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

For projector – confidential information redacted

Technology appraisal committee C [9th September 2025]

Chair: Richard Nicholas

Lead team: Alex Cale (clinical lead), Kate Ren (cost lead), Ugochi Nwulu (lay lead)

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Alice Pritchard, Samuel Slayen, Lorna Dunning

Company: Pierre Fabre

ACM 1 – draft guidance recommendation

Encorafenib plus binimetinib should not be used to treat BRAF V600E mutation-positive advanced non-small-cell lung cancer (NSCLC) in adults.

- Committee concluded that the cost-effectiveness estimates could not be estimated because of uncertainties in the economic model and further analysis was required

Key issues

	Key Issues	ICER impact
1	Lack of adjustment for important prognostic variables in MAIC analysis	Unknown
2	Extrapolation of OS	Large
3	Treatment waning effect	Large
4	Extrapolation of TTD enco-bini	Large
5	Extrapolation of TTD dab-tram	Large

	Other issues	ICER impact
5	Extrapolation of PFS	Moderate
6	Uncertainty in the source to inform the modelling of health state utilities	Moderate

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Abbreviations: ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; TTD, time to treatment discontinuation; OS, overall survival; PFS, progression free survival

Key issues from 1st Committee Meeting and Company's Response 1/2

Key issues and company response

Key issue ACM1	Committee request	Company response
Lack of adjustment of prognostic variables and ITC methods	Comparison of baseline characteristics between PHAROS and IFCT Provide updated MAIC: ❖ Adjust for liver metastasis and all available prognostic variables ❖ MAIC for IFCT alone ❖ Alternative approach for pooled data in MAIC	• Liver metastasis not collected in PHAROS, so not adjusted • Did a MAIC for IFCT alone • Meta-analyses to pool HRs of PHAROS and IFCT study
Extrapolation OS and PFS	• Alternative modelling approaches for long term OS and PFS, could explore flexible parametric modelling	• independently fitted parametric curves to extrapolate OS and PFS in each arm and flexible curves • Scenarios using IFCT alone and independently fitted curves
Treatment effect waning	• Uncertain whether treatment effect would wane in long term. • Requested company provide various treatment effect waning scenarios.	• Updated scenario at ACM1 to include March 2025 DCO • Applied treatment effect from max follow-up PHAROS for duration 3 months after the risks are equivalent between arm

Abbreviations : DCO, data cut-off; HR, hazard ratio; IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group); MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

Key issues from 1st Committee Meeting and Company's Response 1/2

Key issues and company response

Key issue ACM1	Committee request	Company response
Extrapolation TTD	• Committee requested alternative modelling approaches for enco-bini TTD and expert input	• Provided alternative approaches to modelling dab+tram time to TTD
Line of therapy and comparators	• Aligned with company base-case: first-line use only, dabrafenib plus trametinib most appropriate comparator	• Maintained assumption
Source to inform utility values	• Considered the scenario which uses utility values from IFCT study	Presents both options
Treatment costs	• Per pack cost approach, applied every 28 days	Aligned with committee

Abbreviations : IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group); TTD, time to treatment discontinuation

Response to DG consultation

Summary of responses from stakeholders

Stakeholder comments (Oncogene Cancer Research)

Tolerability of treatment and quality of life paramount to people living with BRAF V600E NSCLC

- Underserved group with limited treatment options, uncertainty leads to emotional burden
- If a more tolerable treatment available, this allows people to spend more time with family and live life more fully
- Reduced side effects, such as pyrexia, leads to fewer hospitalisations

Abbreviations: NSCLC, non-small-cell lung cancer

Decision flow chart of some outstanding key issues

Key decisions to be made. Please note, some slides may not be needed depending on decisions made by committee during meeting.

Preferred data source for comparative efficacy: What data should inform indirect treatment comparison? e.g., PHAROS, IFCT, pooled data?

↓

Choice of MAIC: Which prognostic variables should inform the MAIC e.g., all available prognostic variables or ECOG-PS and smoking status only?

↓

Proportional hazards assumption: Has the proportional hazards assumption been met? Proportional hazards or independently fitted curves?

↓

Choice of clinical data: Which trial KM data curves are most appropriate to extrapolate OS and PFS?

↓

Curve selection: Which distributions should be used?

Abbreviations: ECOG-PS, Eastern cooperative oncology group performance status; IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group); ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

Clinical Effectiveness

NICE National Institute for Health and Care Excellence

Updated clinical trial results- OS and TTD, treatment naïve cohort

More mature data for OS and TTD provided (previous data-cut April '24)

PHAROS OS, March 2025 DCO (n=59)

	April 24	March 25
Median (95% CI)	[redacted] months	[redacted] months
Median follow up	[redacted]	[redacted]
Data maturity	[redacted]%	[redacted]

PHAROS TTD, March 2025 DCO

	April 24	March 25
Median (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DCO, data cut-off; KM, Kaplan-Meier; n, number; NE, not estimable; NR, not reported; OS, overall survival; TTD, time to treatment discontinuation; *IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group)

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Key Issue: Company ITCs

Company updates MAIC to include March 2025 DCO for OS

ICER impact: Large

Recap

- Concerns that not all prognostic variables adjusted for in MAIC
- Committee requested: baseline characteristic comparison between PHAROS and IFCT, all available prognostic variables adjusted for, including liver metastasis, MAIC for IFCT alone and alternative approach for pooled data

Company

- Did not adjust for presence of liver metastases data not collected in PHAROS. Clinical experts told company most important prognostic variables in this population are brain metastasis and ECOG-PS
- Pooled data approach: Meta-analyses of HRs for OS and PFS from PHAROS and IFCT vs BRF113928. Fixed effects models with inverse variance method for pooling used as only 2 HRs were pooled, in line with TSD 18. Time to event outcomes, reported HRs and corresponding 95% CI were extracted and log-transformed to obtain log HRs and standard errors.

EAG comments

- Results from updated pooled analyses similar to original analyses in company submission
- Results using PHAROS favourable for enco-bini, particularly PFS
- EAG supports using pooled estimates, can not be ruled out there might be no advantage to enco-bini PFS
- Prefers applying the pooled HRs from the meta-analysis of PHAROS and IFCT versus BRF113928 to model relative effectiveness.

Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IIT, investigator-initiated trial; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PH, proportional hazards; PFS, progression-free survival; OS, overall survival; TSD, technical support document

Supplementary slides: 1. Baseline characteristics

Company ITCs: full results

Company updates MAIC to include March 2025 DCO for OS

ICER impact: Large

Company: updated ITC results, base case includes March 2025 OS DCO, details of adjustment

ITC method	PFS (HR, 95% CI)	OS (HR, 95% CI)
PHAROS alone adjusted (company base case)	0.47 (0.26, 0.85)	[redacted]
IFCT alone adjusted	[redacted]	[redacted]
Pooled Meta-analyses HRs (EAG base case)	[redacted]	[redacted]

ITC results for sensitivity analysis – adjusted for ECOG and smoking status

ITC method	PFS (HR, 95% CI)	OS (HR, 95% CI)
MAIC PHAROS sensitivity	[redacted]	[redacted]
MAIC IFCT alone sensitivity	[redacted]	[redacted]
Sensitivity Meta-analyses HRs	[redacted]	[redacted]

ITC results for unadjusted values

ITC method Enco+bini vs dab+tram	PFS (HR, 95% CI)	OS (HR, 95% CI)
MAIC unadjusted PHAROS	[redacted]	[redacted]
MAIC unadjusted IFCT	[redacted]	[redacted]

Which data source and which ITC should be used for decision making?

Abbreviations: CI, confidence interval; DCO, data cut-off; ECOG-PS, Eastern cooperative oncology group performance status; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PH, proportional hazards; PFS, progression-free survival; OS, overall survival;

Cost Effectiveness

NICE National Institute for Health and Care Excellence

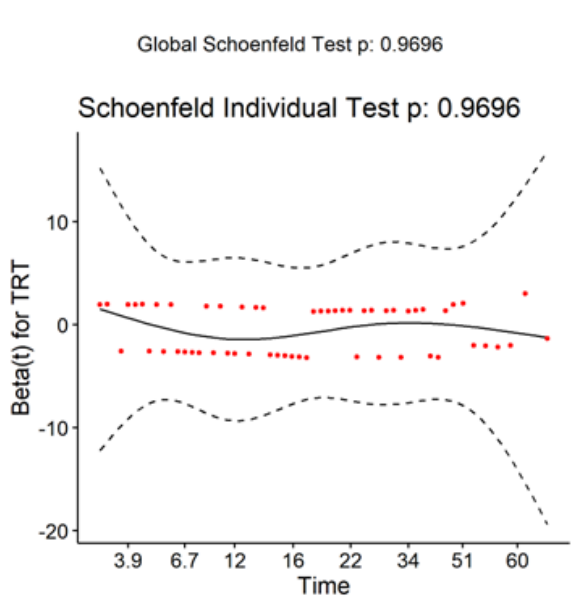
Key issue: Assessment of PH

ICER Impact: Large

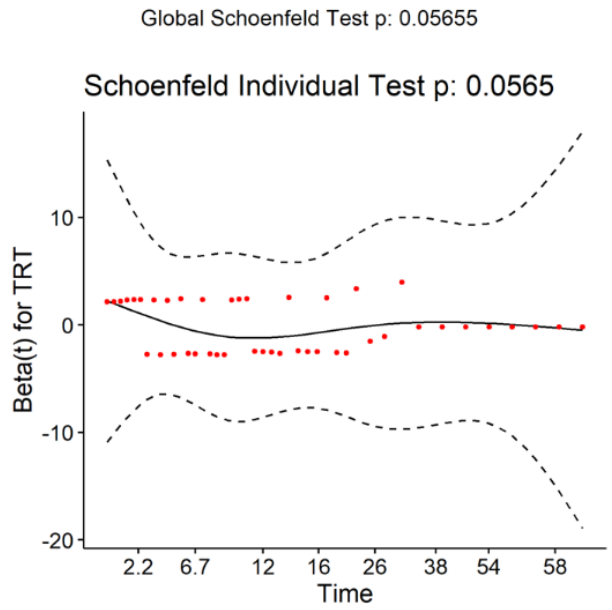
Recap

- Committee: PH assumption likely appropriate but uncertain, requested exploration of independent curves.

PHAROS vs BRF113928 PH assessment



IFCT vs BRF113928 PH assessment



Is the proportional hazards assumption appropriate for the PHAROS comparison?
Is the proportional hazards assumption appropriate for the IFCT comparison?

Proportional hazards modelling: Slides 14 to 19

Non-proportional hazards modelling: Slides 20 to 21

Abbreviations: DG, draft guidance; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison, OS, overall survival; PH, proportional hazard

ICER Impact: Large

Key issue: Extrapolation of OS using PHAROS (1/3)

Company used March 2025 DCO in analysis (proportional hazards modelling)

Recap

- Immature data, DCO at submission was April 2024. DCO for OS data March 2025, updated survival curves

PHAROS predicted OS of different distributions for enco-bini

	Median OS (yr)	OS 5 yr	OS 10yr	OS 15 yr	OS 20yr
Average clinical expert estimates	-	18%	13%	4%	4%
Exponential company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company

Base case: dab-tram curves obtained by applying OS MAIC HR of [redacted] to enco-bini curve

If assuming PH, long term OS estimates for dab-tram depend on selected OS curve for enco-bini

Clinicians noted that high OS survival in PHAROS could be linked to trial selection (ECOG status)

Abbreviations: DCO, data cut-off; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison, OS, overall survival; PH, proportional hazard

Key issue: Extrapolation of OS using PHAROS (2/3)

Company used March 2025 DCO in analysis (proportional hazards modelling)

[redacted]

EAG: Expert opinion should be treated with caution due to limited experience with enco-bini in this indication.

Abbreviations: EAG, external assessment group; DCO, data-cut off; KM, Kaplan-Meier; OS, overall survival

Key issue: Extrapolation of OS using PHAROS (3/3)

Company used March 2025 DCO in analysis (proportional hazards modelling)

Company

- Clinicians predict enco-bini survival of 13% at year 10 and 4% at 15 years and 20 years. Noted that survival outcomes in PHAROS may be due to either trial design or a fitter population in this trial who have better ECOG-PS, raised concerns about real world applicability of high OS rate in PHAROS.
- Base case: exponential used because good statistical fit and most conservative estimate. All distributions including exponential overpredict survival slightly in first 6 months.
- March '25 DCO goes beyond 5 yrs [redacted] month max follow up, therefore appropriate to use data as observed
- Dab-tram survival experts predicted 16% alive at 5 years and 9% alive at 10 years, modelling overpredicts clinical estimates, predictions at 10 yr align with TA898

EAG comments

- PHAROS 5 year OS data ([redacted]) is higher than average of 18% estimated by clinical experts, PHAROS might not be generalisable to a UK population.
- EAG adopted exponential in its base-case because it generates the most conservative long-term OS projections. All survival models fitted to observed PHAROS may over predict OS for enco-bini compared to clinical expert opinion, but use limited over this duration.
- Smoothed hazard curves for OS decline over time, indicating non-constant hazards that are not well captured by exponential distribution. EAG scenarios for gamma

What is the most appropriate distribution to extrapolate OS of enco-bini?

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Abbreviations: DCO, data cut-off; EAG, external assessment group; ECOG-PS, Eastern cooperative oncology group performance status; OS, overall survival, TA, technology appraisal

Key issue: Extrapolation of OS IFCT study

ICER Impact: Large

IFCT study alone when extrapolating OS, assumes proportional hazard modelling

Recap

- DG requested company provides analysis using IFCT only to estimate enco-bini survival

Company

- PH assumed between IFCT and BRF113928
- IFCT study immature- median OS not reached. Median follow up 18.0 months, [redacted] died. Results here
- IIT studies should complement results to sponsor led trial. Key differences between IFCT IIT and sponsor studies (PHAROS). IITs have more limited resource for recruitment, protocol monitoring, more limited access to specialist expertise, may have less rigorous data monitoring and quality assurance
- Provided modelling anyway. IFCT data for enco-bini with IFCT only MAIC HR.
- No clinical consensus of preferred dataset. IFCT more representative of UK population due to proportion of brain metastasis (17% in IFCT compared to 7% in PHAROS)

EAG comments

- IFCT estimated 5-year OS higher for all extrapolations compared to expert opinion but to lesser extent than in PHAROS. Gamma curve 10, 15, 20 year OS in line with expert predictions

1. Assumption PH IFCT and BRF113928 2. Graphical data for OS extrapolation IFCT 3. Scenario: independent fitted curves IFCT

Abbreviations: EAG, external assessment group; IIT, investigator-initiated trial; KM, Kaplan-Meier; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PH, proportional hazard

Key issue: Extrapolation OS IFCT, PH modelling

Unadjusted IFCT enco-bini- observed data and company and EAG preferred models

	Median OS (yr)	2 year OS	5 year OS	10 year OS	15 year OS	20 year OS
Average clinical expert estimates enco-bini	-	-	18%	13%	4%	4%
IFCT KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential (scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma (scenario, EAG preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Median OS (yr)	2 year OS	5 year OS	10 year OS	15 year OS
KM	-	-	-	-	-
TA898 exponential	-	-	-	4.5%	-
Model predicted HR vs IFCT (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival, PH, proportional hazard; TA, technology appraisal

Graphical version-see appendix

Key issue: Extrapolation of OS-PHAROS independently fitted curves (enco-bini), assuming non-PH

Recap

- DG requested company provides scenarios for independently fitted curves to estimate enco-bini OS. This assumed non-PH

Company

- For enco-bini OS independent extrapolation, exponential best statistical fit and more closely aligned with expert predictions. Enco-bini scenarios provided for exponential and spline hazard (2 knots)

	Median OS (yr)	2 year OS	5 year OS	10 year OS	15 year OS	20 year OS
Average clinical expert estimates enco-bini	-	-	18%	13%	4%	4%
PHAROS KM unadjusted	[redacted]	[redacted]	[redacted]	-	-	-
PHAROS KM adjusted	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Independently fitted curves over predict long term OS in enco-bini compared to clinical expert predicted OS

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazard

Graphical version-see appendix

Key issue: Extrapolation of OS- independently fitted curves (dab-tram), assuming non-PH

Recap

- DG requested company provides scenarios for independently fitted curves to estimate dab-tram OS

Company

- For dab-tram OS independently fitted curves, log-normal has best statistical fit. Exponential more closely aligned with expert predictions. Dab-tram scenarios provided for exponential and Weibull

	Median OS (yr)	2 year OS	5 year OS	10 year OS	15 year OS	20 year OS
Average clinical expert estimates dab-tram	-	-	16%	9%	1%	1%
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%
Spline hazard (1 knot)	1.84	47.5%	22.3%	9.0%	4.2%	2.1%
Spline normal (2 knots)	1.92	49.1%	22.8%	9.2%	4.7%	2.8%

EAG comments

- Independently fitted curved to BRF113928 study generated higher 5-year OS estimates than the clinical experts' average OS predictions. Spline hazard 1 knot and spline normal (2 knots) 10-year OS match well with clinical expert average, but 15 and 20 year for these curves seems optimistic.

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazard

Key Issue: Treatment effect waning

ICER impact: Large

Updated base case to include March 2025 DCO

Recap

- Company scenario to model treatment effect waning from [redacted] months for duration of 2 years
- Committee requested company present alternative treatment effect waning scenarios

Company

- At end of PHAROS follow-up, [redacted]% people still receiving treatment in treatment naive cohort
- Many people stop treatment, smoothed hazards for enco-bini OS and PFS show no increase in death or progression after follow-up. PFS hazard plots for enco-bini and dab-tram diverge, remain parallel for OS
- People may benefit from BRAF/MEK after stopping due to ongoing tumour microenvironment activity
- Updated scenario provided at ACM1 to include March 2025 DCO, max follow-up [redacted] months
- Further scenario applies treatment effect from max follow-up PHAROS for duration of 3 months after which the risks are equivalent between arms

EAG comments

- Agree with company that evidence suggests no treatment effect waning in observed period, company's additional scenario analysis conservative.
- No explanation why health gains substantially larger for enco-bini compared to dab-tram in period beyond observed evidence and why this would be plausible based on available evidence.

Should any explicit treatment effect waning be modelled, or otherwise accounted for?

Abbreviations: ACM1, appraisal committee meeting 1; DCO, data cut-off; EAG, external assessment group; OS, overall survival; PFS, progression free survival

Smoothed hazards OS and PFS

Key Issue: Extrapolation of TTD enco-bini arm

ICER impact: Large

All TTD analysis updated to include March 2025 DCO

Recap

- TTD enco-bini arm: No TTD data collected in PHAROS, post-hoc analysis done

Company

Modelling TTD for enco-bini:

- After median follow-up of [redacted] months [redacted]% people discontinued treatment. Median TTD [redacted] months
- Experts aligned most closely with Spline hazards (2 knots) distribution, most extrapolations over-predict proportion on treatment after 5 years. Company retained exponential

EAG comments

- Reject exponential as smoothed hazards decline over time. The 5 years TTD for enco+bini as observed in PHAROS ([redacted]) is higher than 6% estimated by clinical experts. All curves overpredict 5-year TTD compared to clinical expert estimates, EAG prefer the spline-odds (2 knots) which has 10 and 15 year estimates that match clinical experts.

TTD	5 year	10 year	15 year
Clinical expert estimates	6%	2%	1%
PHAROS KM	[redacted]	[redacted]	[redacted]
Exponential (company base case)	[redacted]	[redacted]	[redacted]
Spline hazard (2-knot)	[redacted]	[redacted]	[redacted]
Gompertz scenario	[redacted]	[redacted]	[redacted]
Spline odds (2-knots) EAG base-case	[redacted]	[redacted]	[redacted]

What distribution should be used to extrapolate TTD for enco-bini?

Abbreviations: DCO, data cut-off; EAG, external assessment group; KM, Kaplan-Meier; RWE, real world evidence; TTD, time to treatment discontinuation

Graphical version

Key Issue: Extrapolation of TTD dab-tram arm

ICER impact: Large

Company updated base case using RWE

Recap

- Committee requested alternative modelling approaches for dab-tram TTD and expert input

Company

Modelling TTD for dab-tram:

- Base case: weighted average of median TTD from Auliac et al and Swalduz et al. used to estimate dab-tram TTD -includes all 1st line TTD for people receiving dab-tram (approach 1 below)

3 approaches:

1. **Real world treatment duration**: Weighting each studies median treatment duration by sample size (Swalduz et al 2024 and Auliac et al 2020).
2. **Real world treatment duration**: Swalduz et al 2024 and Auliac et al 2020 using adjustment for discontinuation due to toxicity. This approach accounts for toxicity-related discontinuations by estimating median treatment duration: people who discontinue to toxicity assumed to have median treatment duration equal to 50% of median PFS, people who do not discontinue due to toxicity assumed to have median treatment duration equal to full median PFS.
   - ❖ Swalduz: Median PFS 18.2 months, 15.6% stopped due to toxicity, median TTD was 11.4 months.
   - ❖ Auliac: Median TTD for dab-tram was 17.5 months, aligned closely with median PFS of 16.8 months.
   - ❖ IFCT study for enco-bini median TTD was [redacted] months, aligns with investigator PFS 10.9 months
3. **Equivalence of treatment duration** between dab-tram and enco-bini

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Abbreviations: PFS, progression-free survival; RWE, real world evidence; TTD, time to treatment discontinuation

Graphical version | Baseline characteristics of RWE studies

Key Issue: Extrapolation of TTD dab-tram arm

ICER impact: Large

Company updated base case using RWE

Scenario / Years	Predicted TTD	2 year	5 years	10 years	15 years
Average clinical expert estimates	-	-	5-10%	<5%	<1%
Planchard et al	10.55	20.8%	2.0%	0.0%	0.0%
RWE Auliac 2020	17.50	38.8%	9.4%	0.9%	0.1%
RWE Swalduz et al 2024	11.40	23.4%	2.6%	0.1%	0.0%
Auliac weighted PFS and TTD	15.50	34.3%	6.9%	0.5%	0.0%
Weighted average from Auliac et al and Swalduz et al (company base case)	12.44	26.4%	3.6%	0.1%	0.0%
Swalduz et al, weighted PFS and TTD	16.90	37.5%	8.6%	0.7%	0.1%
HR applied between PFS and TTD (EAG base case)	-	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Company opted for weighted average median treatment duration from (Swalduz et al and Auliac), EAG note these studies conducted in France and different compared to BRF113928 for population characteristics.
- EAG retains base-case of applied HR between PFS and TTD for enco-bini to PFS for dab-tram

What distribution should be used to extrapolate TTD for dab-tram?

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Abbreviations: HR, hazard ratio; RWE, real world evidence; PFS, progression-free survival; TTD, time to treatment discontinuation

Key Issue: utility values

Type here

Recap

- Utility values from Chouaid et al (TA898) to inform PF and PD health states.–cross-sectional study, health-states in advanced NSCLC, n=263, included UK EQ-5D and EQ-VAS Committee requested scenario for utility values from IFCT

Company

- Scenario using IFCT utility values and using IFCT + Chouaid 2013 utility decrement

EAG comments

- Company did not change base case and no more appropriate data were identified to inform health state utilities
- No compelling new arguments or evidence provided by company to address this issue

What is the most appropriate source to model health state utility values?

Abbreviations: EQ-5D, EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; n, number; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressed disease; PF, progression-free; TA, technology appraisal

Summary of company and EAG base case assumptions

	Company	EAG
ITC	Not adjusted for liver metastasis due to lack of data in PHAROS. MAIC adjusted PHAROS only HRs used	Apply the pooled HRs from the meta-analysis of PHAROS and IFCT versus BRF113928 to model relative effectiveness.
OS extrapolation	Exponential distribution assumes PH	Assume PH , exponential distribution
PFS	Assumes PH, original company base case-exponential distribution	Exponential distribution
TTD	Weighted average from Auliac et al and IFCT BLaDE (base case dab-tram). For enco-bini company retained exponential base case	Enco-bini: Spline odds (2 knots) model to extrapolate TTD Dab-tram: Apply HR between PFS and TTD for enco+bini to PFS for dabra+tram
Treatment effect waning	No treatment effect waning in base case. Scenarios provided	No treatment waning effect. Scenario provided at end of trial period over 3 months
Treatment costs	Cost per pack approach, modelled every 28 days	Align with company
Utility values	Base case TA898 utility values	Align with company

- At ACM1 committee concluded there may be uncaptured benefit of reduced pyrexia and accompanying hospital admissions and potentially reduced antibiotic use to treat suspected sepsis.

Abbreviations: EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PH, proportional hazard; TA, technology appraisal; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

Both the EAG and Company's base case ICERs are above the range that NICE usually considers an acceptable use of NHS resources.

Encorafenib in combination with binimetinib for treating advanced BRAFV600E mutation-positive NSCLC

Supplementary appendix

NICE National Institute for Health and Care Excellence

Company ITCs: baseline characteristics

Main slides, Key issue ITC

Company updates MAIC to include March 2025 DCO for OS

Recap

- Company updated MAIC to include March 2025 OS data
- Provided a MAIC using IFCT study alone

Baseline characteristics treatment naive cohorts

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]

Abbreviations: BSA, body surface area; DCO, data cut-off; ECOG-PS, Eastern cooperative oncology group performance status; ITC, indirect treatment comparison; kg, kilogram; m, metre; MAIC, matching-adjusted indirect comparison; OS, overall survival

Factors adjusted for in base case ITC

Comparison	Base case Adjustment factors
PHAROS treatment naive vs Planchard 2017 treatment naive Cohort C	• Age • Race • Gender • Smoking status • ECOG PS • Adenocarcinoma • Brain metastases
IFCT treatment naïve vs Planchard 2017 cohort C	• Age • Gender • Smoking status • Adenocarcinoma • Brain metastases

Main slides, Company ITCs

Baseline characteristics IFCT and PHAROS

Company provides baseline characteristics comparison

Recap

- Committee requested comparison of baseline characteristics between PHAROS and IFCT

PHAROS and IFCT baseline characteristics – adjusted and unadjusted values

Characteristic	PHAROS base case	PHAROS MAIC adjusted	IFCT n=64	IFCT MAIC adjusted	BRF113928 trial	NHS population
Age (years)	66.5	67.0	[redacted]	[redacted]	[redacted]	[redacted]
Male (%)	44.1	39.0	46.9	38.9	38.9	NA
ECOG % ECOG=0	32	36	NA	NA	36	[redacted]
ECOG % ECOG=1	68	NA	NA	NA	61	[redacted]
ECOG % ECOG=2	0	NA	NA	NA	3	[redacted]
Smoking status, % never smoked	31	28	35.9	NA	28	NA
Race, % white	90	89	NA	NA	83	NA
Adenocarcinoma %	97	89	98.4	NA	89	[redacted]
Brain metastasis % yes	7	[redacted]	17.2	NA	6	NA

Abbreviations: BSA, body surface area; ECOG-PS, Eastern cooperative oncology group performance status; ITC, indirect treatment comparison; NA, not available; n, number

Predicted OS dab-tram estimates

Company

- Dab-tram survival experts predicted 16% alive at 5 years and 9% alive at 10 years, model overpredicts clinical estimates, predictions at 10 yr align with TA898

Predicted and TA898 OS (dab-tram)

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

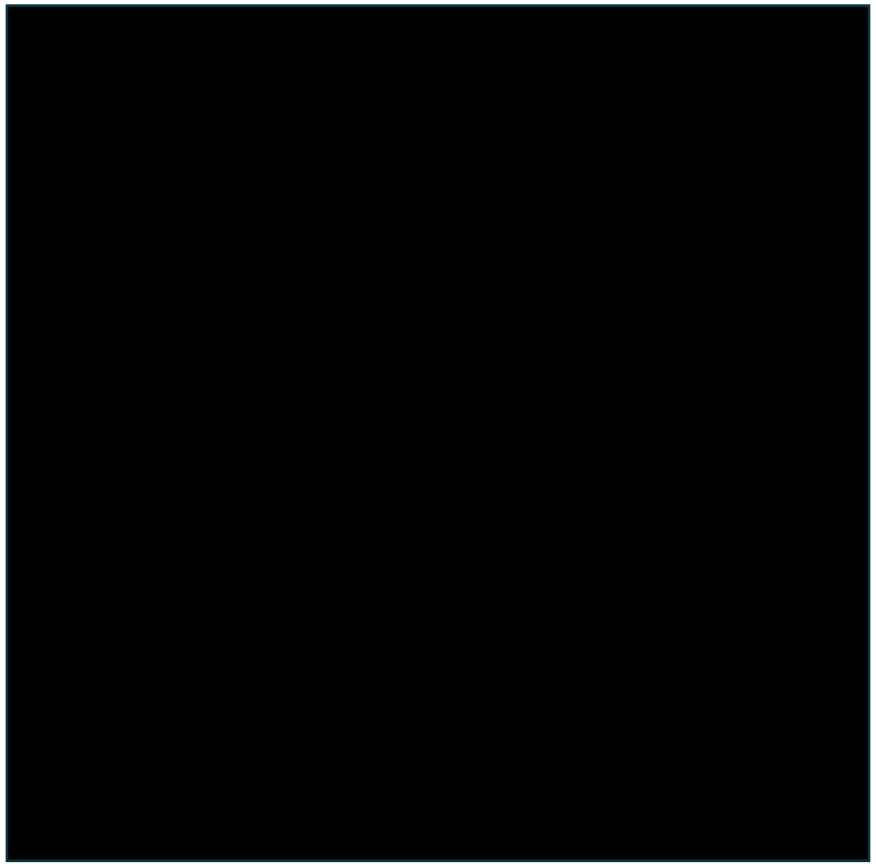
Main slides, extrapolation of OS

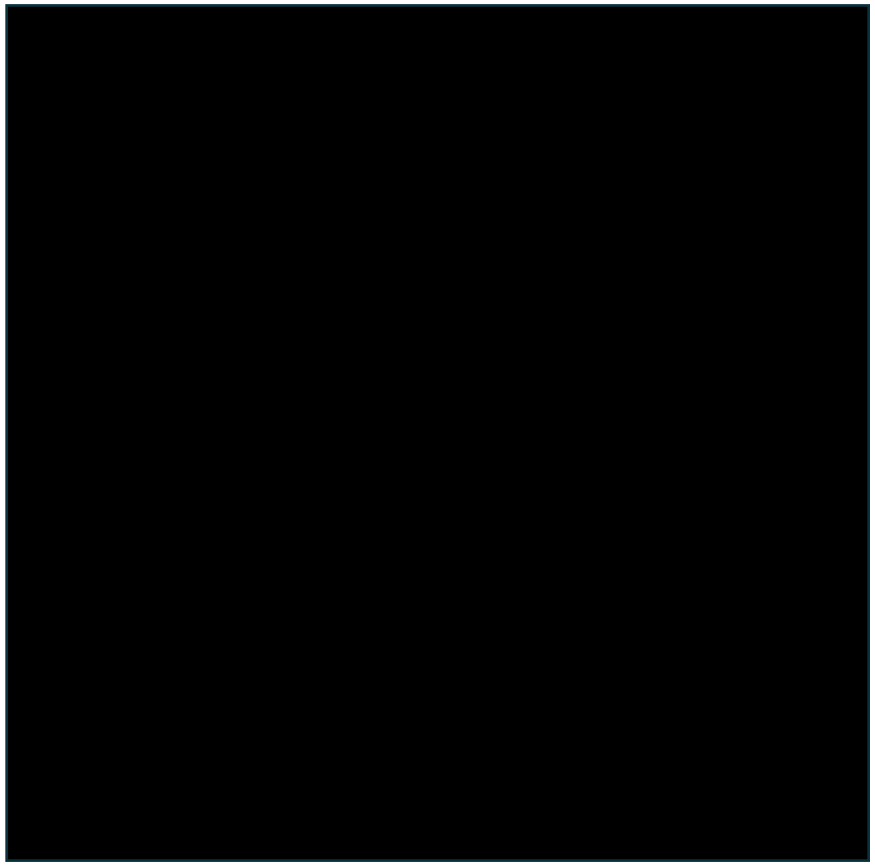
NICE

Abbreviations: OS, overall survival, TA, technology appraisal

Treatment effect waning – Observed hazards

Hazards suggest no waning of treatment effect in observed data





Back to treatment effect waning

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

Key issue: Enco-bini smoothed OS hazard plot

Enco-bini smoothed OS hazard plot

[redacted]

Predicted and TA898 OS (dab-tram)

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

[redacted]

Link to main slides: 1. Extrapolation of OS

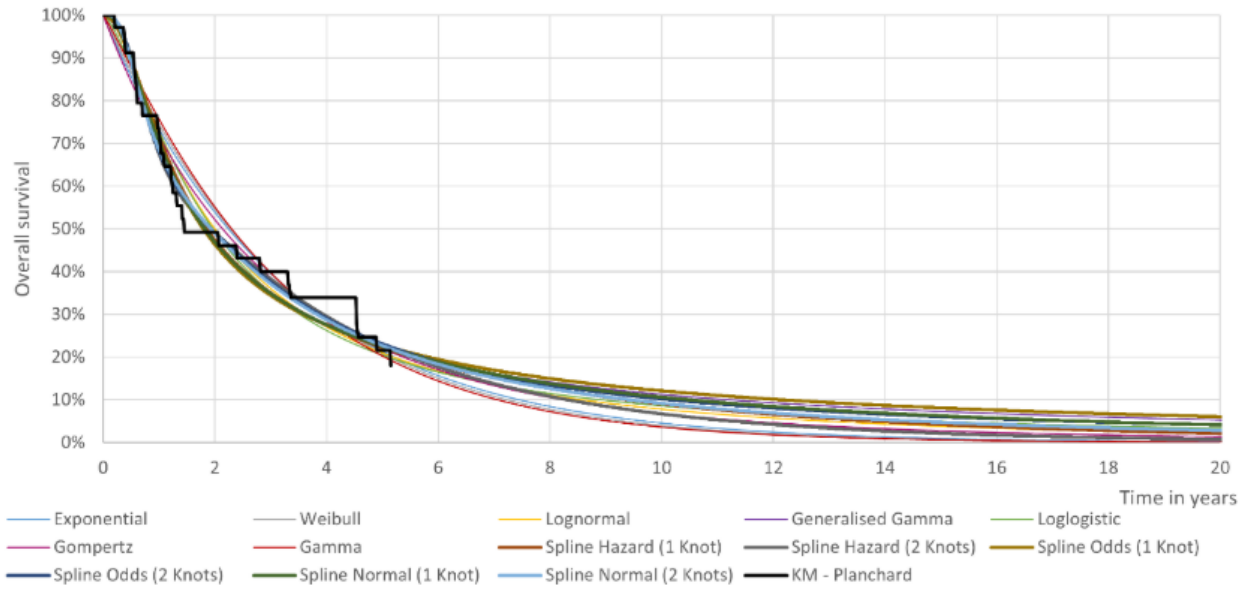
Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; TA, technology appraisal

Extrapolation OS: Independent curves fitted

MAIC adjusted PHAROS enco-bini

[redacted]

Long term OS estimates dab-tram



Main slides, Extrapolation OS: Independent curves fitted

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; OS, overall survival,

Extrapolation OS: IFCT

MAIC unadjusted IFCT enco-bini

Long term OS estimates dab-tram HR versus IFCT

Main slides, Extrapolation OS: IFCT

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; OS, overall survival,

Key issue: Extrapolation of OS IFCT study-independent curves

Type here

ICER Impact: Large

Recap

- DG requested company provides analysis using IFCT and relaxing PH assumption

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

Company

- Gamma distribution most aligned with clinician estimates

Landmark OS estimates IFCT independent fit
Main slides, extrapolation OS IFCT study

NICE Abbreviations: DG, draft guidance; EAG, external assessment group; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison, OS, overall survival; PH, proportional hazard

Key issue: Independent curves fitted, survival estimates OS

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

	Median OS (yr)	2 year OS	5 year OS	10 year OS	15 year OS	20 year OS
IFCT KM unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFCT KM adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma (scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Supplementary slides, Extrapolation of OS IFCT study-independent curves

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival,

Key issue: Extrapolation of OS IFCT study

ICER Impact: Large

IFCT study alone when extrapolating OS, assumes proportional hazard modelling

Unadjusted IFCT predicted OS for enco-bini

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; HR, hazard ratio; OS, overall survival; PH, proportional hazard

Key issue: Modelling TTD for enco-bini

ICER Impact: Large

Company use exponential distribution in base case

Long-term TTD projections enco-bini PHAROS

Main slides, Landmark TTD estimates for enco-bini and dab-tram

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; TTD, time to treatment discontinuation

Baseline characteristics for included TTD studies dab-tram

Company updated base case using RWE

Baseline characteristics for first-line BRAF V600E MT NSCLC

Characteristic	Planchard 2022	Swalduz et al	Auliac et al	IFCT-1904
Number of people	36	44	9	64
Age	Median 67	Median 71.6	Mean 74.3	Median 70.7
Gender % male	39%	50%	44%	46.9%
Histology % Adenocarcinoma	89%	95.5%	100%	98.4%
% never smoked	28%	27.3%	44%	35.9%
ECOG-PS	ECOG-0: 36% ECOG-PS 1: 61% ECOG-PS 2: 3%	ECOG-PS 0-1: 75.7% ECOG-PS 2-3: 24.2%	ECOG-PS 0-1: 67% ECOG-PS ≥2: 33%	ECOG-PS 0: 43.8% ECOG-PS 1: 56.3%

Abbreviations: ECOG-PS, Eastern cooperative oncology group performance status; TTD, time to treatment discontinuation; RWE, real world evidence; NSCLC, non-small-cell lung cancer

Main slides, extrapolation of TTD dab-tram arm

How should TTD be extrapolated in each arm?

Abbrevations: TTD, time to treatment discontinuation

Main slides, TTD dab-tram arm

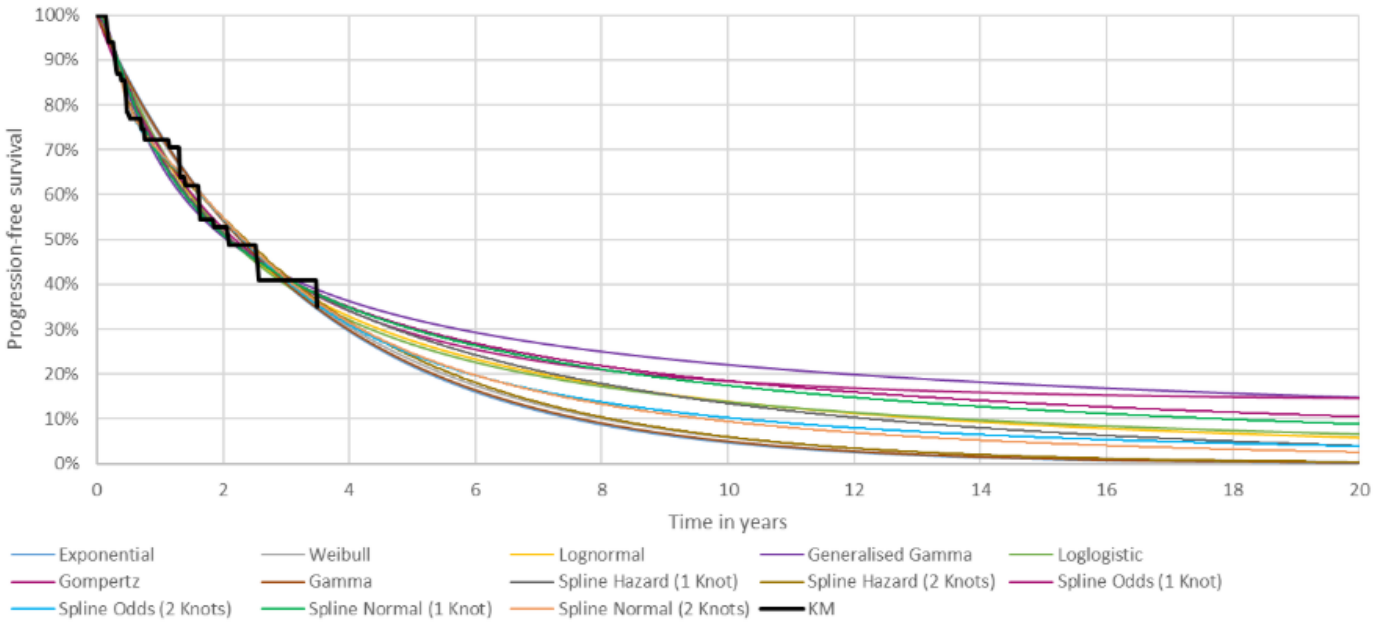
Key issue: Extrapolation of PFS

Company maintain base case, PH assumption, exponential extrapolation

Recap

- Committee requested independent fitted curves and scenarios including IFCT data alone

PHAROS unadjusted predicted PFS of different distributions for enco-bini



Company

- Base case: dab-tram curves are obtained by applying the PFS MAIC HR of [redacted] to the enco-bini curve and so depends on the curve choice for enco-bini

EAG comments

- Exponential (EAG base case) most conservative and long-term (10-year plus) projections align with expert estimate.

What is the most appropriate extrapolation assumption for PFS of enco-bini and dab-tram?

Abbreviations: EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison, OS, overall survival; PFS, progression-free survival; PH, proportional hazard

Key issue: Landmark survival estimates PFS

Company

- Clinicians predict enco-bini PFS at 5 years would be 18%, 10 years PFS would be 5%, 1% at 15 years. Exponential aligns more closely with these estimates. Base case: exponential good statistical fit and most conservative estimate
- Dab-tram PFS experts predictions align with base case predictions

PHAROS Predicted enco-bini PFS

	Median PFS yr	PFS 5yr	PFS 10yr	PFS 15 yr	PFS 20yr
Clinical experts	-	18%	5%	1%	-
Exponential base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Predicted and TA898 PFS (dab-tram)

	Median OS (years)	1yr	2yr	5yr	10yr	15 yr
Clinical experts	-	-	-	5%	1%	0%
BRF113928	0.9	42%	13%	10%	-	-
Model base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; PFS, progression-free survival; TA, technology appraisal

Key issue: Extrapolation of PFS- independently fitted curves

Type here

ICER Impact: Large

Recap

- DG requested company provides independently fitted curves to estimate enco-bini and dab-tram PFS
- Base case remains assuming PH assumption is met

Company

- For enco-bini PFS, exponential best statistical fit and more closely aligned with expert predictions.
- Enco-bini PFS scenarios provided for Weibull, gamma and spline hazard (2 knots)
- For dab-tram PFS independently fitted curves, log-normal has best statistical fit. Exponential more closely aligned with expert predictions.
- Dab-tram scenarios provided for generalised gamma, exponential and spline normal (1 knot)

EAG comments

- 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.

 Abbreviations: EAG, external assessment group; PH, proportional hazard; PFS, progression-free survival

Key issue: Extrapolation PFS: Independent curves fitted

MAIC adjusted PHAROS enco-bini- observed data and company and EAG preferred models

	Median PFS (yr)	2 year PFS	5 year PFS	10 year PFS	15 year PFS	20 year PFS
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%
Spline hazard (2 knots)	2.36	55.0%	24.0%	6.0%	1.5%	0.4%
EAG PREFERRED						

Long term PFS estimates dab-tram- observed data and company and EAG preferred models

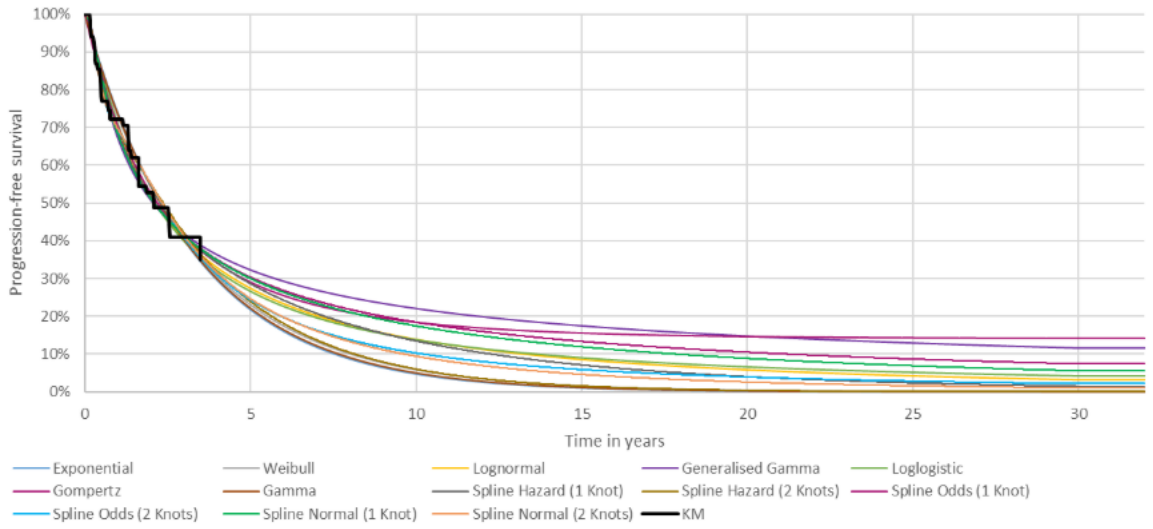
	Median PFS (yr)	2 year PFS	5 year PFS	10 year PFS	15 year PFS	20 year PFS
KM	1.22	-	-	-	-	-
Generalised gamma	0.98	24.0%	4.7%	0.7%	0.2%	0.0%
exponential	1.02	25.9%	3.4%	0.1%	0.0%	0.0%
Spline normal (1 knot)	0.96	24.2%	5.5%	1.1%	0.4%	0.2%

NICE Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; PFS, progression-free survival;

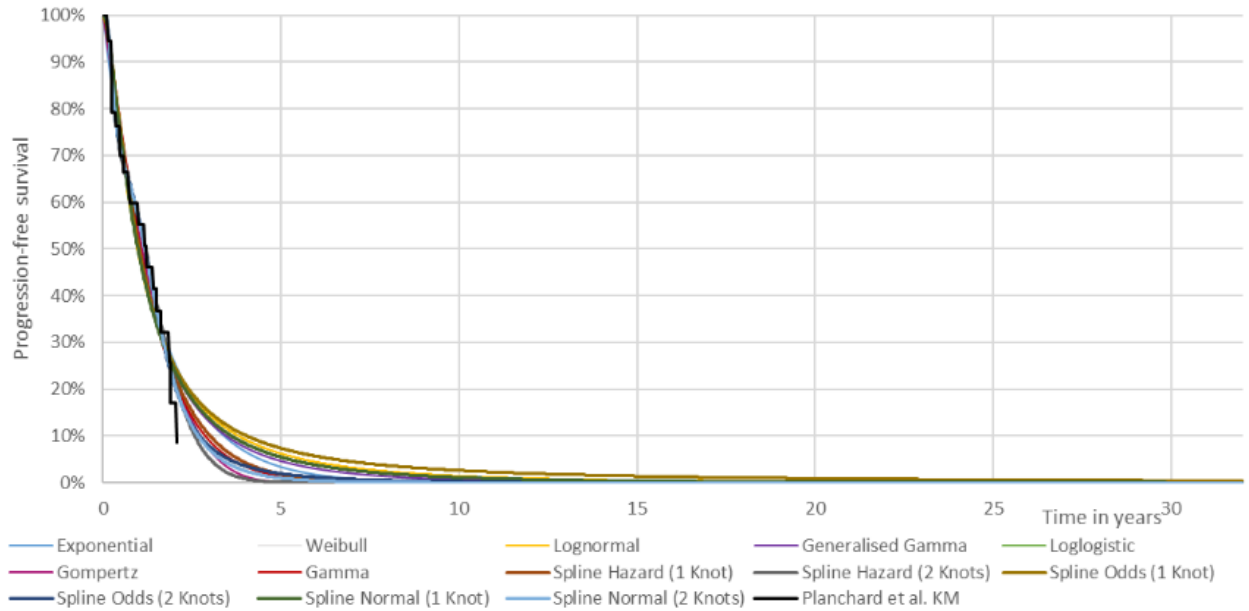
Graphical version-see appendix

Extrapolation PFS: Independent curves fitted

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



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



Extrapolation PFS: Independent curves fitted

NICE

Abbreviations: EAG, external assessment group; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison PFS, progression-free survival

Key issue: Extrapolation of PFS- IFCT

Type here

ICER Impact: Large

Recap

- DG requested company provides scenarios only using IFCT data to inform extrapolation of PFS

Company

- At the end of follow-up in IFCT study, [redacted]% of patients experienced a PFS event in the treatment-naïve population, and median PFS was **** months (95% CI: [redacted])
- Spline odds (2 knots) more closely aligned with expert predictions, modelled as a scenario
- Assumption of PH re-assessed, could not be rejected based on Schoefield residuals (p=0.185) but log-log plot show curves crossing.
- MAIC HR ([redacted]) was applied to the enco+bini PFS curve to derive long-term PFS estimates for dabra+tram. 5 year PFS estimates align with clinician predictions.

EAG comments

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

Abbreviations: DG, draft guidance; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison, PFS, progression-free survival

Key issue: Extrapolation PFS: IFCT

MAIC adjusted IFCT enco-bini- observed data and company and EAG preferred models

	Median PFS (yr)	2 year PFS	5 year PFS	10 year PFS	15 year PFS	20 year PFS
KM IFCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Long term PFS estimates dab-tram- observed data and company and EAG preferred models

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

NICE

Abbreviations: EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival;