ENCORAFENIB PLUS BINIMETINIB VERSUS DABRAFENIB PLUS TRAMETINIB IN FIRST-LINE FOR PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER HARBORING BRAF V600E MUTATION: MATCHING ADJUSTED INDIRECT COMPARISON OF PHAROS AND BRF113928

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BACKGROUND

- BRAF mutations are present in 3-4% of non-small cell lung cancer (NSCLC) and BRAF V600E mutations represent approximately 50% of all those mutations in lung cancer, meaning that around 2% of all NSCLC cases are BRAF V600E mutant patients[1].
- BRAF mutations may often present as adenocarcinoma with histologically aggressive micropapillary growth pattern[2].
- Combination of BRAF and MEK inhibitors is a standard of care for BRAF V600E mutant metastatic NSCLC. Dabrafenib in combination with trametinib (D+T) is approved in this population based on a phase II BRF113928 study (NCT01336634).
- Encorafenib in combination with binimetinib (E+B) has been recently approved for treating advanced BRAF V600E mutant NSCLC patients and has shown meaningful clinical benefit in this population based on the Phase II PHAROS trial (NCT03915951).

OBJECTIVE AND METHODS

Objective: The analysis aimed to assess the relative efficacy and safety of E+B versus D+T in treatment-naïve BRAF V600E mutant metastatic NSCLC, using data from the clinical trials of E+B and D+T.

Study design

- **PHAROS** (NCT03915951) is an ongoing Phase 2, single-arm, multicenter, open-label, global, registrational study of E+B.
- **BRF113928** (NCT01336634) is a Phase 2, single-arm, multicenter, open-label, global, registrational study of D+T

Method

- As PHAROS is a single-arm trial, an unanchored matching-adjusted indirect comparison (MAIC) was conducted using patient-level data from PHAROS (data cutoff date: 19 July 2023) and from the most recent aggregated data from D+T trial BRF113928 (NCT01336634) with a minimum of 5-year follow-up[3].
- All patients included in PHAROS met the eligibility criteria of BRF113928
- Individual patient data (IPD) from 1st line patients in PHAROS were weighted to match the aggregated baseline characteristics of D+T patients in 1st line in BRF113928.
- The adjustment factors were selected based on evidence collected in a systematic literature review (SLR), inputs from clinicians and availability of data in the trials. They were ECOG performance status, smoking status, age, gender, race, histology and presence of brain metastases.
- The Kaplan-Meier (KM) curves of D+T[3] were digitized and pseudo IPD were recreated using the Guyot algorithm[4].
- Weighted Hazard proportional Cox and logistic regression models were fitted to estimate the relative efficacy of E+B vs D+T for time to progression (assessed by independent radiographic review [PFS IRR]), overall survival [OS]), objective response rate [ORR IRR], and serious adverse events [SAE] endpoints.
- The analyses were performed on unweighted data (unadjusted comparison) and on weighted data (adjusted comparison).
- Bootstrap analyses are conducted to improve the estimation of uncertainty and the robustness of the results and to ensure that conclusions are not excessively influenced by bias or variations in adjusted weights.

RESULTS

Patient characteristics

- Before matching, imbalances were observed between the studies (mainly on gender, race and histology).
- After matching on all adjustment factors, the patient characteristics between the two studies were perfectly aligned (**Table 1**). This resulted only in a loss of sample size for the PHAROS study of approximately 25% (estimated sample size ESS=44).
- The validity of the proportional hazard (PH) assumption was graphically assessed using log-log plots and tested using the Schoenfeld residuals. The PH assumption was deemed acceptable in all models.

Table 1. Baseline characteristics for E+B, before and after weighting versus D+T trial.

	Original data		Matched data for PHAROS
Characteristics	PHAROS (N=59)	BRF113928 (N=36)	All factors (ESS=44)
Age (years)	68	67	67
Gender - % Male	44	39	39
ECOG - %ECOG=0	32	36	36
Smoking status - %Never smoked	31	28	28
Race - % White	90	83	83
Histology - % Adenocarcinoma	97	89	89
Brain metastases - % Yes	7	6	6

- The impact of the adjustment on all factors on the difference between both trials is presented in Figure 1 for OS and Figure 2 for PFS, and it leads to an increased benefit of E+B vs D+T in terms of overall survival (OS).

Figure 1. OS curves of E+B and D+T

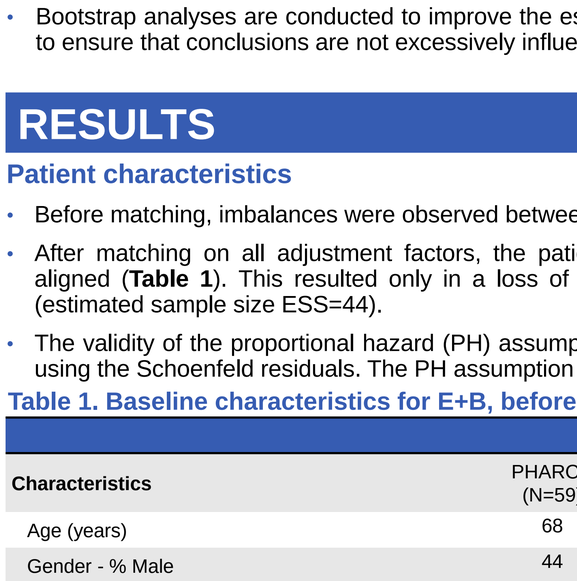
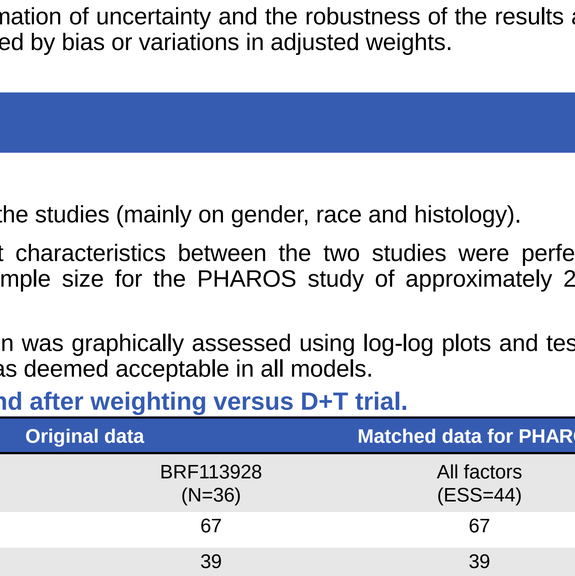


Figure 2. PFS curves of E+B and D+T



RESULTS

Overall Survival (OS)

- The unadjusted comparison showed a non-significant difference in favor of E+B; however, after adjustment on all factors, E+B showed a statistically significant reduction in death of over 50% compared to D+T (adjusted HR=0.48; 95%CI:0.25, 0.90) (**Table 2**).

Table 2. OS results of E+B vs D+T

OS - encorafenib + binimetinib versus dabrafenib + trametinib	
Unadjusted comparison – Unweighted results	
Mean HR (95% CI)	0.562 (0.308 to 1.023)
p-value	p=0.059
MAIC - Weighted results	
Mean HR (95% CI)	0.476 (0.251 to 0.902)
p-value	p=0.023
MAIC – Bootstrapping results	
Median HR (95% percentile CI)	0.493 (0.289 to 0.776)
95% bias-corrected and accelerated CI	(0.277 to 0.764)

Progression-Free Survival (PFS)

- Both the unadjusted and the adjusted comparisons showed a statistically significant reduction in disease progression or death of over 50% compared to D+T (adjusted HR=0.47; 95%CI: 0.26, 0.85) (**Table 3**).

Table 3. PFS results of E+B vs D+T

PFS - encorafenib + binimetinib versus dabrafenib + trametinib	
Unadjusted comparison – Unweighted results	
Mean HR (95% CI)	0.479 (0.265 to 0.866)
p-value	p=0.015
MAIC - Weighted results	
Mean HR (95% CI)	0.471 (0.262 to 0.846)
p-value	p=0.012
MAIC – Bootstrapping results	
Median HR (95% percentile CI)	0.467 (0.269 to 0.713)
95% bias-corrected and accelerated CI	(0.278 to 0.726)

Objective Response Rate (ORR)

- The indirect comparison showed that E+B was numerically superior to D+T (unadjusted OR=1.66; 95%CI: 0.67 to 4.07 and adjusted OR=1.81; 95%CI: 0.71 to 4.59) (**Table 4**).

Table 4. ORR results of E+B vs D+T

ORR - encorafenib + binimetinib versus dabrafenib + trametinib	
Unadjusted comparison – Unweighted results	
Mean OR (95% CI)	1.658 (0.676 to 4.069)
p-value	p=0.270
MAIC - Weighted results	
Mean OR (95% CI)	1.808 (0.712 to 4.588)
p-value	p=0.213
MAIC – Bootstrapping results	
Median OR (95% percentile CI)	1.711 (0.892 to 3.673)
95% bias-corrected and accelerated CI	(0.955 to 4.028)

Safety

- The unadjusted comparison showed a significant difference in favor of E+B and after adjustment on all factors, this difference was larger and associated with a narrower confidence interval (adjusted OR=0.34; 95%CI:0.14, 0.81) (**Table 5**).

Table 5. Serious adverse events

SAEs - encorafenib + binimetinib versus dabrafenib + trametinib	
Unadjusted comparison – Unweighted results	
Mean OR (95% CI)	0.422 (0.178 to 0.999)
p-value	p=0.050
MAIC - Weighted results	
Mean OR (95% CI)	0.335 (0.138 to 0.813)
p-value	p=0.016
MAIC – Bootstrapping results	
Median OR (95% percentile CI)	0.349 (0.187 to 0.666)
95% bias-corrected and accelerated CI	(0.166 to 0.593)

CONCLUSION

- This is the first analysis indirectly comparing the efficacy and safety of E+B and D+T in 1st line in adult patients with BRAFV600E mutant metastatic NSCLC.
- This MAIC suggested that E+B improved clinical outcomes compared with D+T in terms of efficacy and safety. The clinical benefit is statistically significant in terms of OS and PFS.
- Due to the inherent limitations of indirect comparison, results should be interpreted with caution. The results are consistent according unadjusted comparison, weighted results and bootstrapping results, which suggest a limited uncertainty.

REFERENCES

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ABBREVIATIONS

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IPD = individual patient data; KM = Kaplan Meier; HR = hazard ratio; IRR = independent radiographic review; MAIC = matching adjusted indirect comparison; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SLR = systematic literature review

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