute OS (rather than surrogacy based on relative effect as recommended in NICE methods guide). This relationship may be weak and has not been externally validated in the target population, although internal validity is acceptable. It is unclear to what extent this relationship produces valid predictions for KRYSTAL-12 OS. A key requirement for using a surrogate in place of the relevant clinical endpoint is that the effect of the treatment on the surrogate endpoint reliably predicts the effect of the treatment of the endpoint of interest.[27] This has not been demonstrated for the relevant population and interventions.

The company's predictions of OS for KRYSTAL-12 are used to inform the NMA and cost-effectiveness analysis. These predictions are based on a surrogacy analysis from one study with a single arm, expressed in terms of the relationship between absolute outcomes rather than relative effects, and based on a single method that has been adapted from a different meta-analytic context and applied to a single study. The EAG is, therefore, concerned with the high level of uncertainty in the OS results.

3.3 Critique of comparator trials identified and included in the network meta-analysis

As KRYSTAL-12 only provides evidence on the efficacy and safety of adagrasib against docetaxel, an NMA was conducted to compare the relative efficacy and safety of adagrasib to nintedanib+docetaxel and sotorasib.

3.3.1 Study selection

The company's SLR of clinical effectiveness evidence (CS, Section B.2.1 and Appendix D) identified 196 unique RCTs and 123 unique single-arm/non-randomised trials. This included 95 RCTs and 7 non-RCTs of docetaxel monotherapy, one RCT and one non-RCT of docetaxel+nintedanib, and one RCT and one non-RCT of sotorasib. Among these results, two RCTs were considered relevant and retained for the company's NMA: LUME-Lung 1,[32] and CodeBreaK 200.[11] Reasons for the exclusion of most of the RCT evidence were not reported. The EAG checked the table of studies that were included in the company SLR and subsequently excluded from the NMA. Most of the evidence identified included populations and interventions outside of the NICE final scope. The EAG clinical adviser considered that it is unlikely that relevant studies were missed, and the EAG is not aware of any other relevant RCTs for inclusion in the NMA.

Three RCTs were included in the company's NMA, including one trial of adagrasib vs. docetaxel (KRYSTAL-12), one trial of docetaxel+nintedanib vs. docetaxel+placebo (LUME-Lung 1),[32] and one trial of sotorasib vs. docetaxel.[11] In addition, data from KRYSTAL-1 was used to inform OS estimates for adagrasib via a surrogacy relationship between TTP and OS (see Section 3.2.3).

The company argued that it was necessary to include sotorasib in the indirect comparison as it was included in the final scope issued by NICE as subject to managed access review. As discussed in Section 2.3, the EAG agrees with the company that, as sotorasib is only available in the CDF and timelines for the review of sotorasib (TA781) are not publicly available, sotorasib is not a relevant comparator within the context of this appraisal. Due to the absence of loops in the network (i.e. adagrasib, docetaxel+nintedanib and sotorasib are only directly compared with docetaxel), the inclusion of CodeBreaK 200 does not affect the summary estimates of relative effectiveness between the other interventions included in the network.

3.3.2 Design, applicability and risk of bias of comparator trials

3.3.2.1 LUME-Lung 1

The design of LUME-Lung 1 is summarised in CS Section B.2.9.3. LUME-Lung 1 is a phase 3 multi-centre RCT that enrolled a total of 1,314 patients, of whom 655 were assigned to treatment with docetaxel + nintedanib and 659 were assigned to treatment with docetaxel + placebo. Docetaxel was administered 75 mg/m² by intravenous infusion on day 1 plus either nintedanib 200 mg orally twice daily or matching placebo on days 2–21, every 3 weeks until unacceptable adverse events or disease progression. Eligible patients had stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy. Randomisation was stratified by ECOG status, previous bevacizumab treatment, histology, and presence of brain metastases. Participants were included irrespective of their *KRAS* mutation status or histology, with only platinum-based exposure in prior lines but no anti-PD-(L)1 therapy exposure.

In the company's clarification response, Table 27 presents the characteristics of the LUME-Lung 1 population. The proportion of *KRAS* mutation in LUME-Lung 1 is unknown. Half of the patients had adenocarcinoma, which is significantly smaller than in UK practice, where most patients with *KRAS* G12C mutation have adenocarcinoma. A subgroup analysis of patients with adenocarcinoma only was reported in the trial publication for OS and PFS, but the baseline participant characteristics of this subgroup were not presented. Patients were recruited between December 2008 and February 2011, which precedes the era of anti-PD-(L)1 therapy, and nearly all patients had only received a platinum agent as their prior line of systemic therapy. The trial was conducted in 27 countries and the number of UK sites was unknown. Overall, the applicability of the LUME-Lung 1 population to the NICE scope population is limited. The adenocarcinoma-only subgroup population is likely to be more applicable to the decision problem, although it remains limited due to the lack of *KRAS* G12C specific data and lack of prior anti-PD-(L)1 exposure. Concerns about potential differences in effect modifiers between LUME-Lung 1 and KRYSTAL-12 are discussed in Section 3.4.1.

The company's critical appraisal of LUME-Lung 1 is reported in CS Appendix D.2.4. Overall, the company found that LUME-Lung 1 was at low risk of bias. The EAG agrees with this assessment, which is also consistent with the company's and EAG's assessment in TA347.[1] Although the

characteristics of the adenocarcinoma subgroup were not presented, the trial publication reported that demographics and baseline characteristics, including the predefined stratification factors, were balanced across treatment groups in this subgroup.[32]

3.3.2.2 CodeBreaK 200

The design of CodeBreaK 200 is summarised in CS Section B.2.9.3. CodeBreaK 200 is a phase 3, open-label multi-centre RCT that enrolled 345 participants, of which 171 were randomised to sotorasib and 174 to docetaxel. Sotorasib was administered 960 mg once daily and docetaxel or intravenously 75 mg/m² once every 3 weeks. Eligible patients had *KRAS* G12C-mutated locally advanced and unresectable or metastatic NSCLC, who progressed after previous platinum-based chemotherapy and an anti-PD-(L)1 inhibitor. Randomisation was stratified by number of previous lines of therapy in advanced disease, ethnicity (Asian vs non-Asian), and history of CNS metastases. Crossover from docetaxel to sotorasib was permitted.

In the company's clarification response, Table 27 presents the baseline characteristics of CodeBreaK 200 participants. It is unclear whether any patients were recruited in UK centres and details about age distribution were limited, although overall, the EAG clinical adviser considered the reported baseline characteristics to be broadly reflective of 2L+ *KRAS* G12C patients in UK practice.

The EAG generally agreed with the company's quality assessment of CodeBreaK 200 (CS Appendix D.2.4), except for the allocation concealment item. Unlike the company's assessment, the EAG has no significant concerns about allocation concealment in CodeBreaK 200. As per Cochrane guidance, allocation concealment can always be successfully implemented regardless of the RCT design, therefore the EAG disagrees with the company that the open-label design prevented CodeBreaK 200 from having adequate allocation concealment.[33] Random allocation was performed via interactive response technology (IRT) and the study protocol indicated that randomization numbers were to be provided to study sites by the IRT system. Although no further details were reported, the EAG found no evidence that allocation concealment was inadequate.

However, the EAG has several concerns about the quality of the CodeBreaK 200 trial, notably due to early asymmetric dropout, censoring and crossover, the duration of interval between assessments, and lack of blinding. Overall, the EAG considers the CodeBreaK 200 to be at high risk of bias.

Early asymmetric dropout, censoring and crossover

Early asymmetric dropout was observed before patients received their first dose (1.2% in the sotorasib arm, vs. 13% in the docetaxel arm). The EAG believes this may have been influenced by patients and investigators' knowledge of the intervention assigned and the perception that docetaxel may perform poorly compared with a newer generation, targeted therapy. Olivier et al. (2023) estimated that 16% of patients in the sotorasib arm were censored during the first 6 months, compared with 33% of patients in the docetaxel arm.[34] It is unclear whether the prognosis of patients with early dropout differed

systematically from those who remained in the trial, therefore the potential impact of early asymmetric dropout on the trial results is uncertain.

Overall, 26% of patients in the docetaxel arm crossed over to sotorasib; in 11%, early crossover by investigators was observed in the docetaxel arm before confirmation of PD. An exploratory comparison of survival reported by the FDA indicated that early crossover patients may be healthier than those who did crossover after BICR assessed PD (HR of 0.42 with 95% CI: 0.19, 0.95).[14] The FDA also performed additional sensitivity analyses suggesting no significant impact of early dropout or crossover on OS, but also indicating that crossover to sotorasib is unlikely to explain the lack of OS benefit observed in the trial.[13]

To explore the impact of crossover on OS in CodeBreaK 200, the German Gemeinsamer Bundesausschuss (G-BA) submission presented OS results adjusted for crossover.[35] Results are presented in Table 6 and were somewhat inconsistent across the different adjustment methods used.

Table 6 CodeBreaK 200 crossover adjusted OS results in the G-BA submission

OS analysis	*HR (95% CI)*
ITT (primary)	1.010 (0.766, 1.331)
Cross-over adjusted	
RPSFT	1.010 (0.660, 1.492)
IPCW	0.990 (0.733, 1.337)
Two-step	0.885 (0.172, 1.328)

Source: AMGEN submission to G-BA[35]

Abbreviations: IPCW, inverse-probability-of-censoring weighting; ITT, intention to treat; RPSFT, rank preserving structural failure time model.

The EAG agrees with Olivier et al. (2023)[34] that allowing for crossover is particularly problematic in the absence of any other evidence establishing the OS treatment benefit of sotorasib vs. docetaxel in a randomised setting. This limitation hinders the interpretation of how crossover to the control arm impacted on the sotorasib treatment effect.

Interval between assessments of disease progression

As per protocol, disease progression assessments were performed every six weeks in all patients. Disease progression events could have occurred any time within this interval before being detected. The observed median PFS benefit was 1.1 months (median PFS was 5.6 months in the sotorasib arm, vs. 4.5 months in the docetaxel arm), which is less than the six-weeks assessment interval. Using an interval-censoring analysis which randomises the timing of PFS events, the FDA showed that the PFS benefit of sotorasib over docetaxel could be as little as five days, which is significantly shorter than the observed PFS benefit. The risk that PFS estimates may have been biased by the interval in disease progression assessments cannot be excluded.

Lack of blinding

As with KRYSTAL-12, the fact that response outcomes were assessed by BICR limits the risk of performance bias due to lack of blinding of participants and study personnel. However, the subjective nature of PROs means that HRQoL outcomes in CodeBreaK 200 may have been overestimated.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Similarity of trials included in the company NMA

Details of trial designs and populations are summarised in CS Section B.2.9.3, with further details in CS Appendix D.3.1.

3.4.1.1 Populations

The NMA requires that the distribution of patient characteristics that predict the relative treatment effects (treatment effect modifiers) is similar across treatment comparisons in the network (exchangeability assumption). The trial participant populations of the three RCTs included in the NMAs are presented in the company's response to clarification question A13, Table 27. This shows that the population of the LUME-Lung 1 trial differs substantially from KRYSTAL-12[36] and CodeBreaK 200, most notably in prior immunotherapy exposure and histology. Other notable differences include age, metastases and number of prior therapies.

Prior immunotherapy exposure

All patients in the KRYSTAL-12 or CodeBreaK 200 trials were required to have received immunotherapy and platinum chemotherapy prior to *KRAS* G12C-targeted treatment. Most patients (> 95%) in LUME-Lung 1 had received platinum chemotherapy, however, the trial was conducted before immunotherapy was approved as 1L therapy in NSCLC and therefore patients had no prior treatment with checkpoint inhibitors.

In response to request for clarification, the company discussed whether prior immunotherapy might predict outcomes of nintedanib+docetaxel. They noted that the results of J-ALEX, a phase 3 RCT of patients with advanced NSCLC previously treated with cytotoxic chemotherapy, showed no significant difference in OS between docetaxel and pemetrexed in patients without prior immunotherapy (HR 0.91; 95% CI 0.72-1.14), whereas a strong treatment effect was observed in patients with prior immunotherapy (HR 0.43; 95% CI 0.24-0.79). PFS results were similar between the subgroups. The company recognised that prior immunotherapy might predict outcomes of nintedanib + docetaxel, although they noted that any reliable inferences on the effect of between-study differences on NMA results were challenging. The EAG agrees with the company's interpretation. Overall, given the limited evidence, it is uncertain whether prior immunotherapy exposure may affect the relative OS benefits of nintedanib+docetaxel compared with docetaxel monotherapy.

Histology

Only 50% of LUME-Lung 1 patients had adenocarcinoma, unlike most of the KRYSTAL-12 population (95%), and most of CodeBreaK 200 patients (97%) who had non-squamous carcinoma. LUME-Lung 1 subgroup analyses showed improved OS with nintedanib in patients with adenocarcinoma (HR 0.83 95% CI 0.70 to 0.99) and no OS benefit in patients with squamous cell carcinoma (HR 1.01 95% CI 0.85 to 1.21) or other histologies. Subgroup analyses by PFS showed no differences by histology. In response to a request for clarification from the EAG, the company conducted an NMA sensitivity analysis of OS and PFS excluding patients without adenocarcinoma from LUME-Lung 1. The results are presented in response to clarification A13c. The relative OS differences between adagrasib and nintedanib+docetaxel were non-statistically significant in both the primary analysis and the sensitivity analysis, although the effect estimate was numerically [redacted] to adagrasib in the primary analysis (HR [redacted]) than the sensitivity analysis (HR [redacted]), and credible intervals wider (likely due to the reduced sample size). The EAG also notes that nintedanib+docetaxel is only recommended in patients with adenocarcinoma.[1, 37] Overall, adenocarcinoma histology might be a treatment effect modifier for NMA comparisons between nintedanib+docetaxel against adagrasib or docetaxel, although the evidence is limited and uncertain.

KRAS mutation status

The company noted that it is likely that LUME-Lung 1 included patients with mutated and wild-type *KRAS*, although the proportion of patients with *KRAS* mutations was not reported as the trial was conducted before *KRAS* inhibitors were approved in clinical practice. However, given that nintedanib + docetaxel is not a *KRAS* targeted therapy, the EAG agrees with the company that *KRAS* G12C status is not be expected to impact the treatment effect of nintedanib + docetaxel.

Brain metastases

The proportion of patients with brain metastasis was [redacted] in KRYSTAL-12 ([redacted]) and higher in CodeBreaK 200 (34% with history of CNS involvement) than in LUME-Lung 1 (6%). Subgroup analyses in KRYSTAL-12 showed a [redacted] adagrasib treatment effect on PFS in patients without baseline brain metastasis (HR [redacted]) versus patients with baseline brain metastasis (HR [redacted]). CodeBreaK 200 showed that PFS was more favourable to patients with a history of CNS involvement (HR 0.53; 95% CI 0.34 to 0.82) than those without (HR 0.74; 95% CI 0.53 to 1.03), although confidence intervals overlapped. Neither trial reported subgroup analyses for OS. Results from LUME-Lung 1 were limited by the small proportion of patients with brain metastases and resulting imprecision. Overall, it is uncertain whether between-trial differences in brain metastases at baseline may affect the NMA results.

Other variables

The median age of KRYSTAL-12 and CodeBreaK 200 patients ([redacted]) was [redacted] than in LUME-Lung 1 (60 years). Patients in CodeBreaK 200 and KRYSTAL-12 had received [redacted] prior lines of therapy than LUME-Lung 1 overall. There was [redacted] that PFS differed by age or number of prior treatments in any of the trials, although no OS subgroup analyses were available for KRYSTAL-12 and CodeBreaK 200. Overall, the EAG agrees with the company that there is no evidence to suggest that these differences between trials may impact the NMA results.

3.4.1.2 Interventions

Crossover from the docetaxel arm to the intervention arm occurred in KRYSTAL-12 (29%) and CodeBreaK 200 (26%) but was not reported for LUME-Lung 1. Concerns about crossover and subsequent therapies in KRYSTAL-12 and CodeBreaK 200 have been discussed above (Sections 3.2.1.1 and 3.3.2). LUME-Lung 1 patients were recruited between 2008 and 2011 and may not have benefited from improvements in treatment and management of tolerability and safety over the past decade, although it is uncertain to what extent this may impact the NMA results.

3.4.1.3 Outcomes

Progression outcomes were assessed by BICR in KRYSTAL-12 and CodeBreaK 200, and by central independent review in LUME-Lung 1. Outcome assessment schedules were comparable between trials, although follow-up duration differed significantly. Median follow-up was 7.2 months in KRYSTAL-12, 17.7 months for CodeBreaK 200, and 31.7 months for LUME-Lung 1. The company attempted to address the immaturity of KRYSTAL-12 by incorporating results from the surrogacy into the NMA, although this approach has limitations as discussed in Section 3.2.3. The extent to which differences in follow-up duration between the trials may have impacted the NMA results is uncertain although PFS and OS data from CodeBreaK 200 and LUME-Lung 1 were mature.

3.4.2 Proportional hazards assumption

The PH assessment for PFS and OS endpoints are presented in CS Document B Table 26, and in the company's response to clarification question A11a.

To assess the PH assumption, the company used the Grambsch-Therneau test and visual inspection of the log-cumulative hazard plots, Schonfeld residual plot and smoothed hazard plots using individual participant data (IPD) from KRYSTAL-12 and generated pseudo IPD from KM curves from CodeBreaK 200 and LUME-Lung 1.

3.4.2.1 Progression-free survival

The company consider that the PH assumption for KRYSTAL 12 and CodeBreaK 200 was not violated (CS Document B Table 26). The treatments' curves on the log-cumulative hazard plots remain parallel at all timepoints (company's response to clarification question A11a, Figures 2 and 3).

However, the PH assumption for LUME-Lung 1 was violated with a Grambsch-Therneau p-value of 0.036 and a Wald test p-value is 0.030 (CS Document B, Table 26). The treatments' curves on the log-cumulative hazard plots crossed at some timepoints (Company's response to clarification question A11a, Figure 5).

The EAG agrees with the company that the PH assumption is likely to hold for the comparison between adagrasib and docetaxel (KRYSTAL-12), and between sotorasib and docetaxel (CodeBreaK 200), while it is unlikely to hold for the comparison between docetaxel + nintedanib and docetaxel alone (LUME-Lung 1).

3.4.2.2 Overall survival

No PH assessment was reported for KRYSTAL-12 because of the immaturity of the OS data. As per Section 3.2.3, OS data from KRYSTAL-12 was not included in the NMA, only simulated OS data based on the surrogacy analysis was used.

The company considered the PH assumption for LUME-Lung 1 and CodeBreaK 200 (CS Document B, Table 26) and noted that the PH assumption was not violated for LUME-Lung 1. However, the treatments' curves on the log-cumulative hazard plots overlapped (Company's response to clarification question A11a, Figure 4). The company consider that the PH assumption for CodeBreaK 200 (ITT two-stage adjusted OS and unadjusted OS) was violated. The Wald test p values for ITT, two-stage adjusted OS (0.022) and unadjusted OS (0.042) are ≤ 0.05. However, the Grambsch-Therneau p value for the unadjusted OS (0.051) is equal to 0.05 and the Grambsch-Therneau p value for the ITT two-stage adjusted OS (0.098) is above 0.05. The treatments' curve on the log-cumulative hazard plots for ITT two-stage adjusted OS crossed (Company's response to clarification question A11a, Figure 1).

The EAG broadly agrees with the company's position that the PH assumption for LUME-Lung 1 is not violated. Overall, the EAG agrees with the company's consideration that the PH assumption is unlikely to hold for the comparison between sotorasib and docetaxel.

Therefore, the EAG agrees with the company's decision to conduct both a time-varying and a proportional hazard NMA. The time-varying NMA evaluates the clinical effectiveness (PFS and OS) of the treatments at varying timepoints. This allows the hazards to change over time, whereas the proportional hazard NMA assumed the hazards remain constant over time.

3.4.3 Network and methodology

NMA was conducted for PFS, Grade ≥ 3 TEAEs, serious TEAE, serious TRAEs, and grade ≥ 3 hepatoxicity using available data from the most recent data cut-offs from KRYSTAL12, LUME-Lung1 and CodeBreaK 200. However, for the NMA of the OS endpoint, most recent data cut-off from LUME-Lung1 and CodeBreaK 200 were used while estimates from the surrogacy analysis of

KRYSTAL-1 was used for KRYSTAL-12 (CS Section B.2.9.5 and company's response to point of clarification A12).

A network diagram is presented in CS Figure 23. It was not possible to assess the consistency (coherence/agreement) of direct and indirect evidence statistically as there were no trials directly comparing adagrasib, nintedanib + docetaxel and sotorasib.

The company performed both two-stage time-varying NMA[38, 39] (which assumes non-proportional hazards) and standard NMA (which assumes proportional hazards) using a Bayesian framework to evaluate the clinical efficacy of PFS and OS. In the time varying NMA, the company explored various statistical survival distribution such as Weibull, gamma, log-normal and log-logistic and chose the gamma distribution "based on goodness-of-fit measures such as Akaike information criterion (AIC) and clinical expert opinion on the long-term plausibility of the extrapolated curves" (see CS Document B, p79). The company employed both a fixed and random effect model in the time-varying and standard NMA. The company preferred the fixed effect time varying NMA to inform the economic model because of the violation of the PH assumption in PFS for LUME-Lung1 and OS endpoints for CodeBreaK 200, and the fixed effect model had a "better fitting (with lower deviance information criterion – DIC) compared to the random effect model" (pg. 79 Document B of CS).

The EAG agrees that the methods employed were appropriate. The choice of a Bayesian NMA was the most appropriate given the small network size. As the PH assumption is unlikely to hold for all the time-to-event outcomes included in the NMAs (Table 26, Document B of CS, and Company's response to points for clarification, A11a), the EAG agrees with the company's consideration to use the time-varying NMA. Regarding the choice of survival distribution for the time-varying NMA, the lognormal distribution seems to be a better fit given the AIC results reported on Table 35 and 37 in the company's response to clarification question B5. However, given clinical plausibility for extrapolations based on this distribution was low, the choice of a gamma distribution is appropriate (see also Section 4.2.6). The EAG agrees that using a fixed effect approach is appropriate because of the limited number of studies (3 studies) in the network and the lack of relevant informative prior distributions for the between-study heterogeneity in this context. However credible intervals in the NMA results may be too narrow given the heterogeneity in the characteristics of the studies included, which is not considered.

The EAG was able to replicate the results of the NMA using the datasets and the code provided by the company and had no concerns about implementation.

3.4.4 NMA results

3.4.4.1 Overall Survival

The OS results from the fixed effect proportional-hazards NMA and fixed effect time-varying NMA are summarised in CS Section B.2.9.6.2 and CS Section B.2.9.6.2.2 respectively and presented in Table 28 and Table 30 in the CS Document B. The OS from the random effect proportional hazard NMA is presented in Appendix D (D.3.4.3). The EAG notes that the KRYSTAL 12 OS results were simulated via surrogacy analysis using KRYSTAL 1. This approach has been critiqued by the EAG in Section 3.2.3. No OS results from the random effect time varying NMA were presented by the company. Adagrasib showed no statistically significant improvement in OS compared to docetaxel with or without nintedanib, and sotorasib.

3.4.4.2 Progression-free survival

PFS results from the proportional-hazards NMA and time-varying NMA (both modelled using the fixed effect model) are summarised in CS Section B.2.9.6.1 and CS Section B.2.9.6.2.1 respectively and presented in Table 27 and Table 29 in the CS Document B. The PFS results of the proportional hazard NMA via the random effect model is presented in Appendix D (Section D.3.4.2, Table 21). No PFS results from the random effect time-varying NMA are presented by the company. The EAG believes that the point estimates of PFS from the random effect time-varying model may not significantly vary from the point estimates from the fixed effect time-varying model. However, the random effect model would take into consideration the between study differences and heterogeneity as compared to the fixed effect model, thus, reflecting this heterogeneity in the precision of the estimates (i.e. size of the credible interval).

In the fixed effect proportional hazards NMA, adagrasib showed a statistically significant improvement in PFS compared to docetaxel with or without nintedanib, and a statistically non-significant improvement compared to sotorasib. In the random effect proportional hazards NMA, adagrasib showed a statistically non-significant improvement compared to sotorasib, and docetaxel with or without nintedanib.

Six time-points are considered by the company – 3 months, 6 months, 9 months, 12 months, 18 months and 24 months – in the time varying NMA. The PFS point estimates from the fixed effects time-varying NMA are similar to the PFS point estimates from the fixed effect proportional hazards NMA. Adagrasib showed a statistically significant improvement in the PFS compared to docetaxel throughout the time points but showed no statistically significant improvement compared to sotorasib throughout the timepoints. Adagrasib showed a statistically significant improvement compared to docetaxel + nintedanib in two time points – 3 months and 6 months, and statistically non-significant improvement from 9 months.

The EAG agrees with the company that there are some uncertainties in the indirect comparison; including heterogeneity in the patient characteristics of LUME-Lung compared to CodeBreaK 200 and KRYSTAL 12, and the simulation of KRYSTAL12 OS data via surrogacy analysis. Therefore, the results should be interpreted with caution. Additional NMA analyses provided by the company include ORR (Appendix D Section D.3.4.1).

3.4.4.3 Safety outcomes

Results for Grade ≥ 3 treatment emergent adverse events, Grade ≥ 3 hepatoxicity, serious TEAE and serious treatment related adverse events (TRAEs) were presented in the company's response to points for clarification, A12 and are summarised in Table 7. The adverse events were measured using the number of patients who experienced the event and not the number of events because a patient could experience multiple adverse events with varying intensity. The EAG considers the NMA approach (binomial modelling) employed by the company to estimate the safety outcomes to be appropriate. It is plausible that the odds of grade ≥ 3 hepatoxicity is higher for docetaxel compared to adagrasib (in the fixed effect and random effect NMA). All NMA results for safety outcomes were imprecise as shown by the wide credible intervals.

Table 7 NMA results: safety outcomes

	Grade ≥ 3 TEAEs		sTEAEs		sTRAEs		Grade ≥ 3 hepatoxicity	
Odd ratios (95% CrI) for adagrasib versus relevant comparators*								
	Fixed effects	**Random effects**	**Fixed effects**	**Random effects**	**Fixed effects**	**Random effects**	**Fixed effects**	**Random effects**
Docetaxel	1.26 (0.82, 1.95)	1.27 (0.33, 4.87)	**1.81 (1.20, 2.74)**	1.81 (0.50, 6.69)	1.35 (0.80, 2.32)	1.35 (0.34, 5.28)	**10.26 (3.54, 45.73)**	**10.39 (1.98, 70.49)**
Docetaxel + Nintedanib	0.91 (0.56, 1.49)	0.92 (0.14, 6.07)	1.58 (0.99, 2.55)	1.59 (0.26, 9.72)	**3.33 (1.49, 7.66)**	3.33 (0.47, 23.25)	NA	NA
Sotorasib	0.76 (0.40, 1.43)	0.76 (0.11, 5.25)	NA	NA	NA	NA	0.50 (0.06, 3.53)	0.50 (0.03, 6.82)

Note: All estimates below 1 favour adagrasib, and estimates above 1 favour the comparator

Abbreviations: CrI, credible interval; NMA, network meta-analysis; TEAEs, treatment emergent adverse events; sTEAEs, serious treatment emergent adverse events; sTRAEs, serious treatment related adverse events; NA, not available.

3.5 Additional work on clinical effectiveness undertaken by the EAG

No additional analysis on clinical effectiveness was undertaken by the EAG.

3.6 Conclusions on clinical effectiveness and safety

The EAG's primary concern with the clinical effectiveness evidence relates to the limitations of the OS evidence from KRYSTAL-12. The company conducted a pre-planned interim analysis for OS at the time of the primary PFS analysis (31 December 2023 data cut). However, the CS did not present the results of this analysis because the data were highly immature and results inconclusive, and due to [redacted] Although KRYSTAL-12 found a statistically significant PFS benefit favouring adagrasib over docetaxel (HR 0.58 [95% CI, 0.45 to 0.76]), [redacted] Given the immaturity of KRYSTAL-12 OS data, the company used the KRYSTAL-1 single-arm phase 1/2 study to inform a patient-level surrogacy analysis to predict OS for the separate arms of adagrasib and docetaxel from KRYSTAL-12, even though no evidence exists to support the use of a surrogacy relationship to inform OS in *KRAS* G12C mutation-positive NSCLC.

To this date, the CodeBreaK 200 trial is the only RCT with mature OS data to assess the clinical treatment effectiveness of a *KRAS* G12C inhibitor (sotorasib) versus a relevant comparator (docetaxel) in the population under the NICE scope. Although the EAG found CodeBreaK 200 to be at high risk of bias, and there are differences in half-life between the two *KRAS* G12C inhibitors (5 hours for sotorasib and 24 hours for adagrasib), both drugs have a similar mechanism of action, and therefore the EAG believes that CodeBreaK 200 provides relevant contextual information to consider the plausibility of an OS benefit for adagrasib in the NICE scope population. CodeBreaK 200 showed a statistically significant treatment effect for sotorasib vs. docetaxel on PFS, similarly to what was observed in KRYSTAL-12 for adagrasib vs. docetaxel. However, there was no evidence of a difference in OS between sotorasib and docetaxel. Although crossover was allowed in CodeBreaK 200, there is no conclusive evidence that crossover from docetaxel to sotorasib had a significant confounding impact on OS estimates.

Although the EAG found that CodeBreaK 200 was at higher risk of bias than KRYSTAL-12 overall, both trials allowed for crossover from the docetaxel arm to the intervention arm, and the EAG is concerned that this may affect the interpretability of OS estimates in both trials. The EAG is concerned that the existence of a treatment benefit on OS for adagrasib compared to docetaxel cannot be demonstrated, and that the available evidence for sotorasib does not support the existence of an OS

treatment benefit for *KRAS* G12C inhibitors in the relevant population. Overall, there is currently no evidence that improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC.

The EAG is concerned that the lack of blinding may have introduced bias and favoured adagrasib (a new-generation targeted therapy) over docetaxel chemotherapy (an older treatment with known toxicity) in KRYSTAL-12. Although the EAG agrees with the company that there is no evidence that [redacted] it is unclear whether the prognosis of patients who remained in the control group was balanced with those remaining in the adagrasib group. It is also uncertain whether withdrawal may have biased estimates of OS, ORRs , and safety outcomes. KRYTAL-12 showed that patients randomised to adagrasib had improved HRQoL compared with docetaxel, and the differences reached MID thresholds. However, the subjective nature of patient reported outcomes (PROs) and the lack of blinding means that HRQoL outcomes in KRYSTAL-12 may have been overestimated.

Despite the fact adagrasib is a targeted therapy and given the known toxicity of docetaxel, there is currently no evidence to suggest that the overall safety profile of adagrasib is superior to that of docetaxel with or without nintedanib. In KRYSTAL-12, fatal TEAES, Grade ≥ 3 TEAEs and serious TEAEs were all more frequent in the adagrasib arm than the docetaxel arm.

In the absence of direct evidence comparing adagrasib and docetaxel+nintedanib or sotorasib, the company conducted a network meta-analysis (NMA). The EAG's concerns with the validity of the NMA relate mostly to the quality of the evidence informing it. Most importantly, the validity of OS estimates from the NMA are highly uncertain due to concerns about the validity of the surrogacy relationship used to simulate OS data for KRYSTAL-12.

Mature OS evidence from KRYSTAL-12 is required to address the uncertainty around the survival benefits from adagrasib relative to docetaxel. The company stated that the final OS analysis is projected to occur in approximately [redacted], and outputs/reports availability are planned for [redacted] or [redacted]. However, the EAG is concerned that, in view of the [redacted] and results from the CodeBreaK 200 trial of sotorasib, it is uncertain whether KRYSTAL-12 will demonstrate that adagrasib leads to superior OS compared with docetaxel.

[redacted] and [redacted] uptake of *KRAS* G12C inhibitors following docetaxel therapy in the control arm ([redacted]), KRYSTAL-12 may not be able to demonstrate that adagrasib has superior (or even non-inferior) OS compared to docetaxel. Similar

concerns have been raised regarding CodeBreaK 200 following the publication of non-statistically significant OS results for sotorasib versus docetaxel, and it has been argued that the sample size of CodeBreaK 200 is significantly smaller than what would be required to demonstrate that sotorasib is non-inferior to docetaxel.[34]

Longer-term follow-up from KRYSTAL-12 and surveillance data will provide further information on the safety profile of adagrasib, although this is not expected within the timeline of this appraisal.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify published economic evaluations, cost-effectiveness studies, and healthcare resource use studies in advanced/metastatic (Stage III or IV) NSCLC adult patients receiving any 2L+ therapy (see Appendix G of the CS for a detailed description of the searches conducted on the 2nd of July 2024, inclusion criteria, study selection process, critical appraisal of the identified studies and results of the review). In response to EAG's points for clarification, the company provided additional information and corrections to errors identified in the searches, including an updated PRISMA flow diagram (Response to clarification question C7, Figure 19).

A total of 90 publications met the review inclusion and exclusion criteria, of which 58 were economic evaluations and budget impact analyses. The remainder were economic burden and healthcare resource utilisation studies. Of these, the company only deemed relevant those studies that were UK-specific cost-utility/cost-effectiveness analyses for a population with *KRAS* G12C mutation-positive NSCLC and only one publication met these criteria following rescreening. This was a previous NICE technology appraisal, TA781[4] (see Table 40, Appendix G of the CS), which compared sotorasib against i) docetaxel and ii) docetaxel + nintedanib. The company did not identify any economic evaluations of adagrasib in a UK setting.

Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 1 for details. The EAG considers that all relevant publications are likely to have been identified, although restricting the identification strategy to only include UK-specific studies for a *KRAS* G12C population curtailed the inclusion of potentially relevant HTA submissions in other jurisdictions. The EAG identified HTAs of sotorasib in the relevant population by the Canada's Drug Agency (CDA)[40] and the Australian Pharmaceutical Benefits Advisory Committee (PBAC).[41] The economic evidence included in the PBAC submission was largely consistent with that used in NICE TA781. However, the CDA assessment incorporates evidence from the phase 3 CodeBreaK 200 trial comparing adagrasib to docetaxel, which was not

available when NICE assessed sotorasib. The CDA did not recommend sotorasib for reimbursement as the clinical evidence was considered insufficient to conclude that sotorasib results in a clinically meaningful delay in disease progression compared with docetaxel. Furthermore, the CDA considered it impossible to assess whether sotorasib would provide an OS benefit compared to docetaxel.[42]

The EAG also notes that it is unclear why the company did not include the Scottish Medicines Consortium (SMC) assessment of sotorasib [43] as it reports a UK-specific study in the population of interest. Nevertheless, the economic evidence informing the SMC assessment was consistent with that of NICE TA781.

The EAG did not identify any relevant cost-effectiveness studies of adagrasib in the population of interest.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de novo* model to evaluate the cost-effectiveness of adagrasib compared to docetaxel monotherapy and docetaxel plus nintedanib in adult patients with *KRAS* G12C mutation-positive NSCLC, whose disease has progressed after prior treatment with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

The model is structured as a partitioned survival analysis (PartSA) and is used to estimate the long-term health outcomes and costs associated with progression and the clinical pathway of advanced NSCLC in the UK. In the PartSA, the time-dependent risk associated with disease progression and death is modelled using the survival functions that are parameterised by the time varying NMA (see Section 3.4.3). OS and PFS are independently modelled to determine the proportion of patients alive and in the progressed (or progression-free) health state over time. Treatment discontinuation is derived from the extrapolated PFS curves for each treatment and adjusted to reflect the relationship between time-to-treatment discontinuation (TTD) and PFS. The costs of subsequent therapies in progression are applied as a one-off cost included at the point of disease progression.

Adagrasib is modelled to affect QALYs by increasing the proportion of patients who are alive and progression-free over time relative to the comparators, which is associated with improved HRQoL. In addition, the company's base case analysis assumes a higher utility value for patients treated with adagrasib compared to docetaxel +/- nintedanib in the progression-free and progressive disease health states. Only a small difference in QALYs is associated with adverse events.

Adagrasib is modelled to affect costs by increasing the time on treatment compared to the comparators and the proportion of the cohort who remain progression-free for longer, with associated drug acquisition costs, while decreasing the proportion with progressive disease and associated costs of subsequent therapies upon progression. The largest component of cost difference between adagrasib and its comparators is drug acquisition costs, health state (progression-free (PF) and

progressed disease(PD)) resource use, and costs of subsequent treatments, while only a small difference in costs is associated with adverse events.

The company's de novo model uses a similar approach to that used in NICE TA781[4] (and other NICE TAs in NSCLC more generally) with the same PartSA model structure and a lifetime horizon. The source of data used to inform treatment effectiveness and utility values in the model is based on evidence from the relevant treatment-specific clinical studies (see Table 37 of CS for a comparison of key features of the company's analysis with TA781.[4]

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 8.

Table 8 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime.
Synthesis of evidence on health effects	Based on systematic review	The use of simulated OS data for adagrasib and docetaxel (assuming a surrogacy relationship between TTP and OS) to inform the evidence synthesis of OS treatment effects in the absence of comparative OS evidence for adagrasib vs. the comparator treatments is an area of considerable uncertainty.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of HRQoL in adults.	The CS is appropriate. EQ-5D-5L data collected in KRYSTAL-12 was mapped to EQ-5D-3L using the Hernández-Alava et al (2017)[44] algorithm, and used to inform health state utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other	The CS is appropriate.

	characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome; TTP, time to disease progression.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The company's economic model is a PartSA which is used to simulate the time in three mutually exclusive health states: PF, progressed disease PD and death (see CS Figure 24). The model cohort starts in the PF health state and the transitions to the other health states are governed by parametric models fitted to time-dependent PFS and OS curves over a lifetime horizon. Data from the KRYSTAL-12 trial was the key source of clinical evidence used to inform the treatment effect of adagrasib vs. docetaxel (using observed data for PFS and predicted KRYSTAL-12 OS in censored patients based on the surrogacy analysis - see Section 3.2.3). The PD health state captures the costs and health-related quality of life of subsequent treatments received after disease progression, while the OS curve already reflects the effects of subsequent treatment use. Transitions to the death state capture end of life care costs. A model cycle length of one week is used to capture differences in the frequency and timing of the treatments under comparison.

Points for critique

The company's base case model structure is consistent with the models used in previous NICE TAs in advanced and metastatic NSCLC at second-line of treatment.[1, 4, 45]

The appropriateness of the company's PartSA is largely dependent on the completeness and maturity of the observed data informing survival outcomes and the extrapolation of these outcomes over a lifetime horizon. In the current appraisal, the magnitude of the uncertainty surrounding the OS extrapolations is magnified by the unavailability of direct comparative OS data between adagrasib and any of the comparators, leading to considerable uncertainty in the estimates of cost-effectiveness.

4.2.3 Population

The company defines the patient population as comprising adult patients with advanced NSCLC with *KRAS* G12C mutation and progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy, which is in line with adagrasib's

conditional marketing authorisation and the NICE scope for this appraisal. The baseline characteristics of the modelled population are informed by the overall ITT population from KRYSTAL-12 with a mean age of 63.7 years, percentage of females 33.1%, and mean body surface area of 1.82 m^2 (see Table 39, CS).

The NICE scope specified the following subgroups, if evidence permits: i) disease stage, ii) histology, iii) previous treatment, and iv) newly diagnosed or recurrent distant metastatic disease. However, the company does not evaluate the cost-effectiveness of adagrasib in any subgroups.

Points for critique

As noted in Section 2.3.1, the population of KRYSTAL-12 and KRYSTAL-1 is narrower than the population defined by the NICE scope and adagrasib indication according to its anticipated license. KRYSTAL-12 (and KRYSTAL-1) do not provide clinical evidence on adagrasib for the subset of patients with i) intolerance to platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy, or ii) have received an anti-PD-1/PD-L1 immunotherapy (without platinum-based chemotherapy).

The exclusion of subgroups from the cost-effectiveness analysis seems reasonable given the limited availability of clinical evidence to inform the subgroups specified in the NICE scope across treatments and the immaturity of the OS data. However, it is worth noting that docetaxel + nintedanib is only a relevant comparator in the subpopulation with adenocarcinoma as its license is specific to this histology (see Section 2.2). Furthermore, LUME-Lung 1, the study which informs the treatment effectiveness of docetaxel + nintedanib in the NMA, suggests that this therapy may be more effective vs. docetaxel in the subgroup with adenocarcinoma histology than in the ITT population. This is the case for the treatment effect on OS (HR for docetaxel + nintedanib vs. docetaxel is 0.94 [95% CI 0.83–1.05] and 0. 83 [95% CI 0. 70‑0. 99] for the ITT and adenocarcinoma histology subgroup, respectively). In response to clarification question A13c, the company reported results of a PH NMA sensitivity analysis of OS and PFS for the subgroup with adenocarcinoma only from LUME-Lung 1. The other studies in this NMA were not similarly restricted by histology, but adenocarcinoma was the predominant histology in both CodeBreaK 200 and KRYSTAL-12. Since the company did not provide corresponding subgroup analyses for the time varying HR NMAs, it is not possible to explore the impact of using treatment effectiveness estimates for the adenocarcinoma subgroup of LUME-Lung 1 on the company's base-case cost-effectiveness results, without also assuming that the proportional hazards assumption holds for all treatments. As detailed in Section 3.4.2, the proportional hazards assumption is likely to be violated for PFS in LUME-Lung 1.

Overall, the EAG agrees that it is not possible to conduct meaningful cost-effectiveness subgroup analyses due to limitations with the data available, but the EAG notes the additional uncertainty in the treatment effectiveness when considering the subpopulation of patients who are eligible to be treated with nintedanib + docetaxel.

4.2.4 Intervention and comparator

The intervention is adagrasib which is available in 200mg tablets in packs of 180 units. The SmPC recommended dose is 600 mg orally twice daily (b.i.d.), with dose reductions (first reduction to 400mg b.i.d. and second to 600mg once daily) and delays recommended if specified adverse events occur, for example, hepatotoxicity with Grade≥2 AST or ALT, or any adverse events at grade ≥3. The company have incorporated dose reductions to manage toxicity and tolerability of adagrasib and comparators, which is accounted for via a 'relative dose intensity' (RDI) parameter (see Section 4.2.10). According to the SmPC, treatment should be administered until disease progression or unacceptable toxicity.

The comparators included in the company's model correspond to the two treatments currently available under routine NHS commissioning for advanced NSCLC at 2L, regardless of previous treatment received, i.e., docetaxel monotherapy (75 mg/m^2 on day 1 of every 21-day cycle) and docetaxel in combination with nintedanib (adding nintedanib 200 mg orally twice daily on days 2–21, of the 21 days docetaxel cycle as above). Although these two treatments can both be used to treat advanced NSCLC with *KRAS* 12GC mutation at 2L, docetaxel + nintedanib is only recommended by NICE for tumours with adenocarcinoma histology. In addition to docetaxel and docetaxel + nintedanib, the NICE scope also includes sotorasib, which is not considered relevant because it is only available within the CDF (see Section 2.3.2).

Subsequent treatment use after discontinuation from primary treatment is not explicitly modelled, but a one-off subsequent treatment cost is applied upon progression from 2L treatment. The cost of subsequent treatments is assumed to be the same for docetaxel and docetaxel + nintedanib but differ for adagrasib, as the distribution of subsequent treatments is the same across all treatments under comparison (see Section 4.2.10.7).

Points for critique

The EAG considers the exclusion of sotorasib from the set of relevant comparators to be appropriately justified because sotorasib is only available within the CDF at the time of writing the EAR (see Section 2.3.2).

The EAG considers the comparators included in the CS to be appropriate, but notes, as mentioned in Section 2.3.2, that the set of relevant comparators differ by tumour histology due to docetaxel + nintedanib only being licensed for the treatment of tumours of adenocarcinoma. This does not affect the interpretation of the company's fully incremental base case results, as these suggest that docetaxel + nintedanib is extendedly dominated (so the fully incremental analysis reduces itself to the comparison of adagrasib vs. docetaxel). Uncertainties in the clinical effectiveness of docetaxel + nintedanib were also noted in Section 3.3.2, which increase the uncertainty of the cost-effectiveness estimates for adagrasib compared to nintedanib + docetaxel.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a lifetime time horizon of 20 years (starting age of 63.7 years). A 3.5% annual discount rate is used for both costs and health effects.

Points for critique

The CS adheres to the NICE health technology evaluations manual[27] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The model includes three elements relating to treatment effectiveness and extrapolation of effects over time for adagrasib and comparator treatments:

i. PFS , i.e., the probability of not progressing to the progressive disease health state.
ii. OS , i.e., the probability of all-cause death; and
iii. Time to treatment discontinuation (TTD), i.e., the expected duration on treatment until discontinuation due to disease progression, intolerability, or other reasons.

The data sources informing each of these elements for each treatment are described below and the corresponding time-dependent curves used in the company's base case analysis are presented in Figure 4 (PFS), Figure 5 (OS), Figure 6 (TTD) for adagrasib, docetaxel and docetaxel + nintedanib.

Figure 4 Company's base-case PFS curves

Figure 5 Company's base-case OS curves

Figure 6 Company's base-case TTD curves

The effectiveness of adagrasib and docetaxel for PFS is informed by the time-to-event data from KRYSTAL-12 (as assessed by BICR; ITT analysis for the data cut-off 31st December 2023). Given that KRYSTAL-12 interim OS data was immature (see Section 3.2.1.2), the company relied on the use of data from a phase 1/2 single arm study of adagrasib (KRYSTAL-1) to predict OS in censored patients of KRYSTAL-12 for both adagrasib and docetaxel by informing a patient-level surrogacy analysis of the relationship between TTP and OS for patients with previously treated advanced *KRAS* G12C mutation-positive NSCLC in KRYSTAL-1. The methodology and evidence for the surrogacy analysis are discussed in Section 3.2.3.

The predicted KRYSTAL-12 OS curves for adagrasib and docetaxel are presented in Figure 26 of CS. These resulted in a median survival of [redacted] for adagrasib and [redacted] for docetaxel, with [redacted]. The predicted KRYSTAL-12 OS curves were extrapolated using standard parametric models to inform the cost-effectiveness model. For KRYSTAL-12, the parametric distributions were fit to each OS sample from the surrogacy analysis, with the distributional parameters calculated as the average across the predicted samples (adjusting the associated variance using Rubin's rules as described in the technical specification of the surrogacy analysis in Appendix P of the CS).

Parametric survival curves from the time-varying NMA (see Section 3.4.4) were used to inform PFS and OS outcomes in the company's base case analysis. The company considered six alternative survival distributions (namely, the exponential, Weibull, gamma, Gompertz, log-normal and log-logistic distributions). The methodology used by the company to conduct the time-varying NMA assumes a common parametric distribution across all arms of the studies in the evidence network for OS and PFS independently. Therefore, the extrapolated survival curves for each outcome (PFS or OS) all follow the same distribution in the economic model. The selection of survival distribution was based on goodness-of-fit measures of Akaike information criterion (AIC) and clinical expert opinion on the long-term plausibility of the extrapolated curves. The company justified the use of the time-varying NMA to inform the base-case analysis due to violation of the PH assumption for PFS in LUME-Lung 1 and OS in CodeBreaK 200 (see assessment of PH assumption in Section 3.4.2).

The extrapolated TTD curves are used in the model to determine treatment costs. These are derived by adjusting the adagrasib and docetaxel extrapolated PFS curves by a treatment-specific HR for TTD vs. PFS, which is based on observed PFS and TTD data from KRYSTAL-12. For docetaxel + nintedanib, the HR for TTD vs. PFS is assumed the same as for docetaxel.

The company considered a number of alternative approaches in scenario analyses. These include:

- Use of the PH NMA based on constant HRs (rather than the time-varying NMA used in the base case).
- Use of alternative parametric survival distributions in the time-varying NMA.
- The use of unadjusted external OS data as a proxy for KRYSTAL-12 OS data. For adagrasib, KRYSTAL-1 OS data were applied directly in the cost-effectiveness model. For docetaxel, the model considers external OS data directly from SELECT-1, which was a multinational RCT including a docetaxel arm in patients with *KRAS* G12C-mutated advanced NSCLC.
- The use of independent curve fits for the comparison of adagrasib vs. docetaxel and PH NMA for adagrasib vs. docetaxel + nintedanib. The independent curve fits were based on KRYSTAL-12 PFS data and simulated KRYSTAL-12 OS data, KRYSTAL-1 OS data for adagrasib and SELECT-1 OS data for docetaxel.

Table 38 in the CS summarises the company's base-case extrapolation approach and alternative scenarios for PFS and OS.

4.2.7 Progression-Free Survival

The company's base-case approach consists of using the survival curves obtained from the time-varying NMA (see Section 3.4.3) to estimate PFS for each treatment under comparison. The company presents their assessment of the statistical goodness-of-fit of alternative distributions in Table 41 of CS. The distribution selected for the company's base-case analysis (gamma distribution) is the third

ranked model according to the sum of AICs across all arms of the studies in the global evidence network (see Figure 23, CS). Clinical opinion obtained by the company suggested that very few patients were expected to be in PFS at 5 years with adagrasib, while all patients were expected to have progressed by 5 years when treated with docetaxel. Therefore, the company selected the gamma distribution because it resulted in more plausible PFS over the long-term than the log-normal and log-logistic distributions (first and second ranked models, respectively).

In a scenario analysis, the company explored the time-varying NMA log-normal estimates as an alternative. Table 9 contrasts the landmark PFS predictions using the company's base-case and scenario distributions with the observed KRYSTAL-12 data.

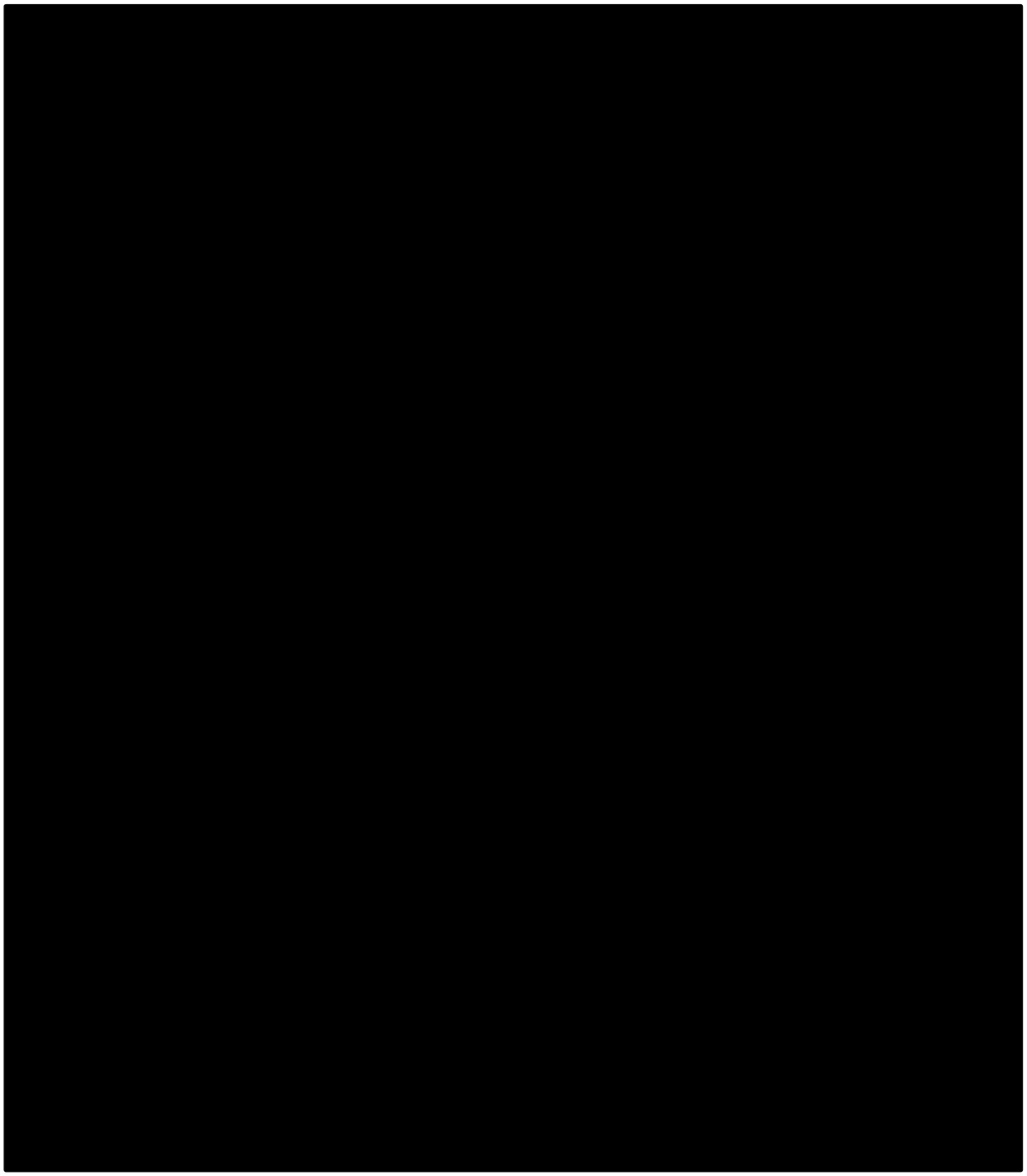
Table 9 Comparison of PFS landmark estimates over time and median PFS for alternative analyses

Analysis	Treatment	Landmark PFS estimates				Median PFS (months)
		1 year	2 years	3 years	5 years	
Base-case: Time varying NMA, gamma	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis: Time varying NMA, Log-normal	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis: PH NMA, independently fitted gamma for adagrasib and docetaxel	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed KM KRYSTAL-12	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; PH, proportional hazards.

In CS Appendix Q (pages 110-113) the company presents an assessment of alternative independent parametric distributions to the KRYSTAL-12 PFS data, which are applied in scenario analysis to extrapolate PFS for adagrasib and docetaxel. The assessment of the alternative distributions to the observed data was based on statistical goodness-of-fit as informed by AIC and BIC (see Tables 54 and 56, Appendix Q of the CS), visual fit (see Figure 26, CS Appendix Q) and clinical plausibility of long-term predictions (see Tables 55 and 57, Appendix Q of the CS). In these scenarios, the HR for docetaxel + nintedanib vs. docetaxel from the PH NMA (HR=[redacted], see section 3.4.4) was applied to the docetaxel extrapolated PFS curve to derive the equivalent PFS curve for docetaxel+nintedanib. In the company's scenario analysis, the gamma distribution was selected for the PFS extrapolation of both adagrasib and docetaxel. The EAG notes that under the assumptions of this scenario, the landmark predictions over time and median PFS for all treatments under comparison are very similar to those of the base-case analysis (see Table 9).

Figure 7 PFS independent fitted extrapolations: adagrasib (A) and docetaxel (B) (adapted from Figures 26 and 27, Appendix Q of CS



Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival.

Points for critique

The EAG considers the use of the time-varying NMA to inform the extrapolation of PFS to be appropriate, given the violation of the PH assumption for LUME-Lung 1 PFS data. The selection of distribution function for the base-case analysis, i.e., gamma, also seems reasonable in light of the

long-term predictions and visual fit (see Figure 7) for all treatments under comparison. The EAG notes that it is not possible to fit different parametric distributions to each treatment group in the context of a time-varying NMA, as noted in Section 3.4.4. The EAG acknowledges, however, that this does pose additional methodological challenges and that there is not yet standard guidance on how to best implement the evidence synthesis model across different survival distributions. At the clarification stage, the EAG requested disaggregated AIC estimates to assess whether there was agreement on goodness-of-statistical fit across treatments for each parametric distribution (see Table 36, response to clarification question B5). The EAG concluded that the interpretation of the AIC estimates by treatment group is similar to that of the aggregated estimates, and, therefore, it is not problematic to use the same distribution function for all treatments when extrapolating the PFS outcome. The EAG is further reassured of the appropriateness of using the same distribution across treatments based on the assessment of the independently fitted parametric functions to KRYSTAL-12 PFS data, which also considers the gamma the best fitting distribution.

In Section 2.3.2, the EAG highlighted that the combination treatment of docetaxel + nintedanib is only a relevant comparator for the subpopulation with the adenocarcinoma histology. The clinical evidence used to inform PFS in the economic model is not specific to any particular histology. In LUME-Lung 1, the main trial informing the effectiveness of the combination treatment, only 50% of patients were classified as having an adenocarcinoma histology while non-squamous histology, which includes adenocarcinomas, was largely predominant (over 90% of participants) in CodeBreaK 200 and KRYSTAL-12. In Section 4.2.3, the EAG also noted that it is not possible to conduct meaningful cost-effectiveness subgroup analyses according to histology due to data availability limitations and that this is an additional source of uncertainty when considering the subpopulation of patients who are eligible to be treated with nintedanib + docetaxel. The EAG considers that the impact of this uncertainty on the PFS treatment effect is potentially smaller, as the PFS HRs estimated in LUME-Lung 1[32] for combination treatment vs. docetaxel suggests that the treatment effectiveness for PFS is similar for the overall population (HR= 0.79 [95% CI 0.68‑0.92]) and the adenocarcinoma histology subgroup (HR= 0. 77 [95% CI 0.62‑0.96]).

4.2.7.1 Overall Survival

The company's base-case approach consists of using the survival curves obtained from the time-varying NMA (see Section 3.4.4.1) to estimate OS for each treatment under comparison. The company presents their assessment of the statistical goodness-of-fit of alternative distributions in Table 43 of CS. The gamma distribution is the second ranked model, while the log-logistic is ranked first according to the sum of AICs across all arms of the studies in the global evidence network (see Figure 23, CS). The company chose the gamma distribution but noted that the Weibull (third ranked model) and gamma were both considered by clinical experts to fit the data well and provide plausible long-term extrapolations.

The company explores in scenario analyses the time-varying NMA Weibull estimates as an alternative to inform the economic model. Table 10 contrasts the landmark OS predictions using the company's base-case and scenario distributions with the simulated KRYSTAL-12 OS data (based on the surrogacy analysis described in Section 3.2.3).

Table 10 Comparison of OS landmark estimates over time and median OS for alternative analyses

Analysis	Treatment	Landmark OS estimates					Median OS (months)
		1 year	2 years	3 years	5 years	10 years	
Base-case: Time varying NMA, gamma	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis: Time varying NMA, Weibull	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis: PH NMA, independently fitted to simulated KRYSTAL-12; generalised gamma for adagrasib and Weibull for docetaxel	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis: PH NMA, independent parametric curves fitted to KRYSTAL-1 for adagrasib (exponential) and SELECT-1 for docetaxel (gamma)	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simulated KM KRYSTAL-12	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KRYSTAL-1 KM	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SELECT-1	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* extracted from Kaplan-Meier data in the economic model

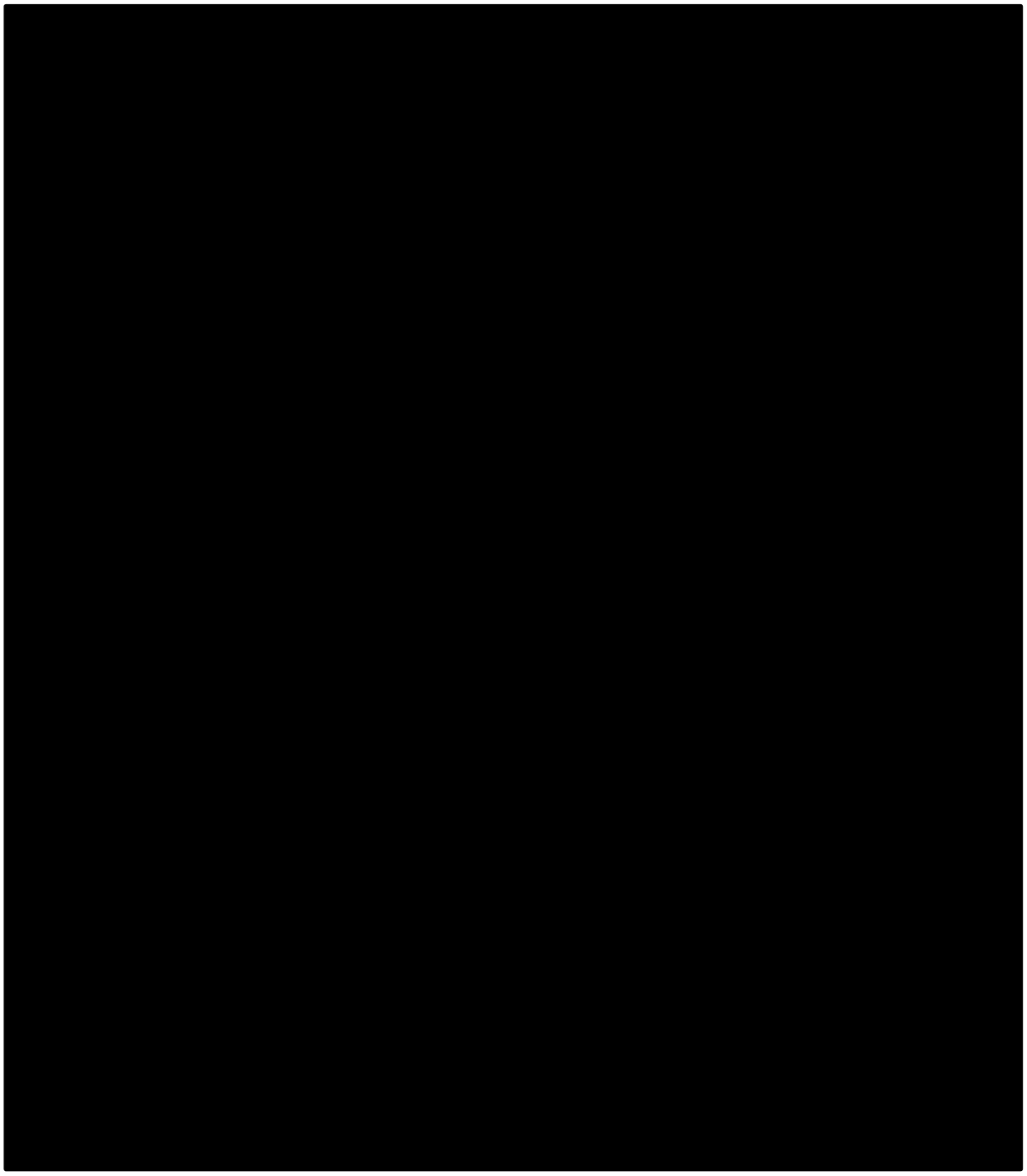
Abbreviations: KM, Kaplan-Meier; NA, not applicable; PH, proportional hazards.

The company presents in Appendix Q of the CS (page 114-113) the assessment of alternative independent parametric distributions to the simulated KRYSTAL-12 OS data, which are applied in scenario analysis to extrapolate OS for adagrasib and docetaxel. The assessment of the alternative distributions was based on statistical goodness-of-fit as informed by AIC and BIC (see Tables 58 and 60, Appendix Q of the CS), visual fit (see Figure 29 of Appendix Q, CS) and clinical plausibility of long-term predictions (see Tables 59 and 61 of Appendix Q, CS). In this scenario, the HR for docetaxel + nintedanib vs. docetaxel from the PH NMA (HR=[redacted], see Section 3.4.4) was applied to the docetaxel extrapolated OS curve to derive the OS curve for the comparator treatment not included in KRYSTAL-12. In the company's scenario analysis, the Weibull and the generalised gamma

distributions were selected for the OS extrapolation of docetaxel and adagrasib, respectively. The EAG notes that under the assumptions of this scenario, the landmark predictions over time for all treatments under comparison are fairly similar to those of the base-case analysis but consistently lower than the base-case estimates for all treatments under comparison (see Table 10).

Figure 8 OS independently fitted extrapolations: adagrasib (A) and docetaxel (B) (adapted from Figures 29 and 30, Appendix Q of the CS)

Abbreviations: KM, Kaplan–Meier; OS, overall survival.



The company also presents a scenario analysis whereby the OS extrapolation is conducted by fitting independent parametric distributions to KRYSTAL-1 KM data for adagrasib and to SELECT-1 KM (pseudo-individual patient) data for docetaxel. The company did not explore other potential sources of observed OS data to inform the docetaxel extrapolation. At the clarification stage, the company justified this choice by stating that: i) SELECT-1 was conducted in patients previously treated with advanced *KRAS* mutant NSCLC and identified systematically, ii) reported mature OS data for the docetaxel arm, and iii) SELECT-1 OS data had been used in the NICE TA of sotorasib in the population of interest (TA781). The company acknowledged that CodeBreaK 200 assesses docetaxel in previously treated with advanced *KRAS* G12C mutated NSCLC but noted that these data were not used due to issues with trial design (e.g., treatment crossover from the docetaxel to sotorasib arm) and results (see Section 3.2). The company presents the assessment of alternative parametric models to the external data in Appendix Q of the CS (page 118-121), which is conducted similarly with the approach taken to assess the fit of alternative models to the simulated KRYSTAL-12 data. The parametric distributions selected for this scenario analysis are the exponential for adagrasib and the gamma for docetaxel. The OS for docetaxel + nintedanib was estimated by applying the HR for docetaxel + nintedanib vs. docetaxel from the PH NMA (HR=[redacted]) to the docetaxel extrapolated OS curve in this scenario analysis.

Points for critique

The EAG's primary concern is the lack of mature survival data to quantify the treatment effect on OS for adagrasib compared to docetaxel+/- nintedanib, which leads to substantial uncertainty in the assessment of cost-effectiveness for adagrasib relative to docetaxel+/- nintedanib. In this Section the EAG discusses the issues affecting the treatment effectiveness evidence for (i) the comparison between adagrasib vs. docetaxel, and (ii) in the subpopulation eligible for docetaxel + nintedanib.

4.2.7.2 Adagrasib vs. docetaxel

As detailed in Section 3.2.3 there is a lack of mature OS evidence for adagrasib vs. docetaxel from KRYSTAL-12, the only phase 3 RCT evaluating adagrasib. The interim OS data from this trial, is immature [redacted] Furthermore, the available evidence for sotorasib, the only other *KRAS* G12C inhibitor with RCT evidence (CodeBreaK 200) in the relevant population shows very limited, or no, OS benefit for sotorasib compared to docetaxel. Therefore, the existence of an OS treatment effect for *KRAS* G12C inhibitors compared to docetaxel has not been established to date.

The company did not consider it appropriate to extrapolate the interim OS data from KRYSTAL-12 (December 2023 data cut-off) to inform the OS curves in the model for adagrasib and docetaxel, given the

[redacted] Whilst the EAG understands the company's rationale and concerns regarding the extrapolation of the interim KRYSTAL-12 OS data for use in the model, it should also be noted that the interim analysis does not currently provide evidence to support a potential survival advantage with adagrasib compared to docetaxel and/or the proposed surrogacy relationship between progression and survival (see Section 3.2.3).

The company included external OS data for docetaxel from SELECT-1 in a scenario analysis. However, SELECT-1 does not provide evidence to inform treatment effectiveness and the EAG considers it more consistent to use the same source and approach for both adagrasib and docetaxel. In addition, the resulting predictions from the simulated KRYSTAL-12 OS for docetaxel appear reasonably aligned to SELECT-1 OS.

Whilst the predictions of OS for docetaxel based on the surrogacy analysis may be reasonable, the corresponding predictions for adagrasib have not been validated against external data (other than that provided by clinical opinion) and remain highly uncertain. The OS treatment effect for adagrasib vs. docetaxel predicted by the individual-level surrogacy analysis [redacted] suggests a much [redacted] treatment effect than that of sotorasib vs. docetaxel in the two-stage crossover adjusted analysis of CodeBreaK 200 (0.885 (95% CI: 0.172- 1.328)). Furthermore, based on the company's analysis (see response to clarification question A2.c) estimation of the conditional probability of observing a positive OS trend at final OS analysis, given the observed interim OS, suggests that the probability of the OS HR for adagrasib vs. docetaxel being [redacted], as shown in Table 11. Although the results of the analysis need to be interpreted cautiously, this emphasises the uncertainty in the OS treatment effect implied by the surrogacy analysis used to inform the cost-effectiveness analysis.

Table 11 Conditional probability of observing a positive OS trend at final OS analysis given observed interim OS HR (Table 4, response to clarification question A2.c)

Positive trend with different HR cutoff	Probability of observing the trend (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] As noted in Section 3.2.3, the predicted KRYSTAL-12 OS based on the surrogacy analysis for adagrasib and docetaxel is likely to be over-precise and underestimating the true uncertainty in OS.

4.2.7.3 Subpopulation eligible for docetaxel + nintedanib

The clinical evidence used to inform OS in the economic model is not specific to any particular histology, the combination treatment of docetaxel + nintedanib is only a relevant comparator for the subpopulation with the adenocarcinoma histology. However, in LUME-Lung 1 there may be

differences in the treatment effectiveness for docetaxel + nintedanib vs. docetaxel in the overall population ((HR= 0.94 [95% CI 0.83‑1.05]) and the adenocarcinoma histology subgroup (HR= 0. 83 [95% CI 0.70‑0.99]), even if the 95% confidence intervals for the HRs partially overlap.

As noted in Section 4.2.3 , the EAG does not consider it possible to conduct meaningful cost-effectiveness subgroup analyses according to histology due to limitations in the data available and that this is an additional source of uncertainty when considering the subpopulation of patients who are eligible to be treated with nintedanib + docetaxel. The impact of this uncertainty on the OS treatment effect cannot be meaningfully explored, but the EAG notes that the treatment effectiveness of docetaxel + nintedanib in the population eligible for this treatment may have been underestimated in the company's cost-effectiveness analysis.

4.2.7.4 Time to Treatment Discontinuation

Time to treatment discontinuation (TTD) curves are used to capture treatment acquisition and administration costs in the model. The company's approach to derive the extrapolated TTD curves for each treatment consisted of adjusting the corresponding PFS curve by a HR based on the relationship between observed PFS and TTD. For adagrasib, the company assumed a HR equal to one because the observed TTD and PFS curves from KRYSTAL-12 do not differ substantially (see Figure 9). In response to clarification question B8, the company clarified that the [redacted] is *"largely an artefact of differences in assessment or timing between PFS-INV and PFS-BICR, and these are the likely cause of the slight difference between the TTD and PFS curves*". For docetaxel, the estimated HR for TTD vs. PFS was [redacted] based on KRYSTAL-12 data (i.e., shorter TTD than PFS – see Figure 9). In the absence of TTD data for docetaxel + nintedanib, the company assumed the same HR of [redacted] as docetaxel monotherapy.

Figure 9 Comparison of TTD and PFS KM curves from KRYSTAL-12 (reproduced from Figure 34, CS)

Abbreviations: PFS, progression-free survival; TTD, time to (treatment) discontinuation.

Points for critique

The EAG considers that the company's approach to model TTD for each treatment provides a reasonable approximation of how treatment duration for each treatment is likely to be in NHS practice.

4.2.8 Adverse events

Table 45 of the CS presents the adverse event rates by treatment arm included in the company's base case analysis. The TRAE rates for adagrasib and docetaxel are informed by KRYSTAL-12, while LUME-Lung 1 is used to inform the safety of docetaxel + nintedanib. Only Grade 3 or higher TRAEs occurring in at least 5% of participants were included, in line with the approach used in TA781.[4] Given only TEAEs were reported in LUME-Lung 1, the company assumed that these were equivalent to TRAEs. Furthermore, for adverse events not reported in LUME-Lung 1, but included in KRYSTAL-12, the company assumed a rate of 0% for docetaxel + nintedanib.

The impact of adverse events is modelled as a one-off HRQoL decrement (see Section 4.2.9) and cost (see Section 4.2.10) applied in the first cycle of the model.

Points for critique

The EAG considers that the inclusion of only TRAEs for adagrasib and docetaxel in the company's model, while treatment emergent adverse events are considered for docetaxel + nintedanib, is inconsistent and may underestimate the rates of AEs considered in the model for adagrasib and docetaxel. However, the impact of adverse events on the cost-effectiveness of adagrasib relative to the comparators is limited because they are modelled as a one-off cost and HRQoL decrement (e.g., an increase of 200% in the adagrasib adverse event rates results in only a marginal impact on the estimates of cost-effectiveness).

4.2.9 Health-related quality of life

4.2.9.1 Summary of company's submission

The elements of HRQoL considered in the CS are: (i) health state utility values (PF and PD), stratified by treatment, and (ii) disutilities associated with adverse events. Health state utility values are applied to time spent in the PF and PD health states to calculate quality-adjusted life years (QALYs) that reflect the improvement in HRQoL associated with treatment.

The company conducted a systematic literature review (SLR) to identify any relevant published HRQoL studies for previously treated patients with NSCLC with *KRAS* G12C mutation (see Appendix H of CS for details about the systematic literature review, including methodology, inclusion criteria and results). The EAG appraisal of the SLR for identification of health-related quality of life evidence is presented in Appendix 1. The company SLR didn't identify any studies reporting UK-specific HRQoL outcomes, or utility values for a *KRAS* G12C NSCLC population, but considered the health utility values reported in TA781 (Sotorasib)[4] suitable for inclusion in a scenario analysis.

The company provides an analysis of EQ-5D data from KRYSTAL-12 from the ITT population, by health state and treatment arm. Patients who crossed over to receive adagrasib after progression in the docetaxel arm of KRYSTAL-12 were censored from the analysis at the time of progression. HRQoL outcomes were assessed using the EQ-5D-5L instrument with questionnaires completed on Days 1 and 15 of Cycles 1 to 4 and on Day 1 of subsequent cycles. There were [redacted] questionnaires collected from [redacted] participants in the PF state and [redacted] collected from [redacted] participants in the PD state (company response to EAG clarifications, question B6a). To align with the NICE reference case, the responses were mapped to the EQ-5D-3L using the approach by Hernández-Alava *et al.*[44] A mixed model for repeated measures (MMRM) including progression status, treatment arm, age, sex, and an interaction term for progression status and treatment arm was used to analyse mapped EQ-5D-3L utility values. Details on the methodology and output are reported in section 3.4.2 of the CS.

Table 12 summarises the treatment-specific health state utility values used in the company's base case analysis.

Table 12 - Health state utility values used in the company's base case analysis

Treatment	Progression-free	Progressed disease	Source
Adagrasib	[redacted]	[redacted]	KRYSTAL-12
Docetaxel	[redacted]	[redacted]	KRYSTAL-12
Docetaxel + nintedanib	[redacted]	[redacted]	Assumption*

*The same utility values for docetaxel monotherapy are applied to docetaxel + nintedanib by assuming a class effect.

Disutilities for adverse events were applied as a one-off QALY decrement in the first model cycle by multiplying the proportion of patients experiencing the adverse event from the relevant clinical trials (Table 45 in CS) with the adverse event disutility values presented Table 52 in CS. The resulting one-off QALY decrements for adverse event applied in the model are [redacted] (adagrasib), [redacted] (docetaxel), and [redacted] (docetaxel + nintedanib). The model also incorporates a reduction in HRQoL associated with aging by applying the appropriate age-adjustment factors from Hernández Alava et al. 2022 [46] to the health state utility values.

Points for critique

The EAG considers it appropriate to use the EQ-5D data from KRYSTAL-12 to inform the utility values in the model. The company applied treatment-specific health state utility values to the pre-progression and progressive disease health states based on the MMRM model of EQ-5D responses from KRYSTAL-12 (Table 48 of CS). The coefficient for the adagrasib arm was positive, suggesting that patients in the intervention arm have higher utility than docetaxel, while controlling for progression status and other variables of age and sex. Consequently, the company applied a utility increment for adagrasib compared to docetaxel for both the progression-free and progressive disease health states. The company justified the increment in utility for adagrasib on the basis that it is an oral treatment that is administered at home, whereas docetaxel is administered intravenously as hospital-based chemotherapy, which may increase the burden on patients and decrease their HRQoL. The company also referred to an observational study that suggests more favourable HRQoL over time (based on EORTC-QLQ-C30) in Stage IV NSCLC patients with a targetable driver mutation compared to patients without a targetable driver mutation;[47] although in this study the EAG notes that patients with a significant decline in HRQoL at 6 months of follow-up also had significantly shorter PFS, as well as significantly shorter OS, suggesting that the differences in HRQoL in this study are driven by the health state.

The EAG considers that the assumption of a utility increment for adagrasib compared to docetaxel for the same health state can only be justified by the mode of drug administration, i.e., oral administration for adagrasib vs. IV for docetaxel, because differences in HRQoL based on progression and survival status are already reflected in differential utility values for the PF and PD health states, where PF is associated with an increment in utility compared to PD. The EAG is reasonably satisfied that adagrasib may be associated with an increment in utility in the PF health state compared to docetaxel

in the same health state, due to its oral treatment at home, but the EAG is not satisfied with a treatment-specific uplift in utility for adagrasib in the PD health state because patients have discontinued their initial treatment upon progression (i.e., discontinued adagrasib) and have moved to subsequent treatments (for adagrasib, 50% of patients are assumed to receive BSC, 40% docetaxel and 10% cisplatin, while for docetaxel 70% of patients are assumed to receive BSC and 30% cisplatin). Furthermore, patients in the docetaxel arm of KRYSTAL-12 that crossed over to adagrasib were censored from the company's HRQoL analysis resulting in potential selection bias in the post-progression analysis. Therefore, given that a large proportion of patients in the adagrasib arm are assumed to receive docetaxel in the PD health state and are no longer receiving adagrasib upon progression, the EAG considers it inappropriate to apply an increment in utility for adagrasib compared to docetaxel in the PD health state.

In TA781, the argument based on administration method was challenged for sotorasib which is also an oral treatment. The adagrasib dose is comprised of three 200-mg tablets (600 mg) which are taken orally, twice daily compared to docetaxel which despite being IV administered is only taken once every 3 weeks. There may also be disutility associated with taking multiple tablets multiple times daily; however, the extent to which this disutility differs compared to less frequent IV administration is unclear.

In summary, the EAG does not consider that the evidence presented is sufficient to support the use of differential utilities in the PD health state.

Given the absence of HRQoL evidence for docetaxel + nintedanib, the company assumed the same utility value as docetaxel monotherapy. The EAG's clinical advisor considered the assumption of a class effect for docetaxel +/- nintedanib to be reasonable.

4.2.10 Resource use and costs

4.2.10.1 Resource use and cost evidence in the published literature

The company conducted a SLR to identify evidence on cost and healthcare resource use for treatments in 2L+ advanced/metastatic NSCLC. The searches were conducted in July 2024. Relevant studies were identified by searching the following databases: MEDLINE®, Embase, NHS economic evaluation database (NHS EED), and EconLit (via EBSCOhost). Studies or publications were only deemed relevant if they were UK-specific cost-utility/cost-effectiveness analyses for a *KRAS* G12C population. After full-text screening, 90 publications were included, with 58 corresponding to economic evaluations/budget impact analyses and 31 studies about economic burden and health care resource utilisation. A detailed description of the searches, methods, and results were included in Appendix G of CS.

Points for critique

The EAG is satisfied that all relevant literature is likely to have been considered, with the review targeted to UK-specific cost-utility/cost-effectiveness analyses for *KRAS* G12C population. While the searches were conducted in July 2024, there is no indication of whether any recent evidence (e.g., publications in late 2024) was considered, particularly as the field of NSCLC is rapidly evolving.

4.2.10.2 Confidential pricing arrangements

The EAG highlights that there are confidential commercial arrangements in place for one of the comparator treatments. The drug acquisition cost used in the CS and in Section 4.2.10.4 of this report includes only the confidential pricing agreement for adagrasib. Table 13 details treatments with confidential prices, differing from public list prices used in this report. The EAG accessed these prices to replicate all EAR analyses for the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of November 29, 2024.

Table 13 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Adagrasib	Simple PAS
Nintedanib	Simple PAS

Abbreviation: PAS, patient access scheme

4.2.10.3 Summary of company's submission

The company's base case analysis includes resource use and costs relating to: (i) treatment acquisition; (ii) treatment administration; (iii) health state specific resource consumption (comprising those associated with disease management conditional on health state membership); (iv) treatment related adverse events; and (v) end of life costs. Cost of test monitoring is not included in the analysis, since testing for *KRAS* G12C mutation is routine in NHS England practice and in line with NICE TA781 in the same patient population.

Costs are inflated to 2022/23 prices using inflation indices reported in the PSSRU Unit Costs of Health and Social Care 2023.[48] Costs are discounted at an annual rate of 3.5%. Table 14 summarises the costs included in the company's base case analysis.

Table 14 - Costs used in the company's base case analysis

Category of cost	Value	Source
Acquisition		
Drug cost, adagrasib 200 mg (per model cycle)	[redacted]	Estimated by the model, unit cost informed by BMS (PAS price)
Drug cost, docetaxel, 20 mg / 1 ml (per model cycle)	£28.89*	Estimated by the model, unit cost informed by eMIT [49]

Drug cost, nintedanib, 100 mg (per model cycle)	£66.04*	Estimated by the model, unit cost informed by BNF [49]
Administration		
IV	£449.26	National Cost Collection (2022/23) [50]
Oral	£0.00	Assumption
Healthcare resource		
Pre-progression (per model cycle)	£84.37	Estimated by the model, resource use assumption informed by TA781[4]
Progressed disease (per model cycle)	£49.32	
Treatment initiation (one-off)	£1,070.43	
Upon progression (one-off)	£303.28	
Adverse events		
Adagrasib (one-off at first cycle)	£170.00	National Cost Collection (2022/23) [50]
Docetaxel	£352.65	National Cost Collection (2022/23) [50]
Docetaxel + nintedanib	£852.71	National Cost Collection (2022/23) [50]
Subsequent treatment use (by initial treatment received)		
Acquisition		
Adagrasib (one-off at progression)	£82.77**	Estimated by the model, resource use assumption informed by TA781[4], TA347[1] and TA428 [51]
Docetaxel (one-off at progression)	£72.96	
Docetaxel + nintedanib (one-off)	£72.96	
Administration		
Adagrasib (one-off)	£1,020.69	Estimated by the model, resource use assumption informed by TA781 .[4], TA347[1] and TA428 [51]
Docetaxel(one-off)	£483.49	
Docetaxel + nintedanib (one-off)	£483.49	
End of life cost		
End-of life (one-off)	£5,554	[52]

* Note that for docetaxel and combination cost does not apply at all model cycles.

** These estimates do not match those presented in Table 60 of the CS and have been extracted by the EAG from the electronic version of the model; this discrepancy seems to arise from a reporting error in the CS.

4.2.10.4 Drug acquisition and administration costs

The drug acquisition and administration costs per cycle for each treatment under comparison are calculated in the model by applying the unit costs to the resource use estimates (derived from the dosing regimens adjusted for relative dose intensity (RDI)). These costs are applied while patients remain in the PF health state on-treatment, as informed by the TTD curves (see Section 4.2.6).

The company presents drug unit costs for the treatments under comparison in Table 53 of the CS. The unit cost for adagrasib is inclusive of a simple PAS discount of [redacted] over its list price. The dosing regimen schedules (see Section 4.2.4) were sourced from the clinical trial studies (KRYSTAL-1 and KRYSTAL-12) for adagrasib, while for docetaxel and nintedanib these were sourced from their corresponding SmPCs. The dosing schedules for each drug were adjusted for the corresponding RDI,

sourced from KRYSTAL-12 CSR [53] for adagrasib (RDI: [redacted]) and docetaxel (RDI: [redacted]), and from TA781 [8] for docetaxel + nintedanib (RDI: 92.10%).

The drug acquisition costs applied in the model assume vial wastage for IV administered drugs (i.e., docetaxel). The model assumes an average number of vials needed to allow administering the dose per docetaxel treatment cycle (136.18 mg), assuming no vial sharing across patients and the average patient body surface area (BSA) in KRYSTAL-12 (1.82 m^2). In the base-case analysis, this corresponds to 7 vials of docetaxel 20mg/mL (1 mL vial) per 21 days treatment cycle of docetaxel 75mg/m^2. For orally administered treatments (i.e., adagrasib and nintedanib), the full cost of a new pack is incurred in any model cycle in which there would not otherwise be enough tablets remaining to complete treatment, based on the required dose and cycle length.

The administration unit costs applied in the model and sources used to inform these are reported in Table 54 of the CS. For IV delivered treatments the cost of a simple parental chemotherapy (day case, first attendance) [50] is applied, in line with TA781. [8] Oral treatments are assumed to incur no administration costs.

Points for critique

The EAG considers that the acquisition and administration costs of the treatments under comparison are, for the most part, appropriately modelled and in line with TA781. Notwithstanding, the EAG notes that different IV formulations of docetaxel are available in the NHS,[49] as illustrated in Table 15. The docetaxel cost per mg and cost per treatment cycle (assuming vial wastage), varies across formulations (see Table 15), and suggests that the unit cost of the docetaxel formulation assumed by the company (docetaxel 20mg/mL,1mL vial) may lead to the acquisition cost of this drug being overestimated in the model, compared to what it would be expected in clinical practice. While this is likely to favour adagrasib vs. docetaxel +/- nintedanib, the EAG considers that, given the magnitude of the cost differences this is unlikely to have any meaningful impact on the estimates of cost-effectiveness.

Table 15 Costs of alternative docetaxel formulations

Drug	Unit	Cost	Cost per mg	Number of vials per treatment cycle	Cost per treatment cycle*
Docetaxel	20 mg/1 ml	£4.49	£4.13	7	£31.43
	80 mg/ 4 ml	£9.73	£2.43	2	£19.46
	160mg / 8ml	£19.70	£2.46	1	£19.70

*Assuming vial wastage

4.2.10.5 Health state costs

The company's model incorporates costs related to healthcare resource use at different stages of disease progression (pre- or post-), and one-off costs associated with treatment initiation and managing disease progression. Tables 55 and 56 of the CS report the resource use frequency and unit costs considered to estimate these costs, while Table 57 of the CS shows the per cycle and one-off costs included in the model. Unit cost data were derived from the NHS reference costs for 2022/23 and PSSRU 2023 reports [48], while resource use estimates were based on TA781. [8]

Points for critique

The EAG was not able to fully reconcile the resource use and unit costs in the CS with those in TA781. However, the health state and one-off routine care costs seem broadly aligned with those included in TA781, as shown in Table 16.

Table 16 Comparison of health state costs included in the CS and TA781

Health state	CS	TA781
Pre-progression (per model cycle)	£84.37	£77.04
Progressed disease (per model cycle)	£49.32	£39.98
Treatment initiation (one-off)	£1,070.43	£834.25
Upon progression (one-off)	£303.28	£116.53

4.2.10.6 Adverse event costs

The cost of adverse events included in the company's model (see section 4.2.8) are estimated by combining the adverse event rates (Table 45 of the CS) with the unit cost for each type of adverse events and applied as a one-off cost in the first model cycle. The unit costs of managing adverse events were informed by the latest NHS National Cost Collection (2022/23) [50] and are presented in Table 58 of the CS. The adverse events calculated for each treatment are: £170.94 for adagrasib, £352.65 for docetaxel, and £852.71 for docetaxel + nintedanib.

In response to EAG clarifications question B11, the company updated the model to include the costs of monitoring for hepatoxicity for adagrasib in a scenario analysis. The costs in this scenario were estimated by combining the frequency of medical tests required per week with the unit costs of each test. The frequency of tests was informed by the SmPC for each treatment under comparison. For each treatment regimen, the number of liver function tests, complete blood counts, and proteinuria tests needed weekly was calculated separately for the first 3 months of treatment and beyond. The unit costs, sourced from NHS National Cost Collection (2022/23).[50] These costs were not included in the company's base-case analysis but had a marginal impact on the estimates of cost-effectiveness (see Table 42, response to clarification question B11).

Points for critique

The EAG is concerned that the company's scenario including the costs of monitoring for hepatotoxicity for adagrasib is insufficiently described to ascertain whether it reflects the likely costs in clinical practice. First, it is unclear why additional monitoring costs were included for docetaxel +/- nintedanib in this scenario, as the risk of hepatotoxicity is a particular concern for *KRAS* G12C inhibitors but not necessarily for docetaxel +/- nintedanib. Second, monitoring costs only included the costs of blood tests, it is unclear why other categories of healthcare resource use were not included (e.g., contacts with healthcare professionals). While it may be that these contacts were already reflected in the health states and would not be incremental costs, the EAG notes that the health state costs are not treatment specific. Furthermore, the company scenario suggests lower monitoring costs for adagrasib compared to docetaxel (-£5) and docetaxel + nintedanib (-£90), and, therefore, the EAG is concerned that the company may not have adequately incorporated the costs of monitoring for hepatotoxicity for adagrasib, but the impact on overall cost-effectiveness is likely to be negligible.

The EAG has identified concerns regarding some adverse event costs used in the company's model. In Table 58 of the CS, the company provided a list of adverse event costs utilised in the model, which were sourced from the latest NHS National Cost Collection (2022/23). When multiple treatment codes were available based on the CC score, a weighted average was calculated using the reported unit costs and frequencies. However, the cost for decreased neutrophil count and neutropenia appears to be overestimated, while the costs for febrile neutropenia and diarrhoea seem to be underestimated when compared to the TA781 appraisal. Despite these discrepancies, the EAG recalculated the model results using adverse event costs from TA781 and found that these adjustments had no significant impact on overall cost-effectiveness results.

4.2.10.7 Subsequent treatment costs

The drug acquisition and administration costs of subsequent treatments are considered in the model as a one-off cost applied to the proportion of patients moving to the PD health state at each cycle. The proportion of patients receiving subsequent treatments and the assumed treatment duration (14 weeks) were informed by TA781 and reported in Table 59 of the CS. In Table 60 of the CS, the company presents the resulting subsequent treatment acquisition and administration costs used in the base case analysis.

The company's model incorporates subsequent treatments as a distribution of treatments to estimate the weighted average cost per treatment arm. The treatments considered include best supportive care (BSC), platinum chemotherapy (cisplatin, 100 mg/m^2 monthly), and docetaxel (75mg/m^2 every 21 days). The same subsequent treatments distribution is assumed for docetaxel and docetaxel + nintedanib, with 70% of patients receiving BSC and 30% cisplatin. For adagrasib, patients were assumed to receive BSC (50%), docetaxel (40%) and cisplatin (10%), consistent with the assumptions

used for sotorasib in TA781. Best supportive care is assumed to have no acquisition or administration costs, while platinum chemotherapy is assumed to correspond to cisplatin.

Points for critique

The costs of subsequent treatment costs in the company's model seem reasonably aligned with those in TA781. Clinical advice to the EAG suggests that the assumed distribution of treatments is fairly consistent with NHS clinical practice. Therefore, the EAG considers the distribution of subsequent treatments included to be appropriate.

The EAG notes that there is a discrepancy between the acquisition cost of subsequent treatments presented in Table 60 of the CS and the corresponding estimates applied in the economic model. The EAG verified the company's calculations in the model and concluded that the discrepancy is likely to be due to a reporting error in the CS. Table 14 report the subsequent treatment costs applied in the company's model.

4.2.10.8 End of life costs

The company's model applies end-of-life (EOL) care costs as a one-time cost when patients transition to the death health state. This cost includes health and social care costs and is informed by lung cancer-specific estimates reported in Round et al. (2015)[52] in the company's base case analysis (see details in Tables 61 of the CS) with alternative evidence sources used in scenario analysis (see Tables 62 and 63 of the CS for details). Costs in the original data sources were uprated to 2022/23 costs, according to inflation indices reported in the PSSRU Unit Costs of Health and Social Care 2023.[48]

Points for critique

The EAG considers the EOL care costs used in the company's model to be appropriate since they are based on lung cancer-specific EOL costs. The impact of the alternative sources used in scenario analyses, including TA781, is marginal on the overall cost-effectiveness results.

5 COST EFFECTIVENESS RESULTS

5.1 Summary of company's submission

All analyses presented in the CS include the confidential simple PAS discount of [redacted] over adagrasib's list price (see Section 4.2.10.2). A summary of the inputs and variables used in the company's base case analysis is presented in Appendix R of the CS and the assumptions used in the model are summarised in Table 67 of the CS.

At the clarification stage, the company submitted a revised version of the economic model. The key revisions were:

- Inclusion of the health state utility regression variance-covariance matrix in the cost-effectiveness model to allow for the joint health state utility uncertainty to be considered in the probabilistic sensitivity analysis using a multinormal distribution. The company also updated the results of the fully incremental probabilistic base case analysis to reflect this change (see response to clarification question B6.h).
- Functionality to perform additional scenario analyses relating to:
    - OS modelling.
    - Treatment duration.
    - Health state utilities.
    - Monitoring costs for hepatotoxicity.
- Updated univariate one-way sensitivity analysis (OWSA) excluding the health state utility values, which are jointly correlated in the revised model.

The company presents base case cost-effectiveness results as:

- Pair-wise comparisons against each comparator: Table 68 and 69 of the CS for adagrasib vs. docetaxel and adagrasib vs. docetaxel + nintedanib, respectively; and
- Fully incremental analysis against all comparators: Table 70 of the CS and Table 49 of the appendix submitted in response to clarification question B6h for the deterministic and probabilistic analysis, respectively.

Table 17 shows the base case results for the fully incremental deterministic and probabilistic analysis (with probabilistic results updated in response to clarification question B6h). The analysis suggests that docetaxel + nintedanib is extendedly dominated by adagrasib, with docetaxel becoming the only relevant comparator for the full incremental analysis. The deterministic ICER for adagrasib compared to docetaxel is [redacted], while the probabilistic ICER is [redacted]; both ICER estimates are inclusive of a severity weight on QALYs of 1.7 (see Section 7). The cost effectiveness acceptability curve and plane are presented in Figures 20 to 22 (in response to clarification question B6h). The probabilistic analysis suggests that adagrasib has a probability of being cost-effective of approximately [redacted] at cost-effectiveness thresholds of £20,000 and £30,000 per additional QALY, respectively. The probabilistic analysis was conducted by jointly varying uncertain parameters according to assigned probability distributions (distributions for the parameters are reported in Appendix R of the CS) over 1,000 interactions using Monte-Carlo simulation.

Table 17 Company's base case fully incremental cost-effectiveness analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental analysis (£/QALY)

Deterministic							
Docetaxel	[redacted]	[redacted]	[redacted]				
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,107
Probabilistic							
Docetaxel	[redacted]	[redacted]	[redacted]				
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,590

*Including a severity weight of 1.7

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The company reports a summary of the disaggregated deterministic costs, life years (LYs) and QALYs for the base-case analysis (Table 46 to 48 in Appendix J of the CS), which are reproduced in Table 18 to Table 20. For adagrasib, [redacted] compared to docetaxel and docetaxel + nintedanib appear to be driven by drug acquisition and, to less extent, by costs in the PF health state. Compared to docetaxel + nintedanib, [redacted]. Adverse event and administration costs are [redacted] for adagrasib compared to docetaxel and docetaxel + nintedanib, but these [redacted]. The QALY gains with adagrasib are driven by [redacted]. Adverse events have a small impact on total QALYs for all treatments under comparison but are [redacted].

Table 18 Discounted costs by category of resource use (reproduced from Table 46, Appendix J of the CS)

Treatment	Total costs	Acquisition	Administration	AE cost	PF HCRU	PD HCRU	EOL care	Sub tx acquisition	Sub tx admin
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event, EOL, end of life, HCRU, healthcare resource use; PD, progressed disease; PF, progression free; tx treatment

Table 19 Discounted QALYs by health state (reproduced from Table 47, Appendix J of the CS)

Treatment	Total QALYs	Progression-free	Progressed disease	Adverse events
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years

Table 20 Discounted LYs by health state (reproduced from Table 48, Appendix J of the CS)

Treatment	Total LYs	Progression-free	Progressed disease
Adagrasib	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]

Abbreviations: LYs, life years

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company conducted one-way deterministic sensitivity analyses (OWSA) on individual model inputs; each input was sequentially varied between a lower and upper bound while holding remaining inputs constant. Lower and upper bounds reflected 95% CIs or published ranges for each input. For parameters without an appropriate estimate to inform the range of variation in the OWSA, upper and lower bounds were calculated by assuming a standard error of 0.1 over the point estimate. Correlated inputs with joint uncertainty (e.g. survival model parameters) were excluded from OWSA.

The company reports results of the updated univariate OWSA for the 10 parameters with greater impact on the estimates of cost-effectiveness tornado plots (Figures 23 and 24 of the Appendix to the company's response to EAG clarification questions); the analysis reports incremental net benefits at a cost-effectiveness threshold of £30,000 per additional QALY.

The company conducted deterministic scenario analyses whereby key model assumptions and evidence sources were varied; these are described in Table 72 of the CS and results are presented in Table 73 of the CS. Additional scenarios requested by the EAG at the clarification stage are presented in Tables 35, 39, 41 and 42 of the company's response (see question B4, B6g, B9 and B11).

The EAG considers the scenarios with alternative approaches to model OS of most interest given the lack of mature OS from KRYSTAL-12 to inform the treatment effectiveness for adagrasib vs. docetaxel. In the scenario assuming an alternative survival distribution to extrapolate OS (which uses a Weibull distribution rather than gamma distribution used in the company's base case analysis) the

ICER for adagrasib versus docetaxel (£28,748 per additional QALY) was slightly lower than the company's base case estimate (£29,107 per additional QALY). When the distributions used to inform the PFS and OS extrapolations were both varied (log-normal for PFS and Weibull for OS rather than gamma for both outcomes in the company's base case) the ICER for adagrasib vs. docetaxel increased to £32,569 per additional QALY. The scenario where the PH NMAs was used to inform the OS and PFS extrapolations for docetaxel + nintedanib, while independently fitted curves were used to extrapolate OS and PFS for adagrasib and docetaxel, the ICER for adagrasib vs. docetaxel was £20,289 per additional QALY (when the PFS of both treatments assumed a gamma distribution, while the OS assumed a Weibull distribution for docetaxel and a generalised gamma for adagrasib). The corresponding scenario assuming a gamma distribution to extrapolate the OS for adagrasib and docetaxel resulted in an ICER of £29,007 per additional QALY for adagrasib. The scenario where KRYSTAL-1 and SELECT-1 were used to inform the OS extrapolation for adagrasib (exponential distribution) and docetaxel (gamma distribution), respectively, the resulting ICER is £17,029 per additional QALY for adagrasib vs. docetaxel (incorrectly reported in Table 72 of the CS as £15,084 per additional QALY). In this last scenario, the severity weight applied to the QALYs is 1.2 rather than 1.7 that is used for the majority of the company's analyses (see section 7).

The scenario analyses assuming non-treatment specific health state utilities (rather than treatment specific health state utilities) from KRYSTAL-12 (company's scenario 12) and from TA781 (company's scenario 13) are also of interest given its impact on the estimates of cost-effectiveness and the uncertainties associated with the health state utilities). The ICER for adagrasib vs. docetaxel increased to £59,830 and £55,601 per additional QALY for the company's scenarios 12 and 13, respectively. In both these scenarios the severity weight applied to QALYs was 1.2.

Docetaxel + nintedanib remained dominated by adagrasib across all scenario analyses.

Points for critique

The EAG's main concern is that the company's scenario analyses do not sufficiently explore alternative approaches to model the size of the treatment effect for adagrasib on OS. The EAG considers that the company's preferred approach to model OS, implies the existence of treatment effect for adagrasib vs. docetaxel that is highly uncertain given the lack of i) mature comparative OS evidence from KRYSTAL-12 and ii) supportive evidence from other *KRAS* G12C inhibitors in the relevant population. The EAG explores alternative approaches to model the treatment effect of adagrasib vs. docetaxel in Section 6.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company's validation of the model implementation followed a structured three-stage approach: (i) extreme value testing to explore how the model behaves under unusual or extreme conditions; (ii)

logical relationship testing to confirm that changes in key inputs, such as drug costs, produce predictable and rational impacts on outcomes; and (iii) consistency checks to ensure that all inputs were applied uniformly and accurately across the model.

For clinical validation, the company sought expert input to verify the survival extrapolations used in the economic analysis for the OS and PFS. Three one-on-one interviews were held with UK clinical experts who reviewed and recommended parametric models that aligned with clinically realistic and plausible long-term outcomes. [54]

Points for critique

The EAG considers the company's validation procedure to be reasonable. In addition to the company's thorough validation process, the EAG conducted independent checks to ensure the robustness and accuracy of the model. This included verifying that analyses, such as the base-case and key scenarios, could be reproduced reliably using the company's model. Inputs such as drug acquisition costs, resource use, and health state utilities were cross-checked against their original sources were possible to confirm their accuracy and correct implementation. The EAG also reviewed the model's structure to ensure it aligned with the decision problem, assessing the appropriateness of health states, transitions, and the time horizon used. Furthermore, additional scenario analyses were conducted to test the model's sensitivity to variations in key assumptions (see Section 6).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified two key areas of uncertainty in the company's cost-effectiveness analysis: (i) the effect of adagrasib relative to docetaxel +/- nintedanib on OS; and (ii) the use of treatment-specific health-related quality of life utility values in the model. The EAG considers alternative scenarios to the company's base case assumptions in these two areas of uncertainty and explores the impact of uncertainty on the cost-effectiveness of adagrasib relative to docetaxel +/- nintedanib.

A description of the EAG exploratory analyses is presented in Section 6.1 and the impact of these analyses on the company's base case results reported in Section 6.2. The EAG's preferred base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of adagrasib relative to docetaxel +/- nintedanib. Where the EAG is unable to provide a judgement in the absence of robust evidence (e.g., the effect of adagrasib on OS), the EAG have presented alternative base case scenarios. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions are presented in Section 6.3.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following exploratory analyses.

1. The effect of adagrasib relative to docetaxel +/- nintedanib on OS

As described throughout this report, one of the key areas of uncertainty is the absence of mature OS data from KRYSTAL-12 to inform the treatment effect of adagrasib on OS. [redacted] The final OS analysis is projected to be reported in [redacted] Consequently, the company relied on the use of data from a phase 1/2 single arm study of adagrasib (KRYSTAL-1) to predict OS in censored patients of KRYSTAL-12 for both adagrasib and docetaxel based on a patient-level surrogacy analysis of the relationship between TTP and OS for patients with previously treated advanced *KRAS* G12C mutation-positive NSCLC derived from KRYSTAL-1. The predicted KRYSTAL-12 OS from the surrogacy analysis was used to inform the company's NMA and the company's cost-effectiveness analysis. This means that the company's cost-effectiveness results hinge on the appropriateness and plausibility of the surrogacy analysis used to estimate KRYSTAL-12 OS, and the resulting treatment effect inferred for adagrasib relative to docetaxel +/- nintedanib for OS. Therefore, the predicted OS from the surrogacy analysis is the most critical parameter in the company's base case model.

In Section 3.2.3, the EAG critiqued the company's surrogacy analysis and concluded that: (i) no evidence currently exists to support the use of a surrogacy relationship between progression and survival in the target population with *KRAS*-mutations or with KRAS inhibitors; (ii) the key requirement for using a surrogate in place of the relevant clinical endpoint had not been demonstrated for the target population and treatments, i.e., that the relative effect of the treatment on the surrogate endpoint reliably predicts the relative effect of the treatment on the endpoint of OS; and (iii) that the predicted KRYSTAL-12 OS data for adagrasib and docetaxel based on the surrogacy analysis is likely to be over-precise and underestimating the true uncertainty in OS. For these reasons, the EAG is not confident that the predicted effect of adagrasib on OS used in the company's base case analysis is a sound basis to inform the cost-effectiveness of adagrasib relative to docetaxel +/- nintedanib. Furthermore, the EAG notes that the CodeBreaK 200 trial, which is the only trial to examine the relative effect of a targeted *KRAS* inhibitor (sotorasib) vs. docetaxel for *KRAS* G12C mutation-positive NSCLC, did not provide sufficient evidence to support a relationship between PFS and OS (crossover adjusted analysis), where despite statistically significant PFS for sotorasib vs. docetaxel, very limited, or no, OS benefit had been shown for sotorasib compared to docetaxel.

In the absence of conclusive OS evidence for adagrasib, and uncertainties concerning the validity of the company's proposed surrogacy approach, the EAG explores the impact of three alternative estimates for the OS HR of adagrasib vs. docetaxel on the cost-effectiveness of adagrasib, which the EAG considers reflects the range of likely scenarios from least to most optimistic OS estimates based on information currently available:

- Scenario 1.1 (least optimistic), no effect of adagrasib on OS. In this scenario, the OS HR for adagrasib vs. docetaxel is set equal to 1.0. This is based [redacted] the primary ITT analysis from CodeBreaK 200 for the more mature sotorasib data, which show a HR greater than one for sotorasib vs. docetaxel.
- Scenario 1.2 (mid-range optimistic), same effect of adagrasib on OS as identified for sotorasib. In this scenario, the OS HR for adagrasib vs. docetaxel is set equal to 0.89 based on the effect from the two-step crossover adjusted analysis for sotorasib vs. docetaxel from CodeBreaK 200.
- Scenario 1.3 (most optimistic), effect of adagrasib on OS based on the company's surrogacy analysis, which is over-precise. In this scenario, the OS HR for adagrasib vs. docetaxel is set equal to [redacted] based on the company's proportional hazards NMA, which avoids the additional uncertainty introduced by using the time-varying HRs for this comparison, where the PH assumption appears to hold. This approach also incorporates more mature OS evidence from KRYSTAL-1 for adagrasib and assumes that there is no class effect for KRAS G12C inhibitors (i.e. it excludes evidence related to sotorasib).

In all three scenarios, the independent simulated KRYSTAL-12 OS curve for docetaxel is used as the baseline survival curve, with the best fitted Weibull extrapolation based on AIC/BIC goodness-of-fit scores. Although the docetaxel OS curve is derived from the surrogacy analysis, the EAG's primary concerns regarding the surrogacy analysis are not based on its predictive effect of OS, but rather its use to derive a relative treatment effect for adagrasib. The choice of baseline curve will impact on the estimates of absolute effect on survival, but it is the estimates of relative treatment effect on survival that are important for the cost-effectiveness assessment of adagrasib relative to docetaxel +/- nintedanib.

For the comparison of adagrasib vs. combination therapy of docetaxel plus nintedanib, the HR from the company's proportional hazards NMA for docetaxel plus nintedanib vs. docetaxel of [redacted] is applied to the docetaxel baseline to derive the corresponding OS curve for docetaxel plus nintedanib.

2. Health-related quality of life utility values for the PD disease health state

As discussed in Section 4.2.9, the company applied treatment-specific health state utility values to the PF and PD health states based on a MMRM model of EQ-5D responses from KRYSTAL-12. The coefficient for the adagrasib arm was positive, suggesting that patients in the intervention arm have higher utility than docetaxel, while controlling for progression status and other variables of age and sex. Therefore, the company applied a utility increment for adagrasib compared to docetaxel for both the PF and PD health states. The company justified the increment in utility for adagrasib on the basis that it is an oral treatment that is administered at home, whereas docetaxel is administered intravenously as hospital-based chemotherapy, which may increase the burden on patients and decrease their HRQoL. The company also referred to an observational study that suggests more favourable HRQoL over time (based on EORTC-QLQ-C30) in Stage IV NSCLC patients with a targetable driver mutation compared to patients without a targetable driver mutation;[47] although in this study patients with a significant decline in HRQoL at 6 months of follow-up also had significantly shorter PFS, as well as significantly shorter OS, suggesting that the differences in HRQoL in this study were driven by the health state.

The EAG is reasonably satisfied that adagrasib may be associated with an increment in utility in the PF health state compared to docetaxel in the same health state because of its oral administration at home, but the EAG is not satisfied with a treatment-specific uplift in utility for adagrasib in the PD health state because patients have discontinued their initial treatment of adagrasib upon progression and have moved to subsequent treatments (for adagrasib, 50% of patients are assumed to receive BSC, 40% docetaxel and 10% cisplatin, while for docetaxel 70% of patients are assumed to receive BSC and 30% cisplatin). Furthermore, patients in the docetaxel arm of KRYSTAL-12 that crossed over to adagrasib were censored from the company's HRQoL analysis resulting in potential selection bias in the post-progression analysis of KRYSTAL-12 data. Therefore, the EAG considers it inappropriate to apply an increment in utility for adagrasib compared to docetaxel in the PD health state.

The EAG explores the impact of using a single treatment-independent utility value for the PD health state on the cost-effectiveness of adagrasib relative to docetaxel +/- nintedanib, while maintaining a treatment-specific utility value for the PF health state. Two scenarios are considered:

- Scenario 2.1, PD utility value is the same for all treatments based on the value of [redacted] for adagrasib used in the company's base case analysis. This would appear the most suitable estimate for use in the model because it is derived directly from KRYSTAL-12 data and is not subject to the censoring concerns noted for the docetaxel arm. In this scenario, the decrement for PD relative to PF is [redacted] for adagrasib and [redacted] for docetaxel due to the increased utility associated with adagrasib in the PF health state.
- Scenario 2.2, PD utility value is the same for all treatments based on the value of [redacted] for docetaxel in the company's base case analysis. In this scenario, the decrement for PD relative

to PF is [redacted] for adagrasib and [redacted] for docetaxel due to the increased utility associated with adagrasib in the PF health state.

In both scenarios, as per the company's base case, the same utility values for docetaxel monotherapy are applied to docetaxel plus nintedanib due to an absence of HRQoL utility data for combination therapy. The EAG's clinical advisor considered the assumption of a class effect for docetaxel +/- nintedanib to be reasonable.

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 21 shows the results of the EAG scenarios for the fully incremental comparison of adagrasib with docetaxel monotherapy and docetaxel plus nintedanib. Across all analyses, the total QALYs are adjusted by applying the 1.7 severity weight, which holds under all scenarios.

In the fully incremental deterministic analysis, docetaxel plus nintedanib is either strictly or extendedly dominated by adagrasib under all scenarios, including the company's base case analysis, where it produces [redacted] compared to adagrasib. Therefore, the most relevant comparison for the cost-effectiveness of adagrasib is with docetaxel monotherapy. In the company's base case results, the ICER for adagrasib compared to docetaxel is £29,107, [redacted]. Under EAG scenario 1.3, the results are very similar to the company's base case (with an ICER of £30,853/QALY) because the effect of adagrasib on OS is based on the company's surrogacy analysis; the EAG considers this scenario to represent the most optimistic effect of adagrasib on OS, which is estimated with over precision and subject to several important uncertainties as outlined previously. The small differences between EAG scenario 1.3 and company base case are due to (i) the use of the proportional hazard assumption for the OS HR from the surrogacy analysis in scenario 1.3 rather than the time-varying HRs from the NMA, and (ii) the use of the best fitted Weibull distribution for the extrapolation of the independent OS curve for docetaxel in scenario 1.3 rather than the gamma distribution, which was selected for all models for consistency with PFS in the company's base case analysis. EAG scenarios 1.1 and 1.2 have the largest impact on the cost-effectiveness of adagrasib compared to docetaxel. Under these scenarios, less optimistic assumptions regarding the effect of adagrasib on OS are considered, where the company have not presented sufficient evidence to justify the expected effect under the surrogacy analysis and it can only be concluded that the effect of adagrasib on OS remains unknown, at least until the final OS analysis from KRYSTAL-12 is complete. When no effect of adagrasib relative to docetaxel on OS is assumed under scenario 1.1, the ICER increases to £67,571 per additional QALY. The EAG also notes that it remains to be seen if adagrasib results in a positive impact on

OS [redacted] When some positive effect on OS is assumed for adagrasib relative to docetaxel, in line with that observed for sotorasib under the best-case analysis from CodeBreaK 200 (two-step crossover adjusted analysis), the ICER increases by £15,468/QALY from the company's base case analysis to £44,575/QALY.

EAG scenarios 2.1 and 2.2 demonstrate that the company's assumption of an increment in utility for adagrasib relative to docetaxel in the PD health state, even though patients have discontinued adagrasib treatment in this health state, has an important material impact on the ICER. Under the assumption of treatment-independent utility values for the PD health state, the ICER for adagrasib increased by £5,658 in scenario 2.1 and £5,513 in scenario 2.2 from the company's base case analysis. The small difference in results between scenarios 2.1 and 2.2 suggests that the absolute value of the PD utility is less important than the relative difference in utility value between treatments.

Table 21 Cost-effectiveness results of EAG scenario analyses – fully incremental deterministic analysis

Scenario #	Name	Option	Total costs	Total QALYs*	Inc. Costs	Inc. QALYs	ICER (/QALY)
	Company's base-case results	Docetaxel	[redacted]	[redacted]			
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£29,107
1.1	No effect of adagrasib on OS (HR = 1.0 for adagrasib vs. docetaxel)	Docetaxel	[redacted]	[redacted]			
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£67,571
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
1.2	Same effect of adagrasib on OS as identified for sotorasib (HR = 0.89 for adagrasib vs. docetaxel based on the effect from the two-step crossover adjusted analysis for sotorasib vs. docetaxel from CodeBreaK 200)	Docetaxel	[redacted]	[redacted]			
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£44,575
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
1.3	Effect of adagrasib on OS from the company's surrogacy analysis (HR = [redacted] for adagrasib vs. docetaxel based on proportional hazards NMA)	Docetaxel	[redacted]	[redacted]			
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£30,853
2.1	Same PD utility value for all treatments based on the value of [redacted] for adagrasib in the company's base case analysis	Docetaxel	[redacted]	[redacted]			
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£34,765
2.2	Same PD utility value for all treatments based on the value of [redacted] for docetaxel in the company's base case analysis	Docetaxel	[redacted]	[redacted]			
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£34,620

*Adjusted by applying a 1.7 severity weight

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes to the company's base case:

- Treatment-independent utility value for PD health state, rather than the increment applied to adagrasib in the PD health state in the company's base case – Scenario 2.1
- Effect of adagrasib on OS is lower than the company's surrogacy analysis – Scenarios 1.1 and 1.2

The selection of changes made to the EAG base case is based on the evidence currently available; however, one key uncertainty remains, which is the unknown effect of adagrasib relative to docetaxel on OS. Given that this effect remains unknown, the EAG considers two alternative base cases:

- EAG base case 1: Includes scenarios 2.1 and 1.1, with no effect of adagrasib on OS.
- EAG base case 2: Includes scenarios 2.1 and 1.2, with some effect of adagrasib on OS, which is commensurate with the effect observed for sotorasib under the best-case analysis from CodeBreaK 200 (two-step crossover adjusted analysis).

Table 22 and Table 23 show the cumulative impact of the EAG's preferred assumptions on the ICER for the fully incremental deterministic and probabilistic analysis, respectively.

Table 22 Cumulative cost-effectiveness results for the EAG's preferred assumptions – fully incremental deterministic analysis

Name	Option	Total costs	Total QALYs*	Inc. Costs	Inc. QALYs	ICER (/QALY)
Company's base-case results	Docetaxel	[redacted]	[redacted]			
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£29,107
EAG base case 1 (scenarios 1.1 + 2.1, no effect of adagrasib on OS and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£108,086
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2 (scenarios 1.2 + 2.1, same effect of adagrasib on OS as observed for sotorasib and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£58,794
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

*Adjusted by applying a 1.7 severity weight

Table 23 Cumulative cost-effectiveness results for the EAG's preferred assumptions – fully incremental probabilistic analysis

Name	Option	Total costs	Total QALYs*	Inc. Costs	Inc. QALYs	ICER (/QALY)
Company's base-case results	Docetaxel	[redacted]	[redacted]			
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£27,590
EAG base case 1 (scenarios 1.1 + 2.1, no effect of adagrasib on OS and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£66,744
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2 (scenarios 1.2 + 2.1, same effect of adagrasib on OS as observed for sotorasib and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£43,554
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

*Adjusted by applying a 1.7 severity weight

6.4 Conclusions of the cost effectiveness section

The company submitted a partitioned survival analysis to compare the cost-effectiveness of adagrasib with docetaxel monotherapy and docetaxel plus nintedanib in adult patients with *KRAS* G12C mutation-positive NSCLC, whose disease has progressed after prior treatment with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. The EAG notes that docetaxel + nintedanib is only a relevant comparator in the subpopulation with adenocarcinoma as its license is specific to this histology.

The company's base case model is consistent with the model structure used in TA781 (sotorasib) and is generally considered appropriate. However, the main limitation is the lack of mature OS data to inform the comparisons. The uncertainty surrounding the OS extrapolations in the model is magnified by the unavailability of mature comparative OS data between adagrasib and any of the comparators, leading to considerable uncertainty in the estimates of cost-effectiveness of adagrasib relative to its comparators. The EAG is concerned that [redacted] Consequently, the effects of adagrasib relative to the comparators remains unknown.

The predicted OS for KRYSTAL-12 from the surrogacy analysis is the most critical parameter in the company's base case model. However, the company's surrogacy analysis is subject to several important limitations, as outlined in Section 3.2.3 The company's cost-effectiveness results hinge on the appropriateness and plausibility of the surrogacy analysis used to estimate KRYSTAL-12 OS, and the resulting treatment effect inferred for adagrasib relative to docetaxel +/- nintedanib for OS. The company's PFS evidence from KRYSTAL-12 is mature, but robust evidence is required to show that the improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC. Without this evidence, it cannot be assumed that a surrogacy relationship holds in the target population.

A further concern relates to uncertainty in the utility values for the PD health state of the model, where the company applied a treatment-specific uplift in utility for adagrasib due to its oral administration. However, the EAG notes that patients in the PD health state have discontinued their initial treatment of adagrasib upon progression and have moved to subsequent treatments, which include IV administration. In addition, patients in the docetaxel arm of KRYSTAL-12 that crossed over to adagrasib were censored from the company's HRQoL analysis resulting in potential selection bias in the post-progression analysis of KRYSTAL-12 data. Therefore, the EAG considers it inappropriate to apply an increment in utility for adagrasib compared to docetaxel in the PD health state.

In summary, the two critical parameters in the partitioned survival analysis impacting the cost-effectiveness of adagrasib relative to the comparators are:

- The magnitude of OS benefit for adagrasib relative to docetaxel +/- nintedanib.
- Treatment-specific utility values in the PD health state.

When no effect of adagrasib on OS based on [redacted] the primary ITT analysis from CodeBreaK 200 for sotorasib (the only other KRAS inhibitor with data in the relevant population) is applied, the company's base case ICER increases to £67,571 per additional QALY (with a severity weight of 1.7 and holding all other parameters the same as company base case). When some positive effect on OS is assumed for adagrasib relative to docetaxel, in line with that observed for sotorasib under the best-case analysis from CodeBreaK 200 (two-step crossover adjusted analysis), the company's base case analysis ICER increases to £44,575 per additional QALY (with a severity weight of 1.7 and holding all other parameters the same as company base case). Docetaxel + nintedanib is dominated by adagrasib under these scenarios. Under the assumption of treatment-independent utility values for the PD health state, the ICER for adagrasib increases by around £5,500 from the company's base case analysis. When these scenarios are combined in the EAG's preferred base case assumptions, the [redacted]

7 SEVERITY MODIFIER

The company estimated the proportional and absolute QALY shortfall for patients with advanced NSCLC with *KRAS* G12C mutation who have progressive disease after prior therapy compared to a population without the condition (i.e., expected health without the condition in the general population over the remaining lifetime of patients).

The baseline participant mean age (63.7 years) and proportion of females (33.1%) in KRYSTAL-12 were used to estimate expected lifetime QALYs for an equivalent population without the condition using general population mortality estimates from UK lifetables and age and sex-adjusted utility values.[46] The corresponding QALYs (discounted at an annual rate of 3.5%) gained for a population without the condition is 11.28.[55]

Docetaxel was considered the standard of care in the company's QALY shortfall calculations, with a median OS in the docetaxel arm from the company's base case assumptions of approximately [redacted]. The total expected QALYs for docetaxel in the company's base case assumptions was [redacted] (discounted at an annual rate of 3.5%).

Table 24 provides the results of the QALY shortfall analysis using the company's base case assumptions. Patients with advanced NSCLC with *KRAS* G12C mutation who have progressive disease after prior therapy meet the proportional shortfall criteria, at the QALY weight of 1.7. Consequently, the company applied a severity weight of 1.7 to its base case results. The severity weight of 1.7 was also consistent across the majority of the company's scenario analyses.

Table 24 Company's QALY shortfall analysis (adapted from Table 66 of CS)

	Start age	% females	QALYs (model output)	QALYs for general population	Absolute QALY shortfall	Proportional QALY shortfall	NICE severity weighting
Docetaxel	63.7	33.1%	[redacted]	11.28	[redacted]	[redacted]	1.7

Points for critique

The company's QALY shortfall calculations and implementation of the severity modifier are in line with NICE methodological guidance.[27] However, the EAG notes that the company have considered docetaxel to be the standard of care in the QALY shortfall analysis. The company highlighted in Section B.1.3.3.5 of the CS that most patients in the relevant population receive sotorasib (85%) at 2L and that most patients who receive a docetaxel-based regimen would receive docetaxel + nintedanib (60–80%). The EAG notes that sotorasib cannot be considered the standard of care treatment while it is not in routine commissioning for the NHS, which would suggest that docetaxel + nintedanib is

considered the standard of care in the patient subpopulation eligible to receive it (i.e., adenocarcinoma histology). However, the EAG checked if using docetaxel + nintedanib as the standard of care treatment had implications for the selection of the severity modifier in the company's and EAG base case analyses and found that the same severity weight of 1.7 would apply across the analyses.

Table 25 summarises the EAG base case QALY shortfall analysis using docetaxel +/- nintedanib as the standard of care. The EAG concludes that the population in the CS meets the NICE criteria for severity weighting, and the QALY weight is 1.7. This weight has been applied to the results reported in Sections 5 and 6 of the EAR. Appendix 2 presents the results of the company and EAG base case without a severity modifier.

Table 25: EAG base case QALY shortfall analysis

	Start age	% females	QALYs (model output)	QALYs for general population	Absolute QALY shortfall	Proportional QALY shortfall	NICE severity weighting
Docetaxel	63.7	33.1%	[redacted]	11.28	[redacted]	[redacted]	1.7
Docetaxel + nintedanib	63.7	33.1%	[redacted]	11.28	[redacted]	[redacted]	1.7

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APPENDIX 1. APPENDICES CRITIQUE OF LITERATURE SEARCHES TO INFORM THE COST-EFFECTIVENESS SECTION OF THE CS

Table 26 EAG appraisal of evidence identification of the cost-effectiveness searches

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, search strategies were not provided for conference proceedings or health technology assessment agency websites. This was raised with the company, who responded with the strategies for the health technology assessment agency websites. The company clarified that conference proceedings were searched as part of the database strategies, although the section on 'congress searches' in Appendix G, section G.1.1.1, suggested otherwise. In the original company submission, health technology assessment agency websites were included in multiple places in the PRISMA. This was raised with the company, who provided a clearer and more detailed PRISMA.
Were appropriate sources searched?	YES	A small range of relevant databases, conference proceedings, and health technology assessment agency websites were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition and the study type.
Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. In the population terms, there was no hyphenation of 'non-small-cell' or 'non-small cell' and the terms for cancer could have been more sensitive (e.g., including tumor* and tumour*). There are also several types of non-small cell lung cancer which were not searched for: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma, adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, salivary gland carcinoma, carcinoid tumour, and unclassified carcinoma. Moreover, the concept of metastasis could have been expanded to include terms for mutation,

		progressive disease, or previously treated, etc. This was raised with the company, who performed additional searches which found no new relevant records.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper and publication types were removed in several of the search strategies.
Were any search filters used, validated and referenced?	UNCLEAR	Search filters were used but not referenced. Therefore, it was unclear if the filters used were validated.

Table 27 EAG appraisal of evidence identification of the health-related quality of life searches

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, search strategies were not provided for conference proceedings or health technology assessment agency websites. This was raised with the company, who responded with the strategies for the health technology assessment agency websites. The company clarified that conference proceedings were searched as part of the database strategies, although the section on 'congress searches' in Appendix H, section H.1.1.1, suggested otherwise.
Were appropriate sources searched?	YES	A small range of relevant databases, conference proceedings, and health technology assessment agency websites were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition and the study type.

Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. In the population terms, there was no hyphenation of 'non-small-cell' or 'non-small cell' and the terms for cancer could have been more sensitive (e.g., including tumor* and tumour*). There are also several types of non-small cell lung cancer which were not searched for: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma, adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, salivary gland carcinoma, carcinoid tumour, and unclassified carcinoma. Moreover, the concept of metastasis could have been expanded to include terms for mutation, progressive disease, or previously treated, etc. This was raised with the company, who performed additional searches which found no new relevant records.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper and publication types were removed in several of the search strategies.
Were any search filters used, validated and referenced?	UNCLEAR	Search filters were used but not referenced. Therefore, it was unclear if the filters used were validated.

Table 28 EAG appraisal of evidence identification of the cost and healthcare resource identification, measurement and valuation searches

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, search strategies were not provided for conference proceedings or health technology assessment agency websites. This was raised with the company, who responded with the strategies for the health technology assessment agency websites. The company clarified that conference proceedings were searched as part of the database strategies, although the section on 'congress searches' in Appendix G, section G.1.1.1, suggested otherwise. In the original company submission, health technology assessment agency websites were included in multiple places in the PRISMA. This was raised with the company, who provided a clearer and more detailed PRISMA.

Were appropriate sources searched?	YES	A small range of relevant databases, conference proceedings, and health technology assessment agency websites were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition and the study type.
Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. In the population terms, there was no hyphenation of 'non-small-cell' or 'non-small cell' and the terms for cancer could have been more sensitive (e.g., including tumor* and tumour*). There are also several types of non-small cell lung cancer which were not searched for: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma, adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, salivary gland carcinoma, carcinoid tumour, and unclassified carcinoma. Moreover, the concept of metastasis could have been expanded to include terms for mutation, progressive disease, or previously treated, etc. This was raised with the company, who performed additional searches which found no new relevant records.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper and publication types were removed in several of the search strategies.
Were any search filters used, validated and referenced?	UNCLEAR	Search filters were used but not referenced. Therefore, it was unclear if the filters used were validated.

APPENDIX 2. COST EFFECTIVENESS RESULTS WITHOUT SEVERITY MODIFIER

Table 29 Cost-effectiveness results of EAG scenario analyses – fully incremental deterministic analysis (no severity modifier)

Scenario #	Name	**Option**	**Total costs**	**Total QALYs**	**Inc. Costs**	**Inc. QALYs**	**ICER (/QALY)**
	Company's base-case results	Docetaxel	[redacted]	[redacted]			-

		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£49,481
1.1	No effect of adagrasib on OS (HR = 1.0 for adagrasib vs. docetaxel)	Docetaxel	[redacted]	[redacted]			-
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£114,872
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
1.2	Same effect of adagrasib on OS as identified for sotorasib (HR = 0.89 for adagrasib vs. docetaxel based on the effect from the two-step crossover adjusted analysis for sotorasib vs. docetaxel from CodeBreaK 200)	Docetaxel	[redacted]	[redacted]			-
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£75,778
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
1.3	Effect of adagrasib on OS from the company's surrogacy analysis (HR = [redacted] for adagrasib vs. docetaxel based on proportional hazards NMA)	Docetaxel	[redacted]	[redacted]			-
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£52,451
2.1	Same PD utility value for all treatments based on the value of [redacted] for adagrasib in the company's base case analysis	Docetaxel	[redacted]	[redacted]			-
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£59,100
2.2	Same PD utility value for all treatments based on the value of [redacted] for docetaxel in the company's base case analysis	Docetaxel	[redacted]	[redacted]			-
		Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
		Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£58,854

Table 30 Cumulative cost-effectiveness results for the EAG's preferred assumptions – fully incremental deterministic analysis

Name	**Option**	**Total costs**	**Total QALYs**	**Inc. Costs**	**Inc. QALYs**	**ICER (/QALY)**
Company's base-case results	Docetaxel	[redacted]	[redacted]			-
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£49,481
EAG base case 1 (scenarios 1.1 + 2.1, no effect of adagrasib on OS and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			-
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£183,746
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2 (scenarios 1.2 + 2.1, same effect of adagrasib on OS as observed for sotorasib and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			-
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£99,950
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

Table 31 Cumulative cost-effectiveness results for the EAG's preferred assumptions – fully incremental probabilistic analysis

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (/QALY)
Company's base-case results	Docetaxel	[redacted]	[redacted]			-
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly Dominated
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£46,904
EAG base case 1 (scenarios 1.1 + 2.1, no effect of adagrasib on OS and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			-
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£113,465
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
EAG base case 2 (scenarios 1.2 + 2.1, same effect of adagrasib on OS as observed for sotorasib and same PD utility value for all treatments)	Docetaxel	[redacted]	[redacted]			-
	Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	£74,042
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 6 February 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Implications of a class effect for *KRAS* G12C inhibitors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3, page 46 "CodeBreaK 200 found a statistically significant improvement in PFS for sotorasib compared with docetaxel monotherapy, but no statistically significant improvement in OS. There was no evidence that crossover from the docetaxel arm to sotorasib had a significant impact on OS. A critique of CodeBreaK 200 is provided in Section 3.3. Therefore, there is currently no evidence that improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC."	The Company proposes that the text is amended to: "CodeBreaK 200 found a statistically significant improvement in PFS for sotorasib compared with docetaxel monotherapy, but no statistically significant improvement in OS. Crossover adjustment for OS did not lead to statistically significant OS, although a reduction in the HR was observed. A critique of CodeBreaK 200 is provided in Section 3.3. Therefore, there is currently limited evidence that improvements in PFS observed with <u>sotorasib</u> translate into OS improvements."	This language implies that there is a class effect for efficacy for *KRAS* G12C inhibitors. While clinical evidence for sotorasib has not demonstrated an OS benefit, further data are needed to confirm the efficacy of adagrasib. It is therefore not factually accurate to imply an unproven class effect, and the Company requests that the statement is clarified as suggested. Removing the suggestion of a parallel between the two therapies avoids the implication that the efficacy of sotorasib predicts that of adagrasib. Further, it is considered misleading to state that there is no evidence that crossover has a significant impact on OS. This misses the broader	Not a factual inaccuracy. This is a matter of interpretation of the evidence and the wording reflects the EAG's position on this issue.

		context that crossover-adjustment reduced the OS HR in CodeBreaK 200.	
Section 3.6, page 62–63 "The EAG is concerned that the existence of a treatment benefit on OS for adagrasib compared to docetaxel cannot be demonstrated, and that the available evidence for sotorasib does not support the existence of an OS treatment benefit for *KRAS* G12C inhibitors in the relevant population. Overall, there is currently no evidence that improvements in PFS observed with *KRAS* G12C inhibitors translate into OS improvements and that PFS is a reliable surrogate outcome for OS in 2L+ *KRAS* G12C mutated NSCLC."	The Company proposes that the text is amended to: "The EAG is concerned that the existence of a treatment benefit on OS for adagrasib compared to docetaxel cannot be demonstrated, and that the available evidence does not support the existence of an OS treatment benefit <u>for sotorasib</u> in the relevant population. Overall, there is currently limited evidence that improvements in PFS observed with <u>adagrasib or sotorasib</u> translate into OS improvements."	As above	As above.
Section 4.2.7.2, page 79 "Furthermore, the available evidence for sotorasib, the only other *KRAS* G12C	The Company proposes that the text is amended to: "Furthermore, the available evidence for sotorasib, the only other *KRAS*	As above	As above.

inhibitor with RCT evidence (CodeBreaK 200) in the relevant population shows very limited, or no, OS benefit for sotorasib compared to docetaxel. Therefore, the existence of an OS treatment effect for *KRAS* G12C inhibitors compared to docetaxel has not been established to date."	G12C inhibitor with RCT evidence (CodeBreaK 200) in the relevant population shows very limited OS benefit for sotorasib compared to docetaxel. Therefore, a statistically significant OS treatment effect for sotorasib or adagrasib compared to docetaxel has not been established to date."		
Section 6.1, page 97 "(i) no evidence currently exists to support the use of a surrogacy relationship between progression and survival in the target population with *KRAS*-mutations or with *KRAS* inhibitors…"	The Company proposes that the text is amended to: "(i) limited evidence currently exists to support the use of a surrogacy relationship between progression and survival in the target population with *KRAS*-mutations or with adagrasib or sotorasib…"	As above	As above.

Issue 2 Incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1.1, page 31 "The subset of patients in the docetaxel arm who crossed over to adagrasib or received another *KRAS* G12C inhibitor tended to be fitter at baseline than the overall docetaxel arm population (ECOG 0: 33.9% vs. 15.5%) and had shorter mean time since metastatic diagnosis (11.5 months vs. 15.0 months)."	The Company proposes that the text is amended to: "The subset of patients in the docetaxel arm who crossed over to adagrasib or received another *KRAS* G12C inhibitor had shorter mean time since metastatic diagnosis (11.5 months vs. 15.0 months)."	To correctly reflect that the proportion of patients with ECOG 0 in the crossover/*KRAS* G12C inhibitor group (33.9%) is comparable to the proportion in the overall docetaxel arm population (30.9%; CSR page 98). Therefore, fitness as a point of difference between the subset of patients and the full population is not factually accurate and can be eliminated from this sentence.	Thank you, this has been amended.
Section 4.2, page 65	The Company proposes that the text is amended to:	Although drug acquisition costs	This is not a matter of

"The largest component of cost difference between adagrasib and its comparators is drug acquisition costs, health state (progression-free and progressed disease) resource use, and costs of subsequent treatments, while only a small difference in costs is associated with adverse events."	"The largest component of cost difference between adagrasib and its comparators is drug acquisition costs, health state (progression-free and progressed disease) resource use, and costs of subsequent treatments, while only a small difference in costs is associated with adverse events. [redacted]"	differ in the adagrasib and docetaxel monotherapy arms, they are more similar between the adagrasib and docetaxel + nintedanib arms.	factual accuracy.
Section 4.2.4, page 69 "The cost of subsequent treatments is assumed to be the same for docetaxel and docetaxel + nintedanib but differ for adagrasib"	The Company proposes that the text is amended to the following: "The cost of subsequent treatments is <u>calculated</u> to be the same for docetaxel and docetaxel + nintedanib but differ for adagrasib"	This change of wording correctly reflects calculations and assumptions taken from the economic model.	We have amended the text to increase clarity.

<table>
<tr>
<td>Section 4.2.7, page 75
“The EAG notes that it is possible to fit different parametric distributions to each treatment group in the context of a time-varying NMA”</td>
<td>The Company believe that the text should instead read:
“The EAG notes that it is <u>not</u> possible to fit different parametric distributions to each treatment group in the context of a time-varying NMA”</td>
<td>The time-varying NMA was based on one specific parametric distribution that was assumed to apply to all arms of all trials within the network of evidence.</td>
<td>Thank you, this has been amended.</td>
</tr>
<tr>
<td>Section 4.2.7, page 77
“Scenario analysis: PH NMA, independent parametric curves fitted to KRYSTAL-1 for adagrasib (exponential) and SELECT-1 for docetaxel (gamma)” in Table 10</td>
<td>The Company notes that the landmark estimates and median OS for this scenario are incorrect, and should instead read:
<table>
<tr><th>Tx*</th><th>1yr</th><th>2yr</th><th>3yr</th><th>5yr</th><th>10yr</th><th>mOS</th></tr>
<tr><td>Ada.</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Doc.</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Doc.+nin.</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
*Table headings shortened for simplicity.</td>
<td>To align with the correct landmark estimates and median OS as calculated in the cost-effectiveness model.</td>
<td>Thank you, this has been amended.</td>
</tr>
<tr>
<td>Section 4.2.7, page 77</td>
<td>The Company proposes that the EAG removes the “Docetaxel” row from the merged “Simulated KM KRYSTAL-12” analysis rows in Table 10.</td>
<td>Currently, incorrect data populates the “SELECT-1” row of</td>
<td>Thank you, we have amended both rows.</td>
</tr>
</table>

The final three rows of Table 10.	Instead, the correct SELECT-1 inputs should populate the "SELECT-1" row. On the "SELECT-1" row, the 1-year landmark estimate should read "[redacted]" and median OS should read "[redacted]".	Table 10 and also duplicates a row in this table. This change alleviates the need for two rows displaying the SELECT-1 data, while also correcting two typographical errors.	
Section 4.2.7.2, page 80 "Whilst the predictions of OS for docetaxel based on the surrogacy analysis may be reasonable, the corresponding predictions for adagrasib have not been externally validated and remain highly uncertain."	The Company proposes the following amendment to the text: "Whilst the predictions of OS for docetaxel based on the surrogacy analysis may be reasonable, the corresponding predictions for <u>adagrasib remain</u> highly uncertain."	The Company consulted clinical experts in order to externally validate docetaxel and adagrasib parametric survival model choices, thus adagrasib OS predictions were externally validated.	We have adapted the text to clarify that the extrapolation was not validated against external data (other than clinical opinion).
Section 5.2.1, page 95	The Company proposes the following amendment to the text:	An ICER of £15,084 is calculated when	The EAG corrected the

"The scenario where KRYSTAL-1 and SELECT-1 were used to inform the OS extrapolation for adagrasib (exponential distribution) and docetaxel (gamma distribution), respectively, the resulting ICER is £15,084 per additional QALY for adagrasib."	"The scenario where KRYSTAL-1 and SELECT-1 were used to inform the OS extrapolation for adagrasib (generalized gamma distribution) and docetaxel (Weibull distribution), respectively, the resulting ICER is £15,084 per additional QALY for adagrasib."	using the distributions named in the amended text.	ICER to £17,029 per additional QALY for adagrasib vs. docetaxel, as this was misreported as £15,084 per additional QALY in the CS. The distributions are correct according to the company's description of scenario 10 in Table 72 of the CS.

Issue 3 Amendments to report text for greater clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1.2, page 35 "A total of [redacted] patients were censored within first 6 months across both treatment arms; the most common	The Company proposes that the text is amended to: "A total of [redacted] patients were censored within the first 6 months across both treatment	Combining these two factually correct statements into	The sentence has been amended to

reason for censoring was [redacted] treatment arms.”	arms. Across the full follow-up period, the most common reason for censoring was [redacted] treatment arms.”	one sentence may give the incorrect impression that the proportions of censored patients correspond to the first 6 months of follow-up, when in fact, these proportions correspond to the full follow-up period. Breaking these statements into two sentences and stating the timeframe for the reported proportions avoids potential misunderstanding.	avoid potential confusion.
Section 3.2.1.2, page 37 “The difference was statistically significant and was above the UK	The Company proposes that the text is amended to: “The difference was statistically significant. For patients receiving docetaxel, the change in index score surpassed the minimally important	It is not the difference between the groups that is compared to the	The statistical analysis plan (v2.0), p.20, states:

minimally important difference (MID) thresholds.”	difference (MID) threshold, indicating a worsening of QoL. In contrast, the MID was not reached for patients receiving adagrasib, suggesting maintained QoL.”	MID, but the change from baseline in the docetaxel group. It is not the MIDs that are UK-specific, but the utility scores used in the analysis. As the utility scores are not discussed here, “UK” can be removed from this text.	“The MID was defined as a score difference of […] 7 points for the VAS” for EQ-5D-5L. Therefore, the sentence was changed to “The difference was statistically significant; however, the minimally important difference specified in the SAP (7 points score difference on the VAS scale) was not met.”
Section 4.1, page 64 “(see Table 40, Appendix G)”	The Company proposes that the text is amended to: “(see Table 40, Appendix G of the CS)”	This is for full contextual clarity to correctly identify the referenced appraisal.	This has been added for clarity.

Section 4.2, page 65 "In the PartSA, the time-dependent risk associated with disease progression and death is modelled using the survival functions that are parameterised by the time varying NMA (see Section 3.4.3) to independently determine the proportion of patients alive and in the progressed (or progression-free) health state over time."	The Company proposes for additional clarity in this wording: "In the PartSA, the time-dependent risk associated with disease progression and death is modelled using the survival functions that are parameterised by the time varying NMA (see Section 3.4.3). OS and PFS are independently modelled to determine the proportion of patients alive and in the progressed (or progression-free) health state over time."	The underlined wording amendment is suggested for clarity.	This has been added for clarity.
Section 4.2.6.1, page 73 "The methodology used by the company to conduct the time-varying NMA assumes a common parametric distribution across all arms of the studies in the evidence network, and, therefore, the extrapolated survival curves for PFS and OS all follow the same distribution in the economic model."	The Company proposes the following wording amendment: "The methodology used by the company to conduct the time-varying NMA assumes a common parametric distribution across all arms of the studies in the evidence network for OS and PFS independently. Following clinical validation input, the extrapolated survival curves for PFS and OS all follow the same distribution in the economic model"	The underlined wording amendment is suggested for clarity that different parametric curves could be selected for OS and PFS.	This has been amended for clarity.
Section 6.2, page 100 "[redacted]"	The Company propose the following amendment to the text: "[redacted]."	Removing the word [redacted] ensures that there is no implication of	The word "significantly" has been replaced by "substantially".

		[redacted].	

Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAR	Defining abbreviations (i.e., OS, PFS) once throughout the document.	The Company note that several abbreviations are redefined throughout the document, and that repeat instances may be removed.	Amended
Section 1.5, page 18 "docetaxel+nintedanib"	"docetaxel +/- nintedanib"	Typographical error	Amended.
Section 3.2.1.2, page 37 "docetael"	"docetaxel"	Typographical error	Amended.
Section 3.6, page 62 "23 hours for adagrasib"	"24 hours for adagrasib"	Typographical error: 24 hours is correctly reported in Section 2.2.1	Amended.
Section 4.2.1, page 67 "EQ-5D-5L data collected in KRYSTAL-12 was mapped to EQ-5D-5L using the	"EQ-5D-5L data collected in KRYSTAL-12 was mapped to EQ-5D-3L using the Hernández-Alava et al (2017)[45] algorithm"	Typographical error	Amended.

Hernández-Alava et al (2017)[45] algorithm”			
Section 4.2.6.1, page 72 “BICR”	“blinded independent central review (BICR)”	Abbreviation is not defined before use.	This abbreviation had been previously defined in page 23 (Section 2.2.1, EAR)
Section 4.2.7.1, page 76 “network (see figure 23, CS)”	“network (see Figure 23, CS)”	Typographical error	Amended.
Section 4.2.7.2, page 79 “relationship between progression and survival (see Section 3.2.3”	“relationship between progression and survival (see Section 3.2.3).”	Missing punctuation following in-text reference	Amended.
Section 4.2.7.4, page 81 “(see Figure X)”	“(see Figure 9)”	Cross-referencing error	Amended.

Confidentiality markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.4, page 14	“No effect of adagrasib on OS based on [redacted]”	“[redacted]”	Amended.

Section 1.4, page 14 Interim OS data may currently be inferred.	"However, the EAG is concerned that, in view of the interim OS analysis, [redacted] it is uncertain whether KRYSTAL-12 will be able to demonstrate that adagrasib leads to superior OS compared with docetaxel."	"[redacted]."	Amended.
Section 3.6, page 62 Interim OS data may currently be inferred.	"The company conducted a pre-planned interim analysis for OS at the time of the primary PFS analysis (31 December 2023 data cut). However, the CS did not present the results of this analysis because the data were highly immature and results inconclusive, and due to the potential confounding effect of crossover which was not adjusted for in the interim analyses. Following a request from the EAG the company provided the results of the interim analyses."	"The company conducted a pre-planned interim analysis for OS at the time of the primary PFS analysis (31 December 2023 data cut). However, the CS did not present the results of this analysis because the data were highly immature and results inconclusive, [redacted]."	Amended.
Section 3.6, page 62 Interim OS data may currently be inferred.	"Although KRYSTAL-12 found a statistically significant PFS benefit favouring adagrasib over docetaxel (HR 0.58 [95% CI, 0.45 to 0.76]), there was a [redacted] in	"Although KRYSTAL-12 found a statistically significant PFS benefit favouring adagrasib over docetaxel (HR 0.58 [95% CI, 0.45 to 0.76]), [redacted]	Amended.

	the adagrasib arm and [redacted] of an OS benefit for adagrasib [redacted] However, these OS results are from an interim analysis of immature data and are inconclusive."	[redacted]	
Section 3.6, page 63 Interim OS data may currently be inferred.	"However, the EAG is concerned that, in view of the interim OS analysis, [redacted] of crossover/subsequent KRAS G12C inhibitors in the docetaxel arm [redacted] and results from the CodeBreaK 200 trial of sotorasib, it is uncertain whether KRYSTAL-12 will demonstrate that adagrasib leads to superior OS compared with docetaxel."	"However, the EAG is concerned that, in view of the [redacted] results from the CodeBreaK 200 trial of sotorasib, it is uncertain whether KRYSTAL-12 will demonstrate that adagrasib leads to superior OS compared with docetaxel."	Amended.
Section 3.6, page 64 Interim OS data may currently be inferred.	"In view of the interim OS analysis results ([redacted])"	"[redacted])"	Amended.
Section 4.2.7, page 74	"(HR=0.79, see section 3.4.4)"	"(HR=[redacted], see section 3.4.4)"	Amended.

Section 4.2.7, page 76	“(HR= 0.79 [95% CI 0.68–0.92])”	“(HR= [redacted])”	This is information from LUME-Lung 1 trial, which has been published and is therefore not CON. We have added the reference to the text for clarity.

SUPPLEMENTARY APPENDIX

Adagrasib for previously treated *KRAS* G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Addendum to the Evidence Assessment Report

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Date completed	26/03/2025

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined.

This addendum reports quality-adjusted life years (QALYs) and life years (LYs) disaggregated by health state in the model for the company's and the Evidence Assessment Group's (EAG)

deterministic base-case analyses (Table 22 of the Evidence Assessment Report [EAR]). The undiscounted and discounted (at 3.5% per annum) disaggregated outcomes for each analysis are presented in Table 1. Please note that QALY estimates do not include the severity adjustment that is applied to derive the incremental cost-effectiveness results reported in the main body of the EAR.

Table 1 Disaggregated QALYs and LYs

Treatment	QALYs undiscounted		LYs undiscounted		QALYs discounted*		LY discounted*	
	PF	PD	PF	PD	PF	PD	PF	PD
Company's base-case								
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case 1: scenarios 1.1 + 2.1, no effect of adagrasib on OS and same PD utility value for all treatments								
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case 2: scenarios 1.2 + 2.1, same effect of adagrasib on OS as observed for sotorasib and same PD utility value for all treatments								
Adagrasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* at 3.5% per annum.

Abbreviations: LYs, life years; PD, progressed disease; PF, progression-free; QALYs, quality-adjusted life years; OS, overall survival.