Single Technology Appraisal

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 Pierre Fabre:**
   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
   c. British Thoracic Oncology Group

4. **Expert personal perspectives** from:
   a. Dr Thomas Newsom-Davis – clinical expert, nominated by the British Thoracic Oncology Group
   b. Dr Toby Talbot – clinical expert, nominated by Pierre Fabre

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews

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

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

Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177] [CiC marked]

Document B

Company evidence submission

May 2025

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ID6177 Enco+Bini BRAFm NSCLC_Doc B_v4.0_[REDACTED]	4.0	Redacted	01.05.2025

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Abbreviations

1L	First-line/treatment-naive
2L+	Second line or more
AE	Adverse events
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	Bayesian Information Criterion
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BRAF	v-Raf Murine Sarcoma Viral Oncogene Homolog B
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
ChT	Chemotherapy
CR	Complete response
CRF	Case report form
Dabra+tram	Dabrafenib with trametinib
DCO	Data Cut Off
DCR	Disease control rate
DOR	Duration of response
DSU	Decision support unit
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG-PS	Eastern cooperative oncology group-Performance Status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
Enco+bini	Encorafenib in combination with binimetinib
EORTC QLQ-C30	European Organisation Core Quality of Life questionnaire
EQ-VAS	EQ visual analogue scale
ESCAT I-B	European Society for Medical Oncology Scale of Clinical Actionability for molecular Targets
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
FA	Feasibility assessment
FACT-L	Functional Assessment of Cancer Therapy-Lung
HR	Hazard ratio

HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Investigator assessment
ICER	Incremental cost-effectiveness ratio
IFCT	French Cooperative Thoracic Intergroup
IO	Immunoncology
IPD	Individual patient data
IRB	Institutional review board
IRC	Independent Review Committee
IRR	Independent radiology review
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma virus
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical dictionary for regulatory activities
MET	Mesenchymal-epithelial transition factor receptor
MMRM	Mixed model with repeated measures
mNSCLC	Metastatic non-small cell lung cancer
MRU	Medical resource use
MT	Mutation positive
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHB	Net Health Benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year

QD	Once daily
QoL	Quality of life
RAS	Rat sarcoma Virus
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
ROS1	ROS proto-oncogene 1
RTK	Receptor tyrosine kinase
RWE	Real-world evidence
SAE	Serious adverse event
SCLC	Small-cell lung cancer
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
SS	Safety set
TEAE	Treatment emergent adverse event
TFL	Tables, figures, and listings
TP53	Tumour Protein p53
TRAE	Treatment-related adverse event
TSD	Technical support document
TTD	Time-to-treatment discontinuation
TTR	Time-to-response
UK	United Kingdom
USA	United Staes of America
WTP	Willingness-to-pay threshold

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

In England, malignancies affecting the lungs are still the leading cause of Death (1)

- Lung carcinomas can be broadly categorised into small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) (2).
- NSCLC is the most common type of lung cancer, representing up to an estimated 85% of all cases (3, 4).
- NSCLC is further sub-classified into three histological types; adenocarcinoma (~40% of all lung cancers), squamous cell carcinoma (~30% of all lung cancers), and large cell carcinoma (~10–15% of all lung cancers) (2, 5).
- Mutations in the v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) gene lead to disease pathology. *BRAF* mutations are present in 3–4% of patients with NSCLC. The most common *BRAF* mutation is V600E (valine [V] substituted by glutamic acid [E]), with *BRAF* V600E mutations representing an estimated 50% or more of the *BRAF* mutations detected in NSCLC (6-8).

NSCLCs are associated with significant clinical, humanistic, and economic burden

- When comparing patients with *BRAF* V600E mutation-positive (MT) disease to those with *BRAF* V600 wild type disease, disease-free survival is significantly shorter in patients with *BRAF* mutation (7).
- Compared with healthy controls, patients with NSCLC report a lower quality of life (QoL) as measured by the EQ-5D-3L utility index, EQ visual analogue scale (EQ-VAS), and European Organisation Core Quality of Life questionnaire (EORTC QLQ-C30) global health status scores (9).
- NSCLC is associated with high medical costs. The overall healthcare resource consumption (including specialist visits, hospitalisations, access to emergency care, pharmacological treatment, laboratory tests and palliative care) for patients with NSCLC is approximately £22,660 (cost year 2017) per patient, requiring a significant level of care in each stage of the disease (10).

Treatment options for patients with advanced (stage IV) NSCLC with a *BRAF* V600E mutation are limited and may be associated with severe side effects

Current standard of care for first-line treatment for patients with *BRAF* V600E MT advanced NSCLC is targeted treatment with dabrafenib in combination with trametinib (dabra+tram). However, dabra+tram can lead to serious side effects that may result in treatment discontinuation, which is why there continues to be an unmet need for this patient group (11, 12).

- Alternatives to dabra+tram include chemotherapy (ChT) with or without immunotherapy (IO). However, there is a lack of evidence of treatment benefit with IOs

in patients with advanced NSCLC with a *BRAF* V600E mutation (11). After ChT and IO, remaining treatment options for patients can be limited and often poorly tolerated (39).

Encorafenib in combination with binimetinib (enco+bini) is a targeted treatment with a manageable safety profile (see Section B.2.11.1), indicated for adult patients with advanced NSCLC with a *BRAF* V600E mutation (13, 14)

- As an orally administered treatment, enco+bini is a convenient alternative to ChT and IO which are administered via intravenous (IV) infusion (15)

There is an unmet clinical need for an additional, well-tolerated targeted treatment option for patients with *BRAF* V600E MT advanced NSCLC, as current treatment options do not fully address this need. The availability of an additional first-line treatment option could benefit the National Health Service (NHS) by alleviating capacity issues and improving patient experience.
Enco+bini offers a novel, targeted therapy as an additional first-line treatment option for patients with advanced (stage IV) *BRAF* V600E MT NSCLC.

B.1.1. Decision problem

Encorafenib in combination with binimetinib (enco+bini) received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 25th July 2024. The objective of this appraisal is to determine the clinical and cost-effectiveness of enco+bini in line with its marketing authorisation, for the treatment of adult patients with advanced (stage IV) v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) V600E mutation-positive (MT) non-small cell lung cancer (NSCLC). The submission covers part of the technology's full marketing authorisation for this indication, targeting the first-line (or treatment naïve) population. The proposed position in the treatment pathway is narrower than the marketing authorisation because the first-line setting reflects where enco+bini provides most clinical benefit.

Furthermore, the proposed position in the treatment pathway is endorsed by United Kingdom (UK) clinical expert opinion as this is where targeted therapy is currently used in UK clinical practice and where there is most need for an alternative treatment option (16)

The decision problem addressed in this submission is provided in Table 1, which also outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope.

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced NSCLC that is positive for a *BRAF* V600E mutation	Treatment-naïve patients with advanced NSCLC with a *BRAF* V600E mutation.	Most patients with advanced *BRAF* V600E MT NSCLC are expected to receive enco+bini targeted therapy as a first-line therapy because: • *BRAF* V600E testing is included in NHS England's national genomic testing directory, making it a part of routine clinical practice. This ensures eligible patients are identified early and can begin targeted therapies at first-line • Patients receiving targeted therapies in first-line would not be eligible to receive a further targeted therapy in second-line. As a result, the number of patients eligible to receive enco+bini in second-line will likely decrease over time, with the majority of eligible patients receiving targeted therapies in the first-line. The pivotal PHAROS phase 2 trial (17) which included both first-line and second-line patients, reflects this anticipated trend. The higher proportion of first-line patients in the trial aligns with expected clinical practice due to routine genomic testing.
Intervention	Encorafenib with binimetinib	Encorafenib capsule 450 mg QD + binimetinib tablet 45 mg BID	N/A – in line with the NICE final scope
Comparator(s)	For people with untreated advanced NSCLC • Dabrafenib with trametinib • Pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either	Dabrafenib with trametinib	Dabrafenib with trametinib, as the only other available targeted therapy, is considered the most relevant comparator. Routine genome testing will identify patients with *BRAF* V600E mutations who are therefore eligible for targeted therapies, at first-line.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	gemcitabine, vinorelbine, docetaxel or pemetrexed) • Pembrolizumab monotherapy • Atezolizumab monotherapy For people with previously treated advanced NSCLC • Atezolizumab monotherapy • Pembrolizumab monotherapy • Nivolumab monotherapy • Docetaxel with nintedanib • Docetaxel • Platinum doublet chemotherapy		Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are currently recommended as treatment options where dabrafenib with trametinib cannot be used, such as in the case of delays in *BRAF* testing. In TA898, the committee noted delays to *BRAF* testing were no longer a concern as it is included in NHS England's national genomic testing directory. Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are therefore not relevant comparators. Monotherapies are also not considered relevant comparators, as these are indicated for previously treated patients with advanced NSCLC, and not the first-line population.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Time to treatment discontinuation • Time to subsequent therapy • Adverse effects of treatment • Health-related quality of life	**Primary outcomes** • ORR as determined by independent IRR in the treatment-naïve setting • ORR as determined by IRR in the previously treated setting **Secondary outcomes** *Efficacy* • Confirmed ORR by IA • DOR (by IRR and by IA) • DCR (by IRR and by IA) • PFS (by IRR and by IA) • TTR (by IRR and by IA) • Time to progression	N/A – in line with the NICE final scope

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		• Overall survival *Safety* • Incidence and severity of AEs graded according to the NCI CTCAE v4.03 • Changes in clinical laboratory parameters, vital signs, ECGs, and echocardiogram/MUGA scans	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	As per final scope	N/A – in line with the NICE final scope

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Line of therapy (treated or untreated) • Histology (squamous or non-squamous) • PD-L1 expression	No subgroups are considered	Adult patients with *BRAF* V600E mutation-positive advanced NSCLC would be offered targeted therapy at first-line. Patients would receive targeted therapy with either enco+bini or dabra+tram regardless of histology of PD-L1 expression. Patients treated with a targeted therapy at first-line would not receive targeted therapy in subsequent lines. Therefore, these subgroups are not appropriate for this submission.

Abbreviations: AEs, adverse events; BID twice daily; BRAF, v-Raf Murine Sarcoma Viral Oncogene Homolog B; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; ECG, echocardiogram; FA, feasibility assessment; IRR independent radiology review; IA, investigator assessment; MUGA, multigated acquisition; N/A, not applicable; NCI, National Cancer Institute; NSCLC non-small cell lung cancer NICE, National Institute for Health and Care Excellence; ORR, objective response rate; PD-L1, Programmed death-ligand 1; PFS, progression-free survival; QD, once daily; SLR, systematic literature review.

B.1.2. Description of the technology

The technology being appraised in this submission (enco+bini) is described in Table 2, and the mechanism of action is outlined in Figure 1. The summary of product characteristics or information for use, and the UK public assessment report, scientific discussion or drafts are provided in Appendix C.

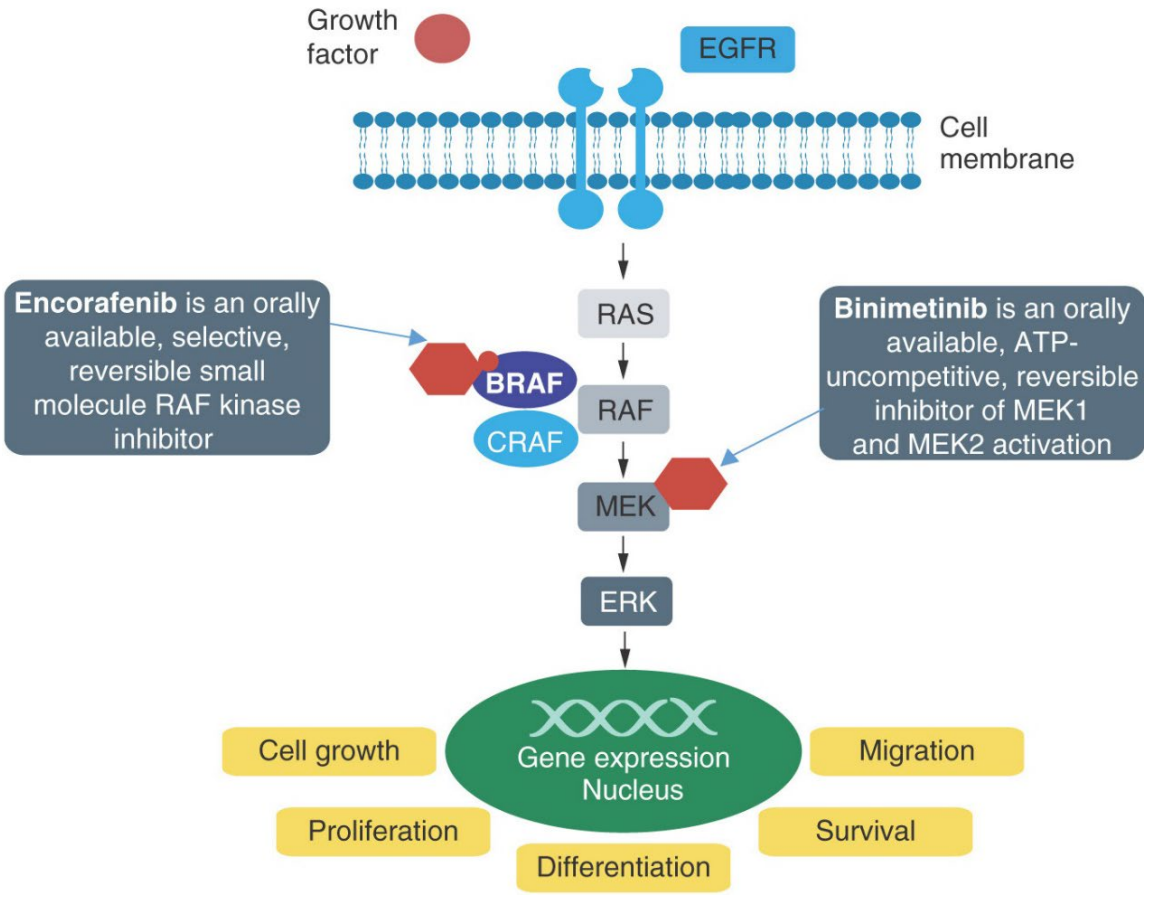
Table 2: Technology being appraised

UK approved name and brand name	Encorafenib (Braftovi®)+binimetinib (Mektovi®)
Mechanism of action	Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K) (14) Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of MEK1 and MEK2. Binimetinib inhibits growth of *BRAF* V600E mutant melanoma cell lines and demonstrates anti-tumour effects in *BRAF* V600E mutant melanoma animal models (13)
Marketing authorisation/CE mark status	Enco+bini received a CHMP opinion on the 25th July 2024, and EC approval on the 29th August 2024. Encorafenib and binimetinib received MHRA approval for NSCLC indication extension on the 14th and 28th of November 2024, respectively.
Indications and any restriction(s) as described in the summary of product characteristics	Encorafenib in combination with binimetinib is anticipated to be indicated for the treatment of adult patients with advanced NSCLC with a *BRAF* V600E mutation (see Appendix C).
Method of administration and dosage	Enco+bini are administered orally as capsules and tablets, respectively. **Encorafenib:** • The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib(14) **Binimetinib:** • The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart (13). In both instances the management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see Appendix C).
Additional tests or investigations	Patients must have confirmation of a *BRAF* V600E mutation using a validated test. In England, patients diagnosed with non-squamous NSCLC are routinely tested for common driver mutations, including *BRAF* V600E mutations, via NGS panel testing. As such, the need to identify patients with NSCLC with a

	BRAF V600E mutation would not result in any additional testing costs.
List price and average cost of a course of treatment	List price: • Encorafenib: £1,400 per pack of 42 tablets • Binimetinib: £2,240 per pack of 84 tablets Average cost of a course of treatment at list price: £[redacted] • Assuming a median treatment duration [redacted] months, derived from PHAROS (18)
Patient access scheme (if applicable)	• Encorafenib: [redacted] per pack of 42 tablets • Binimetinib: [redacted] per pack of 84 tablets Average cost of a course of treatment at PAS price: [redacted] • Assuming a median treatment duration [redacted] months, derived from PHAROS (18)

Source: Braftovi SmPC, 2024 (13); Mektovi SmPC, 2024 (13).
Abbreviations: ATP, adenosine tri-phosphate; BRAF, v-Raf Murine Sarcoma Viral Oncogene Homolog **B;** CE, Conformité Européene; CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; Enco+bini, encorafenib in combination with binimetinib; ERK, extracellular signal-regulated kinase; MEK1, mitogen-activated extracellular signal regulated kinase 1; MHRA, Medicines and Healthcare products Regulatory Agency; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PAS, patient access scheme; RAF, rapidly accelerated fibrosarcoma.

Figure 1: Mechanism of action of encorafenib in combination with binimetinib in BRAF V600E MT advanced NSCLC



Source: Riely et al 2022 (17)
Abbreviations: ATP, adenosine tri-phosphate; BRAF, v-Raf Murine Sarcoma Viral Oncogene Homolog B; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; MEK, mitogen-activated protein kinase; NSCLC, non-small cell lung cancer; RAS, rat sarcoma Virus; RAF, rapidly accelerated fibrosarcoma.

B.1.3. Health condition and positioning

B.1.3.1. Disease overview

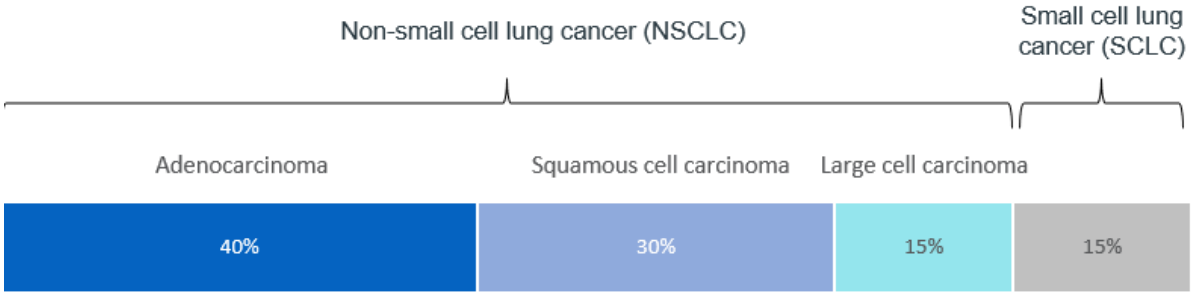
Lung carcinomas begin in cells that line the lung airways (19) and are categorised into two main subtypes, depending on the cell type the cancer originates from: small-cell lung carcinoma (SCLC) and NSCLC (8, 9, 20, 21) (see Figure 2).

NSCLC can be sub-classified into three histological types (2):

- adenocarcinoma (~40% of all lung cancers): found in the outer lung in the cells lining the alveoli

- squamous cell carcinoma (~30% of all lung cancers): found in the centre of the lung next to the main airway (bronchus)
- large cell carcinoma (~10–15% of all lung cancers): can occur in any part of the lung.

Figure 2: Lung cancer and histological subtypes



Source: Internal figure designed using external data (22, 23)
Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.

B.1.3.2. Pathophysiology

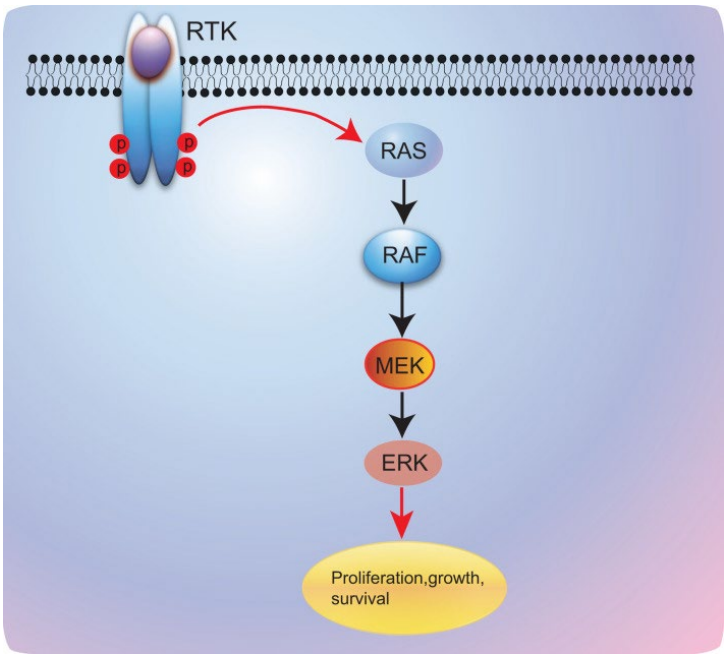
The pathophysiology of lung cancer involves the uncontrolled growth of abnormal cells in the lungs. In NSCLC, high rates of somatic mutation (such as tumour protein p53 [*TP53*] and Kirsten rat sarcoma virus [*KRAS*] mutations), genomic rearrangements (24) and a number of driver genes, including epidermal growth factor receptor (*EGFR*), *BRAF*, *KRAS*, mesenchymal-epithelial transition factor receptor (*MET*), anaplastic lymphoma kinase (*ALK*), and ROS proto-oncogene 1 (*ROS1*) have been identified (24-26).

One mutation occurring in the *BRAF* gene occurs in 3–4% of NSCLCs. The most common *BRAF* mutation is V600E (valine [V] substituted by glutamic acid [E]) (6-8). The *BRAF* gene encodes the protein kinase BRAF, which is an important mediator of the RAS-RAF-MEK-ERK signalling pathway, facilitating cell proliferation and survival in normal cells (27).

The MAPK pathway consists of a series of protein kinases (such as receptor tyrosine kinase [RTK] in Figure 3) that relay signals from the cell surface by external signals like growth factors. Activated RTKs initiate signalling cascades that then lead to rat sarcoma virus ([RAS] a small GTPase protein) activation (28-30). Cells with the

BRAF V600E mutation leads to constitutive activation of BRAF kinase activity (BRAF being one version of the rapidly accelerated fibrosarcoma (RAF) proteins, referred to as RAF in Figure 3), regardless of upstream inputs from RTKs or RAS (31). Activated BRAF is constitutively "on" and therefore continually phosphorylates mitogen-activated protein kinase (MEK), which then phosphorylates and activates extracellular signal-regulated kinase (ERK), which translocate to the nucleus to promote cell growth and proliferation (28-30).

Figure 3: RAS/RAF/MEK/ERK signalling pathway



Abbreviations: ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RTK, receptor tyrosine kinase
Source: Ningning et al. 2022 (32)

BRAF mutations can be further stratified into three functional classes (33, 34):

- Class 1, consisting of V600E mutations that enable RAS independent, monomeric signalling
    - Overall, *BRAF* V600E is the most prevalent Class I mutation and accounts for ~50% of all *BRAF* mutations in NSCLC (7, 35-37).
- Class 2 and Class 3, which are classified based on RAS-independence or -dependence and the level of RAF kinase activity

- RAS-independent Class 2 signalling results in high kinase activity
- RAS-dependent Class 3 mutations are characterised by impaired RAF kinase activity
- RAS alteration only coexists with Class 2 and Class 3 *BRAF* mutations.

There is some evidence that *BRAF* V600E MT tumours are associated with an aggressive phenotype and poor prognosis (38). *BRAF* mutations are much more common in adenocarcinoma than in other lung cancer subtypes and are reported to be mutually exclusive to *EGFR* and *KRAS* mutations, and *ALK*, and *ROS1* rearrangements (20, 39). There is also an increased risk of *BRAF* mutations in women and in people with a history of smoking (6, 28, 40, 41).

Predictive biomarker testing is recommended by the European Society for Medical Oncology (ESMO), particularly for programmed death ligand-1 (*PD-L1*), *EGFR*, *ALK*, *ROS1*, *BRAF*, and neurotrophic tyrosine receptor kinase (*NTRK*) mutations. The importance of biomarker testing is highlighted by the presence of the *BRAF* mutations in NSCLC being predictive for effective treatment with targeted therapies, namely BRAF and MEK inhibitors (42).

B.1.3.3. Epidemiology

The European Cancer Information System reported that in 2020, lung cancer accounted for 11.9% of all new cancer diagnoses (excluding non-melanoma skin cancers) across all EU-27 countries, making it the fourth most frequently occurring cancer after prostate, breast, and colorectal cancers (43). These European data align with global figures, which estimate lung cancer to comprise 11.4% of all new cancer diagnoses in 2020 across all age groups and sexes (44). National Health Service (NHS) statistics estimate that more than 43,000 people per year (2022) are diagnosed with lung cancer, making it one of the most common types of cancer. This, combined with being the most common cause of cancer death in the UK (accounting for 21% of all 2017–2019 cancer deaths), means that there is a significant burden associated with the disease (45).

However, overall, recent lung cancer incidence rates have been decreasing in many EU countries. This trend is primarily driven by a reduction in incidence among men, attributed to declining cigarette consumption per capita, largely due to effective smoking prevention activities/campaigns (40, 43, 46).

B.1.3.4. Disease burden

B.1.3.4.1. Clinical burden

NSCLC can cause a range of symptoms including shortness of breath, cough, distress, fatigue, pain, loss of appetite, dyspnoea, blood in sputum, and constipation, resulting in a negative impact on quality of life (QoL) (47-49). In patients receiving chemotherapy (ChT), treatment-related symptoms, including neuropathy and sore mouth are also commonly noted. These symptoms can interfere with daily activities, relationships, life plans, treatment adherence, and mood (50).

At diagnosis, approximately 57% of patients with NSCLC are estimated to present with advanced or metastatic disease (3, 51, 52). Although there have been recent advances in treatment development for patients with advanced NSCLC, survival rates are still poor. According to the 2017 National Lung Cancer Audit from the Royal College of Physicians, the one-year survival rate of patients with advanced disease (Stage IV) is 15.5% compared with 81.7%, 64.1%, and 42.5% for Stage I, Stage II, and Stage III disease, respectively (48).

B.1.3.4.2. Quality of life

Due to the severity and quantity of symptoms specific to lung cancer, QoL for patients with lung cancer is generally poor and lower when compared with that of patients with other malignancies (53). Symptoms such as fatigue and respiratory problems decrease psychological QoL and cause sleep problems, leading to reduced cognitive functioning. Lung cancer also negatively impacts social relations with many patients unable to continue with family and social roles (47).

Compared to healthy controls, patients with NSCLC also report lower QoL as measured by the EQ-5D-3L utility index, EQ visual analogue scale (EQ-VAS), and European Organisation (EORTC QLQ-C30) global health status scores, as well as

greater work and activity impairment with worsening Eastern Cooperative Oncology Group–Performance Status (ECOG-PS) (all p<0.05) (9).

Significant predictors (p<0.001) of poor NSCLC-specific QoL, as indicated by the Functional Assessment of Cancer Therapy-Lung (FACT-L) total score, include fatigue, loss of appetite, pain, and shortness of breath (54). Additionally, the frequent occurrence of these symptoms reported by patients suggests a notably reduced QoL in the majority of patients with NSCLC (55).

Overall, the poor QoL observed in patients with NSCLC is mainly due to the clinical symptoms caused by the disease, as well as ChT and its associated serious adverse events (SAE). The significantly worse scores across various QoL measures highlight the severity of NSCLC-related symptoms and the need to address this issue in adult patients with advanced NSCLC with a *BRAF* V600E mutation (56, 57).

Additionally, chemotherapy administered via intravenous (IV) infusion requires hospital visits, which impacts QoL by reducing independence and disrupting daily life, often leading to lower treatment adherence (58, 59). In contrast, oral treatments are preferred for their convenience and perceived efficacy (60).

B.1.3.4.3. Economic burden

From an NHS perspective, monthly costs per line of NSCLC treatment can range between £1,289 (cost year 2017, first-line) and £1,566 (cost year 2017, third line) (10).

The overall healthcare cost for patients with NSCLC is approximately £22,660 per patient (cost year 2017) with a significant level of care required in each stage of the disease (10). Overall, oncology therapy is the predominant cost driver in NSCLC, although the composition of medical costs changes across the different lines of treatment, with costs for concomitant medication and palliative care being predominant in late phase of the disease (10).

B.1.3.5. Clinical pathway of care

B.1.3.5.1. Current treatment

Current treatment aims for advanced NSCLC are to halt tumour progression for as long as possible and to alleviate symptoms. Treatment options for patients with NSCLC generally include surgery, ChT, radiotherapy, chemoradiation and immunotherapy (IO) (61). For patients with advanced *BRAF* V600E mutation-positive (MT) NSCLC, treatment options are more limited but do include targeted treatments (15). Choice of treatment is influenced by the histology or disease type (squamous or non-squamous) and by previous treatments (62).

The current treatment pathway for patients with advanced NSCLC in England and Wales is separated by targeted and non-targeted treatment options. The National Institute for Health and Care excellence (NICE) and ESMO clinical guidelines for lung cancer (see Figure 4) recommend dabrafenib with trametinib (dabra+tram) for first-line treatment of advanced *BRAF* V600E MT NSCLC (Table 3). In the July 2024 update of the ESMO Living Guidelines (63), enco+bini is included in the guidelines as a treatment option for Stage IV *BRAF* V600E MT NSCLC. It is also worth noting that enco+bini has been assigned an ESMO-Magnitude of Clinical Benefit Scale (MCBS) score of 3 (64), in contrast to the score of 2 (65) allocated to the dabra+tram combination (after adjustment for toxicity).

When dabra+tram is not used due to side effects such as pyrexia, which has been reported to cause high rates of treatment discontinuation in patients with advanced NSCLC (66), or cannot be used due to delays in receiving *BRAF* V600E mutation testing results and there is a need for urgent clinical intervention, NICE guidelines recommend alternative treatments such as pembrolizumab with carboplatin and paclitaxel, platinum doublet chemotherapy for patients with tumours expressing cells less than 50% PD-L1 expression, and pembrolizumab or atezolizumab as an alternative first-line treatment for patients with tumours expressing cells with 50% or more PD-L1 expression (Table 3).

Given the above, enco+bini is expected to offer an alternative first-line targeted treatment option to dabra+tram. Therefore, dabra+tram is the most relevant

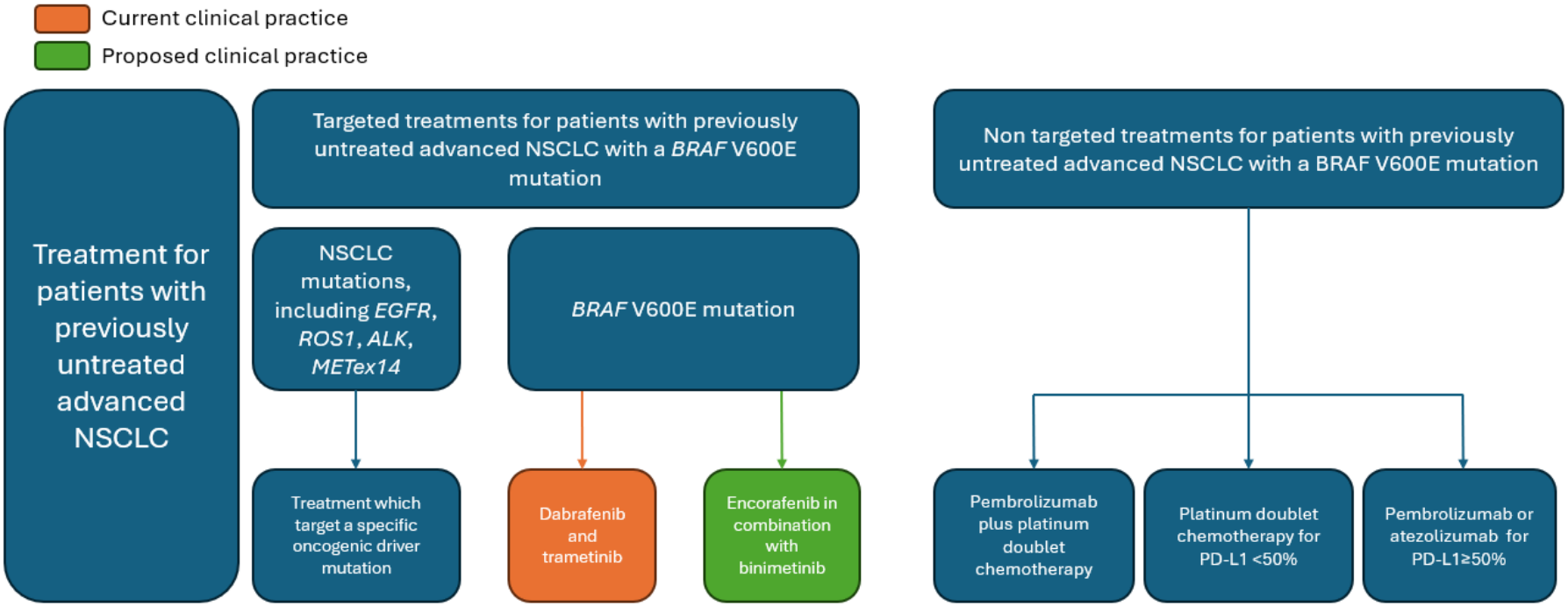
comparator for enco+bini for the treatment of *BRAF* V600E MT advanced (15 ESMO, 2020 #28, 67)

Table 3: NICE and ESMO guidelines for the treatment of patients with BRAF V600E MT NSCLC

NICE – population	**First-line**	**Second-line**
Patients with *BRAF* V600 MT tumours	• Dabra+tram • Pembrolizumab with carboplatin and paclitaxel • Platinum doublet chemotherapy (for tumours expressing <50% of PD-L1), • Pembrolizumab or atezolizumab (for tumours expressing ≥50% of PD-L1)	• Platinum doublet chemotherapy • Docetaxel • Pembrolizumab (if PD-L1 above 1%) or • Atezolizumab (any PD-L1 0% to 100%) or • Nivolumab ((any PD-L1 0% to 100%)[†]
ESMO – population	**First-line**	**After systemic progression**
Patients with advanced NSCLC with a *BRAF* V600 mutation	• BRAF-MEK inhibition using dabra+tram • Enco+bini (for Stage IV mNSCLC with a *BRAF* V600 mutation)	• If no smoking history: platinum-based ChT with or without immunotherapy • If smoking history, immunotherapy with or without platinum-based ChT • Dabra+tram if not received in first-line

[†]Within the submission, the 2L treatment options are based on having initial treatment with dabra+tram.
Abbreviations: BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; ChT, chemotherapy; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.
Source: NICE NSCLC guidelines (68); ESMO guidelines (69).

Figure 4: Current/proposed treatment pathway for previously untreated advanced NSCLC in UK clinical practice



Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, v-Raf Murine Sarcoma Viral Oncogene Homolog B; EGFR, epidermal growth factor receptor; METex14, Hepatocyte growth factor receptor exon 14 skipping; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; TA, Technology Appraisal; UK, United Kingdom.
Source: NICE NSCLC guidelines (68); ESMO guidelines (69).

B.1.3.5.2. Unmet need

Lung cancer is the fourth most commonly diagnosed cancer in Europe, with NSCLC making up about 85% of cases (70). In England and Wales, NSCLC accounts for approximately 88% of lung cancers (48). *BRAF* alterations are responsible for around 4.4% of all lung cancers (71) and are found in 2% of patients with advanced NSCLC (6). Among these, V600E mutations represent one-third of the *BRAF* mutations detected in patients with advanced NSCLC (72).

BRAF V600E mutations are associated with an aggressive phenotype and poor prognosis (48) and effective therapeutic options are limited in this patient population. When dabra+tram is not used in patients with advanced NSCLC with a *BRAF* V600E mutation, treatment typically involves regimens that are applicable regardless of mutation status, such as chemotherapy ± immunotherapy. However, there is a lack of clinical evidence supporting the treatment benefit of immunotherapies in adult patients with advanced NSCLC with a *BRAF* V600E mutation (15). Current evidence suggests that patients with *BRAF* V600E MT advanced NSCLC show a limited response and low efficacy to immunotherapies. Available data indicates that the overall survival (OS) and progression-free survival (PFS) outcomes in this patient population remains low (73).

In non-BRAF V600E mutant NSCLC, there is limited evidence for the efficacy of chemotherapy, largely due to the high doses required to eradicate tumours, which often leads to irreversible tissue damage (74). Additionally, there is a current lack of evidence surrounding the use of chemotherapy in treating *BRAF* MT NSCLC (75).

Immunotherapy treatment options for *BRAF* V600E MT NSCLC are associated with various side effects. For example, treatment with pembrolizumab, can lead to adverse events (AE) such as hypothyroidism, colitis, diarrhoea, pneumonitis, abdominal pain, immunotoxicity, infusion-related reactions, or discomfort associated with administration. These AEs can have a detrimental and potentially long-term impact on a patient's QoL (76, 77). Furthermore, pembrolizumab is administered via IV infusion, requiring nursing staff and in-patient hospital visits, which can impose an

additional burden on patients and the healthcare system. There is also an increased risk of IV cannulation-related infections for patients treated in hospitals (78).

Targeted treatments for patients with *BRAF* V600E MT NSCLC also come with side effects such as fatigue and nausea (79). Clinical experts have noted that dabra+tram, in particular, has been associated with pyrexia, which is a common reason for treatment interruption or discontinuation (16).

Given that current treatment options can have significant side effects and, in the case of chemotherapy and immunotherapy, can present challenges in delivery to patients, there is a strong unmet need for more accessible oral therapy options that are more effective, have a more manageable safety profile, and are easier to administer. Specifically, for patients with advanced NSCLC with a *BRAF* V600E mutation, there is a pressing need for alternative targeted combination therapies to provide clinicians with more prescribing options (15)

Enco+bini is a well-established targeted treatment combination, recently approved for *BRAF* V600E MT advanced NSCLC, that has demonstrated rapid and sustained responses resulting in meaningful clinical benefit in terms of objective response rate (ORR) and PFS (18). Therefore, it presents a viable first-line treatment option for patients with *BRAF* V600E MT advanced NSCLC.

B.1.3.5.3. Positioning of encorafenib in combination with binimetinib

Enco+bini is expected to be used in clinical practice for the first-line treatment of patients with advanced NSCLC with a *BRAF* V600E mutation, in line with guidance that recommends targeted therapy (currently dabra+tram) for patients with a *BRAF* V600E mutation. Although existing guidelines also include chemotherapy± immunotherapy as first-line treatment options, clinical experts have confirmed that patients are routinely tested for *BRAF* V600E mutations and, if present, are offered targeted therapy as first-line treatment. Currently, the only option for targeted therapy is dabra+tram, therefore making it the relevant comparator for first-line treatment in the context of this appraisal.

The proposed positioning of enco+bini within the current clinical care pathway is as a first-line treatment option (Figure 4). This positioning is supported by clinical expert opinion (16).

B.1.4. Equality considerations

None.

B.2. Clinical effectiveness

Encorafenib in combination with binimetinib (enco+bini) demonstrated meaningful clinical benefit in the pivotal Phase 2 PHAROS trial, which was designed for patients with *BRAF* V600 MT metastatic NSCLC. The PHAROS trial showed substantial anti-tumour activity and significant survival benefits in treatment-naïve patients, as assessed by an Independent Radiological Review (IRR).

- The efficacy and safety evidence base to support the use of enco+bini in this indication primarily comes from the pivotal PHAROS trial (a Phase 2, open-label, multicentre trial)
  In PHAROS,
  - 98 patients were enrolled (59 treatment-naïve and 39 previously treated)
  - The primary endpoint was objective response rate (ORR) based on IRR
    - 74.6% of patients (95% confidence interval [CI]: 61.6–85.0) achieved an ORR by IRR

- In the absence of a head-to-head trial comparing enco+bini with dabra+tram, an indirect treatment comparison (ITC) was conducted with results demonstrating:
  - Non-significant difference in favour of enco+bini for ORR
  - Statistically significant difference in favour of enco+bini for progression-free survival (PFS)
  - Non-significant difference in favour of enco+bini for overall survival (OS)

The overall safety profile observed in PHAROS aligns with that observed for enco+bini in other approved indications (80, 81)
In PHAROS: The overall safety profile observed in PHAROS aligns with that observed for enco+bini in other approved indications (80, 81)
In PHAROS:

- Most patients had at least [redacted] all-causality adverse event ([redacted] %) and at least [redacted] treatment related AE ([redacted] %).
- [redacted] % of patients had maximum Grade 3 or 4 all causality treatment-emergent adverse events (TEAE) and [redacted] % of patients had maximum Grade 3 or 4 treatment-related TEAEs

- Additional supporting evidence is provided from the Intergroupe Francophone de Cancérologie Thoracique (IFCT) study (NCT04526782), demonstrating additional safety and efficacy data that was consistent with PHAROS (82)

B.2.1. Identification and selection of evidence

To identify evidence for the treatment of patients with *BRAF* V600 MT advanced NSCLC, a clinical systematic literature review (SLR) was first performed in October 2021 and subsequently updated in May 2023 and July 2023. In preparation for the submission, a further update was performed in May 2024.

As described in section B.1.3.5.3, dabra+tram is the most relevant comparator for enco+bini and this section therefore focusses on evidence for either enco+bini or dabra+tram in treatment-naïve patients with advanced NSCLC with a *BRAF* V600E

mutation. The scope of the SLR was broad: the population included studies in patients with advanced NSCLC with any *BRAF* mutation as well as including any treatment in any line. All identified studies were reviewed for relevance to this submission and studies not reporting on use of enco+bini or dabra+tram for patients with *BRAF* V600E MT NSCLC were not considered further.

Through the original SLR (6/10/2021), the first SLR update (04/05/2023), the second SLR update (11/07/2023) and the third SLR update (15/05/2024), a total of 99 publications were identified for inclusion. Of these, there were 77 full publications (18-94), 20 conference abstracts (of which three were additionally identified as posters), and two clinicaltrials.gov records.

- A total of 18 records reporting on ten interventional trials, of which two were clinicaltrials.gov records for PHAROS (encorafenib plus binimetinib) and Study 113928 (dabrafenib plus trametinib) (Appendix D)

- Overall, nine records (over three unique trials) reported clinical outcomes for patients with *BRAF* V600E/V600 as the target population. Nine publications for seven interventional trials included patients with *BRAF* V600E/V600 as a subgroup of the whole population

- One trial record for the ongoing Intergroupe Francophone de Cancérologie Thoracique (IFCT) trial (enco+bini) was identified during handsearching, however this was excluded as there were no results posted.

- Additionally, there were 81 publications reporting data for 80 unique observational studies. Sixteen publications from 15 unique studies reported on patients with *BRAF* V600E/V600 as their target population. Sixty-five publications from 65 unique studies included patients with *BRAF* V600E/V600 as sub-group of the whole population.

- No RCTs and no studies reporting health-related quality of life (HRQoL) outcomes for patients with *BRAF* V600/V600E were identified.

A full list of studies identified in the SLR is available in Appendix D.

Enco+bini and dabra+tram

There was a total of nine records reporting on four interventional trials for enco+bini (n=1 trial) or dabra+tram (n=3 trials). In addition, 18 observational studies reporting data for enco+bini or dabra+tram were identified (Appendix D).

No direct trial data comparing enco+bini with dabra+tram were available, therefore a feasibility assessment (FA) was conducted to explore whether there were any comparator studies that could be compared to enco+bini in an indirect comparison (see Section B.2.9.1 and Appendix D).

B.2.2. List of relevant clinical effectiveness evidence

The primary source of clinical data for enco+bini is the pivotal Phase 2 PHAROS trial, which was used to support the marketing authorisation for enco+bini in this indication.

Table 4: Clinical effectiveness evidence

Study	PHAROS (NCT03915951)
Study design	Phase 2, open-label, multicentre study
Population	Male and female participants at least 18 years of age with advanced *BRAF* V600E MT NSCLC
Intervention(s)	Encorafenib in combination with binimetinib
Comparator(s)	N/A
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	**Efficacy** Primary outcomes: • ORR as determined by IRR in the treatment-naïve setting • ORR as determined by IRR in the previously treated setting Secondary outcome: • ORR using IA • DOR

	• DCR
	• PFS
	• TTR
	• OS
	Safety
	• Safety and tolerability of enco+bini in treatment-naïve and previously treated patients with *BRAF* V600E MT NSCLC
	  ○ AEs
	  ○ Deaths
	  ○ Significant and other SAEs

All other reported outcomes	N/A

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83)
Abbreviations: AE, adeverse event; BRAF, v-raf murine sarcoma viral oncogene homolog B; DCR, disease control rate; DOR, duration of response; EQ-5D-5L, EuroQol 5 Dimension; IA, investigator assessment; IRR, independent radiology review; MT, mutation-positive; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SAE, serious adverse event; TTR, time to response;.

B.2.2.1. Data presented in the submission

B.2.2.1.1. PHAROS

The key PHAROS study data considered in this submission are derived from a series of different data cut-off (DCO) dates (see Table 5). Clinical efficacy DCO dates are 01 April 2024, 19 July 2023, and 22 September 2022. Safety data are derived from three DCO dates: 01 April 2024, 19 January 2023, and 22 September 2022. The 01 April 2024 cutoff is presented as the primary data source as this is the most recent, and therefore most mature, aligning with the data used in the cost effectiveness model.

Data available at each DCO is outlined in Table 6.

The submission primarily focuses on the treatment-naïve population, and is therefore presented as the main clinical efficacy and safety data in sections B.2.6 and B.2.11, respectively. Data are presented for the previously treated and total populations in Appendix N.

Table 5: PHAROS data cut offs and their respective unpublished/published sources

Data Cut-off	Data	Reason	Unpublished source	Published source
01 April 2024	Clinical efficacy	Represents more mature data	PHAROS update_DCO 01 April 2024 (84)	ESMO Congress 2024 presentation (85)
19 July 2023	Clinical efficacy	EMA license	PHAROS EMA update_DCO 19 July 2023 (86)	EMA documents (87)
19 January 2023	Safety	FDA request Safety update only	Pierre Fabre, PHAROS CSR (88)	EMA documents (87)
22 September 2022	Clinical efficacy and safety	Primary trial endpoint	PHAROS CSR_DCO 22 September 2022 (83)	Phase II, open-label study of encorafenib plus binimetinib in patients with BRAF V600E MT metastatic non-small-cell lung cancer (18)

PHAROS CSR_DCO 22 September 2022 [Data on file] (83); PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); PHAROS update_DCO 01 April 2024 [Data on file] (84); PHAROS FDA update_DCO 19 January 2023 [Data on file] (89); ESMO Congress 2024 presentation (85).
Abbreviations: BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; CSR, clinical study report; NSCLC, non-small cell lung cancer.

Table 6: PHAROS outcome data available for each data cut off

	April 2024	July 2023	January 2023	September 2022
ORR by IRR	✓	✓	×	✓
Investigator confirmed ORR	✓	✓	×	✓
DOR	✓	✓	×	✓
DCR	✓	✓	×	✓
OS	✓	✓	×	✓
PFS	✓	✓	×	✓
TTR	✓	✓	×	✓
Adverse reactions (safety data)	✓	×	✓	✓

Abbreviations: DCR, disease control rate; DOR, duration of response; IRR; Independent radiology review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.

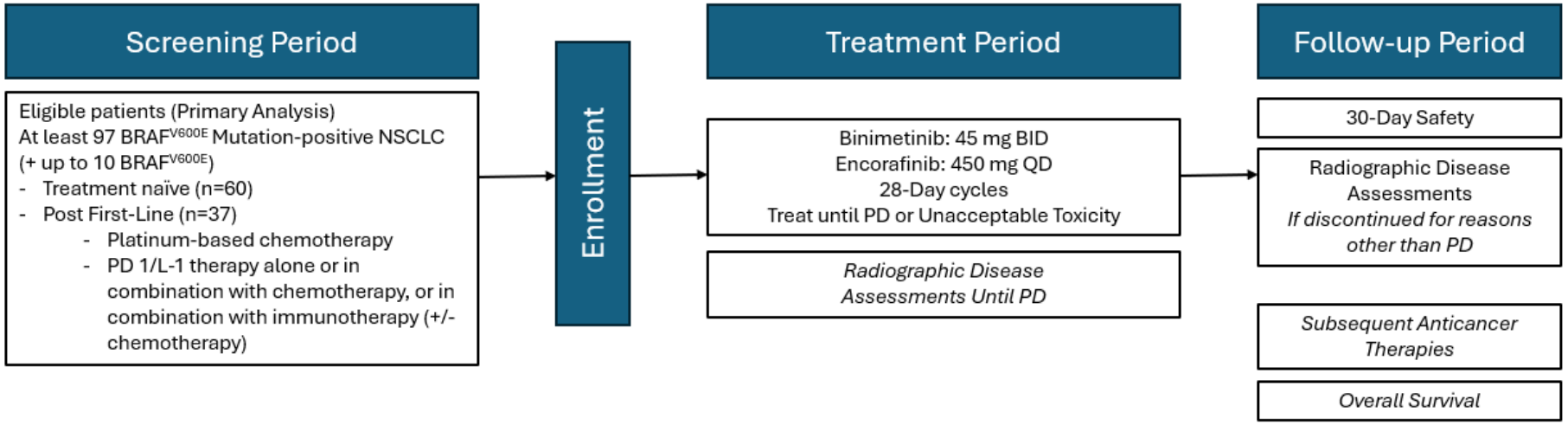
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. PHAROS

B.2.3.1.1. Study Design

PHAROS is an ongoing multicentre, multi-cohort pivotal Phase 2, open-label trial evaluating the safety, tolerability, and efficacy of enco+bini in treatment-naïve and previously treated participants with advanced/metastatic *BRAF* V600E MT NSCLC (18, 90). The primary analysis date was 22nd September 2022, and the most recent data-cut is from 01 April 2024. The study is anticipated to complete by 30th October 2025. The study design is summarised in Figure 5.

Figure 5: Study design for PHAROS



Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83)
Abbreviations: BRAF, B-RAF proto-oncogene, serine/threonine-protein kinase; BID, twice daily; NSCLC, non-small cell lung cancer; PD, progressive disease; QD, once daily.

B.2.3.1.2. Eligibility criteria

The key inclusion and exclusion criteria are outlined in Table 7, with the full detailed criteria outlined in Appendix M.

Table 7: Key inclusion and exclusion criteria - PHAROS

Inclusion criteria	Exclusion criteria

• Male or female aged ≥18 years
• Histologically confirmed diagnosis of NSCLC at Stage IV
• Presence of a *BRAF* V600E mutation in lung cancer tissue as determined by a local laboratory assay or the presence of other *BRAF* V600 mutations other than V600E (i.e. K or D) will be considered
• Patients who are either treatment-naïve (e.g., no prior systemic therapy for advanced/metastatic disease), OR who have received
  ○ 1) first-line platinum-based chemotherapy OR
  ○ 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy
• Presence of measurable disease based on RECIST v1.1
• ECOG performance status of 0 or 1
• Adequate bone marrow function characterized by the following at screening:
  ○ ANC ≥ 1.5 multiplied by 10^9/L;
  ○ Platelets ≥ 100 multiplied by 10^9/L;
  ○ Haemoglobin ≥ 8.5 g/dL (with or without blood transfusions)
• Adequate hepatic and renal function characterized by the following at screening:
  ○ Total bilirubin ≤1.5 multiplied by the ULN
  ○ ALT and AST ≤2.5 multiplied by ULN, or ≤5 multiplied by ULN in presence of liver metastases; Serum creatinine ≤1.5 multiplied by ULN; or calculated creatinine clearance ≥50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m²
	• Patients who have documentation of any of the following:
	  ○ *EGFR* mutation
	  ○ *ALK* fusion oncogene or
	  ○ *ROS1* rearrangement
	• Patients who have received more than one prior line of systemic therapy in the advanced/metastatic setting
	• Previous treatment with any BRAF inhibitor (e.g., dabrafenib, vemurafenib, XL281/BMS-908662, etc.), or any MEK inhibitor (e.g., trametinib, cobimetinib, selumetinib, RDEA119, etc.) prior to screening and enrolment
	• Impaired cardiovascular function or clinically significant cardiovascular diseases
	• History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to the first dose of study treatment. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli
	• History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease
	• Concurrent neuromuscular disorder that is associated with the potential of elevated phosphor-CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
	• Evidence of active non-infectious pneumonitis or history of interstitial lung disease
	• Patients with symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases are not eligible

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83).
Abbreviations: ANC, absolute neutrophil count; ALK, anaplastic lymphoma kinase; ALT, alanine

aminotransferase; AMC, absolute neutrophil count; AST, aspartate aminotransferase; CK, creatine kinase; CNS, central nervous system; ECOG, Eastern Cooperation Oncology Group; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; ROS1, ROS proto-oncogene 1; RVO, retinal vein occlusion; ULN, upper limit of normal.

B.2.3.1.3. Treatments administered

Encorafenib (450 mg once daily [QD]) in combination with binimetinib (45 mg twice a day [BID]) treatment was administered in 28-day (±3 days) cycles and continued until the patient met protocol-defined criteria for withdrawal, which included withdrawal of consent, unacceptable AEs or failure to tolerate study treatment, patient missed >6 weeks of dosing, disease progression per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) (91), clinical progression as determined by the Investigator, pregnancy or breastfeeding, significant protocol deviation, patient non-compliance with study procedures, lost to follow-up, and death. Specifically, patients were considered as having withdrawn from the study if any of the following criteria were met:

- Withdrawal of consent. Patients had the option of withdrawing consent for study treatment but continued in the follow-up period of the study for safety/efficacy assessments.
- Unacceptable AEs or failure to tolerate study treatment was defined as:
    - Grade 4 or life-threatening AE
    - Toxicity requiring more than the allowed number of dose reductions for enco+bini as described in Table 8
- Occurrence of an AE that was related to study treatment and, in the judgment of the investigator, compromised the patient's ability to continue study-specific procedures or was considered to not be in the patient's best interest.

Table 8: Dose reductions for encorafenib and binimetinib

Dose level	Encorafenib
0 (starting dose)	450 mg QD
–1	300 mg QD
–2	225 mg QD

Dose level	Binimetinib
0 (starting dose)	45 mg BID
–1	30 mg BID

± Dose reduction below 225 mg QD of encorafenib was not allowed
Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83).
Abbreviation: QD, once a day.± Dose reduction below 225 mg QD of encorafenib was not allowed

B.2.3.1.4. Prior and concomitant medications

Permitted and prohibited concomitant therapies are summarised in Table 9.

In the treatment-naïve group, 52 (88.1%) received at least 1 prior medication for conditions other than NSCLC prior to study treatment. The most frequently (≥10% of participants) received prior medications for conditions other than NSCLC were paracetamol (16.9%), colecalciferol, and acetylsalicylic acid (13.6% each), atorvastatin, and amlodipine (11.9% each), and metformin, and simvastatin (10.2% each).

In the previously treated group, 32 (82.1%) participants received at least one prior medication for conditions other than NSCLC prior to study treatment. The most frequently (≥10% of participants) received prior medications for conditions other than NSCLC were paracetamol (17.9%), atorvastatin (15.4%), colecalciferol, and folic acid (12.8% each), and acetylsalicylic acid, amlodipine, lorazepam, omeprazole, vitamins not otherwise specified (NOS), and salbutamol (10.3% each).

Table 9: PHAROS – Permitted and prohibited concomitant therapies

Permitted concomitant therapies	Prohibited concomitant therapies

• CYP and UGT Substrates and Inhibitors
  ○ Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib
  ○ If use of a moderate CYP3A4 inhibitor is unavoidable, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with an accompanying dose reduction to one half of the encorafenib dose prior to use of the moderate CYP3A4 inhibitor. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor
• Transporter substrates and inhibitors
• Drugs with a conditional or possible risk to prolong QT interval and/or induce torsade de pointes
	The following therapies were prohibited during the Screening and Treatment Periods of this study (unless otherwise noted). There were no prohibited therapies during the post-treatment Follow-up Period:
	• No additional anticancer agents such as cytotoxic chemotherapy, small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy are to be administered to patients while they are receiving study treatment
	• Investigational drugs and devices
	• Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤10% of the bone marrow reserve)
	• Concomitant strong systemic CYP3A4 inhibitors, which could significantly increase the exposure of encorafenib
	• Concomitant moderate or strong systemic CYP3A4 inducers, which could significantly decrease the exposure of encorafenib

Source: PHAROS protocol (92)
Abbreviations: CYP, Cytochrome P450; UGT, UDP-glucuronosyltransferase enzymes; QT, duration of ventricular electrical systole.

Prior anticancer therapies are summarised in Table 10. Of note, neoadjuvant and adjuvant treatments were considered first-line metastatic treatment if a patient had new lesions or evidence of disease recurrence (such as metastatic disease) within 12 months of completing treatment.

Patients may also have had more than one neoadjuvant treatment and more than one adjuvant treatment. In addition, prior therapies recorded in the case report form (CRF) as “palliative” and/or “locally advanced” were considered first-line metastatic treatment.

In treatment-naïve patients, four (6.8%) patients had received at least one prior systemic therapy, three (5.1%) patients had received one regimen of chemotherapy without immunotherapy in the adjuvant setting, and one (1.7%) patient received one regimen of chemotherapy without immunotherapy in the neoadjuvant setting.

In the previously treated patients, all 39 patients had received at least one prior systemic therapy for metastatic NSCLC. The most frequent was PD-1/PD-L1 therapy as monotherapy (13 [33.3%]) and combination therapy (11 [28.2%]). No patients received prior treatment only in the neoadjuvant/adjuvant setting that met the criteria to be considered first-line metastatic treatment. Of note, 2 (12.8%) participants received 2 prior regimens for metastatic NSCLC and 1 (2.6%) participant received 3 prior regimens for metastatic NSCLC.

Table 10: PHAROS - Prior Anticancer Therapy - Systemic Treatment (safety set)

	Enco+bini		
	Treatment Naive N=59	**Previously Treated N=39**	**Total N=98**
Number of patients with at least one prior systemic treatment, n (%)	4 (6.8)	39 (100)	43 (43.9)
Received at least one regimen of prior immunotherapy (monotherapy or combination therapy)	0	24 (61.5)	24 (24.5)
Received monotherapy PD1/L1	0	13 (33.3)	13 (13.3)
Received combination PD1/L1 therapy (with chemotherapy or other immunotherapy)	0	11 (28.2)	11 (11.2)
Received at least one regimen of chemotherapy without immunotherapy	4 (6.8)	20 (51.3)	24 (24.5)
Received at least one regimen of TKI	0	0	0
Total number of regimens, n (%)			
1	2 (3.4)	33 (84.6)	35 (35.7)
2	2 (3.4)	5 (12.8)	7 (7.1)
3	0	1 (2.6)	1 (1.0)
Total number of regimens			
N	4	39	43
Mean	1.5	1.2	1.2
SD	0.58	0.45	0.47
Median	1.5	1.0	1.0
Minimum	1	1	1

	Enco+bini		
	Treatment Naive N=59	**Previously Treated N=39**	**Total N=98**
Maximum	2	3	3
Setting at last medication			
Neoadjuvant	1 (1.7)	0	1 (1.0)
Adjuvant	3 (5.1)	0	3 (5.1)
Metastatic	0	29 (74.4)	29 (29.6)
Maintenance	0	3 (7.7)	3 (3.1)
Locally advanced	0	3 (7.7)	3 (3.1)
Palliative	0	4 (10.3)	4 (4.1)
Other	0	0	0

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83).
Abbreviations: PD-1, Programmed cell death protein-1; SD, Standard deviation; TKI, tyrosine kinase inhibitor.

B.2.3.1.5. Outcomes

All outcomes were reported separately for the treatment-naïve and previously treated settings.

B.2.3.1.5.1 Primary endpoints

- ORR as determined by independent radiology review (IRR).

B.2.3.1.5.2 Secondary endpoints

- Confirmed ORR by investigator assessment (IA[a], defined as the proportion of patients who have achieved a confirmed best objective response (complete response [CR] or partial response [PR]) as determined by IRR per RECIST v1.1.
- Duration of response (DOR) (by IRR and by IA),[a] defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed

[a] Endpoints for derived investigator assessment were derived programmatically

(by IRR and by IA, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause.

- Disease control rate (DCR) (by IRR and by IA),[a] defined as the proportion of patients who have a confirmed CR or confirmed PR, or stable disease (SD) per RECIST v1.1

- Overall survival (OS)

- Progression free survival (PFS) by IRR and by IA, defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause

- Time to response (TTR) by IRR and by IA, defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by IA, respectively).

B.2.3.1.6. Baseline characteristics

Key patient demographics and baseline disease characteristics (from the published Riely *et a*l. 2022 data) (17) are presented in Table 11. Demographics were generally well-balanced between the patient cohorts. The median age of patients previously treated or treatment-naïve was 71 years (range 53–86) and 68 years (range 47–83), respectively. In total, most of the patients were White (88%) and there were more female than male patients (53% vs 47%). None of the patients had an Eastern Cooperation Oncology Group-Performance Status (ECOG-PS) score above one at study entry. In terms of smoking status, the majority (56 [57%]) of patients were former smokers, while 29 (30%) of patients had never smoked, and the rest (13 [13%]) were current smokers (83). In terms of smoking status, the majority (56 [57%]) of patients were former smokers, while 29 (30%) of patients had never smoked, and the rest (13 [13%]) were current smokers (83).

The predominant American Joint Committee on Cancer (AJCC) staging at diagnosis was stage IV (28.6%), followed by IV-A (25.5%), and then IV-B (24.5%). The majority of patients presented with an adenocarcinoma (96.9%) and 8.2% of patients had brain metastases (18).

Table 11: Baseline demographic and clinical characteristics – PHAROS

Variable	Enco+bini		
Baseline demographic characteristics	**Treatment-naive N=59**	**Previously treated N=39**	**Total N=98**
Age, years, median (range)	68 (47–83)	71 (53–86)	70 (47–86)
Sex, No. (%)			
Women	33 (56)	19 (49)	52 (53)
Men	26 (44)	20 (51)	46 (47)
Ethnicity, No. (%)			
White	53 (90)	33 (85)	86 (88)
Asian	3 (5)	4 (10)	7 (7)
Black	1 (2)	2 (5)	3 (3)
American Indian	1 (2)	0	1 (1)
Unknown	1 (2)	0	1 (1)
ECOG PS, No. (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72(73)
Smoking status, No. (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
BRAF V600E status, No. (%)			
V600E	59 (100)	39 (100)	98 (100)
V600D[a]	0	1 (3)	1 (1)
Method of local *BRAF* testing, No. (%)			
PCR	15 (25)	11 (28)	26 (26)
Tissue NGS	44 (75)	27 (69)	71 (72)
Plasma NGS	0	1 (3)	1 (1)
Tumour histology, No. (%)			
Adenocarcinoma	57 (97)	38 (97)	95 (97)
Squamous cell carcinoma	1 (2)	1 (3)	2 (2)
Other	1 (2)	0	1 (1)
Brain metastases, No. (%)			
No	55 (93)	35 (90)	90 (92)
Yes	4 (7)	4 (10)	8 (8)
Prior systemic treatment for metastatic disease, No. (%)	0	39 (100)	39 (40)
Immunotherapy	NA	24 (62)[b]	24 (24)[b]
Monotherapy PD-(L)1	NA	12 (31)	12 (12)
Combination PD-(L)1	NA	12 (31)	12 (12)
Chemotherapy	NA	18 (46)	18 (18)
Prior radiotherapy, No. (%)			
No	50 (85)	22 (56)	72 (73)

Variable	Enco+bini		
Baseline demographic characteristics	**Treatment-naive N=59**	**Previously treated N=39**	**Total N=98**
Yes	9 (15)	17 (44)	26 (27)

Source: Riely et al. 2022 (18).
Abbreviations: AJCC, American Joint Committee on Cancer; BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; TNM, tumour nodes and metastasis.
Note: one previously treated patient had both V600E and V600D mutations and was considered as V600E for data analysis purposes

B.2.3.2. Supporting evidence

Supportive evidence is provided by the IFCT academic study (see Appendix M). The IFCT study (DCO: 22 January 2024) was conducted to generate further data on the efficacy and safety of enco+bini in patients with advanced NSCLC with a *BRAF* V600E mutation, and to evaluate QoL in these patients (QoL was not collected in the PHAROS study) (82). The results from the IFCT trial are presented from the Cohort A, as this was the treatment-naïve population (Cohort B received first-line treatment of either platinum-based ChT, or an anti-PD-1/L-1 inhibitor given alone or in combination with immunotherapy [eg, ipilimumab] with or without platinum-based chemotherapy).

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

B.2.4.1. PHAROS

B.2.4.1.1. Analysis populations

The sets of analysis populations defined in the trial are presented in Table 12.

Table 12: Definition of analysis populations

Analysis populations	Definition	Reported in submission
Screened	All participants who signed the ICD	Yes
SS	All participants who received at least 1 dose of study treatment	Yes
PK	All participants in the SS who had at least 1 post dose PK blood collection with associated bioanalytical results after the first dose of study treatment	Yes

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83).
Abbreviations: ICD, informed consent document; PK, pharmacokinetic; SS, Safety Set.

B.2.4.1.2. Sample size

The sample size calculation was based on the primary endpoint of ORR as determined by incidence rate ratio (17, 18).

With 60 evaluable treatment-naïve patients with *BRAF* V600E MT NSCLC, the power was greater than 95% to test the null hypothesis that the ORR was less than or equal to 39% vs the alternative hypothesis that it was greater than 39%, assuming an alternative target rate of 65% with a one-sided $\alpha \leq 0.025$ based on a single-stage design using exact test. The null hypothesis was to be rejected if ≥32 confirmed objective responses were observed (17, 18).

With 37 evaluable previously treated patients with *BRAF* V600E MT NSCLC, there was at least 90% power to test the null hypothesis that the ORR was less than or equal to 20% vs the alternative hypothesis that it was greater than 20% assuming an alternative target rate of 45% with a one-sided $\alpha \leq 0.025$ based on a single stage design using exact test. The null hypothesis was to be rejected if ≥13 confirmed objective responses were observed (17, 18).

At least 60 treatment-naïve and 37 previously treated patients with *BRAF* V600E MT NSCLC were enrolled and treated. It was not expected that more than 107 patients with any *BRAF* V600E mutation were to be enrolled and treated (17, 18).

B.2.4.1.3. General methodology

B.2.4.1.4. Analysis of efficacy parameters

The safety analysis set (SS) was the primary population for the analysis of all efficacy endpoints. Data were summarised for treatment-naïve participants, previously treated participants, and overall (83).

All efficacy endpoints, except OS, were evaluated by IRR and by derived IA in participants with advanced/metastatic *BRAF* V600E MT NSCLC, as determined by local testing. Endpoints for derived IA were derived programmatically from the target lesion measurements, non-target lesion status, and new lesions recorded on the electronic CRF (83).

For ORR by IRR and IA, additional subgroup analyses may have been performed to explore the influence of various baseline characteristics (age group [<65 years and ≥65 years], gender, race group [Asian and non-Asian], and ECOG-PS [0 and 1]) (83).

B.2.4.1.5. Analysis of pharmacokinetic parameters

Since there was only one common timepoint between the serial and sparse pharmacokinetic (PK) sampling schedules, separate PK analyses were presented for each sampling schedule (83).

B.2.4.1.6. Safety

Treatment emergent adverse events (TEAE) were defined as AEs with onset date during the on-treatment period. The on-treatment period was defined as the time from the first dose date of study treatment to the last dose of study drug administration date (when both drugs were permanently discontinued) plus 30 days or the earliest date of subsequent anti-cancer drug therapy minus 1 day, whichever occurred first.

AEs and serious adverse events (SAE were coded by preferred term (PT) and system organ class (SOC) medical dictionary for regulatory activities (MedDRA) version 25.0. For summaries by SOC and PT, each participant was counted at most once per SOC and at most once per PT. For summaries by PT, each participant was counted at most once per PT. For summary tables in the clinical study report (CSR) presenting only AEs with a specific frequency cutoff, the “Any AE” row is without consideration for the minimum percent frequency cut-off specified in each table.

The severity of an AE was assessed by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. For participants with more than 1 AE within an SOC or PT, only the maximum grade was included in by-severity summaries (designated as such in some tables) and only the maximum grade is described in text.

The investigator assessed whether an AE was considered related to study drugs (i.e., treatment-related AEs [TRAEs]). For participants with more than 1 AE within a

SOC or PT, the highest level of relationship (treatment related > all causality) was included in the by-relationship summaries.

B.2.4.1.7. Interim analysis

One interim analysis was to be performed for treatment-naïve participants after about 90% (N=54) of the planned treatment-naïve participants (N=60) were enrolled (83). The posterior probability for the expected number of participants and the observed responses at the first look is outlined in Table 13.

Table 13: Posterior probabilities

Enrolled Participants	Observed Responses	Posterior Probability for True ORR >39%
54	24	79.5
54	25	86.4
54	26	91.5
54	27	95.0
54	28	97.2
54	29	98.6

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83).
Abbreviation: ORR, objective response rate.

At the time of the interim analysis, if the posterior probability that the true ORR exceeded 39% was ≥80%, assuming a non-informative Beta (0.5, 0.5) prior, then the data were to be considered for discussions with regulatory authorities (83).

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the included studies can be found in Appendix D.

B.2.6. Clinical effectiveness results of the relevant studies

Although licensed for use in first-line and second-line or more, as noted in section B.1.2, enco+bini is likely to be used primarily in the first-line setting. This is because patients have routine genome testing which includes screening for the *BRAF* V600E mutation on diagnosis of NSCLC, meaning most patients with NSCLC can receive targeted therapies at first-line. This aligns with the proposed positioning of enco+bini as an alternative targeted treatment in first-line where dabra+tram is currently the

mainstay option. This proposed positioning is supported by UK healthcare professional (HCP) clinical expert opinion (16)

This section therefore reports results for the treatment-naïve population at all available DCOs (01 April 2024, 19 July 2023; 22 September 2022) from PHAROS with results for the previously treated and total populations for reported in Appendix N.

Summary results from Cohort A (treatment naïve) from the IFCT academic study are reported with detailed results available in Appendix N.

B.2.6.1. PHAROS

Clinical efficacy data were available from three separate DCOs: 01 April 2024, 19 July 2023 and 22 September 2022.

B.2.6.1.1. Primary endpoint

B.2.6.1.1.1 Confirmed ORR by IRR

A summary of best overall response (BOR) per RECIST v1.1 according to IRR for treatment-naïve patients is provided in Table 14. The ORR was consistent across all DCOs (01 April 2024,19 July 2023; 22 September 2022). The ORR was 74.6 (95% CI 61.6–85.0) including 9 (15.3%) CRs and 35 (59.3%) PRs. Ten patients (16.9%) had stable disease.

Table 14. Summary of Best Overall Response - per RECIST v1.1 According to IRR (SS) – Treatment naïve population

Treatment naïve N=59 n (%)			
Data cut-off	**01 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
Best overall response (based on a confirmed response)†			
CR	9 (15.3)	9 (15.3)	9 (15.3)
PR	35 (59.3)	35 (59.3)	35 (59.3)
Stable disease	10 (16.9)	[redacted]	10 (16.9)
PD	2 (3.4)	[redacted]	2 (3.4)
NE	[redacted]	[redacted]	3 (5.1)
Number of patients with best overall response non-evaluable‡			
No post-baseline assessments due to early death (defined as	[redacted]	[redacted]	0

Treatment naïve N=59 n (%)			
Data cut-off	**01 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
death prior to 6 weeks after date of first dose)			
No post-baseline assessments due to other reason	[redacted]	[redacted]	1 (33.3)
Stable disease occurred <6 weeks after the start of treatment and no subsequent tumour assessments	[redacted]	[redacted]	2 (66.7)
Objective response rate (confirmed) (ORR: CR+PR)	44 (74.6)	44 (74.6)	44 (74.6)
95% CI¶	61.6, 85.0	61.6, 85.0	61.6, 85.0

Source: Table 10 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.1 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.1 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (April DCO) PHAROS ESMO presentation (93); (July DCO) BRAFTOVI EPAR documentation (87); (Sept DCO) Riely 2022 (92).
†Best overall response was based on IRR using RECIST v1.1; ‡The denominator of subcategories is the total number of participants with best overall response=Not evaluable (NE) according to RECIST v1.1 per IRR; Estimated 95% CIs for ORR were obtained using the exact Clopper-Pearson method.
Abbreviations: CI, confidence interval; CR, complete response; IRR, independent radiology review; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SS, safety set

B.2.6.1.2. Secondary endpoints

Secondary outcome results for all DCO dates (01 April 2024, 19 July 2023 and 22 September 2022), for treatment naïve-patients are reported within the main submission, with results for previously treated and total populations reported in Appendix N.

B.2.6.1.2.1 Confirmed ORR by IA

The results of ORR based on IA for treatment-naïve patients (all DCOs) are summarised in Table 15.

In the treatment-naïve population, the ORR based on IA was [redacted], and [redacted] shown in B.2.6.1.1.1. The ORR by IA at the most recent DCO was [redacted] ([redacted]% [95% CI: [redacted]–[redacted]]) including [redacted] ([redacted]%) CRs and [redacted] ([redacted]%) PRs. Total agreement between IRR-assessed and IA responses and non-responses was [redacted]% (see Table 16).

Table 15: Summary of Best Overall Response per RECIST v1.1 According to Derived IA (SS) – Treatment naïve population

Treatment naïve N=59 n (%)			
Data cut date	**01 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
Best overall response (based on confirmed response†)			
CR	[redacted]	[redacted]	2 (3.4)
PR	[redacted]	[redacted]	35 (59.3)
Stable disease	[redacted]	[redacted]	16 (27.1)
PD	[redacted]	[redacted]	4 (6.8)
NE	[redacted]	[redacted]	2 (3.4)
Number of patients with best overall response non-evaluable‡			
No post-baseline assessments due to early death (defined as death prior to six weeks after date of first dose)	[redacted]	[redacted]	[redacted]
No post-baseline assessments due for other reason	[redacted]	[redacted]	[redacted]
Stable disease occurred < 6 weeks after the start of treatment and no subsequent tumour assessments	[redacted]	[redacted]	[redacted]
ORR (confirmed) (CR+PR)	[redacted]	[redacted]	37 (62.7)
95% CI¶	[redacted]	[redacted]	(49.1–75.0)

Source: Table 14.2.2 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.2 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.2 in PHAROS update_DCO 01 April 2024 [Data on file] (84); PHAROS ESMO presentation (93); (Sept DCO) Riely 2022 (92).
†Best overall response is based on derived investigator's assessment using RECIST v1.1; ‡The denominator of subcategories is the total number of participants with best overall response=Not evaluable (NE) according to RECIST v1.1 per derived investigator assessment; ¶ Estimated 95% CIs for ORR were obtained using the exact Clopper-Pearson method.
Abbreviations: CI, confidence interval; CR, complete response; IRR, independent radiology review; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SS, safety set.

Table 16: Summary of agreement and disagreement between response results based on derived IA and IRR in participants with BRAF V600E mutant NSCLC (SS) – Treatment naïve population

Treatment naïve N=59 n (%)			
Data cut date	**01 April 2024**	**19 July 2023**	**22 September 2022**
Discrepancy (%)			
IRR response/investigator no response	[redacted]	[redacted]	9 (15.3)

Treatment naïve N=59 n (%)			
Data cut date	**01 April 2024**	**19 July 2023**	**22 September 2022**
IRR no response/investigator response	[redacted]	[redacted]	2 (3.4)
Total event disagreement rate†	[redacted]	[redacted]	11 (18.6)
Agreement (%)			
IRR response/investigator no response	[redacted]	[redacted]	35 (59.3)
IRR no response/investigator response	[redacted]	[redacted]	13 (22.0)
Total event agreement rate‡	[redacted]	[redacted]	48 (81.4)

Source: Table 14.2.5 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.5 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.5 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (Sept DCO) Riely 2022 (92).
Note: Response refers to confirmed CR or PR. †The total event disagreement rate measures the proportion of participants for whom there is a discrepancy between the IRR and investigator; ‡The total event agreement rate measures the proportion of participants for whom there is a concordance between the IRR and investigator
Abbreviation; IRR, independent radiology review.

B.2.6.1.2.2 Duration of response

DOR by IRR for all DCOs in the treatment-naïve population are summarised in Table 17. In the treatment-naïve population, the median DOR, according to IRR at the most recent DCO for the [redacted] treatment-naïve responding patients was 40 months (95% CI: 23.1, NE), with [redacted] ([redacted]%) patients having disease progression and [redacted] ([redacted]) death after the initial response (DCO: 01 April 2024). The percentages of responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and [redacted]%, respectively (DCO: 01 April 2024).

Table 17: Duration of response per RECIST v1.1 according to IRR (SS, Confirmed Responders) – Treatment naïve population

Treatment naïve			
Data cut date	**01 April 2024 (n=[redacted])**	**19 July 2023 (n=44)**	**22 September 2022 (n=44)**
Number of patients with confirmed response, n (%)	[redacted]	44 (100)	44 (100)
Number of events, n (%)	[redacted]	17 (38.6)	12 (27.3)
Progression	[redacted]	16 (36.4)	11 (25.0)
Death due to any use	[redacted]	1 (2.3)	1 (2.3)

Treatment naïve			
Data cut date	**01 April 2024 (n=[redacted])**	**19 July 2023 (n=44)**	**22 September 2022 (n=44)**
Number of censored, n (%)	[redacted]	27 (61.4)	32 (72.7)
Percentiles of duration of response (months) (95% CI)†			
25th	[redacted]	14.0 (4.5, 23.2)	14.0 (4.5, NE)
50th	40.0 (23.1, NE)	40.0 (23.1, NE)	NE (23.1, NE)
75th	[redacted]	NE (40.0, NE)	NE (NE, NE)
Duration of response (months), n (%)			
<3	[redacted]	3 (6.8)	3 (6.8)
≥3	[redacted]	41 (93.2)	41 (93.2)
≥6	[redacted]	33 (75.0)	33 (75.0)
≥9	[redacted]	31 (70.5)	31 (70.5)
≥12	[redacted]	28 (63.6)	26 (59.1)
≥24	[redacted]	13 (29.5)	7 (15.9)

Source: Table 12 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table in 14.2.8 PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.8 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (July DCO) BRAFTOVI EPAR documentation (87); (Sept DCO) Riely 2022 (92).
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Abbreviations; CI, confidence interval; NE, not evaluable.

DOR based on IA for all DCOs for treatment-naïve patients is summarised in Table 18. For treatment-naïve patients, the median DOR, based on IA was:

- [redacted] (95% CI: [redacted], [redacted]), with [redacted] of [redacted] ([redacted]%) patients having disease progression after the initial response. The percentages of responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and [redacted]%, respectively (DCO: 01 April 2024).
- [redacted] ([redacted]; [95% CI: [redacted], [redacted]]), with [redacted] of [redacted] ([redacted]%) patients having disease progression after the initial response. The percentages of responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and [redacted]%, respectively (DCO: 19 July 2023).
- [redacted] months (95% CI: [redacted], [redacted]), with [redacted] of [redacted] ([redacted]%) patients having disease progression or death after the initial response. The percentages of

responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and 62.2%, respectively (DCO: 22 September 2022).

Table 18: Duration of Response per RECIST v1.1 According to Derived IA (SS, Confirmed Responders) – Treatment naïve population

Treatment naïve			
Data cut date	**01 April 2024 (n=[redacted])**	**19 July 2023 (n=[redacted])**	**22 September 2022 (n=[redacted])**
Number of patients with confirmed response, n (%)	[redacted]	[redacted]	[redacted]
Number of events, n (%)	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]
Death due to any cause	[redacted]	[redacted]	[redacted]
Number of censored, n (%)	[redacted]	[redacted]	[redacted]
Percentiles of duration of response (months) (95% CI)†			
25th	[redacted]	[redacted]	[redacted]
50th	[redacted]	[redacted]	[redacted]
75th	[redacted]	[redacted]	[redacted]
Duration of response (months), n (%)			
<3	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]
≥9	[redacted]	[redacted]	[redacted]
≥12	[redacted]	[redacted]	23 (62.2)
≥24	[redacted]	[redacted]	6 (16.2)

Source: Table 14.2.9 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.9 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.9 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (Sept DCO) Riely 2022 (92).
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Abbreviations; CI, confidence interval; NE, not evaluable.

B.2.6.1.2.3 Disease control rate

DCR at 24 weeks by IRR is presented in Table 19 for treatment-naïve patients.

In these patients, DCR by IRR and DCR by IA were consistent across all DCOs.

DCR by IRR at 24 weeks was 64.4% (95% CI: 50.9, 76.4) and DCR by IA at

24 weeks was [redacted]% (95% CI: [redacted], [redacted]) for the most recent DCO (01 April 2024). The results of DCR based on IA were [redacted] with those based on IRR for all DCOs (see Appendix N).

Table 19: Disease Control Rate per RECIST v1.1 According to IRR (SS) – treatment naïve population

Treatment naïve N=59			
Data-cutoff date	**01 April 2024**	**19 July 2023**	**22 September 2022**
Disease control rate after 24 weeks (DCR: CR + PR + Stable Disease) (95% CI)†	38 (64.4% [95% CI: 50.9,76.4)	[redacted] ([redacted] % [95% CI: [redacted], [redacted])	38 (64.4% 95% CI [50.9,76.4])

Source: Table 14.2.1.1 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.1.1 PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.2.1 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (Sept DCO) Riely 2022 (92).
†Estimated 95% CIs for DCR were obtained using the exact Clopper-Pearson method.
Abbreviations; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not estimable; PR, partial response; SS, safety set.

B.2.6.1.2.4 Time to response

TTR by IRR is summarised in Table 20 for treatment-naïve patients and in Appendix N for previously treated and total populations. Results were consistent across all DCOs. In the treatment naïve patient group, the median TTR by IRR was 1.86 months (range: 1.1 to 19.1 months) (DCO: 01 April 2024). Almost all objective responses ([redacted] of [redacted]) were reached within [redacted] months from study treatment start (at the first or second tumour assessment after baseline evaluation). The results of TTR based on IA [redacted] with those based on IRR across all populations (see Appendix N).

Table 20: Time to Response According to IRR (SS, Confirmed Responders) – treatment naïve population

Treatment-naïve N=59			
Data-cutoff date	**01 April 2024 (n=[redacted])**	**19 July 2023 (n=[redacted])**	**22 September 2022 (n=[redacted])**
Time to response (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	1.86	1.86	1.86

Minimum, maximum	1.1, 19.1	1.1, 19.1	1.1, 19.1
Time to response (months), n (%)			
<2	[redacted]	[redacted]	[redacted]
2 to <4	[redacted]	[redacted]	[redacted]
4 to <6	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]

Source: Table 14.2.10 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.10 PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.10 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (Sept DCO) Riely 2022 (92).
Abbreviation; SD, standard deviation.

B.2.6.1.2.5 Progression free survival

PFS by IRR for all DCOs for the treatment-naïve population are summarised in Table 21 and the Kaplan-Meier (KM) plot for the most recent DCO (01 April 2024) is presented in Figure 6. An overview on the duration of follow-up for PFS are summarised in-text below.

In treatment-naïve patients, median PFS by IRR at each DCO was:

- 30.2 months (95% CI: 15.7, NE). A total of 28 (47.5%) patients had PFS events and [redacted] ([redacted] %) patients were still in follow-up for disease progression at the time of data cut-off. The median duration of follow-up for PFS was 33.3 months (95% CI: 30.4, 41.3) based on the reverse KM method (DCO: 01 April 2024).

- 24.9 months (95% CI: 15.7, 44.0). A total of 27 (45.8%) patients had PFS events and 18 (30.5%) patients were still in follow-up for disease progression at the time of DCO. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse KM method (DCO: 19 July 2023).

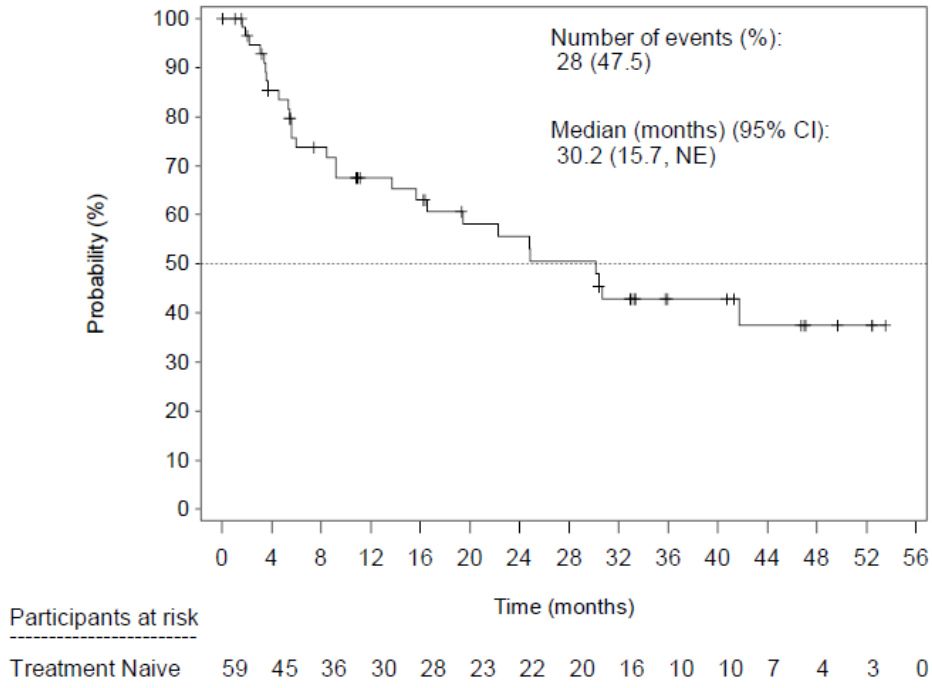
- Not estimable (NE [95% CI: 15.7 months, NE]). PFS data by IRR were immature at the time of the data cutoff, with 21 (35.6%) patients having PFS events and 25 (42.4%) patients still in follow-up for disease progression. The median duration of follow-up for PFS was 18.2 months (95% CI: 16.4, 22.3) based on the reverse KM method (DCO: 22 September 2022).

Table 21: Progression-Free Survival per RECIST v1.1 According to IRR (SS) – treatment naïve population

Treatment Naïve (n=59)			
	01 April 2024	**19 July 2023**	**22 September 2022**
Number of PFS events, n (%)	28 (47.5)	27 (45.8)	21 (35.6)
Progression	[redacted]	24 (40.7)	18 (30.5)
Death without progression	[redacted]	3 (5.1)	3 (5.1)
Number of censored, n (%)	[redacted]	32 (54.2)	38 (64.4)
No adequate baseline assessment	[redacted]	0	0
Start of new anticancer therapy	[redacted]	11 (18.6)	11 (18.6)
Event after missing or inadequate assessments	[redacted]	1 (1.7)	1 (1.7)
Withdrawal of consent	[redacted]	1 (1.7)	1 (1.7)
Lost to follow-up	[redacted]	1 (1.7)	0
No adequate postbaseline tumour assessment	[redacted]	0	0
Ongoing without an event	[redacted]	18 (30.5)	25 (42.4)
Kaplan-Meier estimates of time to event (months), percentiles (95% CI)†			
25th	[redacted]	6.0 (4.6, 16.6)	6.0 (4.6, 19.5)
50th	30.2 (15.7, NE)	24.9 (15.7, NE)	NE (15.7, NE)
75th	[redacted]	44.0 (41.8, NE)	NE (NE, NE)

Source: Table 14.2.12 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.12 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.12 in PHAROS update_DCO 01 April 2024 [Data on file]; (July DCO) BRAFTOVI EPAR documentation (87); (Sept DCO) Riely 2022 (92).
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using the Brookmeyer and Crowley method (1982).
Abbreviations; CI, confidence interval; PFS, progression free survival; NE, not estimable.

Figure 6: Kaplan-Meier Plot of Progression-Free Survival in patients per RECIST v1.1 According to IRR (SS; 01 April 2024) – treatment naïve population



Source: PHAROS update_DCO 01 April 2024 [Data on file] (84).
Abbreviations; CI, confidence interval

PFS based on IA for the treatment naïve-population is summarised in Table 22 for all DCOs and the KM plot for the 01 April 2024 DCO is presented in Figure 7.
In the treatment-naïve patients, the median PFS by IA at each DCO was:

- [redacted] months (95% CI: [redacted], [redacted]). A total of [redacted] ([redacted] %) patients had PFS events and [redacted] ([redacted] %) patients were still in follow-up for disease progression at the time of the data cut-off. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted], [redacted]) based on the reverse KM method (DCO: 01 April 2024).

- [redacted] months (95% CI: [redacted]). A total of [redacted] ([redacted] %) patients had PFS events and [redacted] ([redacted] %) patients were still in follow-up for disease progression at the time of the data cut-off. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse KM method (DCO: 19 July 2023).

- [redacted] months (95% CI: [redacted]). A total of [redacted] ([redacted] %) patients had PFS events and [redacted] ([redacted] %) patients were still in follow-up for disease progression at the time of the data cutoff. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse Kaplan-Meier method (DCO: 22 September 2022).

Table 22: Progression-Free Survival per RECIST v1.1 According to Derived IA (SS)

Treatment Naïve (n=59)			
	01 April 2024	**19 July 2023**	**22 September 2022)**
Number of PFS events, n (%)	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]
Death without progression	[redacted]	[redacted]	[redacted]
Number of censored, n (%)	[redacted]	[redacted]	[redacted]
No adequate baseline assessment	[redacted]	[redacted]	[redacted]
Start of new anticancer therapy	[redacted]	[redacted]	[redacted]
Event after missing or inadequate assessments	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
No adequate postbaseline tumour assessment	[redacted]	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of time to event (months), percentiles (95% CI)†			
25th	[redacted]	[redacted]	[redacted]
50th	[redacted]	[redacted]	[redacted]
75th	[redacted]	[redacted]	[redacted]

Source: PHAROS CSR_DCO 22 September 2022 [Data on file] (83); PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); PHAROS update_DCO 01 April 2024 [Data on file] ; (July DCO) BRAFTOVI EPAR documentation (87); (Sept DCO) Riely 2022 (92).
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Abbreviations; CI, confidence interval; PFS, progression free survival; NE, not estimable.
Publicly available data: (July DCO) BRAFTOVI EPAR documentation (87); (Sept DCO) Riely 2022 (92).

Figure 7: Kaplan-Meier Plot of Progression-Free Survival per RECIST v1.1 According to Derived IA (SS, 01 April 2024) – treatment naïve population

Source: PHAROS update_DCO 01 April 2024 [Data on file] (84).
Abbreviations; CI, confidence interval; PFS, progression free survival; NE, not evaluable.

B.2.6.1.2.6 Overall survival

OS for all DCOs for the treatment-naïve population are summarised in Table 23 and KM plots are presented in Figure 8. Data relating to median duration of follow up is provided in Appendix N.

At the most recent DCO (01 April 2024), the OS rate was [redacted] % in the overall population during a median follow-up of [redacted] months. OS data were immature for both treatment-naïve patients and previously treated patients.

In treatment-naïve patients the median OS at each DCO was:

- NE (95% CI: 31.3, NE). 26 (44.1%) in respect to patient deaths. [redacted] ([redacted] %) patients were censored for OS analysis, with [redacted] [[redacted] %]) patients being alive

and still in follow-up for survival. Median duration of follow-up was [redacted] months (DCO: 01 April 2024).

- NE (95% CI: 26.7, NE). In total, 22 (37.3%) patients had died. 37 (62.7%) patients were censored for OS analysis, with the majority of patients (34 [57.6%]) being alive and still in follow-up for survival (DCO: 19 July 2023).

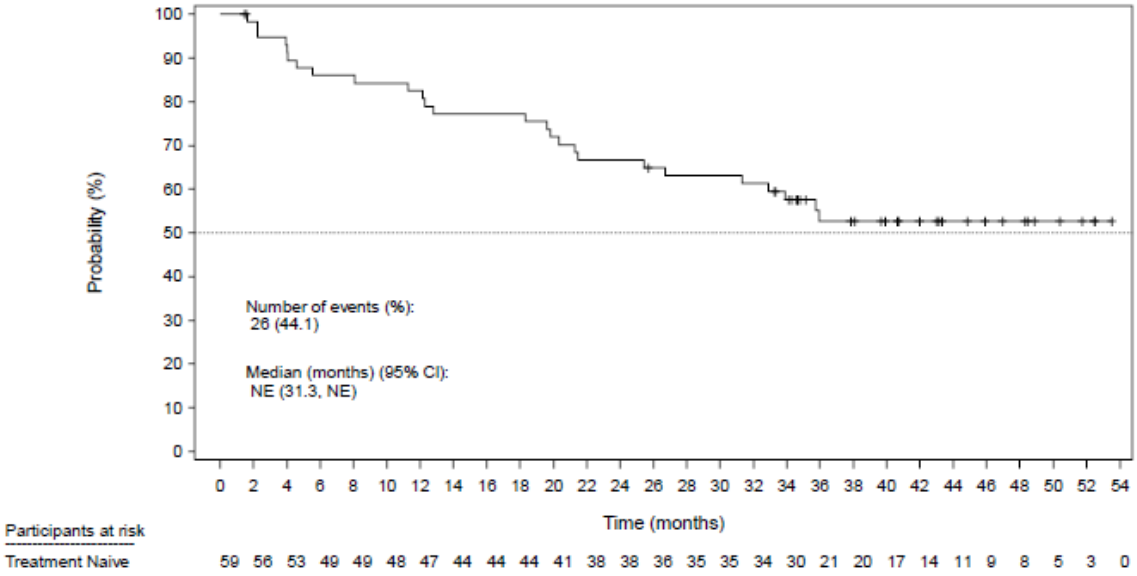
- Immature at the time of DCO, with 17 (28.8%) patients who died and the majority of patients ([redacted]) alive and still in follow-up for survival (DCO: 22 September 2022).

Table 23: Overall Survival (SS) – treatment naïve population

Treatment Naïve (n=59)			
	01 April 2024	**19 July 2023**	**22 September 2022**
Number of deaths, n (%)	26 (44.1)	22 (37.3)	17 (28.8)
Number of censored, n (%)	[redacted]	37 (62.7)	[redacted]
Withdrawal of consent	[redacted]	1 (1.7)	[redacted]
Lost to follow-up	[redacted]	2 (3.4)	[redacted]
No longer followed for survival†	[redacted]	0	[redacted]
Ongoing and no death	[redacted]	34 (57.6)	[redacted]
Kaplan-Meier Estimates of Time to Event (Months) Percentiles (95% CI)‡			
25th	[redacted]	19.6 (8.0, 33.9)	[redacted]
50th	NE (31.3, NE)	NE (26.7, NE)	[redacted]
75th	[redacted]	NE (NE, NE)	[redacted]

Source: Table 14.2.14 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.2.14 in PHAROS EMA update_DCO 19 July 2023 [Data on file] (86); Table 14.2.14 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (July DCO) BRAFTOVI EPAR documentation (87).
†Alive participants who discontinued from the study for reason different from withdrawal consent and lost to follow-up; ‡Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Abbreviation; CI, confidence interval.

Figure 8: Kaplan-Meier Plot of Overall Survival in patients (SS, 01 April 2024) – treatment naïve population



Source: Figure 14.2.14.1 in PHAROS update_DCO 01 April 2024 [Data on file] (84).
Abbreviations: CI, confidence interval; NE, not evaluable.

B.2.6.1.2.7 Time to treatment discontinuation (Post hoc analysis)

Time to treatment discontinuation (TTD) was not produced as a CSR output from the study directly, however a post-hoc analysis was conducted, which assessed TTD. At the 01 April 2024 DCO of PHAROS, median TTD for enco+bini was reached at approximately [redacted] months (95% CI: [redacted], [redacted]) (see Figure 9). TTD data utilised within the economic model in section B.3 was taken from the excel output which is on file and available upon request.

Figure 9: Enco+bini TTD – PHAROS

Source: TTD was not produced as a CSR output from the study directly, however a post-hoc analysis was conducted, which assessed TTD
Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; TTD, time to discontinuation.

B.2.6.2. IFCT

A summary of the results from the IFCT academic study is provided with detailed results reported in Appendix N.

B.2.6.2.1. Primary endpoint

B.2.6.2.1.1 Confirmed ORR by the IA

In the intention-to-treat (ITT) set, the ORR was [redacted] % (95% CI: [redacted] –[redacted] %) including [redacted] patients with PR and no patients with CR. [redacted] ([redacted] %) patients had SD and [redacted] ([redacted] %) had progressive disease (PD).

Secondary endpoints

B.2.6.2.1.2 Progression-free survival

Overall, the total number of PFS events by IA was [redacted] ([redacted] %), with a median PFS of [redacted] months.

B.2.6.2.1.3 Overall survival

In the ITT set, the number of OS events was [redacted] ([redacted] %). Median OS was [redacted] (95% CI: [redacted], [redacted]).

B.2.6.2.1.4 Time to treatment discontinuation (post hoc analysis)

The number of TTD events in the ITT set was [redacted], with the median TTD being [redacted] months (95% CI: [redacted], [redacted]]. Number of TTD events and median TTD was calculated using duration of IFCT exposure observance data presented in Appendix F.

B.2.6.2.1.5 Quality of life (EQ-5D)

A total of [redacted] patients were included in the EQ-5D analysis (cohort A patients meeting all the inclusion criteria). In cohort A, [redacted] patients reported at least one EQ-5D complete measurement, with the number of visits per patient ranging from [redacted] to [redacted] (Appendix N).

No data were reported for EQ-5D in post-progression health state at baseline. However, post-baseline, [redacted] patients reported EQ-5D utility values at post-progression. EQ-5D 5L mean utility at baseline was [redacted], while when considering the complete follow up period, mean utilities were [redacted], and [redacted] pre- and post-progression, respectively. EQ-5D-3L mean utility at baseline was [redacted], while when considering the complete follow up period, mean utilities were [redacted] and [redacted] pre- and post-progression, respectively.

B.2.7. Subgroup analysis

B.2.7.1. PHAROS

For ORR by IRR (primary endpoint) and IA (secondary endpoint) (see Section B.2.3.1.5) additional subgroup analyses were performed to explore the influence of various baseline characteristics (age group <65 years and ≥65 years, gender, race (Asian and non-Asian), and ECOG-PS [0 and 1]). Subgroup analyses of ORR by IRR are provided in Appendix E.

B.2.8. Meta-analysis

Not applicable.

B.2.9. Indirect and mixed treatment comparisons

In first-line treatment of patients with advanced NSCLC with a *BRAF* V600E mutation, enco+bini demonstrated numerically improved clinical outcomes compared with dabra+tram within the ITC.

- In the absence of a head-to-head trial comparing enco+bini with other comparators, a systematic literature review (SLR) and matching-adjusted indirect comparison (MAIC) was conducted to determine the relative efficacy in adult patients with advanced *BRAF* V600E MT NSCLC vs dabra+tram.

The clinical benefits of enco+bini were compared with dabra+tram via a naïve comparison; this translated into enco+bini exhibiting an extended median PFS (30.2 months vs 14.6 months) and a higher ORR (75% vs 64%).

- The MAIC results provide an indication of the relevant benefit of enco+bini compared with dabra+tram, with numerical but non-significant differences in favour of enco+bini for ORR and OS, as well as a statistically significant difference in favour of enco+bini for PFS:
    - ORR: there was a trend towards increased odds of >80% of achieving ORR with enco+bini compared with dabra+tram (adjusted odds ratio [OR]=1.81; 95% CI: 0.71 to 4.59)
    - PFS: enco+bini showed a statistically significant reduction in disease progression by over 50% compared with dabra+tram (adjusted hazard ratio [HR]=0.47; 95% CI: 0.26, 0.85)
    - OS: enco+bini showed statistically significant reduction in death by 45% compared with dabra+tram (adjusted HR=0.55; 95% CI:0.30, 1.01).

- The results of both unadjusted and adjusted models were consistent and robust.

B.2.9.1. Feasibility assessment

In the absence of direct head-to-head evidence comparing the efficacy of enco+bini with dabra+tram, an indirect treatment comparison (ITC) was conducted to assess relative efficacy in line with the recommendations in NICE Decision Support Unit (DSU) technical support document (TSD) 18.

A feasibility assessment (FA) was conducted to explore whether there were any comparator studies that are suitable to be compared with enco+bini in an indirect comparison, for the treatment of *BRAF* V600 MT advanced NSCLC in first- and second-line settings, and to evaluate the feasibility of analyses for each of the key outcomes of interest, considering methodological and population heterogeneity as well as availability of data. Clinical efficacy was identified through a clinical SLR that all available evidence evaluating the efficacy and safety of enco+bini and relevant comparators for the treatment of patients with BRAF V600 MT advanced NSCLC, as described in Section B.2.1 and Appendix D.

The FA focuses on the following outcomes:

- ORR (by IRR, by IA)
- DOR (by IRR, by IA)
- DCR (by IRR and IA)
- PFS (by IRR and IA)
- OS
- AEs, including but not limited to: Any TEAE, treatment-related TEAE, Grade 3, 4, or 5 TEAE, SAE, treatment-related SAE, discontinuation due to AEs.

The FA assesses the comparability of studies with respect to patient characteristics with a focus on confounding factors. A list of relevant confounding factors was identified in the SLR (Appendix D). In addition to the factors identified in the SLR, presence of liver metastases and presence of M1a metastases were also included

based on those identified in TA898 (15). The list of confounding factors considered in this FA is therefore:

- Age
- Gender
- Race
- Smoking history
- ECOG-PS
- Number of previous treatments received (not relevant for analyses in first-line)
- Concomitant mutation in the P13K pathway
- Presence of metastases in the thoracic cavity
- Presence of brain metastases
- Previous treatment with immunotherapy (not relevant for analyses in first-line)
- PD-L1 ≥1% expression
- Histology type
- Presence of liver metastases
- Presence of M1a metastases

This list was validated by clinical experts at the June 2024 UK advisory board (16) and further validated by one clinical expert at the November 2024 virtual consultancy meeting (16). When asked what factors were considered the most important for survival in patients with *BRAF* V600E MT advanced NSCLC, one clinical expert noted that liver metastases, brain metastases, age and performance status are key factors but did not consider 'presence of metastases in the thoracic cavity' an appropriate confounding factor (16). One clinical expert indicated the burden/volume

of metastatic disease is very important, however difficult to quantify. Clinical experts stated that the list of confounding factors identified in the SLR was appropriate and captured all relevant factors. Clinical experts also highlighted smoking status as key confounding factor (16).

The NCT01336634-cohort, dabra+tram study, was identified in the SLR that was eligible for inclusion in the analysis (Appendix D). An outline of the key cohort features from the PHAROS enco+bini study and NCT01336634 dabra+tram study is summarised in Table 24.

Table 24: Key cohort features in the PHAROS and NCT01336634

Cohort	Description
PHAROS	
Treatment naïve patients	Patients who had received no prior systemic therapy for advanced/metastatic disease
Previously treated participants	Patients who had received either: • First-line platinum-based chemotherapy • First-line treatment with an anti-PD-1/PD-L1 inhibitor given alone or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy
NCT01336634	
Cohort A – dabrafenib monotherapy population (pre-treated)	• Prior to enrolment, this cohort was required to have relapsed or progressed on at least one platinum-based chemotherapy regimen for metastatic disease (i.e. dabrafenib was no less than second line treatment for metastatic disease) • Additional lines of prior anti-cancer therapy were allowed (including chemotherapy, radiation therapy, immunotherapy, biological therapy, or major surgery) • Patients received dabrafenib as a single agent at the recommended dose of 150 mg BID • A two-stage design with a planned sample size of 40 patients was initially used for Cohort A
Cohort B – dabrafenib plus trametinib second-line population (pre-treated)	• Prior to enrolment, this cohort was required to have relapsed or progressed on at least one platinum-based chemotherapy for metastatic disease, but cannot have received more than three prior systemic anti-cancer therapies (i.e. dabrafenib plus

Cohort	Description
	trametinib were second, third-, or fourth-line treatment for metastatic disease) • Patients received the recommended dose of both drugs (dabrafenib 150 mg BID and trametinib 2 mg QD)
Cohort C – dabrafenib plus trametinib treatment-naïve population (treatment-naïve)	• This cohort did not receive prior systemic anti-cancer therapies for metastatic disease (i.e. dabrafenib plus trametinib was first-line treatment for metastatic disease) • Patients received the recommended dose of both drugs (dabrafenib 150 mg BID and trametinib 2 mg QD)

Source: ClinicalTrials.gov - NCT01336634 (94); Enco+bini GVD [Data on file] (88).
Abbreviations: BID, twice daily; PD-L1, programmed cell death protein ligand 1; PID-1, programmed cell death protein 1; QD, once daily.

A qualitative analysis on heterogeneity in terms of patient characteristics and study outcomes was conducted to compare PHAROS and NCT01336634 for suitability for an ITC. To provide a robust summary of relative treatment effects, the ITC should include studies that are sufficiently homogeneous in terms of participants and outcomes. A FA for an ITC comparing PHAROS with Planchard 2017 was conducted and concluded that matching-adjusted indirect comparison (MAIC) was feasible in first-line. A comparison of key inclusion and exclusion criteria is presented in Table 25. Inclusion and exclusion criteria were very similar between PHAROS and BRF113928. The main difference in the eligibility criteria between both trials is that patients with an ECOG-PS of 2 were eligible for inclusion in NCT01336634- Cohort C but not in PHAROS. Outcomes were considered well aligned between the two trials; further detail is presented in Section B.2.9.1.1.3.

Table 25: Key inclusion and exclusion criteria for PHAROS and NCT01336634/113928 – Cohort C

PHAROS	NCT01336634/113928- Cohort C-first-line (Planchard 2017)
Inclusion criteria	
• Adult patients (age 18 years and older) with histologically confirmed stage IV • Treatment-naïve patients • Measurable disease on the basis of RECIST 1.1 • ECOG performance status of 0 or 1	• Adults (≥18 years) with metastatic *BRAF* V600E mutant NSCLC. • No previous systemic treatment for metastatic disease • Measurable disease on the basis of RECIST 1.1 • ECOG performance status <= 2

• Presence of a *BRAF* V600E mutation in lung cancer tissue as determined by a local laboratory assay	
Exclusion criteria	
• Patients with symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases are not eligible Note: Patients with previously treated or not treated brain metastases may participate provided they are stable and any neurologic symptoms must have returned to baseline at least 28 days before the first dose of study treatment. Patients must have no evidence of new or enlarging brain metastases or CNS oedema	• Brain metastases were not permitted unless they were asymptomatic, untreated, and measured less than 1 cm, or, if treated, were clinically and radiographically stable 3 weeks after local therapy

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: BID, twice daily; PD-L1, programmed cell death protein ligand 1; PID-1, programmed cell death protein 1; QD, once daily.

It was determined that indirect comparisons were possible in first-line, and that no indirect comparison was possible in second-line between enco+bini and dabra+tram based on the most recent individual patient data (IPD) from PHAROS (DCO April 2024) and published data from NCT01336634/113928-Cohort C. Whenever available, results on time-to-event outcomes presented as KM curves in Planchard 2021 were preferred over curves in Planchard 2017 as they correspond to a longer follow-up period and therefore more mature data.

B.2.9.1.1. Indirect comparison between PHAROS and NCT01336634 (based on the SLR)

Given the presence of time-to-event outcomes and that there is one comparator study that presents data on multiple outcomes, a MAIC was the recommended approach, as per the FA. As both studies are single arm studies, an unanchored MAIC was identified as the preferred approach. Pseudo-IPD for time-to-event data were recreated from published KM curves for NCT01336634/113928-Cohort C using the Guyot algorithm.

B.2.9.1.1.1 Populations

The relative efficacy and safety of enco+bini compared to dabra+tram was aimed to be evaluated in first-line, using the:

- PHAROS treatment naïve cohort – 59 patients

- NCT01336634/113928 Cohort C – 36 patients.

B.2.9.1.1.2 Adjustment factors

Based on the availability of data in the NCT01336634/113928 Cohort C trial, it was only possible to adjust for the following list of variables in the analysis:

- ECOG-PS (used as proportion of patients with ECOG 0)
- Smoking status (used as proportion of patients who never smoked)
- Age
- Gender
- Race (used as proportion of white patients)
- Histology (used as proportion of patients with adenocarcinoma)
- Presence of brain metastases
- Line of treatment (for second-line analysis only).

At the June 2024 UK Advisory Board, clinical experts considered this list of confounding factors appropriate for patients with BRAF V600E MT advanced NSCLC (16). A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis.

B.2.9.1.1.3 Outcomes

Table 26 presents the outcomes that were selected for the ITC. Definitions were aligned between the two trials. The primary outcome in PHAROS was confirmed ORR as determined by IRR per RECIST v1.1.

Table 26: Outcomes definitions

Outcomes	PHAROS	NCT01336634/113928
OS	Time from first dose of study treatment to death	The time from first dose of study drug to death from any cause

Outcomes	PHAROS	NCT01336634/113928
PFS	Time from first dose of study drug to earliest instance of disease progression or death	The interval between the first dose of study drug and the earliest date of disease progression or death from any cause
ORR	Proportion of patients achieving a confirmed best overall response (CR or PR) according to RECIST v1.1 criteria	Percentage of patients who achieved a confirmed CR or PR per RECIST v1.1
Grade 3-4 AE	Patients with a maximum Grade AE of 3 or 4	Patients with a maximum Grade AE of 3 or 4
SAE	Patients experiencing at least one SAE	Patients experiencing at least one SAE
Permanent discontinuation due to AE	Patients who discontinue both enco+bini because of AE	Patients who discontinue dabra+tram because of AE

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: AE, adverse event; dabra+tram, dabrafenib with trametinib; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; IRC, independent review committees; IRR, independent radiological review; SAE, serious adverse event.

B.2.9.1.2. Data

All data used for PHAROS were IPD from the DCO April 2024. All data used for NCT01336634 were extracted from the Planchard publications (95-97), as detailed in Section B.2.9.1

Detailed KM curves for OS and PFS were available in the Planchard publications, as well as information on total number of events, number of patients and events at different timepoints, and indication of censored observations on the curves. Based on this, pseudo patient level data were recreated for the OS and PFS outcomes in NCT01336634 using the algorithm developed by Guyot (206), implemented in R. The patient level data recreated by the algorithm were plotted next to the digitised curves for validation and summary statistics were calculated and compared to the published statistics.

Evidence derived from the supportive study, IFCT, was used alongside data from the pivotal PHAROS study to conduct the pooled MAIC analysis (Section B.2.9.2.4).

B.2.9.1.2.1 Comparison between PHAROS and NCT01336634 in first-line

An overview of the data used in the comparison between PHAROS and NCT01336634-C in first-line is presented in the Table 27.

Table 27: Data for analysis

	PHAROS – Cohort 1 (N=59)	NCT01336634 – Cohort C (N=36)
Efficacy outcomes		
OS	Median follow-up time: [redacted] months 26 events observed (44.1%) Median OS: Not reached	Median follow-up time: 16.4 months 27 events observed (75.0%) median OS: 17.3 months
PFS (IRR)	Median follow-up time: 33.3 months 28 events observed (47.5%) Median PFS: 30.2 months	Median follow-up time 9.3 months 22 events observed (61.1%) Median PFS 14.6 months
ORR (IRR)	44 (74.6%)	23 (63.9%)
Safety outcomes		
Grade 3-4 AE	[redacted]	25 (69.4%)
SAE	[redacted]	24 (66.7%)
Permanent discontinuation due to AE	[redacted]	8 (22.2%)

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: AE, adverse event; ORR, objective response rate; PFS, progression-free survival; IRR, independent radiological review; SAE, serious adverse event.

B.2.9.2. Indirect treatment comparison results

B.2.9.2.1. Comparison between PHAROS and NCT01336634-C (first-line)

B.2.9.2.1.1 Matching and adjustment of populations characteristics

The characteristics of the two populations, before and after weighting are presented in Table 28.

Table 28: Population adjustment in 1L

Variable	Original data		Matched data for PHAROS 1L	
	PHAROS first-line (N=59)	NCT01336634-C (N=36)	Matched on all factors (ESS=44)	Matched on ECOG and smoking status (ESS=58)
Age (years)	68	67	67	66
Gender, % Male	44	39	39	45
ECOG, % ECOG=0	32	36	36	36
Smoking status, % Never smoked	31	28	28	28
Race, % White	90	83	83	90
Histology, % Adenocarcinoma	97	89	89	97
Brain metastases, % Yes	7	6	6	7

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, estimated sample size.

Before matching, imbalances were observed between the two studies primarily on gender, race, and histology, as well as, to a lesser extent, on ECOG and smoking status. At the June 2024 UK Advisory Board, clinical experts commented on the differences in histology between trials but considered this to be a factor of greater patient numbers in PHAROS resulting in smaller proportions (16). One clinical expert noted that the trial population in PHAROS may be closer aligned with UK clinical practice when considering race. In general, clinical experts considered the trial populations to be similar and relatively balanced between the PHAROS first-line population and cohort C of the NCT01336634 study (16).

After matching on all adjustment factors, the characteristics in the weighted PHAROS population were fully aligned with those in Cohort C of the NCT01336634 study. This resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 patients instead of the original 59. This was deemed acceptable by health economic experts at the June 2024 UK advisory board (16).

In this analysis, the rescaled weights ranged from 0.48 to 3.32, with a median of 0.81. The median weight was relatively close to 1, there were no weights equal or close to zero (meaning that all observations contributed to the analyses), and there were no very large weights, which would have indicated that some individual observations had a disproportionate impact on the entire matched population. The matching was therefore deemed satisfactory.

B.2.9.2.2. Safety results

B.2.9.2.2.1 Grade 3-4 adverse events

The results of the naïve comparison between enco+bini and dabra+tram on the proportion of patients experiencing AE of a maximum Grade of 3–4, and of the MAICs using both sets of weights, are presented in Table 29.

Table 29: Results in first-line - Grade 3–4 AEs

Grade 3–4 AE† - Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	1.00 (0.41, 2.47) p=0.996	[redacted]
MAIC – Weighted results		
Mean OR (95% CI), p-value	0.93 (0.37, 2.32) p=0.87	[redacted]

Source: Enco+bini GVD [Data on file] (88).
†Maximum TEAE grade 3 or 4
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; MAIC, matching-adjusted indirect comparison; OR, odds ratio; PFS, progression-free survival.Source: Enco+bini GVD [Data on file] (88).

The unadjusted comparison showed an equivalence between enco+bini and dabra+tram on Grade 3–4 AEs. The unadjusted comparison showed equivalent rates of Grade 3–4 AEs between enco+bini and dabra+tram. After adjusting for all factors, a small difference emerged, but it still did not reach statistical significance.

Enco+bini was slightly favoured compared with dabra+tram for Grade 3–4 AEs (adjusted OR=0.93; 95%CI:0.37, 2.32). The results of both unadjusted and adjusted models were consistent. The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison.

B.2.9.2.2.2 Serious adverse events

The results of the naïve comparison between enco+bini and dabra+tram on the proportion of patients experiencing serious adverse events (SAE), and of the MAICs using both sets of weights, are presented in Table 30.

Table 30: Results in first-line – SAE

SAE – Enco+bini vs dabra+tram	Using all adjustment factors	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	0.45 (0.19, 1.07) p=0.07	[redacted]
MAIC – Weighted results		
Mean OR (95% CI), p-value	0.35 (0.14, 0.85) p=0.02	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; SAE, serious adverse event.Source: Enco+bini GVD [Data on file] (88).

The unadjusted comparison showed a difference in favour of enco+bini. After adjustment on all factors, this difference was larger, statistically significant and associated with a narrower CI. Enco+bini was found to be superior to dabra+tram for SAEs (adjusted OR=0.35; 95%CI:0.14, 0.85). The results of both unadjusted and adjusted models were consistent.

B.2.9.2.2.3 Discontinuation due to adverse events

The results of the naïve comparison between enco+bini and dabra+tram, as well as the MAICs, for the proportion of patients discontinuing treatment because of AE are presented in Table 31.

Table 31: Results in first-line – Discontinuation due to AE

Discontinuation due to AE - Enco+bini vs dabra+tram	Using all adjustment factors	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	0.71 (0.25, 2.02) p=0.53	[redacted]
MAIC - weighted results		
Mean OR (95% CI), p-value	0. 71 (0.24, 2.06) p=0.53	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: AE, adverse event; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; MAIC, matching-adjusted indirect comparison; OR, odds ratio.

The unadjusted comparison showed a non-significant difference in favour of enco+bini. After adjustment on all factors, this difference was slightly larger, in favour of enco+bini, but still did not reach significance (adjusted OR=0.71; 95% CI:0.24, 2.06).

B.2.9.2.3. Efficacy results

The results of the two analyses run for this population, one using the full list of adjustment variables (base case) and one restricted to ECOG-PS and smoking status (sensitivity analysis), are presented together in sections B.2.9.2.3.1, B.2.9.2.3.2 and B.2.9.2.3.3.

B.2.9.2.3.1 Objective response rate

The results of the naïve comparison between enco+bini and dabra+tram on ORR, and of the MAICs using both sets of weights, are presented in Table 32.

Table 32: Results in first-line – ORR

ORR (IRR) – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – Unweighted results		
Mean OR (95% CI), p-value	1.66 (0.68, 4.07), p=0.27	[redacted]
MAIC – Weighted results		
Mean OR 95% CI, p-value	1.81 (0.71, 4.59), p=0.21	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IRR, Independent radiology review; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

The unadjusted comparison showed a non-significant difference in favour of enco+bini. After adjustment on all factors, this difference was slightly larger but still did not reach significance. Enco+bini was favoured compared with dabra+tram for ORR (adjusted OR=1.81; 95%CI: 0.71, 4.59). The results of both unadjusted and adjusted models were consistent.

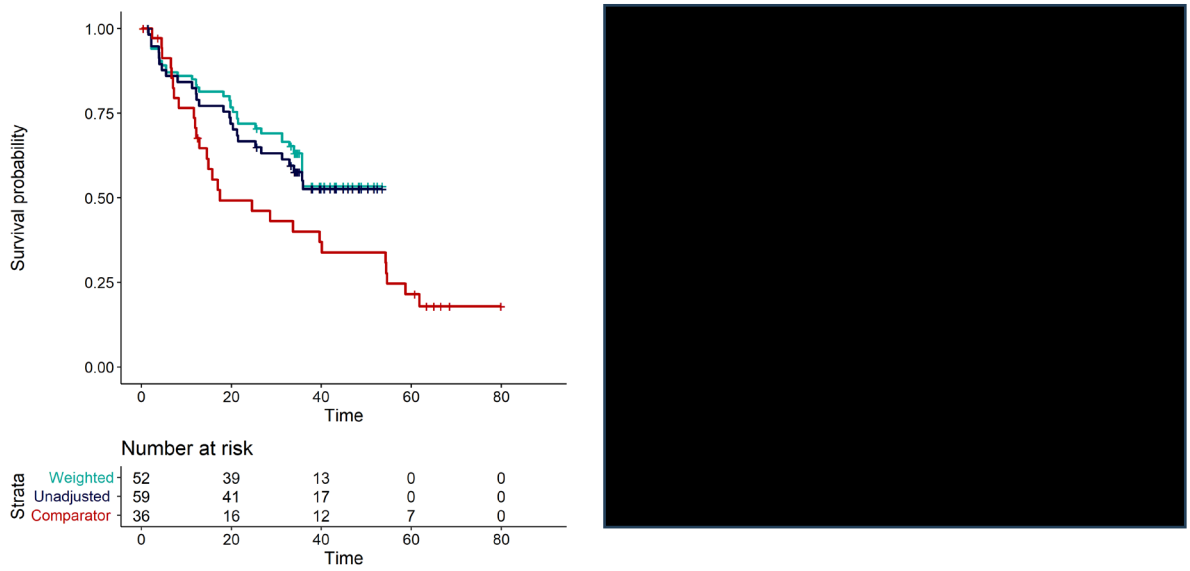
The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison. Sensitivity analyses conducted with bootstrapping method confirmed the base-case results.

B.2.9.2.3.2 Overall survival

OS data in both studies of interest are plotted below, before and after weighting.

Figure 10: Kaplan-Meier curves for overall survival in first-line

A: Impact of adjustment on all factors B: Impact of adjustment on ECOG and smoking status



Source: Enco+bini GVD [Data on file] (88).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; OS, overall survival.

Figure 10A shows the impact of the adjustment on all factors on the difference between PHAROS and NCT01336634. OS was improved with enco+bini compared with dabra+tram (log-rank p-value of [redacted]) based on the unweighted data. This difference was increased by the weighting of the PHAROS population and reached significance (log-rank p-value p=[redacted]). Figure 10B shows that the impact of the adjustment on ECOG and smoking status was minimal. The OS curve for the weighted PHAROS population was almost identical to the curve without any adjustment (log-rank p-value compared to dabra+tram: p=[redacted]). The results of the naïve comparison and of the MAICs using both sets of weights are presented in Table 33.

Table 33: Results in first-line – OS

OS – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – Unweighted results		
Mean HR (95% CI), p-value	0.60	[redacted]

OS – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
	(0.34,1.07) p=0.08	[redacted]
MAIC – Weighted results		
Mean HR, 95% CI, p-value	0.55 (0.30, 1.01) p=0.05	[redacted]

Source: Enco+bini GVD (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

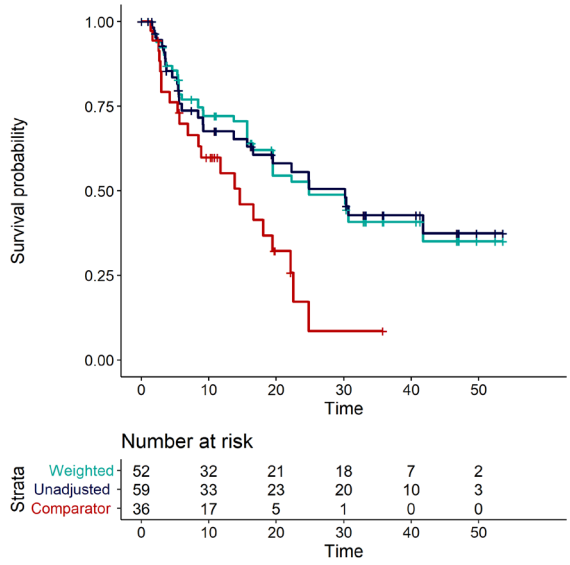
The unadjusted comparison showed a non-significant difference in favour of enco+bini. After adjustment on all factors, this difference was larger but still statistically non-significant. Enco+bini showed a statistically non-significant reduction in death by 45% compared to dabra+tram (adjusted HR=0.55; 95% CI:0.30, 1.01). The results of both unadjusted and adjusted models were in line with the observations made on the KM curves. The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared to the unadjusted comparison.

B.2.9.2.3.3 Progression free survival

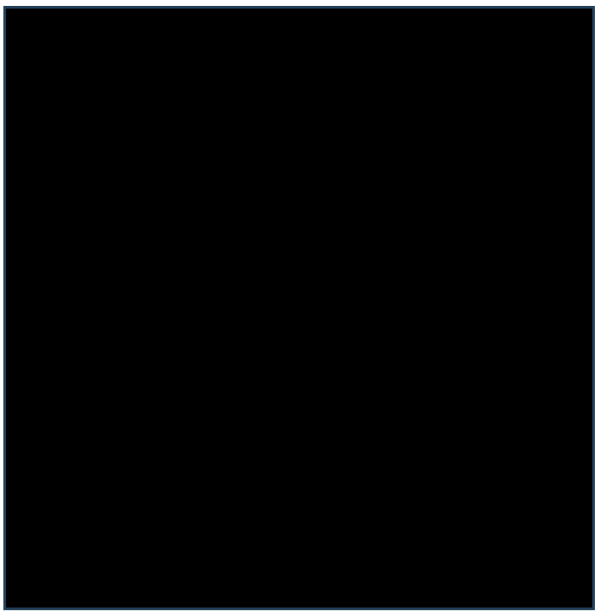
PFS data in both studies of interest are plotted below (Figure 11), before and after weighting.

Figure 11: Kaplan-Meier curves for PFS in first-line

A: Impact of adjustment on all factors



B: Impact of adjustment on ECOG and smoking status



Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.Source: Enco+bini GVD [Data on file] (88).

Figure 11A shows the impact of the adjustment on all factors on the difference between PHAROS and NCT01336634. PFS was improved with enco+bini compared with dabra+tram (log-rank p-value of 0.014) when using unweighted data. When adjusting on all confounding factors, the difference in PFS between enco+bini and dabra+tram remained significant (log-rank p-value p=0.012). Figure 11B shows that the impact of the adjustment on ECOG and smoking status was minimal. The PFS curve for the weighted PHAROS population was almost identical to the curve without any adjustment (log-rank p-value compared to dabra+tram p=0.015). The results of the naïve comparison and of the MAICs using both sets of weights are presented in Table 34.

Table 34: Results in first-line – PFS results

PFS (IRR) – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – Unweighted results		
Mean HR (95% CI), p-value	0.48 (0.27, 0.87)	[redacted]

PFS (IRR) – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
	p=0.01	[redacted]
MAIC – Weighted results		
Mean HR (95% CI), p-value	0.47 (0.26, 0.85) p=0.01	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

The unadjusted comparison showed a statistically significant difference in favour of enco+bini. After adjustment on all factors, this difference was slightly larger and still statistically significant. Enco+bini showed a statistically significant reduction in disease progression of over 50% compared with dabra+tram (adjusted HR=0.47; 95%CI:0.26, 0.85). The results of both unadjusted and adjusted models were consistent and in line with the observations made on the KM curves. As expected, the population adjustment restricted to ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison.

B.2.9.2.4. Comparison between pooled PHAROS and IFCT and NCT01336634-C (first-line)

B.2.9.2.4.1 Matching and adjustment of populations characteristics

A scenario analysis was conducted to compare enco+bini and dabra+tram using pooled data from the first-line cohorts of PHAROS and IFCT to inform the enco+bini arm, and NCT01336634-C to inform the dabra+tram arm. For consistency with the base-case analysis, two MAICs were estimated using the same list of confounding factors as presented in Section B.2.9.1.2.1, aside from race (% white patients) as this data was not available from IFCT. The characteristics of the two populations before and after weighting are presented in Table 35.

Table 35: Population adjustment in first-line, pooled PHAROS and IFCT

Variable	Original data		Matched data for PHAROS and IFCT first-line	
	PHAROS and IFCT first-line (N=120)	NCT01336634-C (N=36)	Matched on all factors (ESS=88)	Matched on ECOG and smoking status (ESS=118)
Age	[redacted]	[redacted]	[redacted]	[redacted]
Gender, % Male	[redacted]	[redacted]	[redacted]	[redacted]
ECOG, % ECOG=0	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, % Never smoked	[redacted]	[redacted]	[redacted]	[redacted]
Histology, % Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases, % Yes	[redacted]	[redacted]	[redacted]	[redacted]

Source: Enco+bini GVD [Data on file] (88); Pierre Fabre data for model ITC & extrapolations [Data on file] (98).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, estimated sample size.

B.2.9.2.5. Efficacy results

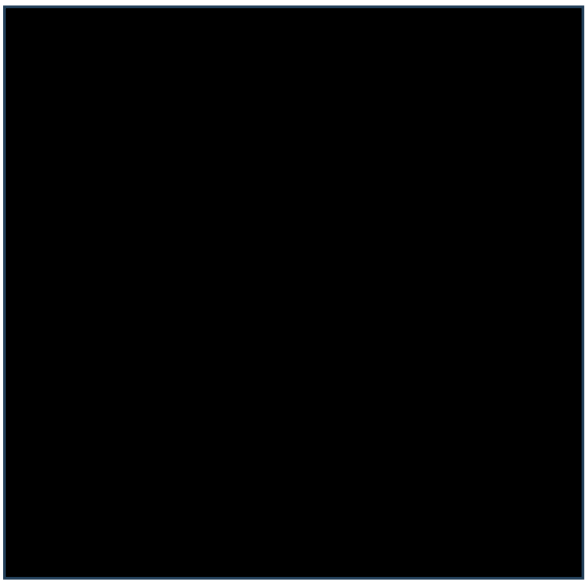
B.2.9.2.5.1 Overall survival

OS data in both studies of interest are plotted below, before and after weighting.

Figure 12: Kaplan-Meier curves for overall survival in first-line, pooled PHAROS and IFCT

A: Impact of adjustment on all factors

B: Impact of adjustment on ECOG and smoking status



Source: Enco+bini GVD [Data on file] (88); Pierre Fabre data for model ITC & extrapolations [Data on file] (98).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; OS, overall survival.

Figure 12A shows the impact of the adjustment on all factors on the difference between pooled PHAROS and IFCT data, and NCT01336634. OS was improved with enco+bini compared with dabra+tram (log-rank p-value of [redacted]) based on the unweighted data. This difference was increased by the weighting of the pooled PHAROS and IFCT population and reached significance (log-rank p-value p=[redacted]). Figure 12B shows that the impact of the adjustment on ECOG and smoking status was minimal. The results of the naïve comparison and of the MAICs using both sets of weights are presented in Table 36.

Table 36: Results in first-line – OS

OS – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – Unweighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]
MAIC – Weighted results		
Mean HR, 95% CI, p-value	[redacted]	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

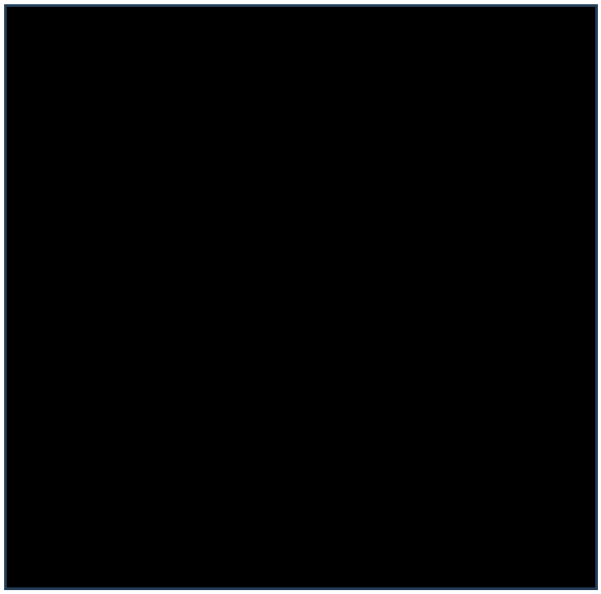
The unadjusted comparison showed a numerical difference in favour of enco+bini (mean HR: [redacted]). After adjustment on all factors, this difference was larger but still statistically non-significant ([redacted]). Enco+bini showed a statistically non-significant reduction in death by [redacted]% compared with dabra+tram (adjusted HR=[redacted], 95%CI: [redacted], [redacted]). The results of both unadjusted and adjusted models were in line with the observations made on the KM curves. The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared to the unadjusted comparison.

B.2.9.2.5.2 Progression free survival

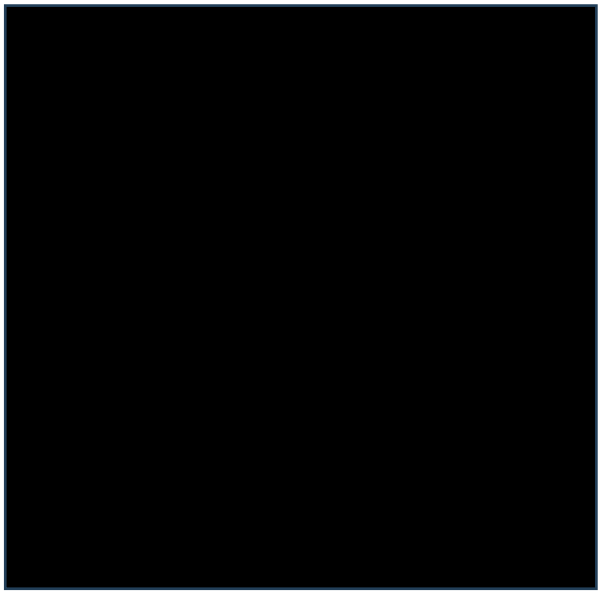
PFS data in both studies of interest are plotted below (Figure 13), before and after weighting.

Figure 13: Kaplan-Meier curves for PFS in first-line, pooled PHAROS and IFCT

A: Impact of adjustment on all factors



B: Impact of adjustment on ECOG and smoking status



Source: Enco+bini GVD [Data on file] (88); Pierre Fabre data for model ITC & extrapolations [Data on file] (98).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 13A shows the impact of the adjustment on all factors on the difference between pooled PHAROS and IFCT data, and NCT01336634. Figure 13B shows that the impact of the adjustment on ECOG and smoking status was minimal. The results of the naïve comparison and of the MAICs using both sets of weights are presented in Table 34.

Table 37: Results in first-line – PFS results, pooled PHAROS and IFCT

PFS (IRR) – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – Unweighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]
MAIC – Weighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]

Source: Enco+bini GVD [Data on file] (88).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

The unadjusted comparison showed a numerical difference in favour of enco+bini (mean HR: [redacted]). Enco+bini showed a numerical reduction in disease progression of [redacted] % compared to dabra+tram (adjusted HR=[redacted]; 95%, CI: [redacted]). The results of both unadjusted and adjusted models were consistent and in line with the observations made on the KM curves. As expected, the population adjustment restricted to ECOG and smoking status did not greatly impact the results compared to the unadjusted comparison.

B.2.10. Uncertainties in the indirect and mixed treatment comparisons

Enco+bini has a more robust assessment of clinical outcomes relying on assessments by both the IRR (primary endpoint) and IA. By contrast in dabra+tram pivotal trial, only an IA was required per protocol, which may lead to some uncertainty in the evaluation of clinical benefit (Independent Review Committee [IRC] in sensitivity analysis only).

B.2.11. Adverse reactions

The combination of enco+bini is associated with a tolerable safety profile

- The overall safety profile of enco+bini in patients with advanced NSCLC with a BRAF V600E mutation is consistent with the safety profile observed in adult patients in approved indications (80, 81).
- [redacted] patients had at least [redacted] all-causality AE ([redacted] %) and at least [redacted] treatment related AE ([redacted] %).
- Slightly [redacted] of patients ([redacted] %) had maximum Grade 3 or 4 all causality AEs, and slightly [redacted] of patients ([redacted] %) had maximum Grade 3 or 4 treatment related AEs.
- Many adverse events are considered clinically inconsequential, such as biochemical abnormalities (for example, alanine aminotransferase increased and aspartate aminotransferase increased) that do not impact patient QoL or treatment costs (16)

B.2.11.1. PHAROS

B.2.11.1.1. Duration of exposure

The duration of exposure to study drug in the treatment-naïve populations is outlined in Table 38 and in Appendix F for previously treated and total populations for all DCOs.

At the 01 April 2024 DCO in the treatment-naïve patient group (N=59)

- [redacted] ([redacted]%) patients received encorafenib and [redacted] ([redacted]%) received binimetinib for >6 to ≤12 months. [redacted] ([redacted]%) patients received encorafenib and [redacted] ([redacted]%) received binimetinib for >12 to ≤24 months. [redacted] patients ([redacted]) received both encorafenib and binimetinib for >24 months

- The median duration of treatment for both encorafenib and binimetinib was [redacted] (range: [redacted] to [redacted]).

Table 38: Duration of Exposure to Study Drug – treatment naïve (SS)

Treatment naïve N=59						
	Enco	**Bini**	**Enco**	**Bini**	**Enco**	**Bini**
	01 April 2024		**19 January 2023**		**22 September 2022**	
Actual treatment duration (months)						
n	59	59	59	59	59	59
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration (months), n (%)						
≤1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>1 to ≤3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>3 to ≤6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<6 to ≤12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>12 to ≤24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>24	24 (40.7)	24 (40.7)	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity[†], %						
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment naïve N=59						
	Enco	Bini	Enco	Bini	Enco	Bini
	01 April 2024		19 January 2023		22 September 2022	
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16 and Table 17 PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.4.1.1 and Table 14.4.1.4 for PHAROS FDA update_DCO 19 January 2023 [Data on file] (89); Table 14.4.1.1 for PHAROS update_DCO 01 April 2024 [Data on file] (84).
[†]Relative dose intensity is defined as 100*(actual dose intensity/intended dose intensity).
Notes: This table summarises participants who received at least one dose of study drug at any given time.
Abbreviation: SD, standard deviationn

B.2.11.1.2. Overall summary of adverse events

An overview of TEAEs for all DCOs for the treatment naïve population is provided in Table 39 and in Appendix F for previously treated and total populations.

As of the 01 April 2024 DCO, in the treatment-naïve population (N=59):

- All patients had at least [redacted] all-causality TEAE and most patients had at least [redacted] treatment-related TEAE ([redacted]%) (83).
- More than [redacted] of patients ([redacted]%) had maximum Grade 3 or 4 all causality TEAEs, and slightly more than [redacted] of patients ([redacted]%) had maximum Grade 3 or 4 treatment-related TEAEs.

Table 39: Summary of AEs in treatment naïve patients, SS

Treatment naïve N=59 n (%)			
Category†	**Enco+bini**	**Enco+bini**	**Enco+bini**
	01 April 2024	**19 January 2023**	**22 September 2022**
Patients with TEAEs	[redacted]	[redacted]	[redacted]
Patients with treatment-related TEAEs	[redacted]	[redacted]	[redacted]
Patients with maximum grade 3 or 4 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with maximum treatment-related grade 3 or 4 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with grade 5 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with treatment-related grade 5 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with SAEs	[redacted]	[redacted]	[redacted]
Patients with treatment-related SAEs	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini permanent discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini dose reduction	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini dosing interruption	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to encorafenib discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to binimetinib discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to encorafenib dose reduction	[redacted]	[redacted]	[redacted]

Treatment naïve N=59 n (%)			
Category†	**Enco+bini**	**Enco+bini**	**Enco+bini**
	01 April 2024	**19 January 2023**	**22 September 2022**
Patients with TEAEs leading to binimetinib dose reduction	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to encorafenib dose interruption	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to binimetinib dose interruption	[redacted]	[redacted]	[redacted]

Source: Table 20, Table 23, Table 26, and Table 29 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.3.1.1.1, Table 14.3.1.1.10 and Table 14.3.1.1.7, and Table 14.3.1.1.16 for PHAROS FDA update_DCO 19 January 2023 [Data on file] ; Table 14.3.1.1.1, Table 14.3.1.1.10, Table 14.3.1.1.13, Table 14.3.1.1.16 and 14.3.1.1.7 PHAROS update_DCO 01 April 2024 [Data on file] .

†Categories are not mutually exclusive. Participants with multiple events in the same category are counted only once in that category; ‡For participants reporting more than one adverse event, the adverse event with the maximum grade is considered.

Abbreviations**:** SD, standard deviation; SS, safety set; TEAE, treatment emergent adverse event.(89);

B.2.11.1.3. Incidence and severity of adverse events

For the treatment-naïve population, the most frequent (all grades) AEs (all causality and treatment-related; ≥10% of total participants), are reported in Table 40 and Table 41.

Most frequent AEs for the treatment-naïve population for previous DCOs (Jan 2023; Sept 2022) and most frequent AEs for previously treated patients and total populations (all DCOs) are reported in Appendix F.

As of the 01 April 2024 DCO, in the treatment-naïve population (N=59), the most frequent

- All-causality TEAEs in the enco+bini arm were nausea ([redacted]%), diarrhoea ([redacted]%), fatigue ([redacted]%), vomiting ([redacted]%), anaemia ([redacted]%) and constipation ([redacted]%)
- Treatment-related TEAEs in the enco+bini arm were nausea ([redacted]%), diarrhoea ([redacted]%), fatigue ([redacted]%), vomiting ([redacted]%), vision blurred ([redacted]%), alanine aminotransferase increased (18.6%), aspartate aminotransferase increased ([redacted]%), and anaemia ([redacted]%).

Table 40: Treatment-Emergent Adverse Events, by Preferred Term (All causality, SS)

Treatment naïve (n=59) **Data cut off: 01 April 2024**	
Preferred term	**All causality n (%)**
Any AE	[redacted]
Nausea	[redacted]
Diarrhoea	[redacted]
Fatigue	[redacted]
Vomiting	[redacted]
Anaemia	[redacted]
Constipation	[redacted]
Dyspnoea	[redacted]
Pyrexia	[redacted]
Oedema peripheral	[redacted]
Abdominal pain	[redacted]
Back pain	[redacted]
Vision blurred	[redacted]
Cough	[redacted]
Asthenia	[redacted]
Blood creatinine increased	[redacted]
Dizziness	[redacted]
Arthralgia	[redacted]
Aspartate aminotransferase increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Lipase increased	[redacted]
Pruritus	[redacted]
Decreased appetite	[redacted]
Alanine aminotransferase increased	[redacted]
Dry skin	[redacted]
Pain in extremity	[redacted]
Alopecia	[redacted]
Hyponatraemia	[redacted]
Muscle spasms	[redacted]
Blood alkaline phosphatase increased	[redacted]
Productive cough	[redacted]
Rash	[redacted]

Treatment naïve (n=59) Data cut off: 01 April 2024	
Preferred term	**All causality n (%)**
Weight increased	[redacted]
Headache	[redacted]
Hypertension	[redacted]
Insomnia	[redacted]
Myalgia	[redacted]

Source: PHAROS TEAE excel document [Data on file] (99).
Abbreviations: TEAE, treatment emergent adverse events; SD, standard deviation; SS, safety set

Table 41: Treatment-Emergent Adverse Events, by Preferred Term (Treatment related, SS)

Treatment naïve (n=59) Data cut off: 01 April 2024	
Preferred term	**Treatment related n (%)**
Any AE	[redacted]
Nausea	[redacted]
Diarrhoea	[redacted]
Fatigue	[redacted]
Vomiting	[redacted]
Anaemia	[redacted]
Constipation	[redacted]
Dyspnoea	[redacted]
Pyrexia	[redacted]
Oedema peripheral	[redacted]
Abdominal pain	[redacted]
Back pain	[redacted]
Vision blurred	[redacted]
Cough	[redacted]
Asthenia	[redacted]
Blood creatinine increased	[redacted]
Dizziness	[redacted]
Arthralgia	[redacted]
Aspartate aminotransferase increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Lipase increased	[redacted]
Pruritus	[redacted]

Treatment naïve (n=59) **Data cut off: 01 April 2024**	
Preferred term	**Treatment related** **n (%)**
Decreased appetite	[redacted]
Alanine aminotransferase increased	[redacted]
Dry skin	[redacted]
Pain in extremity	[redacted]
Alopecia	[redacted]
Hyponatraemia	[redacted]
Muscle spasms	[redacted]
Blood alkaline phosphatase increased	[redacted]
Productive cough	[redacted]
Rash	[redacted]
Weight increased	[redacted]
Headache	[redacted]
Hypertension	[redacted]
Insomnia	[redacted]
Myalgia	[redacted]

Source: Table 14.3.1.3.1 in PHAROS April data cut tables [Data on file] (84).
Abbreviations: TEAE, treatment emergent adverse events; SD, standard deviation; SS, safety set.

B.2.11.1.4. Permanent treatment discontinuations associated with adverse events

Table 42 provides all causality AEs and TEAEs associated with permanent discontinuation of enco+bini, and of encorafenib and binimetinib separately, for the latest DCO (01 April 2024) in the treatment-naïve population; results for the other DCO / all DCOs for previously treated and total populations are provided in Appendix F. All of the most frequent all-causality AEs associated with permanent discontinuation of both encorafenib and binimetinib were also considered treatment related.

As of the 01 April 2024 DCO, in the treatment-naive patient population:

- TEAEs associated with permanent discontinuation of both encorafenib and binimetinib were reported in [redacted] ([redacted]%) patients; no AEs were experienced by more than [redacted] ([redacted]%) patient.
- TEAEs associated with permanent discontinuation of encorafenib were reported in [redacted] ([redacted]%) patients; the most frequent were instances of myalgia, exhibited by [redacted] ([redacted]%) patients. No other AEs were exhibited more than once ([redacted]%).
- TEAEs associated with permanent discontinuation of binimetinib were reported in [redacted] ([redacted]%) patients; the most frequent were ejection fraction decreased ([redacted] [[redacted]%]).

Table 42: Treatment-emergent AEs leading to permanent discontinuation of both encorafenib and binimetinib, and of encorafenib and binimetinib separately in of treatment-naive patients by patient in decreasing frequency (SS)

Treatment naïve n=59 **Data cut-off: 01 April 2024**		
Preferred term	**All causality n (%)**	**Treatment-related n (%)**
Enco+bini		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]

Treatment naïve n=59 Data cut-off: 01 April 2024		
Preferred term	**All causality n (%)**	**Treatment-related n (%)**
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Source: Table 14.3.1.1.4, Table 14.3.1.1.2, and Table 14.3.1.1.3 in PHAROS April data cut tables (84).
Abbreviations: AE, adverse event; SS, safety set.

B.2.11.1.5. Dose reductions associated with adverse events

All causality AEs associated with dose reduction of enco+bini, reported by patients for the latest DCO (01 April 2024) for the treatment-naïve population are outlined in Table 43. Data for earlier DCOs for treatment-naïve and for all DCO for previously treated and total populations are reported in Appendix F.

As of the 01 April 2024 DCO, in the treatment naïve population:

- TEAEs leading to a dose reduction of both enco+bini were reported in [redacted] ([redacted] %) patients. The most frequent AEs were nausea ([redacted] %), increased aspartate aminotransferase (AST; [redacted] %), diarrhoea ([redacted] %), and alanine aminotransferase (ALT) increased ([redacted] %). Of these, most were considered treatment related.

- TEAEs leading to a dose reduction of encorafenib were reported in [redacted] ([redacted] %) patients. The most frequent AEs (≥5% of patients) were nausea ([redacted] %), diarrhoea ([redacted] %), and AST increased ([redacted] %), ALT increased ([redacted] %), and vomiting ([redacted] %). Of these, most were considered treatment related.

- TEAEs leading to a dose reduction of binimetinib were reported in [redacted] ([redacted] %) patients, and the most frequent (≥5% of patients) were diarrhoea ([redacted] %), nausea ([redacted] %), AST increased ([redacted] %), ALT increased ([redacted] %). Of these, most were considered treatment related.

Table 43: Treatment-emergent AEs requiring dose reduction of both enco+bini, and of encorafenib and binimetinib separately in treatment naïve patients by patient in decreasing frequency (SS)

Treatment naïve (n=59) **Data cut off: 01 April 2024**		
	All causality n (%)	**Treatment related n (%)**
Enco+bini		
Any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

Treatment naïve (n=59) Data cut off: 01 April 2024		
	All causality n (%)	**Treatment related n (%)**
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

Source: Table 14.3.1.1.8, Table 14.3.1.1.9, and Table 14.3.1.1.9 in PHAROS April data cut tables (84).
Abbreviations: AE, adverse event; SS, safety set.

B.2.11.1.6. Dosing interruptions associated with adverse events

All causality TEAEs associated with dosing interruptions of enco+bini, and each of encorafenib and binimetinib separately for the treatment-naïve population for the latest (01 April 2024) DCO are reported in Table 44. Details for earlier DCOs are reported in Appendix F.

Table 44 Treatment-emergent AEs requiring dose interruption of both enco+bini, and of encorafenib and binimetinib separately in treatment naïve patients by patient in decreasing frequency (SS)

Treatment naïve (n=59) **Data cut off: 01 April 2024**		
	All causality n (%)	**Treatment related n (%)**
Enco+bini		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]

Treatment naïve (n=59) Data cut off: 01 April 2024		
	All causality n (%)	**Treatment related n (%)**
Fatigue	[redacted]	[redacted]
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

Source: Table 14.3.1.1.16, Table 14.1.1.15, and Table 14.3.1.1.14 in PHAROS April data cut tables (84).
Abbreviations: AE, adverse event; SS, safety set.

B.2.11.1.7. Deaths

Deaths by primary reason for all DCOs in the treatment-naïve population are outlined in Table 45 and for previously treated and total populations in Appendix F.

As of the 01 April 2024 DCO, in the treatment-naïve population:

- A total of [redacted] ([redacted]%) patients died during the study, and [redacted] ([redacted]%) patients died while on-treatment (≤30 days after last dose of study treatment)
- [redacted] ([redacted]%) patients died during the on-treatment period due to disease progression
- [redacted] ([redacted]%) patient died during the on-treatment period due to AEs.

Table 45: Deaths by primary reason – treatment naïve population (SS)

Treatment naïve N=59 n (%)			
Preferred term	**01 April 2024**	**19 January 2023**	**22 September 2022**
All deaths	[redacted]	[redacted]	17 (28.8)

Treatment naïve N=59 n (%)			
Preferred term	**01 April 2024**	**19 January 2023**	**22 September 2022**
Primary reason for death			
Disease progression	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Death ≤30 days after last dose of study treatment	[redacted]	[redacted]	[redacted]
Primary reason for death			
Disease progression	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death >30 days after last dose of study treatment	[redacted]	[redacted]	[redacted]

Source: Table 32 in PHAROS CSR_DCO 22 September 2022 [Data on file] (83); Table 14.3.2.2.1 in PHAROS FDA update_DCO 19 January 2023 [Data on file] (89); Table 14.3.2.2.1 in PHAROS update_DCO 01 April 2024 [Data on file] (84); (Sept DCO) Riely 2022 (92).
Abbreviation: SS, safety set.

B.2.11.1.8. SAEs

Data for SAEs for the 01 April 2024 DCO in the treatment naïve population were not reported. SAEs were calculated for the MAIC/ITC using IPD however, there are no tables figures and listings (TFL) with SAE by preferred term. SAEs for earlier DCOs are reported in Appendix F.

B.2.11.1.9. Adverse events of special interest

Adverse events of special interest (AESI) for the 01 April 2024 DCO in the treatment-naïve population are reported in Table 46. Details for previously treated and total population and for earlier DCOs are reported in Appendix F.

Table 46 Overview of treatment-emergent AESIs (safety set)

Treatment Naïve (n=59)		
01 April DCO		
Category	**Encorafenib n (%)**	**Binimetinib n (%)**
Pts with AESIs	[redacted]	[redacted]

Treatment Naïve (n=59)		
01 April DCO		
Category	**Encorafenib n (%)**	**Binimetinib n (%)**
Pts with Treatment-related AESIs	[redacted]	[redacted]
Pts with Maximum Grade 3 or 4 AESIs	[redacted]	[redacted]
Patients with Maximum Treatment-related Grade 3 or 4 AESIs	[redacted]	[redacted]
Patients with Grade 5 AESIs	[redacted]	[redacted]
Patients with Treatment-related Grade 5 AESIs	[redacted]	[redacted]
Patients with Serious AESIs	[redacted]	[redacted]
Patients with Treatment-related Serious AESIs	[redacted]	[redacted]

Source: Table 14.3.1.4.1 in PHAROS update_DCO 01 April 2024 [Data on file] (84).
† Categories are not mutually exclusive. Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories
‡ For participants reporting more than one adverse event, the adverse event with the maximum grade is considered
Abbreviation: AESIs, adverse events of special interest; DCO, data cut-off; Pts, patients; SS, safety set.

B.2.11.2. IFCT

B.2.11.2.1. Adverse events

An overview of AEs for all-causality AEs, and treatment-related AEs is reported below with full details reported in Appendix F.

For all-causality AEs, [redacted] ([redacted]%) patients experienced any grade of AE, with the most common being Grade 3, which was experienced by [redacted] ([redacted]%) patients. Regarding TEAEs, [redacted] ([redacted]%) patients experienced any grade of AE, with the most common being Grade 3, which was experienced by [redacted] ([redacted]%) patients.

B.2.11.2.2. Observance

Full details for duration of exposure to study drug, dose reductions, interruptions, and summary of exposure are outlined in Appendix F and summarised briefly below.

In the safety set (Cohort A), [redacted] ([redacted]%) patients received enco+bini each for at least 6 months, with the mean actual treatment duration for encorafenib and binimetinib being [redacted] and [redacted] months, respectively. The number of patients experiencing at least one dose reduction for encorafenib and binimetinib was [redacted] ([redacted]%) and [redacted]

([redacted]%). Dosing interruptions for encorafenib and binimetinib occurred in [redacted] ([redacted]%) and [redacted] ([redacted]%) patients, respectively.

B.2.12. Ongoing studies

Encorafenib in combination with binimetinib is currently being evaluated in the OCEANII study (Table 47).

Table 47: Ongoing trials with encorafenib in combination with binimetinib

Study	Population	Description
OCEANII (NCT05195632)	Adult Chinese patients with metastatic unresectable stage IV *BRAF* V600E mutant NSCLC, who are *BRAF*- and *MEK*-inhibitor treatment-naïve and are either previously untreated or have had one line of prior therapy in metastatic setting	A phase 2, multicentre, single-arm study with a safety lead-in to investigate the efficacy, safety and pharmacokinetics of encorafenib 450 mg QD in combination with binimetinib 45 mg BID (Combo450)

Abbreviations: BID, twice daily; NSCLC, non-small cell lung cancer, QD, once daily.

B.2.13. Interpretation of clinical effectiveness and safety evidence

BRAF V600E MT advanced NSCLC represents a small but clinically significant proportion of patients with NSCLC (43). Patients diagnosed with NSCLC are routinely tested for mutations including *BRAF* to determine whether targeted treatments would be appropriate. However, targeted treatment options for patients with *BRAF* V600E mutations are limited, with dabra+tram the only targeted treatment currently available (16). Enco+bini shows clinical benefits in terms of ORR and PFS. Clinical experts indicated that dabra+tram is associated with severe pyrexia, often leading to treatment discontinuation. They believe that enco+bini would be better tolerated, and offer a less toxic alternative as a first-line targeted therapy (16). Enco+bini is therefore a plausible alternative first-line treatment option for advanced *BRAF* V600E MT NSCLC.

B.2.13.1. Principal findings from the available clinical evidence

The pivotal Phase 2 trial PHAROS indicates that enco+bini is associated with clinically meaningful benefits for patients with *BRAF* V600E MT advanced NSCLC in the first-line setting (Section B.2.6.1). These findings are supported by the results of indirect treatment comparisons (ITC) in treatment-naïve patients (Section B.2.9.2)

which indicate a non-significant difference in terms of ORR and OS in favour of enco+bini, and a significant difference in PFS in favour of enco+bini (compared with dabra+tram). The supporting evidence from the IFCT academic study also indicates that enco+bini is associated with clinically meaningful benefits.

In terms of safety, enco+bini demonstrated a strong safety profile consistent with use in other approved indications and other similar therapies (80, 81) (DCO: 01 April 2024). Results of the ITCs again indicated a non-significant difference in terms of grade 3–4 AEs and discontinuation due to AEs in favour of enco+bini compared with dabra+tram, and a significant difference in terms of SAEs in favour of enco+bini compared with dabra+tram. One clinical expert reported that while both dabra+tram and enco+bini were associated with AEs, dabra+tram was particularly associated with severe side effects such as pyrexia, resulting in treatment discontinuations but that AEs associated with enco+bini were manageable.

B.2.14. Strengths and limitations of the data package

The efficacy and safety evidence base primarily comes from the pivotal phase 2 PHAROS trial. PHAROS is a relatively large-scale single-arm study of the combination enco+bini in both treatment-naïve and previously treated *BRAF* V600E MT advanced NSCLC. The supporting evidence base also comes from the IFCT study. The IFCT study was similarly designed to evaluate the efficacy, safety of enco+bini in first-line, and in second-line, with the additional inclusion of QoL as an outcome. The primary endpoint of both the PHAROS trial and the IFCT study is ORR; because spontaneous remission is rare, ORR provides clear evidence of antitumor activity.

The pivotal Phase 2 trial PHAROS, as well as the supporting academic IFCT trial, are both open-label, single-arm, Phase 2 clinical studies which may be seen as a potential limitation. The rarity of the *BRAF* mutation in NSCLC and the commercial availability of the BRAF/MEK combination dabra+tram, however, impedes the feasibility of an adequately powered randomised clinical trial. Recent advances in the treatment of patients with NSCLC with unique molecular drivers including the BRAF/MEK combination dabra+tram, have been founded on regulatory approvals

based on non-randomised, non-comparative clinical trials showing clinically meaningful and durable ORR. Results from PHAROS and IFCT both indicate a clinically meaningful benefit for patients and while a comparative study with dabra+tram would have required a very high number of patients and a long study duration, results from the ITC comparing enco+bini and dabra+tram indicate a non-significant difference in favour of enco+bini.

The PHAROS trial is a multinational study, 48 clinical sites in 5 countries (Spain, Italy, Netherlands, Republic of Korea, and the United States of America [USA]): 18 sites in Europe, 29 sites in North America and 1 site in South Korea and IFCT is also a multicentre study though conducted only in France. Although no UK sites or patients were included in either study, clinical experts noted in the June 2024 UK advisory board that patient demographics and characteristics at trial baseline in both studies were very similar and are generally reflective of the patient population expected in UK clinical practice (16). Furthermore, patient characteristics of the *BRAF* V600E MT NSCLC population analysed in the SLR are comparable to the patient characteristics of the PHAROS trial as described in the FA of the ITC (Section 8.6.2). The clinical evidence is therefore considered to be generalisable to the NHS. (16).

In conclusion, while long-term follow-up is needed for maturity of PFS and OS and long-term side effects, clinical evidence indicates that enco+bini is a suitable additional treatment option for patients with advanced *BRAF* V600E MT NSCLC, offering patients and clinical experts a greater choice of treatments in the first-line setting.

B.3. Cost Effectiveness

The combination of enco+bini is a cost-effective use of NHS resources for treating treatment-naïve adult patients with advanced NSCLC with a *BRAF* V600E mutation, at a willingness to pay (WTP) threshold of £30,000 per quality-adjusted life-year (QALY) gained.

- A cost-utility analysis with a lifetime horizon (33.5 years) was conducted to evaluate the cost-effectiveness of enco+bini vs dabra+tram.
- The population considered is a subset of the marketing authorisation of enco+bini; treatment-naïve adult patients with advanced NSCLC with a *BRAF* V600E mutation, and enco+bini is only compared with dabra+tram. This is because:
    - As mutation status is typically determined at diagnosis, patients are likely to receive targeted treatment, such as enco+bini in the first-line setting. This was noted in TA898 (15) and supported by clinical expert opinion from the June and October 2024 UK advisory boards (16). Dabra+tram is therefore considered to be the only comparator relevant to a population with treatment-naïve advanced NSCLC with a BRAF V600E mutation.
    - As noted in TA898 (15), and confirmed by clinical expert opinion (16), only a small group of patients would receive a non-targeted therapy at first-line due to BRAF V600E testing delays. Furthermore, this population is expected to significantly reduce over time as access to BRAF V600E testing improves.
- The model is structured as an area under the curve (AUC) partitioned survival model (PSM), comprised of three mutually exclusive health states: progression-free, post-progression, and death.
- Clinical inputs for enco+bini data are derived primarily from the pivotal Phase 2 trial PHAROS.
- Parametric curves were fitted to PFS, OS and time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) curves for enco+bini.
- In the absence of direct evidence comparing the efficacy of enco+bini with dabra+tram, a MAIC was conducted. The resulting hazard ratios (HR) vs enco+bini were used to predict PFS and OS for dabra+tram.
- In the base case (including the patient access scheme [PAS] price), enco+bini was associated with cost savings of [redacted] and an incremental QALY gain of [redacted] vs dabra+tram, meaning enco+bini was dominant when compared with dabra+tram.
- In all scenario analysis, enco+bini is associated with a cost saving and increased QALYs compared with dabra+tram and is therefore dominant in all analyses.

B.3.1. Published cost effectiveness studies

A SLR was conducted to identify relevant cost-effectiveness studies from the published literature. Four economic evaluations were identified reporting analyses of dabra+tram adult patients with *BRAF* V600E MT NSCLC. The economic evaluations consisted of three health technology assessment (HTA) reports (15 CADTH, 2017 #180, 100) and one conference abstract (101). Only one study, a submission to NICE (TA898) for dabra+tram is immediately relevant to a UK population and is summarised in Table 48, comparing dabra+tram vs pembrolizumab plus platinum chemotherapy in patients with *BRAF* V600E MT NSCLC. Dabra+tram efficacy was informed by MAIC adjusted data from Cohort C from BRF113928, matching-adjusted to KEYNOTE-189, and pembrolizumab plus platinum chemotherapy efficacy was informed by KEYNOTE-189. The manufacturer reported that dabra+tram dominated pembrolizumab plus platinum chemotherapy over a lifetime horizon. The other economic evaluations were HTA reports from Canada, and the US (15 CADTH, 2017 #180, 100). A complete summary of the SLR is presented in Appendix G.

Table 48: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	*ICER (per QALY gained*)
NICE TA898 (15)	2023	Model details: Model: Partitioned survival model Health states: Three (progression free, progressed disease, death) Cost-effectiveness threshold: NR Dominant or most cost-effective treatment: NR Other details: Model did not include the costs of genomic testing of tumours for a *BRAF* V600 mutation in its base case because it said this test is already done in routine practice	NSCLC *BRAF* V600 mutation Mean age: 67.8	QALYs are reported as commercial in confidence	Costs are reported as commercial in confidence	Dominant. ICERs are reported as commercial in confidence

Abbreviations: ICER, incremental cost-effectiveness ratio; NR, not reported; NSCLC, non-small cell lung cancer; QALYs, quality adjusted life years.

B.3.2. Economic analysis

Since no prior published economic evaluations of enco+bini in patients with advanced NSCLC with a *BRAF* mutation were identified in the economic SLR (Section B.3.1), a de novo cost-effectiveness analysis was developed. Two UK advisory boards were held in June and October 2024 with three clinical experts and two health economists and one follow-up consultation was held in November 2024 to support its development (16).

B.3.2.1. Patient population

The population considered in the analysis is treatment-naïve adult patients with *BRAF* V600E MT NSCLC. This population is aligned with the treatment-naïve cohort of the pivotal PHAROS study and a subset of the full marketing authorisation for enco+bini, for treatment of adult patients with *BRAF* V600E MT NSCLC. Treatment was modelled for this population on the basis that clinical experts agreed (at both the June and October 2024 UK advisory boards) that most patients would start on a targeted therapy except in the case of delayed test results or inadequate biopsy and an urgent need to start treatment (16). Experts stated there was no clinical rationale to not use a targeted therapy if a *BRAF* V600E mutation is present. This view is aligned with TA898, where both the committee and clinical experts noted that only a few people with a *BRAF* V600E mutation have delayed screening results and start a treatment other than targeted therapy (15). Therefore, it is expected that the number of people receiving targeted therapy at second line will fall substantially over time as access to testing improves. This is also aligned with NICE guidance for dabra+tram, which recommends dabra+tram as an option for treating patients with *BRAF* V600E MT NSCLC, only if it is used as first-line treatment (15).

At both the June and October 2024 UK advisory boards, clinical experts also agreed that sequencing of targeted therapies would not be an option (16). Once a patient has failed first-line treatment with a targeted therapy there would be a biological resistance mechanism, making treatments with similar mechanisms of action ineffective. Clinical experts advised that patients switching from one targeted therapy to another may be due to toxicity rather than treatment failure, so would not be considered second-line in that scenario.

B.3.2.2. Model structure

The de novo cost-effectiveness model was developed in Microsoft® Excel 2019 using an area under the curve (AUC) partitioned survival model (PSM) approach. The model is comprised of three mutually exclusive health states: progression-free, post-progression, and dead (Figure 14). Progression-based models are common in economic analyses of oncology treatments as they align with typically reported trial endpoints, accurately reflect the progressive nature of the disease with separate pre- and post-progression states and reflect the clinical pathway of care in NSCLC. The model structure is also consistent with previous HTAs in NSCLC (15, 102-110), including the recent dabra+tram (TA898) appraisal, which was accepted as appropriate for decision-making by NICE (15). As such, a PSM was considered the most appropriate model structure for this analysis.

All patients enter the model in the ‘progression-free” state and receive treatment with either enco+bini or dabra+tram. Individuals experience disease progression and transition to the ‘post-progression’ state. Patients can transition to the ‘Dead’ state from any state in the model; this is an absorbing state.

Health state occupancy is calculated using the AUC approach, using extrapolated KM OS and PFS data for enco+bini from PHAROS, and data for dabra+tram is informed by a MAIC comparing PHAROS with the BRF113928 trial (Section B.2.9.2). The PFS curve is used to inform the proportion of individuals in the progression-free health states over time. The TTD curve is used to inform the number of individuals who are on treatment. The OS curve is used to inform the proportion of individuals in the ‘Dead’ health state over time.

Long-term OS estimates are constrained by general population mortality informed by life tables for England and Wales (Section B.3.3.3) (111); the probability of death in the model is prevented from falling below that of the general population. Logical inconsistencies in the survival extrapolations were adjusted for such that the PFS curve is not permitted to exceed the OS curve (111); the probability of death in the model is prevented from falling below that of the general population. Logical

inconsistencies in the survival extrapolations were adjusted for such that the PFS curve is not permitted to exceed the OS curve.

Figure 14: Model schematic

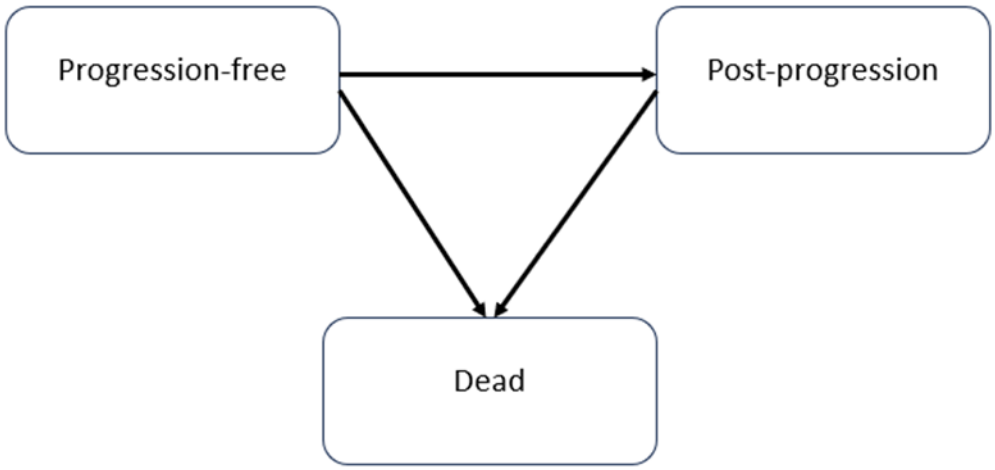


Table 49: Features of the economic analysis

Factor	Previous evaluations	Current evaluation	
	TA898 (15)	Chosen values	Justification
Model type	CUA (PSM)	CUA (PSM)	The NICE reference case specifies CUA as the preferred form of economic evaluation (112).
Time horizon	Lifetime	Lifetime	The NICE reference case recommends a lifetime horizon to capture all expected differences in costs and benefits between treatments (112). The lifetime horizon in the model was defined at 33.5 years. Based on the base-case exponential extrapolation after 33.5 years, less than 1% of patients are expected to be alive, therefore this time horizon will capture the expected long-term survival of treated patients. Additionally, this is aligned with prior NSCLC appraisals.
Cycle length	7 days	7 days	Accounts for the different dosing schedules for relevant comparators and subsequent therapies for patients with advanced NSCLC with a *BRAF* V600E mutation and is sufficiently short to capture all relevant differences between enco+bini and dabra+tram.

Factor	Previous evaluations	Current evaluation	
	TA898 (15)	Chosen values	Justification
Source of utilities	Chouaid et al. 2013 (113)	Chouaid et al. 2013 (113)	Aligns with base case of the dabra+tram appraisal (15).
Source of costs	• NHS reference costs • PSSRU • BNF/eMIT	• NHS reference costs • PSSRU • BNF/eMIT	As per NICE reference case (112).

Abbreviations: BNF, British National Formulary; CUA, cost utility analysis; dabra+tram, dabrafenib plus trametinib; eMIT, electronic marketing information tool; enco+bini, encorafenib in combination with binimetinib; HRQoL, health-related quality of life; HTA, health technology appraisal; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PSM, partitioned survival model; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.3. Intervention technology and comparators

The intervention considered in the analysis is enco+bini, comprised of encorafenib which is administered orally at a dose of 450 mg QD in combination with binimetinib, administered orally at a dose of 45 mg BID. Treatment with enco+bini should be continued until disease progression or unacceptable toxicity (13, 14, 17, 114). At the time of submission, dabra+tram is the only NICE approved targeted therapy for treating treatment-naïve adult patients with *BRAF* V600E MT NSCLC (15). At the June and October 2024 UK advisory boards (16), clinical experts stated that dabra+tram is the only relevant comparator to enco+bini in patients with BRAF V600E MT NSCLC, as:

- There is no clinical rationale to use a non-targeted therapy if a *BRAF* V600E mutation is present
- The only scenario in which a patient would not receive targeted treatment at first-line would be due to delays in receiving genomic screening results and where there is a clinical urgency for the patient to begin treatment
    - As agreed by the committee in TA898 (15), the number of patients experiencing testing delays is expected to fall substantially over time as testing issues are resolved, and therefore the number of patients receiving non-targeted treatments at first-line is expected to be very small.

Clinical expert opinion therefore supports that patients would be offered targeted therapy with dabra+tram prior to other treatment options reserved in second- or later-lines of therapy. Therefore, the only relevant comparator for this analysis is dabra+tram, as described in Section B.1.3.5. Dabrafenib is administered orally at a dose of 150 mg BID, and trametinib is administered orally at a dose of 2 mg QD, in line with the summary of product characteristics (SmPC) and BRF113928 trial (80, 97).

B.3.3. Clinical parameters and variables

As discussed in Section B.2.3, clinical data for enco+bini are available from PHAROS (the pivotal Phase 2 trial), as well as the supporting academic IFCT study.

Patient level data for the treatment naïve subgroup from PHAROS has been used as the primary source of clinical data for the model. This approach aligns with the European Medicines Agency (EMA) regulatory submission and leverages the more mature data available in PHAROS compared with IFCT. At the time of DCO, median duration of follow-up was longer with PHAROS for OS ([redacted] months, CI: [redacted]), and PFS by IRR (33.3 months, CI: 30.4, 41.3) compared with IFCT OS ([redacted] months, CI: [redacted] and PFS by IRR ([redacted] months, CI: [redacted]). Additionally, in PHAROS, 26 (44.1%) patients had died, and [redacted] %) patients were censored for OS analysis. In IFCT, [redacted] ([redacted] %) patients had died, and [redacted] ([redacted] %) were censored for OS analysis.

An unanchored MAIC was performed against the BRF113928 trial to inform clinical inputs for dabra+tram (Section B.2.9). A scenario analysis was also conducted using a pooled PHAROS and IFCT dataset to inform clinical inputs for enco+bini.

B.3.3.1. Patient characteristics

In the base case, patient baseline characteristics were derived from the treatment-naïve cohort of PHAROS (83), a summary is presented in Table 50. The mean age at baseline was 66.5 years, mean patient body weight was 74.6kg, and mean body surface area (BSA) was 1.67m^2. The proportion of male patients in PHAROS was 44.1%. These values were varied in the one-way sensitivity analysis (Section B.3.10.2).

Table 50: Patient baseline characteristics

Characteristic	PHAROS trial, treatment naïve cohort (83)
Age (years)	66.5
Proportion male (%)	44.1%
Mean weight (kg)	74.6
Mean height (m)	1.67
BSA (m^2)†	1.86

†Calculated using the Mosteller formula
Abbreviations: BSA, body surface area.

B.3.3.2. Survival extrapolations

As median follow-up from PHAROS (DCO: 1st April 2024) was shorter than the model time horizon, extrapolations were required to predict long-term estimates of survival (Table 51). As is standard with PSMs, the proportion of patients in each health state at any given time were derived using the OS and PFS curves, whereas the proportion of patients on treatment was determined using the TTD curve.

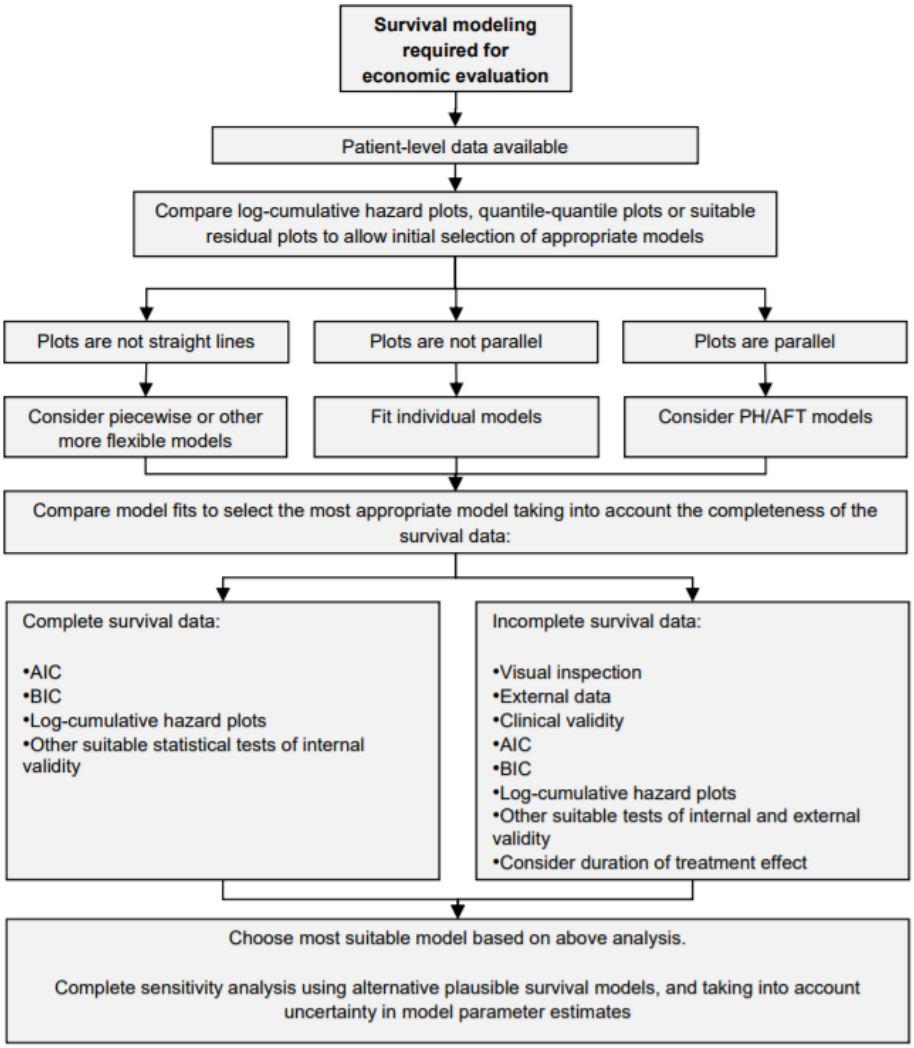
Table 51: Median follow-up PHAROS

	Median follow-up (months)	
	OS	PFS
PHAROS, treatment naïve cohort	[redacted]	33.3

Abbreviations: OS, overall survival; PFS, progression-free survival.

Parametric curves were fitted to OS, PFS, and TTD KM curves for enco+bini and dabra+tram to extrapolate these over a lifetime time horizon. All parametric survival analyses for enco+bini were conducted in line with NICE TSD 14 (Figure 15) (115).

Figure 15: NICE DSU TSD14 – recommendations for the analysis of survival data (115)



Abbreviations: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DSU, Decision Support Unit; NICE, National Institute for Health and Care Excellence; PH, proportional hazards; TSD, technical support document.

The standard seven parametric models; exponential, Weibull, lognormal, generalised gamma, loglogistic, Gompertz, and gamma were estimated for each of OS, PFS and TTD for enco+bini. As the standard parametric distributions provided a good visual fit to the KM curves, flexible models, such as splines, were not considered.

To select the base-case parametric distribution for OS, PFS, and TTD for enco+bini, the following approach was taken:

- Review of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness of fit statistics to assess the model fit to the observed data
- Visual inspection of curves vs the observed data
- Comparison with published data, where available
- Clinical plausibility of long-term projections, based on clinical expert advice from the October 2024 UK advisory board (16).

To prevent implausible estimates, PFS was capped such that it did not exceed OS, and OS was bound by age- and gender-matched general population mortality rates (Section B.3.3.2.3.2). At the October 2024 UK advisory board, clinical experts advised that a proportion of patients may continue with treatment beyond progression if they are still deriving a benefit (16). Therefore, the TTD curve is not capped by the PFS curve.

OS and PFS in the dabra+tram arm were estimated by applying HRs from the MAIC (Section B.2.9.1.1) to the enco+bini survival curves (Section B.3.3.2.1.2). TTD in the dabra+tram arm was assumed equal to PFS (Section B.3.3.2.3.2). A summary of base-case modelling approaches is presented in Table 52.

Table 52: Summary of survival analysis approach

		Base case approach	Source	Reference to section in submission
OS	Enco+bini	Exponential	PHAROS	Section B.3.3.2.1.1
	Dabra+tram	HR: 0.55	MAIC (PHAROS vs BRF113928)	Section B.3.3.2.1.2
PFS	Enco+bini	Exponential	PHAROS	Section B.3.3.2.1.1
	Dabra+tram	HR: 0.47	MAIC (PHAROS vs BRF113928)	Section B.3.3.2.1.2
TTD	Enco+bini	Exponential	PHAROS	Section B.3.3.2.3.1
	Dabra+tram	Equal to PFS	–	Section B.3.3.2.3.2

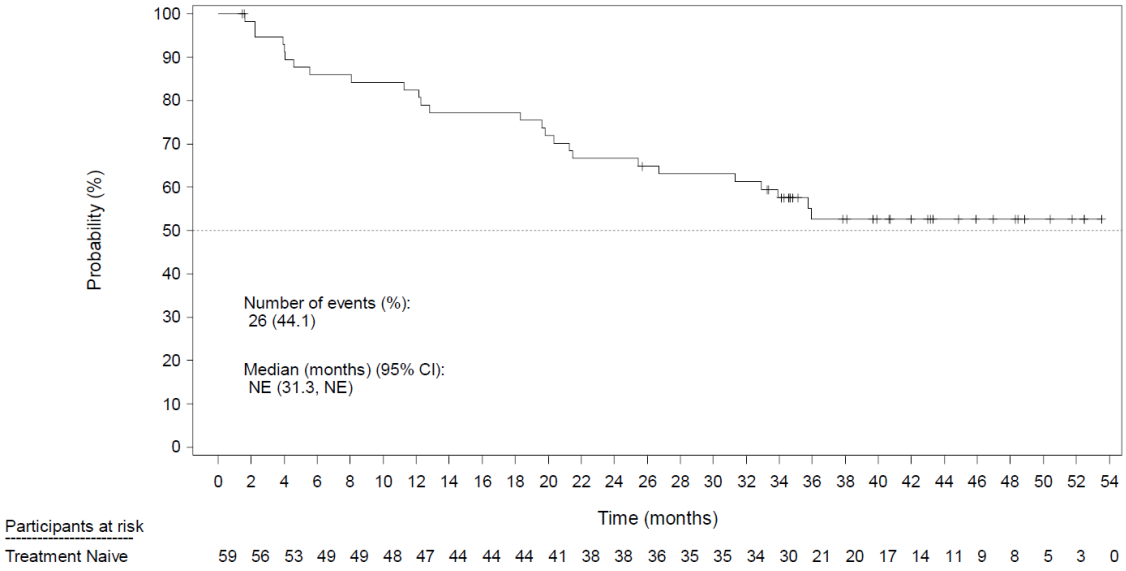
Abbreviations: CI, confidence interval; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; MAIC, matching-adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

B.3.3.2.1. Survival estimates – enco+bini

B.3.3.2.1.1 Overall survival

At the 1st April 2024 DCO of PHAROS, after a median follow-up of [redacted] months, 44.1% of patients experienced an OS event in the treatment-naïve population however, median OS had not been reached (Figure 16).

Figure 16: Enco+bini OS - PHAROS (DCO: 1st April 2024)



Abbreviations: CI, confidence interval; DCO: data cut-off; enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; NE, not estimable; OS, overall survival.

Statistical goodness of fit

The exponential, Weibull, lognormal, generalised gamma, loglogistic, Gompertz and gamma distributions were fitted to the KM data from the treatment-naïve cohort of PHAROS and extrapolated over a lifetime horizon. Statistical goodness of fit was assessed using AIC and BIC statistics. All distributions provided a good statistical fit to the data (within 3 points based on AIC), however, the log-normal and exponential distributions were associated with the best statistical fit based on minimisation of the AIC and BIC statistics, respectively (Table 53).

Table 53: Enco+bini OS, goodness of fit statistics†

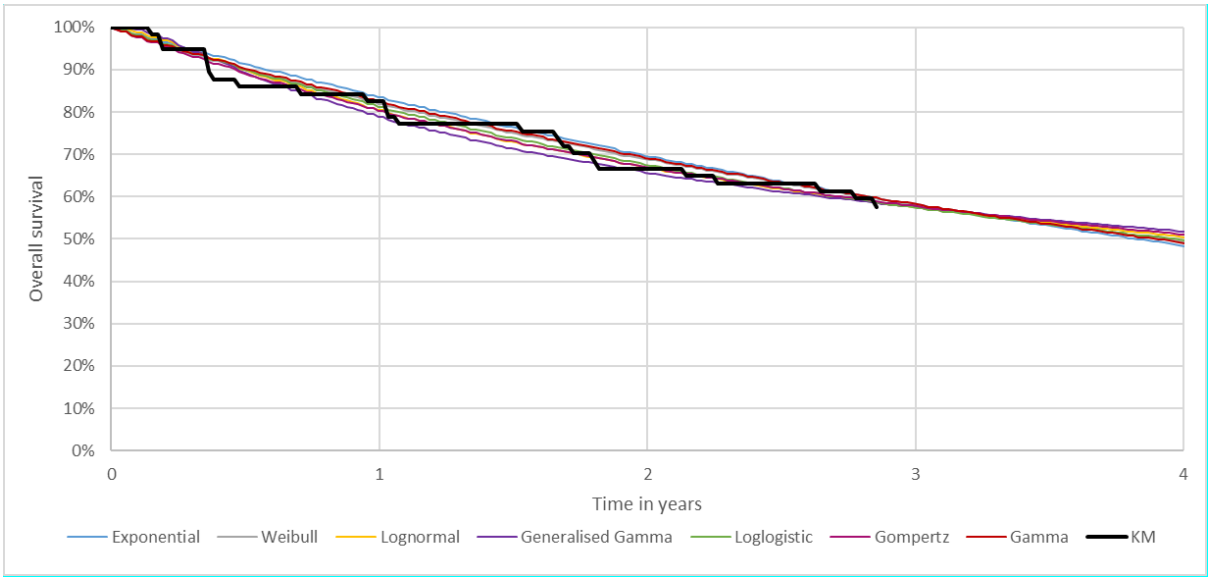
	Goodness of fit statistic	
	AIC	**BIC**
Exponential	271.91	**273.98**
Weibull	273.64	277.79
Log-normal	**271.66**	275.82
Generalized gamma	273.20	279.43
Log-logistic	272.80	276.95
Gompertz	272.81	276.97
Gamma	273.75	277.91

† Lowest AIC and BIC denoted in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Visual inspection

The visual fit of the survival distributions to the observed data from PHAROS was evaluated. Projections of OS from the seven parametric models over the trial period are presented in Figure 17 and landmark survival estimates from each distribution are presented in Table 54. All distributions slightly over-predict survival compared with the observed data at 6 months, but then are well aligned with the observed data from 6 months onwards. Both the exponential and Weibull distributions are associated with the best visual fit, predicting the observed data within 3.0% from 12 to 30 months.

Figure 17: Short-term OS projections – enco+bini



Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; OS, overall survival.

Table 54: Enco+bini OS – parametric distribution and observed data

	Month				
	6	12	18	24	30
KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; OS, overall survival.

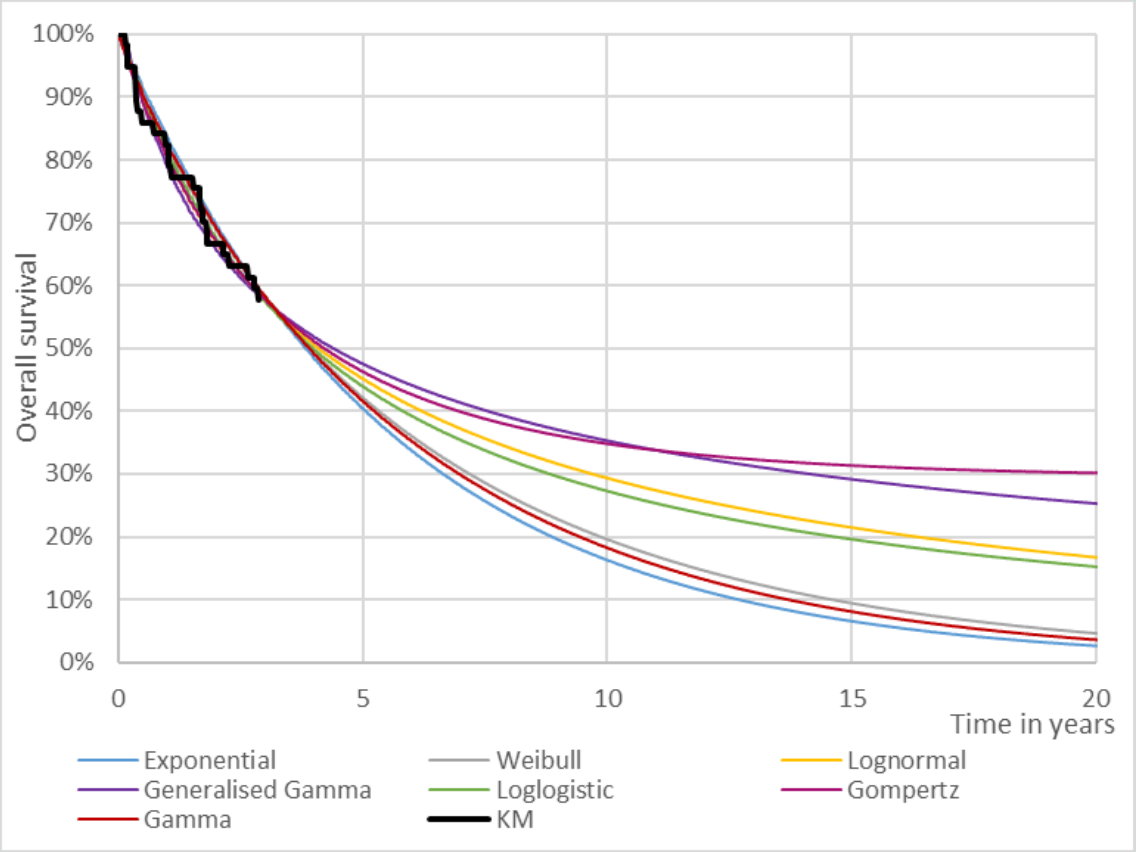
Clinical expert opinion

Long-term extrapolations were presented in a UK advisory board (held in October 2024) to three clinical experts and two health economists (98).

Long-term OS estimates are presented in Figure 18 and Table 55. The generalised gamma and Gompertz distributions provided the most optimistic predictions of median OS, with estimated medians of [redacted] and [redacted] years, respectively. The loglogistic, Weibull and gamma distributions all predicted similar median survival ([redacted], [redacted] and [redacted], respectively). The Weibull, gamma, and exponential

distributions resulted in similar estimates of long-term survival after 10-years at [redacted], [redacted], and [redacted] respectively. The generalised gamma and Gompertz distributions produced the most optimistic long-term survival estimates, predicting [redacted] and [redacted] of patients alive at 10 years, respectively.

Figure 18: Long-term OS projections – enco+bini



Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; OS, overall survival.

Table 55: Long-term OS estimates - enco+bini

	Predicted median OS (years)	Estimated % alive at time (years)				
		1	2	5	10	20
Exponential	3.81	83.4%	69.6%	40.6%	16.3%	2.7%
Weibull	3.93	82.0%	68.8%	42.3%	19.6%	4.6%
Log-normal	4.06	80.4%	66.8%	45.3%	29.4%	16.8%
Generalised gamma	4.37	78.8%	65.7%	47.6%	35.3%	25.3%
Log-logistic	3.97	81.2%	67.4%	44.1%	27.3%	15.3%
Gompertz	4.20	80.2%	67.0%	46.4%	34.8%	30.2%
Gamma	3.89	82.4%	69.1%	41.7%	18.2%	3.6%

Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Clinical experts did not expect many patients to be alive at 20 years, and therefore considered that the Gompertz, generalised gamma, log-logistic and log-normal distributions produced clinically implausible estimates of survival. Clinical experts noted that of the distributions presented, the Weibull, exponential and gamma distributions provided the most clinically plausible estimates of long-term survival for patients treated with enco+bini (16).

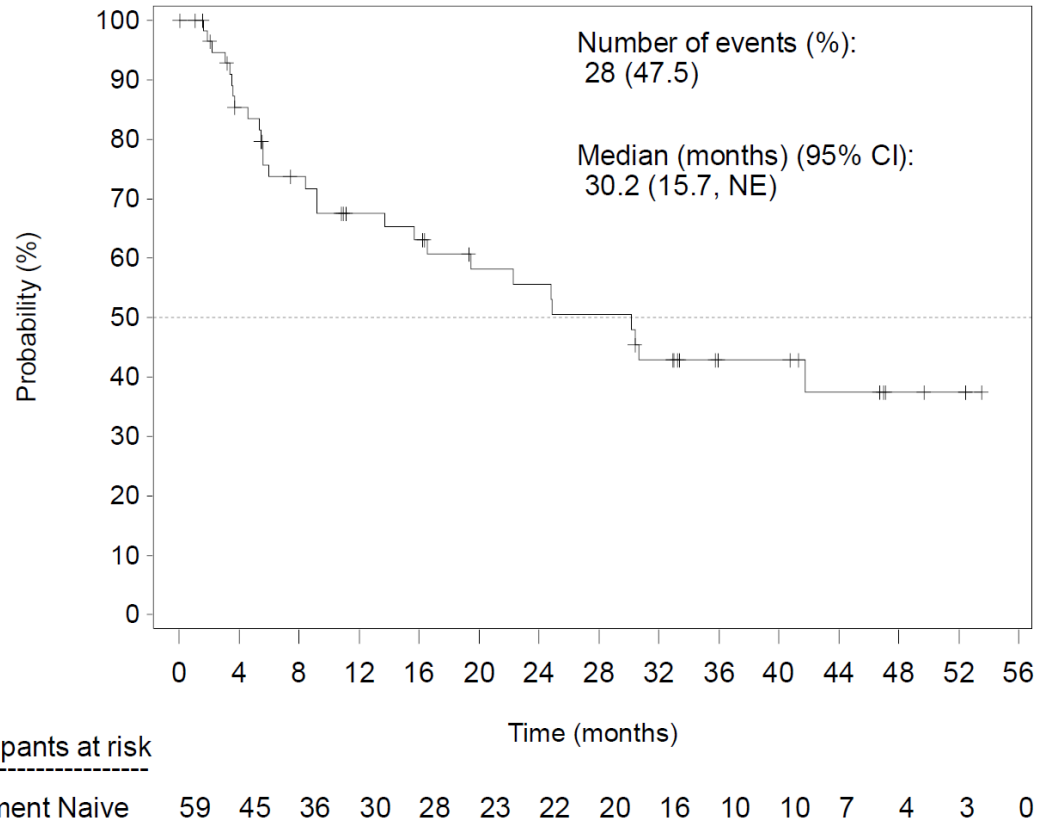
Selected OS distribution

The exponential distribution was selected for the base-case extrapolation because it provided the most clinically plausible long-term estimates of survival, provided predicted landmark survival estimates consistent with the PHAROS trial, and demonstrated a good statistical fit to the trial data. As the Weibull and gamma distributions also produced clinically plausible long term survival estimates, the use of both distributions was considered in scenario analysis.

B.3.3.2.1.2 Progression-free survival

At the 1st April 2024 DCO of PHAROS, after median follow-up of 33.3 months, median PFS (assessed by IRR) was 30.2 months (95% CI, 15.7, NE) in the treatment-naïve population (Figure 19), and 47.5% of patients had experienced a progression event (Figure 19).

Figure 19: Enco+bini PFS - PHAROS (DCO: 1st April 2024)



Abbreviations: CI, confidence interval; DCO: data cut-off; enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; PFS, progression-free survival.

Statistical goodness of fit

Goodness of fit statistics for extrapolations of PFS are presented in Table 56. The generalised gamma distribution provided the best statistical fit based on AIC and BIC respectively. However, all distributions were associated with a good statistical fit to the trial data, with all distributions falling within 8 points of each other on both AIC and BIC statistics.

Table 56: Enco+bini PFS, goodness of fit statistics†

	Goodness of fit statistic	
	AIC	BIC
Exponential	265.25	267.32
Weibull	266.45	270.60
Log-normal	261.67	265.83
Generalised gamma	**259.57**	**265.80**
Log-logistic	264.01	268.17

	Goodness of fit statistic	
	AIC	BIC
Gompertz	264.12	268.27
Gamma	266.85	271.00

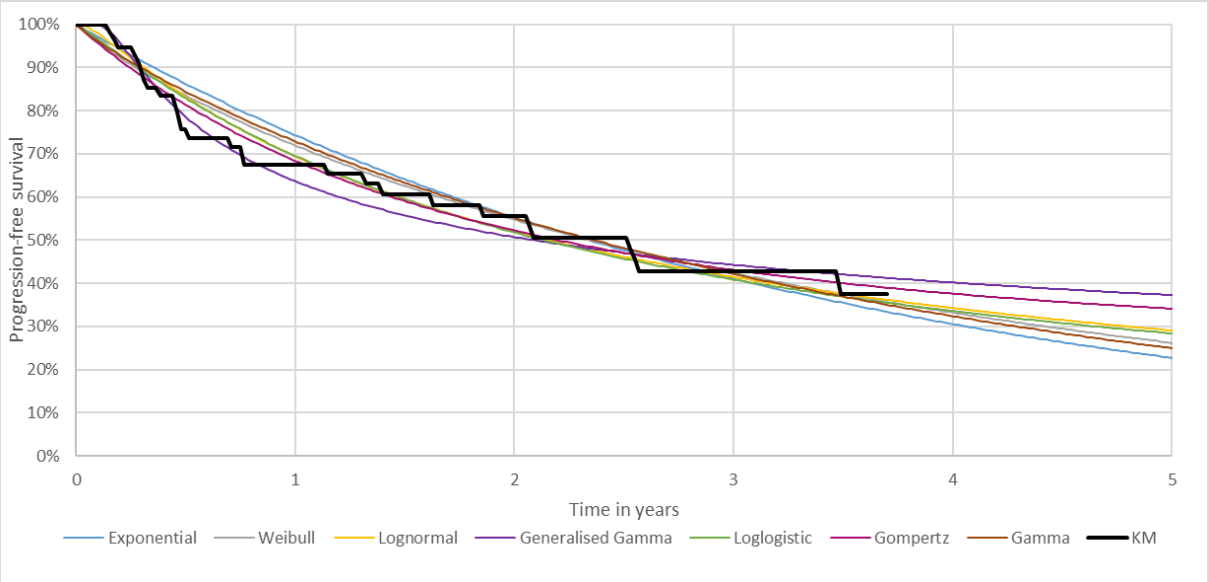
† Lowest AIC and BIC in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

Visual inspection

Projections of PFS from the seven parametric models over the trial period are presented in Figure 20; estimates of PFS are presented in Table 57. All distributions underpredict median PFS estimates compared with the median PFS from PHAROS (30.2 months). All distributions provide estimates of PFS that are relatively aligned with the observed data from Year 1 onwards.

Generally, all distributions provide an overestimation of PFS between zero and 1 year, compared with the observed data. However, distributions are relatively aligned with the observed data from Year 1 onwards. The log-normal and Gompertz distributions are associated with the closest estimation of PFS from 12–42 months of the trial period, predicting the KM data within 4%. The exponential, Weibull and gamma distributions slightly underpredict survival towards the end of the observed period, however there are fewer than [redacted] patients at risk from 42 months.

Figure 20: Short-term PFS projection – enco+bini



Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; PFS, progression-free survival.

Table 57: Enco+bini PFS – parametric distribution and observed data

	Predicted median PFS (months)	Month						
		6	12	18	24	30	36	42
KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

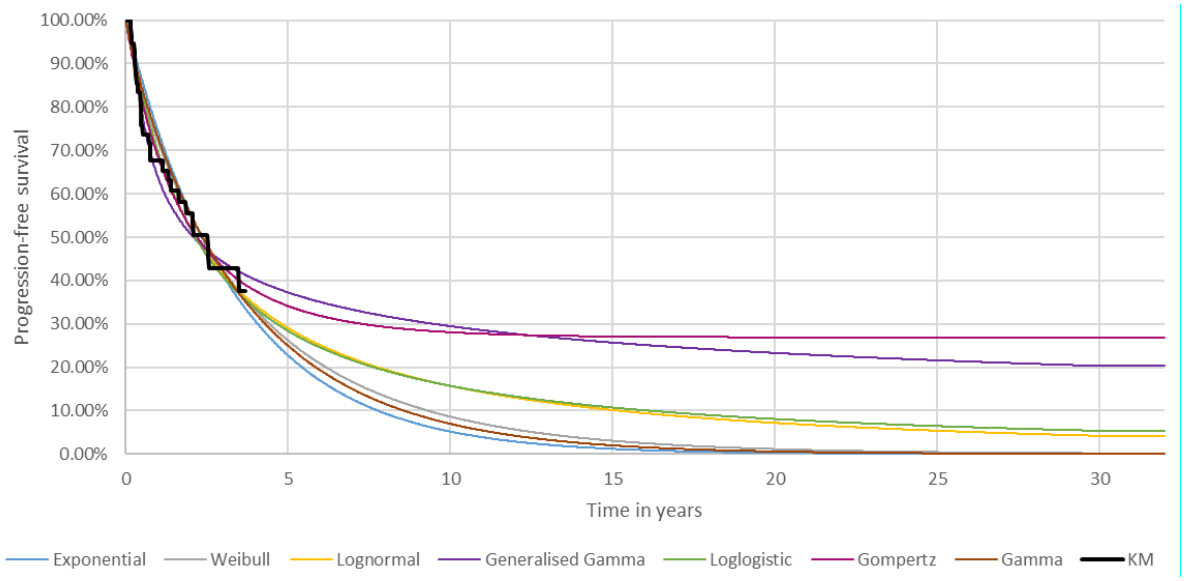
Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

Clinical expert opinion

Long-term extrapolations were presented in a UK advisory board, held in October 2024, and are presented in Figure 21 and Table 58 (16) (98). Clinical experts stated that a proportion of patients would be 'super responders' and therefore some patients would be responders long-term. However, experts predicted that few patients would be progression-free at 5 and 10 years. Therefore, the Gompertz ([redacted] % at 10 years), generalised gamma ([redacted] % at 10 years), log-logistic ([redacted] % at

10 years), and log-normal ([redacted] % at 10 years) distributions were considered clinically implausible and not considered for the base case, all predicting above [redacted] % of patients would be progression-free at 10 years. Clinical experts considered the exponential, Weibull and gamma distributions predicted PFS at 2, 5 and 10 years that were the most clinically plausible, and were therefore considered for the base case.

Figure 21: Long-term PFS projection – enco+bini



Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; PFS, progression-free survival.

Table 58: Long-term PFS estimates - enco+bini

	Predicted median PFS (years)	Estimated % alive and progression-free at time (years)			
		1	2	5	10
Exponential	2.34	74.4%	55.4%	22.8%	5.2%
Weibull	2.34	72.0%	54.8%	26.3%	8.6%
Log-normal	2.15	69.5%	52.1%	29.1%	15.7%
Generalised Gamma	2.07	63.7%	50.8%	37.3%	29.5%
Log-logistic	2.13	69.6%	51.9%	28.5%	15.7%
Gompertz	2.18	68.5%	52.3%	34.2%	28.1%
Gamma	2.36	72.9%	55.3%	25.1%	7.0%

Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

Selected PFS distribution

The exponential distribution was selected for the base-case extrapolation as it provided the most clinically plausible long-term estimates of PFS, provided predicted median and landmark survival estimates that were consistent with PHAROS, and demonstrated a good statistical fit to the trial data. As the Weibull and gamma distributions also produced the most clinically plausible long term survival estimates, the use of both distributions is considered in scenario analysis.

B.3.3.2.2. Survival estimates – dabra+tram

As there are no direct head-to-head trials, a MAIC was conducted comparing the efficacy of enco+bini with dabra+tram. Details regarding the MAIC methods are described in Section B.2.9. Two MAIC analyses were considered for use in the model:

- Adjusting for all available confounding factors identified in the feasibility assessment
    - Age, gender, ECOG, smoking status, race, histology, brain metastases
- Adjusting for only key factors identified by clinical experts (16)
    - ECOG and smoking status

At the June 2024 UK advisory board, clinical experts advised that all of the variables identified in the feasibility assessment as confounding factors were clinically relevant for adult patients with *BRAF* V600E MT NSCLC, and therefore should be included in the analysis (16). These factors are also in line with the MAIC conducted in TA898, which adjusted for age, gender, ECOG, smoking status, histology, presence of liver metastases, presence of M1a metastases and presence of brain metastases (PFS only) (16). Therefore, in the base case, the MAIC adjusting for all available factors between PHAROS and BRF113928 was used. The MAIC HRs after adjustment for only ECOG and smoking status were considered in scenario analysis.

Results from the MAIC adjusting for all factors and for ECOG and smoking status only are presented in Table 59. Enco+bini was associated with an improvement in

both OS and PFS survival compared with dabra+tram with HRs of 0.55 (95% CI: 0.30, 1.01) and 0.47 (95% CI: 0.26, 0.85), respectively when adjusting for all factors. Results when adjusting for ECOG and smoking status only were consistent with the base case analysis with HRs of [redacted] and [redacted] for OS and PFS, respectively.

Table 59: MAIC results, enco+bini vs dabra+tram

	HR (95% CI)	
	Base case - adjusting for all factors	**Scenario – adjusting on ECOG & smoking status**
OS	0.55 (0.30, 1.01)	[redacted]
PFS	0.47 (0.26, 0.85)	[redacted]

Abbreviations: CI, confidence interval; dabra+tram, dabrafenib in combination with trametinib; ECOG, Eastern Cooperative Oncology Group; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival.

The assumption of proportional hazards (PH) was assessed between the PHAROS and BRF113928 data using log-log plots, global test of Schoenfeld residuals, and clinical expert opinion. For OS, the assumption of PH could not be rejected based on the results of the test carried out on the Schoenfeld residuals (p=[redacted]). The plot of the Schoenfeld residuals (Figure 22) shows a relatively flat pattern at 0, suggesting the residuals are independent of time, and the PH assumption may hold. The log-log plots (Figure 23) show curves crossing in the first half of the observation period however, the curves settle in a more parallel pattern in the second half. Furthermore, clinical experts at the June and October 2024 UK advisory boards stated that there would be no clinical reason to expect PH not to hold between enco+bini and dabra+tram (16). Based on this, the assessment of log-log plots, and the non-significance of the p-values associated with the Schoenfeld residuals test, it was considered acceptable to assume PH between enco+bini and dabra+tram for OS and estimate dabra+tram OS by applying the MAIC HRs to the unadjusted PHAROS data.

Figure 22: OS – Schoenfeld residuals, PHAROS vs BRF113928

Abbreviations: OS, overall survival.

Figure 23: OS - Log-log plots, PHAROS vs BRF113928

Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

For PFS, the Schoenfeld residuals (p=[redacted]) suggested the assumption of PH could not be rejected. Schoenfeld residuals (Figure 24) shows a relatively flat pattern at 0, suggesting the residuals are independent of time, and the PH assumption may hold. Furthermore, the log-log plot curves (Figure 25) do not cross and are parallel throughout. Clinical experts also advised that they would expect PH to hold between enco+bini and dabra+tram (16). Based on this, the assessment of log-log plots, and the non-significance of the p-values associated with the Schoenfeld residuals test, it was considered acceptable to assume PH between enco+bini and dabra+tram for PFS and estimate dabra+tram PFS by applying the MAIC HRs to the unadjusted PHAROS data.

Figure 24: PFS – Schoenfeld residuals, PHAROS vs BRF113928

Abbreviations: PFS, progression-free survival.

Figure 25: PFS - Log-log plots, PHAROS vs BRF113928

Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

B.3.3.2.2.1 Overall survival

The MAIC HR (0.55) was applied to the enco+bini OS curve to derive long-term survival estimates for dabra+tram. Long-term projections of OS over a lifetime horizon are presented in Figure 26, and median and long-term survival estimates are presented in Table 60.

Figure 26: Long-term base case OS projection – dabra+tram

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; OS, overall survival.

Table 60: Dabra+tram – median and long-term OS model and trial comparison

	Median OS (years)	1 year	2 years	5 years	10 years
BRF113928†	1.44	74%	49%	22%	-
TA898 – exponential (15)	-	-	-	-	4.5%
Model predicted – base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Median OS reported:17.3 months in the treatment naïve population (Cohort C) (96)

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; OS, overall survival.

The base case slightly over-predicts survival compared with BRF113928 (median: [redacted] years vs 1.44 years). However, as the MAIC attempts to adjust for population imbalances between trials, comparisons between predicted survival and observed survival should be treated with caution. Model estimates are well aligned (within 3%) with published estimates of BRF113928 at 1 year ([redacted] % vs 74%), 2 years ([redacted] % vs 49%), and 5 years ([redacted] % vs 22%) (116). The base case also produces estimates of 10-year survival that are aligned with the exponential distribution presented in TA898 ([redacted] % vs 4.5%). In TA898, the exponential distribution was considered to produce a clinically plausible estimate of long-term survival for patients receiving dabra+tram.

B.3.3.2.2.2 Progression-free survival

The MAIC HR (0.47) was applied to the enco+bini PFS curve to derive long-term estimates for dabra+tram. Base-case projections of PFS over a lifetime time horizon are presented in Figure 27, and median and long-term survival estimates are presented in Table 61. The model base case is relatively well aligned with dabra+tram median survival compared with the observed median survival in BRF113928 (10.8 months), with the base case predicting a median of [redacted] months) (96), however slightly overpredicts PFS compared with published estimates from BRF113928 at 1, 2, and 5 years (116).

Figure 27: Long-term PFS projections – dabra+tram

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; PFS, progression-free survival.

Table 61: Dabra+tram – median and long-term PFS model and trial comparison

	Median PFS (years)	1 year	2 years	5 years	10 years
BRF113928 (96)	0.9	42%	13%	10%	-
Base case estimation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; PFS, progression-free survival.

B.3.3.2.3. Time to discontinuation

B.3.3.2.3.1 Time to discontinuation – enco+bini

No TTD data were collected in the pivotal PHAROS study, however, a post-hoc analysis was conducted. At the 1st April 2024 DCO of PHAROS, median TTD for enco+bini was reached at approximately [redacted] months (CI: [redacted], [redacted]).

Statistical goodness of fit

Goodness of fit statistics for TTD distributions are presented in Table 62. The exponential distribution provided the best statistical goodness of fit to the observed TTD data from PHAROS. However, all distributions provided a good statistical fit to the data and were all within 4 AIC points and 7 BIC points.

Table 62: Enco+bini TTD, goodness of fit statistics†

	Goodness of fit statistic	
	AIC	**BIC**
Exponential	**410.51**	**412.59**
Weibull	410.88	415.04
Log-normal	414.69	418.85
Generalised Gamma	412.87	419.10
Log-logistic	413.24	417.39
Gompertz	411.92	416.08
Gamma	410.94	415.09

† Lowest AIC and BIC in bold.

Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib in combination with binimetinib; TTD, time to discontinuation.

Visual inspection

Estimates of treatment discontinuation over the trial period are presented in Figure 28 and Table 63. Most distributions slightly over-predict time on treatment from 0–6 months but are well aligned with the PHAROS KM data for the reminder of trial period. The Gompertz, Weibull, gamma, and generalised gamma distributions resulted in similar median estimates of TTD as the PHAROS trial ([redacted] months), with medians of [redacted], [redacted], [redacted] and [redacted] months, respectively. The log-normal distribution provided the best visual fit to the observed data and was associated with predictions of TTD that were within 5% of the observed data.

Figure 28: Short-term TTD estimates – enco+bini

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; TTD, time to discontinuation.

Table 63: Enco+bini TTD – parametric distribution and observed data

	Median (months)	Month			
		6	12	18	24
KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; TTD, time to discontinuation.

Clinical expert opinion

Long-term extrapolations were presented in the October 2024 UK advisory board (16). Figure 28 and Table 64 present long-term estimates of TTD. All distributions provide consistent estimates from 0–2 years, all predicting [redacted] % patients remaining on treatment at 2 years. However, from 5 to 10 years, the Gompertz and log-logistic distributions all produce far more optimistic estimates of time on

treatment compared with other distributions, with each distribution predicting TTD of approximately [redacted] % at [redacted] years.

Figure 29: Long-term TTD estimates – enco+bini

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan Meier; TTD, time to discontinuation.

Table 64: Long-term TTD estimates - enco+bini

	Estimated % discontinuation at time (years)			
	1	2	5	10
Exponential	[redacted]	[redacted]	10.0%	1.0%
Weibull	[redacted]	[redacted]	12.4%	2.3%
Log-normal	[redacted]	[redacted]	18.1%	8.9%
Generalised Gamma	[redacted]	[redacted]	12.7%	2.6%
Log-logistic	[redacted]	[redacted]	17.6%	9.0%
Gompertz	[redacted]	[redacted]	12.6%	3.7%
Gamma	[redacted]	[redacted]	11.9%	1.8%

Abbreviations: enco+bini, encorafenib in combination with binimetinib; TTD, time to discontinuation.

Clinical expert opinion elicited at the June 2024 UK advisory board advised that very few patients would remain on treatment at 10 years (16), and therefore the Gompertz, log-normal, and log-logistic distributions were considered clinically implausible and not considered for the base case. The exponential, Weibull, generalised gamma and gamma distributions predicted survival at 2, 5 and 10 years

were more consistent with clinical expert opinion. The exponential distribution aligns best with clinical feedback that few patients would remain on treatment at 10 years.

Selected TTD distribution

The exponential distribution was selected for the base-case extrapolation as it provided clinically plausible long-term estimates of time on treatment, aligned with clinical expert opinion, provided predicted landmark survival estimates that were consistent with the PHAROS trial, and demonstrated a good statistical fit to the trial data. Furthermore, the exponential distribution was selected to align with the base-case PFS distribution, due to the inherent relationship between PFS and TTD. As the Weibull and gamma distributions also produced clinically plausible long term survival estimates, the use of each distribution was considered in scenario analysis.

B.3.3.2.3.2 Time to discontinuation – dabra+tram

For TTD, a MAIC could not be performed due to lack of publicly available TTD data for dabra+tram. Furthermore, only median TTD data is available for the combined cohort from the BRF113928 trial (96).

At the October 2024 UK advisory board, clinical experts advised that some patients would be treated beyond progression if they are still deriving a benefit. This is in line with the BRF113928 trial, in which treatment beyond progression was allowed in patients who had a confirmed response per RECIST v1.1 or SD for 12 weeks or more during study treatment and were considered by the investigator to be clinically benefiting from therapy, and median PFS (10.8 months) was within a week of median TTD (10.6 months) (96). This is also aligned with real word data on dabra+tram use; in a real-world evidence (RWE) study of dabra+tram in patients with *BRAF* V600E-mutant NSCLC in France, median TTD in first-line patients was longer (17.5 months) than median PFS (16.8 months) (116 Auliac, 2020 #223). Taken together, it was considered appropriate to assume treat to progression in the dabra+tram arm. Therefore, TTD for dabra+tram was assumed to be equal to PFS.

To test the uncertainty of this assumption, a scenario is presented that estimate dabra+tram TTD using an exponential curve that passes through median TTD

reported in the combined cohort of the BRF113928 trial (10.55 months) (116). It should be noted that this approach to TTD is likely to be conservative as there is no adjustment for the observed differences between trial populations, as was done with OS and PFS, therefore this may underestimate treatment costs in the dabra+tram arm. Additionally, this data also includes second-line patients, and therefore it is likely that this underestimates the median TTD for a first-line only population.

A further scenario is presented that estimates TTD using an exponential curve to pass through median TTD from the RWE Auliac 2020 study (17.5 months) (117). Predicted median TTD from each modelling option is presented in Table 65.

Table 65: Dabra+tram TTD

Approach	Predicted median TTD (months)
Base case - treat to progression†	[redacted]
Scenario - exponential curve through the median TTD in the BRF113928 trial (116)	10.58
Scenario - exponential curve through the median TTD in the RWE Auliac 2020 study (117)	17.48

†Assuming an exponential distribution.
Abbreviations: dabra+tram, dabrafenib in combination with trametinib; TTD, time to discontinuation.

B.3.3.2.4. Scenario – pooled PHAROS & IFCT

A scenario was conducted in which clinical efficacy estimates for enco+bini were derived from pooling the PHAROS and IFCT trials. The pooled cohort was derived from the treatment naïve cohort of the pivotal PHAROS study and Cohort A of the supportive IFCT study. Baseline characteristics from the pooled PHAROS and IFCT cohort are presented in Table 66. OS and PFS KM curves from the pooled cohort are presented in Figure 30.

Table 66: Patient baseline characteristics, pooled PHAROS and IFCT data

Characteristic	Pooled PHAROS & IFCT
Age (years)	[redacted]
Proportion male (%)	[redacted]
Mean weight (kg)	[redacted]
Mean height (m)	[redacted]
BSA (m^2)†	[redacted]

†Calculated using the Mosteller formula
Abbreviations: BSA, body surface area.

Figure 30: OS & PFS KMs – enco+bini, pooled PHAROS & IFCT

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

A comparison of KMs from PHAROS and pooling PHAROS and IFCT are presented in Figure 31. The pooled scenario was conducted to maximise the use of available data in the relatively small population with *BRAF* V600E MT NSCLC. At time of DCO (1st April 2024), median duration of follow-up was increased with PHAROS for OS (months, CI: ,), and PFS by IRR (33.3 months, CI: 30.4, 41.3) compared with IFCT (OS (months, CI: ,). In PHAROS, 26 (44.1%) patients had died and (%) patients were censored for OS analysis. In IFCT, only (%) patients had died, and (%) were censored for OS analysis. Therefore, the IFCT data was considered to be associated with more uncertainty than PHAROS, and it is maintained that PHAROS is the most appropriate source of data to inform clinical efficacy estimates due to the limitations associated with the IFCT study (Section B.3.3.).

Figure 31: Comparison of enco+bini KMs – PHAROS vs pooled PHAROS & IFCT

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

B.3.3.2.4.1 Overall survival & progression-free survival

OS and PFS distributions were selected based on statistical goodness of fit, visual inspection of curves vs the observed data, clinical plausibility of long-term projections, and consistency with the base case. All distributions provided a good statistical fit to the data. As with the base-case extrapolations (Sections B.3.3.2.1.1 and B.3.3.2.1.2 for OS and PFS, respectively), the exponential distribution provides the most conservative estimates of OS (Figure 33) and PFS (Figure 34) for enco+bini using the pooled PHAROS and IFCT data. Therefore, the exponential distribution was selected as the OS and PFS distribution, respectively, in the pooled scenario, and are presented in Figure 34.

Figure 32: Pooled PHAROS & IFCT, OS curves

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 33: Pooled PHAROS & IFCT, PFS curves

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 34: Pooled PHAROS & IFCT, OS and PFS extrapolations

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

A MAIC was conducted comparing the efficacy of enco+bini, derived from pooled data from the pivotal PHAROS trial and the supportive IFCT study, and dabra+tram, derived from the BRF113928 trial. Details regarding the MAIC methods are described in Section B.2.9. In line with the base case (Section B.3.3.2), the MAIC adjusting for all available factors between pooled PHAROS and IFCT, and BRF113928. Results from the MAIC are presented in Table 67. Enco+bini is associated with improvement in OS and PFS compared with dabra+tram with HRs of [redacted] and [redacted], respectively. The associated dabra+tram curves for OS and PFS are presented in Figure 35.

Table 67: MAIC results, enco+bini vs dabra+tram

	HR (95% CI) – base case adjusting for all factors
OS	[redacted]
PFS	[redacted]

Abbreviations: CI, confidence interval; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival.

In the scenario the MAIC HRs were applied to the enco+bini OS and PFS curves to derive long-term estimates for dabra+tram. Survival projections for dabra+tram over the time horizon are presented in Figure 35 for OS and PFS.

Figure 35: Long-term OS and PFS projections – dabra+tram, HR vs pooled PHAROS & IFCT data

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

B.3.3.2.4.2 Time to discontinuation

TTD estimates in the pooled scenario were derived from pooled PHAROS and IFCT data for enco+bini, and treat to progression was assumed for dabra+tram as per the base-case analysis (Section B.3.3.2.3.2) (96).

Figure 36: TTD enco+bini – pooled PHAROS & IFCT

Abbreviations: enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; TTD, time to discontinuation.

The Weibull and exponential distributions were associated with the best statistical fit by AIC and BIC statistics, respectively. The exponential distribution was considered in the scenario analysis as it is associated with the best statistical fit by BIC, provided TTD estimates most consistent with clinical expert opinion, and was aligned with the selected PFS distribution (Section B.3.3.2.4.1).

B.3.3.3. General population mortality

In line with NICE DSU TSD 23, age- and sex-matched general population mortality values were derived from 2017-19 lifetables for the UK, as reported by the Office for National Statistics (ONS) (111, 118). Mortality rates, as predicted by the OS extrapolations, were bound such that they did not fall below that for the age- and sex-matched general population.

B.3.3.4. Adverse events

AE data were taken from the treatment-naïve populations in PHAROS for enco+bini and data for dabra+tram were taken from the full population of BRF113928, as reported in TA898 (96 National Institute for Health and Care Excellence, 2023 #65). AE data in the treatment naïve cohort of BRF113928 were not available, however as

stated in TA898 it is not expected that the AE profile for dabra+tram would differ depending on whether patients had previously untreated or previously treated disease. Grade ≥3 TEAEs with an incidence of ≥3% in either arm were considered; this approach was considered appropriate by clinical experts in the October 2024 UK advisory board who stated that the analysis captured the events of concern when treating patients with advanced NSCLC with a *BRAF* V600E mutation (15 Pierre Fabre., 2024 #221). All-causality AEs were considered to align with the available data on dabra+tram, as presented in TA898, however this may overstate the toxicity of treatment as these events aren't necessarily treatment related. However, as treatment-related TEAE were not available for dabra+tram, all-casualty events were selected for the base case.

At the October 2024 UK advisory board, a clinical expert with experience using enco+bini and dabra+tram stated that in their experience, dabra+tram is a more toxic treatment, and patients are able to tolerate enco+bini better (16). In particular, the clinical expert highlighted pyrexia as an event of concern when treating patients with dabra+tram. Clinical experts stated that even Grade 1–2 pyrexia greatly impacts patient's QoL. One clinical expert with experience of using both treatments stated that pyrexia associated with dabra+tram can lead to hospital admissions, which are costly and problematic given current pressures on the NHS. Greater than half of patients (56%) experienced pyrexia of any grade in BRF113928 (116), and as described by Thawer et al, pyrexia significantly effects patients QoL, has the potential to worsen and can result in hypotension (secondary to dehydration), and associated organ-related complications (119).

As described in Section B.2.9, a MAIC was conducted comparing safety outcomes (patients experiencing AEs of a maximum grade of 3–4) between enco+bini and dabra+tram. A scenario was conducted that estimates AE rates in the dabra+tram arm by applying the OR of 0.93, estimated from the safety MAIC.

The disutility and costs associated with the AEs included within the model are detailed in Section B.3.4.4 and Section B.3.5.5, respectively.

Table 68: Proportion of patients with Grade ≥3 AEs in ≥3% of patients

	% of patients experiencing AE			
	Enco+bini		Dabra+tram	
	Base case: PHAROS	Scenario: Pooled PHAROS and IFCT data	Base case: BRF113928, in line with TA898 (15)	Scenario: safety OR (enco+bini vs dabra+tram): [redacted], applied to PHAROS data
Alanine aminotransferase increased	[redacted]	[redacted]	6.45%	[redacted]
Amylase increased	[redacted]	[redacted]	0.00%	[redacted]
Anaemia	[redacted]	[redacted]	5.37%	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	3.23%	[redacted]
Asthenia	[redacted]	[redacted]	4.30%	[redacted]
Back pain	[redacted]	[redacted]	3.23%	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	1.08%	[redacted]
Blood creatinine phosphokinase increased	[redacted]	[redacted]	0.00%	[redacted]
Bronchitis	[redacted]	[redacted]	0.00%	[redacted]
Colitis	[redacted]	[redacted]	0.00%	[redacted]
Decreased appetite	[redacted]	[redacted]	0.00%	[redacted]
Diarrhoea	[redacted]	[redacted]	2.15%	[redacted]
Dyspnoea	[redacted]	[redacted]	7.53%	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	0.00%	[redacted]
Fatigue	[redacted]	[redacted]	3.23%	[redacted]
Gamma-gluamyltransferase increased	[redacted]	[redacted]	0.00%	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	0.00%	[redacted]

	% of patients experiencing AE			
	Enco+bini		Dabra+tram	
	Base case: PHAROS	Scenario: Pooled PHAROS and IFCT data	Base case: BRF113928, in line with TA898 (15)	Scenario: safety OR (enco+bini vs dabra+tram): [redacted], applied to PHAROS data
Herpes zoster	[redacted]	[redacted]	0.00%	[redacted]
Hypertension	[redacted]	[redacted]	9.68%	[redacted]
Hyponatraemia	[redacted]	[redacted]	9.68%	[redacted]
Hypotension	[redacted]	[redacted]	4.30%	[redacted]
Leukocytosis	[redacted]	[redacted]	0.00%	[redacted]
Lipase increased	[redacted]	[redacted]	0.00%	[redacted]
Loss of conciousness	[redacted]	[redacted]	0.00%	[redacted]
Myalgia	[redacted]	[redacted]	0.00%	[redacted]
Nausea	[redacted]	[redacted]	0.00%	[redacted]
Neutropenia	[redacted]	[redacted]	7.53%	[redacted]
Pain in extremity	[redacted]	[redacted]	1.08%	[redacted]
Pneumonia	[redacted]	[redacted]	1.08%	[redacted]
Pulmonary embolism	[redacted]	[redacted]	0.00%	[redacted]
Pyrexia	[redacted]	[redacted]	6.45%	[redacted]
Retinal detachment	[redacted]	[redacted]	0.00%	[redacted]
Vomiting	[redacted]	[redacted]	3.23%	[redacted]
Weight increased	[redacted]	[redacted]	3.23%	[redacted]

Abbreviations: AEs, adverse events; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; OR, odds ratio.

B.3.4. Measurement and valuation of health effects

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

Health-related quality of life (HRQoL) was measured in the IFCT study only. Although HRQoL data were not collected in the PHAROS trial, IFCT is a Phase 2 study assessing enco+bini in the population of interest (N=64). However, IFCT was an investigator-initiated trial that was only conducted in France. Patient reported data were collected using the EQ-5D-5L questionnaires administered at:

- The pre-treatment evaluation visit, then
- Every 8 weeks ± 7 days for 12 months, then
- Every 12 weeks ± 7 days until disease progression
- At the end of treatment visit.

Table 69 shows the completion rate of the EQ-5D-5L questionnaire at each visit. Generally, the compliance rate was high, and 62 patients reported at least one EQ-5D complete measurement (354 observations). The number of visits per patient ranged from 1 to 17. No data were reported for EQ-5D in the post-progression health state at baseline. Post-baseline, 45 patients reported EQ-5D utility values at post-progression (50 observations).

Table 69: EQ-5D questionnaire completion rate

	Visit 1, n (%)	Visit 2	Visit 3	Visit 4
Completion rate	[redacted]	[redacted]	[redacted]	[redacted]

B.3.4.2. Mapping

EQ-5D-5L data collected in IFCT were mapped to EQ-5D-3L using the function developed by Hernández Alava, in line with NICE guidance (120, 121).

The estimated mean EQ-5D-5L score at baseline was [redacted] (standard error [SE]: [redacted]) for patients receiving enco+bini. When considering the complete follow-up period the estimated mean EQ-5D-5L score was [redacted] (SE: [redacted]) and [redacted] (SE: [redacted]) pre- and post-progression, respectively. The estimated mean EQ-5D-3L mean utility at baseline was [redacted] (SE: [redacted]). When considering the complete follow-up period,

the estimated mean EQ-5D-3L was [redacted] (SE: [redacted]) and [redacted] (SE: [redacted]) pre- and post-progression, respectively.

B.3.4.3. Health-related quality of life studies

As detailed in Appendix H, no studies were identified in the economic SLRs that reported utility value estimates for patients with NSCLC with a *BRAF* mutation. As such, utility values for the economic model were derived from TA898 and IFCT.

B.3.4.4. Adverse reactions

As described in Section B.3.3.4 the base case considered Grade ≥3 AEs with an incidence of ≥3% and were derived from the treatment-naïve population in PHAROS for enco+bini and the full population in BRF113928 for dabra+tram. To accurately account for the impact of these events on patient HRQoL, the disutility and duration of each event were applied to the frequencies reported in Section B.3.3.4.

Disutilities and durations associated with AEs are presented in Table 70. TA898 sourced data from the most recent appraisals in targeted therapies for NSCLC (tepotinib for treating advanced NSCLC with MET gene alterations [TA789] and pralsetinib for treating RET fusion-positive advanced NSCLC [TA812]) and the published literature where necessary (15, 106, 110, 122). Weight increased was assumed to have a disutility and duration of zero. As no more appropriate data were identified in the HRQoL SLR (Appendix H), disutilities were aligned with TA898 as this is the most recent appraisal in advanced NSCLC with a *BRAF* V600E mutation. Where AEs were not included in TA898, disutilities and durations were sourced from the literature, or assumed equivalent to a similar AE.

During the June and October 2024 UK advisory boards, clinical experts noted that pyrexia, diarrhoea, colitis and GI bleeding were the key TEAEs of concern when treating patients with advanced NSCLC with a BRAF V600E mutation (16). Clinical experts highlighted diarrhoea as a major reason for discontinuation of dabra+tram and colitis and GI bleeding the main reason for discontinuation of enco+bini. Clinical experts also highlighted anaemia is a major reason for treatment interruptions for both treatments, and that lower grade AEs still matter for patients, specifically for pyrexia, as this can be very burdensome for patients. However, conservatively, and

to align with TA898, only disutilities for Grade ≥3 AEs were considered in the analysis. Clinical experts highlighted that many of the TEAEs in the enco+bini arm were ‘clinically inconsequential’ and would have minimal impact on QoL and treatment costs. Clinical experts highlighted increased alanine aminotransferase, increased amylase, increased blood alkaline phosphatase, increased blood creatinine phosphokinase, raised lipase, and herpes zoster, stating they are not routinely measured in UK practice; therefore, these events were set to zero disutility and duration in the base case.

Table 70: Grade 3/4 AEs - disutilities and durations

	Disutility		Duration (days)	
	Value	Source	Value	Source
Alanine aminotransferase increased	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Amylase increased	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Anaemia	0.07	Derived from TA789 (Table 49), assumed same as fatigue as per TA181 (106)	3.0	NICE TA789, VISION trial (106)
Aspartate aminotransferase increased	0.05	Derived from NICE TA760 (Table 58), NICE TA621 (109)	54.8	TA898 (15)
Asthenia	0.07	Assumed same as fatigue	52.0	NICE TA789, VISION trial (106)
Back pain	0.07	Assumed same as abdominal pain	31.0	Assumed same as abdominal pain
Blood alkaline phosphatase increased	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Blood creatinine phosphokinase increased	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Bronchitis	0.00	Assumption	0.00	Assumption
Colitis	0.11	TA898 Assumed same as diarrhoea (15)	3.0	Assumed same as diarrhoea
Decreased appetite	0.09	Derived from NICE TA760 (Table 58), KEYNOTE-010/TA428	10.5	Assumed same as nausea

	Disutility		Duration (days)	
	Value	Source	Value	Source
Diarrhoea	0.05	Derived from NICE TA789 (Table 49), Nafees et al. (122) (106)	3.0	NICE TA789, VISION trial (106)
Dyspnoea	0.05	TA898 (15)	18.8	TA898 (15)
Ejection fraction decreased	0.03	Assumed equal to hypertension	150.0	Assumed equal to hypertension
Fatigue	0.07	Derived from NICE TA789 (Table 49), Nafees et al. (2008) (106) (122)	212.0	NICE TA789, VISION trial (106)
Gamma-gluamyltransferase increased	0.05	Assumed same as aspartate aminotransferase increased	54.8	Assumed same as aspartate aminotransferase increased
Gastrointestinal haemorrhage	0.07	Assumed equal to abdominal pain	31.0	Assumed equal to abdominal pain
Herpes zoster	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Hypertension	0.03	Derived from NICE TA789 (Table 49), Paracha et al., Nafees et al. (106) (122)	150.0	NICE TA789, VISION trial (106)
Hyponatraemia	0.09	Derived from NICE TA760 (Table 58), KEYNOTE-010/TA428 (109)	7.0	NICE TA789, VISION trial (106) (assumed same as hypomagnesemia)
Hypotension	0.03	TA898; Assumed equal to hypertension (15)	150.0	TA898; Assumed equal to hypertension (15)
Leukocytosis	0.05	Assumed same as aspartate aminotransferase increased	54.8	Assumed same as aspartate aminotransferase increased
Lipase increased	0.00	Assumption - clinical expert opinion (16)	0.00	Assumption - clinical expert opinion (16)
Loss of consciousness	0.00	Assumption	0.00	Assumption
Myalgia	0.07	Assumed same as abdominal pain	31.0	Assumed same as abdominal pain
Nausea	0.05	Derived from NICE TA789 (Table 49), Nafees et al (106) (122)	10.5	NICE TA789, VISION trial (106)
Neutropenia	0.09	Derived from NICE TA789 (Table 49), Nafees et al (106) (122)	158.0	NICE TA789, VISION trial (106) (assumed same as hypomagnesemia)

	Disutility		Duration (days)	
	Value	Source	Value	Source
Pain in extremity	0.07	TA898 Assumed same as abdominal pain (15)	31.0	TA898 Assumed same as abdominal pain (15)
Pneumonia	0.01	Derived from combined disutility for "pneumonitis/pneumonia" from TA789 (Table 49), Source: Marti et al. (2013) as per NICE TA655 and NICE TA520 (106)	19.6	NICE TA789, VISION trial (106)
Pulmonary embolism	0.09	TA911, assumed equal to Chronic obstructive pulmonary disease KEYNOTE-010/TA42); (123)	15.0	TA911, assumed equal to Chronic obstructive pulmonary disease (123)
Pyrexia	0.11	Wehler et al. (2018) (124)	7.6	BRF113928 duration of pyrexia (15)
Retinal detachment	0.00	Assumption	0.00	Assumption
Vomiting	0.05	Derived from NICE TA789 (Table 49), Nafees et al (106) (122)	2.0	NICE TA789, VISION trial (106)
Weight increased	0.00	TA898. Assumption (15)	0.00	TA898. Assumption (15)

Abbreviations: AEs, adverse events; NICE, National Institute for Health and Care Excellence.

To consider the impact of AEs on QoL, a one-off QALY decrement was calculated by adjusting the disutility by the event duration, applied at the beginning of the model. This approach is also aligned with the committee accepted approach in TA898 (15). The average AE utility decrement applied for each treatment is reported in Table 71.

Table 71: Total AE QALY decrement per treatment applied in the model

Treatment	Total AE QALY decrement
Enco+bini	0.005
Dabra+tram	0.008

Abbreviations: AE, adverse event; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimentinib; QALY, quality-adjusted life year.

B.3.4.5. Health-related quality of life data used in the cost-effectiveness model

To align with the dabra+tram submission, the base case uses utility values aligned with the committee preferred assumptions in TA898 (15). The committee preferred utility values were derived from Chouaid et al. (2013), a cross-sectional, multi-site study that prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK using EQ-5D and EQ-visual analogue scale (VAS) (113).

A scenario is presented that uses values estimated from the supportive IFCT study. Mixed model with repeated measures (MMRM) were carried out to estimate health state utility values for patients receiving enco+bini in the IFCT trial. An MMRM analysis accounts for the correlations between repeated measures within each patient. Random effects were applied to the questionnaire within-subject errors, to account for the correlations between EQ-5D questionnaires for the same patients at the different visit. A random intercept model was fitted, assuming independent within-subject errors. A univariate model was fitted assuming utility is equal to progression status. Degree of freedom was estimated with the Kenward-Roger approximation (125). The variance covariance matrix for the fixed-effects parameters was explored using classic maximum of likelihood method and Huber-White sandwich robust estimator (125, 126).

Results from MMRM using random effects are presented in Table 72. Higher mean utilities were observed pre-progression compared to post-progression. The

difference between the least squares means for pre- and post-progression health status was statistically significant, with a p-value of 0.0089.

Table 72: IFCT MMRM utility analysis

Progression status	Mean estimate	SE	95% CI
Pre-Progression	[redacted]	[redacted]	[redacted]
Post-Progression	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures; SE, standard error.

A summary of health state utility values from previous NICE appraisals in NSCLC is presented in Table 73.

Table 73: NSCLC NICE appraisals – health state utility values

TA	Intervention	Population	Utility value	
			Progression-free	Progressed disease
-	Enco+bini	Untreated advanced NSCLC and a *BRAF* mutation	[redacted]	[redacted]
TA898 (15)	Dabra+tram	Untreated advanced NSCLC and a *BRAF* mutation	0.71	0.67
TA812 (110)	Pralsetinib	*RET* fusion-positive advanced NSCLC	0.794	0.678
TA789 (106)	Tepotinib	Advanced NSCLC with *MET* gene alterations	0.719	0.638
TA781 (107)	Sotorasib	Previously treated *KRAS* G12C mutation-positive advanced NSCLC	0.739	0.655
TA654 (127)	Osimertinib	Untreated *EGFR* mutation-positive NSCLC	0.794	0.678
TA643 (128)	Enrecetinib	*ROS1*-positive advanced NSCLC	0.780	0.660
TA310 (129)	Afatinib	*EGFR* mutation positive advanced NSCLC	0.784	0.725

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer.

The value estimated from IFCT are closely aligned with previous NSCLC submissions, including the committee preferred assumptions in TA898. Progression-free utility values ranged from 0.71 to 0.794 in previous appraisals, and progressed

disease values ranged from 0.638 to 0.725. The values estimated from IFCT [redacted] and [redacted] for progression-free and progressed disease, respectively) sit close to the midpoint of these ranges (0.75 and 0.68, respectively). Although the utility value estimates from IFCT data are marginally higher than the committee preferred assumptions in TA898 for the progression-free state ([redacted] vs 0.71, respectively), the utility values for the progressed disease state are closely aligned. At the October 2024 UK advisory board, clinical experts considered the utility values to be aligned with previous appraisals in NSCLC, and appropriate for patients with advanced NSCLC with a *BRAF* V600E mutation. A further scenario is presented that applied the progressed disease decrement from TA898 (0.04) to the IFCT MMRM derived progression-free value. A summary of base-case and scenario utility values are presented in Table 74.

Table 74: Health state utility values

	Utility value	
	Progression-free	**Progressed disease**
Base case: Chouaid 2013 (TA898)	0.71	0.67
Scenario: IFCT MMRM analysis	[redacted]	[redacted]
Scenario: IFCT + Chouaid 2013 (TA898) progressed decrement	[redacted]	[redacted]

Abbreviations: MMRM, mixed model for repeated measures.

A summary of all modelled utility values is presented in Table 75.

Table 75: Summary of utility values for cost-effectiveness analysis

State	**Utility value: mean (standard error)†**	**95% confidence interval‡**		**Reference in submission (section and page number)**	**Justification**
		Lower value	**Upper value**		
Health state utility value: progression-free	0.71 (NR)	0.57	0.85	Section B.3.4.5, Page 164	Committee preferred assumptions in TA898 (15), utility values were based on progression status and assumed to be independent of treatment.
Health state utility value: progressed disease	0.67 (NR)	0.54	0.80		
Alanine aminotransferase increased	0.00 (0.00)	0.00	0.00	Section B.3.4.4, Page 159	Estimates were derived from previous submissions to NICE where possible, and from literature.
Amylase increased	0.00 (0.00)	0.00	0.00		

State	Utility value: mean (standard error)†	95% confidence interval‡		Reference in submission (section and page number)	Justification
		Lower value	Upper value		
Anaemia	0.07 (0.01)	0.06	0.09		
Aspartate aminotransferase increased	0.05 (0.01)	0.04	0.06		
Asthenia	0.07 (0.01)	0.06	0.09		
Back pain	0.07 (0.01)	0.06	0.08		
Blood alkaline phosphatase increased	0.00 (0.00)	0.00	0.00		
Blood creatinine phosphokinase increased	0.00 (0.00)	0.00	0.00		
Bronchitis	0.00 (0.00)	0.00	0.00		
Colitis	0.11 (0.01)	0.09	0.13		
Decreased appetite	0.09 (0.01)	0.07	0.10		
Diarrhoea	0.05 (0.00)	0.04	0.06		
Dyspnoea	0.05 (0.01)	0.04	0.06		
Ejection fraction decreased	0.03 (0.00)	0.02	0.04		
Fatigue	0.07 (0.01)	0.06	0.09		
Gamma-glutamyl transferase increased	0.05 (0.01)	0.04	0.06		
Gastrointestinal haemorrhage	0.07 (0.01)	0.06	0.08		
Herpes zoster	0.00 (0.00)	0.00	0.00		
Hypertension	0.03 (0.00)	0.02	0.04		
Hyponatraemia	0.09 (0.01)	0.07	0.10		
Hypotension	0.03 (0.00)	0.02	0.04		
Leukocytosis	0.05 (0.00)	0.05	0.05		

State	Utility value: mean (standard error)†	95% confidence interval‡		Reference in submission (section and page number)	Justification
		Lower value	Upper value		
Lipase increased	0.00 (0.00)	0.00	0.00		
Loss of consciousness	0.00 (0.00)	0.00	0.00		
Myalgia	0.07 (0.01)	0.06	0.08		
Nausea	0.05 (0.00)	0.04	0.06		
Neutropenia	0.09 (0.01)	0.07	0.11		
Pain in extremity	0.07 (0.01)	0.06	0.08		
Pneumonia	0.01 (0.00)	0.01	0.01		
Pulmonary embolism	0.09 (0.01)	0.07	0.10		
Pyrexia	0.11 (0.01)	0.09	0.13		
Retinal detachment	0.00 (0.00)	0.00	0.00		
Vomiting	0.05 (0.00)	0.04	0.06		
Weight increased	0.00 (0.00)	0.00	0.00		

†Standard errors were calculated in the absence of data; ‡In the absence of 95% CIs, an arbitrary ±20% range was assumed.
Abbreviations: NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; TA, technology appraisal.

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

B.3.5.1. Intervention and comparators' costs and resource use

All primary therapies in the model were costed as per the doses outlined in Section B.3.2.3. All acquisition costs were sourced from the electronic marketing information tool (eMIT) the British National Formulary (BNF) (130 National Institute for Health and Care Excellence, 2024 #128). The dosing schedules associated with all therapies are consistent with the SmPC recommended dosing, as detailed in Section B.3.2.3. The costs per pack and dosing schedules of all primary treatments are presented in Table 76. In the base case, a simple discount patient access scheme

(PAS) of [redacted] and [redacted] was applied to the list price of encorafenib and binimetinib, respectively.

Table 76: Acquisition costs

Drug	Dose	mg/tablet	Pack price	Pack size (number of tablets)
Encorafenib (list price)	450mg once daily	75	£1,400.00	42
Encorafenib (PAS price)			[redacted]	
Binimetinib (list price)	45mg twice daily	15	£2,240.00	84
Binimetinib (PAS price)			[redacted]	
Dabrafenib	150mg twice daily	75	£1,400.00	28
Trametinib	2mg once daily	2	£4,800.00	30
			£1,120.00	7

Abbreviations: PAS, patient access scheme.

Treatment costs were calculated based on the TTD curves, as described in Section B.3.3.2.3.1 and Section B.3.3.2.3.2.

In PHAROS and BRF113928, not all patients received the full dose of enco+bini or dabra+tram respectively. Therefore, acquisition costs were adjusted based on relative dose intensity (RDI) for all treatments. For enco+bini, RDI was sourced from PHAROS to align with the efficacy data informing the analysis (Section B.3.3). For dabra+tram, RDI was sourced the BRF113928 trial, as reported in TA898 (15). The RDI of each primary therapy as applied in the model is presented in Table 77.

Table 77: RDI

Drug	RDI (%)	Source
Encorafenib	[redacted]	PHAROS (83)
Binimetinib	[redacted]	
Dabrafenib	83%	NICE TA898 (15)
Trametinib	90%	

Abbreviations: NICE, National Institute for Health and Care Excellence; RDI, relative dose intensity.

A scenario is presented that uses RDI as per pooled PHAROS and IFCT data for encorafenib ([redacted]%) and binimetinib ([redacted]%).

B.3.5.2. Administration costs

Enco+bini and dabra+tram are administered orally, therefore no cost of administration was applied. This assumption is aligned with the committee accepted assumptions in the dabra+tram appraisal (TA898), and other recent oncology NICE appraisals (15, 102-110).

B.3.5.3. Subsequent therapy costs

Subsequent therapy costs were included in the analysis to align with the clinical pathway of care in *BRAF* V600E MT NSCLC as described in Section B.1.3.5. Subsequent therapy proportions in the enco+bini arm were derived from PHAROS data. Subsequent therapies received by ≥1% of patients in the treatment naïve cohort of PHAROS were included in the analysis (Table 78).

Table 78: Subsequent therapy data - PHAROS

Drug	Value
Proportion receiving any subsequent therapy	[redacted]
Encorafenib + binimetinib	[redacted]
Dabrafenib + trametinib	[redacted]
Pembrolizumab	[redacted]
Nivolumab	[redacted]
Nivolumab + ipilimumab	[redacted]
Pembrolizumab + cisplatin + pemetrexed	[redacted]
Nivolumab + ipilimumab +	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]
Chemotherapy only	[redacted]

Clinical experts at the June and October 2024 UK advisory boards advised that patients who receive enco+bini in first-line would not be eligible to receive enco+bini at second line in UK clinical practice, therefore PHAROS data were re-weighted to exclude re-treatment with enco+bini (83). In the June 2024 UK advisory board, all clinical experts agreed that there is a high rate of attrition from first-line to second-line treatment, making the [redacted]% attrition rate a reasonable assumption. They also noted there would be no reason to expect a different proportion of patients receiving subsequent therapy between patients treated with enco+bini and those treated with dabra+tram. Clinical experts also advised there would be no significant difference in the types of therapies received by patients in both treatment groups at first-line. As a

result, the subsequent therapy proportions for the dabra+tram arm were assumed to be the same as for the enco+bini arm, with reweighting performed to exclude any subsequent use of dabra+tram. Base-case subsequent therapy distributions are presented in Table 79.

Table 79: Subsequent therapies - base case

Drug	Enco+bini	Dabra+tram
Proportion receiving any subsequent therapy	[redacted]	[redacted]
Encorafenib + binimetinib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Pembrolizumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]	[redacted]
Chemotherapy only	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

A scenario analysis is presented that uses data from the BRF113928 trial as reported in TA898 for the dabra+tram arm. In TA898, it was reported that 55% of patients received chemotherapy and 45% received immunotherapy in the BRF113928 trial (15). However, the proportion of patients receiving any subsequent therapy, and the individual therapies received at second-line post dabra+tram in the BRF113928 trial, were redacted. Therefore, 45% was equally distributed among the immunotherapy regimens received in PHAROS (pembrolizumab, nivolumab, nivolumab+ipilimumab, pembrolizumab+cisplatin, nivolumab+ipilimumab+cisplatin). It should be noted that nivolumab+ipilimumab+cisplatin was assumed representative of nivolumab+ipilimumab+platinum therapy.

Clinical experts at the June 2024 UK advisory board advised that chemotherapy with immunotherapy is the most common option at second-line and monotherapy chemotherapies may also be used (16). Clinical experts also advised that nivolumab + ipilimumab and nivolumab + chemotherapy would not be used after enco+bini or dabra+tram as nivolumab is not recommended for use at second-line after dabra+tram (16), therefore a further scenario is considered assuming 50% chemotherapy monotherapy and 50% pembrolizumab + cisplatin in both arms.

Although PHAROS included some therapies that are not recommended by NICE at second line for adult patients with *BRAF* V600E MT NSCLC, clinical experts did not consider any of the therapies used to have a significant impact on survival, therefore no cross-over adjustment analyses were considered.

Table 80: Subsequent therapies, scenario analysis

Drug	Enco+bini	Dabra+tram	
	Scenario 1: clinical expert opinion	Scenario 1 – clinical expert opinion	Scenario 2: TA898
Proportion receiving any subsequent therapy	[redacted]	[redacted]	[redacted]
Encorafenib + binimetinib	0.0%	0.0%	0.0%
Dabrafenib + trametinib	0.0%	0.0%	0.0%
Pembrolizumab	0.0%	0.0%	9.0%
Nivolumab	0.0%	0.0%	9.0%
Nivolumab + ipilimumab	0.0%	0.0%	9.0%
Pembrolizumab + cisplatin	50.0%	50.0%	9.0%
Nivolumab + ipilimumab + cisplatin	0.0%	0.0%	9.0%
Nivolumab + ipilimumab + carboplatin	0.0%	0.0%	0.0%
Chemotherapy only	50.0%	50.0%	55.0%

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

Patients in both arms are assumed to receive subsequent therapies for the duration of subsequent therapy received in PHAROS ([redacted] weeks). This is also aligned with clinical advice to the Company in TA898 stating that the average duration of immunotherapy monotherapy in patients with previously treated advanced NSCLC would be approximately 12–15 weeks (15).

Two scenarios are presented to test the impact of subsequent therapy duration assumptions on results:

1. Assuming equivalent subsequent therapy durations aligned with the committee accepted assumption in TA898, 13.5 weeks (15)

2. Using the subsequent therapy durations presented as a scenario in TA898 (Table 81).

Table 81: Subsequent therapy duration, scenario analysis

Drug	Duration (weeks)	Source
Dabrafenib + trametinib	[redacted]	PHAROS (83)
Pembrolizumab	23.4	TA898 (Table 44) (15)
Nivolumab	25.3	TA898 (Table 44) (15)
Nivolumab + ipilimumab	25.3	Assumed equal to nivolumab
Pembrolizumab + cisplatin	23.4	Assumed equal to pembrolizumab
Nivolumab + ipilimumab + cisplatin	25.3	Assumed equal to nivolumab
Nivolumab + ipilimumab + carboplatin	25.3	Assumed equal to nivolumab
Chemotherapy only (carboplatin)	15.0	TA898 (Table 44) (15)

As described in Section B.3.3, a scenario analysis is presented in which clinical data were taken from pooled PHAROS and IFCT data. Therefore, in this scenario, subsequent therapies in the enco+bini arm are aligned with pooled PHAROS and IFCT data. Subsequent therapies received in >1% of patients in both PHAROS and IFCT are presented in Table 82.

Table 82: Subsequent therapies, pooled PHAROS and IFCT

Drug	Proportion of patients (%)	
	Enco+bini	Dabra+tram
Proportion receiving any subsequent therapy	[redacted]	[redacted]
Encorafenib + binimetinib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Pembrolizumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]	[redacted]
Chemotherapy only	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Carboplatin + pembrolizumab+pemetrexed	[redacted]	[redacted]
Carboplatin + bevacizumab+ pemetrexed	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Carboplatin + pemetrexed	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

The unit costs of subsequent therapies are presented in Table 83. RDI for immunotherapies were assumed equal to that of pembrolizumab (96%), as reported in TA683, and 100% for all remaining subsequent therapies.

Radiotherapy was assigned a cost of £1,756.95 based on a weighted average of NHS reference costs for outpatient radiotherapy (cost codes: SC21Z:SC57Z, £351.39), assuming a course of five doses, based on a one-week subsequent therapy duration and short-course radiotherapy schedule (131). RDIs for subsequent therapies are assumed equivalent to first-line for enco+bini and dabra+tram. (131). RDIs for subsequent therapies are assumed equivalent to first-line for enco+bini and dabra+tram.

Table 83: Subsequent therapy acquisition costs

Drug	mg/unit	Pack price	Pack size (number of units)
Pembrolizumab	100 mg	£2,630.00	1
Nivolumab	40 mg	£439.00	1
	100 mg	£1,097.00	1
	120 mg	£1,317.00	1
	240 mg	£2,633.00	1
Ipilimumab	50 mg	£3,750.00	1
	200 mg	£15,000.00	1
Cisplatin	10 mg	£3.23	1
	50 mg	£27.98	1
	100 mg	£29.27	1
Carboplatin	50 mg	£9.28	1
	150 mg	£20.22	1
	450 mg	£48.09	1
	600 mg	£71.44	1
Pemetrexed	500 mg	£40.77	1
Cemiplimab	350 mg	£4,650.00	1
Bevacizumab	100 mg	£205.55	1

Administration costs for subsequent therapies are described in Table 84. Therapies with long (>6 hours) infusion times are assigned the cost of delivering a complex parenteral chemotherapy, all others are assigned the cost of delivering a simple parenteral chemotherapy. Oral therapies are assumed to incur no administration cost as per primary therapies (Section B.3.5.2).

Table 84: Subsequent therapy administration costs

Route of administration	Administration cost (per dose)	Source
Outpatient: Simple parenteral administration	£249.65	NHS reference costs 2022/23, Deliver simple parenteral chemotherapy at first attendance, SB12Z (132, 133)
Outpatient: More complex parenteral chemotherapy	£382.08	NHS reference costs 2022/23, Deliver more complex parenteral chemotherapy at first attendance, SB13Z (132, 133)
Oral	£0	Assumption

Abbreviations: NHS, National Health Service.

Table 85: Subsequent therapy costs

Drug		Dose	Cycle length (days)	Doses per cycle	Drug cost (one week cycle)	Admin cost (one week cycle)
Pembrolizumab	-	240 mg	21	1	£1,676.19	£83.22
Nivolumab	-	240 mg	14	1	£3,913.87	£124.83
Nivolumab + ipilimumab	Nivolumab	240 mg	14	1	£3,164.21	£124.83
	Ipilimumab	1 mg/kg	21	1		
Pembrolizumab + cisplatin + pemetrexed	Pembrolizumab	200 mg	14	1	£1,733.50	£127.36
	Cisplatin	20 mg/kg	28	1		
	Pemetrexed	500 mg/m^2	21	1		
Nivolumab + ipilimumab + cisplatin	Nivolumab	240 mg	21	1	£1,301.94	£127.36
	Ipilimumab	1 mg/kg	21	1		
	Cisplatin	20 mg/kg	28	1		
Nivolumab + ipilimumab + carboplatin	Nivolumab	240 mg	21	1	£3,197.10	£127.36
	Ipilimumab	1 mg/kg	21	1		
	Carboplatin	300 mg/m^2	28	1		
Chemotherapy only	Carboplatin	300 mg/m^2	28	1	£25.45	£127.36
Carboplatin + pembrolizumab + pemetrexed	Pembrolizumab	200 mg	14	1	£1,740.95	£127.36
	Carboplatin	300 mg/m^2	28	1		
	Pemetrexed	500 mg/m^2	21	1		
Carboplatin + bevacizumab + pemetrexed	Carboplatin	300 mg/m^2	28	1	£912.19	£127.36
	Bevacizumab	15 mg/kg	21	1		
	Pemetrexed	500 mg/m^2	21	1		
Dabrafenib	Dabrafenib	150 mg	1	2	£1,162.00	£0.00
Carboplatin + pemetrexed	Carboplatin	300 mg/m^2	28	1	£64.76	£127.36
	Pemetrexed	500 mg/m^2	21	1		

B.3.5.4. Health-state unit costs and resource use

No additional medical resource use (MRU) data were identified by the cost and resource use SLR (Appendix I) to those presented in NICE TA898 (15). Therefore, MRU frequencies were sourced from NICE TA898. Clinical experts also agreed that resource use for all active therapies is the same in UK clinical practice, and that resource use post-progression is the same regardless of treatment. Costs were sourced from the NHS reference costs for 2022/23 and the 2023 Personal Social Services Research Unit (PSSRU) costs (132, 134). Resource use estimates are summarised in Table 86. At the October 2024 UK advisory board, clinical experts confirmed that the estimates were broadly aligned with UK practice, and there would be no difference in resource use between enco+bini and dabra+tram (16).

Table 86: Medical resource use and costs

Element of resource use	Progression-free (annual)	Post-progression (annual)	Unit costs	Source
Outpatient visit	9.61	7.91	£148.19	NHS reference costs 2022/23. Total Outpatient Attendances, 800 - Clinical Oncology Service, Consultant Led. (133)
Chest X-ray	6.79	6.50	£49.00	NHS reference costs 2022/23. Total Outpatient Attendances, 812 - Diagnostic Imaging Service, Consultant Led. (133)
CT scan (chest)	0.62	0.24	£151.03	NHS reference costs 2022/23. Diagnostic Imaging, RD24Z. Computerised Tomography Scan of Two Areas, with Contrast (133)
CT scan (other)	0.36	0.42	£125.39	NHS reference costs 2022/23. Diagnostic Imaging, RD25Z. Computerised Tomography Scan of Three Areas, without Contrast (133)
ECG	1.04	0.88	£155.69	NHS reference costs 2022/23. HRG data. HRG data - EY51Z - Electrocardiogram Monitoring or Stress Testing (133)
Community nurse visit	8.70	8.70	£76.00	PSSRU, 2023 band 8a nurse, cost per working hour (134)

Element of resource use	Progression-free (annual)	Post-progression (annual)	Unit costs	Source
Clinical nurse specialist	12.00	12.00	£88.00	PSSRU, 2023 band 8b nurse, cost per working hour (134)
GP surgery	12.00	0.00	£56.00	PSSRU, 2023 Unit costs for a GP per surgery consultation lasting 10 minutes (including indirect costs) (134)
GP home visit	0.00	26.09	£96.60	PSSRU 2023 GP cost per home visit allowing 10 minutes of patients contact, and 12 minutes for travel (costed using cost per hour of GMS activity) (134)
Therapist visit	0.00	26.09	£52.00	PSSRU, 2023 cost per hour for community occupational therapist (134)

Abbreviations: ECG: electrocardiogram; CT, computerised tomography; GP, general practitioner; HRG: healthcare resource group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

All resource use costs are converted and applied as weekly cycle costs. The total per cycle resource use costs for the progression-free and progressed disease states are presented in Table 87.

Table 87: Resource use cost summary

	Progression-free	Post-progression
Weekly resource use cost	£85.22	£140.11

B.3.5.5. Adverse reaction unit costs and resource use

A list of the TEAEs included in the model, and the corresponding frequencies are presented in Table 88. AE costs were obtained from NHS reference costs 2022/23 (133) and are well aligned with TA898. Unit costs for Grade 3 or above AEs are presented in Table 88. The cost of AEs is applied as a one-off cost in the first cycle of the model as per the committee accepted assumption in TA898. AEs highlighted by clinical experts at the October 2024 UK advisory board as having an inconsequential impact on treatment are assigned zero cost, as discussed in Section B.3.4.4.

Table 88: Grade 3/4 AEs - costs

Adverse event	Unit cost	Source
Alanine aminotransferase increased	£0	Assumption – clinical expert opinion (16)
Amylase increased	£0	Assumption – clinical expert opinion (16)
Anaemia	£1,978	Weighted average of Total HRGs SA01G-K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia) (133)
Aspartate aminotransferase increased	£2,313	TA898 (15)
Asthenia	£855	Assumed equal to fatigue.
Back pain	£826	Total HRGs, HC32 - Low Back Pain without Interventions, with CC Score 0-2 (133)
Blood alkaline phosphatase increased	£0	Assumption – clinical expert opinion (16)
Blood creatinine phosphokinase increased	£0	Assumption – clinical expert opinion (16)
Bronchitis	£602	Total HRGs, DZ65K - Chronic Obstructive Pulmonary Disease or Bronchitis (133)
Colitis	£1,857	Assumed same as diarrhoea
Decreased appetite	£0	Assumption, derived from TA898 (15)
Diarrhoea	£1,857	Total HRGs, weighted average of Total HRGs FD01A-J - Gastrointestinal Infections (133)
Dyspnoea	£831	Total HRGs, weighted average of Total HRGs DZ19H-N - Other Respiratory Disorders (133)
Ejection fraction decreased	£468	Total HRGs, EB03E - Heart Failure or Shock, with CC Score 0-3. Non-elective short stay. (133)
Fatigue	£855	Total HRGs, weighted average of Total HRGs SA04G-L - Iron Deficiency Anaemia (133)
Gamma-gluamyltransferase increased	£2,313	Assumed equal to aspartate aminotransferase increased
Gastrointestinal haemorrhage	£157	Total Outpatient Attendances, 301 - Gastroenterology outpatient visit (133)
Herpes zoster	£0	Assumption – clinical expert opinion (16)
Hypertension	£721	Total HRGs, EB04Z – Hypertension (133)
Hyponatraemia	£0	TA898 – assumed no cost (15)
Hypotension	£721	Assumed equal to hypertension.
Leukocytosis	£2,313	Assumed equal to aspartate aminotransferase increased
Lipase increased	£0	Assumption – clinical expert opinion (16)
Loss of consciousness	£0	Assumption
Myalgia	£826	Total HRGs, HC32K - Low Back Pain without Interventions, with CC Score 0-2 (133)

Adverse event	Unit cost	Source
Nausea	£732	Assumed equal to abdominal pain. NHS Reference Costs: Weighted average of Total HRGs FD05A-B - Abdominal Pain Without Interventions (133)
Neutropenia	£2,421	Total HRGs, weighted average of SA35A-E – Agranulocytosis (133)
Pain in extremity	£1,438	Total HRGs, weighted average of WH08A-B - Unspecified Pain (133)
Pneumonia	£2,628	Total HRGs, weighted average of DZ11K-V - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions (133)
Pulmonary embolism	£602	Total HRGs, DZ65K - Chronic Obstructive Pulmonary Disease or Bronchitis (133)
Pyrexia	£1,304	Total HRGs, weighted average of WJ07A-D - Fever of Unknown Origin (133)
Retinal detachment	£561	Total HRGs, BZ74Z - Minor Ocular Motility Procedures (133)
Vomiting	£732	Total HRGs, weighted average of Total HRGs FD05A-B - Abdominal Pain Without Interventions (133)
Weight increased	£0	Assumption, in line with TA898. (15)

Abbreviations: AEs, adverse events; GP, general practitioner; HRG: healthcare resource group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

The total cost of AEs in each arm applied in the first cycle of the model is presented in Table 89.

Table 89: Adverse event cost summary

	Enco+bini	Dabra+tram
One-off adverse event cost	£1,442.05	£809.25

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

B.3.5.6. Miscellaneous units costs and resource use

A one-off end-of-life care cost was assigned to each patient upon death. As no more recent data were identified to inform the cost of end-of-life care in the cost and resource use SLR (Section B.3.5.4), this was sourced from Brown et al. in line with TA898 (15, 135). Costs were estimated as a weighted average over costs in various care settings and inflated to 2022/23 prices using the PSSRU inflation indices (134). The total one-off cost per death was estimated to be £4,992 and applied to all incident deaths in the model.

Table 90: Terminal care costs

Care setting	Unit cost	Cost source	% of patients in care setting	Frequency		Source
				Value	Unit	
Community nurse visit	£76	PSSRU 2023, Nurse cost per hour, Band 8A (excluding qualifications) (134)	27%	28	Hours	TA898 (15)
GP home visit	£97	PSSRU 2023 GP cost per home visit allowing 10 minutes of patients contact, and 12 minutes for travel (costed using cost per hour of GMS activity) (134)	27%	7	Visits	
Macmillan nurse	£34	Macmillan cancer support, inflated from 2021/22 to 2022/23 (136)	27%	50	Hours	
Drugs and equipment	£667	NICE TA531, inflated from 2015/16 to 2022/23 costs using PSSRU NHSCII index (137)	27%	1	Per patient	
Terminal care in hospital	£4,650	NICE TA531, inflated from 2015/16 to 2022/23 using the PSSRU HCHS index (137)	56%	1	Episode (9.66 days)	
Terminal care in hospice	£5,812	NICE TA531, assumed 25% increase on hospital inpatient care (137)	17%	1	Episode (9.66 days)	
Total one-off cost	£4,992	-	-	-	-	Weighted average

Abbreviations: GMS, General Medical Service; GP, general practitioner; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.

B.3.6. Severity

To assess the severity of *BRAF* V600E MT NSCLC, severity was calculated in line with NICE DSU TSD23 (118). General population utility values were derived from Hernández Alava 2020 (138), and general population mortality values were taken from life tables published by the ONS for the years 2017–19, in line with NICE DSU guidance (111, 118) . Based on a mean age at baseline of 66.5 years and a 44.0% male population, the expected discounted QALYs for people without *BRAF* V600E MT NSCLC is 10.30 and the expected undiscounted life years are 14.49.

Patients treated with dabra+tram would be expected to accrue [redacted] discounted QALYs, resulting in an absolute QALY shortfall of [redacted] and a proportional QALY shortfall of [redacted], resulting in a QALY weighting of 1.0. Therefore, no QALY weighting is applicable to this appraisal.

Table 91: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion male (%)	44.0% (Table 50)	Patient characteristics, Section B.3.3.1
Starting age (years)	66.5 (Table 50)	

Abbreviations: QALY, quality adjusted life year

Table 92: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TA898 (15)	9.871	Redacted	Redacted

Abbreviations: QALY, quality adjusted life year; TA, technology appraisal.

Table 93: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean	Undiscounted life years
Progression-free	0.71	[redacted]
Progressed disease	0.67	[redacted]

Abbreviations: QALY, quality adjusted life year

Table 94: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
10.30	Dabra+tram	[redacted]	[redacted]

Abbreviations: Dabra+tram, dabrafenib in combination with trametinib; QALY, quality adjusted life year

B.3.7. Uncertainty

BRAF V600E MT NSCLC is a rare form of NSCLC, and as a result the treatment-naïve populations in both the PHAROS, IFCT, and the comparative BRF113928

trials are relatively small (N=59, N=64, and N=36 respectively). Therefore, evidence generation is subject to unavoidable uncertainty in outcomes. A scenario was conducted to explore the impact of pooling data from the pivotal phase 2 PHAROS trial and the supportive IFCT study to maximise available data (Section B.3.3). To explore the robustness of the base-case analysis, the impact of structural and parameter uncertainty on model results was explored in deterministic sensitivity analysis, probabilistic sensitivity analysis (PSA) and scenario analysis; details of these are presented in Section B.3.10.

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

B.3.8.1. Summary of base-case analysis inputs

A summary of the base-case inputs is provided in Table 95.

Table 95: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	Section B.3.2
Discount rate, outcomes	3.5%	Fixed	Section B.3.2
Time horizon	Lifetime (33.5 years)	Fixed	Section B.3.2
Baseline age, years	66.5	Fixed	Section B.3.3.1
Male, %	44.1%	Fixed	Section B.3.3.1
Body weight, kg	74.6	Normal (CI: 68.7–80.5)	Section B.3.3.1
Height, m	1.67	Normal (1.64–1.70)	Section B.3.3.1
Survival curves			
OS curve choice, enco+bini	Exponential	-	Section B.3.3.2.1
OS curve, rate parameter, enco+bini	[redacted]	Normal (CI: [redacted], [redacted])	Section B.3.3.2.1
OS HR, enco+bini vs dabra+tram	0.55	Log-normal (CI: [redacted], [redacted])	Section B.3.3.2.2.1
PFS curve chocie, enco+bini	Exponential	-	Section B.3.3.2.1.2
PFS curve, shape parameter enco+bini	[redacted]	Normal (CI: [redacted], [redacted])	Section B.3.3.2.1.2
PFS HR, enco+bini vs dabra+tram	0.47	Log-normal (CI: [redacted], [redacted])	Section B.3.3.2.2
TTD curve, enco+bini	Exponential	-	Section B.3.3.2.3.1
TTD curve, shape parameter	[redacted]	Normal (CI: [redacted],	Section B.3.3.2.3.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
enco+bini		[redacted])	
Adverse events			
Grade ≥3 TEAEs	Table 68	Beta (CI: +/- 20% around mean)	Section B.3.3.4
Utility values			
Utility value – progression-free	0.71	Beta: (CI: 0.57-0.85)	Section 0
Utility value - progressed	0.67	Beta (CI: 0.54- 0.80)	
AE disutilities	Table 70	Beta (CI: +/- 20% around mean)	Section B.3.4.4
AE durations	Table 70	Gamma (CI: +/- 20% around mean)	Section B.3.4.4
Drug costs			
Encorafenib	£1,400.00	Fixed	Section B.3.5.1
Binimetinib	£2,240.00	Fixed	
Dabrafenib	£1,400.00	Fixed	
Trametinib, 7 x 2mg	£1,120.00	Fixed	
Trametinib, 30 x 2mg	£4,800.00	Fixed	
Encorafenib, RDI	[redacted]	Beta (CI: [redacted])	Section B.3.5.1
Binimetinib, RDI	[redacted]	Beta (CI: [redacted])	
Dabrafenib, RDI	0.83	Beta (CI: 0.66–1.00)	
Trametinib, RDI	0.90	Beta (CI: 0.72–1.00)	
Subsequent treatments			
Proportion of patients		Beta (CI: +/- 20% around mean)	Section B.3.5.3
Duration of subsequent therapy, enco+bini	[redacted]	Gamma (CI: +/- 20% around mean)	
Pembrolizumab cost per pack	£2,630.00	Fixed	
Nivolumab cost per pack, 40mg	£439.00	Fixed	
Nivolumab cost per pack, 100mg	£1,097.00	Fixed	
Nivolumab cost per pack, 120mg	£1,317.00	Fixed	
Nivolumab cost per pack, 240mg	£2,633.00	Fixed	
Carboplatin cost per pack, 50mg	£9.28	Fixed	
Carboplatin cost per pack, 150mg	£20.22	Fixed	
Carboplatin cost per pack, 450mg	£48.09	Fixed	
Carboplatin cost per pack,	£71.44	Fixed	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
600mg			
Ipilimumab cost per pack, 50mg	£3,750.00	Fixed	
Ipilimumab cost per pack, 200mg	£15,000.00	Fixed	
Pemetrexed cost per pack, 500mg	£40.77	Fixed	
Cemiplimab, cost per pack, 350mg	£4,650.00	Fixed	
Bevacizumab, cost per pack, 100mg	£205.55	Fixed	
Radiotherapy cost per dose	£351.39	Fixed	
Cisplatin cost per pack, 10mg	£3.23	Fixed	
Cisplatin cost per pack, 50mg	£27.98	Fixed	
Cisplatin cost per pack, 100mg	£29.27	Fixed	
Administration costs			
IV infusion, first attendance	£249.65	Gamma (+/- 20% around mean)	Section B.3.5.3
IV infusion, first attendance, complex infusion	£382.08	Gamma (+/- 20% around mean)	
AE costs			
Unit costs	Table 89	Gamma (CI: +/- 20% around mean)	Section B.3.5.5
Resource use costs			
Chest X-ray, progression-free frequency	6.79	Gamma (+/- 20% around mean)	Section B.3.5.4
CT scan (chest), progression-free frequency	0.62	Gamma (+/- 20% around mean)	
CT scan (other, progression-free frequency	0.36	Gamma (+/- 20% around mean)	
ECG, progression-free frequency	1.04	Gamma (+/- 20% around mean)	
Outpatient visit, progression-free frequency	9.61	Gamma (+/- 20% around mean)	
Community nurse visit, progression-free frequency	8.70	Gamma (+/- 20% around mean)	
Clinical nurse specialist, progression-free frequency	12.00	Gamma (+/- 20% around mean)	
GP surgery, progression-free frequency	12.00	Gamma (+/- 20% around mean)	
GP home visit, progression-free frequency	0.00	Fixed	
Therapist visit, progression-free frequency	0.00	Fixed	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Chest X-ray, progressed frequency	6.50	Gamma (+/- 20% around mean)	
CT scan (chest), progressed frequency	0.24	Gamma (+/- 20% around mean)	
CT scan (other), progressed frequency	0.42	Gamma (+/- 20% around mean)	
ECG, progressed frequency	0.88	Gamma (+/- 20% around mean)	
Outpatient visit, progressed frequency	7.91	Gamma (+/- 20% around mean)	
Community nurse visit, progressed frequency	8.70	Gamma (+/- 20% around mean)	
Clinical nurse specialist, progressed frequency	26.09	Gamma (+/- 20% around mean)	
GP surgery, progressed frequency	0.00	Gamma (+/- 20% around mean)	
GP home visit, progressed frequency	26.09	Gamma (+/- 20% around mean)	
Therapist visit, progressed frequency	0.24	Gamma (+/- 20% around mean)	
GP surgery visit cost	£56.00	Gamma (+/- 20% around mean)	
GP home consultation cost	£96.60	Gamma (+/- 20% around mean)	
Chest X-ray cost	£40.97	Gamma (+/- 20% around mean)	
CT scan (chest) cost	£151.03	Gamma (+/- 20% around mean)	
CT scan (other) cost	£125.39	Gamma (+/- 20% around mean)	
ECG cost	£155.69	Gamma (+/- 20% around mean)	
Outpatient visit cost	£148.19	Gamma (+/- 20% around mean)	
Community nurse visit cost	£76.00	Gamma (+/- 20% around mean)	
Clinical nurse specialist cost	£88.00	Gamma (+/- 20% around mean)	
Therapist visit cost	£52.00	Gamma (+/- 20% around mean)	
End of life costs	£4,992	Gamma (+/- 20% around mean)	Section B.3.5.6

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; TTD, time to treatment discontinuation.

B.3.8.2. Assumptions

A summary of assumptions is presented in Table 96.

Table 96: Assumptions used in the economic model

Assumption	Justification
The exponential distribution was selected to extrapolate the enco+bini OS curve	At time of DCO, median OS had not been reached, and 44.1% of patients had experienced an OS event. Therefore, the long-term estimates of OS are associated with uncertainty. Clinical expert opinion was elicited at the October 2024 UK advisory board to assess the appropriateness of each of the standard distributions estimated in the survival analysis. Clinical experts agreed that the exponential, Weibull and gamma distributions provided the most clinically plausible estimates of long-term survival (16). These distributions also produced statistically good fits to the trial data and good visual fits to the KM curve. The exponential curve was selected in the base case, and Weibull and gamma curves are tested in scenario analysis.
The exponential distribution was selected to extrapolate the enco+bini PFS curve	As with OS, PFS and TTD were incomplete at the time of DCO, therefore extrapolation was required to estimate outcomes for the model time horizon. Clinical expert opinion was elicited at the October 2024 UK advisory board to assess the appropriateness of each of the standard distributions estimated in the survival analysis. Clinical experts agreed that the exponential, Weibull and gamma distributions provided the most clinically plausible estimates of long-term progression-free survival and time on treatment (16). These distributions also produced statistically good fits to the trial data and good visual fits to the KM curve. The exponential curve was selected in the base case for PFS and TTD, due to the inherent relationship between PFS and TTD endpoints The Weibull and gamma curves are tested in scenario analysis.
The exponential distribution was selected to extrapolate the enco+bini TTD curve	
Proportional hazards holds between enco+bini and dabra+tram	The assumption of proportional hazards between enco+bini and dabra+tram was tested on the weighted trial data by assessing the log-log plots and the Schoenfeld residuals for both OS and PFS. Although the log-log plots crossed at the beginning of the plots for OS, they remained parallel for the majority of the trial period. The log-log plots remained parallel for the duration of the PFS data. Furthermore, the results of the global test on the Schoenfeld residuals were insignificant ([redacted]) suggesting that the PH assumption could not be rejected. Clinical experts at the October 2024 UK advisory board also stated that they did not expect any differences in the hazard profile between enco+bini and dabra+tram (16). Therefore, the assumption of PH between treatments was made.
TTD is not capped by PFS	Clinical experts at the October 2024 UK advisory board stated that a proportion of patients would continue to be treated beyond progression (16).
Dabra+tram TTD is assumed equivalent to PFS	A MAIC could not be performed due to lack of publicly available TTD data from dabra+tram, and only median TTD data were available from the combined first-line and second-line cohort of the BRF113928 trial (116). Clinical experts at the October 2024 UK advisory board stated that a proportion of patients would continue to be treated beyond progression

Assumption	Justification
	(16), and RWE data on dabra+tram use showed a longer median TTD than median PFS (117). Therefore, treat to progression was assumed in the dabra+tram arm
Oral therapies are assumed not to incur an administration cost	In line with TA898 (15) and given that all considered primary therapies are administered orally, no administration costs were assigned in the model.
Subsequent therapy costs are based on data from the PHAROS trial.	Clinical experts at the June 2024 UK advisory board advised that the most common therapies used at second-line for patients with advanced NSCLC with a *BRAF* V600E mutation in the UK are chemo-immunotherapy and chemotherapy monotherapy. However, clinical experts stated that they did not consider any of the therapies used in PHAROS or the BRF113928 trial to significantly impact patient survival. Clinical experts further stated they did not expect any significant differences in subsequent therapies received depending on first-line treatment (16).

Abbreviations: AE, adverse event; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation.

B.3.9. Base-case results

As described in Section B.1.3.4 and Section B.3.2.3, the relevant comparator for this appraisal is dabra+tram. Therefore, a pairwise analysis was conducted per the NICE reference case, comparing enco+bini vs dabra+tram.

Results are based on the list prices for dabra+tram and the approved simple discount PAS for enco+bini.

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

The base case cost-effectiveness results are presented in Table 97. Enco+bini was associated with improved mean OS ([redacted] months) and improved mean PFS ([redacted] months) compared with dabra+tram. This translated into [redacted] and [redacted] total QALYs for enco+bini and dabra+tram respectively, yielding an incremental QALY benefit of [redacted] vs dabra+tram. Enco+bini was associated with total costs of [redacted], and a cost saving of [redacted] when compared with dabra+tram (total cost of [redacted]). Enco+bini is therefore dominant when compared with dabra+tram.

Pairwise net health benefit (NHB) estimates are presented in Table 97, based on a WTP threshold of £20,000 and £30,000, as per NICE guidelines. Enco+bini is associated with incremental NHBs of [redacted] and [redacted] compared with dabra+tram at a

WTP of £20,000 and £30,000 respectively. Appendix J presents the clinical outcomes and disaggregated results.

Table 97: Base-case results (deterministic) – enco+bini PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabra+tram	[redacted]	[redacted]	[redacted]	-	-	-	-	–	–
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.10. Exploring uncertainty

B.3.10.1. Probabilistic sensitivity analysis

A summary of the pairwise probabilistic results is presented in Table 98. Enco+bini is associated with incremental QALYs of [redacted] and a cost saving of £[redacted], vs dabra+tram. Enco+bini is therefore dominant when compared with dabra+tram in the probabilistic incremental cost-effectiveness ratio (ICER).

The probabilistic ICER is consistent with the deterministic analysis, where enco+bini was associated with incremental QALYs of [redacted] and cost saving of [redacted], vs dabra+tram, resulting in a dominant ICER. Enco+bini is associated with a probabilistic NHB of [redacted] and [redacted] assuming a WTP threshold of £20,000 and £30,000, respectively. This is consistent with the deterministic analysis, which resulted in a deterministic NHB of [redacted] and [redacted] at a WTP of £20,000 and £30,000, respectively.

The cost-effectiveness plane for enco+bini vs dabra+tram and the cost-effectiveness acceptability curve (CEAC) are presented in Figure 37 and Figure 38, respectively. Uncertainty in the probabilistic results for enco+bini vs dabra+tram arises from the confidence interval associated with the HRs applied to the enco+bini OS and PFS curves to estimate efficacy for dabra+tram. Both HRs were varied independently due to the nature of a partitioned survival analysis approach, which likely overestimates the uncertainty in the model results. As shown in Section B.3.10.2, these parameters are amongst the main drivers of cost-effectiveness. The proportion of simulations considered cost-effective at a WTP threshold of £30,000 per QALY was [redacted]%.

Table 98: Base-case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabra+tram	[redacted]	[redacted]	–	–	–	–	–
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

Figure 37: Cost-effectiveness plane – enco+bini PAS price

Abbreviations: enco+bini, encorafenib plus binimetinib; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 38: Cost-effectiveness acceptability curve – enco+bini PAS price

Abbreviations: enco+bini, encorafenib plus binimetinib; PAS, patient access scheme; WTP, willingness to pay.

B.3.10.2. Deterministic sensitivity analysis

Parameter uncertainty was tested using one-way sensitivity analysis (OWSA), in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±20% of the mean value where no estimates of precision were available. Due to the dominant base-case ICER, the NHB was recorded at the upper and lower values to produce a tornado diagram.

Results for the ten most influential parameters are presented in Table 99, while the tornado diagram is presented in Figure 39. The most influential parameters were the survival curve parameters for PFS, TTD, OS, the MAIC HRs for OS and PFS for dabra+tram vs enco+bini, and RDI. For the majority of parameters, the NHB remains relatively stable other than results for the upper value of the OS HR and PFS HR and survival curve parameters. For all results but one, enco+bini remains dominant when compared with dabra+tram, and the NHB remains above zero.

Table 99: OWSA results – enco+bini PAS price

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
HR - PFS - PHAROS, adjustment on all factors	[redacted]	[redacted]
Encorafenib + binimetinib - PFS (PHAROS) - exponential, Rate	[redacted]	[redacted]
HR - OS - PHAROS, adjustment on all factors	[redacted]	[redacted]
RDI - dabrafenib	[redacted]	[redacted]
RDI - trametinib	[redacted]	[redacted]
Encorafenib + binimetinib - TTD (PHAROS) - exponential, Rate	[redacted]	[redacted]
Utility values, TA898, progression-free	[redacted]	[redacted]
RDI - binimetinib - PHAROS	[redacted]	[redacted]
Encorafenib + binimetinib - OS (PHAROS) - exponential, Rate	[redacted]	[redacted]
RDI - encorafenib - PHAROS	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

Figure 39: Tornado diagram – enco+bini PAS price

Abbreviations: enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

B.3.10.3. Scenario analysis

A summary of scenario analyses performed, along with the justification, is presented in Table 100. All results presented are probabilistic scenario analyses, and results of the deterministic scenario analyses are presented in Appendix O. Due to the dominant base-case ICER, results are presented using NHB. Probabilistic NHB estimates showed a high level of consistency with results of the deterministic analyses.

For probabilistic scenario results of the comparisons of enco+bini with dabra+tram, the NHB lay within the range of [redacted] - [redacted] assuming a WTP threshold of £30,000 per QALY, with most scenarios having little impact on the result. The ICER remained dominant in all scenarios, and the NHB remained positive. In all scenarios, enco+bini is associated with a significant QALY gain, supporting the results of the base-case cost-effectiveness analysis.

Table 100: Scenario analysis results (probabilistic) – enco+bini PAS price

Scenario and cross reference	Base case input	Scenario detail	Brief rationale	Scenario analysis results		
				Incremental costs	Incremental QALYs	NHB
Base case (deterministic)	-	-	-	[redacted]	[redacted]	[redacted]
Base case (probabilistic)	-	-	-	[redacted]	[redacted]	[redacted]
Enco+bini OS curve distribution, B.3.3.2.1.1	Exponential	Gamma	At time of DCO, median OS had not been reached, and 44.1% of patients had experienced an OS event. Therefore, the long-term estimates of OS are associated with uncertainty. Clinical experts at the October 2024 UK advisory board agreed that the Weibull and gamma distributions also provided clinically plausible estimates of long-term survival (16). Therefore, both distributions are explored in scenario analysis.	[redacted]	[redacted]	[redacted]
		Weibull		[redacted]	[redacted]	[redacted]
Enco+bini PFS curve distribution, B.3.3.2.1.2	Exponential	Weibull	At time of DCO, 47.5% had experienced a progression event. Therefore, PFS and TTD extrapolations are associated with uncertainty in long-term estimates. Alternate survival distributions considered clinically plausible by clinical experts are considered as scenarios.	[redacted]	[redacted]	[redacted]
		Gamma		[redacted]	[redacted]	[redacted]
Enco+bini TTD curve distribution, B.3.3.2.3.1	Exponential	Gamma		[redacted]	[redacted]	[redacted]
		Weibull		[redacted]	[redacted]	[redacted]

Scenario and cross reference	Base case input	Scenario detail	Brief rationale	Scenario analysis results		
				Incremental costs	Incremental QALYs	NHB
Enco+bini and dabra+tram TTD curve distribution, B.3.3.2.3.1	Treat to progression	Exponential curve to fit the median TTD reported from BRF113928	No data is available on TTD from the first-line cohort of the BRF113928. RWE from Auliac et al 2020 shows that median TTD and PFS are very similar (117). Clinical advice to the company was that some patients would continue to be treated beyond progression. Therefore, treat to progression was assumed. Scenario analysis is presented that uses the median TTD from BRF113928, although this data is from a combined (first-line and second-line) cohort and therefore may underestimate treatment costs in the dabra+tram arm. A further scenario is presented using median TTD from the RWE study Auliac et al 2020.	[redacted]	[redacted]	[redacted]
		Exponential curve to fit the median from RWE study Auliac et al 2020 (117)		[redacted]	[redacted]	[redacted]
Utility values B.3.4.5	Utility values as per TA898, derived from Chouaid 2013	IFCT MMRM analysis	As detailed in Section B.3.4.5, to align with TA898, the values from Chouaid are considered the most appropriate source of utility values (113). However, to test the impact on results of uncertainty associated with the utility values, as scenario is presented using values from IFCT, which represents data collected in the population relevant to the decision problem.	[redacted]	[redacted]	[redacted]
		IFCT MMRM analysis, with progressed decrement derived from Chouaid 2013 (113)		[redacted]	[redacted]	[redacted]

Scenario and cross reference	Base case input	Scenario detail	Brief rationale	Scenario analysis results		
				Incremental costs	Incremental QALYs	NHB
Dabra+tram subsequent treatment, B.3.5.3	Assume equal to the enco+bini arm after re-weighting to exclude subsequent dabra+tram use	Based on data from the BRF113928 trial, as reported in TA898 (15)	Based on clinical expert feedback, it is expected that there would be no major differences between subsequent treatments received in either arm. Therefore, it was considered appropriate to use PHAROS data to inform subsequent therapies in both arms. However, a scenario is presented using data from the BRF113928 trial.	[redacted]	[redacted]	[redacted]
Dabra+tram and enco+bini subsequent treatment, B.3.5.3	PHAROS data	Clinical expert opinion (16)	Clinical experts stated that chemotherapy and pembrolizumab with chemotherapy are the most common subsequent therapies received by patients in UK clinical practice, therefore a scenario is presented assuming only those therapies are received in both arms (16).	[redacted]	[redacted]	[redacted]
Subsequent therapy duration, B.3.5.3	Based on PHAROS trial data for enco+bini and dabra+tram, respectively	Assume different duration per subsequent therapy as per scenario analysis presented in TA898	As only a mean estimate for all subsequent therapy durations was available from PHAROS and BRF113928, a scenario was conducted to assess the impact of differing subsequent therapy durations on result.	[redacted]	[redacted]	[redacted]

Scenario and cross reference	Base case input	Scenario detail	Brief rationale	Scenario analysis results		
				Incremental costs	Incremental QALYs	NHB
		Assume subsequent therapy duration equal to committee preferred the base case in TA898 (15)		[redacted]	[redacted]	[redacted]
Dabra+tram adverse events, B.3.3.4	Based on data from the BRF113928 trial	Based on Grade 3/4 AE MAIC OR applied to enco+bini data	As discussed in Section B.2.9, enco+bini was associated with a benefit in patients experiencing Grade 3/4 AEs when adjusting for differences in the trial populations. Clinical experts with experience of using both enco+bini and dabra+tram agreed that enco+bini was a more tolerable treatment (16).	[redacted]	[redacted]	[redacted]
MAIC HRs, B.3.3.2.2	MAIC HRs adjusted for all factors	MAIC HRs adjusted for ECOG and smoking status only	Due to the inherent uncertainty in unanchored MAICs, scenario analysis is presented that retains a greater sample size in the analysis.	[redacted]	[redacted]	[redacted]
Source of clinical data, B.3.3.2	Based on the PHAROS trial data for enco+bini, and a MAIC using the BRF113928 trial for dabra+tram	Based on the pooled data from the pivotal study PHAROS & supportive study IFCT for enco+bini, and a MAIC using the	To maximise the use of available data in the relatively small population of patients with *BRAF* V600E MT NSCLC, the pivotal study PHAROS and the supportive study IFCT were pooled.	[redacted]	[redacted]	[redacted]

Scenario and cross reference	Base case input	Scenario detail	Brief rationale	Scenario analysis results		
				Incremental costs	Incremental QALYs	NHB
		BRF113928 trial for dabra+tram				

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; enco+bini, encorafenib in combination with binimetinib; dabra+tram: dabrafenib in combination with trametinib; HR, hazard ratio; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan Meier; MAIC, matching adjusted indirect comparison; NHB, net health benefit; NSCLC, non-small cell lung cancer; OR, odds ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation.

B.3.11. Subgroup analysis

No subgroup analyses were performed.

B.3.12. Benefits not captured in the QALY calculation

Not applicable.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

B.3.13.1.1. Internal validation

Quality control of the economic model was performed by the model developers and by health economists not involved in the development of the model. This included:

- Cell-by-cell checks of formulae
- Rebuilding of key sections of the model
- Logical tests.

The approach to modelling, including long-term survival extrapolations were validated with UK clinical and health economic experts. Expert opinion was sought on the following:

- The current treatment pathway and positioning of enco+bini
- MAIC, including
    - Prognostic factors
    - Treatment effect modifiers.
- Modelling assumptions
- AE inclusion
- Long term estimates of:
    - OS
    - PFS

- TTD.

- Health state utility values.

B.3.13.1.2. External validation

External validation of model outcomes was performed for enco+bini and dabra+tram (Table 101 and Table 102, respectively). The model results were consistent with the results of the PHAROS and BRF113928 studies, however the base case MAIC attempts to adjust for differences seen between populations, so the model slightly overpredicts dabra+tram outcomes.

Table 101: External validation – comparison of enco+bini model outcomes

	PHAROS (DCO: 1st April 2024)	Base case model result – enco+bini
Median OS (months)	NE (95% CI: 31.3, NE)	[redacted]
Median PFS (months)	30.2 (95% CI: 15.7, NE)	[redacted]
Median TTD (months)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; enco+bini, encorafenib in combination with binimetinib; DCO, data cut-off; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

Table 102: External validation – comparison of dabra+tram model outcomes

	BRF113928 (DCO: February 24 2021) (116)	Base case model result – dabra+tram
Median OS (months)	17.3 (95% CI: 12.3, 40.2)	[redacted]
Median PFS (months)	10.8 (95% CI: 7.0, 14.5)	[redacted]
Median TTD (months)	10.55 (range: 0.3, 80)	[redacted]

Abbreviations: CI, confidence interval; dabra+tram, dabrafenib in combination with trametinib; DCO, data cut off; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

B.3.13.1.3. Clinical validation

Clinical expert opinion was obtained to support the assumptions included within the base case economic analysis, as detailed throughout the submission. Two UK advisory boards were held in June 2024 and October 2024 and involved three oncologists representing different centres in England and two health economics experts (16), and one follow-up consultation was held in November 2024.

The following topics were discussed in detail, and expert input was sought on:

- Validation of the treatment pathway in the UK and the current management of patients with advanced NSCLC with a *BRAF* V600E mutation

- Validation of the generalisability of the pivotal PHAROS study and academic IFCT study to UK clinical practice
- Validation of the approach to comparative efficacy estimates against dabra+tram
- Identification of prognostic and treatment effect modifiers relevant to advanced NSCLC with a *BRAF* V600E mutation
- Validation of approach to survival curve extrapolations, and choice of base-case distributions
- Validation of the methodology used to estimate utility values
- Proportion of patients receiving subsequent therapy by treatment arm
- AE management for patients with advanced NSCLC with a *BRAF* V600E mutation and adverse events of concern
- Treatment duration of enco+bini and dabra+tram
- Validation of key assumptions.

B.3.14. Interpretation and conclusions of economic evidence

Clinical experts at the June and October 2024 UK advisory boards advised that the most relevant comparison for decision making was dabra+tram, as patients with *BRAF* V600E MT NSCLC would receive targeted treatment at first-line (16). At the proposed PAS price, enco+bini is associated with incremental QALYs of [redacted] and cost saving of [redacted], resulting in a dominant ICER vs dabra+tram.

Results were found to be robust in the OWSA and in a series of scenario analyses where model assumptions were tested. Enco+bini was dominant when compared with dabra+tram in all scenarios and all OWSA results.

At a WTP threshold of £20,000 and £30,000 per QALY, the NHB associated with enco+bini was [redacted] and [redacted] vs dabra+tram, respectively. Deterministic base case

NHB and ICER estimates were consistent with the probabilistic results (NHB of [redacted] and [redacted], respectively and a dominant ICER). The consistency of results across the deterministic, probabilistic and sensitivity analyses shows that the analysis is robust to uncertainty in the inputs and assumptions, and that enco+bini is a cost-effective use of NHS resources at a WTP threshold of £20,000 and £30,000 per QALY.

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B.5. Appendices

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analyses
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality of life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Price details of treatments included in the submission
- Appendix L: Checklist of confidential information
- Appendix M: Price details of treatments included in the submission
- Appendix N: PHAROS/IFCT methodology – additional information
- Appendix O: Deterministic scenario analysis
- Appendix P: Systematic literature review hand-searching strategies

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from 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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Generic: Encorafenib in combination with Binimetinib (hereafter referred to as enco+bini) Brand name: BRAFTOVI® + MEKTOVI®

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

Enco+bini is intended for use by adult patients with advanced (metastatic) non-small cell lung cancer (NSCLC) who have a specific gene mutation called BRAF V600E. This mutation is a change in the BRAF gene that produces a faulty BRAF protein, which doesn't work properly. The term V600E means that the amino acid valine (V) has been replaced by glutamic acid (E) at position 600 in the DNA sequence.

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.

Enco+bini received CHMP positive opinion on the 25th July 2024. Encorafenib and binimetinib received MHRA approval for NSCLC indication extension on the 14th and 28th of November 2024, respectively.

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:

NA

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. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Condition that the medicine treats Lung cancers begin in cells that cover the lung airways (1) and are categorised into two main subtypes depending on the cell type the cancer originates from: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (2-5). Lung cancer is the fourth most commonly diagnosed cancer in Europe (6). In England and Wales, NSCLC makes up around 88% of all lung cancer cases (7). Approximately 4.4% of all lung cancers have BRAF mutations (8), and these mutations are found in 2% of patients with advanced NSCLC (9). Among those with advanced NSCLC, one-third of the BRAF mutations are specifically the V600E type (10). The way lung cancer develops involves the uncontrolled growth of abnormal cells in the lungs. In lung cancer cells, there are often high rates of DNA mutations of varying types. The following mutations can be associated with the development of lung cancer: EGFR, BRAF, KRAS, MET, ALK, and ROS1 (11-13). BRAF V600E mutations are associated with a biologically aggressive phenotype (how the disease has presented) and a poor prognosis (expected outcome of the disease) (7). Effective treatment options are lacking for patients with advanced NSCLC with a BRAF V600E mutation. **What is the impact of NSCLC on a person's quality of life (QoL)** People with lung cancer experience a range of symptoms and treatment side effects that can have a negative impact on their health. As a result, they usually have a lower QoL compared with people with other types of cancer (14). Symptoms of NSCLC can include chest pain, fatigue, respiratory problems and loss of appetite. Treatments can also cause side effects, such as night sweats, body aches, diarrhoea, headaches,

infections, anaemia, loss of appetite, bruising, and bleeding (15, 16). Lung cancer can also affect relationships, as many patients find it difficult to participate in family and social activities (17) or to work (5).

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?

How is NSCLC diagnosed?

The main method for diagnosing lung cancer is through imaging tests like chest X-rays, MRIs, CT, PET-CT; biopsy techniques such as needle biopsy, bronchoscopy, EBUS; and molecular testing on biopsy samples which can identify specific mutations that can guide treatment options (18).

In England, people diagnosed with NSCLC are regularly tested for gene mutations, including BRAF V600E mutations, which helps physicians to choose the most appropriate treatment. This is so that the most appropriate treatment option can be chosen. Sometimes treatment needs to be initiated with standard chemotherapy or immunotherapy without confirmation of gene status due to delay in gene testing.

2c) Current treatment options:

Treatment is given to help with symptoms and to stop the tumour from spreading and getting worse. Although there are a range of potential treatment options for NSCLC, such as surgery, chemotherapy, radiotherapy, chemoradiation and immunotherapy, the choice of treatment depends on the cancer stage, the presence and type of gene mutations, and any previous treatments the patient may have already received.

As determined by NICE and ESMO guidelines for lung cancer (see Figure 1), the current treatment pathway for patients with advanced NSCLC in England and Wales is divided into targeted and non-targeted treatments. If a patient has a BRAF V600E mutation, targeted therapies such as dabrafenib and trametinib (dabra+tram) are the initial treatment of choice. This is because targeted therapies target the specific mutations found in cancer cells. It is worth also noting that in the July 2024 update of the ESMO Living Guidelines (19), enco+bini is now included as a treatment option for advanced (Stage IV) NSCLC with a BRAF V600 mutation.

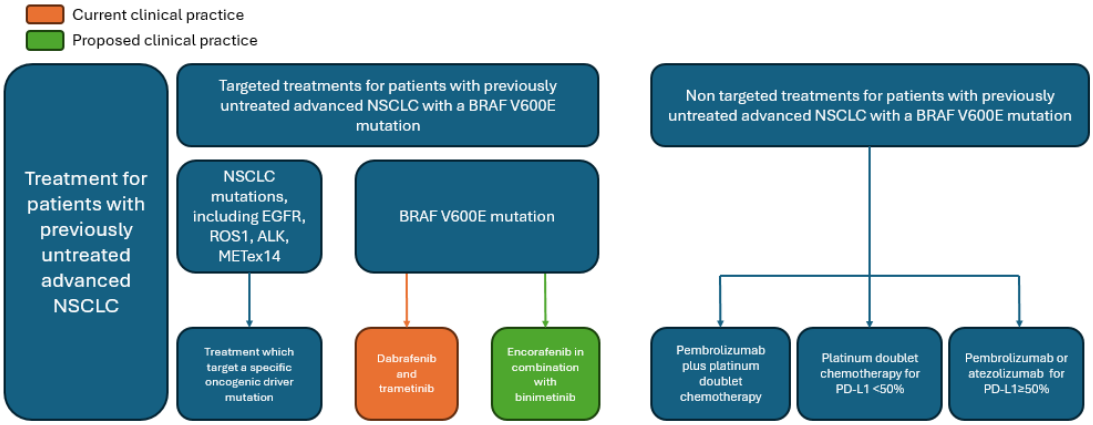
Sometimes dabra+tram can't be used, for instance, if it causes severe side effects (14). In such cases, treatment is given with chemotherapy with or without immunotherapy. However, there is not enough evidence that these treatments are effective, with median overall survival (the average length of time patients are alive after the start of treatment) of around 10 months and a median progression-free survival (the length of time from the start of treatment to the occurrence of disease progression or death) of between 5 to 6.4 months (15, 16).

Enco+bini is a targeted therapy that is similar in mechanism and in the same family of medicines as dabra+tram. Dabra+tram is associated with severe side effects such as pyrexia (fever), resulting in treatment discontinuations. The AEs associated with enco+bini are considered manageable (17, 18).

Despite recent advances in treatment for patients with advanced NSCLC, survival rates are still low. According to the 2017 National Lung Cancer Audit data, only 15.5% of patients with advanced disease (Stage IV) survive for one year, compared to 81.7%, 64.1%, and 42.5% for patients with Stage I, Stage II, and Stage III disease, respectively (46). This shows that there is still a need for new targeted treatments like enco+bini to give patients more treatment options.

The main evidence supporting the case for enco+bini as an additional first-line treatment option comes from the PHAROS trial, and clinical experts also agreed that enco+bini would be used as a first-line treatment (20).

Figure 1: Current/proposed treatment pathway for previously untreated advanced NSCLC in UK clinical practice



Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; METex14, Hepatocyte growth factor receptor exon 14 skipping; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; TA, Technology Appraisal; UK, United Kingdom.
Source: NICE NSCLC guidelines (60); ESMO guidelines (61).

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

The symptoms of advanced NSCLC greatly affect patients' QoL. Studies have shown that advanced NSCLC significantly lowers patients' scores on the EQ-VAS scale (EQ-Visual Analogue Scale) - a questionnaire which measures patient mobility, self-care, daily activities, pain, and anxiety/depression. Patients with worsening advanced NSCLC have lower average scores compared to those whose disease does not worsen. This highlights the need for more first-line treatment options for advanced NSCLC, as stopping the disease from progressing can also improve patients' QoL (21)

SECTION 3: The treatment

3a) How does the new treatment work?

Encorafenib is a potent and highly selective RAF inhibitor that suppresses the RAF/MEK/ERK signalling pathway in cancer cells that contain a faulty version of the BRAF protein (V600E, D and K). It is especially effective against particular mutated forms of this protein found in certain tumours, such as BRAF V600E (22).

Binimetinib is a MEK inhibitor that slows down the growth of cancer cells with the V600E mutation and has shown positive results in animal studies with this type of cancerous growth (23).

Enco+bini are small medical compounds that can enter cancer cells and block the faulty BRAF and MEK proteins. By blocking these proteins, the cancer cells die. Encorafenib (capsules) and binimetinib (tablets) can be taken orally (swallowed) at home. This makes the treatment more convenient and less painful than treatments given through an intravenous (IV) infusion, which is administered in hospital.

Summary of product characteristics are available through the following links:

Encorafenib (https://www.ema.europa.eu/en/documents/overview/braftovi-epar-medicine-overview_en.pdf)

Binimetinib (https://www.ema.europa.eu/en/documents/product-information/mektovi-epar-product-information_en.pdf)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

No

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?

Encorafenib:

The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib (22).

Binimetinib:

The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg, taken approximately 12 hours apart (23).

Enco+bini can be taken orally at home, unlike chemotherapies and immunotherapies, which are administered intravenously in hospital. An oral treatment is more convenient and less painful than an intravenous infusion. It also removes the anxiety and stress associated with hospital visits, therefore improving the QoL for patients and their caregivers.

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.

PHAROS

The clinical efficacy (how well the treatment works) and safety of enco+bini was studied in PHAROS (NCT03915951), a pivotal Phase 2, open-label clinical trial conducted in adult patients with advanced NSCLC with a BRAF V600 mutation (24, 25). Results from the study have been published (26).

The key inclusion criteria for PHAROS included:

- A confirmed NSCLC diagnosis at Stage IV
- Presence of a BRAF V600E mutation
- Patients who were either treatment-naïve (e.g., no prior systemic (targeting the whole body) therapy for advanced/metastatic disease), OR who have received 1) first-line chemotherapy that includes drugs containing platinum ion compounds OR 2) first-line treatment with an anti-programmed cell death protein 1 (PD-1)/ programmed cell death protein ligand 1(PD-L1) inhibitor given alone or in combination with platinum-based chemotherapy
- Presence of measurable disease based on Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1)
- Eastern Cooperation Oncology Group (ECOG) performance status of 0 or 1

The key exclusion criteria for PHAROS included:

- Patients who have documentation of any of the following:
- Epidermal growth factor receptor (EGFR) mutation
- Anaplastic lymphoma kinase (ALK) fusion oncogene or
- ROS1 rearrangement
- Patients who have received more than 1 prior line of systemic therapy in the advanced/metastatic setting
- Previous treatment with any BRAF inhibitor (e.g., dabrafenib, vemurafenib, XL281/BMS-908662, etc.), or any mitogen-activated protein kinase (MEK) inhibitor (e.g., trametinib, cobimetinib, selumetinib, RDEA119, etc.) prior to screening and enrolment
- Impaired cardiovascular function or clinically significant cardiovascular diseases

IFCT

The safety, effectiveness, and QoL of enco+bini in patients with advanced NSCLC with a BRAF V600E mutation were also studied in a separate phase 2, open-label multicentre study called IFCT (NCT04526782). IFCT is an academic investigator-initiated study conducted by the academic group Intergroupe Francophone de Cancérologie Thoracique (IFCT). This study is currently ongoing (27).

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.

PHAROS

Treatment with enco+bini resulted in a clinically meaningful benefit in overall response rate ([ORR] – defined as the percentage of patients whose cancer shrinks or disappears after treatment) in treatment naïve patients (meaning patients who have not yet received any treatment) (see section B.2.6.2 of the main submission).

Key patient characteristics in the PHAROS trial (see Section B.2.3.1.6 of document B):

- Sex was well balanced, with 56% of patients being women and 44% men
- Most of the patients were white (90%)
- None of the patients had an Eastern Cooperation Oncology Group (ECOG) performance (test of functioning in terms of self-care) score above one at study entry (valued 0–3 with higher scores meaning less self-care ability from the patient).
- Most (56%) of the patients were former smokers
- Most (73%) of patients did not have prior radiotherapy
- 24% of patients had prior systemic treatment with immunotherapy
- The predominant American Joint Committee on Cancer (AJCC) staging at diagnosis was stage IV (28.6%), followed by stage IV-A (25.5%), and then stage IV-B (24.5%).
- The majority of patients presented with an adenocarcinoma (96.9%) and 8.2% of patients had brain metastases (28).
- In the treatment-naïve patients, overall response rate (ORR) by independent radiology review (IRR) was 74.6% (percent of patients responding to treatment).

Other secondary endpoints by IRR in treatment naïve patients (see Section B.2.6.1.2 in document B), included:

- Median duration of response (average time that patients continued to respond to treatment)
- Disease control rate (cancer stopped growth or shrank)
- Median time to response
- Median PFS (time before cancer growth began again)
- Nearly half of the patients were alive and in follow-up for survival at the data cut-off

IFCT

In the IFCT study, the primary outcome was ORR in response to treatment with enco+bini (see Section B.2.6.2 in document B for more information).

Indirect treatment comparison

Since there are no studies directly comparing enco+bini with other treatments like dabra+tram, an indirect treatment comparison (ITC) was conducted. When no direct comparison is available, an ITC approach can

provide useful evidence on the difference in efficacy between treatments. In the ITC, evidence from PHAROS and BRF113928 were compared to determine the relative efficacy of enco+bini vs dabra+tram (see section B.2.9.2.3 in document B).

*Refer to Glossary of terms

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.

In the IFCT study, the EQ-5D questionnaire was used during the final evaluation phase to assess the QoL of patients treated with enco+bini. This questionnaire is completed by patients themselves and provides a detailed overview of their current health by assigning numbers to various aspects, such as their ability to stay mobile and fulfil daily tasks (see section B.2.6.2.2.4).

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.

Overall, the enco+bini safety profile was consistent with side effects observed in other approved indications for the population. The most common side effects reported in patients treated with enco+bini are nausea, diarrhoea, vomiting, anaemia, and constipation (20) (see section B.2.11.1.3 in document B).

For more information on the side effects of enco+bini, please refer to the Summary of Product Characteristics (SmPC) (22, 23) and the package leaflet.

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

For adult patients with advanced NSCLC who have a BRAF V600E mutation, there are few first-line treatment options available. Enco+bini is effective and beneficial for patients who have not previously received treatment, providing a sustained response and manageable side effects. In the PHAROS study, patients who had not previously received treatment showed benefits in ORR (percentage of patients whose cancer shrinks or disappears after treatment) as well as survival benefits when taking enco+bini.
Clinical experts report that enco+bini is less toxic compared with other treatments which makes it easier for patients to continue treatment and may improve QoL for patients.
Enco+bini is easy to administer and is convenient for patients because it is an oral treatment and can be taken at home (20, 29)

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.

All medicines can cause side effects. Some side effects that patients might experience with this medicine, like nausea and vomiting, are listed in Section 3G. Clinicians are familiar with the management of these common side effects. There are few serious adverse events (which may be fatal or life-threatening or require that hospital admission or extended hospital stay) reported with enco+bini.

3i) 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.

How the model reflects the condition

The economic model uses a "partitioned survival analysis" to estimate the costs and benefits of treating advanced NSCLC in adults with a BRAF V600E mutation. The model includes three distinct health states: progression-free, post-progression, and dead. These types of models are common in economic analyses of cancer treatments because they match common clinical trial endpoints and accurately reflect how the disease progresses. At the start of the model all patients are in the progression-free state while on treatment. Over time, as the disease spreads, patients may move to the progressed disease state or death. The model is used to calculate and compare the overall costs of treatment with enco+bini versus the current standard-of-care (SoC) therapy. For patients with advanced NSCLC with a BRAF V600E mutation, the current SoC is targeted therapy with dabra+tram as the first treatment option.

Modelling how treatment extends life

Clinical data for enco+bini are available from the pivotal phase 2 clinical trial PHAROS, and the supportive IFCT academic study, and these data are used to inform the model. In the model, the percentage of patients in each of the three health states over time while on enco+bini treatment is defined by OS and PFS data from the PHAROS trial. The number of patients who remain on treatment over time is defined by the time to treatment discontinuation data. Since the trial only provides 41 months of data, the model is used to predict what could happen to a patient for the remainder of their lifetime. To estimate the equivalent proportions over time for patients receiving dabra+tram in the model, a matching-adjusted indirect comparison (MAIC) was conducted to compare the efficacy of dabra+tram from the BRF113928 trial with enco+bini, as described in Section 3e.

Modelling impact on quantity and QoL

Patient outcomes are measured as quality adjusted life-years (QALYs), a measure that reflects the impact of treatment on both life expectancy and QoL. A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

Modelling costs

The health economic model examines the costs of treating and managing NSCLC patients over their lifetime. This includes the costs of treatment itself, monitoring, dealing with side effects, and end-of-life care. The model used the discounted NHS price for enco+bini but could not include discounts for dabra+tram as these prices are confidential. Overall, the total cost of treatment with enco+bini is expected to be lower than with dabra+tram. This is primarily due to the lower price of enco+bini, even though patients stay on treatment with enco+bini for a longer period.

Uncertainty

Healthcare economic modelling can be uncertain. Predicting long-term outcomes is difficult because not all patients are followed until the end of clinical studies. Comparing different treatments is also challenging because there is often no direct head-to-head comparison data available. In these circumstances, indirect comparisons are undertaken to compare the impact of different treatments. To understand how these uncertainties affect the results, the values for data inputs were varied, and the results were assessed at different values.

Cost-effectiveness results

Cost-effectiveness results for enco+bini versus current SoC can be found in Section B.3.9 of the Company Submission.

The economic model predicts that people with advanced NSCLC with a BRAF V600E mutation who are treated with enco+bini will live longer than those treated with dabra+tram. Based on the PHAROS trial data, enco+bini shows improved mean OS and PFS compared with dabra+tram. The trial data also showed that enco+bini was well-tolerated in both the PHAROS trial and the IFCT study, with manageable side effects. The economic model also predicts a QALY benefit for patients treated with enco+bini over dabra+tram, as patients remain progression-free and alive for longer.

In summary, all analyses show that enco+bini treatment is associated with a survival benefit and improved QoL for adult patients with advanced NSCLC with a BRAF V600E mutation. All analysis conducted show that enco+bini is a cost-effective use of NHS resources. Tests around uncertainty did not change these conclusions.

3j) 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)

Enco+bini targets proteins in the same cell signalling pathway as dabra+tram, offering another first-line treatment option that blocks the RAF/MEK/ERK pathway in tumour cells with different mutated forms of BRAF kinase (V600E, D and K). Additionally, enco+bini has shown a clinically meaningful impact on ORR in patients, demonstrating its effectiveness and long-lasting action compared to dabra+tram (see also section 3e) (22, 30-34).

Enco+bini is administered orally, unlike chemotherapies and immunotherapies, which are administered intravenously. Having an oral treatment option helps the NHS by reducing the number of patients who require IV access to chemotherapy in hospital. This also reduces the financial and administrative burden on the NHS and improves the QoL for patients and their caregivers by removing the anxiety and stress associated with hospital visits.

Enco+bini addresses an unmet need for more convenient treatment options for adults with advanced NSCLC with a BRAF V600E mutation.

3k) 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

NA

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.

Further information on NSCLC guidelines:

- The Royal Marsden NHS Foundation trust. Lung cancer https://www.royalmarsden.nhs.uk/your-care/cancer-types/lung-cancer
- European Society for Medical Oncology (ESMO). Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC) Treatment Recommendations https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer-esmo-clinical-practice-guidelines/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations2
- NICE guidance on lung cancer: diagnosis and management Overview | Lung cancer: diagnosis and management | Guidance | NICE

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
- 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/
- The International Network of Agencies for Health Technology Assessment – INAHTA: http://www.inahta.org/

4b) Glossary of terms

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

Disutility: Represents the decrement in utility (valued quality of life) due to a particular symptom or complication.

Duration of response (DOR): The length of time that a tumour continues to respond to treatment without the cancer growing or spreading

First-line: the first treatment given for a disease

Investigator assessment (IA): Refers to data verified by a person involved in running the clinical trial

Incremental cost-effectiveness ratio (ICER): The ICER is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.

Intravenous (IV): A medical technique that administers fluids, medications, and nutrients into a person's vein.

Independent radiology review (IRR): Refers to an unbiased evaluation of the data by radiologists not involved in the trials day to day operations

Mean: In statistics, the mean or average is the sum of numbers divided by the number of numbers. E.g. from adding the following seven numbers together and dividing by seven, the mean is 5.3: 1+3+3+6+7+8+9=37.7; 37.7/7=5.3.

Median: In statistics, the median is the value separating the higher half from the lower half of a data sample. E.g. out of the following numbers, 6 is the median: 1, 3, 3, 6, 7, 8, 9.

NICE: The National Institute for Health and Care Excellence. It is an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England.

Overall response rate (ORR): The total number of patients whose cancer has either gone away (a complete response) or shrunk (a partial response).

Progression-free survival (PFS): The length of time from the start of treatment to the occurrence of disease progression or death.

Patient Reported Outcomes Measurement Information Service (PROMIS): A set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children.

Quality of life (QoL): A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Quality-adjusted life years (QALYs): QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their health-related QoL (measured on a 0–1 scale).

Standard-of-care (SoC): Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease.

Treatment naïve: When a patient has not yet received any treatment for the condition in question

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

Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID6177 encorafenib EAG Clarification letter_response v2.0_[Redacted]	2.0	No - redacted	01/05/2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A 1. Priority question. The population in the decision problem (DP) is narrower than in the NICE scope i.e. treatment-naïve (first line) only. However, the company state that: "the number of patients eligible to receive enco+bini in second-line will likely decrease over time, with the majority of eligible patients receiving targeted therapies in the first-line." (Table 1). This statement suggests that the population in the DP should include 2nd line, even if the number of patients does diminish over time.

a) Please clarify whether the population to be considered in this appraisal is only 1st line or both first and 2nd line.

The population considered is first-line only. Further details on the rationale for this approach are provided in B3.

b) If 2nd line treatment is included then please also include a comparison between encorafenib + binimetinib and comparators that form current

clinical practice for 2nd line in the UK, both in an indirect treatment comparison (ITC) and cost effectiveness analysis (CEA).

NA

A 2. Priority question: Nivolumab with ipilimumab is not recommended for use in the NHS. Given this, please clarify why it has been modelled as a subsequent treatment in the base case analysis. Please could you remove it from the base case analysis in order to reflect NHS clinical practice?

Subsequent treatment types and proportions were modelled in line with the PHAROS trial, with the exception of subsequent enco+bini and dabra+tram after primary treatment with enco+bini and dabra+tram, respectively. This approach was based on clinical expert (CE) opinion received during an advisory board which suggested that patients would not be eligible for re-treatment with a second targeted therapy such as dabra+tram or enco+bini. However, the base case has been updated such that the subsequent therapy proportions are reweighted to remove all therapies not used in UK clinical practice (i.e. removing unused therapies and reweighting assuming the same distribution across the remaining therapies such that they total to one:

- Enco+bini
- Dabra+tram
- Nivolumab with ipilimumab
- Nivolumab with ipilimumab and cisplatin
- Nivolumab with ipilimumab and carboplatin.

Table 1: Subsequent therapy proportions – including and excluding enco+bini, dabra+tram, and nivolumab with ipilimumab

	Company base case		Revised base case – enco+bini, dabra+tram, and nivolumab with ipilimumab subsequent treatments removed	
	Enco+bini	Dabra+tram	Enco+bini	Dabra+tram
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + cisplatin + pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab +	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy only	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

Results of the revised base case are presented in Table 2. This update results in a negligible change to the net health benefit (NHB) and the incremental cost-effectiveness ratio (ICER) remains dominant. Table 2 also presents the revised base case results based on corrections noted in clarification question B27. The revised base case NHB is [redacted]. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 2: Scenario analysis results – subsequent therapies

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS subsequent therapy proportions	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
+ (A2) all non-UK subsequent therapies removed	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

A 3. Priority question. Several comparators in the NICE scope have been omitted for treatment naïve (1st line) patients. This seems to be on the basis of availability of testing for *BRAF* V600E mutations.

a) Please clarify that no patients at 1st line are currently treated in the UK NHS with anything but dabrafenib with trametinib.

b) If even a small number of patients are treated with any other treatment then please perform an ITC and CEA for each of these comparisons.

Gene testing is routinely carried out in the UK by the NHS for NSCLC patients. Therefore, very few patients in the UK may be treated by the NHS at first-line with treatments other than dabrafenib with trametinib (dabra+tram). Pembrolizumab with carboplatin and paclitaxel, pembrolizumab or atezolizumab, or platinum doublet chemotherapy are other first-line options. However, the CEs agreed that dabra+tram was the most appropriate comparator as there is no reason not to choose a targeted therapy if a patient has a known *BRAF* V600E mutation. For this reason, we have determined that is no rationale to complete an ITC and CEA for other treatments (1).

Systematic review

A 4. Please confirm whether the same methodological approach was taken to conduct the SLR during each stage (outlined in Appendix D) for each update of the SLR (October 2021, May 2023, July 2023 and May 2024).

The same methodological approach was taken for the original SLR and updates. Some handsearching methods in the October 2021 original SLR, and May 2023 and

July 2023 SLR updates were not clearly reported (e.g. key words to search sources and any filters used). This means that the handsearching could not be reproduced in the same way in the May 2024 SLR update. Therefore, handsearching was completed without any date limits in May 2024 to ensure all relevant publications were captured. Any relevant publications identified during handsearching that were published prior to 2024 were cross checked with the included studies list of the original SLR and updates. There were no additional relevant publications identified that should have been included in the previous iterations of the SLR as they had already been identified.

A 5. Please explain what is meant by "all extractions including extractions for quality assessment were verified by a second independent reviewer".

Extractions and quality assessment of the included studies were completed by a single reviewer. There was a 100% quality check of all extractions and quality assessment by a second, independent reviewer.

A 6. Appendix D Table 19 indicates that only studies published in English language were included in the SLR. Please explain the impact of exclusion of studies published in non-English languages.

In the May 2024 SLR update, it was not deemed necessary to re-run the October 2021 original SLR, or May 2023 and June 2023 SLR updates to include non-English publications. If the searches for the clinical SLR were run without any language limits, there are very few additional publications.

Language limits were only applied to Embase, MEDLINE, CENTRAL, and DARE/HTAD search strategies. The October 2021 search strings for these databases (detailed in Appendix D) were run in Ovid on the 10th January 2025, once without the English language restriction and once with the English language restriction (Table 3). The difference in the number of hits was screened to check whether any relevant non-English language publications were identified.

The searches from the original SLR were used as there is no date limit in these search strings. The updated SLR search strings would have provided the same results after removing the date limits. The aim of these additional searches is to identify the number

of publications over the same time period allowing the total number of hits to be compared.

Table 3: English language vs no restriction searches

	Search 1	Search 2	Search 2 – search 1
Embase	Search string from Table 2 of Appendix D (including English-language restriction) **Number of hits: 6,308**	Search string from Table 2 of Appendix D changed to remove the English language restriction (therefore including non-English language + English language publications) **Number of hits: 6,366**	6,366 – 6,308 = 58
Medline	Search string from Table 3 of Appendix D (including English-language restriction) **Number of hits: 1,594**	Search string from Table 3 of Appendix D changed to remove the English language restriction (therefore including non-English language + English language publications) **Number of hits: 1,628**	1,628 – 1,594 = 34
CENTRAL	Search string from Table 4 of Appendix D (including English-language restriction) **Number of hits: 502**	Search string from Table 4 of Appendix D changed to remove the English language restriction (therefore including non-English language + English language publications) **Number of hits: 506**	506 – 502 = 4
DARE/HTAD	Search string from Table 6 Appendix D (including English-language restriction) **Number of hits: 8**	Search string from Table 6 Appendix D without English language restriction (therefore including non-English language and English language publications) **Number of hits: 8**	8 – 8 = 0

The difference between the numbers of hits (and therefore the non-English language publications) was 58 in Embase, 34 in MEDLINE, 4 in CENTRAL, and 0 in DARE/HTAD. After removal of 20 duplicates, 76 publications were screened at title/abstract. Seventy-four were excluded at title/abstract and two publications were excluded at the full-text screening stage (Table 4). Therefore, no non-English language publications were identified that were relevant for inclusion in the clinical

SLR. The use of English-language limits in the search strings did not have any impact on the SLR findings.

Table 4: Non-English language publications that were excluded at full-text

Author, year	Title	Exclusion reason
Misch 2022	Erstlinientherapie mit Nivolumab (NIVO) + Ipilimumab (IPI) + 2 Zyklen Chemotherapie (chemo) vs Chemotherapie allein (4 Zyklen) in Patienten (pts) mit metastasiertem nichtkleinzelligem Lungenkarzinom (mNSCLC): 3 Jahre-Update von CheckMate 9LA	Abstract only and no data reported separately for *BRAF* v600e patients
Misch 2022	Erstlinientherapie mit Nivolumab (NIVO) + Ipilimumab (IPI) + 2 Zyklen Chemotherapie (chemo) vs Chemotherapie allein (4 Zyklen) in Patienten (pts) mit metastasiertem nichtkleinzelligem Lungenkarzinom (mNSCLC): 3 Jahre-Update von CheckMate 9LA	Duplicate

Clinical effectiveness evidence

A 7. Please provide subgroup analyses for the overall survival outcome of the PHAROS trial.

Subgroup analyses were not conducted for the overall survival (OS) outcome and was not planned for in the PHAROS trial.

Indirect treatment comparison (ITC)

A 8. Priority question: In Appendix D the company state: *"STC is not recommended for the analysis of non-linear or time-to-event outcomes."* However, no reasoning or references are provided.

a) Please provide supporting references and reasoning for this statement.

b) Please conduct an STC on the basis that it is listed as a method of population adjustment alongside MAIC in NICE TSD 18.

MAIC is the method most commonly used in HTA submissions, especially using an unanchored approach setting and for time-to-event outcomes (2, 3). STC is infrequently used in HTA, Pilkington et al. (4) note that since the 2020 DSU

recommendations were published (and up to 7th June 2023), there were only 4 STCs submitted to NICE, none formed the ITC base case.

In this analysis, an unanchored MAIC was considered more appropriate than a STC for the following reasons:

- The primary outcomes of interest are time-to-event outcomes whereas the secondary outcomes are binary. Technical challenges associated with the application of the unanchored STC method with non-linear outcomes are well documented in the literature (ISPOR poster LeNouveau 2023 (5), Macabeo 2024 (6, 7)). Ren et al. note that *"Further research is required to develop an unbiased unanchored STC approach for time-to-event data (8)"*

- As per Hatswell et al. (9), an unanchored MAIC is appropriate provided there is a large enough effective sample size and there is reasonable overlap between the trial characteristics. During the advisory board, health economic (HE) experts and CEs noted that the trial characteristics were reasonably similar, and after matching the HE experts considered the effective sample size to be appropriate to inform the analysis

- A MAIC is more efficient than other comparison methods when there is only one comparator with multiple outcomes, as the weighting of patients only needs to be done once per comparator.

- The size of the PHAROS population, 59 patients, was considered too small to be able to robustly fit predictive equations predicting each outcome according to the seven adjustment factors identified as relevant, a crucial step in the STC approach.

The Company believe that, although new research has recently been published in this area, there is not yet consensus on which is the most appropriate method for indirect comparison between treatments (3). Moreover, as unanchored MAICs have been widely accepted as a valid approach in previous oncology submissions, the analysis

presented in the original Company submission is sufficient for decision making purposes (10).

A 9. Priority question: In line with question A3, if treatment experienced patients would be eligible for encorafenib + binimetinib, then please also conduct an ITC for a comparison with treatments appropriate for this line of therapy.

The population considered is first-line only based on current expert guidance. Patients with NSCLC with *BRAF* V600E mutation would be treated using targeted therapy (currently dabra+tram) and CEs indicated that patients treated with a targeted therapy in first-line would not be eligible for targeted therapy in second-line. Further details on the rationale for this approach are provided in the response to question B3.

A 10. Priority question. The study by Fan 2022 (NCT04452877) was included in the SLR, but this study was excluded from the ITC. However, it appears that this study includes relevant population, treatment and line of therapy.

a) Please explain why this study was excluded.

b) Please include this study in an ITC if it provides relevant data.

Fan 2022 (NCT04452877) is an interventional study to assess safety and efficacy of dabra+tram in a Chinese population with *BRAF* V600E-mutation positive metastatic NSCLC, in all lines (i.e. first-line and second-line plus). This publication is a conference abstract presenting the preliminary data of the study. Given Fan 2022 was conducted exclusively in a Chinese population, it is not considered suitable for an ITC given the small proportion of Asian patients treated at first-line in PHAROS (5%). In addition, only the overall response rate (ORR) is presented, and other efficacy outcomes of interest are not reached due to the short follow-up period. In a very recent publication (Fan et al. 2024 (11)), the medians were still not reached (median of follow-up 5 months). Kaplan-Meier (KM) curves of OS and progression-free survival (PFS) are presented but only for the full population (first-line and second-line plus combined).

Outcomes are not presented for first-line and second-line separately, which is not aligned with the base case population of this appraisal (treatment-naïve patients only).

Section B: Clarification on cost-effectiveness data

B1. Priority question. The company submission (CS) contains notable repetition, which raises concerns about its clarity and accuracy. For instance, the text on pages 117–118 repeats this statement 4 times within a short section: "*Experts stated there was no clinical rationale to not use a targeted therapy if a BRAF V600E mutation is present. This view is aligned with TA898, where both the committee and clinical experts noted that only a few people with a BRAF V600E mutation have delayed screening results and start a treatment other than targeted therapy (98). Therefore, it is expected that the number of people receiving targeted therapy at second line will fall substantially over time as access to testing improves. This is also aligned with NICE guidance for dabra+tram, which recommends dabra+tram as an option for treating patients with BRAF V600E MT NSCLC, only if it is used as first-line treatment (98)*."

a. **How does the company ensure the accuracy, consistency, and clarity of the CS, particularly in addressing issues of redundancy, such as this example, and potential inconsistencies in the narrative? Please describe the quality assurance processes in place.**

b. **Was ChatGPT or any other large language model (LLM) used in drafting or contributing to any part of the CS? If so, please detail the scope of its use, including any sections generated or edited by AI tools.**

c. **NICE has issued guidance on the use of AI in evidence generation and reporting (see https://www.nice.org.uk/about/what-we-do/our-research-work/use-of-ai-in-evidence-generation--nice-position-statement). Please confirm that the company adheres to this guidance, in general and specifically in relation to transparency, reproducibility, and compliance with point 8 of the statement.**

The repetition noted in the CS was the result of a technical error which can occur when using EndNote with SharePoint tracked changes, which led to synchronisation conflicts when saving the final version of the document. This error has been corrected and a version of the submission with the repeated sections removed has been provided.

To ensure accuracy and consistency within the CS, quality checks and document version control are methods incorporated throughout the submission process to address issues such as inconsistencies or redundancies.

The Company is aware of and adherent to NICE guidance regarding the use of AI in evidence generation, and confirm that ChatGPT or any other LLMs were not utilised during the process of the CS.

Literature reviews

B2 According to CS appendix G, the last systematic literature review (SLR) update on published cost-effectiveness studies occurred in May 2024. Please provide an updated SLR.

As the search strings for the cost-effectiveness and healthcare resource use (HCRU) and cost SLRs are combined, both SLRs were updated in January 2025 for completeness.

Data sources

The electronic databases searched during the original SLR in June 2023 and the SLR update in May 2024 are provided in Appendix G. The electronic databases for the January 2025 SLR update are outlined in Table 5. The Health Technology Assessment Database (HTAD) and National Health Service Economic Evaluation Database (NHS EED) were last updated in 2016 in Ovid and were searched during the June 2023 original SLR. Consequently, no new relevant records would be identified in the January 2025 SLR update, and these databases were not searched during the January 2025 SLR update.

Table 5: Electronic databases included in the January 2025 SLR update

Database	Platform	Span of search	Date searched
Embase	Ovid	**Second SLR update (January 2025)** From 2024 to January 07, 2025	**Second SLR update (January 2025)** 8th January 2025
MEDLINE Daily, In-Process & Other Non-indexed citations, and e-pub ahead-of-print		**Second SLR update (January 2025)** From 2024 to January 06, 2025	
CRD – HTA database†		**Second SLR update (January 2025)** NA	
CRD – NHS EED†		**Second SLR update (January 2025)** NA	
EconLit		**Second SLR update (January 2025)** From 1886 to January 02, 2025	

†The CRD databases are no longer included in the Cochrane library, from 7th August 2018. CRD are maintaining versions of DARE and NHS EED until at least 2021, with records published on DARE and NHS EED until 31st March 2015. From 31st March 2018, CRD is no longer adding records to the HTA database. More details available at: https://www.crd.york.ac.uk/CRDWeb/ and https://onlinelibrary.wiley.com/doi/abs/10.1002/jrsm.1235.
Abbreviations: HTA, health technology assessment; NA, not applicable; NHS EED, National Health Service Economic Evaluation Database; SLR, systematic literature review.

Handsearching

The same sources listed in Section G.1.1.2 of Appendix G were searched during handsearching for the January 2025 SLR update.

SLR search strategy

Other than the addition of date limits, the search strings were identical to the original SLR in June 2023 and the SLR update in May 2024. The search strings for the January 2025 SLR update are provided below.

Database: Embase

Hits: 84

Date searched: 08/01/2025

#	Searches	Results
1	exp lung cancer/	474264
2	((non-small or nonsmall) and cell).ti,ab,kw.	155412
3	nsclc.ti,ab,kw.	125163
4	2 or 3	175524
5	1 and 4	129288
6	exp non-small cell lung cancer/	181402
7	(Lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab,kw.	154493
8	nsclc.ti,ab,kw.	125163
9	6 or 7 or 8	245470
10	5 or 9	245690
11	oncogene ras/	11381
12	oncogene k ras/	13615
13	K ras protein/	32015
14	oncogene ki ras/	65
15	kras gene/	1418
16	"Ras protein"/	28835
17	(k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS or ras or nras or n-ras).mp.	168952
18	"n ras protein"/	358
19	"Oncogene N ras"/	9904
20	B Raf kinase/	37018
21	exp B Raf kinase inhibitor/	18691
22	braf gene/	5041
23	(braf or b raf).mp.	58172
24	"*BRAF*V600E gene"/	66
25	or/11-24	207748
26	10 and 25	20107
27	exp "cost of illness"/ or (cost analysis or cost-analysis).ti,ab,kw. or ((disease$ or sickness or illness) adj2 cost$).ti,ab,kw. or (economic adj5 (burden or cost$ or impact)).ti,ab,kw. or ((direct or medical or indirect or nonmedical or societ* or employe*) adj2 (cost* or resource* or benefit*)).ti,ab,kw. or ((drug$ or healthcare or health care) adj2 (cost$ or price$ or pricing)).ti,ab,kw. or ((hospital$ or re-hospital$ or rehospital$ or admit$ or admission$ or re-admission$ or readmission$) adj2 (cost$ or price$ or rate$ or risk$ or number$)).ti,ab,kw. or length of stay.ab. or exp health care utilization/ or exp hospital utilization/ or exp hospital bed utilization/ or exp drug utilization/ or ((health care or healthcare or resource*) adj2 (use* or utili*)).ti,ab,kw. or exp *productivity/ or (productivity cost$ or productivity).ti,ab,kw. or (productivity loss or (productivity adj2 los*)).ti,ab,kw. or exp *Absenteeism/ or	2159470

#	Searches	Results
	exp *Presenteeism/ or exp *Medical Leave/ or (absenteeism or presenteeism or sick leave).ti,ab,kw. or cost*.ti,ab.	
28	exp economic model/ or exp economic evaluation/ or exp "cost effectiveness analysis"/ or ((cost-effective* adj1 analys*) or (cost adj1 effectiveness adj1 analys*)).mp. or exp "cost benefit analysis"/ or ((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. or exp "cost utility analysis"/ or (cost utility analys* or (cost-utility adj1 analys*)).mp. or exp "cost minimization analysis"/ or (cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. or (cost consequence analys* or (cost consequence adj1 analys*)).mp.	387775
29	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. and (("CEA" or "CMA" or "CBA" or "CUA" or "CCA" or "CEM").mp. or exp decision theory/ or exp "decision tree"/ or decision tree.mp. or economic model.mp. or (markov or deterministic or monte carlo or partition* survival).mp. or ((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. or ((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. or (incremental-cost or incremental cost).mp. or ("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.)	17764
30	27 or 28 or 29	2275008
31	26 and 30	701
32	limit 31 to yr="2024-Current"	84

Database: MEDLINE

Hits: 5

Date searched: 08/01/2025

#	Searches	Results
1	Lung Neoplasms/	275174
2	((non-small or nonsmall) and cell).ti,ab,kw.	97046
3	nsclc.ti,ab,kw.	68182
4	2 or 3	102879
5	1 and 4	71699
6	Carcinoma, Non-Small-Cell Lung/	77376
7	(Lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab,kw.	96411
8	nsclc.ti,ab,kw.	68182
9	or/6-8	113029
10	5 or 9	113163
11	Genes, ras/	12765
12	exp ras Proteins/	26110

#	Searches	Results
13	(k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS or ras or nras or n-ras).mp.	98455
14	Proto-Oncogene Proteins B-raf/	12883
15	(braf or b raf).mp.	25221
16	oncogene ras.mp.	201
17	oncogene k ras.mp.	73
18	K ras protein.mp.	114
19	oncogene ki ras.mp.	8
20	kras gene.mp.	1157
21	"n ras protein".mp.	53
22	"Oncogene N ras".mp.	20
23	B Raf kinase.mp.	173
24	B Raf kinase inhibitor.mp.	10
25	braf gene.mp.	1076
26	"*BRAF*V600E gene".mp.	41
27	or/11-26	114063
28	10 and 27	5433
29	exp "cost of illness"/ or (cost analysis or cost-analysis).ti,ab,kw. or ((disease$ or sickness or illness) adj2 cost$).ti,ab,kw. or (economic adj5 (burden or cost$ or impact)).ti,ab,kw. or ((direct or medical or indirect or nonmedical or societ* or employe*) adj2 (cost* or resource* or benefit*)).ti,ab,kw. or ((drug$ or healthcare or health care) adj2 (cost$ or price$ or pricing)).ti,ab,kw. or ((hospital$ or re-hospital$ or rehospital$ or admit$ or admission$ or re-admission$ or readmission$) adj2 (cost$ or price$ or rate$ or risk$ or number$)).ti,ab,kw. or length of stay.ab. or exp health care utilization/ or exp drug utilization/ or ((health care or healthcare or resource*) adj2 (use* or utili*)).ti,ab,kw. or exp *productivity/ or (productivity cost$ or productivity).ti,ab,kw. or (productivity loss or (productivity adj2 los*)).ti,ab,kw. or exp *Absenteeism/ or exp *Presenteeism/ or (absenteeism or presenteeism or sick leave).ti,ab,kw.	719946
30	exp economic model/ or exp economic evaluation/ or exp "cost effectiveness analysis"/ or ((cost-effective* adj1 analys*) or (cost adj1 effectiveness adj1 analys*)).mp. or exp "cost benefit analysis"/ or ((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. or exp "cost utility analysis"/ or (cost utility analys* or (cost-utility adj1 analys*)).mp. or exp "cost minimization analysis"/ or (cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. or (cost consequence analys* or (cost consequence adj1 analys*)).mp.	290734
31	((economic or pharmacoeconomic) adj2 (evaluation or assessment or analysis or stud*)).mp. and (("CEA" or "CMA" or "CBA" or "CUA" or "CCA" or "CEM").mp. or exp decision theory/ or exp decision tree/ or decision tree.mp. or economic model.mp. or (markov or deterministic or monte carlo or partition* survival).mp. or ((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. or ((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. or (incremental-cost or incremental cost).mp. or ("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.)	9681

#	Searches	Results
32	29 or 30 or 31	899083
33	28 and 32	40
34	exp comment/ or exp note/ or exp editorial/ or exp letter/ or exp case report/ or case report.tw. or Historical article/	3091126
35	33 not 34	39
36	limit 35 to yr="2024-Current"	5

Database: EconLit

Hits: 0

Date searched: 08/01/2025

#	Searches	Results
1	lung cancer.mp. [mp=heading words, abstract, title, country as subject]	178
2	((non-small or nonsmall) and cell).ti,ab,kw.	23
3	nsclc.ti,ab,kw.	11
4	2 or 3	23
5	1 and 4	23
6	non-small cell lung cancer.mp. [mp=heading words, abstract, title, country as subject]	23
7	(Lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab,kw.	23
8	nsclc.ti,ab,kw.	11
9	or/6-8	23
10	5 or 9	23
11	(k ras or kras or k-ras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki ras or Kras1 or Kras2 or KRAS1P or RASK or RASK1 or RASK2 or Kirsten RAS or ras or nras or n-ras).mp.	250
12	(braf or b raf).mp.	5
13	11 or 12	255
14	10 and 13	0
15	limit 14 to yr="2024-Current"	0

Eligibility criteria

The population, intervention, comparator(s), outcomes and study design (PICOS) elements use to assess study eligibility for each SLR can be found in Table 6. The PICOS criteria for the January 2025 SLR update remained the same as the PICOS criteria for the May 2023 SLR update and the June 2023 original SLR except for the date of publication criterion. Here, full publications and conference abstracts from 2024 to 2025 were eligible for inclusion.

Table 6: Eligibility criteria (PICOS) – economic evaluation and HCRU & cost SLR

Criteria	Include	Exclude
Population	Adult patients (aged ≥18 years) with *BRAF*-mutant metastatic NSCLC in the first, second and later lines of treatment • Subgroup of interest are adult patients (aged ≥18 years) with *BRAF* V600E-mutant metastatic NSCLC in the first, second and later lines of treatment	• Paediatric or adolescent patients (<18 years) with *BRAF*/*BRAF* V600E-mutant NSCLC • Patients with cancers other than *BRAF*-mutant NSCLC • Studies reporting data only from mixed NSCLC populations, i.e. not reporting data for the target population separately • Animal/in vitro studies
Intervention/Comparator	No restriction on intervention and comparators, only pharmacological interventions were considered for inclusion in the review	Any non-pharmacological interventions
Outcomes	HCRU and cost outcomes • Cost estimates • Direct medical costs • Direct non-medical costs • Treatment cost/administration cost • Indirect/societal costs • Out of pocket costs expense • Patient, caregiver, family, and societal burden • Estimates of resource use (hospitalisations, length of stay, consultations, day care and outpatient visits, etc)	Outcome(s) not listed

Criteria	Include	Exclude
	• Cost drivers Economic evaluation (models and trial based) outcomes • Model summary (including perspective, time horizon and discounting) and structure, where applicable • Assumptions underpinning model structures. • Estimation of transition probabilities and uncertainty • Key cost drivers • Sources of clinical, cost and QoL inputs • Discounting of costs and health outcomes • Summary health outcomes (e.g., quality adjusted life years [QALYs], disability-adjusted life years [DALYs], life years gained [LYG]) • Incremental cost-effectiveness ratios (ICERs): cost per QALY/DALY/LYG, cost per event avoided • Range of ICERs • Utilities/disutilities associated with treatments and AEs	
Study design/ Publication type	Cost and resource use: • Any studies reporting relevant outcomes. Economic evaluations (trial-based and economic models) including: • Cost-effectiveness analysis (CEA) • Cost-utility analysis (CUA) • Cost-minimisation analysis (CMA) • Cost-consequence analysis (CCA) • Cost-benefit analysis (CBA) • Cost offset analysis (COA) • Budget-impact analyses	• Animal / in-vitro studies • Clinical studies • Editorials • Letters • Case studies • Case reports • Narrative reviews

Criteria	Include	Exclude
	Systematic literature reviews (SLRs) or meta-analyses for reference checking only	
Language of publication	English language publications *Note: English language abstracts of foreign language publications were considered for inclusion*	Non-English language publications
Date of publication	• Full publication: 2024-January 2025 • Conference abstracts: 2024-January 2025	Conference abstracts prior to 2019
Countries	No restriction	-

Abbreviations: CBA, Cost-benefit analysis; CCA, Cost-consequence analysis; CEA, Cost-effectiveness analysis; CMA, Cost-minimisation analysis; COA, Cost offset analysis; CUA, Cost-utility analysis; DALY, disability-adjusted life year; EQ-5D, European Quality of Life-5 Dimensions; HRQoL, Health related quality of life; HUI, Health utilities index; ICER, incremental cost-effectiveness ratio; LYG, life year gained; BRAF V600E NSCLC, BRAF V600E-mutant non-small cell lung cancer; PRO, patient reported outcomes; SF-6D, Short-Form Six-Dimension; QALY, quality adjusted life year; QoL, quality of life; SLR, systematic literature review.

Title/abstract screening, full text screening, data extraction and quality assessment methods

The methods for screening, data extraction, and quality assessment are detailed in Section G.1.4 of Appendix G and remained unchanged in the January 2025 SLR update.

Handsearching results

As stated above, handsearching was completed for sources from 2024 to 2025. A summary of handsearching methods and results is provided in Table 7.

Table 7: Summary of handsearching methods and results

Handsearching source	Date searched	Method	Keyword	Hits	Number included
Conference proceedings					
2024 ASCO Annual Meeting	07/06/2024 (searched in the May 2024 SLR update)	See Appendix P for search methods and results	-		

Handsearching source	Date searched	Method	Keyword	Hits	Number included
2025 ASCO Annual Meeting	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
ESMO congress 2024, Madrid	09/01/2025	Searched in the January 2025 update database searches	-		
ESMO congress 2025, Berlin	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
AACR Annual Meeting 2024	28/05/2024	Searched in the May 2024 SLR update database searches	-		
AACR Annual Meeting 2025	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
World Congress on Lung Cancer 2024	09/01/2025	World congress of lung cancer did not take place before the May 2024 SLR update Abstracts from the 2024 congress were not in the database searched for the 2025 update	Braf	135	0
			Brafv600	17	0
World Congress on Lung Cancer 2025	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
ISPOR Europe 2024	09/01/2025	ISPOR 2024 was not held before the May 2024 SLR update. ISPOR 2024 abstracts were included in the January 2025 update database searches	-		
ISPOR Europe 2025	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
ISPOR International 2024	07/06/2024 (searched in the May 2024 SLR update)	See Appendix P for search methods and results	-		
ISPOR International 2025	NA	Meeting has not taken place yet as of the January 2025 SLR update	-		
HTA submissions					
NICE	09/01/2025	Used the same methods detailed in Appendix P in	Brafv600	0	0

Handsearching source	Date searched	Method	Keyword	Hits	Number included
		addition to filtering on “last updated date” with a date range “07/07/2024 to 09/01/2024”	Braf v600	0	0
			Braf NSCLC	0	0
			Braf-v600	0	0
CADTH	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering “last updated” with a date range of “07/06/2024 to 09/01/2025”	Brafv600	1	0
			Braf v600	0	0
			BRAF NSCLC	0	0
			Braf-v600	0	0
PBAC	09/01/2025	Used the same methods detailed in Appendix P	Brafv600	0	0
			Braf v600	0	0
			Braf-v600	0	0
			Braf NSCLC	0	0
SMC	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering on date to “27/06/2024 to 09/01/2024” in the advanced search	Brafv600	0	0
			Braf v600	1	0
			Braf-v600	1	0
G-BA	09/01/2025	Used the same methods detailed in Appendix P	Dabrafenib	5	0
			Trametinib	4	0
			Encorafenib	3	0
			Binimetinib	2	0
			Vemurafenib	1	0
IQWiG	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering the “period” to the last 12 months	Brafv600	0	0
			Braf v600	9	0
			Braf-v600	9	0
			BRAF NSCLC	2	0
HAS	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering the dates to the past year	Brafv600	0	0
			Braf v600	0	0
PMDA	09/01/2025		Brafv600	0	0

Handsearching source	Date searched	Method	Keyword	Hits	Number included
		Used the same methods detailed in Appendix P	Braf v600	0	0
			Braf-v600	0	0
			BRAF NSCLC	0	0
ICER	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering to the year 2024	NSCLC	0	0
			Brafv600	0	0
			Braf v600	0	0
			Braf-v600	0	0
			BRAF NSCLC	0	0
Additional sources					
EQ-5D	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering to the past year	Braf	1	0
INAHTA	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering to the past year	Braf v600 NSCLC	0	0
			Braf v600 NSCLC	0	0
Google Scholar	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering to the past year	BRAF v600 NSCLC cost effectiveness analysis	NA	0
			BRAF v600 NSCLC health state utility value	NA	0
			BRAF v600 NSCLC resource use	NA	0
			BRAF NSCLC cost	NA	0
			BRAF mutation NSCLC	NA	0
			BRAF-mutated NSCLC	NA	0
NIHR	09/01/2025	Used the same methods detailed in Appendix P	Braf NSCLC	30	0
York CRD	09/01/2025	Used the same methods detailed in Appendix P	Braf NSCLC	0	0
CEA Registry	09/01/2025	Used the same methods detailed in Appendix P in addition to filtering from 2024 to 2025	Braf NSCLC	0	0
			Braf non-small cell	0	0

Handsearching source	Date searched	Method	Keyword	Hits	Number included
EconPapers RePEc	09/01/2025	Used the same methods detailed in Appendix P	"braf nsclc"	0	0
			"braf non-small cell lung cancer"	0	0
			Braf v600 AND NSCLC	0	0

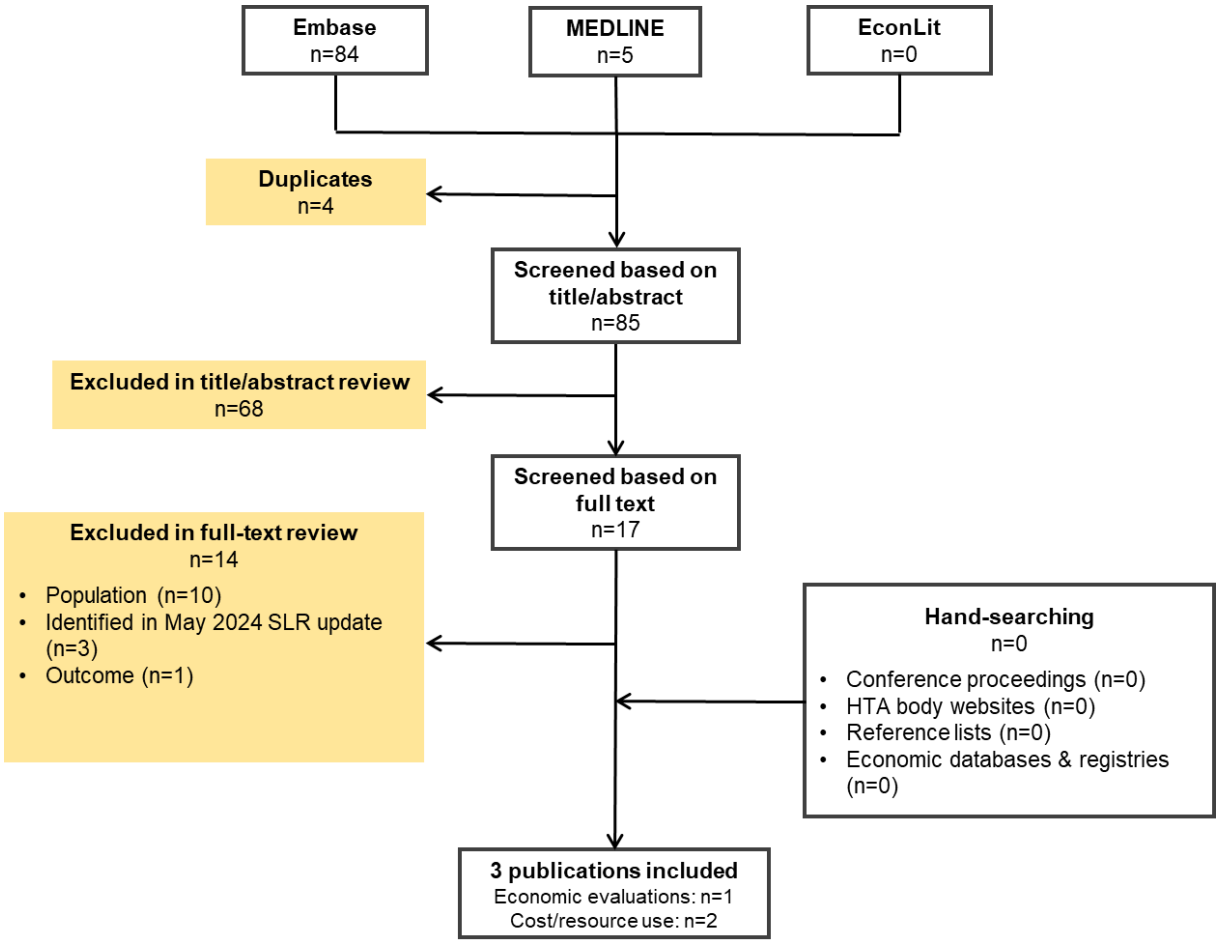
Abbreviations: AACR, American Association for Clinical Research; ASCO, American Society of Clinical Oncology; CADTH, Canada's Drug Agency; CEA, cost-effectiveness analysis; ESMO, European Society for Medical Oncology; EQ-5D, European Quality of Life Questionnaire – 5 Dimensions; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; ICER, Institute for Clinical and Economic Review; INAHTA, International Network of Agencies for Health Technology Assessment; IQWiG, German Institute for Quality and Efficiency in Health Care; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NA, not applicable; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health Research; PBAC, Pharmaceutical Benefits Advisory Committee; PMDA, Pharmaceutical and Medical Devices Agency; RePEc, Research Papers in Economics; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Description of identified studies

Number of included studies – January 2025 SLR update

The searches were run on the 8th January 2025. In total, 89 publications were identified through the electronic database searches. After the removal of 4 duplicates, 85 publications were reviewed based on their titles and abstracts. A total of 68 publications were excluded at the title/abstract review stage, leaving 17 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, a further 14 publications were excluded. A list of publications excluded at the full-text review stage is provided in Table 12, along with a rationale for their exclusion. Hand-searching yielded no additional relevant publications, resulting in a total of 3 publications for final inclusion in the review; a list of all included publications are presented in bold in Table 11. The flow of publications through the January 2025 SLR update is depicted in the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 1.

Figure 1: Flow of publications in the second update of the economic evaluation and HCRU & cost SLR (January 2025)



Abbreviations: HCRU, healthcare resource use; HTA, health technology assessment; SLR, systematic literature review.

Summary of included studies in the January 2025 SLR update

The studies included in the original SLR (June 2023) and first SLR update (May 2024) have been summarised in Appendix G. Only the publications identified in the January 2025 SLR update are summarised here.

One budget impact analysis from Argentina was included in the economic evaluation SLR update. The aim of the budget impact analysis was to compare a scenario in which encorafenib in combination with binimetinib (enco+bini) is available in the market versus a scenario where enco+bini is unavailable. The time horizon was 3 years and took a National Institute of Social Services for Retirees and Pensioners

(INSSJP-PAMI) perspective. Over the 3-year period, the cumulative budget impact was a saving of $155,031. The authors stated that this was mainly due to lower drug acquisition costs.

Table 8: Key characteristics of economic evaluations

Study details	Population, intervention/ comparator	Outcome	Model	Societal perspective taken in a scenario analysis? (Yes/No)	Model inputs	Conclusion
Vega 2024 Argentina BIA Poster	**Population:** advanced *BRAF* V600E NSCLC **Intervention/ comparator:** enco+bini	Budget impact	**Model:** NR **Health states:** NA **Cost-effectiveness threshold:** NA **Dominant or most cost-effective treatment:** NA **Study perspective:** INSSJP-PAMI **Time horizon:** 3 years **Discount rate**: NR	NR	**Clinical:** NR **Costs** (USD): NR **QoL:** NA	Incorporating more patients into *BRAF*-MEK inhibitor therapies represents savings for INSSJP-PAMI and results in a reduction in the healthcare resources allocated for the treatment of *BRAF*m advanced NSCLC patients

Abbreviations: BIA, budget impact analysis; BRAFm, BRAF mutated; enco+bini, encorafenib in combination with binimetinib; INSSJP-PAMI, National Institute of Social Services for Retirees and Pensioners; NA, not applicable; NR, not reported; NSCLC, non-small cell lung cancer; USD, United States Dollar.

Two cost-effectiveness analyses were included in the HCRU & cost SLR as they reported novel cost data. These were not included in the economic evaluation SLR as cost-effectiveness outcomes were not reported for the *BRAF* mutated population.

One of the included studies investigated next-generation sequencing versus single-gene testing in South Korea in patients with advanced EGFR/ALK-negative NSCLC. Only *BRAF* testing costs were reported which were used as cost inputs in the model. The second included study investigated different molecular profiling strategies, including next-generation sequencing. The cost of dabra+tram was the only novel cost reported for *BRAF* mutated NSCLC patients. This was a model input and was taken from local data.

Table 9: Key characteristics of the HCRU & cost studies

Study details	Population	Study Period	Year, Currency	Costs	Total Costs and Cost Drivers	Resource use and disease burden
Kang 2024 South Korea CEA Full text	Patients with EGFR/ALK negative advanced NSCLC	NR	2022, USD	BRAF testing: $82.50	NR	NR
Liu 2024 Singapore CEA Full text	Patients with newly diagnosed advanced NSCLC	NR	NR, SGD	Dab + tram: SGD8,170.2	NR	NR

Abbreviations: CEA, cost-effectiveness analysis; dab + tram, dabrafenib + trametinib; HCRU, healthcare resource use; NR, not reported; NSCLC, non-small cell lung cancer; SGD, Singaporean Dollar; USD, United States Dollar.

Quality assessment

Quality assessment of economic evaluations was only performed where full texts were available; no quality assessment was performed for the January 2025 SLR update as the included study was only available as a poster.

Quality assessment of the HCRU and cost studies is provided in Table 10.

Table 10: Molinier checklist for HCRU & cost studies

	Kang 2024			Liu 2024		
	Y	**P**	**N**	**Y**	**P**	**N**
1. Was a clear definition of the illness given?	Yes			Yes		
2. Were epidemiological sources carefully described?	Yes			Yes		
3. Were direct/indirect costs sufficiently disaggregated?			No			No
4. Were activity data sources carefully described?			No			No
5. Were activity data appropriately assessed?			No			No
6. Were the sources of all cost values analytically described?			No		Partial	
7. Were unit costs appropriately valued?		Partial		Yes		
8. Were the methods adopted carefully explained?		Partial			Partial	
9. Were the major assumptions tested in a sensitivity analysis?			No			No
10. Was the presentation of study results consistent with the methodology of the study?	Yes			Yes		
Total	3	2	5	4	2	4

Abbreviations: Y = Yes; N = No; P = partial.

Complete reference list for included studies

A full list of publications included in the original SLR (June 2023), first SLR update (May 2024), and second SLR update (January 2025) for the economic evaluation and HCRU & cost SLR is presented in Table 11.

Table 11: Publications included across all iterations of the economic evaluations and HCRU & cost SLR (n=13)

Study name	References
Economic evaluation SLR (n=5)	
Zhou 2017	Zhou Z, Bensimon A, Cheng J, Dalal A. Budget Impact Analysis of Dabrafenib and Trametinib Combination Therapy in The Treatment of Braf V600e-Mutant Advanced Non-Small Cell Lung Cancer in The United States. Value in Health. 2017 Oct 1;20(9):A422.
NICE TA898 2023	Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer. Published on 14 June 2023 https://www.nice.org.uk/guidance/ta898
CDA-AMC 2021	Dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600 mutation. Published on May 28, 2021.
CDA-AMC 2017	Dabrafenib (Tafinlar) Trametinib (Mekinist) for non-small cell lung cancer. Published on 02 November 2017
Vega 2024	**Vega, C., et al. Budget-Impact Analysis of Encorafenib Plus Binimetinib As a Treatment for Advanced NSCLC with BRAFV600E-Mutation in Older Adults from Argentina. Value in Health. 2024;27(12): S94.**
HCRU & cost SLR (n=8)	
Dalal 2018	Dalal AA, Guerin A, Mutebi A, Culver KW. Economic analysis of BRAF gene mutation testing in real world practice using claims data: costs of single gene versus panel tests in patients with lung cancer. Journal of Medical Economics. 2018 Jul 3;21(7):649-55.
Desai 2022	Desai A, Scheckel C, Jensen CJ, Orme J, Williams C, Shah N, Leventakos K, Adjei AA. Trends in Prices of Drugs Used to Treat Metastatic Non–Small Cell Lung Cancer in the US From 2015 to 2020. JAMA Network Open. 2022 Jan 4;5(1): e2144923-.
Kelner 2023	Kelner M, da Silva BC, Montella T, Aguiar Jr PN, Lopes G, Ferreira CG, De Marchi P. Discrepancies Between the Cost of Advanced Lung Cancer Treatment and How Much Is Reimbursed by the Brazilian Public Healthcare System. Value in health regional issues. 2023 Jan 1; 33:1-6.
Aparicio 2023	Aparicio I, Iranzo P, Reyes R, Bote H, Saigi M, Bringas M, et al. Brief report: High incidence of peridiagnosis thromboembolic events in patients with BRAF-mutant lung cancer. Thrombosis Research. 2023;232((Aparicio, Bringas, Alvarez, Munoz, Calles) Medical Oncology Department, Hospital General Universitario Gregorio Maranon, Universidad Complutense, Madrid, Spain(Aparicio) Facultad de Medicina, Universidad Francisco de Vitoria, Pozuelo de Alarcon, Madrid):133-7.
Lemmon 2023	Lemmon CA, Zhou J, Hobbs B, Pennell NA. Modeling Costs and Life-Years Gained by Population-Wide Next-Generation Sequencing or Single-Gene Testing in Nonsquamous Non-Small-Cell Lung Cancer in the United States. JCO precision oncology. 2023;7(101705370):e2200294.
Roskoski 2024	Roskoski R. Cost in the United States of FDA-approved small molecule protein kinase inhibitors used in the treatment of neoplastic and non-neoplastic diseases. Pharmacological Research. 2024;199((Roskoski) Blue Ridge Institute for Medical Research, 221 Haywood Knolls Drive, Hendersonville, NC 28791, United States):107036.

Study name	References
Kang 2024	**Kang, D. W., et al. Cost-effectiveness of next-generation sequencing for advanced EGFR/ALK-negative non-small cell lung cancer. Lung Cancer. 2024; 197:107970.**
Liu 2024	**Liu, S., et al. The cost-effectiveness of including liquid biopsy into molecular profiling strategies for newly diagnosed advanced non-squamous non-small cell lung cancer in an Asian population. Lung Cancer. 2024; 191:107794.**

Studies in bold have been included in the January 2025 SLR update

Complete reference list for excluded studies

A full list of publications excluded in the second SLR update (January 2025) for the economic evaluation and HCRU & cost SLR is presented in Table 12.

Table 12: Publications excluded in the January 2025 economic evaluation and HCRU & cost SLR update (n=14)

Study name	References	Reason for exclusion
Abbass 2024	Abbass I.M.; Sheinson D.M.; Shah A.; Gondos A.; Ogale S. Cost-effectiveness of large-panel next-generation sequencing in guiding first-line treatment decisions for patients with nonsquamous advanced non-small cell lung cancer. Journal of Managed Care and Specialty Pharmacy. 2024;30(7): 649EP - 659.	Outcome
Bestvina 2024	Bestvina C.M.; Waters D.; Morrison L.; Emond B.; Lafeuille M.-H.; Hilts A.; Lefebvre P.; He A.; Vanderpoel J. Cost of genetic testing, delayed care, and suboptimal treatment associated with polymerase chain reaction versus next-generation sequencing biomarker testing for genomic alterations in metastatic non-small cell lung cancer. Journal of Medical Economics. 2024;27(1): 292EP- 303	Population
CADTH	Plasma-Based Comprehensive Genomic Profiling DNA Assays for Non-Small Cell Lung Cancer: A Health Technology Assessment. Ontario health technology assessment series. 2024;24(8):1EP – 306.	Population
Cooper 2024	Cooper A.J.; Gorria T.; Conroy M.R.; Ricciuti B.; Pecci F.; Aldea M.; Anagnostou V.; Shaverdian N.; Bott M.; Forde P.M.; Awad M.M.; Schoenfeld A.J.; Chaft J.E. Multi-institution real-world analysis of patients with non-small cell lung cancer (NSCLC) treated with standard of care (SOC) neoadjuvant chemo-immunotherapy (chemoIO). Journal of Clinical Oncology. 2024;42:16 Supplement.	Population
Gamboa 2024	Gamboa O.; Bonilla C.E.; Quitian D.; Torres G.F.; Buitrago G.; Cardona A.F. Cost-Effectiveness of Comprehensive Genomic Profiling in Patients With Non-Small Cell Lung Cancer for the Colombian Health System. Value in Health Regional Issues. 2024;39:115EP - 125	Identified in May 2024 SLR

Study name	References	Reason for exclusion
Goyal 2024	Goyal P.K.; Sangwan K. Pharmacological Profile of FDA-Approved Orphan Drugs in the Year 2022 Current Pharmacology Reports. 2024;10(2):96EP-120	Identified in May 2024 SLR
Ikeda 2024	Ikeda S.; Hasegawa K.; Kachi K.; Yanagisawa A.; Kawakami S.; Hamasaki S.; Watanabe S.; Yoshikawa A.; Takahama T.; Nakagawa K. Patient-Initiated Nationwide Survey on Testing for Actionable Oncogenic Drivers in Non-Small Cell Lung Cancer in Japan. Cancer Medicine. 2024;13(21):e70375	Population
Isla 2024	Isla D.; Alvarez R.; Arnal M.; Arriola E.; Azkarate A.; Azkona E.; Garcia-Campelo R.; Garrido P.; Nadal E.; Ortega A.L.; Carcedo D.; Crespo M.; Lavara J.; Corcoles F.; Bernabe R. Detection of genomic alterations in liquid biopsies from patients with non-small cell lung cancer using FoundationOne Liquid CDx: a cost-effectiveness analysis. Journal of Medical Economics. 2024;27(1):1379EP-1387	Population
Karim 2024	Karim N.; Waterhouse D.; Jones S.; Stollenwerk B. Cost-Effectiveness Analysis of Sotorasib vs. Adagrasib in KRAS G12c-Mutated Previously Treated NSCLC. Journal of Thoracic Oncology. 2024;19(10 Supplement): S719EP - S720	Population
Krebs 2024	Krebs E.; Weymann D.; Regier D. EE566 Real-World Evidence of Multi-Gene Panel Sequencing Effectiveness and Cost-Effectiveness for Advanced Cancers: A Tumor-Agnostic Target Trial Emulation. Value in Health. 2024;27(12 Supplement):S167	Population
Lau-Min 2024	Lau-Min K.S.; Wu Y.; Rochester S.; Bekelman J.E.; Kanter G.P.; Getz K.D. Association between oral targeted cancer drug net health benefit, uptake, and spending. Journal of the National Cancer Institute. 2024;116(9);1479EP-1486	Population
Marrett 2024	Marrett E.; Kwong W.J.; Song J.; Manceur A.; Sendhill S.; Wu E. Treatment Patterns and Resource Use After Osimertinib Discontinuation in Patients with EGFR + Metastatic NSCLC. Oncology and Therapy. 2024(12):3;549EP-563	Population
Roskoski 2024	Roskoski R. Cost in the United States of FDA-approved small molecule protein kinase inhibitors used in the treatment of neoplastic and non-neoplastic diseases. Pharmacological Research. 2024;199:107036	Identified in May 2024 SLR
Sendur 2024	Sendur M.A.; Kockaya G.; Kemal Y.; Ozturk B.; Kaplan M.A.; Aydiner A.; Goker E.; Karadurmus N.; Kurnaz M.; Tibet B.; Okcun S. RWD132 Cost of Treatment of Locally Advanced and Metastatic Non-Small Cell Lung Cancer With Real-World Data in Turkiye. Value in Health. 2024;27(12 Supplement):S599	Population

Patient population

B3. Priority question. The final scope issued by NICE addresses people with advanced NSCLC that are positive for a BRAF V600E mutation (CS Table 1).

Whereas the anticipated indication outlined in the summary of products characteristics (CS Table 2) [redacted] is in line with the final scope issued by NICE, the CS deviates from this final scope in the decision problem, addressing only treatment-naïve patients (CS Table 1).

a) **Please justify the narrower scope, [redacted], the available evidence base for both intervention from the PHAROS (CS Table 24) and IFCT study (CS B.2.3.2.) as well as comparator from the BRF113928 study (CS Table 24) on treatment-experienced patients, and the use of both intervention and comparator as subsequent treatments (CS B.3.5.3.).**

b) **Please provide an updated economic model and scenario analyses also including treatment-experienced patients.**

As stated in the original Company submission Section B.3.2.1, the expected use of enco+bini in UK clinical practice is in treatment naïve-adult patients with BRAF V600E MT NSCLC. This is in alignment with NICE final guidance on the use of dabra+tram in patients with BRAF V600 mutation-positive advanced NSCLC, which states that dabra+tram is recommended only if it is used as a first-line treatment of advanced stage cancer. This is also in alignment with the advice from three UK CEs with experience of treating patients with advanced NSCLC with a BRAF V600E mutation, who stated there is no reason to use anything other than a targeted therapy at first-line if a BRAF V600E mutation is present.

CEs stated that the only rationale to use a non-targeted therapy at first-line would be in the case of delayed test results or inadequate biopsy and where there is a need to start treatment immediately. The committee in TA866 indicated that the delays would be expected to fall over time and the CEs consulted for this submission confirmed that delays are rare. As most, if not all patients will receive either dabra+tram or enco+bini at first-line, patients will not be eligible to receive a targeted therapy at second line, as confirmed by CEs during the advisory board. CEs stated that sequencing, i.e. receiving a targeted therapy at second line after first-line targeted treatment, “was not

considered an option as it would be expected that there would be a biological resistance mechanism with treatments with similar mechanisms of action".

Therefore, as use of enco+bini is expected to be first-line, and those patients who receive dabra+tram at first line would not be eligible to receive enco+bini at second line, the Company does not consider it appropriate to present an analysis in treatment-experienced patients.

B4. Patient population 51.9istics of the CS are based on the PHAROS treatment-naïve cohort (CS B.3.2.1.). The PHAROS study was not conducted in the UK and did not include any UK patients (Study Details | An Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer | ClinicalTrials.gov).

a) **Please clarify whether the modelled patient population was based on the PHAROS treatment-naïve cohort before or after the matching-adjusted indirect comparison (MAIC) on all factors (CS Table 28) and update the economic model settings to reflect the latter patient population. Please provide information on mean weight, height and body surface area for intervention and comparator, adding onto CS Table 28.**

The modelled patient population in the Company submission was based on the PHAROS treatment-naïve population prior to matching adjustment for the MAIC adjusting on all factors. A comparison of patient characteristics based on the unmatched PHAROS and MAIC on all factors are presented in Table 13.

Table 13: Patient characteristics – PHAROS treatment-naïve cohort MAIC unmatched and matched

	PHAROS treatment-naïve cohort	
	MAIC unmatched	MAIC matched on all factors
Age (years)	66.5	67.0
Proportion male (%)	44.1%	39.0%
Mean weight (kg)	74.6	70.6
Mean height (m)	1.67	1.65

	PHAROS treatment-naïve cohort	
	MAIC unmatched	MAIC matched on all factors
Mean BSA (m^2)†	1.86	1.80

†Calculated using the Mosteller formula
Abbreviations: BSA, body surface area; MAIC, matching-adjusted indirect treatment comparison.

The base case has been updated to use patient characteristics derived from the PHAROS treatment-naïve cohort based on the MAIC adjusting on all factors. Results are presented in Table 14. The update is associated with negligible changes to the NHB and the ICER remains dominant. The revised base case, accounting for updates based on clarification question A2, B4, B7, and B27 is associated with a NHB of [redacted].

Table 14: Scenario analysis results - patient characteristics

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – MAIC unmatched	[redacted]	[redacted]	Dominant	[redacted]
+ (B4) MAIC-adjusted population	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect treatment comparison; NHB, net health benefit; QALYs, quality-adjusted life years.

b) Please provide evidence on whether the modelled patient population is reflective of the UK patient population. For this, please use UK real world registry data and distinguish between characteristics for the UK treatment-naïve as well as treatment-experienced patient population with advanced NSCLC that are positive for a BRAF V600E mutation and contrast it with the modelled patient population.

Due to the rarity of the *BRAF* V600E mutation, there is little data available on patients with *BRAF* V600E mutation positive NSCLC. As detailed in Appendix D of the Company submission, no UK registry data on BRAF V600E were identified in the SLR. One UK study was identified that analysed tissue biopsies from 185 NSCLC samples with a *BRAF* mutation from patients referred to the Sarah Cannon Molecular Diagnostics Laboratory between January 2015 and February 2022 from multiple

centres across the UK (12). Only the patient characteristic ‘proportion male’ is available from this study (51.9%), which broadly aligns with the population of PHAROS (44.1%). Data in the wider NSCLC population is available from the 2024 National Lung Cancer Audit (NLCA) report for patients diagnosed in England and Wales in 2022. (13) According to the NLCA report, 39,097 were diagnosed with lung cancer in 2022, of which approximately 90% had NSCLC and 50% had stage IV cancer. Patients with NSCLC were on average 74 years old on diagnosis, which is older than the mean age of the treatment-naïve cohort of PHAROS (66.5). Approximately 10% of patients diagnosed with NSCLC in the NCLA report had never smoked, compared with 18% in the treatment naïve cohort of PHAROS.

All three CEs consulted during both advisory boards stated that the baseline characteristics of the treatment-naïve cohort in the PHAROS study were broadly reflective of the population they would expect to receive enco+bini in UK clinical practice.

B5. NICE DSU TSD 3 recommends to account for heterogeneity between patients, for instance by exploring subgroup analyses. The final scope issued by NICE includes the following subgroups: line of therapy (treated or untreated), histology (squamous or non-squamous) and PD-L1 expression (CS Table 1). However, no such stratified analyses were considered in the CS (CS B.3.11.) besides reflecting the untreated patient population.

a) **In addition to the subgroups mentioned in the NICE scope, please identify potential subgroups of relevance with external evidence, e.g., via systematic literature review and/or expert opinion. Please justify why all those subgroups were not considered in the CS.**

b) **Please provide an updated economic model including the subgroups identified in a) as well as those outlined in the final scope.**

As discussed in response to question B3, three UK CEs with experience of treating patients with NSCLC with a *BRAF* V600E mutation agreed there is no clinical rationale for using a non-targeted therapy at first-line, and patients would not be eligible for

further treatment with targeted therapy at second-line. As enco+bini is expected to be used in a treatment-naïve patient population, a subgroup analysis based on the line of therapy (treated or untreated) is not presented.

As discussed in Section B.1.2 of the company submission, the mechanism of action of enco+bini is independent of other histology types listed in the NICE scope such as PD-L1 expression and squamous or non-squamous histology. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of *BRAF* kinase (V600E, D and K) and binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. The combination of enco+bini inhibits the MAPK pathway resulting in higher anti-tumour activity, compared to treatment with either drug alone (14, 15).

In PHAROS, baseline characteristics (age, gender, race, ECOG) subgroup analyses were performed only for the primary endpoint (ORR by IRR). No powered statistical subgroups analyses were conducted in PHAROS for other endpoints that could be used for modelling.

It should also be noted that PD-L1 expression was not collected in the PHAROS trial, therefore subgroup analysis based on PD-L1 expression is not possible. Furthermore, 97% patients in the treatment naïve cohort (and 97% of patients in the overall population comprised of treatment naïve and treatment experienced patients) had adenocarcinoma tumour type, which is predominantly a non-squamous histology. Therefore, a subgroup analysis based on patients with a squamous tumour histology would be based on one patient. Additionally, CEs in TA898 confirmed that PD-L1 status is not relevant in deciding management strategies as targeted treatment would be used. The BRF113928 trial also did not collect data on PD-L1 status, and therefore it is not possible to present subgroup analyses for enco+bini and dabra+tram based on PD-L1 status.

Finally, as all CEs agreed with the company decision problem that presented no subgroup analyses, the Company does not consider it appropriate to present any subgroup analyses.

Model structure

B6. Priority question. The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period. It also reports the use of STMs in prior STAs to address immature survival outcome data, potentially mitigating extrapolation uncertainty.

a) **Please justify the use of a PSM given the issues highlighted in NICE DSU TSD 19, particularly given the immaturity of the PFS and OS data from the PHAROS and IFCT trials that were used to inform the economic model while assuming structural independence between these endpoints.**

As highlighted in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, partitioned survival models (PSMs) are often preferred to state transition models (STMs) in oncology models due to lack of available data to allow the correct implementation of this type of model. In particular, STMs require estimation of the following transitions for all comparators in the model:

- Progression-free to death
- Progression-free to progressed
- Progressed to dead

These transitions require time to event survival data for time to progression (with pre-progression deaths censored), time to death without prior progression (with progressions censored), and post-progression survival. Although these data can be estimated from the available patient data from the PHAROS trial, none of these data are available for dabra+tram. As noted in TSD19: "*In many instances, external data are only available for the PFS and OS endpoints. These data are not sufficient to allow estimation of individual transition probabilities*". Therefore, the above transitions for dabra+tram would have to be estimated by applying a treatment effect to the survival curves for enco+bini. As these outcomes are not available for dabra+tram to inform an

indirect treatment comparison (ITC) vs enco+bini, a strong assumption would have to made on the treatment effect, either by applying the PFS or OS hazard ratio (HR) to each transition. However, as PFS and OS outcomes are not aligned with the transitions that inform the STM, this is not considered appropriate to accurately model patient movement in the dabra+tram arm.

As noted in Section B.3.2.2, the PSM structure was considered most appropriate as it aligns with the primary and secondary endpoints of the PHAROS and BRF113928 trials which are used directly to inform health state membership over the model time horizon. Furthermore, the model structure is consistent with previous HTAs in NSCLC including the recent dabra+tram (TA898) appraisal, which was accepted as appropriate for decision-making by NICE.

Although median OS had not been reached at the 1st April 2024 DCO of PHAROS, 44.1% of patients experienced an OS event in the treatment-naïve population. Furthermore, median PFS (assessed by IRR) was reached (30.2 months [95% CI, 15.7, NE]), and 47.5% of patients had experienced a progression event. The Company consider these data to be sufficiently mature to inform the analysis, particularly considering previous submissions in oncology have received positive recommendations based on a similar data package using a PSM, including OS and PFS data that are more immature than presented in this submission (16).

b) Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

As discussed in response to part a) of this question, the company consider the PSM approach to be the most appropriate structure for the model, and therefore it is retained in the base case analysis.

However, to test the uncertainty behind these assumptions, the base case curve was validated alongside curves created using the STM approach. Time-to-progression, death from the PFS state, and post-progression survival in PHAROS are presented in Figure 2, Figure 3, and Figure 4, respectively.

Figure 2: Time to progression - PHAROS

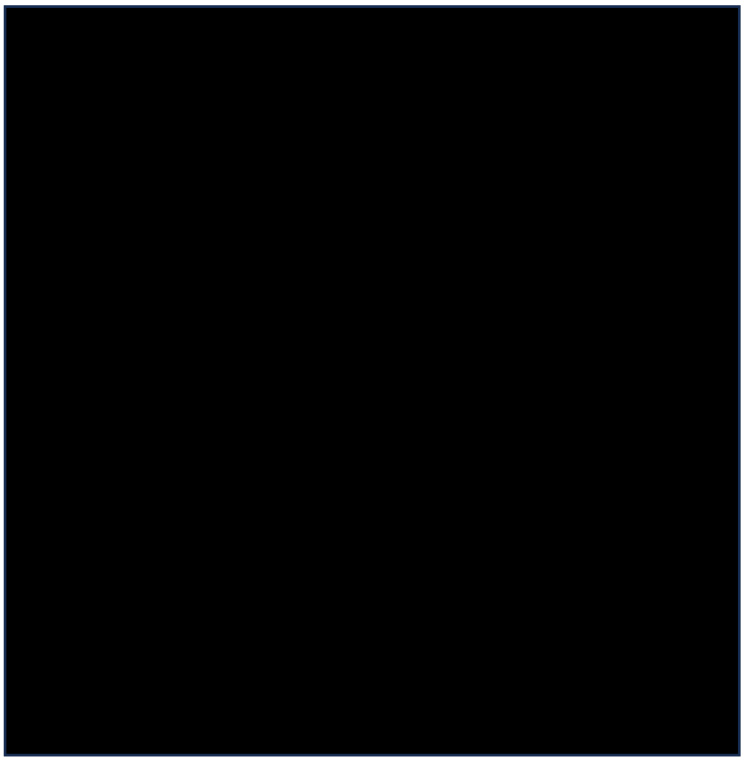
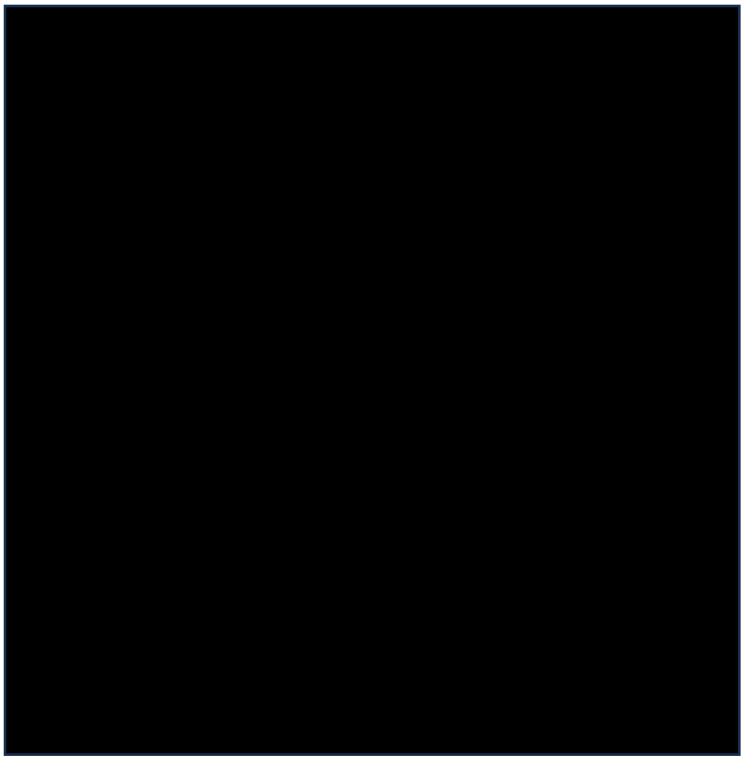
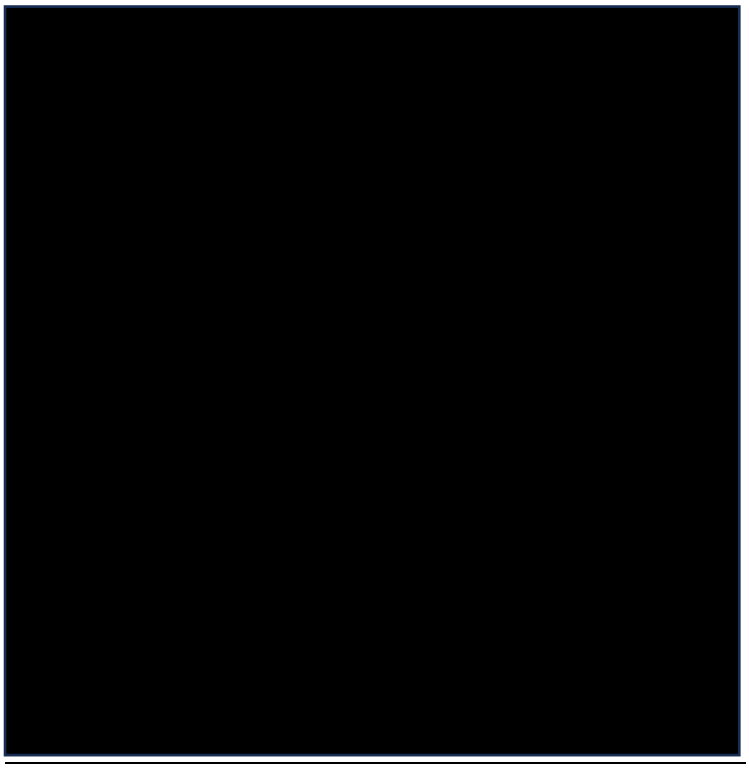


Figure 3: Time-to-death from PFS state - PHAROS



Abbreviations: PFS, progression-free survival.

Figure 4: Post-progression survival - PHAROS



The resulting OS and PFS curves, alongside the Company base case, are presented in Figure 5 and Figure 6, respectively. Exponential curves were fit to the KM data in order to compare to the Company base case curves for OS and PFS. The STM over-predicts survival for the trial period, likely due to the low number of death events from the progression-free state, and the low number of patients informing post-progression survival. The STM is well aligned with progression-free survival estimates in the Company base case.

Figure 5: PSM and STM comparison, OS

Abbreviations: KM, Kaplan Meier; OS, overall survival; PSM, partitioned survival model; STM, state transition model.

Figure 6: PSM and STM comparison, PFS

Abbreviations: KM, Kaplan Meier; PFS, progression-free survival; PSM, partitioned survival model; STM, state transition model.

B7. In the NICE health technology evaluations manual (2022), a time horizon which reflects all important differences in costs or outcomes between the

technologies being compared is recommended. This is usually considered the patient's lifetime and was identified as applicable in the CS. However, the chosen time horizon of 33.5 years resulted in less than 1% of patients from the intervention arm being alive whereas all patients from the comparator arm died.

a) **Please justify the deviation from NICE guidance, particularly addressing important differences in costs and outcomes to be expected.**

In the base case analysis, the time horizon is capped at a maximum age of 100 (time horizon: 33.5 years). This was considered sufficient to capture all important differences in costs and outcomes, as per NICE guidance. At the end of the time horizon the proportion alive in the enco+bini arm is below 0.15% and therefore was considered to have sufficiently minimal effect on model results, particularly given the heavy discount that is applied at 33+ years. However, for completeness, the base case analysis has been updated such that all patients die in the enco+bini arm. Please see the response to part b) of this question for results of this update.

b) **Please provide an updated economic model extending the time horizon such that all patients are dead.**

The base case has been revised to consider a time horizon of 36.0 years such that all patients are dead in the enco+bini and dabra+tram arms. Results of this scenario are presented in Table 15. The impact of this update to the base case analysis is minimal, and enco+bini remains dominant when compared with dabra+tram, and there is a negligible change to the NHB. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 15: Scenario analysis results – time horizon

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – time horizon 33.5 years	[redacted]	[redacted]	Dominant	[redacted]
+ (B7) time horizon 36.0 years	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Revised base case - revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

Intervention and comparator

B8. Priority question. The final scope issued by NICE (CS Table 1) mentions the following treatments as comparators for patients with untreated advanced NSCLC: dabrafenib with trametinib, pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed), pembrolizumab monotherapy, and atezolizumab monotherapy. For patients with previously treated advanced NSCLC, the scope mentions the following treatments as comparators: atezolizumab monotherapy, pembrolizumab monotherapy, nivolumab monotherapy, docetaxel with nintedanib, docetaxel, and platinum doublet chemotherapy. In the CS the comparator reflects solely the intervention arm subgroup of treatment-naïve patients (Cohort C) of the BRF113928 trial, in which they were treated with dabrafenib with trametinib. [redacted].

a) **Please provide justification for not including pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed), pembrolizumab monotherapy, and atezolizumab monotherapy, as comparators in the economic model for treatment-naïve patients.**

As stated in response to question B3, CE advice to the company stated that there was no clinical rationale to use a non-targeted therapy at first-line for patients who have a *BRAF* V600E mutation. Experts stated the only time patients would receive a non-targeted therapy would be in the presence of testing delays with an urgent requirement to begin treatment prior to beginning targeted therapy. However, as discussed by the committee in TA898, and confirmed by CEs during the advisory board for this

submission, these delays are rare. All three CEs with experience of treating patients with advanced *BRAF* V600E mutation positive NSCLC in the UK agreed that dabra+tram was the only relevant comparator in this appraisal.

b) Please provide justification for not including atezolizumab monotherapy, pembrolizumab monotherapy, nivolumab monotherapy, docetaxel with nintedanib, docetaxel, and platinum doublet chemotherapy, as a comparator in the economic model for treatment-experienced patients, despite its anticipated indication described in the summary of products characteristics (CS Table 2) [redacted] being in line with the final scope issued by NICE.

As stated in the response to question B3, the Company do not consider the treatment-experienced population to be a relevant population. Enco+bini is expected to be used in a treatment-naïve patient population, as confirmed by CE opinion. Furthermore, dabra+tram is recommended only in a treatment-naïve patient population, and as patients would not be eligible for re-treatment with a targeted therapy, would not be eligible to receive enco+bini at second-line. Therefore, the Company does not consider it appropriate to present any analysis at second-line.

c) Please provide an updated economic model that includes all relevant comparators listed in the final scope issued by NICE and provide all model analyses and fully incremental analyses, including all sensitivity and scenario analyses for both treatment-naïve and -experienced patients.

As discussed in response to part a) and b) of this question, the Company consider dabra+tram to be the only relevant comparator in this appraisal, and treatment-naïve patients to be the only relevant population and therefore do not consider it appropriate to provide further analyses.

B9. Both intervention and comparators identified in the NICE final scope include combination treatments, i.e., encorafenib with binimetinib and dabrafenib with trametinib for the comparator.

a) **Please justify (and provide evidence) whether patients in UK clinical practice could discontinue one treatment within the combination treatment and continue on the other treatment (e.g. stop having binimetinib and continue having encorafenib or vice versa).**

As per the encorafenib SmPC section 4.2 regarding the use of enco+bini in NSCLC: *"administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 of binimetinib SmPC) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued. If encorafenib is temporarily interrupted, binimetinib should be interrupted. If encorafenib is permanently discontinued (see Tables 3 and 4), then binimetinib should be discontinued."*

In PHAROS, if a participant permanently discontinued treatment with encorafenib, they were also to permanently discontinue treatment with binimetinib; however, if a participant permanently discontinued treatment with binimetinib, treatment with encorafenib could have been continued. Nevertheless, in treatment-naïve patients, median duration of treatment of encorafenib and binimetinib was the same (Figure 7), and differences between duration exposure to encorafenib and duration exposure to binimetinib are negligible.

Figure 7: Duration of exposure to study drug

Abbreviation: SD, standard deviation.

Therefore, it is not anticipated that patients would receive either encorafenib or binimetinib as a single agent in UK clinical practice.

b) If applicable, please provide an updated economic model and scenario analyses using drug-specific TTDs within each combination treatment in the economic model.

As discussed in part a) of this response, patients would not be eligible to receive either encorafenib or binimetinib as a single agent in UK clinical practice. Furthermore, no data is available on treatment duration for dabrafenib or trametinib individually. Therefore, a scenario using drug-specific TTDs within each combination treatment is not presented.

Treatment effectiveness

B10. Priority question. overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTD) data were used to estimate parametric survival models for encorafenib in combination with binimetinib. Please provide, for OS, PFS and TTD separately for both the intervention and comparators:

a. **Tables with the numbers of patients at risk, per 3 months**.

Patients at risk for enco+bini OS, PFS and TTD are presented in Table 16.

Table 16: Patients at risk, enco+bini, PHAROS

Time (months)	Patients at risk, OS	Patients at risk, PFS	Patients at risk, TTD
0	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation.

b. To examine the heuristics of the hazard function over time:

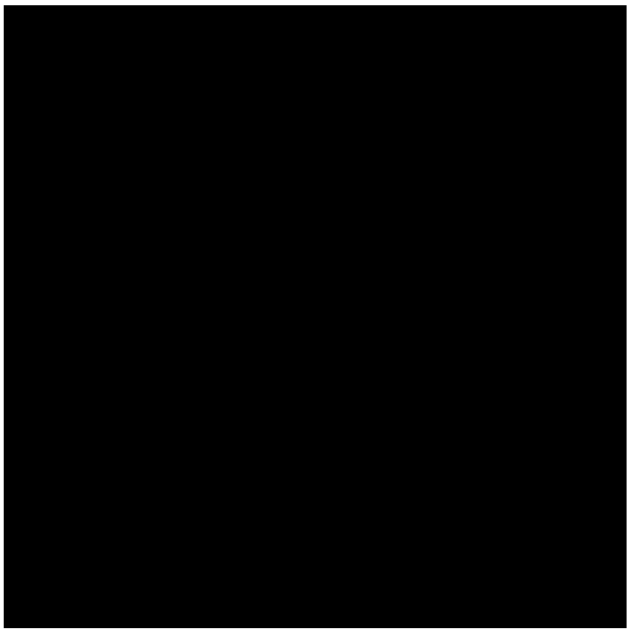
i. Plot the smoothed hazards over time

The smoothed hazard plots for enco+bini OS, PFS, and TTD are presented in Figure 8, Figure 9, and Figure 10, respectively. For OS and PFS, the hazard is decreasing over time. However, the decrease in relatively minor. For TTD, the hazard is decreased for the beginning of the trial period but then levels out to a more constant pattern.

Figure 8: Smoothed hazard plots, enco+bini OS, PHAROS

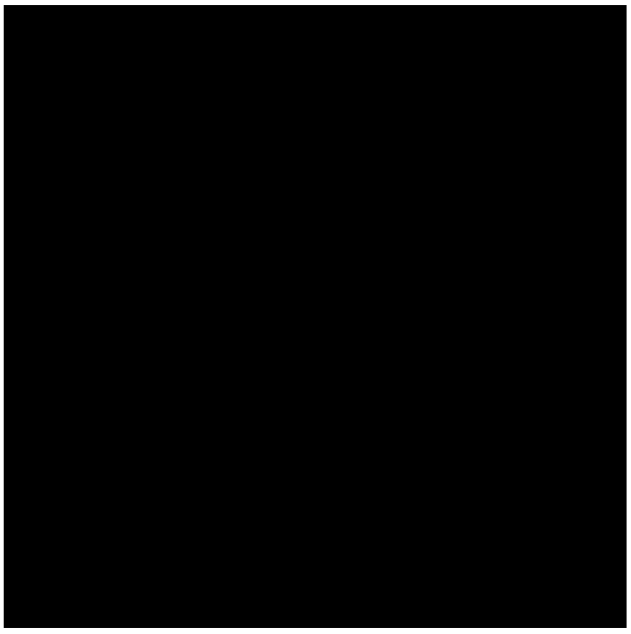
Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Figure 9: Smoothed hazard plots, enco+bini PFS, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

Figure 10: Smoothed hazard plots, enco+bini TTD, PHAROS



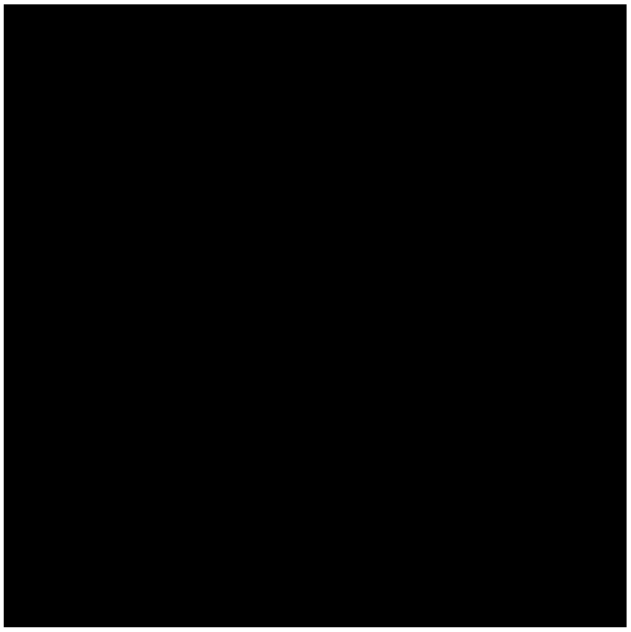
Abbreviations: enco+bini, encorafenib in combination with binimetinib; TTD, time-to-treatment discontinuation.

c. To examine the diagnostics of the parametric survival models (using the observed data), please provide the following Figures (separately for OS, PFS and TTD):

i. Plot the cumulative hazard versus time

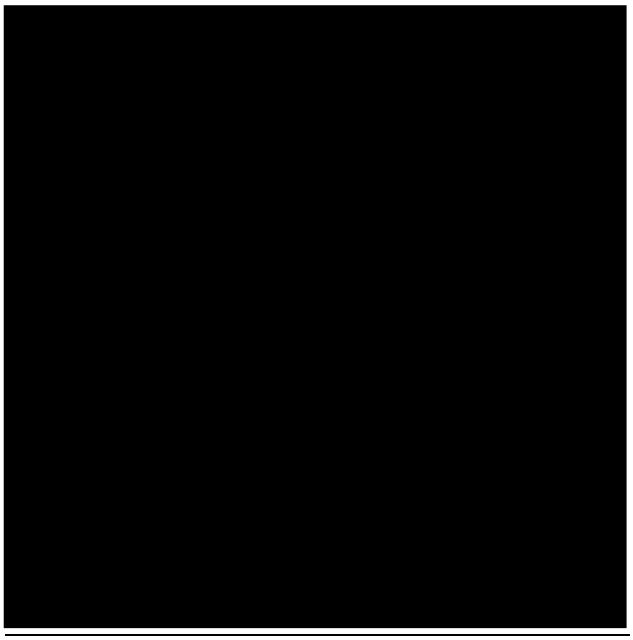
The cumulative hazard plots for enco+bini OS, PFS, and TTD are presented in Figure 11, Figure 12, and Figure 13, respectively. Similarly to the smoothed hazard plots in answer to part b) of this question, these plots show a relatively constant, but slowly decreasing hazard over time for OS, PFS, and TTD.

Figure 11: Cumulative hazard plots, enco+bini OS, PHAROS



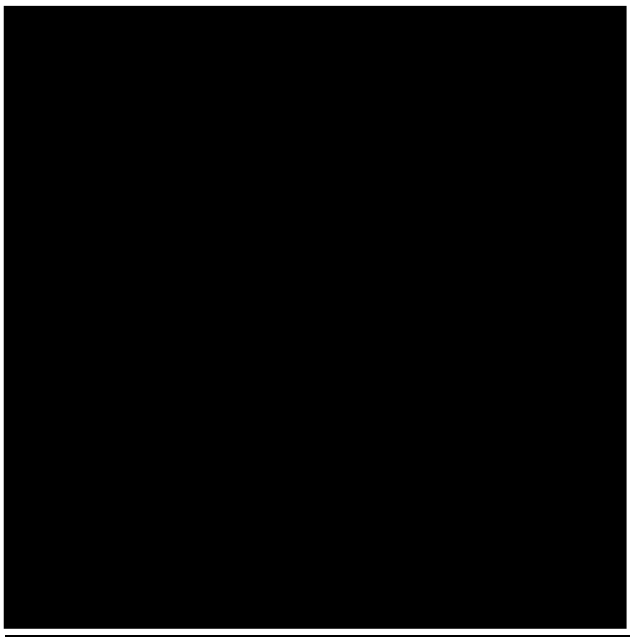
Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Figure 12: Cumulative hazard plots, enco+bini PFS, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

Figure 13: Cumulative hazard plots, enco+bini TTD, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; TTD, time-to-treatment discontinuation.

ii. Plot the log smoothed hazard versus time

The log-smoothed hazard plots for enco+bini OS, PFS, and TTD are presented in Figure 14, Figure 15, and Figure 16, respectively. Similarly to the smoothed hazard

plots in answer to part b) of this question, these plots show a relatively constant, but slowly decreasing hazard over time for OS, PFS, and TTD.

Figure 14: Log-smoothed hazard plots, enco+bini OS, PHAROS

Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Figure 15: Log-smoothed hazard plots, enco+bini PFS, PHAROS

Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival.

Figure 16: Log-smoothed hazard plots, enco+bini TTD, PHAROS

Abbreviations: enco+bini, encorafenib in combination with binimetinib; TTD, time-to-treatment discontinuation.

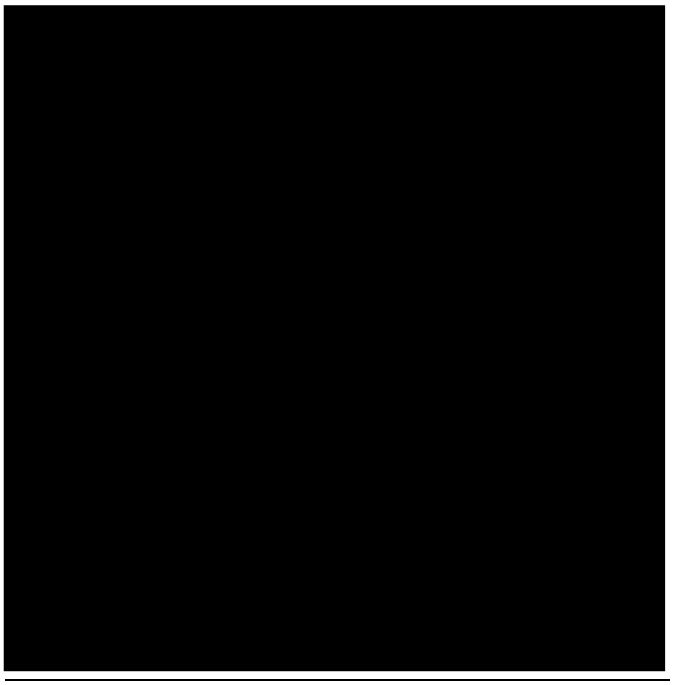
iii. Plot the standard normal quartiles versus log time

The standard normal quartiles for enco+bini OS, PFS, and TTD are presented in Figure 17, Figure 18, and Figure 19 , respectively.

Figure 17: Standard normal quartiles, enco+bini OS, PHAROS

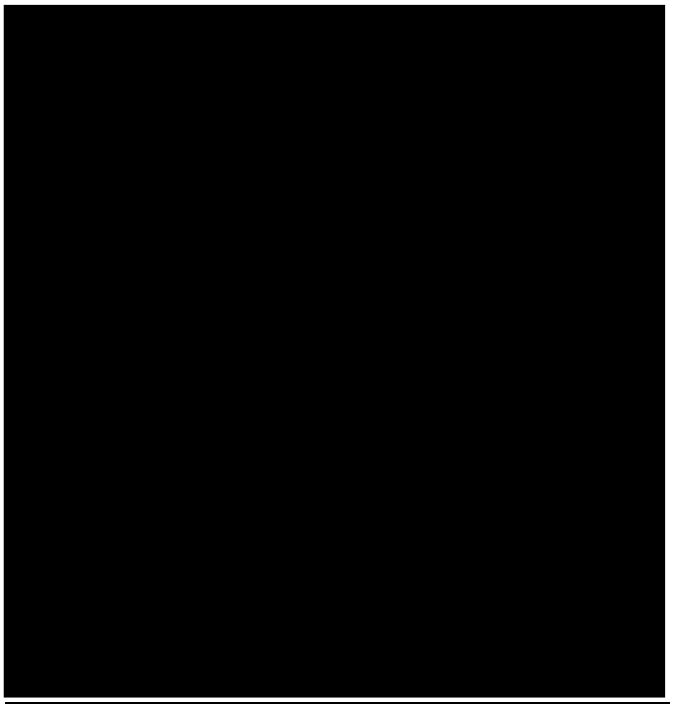
Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Figure 18: Standard normal quartiles, enco+bini PFS, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival**.**

Figure 19: Standard normal quartiles, enco+bini TTD, PHAROS

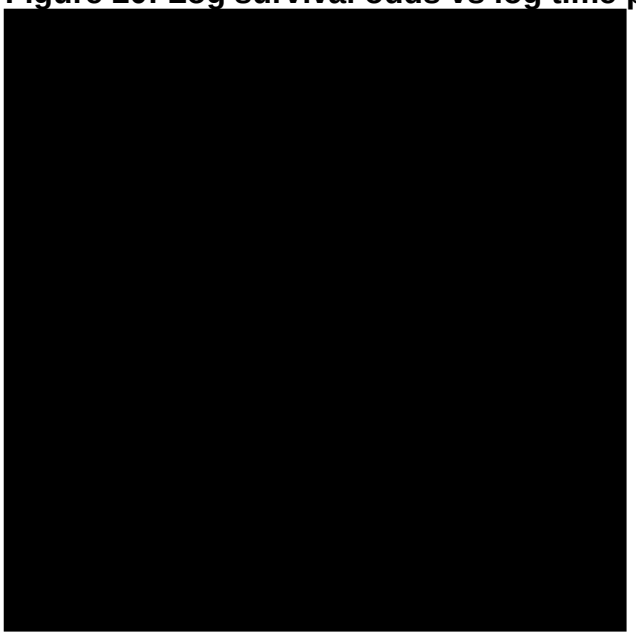


Abbreviations: Enco+bini, encorafenib in combination with binimetinib; TTD, time-to-treatment discontinuation.

iv. Plot the log survival odds versus log time

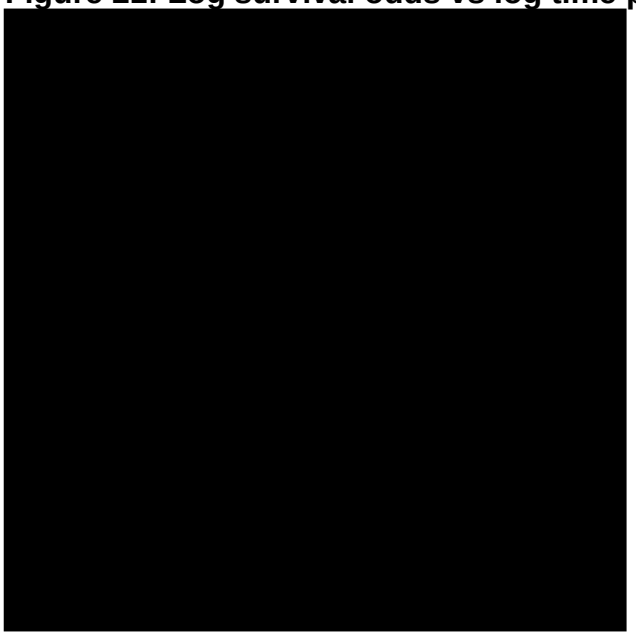
The log survival odds vs log time plots for enco+bini OS, PFS, and TTD are presented in Figure 20, Figure 21, and Figure 22, respectively.

Figure 20: Log survival odds vs log time plots, enco+bini OS, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; OS, overall survival.

Figure 21: Log survival odds vs log time plots, enco+bini PFS, PHAROS



Abbreviations: enco+bini, encorafenib in combination with binimetinib; PFS, progression-free survival**.**

Figure 22: Log survival odds vs log time plots, enco+bini TTD, PHAROS

Abbreviations: Enco+bini, encorafenib in combination with binimetinib; TTD, time-to-treatment discontinuation.

d. To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant external data. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.

A comparison vs available external data is provided in the response to question B38. Details of the advisory board are presented in response to B12.

e. [redacted] justify the selection of the Weibull distribution for both PFS and TTD.

[redacted]

[redacted]

[redacted]. As discussed in Sections B.3.3.2.1.2. and B.3.3.2.3.1, the exponential distribution was selected based on visual inspection, statistical fit to the latest observed data cut (April 2024), and clinical plausibility of long-term predictions.

f. According to CS Figure 23, the Log -Log survival (i.e. cumulative hazard) lines of both treatments cross, which is typically a strong indication of non-proportionality. Please justify the proportional hazards (PH) assumption for OS.

As stated in Section B.3.3.2.2 of the Company submission, the proportional hazards assumption was considered appropriate based on:

- The global test of the Schoenfeld residuals was associated with a p-value >0.05 (p=[redacted]), meaning the proportional hazards assumption could not be rejected.
- The plot of the Schoenfeld residuals were parallel at 0 suggesting the residuals are independent of time and therefore the proportional hazards assumption may be reasonable.
- Advice from CEs at the advisory board, who indicated that they saw no clinical reason for the proportional hazards assumption not to hold between enco+bini and dabra+tram.

Furthermore, as both enco+bini and dabra+tram have a similar mechanism of action, combining a *BRAF* inhibitor (dabrafenib, encorafenib) with a MEK inhibitor (trametinib, binimetinib), the Company consider it reasonable to suggest that both combination therapies would have a similar impact on the hazard of death over time.

Although the log-log plots cross, this is at the early part of the curve (<6 months). This is likely caused by a lack of events, particularly in the enco+bini arm. At 6 months only [redacted] patients had experienced an event in the treatment-naïve subgroup of PHAROS. Therefore, conclusions drawn from the log-log plot up to this point are associated with a high degree of uncertainty. After this point, the plots remain parallel, suggesting that proportional hazards may be an appropriate assumption.

g. Please clarify what external evidence was used to validate the long-term OS, PFS and TTD for both encorafenib with binimetinib and dabrafenib in combination with trametinib and provide justification if no validation with external evidence was performed.

All external evidence used to validate the long-term OS, PFS and TTD for both enco+bini and dabra+tram is presented in the response to question B38.

B11. Priority question. In the CS base-case no treatment waning was assumed, i.e. PFS and OS were assumed to be different for encorafenib in combination with binimetinib and the comparator for the whole duration of the time horizon.

[redacted]**. Moreover, as stated in the published literature "*in the absence of external evidence, a long-term protective treatment effect (even after treatment discontinuation) is a strong assumption when extrapolating beyond clinical trial follow-up*" (Taylor et al 2024; https://doi.org/10.1007/s40273-024-01423-6).**

a. **Please justify the assumption of no treatment waning, i.e. that there is a lifetime difference in PFS and OS based on the initial treatment**.

At the end of follow-up, [redacted]% of patients in the treatment-naïve cohort of PHAROS were still receiving treatment and deriving benefit from enco+bini. Although many patients had discontinued treatment, the smoothed hazard plot for enco+bini OS and PFS for the observed period shows no increase in the risk of death or progression towards the end of the trial period for enco+bini (Figure 23). Furthermore, the hazard plots of enco+bini and dabra+tram diverge for both OS and PFS, and this trend continues throughout the observed period, suggesting treatment effect waning is not appropriate at any point in the observed period for either endpoint.

Figure 23: Smoothed hazard plots, enco+bini (PHAROS) and dabra+tram (BRF113928 trial)

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; OS, overall survival; PFS, progression-free survival.

Furthermore, there is evidence that BRAF/MEK-directed targeted therapy can provide benefit to patients beyond treatment discontinuation. It has been previously reported in analyses of patients with advanced *BRAF* V600 mutant melanoma that BRAF/MEK inhibitor therapy effects the tumour microenvironment (TME) and improves durable tumour surveillance (the body's long-term ability to monitor and supress tumour activity), therefore providing a long-term beneficial effect (17). Studies have previously

shown that patients may still derive benefit from BRAF/MEK-directed targeted therapy after discontinuing treatment, particularly for patients who received treatment for a prolonged period (18). In the treatment-naïve cohort of patients, the majority of patients [redacted]%) received treatment for over 12 months.

However, the company acknowledge the uncertainty associated with long term extrapolations of OS and PFS and have therefore provided scenario analyses assuming waning at different time points after the trial period in response to part d) of this question.

b. Please support the response to the sub question above by plotting the smoothed hazards over time of both treatments (in one plot) separately for OS and PFS.

Please see response to part b) of this question for smoothed hazard plots.

c. Please follow the steps proposed by Taylor et al 2024 (https://doi.org/10.1007/s40273-024-01423-6) to assess the appropriateness of treatment effect waning and present the results.

Step 1 and Step 2a as proposed by Taylor et al 2024 involve collecting external evidence on the treatment effect of the intervention and comparator. As highlighted in the clinical SLR (Appendix D of the submission), beyond publications relating to the PHAROS and IFCT studies, only two observational studies were identified that present data on enco+bini. Patil et al. 2024 reports data from a retrospective chart review of 83 patients with metastatic oncogene-driven NSCLC. Of these, only one patient received enco+bini and survival outcomes are not presented specifically for enco+bini. Perrone et al. 2022 (19) present a multicentre Italian retrospective study involving 44 advanced *BRAF* mutant NSCLC patients. Of these, only one patient received enco+bini and survival outcomes are not presented specifically for enco+bini.

The smoothed hazard plots for enco+bini and dabra+tram are presented in Figure 23 for OS and PFS. These plots show no convergence in the OS hazard during the observed period, therefore it was not considered appropriate to apply treatment

waning at any point before the maximum follow-up of PHAROS ([redacted] months). Therefore, to address uncertainty in the duration of treatment effect beyond the trial period, treatment waning scenario are presented assuming a gradual waning of treatment effect after the PHAROS trial follow-up for 2 years (20). Taylor et al. (20) reviewed treatment effect waning in previous NICE appraisals – 9 of which were in NSCLC. They concluded that where treatment effect waning was preferred by the committee, waning at around 3-5 years was typically used, but acknowledged that this is likely arbitrary and is based on immune-oncology (IO) therapies that have stopping rules at 2 years. Therefore, the Company do not consider it appropriate to implement waning prior to 5 years as enco+bini has no stopping rule in place and the OS hazard shows no sign of waning compared with dabra+tram. As the duration of waning varies in previous appraisals between 1 and 3 years, the scenario analyses uses a midpoint of 2 years.

d. Please provide an updated economic model and scenario analyses while assuming treatment waning (at different time points).

As per the response to part a) of this question, the company maintain that treatment effect waning is not appropriate for the base case analysis but accept there is uncertainty regarding long term estimates of OS and PFS. As such, and in line with part a), waning was considered from [redacted] months for a duration of 24 months.

Results of the scenario are presented in Table 17 and associated with a NHB of [redacted]. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 17: Scenario analysis results – enco+bini treatment effect waning

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – no waning	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – waning from [redacted]	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
months for a duration of 24 months				

Abbreviations: enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

B12. Priority question. Asking experts (to extrapolate their knowledge) requires transparency, structured methodologies, and appropriate validation to ensure the credibility and robustness of the expert inputs.

a. Please clarify in detail how the clinical expert opinion was derived to inform the selection of the parametric survival model approach for OS, PFS and TTD. This should include (but not limited to), per advisor:

i. what advisor was consulted,

ii. why this advisor qualified as expert for this topic,

iii. please provide specific expertise in NSCLC patients with *BRAF* V600E mutations,

iv. what information was provided to the advisor,

v. what questions were asked,

vi. exact statements as well as point estimates (%) and/or ranges provided by the advisor (separately per treatment).

b. Please clarify whether the advisors had access to the Kaplan-Meier curves, or detailed model diagnostics, or detailed analyses underlying the company's proposed models for OS, PFS, and TTD? If not, what level of data granularity was shared, and how was this deemed sufficient to support informed decision-making?

c. Please clarify whether a structured methodology was used to elicit input from the advisors? Please provide details of any employed techniques.

d. **Please clarify whether there any dissenting opinions or variations in advisor input noted? If so, please document these along with their impact on the selection of parametric survival models.**

e. **Please clarify to what extent the advisors were required to extrapolate their expertise and knowledge to areas with limited or no direct clinical experience (e.g., low patient numbers or long-term outcomes)? Please provide details on the assumptions and context provided to the advisors for these extrapolations.**

f. **Please clarify what evidence or rationale supports the credibility of the advisor-derived inputs resulting from such extrapolations? Specifically, describe how these inputs were validated, cross-referenced, or justified against available data or alternative expert opinions.**

g. **Please elaborate on expect biases and uncertainties in the advisor input, considering amongst others that:**

    i. **advisors may inadvertently be influenced by personal biases or overconfidence, leading to overly optimistic or pessimistic estimates,**

    ii. **expertise in one context may not always translate well to unfamiliar situations, especially when the treatment or disease mechanism differs significantly from what the advisor is accustomed to,**

    iii. **the level of uncertainty acknowledged by the advisors.**

h. **Please provide, per advisor, for both the intervention and comparators what the expected % would be for OS, PFS and TTD at 2 year, 3 year, 5 year, 10 year and 20 year.**

i. **Please clarify that the advisor input (response to previous question) supports the CS base-case for OS, PFS and TTD.**

All CEs were selected due to their extensive expertise in the disease area of NSCLC. All CEs are currently working as clinical or medical oncologists in the NHS, diagnosing and treating NSCLC patients with targetable mutations, including *BRAF* V600E mutations. All CEs practise in different geographical areas and NHS trusts, enabling us to maximise the UK coverage of clinical experience in treating the rare *BRAF* V600E-mutant advanced NSCLC patient population. Two of the CEs consulted have experience acting as CEs for NICE appraisals in NSCLC. All CEs have experience of treating NSCLC patients with confirmed mutations such as *BRAF* V600E with targeted therapies. Additionally, one of the experts has experience treating patients with enco+bini in other disease types, such as melanoma. In addition to this all HE experts were selected for their extensive experience with the NICE appraisal processes, having previously served on NICE technology appraisal committees and provided advice on multiple HTAs. Each health economist advisor is an international expert in the field of health economics with appropriate experience in supporting NICE submissions.

The advisors were provided with materials prior to the advisory board meeting, including advisory board presentation slides. We are unable to share the presentation slides due to commercial sensitivity. Further detail of the discussion relating to PFS, OS and TTD is provided below, however, if any further specific queries arise we can review and address these as needed. The documents bulleted below were also shared with the advisors and were provided in the submission reference pack.

- PHAROS publication (Riely et al 2023 JCO). Shared as pre-read ahead of June 2024 advisory board (21).
- IFCT Study Protocol version 6 (Data on File, Confidential) Shared as pre-read ahead of June 2024 advisory board (22).
- Planchard 2021, shared as pre-read ahead of June 2024 and October 2024 advisory boards (23).

During the meeting, advisors were presented with the following for OS, PFS and TTD:

- KM data, including observed median and landmark survival estimates at 1 and 2 years
- Statistical goodness of fit information for each distribution
- Landmark survival estimates at 1, 2, 5, 10, 20 years for each parametric distribution

No structured elicitation techniques were used in the process of estimating long-term survival estimates with the CEs. CEs were asked their opinions on the most clinically plausible estimates of survival over time for enco+bini and dabra+tram, and to estimate plausible survival estimates at 5, 10, 15 and 20 years if they were able to. However, CEs preferred to focus on the curves they were presented during the meeting.

All three CEs noted that the log-normal, log-logistic, Gompertz and generalised gamma produced estimates of survival that are implausible for OS. Two CEs noted that long-term survival at 20 years will be close to zero. Two CEs indicated that the "bottom three" curves (Weibull, exponential, gamma distributions) were the most realistic, and provided long-term estimates at 10 years that were most clinically plausible. However, CEs considered that the estimates of long-term survival may be optimistic. For dabra+tram, all three CEs agreed that the "bottom three" curves (HR vs the enco+bini Weibull, exponential, and gamma distributions) were in line with their expectations for patient survival when receiving treatment with dabra+tram.

Two CEs agreed that the Weibull, exponential and gamma distributions were the most plausible. However, one CE estimated that around 5% of patients could be expected to be progression-free at 5 years. For dabra+tram, CEs agreed that the estimates produced when applying the HR vs the Weibull, exponential and gamma distributions for enco+bini were the most reasonable.

For TTD, CEs noted that some patients would be treated beyond progression with both enco+bini and dabra+tram. One CE noted that this would not be longer than 6 months. Two CEs commented the long-term estimates for all distributions may be overly optimistic for enco+bini, and one CE noted that 10% remaining on treatment at

5 years may be high. However, of the distributions presented, the Weibull, exponential and gamma distributions for enco+bini were the most reasonable.

Validation of the estimates with external data is provided in response to B37 and B38.

B13. Priority question. According to the CS, no TTD data were available for dabrafenib in combination with trametinib. Hence, the company assumed that TTD is equal to PFS for dabrafenib in combination with trametinib. This is a strong assumption that requires further exploration.

a. Please provide an updated economic model with a scenario analysis also assuming TTD is equal to PFS for encorafenib with binimetinib.

The company believe this scenario is not appropriate as PHAROS data are available to inform TTD for enco+bini directly, and therefore the scenario analysis requested ignores the trial data collected on treatment duration for enco+bini. However, for completeness, a scenario has been performed to assume TTD is equal to PFS for enco+bini (Table 18). The scenario results in a NHB of [redacted] and the ICER remains dominant. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 18: Scenario analysis results – enco+bini TTD assumptions

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – TTD derived from PHAROS	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – TTD assumed equal to PFS	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to discontinuation.

b. Please provide an updated economic model with a scenario analysis wherein TTD for dabrafenib in combination with trametinib is estimated

by applying the ratio between PFS and TTD from encorafenib with binimetinib to the PFS for dabrafenib in combination with trametinib.

A scenario has been performed to apply the hazard ratio (HR) between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabra+tram to derive an estimation of dabra+tram TTD. However, this scenario underestimates dabra+tram drug costs, predicting median TTD of 8.51 months compared to median TTD of 10.55 months in the combined cohort of BRF113928. Updated results based on scenarios from the CS are also presented in which TTD for dabra+tram was estimated by fitting an exponential curve through the median TTD reported in the BRF113928 trial (10.55 months) and the real-world evidence (RWE) study by Auliac et al. 2020 (17.50 months) (23, 24).

Results of the scenario are presented in Table 19; the scenario results in a NHB of [redacted] and a dominant ICER. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 19: Scenario analysis results – dabra+tram TTD assumptions

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – TTD equal to PFS	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario 1 – TTD estimated using median from BRF113928	[redacted]	[redacted]	Dominant	[redacted]
Scenario 2 – TTD estimated using median from RWE study Auliac 2020	[redacted]	[redacted]	Dominant	[redacted]
Scenario 3 – TTD derived from enco+bini PFS vs TTD HR	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: dabra+tram, dabrafenib with trametinib; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PFS, progression-free survival; QALYs, quality-adjusted life years; RWE, real-world evidence; TTD, time to discontinuation.

B14. Please provide an updated version of CS Figures 26 and 27 (long-term OS and PFS for dabrafenib in combination with trametinib) that overlay the Kaplan-Meier curves for OS and PFS against the modelled data:

a. **while overlaying the modelled OS with the OS Kaplan-Meier curves for dabrafenib in combination with trametinib.**

b. **while overlaying the modelled PFS with the PFS Kaplan-Meier curves for dabrafenib in combination with trametinib.**

c. **while overlaying the modelled OS with the OS Kaplan-Meier curves for dabrafenib in combination with trametinib + using the unadjusted HRs.**

d. **while overlaying the modelled PFS with the PFS Kaplan-Meier curves for dabrafenib in combination with trametinib + using the unadjusted HRs.**

The updated figures overlaying the modelled dabra+tram survival with the KM curves using the adjusted HRs for OS and PFS are presented in Figure 24 and Figure 25, respectively.

Figure 24: Dabra+tram OS (MAIC adjusted HR on all factors)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

Figure 25: Dabra+tram PFS (MAIC adjusted HR on all factors)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.

The updated figures overlaying the modelled dabra+tram survival with the KM curves using the unadjusted HRs for OS and PFS are presented in Figure 26 and Figure 27, respectively

Figure 26: Dabra+tram OS (unadjusted HR)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.

Figure 27: Dabra+tram PFS (unadjusted HR)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival.

B15. CS Table 100 provides a scenario analysis with MAIC HRs adjusted for ECOG and smoking status only. However, no scenario with the unadjusted HRs was provided. In the summary of section B.2.9. it was stated that "*The results of both unadjusted and adjusted models were consistent and robust*". Please provide scenario analyses using the unadjusted HRs.

The Company would like to clarify that the statement "The results of both unadjusted and adjusted models were consistent and robust" refers to the consistency and robustness of the MAIC analyses, not the economic model. A summary of the unadjusted and adjusted MAIC HRs for enco+bini vs dabra+tram are presented in Table 20.

Table 20: MAIC adjusted and unadjusted HRs

Endpoint	Adjusted		Unadjusted
	Adjustment on all factors	Adjustment on ECOG & smoking status	
OS	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival.

A feasibility assessment was conducted to assess the feasibility of an indirect treatment comparison for enco+bini vs dabra+tram. It concluded that there were imbalances between the PHAROS and BRF113928 trial populations on confounding factors that should be accounted for to generate the most accurate estimate of relative efficacy of enco+bini vs dabra+tram. The recommendations of the feasibility assessment (Section B.2.9.1) suggested the MAIC adjusting for all possible factors was considered the most robust for decision making. CEs at the advisory board also agreed with this conclusion and considered all factors identified in the feasibility assessment relevant to the analysis and therefore should be adjusted for.

Therefore, the company considers the base case analysis adjusting on all factors to be the most relevant for decision making. Furthermore, as per NICE guidance, "*When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate",* also stating that "*the term 'network meta-analysis' includes adjusted indirect comparisons".* Therefore, the Company does not consider it appropriate to inform comparator efficacy using a naïve comparison of trial data.

However, for completeness, scenario results are presented in Table 21 using both adjusted and unadjusted HRs. Results of both adjusted and unadjusted models were consistent and enco+bini remains dominant across analyses. Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 21: Scenario analysis results – MAIC HRs

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS adjusted on all factors	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Scenario 1 – adjusted on smoking & ECOG status	[redacted]	[redacted]	Dominant	[redacted]
Scenario 2 – unadjusted HR	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: dabra+tram, dabrafenib with trametinib; ECOG, Eastern Cooperative Oncology Group; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to discontinuation.

B16. In Section B.3.3.2.1.2 it is stated "Clinical experts stated that a proportion of patients would be 'super responders' and therefore some patients would be responders long-term". Please clarify this statement, when does a patient qualify to be a 'super responder', what is the expected proportion of 'super responders' and what is the expected OS, PFS and TTD for 'super responders'? Please support the response to this question with available empirical evidence.

During an advisory board, CEs were asked to comment on the PFS extrapolations and discuss which was most plausible. The CEs discussed that some estimates were implausibly high. One CE with experience using enco+bini for melanoma noted that PFS of 5% at 5 years seemed plausible as there were 'super-responders in all targeted oncology' but no further discussion or context was provided relating to the term 'super-responders' at the time. Further clarification was sought from the CE following the EAG's query, and the CE noted that there is no fixed definition of a "super responder" but it is a term generally used to describe a patient with a durable, sustained response well over the median duration of response. Patients within this "super responders" group would also be expected to have good tolerance of treatment, as patients experiencing toxicity are less likely to remain on treatment for a sustained period. The CE noted that there are limited trial data available to answer this with accuracy, yet they would estimate 5-10% of patients to experience a durable response and could therefore be classified as "super responders". This is based on clinical observations in other tumour types with BRAF mutations being treated with enco+bini and NSCLC with other driver mutations being treated with other targeted agents. OS, PFS and TTD would all be expected to be better in this group but, without rigid definitions then

survival probabilities would be speculative. Some patients are expected to experience highly sustained benefits with good tolerance of treatment.

B17. The CS provides a pooled scenario combining data from PHAROS and IFCT

a. **Please clarify that the PHAROS and IFCT data are only combined in a scenario analysis (and not in the CS base-case).**

b. **Please describe how the PHAROS and IFCT data are pooled.**

c. **Please clarify that the PHAROS and IFCT data are pooled in a methodologically sound way (e.g. using a multi-level approach).**

The Company can confirm that the base case analysis uses PHAROS data only as this is the pivotal Phase 2 trial, aligns with the European Medicines Agency (EMA) regulatory submission and leverages the more mature data available in PHAROS. The PHAROS and IFCT data are only combined in a scenario analysis. This analysis was carried out for exploratory purposes.

Individual patient data from PHAROS and from IFCT were naively combined to obtain a pooled dataset. CEs at the advisory board considered the populations of both trials to be sufficiently similar, and HE experts considered them to be similar enough to be used in a pool scenario analysis to increase the sample size. This approach to pooling data sources has been accepted in recent NICE appraisals in metastatic colorectal cancer (mCRC) (25). Based on this pooled dataset, a matching-adjusted indirect comparison was conducted comparing the 120 patients receiving enco+bini (59 patients from PHAROS and 61 from IFCT) and the 36 patients receiving dabra+tram.

B18. Some statements in the CS regarding TTD require clarification.

d. **In Section B.3.3.2.3.1 it is stated "*No TTD data were collected in the pivotal PHAROS study, however, a post-hoc analysis was conducted*". Please clarify this statement, how the company conducted a 'post-hoc analysis' while 'no TTD data were collected', i.e without data? Also elaborate on the implications of the post-hoc approach (compared to ad-hoc analyses).**

The Company would like to clarify this statement. TTD was not a specified endpoint in the PHAROS study, and therefore no TTD data were reported in the tables, figures, and listings (TFLs). However, TTD for patients receiving enco+bini was recreated using related data points in PHAROS in a post-hoc analysis. The post-hoc analysis was conducted using the following data points:

- DCTFL: Subject discontinued flag
- TRTEDY: Study day of last exposure to treatment
- DCTADY: Study day of treatment discontinuation

For patients who discontinued treatment (DCTFL='Y'), DCTADY was used for the event time for TTD. For patients who have not discontinued treatment, TRTEDY was used as the censoring point for TTD.

e. **In Section B.3.3.2.3.2 it is stated "*It should be noted that this approach to TTD is likely to be conservative as there is no adjustment for the observed differences between trial populations, as was done with OS and PFS, therefore this may underestimate treatment costs in the dabra+tram arm. Additionally, this data also includes second line patients, and therefore it is likely that this underestimates the median TTD for a first-line only population*". Please clarify this statement, why does the company consider this to be conservative, separately for:**

    i. **no adjustment between the trial populations and;**

    ii. **the inclusion of second line patients.**

In the base case analysis, dabra+tram PFS is estimated by applying the MAIC HR to the enco+bini PFS curve. The MAIC HR is a measure of relative efficacy between the enco+bini and dabra+tram after adjustment for differences in prognostic factors and treatment effect modifiers between the trial populations of the PHAROS and the BRF113928 trials. The observed median PFS in the treatment-naive cohort of BRF113928 trial was 10.8 months, however when applying the MAIC PFS HR to the

enco+bini curve, i.e. after adjustment for the observed differences in characteristics between trial populations, the estimated PFS is [redacted] months. Due to the inherent relationship between PFS and TTD, it may also be expected that the effect of accounting for differences between the PHAROS and the BRF113928 trials would be to also increase the median TTD in the dabra+tram arm marginally, from what was observed in the BRF113928 trial. By using the median TTD from the BRF113928 trial naïvely in the model, these differences are not accounted for and therefore may underestimate treatment costs in the dabra+tram arm.

Furthermore, the observed median TTD reported by Planchard et al. 2021 is a combined estimate for both treatment-naïve and treatment-experienced patients. It is well documented in the literature that outcomes for patients become poorer with each additional line of therapy (26), subsequently it can be expected that median TTD at second-line would be shorter than at first-line, and therefore the combined median TTD would be shorter than at first-line alone. This is true in the PHAROS trial, in which median TTD for the combined population ([redacted] months) and the treatment experienced cohort ([redacted] months) was worse than the treatment naïve cohort ([redacted] months). Similarly, median PFS for the treatment experienced cohort (10.2 months) was worse than the median PFS in the treatment naïve cohort (10.8 months) in the BRF113928 trial. Therefore, using the reported median TTD from the BRF113928 trial from the combined population is likely to underestimate both the true median TTD for a treatment-naïve cohort and treatment costs in the dabra+tram arm.

Adverse events

B19. Grade ≥3 TEAEs with an incidence of ≥3% were taken from the treatment-naïve population in PHAROS for enco+bini. The full population of BRF113928 was used for dabra+tram as AE data in the treatment naïve cohort of BRF113928 were not available.

a) **Please provide an updated economic model and scenario analysis also informing AE incidences for enco+bini based on the full population (i.e. including non-treatment naïve patients) of PHAROS**.

Incidence of Grade ≥3 TEAEs occurring in ≥3% based on both the treatment-naïve and full population of PHAROS are presented in Table 22. It should be noted that some events with frequency of <3% are included in the analysis as they were experienced by ≥3% of patients in the BRF113928 trial.

Table 22: PHAROS - Grade ≥3 TEAEs treatment-naïve and full population

Event	Grade ≥3 TEAEs occurring in ≥3% - PHAROS population	
	Treatment-naïve population	Full population
Alanine aminotransferase increased	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood creatinine phosphokinase increased	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-gluamyltransferase increased	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Leukocytosis	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Loss of consciousness	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]

Event	Grade ≥3 TEAEs occurring in ≥3% - PHAROS population	
	Treatment-naïve population	Full population
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event.

Costs, disutilities, and durations were modelled in line with the base case, as presented in Table 70 and Table 88 of the company submission.

Results of the scenario are presented in Table 23. The scenario resulted in a NHB of [redacted] and a dominant ICER. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 23: Scenario analysis results – PHAROS TEAEs

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS treatment-naïve population	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – PHAROS full population	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; TEAEs, treatment-emergent adverse events.

b) Please provide an updated economic model and scenario analyses including

i. Any grade ≥3 TEAE (i.e. incidence >0%)

ii. Grade ≥3 TEAE with an incidence of ≥5%

Data from BRF113928 are only available in TA898 (company submission Table 19) for events occurring in ≥10% of the population for all grades. Consequently, analysing Grade ≥3 TEAEs occurring in >0% was deemed not possible, as it is expected that a significant number of events would be omitted in the dabra+tram arm due to data unavailability. However, the scenario considering Grade ≥3 TEAE with an incidence of ≥5% was performed using data from the treatment naïve cohort of PHAROS for enco+bini and reported events in TA898 for dabra+tram. Incidences of Grade ≥3 TEAEs occurring ≥5% of patients in PHAROS are presented in Table 24.

Table 24: PHAROS - Grade ≥3 TEAEs with incidence ≥5%

Event	Enco+bini – PHAROS treatment naive population	Dabra+tram - BRF113928
Alanine aminotransferase increased	[redacted]	0.00%
Anaemia	[redacted]	5.38%
Aspartate aminotransferase increased	[redacted]	0.00%
Blood creatinine phosphokinase increased	[redacted]	0.00%
Colitis	[redacted]	0.00%
Diarrhoea	[redacted]	0.00%
Dyspnoea	[redacted]	7.53%
Gamma-gluamyltransferase increased	[redacted]	0.00%
Hypertension	[redacted]	0.00%
Hyponatraemia	[redacted]	0.00%
Lipase increased	[redacted]	0.00%
Nausea	[redacted]	0.00%
Pneumonia	[redacted]	0.00%
Pyrexia	[redacted]	6.45%

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; TEAE, treatment-emergent adverse event.

TEAE costs, disutilities and durations were modelled in line with the model base case as presented in B.3.4.4 and B.3.5.5 of the Company submission. The scenario considering incidence Grade ≥3 TEAEs of ≥5% results in a NHB of [redacted] (Table 25).

Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 25: Scenario analysis results – PHAROS TEAEs

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS treatment-naïve population	XXXXXX	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	XXXXXX	[redacted]	Dominant	[redacted]
Scenario 2 – incidence ≥5%	XXXXXX	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; TEAEs, treatment-emergent adverse events.

c) According to the CS, a clinical expert highlighted that grade 1–2 TEAEs could also substantially impact HRQoL and costs. Please provide justification for not including these in the economic model.

CEs, with experience of using both enco+bini and dabra+tram, noted that Grade 1-2 pyrexia greatly impacts a patient's quality of life (QoL). However, these were not included in the economic model as the equivalent data was not available for dabra+tram. A scenario has been performed in which Grade 1-2 pyrexia is considered in the model for both arms. Event proportions for enco+bini were modelled in line with the treatment-naïve population in PHAROS; for dabra+tram, event proportions were modelled in line with the combined safety population in BRF113928, in the absence of data for cohort C alone, as reported in TA898 (27).

Table 26: TEAEs - pyrexia

	Enco+bini (N=59)	Dabra+tram (N=93)
Proportion experiencing Grade 1-2 pyrexia	[redacted]	46 (49%)
Proportion experiencing Grade 3+ pyrexia	[redacted]	6 (6%)
Total	[redacted]	52 (56%)

Abbreviations: dabra+tram, dabrafenib with trametinib; enco+bini, encorafenib with binimetinib; TEAEs, treatment-emergent adverse events.

For simplicity, it was assumed that the cost, disutility, and duration for Grade 1-2 pyrexia was half of that of Grade 3+ pyrexia. Results of the scenario are presented in Table 27. The scenario is associated with negligible changes to the NHB and enco+bini remains dominant. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 27: Scenario analysis results – Grade 1-2 pyrexia

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS treatment-naïve population	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – including Grade 1-2 pyrexia	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

d) Please provide an updated economic model and scenario analysis also including grade 1-2 TEAEs.

A summary of incidences of Grade 1-2 TEAEs occurring in ≥3% of patients in the treatment naïve population of PHAROS are presented in Table 28. In the absence of other data, it was assumed that Grade 1 and 2 AEs incur a flat cost of £5 per event, a disutility of 0.01, and a one-week duration in line with the committee preferred assumptions in TA866 in mCRC (25). In the absence of data, TEAE proportions which were not reported for dabra+tram in TA898 were assumed to have zero incidence.

Table 28: PHAROS - Grade 1-2 TEAEs occurring in ≥3%

Event	Incidence of Grade 1-2 AEs occurring in ≥3%	
	Enco+bini	Dabra+tram
Abdominal discomfort	[redacted]	NR
Abdominal pain	[redacted]	12.9%
Abdominal pain upper	[redacted]	NR

Event	Incidence of Grade 1-2 AEs occurring in ≥3%	
	Enco+bini	Dabra+tram
Abnormal loss of weight	[redacted]	NR
Actinic keratosis	[redacted]	NR
Acute kidney injury	[redacted]	NR
Alanine aminotransferase increased	[redacted]	NR
Alopecia	[redacted]	NR
Amylase increased	[redacted]	NR
Anaemia	[redacted]	14.0%
Anal haemorrhage	[redacted]	NR
Anxiety	[redacted]	NR
Arthralgia	[redacted]	25.8%
Aspartate aminotransferase increased	[redacted]	NR
Asthenia	[redacted]	24.7%
Back pain	[redacted]	15.1%
Balance disorder	[redacted]	NR
Blood alkaline phosphatase increased	[redacted]	12.9%
Blood creatinine increased	[redacted]	NR
Blood creatinine phosphokinase increased	[redacted]	NR
Blood iron decreased	[redacted]	NR
Cataract	[redacted]	NR
Chills	[redacted]	26.9%
Colitis	[redacted]	NR
Conjunctivitis	[redacted]	NR
Constipation	[redacted]	18.3%
Cough	[redacted]	31.2%
COVID-19	[redacted]	NR
Decreased appetite	[redacted]	33.3%
Deep vein thrombosis	[redacted]	NR
Dehydration	[redacted]	NR
Depression	[redacted]	NR
Dermal cyst	[redacted]	NR
Dermatitis acneiform	[redacted]	NR
Diarrhoea	[redacted]	34.4%
Dizziness	[redacted]	18.3%
Dry skin	[redacted]	37.6%

Event	Incidence of Grade 1-2 AEs occurring in ≥3%	
	Enco+bini	Dabra+tram
Dysgeusia	[redacted]	NR
Dyspepsia	[redacted]	NR
Dysphagia	[redacted]	NR
Dyspnoea	[redacted]	20.4%
Ejection fraction decreased	[redacted]	NR
Erythema	[redacted]	NR
Face oedema	[redacted]	NR
Fall	[redacted]	NR
Fatigue	[redacted]	25.8%
Haemorrhoids	[redacted]	NR
Hair texture abnormal	[redacted]	NR
Headache	[redacted]	19.4%
Hot flush	[redacted]	NR
Hyperglycaemia	[redacted]	NR
Hyperkalaemia	[redacted]	NR
Hyperkeratosis	[redacted]	NR
Hypertension	[redacted]	NR
Hyperuricaemia	[redacted]	NR
Hypoalbuminaemia	[redacted]	NR
Hypocalcaemia	[redacted]	NR
Hyponatraemia	[redacted]	NR
Hypophosphataemia	[redacted]	NR
Hypotension	[redacted]	10.8%
Influenza like illness	[redacted]	NR
Insomnia	[redacted]	NR
Iron deficiency	[redacted]	NR
Keratitis	[redacted]	NR
Lipase increased	[redacted]	NR
Malaise	[redacted]	NR
Melanocytic naevus	[redacted]	NR
Memory impairment	[redacted]	NR
Muscle spasms	[redacted]	NR
Muscular weakness	[redacted]	NR
Musculoskeletal chest pain	[redacted]	NR

Event	Incidence of Grade 1-2 AEs occurring in ≥3%	
	Enco+bini	Dabra+tram
Myalgia	[redacted]	NR
Myoglobin blood increased	[redacted]	NR
Nasal congestion	[redacted]	NR
Nasopharyngitis	[redacted]	15.1%
Nausea	[redacted]	50.5%
Neck pain	[redacted]	NR
Neutrophil count decreaseed	[redacted]	NR
Non-cardiac chest pain	[redacted]	NR
Oedema peripheral	[redacted]	37.6%
Oesophagitis	[redacted]	NR
Oropharyngeal pain	[redacted]	NR
Osteoporosis	[redacted]	NR
Pain in extremity	[redacted]	NR
Palpitations	[redacted]	NR
Paraesthesia	[redacted]	NR
Peripheral embolism	[redacted]	NR
Peripheral sensory neuropathy	[redacted]	NR
Photophobia	[redacted]	NR
Photosensitivity reaction	[redacted]	NR
Platelet count decreased	[redacted]	NR
Pleural effusion	[redacted]	NR
Pneumonia	[redacted]	NR
Pollakiuria	[redacted]	NR
Post herpetic neuralgia	[redacted]	NR
Productive cough	[redacted]	NR
Pruritus	[redacted]	14.0%
Pyrexia	[redacted]	49.5%
Rash	[redacted]	26.9%
Rash macular	[redacted]	NR
Rash maculo-papular	[redacted]	NR
Rash pustular	[redacted]	NR
Respiratory tract infection	[redacted]	NR
Retinal detachment	[redacted]	NR
Rhinitis	[redacted]	NR

Event	Incidence of Grade 1-2 AEs occurring in ≥3%	
	Enco+bini	Dabra+tram
Rhinitis allergic	[redacted]	NR
Rhinorrhoea	[redacted]	NR
SARS-CoV-2 test positive	[redacted]	NR
Seborrhoeic keratosis	[redacted]	NR
Sinusitis	[redacted]	NR
Skin hyperpigmentation	[redacted]	NR
Skin papilloma	[redacted]	NR
Stomatitis	[redacted]	NR
Tachycardia	[redacted]	NR
Tinnitus	[redacted]	NR
Tremor	[redacted]	NR
Upper respiratory tract infection	[redacted]	NR
Urinary incontinence	[redacted]	NR
Vision blurred	[redacted]	NR
Visual acuity reduced	[redacted]	NR
Visual impairment	[redacted]	NR
Vitreous floaters	[redacted]	NR
Vomiting	[redacted]	36.6%
Weight decreased	[redacted]	NR
Weight increased	[redacted]	18.3%
Xerosis	[redacted]	NR

Abbreviations: AEs, adverse events; TEAE, treatment-emergent adverse event; NR, not reported.

The scenario is associated with a NHB of [redacted] and a dominant ICER (Table 29). Although it should be noted that much of the data is unavailable for dabra+tram. Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 29: Scenario analysis results – PHAROS Grade 1-2 TEAEs occurring in ≥3%

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS treatment-naïve population	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – including Grade 1-2 AEs	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; TEAEs, treatment-emergent adverse events.

e) According to the CS "clinically inconsequential" TEAEs that would have minimal impact on HRQoL and costs were set to zero disutility, cost and duration in the company's base case. Please provide evidence to support the statement that these TEAEs would minimally impact HRQoL and costs.

In the October 2024 UK advisory board, one CE noted that dabra+tram is considered a much more toxic treatment (particularly regarding pyrexia), and that increased alanine aminotransferase, increased amylase, increased blood alkaline phosphatase, increased blood creatinine phosphokinase, raised lipase, and herpes zoster can be discounted and have little impact. The CE highlighted these events as inconsequential as they often aren't measured during treatment, and therefore many patients will be unaware they have them in real world clinical practice.

f) Please provide an updated economic model and scenario analysis also including these "clinically inconsequential" TEAEs.

A scenario has been run to consider specified 'clinically inconsequential' TEAEs as specified in part e).

Note that events were considered in the scenario analysis if the incidence was ≥3% in either the enco+bini or dabra+tram arms.

Table 30: Clinically inconsequential Grade ≥3 TEAEs occuring in ≥3%

	Enco+bini – PHAROS (treatment-naïve population)	Dabra+tram - BRF113928 (in line with TA898)
Alanine aminotransferase increased	[redacted]	6.5%
Amylase increased	[redacted]	0.00%
Blood alkaline phosphatase increased	[redacted]	1.08%
Blood creatinine phosphokinase increased	[redacted]	0.0%
Lipase increased	[redacted]	0.0%
Herpes zoster	[redacted]	0.0%

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; TEAEs, treatment-emergent adverse events.

Costs, disutilities and durations of 'clinically inconsequential' TEAEs were derived from previous NICE TAs, where possible, and the published literature and are presented in Table 31.

Table 31: Clinically inconsequential Grade ≥3 TEAEs – cost, disutilities, durations

	Cost		Disutility		Duration	
	Value	Reference	Value	Reference	Value (weeks)	Reference
Alanine aminotransferase increased	£2,313	TA898. Weighted average of Total HRGs GC17A-K (Non-Malignant, Hepatobiliary or Pancreatic Disorders)	0.05	TA898: Derived from TA789 (Table 49), Source: Assumption based on TA347	54.8	TA898: Derived from TA789, Source: VISION trial (27, 28)
Amylase increased	£131	TA789: WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)	0.05	TA789: Assumed same as ALT increased, assumption based on TA347	76.0	TA789: VISION trial (28)

	Cost		Disutility		Duration	
	Value	Reference	Value	Reference	Value (weeks)	Reference
Blood alkaline phosphatase increased	£2,313	TA898. Assumed equal to alanine aminotransferase increased	0.05	TA898: assumed same as alanine aminotransferase increased	54.8	TA898: assumed same as alanine aminotransferase increased (27)
Blood creatinine phosphokinase increased	£2,313	TA898. Assumed equal to alanine aminotransferase increased	0.05	Assumed same as alanine aminotransferase increased	54.8	Assumed same as alanine aminotransferase increased
Lipase increased	£131	TA789: WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)	0.07	TA789: Assumed same as anaemia	38.20	TA789: Assumed same as anaemia (28)
Herpes zoster	£1,993	Total HRGs, weighted average of JD07A-K - Skin disorders	0.00	Assumed equal to severe skin reaction in TA911	0.00	Assumed equal to severe skin reaction in TA911 (29)

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; TEAEs, treatment-emergent adverse events.

Results of the scenario considering 'clinically inconsequential' TEAEs are presented in Table 32, the scenario is associated with negligible changes to the NHB and results in a dominant ICER.

Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 32: Scenario analysis results – Clinically inconsequential TEAEs

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – PHAROS	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
treatment-naïve population				
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – including clinically inconsequential TEAEs	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; TEAEs, treatment-emergent adverse events.

Health-related quality of life

B20. Priority question. In its base-case, the company used health state utility values from Chouaid et al. (2013) to align with the committee preferred assumptions in TA898 (PF 0.710, PD 0.670). Scenarios were presented 1) using values estimated from the IFCT study (PF [redacted], PD [redacted]) and 2) applying the PD decrement from TA898 (0.04) to the PF value derived from the IFCT study.

a) The EAG noticed a number of potential limitations in the study of Chouaid et al (2013):

i. The study was conducted a relatively long time ago (i.e. >10 years)

ii. A substantial number of patients (N=45) were excluded from the analyses because they did not complete the EQ-5D questionnaire

iii. The final regression model used to estimate utility values included 11 covariates

iv. The estimated PF utility value for first-line treated patients (0.71) was lower than the estimated PF utility for second-line treated patients (0.73).

v. The estimated PD utility was based on few patients (N=26)

Please comment on the potential implications of these limitations on the estimated health state utility values.

The company accept the limitations highlighted with respect to the health state utility values from Chouaid et al. (2013) as they were estimated >10 years ago. However, although treatments have evolved in NSCLC over the past decade, the values estimated from Chouaid et al. (2013) are well aligned with the values accepted by the NICE Committee in previous recent appraisals (Table 40). It should be noted that, although 45 patients were excluded from the analysis, the final analysis still contained a significant number of patients (263), 202 more than included in the IFCT analysis (Section B.3.4.1 of the Company submission). Although the regression model included in the analysis by Chouaid et al. (2013) included 11 covariates, these were included after a robust approach to covariate inclusion. Insignificant covariates were removed with backward elimination, and the model was rerun, until all covariates were significant at a 10% level. Furthermore, these covariates are consistent with other publications on determinants of HRQoL in patients with NSCLC (30). As highlighted by the EAG, there are some uncertainties regarding the estimated values due to low patient numbers, specifically the estimated PD utility (N=26) and the estimated PF utility for second-line treated patients (N=47) being higher than the PF utility value for first-line treated patients. Therefore, two further scenario analyses were presented by the Company, using values from IFCT and applying the PD decrement from Chouaid et al. (2013) to the PF utility value from IFCT.

b) Considering the advancements in lung cancer healthcare since the study of Chouaid et al (2013) was published, please discuss whether this study is still considered the best source of published evidence to inform health state utility values in the economic model.

A HSUV SLR was conducted in May 2024 however no studies were identified that reported HRQoL or HSUV data for patients with *BRAF*-mutated advanced NSCLC (Appendix H of the Company Submission). Therefore, HSUVs from the literature were considered appropriate in the company submission given that utility data were not

collected in the pivotal PHAROS trial. Data from Chouaid et al. was considered most appropriate to align with the only and relevant appraisal in *BRAF* V600 mutation positive NSCLC, and to be consistent with the values used in the appraisal of the only comparator for this submission and subsequently accepted by the committee. CEs noted these values were representative of patients with *BRAF* V600E mutation positive NSCLC. However, one CE noted that the difference between PF and PD in the Chouaid et al. study (0.04) was small. Scenario analyses were presented to test the impact of the uncertainty concerning the most appropriate source of HSUVs, including data from IFCT, which estimates a larger difference in HSUV between the PF and PD health states ([redacted]).

c) Please justify why values from Chouaid et al. (2013) were preferred over values from the IFCT study to inform health state utility values in the economic model.

As discussed in part b) of this response, HSUVs were informed by TA898 to align with the most recent and relevant appraisal in *BRAF* V600 mutation positive NSCLC, and to be consistent with the values used in the appraisal of the only comparator for this submission and subsequently accepted by the Committee. Furthermore, the analysis by Chouaid et al. (2013) was conducted on significantly more patients than the IFCT analysis (263 vs 61), and contained patients across a range of countries, including the UK. The IFCT data only contained data from patients in France, and was considered less generalisable to a UK population.

d) The study of Chouaid et al. (2013) was conducted in 25 hospitals in Europe, Canada, Australia, and Turkey. Please provide the number of patients that were from the UK.

Data including number of patients, and results of the utility study by Chouaid et al. (2013) are not available in the published materials. A total of 263 patients were enrolled and included in the study and European study sites included Belgium, France, Italy, The Netherlands, Sweden, and the UK.

e) **Please provide an updated economic model and scenario analysis estimating health state utility values based on only UK patients in Chouaid et al (2013).**

In line with response to part d), it is not possible to perform the requested analysis.

f) [redacted]**. Please provide full details of this study, including patient and disease characteristics of its population, an overview per time point of the data included (i.e. the number of observations in PF and PD), the number and pattern of missingness, how missing data were handled, and details on the methodology of estimating PF and PD utility values.**

g) **details on the methodology of estimating PF and PD utility values.**

OCTOPUS (31) is an ambispective observational study describing diagnosis and treatment patterns in adult *BRAF* V600E-MT mNSCLC patients in Germany, France, Italy, Spain, and the UK with the objective of describing the real-world treatment patterns for first- and second-systemic treatment lines in adult *BRAF* V600E-MT metastatic NSCLC patients. OCTOPUS study design is described in Table 33 and Figure 28.

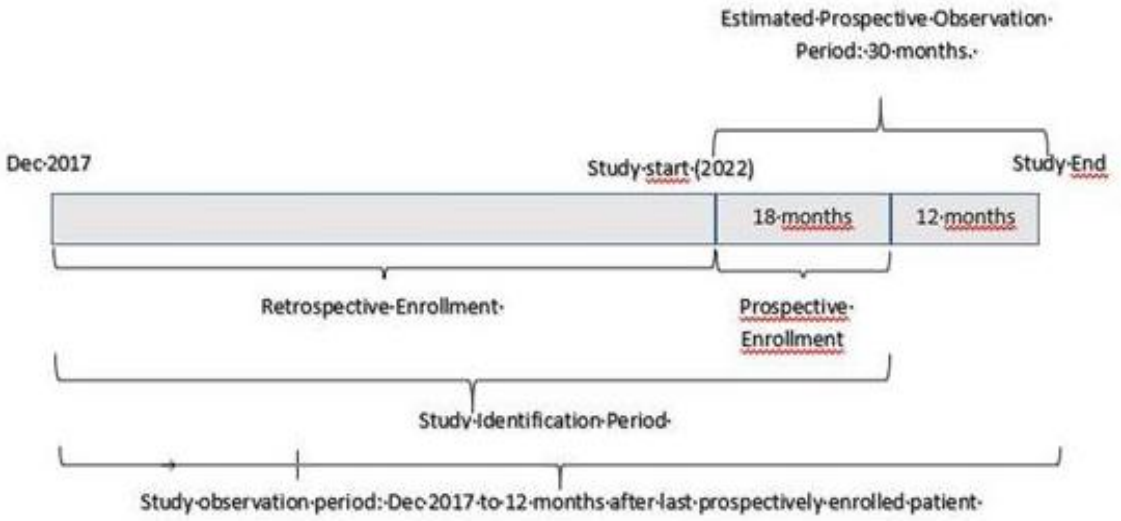
Table 33: OCTOPUS study design description

An ambispective observational study describing diagnosis and treatment patterns in adults with metastatic non-small cell lung cancer with *BRAF* V600E mutation in clinical practice, to assess treatment effectiveness and quality of life (OCTOPUS)	
Clinicaltrial.gov	NCT05546905
Study type	Multi-country, multicenter, observational, descriptive, ambispective study
Location	Germany, France, Italy, Spain, UK
Number of patients	[redacted]
Population	[redacted]

An ambispective observational study describing diagnosis and treatment patterns in adults with metastatic non-small cell lung cancer with *BRAF* V600E mutation in clinical practice, to assess treatment effectiveness and quality of life (OCTOPUS)	
	[redacted]
Treatment regimen	[redacted]
Dates and duration	Ongoing study: [redacted]

Abbreviations: mNSCLC, metastatic non-small cell lung cancer; UK, United Kingdom.

Figure 28: OCTOPUS: study design



Source: OCTOPUS clinical study protocol lay synopsis (32)

Analysis

[redacted]

[redacted]

Results

[redacted]

[redacted]

PROSPECTIVE COHORT

Demographic

[redacted]**Table *34*** [redacted]

Table 34: OCTOPUS: Demographic characteristics at initial diagnosis of NSCLC and at advanced stage of the disease (Prospective Analysis Set)

Characteristic	Prospective population (N=14)
Age at diagnosis of NSCLC	
n	[redacted]
Mean (SD)	[redacted]
Median (Min, Max)	[redacted]
Sex, n (%)	
Male	[redacted]
Female	[redacted]
Primary tumour histology, n (%)	
Adenocarcinoma	[redacted]
Location of metastases, n (%)	
Brain	
Yes	[redacted]
No	[redacted]
Unknown	[redacted]
Performance status (ECOG) at advanced stage of disease, n (%)	

0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Unavailable	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group. Min-Max: Minimum and Maximum. NSCLC: Non-Small Cell Lung Cancer. SD: Standard Deviation.

First line of treatment

[redacted]

Second line of treatment

[redacted]

Quality of life

[redacted]

[redacted]Table

35 [redacted] **Table**

36 [redacted]

Table 35: Time points of EQ-5D measurements and number of patients by health state

Health State	Baseline	3 months	6 months	9 months	12 months
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36: Summary of utility values by time points of EQ-5D-3L measurements and health state

Health State	Baseline	3 months	6 months	9 months	12 months
Pre-progression					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

a) Please provide an updated economic model and scenario analysis estimating health state utility values based on the OCTOPUS study.

As mentioned in the response to part f) of this question, OCTOPUS RWE study [redacted], therefore is not available for use in the economic model.

B21. Priority question. For the company's scenario analysis, EQ-5D-5L data in the IFCT study were mapped to EQ-5D-3L and health state utility values were estimated using a mixed model with repeated measures (MMRM).

a) **Please specify which value set was used.**

The EQ-5D-5L was used with the crosswalk function of Hernández Alava, M. et al (2022) (33) to obtain EQ-5D-3L utility scores; as per the NICE guideline reference case (34).

b) **It is unclear to the EAG whether the EQ-5D completion rate in Table 69 of the CS includes all visits. If not, please provide an updated Table of all visits, including the time points and the number of expected responses.**

c) **Please provide an overview per time point of the data included (i.e. the number of observations in PF and PD), the number and pattern of missingness, and how missing data were handled.**

Table 37 summarises the number of patients with observed and missing data at each visit, stratified by pre- and post-progression status. After completion of the first follow-up visit (at first dose), subjects were followed for EQ-5D-5L questionnaires every 8 weeks ± 7 days for twelve months then every 12 weeks ± 7 days until disease progression. Pre-progression visits consistently show a higher proportion of observed data compared to post-progression visits, with the percentage of missing data progressively increasing over time. These findings highlight a decreasing trend in data completeness over time, attributable to factors such as patient mortality, the timing of the data cut-off, and challenges in maintaining follow-up, particularly within the post-progression cohort.

Table 37: Observed and missing EQ-5D data by visit and progression status

	Pre-progression			Post-progression		
Visit	**N**	**n (%)**	**Missing (%)**	**N**	**n (%)**	**Missing (%)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pre-progression			Post-progression		
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N: Represents the total number of patients eligible for each visit. This number accounts for patient mortality and data cut off (June 2024); once a patient dies, they are no longer considered eligible for subsequent visits., n: Represents the number of patients with available data for the visit. NA: no patients observed

Abbreviations: NA, not available.

The missing data pattern observed in this study was strictly characterized by unit non-response (UNR). In other words, whenever the EQ-5D-3L utility value was not recorded at a particular visit, all corresponding individual item responses (the entire *unit)* for that visit were absent. As a result, there were no instances of partial or item-level missingness within an otherwise completed EQ-5D assessment.

Missing EQ-5D scores were handled by using a Mixed Model for Repeated Measurement (MMRM) (35). MMRM offers a simple alternative to handle missing data under Missing At Random (MAR) assumption without requiring imputations (36). MMRM method is further detailed in answer to part e).

A Linear Mixed Model (LMM) remains the base case method as it directly uses all available observed data under the MAR assumption, without requiring imputation. It is widely regarded as the gold standard for handling missing data in longitudinal studies due to its efficiency and interpretability.

d) Please elaborate on the risk of bias introduced by (handling of) missing data.

The primary risk of bias associated with the missing data in this study stems from the pattern of *unit non-response* (UNR), where the entire EQ-5D-3L assessment was either fully completed or entirely absent at a given visit. This type of missingness could introduce bias depending on the underlying mechanism driving it—whether the data is Missing Completely at Random (MCAR), Missing at Random (MAR), or Not Missing at Random (NMAR). In the primary analysis, a Mixed Model with Repeated Measures (MMRM) was used to include all available data, effectively utilising observed values to estimate population-level trends. This approach assumes that the missing data mechanism is MAR, which is a reasonable but untestable assumption.

Given the high proportion of missing data and the low proportion of observed data in the post-progression state, the pattern of missing data cannot be identified. Any handling method of the missing data (with imputations) would rely on strong and often unverifiable assumptions about the mechanism of missingness or require external data sources or expert input to define priors. Therefore, we maintain that the MMRM under the MAR assumption provides the most reliable and defensible approach for handling missing data and mitigating the risk of bias.

e) Please provide an updated model and scenario analyses using imputed data and elaborate on the method of data imputation used and the reasons it was chosen.

Missing values for the EQ-5D-3L and EQ-5D-5L utilities were addressed through a multiple imputation procedure using Fully Conditional Specification (FCS), with 100 imputations. The EQ-5D-3L and EQ-5D-5L utility scores were imputed via regression models that incorporated the progression status variable and visit variables. This iterative FCS method ensures that each imputation is drawn from a model that reflects observed relationships among the covariates. After generating the imputed datasets,

a MMRM model was fitted to each dataset, and results were subsequently combined to produce pooled estimates. Results after multiple imputation were consistent with results of the base case MMRM analysis.

While imputation allows us to explore the robustness of findings in the presence of a high percentage of missing data, particularly in the post-progression cohort, it does not replace the LMM. The LMM remains the base case method as it directly uses all available observed data under the MAR assumption, without requiring imputation. It is widely regarded as the gold standard for handling missing data in longitudinal studies due to its efficiency and interpretability. The estimated utility values are presented in Table 38.

Table 38: Mean utility derived from MMRM model after multiple imputation of index values

Model	Strata	EQ-5D 5L		EQ-5D 3L (Hernandez algorithm) (33)	
		Mean Estimate	95% CI	Mean Estimate	95% CI
Health State	Pre-Progression	[redacted]	[redacted]	[redacted]	[redacted]
	Post-Progression	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures.

Results of the scenario using imputed IFCT data is presented in Table 39, the scenario is associated with a NHB of [redacted] and a dominant ICER.

Table 39: Scenario analysis results – utility values

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – Chouaid 2013 (TA898)	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario 1 – IFCT	[redacted]	[redacted]	Dominant	[redacted]

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Scenario 2 – IFCT using imputed data	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

f) Please provide details of how the PF and PD utility values were estimated using MMRM, including an overview of which models were considered, which candidate covariates were included, and which model was selected (including rationale)?

A MMRM was employed to estimate utility values separately for pre- and post-progression (PF and PD) while accounting for within-patient correlations over time. A random-intercept structure was selected, assuming independent within-subject errors, and degrees of freedom were derived using the Kenward-Roger approximation method, which provides refined estimates in small samples size and better estimate by correcting for the correlation between random and fixed effects.[1] Given the limited sample size (n=63), only one covariate—progression status—was included in the fixed-effects component to maintain sufficient statistical power. In assessing the variance-covariance structure, both the traditional maximum likelihood approach and the Huber-White (sandwich) robust estimator were evaluated. The Huber-White robust estimator was ultimately selected to accommodate potential violations of model assumptions, such as heteroscedasticity, thereby ensuring greater robustness to slight model misspecifications.

g) The PF and PD health state utility values reported in CS Table 72 are inconsistent with the CS statement: "*When considering the complete follow-up period, the estimated mean EQ-5D-3L was [redacted] (SE: [redacted]) and [redacted] (SE: [redacted]) pre- and post-progression, respectively".* Please explain this potential inconsistency.

The PF and PD health state utility values reported in CS Table 72 are the utilities derived from the MMRM model, while the CS statement quoted are the utilities using simple descriptive statistics.

h) [redacted] mentions base-case utility values based on the IFCT study, while these were presented as a scenario analysis in the economic model. Please justify this discrepancy.

As discussed in response to question B20, HSUVs were informed by TA898 to align with the most recent and relevant appraisal in *BRAF* V600 mutation positive NSCLC, and to be consistent with the values used in the appraisal of the only comparator for this submission and subsequently accepted by the Committee. Furthermore, the analysis by Chouaid et al. (2013) was conducted on significantly more patients than the IFCT analysis, and contained patients across a range of countries, including the UK.

i) [redacted] mentions PF and PD utility values for the previously treated population of the IFCT study. Please elaborate why these were not considered in the economic model.

As discussed in response to question B3, the company do not consider patients who have been previously treated to be a relevant population for this appraisal as enco+bini is expected to be used in patients who are treatment-naïve. Therefore, utility values for the previously-treated population are not considered relevant to this appraisal.

B22. CS Table 73 provides an overview of health state utility values in other NSCLC NICE appraisals.

a) Please elaborate on how the TAs including in Table 73 were selected and justify (NSCLC) TAs that were omitted from this Table?

The TAs listed in Table 73 of the company submission were identified by hand searching of the NICE website for recent TAs for targeted therapies in advanced NSCLC with comparable model structures.

b) Please provide an updated Table including health state utility values of all TAs considering advanced NSCLC.

Please see the updated Table 40, incorporating all additional TAs in advanced NSCLC identified via the NICE website. The base case values used in TA911 were redacted, and therefore the values used for scenario analyses are presented. The values in TA909, TA683, TA653, TA531, TA520, TA347, and TA192 are not included as the model used to inform those appraisals contained either non-comparable health states or utility states. The values in TA724, TA705, TA536, and TA406 are redacted.

Table 40: NSCLC NICE appraisals – health state utility values

TA	Intervention	Population	Utility value	
			Progression-free	Progressed disease
-	Enco+bini	Untreated advanced NSCLC and a *BRAF* mutation	[redacted]	[redacted]
TA911 (29)	Selpercatinib	Untreated RET fusion-positive advanced NSCLC	0.794	0.678
TA898 (27)	Dabra+tram	Untreated advanced NSCLC and a *BRAF* mutation	0.71	0.67
TA850 (37)	Amivantamab	EGFR exon 20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy	0.713	0.569
TA812 (38)	Pralsetinib	*RET* fusion-positive advanced NSCLC	0.794	0.678
TA789 (28)	Tepotinib	Advanced NSCLC with *MET* gene alterations	0.719	0.638
TA781 (39)	Sotorasib	Previously treated *KRAS* G12C mutation-positive advanced NSCLC	0.739	0.655
TA770 (40)	Pembrolizumab	Untreated metastatic squamous NSCLC	Redacted	0.58
TA760 (41)	Selpercatinib	RET fusion-positive advanced NSCLC (first-line)	0.794	0.678
TA713 (42)	Nivolumab	Advanced non-squamous NSCLC after chemotherapy	0.713	0.569
TA683 (43)	Brigatinib	ALK-positive advanced NSCLC	0.793	Progressive disease: 0.624 CNS progressed: 0.543

TA	Intervention	Population	Utility value	
			Progression-free	Progressed disease
				Non-CNS progressed: 0.552
TA654 (44)	Osimertinib	Untreated *EGFR* mutation-positive NSCLC	0.794	0.678
TA643 (45)	Enrecetinib	*ROS1*-positive advanced NSCLC	0.780	0.660
TA628 (46)	Lorlatinib	Previously treated ALK-positive advanced NSCLC	Redacted	0.650
TA571 (47)	Brigatinib	ALK-positive advanced NSCLC after crizotinib	0.793	0.643
TA422 (48)	Crizotinib	Previously treated anaplastic lymphoma kinase-positive advanced NSCLC	NR	0.61
TA411 (49)	Necitumumab	Untreated advanced or metastatic squamous NSCLC	Redacted	0.55
TA403 (50)	Ramucirumab	Previously treated locally advanced or metastatic NSCLC	0.706	0.599
TA310 (51)	Afatinib	*EGFR* mutation positive advanced NSCLC	0.784	0.725
TA258 (52)	Erlotinib	Locally advanced or metastatic EGFR-TK mutation-positive	0.661	0.4302

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; TA, technology appraisal.

B23. CS Table 70 reports the modelled AE disutilities and durations in the economic model. For several AEs its disutility and duration was assumed the same as another AE. Please provide justification and comment on the appropriateness of these assumptions.

In the company submission, AE disutilities and durations were derived from the most recent TAs in targeted therapies for NSCLC (TA789 and TA812), and the published literature where possible. In the absence of data for some AEs, disutilities and/or durations were assumed equal to similar events. A summary of events in which

disutilities and/or duration was assumed equal to a similar event are presented in Table 41.

Table 41: AE disutility and duration - assumptions

	Disutility		Duration (days)		Rationale
	Value	Source	Value	Source	
Anaemia	0.07	Derived from TA789 (Table 49) (28), assumed same as fatigue as per TA181 (28)	3.0	NICE TA789, VISION trial (28)	In line with assumption from TA789 (assumed the same as fatigue per TA181)
Asthenia	0.07	Assumed same as fatigue	52.0	NICE TA789, VISION trial (28)	In line with assumption from TA789 (assumed the same as fatigue per TA181)
Back pain	0.07	Assumed same as abdominal pain	31.0	Assumed same as abdominal pain	In the absence of pain data by location, disutility and durations assumed equal to general pain.
Bronchitis	0.00	Assumption	0.00	Assumption	Assumed as AE is associated with zero incidence for both arms in the base case
Colitis	0.11	TA898 Assumed same as diarrhoea (27)	3.0	Assumed same as diarrhoea	Assumption in line with TA898
Decreased appetite	0.09	Derived from NICE TA760 (Table 58) (41), KEYNOTE-010/TA428 (53)	10.5	Assumed same as nausea	Assumption in line with TA898
Ejection fraction decreased	0.03	Assumed equal to hypertension	150.0	Assumed equal to hypertension	Assumed equal to similar cardiovascular events in the absence of event-specific data
Gamma-gluamyltransferase increased	0.05	Assumed same as aspartate aminotransferase increased	54.8	Assumed same as aspartate aminotransferase increased	Assumed equal to similar hepatic events, in the absence of

	Disutility		Duration (days)		Rationale
	Value	Source	Value	Source	
					event-specific data
Gastrointestinal haemorrhage	0.07	Assumed equal to abdominal pain	31.0	Assumed equal to abdominal pain	Assumed similar to another gastrointestinal symptom AE in the absence of event-specific data.
Hyponatraemia	0.09	Derived from NICE TA760 (Table 58), KEYNOTE-010/TA428 (41)	7.0	NICE TA789, VISION trial (28) (assumed same as hypomagnesemia)	Assumption in line with TA898
Leukocytosis	0.05	Assumed same as aspartate aminotransferase increased	54.8	Assumed same as aspartate aminotransferase increased	Assumed the same as a similar biomarker AE in the absence of event-specific data.
Loss of consciousness	0.00	Assumption	0.00	Assumption	Assumed as AE is associated with zero incidence for both arms in the base case
Myalgia	0.07	Assumed same as abdominal pain	31.0	Assumed same as abdominal pain	In the absence of data for myalgia (muscle pain), disutility and durations assumed equal to general pain.
Neutropenia	0.09	Derived from NICE TA789 (Table 49), Nafees et al (28) (54)	158.0	NICE TA789, VISION trial (28) (assumed same as hypomagnesemia)	Assumption in line with TA898 (derived from TA789)
Pain in extremity	0.07	TA898 Assumed same as abdominal pain (27)	31.0	TA898 Assumed same as abdominal pain (27)	Assumption in line with TA898
Pulmonary embolism	0.09	TA911, assumed equal to Chronic obstructive pulmonary disease	15.0	TA911, assumed equal to Chronic obstructive pulmonary disease (29)	Assumed equal to similar pulmonary events, in the absence of

	Disutility		Duration (days)		Rationale
	Value	Source	Value	Source	
		KEYNOTE-010/TA42); (29)			event-specific data.
Weight increased	0.00	TA898. Assumption (27)	0.00	TA898. Assumption (27)	Assumption in line with TA898.

Abbreviations: AEs, adverse events; NICE, National Institute for Health and Care Excellence.

As these assumptions are not considered to be a key driver of cost-effectiveness, an extreme scenario has been performed in which AEs are removed for dabra+tram. Note that this scenario is overly conservative and is considered informative only.

Table 42: Scenario analysis results – AE disutility and duration

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – no AEs in dabra+tram arm	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: AEs, adverse events; dabra+tram, dabrafenib with trametinib; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

Cost and resource use

B24. Priority question. NICE now takes a more standardised approach for modelling oral treatments to help ensure consistency of cost calculations and better reflect how treatments are dispensed in clinical practice (https://www.nice.org.uk/process/pmg24/chapter/cost-effectiveness) . Oral treatments should be costed on a per pack basis in the economic models, unless clinical experts or other evidence suggests that prescribing and dispensing is done such that there would be no wastage.

a) **Please provide details and justification for the current costing approach (e.g. per mg, per tablet/vial, per pack) for all oral treatments in the economic model.**

In the company submission, oral treatments are costed on a per mg approach, implicitly assuming that there is no wastage for oral treatments. CEs at the advisory board confirmed that treatment adherence was good in practice and patients like oral therapies, therefore treatment wastage is expected to be kept to a minimum. The company recognise the limitations of this approach and therefore, results of a scenario assuming a per pack costing approach are presented in part c).

b) Please provide details on how wastage and vial sharing are currently incorporated in the economic model and justify the approach.

Drugs associated with variable dosing by weight, or BSA are assumed to incur vial wastage. In the economic analysis, vial wastage is calculated using the method of moments approach, in which weight and BSA are modelled as a normal distribution and vials are calculated (55, 56). The method of moments approach is considered appropriate as trial standard deviations for patient characteristics can be used directly to estimate drug costs. The optimal vial size combinations are calculated to minimise wastage across a patient population, using patient characteristics reported in PHAROS. This approach is commonly used and accepted by Committees in NICE appraisals.

c) In line with the NICE statement above, please provide an updated economic model and scenario analysis including a per pack costing approach for all oral treatments.

The following drugs, included in the economic model, are associated with oral administration:

- Encorafenib
- Binimetinib
- Dabrafenib
- Trametinib.

Results of the scenario including a per pack costing approach for all oral treatments are presented in Table 43. The scenario is associated with an increased NHB of [redacted] and a dominant ICER.

Table 43: Scenario analysis results – oral treatment costing approach

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario – cost per pack approach	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: AEs, adverse events; dabra+tram, dabrafenib with trametinib; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

B25. Priority question. Acquisition costs were adjusted based on relative dose intensity (RDI) for all treatments, as not all patients in PHAROS and BRF113928 received the full dose of enco+bini or dabra+tram respectively. Please provide full details of how RDI for all treatments in the economic model were calculated.

Relative dose intensity (RDI) in PHAROS and IFCT was defined as 100*(actual dose intensity/intended dose intensity) and applied to the final drug acquisition costs in the model, as per the approach in TA898, and as described in Section 3.6.1 of the Company Submission. There are no details on the calculation of RDI used in TA898 from the BRF113928 trial.

B26. Priority question. Subsequent therapy proportions for enco+bini were derived from PHAROS data. Subsequent therapies received by ≥1% of patients in the treatment naïve cohort of PHAROS were included in the analysis. Based on clinical expert input, PHAROS data were re-weighted to exclude re-treatment with enco+bini. As clinical experts stated that the types of therapies received by patients in both treatment groups would be similar, the subsequent therapy proportions for the dabra+tram arm were assumed to be the same as for the enco+bini arm, with reweighting performed to exclude any

subsequent use of dabra+tram. Patients in both arms were assumed to receive subsequent therapies for the duration of subsequent therapy received in PHAROS ([redacted] weeks).

a) **For the types, proportions and durations of subsequent treatments in PHAROS, BRF113928 and TA898, please justify whether these are representative of UK clinical practice.**

As noted in the original company submission Section B.3.5.3, PHAROS data were used to inform subsequent therapy use in order to align with the efficacy data used in the model. Re-treatment with the same therapy at second-line, i.e. subsequent enco+bini or dabra+tram, was removed from the analysis as patients would not be eligible for re-treatment with targeted therapy after failing first-line. However, as confirmed by CEs, the PHAROS data contained therapies that were not aligned with UK clinical practice. Patients would not be eligible to receive subsequent targeted therapy or nivolumab-based therapies as they are not recommended for use for patients with NSCLC after first-line treatment. Therefore, several scenarios were presented removing these therapies. CEs advised that pembrolizumab with chemotherapy was the most common therapy after targeted treatment at second line and monotherapy chemotherapy would also be an option for patients. Although the subsequent therapy data in the BRF113928 trial is redacted in TA898, this is aligned with the data used to inform the base case analysis of TA898, which assumed 55% of patients received chemotherapy and 45% received immunotherapy. CEs did however agree that the duration of therapy from PHAROS ([redacted] weeks) was aligned with their expectation of UK clinical practice. This is also aligned with clinical advice to the Company in TA898 stating that the average duration of immunotherapy monotherapy in patients with previously treated advanced NSCLC would be approximately 12–15 weeks.

b) **The CS states that "*subsequent therapy costs were included in the analysis to align with the clinical pathway of care in BRAF V600E MT NSCLC as described in Section B.1.3.5*". However, according to the current clinically pathway of care, patients initially on dabra+tram cannot have subsequent enco+bini. Please justify such deviations in the**

modelling of subsequent treatments and provide an updated economic model and scenario analysis only including subsequent treatments that are in line with the current UK clinical pathway of care.

In line with clarification question A2 and part a) of this question, the base case analysis has been updated in which the following subsequent therapies are removed from both the enco+bini and dabra+tram arms:

- Enco+bini
- Dabra+tram
- Nivolumab with ipilimumab
- Nivolumab with ipilimumab and cisplatin
- Nivolumab with ipilimumab and carboplatin

Therefore, the subsequent therapies received in both arms are aligned with those received in UK clinical practice. Modelled subsequent therapy proportions are presented in Table 44.

Table 44: Subsequent therapies distribution, scenario analysis

Drug	Enco+bini – unweighted PHAROS	Dabra+tram – BRF113928
Encorafenib + binimetinib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Pembrolizumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]	[redacted]
Chemotherapy only	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

c) Please provide an updated economic model and scenario analysis modelling types and proportions of subsequent treatments in line with the types and proportions of subsequent treatments given in the

PHAROS trial (for enco+bini) and BRF113928 trial (for dabra+tram), i.e. without re-weighting.

As noted in Section B.3.5.3. of the Company submission, the proportion of patients receiving any subsequent therapy and the individual therapies received at second-line after dabra+tram in the BRF113928 trial were redacted in TA898 (27).

Therefore, 45% was equally distributed among the immunotherapy regimens received in PHAROS (pembrolizumab, nivolumab, nivolumab+ipilimumab, pembrolizumab+cisplatin, nivolumab+ipilimumab+cisplatin). As such, the scenario considers subsequent therapy proportions from unweighted PHAROS data for enco+bini and derived from BRF113928 in line with the Company's scenario analysis for dabra+tram (Table 45).

Table 45: Subsequent therapies distribution, scenario analysis

Drug	Enco+bini – unweighted PHAROS	Dabra+tram – BRF113928
Encorafenib + binimetinib	[redacted]	0.0%
Dabrafenib + trametinib	[redacted]	0.0%
Pembrolizumab	[redacted]	9.0%
Nivolumab	[redacted]	9.0%
Nivolumab + ipilimumab	[redacted]	9.0%
Pembrolizumab + cisplatin	[redacted]	9.0%
Nivolumab + ipilimumab + cisplatin	[redacted]	9.0%
Nivolumab + ipilimumab + carboplatin	[redacted]	0.0%
Chemotherapy only	[redacted]	55.0%

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib.

The results of the scenario are presented in Table 46; the impact of this scenario is minimal to the NHB. Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Table 46: Scenario analysis results – subsequent therapy proportions

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – subsequent therapy proportions derived from PHAROS and reweighted to remove subsequent primary treatment use	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario analysis – unweighted subsequent therapy proportions	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit.

d) Please justify why patients in both arms were assumed to receive subsequent therapies for the duration of subsequent therapy received in PHAROS in the company's base-case.

As discussed in Section B.3.5.3, all CEs agreed that:

- They expect a high rate of attrition from first-line to second-line treatment for both enco+bini and dabra+tram, and considered 49.2% from PHAROS a reasonable estimate for the amount of patients going on to receive subsequent therapies.
- There would be no reason to expect a different proportion of patients receiving subsequent therapy between patients treated with enco+bini and those treated with dabra+tram at first-line.
- There would be no significant difference in the types of therapies received by patients treated with enco+bini and those treated with dabra+tram at first-line.

Furthermore, the complete subsequent therapy data from the BRF113928 trial is redacted in the TA898 submission. As a result, and given the above feedback from CEs, the subsequent therapy proportions for the dabra+tram arm were assumed to be the same as for the enco+bini arm from the PHAROS trial.

e) Please provide an updated economic model and scenario analysis informing subsequent treatment durations based on trial TTD curves.

A scenario analysis is presented estimating subsequent therapy durations based on individual durations of each therapy from PHAROS (Table 47).

Table 47: Subsequent duration, PHAROS, scenario analysis

Subsequent therapy	Duration – PHAROS (weeks)
Pembrolizumab + chemotherapy	[redacted]
Encorafenib + binimetinib	[redacted]
Pembrolizumab	[redacted]
Dabrafenib + trametinib	[redacted]
Chemotherapy	[redacted]
Nivolumab	[redacted]
Nivolumab + chemo	[redacted]

The results of the scenario are presented in Table 48; the impact of this scenario is negligible to the NHB. Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 48: Scenario analysis results – subsequent therapy durations

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case – mean subsequent therapy duration derived from PHAROS	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario analysis – individual subsequent therapy durations derived from PHAROS	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit.

B27. Priority question. Cost and resource use for first-line treatment was applied to patients on treatment via TTD. However, TTD was not considered

when determining cost and resource use for subsequent treatments. The following sub questions refer to the Comp_encobini and Comp_dabratram sheets.

a. **Drug acquisition costs for subsequent treatments in the economic model were calculated as follows: BF21=IFERROR((X20-X21)*M13,0). Firstly, this difference in PFS includes patients absorbed by the death state. Secondly, it disregards TTD. The ERG suggests: BF21=IFERROR((W20-W21-(Z20-Z21))*M13,0), if TTD is applied for L1. Please justify deviations from this suggestion.**

Subsequent therapies are received by those who experience disease progression and discontinue from their primary treatment. The proposed revision to this clarification question is outlined in part c).

b. **Drug administration costs for subsequent treatments were calculated: BH21= =IFERROR((X20-X21-(Z21-Z20))*N13,0). Firstly, this adds instead of subtracts dead patients. Secondly, this disregards TTD. The ERG suggests: BH21=IFERROR((W20-W21-(Z20-Z21))*N13,0), if TTD is applied for L1. Please justify deviations from this suggestion.**

In line with part a) the proposed revision to this clarification question is outlined in part c).

c. **If not TTD but the share of progression free patients is used to derive L1 treatment costs, the ERG suggests calculating the proportion of patients being eligible for subsequent treatment (acquisition and administration) consistently, as follows: (X20-X21-(Z20-Z21). Please justify deviations from this suggestion.**

The formula for subsequent therapy drug acquisition and administration costs have been amended in the revised economic model. As patients are expected to receive subsequent treatments once they progress and discontinue from their primary treatment, the formula has been amended to account for both PFS and TTD. Additionally, it is noted that the correction suggested by the EAG results in negative

subsequent therapy costs towards the end of the time horizon, which is implausible. This is because the proposed amendment assumes that all patients who die were in the progression-free state.

B28. In the CS it is stated that "In England, patients diagnosed with non-squamous NSCLC are routinely tested for common driver mutations, including BRAF V600E mutations, via NGS panel testing. As such, the need to identify patients with NSCLC with a BRAF V600E mutation would not result in any additional testing costs".

a) Please provide evidence for your statement that identifying patients with NSCLC with a *BRAF* V600E mutation would not result in any additional testing costs.

BRAF V600E mutation testing is a part of routine UK clinical practice and is included in the 2021/2022 National Genomic Test Directory for cancer. Therefore, all patients would receive this test upon diagnosis of NSCLC. This was confirmed by CEs at the advisory board and during the dabra+tram appraisal (TA898) (27)

"The committee concluded that BRAF V600 mutation testing is routine practice and that, in line with NICE methodology, it was not appropriate to include the costs of these tests in the cost-effectiveness analysis".

b) Please provide an updated economic model and scenario analysis including testing costs for *BRAF* V600E mutation.

For completeness, a scenario is included in the model that includes a one-off cost of *BRAF* mutation testing at the beginning of the model for all patients. The costs are aligned with TA898, accounting for the incidence of *BRAF* V600 and *BRAF* V600E mutations. A summary of the scenario analysis inputs is presented in Table 49.

Table 49: BRAF V600 testing costs scenario

Input	Value	Source
Incidence of *BRAF* V600	2.50%	Midpoint of range (1% to 4%): Barlesi et al (2016), Carderella et al. (57, 58) (2013) as per TA898

Input	Value	Source
Incidence of *BRAF* V600E (57, 59-61)	1.25%	*BRAF* V600E mutations account for roughly 50% of all BRAF mutations in NSCLC
Unit cost of *BRAF* mutation test	£34	As per EAG preference in TA898
Total cost of *BRAF* V600 test	£1,360	-
Total cost of *BRAF* V600E test	£2,720	-

Abbreviations: BRAF, v-Raf Murine Sarcoma Viral Oncogene Homolog B; EAG, external assessment group; NSCLC, non-small cell lung cancer.

The results of the scenario analysis are presented in Table 50. Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 50: Scenario analysis results – BRAF V600E testing costs

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario analysis – including *BRAF* V600 and V600E testing costs	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit.

B29. Healthcare resource use in the economic model was informed by TA898, whereas the reported healthcare resource use in [redacted] were based on clinical expert opinion.

a) Please justify why the healthcare resource use values from TA898 were deemed more appropriate to inform the economic model [redacted].

Health care resource use was informed by TA898 to align with the most recent and relevant UK appraisal in *BRAF* V600 mutation positive NSCLC, and to be consistent with the values used in the appraisal of the only comparator for this submission. CEs noted these values were broadly aligned with UK clinical practice.

[redacted]Please provide an updated economic model and scenario analysis informing healthcare resource use based on [redacted]

A scenario analysis is presented including alternate resource use for the treatment-naïve population, as per Table 51.

Table 51: Resource use scenario inputs

Input	Progression-free, frequency per month	Progressed, frequency per month
CT scan (chest)	0.33	0.50
CT scan (other)	0.33	0.50
Outpatient visit	0.33	0.50
Clinical nurse specialist	0.33	1.00

Abbreviations: CT, computed tomography.

The results of the scenario analysis are presented in Table 52. Results of the updated base case, sensitivity analyses and additional scenario analyses performed as part of these responses are presented in Appendix A.

Table 52: Scenario analysis results – resource use

	Incremental costs	Incremental QALYs	ICER	NHB at £30,000
Base case	[redacted]	[redacted]	Dominant	[redacted]
Revised base case – revisions based on A2, B4, B7, and B27	[redacted]	[redacted]	Dominant	[redacted]
Scenario analysis – resource use based on clinical opinion	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit.

Severity

B30. The EAG was unable to reproduce the results reported in CS Table 94, utilising the QALY shortfall calculator (https://shiny.york.ac.uk/shortfall/) recommended in NICE DSU TSD 23.

a. Please provide step-by-step instructions to reproduce the results reported in CS Table 94.

To estimate total QALYs for the general population:

1. The annual rate of death for the general population was derived from the Office for National Statistics (ONS) for the years 2017-2019 in line with NICE DSU guidance and general population utility values were taken from Hernández-Alava 2020. Each of which accounted for the modelled sex distribution (44.1% male).

2. The annual rate of death was converted to an annual probability of death using the following formula $Annual\ probability = -\ln(1 - annual\ rate)$

3. The annual probability of death was used to calculate an alive curve for the general population

4. Total QALYs for the general population were derived using the alive curve and general population utility values

5. General population QALYs were discounted using the discount rate for outcomes (3.5%) and half-cycle corrected.

The calculated total QALYs with the condition were taken from the dabra+tram arm in the economic analysis in order to estimate the absolute and proportional QALY shortfall. Absolute and proportional QALY shortfalls were calculated in line with NICE guidance.

A comparison of shortfall results using the calculator are presented in Table 53. As functionality is only available for inputs to 0 decimal places, inputs were both rounded down and rounded up from the base case value. Results demonstrate that those presented in the Company submission are between results from the calculator when rounding down and up.

Table 53: QALY shortfall results

	Company results	QALY shortfall calculator	
		Rounded down	Rounded up
Inputs			
Age (years)	66.5	66	67
% female	55.9%	55%	56%
Remaining QALYs with disease	[redacted]	[redacted]	[redacted]
Discount rate (%)	3.5%	3.5%	3.5%
Outputs			
Remaining QALYs without the disease	10.30	10.61	10.26
Absolute shortfall	[redacted]	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year.

b. Please justify the difference between the 14.79 expected undiscounted life years in the CS and the 14.49 expected undiscounted life years in the economic model sheet 'QALY shortfall'.

The company economic model is correct that reports 14.49 expected undiscounted *QALYs***.** However, the company note that the 14.79 expected undiscounted life years in the company submission is a reporting error and should instead read “19.50”.

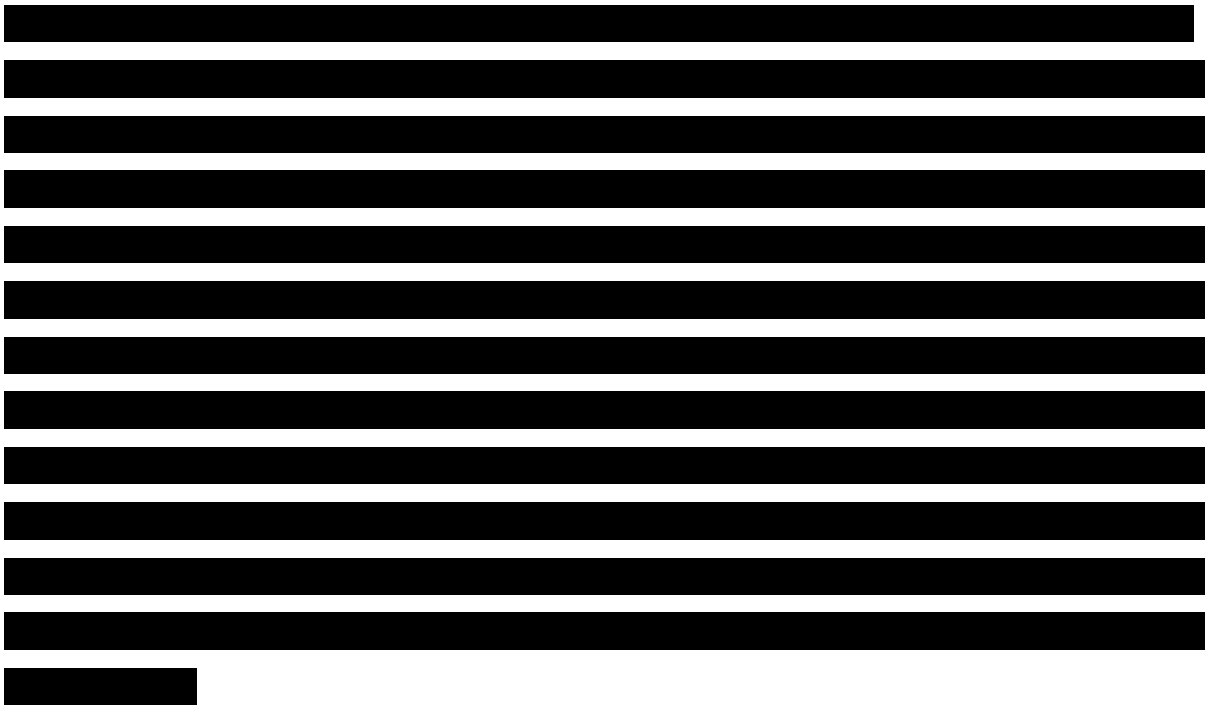
Results

B31. Considering the disaggregated results in Appendix J of the company’s base-case analysis.

a. Considering that all patients in both treatment arms die throughout the model time horizon, please justify the difference in total terminal care costs for encorafenib with binimetinib versus dabrafenib with trametinib.

The Company would like to highlight that there is no error in the terminal care costs in Appendix J. The differences between the terminal care costs identified by the EAG are a result of discounting. The cost of death is applied as a one-off cost at the point of transition into the death state. On average, patients in the enco+bini arm live longer

than in the dabra+tram arm and therefore the impact of discounting is greater in the enco+bini arm compared with the dabra+tram arm. As highlighted by the EAG in question B7, there are a small percentage of patients alive at the end of the time horizon in the base case analysis in the enco+bini arm (<0.15%), whereas the proportion alive in the dabra+tram arm is 0.00%. Therefore, even for undiscounted costs, it would not be expected that the total terminal care costs would be identical between arms.



B32. Considering the CS base-case results in sections 3.9 and 3.10 of the CS.

a. **Please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.**

b. **Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:**

i. Encorafenib in combination with binimetinib

ii. Dabrafenib in combination with trametinib

iii. **Incremental results**

c) Regarding the model estimated differences between the intervention and the comparator; please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

A comparison of RMST at alternate truncation points from the observed data and modelled survival is provided in Table 54. Truncation points for OS and PFS were selected based on the amount of censoring in the PHAROS and the BRF113928 trial, and 90% of the maximum follow-up as suggested in the literature (62). As expected, the proportion beyond the observed data for OS and PFS increased with an increase in truncation point. For OS the proportion increment decreased from [redacted] when considering a 35.8 month truncation to [redacted]% at 53.6 month truncation; for PFS this was [redacted]% and [redacted]%, respectively. The differences between the enco+bini and dabra+tram arms are driven primarily by longer time spent in the progression-free state. The increments are driven by substantial differences in OS, PFS and ORR for patients who were treated with enco+bini in the treatment-naïve cohort of PHAROS compared with cohort C of the BRF113928 trial. ORR was 74.6% in the treatment naïve cohort of PHAROS compared with 63.9% in cohort C of the BRF113928 trial. Median OS was not reached at a median follow-up of [redacted] months and median PFS was 30.2 months in the treatment naïve cohort of PHAROS compared with 17.3 and 10.8 months in cohort C of the BRF113928 trial. When adjusting for observed differences in prognostic factors and treatment effect modifiers between the two trial populations, the differences in ORR, OS and PFS remained significant. As discussed in B11, the risk of OS and PFS did not converge over the observed period between

PHAROS and BRF113928 trial, suggesting no waning of effect during the trial period. There is, however, uncertainty regarding the long-term treatment effect associated with enco+bini due to lack of external, long-term data. Therefore, in response to B11, the Company have provided waning scenarios to test the impact of this uncertainty on results.

Table 54: RMST comparison†

	Observed	Modelled	
	Restricted mean survival time (RMST) (months)	**Estimated (lifetime time horizon) (months)**	**Proportion beyond observed data**
OS - RMST period / truncation point: 36 months before the plateau and a lot of censoring			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: 48.2 months as 90% of max follow-up			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: 53.6 months as max follow-up			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 24 months as just before median OS			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 32.2 months as 90% of max follow-up			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 35.8 months as max follow-up			
Encorafenib + binimetinib	[redacted]	[redacted]	[redacted]

Comparator	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

†Note, results have been run using the revised base case
Abbreviations: OS, overall survival, PFS, progression-free survival, RMST, restricted mean survival time.

Sensitivity and Scenario analysis

B33. The CS stated "For all results but one in the deterministic sensitivity analysis, enco+bini remains dominant when compared with dabra+tram, and the NHB remains above zero" (see CS section B.3.12.2). However, this result seems not presented in the tornado diagram in Figure 39 nor in Table 99. Please explain this discrepancy between the text and the figures in the CS.

This statament should read "for all results in the deterministic sensitivity analysis enco+bini remains dominant when compared with dabra+tram, and the NHB remains above zero". All sensitivity analyses have been updated as per the updated base case analysis, and are presented in Appendix A. In the updated deterministic sensitivity analyses, enco+bini remains dominant when compared with dabra+tram in all analyses.

B34. The EAG was unable to reproduce the results reported for the scenario analyses (see CS section 3.12.3 Table 100 and Appendix O).

a. For all scenario analyses, please provide step-by-step details how to reproduce these in the economic model.

The economic model contains functionality to run automated scenario analyses:

1. Navigate to the "Control" sheet from column AN
2. Enter the new value in the row associated with the parameter explored in scenario analysis
3. In row 2, select whether the scenario is to be run deterministically only, or deterministically and probabilistically
4. Navigate to the "Sensitivity analysis" sheet from row 73
5. Press the "Click to run scenario analysis" button
6. Results of all scenario analyses are presented in the table from row 82.

Scenarios can also be run manually by overwriting the input cell (white cells) and observing the change in results. Base case inputs can be restored using the “Reset to default” button located on each input sheet.

Results of all scenario analyses from the revised company base case are presented in Appendix A.

b. Please provide an updated economic model including a fixed seed to ensure reproducibility of the probabilistic results.

Functionality has been added to the economic model such that probabilistic results for PSA and probabilistic scenarios can be replicated. A dropdown has been added to row 26 of the “Sensitivity analysis” sheet to run the analyses with a set seed or independently.

c. Please justify the difference between the probabilistic results in the economic model sheet 'Sensitivity analysis' and the CS Table 100 for the following two scenarios: 'Subsequent therapy duration – TA898 scenario analysis' and 'Subsequent therapy duration – TA898 base case'.

The company apologise for this inconsistency and note that the NHB is incorrectly reported for these scenarios in error, the corrected values based on the original company submission, and revised base case are presented in Table 55.

Note that results of scenario analysis using the revised base case are presented in Appendix A.

Table 55: Subsequent therapy duration scenario analysis

Scenario and cross reference	Scenario detail	Incremental costs	Incremental QALYs	NHB	
				Company submission	Correction
Based on original company submission					
Subsequent therapy duration, B.3.5.3	Assume different duration per subsequent therapy as per scenario analysis presented in TA898	[redacted]	[redacted]	[redacted]	[redacted]

Scenario and cross reference	Scenario detail	Incremental costs	Incremental QALYs	NHB	
				Company submission	Correction
	Assume subsequent therapy duration equal to committee preferred the base case in TA898 (27)	[redacted]	[redacted]	[redacted]	[redacted]
Based on revised base case					
Subsequent therapy duration, B.3.5.3	Assume different duration per subsequent therapy as per scenario analysis presented in TA898	[redacted]	[redacted]	[redacted]	
	Assume subsequent therapy duration equal to committee preferred the base case in TA898 (27)	[redacted]	[redacted]	[redacted]	

Abbreviations: NHB, net health benefit; QALY, quality-adjusted life year.

d. Please justify the results for the % change from base-case NHB for the probabilistic scenario analyses in the economic model, since the base-case seems to be set equal to scenario 1 (OS distribution – Gamma) instead of the actual base-case (see sheet 'Sensitivity analysis' cell K82).

In the revised economic model, results for the % change from base-case NHB has been corrected for the base case and all scenarios.

e. Please justify the difference between the deterministic results in Appendix O and the economic model sheet 'Sensitivity analysis' of the following scenarios: 'Source of subsequent therapies, dabra+tram, TA898 base case', 'Source of subsequent therapies, clinical opinion', 'Subsequent therapy duration – TA898 scenario analysis' and 'Subsequent therapy duration – TA898 base case'.

Appendix O presents the results of deterministic scenario analysis, the company are unable to identify any inconsistencies between results reported in the economic model and Appendix O.

B35. In section B.10.3.3 of the CS the results of various scenario analyses are presented

b. .Please provide an updated economic model with all relevant scenario analyses,

Scenarios estimating OS, PFS and TTD using alternate parametric distributions are presented in Section B.3.10.1 of the company submission. As per the response to B11, scenario analyses have been included to assess the effect of treatment waning. As per the response to B24, no vial sharing is assumed in the base case. A scenario is included that applies no drug wastage (full vial sharing). For completeness, a further

scenario has been added that assumed a shorter time horizon (25 years). Results of the updated base case, sensitivity analyses and additional scenario analyses presented as part of these responses are presented in Appendix A.

Validation

B36. The (results of the) validity assessments are not described in detail nor are detailed validation exercises (i.e. specific black-box tests) described in CS section B.3.13.

a. **Please provide a detailed description of the validity assessments performed as well as the results.**

b. **Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results to support the computational implementation of the economic model.**

c. **Considering the errors identified by the EAG (e.g. errors related to % change from baseline in scenario analyses and calculation errors in the modelling of administration and acquisition costs for subsequent treatments), please justify how the credibility and accuracy of the economic model can be ensured. Please describe the quality assurance processes in place.**

The economic model was quality-assured through extensive quality checking processes conducted by the model developers and by two other health economists not involved in the development of the model. This was informed by the Drummond checklist, the Phillips checklist (63), HTA methods guides (64), and NICE DSU TSD series, and included cell-by-cell checks, extreme value testing and logical checks, as well as a rebuild of the model engine. A detailed summary of the verification checks and results are provided in the document attached with these responses "ID6177_Encorafenib plus binimetinib_BRAFm_NSCLC_CEM_verification".

B37. Priority question. The CS states that, "The model results were consistent with the results of the PHAROS and BRF113928 studies (see CS table 101 and

102).” Please provide cross validations, i.e. comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g. related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

a. Model structure and assumptions

Table 56: Cross validation – model structure and assumptions

	TA898 & Company submission	Rationale for differences
Model structure	PSM	N/A
Health states	Progression-free Progressed disease Death	N/A
Time horizon	Lifetime	N/A
Cycle length	7 days	N/A
Discount rate	3.5% per annum for costs and outcomes	N/A
Perspective	The NHS and PSS	N/A

Abbreviations: N/A, not applicable; NHS, National Health Service; PSM, partitioned survival model; PSS, Personal Social Services.

b. Input parameters related to:

i. Clinical effectiveness

Table 57: Cross validation – clinical effectiveness

	TA898	Company submission	Rationale for differences
Patient characteristics	Based on Cohort C of BRF113928 38.9% male Mean age 67.8 years	Based on the treatment-naïve population of PHAROS 44.1% male Mean age 66.5 years	Sources align with the primary sources of clinical evidence, patient characteristics are broadly consistent between appraisals.
OS distribution for dabra+tram	Weibull	Exponential	Proportional hazards were assumed for OS and PFS for enco+bini vs dabra+tram. Base case parametric curve was selected based on clinical plausibility, consistent estimates of OS and PFS versus the PHAROS trial and were associated with good statistical goodness of fit.
PFS distribution for dabra+tram	Loglogistic	Exponential	

	TA898	Company submission	Rationale for differences
TTD (ToT) for dabra+tram	Exponential extrapolation BRF113928 trial Cohort C	Treat to progression	In the absence of trial data for BRF113928, treat to progression was assumed based on feedback from CEs, treatment beyond progression permitted in the BRF113928 trial, and RWE.
AE data for dabra+tram	Grade ≥3 AEs occurring in ≥1% of patients derived from BRF113928 trial (Cohort C)	Grade ≥3 AEs occurring in ≥3% of patients derived from BRF113928 trial (Cohort C)	Inclusion of events occurring in ≥3% of patients was considered an appropriate approach by CEs in an advisory board.
UK general population life tables	2018-2020 from the ONS	2017-2019 from the ONS	In line with NICE DSU TSD 23 ((65)), life tables for 2017-2019 were used due to uncertainty around the long-term impact of COVID-19.

Abbreviations: AEs, adverse events; CE, clinical expert; dabra+tram, dabrafenib in combination with trametinib; DSU, Decision Support Unti; enco+bini, encorafenib with trametinib; ONS, Office for National Statistics; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; ToT, time on treatment; TSD, technical support document; TTD, time to treatment discontinuation; UK, United Kingdom.

ii. Health state utility values

Table 58: Cross validation – health state utility values

	TA898	Company submission	Rationale for differences
Health state utility values	Derived from Chouaid 2013		N/A

Abbreviations: N/A, not applicable.

iii. Resource use and costs

Table 59: Cross validation – resource use and costs

	TA898	Company submission	Rationale for differences
Administration costs associated with oral treatments	Oral treatments are not associated with any administration costs		N/A
Relative dose intensity	Applied to acquisition costs based on mean trial relative dose intensity.		N/A
Distribution of subsequent therapies – dabra+tram	Of patients who were assumed to receive subsequent therapies after dabra+tram, 55% received	Assumed equal to PHAROS, data were reweighted such that subsequent dabra+tram use are after primary treatment with dabra+tram was not permitted.	CEs stated that there would be no significant difference in the types of therapies received after

	TA898	Company submission	Rationale for differences
	chemotherapy (carboplatin and pemetrexed) and 45% received immunotherapy (equally distributed between atezolizumab, nivolumab and pembrolizumab monotherapy)		first-line treatment with enco+bini and dabra+tram.
Healthcare resource use	Resource use differs between the progression-free and progressed disease health states but do not differ between treatments. Types of resource use and frequencies are aligned between submissions.		N/A

Abbreviations: CE, clinical expert; dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; N/A, not applicable.

c. Estimated (disaggregated) outcomes per comparator/ intervention

c. PFS

d. OS

e. TTD

f. Life years

g. QALYs

h. Costs

As all results, with the exception of the ICER, are redacted in TA898 therefore cross-validation is not possible.

B38. Priority question. Further external validation of modelled effectiveness would be desirable.

a. Please report on the face validity of the model structure, modelling assumptions, model inputs, intermediate outcomes as well as final

outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).

b. Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using

i. evidence used to develop the economic model.

ii. evidence not used to develop the economic model.

Model outcomes for enco+bini and dabra+tram were compared with observed outcomes of key comparator trials and RWE identified by the clinical SLR (Appendix D), and published evidence in previous NICE appraisals where available.

For all comparators, the predicted outcomes align well with the evidence used to develop the economic model. For enco+bini, the modelled median PFS ([redacted] months) is comparable to the observed data from PHAROS (30.2 months). Although median OS was not reached in the PHAROS, the base case extrapolation was a close visual fit to the observed data. The base case OS extrapolations for enco+bini predict [redacted] % and [redacted] % of patients alive at 1 and 2 years respectively, which is well aligned with the observed PHAROS data ([redacted] % and [redacted] %, respectively). The modelled median TTD ([redacted] months) was slightly increased compared with the observed median in PHAROS ([redacted] months).

For dabra+tram, predicted median OS ([redacted] months) and PFS ([redacted] months) were slightly increased from the reported observed data from the BRF113928 trial (17.2 months and 10.8 months, respectively). Model estimates for OS are well aligned (within [redacted]%) with published estimates of BRF113928 at 1 year ([redacted]% vs 74%), 2 years ([redacted] % vs 49%), and 5 years ([redacted]% vs 22%). Model estimates for PFS over-predict the reported outcomes from the BRF113928 at 1 year ([redacted] % vs 42%), 2 years ([redacted] % vs 13%), and slightly underpredict PFS at 5 years ([redacted] % vs 10%). However, slight differences may be expected considering dabra+tram is modelled by applying a MAIC adjusted HR to the unadjusted enco+bini data. Only TTD data is available from the combined cohort of the BRF113928 trial (10.55 months), a more pre-treated population than relevant to this appraisal.

No external RWE studies were identified in the clinical SLR (Appendix D) that presented efficacy data for patients with *BRAF* V600E mutant positive NSCLC. Therefore, further external validation of model outcomes in the enco+bini arm was not possible. Outcomes from the model for dabra+tram were compared to the external studies identified in the clinical SLR (Appendix D) reporting efficacy outcomes for patients receiving dabra+tram in the first-line. Modelled median OS ([redacted] months) is within half a month from the midpoint of the range of median OS reported in the literature (15.7-34.7 months). The modelled median PFS ([redacted] months) is within a month of the midpoint of the range of median PFS reported in the literature (8.2-19.9 months). The outcomes from Leonetti 2024 only relate to one patient and were therefore not included in the range of medians. Similarly, the modelled median TTD ([redacted] months) is within a month of the midpoint of the range of median TTD reported in the literature (10.4-17.5 months). As discussed in response to question B12, all survival extrapolations were validated by three CEs with experience of treating patients with *BRAF* V600E mutation positive NSCLC in the UK.

Table 60: Comparison of outcomes, dabra+tram

Publication	Study	Median (months)
OS		
Modelled	-	[redacted]
Planchard 2022	BRF113928 trial	17.3
Auliac 2020	GFPC 01-2019	21.8
Leonetti 2024	LiBRA study (GOIRC-03-2020)	18.2
Lips 2020	Lips 2020	479 days
Melosky 2021	Melosky 2021	29.3
Melosky 2021	Melosky 2021	29.3
Melosky 2021	Melosky 2021	34.7
Sbrana 2024	Sbrana 2024	29.9
Swalduz 2022	IFCT-2004 BLaDE	24.1
PFS		
Modelled	-	[redacted]
Planchard 2022	BRF113928 trial	17.3
Auliac 2020	GFPC 01-2019	16.8
Facchinetti 2020	MATCH-R	35

Publication	Study	Median (months)
Facchinetti 2020	MATCH-R	14
Facchinetti 2020	MATCH-R	10
Gibson 2022	Gibson 2022	15.2
Leonetti 2024	LiBRA study (GOIRC-03-2020)	8.2
Melosky 2021	Melosky 2021	9.6
Melosky 2021	Melosky 2021	10.5
Melosky 2021	Melosky 2021	13.7
Mu 2020	Mu 2020	Not reached
Sbrana 2024	Sbrana 2024	19.9
Swalduz 2022	IFCT-2004 BLaDE	18.2
TTD		
Modelled	-	[redacted]
Planchard 2022	BRF113928 trial	10.55 (combined cohort)
Auliac 2020	GFPC 01-2019	17.5
Leonetti 2024	LiBRA study (GOIRC-03-2020)	10.4

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation.

No economic evaluations assessing either dabra+tram or enco+bini were identified in the economic SLR (Appendix G). Therefore, the only source to validate outcomes from the model beyond clinical endpoints is TA898. As discussed in response to B37, all results, with the exception of the ICER, are redacted in TA898, therefore cross-validation is not possible. The exponential distribution used in TA898 predicted 4.5% of patients alive at 10 years, which is well aligned with the model base case for dabra+tram in this appraisal ([redacted]%). In TA898, the exponential distribution was considered to produce a clinically plausible estimate of long-term survival for patients receiving dabra+tram.

B39. Throughout the submission, reference is frequently made to a clinical advisory board (reference 99 in the submission). The reference contains the executive summary of the information from two advisory board meetings held in June and October 2024 and one follow-up consultation from November 2024, which informed the submission. Amongst others, the clinical plausibility of long-term projections was validated by the company

based on clinical expert advice from the advisory board meetings. However, only the executive summary of the advisory board document was provided by the company. The NICE health technology evaluations manual (https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741) states that the reporting of expert opinion should contain information about "the identification and selection of experts, and the reporting of results including the consensus of opinions or data aggregation."

a. **Please clarify how advisors were recruited and selected for the two advisory board meetings, as well as the follow-up consultation. Please provide details on the selection process, including any disclosed conflicts of interest or affiliations with pharmaceutical companies. Please also provide further information if (the selection of) experts differ across the two advisory board meetings and the follow-up consultation.**

b. **Please provide the full advisory board documents as well as all supporting documents/information shared with the participants (including handouts of the presentations).**

c. **Please provide the inputs obtained from the different expert advisory board meetings and the follow-up consultation, including detailed minutes, notes and results supporting modelling assumptions and input parameters,**

A summary of the approach to expert recruitment is provided in the response to B12. The same advisors (three CEs, two HEs) participated in both advisory boards, and one of the CEs also took part in the follow-up consultation. For a non-promotional advisory board and follow-up consultation, we would not request CEs to disclose any conflicts of interest or affiliations with pharmaceutical companies.

The executive summary of the advisory board provides all relevant supporting information relating to the submission, and further details regarding the discussion on survival extrapolations have been provided in the response to question B12. Although the advisory board presentation slides and full report cannot be shared due to

commercial sensitivity, any journal articles used to support points made within the submission (such as Planchard et al or Riley et al) have been provided in the reference pack.

Appendix A – Revised results

Revised company base case

The updated base case cost-effectiveness results are presented in Table 61. Enco+bini was associated with improved mean OS ([redacted] months) and improved mean PFS ([redacted] months) compared with dabra+tram. This translated into [redacted] and [redacted] total QALYs for enco+bini and dabra+tram respectively. Enco+bini was associated with total costs of [redacted], and a cost saving of [redacted] when compared with dabra+tram (total cost of [redacted]). Enco+bini is therefore dominant when compared with dabra+tram.

Pairwise net health benefit (NHB) estimates are presented in Table 61, based on a WTP threshold of £20,000 and £30,000, as per NICE guidelines. Enco+bini is associated with incremental NHBs of [redacted] and [redacted] compared with dabra+tram at a WTP of £20,000 and £30,000 respectively. Appendix J presents the clinical outcomes and disaggregated results.

Table 61: Base-case results (deterministic) – enco+bini PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabra+tram	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

Probabilistic sensitivity analysis

A summary of the pairwise probabilistic results is presented in Table 62. Enco+bini is associated with incremental QALYs of [redacted] and a cost saving of [redacted], vs dabra+tram. Enco+bini is therefore dominant when compared with dabra+tram in the probabilistic ICER. Enco+bini is associated with a probabilistic NHB of [redacted] and [redacted] assuming a WTP threshold of £20,000 and £30,000, respectively. The cost-effectiveness plane for enco+bini vs dabra+tram and the cost-effectiveness acceptability curve (CEAC) are presented in Figure 29 and Figure 30, respectively. The proportion of simulations considered cost-effective at a WTP threshold of £30,000 per QALY was [redacted] %.

Table 62: Base-case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabra+tram	[redacted]	[redacted]	–	–	–	–	–
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; enco+bini, encorafenib in combination with binimetinib; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years

Figure 29: Cost-effectiveness plane – enco+bini PAS price

Abbreviations: enco+bini, encorafenib plus binimetinib; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 30: Cost-effectiveness acceptability curve – enco+bini PAS price

Abbreviations: enco+bini, encorafenib plus binimetinib; PAS, patient access scheme; WTP, willingness to pay.

Deterministic sensitivity analysis

Results for the ten most influential parameters are presented in Table 63, while the tornado diagram is presented in Figure 31. For all results, enco+bini remains dominant when compared with dabra+tram, and the NHB remains above zero.

Table 63: OWSA results – enco+bini PAS price

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
HR - PFS - PHAROS, adjustment on all factors - weighted	[redacted]	[redacted]
Encorafenib + binimetinib - PFS (PHAROS) - exponential, Rate	[redacted]	[redacted]
RDI - dabrafenib	[redacted]	[redacted]
HR - OS - PHAROS, adjustment on all factors - weighted	[redacted]	[redacted]
RDI - trametinib	[redacted]	[redacted]
Encorafenib + binimetinib - TTD (PHAROS) - exponential, Rate	[redacted]	[redacted]
Utility values, TA898, progression-free	[redacted]	[redacted]
RDI - binimetinib - PHAROS	[redacted]	[redacted]
Encorafenib + binimetinib - OS (PHAROS) - exponential, Rate	[redacted]	[redacted]
RDI - encorafenib - PHAROS	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

Figure 31: Tornado diagram – enco+bini PAS price

Abbreviations: enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

Scenario analysis

Scenario analysis results are presented in Table 64. Due to the dominant base-case ICER, results are presented using NHB.

Table 64: Scenario analysis results – enco+bini PAS price

Scenario	Incremental costs	Incremental QALYs	NHB
Original base case	[redacted]	[redacted]	[redacted]
Revised base-case	[redacted]	[redacted]	[redacted]
OS distribution - Gamma	[redacted]	[redacted]	[redacted]
OS distribution - Weibull	[redacted]	[redacted]	[redacted]
PFS distribution - Weibull	[redacted]	[redacted]	[redacted]
PFS distribution - Gamma	[redacted]	[redacted]	[redacted]
TTD distribution, enco+bini - Gamma	[redacted]	[redacted]	[redacted]
TTD distribution, enco+bini - Weibull	[redacted]	[redacted]	[redacted]
Source of subsequent therapies, dabra+tram, TA898 base case	[redacted]	[redacted]	[redacted]
Source of subsequent therapies, clinical opinion	[redacted]	[redacted]	[redacted]
Subsequent therapy duration - TA898 scenario analysis	[redacted]	[redacted]	[redacted]
Subsequent therapy duration - TA898 base case	[redacted]	[redacted]	[redacted]
AEs, dabra+tram - MAIC OR	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (BRF113928)	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (RWE Auliac 2020)	[redacted]	[redacted]	[redacted]
OS & PFS, dabra+tram - MAIC adjusted for ECOG and smoking status	[redacted]	[redacted]	[redacted]
Utility values - IFCT	[redacted]	[redacted]	[redacted]
Utility values - IFCT + Chouaid 2013 progressed decrement	[redacted]	[redacted]	[redacted]
Source of clinical data - Pooled PHAROS & IFCT	[redacted]	[redacted]	[redacted]
EAG Q B11 - waning OS and PFS treatment effect from end of trial period (2 years)	[redacted]	[redacted]	[redacted]
EAG Q B13 - enco+bini TTD = PFS	[redacted]	[redacted]	[redacted]
EAG Q B13 - dabra+tram TTD = HR vs PFS	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	NHB
EAG Q B15 - unadjusted HR	[redacted]	[redacted]	[redacted]
EAG Q B19 - AEs from combined PHAROS trial population	[redacted]	[redacted]	[redacted]
EAG Q B19 - AEs ≥5%	[redacted]	[redacted]	[redacted]
EAG Q B19 - AEs including Grade 1-2 pyrexia	[redacted]	[redacted]	[redacted]
EAG Q B19 - AEs including Grade 1-2	[redacted]	[redacted]	[redacted]
EAG Q B19 - AEs including clinical inconsequential AEs	[redacted]	[redacted]	[redacted]
EAG Q B21 - IFCT utility values using imputed data	[redacted]	[redacted]	[redacted]
EAG Q B23 - no AEs in dabra+tram arm	[redacted]	[redacted]	[redacted]
EAG Q B24 - cost per pack	[redacted]	[redacted]	[redacted]
EAG Q B26 - unweighted PHAROS subs therapies in E&B arm	[redacted]	[redacted]	[redacted]
EAG Q B26 - PHAROS individual subs therapy durations	[redacted]	[redacted]	[redacted]
EAG Q B28 - *BRAF* mutation testing	[redacted]	[redacted]	[redacted]
EAG Q B29 - alternate resource use	[redacted]	[redacted]	[redacted]
EAG Q B35 - time horizon = 25 years	[redacted]	[redacted]	[redacted]

Abbreviations: AEs, adverse events; dabra+tram, dabrafenib in combination with trametinib; EAG, external assessment group; enco+bini, encorafenib in combination with binimetinib; HR, hazard ratio; MAIC, matching-adjusted indirect treatment comparison; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

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].

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- 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	**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)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- 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) - 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?	No
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 2% of patients with non small cell lung cancer (nsclc) have the BRAF V600E mutation.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Clinical investigation of target therapy with BRAF V600E mutant nsclc, began with BRAF inhibitor monotherapy. Clinical benefit, however, was limited. The addition of a MEK inhibitor to a BRAF inhibitor was shown to prolong anti-tumour activity. In June 2023, NICE recommended the use of Dabrafenib plus Trametinib (BRAF plus MEK inhibitor combination), [TA898] as an option for the treatment of patients with BRAF V600 mutation positive advanced non small cell lung cancer (first line, advanced stage). This is the only NICE recommended therapy, specific for this biological target, at this time. Immunotherapy, chemotherapy or a combination are other treatment options.
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?	As in the PHAROS study. 98 people with BRAF V600E mutated metastatic nsclc were treated with the combination of encorafenib and binimetinib. 59 people had not received any treatment for their nsclc and 39 people had received previous anticancer treatment. In treatment naïve patients, the objective response rate was 75%, median duration of response was not estimable and median time to response of 1.9 months. This was based on a median duration follow up for PFS at 18.2 months. Median PFS and median overall survival were not reached. In previously treated patients, the objective response rate was 46%, with median duration of response of 16.7 months and time to response of 1.7 months. The median duration of follow up in this group was 12.8 months. Median PFS was 9.3 months and median OS was not estimable.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects of the treatment. Mose common side effects were nausea, diarrhoea, fatigue and musculoskeletal pain. Adverse events in the study were generally managed by dose reduction and medications such as antiemetics and antidiarrhoeals.

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 people with NSCLC likely to miss doses of oral anti-cancer drugs? **If so, would you consider this to be related to the number of pills taken each day?**	There is, of course, the potential for any patient to miss doses of oral therapies. However, due to the nature of the illness, anecdotally, lung cancer patients report the importance to them of remembering to take anti-cancer medication as prescribed. This can be mitigated by dated blister packs etc… In general, patients prefer oral to iv medications.
14. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Encorafenib plus binimetinib represents an additional option for patients with BRAF-V600E mutated metastatic nsclc.

Thank you for your time.

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Single Technology Appraisal

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

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.

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- 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	[redacted]
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.)	Improve progression free an overall survival. Improve quality of life.
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 in tumour burden,
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The BRAF mutation is relatively new so it is important to have specific treatment options for this group of patients.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	For untreated advanced NSCLC with a BRAF V600 mutation, NICE guidance recommends dabrafenib with trametinib as a first-line treatment (TA898). For previously treated NSCLC NICE guidance recommends nivolumab (TA655 and TA713), atezolizumab (TA520) and pembrolizumab (TA428) monotherapies as well as docetaxel with nintedanib (TA347). Docetaxel alone and platinum doublet chemotherapy may also be offered.
9a. Are any clinical guidelines used in the	See above.

treatment of the condition, and if so, which?	
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.)	Pathway is defined but due to relatively new mutation, it is still being embedded in some areas.
9c. What impact would the technology have on the current pathway of care?	Improve pathway for patients, clear pathway and increase treatment options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be used in the same way as current
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 benefits compared with current care?	Yes
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?	Depends on performance status and comorbidities.

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	May be more difficult to implement initially as not used before, will be some training needs of staff.

affecting patient acceptability or ease of use 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?	Ensure patient is BRAF V600 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?	There are already treatments for this group of patients but results from the PHAROS trial support the use of this new treatment although test numbers were small.
16a. Is the technology a 'step-change' in the management of the condition?	Along the lines of current treatment modalities but would provide alternative treatments for patients who are BRAF positive.

16b. Does the use of the technology address any particular unmet need of the patient population?	This may be useful for patients who are unable to have immunotherapy.
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?	Side effects commonly seen are nausea, fatigue, diarrhoea and vomiting. All may impact quality of life, each patient will be assessed individually and may need differing management of side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, they do.
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Quality of life, progression free survival. Progression free survival measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were	Not that I am aware of.

not apparent in clinical trials but have come to light subsequently?	
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 TA898?	No
21. How do data on real-world experience compare with the trial data?	Some evidence of wider range of side effects – breathlessness, numbness in fingers / toes, headaches.

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.	No

Topic-specific questions

23. Could you estimate what proportion of people with advanced metastatic NSCLC with BRAF V600 mutations do not currently have dabrafenib with trametinib as a first-line treatment?	
24. In your experience are there any issues with adherence to oral anti-cancer drugs? Would you expect people to miss any doses and if so, could you estimate how many?	No, most patients engage well with oral anti cancer therapy and take this as prescribed.
25. Would people be offered a second BRAF and MEK inhibitor combination if their NSCLC progressed after first line treatment with a BRAF and MEK inhibitor combination?	

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Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Evidence suggests this is a good option for treatment of patients with a BRAF mutation • Side effect profile acceptable. • • •

Thank you for your time.

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Professional organisation submission

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- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	[redacted]
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? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. We are funded via sponsorship and registration fees from our annual conference
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.**	None
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.)	To reduce burden of disease and therefore improve symptoms, maintain or improve quality of life, and prolong survival. This is a palliative, not a curative, treatment.
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 in tumour size by 30% or more as determined by cross-sectional imaging. Or Reduction in metabolic activity (SUVmax) of an FDG-avid malignant lesion on PET scan by 30% or more. Or Statistically significant improvement in symptoms as documented on a recognised lung cancer specific, or general oncology, Quality of Life scale
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes 1. Effective targeted therapies for the 2nd line treatment of BRAF V600E mutated lung cancer, after progression on first line Trametinib + Dabrafenib 2. Better tolerated 1st line targeted therapies, with lower incidence and severity of treatment related adverse events

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	NICE TA898 recommends dabrafenib and trametinib for the first line treatment of BRAF V600E non-small cell lung cancer (NSCLC) Following progression on this combination, standard of care would be chemoimmunotherapy with pemetrexed, carboplatin +/- pembrolizumab (in non-squamous) or carboplatin, paclitaxel +/- pembrolizumab (squamous cell carcinoma)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK: NICE TA898 (2023) Europe: ESMO Guidelines for Metastatic NSCLC (2019) USA: NCCN Guidelines for NSCLC (2024)
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.)	In England, where BRAF status is known at the time of diagnosis, Dabrafenib and Trametinib should be the standard of care with little variation in pathway of care. Dabrafenib and Trametinib are not NHS-funded in 2nd or later lines of therapy, and so their use is likely to be exclusively in the 1st line setting. Some oncologists may prefer to use single agent immunotherapy (Pemrbolizumab or Atezolizumab) if the tumour is a very-higher PD-L1 expresser (for example, 90-100%). This is only likely to account for a minority of patients.
9c. What impact would the technology have on the current pathway of care?	It would not change the pathway, beyond the fact that Encorafenib with Binimetinib would be used instead of Dabrafenib and Trametinib.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See answer to 9c

10a. How does healthcare resource use differ between the technology and current care?	Encorafenib with Binimetinib are a different drug combination, but using the same principal, as the existing combination of Dabrafenib and Trametinib. These are both oral drugs, given in the same fashion with the same cycle length and duration (until progression). There are differences in side effect profile, with Encorafenib with Binimetinib causing less pyrexia. As such, in therapy, patients on Encorafenib with Binimetinib may require fewer acute admissions with pyrexia, and this may result in reduced healthcare resource use. However there is no data to confirm what this difference in resource use may be. Otherwise, no anticipated differences in healthcare resource use.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology outpatient clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. All facilities and equipment already in place.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There are no trials directly comparing Encorafenib and Binimetinib with Dabrafenib and Trametinib. All comparison is therefore cross-trial comparison of separate phase 2 studies. The phase 2 PHAROS trial, undertaken in the USA, showed that when used in the treatment naïve population, and when using independent radiology response assessments, Encorafenib with Binimetinib had an overall response rate (ORR) of 75% and median duration of response (DOR) of 40.0 months. Median progression free survival (mPFS) of 30.2 months, but median overall survival (mOS) was not yet reached.

	The French ENCO-BRAF study of Encorafenib with Binimetinib, which used investigator response assessments, showed an ORR 66% and mPFS of 10.9m. mOS was again not reached. In comparison, the 5-year update of the phase 2 BRF113928 study of Dabrafenib and Trametinib showed, in the same treatment naive population, ORR 64% mPFS 10.8m. Median OS was 17.3m. With the caveat that cross-trial comparison is a notoriously unreliable way of assessing different treatment regimens, the data may suggest that Encorafenib with Binimetinib has a clinically significantly longer mPFS than Dabrafenib and Trametinib. However the variation in mFPS between PHAROS and ENCO-BRAF makes it hard to know the exact degree of benefit. It is not known yet whether the mPFS benefit of Encorafenib with Binimetinib in PHAROS will translate into an OS benefit. I have not explored the PHAROS data on 2nd line use of Encorafenib with Binimetinib here, because Dabrafenib and Trametinib is not recommended by NICE in that setting, and as such is not standard of care.
11a. Do you expect the technology to increase length of life more than current care?	We do not have that information yet from the clinical trial data.
11b. Do you expect the technology to increase health-related quality of life more than current care?	We do not have that information yet from the clinical trial data. Although there are differences in side effect profiles, health-related quality of life has not been formally reported or compared in PHAROS, ENCO-BRAF or BRF113928.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only to be used in patients with BRAF V600E mutated, advanced stage, NSCLC. It will be futile in patients without a BRAF V600E mutation.

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 or additional tests or monitoring needed.)	Both are similar in terms of route of administration, frequency and so on. They will therefore be similar in terms of difficulty from the healthcare professionals' point of view. There are differences in side effect profiles: Encorafenib with Binimetinib have a much lower rate of pyrexia, but have a higher rate of gastrointestinal toxicities such as nausea, vomiting, constipation and diarrhoea. Patients on Encorafenib with Binimetinib would therefore be less likely to be contacting oncology teams and acute medical services with pyrexias, but are more likely to require additional anti-emetics and laxative or anti-diarrhoeal. In the PHAROS trial of Encorafenib with Binimetinib, treatment-related dose reductions and cessation occurred in 24%, and 15% respectively. In the BRF113928 study of Dabrafenib and Trametinib, treatment-related dose reductions and cessation occurred in 39%, and 22% respectively. In the absence of quality of life data, but taking the above into consideration, it would seem likely that Encorafenib with Binimetinib will be slightly less difficult for patients (as shown by fewer requiring dose reductions or cessation due to side effects).

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would only be used in those who have a proven BRAF-V600E mutation. BRAF testing is already included in the National Genomics Testing Directory, and so no additional testing is required. Treatment would continue so long as there is clinical benefit (as assessed by radiological response and symptomatic benefit), or until unacceptable toxicity develops.
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?	No. Although Encorafenib with Binimetinib are a novel combination, which may have greater efficacy and a more favourable side effect profile, I do not see it as innovative beyond the existing combination of Dabrafenib and Trametinib.
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the	Please see answer to Q13

technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Response Rate (yes) Duration of Response (in part, yes) Progression Free Survival (yes) Overall Survival (yes, and data not available yet) Safety (yes) Quality of life (no)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The use of median Progression Free Survival has long been used as a surrogate for Overall Survival. The use here is in keeping with that approach, and is affected by the same advantages and limitations as other studies where PFS is (so far) the only survival data available.
18d. Are there any adverse effects that were not apparent in clinical	Not that I am aware of

trials but have come to light subsequently?	
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 TA898?	No
21. How do data on real-world experience compare with the trial data?	There is no significant real-world data experience yet published to compare with trial data.

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.	N/A

Topic-specific questions

23. Could you estimate what proportion of people with advanced metastatic NSCLC with BRAF V600 mutations do not currently have dabrafenib with trametinib as a first-line treatment?	I am not able to estimate this with any certainty.
24. In your experience are there any issues with adherence to oral anti-cancer drugs? Would you expect people to miss any doses and if so, could you estimate how many?	Variable compliance with oral anti-cancer therapies has long been recognised. However in my experience compliance is high, given the importance for patients of the control of their disease. Compliance with Dabrafenib and Trametinib is a little lower that that with other biological therapies such as Osimertinib and Alectinib. This reflects the side effect profile, especially pyrexias. I am not able to estimate the number of missed doses with Dabrafenib and Trametinib.
25. Would people be offered a second BRAF and MEK inhibitor combination if their NSCLC progressed after first line treatment with a BRAF and MEK inhibitor combination?	No. This is not proven to be beneficial, not licensed, and not funded by the NHS.

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Encorafenib with Binimetinib is a novel combination for the treatment of BRAF V600E NSCLC, with the only other targeted treatment combination being Dabrafenib and Trametinib. • There is no head-to-head data, but in cross-trial comparison Encorafenib with Binimetinib appears to have a longer mPFS than Dabrafenib and Trametinib. • The ORR, mDOR and mPFS with Dabrafenib and Trametinib in PHAROS are the longest seen in 1st line treatment of BRAF V600E NSCLC • The data on Encorafenib with Binimetinib is limited by lack of mature OS data. Both regimens also lack formal Quality of Life data, and all trials are small, non-comparative phase 2. • Encorafenib with Binimetinib has a different side effect profile, which is probably slightly easier for patients to tolerate.

Thank you for your time.

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Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm on Friday 18 April 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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.

NICE National Institute for Health and Care Excellence

Part 1: Treating BRAF V600E 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 Tom Newsom-Davis
2. Name of organisation	Chelsea & Westminster Hospital 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 BRAF V600E mutation-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for BRAF V600E 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 BRAF V600E 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)	Answers as per Nominating Organisation (BTOG) submission, with no changes
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)	Answers as per Nominating Organisation (BTOG) submission, with no changes
10. In your view, is there an unmet need for patients and healthcare professionals in BRAF V600E mutation-positive advanced non-small-cell lung cancer?	Answers as per Nominating Organisation (BTOG) submission, with no changes
11. How is BRAF V600E 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?	Answers as per Nominating Organisation (BTOG) submission, with no changes
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?	Answers as per Nominating Organisation (BTOG) submission, with no changes

• 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?	Answers as per Nominating Organisation (BTOG) submission, with no changes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Answers as per Nominating Organisation (BTOG) submission, with no changes
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)	Answers as per Nominating Organisation (BTOG) submission, with no changes
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Answers as per Nominating Organisation (BTOG) submission, with no changes

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	Answers as per Nominating Organisation (BTOG) submission, with no changes
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?	Answers as per Nominating Organisation (BTOG) submission, with no changes
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?	Answers as per Nominating Organisation (BTOG) submission, with no changes
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?	Answers as per Nominating Organisation (BTOG) submission, with no changes

• 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?	Answers as per Nominating Organisation (BTOG) submission, with no changes
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA898]?	There were updates on both PHAROS and ENCO-BRAF at ESMO 2024 annual meeting in September 2024. **PHAROS (Abstract LBA56):** Following an additional 18 months of follow-up, ORR for treatment-naïve patients was 75%, median duration of response (DOR) of 40.0 months. For previously treated patients, the ORR was 46%, median DOR was 16.7 weeks. Median PFS was 30.2 months after a median 33.3 months of follow-up in the treatment-naïve population, and 9.3 months after a median 14.0 months of follow-up in the previously treated population. Median overall survival (OS) was not estimable in the treatment-naïve population and was 22.7 months in the previously treated population. **IFCT-1904 ENCO-BRAF (Abstract 1259MO):** For untreated *BRAF* V600E-mutant NSCLC, at a median follow-up of 18 months, ORR (primary endpoint) was 65.6%, the median DOR was 13 months and disease control rate was 85.2%. Median PFS was 10.9 months, while the median OS was not reached.
23. How does data on real-world experience compare with the trial data?	I am not aware of any new real-world data on Encorafenib / Binimetinib in NSCLC.
24. Looking at the long term projections for encorafenib with binimetinib for:	I cannot answer this because Company Submission Document B was not provided to me on the NICE portal, and so I cannot review the relevant figures.

- **Overall survival (Figure 18 of company submission document B)** - **Progression free survival (Figure 21)** - **Time to discontinuation (Figure 29)** **which distributions on the graphs do you consider to be the most plausible?**	
25. What do you consider might happen to the treatment effect of encorafenib with binimetinib on PFS over time, particularly as people start to discontinue treatment?	I cannot answer this because Company Submission Document B was not provided to me on the NICE portal, and so I cannot review the relevant figures.
26. What do you consider might happen to the treatment effect of encorafenib with binimetinib on OS over time, particularly as people start to discontinue treatment or as their cancer progresses?	I cannot answer this because Company Submission Document B was not provided to me on the NICE portal, and so I cannot review the relevant figures.
27. 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.	No

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. 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:

Encorafenib/Binimetanib is a new treatment combination for 1st line advanced stage BRAF V600E NSCLC, for which we already have Dabrafenib/Trametinib.

There is no head-to-head data to determine whether Encorafenib/Binimetanib is better than Dabrafenib/Trametinib: data on Encorafenib/Binimetanib comes from phase 2 trials.

Encorafenib/Binimetanib is likely to have a longer mPFS than Dabrafenib/Trametinib, although the extent of this, and whether it translates to an OS benefit, it not clear.

Encorafenib/Binimetanib has a more favourable side effect profile, appearing to require fewer dose reductions and cessations

No additional resources or testing, beyond those already in place, are required for use of Encorafenib/Binimetanib.

Thank you for your time.

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Single Technology Appraisal

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

Clinical expert statement

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The deadline for your response is **5pm on Tuesday 22 April 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Treating BRAF V600E 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 Toby Talbot
2. Name of organisation	Royal Cornwall Hospitals NHS Trust
3. Job title or position	Consultant Clinical 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 BRAF V600E mutation-positive advanced non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for BRAF V600E 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 BRAF V600E 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)	To improve survival and reduce symptom burden (improve quality of life)
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)	Any reduction of tumour volume that translates into a reduction in symptoms or improved survival. Response is defined within clinical trials using strict criteria (RECIST criteria)
10. In your view, is there an unmet need for patients and healthcare professionals in BRAF V600E mutation-positive advanced non-small-cell lung cancer?	NHS funded treatment already exists in this space in the form of Dabrafenib and Trametinib (NICE TA898)
11. How is BRAF V600E 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?	Most patients known to have BRAF V600E mutation driven NSCLC will be treated with first line Dabrafenib and Trametinib. The pathway is well established but depends on the genomic analysis being completed and results available at point of first consultation. There may be geographical variation nationally regarding the turnaround time for BRAF analysis; there are seven genomic laboratory hubs (GLH) providing molecular diagnostics for the whole of England and each may have different performance from test to result. The availability of Encorafenib and Binimetinib would not have a meaningful impact on the pathway of care.
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?	Yes – Encorafenib and Binimetinib is used in the same patients as Dabrafenib and Trametinib. There are significant toxicity differences between these agents with (in my clinical experience) better tolerance of Encorafenib and Binimetinib. Healthcare resource use is unlikely to be any different compared to current standard of care.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) – *specialist oncology clinic* • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) - *none*	
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. I have over ten years of experience with BRAF and MEK inhibitors, mostly in the management of patients with metastatic melanoma. The most notable difference between Encorafenib and Binimetinib and the other available agents is of toxicity with a notable reduction in side effects, particularly with drug associate pyrexia which is problematic and impacts on the emergency portals. I do not believe that this technology will increase length of life (overall survival) over currently available treatment other than in those patients for whom Dabrafenib and Trametinib leads to unacceptable toxicity. I believe strongly that quality of life would be likely to be improved with Encorafenib and Trametinib based on my experiences with melanoma.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – this technology would only be applicable to patients with BRAF V600E mutation positive NSCLC; this is a rare mutation in lung cancer, around 1% of all cases.
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)	As above – the main difference would be in frequency and grade of toxicity. The most frequent and clinically significant toxicity with Dabrafenib and Trametinib is drug associated pyrexia. This can cause severe symptoms in those patients for whom it is an issue and frequently results in assessment in the emergency portals and admission for antibiotics to cover the possibility of sepsis; this would be much less frequent an issue with Encorafenib and Binimetinib. No additional monitoring or tests would be required over current standard of care.

	The one point to highlight is that the number of tablets for Encorafenib and Binimetinib (pill burden) is generally higher with Encorafenib and Binimetinib compared to Dabrafenib and Trametinib – this might be an issue for patients with difficulty swallowing.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would expect treatment to continue until loss of clinical benefit or unacceptable toxicity.
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	My clinical experience is that Encorafenib and Binimetinib is a better tolerated BRAF/MEK combination compared to other similar agents. I do not think that the clinical trial data necessarily captured this difference well and therefore QALY calculations are likely to underestimate the better quality of life that patients are likely to experience with this technology.
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?	No – BRAF directed therapy is already available. I do not consider this a step-change but would consider it an enhancement in the available option for these patients with a rare variant of 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?	As above – toxicity is lower with Encorafenib and Binimetinib. The side effect profile is well established with this treatment being available on the NHS for the treatment of metastatic melanoma and robust management guidelines are readily available.

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 – I think that the results are applicable to the UK population. BRAF mutation positive melanoma is very rare and designing and recruiting to clinical trials is very challenging; large randomised trials are not likely to be possible. The most important outcome is overall survival for most clinicians and patients. Quality of life is also very important. Unusually, I think that real world experience has shown reduced adverse effects compared to trial data.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA898]?	No
23. How does data on real-world experience compare with the trial data?	Unknown to me
24. Looking at the long term projections for encorafenib with binimetinib for: - **Overall survival (Figure 18 of company submission document B)** - **Progression free survival (Figure 21)** - **Time to discontinuation (Figure 29)** **which distributions on the graphs do you consider to be the most plausible?**	Documents listed are not currently available to me due to issues with the NICE website.

25. What do you consider might happen to the treatment effect of encorafenib with binimetinib on PFS over time, particularly as people start to discontinue treatment?	Patients who discontinue treatment due to toxicity are likely to experience earlier disease progression
26. What do you consider might happen to the treatment effect of encorafenib with binimetinib on OS over time, particularly as people start to discontinue treatment or as their cancer progresses?	I would not expect a significant overall survival advantage beyond progression once the treatment has stopped though patients may well have further prognosis enhancing treatment options such as chemotherapy.
27. 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.	I do not feel that there are likely to be any equality issues with this technology.

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.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

BRAF V600E NSCLC is a very rare variant of lung cancer

Currently available treatment can be challenging in terms of tolerance for patients

In my extensive clinical experience with Encorafenib and Binimetinib in melanoma, it has the most favourable toxicity profile in comparison to other BRAF/MEK combinations

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors: None.

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Confidential (CON) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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.

This report should be referenced as follows:

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Contributions of authors:

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong also acted as project lead as well as health economist on this assessment and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Teresa Holly, Mabel Wieman and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mubarak Patel acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian and Jiongyu Chen acted as systematic reviewers as well as health economists on this assessment. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

1L	First-line/treatment naïve
2L	Second-line
AACR	American Association for Cancer Research
ABCP	Atezolizumab, bevacizumab, carboplatin and paclitaxel
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
BSC	Best supportive care
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CBR	Clinical benefit rate
CCA	Cost-consequence analysis
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMA	Cost-minimisation analysis
CNS	Central nervous system
COA	Cost offset analysis
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology for Adverse Events
ctDNA	Circulating tumour DNA
CUA	Cost-utility analysis
Dabra+tram	Dabrafenib in combination with trametinib
DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group-performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic information marketing tool
Enco+bini	Encorafenib in combination with binimetinib
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
ESMO	European Society of Medical Oncology

ESS	Estimated sample size
EUA	Emergency Use Authorization
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FE	Fixing error
FV	Fixing violation
G-BA	Gemeinsamer Bundesausschuss
HAS	Haute Autorité de Santé
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health Technology Assessment
HUI2	Health utilities index 2
IA	Investigator assessment
IASLC WCLC	International Association for the Study of Lung Cancer World Conference on Lung Cancer
ICD	Informed consent document
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IQWiG	German Institute for Quality and Efficiency in Health Care
IRR	Independent radiology review
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
JBI	Joanna Briggs Institute
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LY	Life year
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MEKi	Mitogen-activated protein kinase kinase inhibitors
MJ	Matters of judgement
MMRM	Mixed-model repeated measures
MT	Mutation-positive
MUGA	Multi-gated acquisition
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NE	Not estimable
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small-cell lung cancer
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate

OS	Overall survival
PAS	Patient access scheme
PBAC/TGA	Pharmaceutical Benefits Advisory Committee/Therapeutic Goods Administration
PCR	Polymerase chain reaction
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
ROS1	ROS proto-oncogene 1
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SD	Stable disease
SF-6D	Short form-6 dimensions
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SS	Safety set
STA	Single Technology Appraisal
STC	Simulated treatment comparison
STM	State transition model
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TECH-VER	Technical verification
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
UMC+	University Medical Center+
WTP	Willingness-to-pay

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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. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID6177	Summary of issue	Report Sections
1	Uncertainty as to line of therapy	2.1, 2.3, and 2.5
2	Exclusion of comparators in the NICE scope and in the NICE guideline 122	2.3 and 2.5
3	Lack of adjustment for some important prognostic variables in the MAIC analysis	3 and 4
4	Uncertainty related to long-term extrapolation of OS, PFS, and TTD	4.2.6
5	Assumptions related to waning of relative treatment effectiveness	4.2.6
6	Uncertainty in the source to inform the modelling of health state utilities	4.2.8
7	Suboptimal approach of modelling drug acquisition costs of oral treatments	4.2.9
8	Majority of health gains accumulated beyond the observed data	5.1
9	Issues related to (the reporting of) probabilistic and sensitivity analyses	5.2
10	Insufficient technical verification of the economic model	5.3
11	Lack of transparency regarding expert consultation and comparisons with other relevant NICE appraisals	5.3

EAG = External Assessment Group; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS =progression-free survival; TTD = time to treatment discontinuation

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) 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:

- Increased progression-free survival (PFS) with incremental QALYs of [redacted] ([redacted] of the total incremental QALYs).

Overall, the technology is modelled to affect costs by:

- Decreased acquisition costs of encorafenib with binimetinib (enco+bini) (reduced costs of [redacted] of the total costs for the treatment).

The modelling assumptions that have the greatest effect on the ICER are:

- Exponential curve to fit the median time to treatment discontinuation (TTD) reported from BRF113928 ([redacted]% decreased net health benefit (NHB))
- Exponential curve to fit the median TTD reported from real-world evidence (RWE) study Auliac et al. 2020 ([redacted]% increased NHB)
- Assume TTD is equal to PFS for enco+bini ([redacted] decreased NHB, scenario analysis provided in response to the clarification letter)
- Apply the hazard ratio (HR) between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabrafenib with trametinib (dabra+tram) to derive an estimation of dabra+tram TTD ([redacted] decreased NHB, scenario analysis provided in response to the clarification letter).

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue 1: Uncertainty as to line of therapy

Report Sections	**2.1, 2.3, and 2.5**
Description of issue and why the EAG has identified it as important	Treatment with encorafenib with binimetinib at second-line, i.e., of treatment experienced patients, appears not have been ruled out.
What alternative approach has the EAG suggested?	Either ruling out second-line treatment or effectiveness and cost effectiveness analyses at this line.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Either ruling out second-line treatment or use of the treatment experienced subgroup of the PHAROS trial for effectiveness and cost effectiveness analyses at this line.
EAG = External Assessment Group	

Table 1.3: Key issue 2: Exclusion of comparators in the NICE scope and in the NICE guideline

Report Sections	**2.3 and 2.5**
Description of issue and why the EAG has identified it as important	Multiple comparators in the NICE scope and more in NICE guideline 122 for patients at first-line (treatment-naïve) have been excluded from the decision problem. The company cites clinical expert opinion that most patients would receive dabra+tram or enco+bini, which leaves open the possibility that some currently receive treatments other than dabra+tram. The EAG also note that NICE guideline 122 recommends choice of treatment according to histology and PD-L1 status.

Report Sections	2.3 and 2.5
What alternative approach has the EAG suggested?	Include all comparators that are used in clinical practice and provide an updated economic model including fully incremental analyses.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	All comparators as used in clinical practice should be included, and an updated economic model should be provided including fully incremental analyses.
dabra+tram = dabrafenib in combination with trametinib; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed cell death ligand 1	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.4: Key issue 3: Lack of adjustment for some important prognostic variables in the MAIC analysis due to the lack of availability of these variables.

Report Sections	3.4
Description of issue and why the EAG has identified it as important	It should be noted that the prognostic variables of concomitant mutation in the P13K pathway, presence of metastases in the thoracic cavity, previous treatment with immunotherapy (not relevant for analyses in first-line), PD-L1 ≥1% expression, presence of liver metastases, and presence of M1a metastases were not adjusted for in the MAIC analyses due to the lack of availability of these variables in the data. Therefore, the lack of adjustment for these important prognostic variables in the MAIC analysis may have compromised the validity of results of MAIC analysis.
What alternative approach has the EAG suggested?	All-important prognostic variables should be adjusted for in the MAIC analysis and subsequently in the economic model.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that all important prognostic variables should be adjusted for in the MAIC analysis, and subsequently in the economic model.
EAG = External Assessment Group; MAIC = matching-adjusted indirect comparison; PD-L1 = programmed cell death ligand 1	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.5: Key issue 4: Uncertainty related to long-term extrapolation of OS, PFS, and TTD

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Long-term extrapolation of OS, PFS, and TTD beyond the observed data period is critical for estimating cost-effectiveness. The assumptions underpinning the extrapolation are a major source of uncertainty and substantially influence the cost-effectiveness results.
What alternative approach has the EAG suggested?	Providing access to the advisory board presentation slides and full report, as well as comprehensive data sharing related to the obtained expert opinion. Additionally, consideration of external data sources to inform inputs related to long-term extrapolation is recommended.
What is the expected effect on the cost effectiveness estimates?	Adjusting the assumptions for long-term extrapolations may significantly alter NHB estimates as these substantially impact the extrapolated survival benefits and healthcare resource utilisation.
What additional evidence or analyses might help to resolve this key issue?	Clinical input to validate whether extrapolated survival curves for OS, PFS, and TTD align with expert expectations. External validation using real-world evidence to assess the plausibility of long-term extrapolations for OS, PFS, and TTD. If based on this information none of the standard parametric curves are considered appropriate to estimate long-term OS, PFS and TTD more flexible parametric survival models might be explored (see NICE DSU TSD 24).

DSU = Decision Support Unit; EAG = External Assessment Group; NHB = net health benefit; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TSD = technical support document; TTD = time to treatment discontinuation

Table 1.6: Key issue 5: Assumptions related to waning of relative treatment effectiveness

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Current evidence may not adequately support sustained treatment effects beyond the trial duration, leading to uncertainty in long-term relative treatment effectiveness. If the treatment effect diminishes (wanes) in the long term, the cost effectiveness conclusions could be significantly impacted.
What alternative approach has the EAG suggested?	The EAG suggests implementing scenarios with different waning assumptions (e.g., gradual reduction in treatment effect over 1, 2, or 3 years potentially starting at 3, 4 and 5 years) where the hazard of enco+bini converges to the hazard of dabra+tram (not the other way around). Additionally, using external clinical input and/or real-world evidence to validate the duration and pattern of treatment effect waning could improve robustness.
What is the expected effect on the cost effectiveness estimates?	Introducing waning of treatment effect would generally reduce the long-term benefit of the intervention and as a result decrease the NHB.
What additional evidence or analyses might help to resolve this key issue?	Scenario and sensitivity analyses to test the robustness of cost-effectiveness outcomes to varying waning assumptions. Validation of waning assumptions through clinical expert elicitation. Comparative analyses of similar treatments with long-term follow-up data to infer plausible waning patterns.

Dabra+tram = dabrafenib in combination with trametinib; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib

Table 1.7: Key issue 6: Uncertainty in the source to inform the modelling of health state utilities

Report Section	**4.2.8**
Description of issue and why the EAG has identified it as important	Due to the lack of HRQoL data in PHAROS and the limitations of alternative studies, there is uncertainty in the selection of the source to inform the modelling of health state utilities.
What alternative approach has the EAG suggested?	Scenario analyses exploring the plausible range of health state utility values, including 1) relatively high utility values from TA310 (PF = 0.784, PD = 0.725), and 2) relatively low utility values from TA258 (PF = 0.661, PD = 0.4302).
What is the expected effect on the cost effectiveness estimates?	The scenario analysis including the relatively high utility values from TA310 increased the NHB, whereas the scenario analysis including the relatively low utility values decreased the NHB.
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = External Assessment Group; HRQoL = health-related quality of life; N/A = not applicable; NHB = net health benefit; PF = progression-free; PD = progressed disease; TA = technology appraisal	

Table 1.8: Key issue 7: Suboptimal approach of modelling drug acquisition costs of oral treatments

Report Section	**4.2.9**
Description of issue and why the EAG has identified it as important	Contrary to the NICE process and methods guide, which states that the costs of oral treatments dispensed in tablet packs should be evaluated on a per pack basis, the company used a per mg approach in their base-case.
What alternative approach has the EAG suggested?	A scenario analysis using a per pack costing approach for oral treatments in line with the NICE process and methods guide
What is the expected effect on the cost effectiveness estimates?	The company's scenario analysis in which per pack drug acquisition costs were applied every four weeks/model cycles resulted in an increased NHB. The EAG's amended approach in which acquisition costs were modelled every week/model cycle also increased the NHB.
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = External Assessment Group; N/A = not applicable; NHB = net health benefit; NICE = National Institute for Health and Care Excellence	

Table 1.9: Key issue 8: Majority of health gains accumulated beyond the observed data

Report Section	**5.1**
Description of issue and why the EAG has identified it as important	The majority of absolute and incremental health gains for enco+bini and dabra+tram were accumulated beyond the observed data period. Moreover, the proportion of health gains accumulated beyond the observed data for enco+bini was substantially larger than for dabra+tram.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Additional explanation of the mechanism by which the model generated these differences as well as justification for why these are plausible based on the available evidence.
Dabra+tram = dabrafenib in combination with trametinib EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib	

Table 1.10: Key issue 9: Issues related to (the reporting of) probabilistic and sensitivity analyses

Report Section	**5.2**
Description of issue and why the EAG has identified it as important	1) The company's probabilistic analyses results were substantially different than the deterministic analyses results. 2) The results of several scenario analyses could not be reproduced. 3) The run-time of the PSA is relatively long.
What alternative approach has the EAG suggested?	1) None. 2) Correct errors in the economic model that prevented the reproduction of scenario analyses and for every scenario analysis provide step by step details on how to conduct these in the economic model. 3) None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	1) Explore and justify the substantially different deterministic and probabilistic results. 2) Correct errors in the economic model and for every scenario analysis provide step by step details on how conduct these in the economic model. 3) Explore ways of lowering the PSA run-time.
EAG = External Assessment Group; PSA = probabilistic sensitivity analysis	

Table 1.11: Key issue 10: Insufficient technical verification of the economic model

Report Section	5.3
Description of issue and why the EAG has identified it as important	Despite the company's technical verification efforts, the EAG identified errors in the economic model. Furthermore, a completed version of the TECH-VER checklist was not provided.
What alternative approach has the EAG suggested?	Provide sufficient technical verification of the economic model.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Correct all errors in the economic model, further justify why these were not identified during their technical verification and provide a reassessment of technical verification. Provide a completed version of the TECH-VER checklist.
EAG = External Assessment Group; TECH-VER = technical verification	

Table 1.12: Key issue 11: Lack of transparency regarding expert consultation and comparisons with other relevant NICE appraisals

Report Section	5.3
Description of issue and why the EAG has identified it as important	The full meeting minutes of the company's advisory boards and the follow-up consultation were not provided. Furthermore, cross-validation was only provided with TA898, despite that other relevant TAs were mentioned in the company's initial CS.
What alternative approach has the EAG suggested?	The EAG requested providing more transparency regarding expert elicitation. The EAG requested cross-validation with other relevant NICE TAs.
What is the expected effect on the cost effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	Provide the full advisory board meeting minutes. Provide comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g. TA812, TA789, TA781, TA654, TA643, TA310, TA520, TA724, TA705, TA713)
CS = company submission; EAG = External Assessment Group; N/A =, not applicable; NICE = National Institute for Health and Care Excellence; TA = technology appraisal	

1.6 Summary of the EAG's view

The estimated EAG base-case NHB (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted]. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted]% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was applying the HR between PFS and TTD for enco+bini to PFS for dabra+tram to estimate TTD. The NHB decreased most in the scenario analysis with alternative assumptions regarding the source to inform health state utility values.

There is large remaining uncertainty about the effectiveness and cost effectiveness of enco+bini, which can be partly resolved by the company. This includes providing the full documentation of the advisory board, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of life-year gains beyond the observed data, scenarios including different waning assumptions, and the use of external clinical input or real-world evidence to validate the duration and pattern of treatment effect waning. Additionally, the company should explore the substantial difference between the probabilistic and deterministic results, correct all errors in the economic model, further explain why these were not identified during initial technical verification, and provide a thorough reassessment of technical verification. Therefore, according to the EAG, neither the company submission (CS) nor the EAG report contains an unbiased estimate of enco+bini compared with all relevant comparators.

Table 1.13: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Deterministic CS base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Fixing violations (1- Per pack costing approach for oral treatments)						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Matter of judgement (2- dabra+tram TTD using HR between PFS and TTD of enco+bini						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Deterministic EAG base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Probabilistic EAG base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

CS = company submission; dabra+tram = dabrafenib in combination with trametinib; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation; WTP = willingness to pay

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	People with advanced NSCLC that is positive for a *BRAF* V600E mutation.	Treatment-naïve patients with advanced NSCLC with a *BRAF* V600E mutation.	Most patients with advanced BRAF V600E MT NSCLC are expected to receive enco+bini targeted therapy as a first-line therapy because: *BRAF* V600E testing is included in NHS England's national genomic testing directory, making it a part of routine clinical practice. This ensures eligible patients are identified early and can begin targeted therapies at first-line. Patients receiving targeted therapies in first-line would not be eligible to receive a further targeted therapy in second-line. As a result, the number of patients eligible to receive enco+bini in second-line will likely decrease over time, with the majority of eligible patients receiving targeted therapies in the first-line. The pivotal PHAROS phase 2 trial[1] which included both first-line and second-line patients, reflects this anticipated trend. The higher proportion of first-line patients in the trial aligns with expected	The EAG are concerned that population for which the recommendation by NICE could be made might include the wider i.e., treatment experienced population for which evidence has not been presented in the CS.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			clinical practice due to routine genomic testing.	
Intervention	Encorafenib with binimetinib	Encorafenib capsule 450 mg QD + binimetinib tablet 45 mg BID	N/A – in line with the NICE final scope.	The intervention is in line with the NICE scope.
Comparator(s)	For people with untreated advanced NSCLC • Dabrafenib with trametinib • Pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed) Pembrolizumab monotherapy Atezolizumab monotherapy For people with previously treated advanced NSCLC • Atezolizumab monotherapy • Pembrolizumab monotherapy • Nivolumab monotherapy • Docetaxel with nintedanib • Docetaxel • Platinum doublet chemotherapy	Dabrafenib with trametinib	Dabrafenib with trametinib, as the only other available targeted therapy, is considered the most relevant comparator. Routine genome testing will identify patients with BRAF V600E mutations who are therefore eligible for targeted therapies, at first-line. Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are currently recommended as treatment options where dabrafenib with trametinib cannot be used, such as in the case of delays in *BRAF* testing. In TA898, the committee noted delays to *BRAF* testing were no longer a concern as it is included in NHS England's national genomic testing directory. Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are therefore not relevant comparators.	The comparators are in line with the NICE scope, assuming that all patients are tested for the BRAF V600E mutation and, as a result receive dabrafenib with trametinib. However, NICE guideline 122 lists several alternatives, depending on histology and PD-L1 status.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			Monotherapies are also not considered relevant comparators, as these are indicated for previously treated patients with advanced NSCLC, and not the first-line population.	
Outcomes	The outcome measures to be considered include: OS PFS Response rate TTD Time to subsequent therapy Adverse effects of treatment HRQoL	**Primary outcomes** ORR as determined by independent IRR in the treatment-naïve setting ORR as determined by IRR in the previously treated setting **Secondary outcomes** *Efficacy* Confirmed ORR by IA DOR (by IRR and by IA) DCR (by IRR and by IA) PFS (by IRR and by IA) TTR (by IRR and by IA) Time to progression Overall survival *Safety* Incidence and severity of AEs graded according to the NCI CTCAE v4.03 Changes in clinical laboratory parameters, vital signs, ECGs, and	N/A – in line with the NICE final scope.	The outcomes reported are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
		echocardiogram/MUGA scans.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE TA guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per final scope.	N/A – in line with the NICE final scope.	The economic analysis is in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: Line of therapy (treated or untreated) Histology (squamous or non-squamous) PD-L1 expression	No subgroups are considered	Adult patients with *BRAF* V600E mutation-positive advanced NSCLC would be offered targeted therapy at first-line. Patients would receive targeted therapy with either enco+bini or dabra+tram regardless of histology of PD-L1 expression. Patients treated with a targeted therapy at first-line would not receive targeted therapy in subsequent lines. Therefore, these subgroups are not appropriate for this submission.	The EAG have concerns about the lack of any subgroup analyses.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	N/A

Based on Table 1 of the CS[2]

AE = adverse event; BID = twice daily; CS = company submission; BRAF = v-Raf murine sarcoma viral oncogene homolog B; CTCAE = Common Terminology for Adverse Events; dabra+tram = dabrafenib in combination with trametinib; DCR = disease control rate; DOR = duration of response; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib; ECG = electrocardiogram; HRQoL = health-related quality of life; IA = investigator assessment; IRR, independent radiology review; MT, mutation-positive; MUGA = multi-gated acquisition; N/A = not applicable; NCI = National Cancer Institute; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; QALY = quality-adjusted life year; QD = once daily; TA = Technology Appraisal; TTR = time to treatment discontinuation

2.1 Population

The population in the National Institute for Health and Care Excellence (NICE) scope and the decision problem (DP) are: People with advanced non-small-cell lung cancer (NSCLC) that is positive for a v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600E mutation and treatment-naïve patients with advanced NSCLC with a BRAF V600E mutation respectively.[2, 3]

EAG comment: The population in the DP is narrower than in the NICE scope i.e., treatment-naïve (first-line) only. However, the company state that: "*the number of patients eligible to receive enco+bini in second-line will likely decrease over time, with the majority of eligible patients receiving targeted therapies in the first-line.*" (Table 1, company submission (CS)). This statement suggests that the population in the DP should include second-line, even if the number of patients does diminish over time. In the clarification letter the company were therefore asked:[4]

- To clarify whether the population to be considered in this appraisal is only first-line or both first and second-line.
- If second-line treatment is included then to also include a comparison between encorafenib in combination with binimetinib (enco+bini) and comparators that form current clinical practice for second-line in the United Kingdom (UK), both in an indirect treatment comparison (ITC) and cost effectiveness analysis (CEA).

In response, the company stated that the population was first-line only on the basis of the recommendation by NICE for dabrafenib in combination with trametinib (dabra+tram), and clinical expert opinion that: *"As most, if not all patients will receive either dabra+tram or enco+bini at first-line, patients will not be eligible to receive a targeted therapy at second line, as confirmed by CEs during the advisory board. CEs stated that sequencing, i.e. receiving a targeted therapy at second line after first-line targeted treatment, "was not considered an option as it would be expected that there would be a biological resistance mechanism with treatments with similar mechanisms of action."*[5] However, the External Assessment Group (EAG) notes that comparators listed in NICE guideline 122 include several alternatives to dabra+tram for BRAF V600 mutation-positive treatment-naïve patients (see Section 2.5), some of which are not 'targeted therapies'.[6] Therefore, it is firstly not clear that all patients would receive dabra+tram, and therefore, that some might be eligible for targeted therapy, which includes enco+bini. Uncertainty as to line of therapy is therefore a key issue.

2.2 Intervention

The intervention in the NICE scope and the DP is: Encorafenib capsule 450 mg once daily (QD) + binimetinib tablet 45 mg twice daily (BID).[2, 3]

EAG comment: The intervention in the DP is in line with the NICE scope.

2.3 Comparators

The comparators in the NICE scope depend on treatment experience: for people with untreated advanced NSCLC:[3]

- Dabrafenib with trametinib
- Pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed)

- Pembrolizumab monotherapy
- Atezolizumab monotherapy.

For people with previously treated advanced NSCLC:

- Atezolizumab monotherapy
- Pembrolizumab monotherapy
- Nivolumab monotherapy
- Docetaxel with nintedanib
- Docetaxel
- Platinum doublet chemotherapy.

In the DP there is only one comparator, dabrafenib with trametinib.[2]

EAG comment: The DP population is limited to first-line only, which explains the omission of the comparators for the previously treated. However, several comparators in the NICE scope have been omitted for treatment-naïve (first-line) patients. This seems to be on the basis of availability of testing for BRAF V600E mutations (see Table 1). In the clarification letter the company were therefore asked:[7]

- To clarify that no patients at first-line are currently treated in the UK National Health Service (NHS) with anything but dabra+tram.
- If even a small number of patients are treated with any other treatment, then to perform an ITC and CEA for each of these comparisons.

In response the company stated: *"Gene testing is routinely carried out in the UK by the NHS for NSCLC patients. Therefore, very few patients in the UK may be treated by the NHS at first-line with treatments other than dabrafenib with trametinib (dabra+tram). Pembrolizumab with carboplatin and paclitaxel, pembrolizumab or atezolizumab, or platinum doublet chemotherapy are other first-line options. However, the clinical experts (CEs) agreed that dabra+tram was the most appropriate comparator as there is no reason not to choose a targeted therapy if a patient has a known BRAF V600E mutation. For this reason, we have determined that is no rationale to complete an ITC and CEA for other treatments."* However, as reported in Section 2.1, in response to the clarification letter, the company stated: *"As most, if not all patients will receive either dabra+tram or enco+bini at first-line…"*. Therefore, it seems that treatments other than dabra+tram are not entirely ruled out. Also, NICE guideline 122 includes the following alternatives to dabra+tram for BRAF V600 mutation-positive treatment-naïve patients:[6]

- Squamous, programmed cell death ligand 1 (PD-L1) <50%: platinum doublet, pembrolizumab + carboplatin + paclitaxel
- Squamous, PD-L1≥50%: pembrolizumab + carboplatin + paclitaxel (urgent intervention), pembrolizumab, atezolizumab
- Non-squamous: platinum doublet, pemetrexed + platinum chemo, atezolizumab + bevacizumab + carboplatin + paclitaxel, pembrolizumab + pemetrexed + platinum chemo
- Non-squamous, PD-L1≥50%: pembrolizumab atezolizumab

The EAG clinical expert stated: *"I agree with the exclusion of other comparators as if a patient has a confirmed BRAF V600E mutation, lung cancer oncologists would favour a targeted therapy.*

As genomic testing has been rolled out unequally around the UK (onus on centres to set this up themselves) it is possible that a small number of centres will still not have access to it and so patients may not be tested for BRAF-V600E and so they would be treated with standard 1st line therapies.

My guess would be that under 5% of patients would be in a situation where there was insufficient tissue for genomic testing and rebiopsy would not be feasible and so these patients would also be considered for standard non-targeted therapies."

Therefore, given lack of objective data on contemporary clinical practice, lack of inclusion of comparators remains a key issue.

2.4 Outcomes

EAG comment: The outcomes in the CS are in line with those in the NICE scope (see Table 1).

2.5 Subgroups to be considered

The NICE scope specifies the following subgroups:[3]

- Line of therapy (treated or untreated)
- Histology (squamous or non-squamous)
- PD-L1 expression.

The CS does provide any evidence for these subgroups.[2]

EAG comment: As stated in Section 2.1, evidence for only untreated patients has been presented, which therefore remains a concern if treated patients might be eligible for enco+bini. For the untreated population, pembrolizumab (combination or monotherapy) and atezolizumab have also been excluded as a comparator. If patients currently receiving either of these treatments are also eligible for enco+bini, and these patients have been selected for treatment according to PD-L1 status, then a subgroup analysis of the effectiveness of enco+bini according to PD-L1 status might be warranted. As reported in Section 2.3, NICE guideline 122 includes alternatives to dabra+tram for BRAF V600 mutation-positive treatment-naïve patients, the choice for which seems to depend on both histology and PD-L1 status.[6] The EAG therefore considers that lack of subgroup analyses by line, histology and PD-L1 status constitutes a key issue. Unfortunately, only 2% of patients in the key enco+bini trial, PHAROS, were of squamous histology, thus probably precluding a formal subgroup analysis. The PD-L1 status for PHAROS was also not reported in the CS, and the EAG note that it is also not reported in the trial clinical study report (CSR).[8] Therefore, it seems that the only subgroup analysis that might be conducted is for the treatment experienced population, which might be required depending on the resolution of uncertainty regarding line of therapy (see Section 2.1).

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) and other relevant evidence relating to the efficacy and safety of enco+bini for the treatment of patients with BRAF V600 mutated advanced NSCLC.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[2] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D and P of the CS detail the SLR conducted to identify relevant clinical evidence on evidence for the treatment of patients with BRAF V600 mutated advanced NSCLC.[10, 11] The searches were conducted in October 2021, and updated in May 2023, July 2023 and May 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	Incep – Wk 42 2021 2021 – Wk 17 2023 2023 – Wk 27 2023 2023 – 14/5/24	26/10/21 4/5/23 11/7/23 15/5/24
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)		Incep – 22/10/21 2021 – 3/5/23 2023 – 10/7/23 2023 – 14/5/24	
CENTRAL		Incep – Sept 2021 2021 – March 2023 2023 – June 2023 2023 – Apr 2024	
CDSR		Incep – 26/10/21 May 2020 – 2/5/23 July 2022 – 5/7/23 Apr 2022 – 4/4/24	
DARE		Incep – 1st Quarter 2016	
HTA Database		Incep – 4th Quarter 2016	
Conferences			
• ASCO	Embase/ Internet	2018-2024 2018-2023	7/6/24

Resource	Host/Source	Date Ranges	Date searched
• ESMO • IASLC WCLC • AACR		2018-2023 2018-2024	
HTA Agencies			
• NICE • CDA-AMC • PBAC/TGA	Internet	All	7/6/24
Trials registries			
• ClinicalTrials.gov • NCI Clinical Trial Database • EORTC • UK Clinical Trials Gateway • ICTRP	Internet	All	17/6/24 7/6/24 17/6/24 17/6/24 17/6/24
Guidelines organisations			
• NICE • ESMO • ASCO • NCCN • TGA	Internet	All	17/6/24
Additional resources			
• EQ-5D • INAHTA Database • Google Scholar • NIHR	Internet	All	27/6/24

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDA-AMC = Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health); CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = EuroQol-5 Dimensions; ESMO = European Society of Medical Oncology; HTA = Health Technology Assessment; IASLC WCLC = International Association for the Study of Lung Cancer World Congress on Lung Cancer; ICTRP = International Clinical Trials Registry Platform; INAHTA = International Network of Agencies for Health Technology Assessment; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; NICE = National Institute for Health and Care Excellence; NIHR = National Institute for Health and Care Research; PBAC/TGA = Pharmaceutical Benefits Advisory Committee/Therapeutic Goods Administration; TGA = Therapeutic Goods Administration

EAG comment:

- Searches were undertaken in October 2021, and updated in May 2023, July 2023 and May 2024 to identify clinical evidence on clinical, efficacy and safety evidence for the treatment of patients with BRAF V600 mutated advanced NSCLC. The CS, Appendices D and P and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 5, 10, 11]
- An extensive range of bibliographic databases, conferences, Health Technology Assessment (HTA) organisation web sites, guidelines resources, trials registries and other resources were searched. Reference checking was conducted.

- Searches were extremely well documented, and were well structured, transparent and fully reproducible.
- The database searches for the clinical effectiveness SLR combined facets for BRAF mutations and NSCLC. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. A good range of subject headings and free-text terms were employed. Animal-only studies were excluded where possible.
- Conference proceedings were searched for key international conferences between 2018 and 2024 (where available), using a combination of Embase searches and manual searches of online conference proceedings as necessary.
- For Embase and MEDLINE, CENTRAL, and DARE/HTAD the database searches were limited to studies published in English only. Limiting to English language only studies may have introduced language bias. Current best practice states that *'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*[12] and research related to language bias supports the inclusion of non-English studies in systematic reviews.[13, 14]
- The EAG notes that the approach used by the company for the update searches was potentially restrictive, as only the publication year limit was used, rather than also including limits related to the date on which records were added to the database. This could potentially miss records that were added since the last update, but which had an earlier publication year. However, given the extensive range of resources included in this SLR, the EAG considers it unlikely any relevant records were missed due to this approach.

3.1.2 Inclusion criteria

An SLR was conducted to identify relevant clinical evidence for the treatment of patients with BRAF V600 mutated advanced NSCLC. Full details of the SLR search strategy, study selection process and results were reported in Appendix D of the CS.[10]

The eligibility criteria used in the search strategy is presented in Table 3.2.

Table 3.2: Eligibility criteria for the SLR

	Inclusion criteria	Exclusion criteria
Population	Adult patients (aged ≥18 years) with BRAF V600/V600E mutant advanced/metastatic NSCLC in the 1L, 2L and later lines settings[a]	• Paediatric/adolescent populations (<18 years) • Patients with cancers other than NSCLC • Early-stage NSCLC patients • Animals/in vitro data
Interventions/ Comparators	Any pharmacological interventions/comparators were included[b]	–
Outcomes[c]	Efficacy: • OS • Duration of treatment • PFS • TTP • DOR • TTR	Outcomes not listed

	Inclusion criteria	Exclusion criteria

	• Response rates:
	  o CR
	  o PR
	  o SD
	  o ORR
	• DCR or CBR
	• Confounding factors (prognostic factors or treatment effect modifiers) associated with OS and response
	
	Safety and tolerability:
	• All-grade AEs
	• Grade 3/4 AEs
	• Serious AEs
	• Tolerability: dose reductions and interruptions, discontinuation and time-to-discontinuation (any reason, due to AEs)
	
	HRQoL:
	• Utilities derived using generic preference-based instruments (e.g., EQ-5D, SF-6D, HUI2, HUI3, AQoL) for relevant health states
	• Direct utility estimates (e.g., standard gamble, time trade off)
	• Mapping studies, from disease-specific to generic preference-based measures or between different generic preference-based measures
	• Disease-specific or generic non-preference-based QoL questionnaires
	• Descriptive summary of health states, and/or change in health status/QoL results	

Study design	Clinical SLR: • Prospective RCTs (Phase II-IV) with active/placebo/BSC controls (no restriction on blinding) • Non-randomised, case-control, cohort or observational, retrospective studies, case series QoL SLR: • Any studies reporting original QoL/HSUV data	• Animal/in-vitro studies • Reviews/editorials • Case reports • Pilot studies • Letters/comments • SLRs/NMAs • Pharmacokinetic/pharmacodynamic studies • Phase I trials[d]
Date limits	Full publications: Not restricted	–

	Inclusion criteria	Exclusion criteria
	• Original review: From database inception to 26th October 2021 • May 2023 update: From 2021 to 4th May 2023 • July 2023 update: From 2023 to 11th July 2023 • May 2024 update: From 2023 to 15th May 2024 Conference abstracts: • Conference abstracts included in Embase database: No restrictions • Original review: From database inception to 26th October 2021 • May 2023 update: From 2021 to 4th May 2023 • July 2023 update: From 2023 to 11th July 2023 • May 2024 update: From 2023 to 15th May 2024 Hand-searched conference abstracts: 2018 to 2024	
Countries	No restriction	–
Language	English language publications	Non-English language publications

Based on Table 19 of Appendix D of the CS[2, 10]

[a] The SLR protocol was amended to include studies where the target population was NSCLC patients with BRAF V600 mutation. Studies focussing on NSCLC patients with BRAF mutation where the details of the type of BRAF mutation (i.e. BRAF V600E or BRAF V600) were not specified were excluded.

[b] Studies where efficacy outcomes for the target population were not reported in relation to a therapy were excluded.

[c] Post-hoc analyses in relation to prognostic factors were extracted.

[d] Phase I trials are primarily designed to assess dose range and safety. Outcomes reported in Phase I trials were considered less applicable in terms of clinical practice, than those reported in Phase II-Phase IV trials. Therefore, Phase I trials were excluded from the SLR.

1L = first-line; 2L = second-line; AE = adverse event; AQoL = assessment of quality of life; BSC = best supportive care; CBR = clinical benefit rate; CR = complete response; CS = company submission; DCR = disease control rate; DOR = duration of response; EQ-5D = European Quality of Life-5 dimensions; HRQoL = health-related quality of life; HSUV = health state utility value; NMA = network meta-analysis; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; RCT = randomised controlled trial; SD = stable disease; SF-6D = short form-6 dimensions; SLR = systematic literature review; TTP = time to progression; TTR = time to response

The company was asked to confirm whether the same methodological approach was taken to conduct the SLR during each stage (outlined in Appendix D) for each update of the SLR (October 2021, May 2023, July 2023 and May 2024). The company confirmed using the same methodology for all SLR updates. However, handsearching methods in earlier updates (Oct 2021, May/July 2023) were insufficiently documented (e.g., search terms/filters), making replication impossible in May 2024. To

address this, May 2024 handsearching removed date limits and cross-checked results against prior SLR versions. No new relevant studies were identified, confirming all earlier inclusions were complete.

The EAG questioned whether excluding non-English studies (as stated in Appendix D) impacted the SLR results. The company clarified: all 76 non-English hits were excluded during screening (74 at title/abstract, two at full text: duplicates or lacked BRAF-specific data). Including non-English studies would not alter SLR findings, as no relevant publications were missed.

3.1.3 Critique of data extraction

According to the CS, two reviewers independently screened the titles, abstracts, and full texts for eligibility based on the pre-defined selection criteria. Any disagreements were resolved in consultation with a third reviewer.[10]

Data extraction was conducted by a single reviewer and verified by a second independent reviewer. Any disputes were referred to a third, more senior reviewer.

3.1.4 Quality assessment

Quality assessment was performed by one reviewer and quality checked by a second independent reviewer. The quality assessment tools used are provided in Table 3.3

Table 3.3: Quality assessment checklists

Study type	Checklist(s)
RCTs	The seven-criteria checklist provided in the NICE STA user guide
Single-arm trials/ non-randomised studies	Downs and Black checklist
Observational studies	JBI checklist for cross-sectional studies
JBI = Joanna Briggs Institute; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; STA = single technology appraisal	

3.1.5 Evidence synthesis

In the absence of a head-to-head trial comparing enco+bini with other comparators, an SLR and matching-adjusted indirect comparison (MAIC) was conducted to determine the relative efficacy in adult patients with advanced BRAF V600E MT NSCLC versus dabra+tram. Details are provided in Sections 3.3 and 3.4 for the ITC.

EAG comment: The EAG is satisfied with the methodological approach taken by the Company, which reflects best practice in systematic reviews.[15]

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

The flow of evidence identification and selection are presented in Appendix D[10] with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram for the original SLR (October 2021), and subsequent updated SLRs (May 2023, July 2023 and May 2024) also provided.

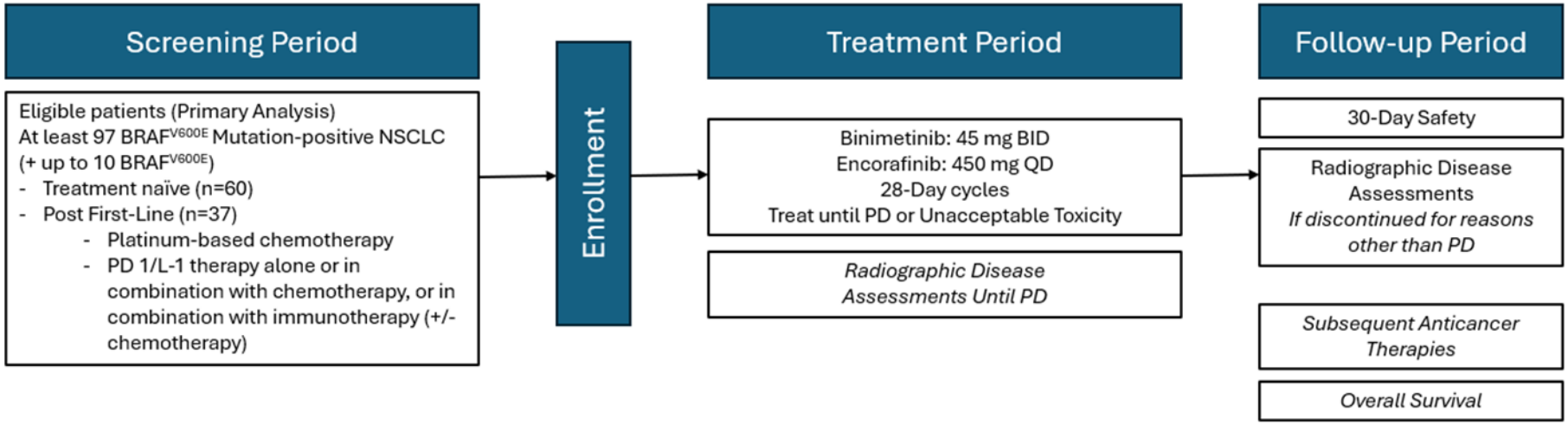
In the original SLR of October 2021, a total of 5,312 records were retrieved by the electronic database searches, of which 936 were duplicates, resulting in 4,376 novel records that were screened at the title/abstract review stage against the eligibility criteria. Subsequently, 310 full publications were screened against the eligibility criteria at full text review. A total of 52 records were found to fulfil the eligibility criteria for the SLR. Of these 52 publications, 42 were full publications and 10 were conference abstracts.

Across the original SLR and all SLR updates (the first SLR update (May 2023), second SLR update (July 2023) and third SLR update (May 2024)), a total of 99 publications reporting on 134 unique studies were included in the SLR. Of these studies there were 77 publications, 20 conference abstracts and two ClinicalTrials.gov records. There were 18 records reporting 10 interventional trials which reported on the efficacy and safety of various therapeutic approaches for BRAF V600/V600E mutation-positive non-small-cell lung cancer. Furthermore, there were nine records across three unique trials which reported clinical outcomes for patients with BRAF V600E/V600 as the target population. There were also nine records for seven interventional trials which included patients with BRAF V600E/V600 as a subgroup of the whole population. Finally, there were 11 publications reporting on five unique trials which reported data for patients in the first-line setting specifically. Whilst five publications covering three trials reported data for patients in the second-line setting specifically.

3.2.2 Details on the PHAROS trial

The CS[2] states that the PHAROS trial is an "*ongoing multicentre, multi-cohort pivotal Phase 2, open-label trial evaluating the safety, tolerability, and efficacy of enco+bini in treatment-naïve and previously treated participants with advanced/metastatic BRAF V600E MT NSCLC*".

Figure 3.1: Study design of PHAROS



Based on Figure 5 of the CS[2]

BRAF = B-RAF proto-oncogene, serine/threonine-protein kinase; BID = twice daily; CS = company submission; NSCLC = non-small-cell lung cancer; PD = progressed disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; QD = once daily

As illustrated in Figure 3.1, the PHAROS trial was comprised of three periods – screening period, treatment period and follow-up period. During the screening period eligible patients with the BRAF V600E mutation who were treatment-naïve (n=60), or post first-line (n=37) were recruited for the trial. Post first-line included platinum-based chemotherapy or PD1 1/L-1 therapy alone or in combination with immunotherapy (+/- chemotherapy).

3.2.2.1 Trial methodology

The PHAROS trial methodology is presented in Table 3.4.

Table 3.4: Clinical effectiveness evidence

Study	PHAROS (NCT03915951)
Study design	Phase 2, open-label, multicentre study
Population	Male and female participants at least 18 years of age with advanced BRAF V600E MT NSCLC
Intervention(s)	Encorafenib in combination with binimetinib
Comparator(s)	N/A
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	Efficacy Primary outcomes: ORR as determined by IRR in the treatment-naïve setting ORR as determined by IRR in the previously treated setting Secondary outcome: ORR using IA DOR DCR PFS TTR OS Safety Safety and tolerability of enco+bini in treatment-naïve and previously treated patients with BRAF V600E MT NSCLC AEs Deaths Significant and other SAEs
All other reported outcomes	N/A

Based on Table 4 of the CS[2]
Source: PHAROS CSR_DCO 22 September 2022 [Data on file][8]
AE = adverse event; BRAF = v-Raf murine sarcoma viral oncogene homolog B; DCR = disease control rate; DOR = duration of response; IA = investigator assessment; IRR, independent radiology review; MT, mutation-positive; N/A = not applicable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; TTR = time to response

EAG comment: The PHAROS trial employs an open-label design, where both investigators and participants are aware of the treatment being administered. This poses a significant limitation, as it increases the risk of performance bias and detection bias, particularly for subjective outcomes like progression-free survival (PFS) and disease control rate (DCR), which rely on investigator assessment. The absence of blinding may also lead to an overestimation of benefits in patient-reported outcomes, such as quality of life, due to the psychological impact of knowing the treatment being received. However, it should be noted that health-related quality of life was not reported despite being listed in the NICE final scope. While open-label designs are often necessary in early-phase trials or rare diseases, the inclusion of blinding or an independent control group would have reduced biases and improved the reliability of the findings.

A key limitation of the PHAROS trial is the absence of a comparator arm. Without a control group receiving either standard of care or placebo, it is challenging to assess the relative efficacy and safety of the intervention. The lack of a comparator also hinders the ability to contextualise outcomes like overall response rate (ORR) or PFS within the broader treatment landscape. Incorporating a control group would have significantly strengthened the study design and provided more robust evidence for comparative analysis.

The trial design includes separate cohorts for treatment-naïve and previously treated patients, which allows for subgroup analyses and insights into different patient populations.

The eligibility criteria of the PHAROS trial are presented in Table 3.5.

Table 3.5: Inclusion and exclusion criteria, PHAROS

Inclusion criteria	Exclusion criteria
Male or female aged ≥18 years Histologically confirmed diagnosis of NSCLC that was currently Stage IV (M1a M1b, M1c-AJCC 8th edition)	Participants who had documentation of any of the following: *EGFR* mutation, *ALK* fusion oncogene, or *ROS1* rearrangement
Presence of a *BRAF* V600E mutation tumour tissue or blood (e.g., ctDNA genetic testing) as determined by a local laboratory assay. Other Class 1 *BRAF* V600 mutations (e.g., K or D) were permitted with prior discussion with the Sponsor. Participants must have had written documentation from a previous local pathology report of *BRAF* V600 mutation in tumour tissue or blood. Only PCR and NGS-based local assay results for tumour tissue or blood were acceptable.	Previous treatment with any BRAF inhibitor (e.g., dabrafenib, vemurafenib, XL281/BMS-908662, etc.), or any MEKi (e.g., trametinib, cobimetinib, selumetinib, RDEA119, etc.) prior to screening and enrolment.
The Investigator must have obtained prior to enrolment adequate tumour tissue for submission to a central laboratory for confirmation of *BRAF* V600 mutation status. Tumour tissue collected after the participant was diagnosed with metastatic disease was preferred Tumour tissue sample must not have been from locations previously radiated	Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment: A: ≤14 days for chemotherapy, targeted small-molecule therapy, radiation therapy, immunotherapy, or antineoplastic biologic therapy (e.g., erlotinib, crizotinib, bevacizumab, etc).

Inclusion criteria	Exclusion criteria
Tumour sample of one block or a minimum of eight unstained slides of analysable tissue was required (up to 15 unstained slides was preferred). Tumour cells from pleural fluid were permitted, provided the sample had been centrifuged to generate a formalin-fixed, paraffin-embedded block with sufficient tumour nuclei (i.e., >20% tumour nuclei). Liquid samples were not permitted. One block or a minimum of eight unstained slides was required (up to 15 unstained slides was preferred). Fine needle aspiration was permitted, provided sufficient material (one block or a minimum of eight unstained slides [up to 15 unstained slides was preferred]) from the same sample used to obtain the local *BRAF* positive result was sent to the central laboratory.	B: ≤14 days or five half-lives (minimum of 14 days) for investigational agents or devices. For investigational agents with long half-lives (e.g., >5 days), enrolments before the fifth half-life required medical monitor approval. COVID-19 vaccinations approved under an EUA (or equivalent) were not considered investigational products by regulatory authorities. C: Palliative radiation therapy must have been completed 7 days prior to the first dose of study treatment.
Participants who were either treatment-naïve (e.g., no prior systemic therapy for advanced/metastatic disease), OR who had received 1) first-line platinum-based chemotherapy OR 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with immunotherapy (e.g., ipilimumab) with or without platinum-based chemotherapy. Alternative chemotherapy regimens were acceptable if the participant was platinum intolerant or ineligible. Participants with early-stage disease (e.g., Stages I-III) who had surgery followed by chemotherapy, radiation therapy and/or immunotherapy (e.g., treatment in the adjuvant setting), and present with new lesions or evidence of disease recurrence (e.g., metastatic disease), within 12 months of completing adjuvant treatment would have been considered as receiving treatment in the first-line setting for metastatic disease. These participants would have started treatment with encorafenib/binimetinib in the previously treated setting. Maintenance therapy given after first-line therapy was not considered a separate regimen, provided there was no documentation of disease progression between completion of first-line therapy and the start of maintenance therapy.	Participants who had major surgery (e.g., inpatient procedure with regional or general anaesthesia) ≤6 weeks prior to start of study treatment. Participants who had received more than 1 prior line of systemic therapy. Prior therapies could have been reviewed with the Sponsor. Generally, treatments that were separated by an event of progression were considered to represent another line of therapy. Any therapeutic intervention including systemic therapy, surgery concurrent with or followed by systemic therapy, radiation concurrent with systemic therapy, or stereotactic radiation/radiosurgery, initiated or added to an existing therapy for oligometastatic disease were considered a new line of therapy. Palliative radiation to solitary lesions was permitted and was not considered a new line of therapy. Surgery/radiosurgery for CNS metastases was permitted and was not considered a line of therapy as long as the surgery/radiosurgery was not given with systemic therapy (neoadjuvant or adjuvant). Surgery followed by chemotherapy was considered a line of therapy.
Presence of measurable disease based on RECIST v1.1	Participant had not recovered to Grade ≤1 from toxic effects of prior therapy and/or

Inclusion criteria	Exclusion criteria
Tumour lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, were not considered measurable unless there had been documented progression of the lesion. If baseline scans from an institution other than the investigational site were used, the site must have obtained copies of the scans prior to enrolment of the participant, or the scans must have been repeated at the investigational site and submitted for independent review.	complications from prior surgical intervention before starting study treatment Stable chronic conditions (Grade ≤2) that were not expected to resolve (e.g., neuropathy, myalgia, alopecia, and prior therapy-related endocrinopathies) were exceptions.
Adequate bone marrow, hepatic, and renal functions'	Evidence of active non-infectious pneumonitis or history of interstitial lung disease. Participants with symptomatic brain metastasis, leptomeningeal disease, or other active CNS metastases were not eligible.
Based on Table 1 of Appendix M[16] and Table 7 of the CS[2] Source: PHAROS CSR, 2024.[8] ALK = anaplastic lymphoma kinase; AJCC, American Joint Committee on Cancer; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CNS = central nervous system; CS = company submission; CSR = clinical study report; ctDNA = circulating tumour DNA; EGFR = epidermal growth factor receptor; EUA = Emergency Use Authorization; MEKi = mitogen-activated protein kinase kinase inhibitor; PD-L1 = programmed cell death protein ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours; ROS1 = ROS proto-oncogene 1	

Encorafenib (450 mg QD) was administered in combination with binimetinib (45 mg BID) in 28-day cycles (±3 days). Treatment continued until patients met protocol-defined withdrawal criteria, which included withdrawal of consent, unacceptable adverse events (AEs), inability to tolerate the study treatment, missing more than six weeks of dosing, disease progression based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, or clinical progression as determined by the investigator. Other reasons for discontinuation included pregnancy or breastfeeding, significant protocol deviations, non-compliance with study procedures, being lost to follow-up, or death. The CS[2] specified that patients were deemed to have withdrawn from the trial if certain criteria were met. This included withdrawal of consent, where patients could choose to stop receiving study treatment but remain in the follow-up period for safety and efficacy assessments. Withdrawal also occurred if a patient experienced unacceptable AEs or was unable to tolerate the treatment. Unacceptable AEs were defined as grade 4 or life-threatening events, or toxicities requiring more dose reductions than permitted for encorafenib and binimetinib, as specified in the protocol and highlighted in Table 3.6. Additionally, if a treatment-related AE, from the investigator's judgment, compromised the patient's ability to continue study-specific procedures or was deemed not in the patient's best interest, the patient was withdrawn from the study.

Table 3.6: Dose reductions for encorafenib and binimetinib

Dose level	Encorafenib
0 (starting dose)	450 mg QD
–1	300 mg QD
–2	225 mg QD
Dose level	**Binimetinib**
0 (starting dose)	45 mg BID
–1	30 mg BID

Based on Table 8 of the CS[2]
± Dose reduction below 225 mg QD of encorafenib was not allowed
BID = twice daily; CS = company submission; QD = once a day

EAG comment: While the eligibility criteria are well-defined, they exclude patients with symptomatic brain metastases, poorer performance status (Eastern Cooperative Oncology Group (ECOG) >1), or prior exposure to BRAF or mitogen-activated protein kinase kinase (MEK) inhibitors. These exclusions limit the generalisability of the findings, as patients with these characteristics are commonly seen in real-world clinical settings. Consequently, the trial results may not fully represent the efficacy or safety profile of encorafenib and binimetinib in a broader NSCLC population.

3.2.2.2 Prior treatment

In the PHAROS trial, the prior treatments used by the previously treated cohort are well-documented in the CS[2]. All 39 patients in this group "*had received at least one prior systemic therapy for metastatic NSCLC*", while none of the treatment-naïve patients had prior systemic treatment for metastatic disease. The most frequently used therapies in the previously treated cohort were PD-1 or PD-L1, administered either as monotherapy (n=13, 33.3%) or in combination with chemotherapy or other immunotherapies (n=11, 28.2%). Additionally, 20 patients (51.3%) had received chemotherapy without immunotherapy, while no patients in either cohort had prior treatment with tyrosine kinase inhibitors (TKIs) (Table 3.7).

The setting of prior treatments varied. Among the previously treated patients, 74.4% (29 patients) had received systemic therapy for metastatic disease, while a smaller proportion had therapies categorised as maintenance (7.7%), locally advanced (7.7%), or palliative (10.3%). Interestingly, some patients in the treatment-naïve cohort had received prior treatments in the neoadjuvant (1.7%) or adjuvant (5.1%) setting, but these were considered systemic therapy only if disease recurrence occurred within 12 months of completing treatment. Table 3.7 has a full breakdown of the prior anticancer therapy from the PHAROS trial.

Table 3.7: PHAROS - prior anticancer therapy - systemic treatment (safety set)

	Enco+bini		
	Treatment Naïve N=59	**Previously Treated N=39**	**Total N=98**
Number of patients with at least one prior systemic treatment, n (%)	4 (6.8)	39 (100)	43 (43.9)
Received at least one regimen of prior immunotherapy (monotherapy or combination therapy)	0	24 (61.5)	24 (24.5)
Received monotherapy PD1/L1	0	13 (33.3)	13 (13.3)
Received combination PD1/L1 therapy (with chemotherapy or other immunotherapy)	0	11 (28.2)	11 (11.2)
Received at least one regimen of chemotherapy without immunotherapy	4 (6.8)	20 (51.3)	24 (24.5)
Received at least one regimen of TKI	0	0	0

	Enco+bini		
	Treatment Naïve N=59	**Previously Treated N=39**	**Total N=98**
Total number of regimens, n (%)			
1	2 (3.4)	33 (84.6)	35 (35.7)
2	2 (3.4)	5 (12.8)	7 (7.1)
3	0	1 (2.6)	1 (1.0)
Total number of regimens			
N	4	39	43
Mean	1.5	1.2	1.2
SD	0.58	0.45	0.47
Median	1.5	1.0	1.0
Minimum	1	1	1
Maximum	2	3	3
Setting at last medication			
Neoadjuvant	1 (1.7)	0	1 (1.0)
Adjuvant	3 (5.1)	0	3 (5.1)
Metastatic	0	29 (74.4)	29 (29.6)
Maintenance	0	3 (7.7)	3 (3.1)
Locally advanced	0	3 (7.7)	3 (3.1)
Palliative	0	4 (10.3)	4 (4.1)
Other	0	0	0

Based on Table 10 of the CS[2]
Source: PHAROS CSR_DCO 22 September 2022 [Data on file][8]
CS = company submission; CSR = clinical study report; DCO = data cut-off; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death ligand 1; SD = standard deviation; TKI, tyrosine kinase inhibitor

EAG comment: The EAG considers the detailing of prior therapies to be appropriate and that it provides a clear understanding of the treatment landscape for the previously treated cohort. The inclusion of a detailed breakdown of the types and settings of prior therapies is a strength, as it aids in interpreting the efficacy of encorafenib and binimetinib in a population that has already been exposed to contemporary treatments. However, it should be noted that no patients in the previously treated group had received TKIs or other targeted therapies prior to enrolment. While this exclusion ensures that the efficacy and safety signals observed for encorafenib and binimetinib are not influenced by factors such as resistance mechanisms developed during earlier treatments, it may limit the generalisability of the findings to patients who have already undergone treatment with BRAF or MEK inhibitors in real-world settings as highlighted in the exclusion criteria in Table 3.5. However, as the PHAROS trial is a phase 2 trial which prioritises establishing the drug's efficacy in a treatment-naïve population, therefore, the approach can be considered scientifically viable.

3.2.2.3 Analysis sets

The key data for the PHAROS study included in the CS[2] are based on several data cut-off (DCO) dates, as summarised in Table 3.6. Clinical efficacy data were collected at three DCO dates: 22 September 2022, 19 July 2023, and 1 April 2024. Safety data were derived from three separate DCO dates: 22 September 2022, 19 January 2023, and 1 April 2024. Among these, the 1 April 2024 cut-off

is highlighted as the primary data source due to its recency and greater maturity, which also aligns with the data used in the cost effectiveness model.

Details on the data available at each DCO are outlined in Table 3.8. The CS[2] primarily emphasises findings from the treatment-naïve population, with these results presented as the main clinical efficacy and safety data in sections of the CS[2], respectively.

Table 3.8: PHAROS data cut-offs and their respective unpublished/published sources

Data cut-off	Data	Reason	Unpublished source	Published source
1 April 2024	Clinical efficacy	Represents more mature data	PHAROS update_DCO 1 April 2024[17]	ESMO Congress 2024 presentation[18]
19 July 2023	Clinical efficacy	EMA license	PHAROS EMA update_DCO 19 July 2023[19]	EMA documents[20]
19 January 2023	Safety	FDA request Safety update only	Pierre Fabre, PHAROS CSR[21]	EMA documents[20]
22 September 2022	Clinical efficacy and safety	Primary trial endpoint	PHAROS CSR_DCO 22 September 2022[8]	Phase II, open-label study of encorafenib plus binimetinib in patients with BRAF V600E MT metastatic non-small-cell lung cancer[22]

Based on Table 5 of the CS[2, 8, 17, 18, 23]
BRAF = v-Raf murine sarcoma viral oncogene homolog B; CS = company submission; CSR = clinical study report; DCO = data cut-off; EMA = European Medicines Agency; ESMO = European Society of Medical Oncology; FDA = Food and Drug Administration; MT = mutation-positive; NSCLC = non-small-cell lung cancer

Table 3.9: PHAROS outcome data available for each data cut-off

	April 2024	July 2023	January 2023	September 2022
ORR by IRR	✓	✓	×	✓
Investigator confirmed ORR	✓	✓	×	✓
DOR	✓	✓	×	✓
DCR	✓	✓	×	✓
OS	✓	✓	×	✓
PFS	✓	✓	×	✓
TTR	✓	✓	×	✓
Adverse reactions (safety data)	✓	×	✓	✓

Based on Table 6 of the CS[2]
CS = company submission; DCR = disease control rate; DOR = duration of response; IRR = independent radiology review; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response

3.2.2.4 Study endpoints

Table 3.10 outlines the primary and secondary endpoints from the PHAROS trial presented in the CS.[2]

Table 3.10: Summary of endpoint definitions from the PHAROS trial

Endpoint	Definition or determination criteria
Primary endpoint	
ORR	*"Determined by independent radiology review (IRR)*"
Secondary endpoints	
ORR by investigator assessment (IA)	"*Defined as the proportion of patients who have achieved a confirmed best objective response (complete response [CR] or partial response [PR]) as determined by IRR per RECIST v1.1*"
DOR	By IRR and by IA. "D*efined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by IA, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause.*"
DCR	By IRR and by IA. "*Defined as the proportion of patients who have a confirmed CR or confirmed PR, or stable disease (SD) per RECIST v1.1*"
OS	
PFS	By IRR and by IA. "*Defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause*".
TTR	By IRR and by IA. "*Defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by IA, respectively)*."

Based on Section B.2.3.1.5 of the CS[2]
CR = complete response; CS = company submission; DCR = disease control rate; DOR = duration of response; IA = investigator assessment; IRR = independent radiology review; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TTR = time to response

3.2.2.5 Baseline characteristics

Baseline demographic and clinical characteristics of patients in the PHAROS trial, are presented in Table 3.11. The characteristics between the two cohorts, treatment-naïve patients and previously treated patients, were generally well-balanced. The median age was 68 years for the treatment-naïve cohort (range: 47 – 83) and 71 years for the previously treated cohort (range: 53 – 86), with an overall median of 70 years. Most patients were white (88%), with smaller proportions being Asian (7%), black (3%), or American Indian (1%). Slightly more women (53%) were included compared to men (47%), and no patients had an ECOG performance status above 1, ensuring that participants were relatively fit at study entry.

The majority of patients (57%) were former smokers, while 30% had never smoked, and 13% were current smokers. The inclusion of former and current smokers aligns with the epidemiology of NSCLC, given the strong association between smoking and lung cancer development. Tumour histology was predominantly adenocarcinoma (97%), with only 2% classified as squamous cell carcinoma and 1% as

"*other*." A small percentage of patients (8%) had brain metastases, which is an important subgroup in advanced NSCLC given its impact on prognosis and treatment.

The disease staging at diagnosis was reflective of an advanced population, with 28.6% of patients presenting at American Joint Committee on Cancer (AJCC) Stage IV, followed by 25.5% at Stage IV-A and 24.5% at Stage IV-B. Notably, all patients had confirmed BRAF V600E mutations, verified primarily through tissue next-generation sequencing (NGS) (72%), polymerase chain reaction (PCR) (26%), or plasma NGS in one case.

Table 3.11: Baseline demographic and clinical characteristics – PHAROS

Variable	**Enco+bini**		
Baseline demographic characteristics	Treatment-naive N=59	Previously treated N=39	Total N=98
Age, years, median (range)	68 (47–83)	71 (53–86)	70 (47–86)
Sex, No. (%)			
Women	33 (56)	19 (49)	52 (53)
Men	26 (44)	20 (51)	46 (47)
Ethnicity, No. (%)			
White	53 (90)	33 (85)	86 (88)
Asian	3 (5)	4 (10)	7 (7)
Black	1 (2)	2 (5)	3 (3)
American Indian	1 (2)	0	1 (1)
Unknown	1 (2)	0	1 (1)
ECOG-PS, No. (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72(73)
Smoking status, No. (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
***BRAF V600E* status, No. (%)**			
V600E	59 (100)	39 (100)	98 (100)
V600D[a]	0	1 (3)	1 (1)
Method of local *BRAF* testing, No. (%)			
PCR	15 (25)	11 (28)	26 (26)
Tissue NGS	44 (75)	27 (69)	71 (72)
Plasma NGS	0	1 (3)	1 (1)
Tumour histology, No. (%)			
Adenocarcinoma	57 (97)	38 (97)	95 (97)
Squamous cell carcinoma	1 (2)	1 (3)	2 (2)
Other	1 (2)	0	1 (1)
Brain metastases, No. (%)			
No	55 (93)	35 (90)	90 (92)

Variable	Enco+bini		
Baseline demographic characteristics	Treatment-naive N=59	Previously treated N=39	Total N=98
Yes	4 (7)	4 (10)	8 (8)
Prior systemic treatment for metastatic disease, No. (%)	**0**	**39 (100)**	**39 (40)**
Immunotherapy	NA	24 (62)[b]	24 (24)[b]
Monotherapy PD-(L)1	NA	12 (31)	12 (12)
Combination PD-(L)1	NA	12 (31)	12 (12)
Chemotherapy	NA	18 (46)	18 (18)
Prior radiotherapy, No. (%)			
No	50 (85)	22 (56)	72 (73)
Yes	9 (15)	17 (44)	26 (27)

Based on Table 11 of the CS[2]
Note: one previously treated patient had both V600E and V600D mutations and was considered as V600E for data analysis purposes.
BRAF = v-Raf murine sarcoma viral oncogene homolog B; CS = company submission; table 3.11 = Eastern Cooperative Oncology Group performance status; NGS = next generation sequencing; PCR = polymerase chain reaction; PD-(L)1 = programmed cell death protein (ligand) 1

EAG comment: The PHAROS trial provides a detailed and well-structured overview of the baseline demographic and clinical characteristics of its enrolled population. This transparency supports the robustness of the data and aids in the interpretation of the efficacy and safety outcomes within the context of the studied population. However, certain limitations in the characteristics raise questions about the trial's generalisability to broader UK patient populations.

The trial population's demographic characteristics, including a median age of 70 years (range: 47–86), align well with the typical age distribution of advanced NSCLC patients. The inclusion of a majority of former smokers (57%) and a significant proportion of current smokers (13%) reflects the smoking-related aetiology of NSCLC and is representative of real-world patient populations. The predominance of adenocarcinoma cases (97%) is consistent with the most common histological subtype of NSCLC and strengthens the relevance of the findings for this subgroup.

The inclusion of advanced-stage patients (predominantly Stage IV) ensures that the trial targets the population most likely to benefit from targeted therapies. However, the small proportion of patients with brain metastases (8%) limits the applicability of the findings to this clinically significant subgroup, which is frequently encountered in advanced NSCLC.

The exclusion of patients with an ECOG performance status above 1 further narrows the generalisability of the trial. While this ensures the trial focuses on a relatively fit population capable of tolerating intensive therapy, it does not represent the broader population of advanced NSCLC patients, many of whom present with poorer performance status due to comorbidities or disease burden.

A notable limitation is the lack of ethnic diversity, with 88% of the trial population being white and only small proportions of Asian (7%) and black (3%) participants. This homogeneity limits the applicability of the findings to ethnically diverse populations, such as those found in England and Wales. Genetic, environmental, and healthcare-related differences among ethnic groups could impact treatment outcomes, and the lack of representation may undercut the trial's external validity in certain regions.

3.2.2.6 Statistical analysis

The analysis populations are defined in Table 3.12

Table 3.12: Definition of analysis populations

Analysis populations	Definition	Reported in submission
Screened	All participants who signed the ICD	Yes
SS	All participants who received at least 1 dose of study treatment	Yes
PK	All participants in the SS who had at least 1 post dose PK blood collection with associated bioanalytical results after the first dose of study treatment	Yes

Based on Table 12 of the CS[2]
Source: PHAROS CSR_DCO 22 September 2022 [Data on file][8]
CS = company submission; CSR = clinical study report; DCO = data cut-off; ICD = informed consent document; PK = pharmacokinetic; SS = safety set

There were clearly defined analysis populations, with the safety set (SS) as the primary analysis group, which included all patients who received at least one dose of study treatment. This ensured that efficacy and safety endpoints are based on treated patients.

Sample size calculations were robust, with the company[2] stating that the treatment-naïve cohort was powered at >95% "*to test the null hypothesis that the ORR was less than or equal to 39% vs the alternative hypothesis that it was greater than 39%"* (target ORR: 65%) and the previously treated cohort powered at 90% "*to test the null hypothesis that the ORR was less than or equal to 20% vs the alternative hypothesis that it was greater than 20%"* (target ORR: 45%), both at a one-sided $\alpha \leq 0.025$.

The single-arm design limits direct comparisons with standard-of-care treatments, and ORR, while a useful endpoint in early-phase trials, is a surrogate measure that does not fully capture long-term clinical outcomes such as OS or quality of life (QoL). These factors reduce the trial's external validity.

The trial also conducted a Bayesian interim analysis for the treatment-naïve cohort after 54 patients (90% of the planned sample size) were enrolled. The analysis set a threshold for the posterior probability, stating in the CS[2] that "*if the posterior probability that the true ORR exceeded 39% was ≥80%, assuming a non-informative Beta (0.5, 0.5) prior, then the data were to be considered for discussions with regulatory authorities*." The posterior probability based on the expected number of participants and the observed responses at the interim analysis is summarized in Table 3.11.

Table 3.13: Posterior probabilities

Enrolled participants	Observed responses	Posterior probability for true ORR >39%
54	24	79.5
54	25	86.4
54	26	91.5
54	27	95.0
54	28	97.2
54	29	98.6

Based on Table 13 of the CS[2]
Source: PHAROS CSR_DCO 22 September 2022 [Data on file][8]
CS = company submission; CSR = clinical study report; DCO = data cut-off; ORR = objective response rate

3.2.2.7 Risk of bias quality assessment

The quality assessment of the PHAROS trial was conducted using the Downs and Black checklist and are provided in Table 3.14, Table 3.15, Table 3.16 and Table 3.17.

Table 3.14: Downs and Black checklist (interventional studies) (1/4)

Study	1. Is the hypothesis/ aim/ objective of the study clearly described?	2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	3. Are the characteristics of the patients included in the study clearly described?	4. Are the intervention (s) of interest clearly described?	5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	6. Are the main findings of the study clearly described?	7. Does the study provide estimates of the random variability in the data for the main outcomes?	8. Have all important adverse events that may be a consequence of the intervention been reported?	9. Have the characteristics of patients lost to follow-up been described?
NCT03915951 [22, 24]	Yes - described in the abstract and introduction sections	Yes - response outcomes, survival, and safety outcomes were reported in the methods section	Yes - inclusion criteria reported	Yes - encorafenib 450 mg QD plus binimetinib 45 mg BID, administered orally in 28-day cycles	Yes	Yes - main findings clearly reported	Yes - range and 95% CI of outcomes reported	Yes - there was a comprehensive attempt to measure AEs	Yes - loss to follow up reported in NCT record

Based on Table 34 of Appendix D[10]

AE = adverse event; BID = twice daily; CI = confidence interval; NCT = National Clinical Trial; QD = once daily

Table 3.15: Downs and Black checklist (interventional studies) (2/4)

Study	10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	14. Was an attempt made to blind study subjects to the intervention they have received?	15. Was an attempt made to blind those measuring the main outcomes of the intervention?	16. If any of the results of the study were based on "data dredging", was this made clear?
NCT03915951 [22, 24]	No - No probability values were reported	Unclear - study does not report the proportion of the source population from which the patients are derived	Unclear - study does not report the proportion of those asked who agreed	Unclear - unclear whether the staff, places and facility where patients were treated was representative of the treatment the majority of patients receive	No – single-arm trial	No – single-arm trial	Yes - no unplanned analyses were reported
Based on Table 35 of Appendix D[10]							

Table 3.16: Downs and Black checklist (interventional studies) (3/4)

Study	17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	18. Were the statistical tests used to assess the main outcomes appropriate?	19. Was compliance with the intervention/s reliable?	20. Were the main outcome measures used accurate (valid and reliable)?	21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	23. Were study subjects randomised to intervention groups?
NCT03915951[22, 24]	Yes - Kaplan-Meier survival analysis	Yes - statistical tests used were appropriate for the data	Unclear - compliance to intervention not reported	Yes - outcome measures are clearly described	N/A – single-arm trial	N/A – single-arm trial	No – single-arm trial
Based on Table 36 of Appendix D[10] N/A = not applicable							

Table 3.17: Downs and Black checklist (interventional studies) (4/4)

Study	24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	26. Were losses of patients to follow-up taken into account?	27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?
NCT03915951 [22, 24]	No – single-arm trial	N/A - not comparative	Yes - number of patients loss to follow up reported in NCT record (participant flow)	Yes - For the primary efficacy end point, the study was designed to test the null hypothesis of ORR ≤ 39% in treatment-naïve patients (n=60, assuming an alternative target rate of 65% and 1-sided a ≤ .025), which was considered not sufficiently clinically meaningful to warrant further investigation in this indication where similar therapies are already available, and ≤20% in previously treated patients (n=37, assuming an alternative target rate of 45% and 1-sided a ≤ .025) with BRAF V600E-mutant metastatic NSCLC

Based on Table 37 of Appendix D[10]
BRAF = v-Raf murine sarcoma viral oncogene homolog B; N/A = not applicable; NCT = National Clinical Trial; NSCLC = non-small-cell lung cancer; ORR = objective response rate

EAG comment: The company in Appendix D[10], determined that the PHAROS trial was well-designed in terms of hypothesis clarity, patient inclusion criteria, and the reporting of outcomes such as response rates, survival, and safety. Statistical methods, including Kaplan-Meier (KM) survival analysis and power calculations, were appropriate for detecting clinically meaningful differences in ORR for both treatment-naïve (ORR >39%) and previously treated cohorts (ORR >20%). Adverse events were comprehensively assessed, and losses to follow-up were reported, ensuring transparency.

However, the single-arm design limits the ability to compare efficacy and safety with standard treatments, and the absence of blinding may introduce bias in subjective assessments. Additionally, compliance with the intervention was not reported, and it is unclear whether the trial setting is representative of real-world clinical practice. Whilst robust within its design limitations, these factors reduce its utility for direct comparisons. The EAG rated the trial of PHAROS as being moderate risk of bias.

3.2.3 Efficacy results of PHAROS

3.2.3.1 Primary endpoint

3.2.3.1.1 Confirmed ORR by IRR

The company reported that for the treatment-naïve patients, "*The ORR was consistent across all DCOs. The ORR was 74.6 (95% CI 61.6–85.0) including 9 (15.3%) CRs and 35 (59.3%) PRs. Ten patients (16.9%) had stable disease.*" [2] Further details can be found in Table 3.18.

Table 3.18: Summary of best overall response - per RECIST v1.1 according to IRR (SS) – treatment-naïve population

Treatment-naïve N=59 n (%)			
Data cut-off	**1 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
Best overall response (based on a confirmed response)†			
CR	9 (15.3)	9 (15.3)	9 (15.3)
PR	35 (59.3)	35 (59.3)	35 (59.3)
Stable disease	10 (16.9)	[redacted]	10 (16.9)
PD	[redacted]	[redacted]	2 (3.4)
NE	[redacted]	[redacted]	3 (5.1)
Number of patients with best overall response non-estimable‡			
No post-baseline assessments due to early death (defined as death prior to 6 weeks after date of first dose)	[redacted]	[redacted]	0
No post-baseline assessments due to other reason	[redacted]	[redacted]	1 (33.3)
Stable disease occurred <6 weeks after the start of treatment and no	[redacted]	[redacted]	2 (66.7)

Treatment-naïve N=59 n (%)			
Data cut-off	**1 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
subsequent tumour assessments			
Objective response rate (confirmed) (ORR: CR+PR)	44 (74.6)	44 (74.6)	44 (74.6)
95% CI¶	61.6, 85.0	61.6, 85.0	61.6, 85.0
Based on Table 14 of the CS [2] Footnote: †Best overall response was based on IRR using RECIST v1.1; ‡The denominator of subcategories is the total number of participants with best overall response=Not estimable (NE) according to RECIST v1.1 per IRR CI = confidence interval; CR = complete response; CS = company submission; IRR = independent radiology review; NE = not estimable; ORR = objective response rate; PD = progressed disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set			

3.2.3.2 Secondary endpoints

The CS only reported secondary outcome results for all DCO dates for treatment-naïve patients, while the results for previously treated and total populations are reported in Appendix N.[25]

3.2.3.2.1 Confirmed ORR by IA

The company reported that for the treatment-naïve patients, "*The ORR based on IA was [redacted]. The ORR by IA at the most recent DCO was [redacted] ([redacted]% [95% CI: [redacted]–[redacted]]) including [redacted] ([redacted]%) CRs and [redacted] ([redacted]%) PRs.*" Further details can be found in Table 3.19.

Table 3.19: Summary of best overall response per RECIST v1.1 according to derived IA (SS) – treatment-naïve population

Treatment-naïve N=59 n (%)			
Data cut date	**01 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
Best overall response (based on confirmed response†)			
CR	[redacted]	[redacted]	2 (3.4)
PR	[redacted]	[redacted]	35 (59.3)
Stable disease	[redacted]	[redacted]	16 (27.1)
PD	[redacted]	[redacted]	4 (6.8)
NE	[redacted]	[redacted]	2 (3.4)
Number of patients with best overall response non-estimable‡			
No post-baseline assessments due to early death (defined as death prior to 6 weeks after date of first dose)	[redacted]	[redacted]	[redacted]
No post-baseline assessments due for other reason	[redacted]	[redacted]	[redacted]

Treatment-naïve N=59 n (%)			
Data cut date	**01 April 2024 (N=59)**	**19 July 2023 (N=59)**	**22 September 2022 (N=59)**
Stable disease occurred <6 weeks after the start of treatment and no subsequent tumour assessments	[redacted]	[redacted]	[redacted]
ORR (confirmed) (CR+PR)	[redacted]	[redacted]	37 (62.7)
95% CI¶	[redacted]	[redacted]	(49.1–75.0)

Based on Table 15 of the CS[2]
†Best overall response is based on derived investigator's assessment using RECIST v1.1
‡The denominator of subcategories is the total number of participants with best overall response = NE according to RECIST v1.1 per derived investigator assessment; Estimated 95% CIs for ORR were obtained using the exact Clopper-Pearson method.
CI = confidence interval; CR = complete response; CS = company submission; IRR = independent radiology review; NE = not estimable; ORR = objective response rate; PD = progressed disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

For the agreement and disagreement between response results based on derived investigator assessment (IA) and independent radiology review (IRR), the company mentioned that "*Total disagreement between IRR-assessed and IA responses and non-responses was* [redacted]*%.*" [2]Further details can be found in Table 3.20.

Table 3.20: Summary of agreement and disagreement between response results based on derived IA and IRR in participants with BRAF V600E mutant NSCLC (SS) – Treatment-naïve population

Treatment-naïve N=59 n (%)			
Data cut-off date	**1 April 2024**	**19 July 2023**	**22 September 2022**
Discrepancy (%)			
IRR response/investigator no response	[redacted]	[redacted]	9 (15.3)
IRR no response/investigator response	[redacted]	[redacted]	2 (3.4)
Total event disagreement rate†	[redacted]	[redacted]	11 (18.6)
Agreement (%)			
IRR response/investigator no response	[redacted]	[redacted]	35 (59.3)
IRR no response/investigator response	[redacted]	[redacted]	13 (22.0)
Total event disagreement rate‡	[redacted]	[redacted]	48 (81.4)

Based on Table 16 of the CS[2]
†The total event disagreement rate measures the proportion of participants for whom there is a discrepancy between the IRR and investigator
‡The total event agreement rate measures the proportion of participants for whom there is a concordance between the IRR and investigator
BRAF = v-Raf murine sarcoma viral oncogene homolog B; CS = company submission; IA = investigator assessment; IRR = independent radiology review; NSCLC = non-small-cell lung cancer; SS = safety set

3.2.3.2.2 Duration of response

The company reported that *"In the treatment-naïve population, the median DOR, according to IRR at the most recent DCO for the [redacted] treatment-naïve responding patients was 40 months (95% CI: 23.1, NE), with [redacted] ([redacted]%) patients having disease progression and [redacted] ([redacted]) death after the initial response (DCO: 01 April 2024). The percentages of responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and [redacted]%, respectively (DCO: 01 April 2024)."*[2] Further details for more DCOs can be found in Table 3.21.

Table 3.21: Duration of response per RECIST v1.1 according to IRR (SS, confirmed responders) – treatment-naïve population

Treatment-naïve			
Data cut-off date	**1 April 2024 (n=[redacted])**	**19 July 2023 (n=44)**	**22 September 2022 (n=44)**
Number of patients with confirmed response, n (%)	[redacted]	44 (100)	44 (100)
Number of events, n (%)	[redacted]	17 (38.6)	12 (27.3)
Progression	[redacted]	16 (36.4)	11 (25.0)
Death due to any use	[redacted]	1 (2.3)	1 (2.3)
Number of censored, n (%)	[redacted]	27 (61.4)	32 (72.7)
Percentiles of duration of response (months) (95% CI)†			
25th	[redacted]	14.0 (4.5, 23.2)	14.0 (4.5, NE)
50th	40.0 (23.1, NE)	40.0 (23.1, NE)	NE (23.1, NE)
75th	[redacted]	NE (40.0, NE)	NE (NE, NE)
Duration of response (months), n (%)			
<3	[redacted]	3 (6.8)	3 (6.8)
≥3	[redacted]	41 (93.2)	41 (93.2)
≥6	[redacted]	33 (75.0)	33 (75.0)
≥9	[redacted]	31 (70.5)	31 (70.5)
≥12	[redacted]	28 (63.6)	26 (59.1)
≥24	[redacted]	13 (29.5)	7 (15.9)

Based on Table 17 of the CS[2]
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
CI = confidence interval; CS = company submission; IRR = independent radiology review; NE = not estimable; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

The company also reported that *"For treatment-naïve patients, the median DOR, based on IA was [redacted] (95% CI: [redacted], [redacted]), with [redacted] of [redacted] ([redacted]%) patients having disease progression after the initial response. The percentages of responding patients with DOR by IRR ≥6 months and ≥12 months were [redacted]% and [redacted]%, respectively (DCO: 01 April 2024)."*[2] Further details for more DCOs can be found in Table 3.22.

Table 3.22: Duration of response per RECIST v1.1 according to derived IA (SS, confirmed responders) – treatment-naïve population

Treatment-naïve			
Data cut-off date	**1 April 2024 (n=[redacted])**	**19 July 2023 (n=[redacted])**	**22 September 2022 (n=[redacted])**
Number of patients with confirmed response, n (%)	[redacted]	[redacted]	[redacted]
Number of events, n (%)	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]
Death due to any cause	[redacted]	[redacted]	[redacted]
Number of censored, n (%)	[redacted]	[redacted]	[redacted]
Percentiles of duration of response (months) (95% CI)†			
25th	[redacted]	[redacted]	[redacted]
50th	[redacted]	[redacted]	[redacted]
75th	[redacted]	[redacted]	[redacted]
Duration of response (months), n (%)			
<3	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]
≥9	[redacted]	[redacted]	[redacted]
≥12	[redacted]	[redacted]	23 (62.2)
≥24	[redacted]	[redacted]	6 (16.2)

Based on Table 18 of the CS[2]
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
CI = confidence interval; CS = company submission; IA = investigator assessment; NE = not estimable; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

3.2.3.2.3 Disease control rate

The company reported that "*DCR by IRR at 24 weeks was 64.4% (95% CI: 50.9, 76.4) and DCR by IA at 24 weeks was [redacted]% (95% CI: [redacted], [redacted]) for the most recent DCO (01 April 2024).*" Further details can be found in Table 3.23.

Table 3.23: Disease control rate per RECIST v1.1 according to IRR (SS) – treatment-naïve population

Treatment-naïve N=59			
Data cut-off date	**1 April 2024**	**19 July 2023**	**22 September 2022**
DCR after 24 weeks (DCR: CR + PR + SD) (95% CI)†	38 (64.4% [95% CI: 50.9,76.4)	[redacted] ([redacted]% [95% CI: [redacted], [redacted]])	38 (64.4% 95% CI [50.9,76.4])

Based on Table 19 of the CS[2]
†Estimated 95% CIs for DCR were obtained using the exact Clopper-Pearson method.

Treatment-naïve N=59			
Data cut-off date	**1 April 2024**	**19 July 2023**	**22 September 2022**
CI = confidence interval; CR = complete response; CS = company submission; DCR = disease control rate; IRR = independent radiology review; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; SS = safety set			

3.2.3.2.4 Time to response

The company stated that *"In the treatment naïve patient group, the median TTR by IRR was 1.86 months (range: 1.1 to 19.1 months) (DCO: 01 April 2024). Almost all objective responses ([redacted] of [redacted]) were reached within [redacted] months from study treatment start (at the first or second tumour assessment after baseline evaluation)."* Further details can be found in Table 3.24.

Table 3.24: Time to response according to IRR (SS, confirmed responders) – treatment-naïve population

Treatment-naïve N=59			
Data cut-off date	**1 April 2024 (n=[redacted])**	**19 July 2023 (n=[redacted])**	**22 September 2022 (n=[redacted])**
Time to response (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	1.86	1.86	1.86
Minimum, maximum	1.1, 19.1	1.1, 19.1	1.1, 19.1
Time to response (months), n (%)			
<2	[redacted]	[redacted]	[redacted]
2 to <4	[redacted]	[redacted]	[redacted]
4 to <6	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]
Based on Table 20 of the CS[2] CS = company submission; IRR = independent radiology review; SD = standard deviation; SS = safety set			

3.2.3.2.5 Progression-free survival

For the treatment-naïve patients, the company reported the median PFS by IA at each DCO as below: *"The median PFS was 30.2 months (95% CI: 15.7, NE). A total of 28 (47.5%) patients had PFS events and [redacted] ([redacted]%) patients were still in follow-up for disease progression at the time of data cut-off. The median duration of follow-up for PFS was 33.3 months (95% CI: 30.4, 41.3) based on the reverse KM method (DCO: 01 April 2024).*

The median PFS was 24.9 months (95% CI: 15.7, 44.0). A total of 27 (45.8%) patients had PFS events and 18 (30.5%) patients were still in follow-up for disease progression at the time of DCO. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse KM method (DCO: 19 July 2023).

The median PFS was not estimable (NE [95% CI: 15.7 months, NE]). PFS data by IRR were immature at the time of the data cutoff, with 21 (35.6%) patients having PFS events and 25 (42.4%) patients still

in follow-up for disease progression. The median duration of follow-up for PFS was 18.2 months (95% CI: 16.4, 22.3) based on the reverse KM method (DCO: 22 September 2022)."

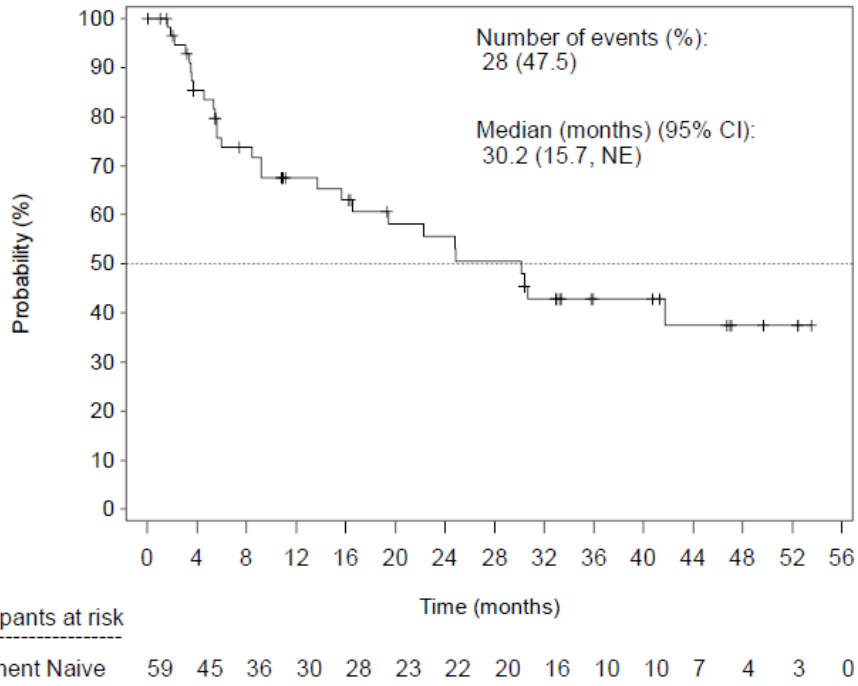
Further details are presented in Table 3.25 and Figure 3.2 below.

Table 3.25: Progression-free survival per RECIST v1.1 according to IRR (SS) – treatment-naïve population

Treatment-naïve (n=59)			
	1 April 2024	**19 July 2023**	**22 September 2022**
Number of PFS events, n (%)	**28 (47.5)**	**27 (45.8)**	**21 (35.6)**
Progression	[redacted]	24 (40.7)	18 (30.5)
Death without progression	[redacted]	3 (5.1)	3 (5.1)
Number of censored, n (%)	[redacted]	**32 (54.2)**	**38 (64.4)**
No adequate baseline assessment	[redacted]	0	0
Start of new anticancer therapy	[redacted]	11 (18.6)	11 (18.6)
Event after missing or inadequate assessments	[redacted]	1 (1.7)	1 (1.7)
Withdrawal of consent	[redacted]	1 (1.7)	1 (1.7)
Lost to follow-up	[redacted]	1 (1.7)	0
No adequate postbaseline tumour assessment	[redacted]	0	0
Ongoing without an event	[redacted]	18 (30.5)	25 (42.4)
Kaplan-Meier estimates of time to event (months), percentiles (95% CI)†			
25th	[redacted]	6.0 (4.6, 16.6)	6.0 (4.6, 19.5)
50th	30.2 (15.7, NE)	24.9 (15.7, NE)	NE (15.7, NE)
75th	[redacted]	44.0 (41.8, NE)	NE (NE, NE)

Based on Table 21 of the CS[2]
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using the Brookmeyer and Crowley method (1982).
CI = confidence interval; CS = company submission; IRR = independent radiology review; NE = not estimable; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

Figure 3.2: Kaplan-Meier plot of PFS in patients per RECIST v1.1 according to IRR (SS; 01 April 2024) – treatment-naïve population



Based on Figure 6 of the CS [2]
CI = confidence interval; CS = company submission; IRR = independent radiology review; NE = not estimable; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

For the treatment-naïve patients, the company reported the median PFS by IA at each DCO as below:[2]

"The median PFS was [redacted] months (95% CI: [redacted], [redacted]). A total of [redacted] ([redacted]%) patients had PFS events and [redacted] ([redacted]%) patients were still in follow-up for disease progression at the time of the data cut-off. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted], [redacted]) based on the reverse KM method (DCO: 01 April 2024).

The median PFS was [redacted] months (95% CI: [redacted]). A total of [redacted] ([redacted]%) patients had PFS events and [redacted] ([redacted]%) patients were still in follow-up for disease progression at the time of the data cut-off. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse KM method (DCO: 19 July 2023).

The median PFS was [redacted] months (95% CI: [redacted]). A total of [redacted] ([redacted]%) patients had PFS events and [redacted] ([redacted]%) patients were still in follow-up for disease progression at the time of the data cutoff. The median duration of follow-up for PFS was [redacted] months (95% CI: [redacted]) based on the reverse Kaplan-Meier method (DCO: 22 September 2022)."

Further details are presented in Table 3.26 and Figure 3.3 below.

Table 3.26: PFS per RECIST v1.1 according to derived IA (SS)

Treatment-naïve (n=59)			
	1 April 2024	**19 July 2023**	**22 September 2022)**
Number of PFS events, n (%)	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]
Death without progression	[redacted]	[redacted]	[redacted]
Number of censored, n (%)	[redacted]	[redacted]	[redacted]
No adequate baseline assessment	[redacted]	[redacted]	[redacted]
Start of new anticancer therapy	[redacted]	[redacted]	[redacted]
Event after missing or inadequate assessments	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
No adequate postbaseline tumour assessment	[redacted]	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of time to event (months), percentiles (95% CI)†			
25th	[redacted]	[redacted]	[redacted]
50th	[redacted]	[redacted]	[redacted]
75th	[redacted]	[redacted]	[redacted]

Based on Table 22 of the CS[2]
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
CI = confidence interval; CS = company submission; IA = investigator assessment; NE = not estimable; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

Figure 3.3: Kaplan-Meier plot of PFS per RECIST v1.1 according to derived IA (SS, 1 April 2024) – treatment-naïve population

Based on Figure 7 of the CS[2]
CI = confidence interval; CS = company submission; IA = investigator assessment; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SS = safety set

3.2.3.2.6 Overall survival

The company reported, *"At the most recent DCO (01 April 2024), the OS rate was [redacted] in the overall population during a median follow-up of [redacted] months. OS data were immature for both treatment-naïve patients and previously treated patients."*[2]

For the treatment-naïve patients, the company reported the median overall survival (OS) at each DCO as below[2]:

"The median OS was NE (95% CI: 31.3, NE). 26 (44.1%) in respect to patient deaths. [redacted] ([redacted]%) patients were censored for OS analysis, with [redacted] /[redacted]%]) patients being alive and still in follow-up for survival. Median duration of follow-up was [redacted] months (DCO: 01 April 2024).

The median OS was NE (95% CI: 26.7, NE). In total, 22 (37.3%) patients had died. 37 (62.7%) patients were censored for OS analysis, with the majority of patients (34 [57.6%]) being alive and still in follow-up for survival (DCO: 19 July 2023).

The median OS was Immature at the time of DCO, with 17 (28.8%) patients who died and the majority of patients ([redacted]/[redacted]%]) alive and still in follow-up for survival (DCO: 22 September 2022)."

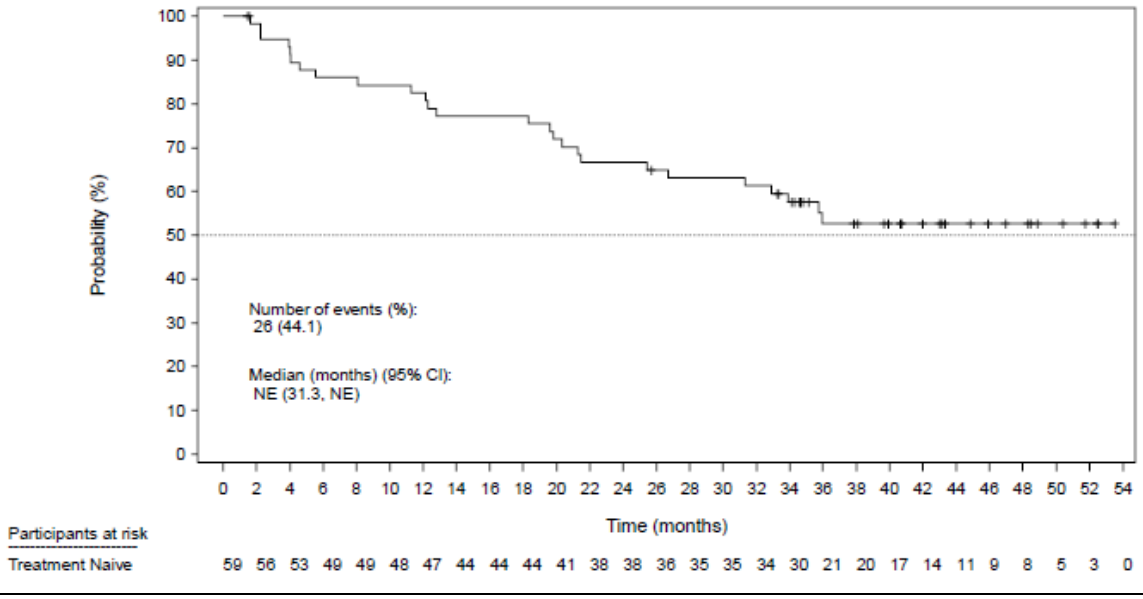
Further details are presented in Table 3.27 and Figure 3.4 below.

Table 3.27: Overall survival (SS) – treatment-naïve population

Treatment-naïve (n=59)			
	1 April 2024	**19 July 2023**	**22 September 2022**
Number of deaths, n (%)	26 (44.1)	22 (37.3)	17 (28.8)
Number of censored, n (%)	[redacted]	37 (62.7)	[redacted]
Withdrawal of consent	[redacted]	1 (1.7)	[redacted]
Lost to follow-up	[redacted]	2 (3.4)	[redacted]
No longer followed for survival†	[redacted]	0	[redacted]
Ongoing and no death	[redacted]	34 (57.6)	[redacted]
Kaplan-Meier Estimates of time to event (months) percentiles (95% CI)‡			
25th	[redacted]	19.6 (8.0, 33.9)	[redacted]
50th	NE (31.3, NE)	NE (26.7, NE)	[redacted]
75th	[redacted]	NE (NE, NE)	[redacted]

Based on Table 23 of the CS[2]
†Alive participants who discontinued from the study for reason different from withdrawal consent and lost to follow-up.
‡Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
CI = confidence interval; CS = company submission; NE = not estimable; SS = safety set

Figure 3.4: Kaplan-Meier plot of OS in patients (SS, 1 April 2024) – treatment-naïve population



Based on Figure 8 of the CS[2]
CI = confidence interval; CS = company submission; NE = not estimable; OS = overall survival; SS = safety set

3.2.3.2.7 Time to treatment discontinuation (Post hoc analysis)

The company stated that "*Time to treatment discontinuation (TTD) was not produced as a CSR output from the study directly, however a post-hoc analysis was conducted, which assessed TTD.*"[2]

The company also reported that *"At the 01 April 2024 DCO of PHAROS, median TTD for enco+bini was reached at approximately* [redacted] *months (95% CI:* [redacted]*)"* [2] Further details are presented in Figure 3.5.

Figure 3.5: Enco+bini TTD – PHAROS

[redacted]

Based on Figure 9 of the CS[2]
CI = confidence interval; CS = company submission; enco+bini = encorafenib plus binimetinib; TTD = time to discontinuation

3.2.4 Efficacy results of IFCT

Detailed results for the IFCT academic study are provided in Appendix N.[25]

3.2.4.1 Primary endpoint

3.2.4.1.1 Confirmed ORR by the IA

The company reported that *"In the intention-to-treat (ITT) set, the ORR was [redacted]% (95% CI: [redacted]–[redacted]%) including [redacted] patients with PR and no patients with CR. [redacted] ([redacted]%) patients had SD and [redacted] ([redacted]%) had progressive disease (PD)."*[2]

3.2.4.2 Secondary endpoints

3.2.4.2.1 Progression-free survival

The company stated, *"Overall, the total number of PFS events by IA was [redacted] ([redacted]%), with a median PFS of [redacted] months."*[2]

3.2.4.2.2 Overall survival

The company explained that *"in the ITT* [intention-to-treat] *set, the number of OS events was [redacted] ([redacted]%). Median OS was [redacted] (95% CI: [redacted], [redacted])".*[2]

3.2.4.2.3 Time to treatment discontinuation (post hoc analysis)

The company reported that, *"The number of TTD events in the ITT set was [redacted], with the median TTD being [redacted] months (95% CI: [redacted], [redacted]."*[2]

3.2.4.2.4 Quality of life (EQ-5D)

The company reported that, *"A total of [redacted] patients were included in the EQ-5D analysis (cohort A patients meeting all the inclusion criteria). In cohort A, [redacted] patients reported at least one EQ-5D complete measurement, with the number of visits per patient ranging from [redacted] to [redacted]."*[2]

The company also added that, *"EQ-5D 5L mean utility at baseline was [redacted], while when considering the complete follow-up period, mean utilities were [redacted], and [redacted] pre- and post-progression, respectively. EQ-5D-3L mean utility at baseline was [redacted], while when considering the complete follow up period, mean utilities were [redacted] and [redacted] pre- and post-progression, respectively.*"[2]

3.2.5 Subgroup analysis

3.2.5.1 PHAROS

3.2.5.1.1 Subgroup analyses of objective response rate

The additional subgroup analyses of ORR by IRR for treatment-naïve, previously treated, and total patient populations were performed to explore the influence of various baseline characteristics (age

group <65 years and ≥65 years, gender, race (Asian and non-Asian), and ECOG-performance status (ECOG-PS) [0 and 1]).[26]

EAG comment: The results of subgroup analyses for the OS outcome of the PHAROS trial were not found in the CS or Appendix E, so the EAG requested that this be provided. The Company noted in their response to clarification questions that "*subgroup analyses were not conducted for the overall survival (OS) outcome and was not planned for in the PHAROS trial*". [5]

3.2.6 Adverse events

3.2.6.1 PHAROS

3.2.6.1.1 Overall summary of adverse events

At the 1 April 2024 DCO in the treatment-naïve patient group (N=59)

[redacted] ([redacted]%) patients received encorafenib and [redacted] ([redacted]%) received binimetinib for >6 to ≤12 months. [redacted] ([redacted]%) patients received encorafenib and [redacted] ([redacted]%) received binimetinib for >12 to ≤24 months. [redacted] patients ([redacted]) received both encorafenib and binimetinib for >24 months.

The median duration of treatment for both encorafenib and binimetinib was [redacted] (range: [redacted] to [redacted]).

An overview of treatment-emergent adverse events (TEAEs) for all DCOs for the treatment-naïve population is provided in Table 3.28.

[redacted] patients had at least [redacted] all-causality TEAE and [redacted] patients had at least [redacted] treatment-related TEAE ([redacted]%). [redacted] of patients ([redacted]%) had maximum Grade 3 or 4 treatment-related TEAEs.

Table 3.28: Summary of AEs in treatment-naïve patients, SS

Category† n (%)	Enco+bini 1 April 2024	Enco+bini 19 January 2023	Enco+bini 22 September 2022
Patients with TEAEs	[redacted]	[redacted]	[redacted]
Patients with treatment-related TEAEs	[redacted]	[redacted]	[redacted]
Patients with maximum grade 3 or 4 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with maximum treatment-related grade 3 or 4 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with grade 5 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with treatment-related grade 5 TEAEs‡	[redacted]	[redacted]	[redacted]
Patients with SAEs	[redacted]	[redacted]	[redacted]
Patients with treatment-related SAEs	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini permanent discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini dose reduction	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to both enco+bini dosing interruption	[redacted]	[redacted]	[redacted]

Category† n (%)	Enco+bini 1 April 2024	Enco+bini 19 January 2023	Enco+bini 22 September 2022
Patients with TEAEs leading to encorafenib discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to binimetinib discontinuation	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to encorafenib dose reduction	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to binimetinib dose reduction	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to encorafenib dose interruption	[redacted]	[redacted]	[redacted]
Patients with TEAEs leading to binimetinib dose interruption	[redacted]	[redacted]	[redacted]

Based on Table 39 of the CS[2]
†Categories are not mutually exclusive. Participants with multiple events in the same category are counted only once in that category.
‡For participants reporting more than one AE, the AE with the maximum grade is considered.
AE = adverse event; CS = company submission; enco+bini = encorafenib plus binimetinib; SAE = serious adverse event; SS = safety set; TEAE = treatment-emergent adverse event

3.2.6.1.2 Incidence and severity of adverse events

Most frequent all-causality TEAEs in the enco+bini arm were nausea ([redacted]%), diarrhoea ([redacted]%), fatigue ([redacted]%), vomiting ([redacted]%), anaemia [redacted]%) and constipation ([redacted]%).

Most frequent treatment-related TEAEs in the enco+bini arm were nausea ([redacted]%), diarrhoea ([redacted]%), fatigue ([redacted]%), vomiting ([redacted]%), vision blurred ([redacted]%) and alanine aminotransferase increased ([redacted]%).

Table 3.29: Treatment-emergent adverse events, by preferred term (SS)

Preferred term	All causality n (%)	Treatment related n (%)
Any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Cough	[redacted]	[redacted]

Preferred term	All causality n (%)	Treatment related n (%)
Asthenia	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Productive cough	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Based on Table 40 and 41 of the CS[2] AE = adverse event; CS = company submission; SS = safety set		

3.2.6.1.3 Permanent treatment discontinuations associated with adverse events

TEAEs associated with permanent discontinuation of both encorafenib and binimetinib were reported in [redacted] ([redacted]%) patients, encorafenib alone in [redacted] ([redacted]%) patients, and binimetinib alone in [redacted] ([redacted]%) patients.

Table 3.30: Treatment-emergent AEs leading to permanent discontinuation of treatment-naive patients by patient in decreasing frequency (SS)

Preferred term	All causality n (%)	Treatment-related n (%)
Enco+bini		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Preferred term	All causality n (%)	Treatment-related n (%)
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Based on Table 42 of the CS[2] AE = adverse event; CS = company submission; enco+bini = encorafenib in combination with binimetinib; SS = safety set		

3.2.6.1.4 Dose reductions associated with adverse events

TEAEs leading to a dose reduction of both enco+bini were reported in [redacted] ([redacted]%) patients, encorafenib alone in [redacted] ([redacted]%) patients, and binimetinib alone in [redacted] ([redacted]%) patients.

Table 3.31: Treatment-emergent AEs requiring dose reduction

Preferred term	All causality n (%)	Treatment related n (%)
Enco+bini		
Any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

Preferred term	All causality n (%)	Treatment related n (%)
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Based on Table 43 of the CS[2] AE = adverse event; CS = company submission; enco+bini = encorafenib in combination with binimetinib; SS = safety set		

3.2.6.1.5 Dosing interruptions associated with adverse events

All causality TEAEs associated with dose interruptions of both enco+bini were reported in [redacted] ([redacted]%) patients, encorafenib alone in [redacted] ([redacted]%) patients, and binimetinib alone in [redacted] ([redacted]%) patients.

Treatment related TEAEs associated with dose interruptions were not reported.

Table 3.32 Treatment-emergent AEs requiring dose interruption

Preferred term	All causality n (%)	Treatment related n (%)
Enco+bini		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Encorafenib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

Preferred term	All causality n (%)	Treatment related n (%)
Vomiting	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Binimetinib		
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

Based on Table 44 of the CS[2]

AE = adverse event; CS = company submission; enco+bini = encorafenib in combination with binimetinib; NR= not reported

3.2.6.1.6 Deaths

A total of [redacted] %) patients died during the study, and [redacted] (%) patients died while on-treatment (≤30 days after last dose of study treatment). [redacted] (%) patients died during the on-treatment period due to disease progression. [redacted] %) patient died during the on-treatment period due to AEs.

Table 3.33: Deaths by primary reason – treatment-naïve population (SS)

Preferred term	1 April 2024	19 January 2023	22 September 2022
All deaths	[redacted]	[redacted]	17 (28.8)
Disease progression	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Death ≤30 days after last dose of study treatment	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death >30 days after last dose of study treatment	[redacted]	[redacted]	[redacted]

Based on Table 45 of the CS[2]

CS = company submission; SS = safety set

3.2.6.1.7 SAEs

At the 19 January 2023 DCO in the treatment-naïve population, [redacted] ([redacted]%) patients had serious treatment-emergent AEs.

Data for SAEs for the 1 April 2024 DCO in the treatment-naïve population were not reported.

Table 3.34: Serious treatment-emergent AEs– treatment-naïve population (all causality, SS)

Preferred term	1 April 2024	19 January 2023	22 September 2022
Any SAE	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Neoplasm progression	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]	[redacted]
Haemothorax	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]

Based on Table 12 of Appendix F.[27]
AE = adverse event; CS = company submission; SAE = serious adverse event; SS = safety set

3.2.6.2 IFCT

3.2.6.2.1 Adverse events

[redacted] patients had at least [redacted] all-causality TEAE and most patients had at least [redacted] treatment-related TEAE ([redacted]%). An overview of AEs for all-causality adverse events, and treatment-related adverse events are outlined in Table 3.35.

Table 3.35: Treatment-emergent adverse events (any grade, SS)

Preferred term	All causality n (%)	Treatment related n (%)
Any adverse event	[redacted]	[redacted]
Serious adverse event	[redacted]	[redacted]
Treatment withdrawn	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]

Preferred term	All causality n (%)	Treatment related n (%)
Investigations	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Based on Table 15 and 16 of Appendix F[27] CS = company submission; SS = safety set		

3.2.6.2.2 Observance

In the safety set (Cohort A), [redacted] ([redacted]%) patients received enco+bini each for at least six months.

The average treatment duration was [redacted] months for encorafenib and [redacted] months for binimetinib.

Dose reductions occurred in [redacted] ([redacted]%) patients taking encorafenib and [redacted] ([redacted]%) patients taking binimetinib. Treatment interruptions affected [redacted] ([redacted]%) patients on encorafenib and [redacted] ([redacted]%) patients on binimetinib.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Indirect treatment comparison was conducted by the company because there were no direct comparative data of enco+bini versus dabra+tram. The included studies in the ITC were identified via an SLR. The company stated that a feasibility assessment was conducted to explore whether there were any comparator studies that were suitable for the comparison with enco+bini in an indirect comparison for the treatment of *BRAF* V600 MT advanced NSCLC in first- and second-line settings, and to assess the feasibility of analyses for each of the key outcomes of interest.[2]The feasibility assessment focused on the following outcomes:

- ORR (by IRR, by IA)
- DOR (by IRR, by IA)
- DCR (by IRR and IA)
- PFS (by IRR and IA)

- OS
- AEs, including but not limited to: any TEAE, treatment-related TEAE, Grade 3, 4, or 5 TEAE, serious adverse event (SAE), treatment-related SAE, discontinuation due to AEs.[2]

The company stated that the feasibility assessment assessed the comparability of included studies relating to patient characteristics with a focus on confounding factors. A list of relevant confounding factors was identified in an SLR. The list of confounding factors considered in this feasibility assessment were:[2]

- Age
- Gender
- Race
- Smoking history
- ECOG-PS
- Number of previous treatments received (not relevant for analyses in first-line)
- Concomitant mutation in the P13K pathway
- Presence of metastases in the thoracic cavity
- Presence of brain metastases
- Previous treatment with immunotherapy (not relevant for analyses in first-line)
- PD-L1 ≥1% expression
- Histology type
- Presence of liver metastases
- Presence of M1a metastases

The company stated that the above list of confounding factors was validated by clinical experts at the June 2024 UK advisory board and further validated by one clinical expert at the November 2024 virtual consultancy meeting.[2]

The company stated that the NCT01336634-cohort study (which assessed the combination treatment of dabra+tram) was eligible for inclusion in the ITC analysis.[2] Table 3.36 presents the key features from the PHAROS enco+bini study and NCT01336634 dabra+tram study.

Table 3.36: Key cohort features in the PHAROS and NCT01336634

Cohort	Description
PHAROS	
Treatment-naïve patients	Patients who had received no prior systemic therapy for advanced/metastatic disease
Previously treated participants	Patients who had received either: First-line platinum-based chemotherapy First-line treatment with an anti-PD-1/PD-L1 inhibitor given alone or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy
NCT01336634	
Cohort A – dabrafenib monotherapy population (pre-treated)	Prior to enrolment, this cohort was required to have relapsed or progressed on at least one platinum-based chemotherapy regimen for metastatic disease (i.e., dabrafenib was no less

Cohort	Description
	than second-line treatment for metastatic disease) Additional lines of prior anti-cancer therapy were allowed (including chemotherapy, radiation therapy, immunotherapy, biological therapy, or major surgery) Patients received dabrafenib as a single agent at the recommended dose of 150 mg BID A two-stage design with a planned sample size of 40 patients was initially used for Cohort A
Cohort B – dabrafenib plus trametinib second-line population (pre-treated)	Prior to enrolment, this cohort was required to have relapsed or progressed on at least one platinum-based chemotherapy for metastatic disease, but cannot have received more than three prior systemic anti-cancer therapies (i.e. dabrafenib plus trametinib were second, third-, or fourth-line treatment for metastatic disease) Patients received the recommended dose of both drugs (dabrafenib 150 mg BID and trametinib 2 mg QD)
Cohort C – dabrafenib plus trametinib treatment-naïve population (treatment-naïve)	This cohort did not receive prior systemic anti-cancer therapies for metastatic disease (i.e. dabrafenib plus trametinib was first-line treatment for metastatic disease) Patients received the recommended dose of both drugs (dabrafenib 150 mg BID and trametinib 2 mg QD)
Based on Table 24 of CS[2] BID = twice daily; CS = company submission; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death protein ligand 1; QD = once daily	

The company further stated that based on the feasibility assessment for an ITC comparing PHAROS with Planchard 2017, matching-adjusted indirect comparison (MAIC) was feasible in first-line therapy.[2]

Table 3.37 presents a comparison of key inclusion and exclusion criteria. Inclusion and exclusion criteria were similar between PHAROS and BRF113928. The main difference in the eligibility criteria between both trials was that patients with an ECOG-PS of 2 were eligible for inclusion in NCT01336634- Cohort C but not in PHAROS.[2]

Table 3.37: Key inclusion and exclusion criteria for PHAROS and NCT01336634/113928 – Cohort C

PHAROS	NCT01336634/113928- Cohort C-first-line (Planchard 2017)
Inclusion criteria	
Adult patients (age 18 years and older) with histologically confirmed stage IV Treatment-naïve patients Measurable disease on the basis of RECIST 1.1 ECOG-PS of 0 or 1	Adults (≥18 years) with metastatic BRAF V600E mutant NSCLC. No previous systemic treatment for metastatic disease Measurable disease on the basis of RECIST 1.1 ECOG-PS <=2

Presence of a BRAF V600E mutation in lung cancer tissue as determined by a local laboratory assay	
Exclusion criteria	
Patients with symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases are not eligible Note: Patients with previously treated or not treated brain metastases may participate provided they are stable and any neurologic symptoms must have returned to baseline at least 28 days before the first dose of study treatment. Patients must have no evidence of new or enlarging brain metastases or CNS oedema	Brain metastases were not permitted unless they were asymptomatic, untreated, and measured less than 1 cm, or, if treated, were clinically and radiographically stable three weeks after local therapy
Based on Table 25 of the CS[2] BRAF = v-Raf murine sarcoma viral oncogene homolog B; CNS = central nervous system; CS = company submission; ECOG-PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small-cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumours	

The company stated that indirect comparisons were possible in first-line therapy. However, no indirect comparison was possible in second-line therapy between enco+bini and dabra+tram on the basis of the most recent individual patient data (IPD) from PHAROS (DCO April 2024) and published data from NCT01336634/113928-Cohort C.[2] The ITC used more mature data of time-to-event outcomes from Planchard 2021 as longer-term follow-up data were included in Planchard 2021.[2]

Because both studies are single-arm studies, an unanchored MAIC was used as the preferred approach.[2] Pseudo-IPD data for time-to-event outcomes were recreated from published KM curves for NCT01336634/113928-Cohort C by using the Guyot algorithm.[2]

3.3.1 Populations

The data of ITC were based on 59 patients from the PHAROS treatment-naïve cohort and 36 patients from the NCT01336634/113928 Cohort C.[2]

3.3.2 Adjustment factors

The company stated that based on the availability of data in the NCT01336634/113928 Cohort C trial, it was only feasible to adjust for the following list of variables in the analysis:[2]

- ECOG-PS (used as proportion of patients with ECOG 0)
- Smoking status (used as proportion of patients who never smoked)
- Age
- Gender
- Race (used as proportion of white patients)
- Histology (used as proportion of patients with adenocarcinoma)
- Presence of brain metastases
- Line of treatment (for second-line analysis only).

The company further made the following statement:

- '*A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis. considered this list of confounding factors appropriate for patients with BRAF V600E MT advanced NSCLC.* '[2]

3.3.3 Outcomes

Table 3.29 presents the outcomes for the ITC. Definitions of outcomes were generally consistent between the two trials.[2]

Table 3.38: Outcomes definitions

Outcomes	PHAROS	NCT01336634/113928
OS	Time from first dose of study treatment to death	The time from first dose of study drug to death from any cause
PFS	Time from first dose of study drug to earliest instance of disease progression or death	The interval between the first dose of study drug and the earliest date of disease progression or death from any cause
ORR	Proportion of patients achieving a confirmed best overall response (CR or PR) according to RECIST v1.1 criteria	Percentage of patients who achieved a confirmed CR or PR per RECIST v1.1
Grade 3-4 AE	Patients with a maximum Grade AE of 3 or 4	Patients with a maximum Grade AE of 3 or 4
SAE	Patients experiencing at least one SAE	Patients experiencing at least one SAE
Permanent discontinuation due to AE	Patients who discontinue both enco+bini because of AE	Patients who discontinue dabra+tram because of AE

Based on Table 26 of the CS[2]
AE = adverse event; CR = complete response; CS = company submission; dabra+tram = dabrafenib with trametinib; enco+bini = encorafenib with binimetinib; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event

3.3.4 Data

The company stated that all data used for the PHAROS trial were IPD from the DCO April 2024. All data used for NCT01336634 were extracted from the Planchard publications.[2] For the NCT01336634 trial, pseudo patient level data were recreated for the OS and PFS outcomes by using the algorithm developed by Guyot et al.[2] The patient level data of the NCT01336634 trial recreated by using the algorithm were plotted against the digitised curves for validation.[2] The summary statistics were calculated and compared to the published statistics.[2] The data which were derived from the supportive study (IFCT) were used together with data from the pivotal PHAROS study to conduct the pooled MAIC analysis.[2] Table 3.39 presents an overview of the data used in the comparison between PHAROS and NCT01336634-C in the first-line setting.

Table 3.39: Data for analysis

	PHAROS – Cohort 1 (N=59)	NCT01336634 – Cohort C (N=36)
Efficacy outcomes		
OS	Median follow-up: time [redacted] 26 events observed (44.1%) Median OS: Not reached	Median follow-up time: 16.4 months 27 events observed (75.0%) median OS: 17.3 months
PFS (IRR)	Median follow-up time: 33.3 months 28 events observed (47.5%) Median PFS: 30.2 months	Median follow-up time 9.3 months 22 events observed (61.1%) Median PFS 14.6 months
ORR (IRR)	44 (74.6%)	23 (63.9%)
Safety outcomes		
Grade 3-4 AE	[redacted]	25 (69.4%)
SAE	[redacted]	24 (66.7%)
Permanent dis-continuation due to AE	[redacted]	8 (22.2%)

Based on Table 27 of the CS[2]
Source: Enco+bini Global Value Dossier
AE = adverse event; CS = company submission; enco+bini = encorafenib with binimetinib; IRR = independent radiological review; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Matching and adjustment of populations characteristics

The characteristics of the two populations for the comparison between PHAROS and NCT01336634-C (first-line setting) before and after weighting are presented in Table 3.40.

Table 3.40: Population adjustment in 1L

Variable	Original data		Matched data for PHAROS 1L	
	PHAROS first-line (N=59)	NCT01336634-C (N=36)	Matched on all factors (ESS=44)	Matched on ECOG and smoking status (ESS=58)
Age (years)	68	67	67	66
Gender, % Male	44	39	39	45
ECOG, % ECOG=0	32	36	36	36
Smoking status, % Never smoked	31	28	28	28
Race, % White	90	83	83	90
Histology, % Adenocarcinoma	97	89	89	97
Brain metastases, % Yes	7	6	6	7

Based on Table 28 of the CS[2]
1L = first-line; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ESS = estimated sample size

The company made the following statements:

- *'Before matching, imbalances were observed between the two studies primarily on gender, race, and histology, as well as, to a lesser extent, on ECOG and smoking status. At the June 2024 UK Advisory Board, clinical experts commented on the differences in histology between trials but considered this to be a factor of greater patient numbers in PHAROS resulting in smaller proportions. One clinical expert noted that the trial population in PHAROS may be closer aligned with UK clinical practice when considering race. In general, clinical experts considered the trial populations to be similar and relatively balanced between the PHAROS first-line population and cohort C of the NCT01336634 study.*
- *After matching on all adjustment factors, the characteristics in the weighted PHAROS population were fully aligned with those in Cohort C of the NCT01336634 study. This resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 patients instead of the original 59. This was deemed acceptable by health economic experts at the June 2024 UK advisory board.*
- *In this analysis, the rescaled weights ranged from 0.48 to 3.32, with a median of 0.81. The median weight was relatively close to 1, there were no weights equal or close to zero (meaning that all observations contributed to the analyses), and there were no very large weights, which would have indicated that some individual observations had a disproportionate impact on the entire matched population. The matching was therefore deemed satisfactory*.'[2]

3.4.2 Efficacy results

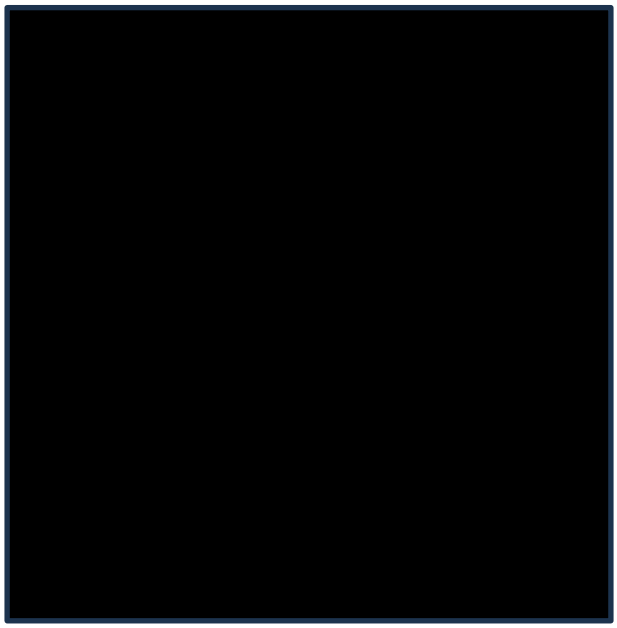
Two analyses were performed: one using the full list of adjustment variables (base-case) and another restricted to ECOG-PS and smoking status (sensitivity analysis).[2]

3.4.2.1 Overall survival

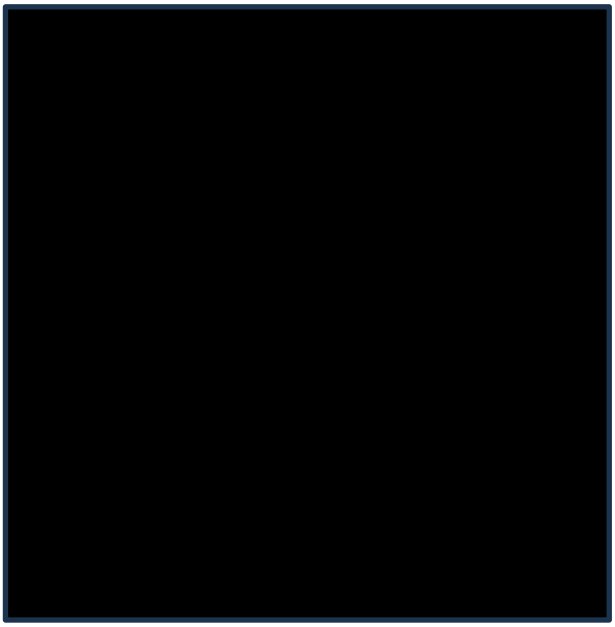
The OS data in PHAROS and IFCT before and after weighting are presented in Figure 3.6. Figure 3.6 A shows the impact of the adjustment on all factors on the difference between pooled PHAROS and IFCT data, and NCT01336634. There was an improvement in OS with enco+bini compared with dabra+tram (log-rank p-value of [redacted]) based on unweighted data. This improvement in OS was increased by the weighting of the pooled data of PHAROS and IFCT trials (log-rank p-value p=[redacted]).[2] Figure 3.6 B shows that the impact of the adjustment on the two factors of ECOG and smoking status was minimal.

Figure 3.6: Kaplan-Meier curves for OS in first-line, pooled PHAROS and IFCT

A: Impact of adjustment on all factors



B: Impact of adjustment on ECOG and smoking status



Based on Figure 12 of the CS[2]
ECOG = Eastern Cooperative Oncology Group; OS = overall survival

The results of the naïve comparison and the results of the MAICs by using the two sets of weights are presented in Table 3.41. After adjustment on all factors, enco+bini was associated with a statistically [redacted] reduction in death by [redacted]% compared with dabra+tram (adjusted [redacted]. The population adjustment based on ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison.[2]

Table 3.41: Results in first-line – OS

OS – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]
MAIC – weighted results		
Mean HR, 95% CI, p-value	[redacted]	[redacted]

Based on Table 36 of the CS[2]
CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; HR = hazard ratio; MAIC = Matching-adjusted indirect comparison; OS = overall survival

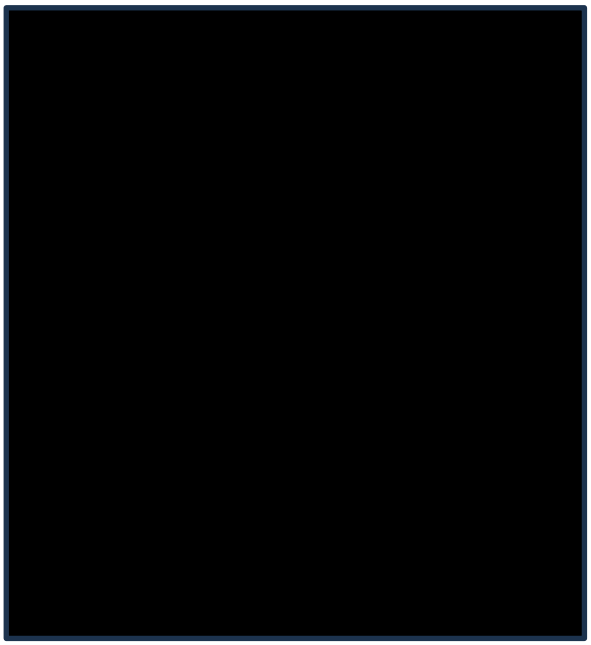
3.4.2.2 Progression free survival

The PFS data in PHAROS and IFCT before and after weighting are presented in Figure 3.7. Figure 3.7 A shows the impact of adjustment based on all factors on the difference between pooled PHAROS

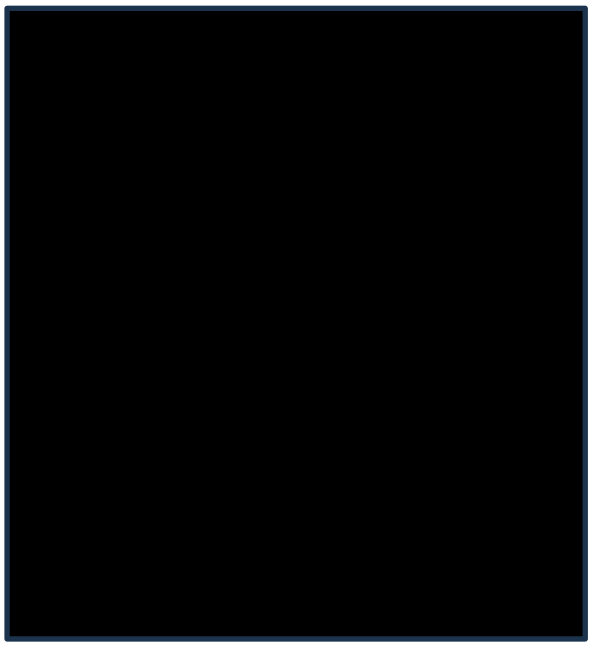
and IFCT data, and NCT01336634. Figure 3.7 B shows that the impact of adjustment based on ECOG and smoking status was minimal.[2]

Figure 3.7: Kaplan-Meier curves for PFS in first-line, pooled PHAROS and IFCT

A: Impact of adjustment on all factors



B: Impact of adjustment on ECOG and smoking status



Based on Figure 13 of the CS[2]

CS = company submission; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival

The results of the naïve comparison and the results of the MAICs by using the two sets of weights are presented in Table 3.42. After adjustment on all factors, enco+bini was associated with a numerical reduction in disease progression of [redacted]% when compared with dabra+tram (adjusted HR=[redacted]; 95%, CI: [redacted]).The adjustment based on ECOG and smoking status did not greatly impact the results in PFS compared with the unadjusted comparison.[2]

Table 3.42: Results in first-line – PFS results, pooled PHAROS and IFCT

PFS (IRR) – enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and smoking status
Unadjusted comparison – unweighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]
MAIC – weighted results		
Mean HR (95% CI), p-value	[redacted]	[redacted]

Based on Table 37 of the CS[2]
CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; HR = hazard ratio; IRR = independent radiology review; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

3.4.3 Objective response rate

The results of the naïve comparison between enco+bini and dabra+tram on ORR, and the results of the MAICs by using the two sets of weights are presented in Table 3.43. After adjustment on all factors, enco+bini was favoured for ORR compared with dabra+tram (adjusted odds ratio (OR)=1.81; 95%CI: 0.71, 4.59, p=0.21). The adjustment based on ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison.[2]

Table 3.43: Results in first-line – ORR

ORR (IRR) – enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	1.66 (0.68, 4.07), p=0.27	[redacted]
MAIC – weighted results		
Mean OR 95% CI, p-value	1.81 (0.71, 4.59), p=0.21	[redacted]

Based on Table 32 of the CS[2]
CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; IRR = independent radiology review; MAIC = matching-adjusted indirect comparison; OR = odds ratio; ORR = objective response rate; OS = overall survival

3.4.4 Safety results

3.4.4.1 Grade 3-4 adverse events

The results of naïve comparison between enco+bini and dabra+tram for the proportion of patients experiencing AE of a maximum Grade of 3–4, and of the MAICs using both sets of weights, are presented in Table 3.44. After adjusting for all factors, there was no statistically significant result in proportions of patients experiencing Grade 3–4 AEs between enco+bini and dabra+tram. The adjustment based on ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison.[2]

Table 3.44: Results in first-line – Grade 3–4 AEs

Grade 3–4 AE† - enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	1.00 (0.41, 2.47) p=0.996	[redacted]
MAIC – weighted results		
Mean OR (95% CI), p-value	0.93 (0.37, 2.32) p=0.87	[redacted]

Based on Table of 29 of the CS[2]
†Maximum TEAE grade 3 or 4
AE = adverse event; CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; MAIC = matching-adjusted indirect comparison; OR = odds ratio; TEAE = treatment-emergent adverse event

3.4.4.2 Serious adverse events

The results of the naïve comparison between enco+bini and dabra+tram for the proportion of patients experiencing serious adverse events (SAE), and of the MAICs using both sets of weights, are presented in Table 3.45. After adjustment of all factors, enco+bini was found to be superior to dabra+tram for SAEs (adjusted OR=0.35; 95% CI:0.14, 0.85; p=0.02).

Table 3.45: Results in first-line – SAE

SAE –enco+bini vs dabra+tram	Using all adjustment factors	Using only ECOG and smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	0.45 (0.19, 1.07) p=0.07	[redacted]
MAIC – weighted results		
Mean OR (95% CI), p-value	0.35 (0.14, 0.85) p=0.02	[redacted]
Based on Table 30 of the CS[2] CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; OR = odds ratio; SAE = serious adverse event		

3.4.4.3 Discontinuation due to adverse events

The results of the naïve comparison between enco+bini and dabra+tram, as well as the MAICs, for the proportion of patients discontinuing treatment because of AE are presented in Table 3.46. After adjustment on all factors, there was no statistically significant result in proportions of patients discontinuing treatment because of AE between enco+bini and dabra+tram.[2]

Table 3.46: Results in first-line – Discontinuation due to AE

Discontinuation due to AE - enco+bini vs dabra+tram	Using all adjustment factors	Using only ECOG and smoking status
Unadjusted comparison – unweighted results		
Mean OR (95% CI), p-value	0.71 (0.25, 2.02) p=0.53	[redacted]
MAIC - weighted results		
Mean OR (95% CI), p-value	0. 71 (0.24, 2.06) p=0.53	[redacted]
Based on Table 31 of the CS[2] AE = adverse event; CI = confidence interval; CS = company submission; dabra+tram = dabrafenib with trametinib; ECOG = Eastern Cooperative Oncology Group; enco+bini = encorafenib with binimetinib; MAIC = matching-adjusted indirect comparison; OR = odds ratio		

EAG comment:

- The ITC analysis was based on the data from two trials (PHAROS treatment-naïve cohort and NCT01336634/113928 Cohort C). The base-case analyses were conducted by adjusting for a full list of eight prognostic factors. These prognostic factors included ECOG performance status (PS), smoking status, age, gender, race (used as proportion of white patients), histology (used as proportion of patients with adenocarcinoma), presence of brain metastases and line of treatment (for

second-line analysis only). The sensitivity analyses were conducted by adjusting for only two prognostic factors (ECOG and smoking status).

- The company stated that matching on the basis of all adjustment factors resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 patients rather than the original 59 for PHAROS (first-line). The EAG considers that the effective sample size for PHAROS (first-line) after matching was relatively small. However, the EAG also acknowledged that matching based on all adjustment factors would result in a reduction in the effective sample size.
- The EAG considers that there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to the lack of availability of these variables. It should be noted that the prognostic variables of concomitant mutation in the P13K pathway, presence of metastases in the thoracic cavity, previous treatment with immunotherapy (not relevant for analyses in first-line), PD-L1 ≥1% expression, presence of liver metastases, and presence of M1a metastases were not adjusted for in the MAIC analyses due to the lack of availability of these variables in the data. Therefore, the lack of adjustment for these important prognostic variables in the MAIC analysis may have compromised the validity of results of MAIC analysis.
- The EAG noted that in Appendix D the company stated: *"STC* [simulated treatment comparison] *is not recommended for the analysis of non-linear or time-to-event outcomes."* However, no reasoning or references are provided. The EAG asked the company to provide supporting references and reasoning for this statement. The EAG also asked the company to conduct an STC on the basis that it is listed as a method of population adjustment alongside MAIC in NICE TSD 18. In responding to the EAG's request, the company stated that the sample size of the population (n=59) from the PHAROS trial was considered too small to be able to robustly fit predictive models predicting each outcome according to the seven adjustment factors identified as relevant. The EAG considers that given that fitting a robust model is important for the STC approach, the STC would be not an optimal approach for the ITC of this project due to the small sample size of the population of the PHAROS trial.
- The EAG found that the study by Fan 2022 (NCT04452877) was included in the SLR, but this study was excluded from the ITC. However, it appears that this study includes a relevant population, treatment and line of therapy. The EAG asked the company to explain why this study was excluded. The EAG also asked the company to include this study in an ITC if it provides relevant data. In responding to the EAG's request, the company made the following statement:[5] *"Fan 2022 (NCT04452877) is an interventional study to assess safety and efficacy of dabra+tram in a Chinese population with BRAF V600E-mutation positive metastatic NSCLC, in all lines (i.e. first-line and second-line plus). This publication is a conference abstract presenting the preliminary data of the study. Given Fan 2022 was conducted exclusively in a Chinese population, it is not considered suitable for an ITC given the small proportion of Asian patients treated at first-line in PHAROS (5%). In addition, only the overall response rate (ORR) is presented, and other efficacy outcomes of interest are not reached due to the short follow-up period. In a very recent publication (Fan et al. 2024 (11)), the medians were still not reached (median of follow-up 5 months). Kaplan-Meier (KM) curves of OS and progression-free survival (PFS) are presented but only for the full population (first-line and second-line plus combined). Outcomes are not presented for first-line and second-line separately, which is not aligned with the base case population of this appraisal (treatment-naïve patients only)."* The EAG considers that given the lack of relevant outcomes for first-line and second-line separately for the study by Fan 2022, excluding this study from the ITC analysis appears to be appropriate.

Therefore, in conclusion, the lack of inclusion of some important prognostic factors in the MAIC is a key issue.

3.5 Additional work

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS, response to clarification and Appendices D and P provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the treatment of patients with BRAF V600 MT advanced NSCLC.[2, 5, 10, 11] Searches were conducted in October 2021, and updated in May 2023, July 2023 and May 2024. Searches were transparent, well-documented and reproducible, and comprehensive strategies were used. An extensive range of bibliographic databases, conference proceedings, HTA and guidelines websites and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although it would have been preferable not to have limited to English language studies only.

The study selection criteria for participants, interventions, comparators and outcomes in the SLR of clinical effectiveness generally encompassed those specified by the NICE final scope. The data extraction process was satisfactory and in line with recommended good practice in SLRs. The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The number of studies retrieved, screened and included was clear based on the PRISMA flow chart.

One unique RCT was identified as being relevant to the SLR: one RCT (PHAROS) provided the main source of evidence. The PHAROS trial was an international, Phase 2, open-label, multicentre study that assessed the efficacy and safety of encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer. The EAG rated the PHAROS trial being at moderate risk of bias.

At DCO (1 April 2024) for the PHAROS trial, for the treatment-naïve patients, ORR assessed by IRR was 44 (95% CI 61.6–85.0) including 9 (15.3%) complete responses (CRs) and 35 (59.3%) partial responses (PRs). Ten patients (16.9%) had stable disease. For the treatment-naïve patients, the median PFS was 30.2 months (95% CI: 15.7, NE). A total of 28 (47.5%) patients had PFS events and [redacted] ([redacted]%) patients were still at follow-up for disease progression at the time of data cut-off. The median duration of follow-up for PFS was 33.3 months (95% CI: 30.4, 41.3). For the treatment-naïve patients, median OS was NE (95% CI: 31.3, NE). There were [redacted] ([redacted]%) patient deaths. Median duration of follow-up for OS was [redacted] months.

The ITC analysis was based on the data from two trials (PHAROS treatment-naïve cohort and NCT01336634/113928 Cohort C). The base case analyses were conducted by adjusting for a full list of eight prognostic factors. These prognostic factors included ECOG performance status, smoking status, age, gender, race (used as proportion of white patients), histology (used as proportion of patients with adenocarcinoma), presence of brain metastases and line of treatment (for second-line analysis only). The sensitivity analyses were conducted by adjusting for only two prognostic factors (ECOG and smoking status).

The company stated that matching on the basis of all adjustment factors resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 patients rather than the original

59 for PHAROS (first-line). The EAG considers that the effective sample size for PHAROS (first-line) after matching was relatively small. However, the EAG also acknowledged that matching based on all adjustment factors would result in a reduction in the effective sample size.

However, there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to the lack of availability of these variables. It should be noted that the prognostic variables of concomitant mutation in the P13K pathway, presence of metastases in the thoracic cavity, previous treatment with immunotherapy (not relevant for analyses in first-line), PD-L1 ≥1% expression, presence of liver metastases, and presence of M1a metastases were not adjusted for in the MAIC analyses due to the lack of availability of these variables in the data. Therefore, the lack of adjustment for these important prognostic variables in the MAIC analysis may have compromised the validity of results of MAIC analysis

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, health-related quality of life (HRQoL) and resource use identification presented in the CS.[2] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

The CS, Appendix G, Appendix I, Appendix P and the company's response to clarification provide details of an SLR conducted to identify relevant studies on cost effectiveness and cost/health care resource use for the treatment of patients with BRAF-mutated advanced NSCLC.[2, 5, 11, 28, 29] The searches were conducted in June 2023, and updated in May 2024 and January 2025. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations/resource use identification

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974 – Wk 22 2023 2023 – 24/5/24 2024-7/1/25	15/6/23 28/5/24 8/1/25
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)		1946 – 5/6/23 2023 – 24/5/24 2024-6/1/25	
International HTA Database		Incep – 4th Q 2016	
NHS EED		Incep – 1st Q 2016	
EconLit		1886 – 25/5/23 2023 – 16/5/24 1886-2/1/25	
Conferences			
• ASCO • ESMO • IASLC WCLC • AACR • ISPOR	Embase/ Internet	2018-2024 2018-2023 2018-2023 2018-2024 2019-2023	7/6/24 8/1/25

Resource	Host/Source	Date Ranges	Date searched
HTA Agencies			
• NICE • CDA-AMC • PBAC/TGA • SMC • HAS • IQWiG • G-BA • PMDA • ICER	Internet	All	7/6/24 8/1/25
Additional resources			
• EQ-5D • INAHTA Database • Google Scholar • NIHR • CRD • CEA Registry • RePEc	Internet	All	27/6/24 8/1/25

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDA-AMC = Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health); CEA Registry = Cost-Effectiveness Analysis Registry; CRD = Centre for Reviews and Dissemination; CS = company submission; ESMO = European Society of Medical Oncology; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; IASLC WCLC = International Association for the Study of Lung Cancer World Congress on Lung Cancer; ICER = Institute for Clinical and Economic Review; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = German Institute for Quality and Efficiency in Health Care; ISPOR = International Society of Pharmacoeconomics and Outcomes Research (European and International meetings); PBAC/TGA = Pharmaceutical Benefits Advisory Committee/Therapeutic Goods Administration; NIHR = National Institute for Health Research; PBAC = Pharmaceutical Benefits Advisory Committee; PMDA = Pharmaceuticals and Medical Devices Agency; RePEc = EconPapers within Research Papers in Economics; TGA = Therapeutic Goods Administration

EAG comment:

- Searches were undertaken in June 2023 and updated in May 2024 and January 2025 to identify evidence on cost effectiveness and cost/health care resource use for the treatment of patients with BRAF V600 mutated advanced NSCLC. The CS, Appendix G, Appendix I, Appendix P and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches. [2, 5, 11, 28, 29]
- An extensive range of bibliographic databases, conferences, HTA organisation web sites and other resources were searched. Reference checking was conducted.
- Searches were extremely well documented, and were well-structured, transparent and fully reproducible.
- The database searches for the cost effectiveness and cost/health care resource use SLR combined facets for BRAF mutations and NSCLC. In the Embase and MEDLINE searches, this was then combined with a study design filter for cost/economic evaluation studies. A good range of subject headings and free-text terms were employed.

- Conference proceedings were searched for key international conferences between 2018 and 2024 (where available), using a combination of Embase searches and manual searches of online conference proceedings as necessary.
- The EAG notes that the approach used by the company for the update searches was potentially restrictive, as only the publication year limit was used, rather than also including limits related to the date on which records were added to the database. This could potentially miss records that were added since the last update, but which had an earlier publication year. However, given the extensive range of resources included in this SLR, the EAG considers it unlikely any relevant records were missed due to this approach.

Appendices H and P of the CS provide details of an SLR conducted to identify relevant HRQoL/health state utility value (HSUV) evidence for the treatment of patients with BRAF-mutated advanced NSCLC.[11, 30] The searches were conducted in October 2021, and updated in May 2023, July 2023 and May 2024.

A summary of the sources searched is provided in Table 4.2.

Table 4.2: Data sources for the HRQoL SLR

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	Incep – Wk 42 2021 2021 – Wk 17 2023 2023 – Wk 27 2023 2023 – 14/5/24	26/10/21 4/5/23 11/7/23 15/5/24
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)		Incep – 22/10/21 2021 – 3/5/23 2023 – 10/7/23 2023 – 14/5/24	
CENTRAL		Incep – Sept 2021 2021 – March 2023 2023 – June 2023 2023 – Apr 2024	
CDSR		Incep – 26/10/21 May 2020 – 2/5/23 July 2022 – 5/7/23 Apr 2022 – 4/4/24	
DARE		Incep – 1st Quarter 2016	
HTA Database		Incep – 4th Quarter 2016	
Conferences			
• ASCO • ESMO • IASLC WCLC • AACR • ISPOR	Embase/ Internet	2018-2024 2018-2023 2018-2023 2018-2024 2019-2023	7/6/24

Resource	Host/Source	Date Ranges	Date searched
HTA Agencies			
• NICE • CDA-AMC • PBAC/TGA • SMC • HAS • IQWiG • G-BA • PMDA • ICER	Internet	All	7/6/24
Additional resources			
• EQ-5D • INAHTA Database • Google Scholar • NIHR • CRD • CEA Registry • RePEc	Internet	All	27/6/24

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDA-AMC = Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health); CEA Registry = Cost-Effectiveness Analysis Registry; CRD = Centre for Reviews and Dissemination; CS = Company submission; ESMO = European Society of Medical Oncology; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; IASLC WCLC = International Association for the Study of Lung Cancer World Congress on Lung Cancer; ICER = Institute for Clinical and Economic Review; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = German Institute for Quality and Efficiency in Health Care; ISPOR = International Society of Pharmacoeconomics and Outcomes Research (European and International meetings); PBAC/TGA = Pharmaceutical Benefits Advisory Committee/Therapeutic Goods Administration; NCCN = National Comprehensive Cancer Network; NIHR = National Institute for Health Research; PBAC = Pharmaceutical Benefits Advisory Committee; PMDA = Pharmaceuticals and Medical Devices Agency; RePEc = EconPapers within Research Papers in Economics; TGA = Therapeutic Goods Administration

EAG comment:

- Searches were undertaken in October 2021, and updated in May 2023, July 2023 and May 2024 to identify relevant HRQoL/HSUV evidence for the treatment of patients with BRAF V600 mutated advanced NSCLC. The CS, Appendix H, Appendix P and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 5, 11, 30]
- An extensive range of bibliographic databases, conferences, HTA organisation web sites and other resources were searched. Reference checking was conducted.
- Searches were extremely well documented, and were well-structured, transparent and fully reproducible.
- The database searches combined facets for BRAF mutations and NSCLC. In the Embase and MEDLINE searches, this was then combined with a study design filter for HRQoL and HSUV. A good range of subject headings and free-text terms were employed. Animal-only studies were excluded where possible.

- Conference proceedings were searched for key international conferences between 2018 and 2024 (where available), using a combination of Embase searches and manual searches of online conference proceedings as necessary.
- For Embase and MEDLINE, the database searches were limited to studies published in English only. Limiting to English language only studies may have introduced language bias. Current best practice states that 'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'[12] and research related to language bias supports the inclusion of non-English language studies in systematic reviews.[13, 14]
- The EAG notes that the approach used by the company for the update searches was potentially restrictive, as only the publication year limit was used, rather than also including limits related to the date on which records were added to the database. This could potentially miss records that were added since the last update, but which had an earlier publication year. However, given the extensive range of resources included in this SLR, the EAG considers it unlikely any relevant records were missed due to this approach.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.3.

Table 4.3: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (aged ≥18 years) with BRAF-mutant metastatic NSCLC in the first, second and later lines of treatment • Subgroup of interest are adult patients (aged ≥18 years) with BRAF V600E-mutant metastatic NSCLC in the first, second and later lines of treatment	• Paediatric or adolescent patients (<18 years) with BRAF/BRAF V600E-mutant NSCLC • Patients with cancers other than BRAF-mutant NSCLC • Studies reporting data only from mixed NSCLC populations, i.e., not reporting data for the target population separately • Animal/in vitro studies
Intervention/ Comparator	No restriction on intervention and comparators, only pharmacological interventions were considered for inclusion in the review	Any non-pharmacological interventions
Outcomes(s) 1 (Published economic evaluations)	• Model summary (including perspective, time horizon and discounting) and structure, where applicable • Assumptions underpinning model structures. • Estimation of transition probabilities and uncertainty	Outcome(s) not listed

	Inclusion criteria	Exclusion criteria
	• Key cost drivers • Sources of clinical, cost and HRQoL inputs • Discounting of costs and health outcomes • Summary health outcomes (e.g., quality adjusted life years [QALYs], disability-adjusted life years [DALYs], life years gained [LYG]) • Incremental cost-effectiveness ratios (ICERs): cost per QALY/DALY/LYG, cost per event avoided • Range of ICERs • Utilities/disutilities associated with treatments and AEs	
Outcomes(s) 2 (Cost/ resource use studies)	HCRU and cost outcomes • Cost estimates • Direct medical costs • Direct non-medical costs • Treatment cost/administration cost • Indirect/societal costs • Out of pocket costs expense • Patient, caregiver, family, and societal burden • Estimates of resource use (hospitalisations, length of stay, consultations, day care and outpatient visits, etc) • Cost drivers	Outcome(s) not listed
Outcome(s) 3 (HRQoL & HSUV)	QoL and utility outcomes • PROs and symptom measures, HRQoL, patient preference • QoL instruments as reported in literature • Disease-specific or generic non-preference based QoL and PRO measures • Descriptive summary of health states, and/or change in health status/QoL results	Outcome(s) not listed

	Inclusion criteria	Exclusion criteria
	• Utilities derived using generic preference-based instruments (e.g., EQ-5D, SF-6D, HUI2, HUI3) for relevant health states Direct utility estimates (e.g., SG, TTO)	
Study design 1 (Cost effectiveness analysis studies)	• CEA • CUA • CMA • CCA • CBA • COA • Budget-impact analyses SLRs or meta-analyses for reference checking only	• Animal/in-vitro studies • Clinical studies • Editorials • Letters • Case studies • Case reports • Narrative reviews
Study design 2 (Cost/resource use studies)	Cost and resource use: • Any studies reporting relevant outcomes.	• Animal/in-vitro studies • Clinical studies • Editorials • Letters • Case studies • Case reports • Narrative reviews
Study design 3 (HRQoL & HSUV)	Any studies reporting relevant outcomes. Systematic literature reviews (SLRs) or meta-analyses for reference checking only	• Animal / in-vitro studies • Clinical studies • Editorials • Letters • Case studies • Case reports • Narrative reviews

Based on Appendix G[28], Table 9; Appendix H, Table 19{Pierre Fabre, 2024 #89}.
AE = adverse event; BRAF V600E NSCLC, BRAF V600E-mutant non-small-cell lung cancer; CBA = cost-benefit analysis; CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; COA = cost offset analysis; CUA = cost-utility analysis; DALY = disability-adjusted life year; HCRU = health care resource utilisation; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LYG = life year gained; QALY = quality-adjusted life year; QoL = quality of life; SLR = systematic literature review

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.4: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with NICE reference case
Perspective on costs	NHS and PSS	Consistent with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Consistent with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with NICE reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear whether the UK tariff was used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with NICE reference case
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	Consistent with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with NICE reference case

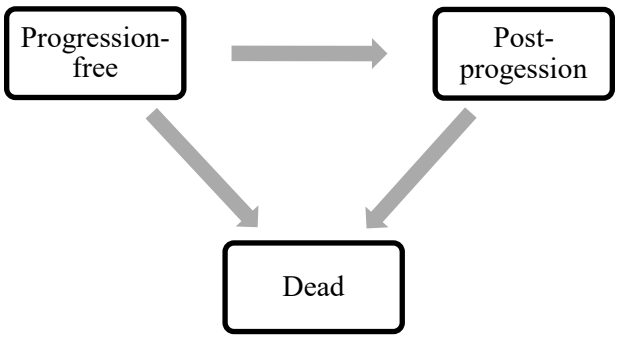
CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQol-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United-Kingdom

4.2.2 Model structure

The company provided a de novo partitioned survival model (PSM) in Microsoft® Excel with three mutually exclusive health states which patients who received either enco+bini or dabra+tram occupy and eventually transition from as presented in Figure 4.1: progression-free (PF), post-progressed disease (PD), and death. A one-week cycle length with half-cycle correction in the company's base-case was implemented. Kaplan-Meier data informed the duration patients occupied the respective health state and were extrapolated with parametric models to satisfy a life-time horizon.

The company justified the chosen modelling structure as follows: it corresponded with trial endpoints, was reflective of the progressive nature and clinical care pathway of NSCLC and had been used in former NICE technology appraisals (TAs) addressing NSCLC.[31-40]

Figure 4.1: Model structure



Based on Figure 14[2]

EAG comment: The main concern of the EAG relates to the lack of a state transition model (STM) to verify the extrapolated outcomes of the PSM.

The company used a support Unit (DSU) Technical Support Document (TSD) 19 advises using state transition modelling de novo PSM with three mutually exclusive health states for this appraisal. The NICE Decision S g alongside PSM to help validate the plausibility of extrapolations and investigate critical clinical uncertainties during the extrapolation period.[41] In response to clarification question B6, the company stated that available survival data and common practice spoke in favour of using a PSM, as PSMs had been accepted in previous HTAs in NSCLC, including the appraisal of dabra+tram.[31] The company argued that missing individual state transition probabilities for the comparator, i.e., time to progression, time to death without progression and post-progression survival, prevented the use of an STM.[5, 41] Applying a treatment effect to the enco+bini survival curves for the dabra+tram transitions was deemed a strong assumption and inappropriate by the company since they would fail to match the original dabra+tram survival curves. However, the company provided insightful individual state transition probabilities over time for enco+bini which in the opinion of the EAG plausibly supported their PSM choice. The STM appears to overpredict Kaplan-Meier data for OS[5] (Figure 5) and PFS[5] (Figure 6) compared to the PSM. The EAG agrees that using an STM would require pre- and post-progression survival estimates, yet it stresses that the available PFS and OS data would allow exploring various assumptions regarding pre- and post-progression survival in as STM. While the EAG recognises that implementing an STM would demand significant time and resources, this approach would be particularly valuable to address the uncertainty associated with the extrapolated curves, which stem from immature PFS and OS data (i.e., 44.1% and 47.5% of patients had experienced OS and PFS events respectively). On this, the EAG disagrees with the company, with the latter perceiving the data

"sufficiently mature."[5] The EAG exemplary refers to Figures 2 and 4 provided by the company in response to clarification question B6[5] which show considerable probability variation over the available time horizon.

4.2.3 Population

The population considered in the CS economic model[2] (Table 1) was treatment-naïve advanced NSCLC patients with a BRAF V600E mutation. It is narrower than the marketing authorisation and the NICE scope considering people with advanced NSCLC that is positive for a BRAF V600E mutation.

The evidence for enco+bini was based on the 59 non-UK, treatment-naïve subgroup of patients participating in the ongoing multicentre, multi-cohort, open-label phase 2 PHAROS trial. For dabra+tram, the BRF113928 trial with five out of 71 study sites in England was used. A MAIC was performed on several factors (age, gender, ECOG performance score, smoking status, race, histology, brain metastases) towards the BRF113928 trial, resulting in 44 treatment-naïve patients contributing to the cost effectiveness evidence of enco+bini.

No subgroup analyses were performed besides singling out treatment-naïve patients. This is contrary to the NICE scope which considers also treated patients, histology (squamous or non-squamous) and PD-L1 expression relevant.

The key baseline patient characteristics in the economic model after MAIC are listed in Table 4.5 below.

Table 4.5: Key baseline treatment-naïve patient characteristics

	MAIC matched on several factors	**Original data**	
Mean	**PHAROS - base case in the economic model (ESS=44)**	**PHAROS (N=59)**	**BRF113928 (N=36)**
Median age (years)	67.0	68	67
Proportion of males (%)	39	44.1	39
Weight (kg)	70.6	74.6	N/A
Height (m)	1.65	1.67	N/A
Body surface area (m^2)	1.8	1.86	N/A
ECOG-PS (% ECOG=0)	36	32.2	36
Smoking status (% Never smoked)	28	30.5	28
Race (% White)	83	90	83
Histology (% Adenocarcinoma)	89	97	89
Brain metastases (% Yes)	6	7	6

Source: Table 28, CS; Table 13, response to clarification letter.[2, 5]
ECOG = Eastern Cooperative Oncology Group; ESS = estimated sample size; kg = kilogram; m = metres; m^2 = square metres; MAIC = matching-adjusted indirect comparison; N/A = not available; PS = performance status

EAG comment: The main concerns of the EAG relate to: a) the modelled population being narrower than the population defined in the NICE scope, b) the lack of subgroup analyses, c) the modelled patient characteristics not being representative of the UK patient population.

a) Contrary to the NICE scope, the company only modelled the treatment-naïve NSCLC patient population with a BRAF V600E mutation. The EAG requested an updated economic model also including treatment-experienced patients, but this was not provided by the company. The company justifies its decision to exclude treatment-experienced patients referencing three clinical experts who identify the expected use of enco+bini as a targeted first-line therapy in presence of a BRAF V600E mutation in UK clinical practice[5]. Only delayed test results for the mutation or insufficient biopsy could cause a non-targeted first-line therapy. Such delays and thus treatment-experienced patients receiving enco+bini would decrease over time according to TA866[2, 42] (Table 1) and were "rare" according to the clinical experts consulted[5]. The majority of patients hence would receive targeted therapy as a first-line treatment and be ineligible for another targeted therapy with a similar action mechanism.[5] Apart from a summary of the advisory board meetings, the company did not provide details of clinical expert elicitation procedures and expert inputs. The clinical expert consulted by the EAG generally agrees with the company and deems testing issues to be small.[43] Additionally, the company stated that the chosen population mirrors NICE guidance on the comparator, i.e., dabra+tram[31]. Nevertheless, the EAG still sees the need to address those patients who priorly received a non-targeted therapy, also identified as a key issue in Section 2.1 of this report.
b) Besides the treatment-naïve subgroup serving as the CS patient population, no further subgroups mentioned in the NICE scope were addressed by the company. Treatment-experienced patients were discarded in line with the argument above. Moreover, PD-L1 expression and histologic subgroups (squamous or non-squamous) were not considered because PD-L1 expression was not collected and only one patient presented with a squamous histology. The clinical expert consulted by the EAG agrees with the company's choice to exclude them, stating that PD-L1 expression "is not considered helpful in patients with driver mutations" [43] and almost all patients with a BRAF V600E mutation would present with adenocarcinoma, i.e., non-squamous histology. Therefore, as highlighted in section 2.6 of this report, the only formal subgroup analysis mentioned in the NICE scope that might be conducted with the data available is for the treatment experienced population. Nevertheless, the lack of subgroup analyses identified as relevant in the NICE scope constitutes a limitation and therefore a key issue for the EAG, see Section 2.6.
   Further subgroup differentiation (e.g., age, gender, race, ECOG) was not deemed possible by the company because subgroups based on baseline characteristics were only analysed for the primary study endpoint and not for other endpoints relevant for modelling. The EAG does not agree with the company's argument, as clinical trials by design are usually not powered for subgroup analyses. Whereas not requested as part of the NICE scope the EAG considers further subgroup differentiation based on patient characteristics to be customary, feasible and informative.
c) In the CS, the company's modelled patient characteristics were obtained from the PHAROS treatment-naïve cohort prior to MAIC adjustment. Upon request of the EAG, these were updated to MAIC adjusted values to reflect the population of the BRF113928 trial. Whereas the latter also included UK patients, it remains unclear whether these patient characteristics are representative of the UK. Although requested by the EAG, the company failed to provide certain relevant patient characteristics for the BRF113928 trial (Table 4.5). The company's SLR did not identify UK registry data on BRAF V600E,[5, 10] and one UK study reported with 51.9%

a higher proportion of males.[44] In the wider UK NSCLC population,[45] patients had a mean age of 74 years and 10% never smoked. The CS modelled patient population was thus younger and had a higher share of patients who never smoked. Here the EAG highlights that the CS clarification response cited 18% of patients who never smoked,[5] yet cross-checking with CS Table 11 and CS Table 28 this was identified as the absolute and not relative value, the latter being 31%.[2] Three clinical experts consulted by the company argued that "the baseline characteristics of the treatment-naïve cohort in the PHAROS study were broadly reflective of the population they would expect to receive enco+bini in UK clinical practice."[5] Apart from a summary of the advisory board meetings, the company did not provide details of clinical expert elicitation procedures and expert inputs. The clinical expert consulted by the EAG aligns with this view, stating since "some study sites were in Europe and North America […], it is feasible to assume that the study population would be representative of the lung cancer population in the UK."[43] Despite the lack of details on clinical expert elicitation in the advisory boards, which should be provided by the company, based on input from the EAG clinical expert, the EAG endorses the modelled patient characteristics in the company's updated economic model as representative of the UK patient population.

4.2.4 Intervention and comparator

The intervention considered in the CS was encorafenib (enco), administered orally at a dose of 450 mg daily, in combination with binimetinib (bini), administered orally at a dose of 45 mg twice daily[2] (Table 2) and discontinued in case of disease progression or intolerable toxicity[2] (B.3.2.3.). The comparator considered was dabrafenib (dabra) administered orally at a dose of 150 mg twice daily, in combination with trametinib (tram) administered orally at a dose of 2 mg daily. Dabra+tram administration was likewise reduced, interrupted or discontinued in case of adverse reactions.[31]

The NICE scope listed the following comparators:

- For people with untreated advanced NSCLC
  - Dabra+tram
  - Pembrolizumab with platinum doublet chemotherapy (cisplatin or carboplatin with either gemcitabine, vinorelbine, docetaxel or pemetrexed)
  - Pembrolizumab monotherapy
  - Atezolizumab monotherapy.
- For people with previously treated advanced NSCLC
  - Atezolizumab monotherapy
  - Pembrolizumab monotherapy
  - Nivolumab monotherapy
  - Docetaxel with nintedanib
  - Docetaxel
  - Platinum doublet chemotherapy.

The company justified the selection of dabra+tram as the sole comparator, such that a targeted therapy was clinically favourable in presence of a BRAF V600E mutation. A non-targeted therapy might only be considered under delayed genomic testing or insufficient biopsy and clinical urgency for treatment initiation. The company stated that these delays were few, and improvements were to be expected. Clinical experts consulted by the company stated that other treatment options were more appropriate for subsequent therapy lines.

EAG comment: The main concerns of the EAG relate to: a) omission of relevant comparators from the NICE scope, b) divergence of treatment administration within each combination treatment.

a) As outlined in EAG report Section 2.3, the NICE scope identified a range of relevant comparators. However, the company opted to include only dabra+tram in their analysis despite an additional request of the EAG. It hereby follows the consulted three clinical experts who saw "no clinical rationale to use a non-targeted therapy" besides BRAF V600E mutation testing issues for treatment-naïve patients[5] and identify dabra+tram as "the only relevant comparator in this appraisal."[5] Apart from a summary of the advisory board meetings, the company did not provide details of clinical expert elicitation procedures and expert inputs. The EAG clinical expert aligns with the company's first statement, commenting that in case of a "confirmed BRAF V600E mutation, lung cancer oncologists would favour a targeted therapy" [43]. Notably, the exclusion of comparators deemed relevant in the NICE scope except for dabra+tram contradicts [redacted] These, the EAG deems relevant for the decision problem at hand since a small group of patients is affected by genomic testing issues, and would therefore rely on "empiric treatment with chemotherapy and/or immunotherapy."[43] This exclusion of presumably relevant comparators hinders a holistic assessment of cost effectiveness of enco+bini in the UK setting, particularly since solely the treatment-naïve subgroup of the overall patient population with advanced NSCLC positive for a BRAF V600E mutation is addressed. Further details on the EAGs view regarding the key issue of omission of these comparators can be found in Section 2.3 of this report.
b) It was unclear to the EAG whether patients could discontinue one treatment within the combination treatments and continue on the other treatment, implying changes in TTD and thus cost modelling. Upon clarification question B9 of the EAG, the company explained based on the Summary of Product Characteristics (SmPC) that for enco+bini, if bini were to be temporarily interrupted, enco could be continued but should be reduced to 300 mg once daily during this period. Both drugs would be simultaneously permanently discontinued. The EAG agrees with the assessment of the company that PHAROS trial data showed little difference in the duration of exposure to enco or bini[5] (Figure 7), yet inferring it on UK clinical practice may be questionable. The company did not provide similar evidence for the dabra+tram combination treatment, explaining that this data was not available. The SmPC on dabra+tram state that both treatments should be "simultaneously dose reduced, interrupted or discontinued"[46] with a few disease-specific exceptions. They further provide recommended dose level reductions[46] (Table 1, Table 2). Reviewing the available evidence, the EAG considers this to be a minor issue that is not expected to be a driver of cost effectiveness in the health economic model.

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was one week with a lifetime time horizon (36 years) and a half-cycle correction was applied to capture all relevant differences in outcomes and costs between intervention and comparator.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators are PHAROS (DCO: 1 April 2024; treatment-naïve subgroup), to inform enco+bimi, and the BRF113928 (NCT01336634) trial to inform dabra+tram.

4.2.6.1 Estimation of parametric survival models for encorafenib with binimetinib

Parametric survival models were estimated for enco+bimi for PFS, OS and TTD. According to the CS, the parametric distributions (considering the seven standard parametric distributions, i.e., exponential, Weibull, log-logistic, log-normal, Gompertz, gamma, and generalised gamma) for PFS, OS and TTD were selected, as per the NICE DSU TSD 14. Specifically, the following criteria was considered for each outcome:

1. Goodness-of-fit statistics based on Akaike information criterion (AIC) and Bayesian information criterion (BIC)
2. Visual assessment of fit based on the Kaplan-Meier curve
3. Comparison with published data, where available
4. Clinical plausibility of long-term projections (based on the October 2024 UK advisory board).

Notably, PFS was capped such that it did not exceed OS, and OS was bound by age- and gender-matched general population mortality rates. According to the CS, clinical experts advised that a proportion of patients may continue with treatment beyond progression, hence TTD is not capped by PFS. The process of selecting the approach to estimate and extrapolate OS, PFS and TTD is summarised in Table 4.6.

Table 4.6: Selection of approach to estimate and extrapolate OS, PFS and TTD

	OS (CS B.3.3.2.1.1)	PFS (CS B.3.3.2.1.2)	TTD (CS B.3.3.2.3.1)
General	Median follow-up: [redacted] months, 44.1% experienced an OS event (in the treatment-naïve population). Median OS was not reached.	Median follow-up: 33.3 months, 47.5% experienced a progression event (in the treatment-naïve population). Median PFS (assessed by IRR) was 30.2 months.	Median TTD was [redacted] months.
Fit to the observed data based on AIC and BIC	All distributions were within 3 points (AIC), however, the log-normal (AIC) and exponential (BIC) distributions had the best statistical fit (CS Table 53)	The generalised gamma distribution had the best statistical fit (AIC and BIC). However, the log-normal distribution was within 3 AIC points. Similarly, all distributions except the Weibull and gamma were within 3 BIC points. (CS Table 56)	All distributions except the log-normal distribution were within 3 points (AIC), however, the exponential distribution (AIC and BIC) had the best statistical fit (CS Table 62).
Fit to the observed data based on visual comparison with the Kaplan-Meier curves	All distributions slightly over-predict OS compared with the observed data at 6 months but then are well aligned with the observed data (CS	All distributions slightly over-predict PFS compared with the observed data at 6 months but are relatively aligned with the observed data from year 1 onwards (CS	All distributions (slightly) over-predict TTD compared with the observed data at 6 months but are relatively aligned with the observed data from

	OS (CS B.3.3.2.1.1)	PFS (CS B.3.3.2.1.2)	TTD (CS B.3.3.2.3.1)
	Figure 17 and CS Table 54).	Figure 20 and CS Table 57).	year 1 onwards (CS Figure 28 and CS Table 63).
Comparison with published data	Not provided in section CS B.3.3.2.1.1.	Not provided in section CS B.3.3.2.1.2.	Not provided in section CS B.3.3.2.3.1.
Clinical plausibility of long-term projections (based on the October 2024 UK advisory board)	It was not expected that many patients are alive at 20 years, and therefore the Gompertz, generalised gamma, log-logistic and log-normal distributions were not supported. It was noted that the Weibull, exponential and gamma distributions provided the most clinically plausible long-term estimates.	It was expected that few patients are progression free beyond 5 year and therefore the Gompertz, generalised gamma, log-logistic and log-normal were not supported. It was noted that the Weibull, exponential and gamma distributions provided the most clinically plausible long-term estimates.	It was not expected that many patients would remain on treatment at 10 years and therefore the Gompertz, log-normal, and log-logistic distributions were not supported It was noted that the Weibull, exponential, gamma and generalised gamma distributions provided the most clinically plausible long-term estimates.
Base-case approach	The exponential distribution was selected as it provided the most clinically plausible long-term estimates.	The exponential distribution was selected as it provided the most clinically plausible long-term estimates.	The exponential distribution was selected as it provided the most clinically plausible long-term estimates.

AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; IRR = independent radiology review; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

4.2.6.2 Proportional hazards assumption

The assumption of proportional hazards (PH) was assessed between the PHAROS and BRF113928 data for OS and PFS by examining the log cumulative hazards (CS Figures 23 and 25), Schoenfeld residuals (CS Figures 22 and 24), and clinical expert opinion.

For OS, the Schoenfeld residuals indicated that the residuals are independent of time, and the PH assumption may thus hold. However, the log cumulative hazards versus time plot shows curves crossing in the first half of the observation period and thus evidence of non-proportionality between enco+bini and dabra+tram. However, the company stated that there is no clinical reason to expect PH not to hold. Given the above, the company considered it acceptable to assume PH for OS by applying the MAIC HRs to the unadjusted PHAROS data.

For PFS, the Schoenfeld residuals indicated that the residuals are independent of time, and the PH assumption may thus hold. Similarly, the log cumulative hazards versus time plot does not show crossing curves. However, the company stated that clinical experts also advised that they would expect PH to hold between enco+bini and dabra+tram. Given the above, the company considered it acceptable to assume PH for PFS by applying the MAIC HRs to the unadjusted PHAROS data.

4.2.6.3 Relative treatment effectiveness

Overall survival and PFS for dabra+tram were estimated by applying HRs (OS HR: 0.55 and PFS HR: 0.47) obtained from the unanchored MAIC (CS Section B.2.9 and Section 3.4 of this report). For dabra+tram TTD was assumed to be equal to PFS.

As there are no direct head-to-head trials, an unanchored MAIC was conducted comparing the effectiveness of enco+bini and dabra+tram (CS Section B.2.9 and Section 3.4 of this report). Two MAIC analyses were considered for use in the model (CS Table 59):

1. Adjusting for all available confounding factors identified in the feasibility assessment: age, gender, ECOG, smoking status, race, histology, brain metastases (CS base case)
2. Adjusting only for key factors based on clinical expert opinion: ECOG and smoking status (CS scenario).

The estimated OS, PFS and TTD for dabra+tram was compared with BRF113928 data and TA898 (CS Tables 60 and 61). The 1-, 5- and 10-year modelled OS was slightly [redacted] compared with BRF113928 data and TA898. The modelled 1- and 2-year PFS was [redacted] compared with BRF113928 data while it was lower for 5-year PFS.

4.2.6.4 Waning of relative treatment effect

No explicit assumptions regarding waning of the relative treatment effect were discussed in the CS.

EAG comment: The main concerns of the EAG relate to: a) selection of parametric distributions based on observed data for OS, PFS and TTD; b) justification of long-term estimates for OS, PFS and TTD; c) proportional hazards assumption d) uncertainty in relative treatment effectiveness; e) waning of relative treatment effectiveness; f) assumption of TTD equal to PFS for dabra+tram; and; g) estimation of TTD in the PHAROS study.

a) Based on the information provided in response to clarification question B10, the EAG believes that the exponential distribution is suboptimal for the modelling of OS, PFS, and TTD when considering fit to the observed data. Specifically, the smoothed hazard curves for OS, PFS and TTD decrease over time, indicating a non-constant hazard, which the exponential distribution does not capture. Moreover, for TTD, the smoothed hazard curve decreased for the beginning of the follow-up period but then levelled out to a more constant pattern. Therefore, the Weibull and Gompertz are also suboptimal for TTD when considering the fit to the observed data (as these are associated with a monotonically increasing/decreasing hazard over time, see Ishak et al. 2013; https://doi.org/10.1007/s40273-013-0064-3).[47] Hence, according to the EAG more flexible parametric models that are non-constant over time (and for TTD can also incorporate non-monotonically increasing/decreasing hazard over time) might be preferred based on the observed data, for instance, based on CS Table 54 the log-logistic and gamma distributions might be plausible alternatives based on the observed data for OS.
b) Long-term estimates for OS, PFS, and TTD represent a key uncertainty. Overall survival and PFS data from PHAROS were immature (i.e., 44.1% and 47.5% of patients had experienced OS and PFS events respectively), introducing significant uncertainty to the extrapolated OS and PFS curves. Next to that, long-term estimates for OS, PFS and TTD were informed by the company through expert opinion. Information on the expert opinion obtained is only scarcely reported in the CS. Therefore, the EAG did ask for further information regarding the obtained expert opinion. However, the company did not provide the advisory board presentation slides and full report (which are typically shared with the EAG) nor did the company provide a full response to

clarification question B12. Instead, the response to clarification question B12 focussing on long-term estimates for OS, PFS, and TTD largely reiterated information already described in the CS. Without access to the advisory board presentation slides and full report, the EAG considers it challenging to evaluate the robustness of the expert opinions informing these estimates. This lack of transparency underscores the need for comprehensive data sharing to ensure that the selected parametric models are justified. Consequently, the EAG believes that the selection of the CS base-case distributions to estimate OS, PFS and TTD are not well-supported. Potentially, none of the standard parametric curves might be appropriate to estimate long-term OS, PFS and TTD. This is illustrated by the statement in the CS that "experts predicted that few patients would be progression-free at 5 and 10 years", which seems to disqualify all long-term PFS estimates provided in CS Table 58 (with all 5-year PFS estimates above 20%). Similarly, the long-term OS estimates (e.g., at 5 and 10 year) provided in CS Table 55 might potentially also be overly optimistic. However, without transparency about the obtained expert opinion it is challenging to assess the appropriateness of long-term OS, PFS and TTD.

c) According to CS Figure 23, the log-log survival (i.e., cumulative hazard) curves for OS of both treatments cross, which is typically a strong indication of non-proportionality. Nevertheless, the company argued in response to clarification question B10 that the proportional hazards assumption was appropriate based on the Schoenfeld residuals and given both enco+bini and dabra+tram have a similar mechanism of action. Moreover, the company stated the log-log plots cross at the early part of the curve (<6 months), which is likely caused by a lack of events in the enco+bini arm (at 6 months only [redacted] patients had experienced an event in the treatment-naïve subgroup of PHAROS). The company stated that after 6 months, the curves remain parallel, suggesting that proportional hazards may be an appropriate assumption. The EAG believes it is reasonable to assume proportional hazards.
d) One key uncertainty is the relative treatment effectiveness, informed by the unanchored MAIC. In response to clarification question B15, the company explored scenarios using alternative HRs: 1) adjusted on smoking and ECOG status and 2) using the unadjusted HRs. Notably, the incremental quality-adjusted life years (QALYs) were substantially lower in these scenarios, compared with the CS base-case, highlighting the substantial impact of assumptions related to the modelling of the relative treatment effectiveness. Although the EAG did adopt the same MAIC in its base-case as the CS base-case, it should be noted that some important prognostic variables were not adjusted for in the MAIC analyses due to the lack of availability of these variables. This may have compromised the validity of results of MAIC analysis. See Section 3.4 of this report for more information on the EAG perspective regarding the unanchored MAIC.
e) Treatment waning was not explored in the CS. According to the company's response to clarification question B11, at the end of follow-up, [redacted] of patients in the treatment-naïve cohort of PHAROS were still receiving treatment with enco+bini. For OS and PFS, during the observed period, the hazards of enco+bini and dabra+tram for both OS and PFS did not converge (clarification response Figure 23). The EAG agrees with the company that indeed this figure suggests that treatment effect waning is not applicable during the observed period. However, it is uncertain whether treatment effect waning would be applicable beyond the observed data period. Despite that the company argues that it has previously been shown "*that patients may still derive benefit from BRAF/MEK-directed targeted therapy after discontinuing treatment, particularly for patients who received treatment for a prolonged period (18). In the treatment-naïve cohort of patients, the majority of patients ([redacted]) received treatment for over 12 months*", the EAG believes that treatment effect waning beyond the observed data period remains uncertain and is therefore informative to explore. Similarly, the company accepts there is uncertainty regarding long-term estimates of OS and PFS and therefore provided a scenario wherein waning was considered from

[redacted] months (maximum follow-up of PHAROS) for a duration of 24 months (duration of waning in previous TAs varies between 1 and 3 years, the company uses a midpoint of 2 years). In this scenario enco+bini remains dominant but the incremental QALY decreased from [redacted].

f) The CS states that no TTD data were available for dabra+tram, leading to the CS base-case assumption that TTD equals PFS for this treatment. The EAG considers that this strong assumption requires further exploration. Consequently, the company provided scenario analyses exploring alternative assumptions in response to clarification question B13 (clarification response Tables 18 and 19), which indicated that the assumptions related to the estimation of TTD for dabra+tram substantially impact the cost effectiveness results. These scenarios included 1) applying the HR between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabra+tram to estimate TTD for dabra+tram and; 2) estimating TTD for dabra+tram by fitting an exponential curve through the median TTD reported in the BRF113928 trial. The EAG considered both scenarios to be more plausible than assuming that TTD is equal to PFS as in the CS base-case. The company stated that the first abovementioned scenario underestimates dabra+tram TTD as the median TTD in the model is 8.51 months compared to median TTD of 10.55 months in the combined cohort of BRF113928. However, this difference in TTD might be related to the difference in context and population between the BRF113928 trial and PHAROS as well as other model choices (e.g., approach to estimate PFS and OS). Therefore, the EAG preferred applying the HR between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabra+tram to estimate TTD for dabra+tram in its base-case. This approach is also considered intuitive given both enco+bini and dabra+tram have a similar mechanism of action (as stated by the company) and might potentially even be conservative as clinical experts stated that dabra+tram is more toxic and hence patients might discontinue treatment earlier compared with enco+bini.

g) In CS Section B.3.3.2.3.1 it is stated "*No TTD data were collected in the pivotal PHAROS study, however, a post-hoc analysis was conducted*". It was unclear to the EAG how the company conducted a "post-hoc analysis" while "no TTD data were collected". In response to clarification question B18, the company clarified that TTD was not a specified endpoint in the PHAROS study. Instead, TTD was estimated using the following data points
    a. DCTFL: Subject discontinued flag
    b. TRTEDY: Study day of last exposure to treatment
    c. DCTADY: Study day of treatment discontinuation

    For patients who discontinued treatment (DCTFL='Y'), DCTADY was used for the event time for TTD. For patients who have not discontinued treatment, TRTEDY was used as the censoring point for TTD. The EAG considers this a reasonable approach to estimate TTD based on the abovementioned data points.

4.2.7 Adverse events

Grade ≥3 all causality TEAEs with an incidence of ≥3% (based on clinical expert inputs in the October 2024 UK advisory board) in the treatment-naïve population of PHAROS and the full population of BRF113928 (treatment-naïve population of BRF113928 was not available) were included in the company's economic model to inform the AE incidence of enco+bini and dabra+tram respectively (CS Table 68). Scenario analyses were conducted informing 1) the AE incidence for enco+bini based on the pooled PHAROS and IFCT data, and 2) the AE incidence for dabra+tram by applying a 0.93 OR from the safety MAIC.

EAG comment: The main concerns of the EAG relate to: a) use of naïve versus full population of enco+bini and dabra+tram respectively to inform AE incidences, b) lack of modelling grade 1-2 TEAEs c) modelling a zero cost and disutility for TEAEs considered clinically inconsequential.

a) The company used the treatment-naïve population in PHAROS to model grade ≥3 TEAEs with an incidence of ≥3% for enco+bini, whereas due to the lack of AE data in the treatment-naïve cohort of BRF113928, the full population was used for dabra+tram. In response to clarification question B19, the company provided a scenario analysis also informing AE incidences for enco+bini based on the full population (i.e., including non-treatment-naïve patients) of PHAROS. Although the impact on the cost effectiveness was minor, the EAG noted that in addition to considering the full population of PHAROS, the company's scenario analysis also included grade ≥3 TEAEs that were considered clinically inconsequential in their initial analysis (e.g., alanine aminotransferase increased, blood creatinine phosphokinase increased, lipase increase and weight increased). Nevertheless, the EAG can confirm that the company's scenario analysis using the full population of PHAROS without inclusion of AEs that were considered clinically inconsequential, the impact on the cost effectiveness results remained negligible. The EAG therefore considers this issue likely not to be a driver of cost effectiveness.
b) The company only included grade ≥3 TEAEs with an incidence of ≥3% in either arm, despite a clinical expert highlighting that grade 1–2 TEAEs could also substantially impact HRQoL and costs. In response to clarification question B19, the company provided scenario analyses 1) including grade 1-2 pyrexia only, and 2) including any grade 1-2 TEAE occurring in ≥3% of the treatment-naïve population in PHAROS. Both scenario analyses had a negligible impact on the cost effectiveness results, indicating that the modelling of grade 1-2 TEAEs is likely not a driver of cost effectiveness.
c) The company modelled a zero cost, disutility and duration for "clinically inconsequential" TEAEs that would have a minimal impact on HRQoL and costs in its base-case. In response to clarification question B19, the company argued that a clinical expert highlighted during an advisory board that increased alanine aminotransferase, increased amylase, increased blood alkaline phosphatase, increased blood creatinine phosphokinase, raised lipase, and herpes zoster are inconsequential as these are usually not measured during treatment and many patients therefore would be unaware of having them in real-world clinical practice. Upon request, the EAGs clinical expert stated that these TEAEs would be more impactful if they occurred as grade 3 or 4. More specifically, the clinical expert stated that grade 1-2 blood biochemical abnormalities would not impact HRQoL or costs but bronchitis, herpes zoster and loss of consciousness may have a much bigger impact, especially if of a higher grade. A scenario analysis was provided by the company including a cost and disutility (derived from previous NICE TAs and published literature) for clinically inconsequential TEAEs, which resulted in a minor net health benefit (NHB) decrease. The EAG, however, noted that the proportion of patients reported for dabra+tram in clarification response Table 30 was inconsistent with the proportion of patients in the economic model, e.g., [redacted]% of patients were reported in Table 30 to have amylase increased whereas [redacted]% of patients were modelled to have amylase increased. The EAG would like to see justification for these inconsistencies.

4.2.8 Health-related quality of life

4.2.8.1 Health-related quality of life data identified in the literature review

According to the CS, the SLR identified no studies reporting utility values for NSCLC patients with a BRAF mutation.

4.2.8.2 Health state utility values

The company used the committee preferred assumptions in TA898 to inform PF and PD utility values in its base-case. These utility values were derived from Chouaid et al. (2013)[48], a cross-sectional, multi-site study that prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK using EuroQol-5 Dimensions (EQ-5D) and EQ-visual analogue scale (VAS).

A scenario analysis included HSUV based on the IFCT study[49], in which European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) data were collected at the pre-treatment visit, every 8 weeks in the first 12 months, every 12 weeks until disease progression and at the end of treatment visit. EQ-5D-5L data from the IFCT study were mapped to EQ-5D-3L data using the function by Hernández-Alava et al.[50] A univariate mixed model with repeated measures (MMRM) was used to estimate HSUV for patients receiving enco+bini in the IFCT trial. The company explored another scenario analysis in which the PD decrement from TA898 (0.04) was applied to the IFCT MMRM derived PF value.[31] A summary of all utility values used in the CEAs is provided in Table 4.7.

Table 4.7: Health state utility values

	Utility value	
	Progression-free	**Progressed disease**
Base-case: Chouaid 2013 (TA898)	0.71	0.67
Scenario: IFCT MMRM analysis	[redacted]	[redacted]
Scenario: IFCT + Chouaid 2013 (TA898) progressed decrement	[redacted]	[redacted]

Based on CS Table 74
CS = company submission; MMRM = mixed model with repeated measures

4.2.8.3 Disutility values

Disutilities and durations in the company's economic model were aligned with TA898.[31] and if not included in TA898, sourced from the literature, clinical expert opinion, or assumed equivalent to a similar AE (CS Table 70). Disutility and duration of each event were applied to the frequencies reported in Section B.3.3.4 of the CS. Based on clinical experts' input, disutility and duration of 'clinically inconsequential' AEs, i.e., AEs that were expected to have minimal impact on QoL and treatment costs, were set to zero in the company's base-case (CS Table 70).

EAG comment: The main concerns of the EAG relate to: a) the source to inform the modelling of health state utilities, and b) assumptions related to TEAE disutilities and durations.

a) To align with TA898 in their base-case,[31] the company informed HSUV from Chouaid et al. 2013[48], a cross-sectional, multi-site study that prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK. The EAG, however, noted a number of limitations in this study, including 1) the study was conducted a relatively long time ago (2013), 2) the risk of selection bias resulting from non-random drop-out, as a substantial number of patients (N=45) was excluded from the analyses because of uncompleted EQ-5D questionnaires, 3) risk of overfitting of the final regression model, which included 11 covariates, and 4) face validity of the lower PF utility for first-line treated patients (0.71) compared to second-line treated patients (0.73). In response to clarification question B20, the company addressed these limitations by stating that 1) utility values from Chouaid et al. well aligned with utility values in more recent appraisals, 2)

although 45 patients were excluded from the analysis, significantly more patients (N=263) were included in the analysis compared to the IFCT analysis (N=61), 3) a robust covariate selection approach (backward elimination) was used, and 4) various scenario analyses were performed to assess uncertainty regarding the estimated utility values due to low patient numbers. The EAG agrees that the estimated Chouaid et al. utility values are within the range of utility values in other NSCLC appraisals as reported in Table 40 of the clarification response. In addition, it acknowledges the lack of HRQoL data collected in PHAROS and the limitations of low patient numbers in French patients only in IFCT.[49] The EAG, however, does not consider the company argument of higher patient numbers in Chouaid et al. compared to IFCT to address the issue of potential selection bias resulting from non-random drop-out in Chouaid et al. Scenario analyses provided by the company (i.e., modelling [imputed] IFCT PF and PD utility values, modelling IFCT PF utility and applying PD decrement from Chouaid et al.) suggest that the company's current base-case approach is conservative. Overall, given the lack of HRQoL data in PHAROS and the limitations of alternative studies, it is unclear to the EAG what would be the appropriate source to inform the HSUV in the economic model. To assess the potential impact of the uncertainty related to the source for utility values, the EAG explored two scenarios including 1) relatively high utility values from TA310 (PF = 0.784, PD = 0.725),[51] and 2) relatively low utility values from TA258 (PF = 0.661, PD = 0.4302).[52] These scenario analyses resulted in probabilistic incremental QALYs ranging between [redacted] and [redacted].

b) For several TEAEs in the economic model, the company assumed its disutility and/or duration to be equal to another TEAE. In response to clarification question B23, the company justified that whenever possible, disutility values and durations of TEAEs were derived from recent TAs in targeted therapies for NSCLC and the published literature. However, if data were absent, disutilities and/or durations were assumed equal to similar events. Based on the minor impact of the extreme (and conservative) scenario analysis assuming no AE impact for dabra+tram on the cost effectiveness results, in addition to other scenario analyses related to the modelling of AEs provided by the company as discussed in Section 4.2.7, the EAG agrees that assumptions regarding the disutility and duration of TEAEs are likely not key drivers of cost effectiveness.

4.2.9 Resources and costs

The cost categories included in the model were medical costs (treatment acquisition costs, administration costs, subsequent treatment costs), health state costs, costs of managing adverse events and end of life costs.

Unit prices were based on the NHS reference prices, British National Formulary (BNF), and Personal Social Services Research Unit (PSSRU).[53-55]

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, the SLR identified no studies reporting UK relevant resource use and cost information.

4.2.9.1.1 Treatment costs (with PAS)

All primary therapies in the company's economic model were costed per dose (consistent with the SmPC recommended dosing) reported in Section 4.2.4 (Table 4.8). Acquisition costs were sourced from the electronic marketing information tool (eMIT) and the BNF.[54, 56]

Treatment costs were calculated based on the TTD curves as described in Section 4.2.6. Acquisition costs of enco+bini and dabra+tram were adjusted based on relative dose intensity (RDI) from PHAROS and BRF113928 respectively, as not all patients received the full dose (CS Table 77).

Table 4.8: Drug acquisition costs

Drug	Dose	Mg/tablet	Pack size (number of tablets)	List price (PAS price) per pack
Encorafenib	450 mg once daily	75	42	£1,400.00 ([redacted])
Binimetinib	45 mg twice daily	15	84	£2,240.00 ([redacted])
Dabrafenib	150 mg twice daily	75	28	£1,400.00
Trametinib	2 mg once daily	2	30	£4,800.00
	2 mg once daily	2	7	£1,120.00
Based on CS Table 76 CS = company submission; PAS = patient access scheme				

No administration costs were applied for enco+bini and dabra+tram, as both combination treatments are administered orally.

For enco+bini, [redacted] of patients were modelled to receive subsequent treatment costs, which were included for therapies received by ≥1% of patients from the treatment-naïve cohort of PHAROS. Based on expert opinion, subsequent treatments from PHAROS were re-weighted to exclude re-treatment with enco+bini. Experts also expected no significant differences in the types of subsequent therapies between the treatment arms and the subsequent therapy proportions for dabra+tram were therefore assumed to be the same as for the enco+bini arm (also re-weighted to exclude subsequent use of dabra+tram). The company's base-case subsequent therapy distributions are reported in Table 4.9 below. For both enco+bini and dabra+tram, duration of subsequent treatments was modelled in line with PHAROS ([redacted] weeks, independent of the subsequent treatment administered). The RDI's for immunotherapies were assumed equal to that of pembrolizumab (96%) as reported in TA683, and 100% for other subsequent treatments. Acquisition and administration costs of all subsequent treatments are reported in CS Tables 83 to 85.

Table 4.9: Company's base-case subsequent treatments

Drug	Enco+bini	Dabra+tram
Proportion receiving any subsequent therapy	[redacted]	[redacted]
Encorafenib + binimetinib	[redacted]	[redacted]
Dabrafenib + trametinib	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Pembrolizumab + cisplatin	[redacted]	[redacted]

Drug	Enco+bini	Dabra+tram
Nivolumab + ipilimumab + cisplatin	[redacted]	[redacted]
Nivolumab + ipilimumab + carboplatin	[redacted]	[redacted]
Chemotherapy only	[redacted]	[redacted]
Based on CS Table 79 CS = company submission		

4.2.9.2 Health state costs

Medical resource use frequencies were sourced from TA898.[31] Clinical experts agreed that resource use pre- and post-progression is the same for all active therapies in UK clinical practice. Costs were sourced from the NHS reference costs for 2022/23 and the 2023 PSSRU costs (Table 4.10).[53, 55] All resource use costs were converted and applied as weekly cycle costs (CS Table 87).

Table 4.10: Health state costs

Element of resource use	Progression-free (annual)	Post-progression (annual)	Unit cost
Outpatient visit	9.61	7.91	£148.19
Chest X-ray	6.79	6.50	£49.00
CT scan (chest)	0.62	0.24	£151.03
CT scan (other)	0.36	0.42	£125.39
ECG	1.04	0.88	£155.69
Community nurse visit	8.70	8.70	£76.00
Clinical nurse specialist	12.00	12.00	£88.00
GP surgery	12.00	0.00	£56.00
GP home visit	0.00	26.09	£96.60
Therapist visit	0.00	26.09	£52.00
Based on CS Table 86 CS = company submission; CT = computed tomography; ECG = electrocardiogram; GP = general practitioner			

4.2.9.3 Event costs

Unit costs of grade 3+ TEAEs (obtained from NHS reference costs 2022/23) included in the economic model are reported in CS Table 88. Treatment-emergent AE costs were applied as a one-off cost in the first cycle of the economic model (CS Table 89).

A one-off end-of-life care cost (£4,992) sourced from Brown et al.[57] (in line with TA898) was assigned to each patient upon death. Costs were estimated as a weighted average over costs in various care settings and inflated to 2022/23 prices using the PSSRU inflation indices.

EAG comment: The main concerns of the EAG relate to: a) per mg rather than per pack modelling of acquisition costs, b) approach taken to model subsequent treatments, c) BRAF V600E testing costs, d) source for modelling healthcare resource use.

a) The NICE process and methods guide states that the costs of oral treatments dispensed in tablet packs should be evaluated on a per pack basis, unless clinical experts or other evidence suggests

that prescribing and dispensing is done such that there would be no wastage.[58] In response to clarification question B24, the company stated that oral treatments were costed on a per mg approach, implicitly assuming no wastage for oral treatments. Upon the request of the EAG, a scenario analysis was provided assuming a per pack costing approach, which substantially increased the incremental costs. The EAG noted, however, that the per pack drug acquisition costs in the economic model were applied every four weeks/model cycles instead of every week/model cycle, which likely resulted in overestimated total acquisition costs due to discounting and survival. Therefore, in line with the NICE process and methods guide, the EAG adopted the per pack costing approach in its base-case, but amended the company's approach to make sure acquisition costs were modelled every week/model cycle.

b) In their initial base-case, the company included subsequent treatments received by ≥1% of patients in the treatment-naïve cohort of PHAROS. Upon request, the EAG's clinical expert agreed on 1) the proportion of patients modelled to receive subsequent treatments ( ) in both arms, 2) the assumption that patients initially on dabra+tram are assumed to get the same subsequent treatment proportions as patients who were initially on enco+bini, 3) the assumption of no re-treatment with enco+bini and dabra+tram in patients who initially received those treatments, 4) the modelled subsequent treatments being in line with what would be expected in UK clinical practice and 5) the modelled duration of subsequent treatments ( ). The EAGs clinical expert further stated that in UK clinical practice "*many centres will treat with carboplatin and cisplatin as it is more convenient to administer with fewer toxicities and better tolerability*". In addition, the clinical expert noted that the ABCP regime (atezolizumab, bevacizumab, carboplatin and paclitaxel) was not included, which is used infrequently in the fittest patients. Lastly, the EAG clinical expert highlighted that nivolumab + ipilimumab ± chemotherapy are not available in the UK. In response to clarification, the company updated its base-case by excluding subsequent treatments that are currently not recommended for use in the NHS, which resulted in the exclusion of enco+bini, dabra+tram, and nivolumab+ipilimumab ± chemotherapy. The EAG considers the modelling of subsequent treatments in the company's updated base-case (i.e., excluding treatments that are currently not recommended for use in the NHS) to be reasonable.

c) In the CS it was stated that "*In England, patients diagnosed with non-squamous NSCLC are routinely tested for common driver mutations, including BRAF V600E mutations, via NGS panel testing. As such, the need to identify patients with NSCLC with a BRAF V600E mutation would not result in any additional testing costs."* In clarification question B28, the EAG requested evidence to support this statement. The company responded that BRAF V600E mutation testing is a part of routine UK clinical practice and is included in the 2021/2022 National Genomic Test Directory for cancer. For completeness, the company provided a scenario analysis including a one-off testing cost at the start of the model of £1,360 for BRAF V600 and £2,720 for BRAF V600E based on incidences of respectively 2.50% and 1.25% and a unit test cost of £34, which had a minor decreasing impact on the incremental costs. The EAG clinical expert agreed with the company's assumption that non-squamous NSCLC are routinely tested for BRAF V600E mutations in the UK, and the EAG therefore considers this assumption sufficiently justified.

d) Healthcare resource use in the economic model was informed by TA898, whereas the reported healthcare resource use in . In response to clarification, the company provided a scenario analysis informing healthcare resource use based , which suggests that the company's current base-case approach is conservative.

4.2.10 Disease severity

The QALY shortfall analysis was calculated in line with NICE DSU TSD 23.[59] The expected general population mortality values were taken from the Office for National Statistics (ONS) Life Tables for the years 2017-19.[60] The expected general population utility values were derived from Hernandez Alava 2020.[61] Total discounted QALYs for treatment-naïve advanced NSCLC patients with a BRAF V600E mutation treated with dabra+tram were derived from the company's economic model. In the revised company base case, the informing sex distribution (% female), starting age (based on the treatment-naive cohort from the PHARHOS study) and discount rate were 61%, 67 and 3.5%, respectively. The results presented in the CS were in between the results from the calculator when rounding down and up.

In the revised company base case, the expected discounted QALYs for people without BRAF V600 MT NSCLC were 9.97 and the expected undiscounted life years were 13.88. Patients treated with dabra+tram were modelled to accrue [redacted] discounted QALYs, resulting in an absolute shortfall of [redacted] and a proportional shortfall of [redacted] (Table 4.11). Hence, a severity modifier of x1.0 was applied in the company's base-case (Table 4.12).

Table 4.11: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality adjusted life year		

Table 4.12: Summary of company QALY shortfall analysis in its revised base-case

Expected total QALYs for the general population	Total expected QALYs for NSCLC patients with a BRAF V600E mutation on dabra+tram	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
9.97	[redacted]	[redacted]	[redacted]	1.0

Based on Table 91,92,93,94 in CS. Clarification letter question B30
BRAF = v-Raf murine sarcoma viral oncogene homolog B; CS = company submission; dabra+tram = dabrafenib in combination with trametinib; NSCLC = non-small-cell lung cancer; QALY = quality-adjusted life year

EAG comment: The EAG was unable to reproduce the company absolute and proportional QALY shortfall results using the QALY shortfall calculator by Schneider et al.[62] Using a starting age of 67 years, proportion female 61%, a 3.5% discount rate, and [redacted] expected discounted QALYs for patients on dabra+tram (in line with the economic model), the EAG found absolute and proportional QALY shortfalls of [redacted] and [redacted] respectively. Although these results deviate from the results reported by the company, this does not affect the modelled severity weight of 1.0x. Finally, the EAG would like to note that the presented QALY shortfall results only apply to the dabra+tram comparator and additional QALY shortfall analyses should also be performed when other relevant comparators mentioned in the NICE scope are introduced.

4.2.11 Uncertainty

According to the company, the key areas of uncertainty were:

- The treatment-naïve populations in PHAROS, IFCT, and the comparative BRF113928 trials are relatively small, since V600E MT NSCLC is a rare form of NSCLC. Therefore, a scenario was conducted to explore the impact of pooling data from the pivotal phase 2 PHAROS trial and the supportive IFCT study to maximise available data.

EAG comment: The EAG broadly agrees with the company's assessment of the key areas of uncertainty. In addition to the uncertainty related to the relatively small studies, the EAG also considers the ITC, the design of the informing PHAROS and IFCT studies being open-label and single-arm, and the lack of TTD data for dabra+tram key areas of uncertainty.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The CS base-case cost effectiveness results (probabilistic) indicated that enco+bini is more effective (incremental QALYs of [redacted]), and less costly (reduced costs of [redacted], including PAS for enco+bini), and therefore a dominant strategy when compared to dabra+tram (Table 5.1). The incremental net health benefits (NHB), at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, were [redacted] and [redacted], respectively.

Table 5.1: Summary of the initial company pairwise probabilistic results

Treatment	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]					

dabra+tram = dabrafenib in combination with trametinib; enco+bini = encorafenib in combination with binimetinib; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year

Overall, the technology is modelled to affect QALYs by:

- Increased PFS with incremental QALYs of [redacted] ([redacted] of the total incremental QALYs).

Overall, the technology is modelled to affect costs by:

- Decreased acquisition costs of enco+bini (reduced costs of [redacted], [redacted] of the total costs for the treatment).

EAG comment: The main comments of the EAG relate to a) the health gains accumulated beyond the observed data, and b) the updated company base-case in response to the clarification letter.

a) In response to clarification question B32, the company provided the observed OS as well as PFS using restricted mean survival time (RMST) with multiple truncation points. Table 54 of the clarification response shows that the proportion of life years (LYs) accumulated beyond the observed data is substantially larger for enco+bini than for dabra+tram. For OS, this was [redacted] for enco+bini versus [redacted] for dabra+tram based on the maximum follow-up of [redacted] months as truncation point. For PFS, this was [redacted] for enco+bini versus [redacted] for dabra+tram based on the 90% of maximum follow-up of 32.2 months as truncation point. It should be noted that the EAG does not report the maximum truncation point of 35.8 months for PFS here, as there seem to be errors for this truncation point in Table 54 (e.g., the observed restricted mean survival time for the comparator is not consistent with the increment, it seems to be too large). Furthermore, the EAG noted that the majority of incremental gains are also accumulated beyond the observed period. The percentage incremental gain for OS was [redacted]% at the [redacted] month truncation point and for PFS it was [redacted] at the 35.8 month truncation point. Considering the uncertainty in the modelled long-term estimates for OS and PFS (see EAG comment in Section 4.2.6 of this report), the EAG would like to see additional explanation of the mechanism by which the model generated these differences as well as justification for why these are plausible based on the available evidence. This includes verifying the plausibility of the model extrapolations of the partitioned survival model extrapolations, as commented on in Section 4.2.2 of this report.

b) The company updated its base-case in response to the clarification letter, including removal of all non-UK subsequent therapies, usage of the MAIC-adjusted patient characteristics, extension of the time horizon to 36 years, and amendment of the formula for subsequent therapy drug acquisition and administration costs. In the company's updated base-case, enco+bini is associated with incremental QALYs of [redacted] and a cost saving of [redacted], versus dabra+tram. The incremental NHB, at WTP thresholds of £20,000 and £30,000 per QALY gained, were [redacted] and [redacted], respectively. Results of the updated probabilistic company base-case are reported in Table 5.2 below.

Table 5.2: Summary of the updated company pairwise probabilistic results

Treatment	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]					

dabra+tram = dabrafenib in combination with trametinib; enco+bini = encorafenib in combination with binimetinib; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. The probabilistic incremental cost-effectiveness ratio (ICER) was consistent with the deterministic analysis. The proportion of simulations considered cost-effective at a WTP-threshold of £30,000 per QALY was [redacted]%.

The parameters that have the greatest impact on the NHB (based on the company's one-way sensitivity analyses) were:

- The parametric survival curve parameters for PFS, TTD and OS
- The MAIC HRs for OS and PFS for enco+bini versus dabra+tram
- The RDIs
- The PF utility value.

Consistently, modelling assumptions that relate to these parameters likely had the greatest effect on the NHB. However, enco+bini remained dominant in all scenarios, and the NHB positive. The following CS scenarios had the largest impact on the NHB:

- Exponential curve to fit the median TTD reported from BRF113928 ([redacted]% decreased NHB, in the original company base case results)
- Exponential curve to fit the median TTD reported from real-world evidence (RWE) study Auliac et al. 2020 ([redacted]% increased NHB, in the original company base case results)
- Assume TTD is equal to PFS for enco+bini ([redacted] decreased NHB, scenario analysis provided in response to the clarification letter).
- Apply the HR between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabra+tram to derive an estimation of dabra+tram TTD ([redacted] decreased NHB, scenario analysis provided in response to the clarification letter).

EAG comment: The main concerns of the EAG relate to: a) issues related to the reporting of the results in sensitivity and scenario analyses, b) issues related to the probabilistic sensitivity analysis, c) lack of modelling all relevant scenarios.

a) The EAG noted issues related to the reporting of the DSA and scenario analyses results. First, in their original submission the company mentioned one result in the DSA where dabra+tram would be dominant instead of enco+bini (see CS B3.12.2). This was, however, not shown in the tornado diagram (CS Figure 39), and the company in response to clarification question B33 corrected this by stating that all DSAs resulted in enco+bini being the dominant strategy. Second, there were inconsistencies between CS Table 100 and the reported scenario analyses results in the economic model. The company apologised for these inconsistencies in response to clarification questions B33 and B34 and reported corrected results. However, the EAG was still unable to reproduce the deterministic results of the following scenario analyses: 'Source of subsequent therapies, dabra+tram, TA898 base case', 'Source of subsequent therapies, clinical opinion', 'Subsequent therapy duration – TA898 scenario analysis' and 'Subsequent therapy duration - TA898'. In addition, the EAG noted that in the subsequent therapies sheet of the updated economic model the drop-down menu related to the source of subsequent treatment duration for enco+bini included the 'TA898-scenario' twice, whereas the 'TA898 base case' option seemed to be missing. Furthermore, for dabra+tram the source of 'clinical opinion' did not show the intended distribution of subsequent therapies, and results of the scenario 'Subsequent therapy duration – TA898 scenario analysis' were reported under another scenario (i.e., subsequent therapy duration - TA898) in the economic model. The company should provide further clarification on all inconsistencies and errors identified by the EAG, accompanied by a corrected economic model.
b) The EAG identified multiple issues related to the company's PSAs. Firstly, the company's probabilistic analyses results were substantially different than the deterministic analyses results, i.e., substantially higher incremental costs and lower increment QALYs. The EAG would like to see this further explored and justified by the company**.** Secondly, the EAG noted that running the PSA is relatively time consuming, and it would therefore appreciate if the company would explore ways of lowering the run-time. Finally, the probabilistic results in the company's initial submission could not be exactly reproduced due to the use of a random seed. In response to clarification, the company resolved this issue by providing an updated economic model including a fixed seed.

[redacted]

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company held two advisory boards and a follow-up consultation with three oncologists and two health economists to ensure that the inputs, assumptions, and outcomes were relevant and plausible to the UK clinical practice. The model inputs which were validated by the clinical experts can be found in CS section B.3.13.1.3.

5.3.2 Technical verification

As per the CS, quality-control procedures for coding, inputs and model assumptions were performed by model developers and health economists not involved in the development of the model. This included cell-by-cell checks of formulae, rebuilding of key sections of the model and logical tests. The utilised checklist, procedures and outputs of the independent review were not detailed in the CS.

5.3.3 Comparisons with other technology appraisals

Cross validation with other technology appraisals was performed for various input parameters (e.g., health state utility values, adverse events), the model structure and other model features (e.g., no administration cost assumption) (see CS section B3.4.4, B3.4.5, B.3.2.2 and B3.5.2 of the CS).

5.3.4 Comparison with external data used to develop the economic model

Validation of extrapolated data was performed by comparing these to observed survival rates from the PHAROS and BRF113928 studies (see Table 101 and 102 of the CS).

5.3.5 Comparison with external data not used to develop the economic model

Supportive evidence for the CS base-case is provided by the IFCT academic study for the OS and PFS long-term extrapolations of enco+bini. Other external data validation was not explicitly mentioned in the CS section B3.13.

EAG comment: The main concerns of the EAG relate to: a) insufficient technical verification of the economic model, b) lack of cross validation with other TAs, and c) transparency issue related to the lack of the full advisory board meeting minutes.

a) The EAG is concerned that the technical verification of the company's economic model was insufficient. The company confirmed that quality-control procedures for coding, inputs and model assumptions were performed by model developers and health economists not involved in the development of the model. In response to clarification question B36, the company confirmed that the Drummond checklist, the Philips checklist, HTA methods guides and NICE DSU TSD series were followed. However, despite the company's effort, the EAG identified errors in formulae within the economic model. The EAG, noted that the reported proportion of patients that had clinically inconsequential TEAEs for dabra+tram in clarification response Table 30 was inconsistent with the proportion of patients in the economic model (see EAG comment in Section 4.2.7). Furthermore, **t**he EAG was unable to reproduce the scenario analyses related to subsequent therapies due to errors in the drop-down menu of the 'Subsequent treatments' sheet (see EAG comment in Section 5.2 of this report). Finally, the EAG requested the company to complete the technical verification (TECH-VER) checklist in clarification letter B36b, but this was not provided.[63] The company should correct all errors in the economic model and further justify why

these were not identified during their technical verification. A reassessment of technical verification should be provided as well as the completed TECH-VER checklist.

b) The company provided cross-validation only with TA898 in response to clarification question B37, despite that other relevant TAs were mentioned in their initial CS (e.g., TA812, TA789, TA781, TA654, TA643, TA310, TA520, TA724, TA705, TA713).[32-37, 40, 51, 64, 65] Although cross validation should ideally take place in the exact same population (i.e., including BRAF V600E MT), given the rarity of BRAF V600E mutations the EAG would also like to see cross-validation with TAs including NSCLC regardless of mutation status.

c) Various modelling assumptions in the CS were justified based on expert opinion from advisory board meetings and the follow-up consultation. The EAG noted, however, that only a summary rather than the full meeting minutes of these advisory boards was provided. Although requested in clarification question B39, the company did not provide the full advisory board details because of commercial sensitivity. The EAG considers this to be a serious transparency issue as it is unable to verify various assumptions made by the company, and the full meeting details should therefore be provided.

6. External Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[66]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

No fixing errors.

6.1.1.2 Fixing violations

1. Approach of modelling drug acquisition costs of oral treatments (Section 4.2.9)
   Per pack instead of per mg costing approach for oral treatments.

6.1.1.3 Matters of judgement

2. Modelling of TTD for dabra+tram (Section 4.2.6)
   Applying the HR between PFS and TTD for enco+bini to PFS for dabra+tram to estimate TTD instead of assuming TTD to be equal to PFS for dabra+tram.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

3. Health state utility values based on alternative evidence (Section 4.2.8)
   Use PF and PD utility from TA310
4. Health state utility values based on alternative evidence (Section 4.2.8)
   Use PF and PD utility from TA258

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Uncertainty related to long-term extrapolation of OS, PFS, and TTD	4.2.6	Transparency/imprecision	Full advisory board and detailed expert opinion. Consideration of external data sources to inform long-term outcomes.	+/-	No	Validate extrapolated curves with expert expectations. External validation of long-term extrapolations Exploration of more flexible parametric survival models.
Assumptions related to waning of relative treatment effectiveness	4.2.6	Unavailability/methods	Scenarios with different waning assumptions. Validate the duration and pattern of treatment effect waning.	+	No	Scenario and sensitivity analyses varying waning assumptions. Validation of waning assumptions Comparative analyses of similar treatments to infer plausible waning patterns.
Uncertainty in the source to inform the modelling of health state utilities	4.2.8	Bias and indirectness	Scenario analyses exploring the plausible range of health state utility values	+/-	Partly	N/A
Approach of modelling drug acquisition costs of oral treatments	4.2.9	Methods	Scenario analysis using a per pack costing approach for oral treatments in line with the NICE process and methods guide	-	Yes	N/A
Majority of health gains accumulated	5.1	Unavailability	Explanation of the mechanism by which the model generated these differences as well as	+/-	No	Explanation of the mechanism by which the model generated these

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
beyond the observed data			justification for why these are plausible based on the available evidence.			differences as well as justification for why these are plausible based on the available evidence.
Issues related to (the reporting of) probabilistic and sensitivity analyses	5.2	Transparency/ imprecision/ unavailability	Correct errors in the economic model that prevented the reproduction of scenario analyses and for every scenario analysis provide step by step details on how to conduct these in the economic model.	+/-	No	Explore and justify the substantially different deterministic and probabilistic results Correct errors in the economic model. Provide step by step details for every scenario analysis Explore ways of lowering the PSA run-time
Insufficient technical verification of the economic model	5.3	Methods/Transparency	Provide sufficient technical verification of the economic model.	+/-	No	Correct errors in the economic model, justify why these were not identified during their technical verification and provide a reassessment of technical verification. Provide a completed version of the TECH-VER checklist.
Lack of transparency regarding expert consultation and comparisons with	5.3	Transparency	Provide more transparency regarding expert elicitation. Cross-validation with other relevant NICE TAs.	+/-	No	Provide full advisory board meeting minutes. Provide comparisons with other relevant NICE TAs focussed on similar,

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
other relevant NICE appraisals						potentially relevant, diseases (other than TA898)

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator

[b] Explored

EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; TA = Technology Appraisal; TECH-VER = technical verification; TTD = time to treatment discontinuation

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic and probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Deterministic CS base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Fixing violations (1- Per pack costing approach for oral treatments)						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Matter of judgement (2- dabra+tram TTD using HR between PFS and TTD of enco+bini						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Deterministic EAG base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Probabilistic EAG base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

CS = company submission; dabra+tram = dabrafenib in combination with trametinib; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation; WTP = willingness to pay

Table 6.3: Probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Probabilistic EAG base-case						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Scenario 1 (Health state utility values based on TA310)						
Enco+bini	[redacted]	[redacted]				

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Scenario 2 (Health state utility values based on TA258)						
Enco+bini	[redacted]	[redacted]				
Dabra+tram	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

dabra+tram = dabrafenib in combination with trametinib; EAG = External Assessment Group; enco+bini = encorafenib in combination with binimetinib; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year; TA = Technology Appraisal; WTP = willingness to pay

6.3 EAG's preferred assumptions

The estimated EAG base-case NHB (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted]. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted]% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was applying the HR between PFS and TTD for enco+bini to PFS for dabra+tram to estimate TTD. The NHB decreased most in the scenario analysis with alternative assumptions regarding the source to inform health state utility values.

6.4 Conclusions of the cost effectiveness section

The CS, response to clarification and Appendices G, H and P provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant cost effectiveness evidence for the treatment of patients with BRAF V600 MT advanced NSCLC.[2, 5, 10, 11] Searches were conducted in June 2023 (updated May 2024 and January 2025) for the economic evaluation/HCRU SLR, and in October 2021 (updated May 2023, July 2023 and May 2024) for the HRQoL SLR. All searches were transparent, well-documented and reproducible, and comprehensive strategies were used. An extensive range of bibliographic databases, conference proceedings, HTA and guidelines websites and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although it would have been preferable not to have limited to English language studies only.

The company's cost effectiveness model partly complied with the NICE reference case. The only deviation from the NICE reference case related to unclarity whether the UK tariff was used to calculate the health state utility values. The most prominent issues highlighted by the EAG are reported in the key issue tables in Section 1.5.

Firstly, long-term estimates for OS, PFS, and TTD represent a key uncertainty. These were informed by the company through expert opinion, but the advisory board presentation slides and full report were not provided, which made it challenging for the EAG to evaluate the robustness of the estimates. In addition, immaturity of the OS and PFS data from PHAROS introduced significant uncertainty related to the extrapolated OS and PFS. This issue was particularly influential due to a large proportion of life-years being gained beyond the available trial data. To support the company's partitioned survival modelling approach, further explanation of the mechanisms by which the economic model generated these results would be informative. Additional uncertainty to the long-term relative treatment effectiveness relates to the current evidence on treatment waning, which may not support sustained treatment effects beyond the trial duration. The EAG suggests implementing scenarios with different waning assumptions, and the use of external clinical input and/or RWE to validate the duration and pattern of treatment effect waning. Moreover, the company assumed that TTD equals PFS for

dabra+tram due to a lack of TTD data for this treatment. The EAG considered that this assumption requires further exploration and preferred the company's scenario analysis applying the HR between PFS and TTD for enco+bini to estimate TTD for dabra+tram. Secondly, there was uncertainty regarding the source to inform the modelling of health state utilities. Health-related QoL data in PHAROS was lacking and the EAG noted serious limitations in alternative studies presented by the company. Two EAG scenario analyses explored modelling a plausible range of health state utility values to quantify this uncertainty, which resulted in probabilistic incremental QALYs ranging between [redacted] and [redacted]. Thirdly, oral treatments in the company's economic model were costed per mg, which is not in line with the NICE process and methods guide stating that the costs of oral treatments dispensed in tablet packs should be evaluated on a per pack basis. A per pack costing scenario analysis was provided by the company in which drug acquisition costs were modelled every four weeks, likely overestimating total acquisition costs. An amended version of this scenario analysis (modelling acquisition costs every week) was therefore adopted in the EAG base-case. Fourthly, several modelling errors and inconsistencies in the company's economic model, including issues related to reproducing the results of scenario analyses, indicated that the company's economic model was insufficiently technically verified. The EAG also noted that the company's probabilistic analyses results substantially differed from the deterministic analyses results, which should be further explored and justified by the company. Finally, the company did not provide the full advisory board report, which was considered a serious transparency issue as it hinders validation of various modelling assumptions informed by clinical experts, including long-term estimates for OS, PFS, and TTD as mentioned above.

The estimated EAG base-case NHB (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted]. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted]% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was applying the HR between PFS and TTD for enco+bini to PFS for dabra+tram to estimate TTD. The NHB decreased most in the scenario analysis with alternative assumptions regarding the source to inform health state utility values.

There is large remaining uncertainty about the effectiveness and cost effectiveness of enco+bini, which can be partly resolved by the company. This includes providing the full documentation of the advisory board, explanation and justification of the mechanisms by which the economic model generated a substantial proportion of life-year gains beyond the observed data, scenarios including different waning assumptions, and the use of external clinical input or real-world evidence to validate the duration and pattern of treatment effect waning. Additionally, the company should explore the substantial difference between the probabilistic and deterministic results, correct all errors in the economic model, further explain why these were not identified during initial technical verification, and provide a thorough reassessment of technical verification. At the moment, according to the EAG, the CS nor the EAG report contains an unbiased estimate of enco+bini compared with all relevant comparators.

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Single Technology Appraisal

Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer [ID6177]

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 Wednesday 5 March 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 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1: Points of clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
N/A	The Company has reviewed the EAG report against the latest and relevant version of its submission: Company evidence submission v3.0 for encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]. The Company would like to remind the EAG that multiple versions of the submission exist, with v3.0 being the most up-to-date. A revised version (v2.0) was submitted on 6th January 2025 to correct a syncing issue that had unintentionally duplicated certain text in v1.0. Subsequently, v3.0 was submitted on 5th February 2025 to address an issue with a confidential reference.	N/A	Not a factual inaccuracy.
Section 1.5, page 17, Table 1.12; Section 4.2.3, pages 94–95; Section 6.1.3, pages 117–118, Table 6.1	The sections listed all contain text which notes the EAG's request for the Company to provide more transparency/details regarding expert elicitation. The Company requests the removal of these statements, as details of the expert elicitation process were provided in responses to clarification questions B12 and B39. Therefore, it is misleading for the EAG to suggest that more	The Company believe that these statements are strong and misleading as information regarding clinical expert elicitation procedures and expert inputs were provided in the responses to clarification questions B12 and B39.	Not a factual inaccuracy.

	transparent/details should be provided when this information has already been submitted.		
Section 1.5, page 14, Table 1.6	The Company suggests that the EAG clarify that the Company provided a scenario analysis including waning in response to clarification questions as suggested. "Scenario and sensitivity analyses to test the robustness of cost-effectiveness outcomes to varying waning assumptions."	The Company would like to emphasise that in response to clarification question B11, a scenario was provided that models treatment waning at [redacted] months (maximum follow-up of PHAROS) for a duration of 24 months. The EAG agreed with the Company's assessment that the smoothed hazard plots provided in response to clarification question B11 suggest that a waning of treatment effect would not be applicable during the observed period. Therefore, a scenario in which waning begins immediately following the observed period represents the most conservative estimate of long-term treatment effectiveness for encorafenib + binimetinib (enco+bini) compared with dabrafenib with trametinib (dabra+tram).	Not a factual inaccuracy.

Section 2, page 19, Table 2.1	The Company suggests that the EAG re-word the following statement, as the basis for their concern is unclear. "The EAG are concerned that population for which the recommendation by NICE could be made might include the wider i.e., treatment experienced population for which evidence has not been presented in the CS."	The Company would like to emphasise that patients with advanced *BRAF* V600E mutation positive NSCLC are expected to receive enco+bini targeted therapy as a first-line therapy. A targeted therapy used in the first-line setting would not be administered again in the second-line. A targeted therapy would only be given in a second-line setting if one was not already administered in the first-line. However, with testing for *BRAF* now standard practice in the UK for NSCLC, the majority of patients would receive targeted therapy in the first-line setting. The Company also highlight that the TA898 recommendation for dabra+tram was for first-line treatment only (1). As noted by the EAG clinical expert, fewer than 5% of	Not a factual inaccuracy.

		patients may not undergo testing and these patients would likely receive a non-targeted treatment. As such, they would be treated according to the 'no-targetable mutations' pathway of the NICE guideline NG122 (2), i.e. without confirmation of a *BRAF* mutation, they would not be eligible for targeted enco+bini treatment.	
Section 2, page 20 and page 26	The EAG's stance on whether or not the comparators are in line with the NICE scope is currently unclear. In Table 2.1 on page 20, the EAG state "The comparators are in line with the NICE scope" However, on page 26 the EAG contradictorily noted "Therefore, given lack of objective data on contemporary clinical practice, lack of inclusion of comparators remains a key issue" Please could the EAG ensure consistency in their statements throughout the report.	There are conflicting statements in the EAG report with regards to whether or not the comparators used in the submission are in line with the NICE scope. As dabra+tram is the only other available targeted therapy, the Company consider it the most relevant comparator. Routine genome testing will identify patients with *BRAF* V600E mutations who are therefore eligible for targeted therapies, at first-line.	Table 2.1 has been amended.

		Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are currently recommended as treatment options where dabra+tram cannot be used, such as in the case of delays in *BRAF* testing. In TA898, the committee noted delays to *BRAF* testing were no longer a concern as it is included in NHS England's national genomic testing directory. Pembrolizumab with platinum doublet chemotherapy, pembrolizumab monotherapy, or atezolizumab monotherapy are therefore not relevant comparators. Monotherapies are also not considered relevant comparators, as these are indicated for previously treated patients with advanced NSCLC, and not a treatment-naïve population.	

Section 2.3, page 26	The language used in the EAG's clinical expert quote is unclear and potentially misleading. "*As genomic testing has been rolled out unequally around the UK (onus on centres to set this up themselves) it is possible that a small number of centres will still not have access to it and so patients may not be tested for BRAF-V600E and so they would be treated with standard 1st line therapies.*" Please could the EAG clarify what the EAG clinical expert meant by "centres". Note that if they are referring to NHS hospitals or trusts, then this statement is incorrect.	The assumption that there are a small number of "centres" without access to genomic testing or access to *BRAF* mutation testing is not accurate. Hospitals and NHS trusts are not responsible for independently setting up genomic testing, as testing is conducted through a network of seven genomic laboratory hubs (GLH), each responsible for coordinating services. These hubs, which have been operational for several years, are located within NHS trusts across England and provide next generation sequencing (NGS) for lung cancer.	Not a factual inaccuracy.
Section 3.2.2.1, page 36	Change from "This poses a **significant** limitation, as it increases the risk of performance bias and detection bias, particularly for subjective outcomes like progression-free survival (PFS) and disease control rate (DCR), which rely on investigator assessment" To	This statement in the EAG report is quite strong. The limitation is not significant, as the primary endpoint was ORR assessed by IRR, which the current wording does not clearly reflect. ORR by IRR ensures an unbiased, standardised evaluation by independent, blinded	Not a factual inaccuracy. The EAG notes that, whilst ORR might be the primary endpoint, it might not be the most clinically relevant outcome, and PFS is a very important input in the economic model.

	"This poses a limitation, as it increases the risk of performance bias and detection bias, particularly for subjective outcomes like progression-free survival (PFS) and disease control rate (DCR) which rely on investigator assessment (IA)**. Nevertheless, IA represents how treatment decisions are made in clinical practice, making the findings applicable to real-world settings. Furthermore, the relatively consistent outcomes observed across both ORR by IA and ORR by independent radiology review (IRR; primary endpoint) assessment approaches, strengthens confidence in trial outcomes**."	radiologists, minimises potential investigator bias, and provides a comparative measure against ORR by IA.	
Section 3.2.2.1, page 36	Remove "The absence of blinding may also lead to an overestimation of benefits in patient-reported outcomes, such as quality of life, due to the psychological impact of knowing the treatment being received."	Several studies have shown that open-label designs do not introduce clinically or statistically significant bias in patient reported outcome (PRO) results (3-8). Also, this sentence is misleading, as PRO outcomes were not collected in the PHAROS trial and are not listed in the NICE scope.	Health-related quality of life is listed in the final NICE scope. The EAG deems the sentence appropriate but acknowledges that PRO was not reported in the PHAROS trial and has now added an additional sentence to highlight this.
Section 3.2.2.2, page 40	Remove "However, it should be noted that no patients in the previously treated group had received TKIs or	The Company suggests removing this text as it discusses concerns that are	Not a factual inaccuracy. There is still some doubt as to

	other targeted therapies prior to enrolment. While this exclusion ensures that the efficacy and safety signals observed for encorafenib and binimetinib are not influenced by factors such as resistance mechanisms developed during earlier treatments, it may limit the generalisability of the findings to patients who have already undergone treatment with BRAF or MEK inhibitors in real-world settings as highlighted in the exclusion criteria in Table 3.5”	not applicable to a treatment-naive patient population. Since enco+bini is intended only for patients with advanced NSCLC with a *BRAF* V600E mutation who have not previously received therapy, mentioning the potential impact on patients who have undergone prior treatment is irrelevant. This change would improve the focus of the EAG report by aligning the discussion strictly with the target population.	whether previously treated patients are relevant.
Section 3.2.5.1.1, page 62	Change from **“EAG comment**：The results of subgroup analyses for the OS outcome of the PHAROS trial were not found in the CS or Appendix E, so the EAG requested that this be provided” To **“EAG comment**：The results of subgroup analyses for the OS outcome of the PHAROS trial were not found in the CS or Appendix E, so the EAG requested that this be provided. **The Company noted in their response to**	The additional information should be shared to clarify that subgroup analyses for OS were not planned for the PHAROS trial.	The EAG has amended the report accordingly. (Page 63 not 62)

	clarification questions that subgroup analyses were not conducted for the overall survival (OS) outcome, and was not planned for in the PHAROS trial"		
Section 3.2.6.2.1, page 69, Table 3.35	Change from "Table 3.35: Treatment-emergent adverse events" To "Table 3.35: Treatment-emergent adverse events **(any grade, SS)**"	Missing detail in table title should be added for clarity.	The EAG has made this amendment. (Page 70 not 69)
Section 4.2.3, page 94	Remove "Overall, the EAG considers further subgroup differentiation based on patient characteristics to be customary, feasible and informative"	The Company would like to clarify that cost-effectiveness subgroup analysis by patient characteristics was not requested as part of the NICE scope.	Sentence adjusted to clarify that the EAG suggestion of further subgroup differentiation was not part of the NICE scope.
Section 4.2.4, page 96	Change from "The company did not provide similar evidence for the dabra+tram combination treatment." To "The company did not provide similar evidence for the dabra+tram combination treatment**, as this data was not available.**"	The current wording in this sentence is misleading; it implies that the Company withheld evidence when, in reality, the necessary data was not available.	Sentence adjusted to incorporate the Company's request

Section 4.2.6.4, page 100	Change from “Notably, the incremental quality-adjusted life years (QALYs) were **substantially lower** in these scenarios, compared with the CS base-case, highlighting the **substantial** impact of assumptions related to the modelling of the relative treatment effectiveness.” To “Notably, the incremental quality-adjusted life years (QALYs) were reduced in these scenarios, compared with the CS base-case, highlighting the impact of assumptions related to the modelling of the relative treatment effectiveness.”	The use of the term ‘substantial’ is misleading, as the incremental QALY was reduced by [redacted].	Not a factual inaccuracy.
Section 4.2.6.4, page 101	Remove: “might potentially even be conservative as clinical experts stated that dabra+tram is more toxic and hence patients might discontinue treatment earlier compared with enco+bini.”	The Company does not consider it accurate to state that a scenario that applies the hazard ratio (HR) between PFS and TTD for enco+bini (HR: [redacted]) to PFS for dabra+tram to estimate TTD for dabra+tram to be conservative. This scenario underestimates TTD for dabra+tram (8.15 months) compared with 10.55 months in the combined cohort of BRF113928, which represents a more heavily	Not a factual inaccuracy.

		pre-treated population, and RWE on the treatment of 1L patients with dabra+tram (17.50 months).	
Section 4.2.9.3, pages 106–107	Revise: "The EAG noted, however, that the per pack drug acquisition costs in the economic model were applied every four weeks/model cycles instead of every week/model cycle, which likely resulted in overestimated total acquisition costs due to discounting and survival. Therefore, in line with the NICE process and methods guide, the EAG adopted the per pack costing approach in its base-case, but amended the company's approach to make sure acquisition costs were modelled every week/model cycle." The current statement implies that the Company approach to per-pack costing is not in line with the NICE methods guide.	The Company would like to highlight that the approach included to drug costing that applies the per pack drug acquisition costs every 4 weeks/model cycles does not likely overestimate drug costs and is in line with the NICE process and methods guide, contrary to the EAG's statement. As per the NICE methods guide oral treatments should be costed in line with dispensing. Both enco+bini and dabra+tram are given in 28-day cycles, as per the respective SmPCs. Furthermore, the EAG's approach to costing implies that patients being treated with enco+bini receive a pack of enco every week and a pack of bini every 2 weeks, while patients receiving	Not a factual inaccuracy.

		dabra+tram receive a pack of each, every week. The Company does not believe this to be an accurate reflection of UK clinical practice and therefore maintain that a 28-day dispensing schedule for both treatments is more appropriate for the base case.	
Section 5.2, page 111	Remove “Firstly, the company's probabilistic analyses results were substantially different than the deterministic analyses results, i.e., substantially higher incremental costs and lower increment QALYs”	The Company does not consider the statement by the EAG to be accurate. Comparator costs and intervention QALYs were within 0.5% of deterministic results. Intervention costs and comparator QALYs were within 3.5% of deterministic results.	Not a factual inaccuracy
Section 5.3.5, pages 112	Revise “Other external data validation was not explicitly mentioned in the CS section B3.13.”	The Company clarified that no external data was available for enco+bini. However, the Company provided comparison with all external data for dabra+tram identified in the SLR in response to clarification question B38.	Not a factual inaccuracy

Section 5.3.5, pages 112–113	Remove “b) The company provided cross-validation only with TA898 in response to clarification question B37, despite that other relevant TAs were mentioned in their initial CS (e.g., TA812, TA789, TA781, TA654, TA643, TA310, TA520, TA724, TA705, TA713).31-36, 39, 50, 63, 64 Although cross validation should ideally take place in the exact same population (i.e., including BRAF V600E MT), given the rarity of BRAF V600E mutations the EAG would also like to see cross-validation with TAs including NSCLC regardless of mutation status”	As first-line *BRAF* V600E mutation positive NSCLC is the only indication of relevance to this submission, the Company do not find the EAGs suggestion for cross validation with TAs regardless of NSCLC mutation status appropriate or in scope for this appraisal.	Not a factual inaccuracy

Issue 2: General inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.1.1, page 29	Change from "For Embase and MEDLINE, the database searches were limited to studies published in English only." To "For Embase, MEDLINE, **CENTRAL, and DARE/HTAD** the database searches were limited to studies published in English only."	The full list of database searches which were limited to studies in English only was incomplete. Furthermore, in the Company response to EAG clarification questions, the Company demonstrated that there were no relevant non-English language publications when searches were performed in these databases without restrictions.	The amendment has been made.
Section 3.2.2.7, page 46, Table 3.14	Change from "Yes - encorafenib 450 mg QD plus **trametinib** 45 mg BID, administered orally in 28-day cycles" To "Yes - encorafenib 450 mg QD plus **binimetinib** 45 mg BID, administered orally in 28-day cycles"	The company submission contained an error in the treatment name that has been replicated in the EAG report.	Amendment made.

Section 3.2.2.7, page 47, Table 3.15	Change from “Based on Table **34** of Appendix D” To “Based on Table **35** Appendix D”	Incorrect table reference. In the Company submission, the Downs and Black checklist tables were split into four separately labelled tables.	Amendment made.
Section 3.2.2.7, page 48, Table 3.16	Change from “Based on Table **34** Appendix D” To “Based on Table **36** Appendix D”	Incorrect table reference. In the Company submission, the Downs and Black checklist tables were split into four separately labelled tables.	Amendment made.
Section 3.2.2.7, page 49, Table 3.17	Change from “Based on Table **34** Appendix D” To “Based on Table **37** Appendix D”	Incorrect table reference. In the Company submission, the Downs and Black checklist tables were split into four separately labelled tables.	Amendment made.
Section 3.2.3.2.4, page 55, Table 3.24	Change from “Based on Table **19** of the CS” To “Based on Table **20** of the CS”	Incorrect table reference.	Amendment made.

<table>
<tr>
<td>Section 3.2.6.1.7, page 68, Table 3.34</td>
<td>Missing the following final row, in Table 3.34
<table>
<tr><th>Preferred term</th><th>1 April 2024</th><th>19 January 2023</th><th>22 September 2022</th></tr>
<tr><td>Pneumonia</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Missing row.</td>
<td>Missing row has been added.</td>
</tr>
<tr>
<td>Section 3.3.4, page 74, Table 3.39</td>
<td>Change from
Source: [redacted]
To
Source: Pierre Fabre. NSCLC Global Value Dossier V0.2 [Data on file] [CON]. 2024”</td>
<td>Correction of source referenced. This reference was updated in the latest Company submission, submitted 5th February 2025 (v3.0)</td>
<td>Ref updated</td>
</tr>
<tr>
<td>Section 4.1.1, page 84</td>
<td>Change from
“The CS, Appendix G, Appendix P and the company’s response to clarification provide details of an SLR…”
To
“The CS, Appendix G, Appendix I, Appendix P, and the company’s response to clarification provide details of an SLR</td>
<td>The HCRU/cost SLR is detailed in Appendix I, which is missing from the list in the EAG report.</td>
<td>Text amended</td>
</tr>
<tr>
<td>Section 4.1.1, page 87, Table 4.2</td>
<td>Remove the following row
<table>
<tr><th colspan="4">Guidelines organisations</th></tr>
<tr><td>• NICE
• ESMO
• ASCO
• NCCN
• TGA</td><td>Internet</td><td>All</td><td>17/6/24</td></tr>
</table>
</td>
<td>Clinical guidelines were exclusively searched in the clinical SLR, making it inaccurate to list these in
Table 4.2.</td>
<td>Rows removed</td>
</tr>
</table>

<table>
<tr>
<td>Section 4.1.2, pages 88–90, Table 4.3</td>
<td>Add the following missing rows

Outcomes 3

<table>
<tr><td>Outcome(s) 3 (HRQoL & HSUV)</td><td>QoL and utility ouctomes
PROs and symptom measures, HRQoL, patient preference
QoL instruments as reported in literature
Disease-specific or generic non-preference based QoL and PRO measures
Descriptive summary of health states, and/or change in health status/QoL results
Utilities derived using generic preference-based instruments (e.g., EQ-5D, SF-6D, HUI2, HUI3) for relevant health states
Direct utility estimates (e.g., SG, TTO)</td><td>Outcomes not listed</td></tr>
</table>

Study design 3

<table>
<tr><td>Study design 3</td><td>Any studies reporting relevant outcomes.</td><td>Animal / in-vitro studies</td></tr>
</table>
</td>
<td>The HRQoL & HSUV SLR outcomes and study design eligibility information are currently missing in Table 4.3.</td>
<td>Included as proposed by the Company</td>
</tr>
</table>

	(HRQoL & HSUV)	• SLRs or meta-analyses for reference checking only	• Clinical studies • Editorials • Letters • Case studies • Case reports • Narrative reviews		
Section 4.1.2, page 90, Table 4.3	Change from "Based on Appendix G, Table 9" To "Based on Appendix G, Table 9; **Appendix H, Table 19**"			Missing source.	Included as proposed by the Company
Section 4.2.1, page 91, Table 4.4	Change from "**Unclear whether the** UK tariff was used." To "UK tariff was used"			The UK tariff was used, as supported by the company submission. There is no indication or reason provided by the EAG for uncertainty with regards to the use of the UK tariff.	Not a factual inaccuracy.
Section 4.2.2, page 91	Change from "The company justified the chosen modelling structure as follows: it corresponded with trial endpoints, was reflective of the progressive nature and clinical care pathway of NSCLC and			Incomplete Company justification for the selected model structure	Not a factual inaccuracy.

	had been used in former NICE technology appraisals (TAs) addressing NSCLC" To "The company justified the chosen modelling structure as follows: it corresponded with trial endpoints, was reflective of the progressive nature and clinical care pathway of NSCLC and had been used in former NICE technology appraisals (TAs) addressing NSCLC. **Additionally, it was the accepted structure used for decision making in the dabra+tram appraisal (TA866) (1)**"		
Section 4.2.2, page 92	Change from "Applying a treatment effect to the enco+bini survival curves for the dabra+tram transitions was deemed a strong assumption and inappropriate by the company since they would fail to match the original dabra+tram survival curves." To "Applying a treatment effect to the enco+bini survival curves for the dabra+tram transitions was deemed a strong assumption and inappropriate by the company since they would fail to match the original dabra+tram survival curves. **In addition, as the Company did not have treatment effect data for these curves, it was not possible to estimate these treatment effects**"	Full explanation of why the company deemed applying treatment effects to enco+bini for the dabra+tram transitions was missing.	Not a factual inaccuracy.
Section 4.2.2, page 92	Change from "While the EAG recognises that implementing an STM would demand significant time and resources, this approach would be	The complete justification for why an STM was not a feasible	Not a factual inaccuracy.

<table>
<tr>
<td></td>
<td>particularly valuable to address the uncertainty associated with the extrapolated curves, which stem from immature PFS and OS data (i.e., 44.1% and 47.5% of patients had experienced OS and PFS events respectively).”

To

“The EAG recognises that implementing an STM would demand significant time and resources, and require treatment effect data for post-progression survival, and PFS without death, endpoints which were not available for dabra+tram. While therefore not feasible, this approach would be particularly valuable to address the uncertainty associated with the extrapolated curves, which stem from immature PFS and OS data (i.e., 44.1% and 47.5% of patients had experienced OS and PFS events respectively).</td>
<td>modeling approach was not provided.</td>
<td></td>
</tr>
<tr>
<td>Section 4.2.3, page 93, Table 4.5</td>
<td>Change row description for “Age (years)” to “Median age (years)”, as shown in example below.
<table>
<tr><td></td><td>MAIC matched on several factors</td><td>Original data</td><td></td></tr>
<tr><td></td><td>PHAROS - base case in the economic model (ESS=44)</td><td>PHAROS (N=59)</td><td>BRF113928 (N=36)</td></tr>
<tr><td>Median Age (years)</td><td>67.0</td><td>68</td><td></td></tr>
</table>
</td>
<td>Missing statistical detail.</td>
<td>Included as proposed by the Company</td>
</tr>
</table>

Section 4.2.3, page 94	Remove “Although requested by the EAG, the company failed to provide relevant patient characteristics for the BRF113928 trial.”	This is not accurate, as the EAG did not request for the Company to provide relevant patient characteristics for the BRF113928 trial.	The EAG did request in clarification question B4. a): “Please provide information on mean weight, height and body surface area for intervention **and comparator**, adding onto CS Table 28.” Table 28 also lists BRF113928 (here labelled NCT01336634). The EAG adjusted the phrasing slightly.
Section 4.2.6.1, page 97, Table 4.6	In column “PFS (CS B.3.3.2.1.2)”; row “Clinical plausibility of long-term projections (based on the October 2024 UK advisory board)” Change from “It was **not** expected that few patients are progression free beyond 5 year and therefore the Gompertz, generalised gamma, log-logistic and log-normal were not supported.”	Incorrect statement.	Amended as proposed by the Company

	To "It was expected that few patients are progression free beyond 5 year and therefore the Gompertz, generalised gamma, log-logistic and log-normal were not supported."		
Section 4.2.6.3, page 99	Change from "The 1-, **2-** and 10-year modelled OS was slightly lower compared with BRF113928 data and TA898" To "The 1- and 10-year modelled OS was slightly lower compared with BRF113928 data and TA898"	Incorrect. The 2-year modelled OS for dabra+tram was not lower compared with BRF113928 data and TA898.	This should have been "1-, 5- and 10-year" instead of "1-, 2- and 10-year", and is amended accordingly.
Section 4.2.7, page 102	Change from "The company only included grade ≥3 TEAEs with an incidence of ≥3% in either arm, despite a clinical expert highlighting that grade 1–2 **TEAEs** could also substantially impact HRQoL and costs." To "The company only included grade ≥3 TEAEs with an incidence of ≥3% in either arm, despite a clinical expert highlighting that grade 1–2 **pyrexia** could also substantially impact HRQoL and costs."	The EAG report does not clearly reflect that the comment made by the clinical expert was specific to pyrexia.	Not a factual inaccuracy.
Section 4.2.10, page 107	Change from "The informing sex distribution, starting age (based on the treatment-naive cohort from the PHARHOS study) and discount rate were **61**%, 67 and 3.5%, respectively."	Incorrect pivotal trial name, and additional clarity on base case inputs.	The EAG amended the text to clarify that the revised company

	To "**In the original CS,** the informing sex distribution (**% female**), starting age (based on the treatment-naive cohort from the **PHAROS** study) and discount rate were **56**%, **66.5** and 3.5%, respectively. **In the revised company base case, as a result of EAG clarification questions, these values were 61%, 67.0, and 3.5%, respectively**"		base case was used.
Section 4.2.10, page 108	Change from "The expected discounted QALYs for people without BRAF V600 MT NSCLC were **9.97** and the expected undiscounted life years were **13.88**" To "The expected discounted QALYs for people without BRAF V600 MT NSCLC **in the original CS** were **10.30** and the expected undiscounted life years were **19.50. In the revised company base case, as a result of the EAG clarification questions, these values were 9.97 and 13.88, respectively.**"	Additional clarity on base case results.	The EAG amended the text to clarify that the revised company base case was used.
Section 4.2.10, page 108, Table 4.12	Change Table 4.12 to the following	Incorrect statement.	The EAG amended the title of the table to clarify that the revised company base case was used.

<table>
<tr><td></td><td>
<table>
<tr><th>Expected total QALYs for the general population</th><th>Total expected QALYs for NSCLC patients with a BRAF V600E mutation on dabra+tram</th><th>Absolute QALY shortfall</th><th>Proportional QALY shortfall</th><th>QALY weight</th></tr>
<tr><td>10.30</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>1.0</td></tr>
<tr><td colspan="5">Based on Table 91,92,93,94 in CS. Clarification letter question B30
BRAF = v-Raf murine sarcoma viral oncogene homolog B; CS = company submission; dabra+tram = dabrafenib in combination with trametinib; NSCLC = non-small-cell lung cancer; QALY = quality-adjusted life year</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Section 5.3.1, page 111</td><td>Change from
“The company held three advisory boards and a follow-up consultation…”
To
“The company held two advisory boards and a follow-up consultation…”</td><td>Incorrect statement.</td><td>Corrected by the EAG as suggested by the company</td></tr>
</table>

Issue 3: Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.3.2.3, page 55, Table 3.33	Remove duplicated table heading.	Please remove the duplicated table heading, as it creates the impression that data may be missing.	The EAG is unsure what the issue is: perhaps Table 3.33 was a typo and the company was referring to another table 3.23. However, the EAG can find no duplicate table headings.
Section 3.3.2, page 73	Change from "A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis. considered this list of confounding factors appropriate for patients with BRAF V600E MT advanced NSCLC. **A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis. considered this list of confounding factors appropriate for patients with BRAF V600E MT advanced NSCLC. A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis. considered this list of confounding factors**	The error in the statement originates from the Company's original submission (v1.0) and includes duplicated text. The Company submitted a revised version (v3.0) on 5th February 2025 after identifying a syncing issue that led to the unintentional duplication of certain text in v1.0.	Amended.

	appropriate for patients with BRAF V600E MT advanced NSCLC. A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis." To • "At the June 2024 UK Advisory Board, clinical experts considered this list of confounding factors appropriate for patients with BRAF V600E MT advanced NSCLC. A restricted list of adjustment factors, including only the two factors identified as the key factors (ECOG-PS and smoking status), was used in a sensitivity analysis."		
Section 3.4.1, page 75	Change from *"Before matching, imbalances were observed between the two studies primarily on gender, race, and histology, as well as, to a lesser extent, on ECOG and smoking status. At the June 2024 UK Advisory Board, clinical experts commented on the differences in histology between trials but considered this to be a factor of greater patient numbers in PHAROS resulting in smaller proportions. One clinical expert noted that the trial population in PHAROS may be closer aligned with UK clinical practice when considering race. In general, clinical experts considered the trial populations to be similar and relatively balanced between the PHAROS first-line population and cohort C of the NCT01336634 study.* ***One clinical expert noted that***	The error in the statement originates from the Company's original submission (v1.0) and includes duplicated text. The Company submitted a revised version (v3.0) on 5th February 2025 after identifying a syncing issue that led to the unintentional duplication of certain text in v1.0.	Amended.

	the trial population in PHAROS may be closer aligned with UK clinical practice when considering race. In general, clinical experts considered the trial populations to be similar and relatively balanced between the PHAROS first-line population and cohort C of the NCT01336634 study." To *"Before matching, imbalances were observed between the two studies primarily on gender, race, and histology, as well as, to a lesser extent, on ECOG and smoking status. At the June 2024 UK Advisory Board, clinical experts commented on the differences in histology between trials but considered this to be a factor of greater patient numbers in PHAROS resulting in smaller proportions. One clinical expert noted that the trial population in PHAROS may be closer aligned with UK clinical practice when considering race. In general, clinical experts considered the trial populations to be similar and relatively balanced between the PHAROS first-line population and cohort C of the NCT01336634 study*."		
Section 3.4.1, page 76	Change from • *"After matching on all adjustment factors, the characteristics in the weighted PHAROS population were fully aligned with those in Cohort C of the NCT01336634 study. This resulted in a loss of sample size of approximately 25%, with the weighted*	The error in the statement originates from the Company's original submission (v1.0) and includes duplicated text. The Company submitted a revised version (v3.0) on	Amended.

	population representing 44 patients instead of the original 59. This was deemed acceptable by health economic experts at the June 2024 UK advisory board. ***This was deemed acceptable by health economic experts at the June 2024 UK advisory board.***" To • *"After matching on all adjustment factors, the characteristics in the weighted PHAROS population were fully aligned with those in Cohort C of the NCT01336634 study. This resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 patients instead of the original 59. This was deemed acceptable by health economic experts at the June 2024 UK advisory board. "*	5th February 2025 after identifying a syncing issue that led to the unintentional duplication of certain text in v1.0.	
Section 4.2.6 and 4.2.6.1, page 96	Change from "enco+bi**m**i" To "enco+bi**n**i"	Correction of intervention treatment abbreviation.	Corrected by the EAG as suggested by the company.
Section 4.2.7, page 102	In point c), remove the following sentences at the end of the paragraph: "Upon request, the EAGs clinical expert stated that these TEAEs would be more impactful if they occurred as grade 3 or 4. More specifically, the clinical expert	Repetition of text from earlier in the paragraph.	Corrected by the EAG as suggested by the company.

	stated that grade 1-2 blood biochemical abnormalities would not impact HRQoL or costs but bronchitis, herpes zoster and loss of consciousness may have a much bigger impact, especially if of a higher grade”		

Issue 4: Errors in reporting of economic model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.2, page 12, and Section 5.2, page 110	Change to: "Exponential curve to fit the median TTD reported from BRF113928 ([redacted]% decreased NHB)"	Incorrect reporting of percentage decrease in NHB	The EAG amended the text to clarify that the original company base case was used
Section 1.2, page 12, and Section 5.2, page 110	Change to: "Exponential curve to fit the median TTD reported from real-world evidence (RWE) study Auliac et al. 2020 ([redacted]% increased NHB)"	Incorrect reporting of percentage decrease in NHB	The EAG amended the text to clarify that the original company base case was used.

Issue 5: Company responses

Location of text	Description of text	Company response	EAG comment
Section 5.2, page 111	"… the EAG was still unable to reproduce the deterministic results of the following scenario analyses: 'Source of subsequent therapies, dabra+tram, TA898 base case', 'Source of subsequent therapies, clinical opinion', 'Subsequent therapy duration – TA898 scenario analysis' and 'Subsequent therapy duration - TA898'." And "…the EAG noted that in the subsequent therapies sheet of the updated economic model the drop-down menu related to the source of subsequent treatment duration for enco+bini included the 'TA898-scenario' twice, whereas the 'TA898 base case' option seemed to be missing." And "for dabra+tram the source of 'clinical opinion' did not show the intended distribution of subsequent therapies, and results of the scenario 'Subsequent therapy duration – TA898 scenario analysis' were reported under another scenario (i.e., subsequent therapy duration - TA898) in the economic model."	Thank you for highlighting these errors, the economic model has now been corrected. Please note that these corrections do not impact the results of the company or EAG base cases.	Thank you for highlighting these errors, the economic model has now been corrected. Please note that these corrections do not impact the results of the company or EAG base cases.

Section 5.3.5, page 112	“The EAG, noted that the reported proportion of patients that had clinically inconsequential TEAEs for dabra+tram in clarification response Table 30 was inconsistent with the proportion of patients in the economic model”	Thank you for highlighting these errors, the economic model has now been corrected. Please note that these corrections do not impact the results of the company or EAG base cases.	Thank you for highlighting these errors, the economic model has now been corrected. Please note that these corrections do not impact the results of the company or EAG base cases.

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10. Riely GJ, Smit EF, Ahn MJ, Felip E, Ramalingam SS, Tsao A, et al. Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With BRAFV600-Mutant Metastatic Non–Small-Cell Lung Cancer. Journal of Clinical Oncology. 2023;41(21):3700-11.

11. Pierre Fabre. Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendix F: Adverse reactions v2.0 [5.2.25]: Pierre Fabre2024.