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

For Projector- confidential information redacted

Technology appraisal committee C [13th May 2025]

Chair: Stephen O' Brien

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

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Technical team: Alice Pritchard, Samuel Slayen, Ross Dent

Company: Pierre Fabre

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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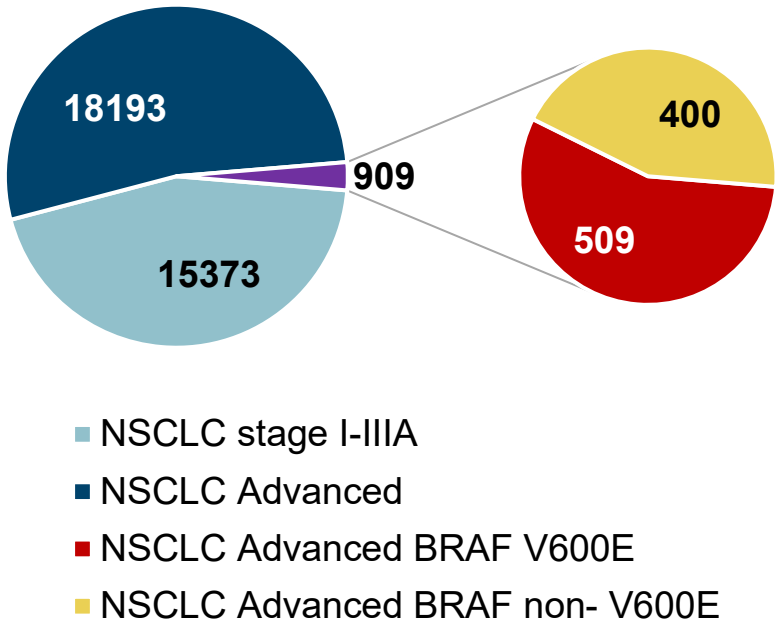
Background on non-small-cell lung cancer

Epidemiology

- Non-small-cell lung cancer (NSCLC) makes up 91% of all lung cancers
- Most NSCLCs are diagnosed at advanced stage (the cancer has spread to lymph nodes or organs in the chest) or metastatic (the cancer has spread to other parts of the body)

Population advanced NSCLC BRAF V600E mutation



Symptoms and prognosis

- Symptoms can include a persistent cough, recurrent chest infections, coughing up blood and persistent tiredness
- Survival rates are relatively low, in England between 2016 and 2020 five year survival for those diagnosed with stage 3 (advanced) and stage 4 (metastatic) lung cancer was 16% and 4% respectively

*Advanced Stage 3B/3C/IV as defined by National Lung cancer audit 2024.

Abbreviations: NSCLC, non-small-cell lung cancer

Patient perspectives

Encorafenib plus binimetinib is a 2nd treatment option for BRAF V600E+ NSCLC

Submission from RCLCF

- Only one therapy recommended by NICE for those with BRAF V600E mutation - dabrafenib plus trametinib
- Other treatment options are immunotherapy, chemotherapy or a combination of the two
- Encorafenib plus binimetinib represents an additional oral treatment option for BRAF V600E mutated NSCLC
- Generally, there is potential to miss doses of oral treatments, but anecdotally people with lung cancer consider it important to take medication as prescribed

"Lung cancer symptoms such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Symptoms can be distressing for loved ones to observe"

Abbreviations: NSCLC, non-small-cell lung cancer; RCLCF, Roy Castle Lung Cancer Foundation; ARN

Clinical perspectives

Encorafenib plus binimetinib better tolerated than dabrafenib plus trametinib

Submissions from BTOG, ARN and clinical experts

Current treatment and unmet need:

- Need for a treatment with lower incidence and severity of adverse events
- Need for an effective targeted therapy 2L after progression on dabrafenib plus trametinib
- If recommended encorafenib plus binimetinib to be used instead of dabrafenib plus trametinib

Encorafenib better tolerated than dabrafenib:

- Encorafenib with binimetinib trial had reduced number of treatment-related dose reductions and fewer people stopping treatment compared to dabrafenib and trametinib trial, less likely to progress if do not discontinue treatment
- Encorafenib with binimetinib slightly better tolerated than dabrafenib with trametinib
- Encorafenib with binimetinib has lower incidence of pyrexia (fever) and this may require less healthcare resource, such as reduced impact on emergency portals and use of antibiotics to treat/prevent sepsis

"In England, where BRAF status is known at the time of diagnosis, dabrafenib and trametinib should be the standard of care with little variation in pathway of care"

Abbreviation: 2L, second line; BTOG, British thoracic oncology group; ARN, association of respiratory nurses; AE, adverse event

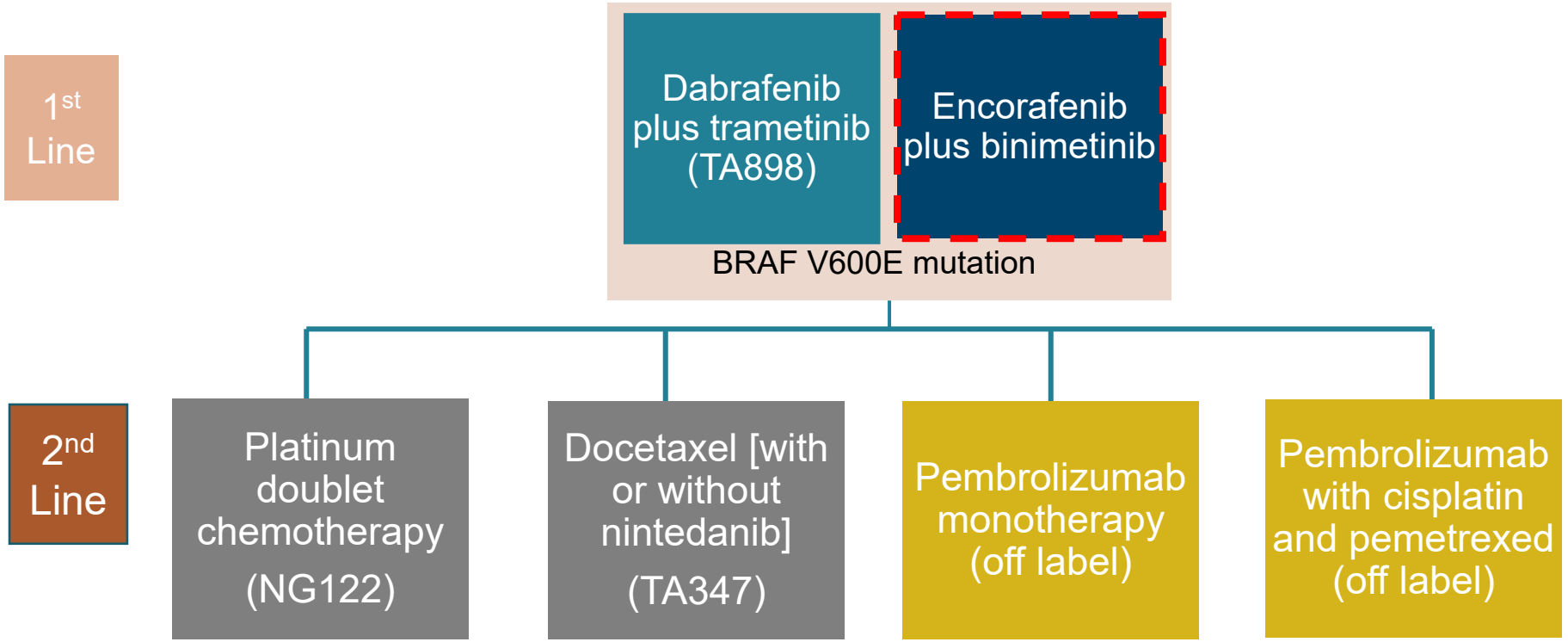
Equality considerations

No known equality issues

- Neither the company, clinical experts or the patient organisation identified any equality considerations for this appraisal.

Treatment options (NSCLC with BRAF V600 mutation)

Various treatment options for NSCLC, only one specific for BRAF mutations



Company positioning - 1L positioning is narrower than MA (which is for all lines of treatment), this assumes most people gets genomic test

Subsequent immunotherapy - Off-label use, as per company and EAG expert opinion

Abbreviations: 1L, first line; MA, marketing authorisation, NG, NICE guideline; NSCLC, non-small-cell lung cancer; TA, technology appraisal. Notes: encorafenib plus binimetinib referred to as enco-bini, dabrafenib plus trametinib referred to as dab-tram. BRAF V600 mutations in NSCLC are considered mutually exclusive to other driver mutations

Encorafenib plus binimetinib (Braftovi and Mektovi, Pierre Fabre)

Technology details

Marketing authorisation (Nov 2024)	• Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small-cell lung cancer with a BRAF V600E mutation
Mechanism of action	• Encorafenib is a selective ATP-competitive small molecule RAF kinase inhibitor. It supresses RAF/MEK/ERK pathway in tumour cells which express a few mutated forms of BRAF kinase (V600E, D and K) • Binimetinib is an ATP-uncompetitive, reversible inhibitor of kinase activity of MEK1 and MEK2. Binimetinib inhibits growth of BRAF V600E mutant melanoma animal models • Together they disrupt cellular growth pathway and reduce uncontrolled cell division
Administration	• Encorafenib and binimetinib are both oral therapies • Encorafenib 450mg (6 capsules) once daily, binimetinib 45 mg (3 tablets) twice daily
Price	• Encorafenib 75mg list price: £1,400 per pack of 42 capsules • Binimetinib 15mg list price: £2,240 per pack of 84 tablets • Encorafenib plus binimetinib has a confidential patient access scheme • Yearly total cost of full course of encorafenib plus binimetinib = £131,040

Note- Comparators in this appraisal have a confidential PAS

Abbreviations: ATP, adenosine triphosphate; ERK, extracellular signal-regulated kinases; MA, marketing authorisation; MEK, mitogen-activated protein kinase; NSCLC, non-small-cell lung cancer

Key issues

	Key Issues	ICER impact
1	Lack of adjustment for important prognostic variables in MAIC analysis	Large
2	Extrapolation of OS	Large
3	Treatment waning effect	Large
4	Extrapolation of TTD	Large

	Other issues	ICER impact
5	Extrapolation of PFS	Moderate
6	Uncertainty in the source to inform the modelling of health state utilities	Moderate
7	Other modelling issues	Unknown
8	Line of therapy and comparators	Unknown

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

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Key clinical trial - PHAROS (NCT03915951)

PHAROS pivotal trial, supplemented by Intergroupe Francophone de Cancérologie Thoracique (IFCT) trial

	PHAROS
Design	Phase 2, open-label, multicentre study
Population	• Adults, aged 18 and over, with advanced BRAF V600E mutation-positive NSCLC. Treatment naive, n=59 • Previously treated, n=39
Intervention	Encorafenib in combination with binimetinib
Comparator(s)	None
Duration	Ongoing
Primary outcome	Overall response rate
Key secondary outcomes	Disease control rate, duration of response, OS, PFS, time to response
Locations	48 sites recruited in 5 countries (Spain, Italy, Holland, Republic of Korea, USA)
Used in model?	Yes (treatment naive cohort only)
Data cut-off	4 data cut-offs: April 2024, July 2023, January 2023, September 2022

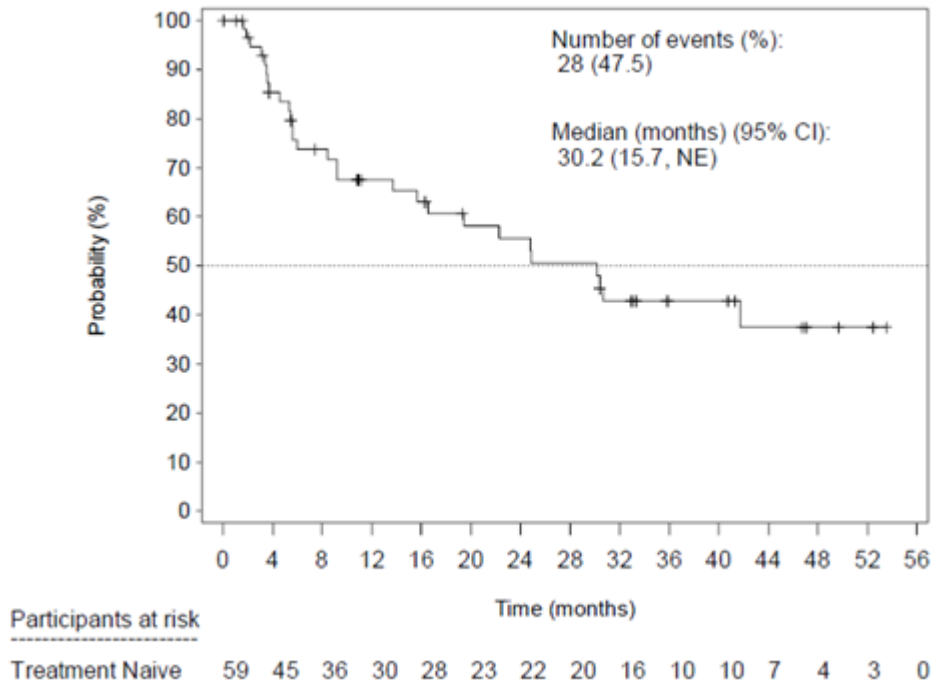
For baseline characteristics, see supplementary appendix baseline characteristics of treatment naïve cohort
For details of additional clinical trial please see supplementary appendix IFCT

Abbreviations: n, number; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival; IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group)

Clinical trial results- PFS, treatment naïve cohorts

Progression free survival appears worse in the IFCT study

PHAROS PFS, April 2024 DCO (n=59)



Estimated PFS, months	
Median (95% CI)	30.2 (15.7, NE)
Median follow up	33.3 months

IFCT PFS, (n=64)

[redacted]

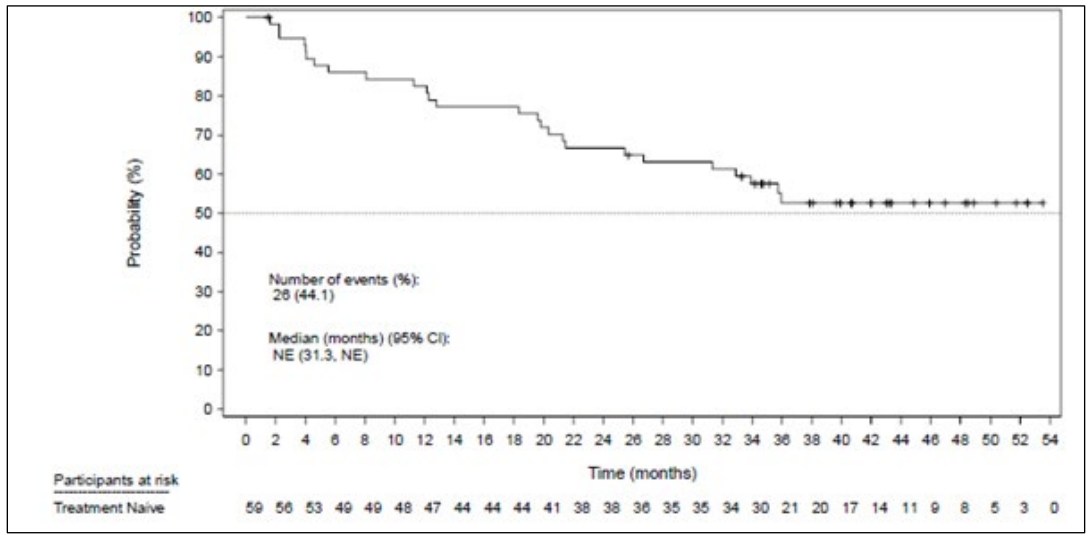
Estimated PFS, months	
Median (95% CI)	[redacted]
Median follow up	[redacted]

Abbreviations: CI, confidence interval; DCO, data cut-off; IA, independent assessment; KM, Kaplan-Meier; IRR, independent radiology review; NE, not estimable; NR, not reported; PFS, progression free survival; *IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group)

Clinical trial results- OS, treatment naïve cohorts

Overall survival appears similar in both clinical trials

PHAROS OS, April 2024 DCO (n=59)



Estimated overall survival	
Median (95% CI)	NE (31.3, NE)
Median follow up	[redacted]

IFCT OS (n=64)

[redacted]

Estimated overall survival	
Median (95% CI)	[redacted]
Median follow up	[redacted]

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

PHAROS results - Time to treatment discontinuation

Trial did not measure TTD directly, company conducted post-hoc analysis

TTD KM curve of treatment naïve cohort

- Post-hoc analysis conducted by company, TTD recreated using related data points from PHAROS. EAG consider approach used was reasonable.
- April DCO: Median TTD was reached at [redacted] months (95% CI: [redacted]

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Abbreviations: CI, confidence interval; DCO, data cut-off; EAG, external assessment group; KM, Kaplan-Meier; NE, not estimable; TTD, time to treatment discontinuation

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Indirect treatment comparison summary

Company did MAICs to compare encorafenib plus binimetinib and dabrafenib plus trametinib

Background: BRF113928

- No direct trials comparing enco-bini and dab-tram in a treatment-naïve population, company did unanchored MAICs to compare encorafenib plus binimetinib with dabrafenib plus trametinib
- BRF113928 was an open label, phase 2, multi-centre trial, participants received dabrafenib with trametinib.
- Company conducted a base case MAIC and several scenarios to generate relative effectiveness estimates
  - PHAROS alone adjusted to BRF113928 for
    - ECOG, smoking status, age, gender, race, histology, brain metastases (base case)
    - ECOG + smoking status only (sensitivity)
  - PHAROS and IFCT pooled and adjusted to BRF113928 for
    - ECOG, smoking status, age, gender, race, histology, brain metastases (scenario)
    - ECOG + smoking status only

Other key MAIC results link to:

1. full ITC results summary
2. PFS MAIC PHAROS
3. PFS Scenario using pooled PHAROS and IFCT

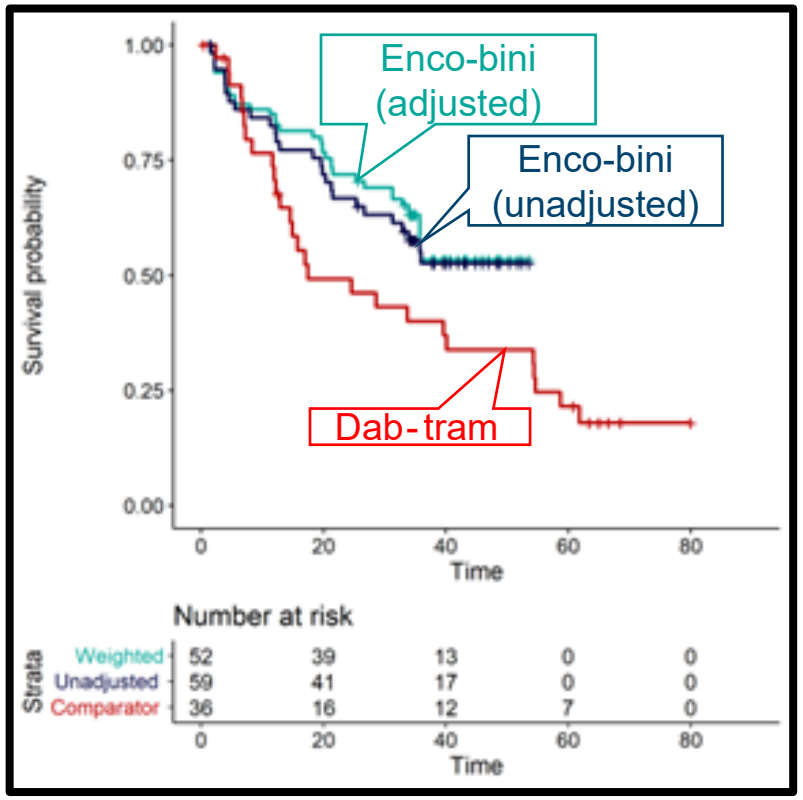
Abbreviations: ECOG, eastern cooperative oncology group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison, IFCT, Intergroupe Francophone de Cancérologie Thoracique (French Thoracic Oncology Group)

Link to supplementary slides: Baseline characteristics summary for ITC

MAIC results – OS – PHAROS vs BRF113928

Adjustment does not greatly affect results

OS – MAIC base case



OS – MAIC sensitivity

[redacted]

Analysis	N/ESS	HR (95% CI)
Unadjusted	59	0.60 (0.34, 1.07)
Base case*	44	0.55 (0.30, 1.01)
Sensitivity analysis**	58	[redacted]

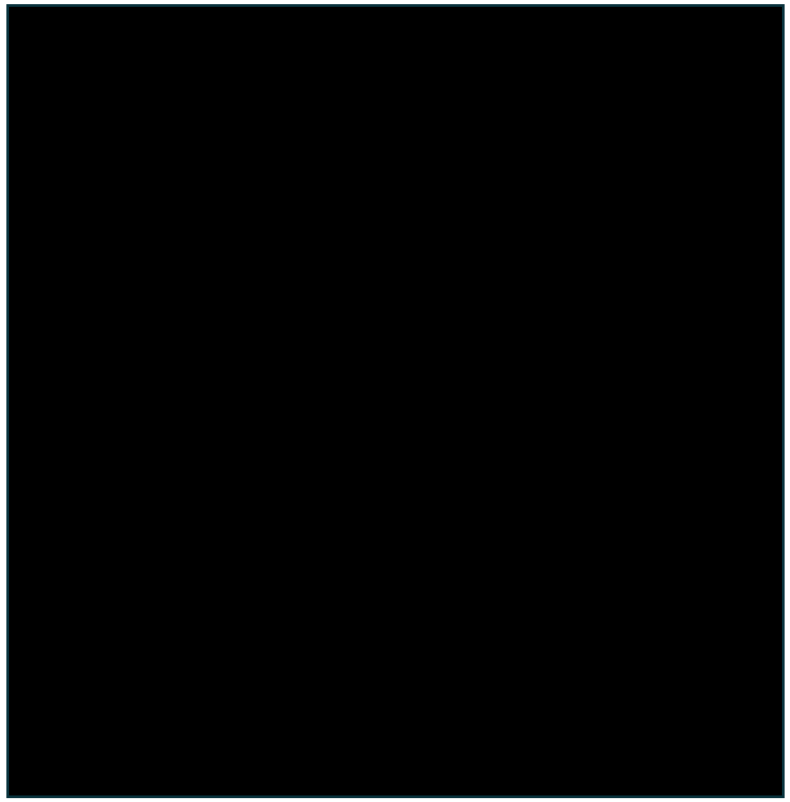
Abbreviations: CI, confidence interval; ESS, estimated sample size; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival

*Base case adjusts for ECOG, smoking status, age, gender, race, histology, brain metastases. **Sensitivity only smoking and ECOG

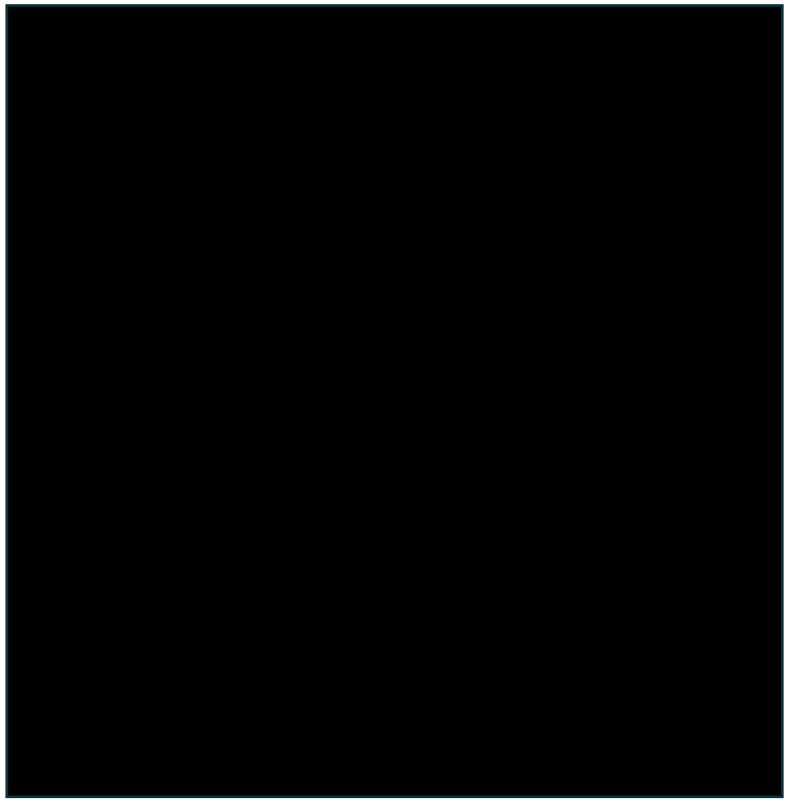
MAIC results – OS – Pooled PHAROS and IFCT vs BRF113928

Adjustment does not greatly affect results

OS – MAIC scenario analysis



OS – MAIC sensitivity analysis



Analysis	N / ESS	HR (95% CI)
Unadjusted	120	[redacted]
Pooled base case*	88	[redacted]
Sensitivity analysis**	118	[redacted]

Abbreviations: CI, confidence interval; ESS, estimated sample size; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; IFCT, intergroup francais cancerologie thoracic (French Thoracic Oncology Group)

* pooled PHAROS and IFCT adjusts for ECOG, smoking status, age, gender, race, histology, brain metastases. **Sensitivity only smoking and ECOG

Key issues: Prognostic variables missing from MAIC

Prognostic variables not adjusted for may affect reliability of MAIC results

Company

- Base case uses the PHAROS versus BRF113928 MAIC with adjustment for 7 variables
- After matching on adjustment factors, resulted in a loss of sample size of approximately 25%, with the weighted population representing 44 people

EAG comments

1. The MAIC substantially reduces the effective sample size for enco-bini (from 59 to 44)
2. Lack of adjustment for some important prognostic variables in the MAIC, due to the lack of availability of these variables.
3. Lack of adjustment for these variables, may have compromised the validity of results

Variables not adjusted for in MAIC
P13K pathway concomitant mutation
Presence of thoracic cavity metastases
PD-L1 ≥1% expression
Liver metastases
M1a metastases

Clinical expert opinion

- Do not believe that encorafenib plus binimetinib will improve overall survival over currently available treatment other than in people for whom dabrafenib plus trametinib leads to unacceptable toxicity

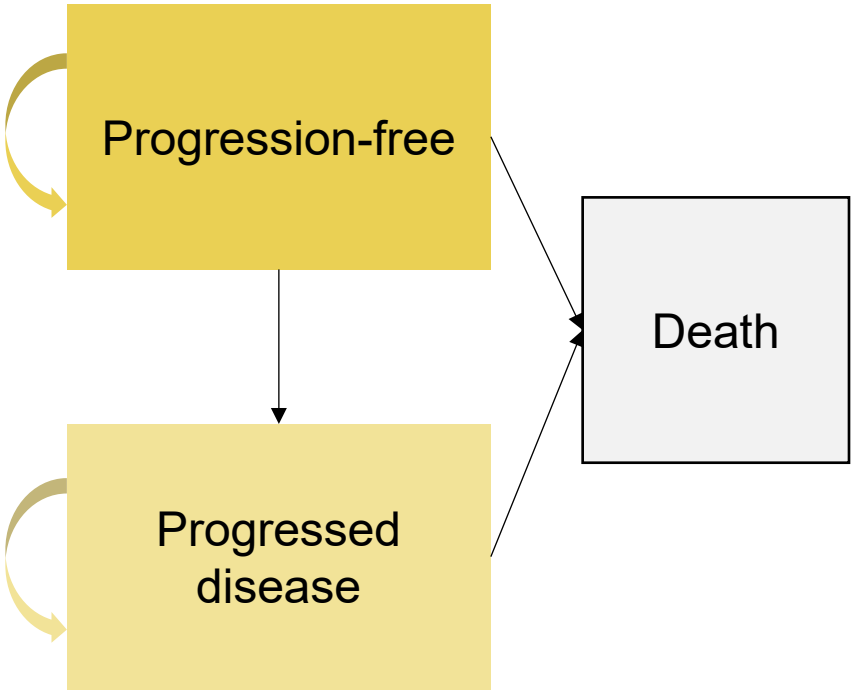
What are committee conclusions on missing variables in the MAICs?
Is a MAIC appropriate for decision making and if so which one?

Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison, PD-L1, programmed cell death ligand 1

Company's model overview

Partitioned survival model

Model structure



- Technology affects costs by:
  - Higher acquisition costs associated with encorafenib plus binimetinib.
- Technology affects QALYs by:
  - Longer time in PFS health state
  - Longer overall survival
- Assumptions with greatest ICER effect:
  - Modelling of time to discontinuation
  - Choice of MAIC

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

How company incorporated evidence into model

Input	Assumption and evidence source (company base case)
Baseline characteristics	Based on treatment naïve population of PHAROS trial after MAIC
Intervention efficacy	Extrapolated from PHAROS trial (unadjusted KM curves)
Comparator efficacy	PH models fitted, PFS and OS HRs from base-case MAIC of patient naïve cohort from PHAROS (matching adjusted to BRF113928)
Utilities	Health state utility values sourced from Chouaid et al. – aligned with TA898
Costs	NHS reference costs, BNF, eMIT; PSSRU
Resource use and treatment discontinuation	• TTD data and dosing regimens from post hoc analysis of PHAROS • For dab-tram TTD was assumed to be equal to PFS
Adverse events	All cause TEAEs grade 3+ experienced by ≥3% of: • PHAROS treatment naïve population (enco-bini) • full population of BRF113928 (dab-tram)
Subsequent treatments	• [redacted] assumed to have subsequent treatments • informed by clinical opinion to align with UK practice

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PH, proportional hazard; PFS, progression free survival; PSSRU, personal social services research unit; TEAE, treatment emergent adverse event; ToT, time on treatment; PSSRU, personal social services research unit

Proportional hazards assumption for OS

log-log plot PH assumption

Schoenfeld residuals

Company

- PH between enco-bini and dab-tram for OS. Applied MAIC HR to unadjusted PHAROS data to estimate OS for dab-tram.
- PH not rejected due to Schoenfeld residuals was associated with a p-value >0.05 (p=[redacted])
- Advisory board experts saw no clinical reason why PH would not hold between these drugs

EAG comments

- Log-log plot shows curves crossing, strong indication of non-proportionality
- Company stated curves cross in first 6 months and could be due to lack of events in enco-bini arm (At 6 months, [redacted] patients experienced event in treatment naive cohort). After 6 months curves remain parallel
- EAG agree that PH assumption reasonable

Does the committee consider the proportional hazards assumption to be appropriate?

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Abbreviations: OS, overall survival; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PH, proportional hazard

Key issue: Extrapolation of OS

Company selected exponential, EAG consider long term OS to be very uncertain

Predicted OS of different distributions for enco-bini and dab-tram

- The dab-tram curves are obtained by applying the OS MAIC HR of 0.55 to the enco-bini curve and so depends on the curve choice for enco-bini
- EAG uses exponential in base case but considers this is associated with substantial uncertainty

OS smoothed hazards

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

Key issue: Landmark survival estimates OS

Predicted enco-bini OS

	Median OS (yr)	OS at 5yr	OS at 10yr	OS at 20yr
Exponential company BC	3.81	40.6%	16.3%	2.7%
Weibull	3.93	42.3%	19.6%	4.6%
Log-normal	4.06	45.3%	29.4%	16.8%
Generalised gamma	4.37	47.6%	35.3%	25.3%
Log-logistic	3.97	44.1%	27.3%	15.3%
Gompertz	4.20	46.4%	34.8%	30.2%
Gamma	3.89	41.7%	18.2%	3.6%

Predicted and TA898 OS (dab-tram)

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

Company

- Exponential predicted lowest median OS of 3.81 years and provided good statistic fit based on AIC and BIC
- Clinical experts: not many people expected alive after 20 years. Weibull, exponential, gamma most plausible.
- Exponential distribution selected as predicted landmark survival estimates consistent with PHAROS trial

Abbreviations: OS, overall survival, TA, technology appraisal

ICER Impact: Large

Key issue: Extrapolation of OS

Parametric modelling might not be suitable to estimate long-term OS

EAG comments

- PHAROS data immature (44.1% OS)
- Exponential distribution suboptimal compared to observed data: smoothed hazard curves for OS decrease over time which indicates non-constant hazard over time and exponential does not capture this.
- Distributions which allow for non-constant hazards (e.g log-logistic and gamma) might be more appropriate
- Suggest using clinical input, external data sources or RWE to validate long term extrapolations for OS
- If, based on this, no standard parametric survival curves are considered appropriate then more flexible methods such as parametric survival models might be explored (TSD 21)
- EAG base case uses exponential curves for OS but considers this to be highly uncertain
- EAG notes that the proportion of health gains that was accrued beyond the observed data is much larger for enco-bini than for dab-tram and would like explanation of why this occurs

What is the preferred approach to modelling OS?

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criterion; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; RWE, real world evidence; TSD, technical support document; TTD, time to treatment discontinuation

Key Issue: Treatment effect waning

ICER Impact: Large

Treatment effect waning may occur beyond observed data

Company

- End of follow up, [redacted] of treatment naïve cohort of PHAROS were still having treatment
- Observed hazards of enco-bini and dab-tram for OS and PFS did not converge. No evidence of waning
- People may derive benefit from BRAF/MEK therapy after stopping treatment due to ongoing effects in the tumour microenvironment. Treatment effect waning was not applied in the dabrafenib plus trametinib appraisal, TA898
- Scenario: waning explored from [redacted] months (max follow-up of PHAROS) for a duration of 2 years

EAG comments

- Agrees that no effect waning during the observed period. Uncertain if waning occurs past observed data. Additional scenarios should explore waning assumptions
  - ❖ Different waning assumptions (e.g., gradual reduction in treatment effect over 1, 2, or 3 years starting at 3, 4 and 5 years) where the hazard of enco-bini converges to the hazard of dab-tram
  - ❖ Use external clinical input and/or RWE to validate the duration and pattern of treatment effect waning could improve robustness.
  - ❖ Comparative analysis of similar treatments with long term follow up data to infer plausible assumptions

Additional graphs on treatment effect waning

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

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MEK, mitogen-activated protein kinase; OS, overall survival; PFS, progression free survival; RWE, real world evidence

Key issue: Modelling TTD for both arms

ICER Impact: Large

Company base-case assumed that for dab-tram that TTD equals PFS

Background

- No estimates available for dab-tram for TTD. Company assumed that TTD equals PFS for dab-tram

Company

Modelling TTD for enco-bini

- TTD enco-bini arm: No TTD data collected in PHAROS, post-hoc analysis done
- Experts stated would not expect many people to be on treatment at 10 years, ruled out Gompertz, log-normal and log-logistic. Selected exponential for enco-bini as most clinically plausible estimates.

Modelling to estimate TTD for dab-tram:

- TTD dab-tram arm: TTD equals PFS. Company also provided scenarios requested by EAG:
  1. TTD by fitting exponential curve through median TTD reported in BRF113928 trial (10.55 months)
  2. TTD by fitting exponential curve through median TTD from RWE study Auliac 2020 (17.50 months)
  3. Apply HR between PFS and TTD for enco-bini (HR [redacted] to PFS for dab-tram to estimate TTD for dab-tram (8.51 months). Company state this scenario underestimates dab-tram TTD compared to the median TTD published in BRF113928 (10.55 months).

Abbreviations: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; RWE, real world evidence; TTD, time to treatment discontinuation

Key issue: Modelling TTD for both arms

Company base-case assumed that for dab-tram that TTD equals PFS

ICER Impact: Large

EAG comments

Modelling TTD for enco-bini

- Exponential distribution suboptimal compared to observed data: smoothed hazard curves for TTD decrease over time- indicates non-constant hazard and exponential does not capture this.
- Parametric models may not be appropriate for TTD extrapolation- more flexible parametric approach might be needed (TSD 21)

Modelling TTD for dab-tram

- Assuming that TTD equals PFS is a strong assumption
- EAG prefer applying HR between PFS and TTD for enco-bini (HR [redacted] to PFS for dab-tram (scenario 3) more plausible to estimate TTD for dab-tram. Due to:
    1. Enco-bini similar mechanism to dab-tram
    2. scenario could be conservative, dab-tram more toxic so people may discontinue earlier compared to enco-bini
- The difference in median TTD between scenario 3 and combined BRF113928 population could be due to differences in context and population between the 2 trials and approaches to estimating PFS and OS.

What are the preferred approaches to modelling TTD for enco-bini and dab-tram?

Abbreviations: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Key issue: Modelling TTD for both arms

ICER Impact: Large

Company use exponential distribution in base case

Long-term TTD projections

TTD smoothed hazard plot (enco-bini)

Landmark TTD estimates for enco-bini and dab-tram

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PFS, progression free survival; TTD, time to treatment discontinuation

Other issues: Utility values

Company used utility values from TA898

ICER Impact: Moderate

Background

- No studies report utility values for people with NSCLC who have a BRAF mutation

Company

- **Base case:** 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
- **Scenario 1:** HSUV on IFCT study, EQ-5D-5L collected and mapped to EQ-5D-3L, MMRM to estimate HSUV for people receiving enco-bini in IFCT trial
- **Scenario 2**: PD decrement from TA898 (0.04) applied to IFCT MMRM derived PF value

EAG comments

- Concerns with Chouaid et al: dated (2013), non-random drop out due to incomplete EQ-5D and excluded from analysis, risk of incorrect fitting of regression model, PF utility for 1st line lower than 2nd line is face validity issue
- EAG scenarios:
  - TA310: relatively high utility values
  - TA258: relatively low utility values

Which utility values should be used?

Health state utility values

	PF	PD
Base case: Chouaid 2023 (TA898)	0.71	0.67
Company scenario 1	[redacted]	[redacted]
Company scenario 2	[redacted]	[redacted]
EAG TA310 scenario*	0.784	0.725
EAG TA258 scenario*	0.661	0.4202

*Values from EGFR mutation+ NSCLC

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Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IFCT, intergroup francais cancerologie thoracic (French Thoracic Oncology Group); MMRM, mixed model with repeated measures; n, number; NSCLC; non-small-cell lung cancer PD, progressed disease; PF, progression free; TA, technology appraisal

Summary of base case assumptions and other issues

Other modelling issues

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PSA, probabilistic sensitivity analysis; mg, milligram; TTD, time to treatment discontinuation;

Modelling issue	Company	EAG	ICER Impact
Sub-optimal modelling of cost	Correct to apply per pack (instead of per mg) costing, applied every 28 days	Apply per pack costing in line with NICE methods, applies this weekly as a per cycle cost	Moderate
Model errors and technical verification	Model with scenarios.	Errors in model, would have preferred TECH-VER checklist to be completed.	Unknown
Deterministic / PSA	Large difference between deterministic and probabilistic results	Explore reasons why large difference and want PSA model with reduced run time	Unknown

Assumptions in company and EAG base case

Assumption	Company base case	EAG exploratory base case
Health state utilities	Chouaid et al (TA898)	Used Chouaid et al with TA310 & TA258 scenarios
Extrapolation of efficacy: OS	Exponential	Exponential (substantial uncertainty)
Extrapolation of efficacy: PFS	Exponential	Exponential (substantial uncertainty)
Extrapolation of efficacy: TTD	Exponential	Exponential (substantial uncertainty)
TTD for dab-tram	TTD equals PFS	Apply HR between PFS and TTD
Acquisition costs	Per mg, applied 28 days	Per pack (modelled weekly). Cost applied weekly

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.

Key issues

	Key Issues	ICER impact
1	Lack of adjustment for important prognostic variables in MAIC analysis	Large
2	Extrapolation of OS	Large
3	Treatment waning effect	Large
4	Extrapolation of TTD	Large

	Other issues	ICER impact
5	Extrapolation of PFS	Moderate
6	Uncertainty in the source to inform the modelling of health state utilities	Moderate
7	Other modelling issues	Unknown
8	Line of therapy and comparators	Unknown

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

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Key issues: Line of therapy and comparators

Some people may not have genomic testing and might have non targeted treatments

Background

- Company narrowed positioning to only 1st line population and only compare with dab-tram

Company

- Routine genetic testing for BRAF V600 in NHS for people diagnosed with NSCLC. People with a BRAF V600 mutation will have targeted treatment (dab-tram) as clinical experts agreed that no reason not to use targeted therapy if person known to have BRAF V600 mutation.
- Second line usage excluded because there is no retreatment with BRAF/MEK inhibitor combinations
- Committee in TA898 identified that delays to BRAF testing were no longer a concern

EAG comments

- Multiple comparators in NICE scope and additional comparators listed in NG122 for 1st line treatment
- Comparators used in clinical practice should be included in model
- EAG Clinical expert: Agrees with excluding other comparators, if BRAF V600E mutation is confirmed, oncologists would favour targeted therapy.
- However a small number of centres may not access genomic testing, standard 1st line therapy offered
- Also, less than 5% people with NSCLC would have insufficient tissue for genetic testing to be done

Which are the most appropriate comparators for this appraisal?

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NG, NICE guideline; NSCLC, non-small-cell lung cancer; MEK, mitogen-activated protein kinase; TA, technology appraisal

Additional clinical trial - IFCT (NCT04526782)

Clinical trial designs and outcomes

	PHAROS
Design	Phase 2, open-label, multicentre study
Population	Adults aged 18 years of age and older with advanced BRAF V600E MT NSCLC
Intervention	Encorafenib in combination with binimetinib
Comparator(s)	No comparator
Duration	ongoing
Primary outcome	Overall response rate using Independent assessment
Key secondary outcomes	ORR using IRR, duration of response, disease control rate, progression free survival, overall survival, time to progression, QoL/EQ-5D-5L, adverse events
Locations	France, 36 sites
Used in model?	Not used in base case

Back to PHAROS trial

Abbreviations: IFCT, intergroup francais cancerologie thoracic (French Thoracic Oncology Group); IRR, independent radiology review; n, number; NSCLC, non-small-cell lung cancer; MT, mutation positive; ORR, objective response rate; QoL, quality of life

PHAROS baseline characteristics: treatment naive cohort

Baseline characteristics for treatment naive cohort n=59

Characteristic	Intervention- treatment naive (n=59)
(Median) age (years)	68 (range 47-83)
Sex %	
% Women	56
% Men	44
Ethnicity %	
% White	90
% Asian	5
% Black	2
Brain metastasis Yes %	7
Tumour histology adenocarcinoma %	97
Smoking status	
% never	31
% current	14
% former	56

Abbreviations: n, number

Link to: main slides, key clinical trail – PHAROS (NCT03915951)

ITC summary data

Background

- Pseudo patient level data recreated for OS and PFS outcomes, algorithm developed by Guyot et al. This patient level data was plotted next to digitised curves for validation and summary statistics were calculated and compared to the published statistics

Summary data used in ITC

	PHAROS (n=59)	BRF113928 (n=36)
Efficacy		
OS		
Median follow up time (months)	[redacted]	16.4
% observed events	44.1	75.0
Median OS (months)	Not reached	17.3
PFS (IRR)		
Median follow up time (months)	33.3	9.3
% observed events	47.5	61.1
Median PFS (months)	30.2	14.6
% ORR (IRR)	74.6	63.9
Safety		
% Grade 3-4 AE	[redacted]	69.4
% SAE	[redacted]	66.7
% Discontinuation due to AE	[redacted]	22.2

Abbreviations: AE, adverse event; IRR, independent radiology review; ITC, indirect treatment comparison; n, number; OS, ORR, objective response rate; overall survival; PFS, progression free survival; SAE, serious adverse event

Link to main slides summary of company ITC

ITC results summary

Abbreviations: ECOG, eastern cooperative oncology group; ESS, estimated sample size; n, number; OS, overall survival; PFS, progression free survival

Back to ITC

Variable	Original data		Matched data for PHAROS and IFCT	
	PHAROS and IFCT (N=120)	BRF113928 (N=36)	All factors (ESS=88)	ECOG + smoking status (ESS=118)
Age	[redacted]	[redacted]	[redacted]	[redacted]
% Male	[redacted]	[redacted]	[redacted]	[redacted]
% ECOG=0	[redacted]	[redacted]	[redacted]	[redacted]
% Never smoked	[redacted]	[redacted]	[redacted]	[redacted]
% Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]
% Brain metastases	[redacted]	[redacted]	[redacted]	[redacted]

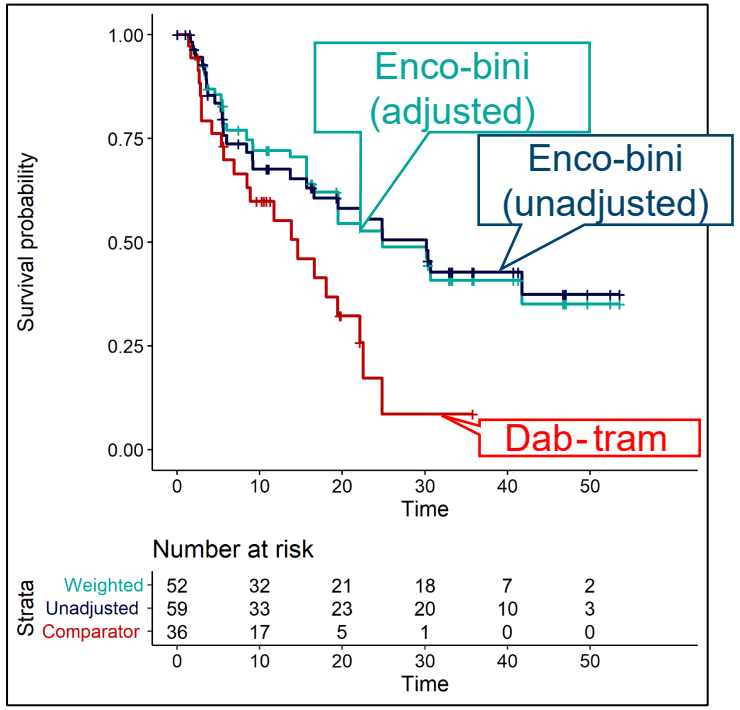
Variable	Original data		Matched data for PHAROS	
	PHAROS (N=59)	BRF113928 (N=36)	All factors (ESS=44)	ECOG + smoking status (ESS=58)
Age (years)	68	67	67	66
% Male	44	39	39	45
% ECOG=0	32	36	36	36
% Never smoked	31	28	28	28
% White	90	83	83	90
% Adenocarcinoma	97	89	89	97
% Brain metastases	7	6	6	7

	PHAROS only			PHAROS and IFCT		
Outcome	Unadjusted (N=59)	All factor adjustment (ESS = 44)	ECOG and smoking status (ESS=58)	Unadjusted (N=120)	All factor adjustment (ESS = 80)	ECOG and smoking status (ESS=118)
OS	0.60 (0.34, 1.07)	0.55 (0.30, 1.01)	[redacted]	[redacted]	[redacted]	[redacted]
PFS	0.48 (0.27, 0.87)	0.47 (0.26, 0.85)	[redacted]	[redacted]	[redacted]	[redacted]

MAIC results – PFS – PHAROS vs BRF113928

Adjustment does not greatly affect results

PFS – MAIC base case



PFS – MAIC sensitivity

[redacted]

Analysis	N / ESS	HR (95% CI)
Unadjusted	59	0.48 (0.27 to 0.87)
Base case*	44	0.47 (0.26 to 0.85)
Sensitivity analysis**	58	[redacted]

Link to: ITC summary

Abbreviations: CI, confidence interval; ECOG, eastern cooperative oncology group; ESS, estimated sample size; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; n, number; PFS, progression free survival;
*Base case adjusts for ECOG, smoking status, age, gender, race, histology, brain metastases. **Sensitivity only smoking and ECOG

MAIC results – PFS – Pooled PHAROS and IFCT vs BRF113928

Adjustment does not greatly affect results

PFS – MAIC scenario analysis

PFS – MAIC scenario sensitivity

Analysis	N / ESS	HR (95% CI)
Unadjusted	120	[redacted]
Pooled base case*	88	[redacted]
Sensitivity analysis**	118	[redacted]

Link to main slides, ITC summary

Abbreviations: CI, confidence interval; ECOG, eastern cooperative oncology group; ESS, estimated sample size; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-meier; PFS, progression free survival

*pooled PHAROS and IFCT adjusts for ECOG, smoking status, age, gender, race, histology, brain metastases. **Sensitivity only smoking and ECOG

Key issue: Enco-bini smoothed OS hazard plot

Enco-bini smoothed OS hazard plot

Predicted and TA898 OS (dab-tram)

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

EAG: Smoothed hazard plot suggests exponential inappropriate for PFS due to non-constant hazards

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression free 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; TTD, time to treatment discontinuation

Landmark TTD estimates of enco-bini and dab-tram

Predicted TTD of different distributions for enco-bini

Years	5	10
Exponential	10.0%	1.0%
Weibull	12.4%	2.3%
Log-normal	18.1%	8.9%
Gen. gamma	12.7%	2.6%
Log-logistic	17.6%	9.0%
Gompertz	12.6%	3.7%
Gamma	11.9%	1.8%

Alternative modelling of TTD for dab-tram

Scenario / Years	2	5	10
Base case: Assume TTD equal to PFS	[redacted]	[redacted]	[redacted]
Scenario 1: Plot exponential through the median TTD from BRF113928	[redacted]	[redacted]	[redacted]
Scenario 2: Plot exponential through the median TTD from Auliac 2020	[redacted]	[redacted]	[redacted]
Scenario 3: Use HR derived from TTD/PFS from PHAROS	[redacted]	[redacted]	[redacted]

Link to main slides: modelling TTD for enco-bini and dab-tram

Abbreviations: HR, hazard ratio; PFS, progression free survival; TTD, time to treatment discontinuation

ICER Impact: Moderate

Other issues: Extrapolation of PFS

Exponential predicted lowest progression free survival after 5 and 10 years

Predicted PFS of different distributions

Company experts: Some patients would be “super responders” and have long term response. However, few would be in PFS at 5 and 10 years. Exponential, Weibull and gamma most clinically plausible

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PFS, progression free survival

Smoothed PFS hazards

Other issues: Extrapolation of PFS

ICER Impact: Moderate

Exponential predicted lowest progression free survival after 5 and 10 years

Enco-bini predicted PFS estimates of different distributions

	Median	PFS at 5 yrs	PFS at 10 yrs
Exponential	2.34	22.8%	5.2%
Weibull	2.34	26.3%	8.6%
Log-normal	2.15	29.1%	15.7%
Generalised gamma	2.07	37.3%	29.5%
Log-logistic	2.13	28.5%	15.7%
Gompertz	2.18	34.2%	28.1%
Gamma	2.36	25.1%	7.0%

Predicted and TA898 PFS (dab-tram)

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

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression free survival; TA, technology appraisal

Other issues: Extrapolation of PFS

ICER Impact: Moderate

Parametric modelling might not be suitable to estimate long-term PFS

Company

- Clinical experts: few people progression free at 5 years. Exponential, Weibull and gamma most plausible.
- Chose exponential, clinically plausible and predicted median survival estimates consistent with PHAROS.

EAG comments

- PHAROS data immature [redacted]
- Exponential distribution suboptimal compared to observed data: smoothed hazard curves for PFS decrease over time which indicates non-constant hazard over time and exponential does not capture this.
- Distributions which allow for non-constant hazards (e.g log-logistic and gamma) might be more appropriate
- Suggest using clinical input, external data sources or RWE to validate long term extrapolations for PFS
- If, based on this, no standard parametric survival curves are considered appropriate then more flexible methods such as parametric survival models might be explored (TSD 21)
- EAG base case uses exponential curves for PFS but considers this to be highly uncertain

What is the preferred approach to modelling PFS?

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; PFS, progression free survival; RWE, real world evidence; TSD, technical support document;

Enco-bini smoothed PFS hazard plot

Enco-bini smoothed PFS hazard plot

Long-term PFS projections of dab-tram vs BRF trial KM

EAG: Smoothed hazard plot suggests exponential inappropriate for OS due to non-constant hazards

Link to main slides: 1.Extrapolation of PFS

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

Subsequent treatment distributions

Proportion of each subsequent therapies modelled – Company and EAG base cases

Subsequent treatment	Distribution
Encorafenib + binimetinib	[redacted]
Dabrafenib + trametinib	[redacted]
Pembrolizumab	[redacted]
Nivolumab	[redacted]
Nivolumab + Ipilimumab	[redacted]
Pembrolizumab + cisplatin + pemetrexed	[redacted]
Nivolumab + Ipilimumab + cisplatin	[redacted]
Nivolumab + Ipilimumab + carboplatin	[redacted]
Chemotherapy only	[redacted]
Radiotherapy	[redacted]
Carboplatin + pembrolizumab + pemetrexed	[redacted]
Carboplatin + bevacizumab + pemetrexed	[redacted]
Dabrafenib	[redacted]
Carboplatin + pemetrexed	[redacted]

Abbreviations: