Single Technology Appraisal

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

Committee Papers

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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]

Contents:

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NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Tuesday 24 June 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pierre Fabre

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Comments

Comment number	Comments
1	The company are concerned that the current description of the BRAF mutation in Section 3.1 of the draft guidance lacks clarity and may be difficult for readers to interpret accurately. As such, the following revision to the draft guidance is proposed: "*The BRAF V600E mutation is one of several mutations that can drive cancer growth. Among all BRAF mutations, approximately one-third to one-half are V600 mutations, with the majority of these being V600E. The clinical experts highlighted that the BRAF V600E mutation is relatively rare in NSCLC, occurring in no more than 2% of all lung cancers cases*." The proposed revision aims to improve the scientific context and readability of this section by clarifying the role of BRAF as a driver mutation, quantifying mutation prevalence, and highlighting the rarity of BRAF V600E in non-small cell lung cancer (NSCLC).
2	The discussion on generalisability in the draft guidance is unclear and potentially misleading. In Section 3.4, the reference to a single patient with Eastern Cooperative Oncology Group performance status (ECOG) performance status (PS) 2 in cohort C of BRF113928 adds little value and does not meaningfully address the broader issue of patient generalisability. It is acknowledged that the pivotal PHAROS trial was restricted to patients with ECOG-PS 0 or 1, and that one patient with ECOG-PS 2 was enrolled in cohort C. Given that ECOG-PS may be a prognostic factor in BRAF V600E NSCLC, this discrepancy might limit the generalisability of the trial and matching-adjusted indirect comparison (MAIC) results to the NHS population. However, this issue is largely unavoidable due to the rarity of the patient population and the challenges associated with conducting clinical trials in such settings, i.e. in patients with poor PS. This limitation and the constraints faced by the company are not adequately reflected in the draft guidance. A more balanced and transparent acknowledgment of this context is warranted to avoid misrepresentation of the evidence base and its applicability to NHS patients.
3	The Company would like to highlight that although thoracic cavity and liver metastasis data are available from TA898, these data were not collected in PHAROS and therefore cannot be adjusted for in the MAIC.
4	The Company would like to clarify the description of the presented scenario analysis in Section 3.13 "That is, the hazard ratio between the 2 treatments returned to 1 after the maximum follow up of the PHAROS trial." In this scenario the hazard ratio between the 2 treatments returns to 1 following a constant two year waning duration that begins at the maximum follow-up of the PHAROS trial.
5	Correction of

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	"alternative modelling approaches and detailed clinical expert input for TTD for encorafenib plus binimetinib (see section 3.12)" To "alternative modelling approaches and detailed clinical expert input for TTD for dabrafenib plus trametinib (see section 3.12)"

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Single technology appraisal

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

Additional post-submission analyses

August 2025

File name	Version	Contains confidential information	Date
ID6177_enco+bini BRAF V600E MT NSCLC analyses_Sept 2025_v3_[Redacted].docx	3.0	No [Redacted]	23rd September 2025

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List of Abbreviations

Abbreviation	Description
ACM	Appraisal committee meeting
AE	Adverse event
BNF	British National Formulary
BRAF	v-Raf Murine Sarcoma Viral Oncogene Homolog B
CI	Confidence interval
CEAC	Cost-effectiveness acceptability curve
Dabra+tram	Dabrafenib + trametinib
DBL	Database lock
DCO	Data cut-off
DSU	Decision Support Unit
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
FE	Fixed effects
HCP	Health care professional
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IFCT	Intergroupe Francophone de Cancérologie Thoracique
IIT	Investigator-initiated trial
IRC	Independent Review Committee
IRR	Independent radiology review
ITC	Indirect treatment comparison
KM	Kaplan-Meier
KOL	Key opinion leader
MT	Mutation positive
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PFS	Progression-free survival
PH	Proportional hazards
PS	Performance status
QALY	Quality-adjusted life year

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Abbreviation	Description
QoL	Quality of life
RE	Random effects
REML	Restricted maximum-likelihood estimator
RWE	Real-world evidence
SE	Standard error
SAS	Safety analysis set
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTD	Time-to-treatment discontinuation
WTP	Willingness-to-pay

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1 Context

A single technology appraisal for encorafenib in combination with binimetinib (enco+bini) for treating BRAF V600E mutation-positive (MT) advanced non-small cell lung cancer (NSCLC) [ID6177] was submitted to the National Institute for Health and Care Excellence (NICE) on the 5th May 2025. Following the first appraisal committee meeting (ACM) held on the 13th May, NICE published negative draft guidance on the 3rd June 2025.

The NICE Committee and external assessment group (EAG) identified key uncertainties with potential impact on cost-effectiveness. As a result, further analyses were requested by the Committee, including:

- Using IFCT as the sole clinical data source
- Alternative methods for pooling IFCT and PHAROS data
- Different modelling assumptions for survival, including flexible models
- Independent extrapolation of each arm i.e. no proportional hazards assumed between enco+bini and dabrafenib in combination with trametinib (dabra+tram)
- Alternative treatment waning scenarios
- Alternative approaches to modelling dabra+tram time to treatment discontinuation (TTD).

Since the original submission, a new data cut-off (DCO; March 2025) for the key evidence base, PHAROS, has become available. Additionally, the company presents contextualisation of the supportive IFCT study, and alternative scenarios for the treatment duration of dabra+tram.

Furthermore, the Company conducted one-to-one interviews with three England-based oncologists with experience in treating NSCLC, including the use of dabra+tram. One of the clinicians also had additional experience in treating patients with melanoma with enco+bini. These consultations were conducted to gather expert insights to inform and validate the additional analyses.

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Leveraging this updated dataset, alongside the revised analyses approaches and clinical validation, the Company has generated revised cost-effectiveness results for submission to NICE.

This updated evidence package is intended to reduce the clinical and economic uncertainties identified by NICE and the EAG.

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2 Additional clinical effectiveness evidence

2.1 PHAROS

This section presents updated clinical effectiveness evidence from the primary evidence base for the submission of enco+bini for BRAF V600E MT NSCLC, namely the PHAROS trial.

Data presented are from the most recent data cut-off (DCO) 14th March 2025 (database lock [DBL] 3rd April 2025) and have been used to inform the updated economic model (1). The March 2025 DCO assessed the maturity of the OS data, with a final DCO anticipated in Q4 2025.

2.1.1 Patient disposition

Of the 59 patients treated with enco+bini at the PHAROS March 2025 DCO, [redacted]% discontinued treatment, primarily due to radiological disease progression ([redacted]%), adverse events ([redacted]%), and clinical disease progression ([redacted]%). Other reasons included consent withdrawal ([redacted]%), investigator or patient decision (each [redacted]%), and other causes ([redacted]%), with [redacted] discontinuations due to death. At the March 2025 DCO, [redacted] ([redacted]%) patients remained on treatment. Following treatment discontinuation, [redacted]% of patients continued to be followed for disease or survival, while [redacted]% discontinued the study. The leading cause of study discontinuation was death ([redacted]%), followed by consent withdrawal ([redacted]%), and loss to follow-up ([redacted]%).

Table 1: PHAROS patient disposition (SAS; March 2025 DCO)

Disposition	Treatment-naïve (N=59), n (%)
Patients treated	[redacted]
Treatment discontinued	[redacted]
Treatment ongoing†	[redacted]
Primary reason for treatment discontinuation	
AE	[redacted]
Disease progression (clinical)	[redacted]
Disease progression (radiological)	[redacted]
Consent withdrawn	[redacted]
Investigator decision	[redacted]

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Disposition	Treatment-naïve (N=59), n (%)
Death	[redacted]
Patient decision	[redacted]
Other	[redacted]
Study evaluation after treatment discontinuation	
Patients who continue to be followed for disease or survival	[redacted]
Patients who discontinued the study	[redacted]
Primary reason for study discontinuation	
Withdrawal of consent	[redacted]
Lost to follow-up	[redacted]
Death	[redacted]
Other	[redacted]

Source: Pierre Fabre. DOF. Table 14.1.1.2 (1).
†Patients ongoing at the time of the DCO.
Abbreviations: AE, adverse event; DCO, data cut-off; SAS, safety analysis set.

2.1.2 Progression-free survival

Progression-free survival (PFS) data are not available from the updated March 2025 DCO, as the intent of this DCO was to check the progress of OS data; the final PHAROS analysis and DCO of all outcomes is planned in Q4 2025.

2.1.3 Overall survival

At the March 2025 DCO, following a further [redacted] months of median follow-up since the latest DCO (April 2024 DCO) presented in the original submission, median OS was reached ([redacted] months; 95% CI: [redacted], [redacted]). Enco+bini showed a continued trend in OS benefit (Table 2, Table 3, Figure 1).

Table 2: PHAROS OS (SAS; March 2025 DCO)

	Treatment-naïve (N=59)
Number of deaths, n (%)	[redacted]
Number of censored, n (%)	[redacted]
Withdrawal of consent	[redacted]
Lost to follow-up	[redacted]
No longer follow for survival (alive patient who discontinued from the study for reason different from withdrawal consent and lost to follow-up)	[redacted]
Ongoing and no death	[redacted]
Event-free probability estimates (95% CI)†	
24 months	[redacted]

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	Treatment-naïve (N=59)
36 months	[redacted]
48 months	[redacted]
60 months	[redacted]
KM estimates of time to event (months), percentiles (95% CI)†	
25th	[redacted]
50th	[redacted]
75th	[redacted]

Sources: Pierre Fabre. DOF. Table 14.2.14 (1).
†Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Abbreviations: CI, confidence interval; DCO, data cut-off; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; SAS, safety analysis set.

Table 3: PHAROS duration of follow-up for OS (SAS; March 2025 DCO)

	Treatment-naïve (N=59)
Number of events, n (%)	[redacted]
Number of censored, n (%)	[redacted]
KM estimate of time to event (months), percentiles (95% CI)†	
25th	[redacted]
50th	[redacted]
75th	[redacted]

Source: Pierre Fabre. DOF. Table 14.2.17 (1).
Abbreviations: CI, confidence interval; DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; SAS, safety analysis set.

Figure 1: PHAROS KM of OS (SAS; March 2025 DCO)


[redacted]

Source: Pierre Fabre. DOF. Figure 14.2.14.1 (1).
Abbreviations: DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; SAS, safety analysis set.

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2.1.4 Time to treatment discontinuation

At the March 2025 DCO, enco+bini demonstrated a meaningful clinical benefit in terms of TTD in treatment-naïve patients, where median TTD was [redacted] months (Figure 2).

Figure 2: PHAROS KM of TTD (SAS; March 2025 DCO)

[redacted]

Source: Pierre Fabre. Post-hoc analysis based on Pierre Fabre DOF (1).
Abbreviations: DCO, data cut-off; KM, Kaplan Meier; SAS, safety analysis set; TTD, time to treatment discontinuation.

2.1.5 Treatment exposure

An overview of the duration of treatment exposure is presented in Table 4. The median actual treatment duration, as well as actual binimetinib and encorafenib treatment durations were [redacted] since the latest DCO presented in the original submission (April 2024 DCO).

Table 4: PHAROS duration of exposure (SAS; March 2025 DCO)

	Binimetinib (n=59)	Encorafenib (n=59)
Actual treatment duration (months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Actual treatment duration (months), n (%)		

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	Binimetinib (n=59)	Encorafenib (n=59)
≤1	[redacted]	[redacted]
>1 to ≤3	[redacted]	[redacted]
>3 to ≤6	[redacted]	[redacted]
>6 to ≤12	[redacted]	[redacted]
>12 to ≤24	[redacted]	[redacted]
>24	[redacted]	[redacted]

Source: Pierre Fabre. DOF. Table 14.4.1.1 (1).
This table summarises participants who received at least one dose of study drug at any given time.
Abbreviations: DCO, data cut-off; SAS, safety analysis set; SD, standard deviation.

2.1.6 Adverse reactions

The proportion of patients with Grade 1–2 treatment emergent adverse events (TEAE) in ≥3% of patients in the treatment-naïve cohort of PHAROS, at the March 2025 DCO is presented in Table 5.

Table 5: Proportion of patients with Grade 1–2 TEAEs in ≥3% of patients

Event	PHAROS, treatment-naïve cohort Grade 1–2 TEAEs
Abdominal discomfort	[redacted]
Abdominal pain	[redacted]
Abdominal pain upper	[redacted]
Abnormal loss of weight	[redacted]
Actinic keratosis	[redacted]
Acute kidney injury	[redacted]
Alanine aminotransferase increased	[redacted]
Alopecia	[redacted]
Amylase increased	[redacted]
Anaemia	[redacted]
Anal haemorrhage	[redacted]
Anxiety	[redacted]
Arthralgia	[redacted]
Aspartate aminotransferase increased	[redacted]
Asthenia	[redacted]
Back pain	[redacted]
Balance disorder	[redacted]
Blood alkaline phosphatase increased	[redacted]
Blood creatinine increased	[redacted]
Blood creatinine phosphokinase increased	[redacted]
Blood iron decreased	[redacted]
Cataract	[redacted]
Chills	[redacted]

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Event	PHAROS, treatment-naïve cohort Grade 1–2 TEAEs
Colitis	[redacted]
Conjunctivitis	[redacted]
Constipation	[redacted]
Contusion	[redacted]
Cough	[redacted]
COVID-19	[redacted]
Decreased appetite	[redacted]
Deep vein thrombosis	[redacted]
Dehydration	[redacted]
Depression	[redacted]
Dermal cyst	[redacted]
Dermatitis acneiform	[redacted]
Diarrhoea	[redacted]
Dizziness	[redacted]
Dry skin	[redacted]
Dysgeusia	[redacted]
Dyspepsia	[redacted]
Dysphagia	[redacted]
Dyspnoea	[redacted]
Ejection fraction decreased	[redacted]
Erythema	[redacted]
Face oedema	[redacted]
Fall	[redacted]
Fatigue	[redacted]
Haemorrhoids	[redacted]
Hair texture abnormal	[redacted]
Headache	[redacted]
Hot flush	[redacted]
Hyperglycaemia	[redacted]
Hyperkalaemia	[redacted]
Hyperkeratosis	[redacted]
Hypertension	[redacted]
Hyperuricaemia	[redacted]
Hypoalbuminaemia	[redacted]
Hypocalcaemia	[redacted]
Hyponatraemia	[redacted]
Hypophosphataemia	[redacted]
Hypotension	[redacted]
Influenza like illness	[redacted]
Insomnia	[redacted]
Iron deficiency	[redacted]
Keratitis	[redacted]
Lipase increased	[redacted]

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Event	PHAROS, treatment-naïve cohort Grade 1–2 TEAEs
Malaise	[redacted]
Melanocytic naevus	[redacted]
Memory impairment	[redacted]
Muscle spasms	[redacted]
Muscular weakness	[redacted]
Musculoskeletal chest pain	[redacted]
Myalgia	[redacted]
Myoglobin blood increased	[redacted]
Nasal congestion	[redacted]
Nasopharyngitis	[redacted]
Nausea	[redacted]
Neck pain	[redacted]
Neutrophil count decreaseed	[redacted]
Non-cardiac chest pain	[redacted]
Oedema peripheral	[redacted]
Oesophagitis	[redacted]
Oropharyngeal pain	[redacted]
Osteoporosis	[redacted]
Pain in extremity	[redacted]
Palpitations	[redacted]
Paraesthesia	[redacted]
Peripheral embolism	[redacted]
Peripheral sensory neuropathy	[redacted]
Photophobia	[redacted]
Photosensitivity reaction	[redacted]
Platelet count decreased	[redacted]
Pleural effusion	[redacted]
Pneumonia	[redacted]
Pollakiuria	[redacted]
Post herpetic neuralgia	[redacted]
Productive cough	[redacted]
Pruritus	[redacted]
Rash	[redacted]
Rash macular	[redacted]
Rash maculo-papular	[redacted]
Rash pustular	[redacted]
Respiratory tract infection	[redacted]
Retinal detachment	[redacted]
Rhinitis	[redacted]
Rhinitis allergic	[redacted]
Rhinorrhoea	[redacted]
SARS-CoV-2 test positive	[redacted]
Seborrhoeic keratosis	[redacted]

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Event	PHAROS, treatment-naïve cohort Grade 1–2 TEAEs
Sinusitis	[redacted]
Skin hyperpigmentation	[redacted]
Skin papilloma	[redacted]
Stomatitis	[redacted]
Tachycardia	[redacted]
Tinnitus	[redacted]
Tremor	[redacted]
Upper respiratory tract infection	[redacted]
Urinary incontinence	[redacted]
Vision blurred	[redacted]
Visual acuity reduced	[redacted]
Visual impairment	[redacted]
Vitreous floaters	[redacted]
Vomiting	[redacted]
Weight decreased	[redacted]
Weight increased	[redacted]
Xerosis	[redacted]

Pierre Fabre. DOF TEAE 2025 (2).
Abbreviations: AE, adverse event.

The proportion of patients with Grade ≥3 TEAEs in ≥3% of patients in the treatment-naïve cohort of PHAROS at the March 2025 DCO are presented in Table 6.

Table 6: Proportion of patients with Grade ≥3 TEAEs in ≥3% of patients

Event	PHAROS, treatment-naïve cohort Grade ≥3 TEAEs
Alanine aminotransferase increased	[redacted]
Amylase increased	[redacted]
Anaemia	[redacted]
Aspartate aminotransferase increased	[redacted]
Asthenia	[redacted]
Back pain	[redacted]
Blood alkaline phosphatase increased	[redacted]
Blood creatinine phosphokinase increased	[redacted]
Bronchitis	[redacted]
Colitis	[redacted]
Decreased appetite	[redacted]
Diarrhoea	[redacted]
Dyspnoea	[redacted]
Ejection fraction decreased	[redacted]
Fatigue	[redacted]
Gamma-gluamyltransferase increased	[redacted]
Gastrointestinal haemorrhage	[redacted]

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Event	PHAROS, treatment-naïve cohort Grade ≥3 TEAEs
Herpes zoster	[redacted]
Hypertension	[redacted]
Hyponatraemia	[redacted]
Hypotension	[redacted]
Leukocytosis	[redacted]
Lipase increased	[redacted]
Loss of conciousness	[redacted]
Myalgia	[redacted]
Nausea	[redacted]
Neutropenia	[redacted]
Pain in extremity	[redacted]
Pneumonia	[redacted]
Pulmonary embolism	[redacted]
Pyrexia	[redacted]
Retinal detachment	[redacted]
Vomiting	[redacted]
Weight increased	[redacted]

Pierre Fabre. DOF TEAE 2025 (2).
Abbreviations: AE, adverse event.

Grade 3/4 treatment-related TEAEs ≥5% are presented in Table 7. The most frequently reported Grade 3 treatment-related TEAEs were [redacted]

Table 7: Grade 3/4 treatment-related TEAEs ≥5% by preferred term in decreasing frequency (SAS; March 2025 DCO)

Preferred Term	Treatment-naïve (N=59)	
	Grade 3, n (%)	Grade 4, n (%)
Lipase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Source: Pierre Fabre. DOF. Table 14.3.1.3.1 (1).
A participant with multiple grade ratings for a TEAE is only counted under the maximum rating.
Abbreviations: DCO, data cut-off; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

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2.2 Indirect treatment comparison

The matching adjusted indirect comparisons (MAICs) that were presented as part of the original company submission (Section B.2.9) were updated using the March 2025 DCO for OS. In the draft guidance, the Committee requested updated MAICs adjusting for liver metastasis and exploring all possible available variables. In the feasibility assessment presented in Section B.2.9.1 of the original company submission, the following were identified as prognostic factors based on the SLRs, and review of TA898:

- Age
- Gender
- Race
- Smoking history
- ECOG-PS
- Number of previous treatments received
- Concomitant mutation in the P13K pathway
- Presence of metastases in the thoracic cavity
- Presence of brain metastases
- Previous treatment with immunotherapy
- PD-L1 ≥1% expression
- Histology type
- Presence of liver metastases
- Presence of M1a metastases

The following factors could not be included in the analysis as they were not collected in the PHAROS:

- Concomitant mutation in the P13K pathway
- Presence of metastases in the thoracic cavity
- PD-L1 ≥1% expression
- Presence of liver metastases
- Presence of M1a metastases

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The following factors were not included in the analysis as they were not relevant for a treatment-naïve population:

- Number of previous treatments received
- Previous treatment with immunotherapy

Therefore, the only factors that could be included in the analysis were:

- Age
- Race
- Gender
- Smoking status
- ECOG PS
- Histology (adenocarcinoma)
- Brain metastases

As such, the adjustment factors included in the analysis remain unchanged from the original company submission. Furthermore, clinical experts consulted during the June 2024 UK Advisory Board agreed that this set of confounding factors is appropriate for patients with BRAF V600E MT advanced NSCLC (3). Among these factors, they highlighted ECOG-PS and smoking status as the most important considerations.

It is not clear how much of an impact the exclusion of the above factors has on the analysis. However, during one of the key opinion leader (KOL) interviews, held in July 2025 to support these additional post-submission analyses (Section 3.2), a clinical expert noted that the presence of liver metastases is not a major prognostic factor in this patient population (4). Instead, brain metastases and ECOG performance status were highlighted as having a greater impact. Therefore, the omission of liver metastases is expected to have limited effect.

As requested by the Committee at draft guidance, MAIC analyses are presented comparing IFCT alone (Section 3.3.4) vs Planchard et al. It should be noted that this analysis represents a comparison of two studies with key design differences (academic investigator-initiated trial [IIT] vs a sponsor led pivotal clinical trial), and therefore the Company considers that these results should be interpreted with caution and should not be used to inform the base case estimates of relative

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effectiveness between enco+bini and dabra+tram. IITs, such as IFCT, often face more challenges than industry-sponsored studies (5). IITs often lack the robust financial backing of industry-sponsored trials, which limits resources for recruitment, protocol monitoring (protocol deviations, standard operating procedures, Good Clinical Practice), infrastructure, and access to specialist expertise. IITs may also suffer from less rigorous data monitoring and quality assurance than industry-sponsored trials.

Planchard et al. is a multicentre and multi-country, Company led clinical trial whereas the IFCT study is an academic led study conducted only in France. These differences in study design cannot be accounted for in an indirect treatment comparison (ITC) and their impact on the robustness of results is unknown. Furthermore, the follow-up available from IFCT is much shorter than in PHAROS. At the time of latest March 2025 DCO, median duration of follow-up was increased with PHAROS for OS ([redacted] months), compared with IFCT (18.0 months). Therefore, conclusions based on comparing IFCT data with Planchard et al. are based on more uncertain data. That said, as requested by the Committee, scenario analyses are presented using IFCT data. The same list of prognostic factors was used in this analysis, however as data on race was not available from IFCT, it is not included in analyses that include IFCT data. A scenario analysis using only ECOG-PS and smoking status is also presented for the IFCT alone analyses. A further analysis that pooled estimates from PHAROS and IFCT data using formal meta-analysis techniques has also been presented in response to the Committees request for alternate methods pooling data from PHAROS and IFCT.

A summary of the adjustment factors and sample size of the analysis is presented in Table 8.

Table 8: MAIC – population adjustment, enco+bini vs dabra+tram

	Adjustment factors	Initial sample size	ESS
PHAROS (enco+bini treatment-naïve cohort; March 2025 DCO) vs	Base case scenario: • Age • Race • Gender • Smoking status • ECOG PS	59	44

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	Adjustment factors	Initial sample size	ESS
Planchard 2017 (treatment-naïve cohort C)	• Adenocarcinoma • Brain metastases		
	Sensitivity analysis: • Smoking status • ECOG PS	59	58
IFCT (enco+bini treatment-naïve cohort) vs Planchard 2017 (treatment-naïve cohort C)	Base case scenario: • Age • Gender • Smoking status • ECOG PS • Adenocarcinoma Brain metastases	61	37
	Sensitivity analysis: • Smoking status • ECOG PS	61	58

Abbreviations: DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

Meta-analyses of hazard ratios (HR) for OS and PFS from PHAROS and IFCT vs Planchard et al. were conducted as requested by the Committee to explore alternate methods for pooling PHAROS and IFCT data. Meta-analysis are considered a more robust methods for estimating pooled efficacy compared with naïve pooling as per NICE Decision Support Unit (DSU) technical support document (TSD) 18 (6). Fixed effects (FE) models with the inverse variance method for pooling were fitted. Analyses were conducted using the netmeta package in R (version 4.4.2). For time-to-event outcomes, reported HRs and their corresponding 95% CIs were extracted and log-transformed to obtain log HRs and standard errors (SE), using the formula: SE = 2 × 1.96 * log(Upper CI) − log(Lower CI). FE models were used throughout as only two HRs were pooled. The meta-analyses were performed using the netmeta() function, specifying the appropriate summary measure (sm = "HR”). Input parameters included the treatment arms, study labels, effect estimates (log HRs), and corresponding SEs. Pooled effect estimates were calculated with 95% CIs.

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2.2.1 Indirect treatment comparison results

2.2.1.1 OS

The updated MAIC results comparing OS for enco+bini vs dabra+tram using the PHAROS only, IFCT only, and meta-analysis, are presented in Table 9.

The unadjusted comparison showed a numerical difference in favour of enco+bini (mean HR: [redacted]; 95% CI: [redacted]) when using the PHAROS data compared with dabra+tram. After adjustment on all factors enco+bini showed a larger, statistically significant reduction in death by [redacted]% compared with dabra+tram (adjusted HR: [redacted]; 95%CI: [redacted]). The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison. For OS, the HRs from PHAROS and IFCT are very similar, with overlapping 95% CIs. When using the IFCT data, enco+bini was associated with a [redacted]% reduction in death (mean HR: [redacted], 95% CI: [redacted]) The HR estimated by the FE meta-analyses for OS for enco+bini vs dabra+tram was [redacted] (95% CI: [redacted]).

Table 9: MAIC of enco+bini vs dabra+tram – OS

Comparison	Study	Individual HRs (95% CI)	Meta-analysis HRs (95% CI)
Enco+bini vs dabra+tram (base-case scenario)	PHAROS† vs Planchard 2017	[redacted]	[redacted]
	IFCT vs Planchard 2017	[redacted]	
Enco+bini vs dabra+tram (sensitivity analysis)	PHAROS† vs Planchard 2017	[redacted]	[redacted]
	IFCT vs Planchard 2017	[redacted]	
Enco+bini vs dabra+tram (unadjusted)	PHAROS† vs Planchard 2017	[redacted]	-
	IFCT vs Planchard 2017	[redacted]	

Bold = statistically significant.
†Based on the PHAROS March 2025 DCO, treatment-naïve cohort.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.

No PFS data were available for the PHAROS March 2025 DCO, therefore the MAIC for PFS using PHAROS results remain unchanged as presented in Section B.2.9 of the original company submission. As requested by the Committee, additional PFS analysis are presented as per OS for IFCT alone and meta-analysis of the PHAROS and IFCT results. Contrary to PHAROS where the primary endpoint was assessed

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by independent radiology review (IRR), the primary endpoint of IFCT study and the primary endpoint of the dabra+tram pivotal study (NCT01336634; BRF113928) were assessed by investigator. In addition, PFS was assessed by an Independent Review Committee (IRC) in the IFCT study and the dabra+tram pivotal study, although only as part of a sensitivity analysis. Therefore, in the context of the exploratory comparison between the IFCT study and the dabra+tram pivotal study, it is recommended to focus on investigator-assessed PFS, rather than PFS by IRR.

2.2.1.2 PFS

MAIC results comparing enco+bini with dabra+tram using the PHAROS only, IFCT only, meta-analysis are presented in Table 10 for PFS. The unadjusted comparison showed a statistically significant difference in favour of enco+bini (mean HR: [redacted]; [redacted]) when using the PHAROS data compared with dabra+tram. After adjustment on all factors enco+bini showed a statistically significant reduction in death by [redacted]% compared with dabra+tram (adjusted HR: 0.47; 95%CI: 0.26, 0.85). The population adjustment restricted to ECOG and smoking status did not greatly impact the results compared with the unadjusted comparison. When using the IFCT data, enco+bini was associated with a mean HR of [redacted] (95% CI: [redacted]). The HR estimated by the FE meta-analyses for PFS for enco+bini vs dabra+tram was [redacted] (95% CI: [redacted]).

Table 10: MAIC of enco+bini vs dabra + tram – PFS

Comparison	Study	Individual HRs (95% CI)	Meta-analysis HRs (95% CI)
Enco+bini vs dabra+tram (base-case scenario)	PHAROS† vs Planchard 2017	**0.47 (0.26, 0.85)**	[redacted]
	IFCT vs Planchard 2017	[redacted]	
Enco+bini vs dabra+tram (sensitivity analysis)	PHAROS† vs Planchard 2017	[redacted]	[redacted]
	IFCT vs Planchard 2017	[redacted]	
Enco+bini vs dabra+tram (unadjusted)	PHAROS† vs Planchard 2017	[redacted]	-
	IFCT vs Planchard 2017	[redacted]	

Bold = statistically significant.
†Based on the PHAROS April 2024 DCO, treatment-naïve cohort.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

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3 Economic analysis

3.1 Patient population

As per the Committee's requested analyses, the model has been updated such that baseline characteristics are aligned with the source of the intervention efficacy for the base case and all scenario analyses. In the base case, enco+bini efficacy is sourced from unadjusted PHAROS data, therefore the baseline characteristics are derived from the treatment-naïve cohort of PHAROS. 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%. Scenario analyses are presented where enco+bini efficacy is sourced from PHAROS after adjustment for the MAIC (Sections 3.3.3 and 3.4.3), and IFCT data alone (Section 3.3.4 and 3.4.4), therefore in these scenarios baseline characteristics are taken from the respective data sources. A full summary of the baseline characteristics used in the base case and scenario analyses are presented in Table 11.

Table 11: Patient baseline characteristics, treatment-naïve cohorts, base case and scenario analyses

Characteristic	PHAROS Base case	PHAROS MAIC adjusted	IFCT	IFCT MAIC adjusted
Age (years)	66.5	67.0	[redacted]	[redacted]
Proportion male (%)	44.1%	39.0%	46.9%	38.9%
Mean weight (kg)	74.6	70.6	[redacted]	[redacted]
Mean height (m)	1.67	1.65	[redacted]	[redacted]
BSA (m^2)†	1.86	1.80	[redacted]	[redacted]

†Calculated using the Mosteller formula.
Abbreviations: BSA, body surface area; IFCT, Intergroupe Francophone de Cancérologie Thoracique; MAIC, matching-adjusted indirect comparison.

3.2 Key opinion leader clinical validation interviews

Three virtual interviews were held with KOLs in July 2025, to support the submission for enco+bini for the treatment of patients with BRAF V600E MT NSCLC to NICE. The interviews engaged three England-based clinicians with experience in treating NSCLC, including the use of dabra+tram. One of the clinicians also had additional

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experience in treating patients with melanoma with enco+bini. The objective of the interviews was to gather the experts' clinical insights to inform and validate the additional analyses requested by the NICE Committee, following the negative draft guidance (4).

Clinicians were invited to provide their expert insights based on the updated PHAROS March 2025 DCO data. Specifically, they were asked to:

- Review the updated PHAROS data OS and assess its clinical relevance
- Comment on the representativeness of the PHAROS and IFCT datasets to UK clinical practice
- Discuss potential factors contributing to differences in outcomes between the PHAROS and IFCT studies, and comment on their generalisability to current UK clinical practice
- Provide survival estimates to support survival extrapolations
- Comment on treatment waning effects and any implications in real-world clinical practice
- Offer any additional supportive information relevant to the interpretation of clinical outcomes or modelling assumptions for enco+bini.

Clinical expert feedback has been integrated throughout this document where relevant and is detailed in the minutes report included as part of the additional analyses package (4).

3.3 Overall survival

As per the Committee requested analysis, further analysis is presented for OS and PFS including:

- Independent fitting of parametric curves to extrapolate PFS and OS in each arm
- Alternative modelling approaches for OS and PFS that might include flexible parametric modelling

All survival analysis of OS data from PHAROS was updated to include the March 2025 DCO of PHAROS (Section 2.1.3). At the March 2025 DCO of PHAROS, after a

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median follow-up of [redacted] months, [redacted]% of patients experienced an OS event in the treatment-naïve population, and median OS had been reached at [redacted] months (95% CI: [redacted]) (Figure 1).

As per the original submission Section B.3.3.2, all parametric survival analyses for enco+bini were conducted in line with NICE Technical Support Document (TSD) 14 (7). Survival curves were assessed based on statistical goodness of fit, visual fit vs the observed data, comparison with published data, and clinical plausibility. As per the Committee's request, flexible survival models were estimated including 1 and 2 knot spline models using the hazard, odds, and normal scale.

3.3.1 Enco+bini

Goodness of fit statistics using the PHAROS unadjusted data for enco+bini OS are presented in Table 12. The exponential distribution was associated with the best statistical fit.

Table 12: Enco+bini OS, PHAROS unadjusted, goodness of fit statistics

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	**314.47**	**316.55**
Weibull	316.19	320.35
Gompertz	315.86	320.01
Log-normal	314.70	318.86
Log-logistic	315.67	319.83
Generalised gamma	316.64	322.87
Gamma	316.29	320.45
Spline hazard 1 knot	317.41	323.64
Spline hazard 2 knots	319.02	327.33
Spline odds 1 knot	317.53	323.76
Spline odds 2 knots	318.91	327.22
Spline normal 1 knot	316.70	322.93
Spline normal 2 knots	318.12	326.43

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

All distributions over-predict the data slightly for the first 6 months but then provide a reasonable fit to the observed data and were within 5% of the KM (Table 13). The Weibull distribution provided a very good fit to the data and was within 2–3% at most time points.

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Table 13: 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]
Spline Hazard (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

The smoothed hazards and log-smoothed hazards plots are presented in Figure 3. The plots show a monotonic decreasing hazard in the observed period, with the log smoothed hazard plot appearing relatively constant. These plots suggest a simple hazard function is appropriate and that complex or flexible distributions are not required.

Figure 3: Smoothed hazard plots, enco-bini OS – PHAROS unadjusted data

Abbreviations: enco+bini, encorafenib plus binimetinib; OS, overall survival.

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Long-term projections for each distribution are presented in Figure 4 and Table 14. During the KOL clinical validation interviews, clinicians were invited to comment on the PHAROS and IFCT data. Overall, the PHAROS survival data were viewed as promising but warrant further scrutiny to confirm their generalisability. Across the three interviews, clinicians highlighted that the OS outcomes for enco+bini in BRAF V600E MT NSCLC were notably strong, especially when compared with other BRAF tumour types and targeted treatments such as dabra+tram. Clinicians noted that the survival outcomes observed may be attributed to PHAROS trial design or patient selection (e.g. a fitter patient population with better ECOG PS). Concerns were raised about the real-world applicability of the high OS rate in PHAROS, given the favourable baseline characteristics of the PHAROS trial population.

Clinicians were also asked to provide their expectations for survival in patients treated with enco+bini at 5, 10, 15, and 20 years; a summary of their estimates of long-term survival are presented in Table 15 (4). On average, clinicians predicted that 13%, 4%, and 4% of patients would be alive after receiving treatment with enco+bini at 10, 15, and 20 years, respectively (4). Of the distributions estimated, the exponential provides the best fit to this data, [redacted] of the clinician average at each time point ([redacted]%, [redacted]% and [redacted]%, respectively). The clinician average for survival at 5 years was 18%, which is below the estimate for the exponential curve ([redacted]%). Although the exponential (and all distributions) over-estimate survival compared with clinician estimates, the exponential is the most conservative of the distributions presented. Furthermore, follow-up from the PHAROS March 2025 DCO goes beyond 5 years (max follow-up of [redacted] months), therefore the Company believes it is appropriate to use the data as observed. The 5-year estimates of survival when using the PHAROS data are also consistent with the 5-year projections when using the IFCT data (Section 3.3.4).

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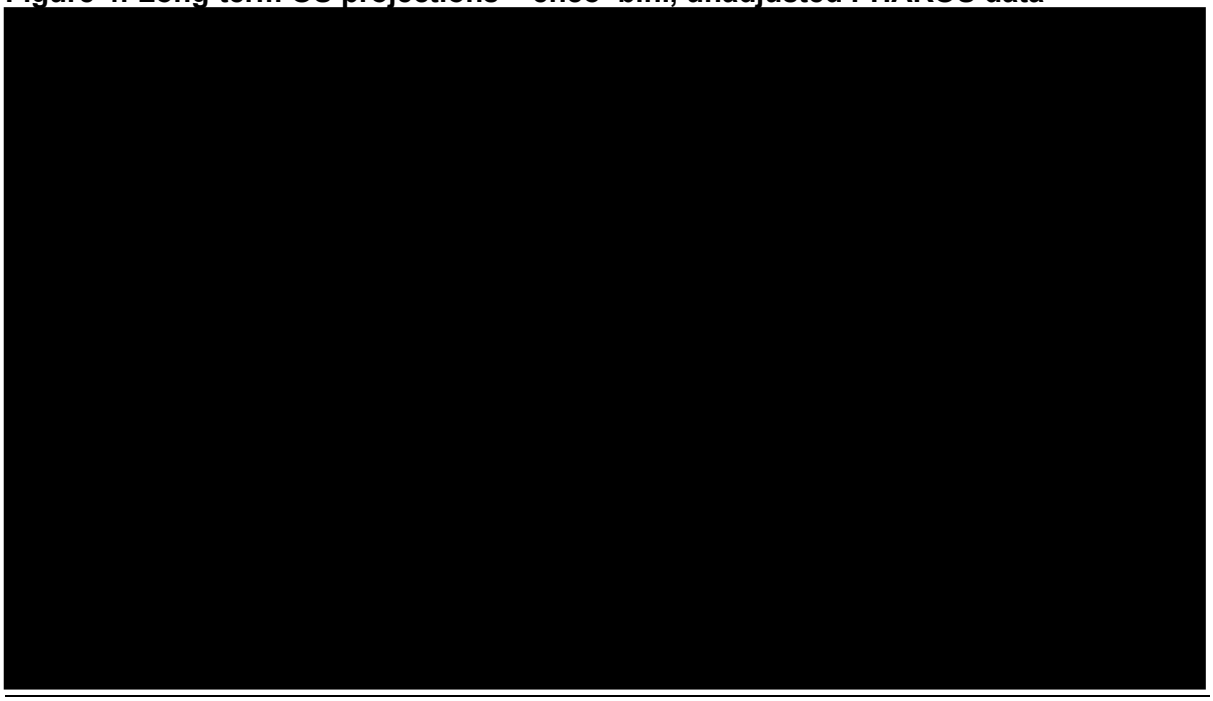
Figure 4: Long-term OS projections – enco+bini, unadjusted PHAROS data



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

Table 14: Long-term OS estimates - enco+bini, PHAROS unadjusted data

	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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Table 15: Long-term OS estimates – clinician interviews, enco+bini

Year	KOL 1	KOL 2	KOL 3	Average
5	~10%	–	25% typical (based on melanoma)	18%
10	~5%	20%	40–50% overly optimistic	13%
15	0%	5–10%	Curve will flatten beyond 10 years	4%
20	0%	5–10%	Curve will flatten beyond 10 years	4%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: enco+bini, encorafenib plus binimetinib; KOL, key opinion leader; OS, overall survival.

Based on statistical and visual fit, and alignment with clinician estimates of survival at 10, 15, and 20 years, the exponential distribution is retained as the base case OS distribution for enco+bini. Scenarios are presented using the gamma, Weibull, and spline hazard (2 knots) distributions, as these distributions also produce estimates consistent with the long-term estimates provided by clinical experts.

3.3.2 Dabra+tram

The assumption of proportional hazards (PH) was re-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=0.9696). The plot of the Schoenfeld residuals (Figure 5) 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 6) show curves crossing in the first half of the observation period however, the curves settle in a more parallel pattern in the second half. A comparison of the smoothed hazard plots in the observed period of PHAROS and Planchard et al. (Figure 7) show that the hazards over time in each arm follow the same shape with a decreasing hazard throughout the trial period, further supporting the assumption of proportional hazards. 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 (3). The EAG also agreed that it was reasonable to assume PH, and at ACM1, the Committee noted that it was not unusual to see crossing of log-log plots at the start or end of trials when there were a small number of events, and concluded that the

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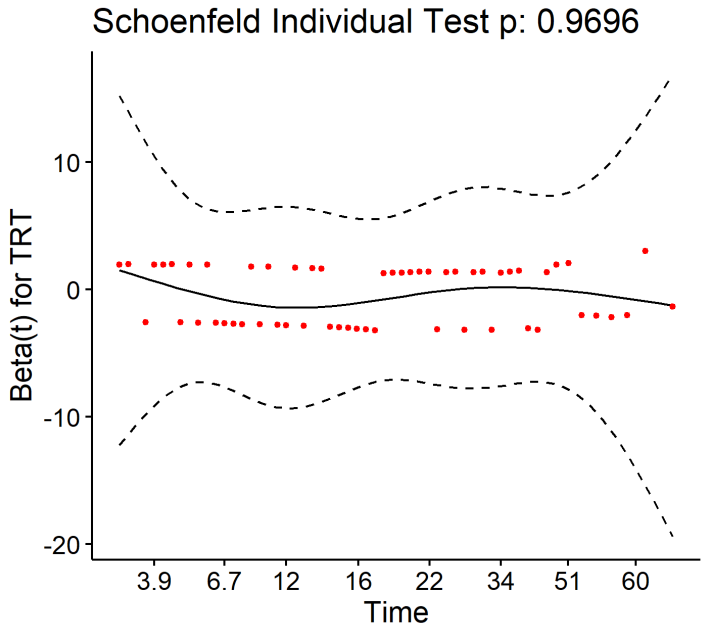
PH assumption was likely to be appropriate. Based on this, the assessment of log-log plots, and the non-significance of the p-values associated with the Schoenfeld residuals test, it was considered acceptable to assume PH between enco+bini and dabra+tram for OS, and estimate dabra+tram OS by applying the MAIC HRs to the unadjusted PHAROS data.

Figure 5: Schoenfeld residuals test, OS – PHAROS vs Planchard et al.

Global Schoenfeld Test p: 0.9696



Abbreviations: OS, overall survival.

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Figure 6: Log-log plot, OS – PHAROS vs Planchard et al.

Abbreviations: enco+bini, encorafenib plus binimetinib; OS, overall survival.

Figure 7: Smoothed hazard comparison, OS – PHAROS vs Planchard et al.

Abbreviations: OS, overall survival

The MAIC HR ([redacted]) was applied to the enco+bini OS curve to derive long-term survival estimates for dabra+tram. A scenario analysis is presented that applies the MAIC HR adjusting for only ECOG and smoking status ([redacted]) and the unadjusted HR

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([redacted]). Long-term projections of OS over a lifetime horizon are presented in Figure 8, and median and long-term survival estimates are presented in Table 16.

Figure 8: Long-term base case OS projection – dabra+tram

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

Table 16: Dabra+tram – median and long-term OS model and trial comparison

	Median OS (years)	1 year	2 years	5 years	10 years	15 years
BRF113928†	1.44	74%	49%	22%	-	-
TA898 – exponential (8)	-	-	-	-	4.5%	-
Model predicted – base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Median OS reported:17.3 months in the treatment naïve population (Cohort C).
Abbreviations: Dabra+tram, dabrafenib + trametinib; OS, overall survival.

Long-term estimates of OS for patients treated with dabra+tram as estimated by clinical experts are presented in Table 17. Clinicians estimated that 16% and 9% of patients would be alive at 5 years and 10 years, respectively. Clinicians stated very few patients (0–1%) would be alive at 15 years. The model base case slightly over-predicts clinician estimates at 5 years, although [redacted] of the trial data and clinician estimates. The model base case ([redacted]%) under predicts the average clinician estimate at 10 years (9%), however is well aligned with 2 out of the 3 clinician estimates. Predictions at 10 years are also well aligned with the exponential distribution presented in TA898, which was considered plausible by the Committee in

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that appraisal. Predictions at 15 and 20 years ([redacted]% and [redacted]%, respectively) are well aligned with clinician estimates.

Table 17: Long-term OS estimates – clinician interviews, dabra+tram

Year	KOL 1	KOL 2	KOL 3	Average
5	~10%	-	Trial data reasonable (22%)	16%
10	2–3%	5%	20%	9%
15	0%	1%	Curve will flatten	1%
20	0%	1%	Curve will flatten	1%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: Dabra+tram, dabrafenib plus trametinib; KOL, key opinion leader; OS, overall survival.

3.3.3 Independent extrapolations

As discussed in Section 3.3.2, the PH assumption is assumed in the base case based on assessment of Schoenfeld residuals, log-cumulative hazard plots, clinician opinion, and comments from the EAG and Committee at ACM1. However, as per the Committee's requested analysis, scenarios are presented relaxing the PH assumption, estimating enco+bini and dabra+tram OS using independent extrapolations of both arms. In these scenarios, parametric distributions are fit to the patient-level data after adjusting in the MAIC (Section 2.2).

3.3.3.1 Enco+bini

Goodness of fit statistics using the PHAROS MAIC adjusted data for enco+bini OS are presented in Table 18. The exponential distribution was associated with the best statistical fit.

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Table 18: Enco+bini OS, PHAROS MAIC adjusted – goodness of fit statistics

	Goodness of fit statistic†	
	AIC	BIC
Exponential	**266.03**	**267.98**
Weibull	267.91	271.83
Gompertz	267.90	271.82
Log-normal	267.66	271.57
Log-logistic	267.99	271.90
Generalised gamma	269.60	275.47
Gamma	267.94	271.85
Spline hazard 1 knot	269.83	275.70
Spline hazard 2 knots	271.36	279.18
Spline odds 1 knot	269.97	275.84
Spline odds 2 knots	271.14	278.97
Spline normal 1 knot	269.39	275.26
Spline normal 2 knots	270.41	278.24

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

All distributions over-predict the data slightly for the first 6 months but then provided a reasonable fit to the observed data (Table 19).

Table 19: Enco+bini OS, PHAROS MAIC adjusted – 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]
Spline Hazard (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

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Long-term projects for each distribution are presented in Figure 9 and Table 20. Of the distributions estimated, the spline hazard (2 knots) provides the best fit to the estimates of long-term survival from clinicians (Table 15) at each time point ([redacted]%, [redacted]% and [redacted]% at 10, 15, and 20 years, respectively). The exponential distribution also provides reasonable predictions compared with the clinician long-term estimates. Therefore, both distributions are presented in scenario analyses.

Figure 9: Long-term OS projections – enco+bini, MAIC adjusted PHAROS data

Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

Table 20: Long-term OS estimates – enco+bini, MAIC adjusted PHAROS data

	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
PHAROS KM (unadjusted)	[redacted]	[redacted]	[redacted]	-	-	-
PHAROS KM (adjusted)	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib in combination with binimetinib; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

3.3.3.2 Dabra+tram

To model dabra+tram OS independently, parametric curves were fit to digitised KM data from Planchard et al. Goodness of fit statistics using the Planchard et al. unadjusted data for dabra+tram OS are presented in Table 21. The log-normal distribution was associated with the best statistical fit by AIC and BIC.

Table 21: Dabra+tram OS, Planchard et al., goodness of fit statistics

	Goodness of fit statistic†	
	AIC	BIC
Exponential	253.56	255.15
Weibull	255.50	258.67
Gompertz	255.40	258.56
Log-normal	**251.72**	**254.89**
Log-logistic	253.20	256.37
Generalised gamma	252.91	257.66
Gamma	255.28	258.45
Spline hazard 1 knot	253.15	257.90
Spline hazard 2 knots	253.48	259.81
Spline odds 1 knot	253.55	258.30
Spline odds 2 knots	254.23	260.57
Spline normal 1 knot	252.72	257.47
Spline normal 2 knots	254.14	260.47

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

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All distributions provide a reasonable fit to the observed data in the first year, however significantly over-estimate the trial data between 18 and 30 months. The log-normal distribution provides the best visual fit to the data.

Table 22: Dabra+tram OS, Planchard et al., parametric distribution and observed data

	Month				
	6	**12**	**18**	**24**	**30**
KM	91.3%	70.6%	49.2%	49.2%	43.1%
Exponential	85.7%	73.5%	63.0%	54.0%	46.3%
Weibull	86.8%	74.6%	64.0%	54.8%	46.8%
Log-normal	88.9%	73.0%	60.1%	50.1%	42.3%
Generalised gamma	89.2%	70.5%	56.9%	47.3%	40.3%
Log-logistic	88.0%	72.8%	59.8%	49.5%	41.4%
Gompertz	84.5%	71.7%	61.1%	52.3%	44.9%
Gamma	87.9%	75.7%	64.8%	55.2%	47.0%
Spline hazard (1 knot)	89.8%	71.7%	57.4%	47.5%	40.4%
Spline hazard (2 knots)	90.1%	67.6%	55.8%	49.2%	43.6%
Spline odds (1 knot)	89.8%	70.9%	56.3%	46.5%	39.6%
Spline odds (2 knots)	89.9%	68.2%	56.5%	49.2%	43.1%
Spline normal (1 knot)	89.6%	70.4%	56.5%	47.0%	40.2%
Spline normal (2 knots)	89.0%	68.6%	56.9%	49.1%	42.7%

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

Long-term projections for each distribution are presented in Figure 10 and Table 23. A summary of clinician estimates of long-term survival estimates are presented in Table 17. Clinicians estimated that 16% and 9% of patients would be alive at 5 and 10 years, respectively, with very few patients alive at 15 and 20 years. All distributions over-predict the clinician average at 5 years, from 15 years; however, most are relatively aligned with estimates of 10-year survival. The exponential is the most aligned with long-term estimates from clinicians that stated very few patients (1%) would be alive at 15 years. The Weibull predicted survival is relatively aligned with clinical expert opinion at 15 and 20 years. Therefore, both the exponential and Weibull distribution are presented in scenario analyses.

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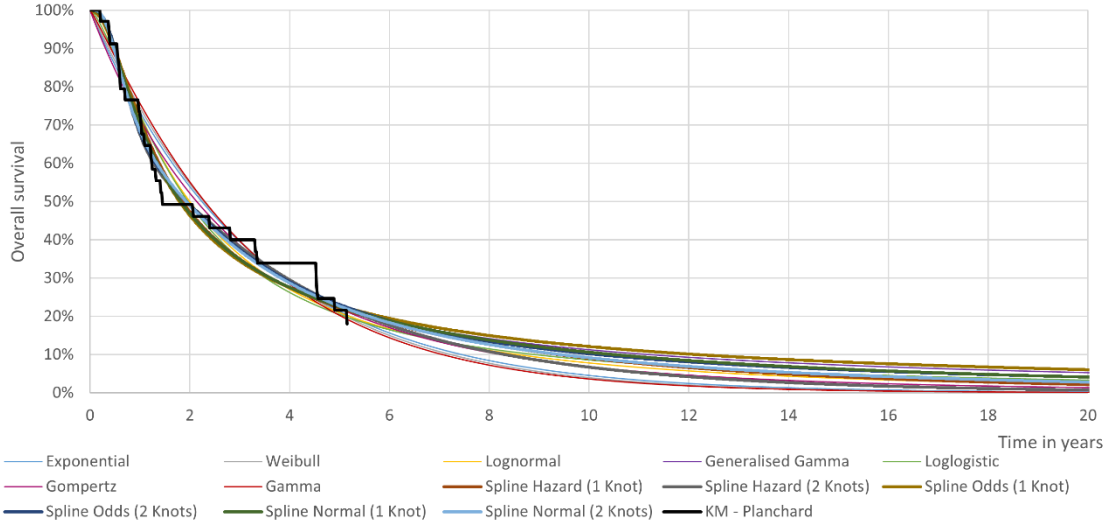
Figure 10: Long-term OS projections – dabra+tram, Planchard et al.



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

Table 23: Long-term OS estimates – dabra+tram, Planchard et al.

	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Planchard KM	-			-	-	-
Exponential	2.22	54.0%	21.4%	4.6%	1.0%	0.2%
Weibull	2.28	54.8%	20.9%	4.0%	0.7%	0.1%
Log-normal	1.99	50.1%	21.1%	7.8%	3.8%	2.1%
Generalised gamma	1.82	47.3%	22.5%	11.3%	7.3%	5.3%
Log-logistic	1.95	49.5%	20.5%	8.6%	5.0%	3.3%
Gompertz	2.13	52.3%	22.2%	6.8%	2.8%	1.4%
Gamma	2.28	55.2%	20.4%	3.6%	0.6%	0.1%
Spline hazard (1 knot)	1.84	47.5%	22.3%	9.0%	4.2%	2.1%
Spline hazard (2 knots)	1.92	49.2%	22.9%	6.7%	2.1%	0.7%
Spline odds (1 knot)	1.78	46.5%	22.9%	12.1%	8.1%	6.0%
Spline odds (2 knots)	1.92	49.2%	23.2%	10.2%	6.0%	4.1%
Spline normal (1 knot)	1.80	47.0%	22.6%	10.6%	6.2%	4.1%
Spline normal (2 knots)	1.92	49.1%	22.8%	9.2%	4.7%	2.8%

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; OS, overall survival.

3.3.4 IFCT

As per the Committee requested additional analysis, a scenario is presented that uses IFCT only to estimate enco+bini survival. The IFCT-1904 ENCO-BRAF study (referred to as IFCT throughout the submission) is a French IIT by the academic

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group: Intergroupe Francophone de Cancérologie Thoracique (IFCT). This study aimed to collect additional data on the efficacy, safety, and quality of life (QoL) of enco+bini in patients with advanced BRAF V600E MT NSCLC, as QoL was not evaluated in the pivotal PHAROS study.

As touched upon in Section 2.2, operational differences are often observed between sponsor-initiated clinical trials and IIT. These differences may for instance include the level of monitoring, evaluation methods, potential for bias (e.g. distribution of study sites), and standard operating procedures. Although the study design and settings may appear similar at first glance, multifactorial operational differences between sponsor-initiated and IITs are frequently observed. Compared with IIT, sponsor-initiated studies, such as the PHAROS study, are therefore often considered to be more rigorous and of the highest quality (9).

The value of conducting an IIT lies in their ability to generate and expand product knowledge, including safety data, and to explore new therapeutic uses for existing treatments that may enhance patient outcomes. Findings from IITs serve as a valuable complement to results from sponsor-initiated trials, especially in medical fields that are often underrepresented in traditional trials, including physiotherapy, psychotherapy, behavioural interventions, and complementary medicine (10).

Notably, variations in treatment landscape, reimbursement, and access conditions across countries can significantly influence the types of patients enrolled in clinical trials. In the PHAROS study, 51% of patients in the treatment-naïve cohort were European (US n=27; the Netherlands n=14; Spain n=9; Italy n=7; Korea n=2) and the inclusion period ran from June 2019 to June 2022. Conversely, the IFCT study only included patients in France enrolled from March 2021 to September 2023. Ddabra+tram was available, reimbursed and recommended as first-line treatment for advanced BRAF V600 MT NSCLC in many countries included in the PHAROS study. In France, dabra+tram is only reimbursed as second-line treatment (since January 2020) (11). Consequently, in the absence of alternative therapeutic options, the IFCT study may have enrolled a higher proportion of patients who would derive clinical benefit from prompt initiation of first-line therapy with a BRAF/MEK inhibitor. In contrast, patients in the PHAROS study were more likely to receive the approved

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combination of dabra+tram in a timely manner, facilitated by reimbursement, rather than the investigational regimen of enco+bini, which may have been associated with delays in treatment initiation.

Since dabra+tram is also reimbursed in the UK as first-line treatment, the population included in the PHAROS study is more generalisable to UK clinical practice than the population included in the IFCT study, given that in France dabra+tram is only reimbursed in second-line.

During the KOL interviews, clinicians were invited to reflect on the differences between PHAROS and IFCT outcomes. There was a broad consensus among clinicians that differences between PHAROS and IFCT outcomes are likely driven by small trial numbers and variations in baseline characteristics, particularly the proportion and nature of brain metastases and patient fitness (e.g. ECOG PS).

Clinicians were also asked to provide their views on whether one of the datasets better reflects current UK clinical practice (4). Ultimately the clinicians did not reach consensus on an optimal dataset for modelling, which remained uncertain. IFCT was viewed as potentially more representative of UK clinical practice, with the proportion of patients with brain metastases better aligned with UK clinical practice (7% in PHAROS vs 17% in IFCT), whereas PHAROS was seen as enrolling a fitter population than observed in practice, likely a result of study design (e.g. stricter screening). PHAROS provides longer-term OS data, although its PFS divergence from IFCT PFS was seen as a potential limitation; clinicians noted that small sample sizes are likely the key reason for this observed variability.

As such, due to the overall differences between IFCT and PHAROS, the results of the IFCT study are of limited comparability. In summary, these differences include, IFCT baseline demographic and clinical characteristics, the restriction to centres in France where dabra+tram is not reimbursed in treatment-naïve patients (unlike in the UK), the difference in the study and sponsor type, and the difference in maturity of the secondary endpoints (median duration of follow-up for OS was [redacted] months in first-line in PHAROS [March 2025 DCO] compared with 18 months in first-line in IFCT [March 2024 DCO]). Nevertheless, it can be concluded that the results of the

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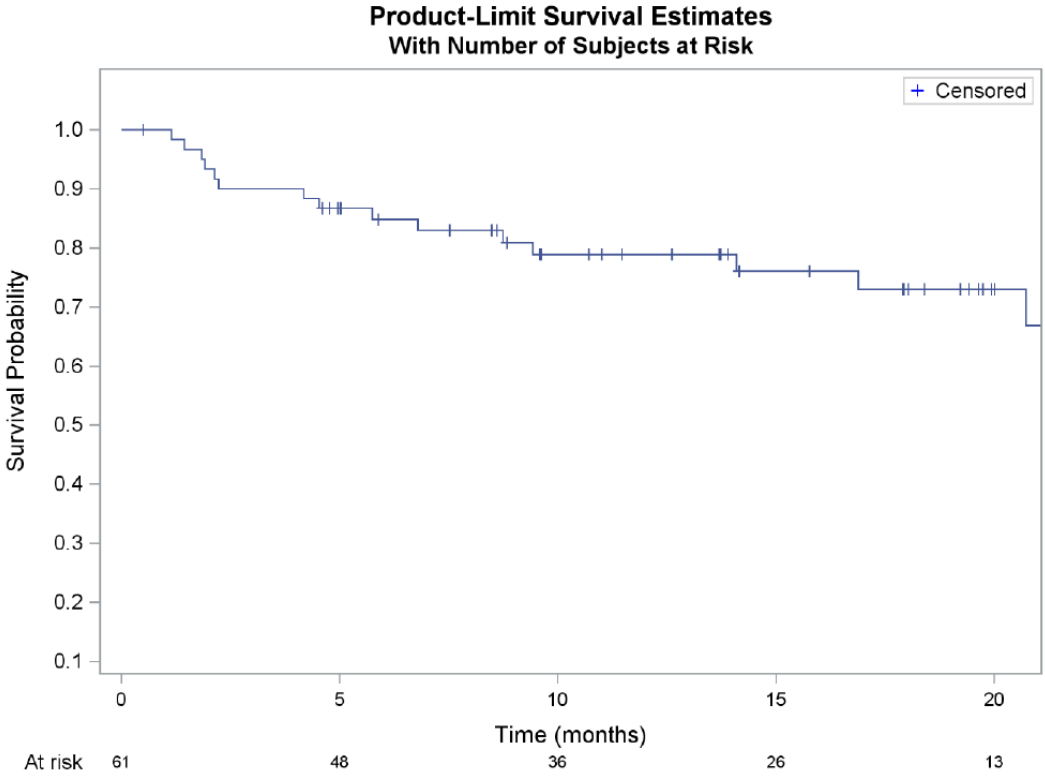
IFCT study generally confirm the favourable effect of enco+bini as first-line treatment in patients with advanced BRAF V600E MT NSCLC.

3.3.4.1 Enco+bini

The IFCT OS data was immature after a median follow-up of 18.0 months, [redacted]% of patients experienced an OS event in the treatment-naïve population, and median OS had not been reached (Figure 11).

Figure 11: IFCT – KM OS



Source: Planchard et al, 2024 (12).
Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan Meier; OS, overall survival.

Goodness of fit statistics using the IFCT unadjusted data for enco+bini OS are presented in Table 24. The log-normal and exponential distribution were associated with the best statistical fit by AIC and BIC, respectively.

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Table 24: Enco+bini OS, IFCT unadjusted, goodness of fit statistics

	Goodness of fit statistic†, ‡	
	AIC	**BIC**
Exponential	169.60	**171.71**
Weibull	171.19	175.41
Gompertz	170.76	174.98
Log-normal	**169.55**	173.77
Log-logistic	170.79	175.02
Spline hazard 1 knot	171.58	177.91
Spline hazard 2 knots	171.28	179.73
Spline odds 1 knot	171.60	177.94
Spline odds 2 knots	171.21	179.65
Spline normal 1 knot	170.88	177.21
Spline normal 2 knots	170.53	178.98

†Lowest AIC and BIC denoted in bold; ‡The generalised gamma distribution did not converge for IFCT OS.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; OS, overall survival.

All distributions provided a reasonable fit to the observed data (Table 25). The spline models all provide a very good fit to the data.

Table 25: Enco+bini OS, IFCT unadjusted – parametric distribution and observed data

	Month†				
	6	**12**	**18**	**24**	**30**
KM	[redacted]	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†The generalised gamma distribution was not estimable for IFCT OS.
Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; OS, overall survival.

Long-term projections for each distribution using the IFCT data are presented in Figure 12 and Table 26. Of the distributions estimated, the gamma, exponential and Weibull are the only distributions that provide predictions that are consistent with clinician estimates at 10 (13%), 15 (4%), and 20 years (4%), respectively. The

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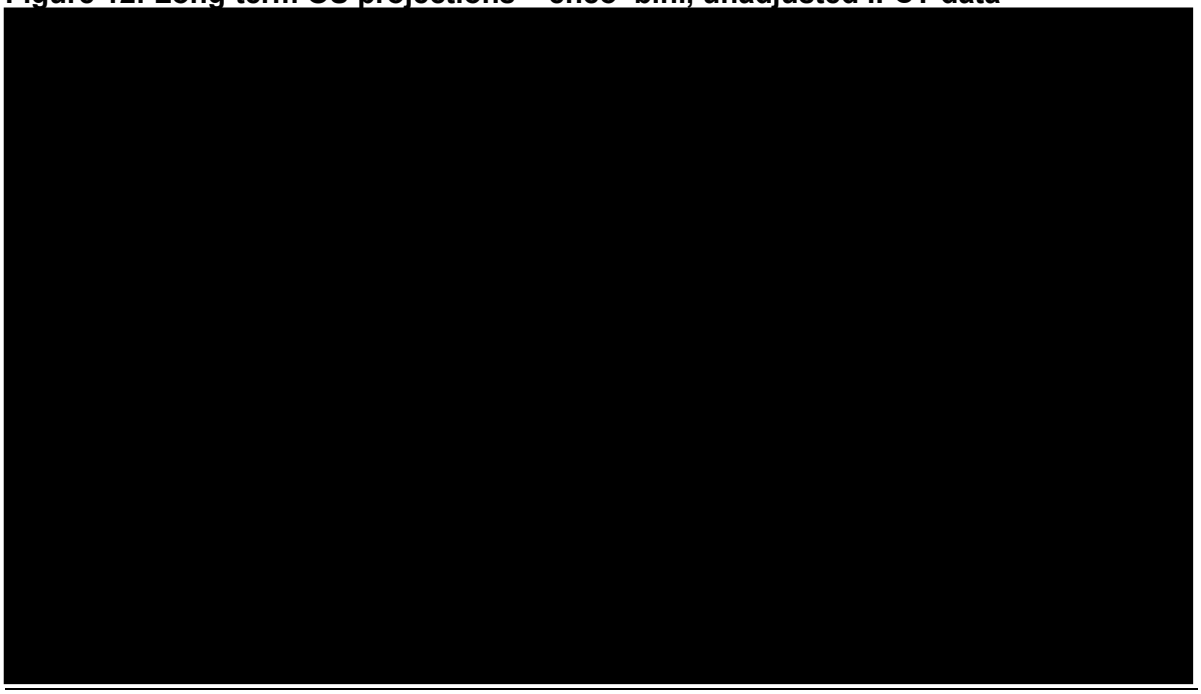
gamma distribution provides the best fit to these estimates ([redacted]%, [redacted]%, and [redacted]% respectively). Therefore, the exponential, gamma and Weibull distributions are presented in scenario analysis using the IFCT data. It should be noted that the IFCT data contains much shorter follow-up than PHAROS, and the data are immature (median OS not reached), and therefore there is greater uncertainty associated with the long-term extrapolations.

Figure 12: Long-term OS projections – enco+bini, unadjusted IFCT data†



†The generalised gamma distribution was not estimable for IFCT OS.
Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan Meier; OS, overall survival.

Table 26: Long-term OS estimates – enco+bini, IFCT unadjusted data

	Predicted median OS (years)	Estimated % alive at time (years)†				
		2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Predicted median OS (years)	Estimated % alive at time (years)†				
		2	5	10	15	20
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†The generalised gamma distribution was not estimable for IFCT OS.
Abbreviations: enco+bini, encorafenib plus binimetinib; OS, overall survival.

3.3.4.2 Dabra+tram

The assumption of PH was re-assessed between the IFCT 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=0.0565). The plot of the Schoenfeld residuals (Figure 13) 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 14) show curves crossing, however the plots show a similar pattern in each arm. As discussed in Section 3.3.2 above, clinical advice to the Company stated that there would be no clinical reason to expect PH not to hold between enco+bini and dabra+tram (3), and comments from the EAG and Committee at ACM1 also support the PH assumption. 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 when using the IFCT data and estimate dabra+tram OS by applying the MAIC HRs to the unadjusted PHAROS data. However, as there is uncertainty in the conclusions, further scenario analyses are presented using independent extrapolations (Section 3.3.4.3).

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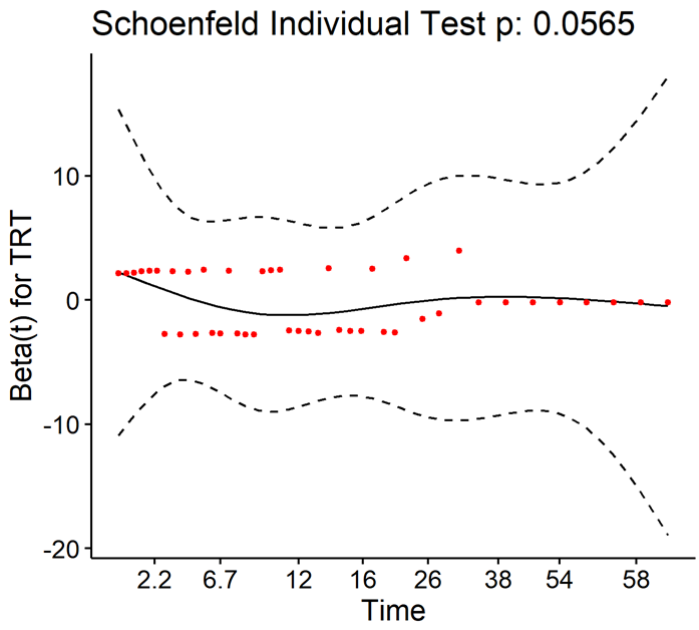
Figure 13: Schoenfeld residuals, IFCT vs Planchard et al.



Abbreviations: IFCT, Intergroupe Francophone de Cancérologie Thoracique.

Figure 14: Log-log plot, IFCT vs Planchard et al.

Abbreviations: enco+bini, encorafenib plus binimetnib; IFCT, Intergroupe Francophone de Cancérologie Thoracique.

The MAIC HR ([redacted]) was applied to the enco+bini OS curve to derive long-term survival estimates for dabra+tram. Scenario analyses are also presented that

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applying the MAIC HR adjusting only for ECOG and smoking status ([redacted]) and the unadjusted HR ([redacted]). Long-term projections of OS over a lifetime horizon are presented in Figure 15, and median and long-term survival estimates are presented in Table 16.

Figure 15: Long-term OS projection, HR vs IFCT – dabra+tram

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

Table 27: Dabra+tram – median and long-term OS model and trial comparison

	Median OS (years)	1 year	2 years	5 years	10 years	15 years
BRF113928†	1.44	74%	49%	22%	-	-
TA898 – exponential (8)	-	-	-	-	4.5%	-
Model predicted, HR vs IFCT (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Median OS reported:17.3 months in the treatment naïve population (Cohort C).
Abbreviations: Dabra+tram, dabrafenib + trametinib; OS, overall survival.

3.3.4.3 Independent extrapolations

As per the Committee's requested analysis, scenarios are presented relaxing the PH assumption, estimating enco+bini and dabra+tram OS using independent extrapolations of both arms.

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3.3.4.3.1 Enco+bini

In these scenarios, enco+bini OS is estimated from the MAIC adjusted IFCT patient level data. The goodness of fit statistics are presented in Table 28. The generalised gamma distribution produces the best statistical fit by both AIC and BIC. The spline odds 2 knots and spline normal 2 knots also provide a good statistical fit to the data.

Table 28: Enco+bini OS, IFCT MAIC adjusted, goodness of fit statistics

	Goodness of fit statistic†	
	AIC	BIC
Exponential	157.81	159.73
Weibull	158.08	161.91
Gompertz	156.66	160.49
Log-normal	155.41	159.24
Log-logistic	157.22	161.06
Generalised gamma	**148.79**	**154.54**
Gamma	158.42	162.26
Spline hazard 1 knot	155.58	161.33
Spline hazard 2 knots	150.24	157.90
Spline odds 1 knot	155.32	161.07
Spline odds 2 knots	149.96	157.63
Spline normal 1 knot	154.04	159.79
Spline normal 2 knots	149.04	156.71

†Lowest AIC and BIC denoted in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; OS, overall survival.

Table 29: Enco+bini OS – parametric distribution and observed data, IFCT MAIC adjusted 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]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Month				
	6	12	18	24	30
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; MAIC, matching-adjusted indirect comparison; OS, overall survival.

Long term projects are presented in Figure 16 and Table 30. The gamma distribution is most aligned with the clinician estimates of survival and is therefore presented as a scenario.

Figure 16: Long-term OS projections – enco+bini, MAIC adjusted IFCT data

[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; MAIC, matching-adjusted indirect comparison; OS, overall survival.

Table 30: Long-term OS estimates - enco+bini, IFCT MAIC adjusted data

	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
IFCT KM (unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFCT KM (adjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Predicted median OS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Spline hazard (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; MAIC, matching-adjusted indirect comparison; OS, overall survival.

3.3.4.3.2 Dabra+tram

In the scenario using IFCT data and independent extrapolations, dabra+tram survival is as per Section 3.3.3.

3.4 Progression-free survival

3.4.1 Enco+bini

As discussed in Section 2.1.2, PFS data were not available from the PHAROS March 2025 DCO, therefore all analysis using the unadjusted PHAROS data are as per the original Company submission (Section 3.3.2.1.2). Spline models were explored as per OS (Section 3.3.1) and the Committee's requested analysis. The long-term extrapolations are presented in Figure 17.

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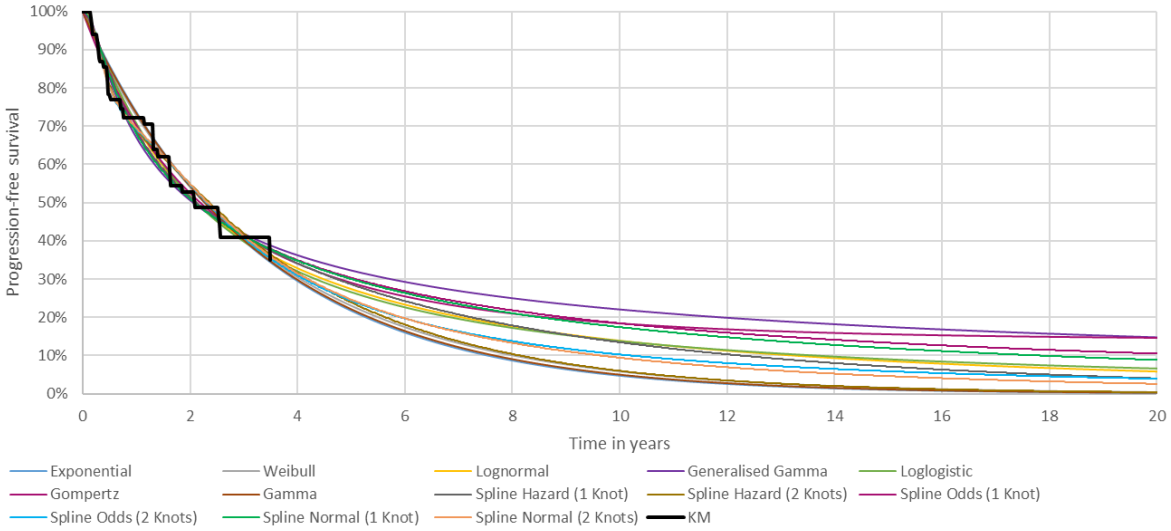
Figure 17: Long-term PFS projections – enco+bini, unadjusted PHAROS data



Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan Meier; PFS, progression-free survival.

Clinician estimates of long-term PFS are presented in Table 31. The average clinician estimates for the proportion of patients who would still be progression-free at 5, 10, and 15 years are 18%, 5% and 1%, respectively. One clinician stated no patients would be progression-free from 10 years and one clinician stated that patients who are progression-free beyond 5 years will likely remain so and there would be minimal change. The exponential distribution produces predictions that are most aligned with the estimates from clinicians with 5, 10 and 15 years PFS estimates of 21.8%, 4.7% and 1.0%, respectively, and is therefore retained for the base case. The Weibull, gamma, and spline hazard (2 knots) models also produce estimates relatively aligned with those from clinical experts and are therefore presented as scenarios.

Table 31: Long-term PFS estimates – clinician interviews, enco+bini

Year	KOL 1	KOL 2	KOL 3	Average
5	~10% (4 years)	30%	10-15%	18%
10	0%	10%	Minimal change long-term if still progression-free	5%
15	0%	2%		1%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: enco+bini, encorafenib plus binimetinib; KOL, key opinion leader; PFS, progression-free survival.

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3.4.2 Dabra+tram

The assessment of PH for PFS is as per the original Company submission (Section B.3.3.2.2.2). Based on this, PH were assumed between PHAROS and Planchard et al. Therefore, the MAIC HR (0.47) was applied to the enco+bini PFS curve to derive PFS estimates for dabra+tram. Scenario analyses are presented that apply the MAIC HR adjusting only for smoking status and ECOG-PS ([redacted]) and the unadjusted HR ([redacted]) Long-term projections of PFS over a lifetime horizon are presented in Figure 18.

Figure 18: Long-term base case PFS projection – dabra+tram

Abbreviations: Dabra+tram, dabrafenib plus trametinib; enco+bini, encorafenib plus binimetinib; HR, hazard ratio; PFS, progression-free survival.

Long-term PFS estimates for the dabra+tram arm are presented in Table 32, and long-term clinician estimates are presented in Table 33. The base case extrapolations are well aligned with the clinical experts estimates at 5, 10, and 15 years.

Table 32: Dabra+tram – median and long-term PFS model and trial comparison

	Median PFS (years)	1 year	2 years	5 years	10 years	15 years
BRF113928†	0.9	42%	13%	10%	-	
Model predicted – base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dabra+tram, dabrafenib plus trametinib; PFS, progression-free survival.

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Table 33: Long-term PFS estimates – clinician interviews, dabra+tram

Year	KOL 1	KOL 2	KOL 3	Average
5	0%	5%	10%	5%
10	0%	0-1%	Minimal change long-term if still progression-free	1%
15	0%	0%		0%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: Dabra+tram, dabrafenib plus trametinib; KOL, key opinion leader; PFS, progression-free survival

3.4.3 Independent extrapolations

As per the Committee's requested analysis, scenarios are presented relaxing the PH assumption, estimating enco+bini and dabra+tram PFS using independent extrapolations of both arms.

3.4.3.1 Enco+bini

Goodness of fit statistics using the PHAROS adjusted data for enco+bini PFS are presented in Table 34. The log-normal and exponential distributions were associated with the best statistical fit by AIC and BIC, respectively.

Table 34: Enco+bini PFS, PHAROS MAIC adjusted, goodness of fit statistics

	Goodness of fit statistic†	
	AIC	BIC
Exponential	246.04	**248.00**
Weibull	247.95	251.86
Gompertz	247.06	250.97
Log-normal	**244.88**	248.79
Log-logistic	246.41	250.32
Generalised gamma	245.87	251.74
Gamma	248.03	251.95
Spline hazard 1 knot	247.46	253.33
Spline hazard 2 knots	247.39	255.22
Spline odds 1 knot	247.39	253.26
Spline odds 2 knots	246.50	254.33
Spline normal 1 knot	246.37	252.24
Spline normal 2 knots	245.92	253.75

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

All distributions over-predict the data slightly for the first 6 months but then provided a reasonable fit to the observed data from 6–30 months (Table 35).

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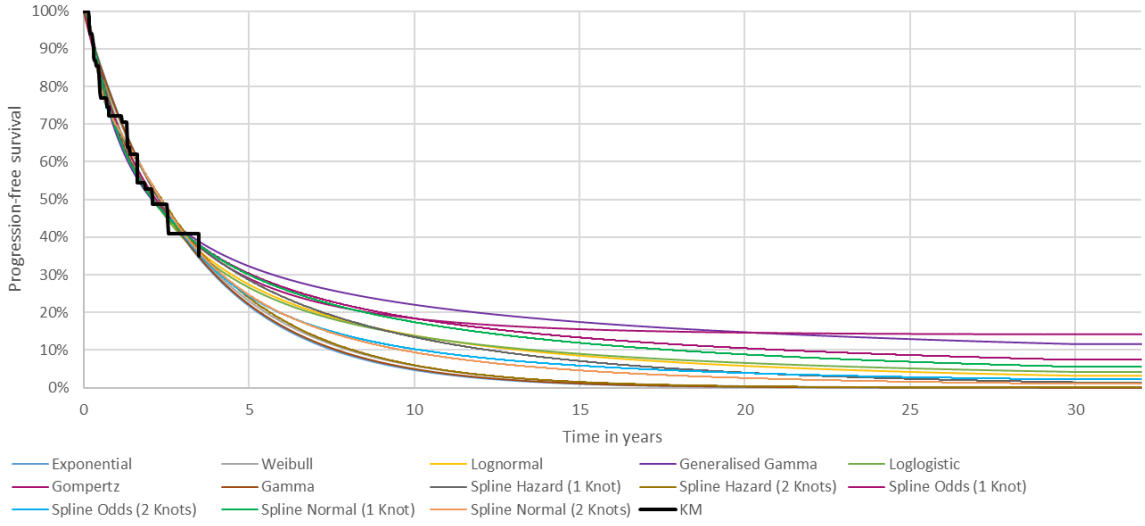
Table 35: Enco+bini PFS – parametric distribution and observed data, PHAROS MAIC adjusted data

	Month				
	6	12	18	24	30
KM	78.4%	72.1%	62.1%	52.7%	48.8%
Exponential	85.9%	73.8%	63.4%	54.4%	46.7%
Weibull	84.9%	72.8%	62.8%	54.2%	46.9%
Log-normal	84.4%	70.1%	59.6%	51.7%	45.5%
Generalised gamma	82.6%	67.1%	57.4%	50.7%	45.8%
Log-logistic	84.6%	70.8%	60.1%	51.7%	45.2%
Gompertz	83.1%	70.2%	60.3%	52.6%	46.4%
Gamma	85.5%	73.5%	63.2%	54.4%	46.8%
Spline hazard (1 knot)	84.1%	68.9%	58.8%	51.6%	46.0%
Spline hazard (2 knots)	80.9%	68.9%	61.9%	55.0%	48.2%
Spline odds (1 knot)	83.9%	68.5%	58.3%	51.2%	45.7%
Spline odds (2 knots)	80.2%	69.3%	62.3%	54.8%	47.4%
Spline normal (1 knot)	83.5%	68.1%	58.2%	51.1%	45.7%
Spline normal (2 knots)	80.2%	69.6%	62.5%	55.0%	47.7%

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

Long-term extrapolations of PFS using the MAIC adjusted PHAROS data are presented in Figure 19 and Table 36. The exponential predicts long-term estimates consistent with the average of the clinical opinion. The Weibull, gamma and spline hazard (2 knots) all provide plausible projects and are therefore presented as scenario analysis.

Figure 19: Long-term PFS projections – enco+bini, MAIC adjusted PHAROS data



Abbreviations: PFS, progression-free survival; MAIC, matching-adjusted indirect comparison.

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Table 36: Long-term PFS estimates – enco+bini, PHAROS MAIC adjusted data

	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
PHAROS KM (unadjusted)	2.52	55.6%	-	-	-	-
PHAROS KM (adjusted)	2.07	52.7%	-	-	-	-
Exponential	2.26	54.4%	21.8%	4.7%	1.0%	0.2%
Weibull	2.26	54.2%	23.1%	5.9%	1.5%	0.4%
Log-normal	2.11	51.7%	27.5%	13.9%	8.6%	5.8%
Generalised gamma	2.05	50.7%	32.3%	22.1%	17.5%	14.8%
Log-logistic	2.11	51.7%	26.7%	13.8%	9.0%	6.6%
Gompertz	2.18	52.6%	29.1%	18.4%	15.6%	14.6%
Gamma	2.26	54.4%	22.2%	5.0%	1.1%	0.3%
Spline hazard (1 knot)	2.11	51.6%	28.7%	13.5%	7.1%	4.0%
Spline hazard (2 knots)	2.36	55.0%	24.0%	6.0%	1.5%	0.4%
Spline odds (1 knot)	2.09	51.2%	30.4%	18.4%	13.3%	10.5%
Spline odds (2 knots)	2.30	54.8%	24.4%	10.3%	5.9%	3.9%
Spline normal (1 knot)	2.07	51.1%	30.1%	17.4%	11.9%	8.8%
Spline normal (2 knots)	2.32	55.0%	24.8%	9.4%	4.6%	2.6%

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

3.4.3.2 Dabra+tram

To model dabra+tram PFS independently, parametric curves were fit to digitised KM data from Planchard et al. Goodness of fit statistics are presented in Table 37. The spline normal 2 knots and exponential distribution provide the best statistical fit to the data by AIC and BIC, respectively.

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Table 37: Dabra+tram PFS, Planchard et al., goodness of fit statistics

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	172.43	**174.01**
Weibull	173.00	176.16
Gompertz	173.54	176.71
Log-normal	172.52	175.69
Log-logistic	173.73	176.89
Generalised gamma	174.47	179.22
Gamma	172.83	176.00
Spline hazard 1 knot	174.65	179.40
Spline hazard 2 knots	171.96	178.30
Spline odds 1 knot	175.73	180.48
Spline odds 2 knots	171.42	177.75
Spline normal 1 knot	174.47	179.22
Spline normal 2 knots	**171.08**	177.42

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

All distributions predict the KM data well for the first 6 months but then provided a relatively poor fit to the observed data from 6–30 months (Table 38).

Table 38: Dabra+tram PFS, Planchard et al., parametric distribution and observed data

	Month				
	6	**12**	**18**	**24**	**30**
KM	69.8%	55.2%	41.4%	17.2%	-
Exponential	71.3%	50.9%	36.3%	25.9%	18.5%
Weibull	76.3%	52.8%	34.8%	22.1%	13.7%
Log-normal	73.0%	48.7%	34.0%	24.8%	18.7%
Generalised gamma	73.9%	49.4%	33.9%	24.0%	17.5%
Log-logistic	74.6%	49.9%	34.6%	25.2%	19.2%
Gompertz	75.1%	53.7%	36.2%	22.8%	13.3%
Gamma	76.1%	52.0%	34.3%	22.2%	14.1%
Spline Hazard (1 Knot)	75.1%	51.0%	34.4%	23.1%	15.4%
Spline Hazard (2 Knots)	69.9%	56.2%	39.0%	22.3%	11.3%
Spline Odds (1 Knot)	74.7%	49.9%	34.5%	25.2%	19.1%
Spline Odds (2 Knots)	70.7%	56.8%	36.9%	21.1%	12.4%
Spline Normal (1 Knot)	73.7%	49.2%	33.9%	24.2%	17.9%
Spline Normal (2 Knots)	70.8%	56.4%	37.2%	21.4%	12.2%

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

Long-term PFS estimates are presented in Figure 20 and Table 39. The generalised gamma provides estimates that are most closely aligned to the average of clinician

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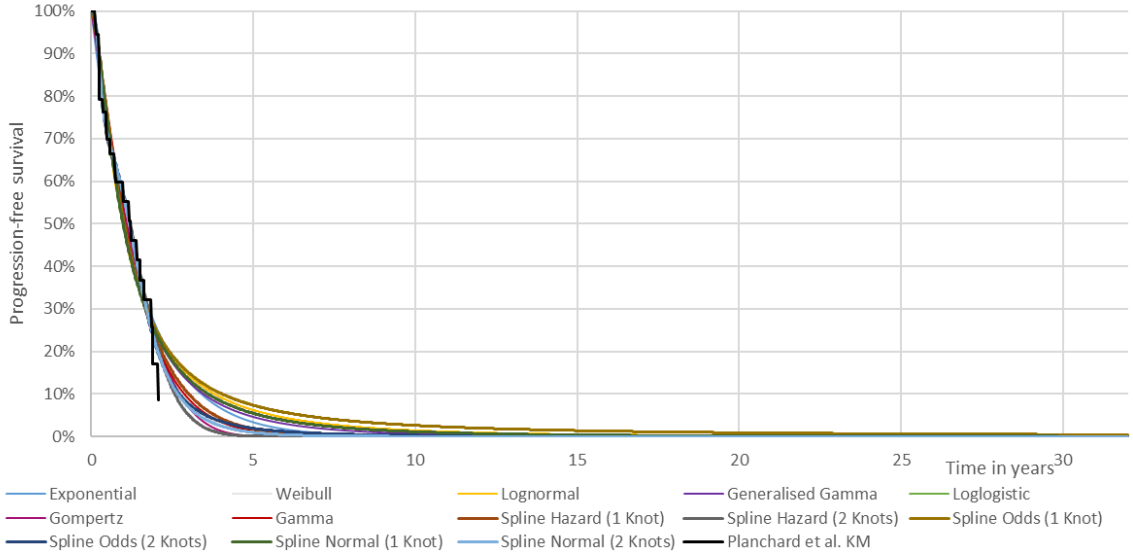
estimates at 5, 10, and 15 years. The exponential and spline normal (1 knots), also produce clinically plausible estimates and are included as further scenario analyses.

Figure 20: Long-term PFS projections – dabra+tram, Planchard et al.



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

Table 39: Long-term PFS estimates – dabra+tram, Planchard et al.

	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Planchard KM	1.22			-	-	-
Exponential	1.02	25.9%	3.4%	0.1%	0.0%	0.0%
Weibull	1.05	22.1%	0.9%	0.0%	0.0%	0.0%
Log-normal	0.96	24.8%	6.3%	1.5%	0.5%	0.2%
Generalised gamma	0.98	24.0%	4.7%	0.7%	0.2%	0.0%
Log-logistic	0.98	25.2%	7.4%	2.6%	1.4%	0.9%
Gompertz	1.09	22.8%	0.2%	0.0%	0.0%	0.0%
Gamma	1.03	22.2%	1.4%	0.0%	0.0%	0.0%
Spline Hazard (1 Knot)	1.02	23.1%	1.8%	0.0%	0.0%	0.0%
Spline Hazard (2 Knots)	1.19	22.3%	0.1%	0.0%	0.0%	0.0%
Spline Odds (1 Knot)	0.98	25.2%	7.4%	2.6%	1.4%	0.9%
Spline Odds (2 Knots)	1.17	21.1%	1.9%	0.3%	0.1%	0.0%
Spline Normal (1 Knot)	0.96	24.2%	5.5%	1.1%	0.4%	0.2%
Spline Normal (2 Knots)	1.17	21.4%	1.0%	0.0%	0.0%	0.0%

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

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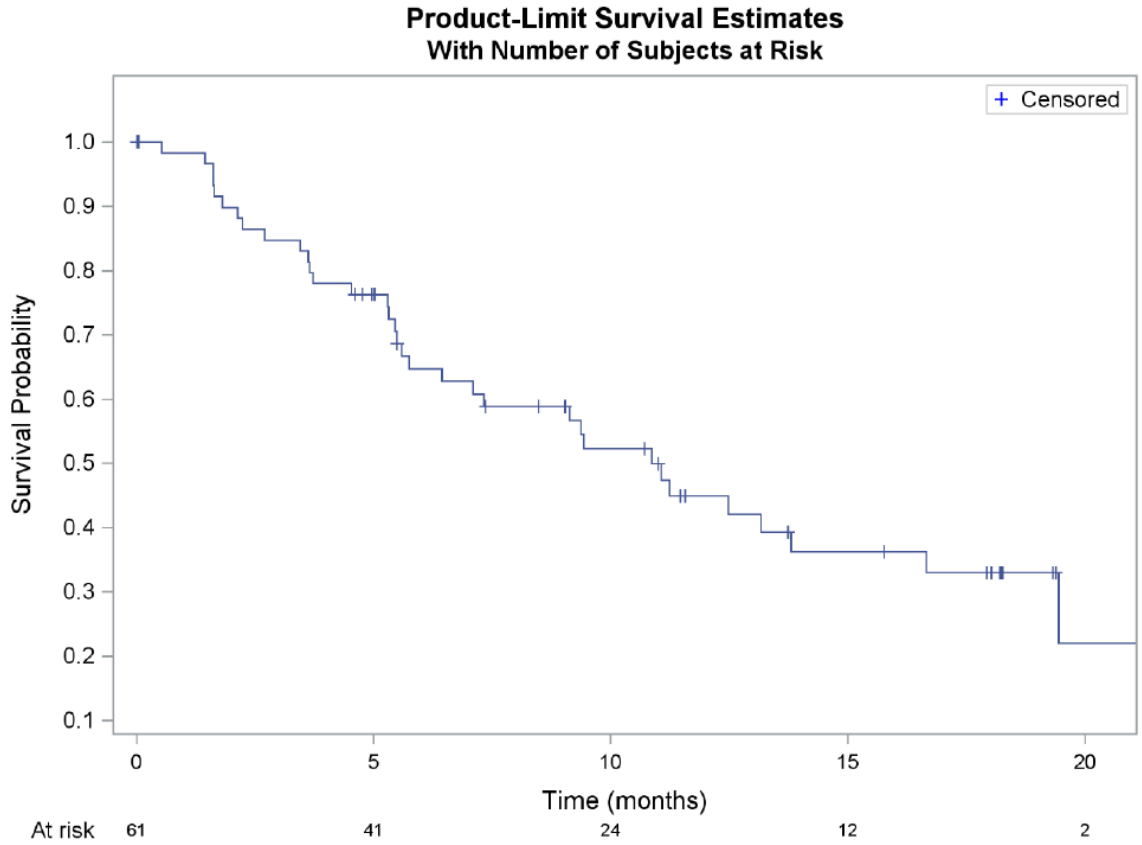
3.4.4 IFCT

3.4.4.1 Enco+bini

As discussed in Section 3.3.4, due to the operational challenges of IIT and treatment practice differences in France, the Company consider the PHAROS trial to be the most appropriate source of data to inform the model estimates. However, as per the Committee requested additional analysis, scenarios are presented that use IFCT only to estimate enco+bini survival. As discussed in Section 2.2.1, due to definition of the primary endpoints of IFCT and Planchard et al., PFS by Investigator is used for the IFCT PFS analysis, rather than PFS by IRR. At the end of follow-up, [redacted]% of patients experienced a PFS event in the treatment-naïve population, and median PFS was 10.9 months (95% CI: 6.4, 16.7) (Figure 21).

Figure 21: IFCT KM – PFS by Investigator



Source: Planchard et al, 2024 (12).
Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

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Goodness of fit statistics using the IFCT unadjusted data for enco+bini OS are presented in Table 40. The log-normal and exponential distributions were associated with the best statistical fit by AIC and BIC.

Table 40: Enco+bini PFS by Investigator, IFCT unadjusted, goodness of fit statistics

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	261.90	**264.01**
Weibull	262.59	266.81
Gompertz	263.53	267.76
Log-normal	**260.94**	265.16
Log-logistic	261.82	266.05
Gamma	262.88	269.21
Spline hazard 1 knot	262.17	266.40
Spline hazard 2 knots	262.95	269.29
Spline odds 1 knot	264.47	272.91
Spline odds 2 knots	263.66	270.00
Spline normal 1 knot	264.91	273.35
Spline normal 2 knots	262.90	269.23

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

All distributions over-predict the data slightly for the first 6 months but then provided a reasonable fit to the observed data (Table 13).

Table 41: Enco+bini PFS by Investigator, IFCT unadjusted – 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]
Spline Hazard (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Hazard (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Odds (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (1 Knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Normal (2 Knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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Long-term projections for each distribution using the IFCT data are presented in Figure 22 and Table 42. All distributions significantly underestimate the survival projects based on clinical opinion. The spline odds (2 knot) distribution is most closely aligned at 10 and 15 years, and is therefore selected for scenario analyses.

Figure 22: Long-term PFS by Investigator projections – enco+bini, unadjusted IFCT data

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

Table 42: Long-term PFS by Investigator estimates – enco+bini, IFCT unadjusted data

	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; PFS, progression-free survival.

3.4.4.2 Dabra+tram

The assumption of PH was re-assessed between the IFCT 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=0.185). The plot of the Schoenfeld residuals (Figure 23) 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 24) show curves crossing, however the plots show a similar pattern in each arm. 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 when using the IFCT data and estimate dabra+tram PFS by applying the MAIC HRs to the unadjusted IFCT data. However, as there is uncertainty in the conclusions, further scenario analyses are presented using independent extrapolations (Section 3.3.4.3).

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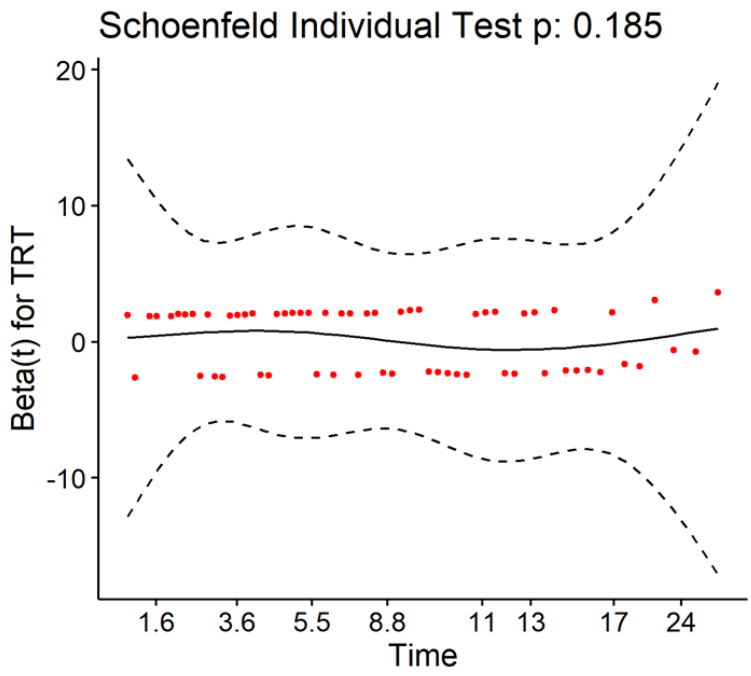
Figure 23: Schoenfeld residuals, IFCT vs Planchard et al.



Abbreviations: IFCT, Intergroupe Francophone de Cancérologie Thoracique.

Figure 24: Log-log plot, IFCT vs Planchard et al.

Abbreviations: enco+bini, encorafenib plus binimetnib; IFCT, Intergroupe Francophone de Cancérologie Thoracique.

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The MAIC HR ([redacted]) was applied to the enco+bini PFS curve to derive long-term PFS estimates for dabra+tram. Scenario analyses are presented using the MAIC adjusting only for smoking status and ECOG-PS ([redacted]) and the unadjusted HR ([redacted]). Long-term projections of PFS over a lifetime horizon are presented in Figure 8, and median and long-term survival estimates are presented in Table 16. Long-term projections of PFS for dabra+tram are presented in Figure 25 and Table 43. Estimates at 5 years are well aligned with clinical input, but the model over-estimates clinical input at 10 years.

Figure 25: Long-term PFS projection – dabra+tram

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

Table 43: Dabra+tram – median and long-term PFS model and trial comparison

	Median PFS (years)	1 year	2 years	5 years	10 years
BRF113928	0.9	42%	13%	10%	-
Model predicted, HR vs IFCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dabra+tram, dabrafenib + trametinib; HR, hazard ratio; IFCT, Intergroupe Francophone de Cancérologie Thoracique; PFS, progression-free survival.

3.4.4.3 Independent extrapolations

As per the Committee's requested analysis, scenarios are presented relaxing the proportional hazards assumption, estimating enco+bini and dabra+tram PFS using independent extrapolations of both arms.

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3.4.4.3.1 Enco+bini

In these scenarios, enco+bini PFS is estimated from the MAIC adjusted IFCT patient level data. The goodness of fit statistics are presented in Table 28. The exponential and log-normal distributions produce the best statistical fit by BIC and AIC, respectively.

Table 44: Enco+bini PFS by Investigator, IFCT MAIC adjusted, goodness of fit statistics

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	216.73	**218.65**
Weibull	218.65	222.48
Gompertz	218.72	222.55
Log-normal	**215.85**	219.68
Log-logistic	217.56	221.40
Generalised gamma	217.51	223.26
Gamma	218.50	222.33
Spline hazard 1 knot	218.39	224.14
Spline hazard 2 knots	216.97	224.64
Spline odds 1 knot	218.84	224.59
Spline odds 2 knots	217.12	224.78
Spline normal 1 knot	217.57	223.33
Spline normal 2 knots	217.15	224.81

† Lowest AIC and BIC denoted in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; PFS, progression-free survival.

All distributions provide a reasonable fit to the data from 0–24 months (Table 45).

Table 45: Enco+bini PFS by Investigator – parametric distribution and observed data, IFCT MAIC adjusted 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]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Month				
	6	12	18	24	30
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan-Meier; PFS, progression-free survival.

Long-term projections when using the MAIC adjusted IFCT data for enco-bini PFS are presented in Figure 26 and Table 46. Most distributions significantly underestimate clinical expert predictions. The spline odds (2 knots) provides the most plausible predictions and therefore is presented in scenario analysis.

Figure 26: Long-term PFS projections – enco+bini, MAIC adjusted IFCT data

Abbreviations: IFCT, Intergroupe Francophone de Cancérologie Thoracique; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Table 46: Long-term PFS estimates – enco+bini, IFCT MAIC adjusted data

	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
IFCT KM (unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFCT KM (adjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Predicted median PFS (years)	Estimated % alive at time (years)				
		2	5	10	15	20
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan-Meier; PFS, progression-free survival.

3.4.4.3.2 Dabra+tram

In the scenario using IFCT data and independent extrapolations, dabra+tram survival is as per Section 3.3.3.

3.5 Treatment effect waning

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 27). Furthermore, the hazard plots of enco+bini and dabra+tram diverge for PFS, and remain parallel for OS for the majority of the trial follow-up. At approximately 40 months, the risk of an OS event begins to decline in both arms, albeit at a slightly reduced rate compared with the beginning of follow-up. After this point the hazard curve flattens out slightly quicker in the enco+bini arm compared with the dabra+tram arm, although there are fewer patients at risk at this point in the analysis. Taken together, it is not considered appropriate to apply a waning of effect during the trial follow-up (max treatment exposure of [redacted] months).

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Figure 27: Smoothed hazards, enco+bini (PHAROS) and dabra+tram (Planchard et al.)

Abbreviations: Enco+bini, encorafenib and binimetinib; dabra+tram, dabrafenib and trametinib; OS, overall survival; PFS, progression-free survival.

At EAG clarification response (Question B11), a scenario was presented that applied waning for a duration of 2 years (based on previous appraisals in NSCLC) at the end of PHAROS follow-up (max of [redacted] months). The EAG agreed with the assessment that there was no evidence of waning during the trial period. This scenario has been updated to match the March 2025 DCO max follow-up of [redacted] months.

As per the response to B11, there are little external data on enco-bini beyond IFCT and PHAROS. 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 (13). Of these, only one patient received enco+bini and survival outcomes are not presented specifically for enco+bini. Perrone et al. 2022 present a multicentre Italian retrospective study involving 44 advanced BRAF mutant NSCLC patients (14). Of these, only one patient received enco+bini and survival outcomes are not presented specifically for enco+bini.

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 affects the tumour microenvironment (TME) and

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improves durable tumour surveillance (the body's long-term ability to monitor and supress tumour activity), therefore providing a long-term beneficial effect (15). 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 (16).

It should be noted also that in the appraisal for enco+bini in melanoma (TA562) (17), no treatment waning was included in the analysis which also compared enco+bini vs dabra+tram based on a similar evidence base. In TA562, a treatment effect for enco+bini vs dabra+tram was applied for the model duration and this was accepted for decision making by the Committee. However, as per the Committee's requested analysis, and due to a lack of evidence on treatment effect waning, clinical experts were consulted on the expect treatment effect waning over time (4). During the July 2025 KOL interviews, clinicians were asked whether they thought waning was relevant for enco+bini in this patient population, and if so, at what point it would occur (4). One clinician thought that waning would be minimal and dependent on the reason for discontinuation, one clinician said they did not think treatment effect waning was relevant, while one clinician thought that the duration of waning would be very short (3 months). Therefore, a further scenario analysis is included that applies treatment effect waning at max follow-up of PHAROS for a duration of 3-months after which point the risks are equivalent between arms. It should be noted, however, that all clinicians highlighted the consistently better tolerability of enco+bini compared with dabra+tram, which they felt is likely to lead to improved outcomes.

3.6 Time-to-treatment discontinuation

3.6.1 Enco+bini

All survival analysis of TTD data from PHAROS was updated to include the March 2025 DCO of PHAROS (Section 2.1.4). At the March 2025 DCO of PHAROS, after a median follow-up of [redacted] months, [redacted]% of patients had discontinued in the treatment-naïve population and median TTD was [redacted] months (95% CI: [redacted]) (Figure 2).

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3.6.1.1 PHAROS

Goodness of fit statistics using the PHAROS unadjusted data for enco+bini TTD are presented in Table 47. The exponential distribution was associated with the best statistical fit.

Table 47: Enco+bini TTD, goodness of fit statistics – PHAROS

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	**456.52**	**458.60**
Weibull	457.80	461.96
Gompertz	458.52	462.67
Log-normal	465.74	469.89
Log-logistic	464.11	468.26
Generalised gamma	459.03	465.26
Gamma	457.63	461.79
Spline hazard 1 knot	459.77	466.00
Spline hazard 2 knots	458.07	466.38
Spline odds 1 knot	464.15	470.38
Spline odds 2 knots	460.09	468.40
Spline normal 1 knot	461.91	468.14
Spline normal 2 knots	460.35	468.66

†Lowest AIC and BIC denoted in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib plus binimetinib; TTD, time to treatment discontinuation.

All distributions over-predict the data slightly for the first 6 months but then provided a reasonable fit to the observed data (Table 48).

Table 48: Enco+bini TTD – parametric distribution and observed data, PHAROS

	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]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Month				
	6	12	18	24	30
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; TTD, time to treatment discontinuation

Long-term projections for each distribution are presented in Figure 28 and Table 49. During the KOL clinical validation interviews, clinicians were asked to provide their expectations for TTD in patients treated with enco+bini at 5, 10, and 15 years; a summary of their estimates of long-term survival are presented in Table 50 (4). On average, clinicians predicted that 6%, 2%, and 1% of patients would still be receiving treatment with enco+bini at 5, 10, and 15 years, respectively (4). Of the distributions estimated, the spline hazard (2 knots) provides the best fit to this data ([redacted]%, [redacted]% and [redacted]%, respectively). The exponential and Gompertz distributions also provide similar estimates, however most distributions over-estimate patients on treatment at 5 years compared with clinician estimates. The exponential distribution was retained in the base case due to the inherent relationship between PFS and TTD. The Gompertz and spline hazard (2-knot) models are presented as scenarios.

Figure 28: Long-term TTD projections – enco+bini, PHAROS

Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

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Table 49: Long-term TTD estimates - enco+bini, PHAROS

	Predicted median TTD (years)	Estimated % on treatment at time (years)				
		2	5	10	15	20
PHAROS KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib plus binimetinib; KM, Kaplan Meier; TTD, time to treatment discontinuation.

Table 50: Long-term TTD estimates – clinician interviews, enco+bini

Year	KOL 1	KOL 2	KOL 3	Average
5	5–10%	5%	-	6%
10	-	2%	Minimal drop-off if still receiving treatment at 5 years	2%
15	-	1%		1%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: Enco+bini, encorafenib plus binimetinib; KOL, key opinion leader; TTD, time-to-treatment discontinuation.

3.6.1.2 IFCT

As per the Committee's request for additional analysis, a scenario is presented that uses IFCT only to estimate enco+bini TTD. Median TTD was [redacted] months (95% CI: [redacted]) (Figure 29).

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Figure 29: IFCT KM of TTD

Abbreviations: IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Goodness of fit statistics using the PHAROS unadjusted data for enco+bini OS are presented in Table 51. The Weibull and exponential distribution were associated with the best statistical fit by AIC and BIC, respectively.

Table 51: Enco+bini TTD, goodness of fit statistics – IFCT

	Goodness of fit statistic†	
	AIC	**BIC**
Exponential	289.81	**291.97**
Weibull	**289.58**	293.89
Gompertz	289.66	293.98
Log-normal	293.07	297.38
Log-logistic	290.02	294.34
Generalised gamma	291.57	298.04
Gamma	289.68	294.00
Spline hazard 1 knot	291.56	298.04
Spline hazard 2 knots	293.40	302.04
Spline odds 1 knot	290.99	297.47
Spline odds 2 knots	292.96	301.60
Spline normal 1 knot	291.02	297.50
Spline normal 2 knots	293.01	301.65

†Lowest AIC and BIC denoted in bold.
Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; TTD, time to treatment discontinuation.

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All distributions provided a reasonable fit to the observed data (Table 52).

Table 52: Enco+bini TTD – parametric distribution and observed data, IFCT

	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]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Long-term projections for each distribution are presented in Figure 30 and Table 53. Of the distributions estimated, the gamma distribution provides the best fit to the clinician estimates at 5, 10 and 15 years and is therefore presented as a scenario analysis.

Figure 30: Long-term TTD projections – enco+bini, IFCT

Abbreviations: enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique KM, Kaplan-Meier; TTD, time to treatment discontinuation.

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Table 53: Long-term TTD estimates - enco+bini, IFCT

	Predicted median TTD (years)	Estimated % alive at time (years)				
		2	5	10	15	20
IFCT KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KM, Kaplan-Meier, TTD, time to treatment discontinuation.

3.6.2 Dabra+tram TTD

Regarding the dabra+tram treatment duration, the NICE Committee, in its draft guidance, "*thought that it was not plausible to assume that TTD is equal to PFS*", reflecting clinical expert feedback "*that assuming TTD is equal to PFS was too simplistic*". The Committee also indicated they would consider alternative scenarios that provide plausible results with clinical expert validation. Following this feedback, alternative scenarios for the treatment duration of dabra+tram are presented.

Alternative scenarios were presented during the KOL interviews in July 2025. When asked which of the scenarios they preferred, responses varied among the three UK clinical experts consulted: one clinician preferred simpler real-world assumptions (i.e. real-world treatment duration of dabra+tram and equivalence of treatment duration between dabra+tram and enco+bini), while others found all approaches speculative.

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3.6.2.1 Overview of evidence

Planchard 2022 is the pivotal prospective Phase 2 single-arm study for dabra+tram. The Swalduz et al, 2024 BLaDE study (18) and study by Auliac et al, 2020 (19) are the two most relevant retrospective RWE studies – these studies were conducted across multiple centres in France. Table 54, Table 55, and Table 56 present comparisons of study design, population characteristics, and treatment duration and outcomes, respectively, between the three studies evaluating dabra+tram. The RWE of dabra+tram has been evaluated in the context of the IFCT academic study (i.e. IFCT-1904 ENCO-BRAF [March 2024]) evaluating enco+bini, as according to the NICE draft guidance, the IFCT study may have included a patient population more reflective of real-world clinical practice.

Table 54 Study design for first-line BRAF V600E MT NSCLC population

Aspect	Planchard 2022 (NCT01336634; BRF113928) (20)	Swalduz et al., 2025 BLaDE Study (18)	Auliac 2020 (19)	IFCT-1904 ENCO-BRAF (March 2024)
Type	Phase 2, multicohort, multicentre, non-randomised, open-label study	Retrospective, non-interventional, French multicentre study	Retrospective observational multicentre study	Phase 2 study of enco+bini in BRAF V600E MT NSCLC
Objective	Assess activity and safety of dabra+tram in treatment-naive BRAF V600E MT NSCLC	Collect real-world data on treatment-naive BRAF V600E MT NSCLC patients treated with dabra+tram	Describe clinical characteristics and outcomes of treatment-naive patients treated with dabra+tram	Assess efficacy and safety of enco+bini in NSCLC
Country and centres	Conducted internationally across multiple centres. 19 centres in eight countries within North America, Europe, and Asia	Conducted in France across multiple centres	Conducted in French centres	Conducted in French centres

Abbreviations: BRAFV600E, v-Raf murine sarcoma viral oncogene homolog B, valine to glutamic acid substitution at amino acid 600; (m)NSCLC, (mutant) non-small cell lung cancer.

In Planchard 2022, 36 patients were included, with 61% having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, and 3% with a status of 2. Swalduz et al, 2024 reported on a larger cohort of 44 patients, of whom 75.7% had an ECOG PS of 0–1 and 24.2% had a status of 2–3, indicating a

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generally poorer PS. Auliac et al, 2020, which included the smallest cohort (9 patients), reported that 33% had an ECOG status of ≥2.

Table 55: Population characteristics for first-line BRAF V600E MT NSCLC population

Characteristic	Planchard 2022 (NCT01336634; BRF113928) (20)	Swalduz et al., 2025 BLaDE Study (18)	Auliac 2020 (19)	IFCT-1904 ENCO-BRAF (March 2024) (12)
Total patients	36	44	9	64
Age (years)	Median: 67 (range: 44–91)	Median: 71.6	Mean: 74.3	Median: 70.7 (range: 39.1–90.3)
Gender	Female: 61%; Male: 39%	Female: 50%; Male: 50%	Female: 56%; Male: 44%	Female: 53.1%; Male: 46.9%
Histology	Adenocarcinoma: 89%	Adenocarcinoma: 95.5%	Adenocarcinoma: 100%	Adenocarcinoma: 98.4%
Smoking Status	Never: 28%; Current: 14%; Former: 58%	Never: 27.3%; Current/Former: 72.7%	Never: 44%; Current/Former: 56%	Never: 35.9%; Current: 12.5%; Former: 51.6%
ECOG PS	0: 36% 1: 61% 2: 3%	0–1: 75.7% 2–3: 24.2%	0–1: 67% ≥2: 33%	0: 43.8% 1: 56.3%

Abbreviations: BRAF V600E, v-Raf murine sarcoma viral oncogene homolog B, valine to glutamic acid substitution at amino acid 600; ECOG, Eastern Cooperative Oncology Group; (m)NSCLC, (mutant) non-small cell lung cancer; PS, performance status.

The median treatment duration varied notably across studies: 10.55 months in Planchard 2022, 11.4 months in Swalduz et al, 2024 BLaDE Study, and 17.5 months in Auliac 2020. Also, Planchard 2022 reported the highest rate of treatment discontinuation (22%) compared with Swalduz et al, 2024 (15.6%) and Auliac 2020 (18%). However, the safety endpoints when evaluated in RWE studies have limitations inherent to those studies (21-24).

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Table 56: Treatment duration and outcomes for first-line BRAF V600E mNSCLC population

Aspect	Planchard 2022 (NCT01336634; BRF113928) (20)	Swalduz et al., 2025 BLaDE Study (18)	Auliac 2020 (19)	IFCT-1904 ENCO-BRAF (March 2024) (12)
Median follow-up	16.3 months	27.4 months	16.5 months	18 months
Median treatment duration (combination)	10.55 months	11.4 months	17.5 months	[redacted]
Median PFS	Investigator-assessed: 10.8 (95% CI: 7.0, 14.5) months IRR assessed: 14.6 (95% CI: 7.0, 22·1) months	Investigator-assessed: 18.2 (95% CI: 7.7, 21.3) months	Investigator-assessed: 16.8 (95% CI: 6.1, 23.2) months	Investigator-assessed: 10.9 (95% CI: 6.4, 16.7) months [redacted]
Median OS	17.3 (95% CI: 12.3, 40.2) months	24.1 months	21.8 months	NR [95% CI: 20.7, NR]
Treatment discontinuation due to toxicity	22%	15.6%	18%	[redacted]
Treatment interruption or delay due to toxicity	75%	Not specified	20%	34.4% for encorafenib; 35.9% for binimetinib
Treatment reduction due to toxicity	39%	Not specified	30%	34.4% for encorafenib; 32.8% for binimetinib

Abbreviations: BRAFV600E, v-Raf murine sarcoma viral oncogene homolog B, valine to glutamic acid substitution at amino acid 600; CI, confidence interval; IRR, independent radiology review; (m)NSCLC, (mutant) non-small cell lung cancer; NR, not reached; PFS, progression-free survival.

In real-world studies (Swalduz et al., 2024 and Auliac 2020), patients receiving dabra+tram experienced longer treatment durations compared with those in NCT01336634 (Planchard 2022).

Alternative methods are proposed for modelling the treatment duration of dabra+tram, utilising RWE data. These approaches are outlined in Sections 3.6.2.2–3.6.2.4.

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3.6.2.2 Approach 1 – Real-world treatment duration of dabra+tram

To determine a conservative and plausible median treatment duration for dabra+tram, a weighted average approach may be applied to the two RWE studies: Swalduz et al, 2024 and Auliac 2020. This involves weighting each study's median treatment duration by its sample size, ensuring that studies with larger populations have a proportionally greater influence on the final estimate. By aggregating the weighted durations, a single median treatment duration can be derived that reflects the combined insights from all studies. Using this methodology, the calculated weighted median treatment duration across the two RWE studies of dabra+tram is:

$\frac{11.4*44+17.5*9}{44+9} = \mathbf{12.44\ months}$.

3.6.2.3 Approach 2 – Real-world treatment duration of dabra+tram using the adjustment for discontinuation due to toxicity

In RWE studies (Swalduz et al., 2024 and Auliac 2020 [dabra+tram] and IFCT study [enco+bini]), the median treatment duration was similar to the median PFS by investigator:

- In the Auliac 2020 study, the mTTD for dabra+tram was 17.5 months, closely aligning with the median median PFS of 16.8 months as assessed by investigators,
- In the Swalduz et al, 2024 study, the median TTD for dabra+tram was reported as 11.4 months, while the investigator assessed median PFS was 18.2 months. Although these figures differ, a closer examination of the Kaplan-Meier (KM) PFS curve for first-line treatment (N=44) reveals a plateau occurring just before the median. Had the curve followed the same exponential trajectory as observed in second-line treatment (N=119), the median PFS for first-line treatment would likely have been less than 15 months, aligning more closely with the median TTD. This plateau could be attributed to various factors, for instance statistical artifacts, real-world variability, heterogeneity in patient responses, or censoring and data maturity. However, it is highly uncertain that this rebound is linked to a delayed treatment effect specific to first-line patients,

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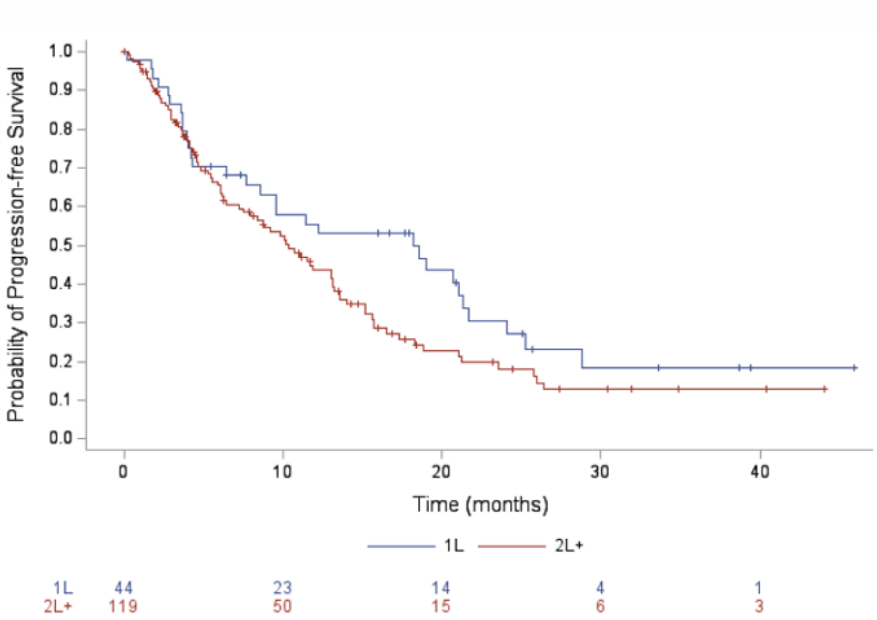
Figure 31: KM curve for PFS (Swalduz et al, 2024)



Abbreviations: 1L, first-line; 2L, second-line; KM, Kaplan-Meier; PFS, progression-free survival.

- In the IFCT study for enco+bini, a median TTD of [redacted] months was reported, which is closely aligned with the investigator assessed median PFS of [redacted] months.

During the NICE Committee meeting, clinical experts emphasised that patients who discontinue treatment due to toxicity are unlikely to have a treatment duration equivalent to their PFS; rather, their treatment duration is typically shorter. Additionally, for ethical reasons, treatment is often continued beyond disease progression in other patients to avoid leaving them without therapeutic options. As a result, assuming that treatment duration is equal to PFS may not accurately reflect real-world treatment patterns.

To address this, and in line with clinical observations of dabra+tram noted in the NICE draft guidance and supported by real-world evidence (RWE) studies, a revised methodology was developed. This approach accounts for toxicity-related discontinuations by estimating median treatment duration as follows:

- Patients who discontinue due to toxicity are assumed to have a median treatment duration equal to 50% of the median PFS
- Patients who do not discontinue due to toxicity are assumed to have a median treatment duration equal to the full median PFS.

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This approach is conservative, particularly as treatment may continue beyond progression in clinical practice.

3.6.2.3.1 Dabra+tram

In the Swalduz et al, 2024 BLaDE Study (N=44), a median PFS by investigator of 18.2 months was reported. With 15.6% of patients discontinuing due to toxicity, the initial estimated median treatment duration was approximately 16.9 months. However, adjusting for the KM PFS curve artifact in the first-line treatment, a median PFS of 15 months is proposed, resulting in a revised estimated median treatment duration of approximately 13.8 months. The Auliac 2020 study (N=9) reported a median PFS of 16.8 months, and with 18% of patients discontinuing due to toxicity, the estimated median treatment duration is approximately 15.5 months. These estimates provide valuable insights into how adverse events influence treatment duration, highlighting the importance of effective toxicity management to maximise treatment benefits for patients.

3.6.2.4 Approach 3 – Equivalence of treatment duration between dabra+tram and enco+bini

Considering the real-world treatment durations of dabra+tram and enco+bini, along with the significant variability and the impact on the incremental cost-effectiveness ratio (ICER), a reasonable assumption is to consider equivalent treatment durations for both combinations.

A comparison of long-term TTD estimates for dabra+tram per scenario are presented in Table 57. Using the Planchard et al. data underestimates clinician estimates at every time point, therefore is not considered appropriate for the base case. The weighted PFS and TTD scenario using Auliac et al is most aligned with the estimates from clinical experts that 5–10%, <5% and <1% of patients would be on treatment with dabra+tram at 5, 10 and 15 years, respectively. However, it should be noted that one clinician noted that very few patients would make it to 5 years on treatment.

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Table 57: Long-term TTD estimates – dabra+tram, IFCT

Method	Predicted median TTD (years)	Estimated % on-treatment at time (years)				
		2	5	10	15	20
Planchard et al.	10.55	20.8%	2.0%	0.0%	0.0%	0.0%
RWE Auliac 2020 study	17.50	38.8%	9.4%	0.9%	0.1%	0.0%
RWE Swalduz et al, 2024	11.40	23.4%	2.6%	0.1%	0.0%	0.0%
Auliac 2020 weighted PFS and TTD	15.50	34.3%	6.9%	0.5%	0.0%	0.0%
Weighted average of median TTD from Auliac 2020 and IFCT BLaDE	12.44	26.4%	3.6%	0.1%	0.0%	0.0%
Swalduz et al, 2024, weighted PFS and TTD	16.90	37.5%	8.6%	0.7%	0.1%	0.0%

Abbreviations: Dabra+tram, dabrafenib + trametinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; TTD, time to treatment discontinuation.

Table 58: Long-term TTD estimates – clinician interviews, dabra+tram

Year	KOL 1	KOL 2	KOL 3	Average
5	Very few patients reach 5 years	5–10%	TTD would be similar to PFS, but dabra+tram not as tolerable as enco+bini	5–10%
10		<5%		<5%
15		<1%		<1%

Source: Pierre Fabre, KOL interview minutes DOF (4).
Abbreviations: dabra+tram, dabrafenib plus trametinib; KOL, key opinion leader; TTD, time-to-treatment discontinuation.

In the base case, the weighted average of median TTD from the RWE is used to estimate dabra+tram TTD as this scenario represents use of all of the available first-line TTD for patients receiving dabra+tram. All other methods are presented as scenarios.

3.7 Adverse events

The updated analyses using PHAROS data includes updated TEAE data for the treatment-naïve cohort. Grade ≥3 TEAEs are presented in Table 6. The TEAEs used in scenario analyses using Grade 1–2 AEs are presented in Table 5.

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3.8 Treatment costs

Primary therapy acquisition costs have been updated as per the Committee's preferred assumptions. Acquisitions costs are modelled per pack and applied every 28 days as per the prescribing of enco+bini and dabra+tram. Costs are sourced from the British National Formulary (BNF) and are presented in Table 59.

Table 59: Acquisition costs

Drug	Dose	mg/tablet	Pack price	Pack size (number of tablets)	Cost per 28 days
Encorafenib (list price)	450mg once daily	75	£1,400.00	42	£5,600.00
Binimetinib (list price)	45mg twice daily	15	£2,240.00	84	£4,480.00
Encorafenib (PAS price)	450mg once daily	75	[redacted]	42	[redacted]
Binimetinib (PAS price)	45mg twice daily	15	[redacted]	84	[redacted]
Dabrafenib	150mg twice daily	15	£1,400.00	28	£5,600.00
Trametinib	2mg once daily	2	£4,800.00	30	£4,480.00
			£1,120.00	7	

Abbreviations: PAS, patient access scheme.

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4 Cost-effectiveness results

4.1 Summary of changes to Company base case

A summary of the adjustments made to the Company base case submitted at EAG clarification questions is presented in Table 60. As per Section 3.16 of the draft guidance the Committee's preferred assumptions are:

- Enco+bini positioned for first-line use only
- Dabra+tram as the most appropriate comparator
- Drug acquisition costs modelled per pack and applied every 28 days

The revised Company base case is aligned with these assumptions.

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Table 60: Summary of updates to Company base case – enco+bini PAS price

Scenario	Related ACD comment	Description	Justification	Model implementation	Inc. costs	Inc. QALYs	NHB	Cross reference
Original Company base case (submitted at EAG clarification questions)	–	–	–	–	[redacted]	[redacted]	[redacted]	–
1.1 – Updated data from the March 2025 DCO of PHAROS	In response to the Committee's comment that there is "substantial uncertainty" relating to the "modelling of long-term OS, PFS (Section 3.9) and TTD for enco+bini (Section 3.10)"	Incorporation of the most recent data cut of PHAROS (March 2025): • Updated enco+bini OS and TTD data • Updated enco+bini AE data Updated MAIC (adjusted for all factors) OS HR vs dabra+tram.	The Committee highlighted that there was uncertainty associated with long-term estimates of enco+bini survival. Therefore, the updated base case incorporates a further PHAROS DCO (March 2025 DCO), which provides a further [redacted] months of follow-up, which means median OS has been reached and enco+bini is now associated with a significant reduction in death compared with dabra+tram.	• Updated covariates for the enco+bini OS and TTD survival curves (Column BG and CT of the 'data_curves' sheet) • Updated AE data (H27:61 of the 'Safety' sheet) • Updated OS MAIC HR (F19 of the 'Relative efficacy sheet')	[redacted]	[redacted]	[redacted]	Section 3.3, Section 3.7, Section 2.2.1.1
1.2 – Baseline characteristics to match efficacy data	Committee request: "Use of baseline characteristics from the same source as for the intervention efficacy", Section 3.8	The model baseline characteristics have been updated to align with the unadjusted data from PHAROS	The updated base case aligns the source of baseline characteristics with the source of efficacy data (i.e. the unadjusted PHAROS data), as per the Committee's request.	Select 'PHAROS' from the data source drop down (D29 of the 'Dashboard' sheet), and 'HR vs enco+bini' from the modelling approach drop down (D30 of the 'Dashboard' sheet). The model has been updated such that the baseline characteristics (K18:22 of the 'Dashboard' sheet) match the source of efficacy data selected.	[redacted]	[redacted]	[redacted]	Section 3.1

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Scenario	Related ACD comment	Description	Justification	Model implementation	Inc. costs	Inc. QALYs	NHB	Cross reference
1.3 – Cost per pack approach for oral therapies	Committee preferred assumptions: "Drug acquisition costs modelled per pack and applied every 28 days", Section 3.15	Acquisitions costs are modelled per pack and applied every 28 days.	Aligns with the prescribing of enco+bini and dabra+tram and aligns with the Committee's preferred assumptions.	Select 'Cost per pack approach' from the oral treatment costing approach drop down on C64 of the 'Dosing & Admin' sheet.	[redacted]	[redacted]	[redacted]	Section 3.8
1.4 – Dabra+tram TTD: median from Swalduz et al. (18), and Auliac et al. (19)	Committee request: "alternative modelling approaches and detailed clinical expert input for TTD for encorafenib plus binimetinib", Section 3.12	Dabra+tram TTD is estimated by fitting an exponential curve to fit through weighted median (12.4 months) from Swalduz et al.(18), and Auliac et al. (19)	The Committee "thought that it was not plausible to assume that TTD is equal to PFS", reflecting clinical expert feedback "that assuming TTD is equal to PFS was too simplistic". Therefore, the updated base case uses all available evidence on TTD for the first-line only treatment of dabra+tram to estimate treatment duration.	Addition of further median TTD options on row 29 of the 'Relative Efficacy' sheet. Select 'Exponential to fit through the median TTD' from the TTD drop down on F25 and 'Weighted average of median TTD from Auliac and IFCT BLaDE' from the drop down on F26 of the 'Relative Efficacy' sheet.	[redacted]	[redacted]	[redacted]	Section 3.6.2
Revised Company base case	–	Original base case + adjustments 1.1–1.4			[redacted]	[redacted]	[redacted]	Section 4.2

Abbreviations: ACD, appraisal consultation document; AE, adverse event; dabra+tram, dabrafenib plus trametinib; DCO, data cut-off; EAG, external assessment group; enco+bini, encorafenib plus binimetinib; HR, hazard ratio; IFCT, Intergroupe Francophone de Cancérologie Thoracique; Inc., incremental; MAIC, matching-adjusted indirect treatment comparison; NHB, net health benefit; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation.

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A summary of the differences between the revised Company base case and the EAG base case is provided in Table 61.

Table 61: Differences between revised Company base case and EAG base case

Model setting	EAG base case	Company base case	Justification	Cross reference
Drug acquisition costs	Cost per pack approach every 28-days	Cost per pack approach every 28-days	This has been updated in the revised company base case to align with the Committee's preferred assumptions.	Section 3.8
Baseline characteristics	Baseline characteristics from PHAROS after MAIC adjustment.	Baseline characteristics from unadjusted PHAROS data.	This has been updated in the revised company base case to align with the Committee's preferred assumptions that the baseline characteristics should match the source of efficacy data	Section 3.1
Dabra+tram TTD	Applied the PFS HR vs enco+bini TTD.	Weighted median from Swalduz et al. (18), and Auliac et al. (19)	The revised Company base case uses all of the available data for first-line TTD for dabra+tram. The EAG base case predicted a median TTD of 8.51 months for dabra+tram which is well below the reported range of TTD identified in the SLR (11.4–17.5 months) based on 3 studies reporting TTD for patients receiving dabra+tram (18-20). This estimate is also lower than the median TTD of 10.55 months in the combined cohort (first-line and second-line) of BRF113928 (20).	Section 3.6

Abbreviations: Dabra+tram, dabrafenib plus trametinib; EAG, external assessment group; HR, hazard ratio; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; SLR, systematic literature review; TTD, time-to-treatment discontinuation.

The revised Company base case also includes a more recent PHAROS DCO (March 2025), which was not available at the time of the EAG report. A summary of the Company responses to the key issues identified in the EAG report are presented in Table 62.

Table 62: Summary of EAG key issues and related updates

Key issue	Summary of issue	EAG report Sections	Response	Cross reference
1	Uncertainty as to line of therapy	2.1, 2.3, and 2.5	No change to the Company base case as per the Committee's preferred assumption that enco+bini is positioned for first-line use only	–
2	Exclusion of comparators in the NICE scope and in the NICE guideline 122	2.3 and 2.5	No change to the Company base case as per the Committee's preferred assumption that dabra+tram is the most appropriate comparator	–

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Key issue	Summary of issue	EAG report Sections	Response	Cross reference
3	Lack of adjustment for some important prognostic variables in the MAIC analysis	3 and 4	Clarification has been provided that adjustment for concomitant mutation in the P13K pathway, presence of metastases in the thoracic cavity, PD-L1 ≥1% expression, presence of liver metastases, presence of M1a metastases was not possible as these data were not collected in PHAROS. All other variables from the list identified during the feasibility assessment were included in the MAIC as per clinical opinion.	Section 2.2
4	Uncertainty related to long-term extrapolation of OS, PFS, and TTD	4.2.6	A more recent data cut from PHAROS providing a further [redacted] months of follow-up for OS and TTD has been provided. Further scenarios have been provided using independent extrapolation of enco+bini and dabra+tram survival curves, flexible survival modelling approaches, and IFCT data only. A full assessment of the updated analyses has been provided in this response including clinical validation.	Section 3.3, 3.4, and 3.6
5	Assumptions related to waning of relative treatment effectiveness	4.2.6	A further scenario analysis exploring the impact of waning of relative treatment effectiveness has been provided based on discussion with clinical experts.	Section 3.5
6	Uncertainty in the source to inform the modelling of health state utilities	4.2.8	No change to the Company base case. No more appropriate data were identified to inform health state utilities. A scenario analysis is included that uses utility data sourced from the IFCT study.	Section 4.5
7	Suboptimal approach of modelling drug acquisition costs of oral treatments	4.2.9	The revised Company base case has been brought in line with the EAG's comments that drug acquisition costs should be on a per-pack basis. However, costs are applied every 28-days as per the Committee's preferred assumptions.	Section 3.8
8	Majority of health gains accumulated beyond the observed data	5.1	A further [redacted] months of follow-up was available from the March 2025 DCO of PHAROS for OS and TTD. The uncertainty in long-term extrapolations has been explored using various scenario analyses including independent extrapolation of each treatment arm, flexible survival models, and IFCT data.	Section 3.2, 3.3, 3.4, and 3.6
9	Issues related to (the reporting of) probabilistic and sensitivity analyses	5.2	The Company have made adjustments to the cost-effectiveness model to reduce the run time of probabilistic sensitivity analysis, including removal of unnecessary calculations, tables, and formatting. Corrections have been made to the subsequent therapy drop down to correct the errors in the reporting of scenario analyses identified by the EAG. The Company have investigated the differences in probabilistic results and deterministic results and have provided further justification.	Section 4.3 and 4.5

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Key issue	Summary of issue	EAG report Sections	Response	Cross reference
10	Insufficient technical verification of the economic model	5.3	The validation checklist undertaken by the company was provided at EAG clarification question stage and is aligned with the TECH-VER checklist. This checklist was repeated alongside the revised base case. In the revised model the Company corrected the error in the drop down for alternate subsequent therapy options.	–
11	Lack of transparency regarding expert consultation and comparisons with other relevant NICE appraisals	5.3	A full summary of the KOL clinical validation interviews has been provided.	Section 3.2

Abbreviations: Dabra+tram, dabrafenib plus trametinib; DCO, data cut-off; EAG, external assessment group; enco+bini, encorafenib plus binimetinib; IFCT, Intergroupe Francophone de Cancérologie Thoracique; KOL, Key opinion leader; MAIC, matching-adjusted indirect treatment comparison; NICE, National Institute of Health and Care Excellence. OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; P13K, phosphoinositide 3-kinase; TTD, time-to-treatment discontinuation.

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4.2 Base case results

The revised base case cost-effectiveness results are presented in Table 63. Enco+bini and dabra+tram were associated with [redacted] and [redacted] total quality-adjusted life years (QALY), respectively, yielding an incremental QALY benefit of [redacted] for enco+bini 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 63, based on a willingness-to-pay (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.

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Table 63: 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 plus trametinib; enco+bini, encorafenib plus binimetinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

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4.3 Probabilistic sensitivity analysis

A summary of the pairwise probabilistic results is presented in Table 64. 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.

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. The cost-effectiveness plane for enco+bini vs dabra+tram and the cost-effectiveness acceptability curve (CEAC) are presented in Figure 32 and Figure 33, 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. The proportion of simulations considered cost-effective at a WTP threshold of £30,000 per QALY was [redacted]%. When using the updated data cut for PHAROS, the differences between the probabilistic and deterministic analyses are minimal. The rate parameter for the exponential curve ([redacted]) is close to 0, and therefore there is a natural skew to longer survival (and therefore longer QALYs) in the PSA. Although in the PSA the rate parameter is centred around the mean value, values below the rate parameter produce very large mean survival times, whereas values above the rate parameter produce smaller mean survival times but the difference is not as dramatic as seen with values of the rate parameter below the mean. A comparison of OS curves at values of the rate parameter 25% above and below the mean are presented in Figure 34 to illustrate the skew to longer survival in the probabilistic results.

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Table 64: 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 plus trametinib; enco+bini, encorafenib plus binimetinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

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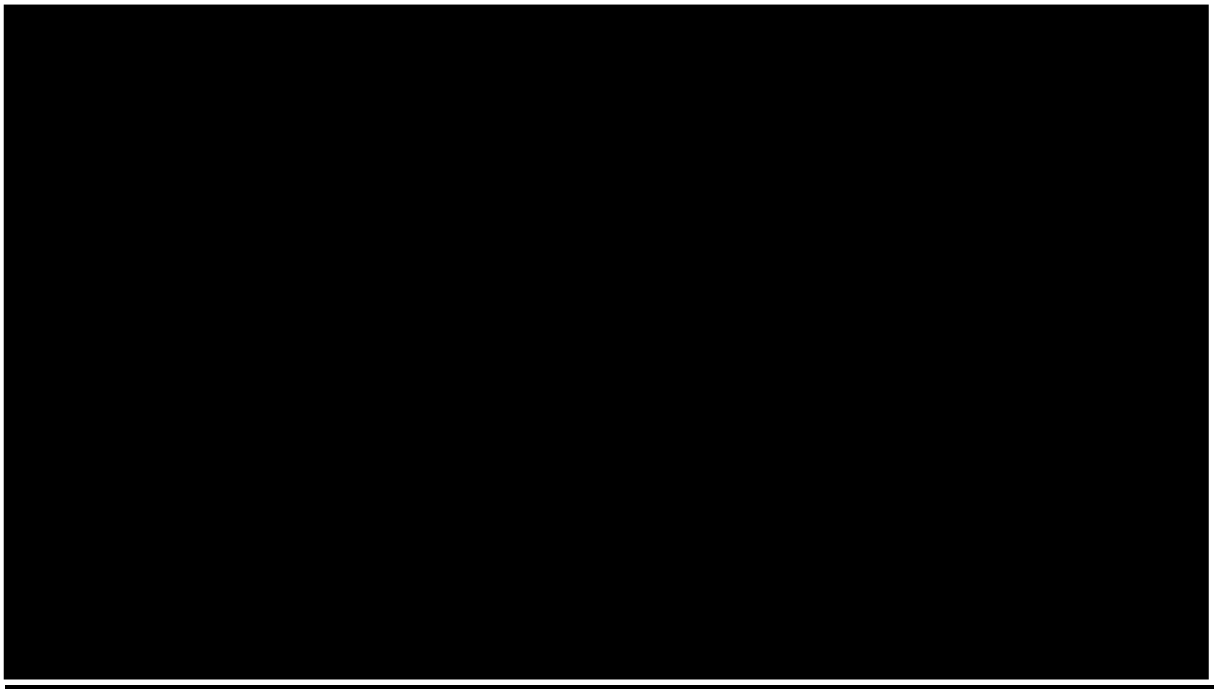
Figure 32: Cost-effectiveness plane – enco+bini PAS price

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

Figure 33: Cost-effectiveness acceptability curve – enco+bini PAS price



Abbreviations: enco+bini, encorafenib plus binimetinib; PAS, patient access scheme

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Figure 34: Comparison of OS curves at +25% and -25% of mean value of rate parameter

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

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4.4 Deterministic sensitivity analyses

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 65, while the tornado diagram is presented in Figure 35. The most influential parameters were the survival curve parameters for TTD, OS, PFS, the MAIC HRs for OS and PFS for dabra+tram vs enco+bini, and the utility values for progression-free. For the majority of parameters, the NHB remains relatively stable. For all results, enco+bini remains dominant when compared with dabra+tram, and the NHB remains above zero.

Table 65: OWSA results – enco+bini PAS price

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
TTD - dabra+tram - median TTD (months) - Weighted average of median TTD from Auliac 2020 and IFCT BLaDE	[redacted]	[redacted]
Enco+bini - TTD (PHAROS) - exponential, Rate	[redacted]	[redacted]
HR - OS - PHAROS, adjustment on all factors - weighted	[redacted]	[redacted]
Utility values, TA898, progression-free	[redacted]	[redacted]
Enco+bini - OS (PHAROS) - exponential, Rate	[redacted]	[redacted]
HR - PFS - PHAROS, adjustment on all factors - weighted	[redacted]	[redacted]
Enco+bini - PFS (PHAROS) - exponential, Rate	[redacted]	[redacted]
Utility values, TA898, progressed	[redacted]	[redacted]
Disease management costs - Outpatient visit	[redacted]	[redacted]
Healthcare Resource Use - PF frequency - Outpatient visit - TA898	[redacted]	[redacted]

Abbreviations: dabra+tram, dabrafenib plus trametinib; enco+bini, encorafenib plus binimetinib; HR, hazard ratio; NHB, net health benefit; OWSA, one-way sensitivity analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; TTD, time-to-treatment discontinuation.

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Figure 35: Tornado diagram – enco+bini PAS price

Abbreviations: enco+bini, encorafenib plus 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.

4.5 Scenario analysis

Scenario analysis results are presented in Table 66. Due to the dominant base-case ICER, results are presented using NHB. In all scenarios, enco+bini remains dominant when compared with dabra+tram.

Table 66: Scenario analysis results – enco+bini PAS price

Scenario	Incremental costs	Incremental QALYs	NHB
Original base case (submitted at EAG clarification questions)	[redacted]	[redacted]	[redacted]
Revised base-case	[redacted]	[redacted]	[redacted]
OS distribution - Gamma	[redacted]	[redacted]	[redacted]
OS distribution - Weibull	[redacted]	[redacted]	[redacted]
OS distribution - spline hazard (2 knot)	[redacted]	[redacted]	[redacted]
PFS distribution - Weibull	[redacted]	[redacted]	[redacted]
PFS distribution - Gamma	[redacted]	[redacted]	[redacted]
PFS distribution - spline hazard (2 knot)	[redacted]	[redacted]	[redacted]
TTD distribution, enco+bini - Gompertz	[redacted]	[redacted]	[redacted]
TTD distribution, enco+bini - spline hazard (2 knot)	[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]

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Scenario	Incremental costs	Incremental QALYs	NHB
AEs, dabra+tram - MAIC OR	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - treat to progression	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (RWE Swalduz 2024)	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (RWE Auliac 2020, weighted PFS)	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (RWE Auliac 2020)	[redacted]	[redacted]	[redacted]
TTD, dabra+tram - exponential to fit through reported median (RWE Swalduz 2024, weighted PFS)	[redacted]	[redacted]	[redacted]
TTD, dabra+tram = enco+bini	[redacted]	[redacted]	[redacted]
OS & PFS, dabra+tram - MAIC adjusted for ECOG and smoking status	[redacted]	[redacted]	[redacted]
OS & PFS, dabra+tram - MAIC meta-analysis	[redacted]	[redacted]	[redacted]
Utility values - IFCT	[redacted]	[redacted]	[redacted]
Utility values - IFCT + Chouaid 2013 progressed decrement	[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]
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 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]
Independent extrapolations, PHAROS, OS, PFS enco+bini – spline hazard (2-knots), dabra+tram distribution (exponential)	[redacted]	[redacted]	[redacted]
Independent extrapolations, PHAROS, OS, PFS enco+bini – spline hazard (2-knots), dabra+tram distribution OS (Weibull), PFS (exponential)	[redacted]	[redacted]	[redacted]
Independent extrapolations, PHAROS, OS, enco+bini and dabra+tram distribution –	[redacted]	[redacted]	[redacted]

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Scenario	Incremental costs	Incremental QALYs	NHB
exponential; PFS enco+bini (spline hazard 2 knots), dabra+tram (spline normal 1 knot)			
Independent extrapolations, PHAROS, PFS, enco+bini distribution - exponential; OS - spline hazards 2 knots); dabra+tram distribution OS and PFS (exponential)	[redacted]	[redacted]	[redacted]
Independent extrapolations, PHAROS, PFS, enco+bini distribution - Weibull; OS - spline hazards 2 knots); dabra+tram distribution OS and PFS (exponential)	[redacted]	[redacted]	[redacted]
Independent extrapolations, PHAROS, PFS, enco+bini distribution – gamma; OS - spline hazards 2 knots); dabra+tram distribution OS and PFS (exponential)	[redacted]	[redacted]	[redacted]
IFCT data, OS (exponential), PFS (spline odds 2 knots), TTD (gamma)	[redacted]	[redacted]	[redacted]
IFCT data, OS (Weibull), PFS (spline odds 2 knots), TTD (gamma)	[redacted]	[redacted]	[redacted]
IFCT data, OS (gamma), PFS (spline odds 2 knots)	[redacted]	[redacted]	[redacted]
IFCT data, independent extrapolations enco+bini OS (gamma), dabra_t tram OS (exponential) enco+bini PFS (spline odds 2 knots) dabra+tram PFS (exponential	[redacted]	[redacted]	[redacted]
IFCT data, OS (exponential), PFS (spline odds 2 knots) + MAIC adjusted for ECOG and smoking status	[redacted]	[redacted]	[redacted]
IFCT data, OS (exponential), PFS (spline odds 2 knots) + MAIC adjusted for ECOG and smoking status + unadjusted HR	[redacted]	[redacted]	[redacted]
IFCT data, OS (exponential), PFS (spline odds 2 knots) + MAIC adjusted for ECOG and smoking status + meta-analysis HR	[redacted]	[redacted]	[redacted]
Treatment waning at end of trial period (3-month duration)	[redacted]	[redacted]	[redacted]

Abbreviations: AEs, adverse events; dabra+tram, dabrafenib plus trametinib; EAG, external assessment group; enco+bini, encorafenib plus 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.

4.5.1 Pooling of PHAROS and IFCT results

As requested by the Committee, an alternate method of pooling results from PHAROS and IFCT is presented. A meta-analysis to pool the HRs was conducted as presented in Section 2.2, and scenarios using these HRs to estimate survival are presented in Table 66. A further scenario is presented that weights the overall costs and QALYs in the base case using PHAROS (OS and PFS, exponential) and the IFCT data alone scenario (OS: gamma; PFS: spline odds, 2 knots) by the respective number of patients in the analyses (N=59 and N=61 in PHAROS and IFCT, respectively). The results of this scenario are presented in Table 67.

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Table 67: Pooled PHAROS and IFCT results

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

Abbreviations: Dabra+tram, dabrafenib plus trametinib; enco+bini, encorafenib plus binimetinib; ICER, incremental cost-effectiveness ratio; IFCT, Intergroupe Francophone de Cancérologie Thoracique; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

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5 Conclusions

In response to the draft guidance from the Committee, the Company have updated their base case to align with the Committee's preferences:

- Baseline characteristics match the source of efficacy data
- Cost per pack costing approach

In addition, the Company have provided several scenario analyses in response to the Committee's request:

- Alternate methods to extrapolating enco+bini OS, PFS and TTD, including flexible survival modelling
- Scenarios relaxing the proportional hazards assumption, i.e. modelling enco+bini and dabra+tram OS and PFS independently
- Using IFCT alone as the source of clinical data
- Alternate methods to estimating dabra+tram TTD
- Alternate methods of pooling PHAROS and IFCT data

To validate the above analyses, the Company have conducted further interviews with England-based clinical experts (Section 3.2). Furthermore, a key discussion point at ACM1 was the uncertainty associated with long-term estimates of enco+bini survival. It should be noted that the analysis presented in this document incorporates a further PHAROS DCO (March 2025 DCO), which provides a further [redacted] months of follow-up to this pivotal Phase 2 study of enco+bini and, crucially, means median OS has been reached ([redacted] months; 95% CI: [redacted]). This is a substantial numerical improvement ([redacted] months) when compared with the first-line population of the Planchard et al. study (17.3 months; 95% CI: 12.3,40.2), particularly considering clinical experts considered the populations in each cohort to be extremely similar (3). Furthermore, with the additional [redacted] months of follow-up from PHAROS:

- The MAIC HRs vs Planchard et al. adjusting for all available prognostic factors for OS are slightly improved ([redacted]) when compared with the April 2024 DCO (0.55; 95% CI: 0.30, 1.01), and enco+bini is now associated with a significant reduction in death compared with dabra+tram.

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- The updated OS KM (Figure 1) show a continued trend in OS benefit, aligned with the base case extrapolations presented in the original Company submission.

The Company believes that the additional data available from the PHAROS pivotal trial for OS and TTD will help provide greater certainty in the estimated benefits associated with enco+bini. In the updated base case, enco+bini is associated with an improved QALY gain ([redacted], [redacted] respectively) vs the original company submission, and a larger reduction in costs ([redacted] and [redacted], respectively). Enco+bini remains dominant vs dabra+tram in the base case analysis.

Although the Company consider the PHAROS pivotal trial to be the most robust source of clinical data to inform the model, the Company have provided further exploratory analysis using IFCT data, comparing RWE for enco+bini (IFCT), with robust trial data (Planchard et al.) for dabra+tram. Even though the Company do not consider these scenarios as appropriate (Section 3.3.4), in all scenarios presented, enco+bini was dominant vs dabra+tram. This was also consistent with the feedback received during the KOL interviews, during which clinicians noted that enco+bini is likely a superior product compared with dabra+tram due to its improved tolerance (4).

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, and provided a substantial QALY and LY gain in a population with substantial unmet need. 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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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Tuesday 24 June 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Oncogene Cancer Research**

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** NICE has an obligation to ensure that the treatments it recommends for NHS use are clinically effective and provide value for money. We recognise the importance of that responsibility. However, we urge NICE and NHS England to reconsider the recent decision not to recommend

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	the combination therapy encorafenib plus binimetinib for people living with BRAF V600E–mutant non-small cell lung cancer (NSCLC) in England. As a patient-led organisation representing people living with BRAF V600E mutation-positive advanced NSCLC, we want to emphasise the critical importance of including patient experience and quality of life data alongside clinical outcomes. People affected by this rare cancer subtype face significant challenges, including limited treatment options and the emotional burden of uncertainty. We urge NICE to consider real-world impacts such as treatment tolerability, side effects, and the effect on daily living in their decision making. For people living with this type of lung cancer, this translates into more time with loved ones, fewer side effects, and the ability to live more fully with their diagnosis. We feel it's important to consider tolerability over other options.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** While we do not have the expertise to comment on economic evaluations, we want to highlight that from a patient perspective, tolerability and quality of life are paramount. Treatments that reduce hospital admissions, side effects like pyrexia, and interruptions to therapy significantly improve patients' lived experience and ability to maintain everyday activities and relationships.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** We are concerned that the current recommendation not to use encorafenib plus binimetinib may limit access to a well-tolerated treatment option for a small but underserved patient group. Patients with this mutation urgently need access to therapies that offer the best chance of control with manageable side effects. We hope NICE will consider pathways that allow patient access while additional evidence is collected.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We welcome the recognition that this is a rare cancer subtype and the committee's attention to equality issues. We encourage ongoing vigilance to ensure all patients have equitable access to diagnosis and treatment regardless of age, gender, ethnicity, or other factors, and to minimise barriers to care in this underserved population.

Insert extra rows as needed

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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]

Draft Guidance additional analyses critique

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. Additional clinical effectiveness evidence

1.1 PHAROS

The updated analyses in response to the Draft Guidance (DG)[1] are from the most recent data cut-off (DCO) 14th March 2025 (database lock [DBL] 3rd April 2025) and have been used to inform the updated economic model.[2] Only further OS data i.e. no PFS data were presented. A final DCO for all outcomes is anticipated in Q4 2025.

1.1.1 Overall survival

The OS results from the original CS, as reported in the EAG report (EAR), and the additional analyses are shown below.[2, 3]

Table 1.1: Overall survival (SS) – treatment-naïve population

Treatment-naïve (n=59)				
	1 April 2024	19 July 2023	22 September 2022	March 2025
Number of deaths, n (%)	26 (44.1)	22 (37.3)	17 (28.8)	[redacted]
Number of censored, n (%)	[redacted]	37 (62.7)	[redacted]	[redacted]
Withdrawal of consent	[redacted]	1 (1.7)	[redacted]	[redacted]
Lost to follow-up	[redacted]	2 (3.4)	[redacted]	[redacted]
No longer followed for survival†	[redacted]	0	[redacted]	[redacted]
Ongoing and no death	[redacted]	34 (57.6)	[redacted]	[redacted]
Kaplan-Meier Estimates of time to event (months) percentiles (95% CI)‡				
25th	[redacted]	19.6 (8.0, 33.9)	[redacted]	[redacted]
50th	NE (31.3, NE)	NE (26.7, NE)	[redacted]	[redacted]
75th	[redacted]	NE (NE, NE)	[redacted]	[redacted]

Based on Table 3.27 of the EAR, and additional analyses.[2, 3]

†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; EAR = Evidence Review Group report; NE = not estimable; SS = safety set

EAG comment: For the first time, survival data were mature enough so that median survival could be estimated, and was: [redacted] months.

1.2 Indirect treatment comparison

The matching-adjusted indirect comparison (MAIC) from the original company submission (CS) was updated with the March 2025 DCO. The DG requested that additional variables be included, specifically

liver metastases,[1] but the company stated that no further data were available than had been used in the CS:

- 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

The company performed a fixed effect invariance meta-analysis to pool comparisons between enco+bini and dabra+tram using the two main sources for enco+bini i.e. PHAROS versus Planchard 2017 and Intergroupe Francophone de Cancérologie Thoracique (IFCT) versus Planchard.

The updated pooled analyses in response to the DG employ a better method of pooling, as requested in the DG.[1] As also requested in the DG,[1] the results have been presented separately for the two data sources, PHAROS and IFCT.

1.2.1 Overall survival

The OS results from the original CS, and the additional analyses are shown below, from the pooled analyses in Table 1.2, and each comparison separately in Table 1.3.

Table 1.2: Results in first-line – OS

	Original CS		Updated analyses – pooled using fixed effect meta-analysis	
OS – Enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results				
Mean HR (95% CI), p-value	[redacted]	[redacted]	NR	NR
MAIC – weighted results				
Mean HR, 95% CI, p-value	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3.41 of the EAR, and Additional post-submission analyses.[2, 3]
CI = confidence interval; EAR = Evidence Review Group report; 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

Table 1.3: MAIC of enco+bini vs dabra+tram – OS, comparison of PHAROS with IFCT

Comparison	Study	Individual HRs (95% CI)
Enco+bini vs dabra+tram (base-case scenario)	PHAROS† vs Planchard 2017	[redacted]
	IFCT vs Planchard 2017	[redacted]
Enco+bini vs dabra+tram (sensitivity analysis)	PHAROS† vs Planchard 2017	[redacted]
	IFCT vs Planchard 2017	[redacted]
Enco+bini vs dabra+tram (unadjusted)	PHAROS† vs Planchard 2017	[redacted]
	IFCT vs Planchard 2017	[redacted]

Source: Table 9, Additional post-submission analyses.[2]
†Based on the PHAROS March 2025 DCO, treatment-naïve cohort.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.

1.2.2 Progression free survival

The PFS results from the original CS, and the additional analyses are shown below, from the pooled analyses in Table 1.4, and each comparison separately in Table 1.5.

Table 1.4: Results in first-line – PFS results, pooled PHAROS and IFCT

	Original CS		Updated analyses	
PFS (IRR) – enco+bini vs dabra+tram	Using all adjustment factors (base-case)	Using only ECOG and Smoking status	Using all adjustment factors (base-case)	Using only ECOG and Smoking status
Unadjusted comparison – unweighted results				
Mean HR (95% CI), p-value	[redacted]	[redacted]	NR	NR
MAIC – weighted results				
Mean HR (95% CI), p-value	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3.42 of the EAR, and Additional post-submission analyses.[2, 3]
CI = confidence interval; EAR = Evidence Review Group report; 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

Table 1.5: MAIC of enco+bini vs dabra+tram – PFS, comparison of PHAROS with IFCT

Comparison	Study	Individual HRs (95% CI)
	PHAROS† vs Planchard 2017	0.47 (0.26, 0.85)

Comparison	Study	Individual HRs (95% CI)
Enco+bini vs dabra+tram (base-case scenario)	IFCT vs Planchard 2017	[redacted]
Enco+bini vs dabra+tram (sensitivity analysis)	PHAROS† vs Planchard 2017	[redacted]
	IFCT vs Planchard 2017	[redacted]
Enco+bini vs dabra+tram (unadjusted)	PHAROS† vs Planchard 2017	[redacted]
	IFCT vs Planchard 2017	[redacted]

Source: Additional post-submission analyses.[2]
†Based on the PHAROS March 2025 DCO, treatment-naïve cohort.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.

EAG comment: The results of the pooled analyses are almost identical to the original ones from the CS. However, the results are more favourable to enco+bini using PHAROS, particularly for PFS. The EAG is inclined to support the committee opinion expressed in the DG in preferring the pooled estimates, although it cannot be ruled out that there might be no advantage to enco+bini in PFS.

The analyses requested in the DG using additional covariates for the MAIC could not be completed due to the lack of availability of data, therefore the EAG can offer no further comment.

2. Additional cost effectiveness evidence

2.1 Key issue: 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	

In response to the DG, the company conducted interviews with three England-based oncologists with experience in treating NSCLC to gather expert insights to inform and validate its additional analyses, and shared the full interview minutes with the EAG. No external validation of long-term OS, PFS and TTD extrapolations based on real-world evidence was provided. Independently fitted models, as well as more flexible spline-based models were explored as alternative to standard parametric curves for the modelling of OS, PFS and TTD.

EAG comment: The long-term OS, PFS and TTD clinical expert estimates for enco+bini and dabra+tram provided by the company are reported in Table 2.1 below. The EAG noted that clinical expert statements such as "*curve will flatten*", "*minimal change long-term if still progression-free"*, "*very few patients reach 5 years*", and "*TTD would be similar to PFS"* were not used for the calculation of the average long-term clinical expert values as reported in Table 2.1. Hence, not all values reported in Table 2.1 below represent the average of the three clinical experts. In addition, individual clinical expert estimates varied substantially. For example, the range for 5-year OS expert estimates with enco+bini was 10%–25%, while the ranges for 5- and 10-year OS expert estimates with dabra+tram were 10%–22% and 2-3%–20%, respectively. For PFS, also differences between individual clinical experts estimates of around 10% were observed for both enco+bini and dabra+tram. While the EAG considers clinical expert input informative, particularly when there is a lack of alternative long-term evidence, its use to validate long-term extrapolations should be taken with caution as there is limited experience with enco+bini in NHS practice and expert opinions may differ.

Table 2.1: Long-term OS, PFS and TTD clinical expert estimates for encorafenib + binimetinib and dabrafenib + trametinib.

Clinical experts	**5 years**	**10 years**	**15 years**	**20 years**
Encorafenib + binimetinib				
Average OS	18%	13%	4%	4%
Average PFS	18%	5%	1%	NR
Average TTD	6%	2%	1%	NR
Dabrafenib + trametinib				
Average OS	16%	9%	1%	1%
Average PFS	5%	1%	0%	NR
Average TTD	5-10%	<5%	<1%	NR

OS

Enco+bini

The EAG noted that the 5 years OS as observed in PHAROS ([redacted]) is substantially higher than the average of 18% estimated by the clinical experts, which indicates that the PHAROS trial results may not be generalisable to UK clinical practice. All survival models fitted to the observed PHAROS data (including the more flexible models) seem to substantially overpredict long-term OS for enco+bini.

Also based on IFCT, the estimated 5 years OS is substantially higher for all provided curves compared to the average clinical expert estimate, but to a lesser extent than in PHAROS. The Gamma curve generates 10, 15 and 20 years estimates that are reasonably in line with expert estimates.

Dabra+tram

If hazards are assumed to be proportional, long-term OS estimates for dabra+tram depend on the selected OS curve for enco+bini.

Independently fitted curves to the BRF113928 data all generated higher 5-years OS estimates than the clinical experts' average. The spline hazard (1 knot) and spline normal (2 knots) 10 years OS match well with the clinical expert average, but 15 years and 20 years estimates for these curves seem optimistic.

PFS

Enco+bini

The EAG noted that the updated long-term clinical expert estimates (18% and 5% at 5 years and 10 years respectively) seem more optimistic than the clinical expert estimates in the initial company submission stating: "*experts predicted that few patients would be progression-free at 5 and 10 years*". In addition, for the jointly fitted spline-based PFS models to PHAROS data, details (e.g. AIC/BIC statistics, overview of long-term estimates) were missing in section 3.4.1 of the company's additional post-submission analyses document.

The exponential and gamma curves based on PHAROS generate long-term enco+bini PFS estimates that match with the clinical expert averages.

Based on IFCT, all fitted curves substantially underestimate long-term enco+bini PFS.

Dabra+tram

If hazards are assumed to be proportional, long-term PFS estimates for dabra+tram depend on the selected PFS curve for enco+bini.

Independently fitted spline normal (1 knot) and generalised gamma curves generated 5 years, 10 years and 15 years estimates that match with the clinical expert averages.

TTD

Enco+bini

For TTD, the 5 years TTD for enco+bini as observed in PHAROS ([redacted]%) is somewhat higher than the average of 6% estimated by the clinical experts. Consequently, all curves overpredict 5-year TTD compared to the clinical expert estimates, but the spline-odds (2 knots) generates 10 years and 15 years estimates that match with the clinical expert averages.

Based on IFCT, the 5 years estimates of the Gamma and spline hazard (1 knot) reasonably match the clinical expert estimate. However, these curves seem to underestimate TTD at 10 years and 15 years.

Dabra+tram

The various scenario-analyses provided by the company resulted in 5 years TTD estimates for dabra+tram ranging from 2.0% to 9.4%, and 10 years TTD estimates ranging from 0.0% to 0.9% (Table 57 of the company's additional post-submission analyses document).

2.2 Key issue: 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	

In response to the DG, the company interviewed clinical experts for the validation of waning assumptions. One clinician thought waning would be minimal and dependent on the reason for discontinuation, one clinical stated treatment waning was not relevant at all, and one clinician thought that the duration of waning would be very short (3 months). Following expert inputs, the company provided an additional scenario analysis that applies treatment effect waning at the maximum follow-up of PHAROS for a duration of 3-months after which the risks are equivalent between arms.

EAG comment: The EAG reiterates that it agrees with the company that the provided evidence suggests that treatment effect waning is not applicable during the observed trial period. It considers the company's additional scenario analysis to explore treatment waning beyond the observed data to be conservative. In this scenario analysis, enco+bini remains dominant but the incremental QALYs in the company's base-case decreased from [redacted] to [redacted]. The EAG also explored this scenario conditional on its EAG base-case.

2.3 Key issue: 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	

In response to the DG, the company stated that it did not change its base case. No more appropriate data were identified to inform health state utilities. A scenario analysis was included that uses utility data sourced from the IFCT study.

EAG comment: No compelling new arguments or evidence were provided by the company to address this issue.

2.4 Key issue: 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

Report Section	4.2.9
	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	

In response to the DG, the company updated its base-case using the per pack costing approach.

EAG comment: The EAG agrees that the company's base-case and committee's preferred approach of per-pack costing for 28 days is reasonable and aligns its base-case accordingly.

2.5 Key issue: 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	

In response to the DG, the company stated that a further [redacted] months of follow-up was available from the March 2025 DCO of PHAROS for OS and TTD, and that uncertainty in long-term extrapolations was explored using various scenario analyses including independent extrapolation of each treatment arm, flexible survival models, and IFCT data.

EAG comment: The EAG appreciates the provided updated follow-up data and scenario analyses. However, no further explanation of the mechanism by which the model generated the majority of absolute and incremental health gains for enco+bini and dabra+tram beyond the observed data period, nor why this was substantially larger for enco+bini compared to dabra+tram, was provided. Justification for why this would be plausible based on the available evidence was also lacking.

2.6 Key issue: 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	

In response to the DG, the company made adjustments to the cost-effectiveness model to reduce the run time of probabilistic sensitivity analysis, including removal of unnecessary calculations, tables, and formatting. Corrections have been made to the subsequent therapy drop down to correct the errors in the reporting of scenario analyses identified by the EAG. The company further stated that, when using the updated data cut for PHAROS, the differences between the probabilistic and deterministic analyses are minimal. It was further stated that uncertainty in the probabilistic results arises from independently varying the OS and PFS HRs in the PSA to estimate efficacy for dabra+tram due to the nature of partitioned survival analysis models. Next to that, the company explained that the rate parameter for the exponential curve is close to 0, and therefore naturally skews to longer survival in the PSA.

EAG comment: The EAG considers the company's justification for the differences between deterministic and probabilistic results to be plausible. Although differences are substantially smaller compared to the company's initial base-case results, deterministic and probabilistic incremental costs (i.e. deterministic: [redacted]; probabilistic: [redacted]) and QALYs (i.e. deterministic: [redacted]; probabilistic: [redacted]), as well as the NHB (deterministic: [redacted], probabilistic: [redacted]) remain different.

In the updated company model in response to the DG, the EAG was unable to reproduce the company's probabilistic base-case results, despite the fixed seed button activated in the sensitivity analyses sheet.

Likewise, results of probabilistic EAG analyses vary every time the EAG reruns the same analysis probabilistically. Variation in results seems minor, but it is unclear to the EAG what causes this discrepancy. An additional issue related to the PSA is that the probabilistic setup of the company's economic model transforms EAG-defined flexible inputs (i.e. if-statements) for its base-case and scenario analyses back into hard-coded values, hampering the next probabilistic EAG analysis.

2.7 Key issue: 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	

In response to the DG, the company stated that the validation checklist was provided at EAG clarification question stage and is aligned with the TECH-VER checklist. It further stated that this checklist was repeated alongside the revised base case. In the revised model, the company corrected the error in the drop down for alternate subsequent therapy options.

EAG comments: The company did not provide further technical verification of the economic model, nor provided the checklist that was repeated alongside the revised base-case.

2.8 Key issue: 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	

In response to the DG, the company conducted interviews with three England-based oncologists with experience in treating NSCLC to gather expert insights to inform and validate its additional analyses, and shared the full interview minutes with the EAG. Cross-validation with other relevant NICE TAs was not provided.

EAG comment: The EAG considers the clinical expert documentation provided by the company sufficient to verify modelling assumption that were based on expert opinion. However, cross-validation with other relevant NICE TAs was not provided.

3. Committee's preferred assumptions for the cost effectiveness analysis

After the first committee meeting, the committee's preferred assumptions were as follows:

- Encorafenib plus binimetinib positioned for first-line use only
- Dabrafenib plus trametinib as the most appropriate comparator
- Drug acquisition costs modelled per pack and applied every 28 days

Despite its preferred assumptions, substantial uncertainty remained, including:

- Modelling of long-term OS, PFS and TTD for encorafenib plus binimetinib
- Relative treatment effectiveness and TTD for dabrafenib plus trametinib
- Source of most appropriate health-state utility values
- Treatment-effect waning

The committee therefore requested additional analyses and further evidence:

3.1 Exploration of differences between deterministic and probabilistic results

EAG comment: EAG comments are provided in section 2.6.

3.2 Use of baseline characteristics from the same source as for the intervention efficacy

EAG comment: In response to the DG, the company aligned its modelled baseline characteristics with the source of the intervention efficacy (PHAROS) for their base case and all scenario analyses.

3.3 Exploration of independent fitting of parametric curves to extrapolate PFS and OS in each arm

EAG comment: In response to the DG, the company explored various scenario analyses using independently fitted parametric survival curves to separately extrapolate PFS and OS data from PHAROS and IFCT (enco+bini), and BRF113928 (dabra+tram), which all slightly increased the NHB. The EAG, however, prefers applying the pooled HRs from the meta-analysis of PHAROS and IFCT versus BRF113928 to model relative effectiveness.

3.4 Alternative modelling approaches for OS, PFS and TTD that might include flexible parametric modelling and provide full justification and expert elicitation for the choice of preferred curves

EAG comment: In response to the DG, the company explored the use of more flexible spline models to extrapolate PFS, OS, and TTD as alternatives to standard parametric models. However, the company did not revise its preferred base-case extrapolations for enco+bini and continued to apply exponential distributions for OS, PFS, and TTD. The EAG's concerns regarding the appropriateness of the exponential distribution, as detailed in its EAG report, remain unchanged. Specifically, the smoothed hazard curves for OS, PFS, and TTD decline over time, indicating non-constant hazards that are not well captured by the exponential distribution.

All OS extrapolations for enco+bini based on the PHAROS trial produced substantially higher survival estimates than those estimated by clinical experts. Consequently, despite the exponential model being

suboptimal in light of the observed hazards, the EAG adopted it in its base-case because it generates the most conservative long-term OS projections. Similarly, all PFS extrapolations for enco+bini based on PHAROS overestimated five-year PFS. Again, the exponential distribution provided the most conservative long-term estimates, and its long-term projections (10 years and beyond) were broadly consistent with clinical expert estimates. The EAG therefore also adopted the exponential curve in its base-case for the extrapolation of enco+bini PFS. For enco+bini TTD based on the PHAROS trial, the company's selected exponential distribution overestimated five-year TTD while underestimating TTD at 10 and 15 years compared with clinical expert averages. In contrast, the spline odds (2 knots) model produced slightly higher estimates at five years but generated 10- and 15-year values that aligned more closely with clinical expert opinion. Therefore, the EAG preferred the spline odds (2 knots) model in its base-case for the extrapolation of enco+bini TTD.

As long-term outcomes generated by extrapolating PHAROS data overall were substantially higher than clinical expert predictions, the EAG performed a scenario analysis in which enco+bini efficacy was modelled based on IFCT data. As highlighted in section 2.1 above, the survival curves extrapolating IFCT data also generated long-term OS estimates that were substantially higher than clinical expert predictions, but to a lesser extent, and long-term PFS extrapolations seemed underestimated compared to expert inputs. In its scenario analysis, the EAG selected the gamma, spline-odds (1 knot) and spline hazard (1 knot) to extrapolate OS, PFS and TTD for enco+bini respectively, mainly because long-term estimates from these curves provided the most reasonable match with clinical expert averages.

Finally, as noted in Section 1.2, the EAG preferred to inform the OS and PFS of dabra+tram by applying the pooled HRs from a meta-analysis of PHAROS and IFCT versus BRF113928 to the estimated enco+bini OS and PFS curves.

3.5 Alternative modelling approaches and detailed clinical expert input for TTD for dabrafenib plus trametinib

EAG comment: In response to the DG, the company provided alternative TTD scenario analyses for dabra+tram. In its revised base-case the company preferred using the weighted average median treatment duration from two RWE studies (Swalduz et al. 2024 and Auliac 2020), stating that this represents use of all the available first-line TTD for patients receiving dabra+tram. The EAG, however, noted that these studies were retrospectively conducted in France, and were substantially different compared to BRF113928 in terms of population characteristics (Table 55 of the company's DG additional post-submission analyses). The EAG therefore retains its initial base-case approach of applying the HR between PFS and TTD for enco+bini to PFS for dabra+tram in BRF113928 (which is also the source that informs dabra+tram efficacy in the indirect treatment comparison) to estimate TTD for dabra+tram.

3.6 Further exploratory analyses that present different treatment-effect waning assumptions

EAG comment: EAG comments are provided in section 2.2.

4. Updated EAG base-case and scenario analyses

Adjustments made by the EAG, to derive the updated EAG base-case (using the company's revised base-case as starting point) are listed below. Table 4.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case.

- Matter of judgement: use updated MAIC results based on meta-analyses of HRs for OS and PFS from PHAROS and IFCT vs Planchard et al. (adjustment on all factors) instead of using MAIC results based on PHAROS vs Planchard et al. (adjustment on all factors).
- Matter of judgement: use the spline odds (2 knots) model to extrapolate enco+bini TTD instead of the exponential model.
- Matter of judgement: use the HR between PFS and TTD for enco+bini to PFS for dabra+tram to estimate TTD instead of fitting an exponential curve through the weighted median from Swalduz et al., and Auliac et al.

In addition, the EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

- Waning of the enco+bini treatment effect at the end of the observed data period over three months.
- Use of IFCT instead of PHAROS as the clinical data source to inform OS, PFS and TTD for enco+bini.

Table 4.1: Updated deterministic EAG base-case and scenario analyses.

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Deterministic company base-case						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-
Matter of judgement (EAG_1, pooled PHAROS/IFCT vs BRF113928 HR)						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-
Matter of judgement (EAG_2, enco+bini TTD use spline odds (2 knots)						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-
Matter of judgement (EAG_3, dabra+tram TTD is ratio PFS:TTD of enco+bini)						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-
Deterministic EAG base-case						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (WTP £30,000/QALY)
Scenario 1 (Treatment waning at end of observed period gradually over 3 months)						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-
Scenario 2 (Use IFCT as the source to inform OS, PFS and TTD for enco+bini)						
Enco+bini	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabra+tram	[redacted]	[redacted]	-	-	-	-

Abbreviations: dabra+tram, dabrafenib in combination with trametinib; EAG, evidence 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;

5. References

[1] National Institute for Health and Care Excellence. *Encorafenib with binimetinib for treating BRAF V600E mutation-positive advanced non-small-cell lung cancer: Draft guidance consultation*. London: NICE, 2025. 22p.

[2] National Institute for Health and Care Excellence. *Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]: Additional post-submission analyses*. London: NICE, 2025. 101p.

[3] Yang H, Witlox W, Ramaekers B, Holly T, Wieman M, Patel M, et al. *Encorafenib in combination with binimetinib for the treatment of advanced BRAF V600E mutation-positive non-small-cell lung cancer [ID6177]: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd., 2024. 126p.