Matching-adjusted indirect comparison (MAIC) of dabrafenib plus trametinib versus pembrolizumab plus chemotherapy in patients with treatment-naive metastatic BRAF V600 mutation-positive non-small cell lung cancer (NSCLC)

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INTRODUCTION

- BRAF V600 is a rare variant among non-small cell lung cancer (NSCLC) driver mutations and present in around 1% to 3% of patients with NSCLC[1-6].
- Patients with BRAF V600 mutations have poor prognosis compared with other driver mutations and there is limited treatment option specifically for BRAF V600 mutation[1,7].
- The combination of dabrafenib + trametinib (subsequently referred to as Dab-Tram), inhibitors of BRAF V600 and MEK, has been approved for treating metastatic BRAF V600 mutant NSCLC patients. The efficacy of this combination was evaluated in a Phase II study (NCT01336634), demonstrating clinically meaningful efficacy and a manageable safety profile in both previously treated and untreated metastatic NSCLC patients with BRAF V600 mutations[8,9].
- Pembrolizumab plus platinum-based doublet chemotherapy (subsequently referred to as Pembro+PDC) is considered as the most commonly used therapy for this population when Dab-Tram is unavailable[10].

OBJECTIVE

- This study aimed to evaluate the relative efficacy of Dab-Tram versus Pembro+PDC in patients with treatment-naive metastatic BRAF V600 mutant NSCLC .

METHOD

- Due to Dab-Tram trial being a single-arm trial, unanchored matching adjusted indirect comparison (MAIC) was used. The outcomes of interest were overall survival (OS) and progression-free survival (PFS).
- Individual patient data (IPD) from Cohort C of the Dab-Tram trial (NCT01336634)[8,9] were weighted to match the aggregate baseline characteristics of the Pembro+PDC arm from the KEYNOTE-189 trial (NCT02578680)[11].
- The prognostic variables were selected based on literature and Cox-regression analysis (Table 1), and included age, gender, ECOG, smoking status, histology, liver metastases, brain metastases and extent of metastasis.
- Pseudo IPD of Pembro+PDC was obtained by digitizing Kaplan-Meier (KM) curves from the most recent cut-off (5-year follow-up) of KEYNOTE-189 trial using the Guyot algorithm[12,13].
- After matching, hazard ratios (HRs) were estimated using a weighted Cox proportional hazard model. Success of matching was assessed by inspecting distributions of weights and effective sample size (ESS).

Table 1. Prognostic value of covariates

Covariate	Reference	HR (P-value) for OS	HR (P-value) for PFS
Median age	< vs >= median age	0.577 (0.184)	0.799 (0.625)
Sex	Male vs female	1.132 (0.757)	1.076 (0.867)
Region	Europe vs other	1.038 (0.933)	0.983 (0.973)
	North America vs other	0.826 (0.681)	0.826 (0.73)
ECOG PS	0 vs other	0.229 (0.003)	0.195 (0.004)
Smoking history	Smoker vs never smoked	0.848 (0.709)	1.048 (0.927)
Histology	Adenocarcinoma vs other	0.801 (0.717)	1.152 (0.85)
Brain metastases	Present vs absent	1.051 (0.946)	4.124 (0.078)
Liver metastases	Present vs absent	53.625 (0)	19.727 (0)
Metastasis staging	M1a vs other	0.409 (0.103)	0.378 (0.121)

[1] We defined covariates with p-value < 0.2 as potential prognostic factor

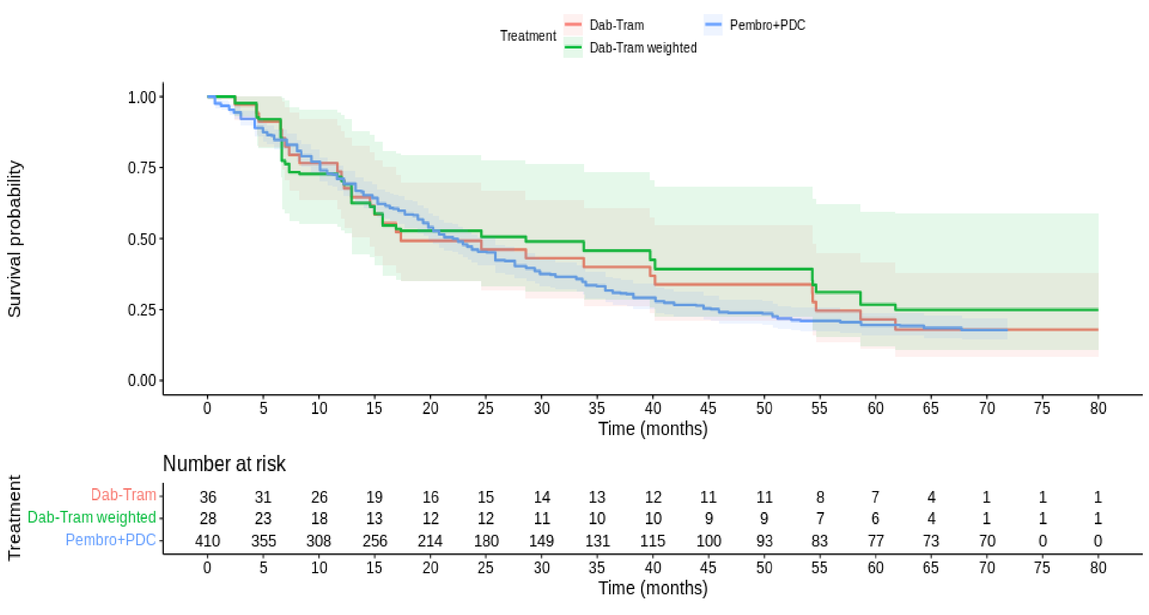
RESULTS

- The MAIC successfully balanced baseline characteristics between Dab-Tram and Pembro+PDC (Table 2, Table 3).
- Before matching, OS was similar between Dab-Tram and Pembro+PDC (HR 0.944 [95% CI 0.638 - 1.398]) while adjusted HR numerically favored Dab-Tram (HR 0.817 [95% CI 0.454 - 1.471]).

Table 2. Baseline characteristics for Dab-Tram trial Cohort C, before and after weighting, compared with KEYNOTE-189 trial, for OS

Characteristics	Dab-Tram Before Weighting	Dab-Tram After Weighting	KEYNOTE-189
ESS	36	22.8	410
Median age, years	67	65	65
Male	38.9%	62.0%	62.0%
ECOG PS 0	36.1%	45.1%	45.1%
Smokers	72.2%	88.3%	88.3%
Adenocarcinoma histology	88.9%	96.1%	96.1%
Liver metastases	11.1%	16.1%	16.1%
M1a metastasis	25.0%	30.0%	30.0%

Figure 1. KM curves of OS for Dab-Tram vs Pembro+PDC

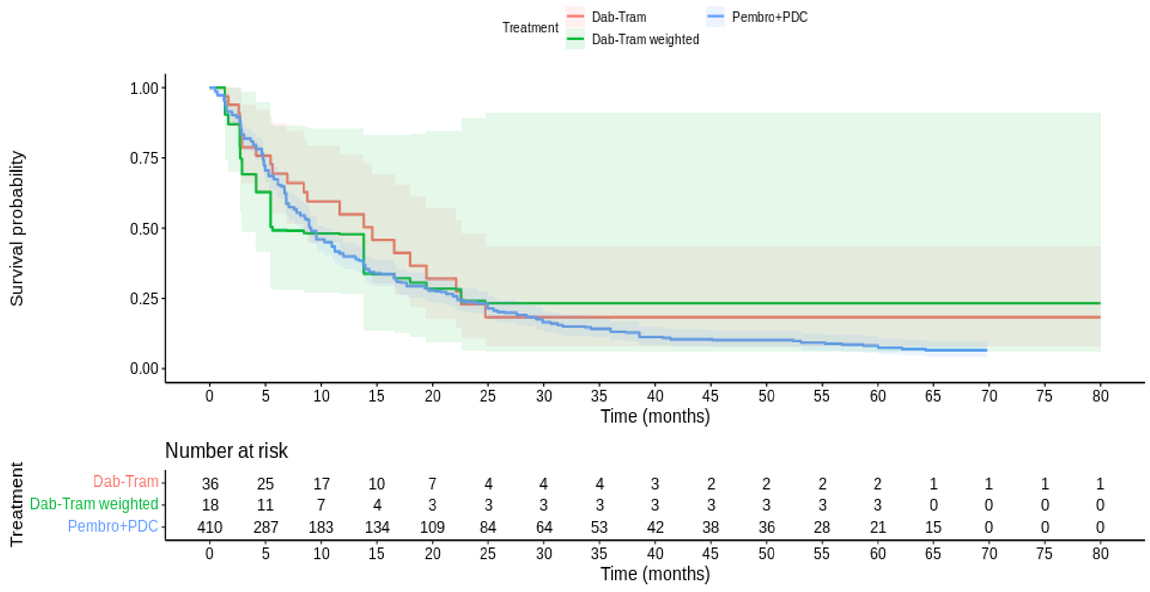


- Dab-Tram appeared to prolong PFS compared with Pembro+PDC both before and after matching but the difference was not significant (naive HR 0.759 [95% CI 0.493 - 1.167]; adjusted HR 0.842 [95% CI 0.295 - 2.402])

Table 3. Baseline characteristics for Dab-Tram trial Cohort C, before and after weighting, compared with KEYNOTE-189 trial, for PFS

Characteristics	Dab-Tram Before Weighting	Dab-Tram After Weighting	KEYNOTE-189
ESS	36	13.6	410
Median age, years	67	65	65
Male	38.9%	62.0%	62.0%
ECOG PS 0	36.1%	45.1%	45.1%
Smokers	72.2%	88.3%	88.3%
Adenocarcinoma histology	88.9%	96.1%	96.1%
Brain metastases	5.6%	17.8%	17.8%
Liver metastases	11.1%	16.1%	16.1%
M1a metastasis	25.0%	30.0%	30.0%

Figure 2. KM curves of PFS for Dab-Tram vs Pembro+PDC



CONCLUSION

- The MAIC showed that Dab-Tram has numerically better OS and PFS than Pembro+PDC in treatment-naive metastatic BRAF V600 mutation-positive NSCLC patients; however results are not statistically significant.

DISCUSSION

- MAIC is often used to evaluate relative treatment effect when there are substantial differences in patient composition between trials or when there is a lack of common comparator. In our case, unanchored MAIC was employed due to Dab-Tram being a single-arm trial.
- In this analysis, we identified baseline variables which may be treatment effect modifiers or prognostic factors. Although there were differences in the baseline characteristics between the two data sources, adjusting for many of these characteristics did not fundamentally alter the conclusion – Dab-Tram is comparable to Pembro+PDC. It is worth noting that the confidence interval was wide in naive and adjusted analyses which might be because of small sample size of Dab-Tram trial Cohort C.
- We presented two sets of results: in the scenario analysis (presented in the supplementary materials), we matched on variables with significant prognostic value determined in our Cox PH regression and in base-case we matched on more complete sets of variables. Matching improved point estimates of OS HR in both base-case and scenario analysis while PFS HR was worsened in base-case (in which case the effective sample size was substantially reduced making the results unreliable) and unchanged in scenario analysis.
- A limitation of this study is that it was not possible to match for BRAF mutation, PD-L1 and any unobserved factors. Despite this limitation, it remains informative to understand relative treatment effect where a standard indirect comparison is not feasible.

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