Estimating treatment effect on survival outcomes from real-world data: inverse probability of treatment weighting with missing data and non-proportional hazards

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INTRODUCTION

There are several available first-line treatment options for BRAF-mutated advanced melanoma (aM): targeted therapy with BRAF±MEK-inhibitors and immunotherapy with anti-PD-1/PD-L1±anti-CTLA-4 agents. Currently, there are insufficient data on their relative effect on overall (OS) and progression-free (PFS) survival in clinical trials. Its evaluation is complicated by non-proportional hazards which stems from differences in a mechanism of action between these options. Real-world practice provide data for indirect comparisons, but involves additional concerns about missing values and confounding.

OBJECTIVES

To compare OS and PFS between mono anti-PD1 and mono BRAF-inhibitors (monoBRAFi) or combination of BRAF- and MEK-inhibitors (BRAFi+MEKi) in the first-line treatment of patients with BRAF-mutated aM in the routine clinical practice in the Russian Federation (RF).

METHODS

For this analysis, we selected 115 patients with BRAF-mutated aM who received anti-PD-1 drug prolgolimab (approved in the RF for aM in 2020) as the first-line therapy from 700 participants enrolled in the multicenter prospective cohort study FORA (NCT05120024) and 130 patients treated with BRAFi+MEKi (dabrafenib+trametinib or vemurafenib+cobimetinib) and 76 patients treated with monoBRAFi (dabrafenib or vemurafenib) in the first line from 382 participants included into the multicenter retrospective cohort study ADMIRE (NCT03663647).

Due to non-proportionality of hazards for OS and PFS a difference in the restricted mean survival time (rmstD) over 30 months was used as an estimand. Marginal RMST was assessed as an area under a Kaplan-Meier curve adjusted by the inverse probability of treatment weighting (IPTW) computed from propensity scores. Covariates for the latter included sex, age, AJCC M-stage, ECOG and LDH elevation above the upper limit of the norm.

38/115 (33%), 76/130 (66%) and 59/76 (78%) patients in prolgolimab, BRAFi+MEKi and monoBRAFi groups, respectively, have no data either on LDH elevation or ECOG. Therefore, the analysis was preceded by multiple imputation of these missing values using chain equations (MICE) with covariates for treatment group, sex, age, AJCC M-stage, year of treatment start, duration of disease from the aM diagnosis, type of BRAF mutation (V600E or V600 non-E), disease progression at the first line, death and Nelson-Aalen estimates of cumulative hazard of progression and death. IPTW-adjusted survival and rmstDs with bootstrapped standard errors from 50 imputed datasets were pooled according to the Rubin's rules.

RESULTS

Averaged over imputations, effective sample size (ESS) for prolgolimab, BRAFi+MEKi and monoBRAFi was 79/115 (69%), 102/130 (78%) and 61/76 (80%) patients, accordingly. Initially, there were less patients with metastases to CNS (M1d stage), ECOG 2-3 and elevated LDH in prolgolimab group compared to BRAFi±MEKi, although they were older, on average (Fig.1A). Weighting balanced all groups by all covariates used to calculate propensity scores (Fig.1B). Adjustment with IPTW more thoroughly affected survival in targeted therapy groups, especially monoBRAFi (Fig.2, Fig.3).

IPTW-adjusted 30-month mean survival time and mean progression-free survival time were 23.9 and 15.2 months on prolgolimab, 23.1 and 14.2 months on BRAFi+MEKi, 21.0 and 11.2 months on monoBRAFi, respectively. 30-month rmstD in prolgolimab group compared to BRAFi+MEKi and monoBRAFi was 0.8 (95% CI, -2.0, 3.6, p=0.566) and 2.9 (95% CI, -0.4, 6.2, p=0.085) months for OS (Fig.4A), 0.9 (95% CI, -2.6, 4.5, p=0.597) and 4.0 (95% CI, 0.5, 7.8, p=0.027) months for PFS (Fig.4B), respectively.

CONCLUSIONS

Due to high population heterogeneity, small ESS and non-proportionality of hazards, further analysis on the long-term data is necessary for more precise estimates of differences in survival between anti-PD1 and targeted therapy for patients with BRAFV600-mutated advanced melanoma in the routine clinical practice.

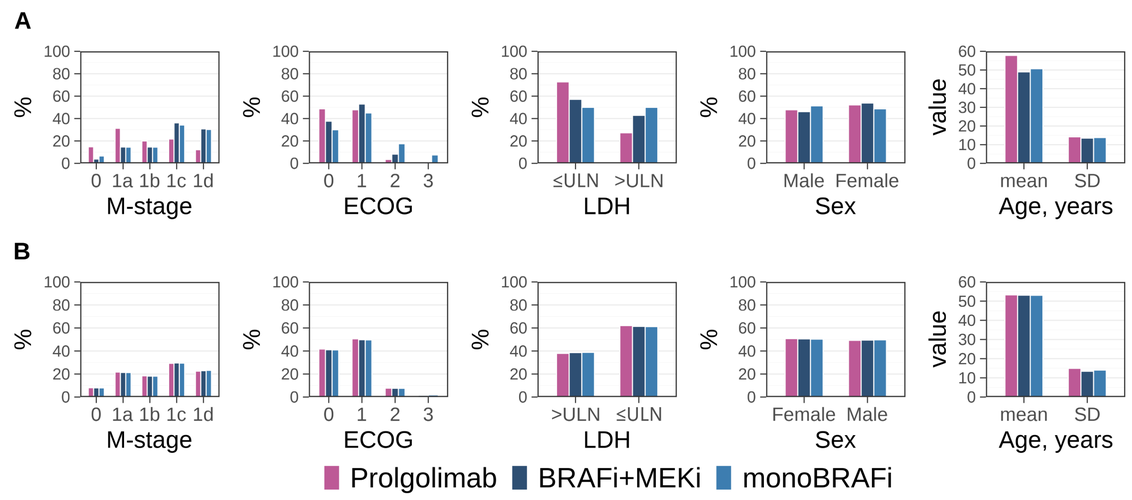

Figure 1. Descriptive statistics before (A) and after (B) MICE and IPTW-adjustment

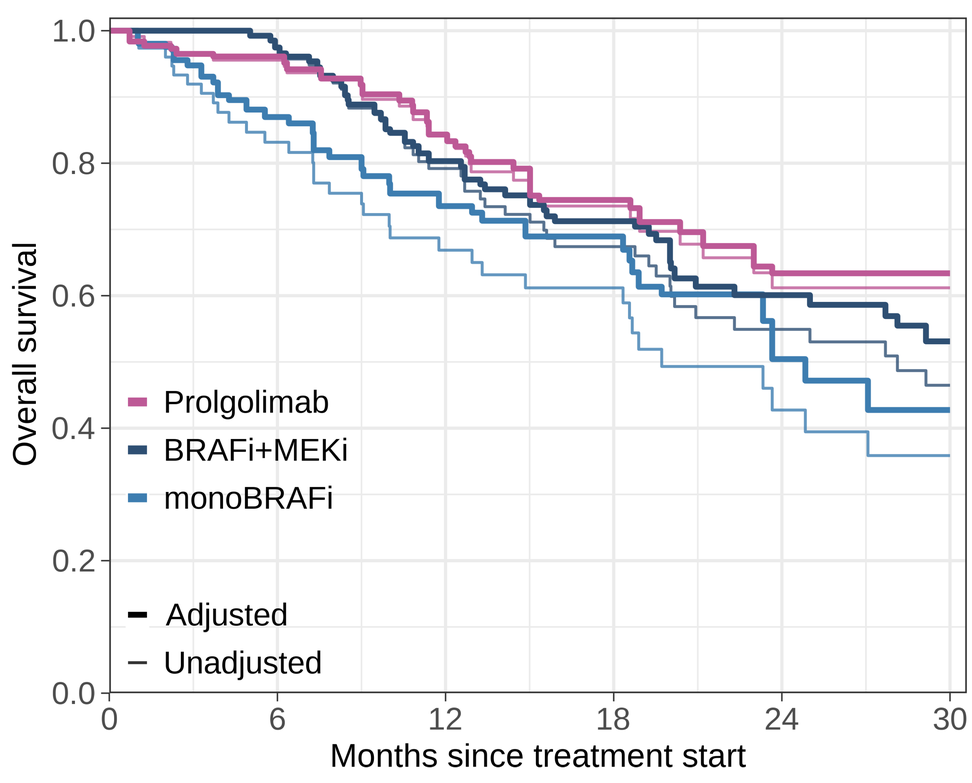

Figure 2. Overall survival before and after IPTW-adjustment

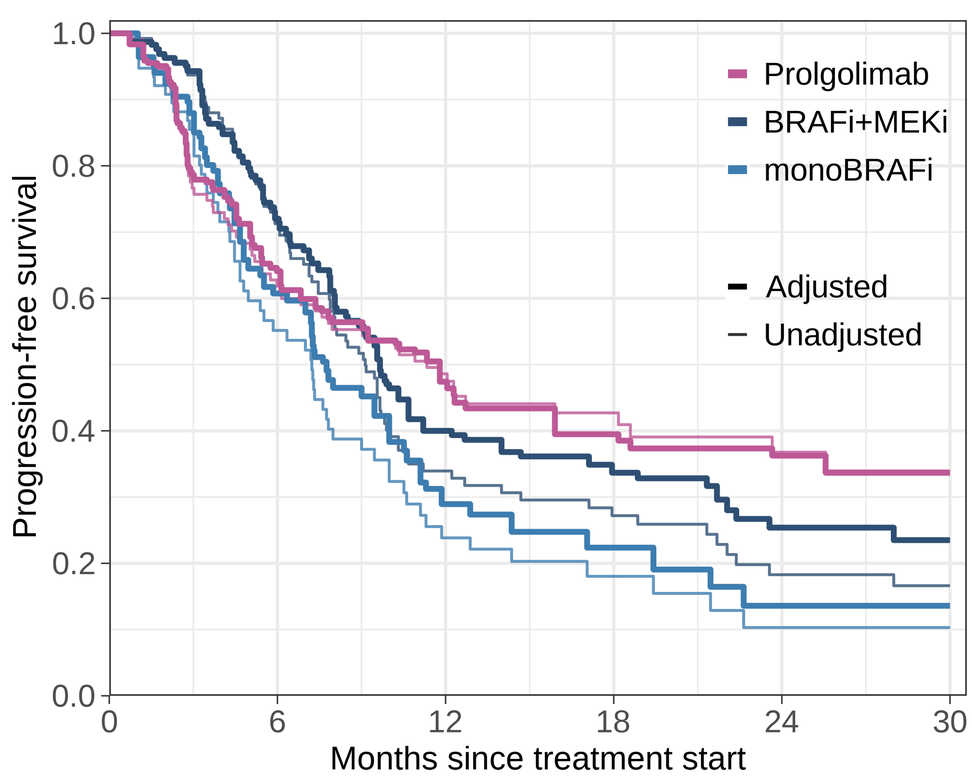

Figure 3. Progression-free survival before and after IPTW-adjustment

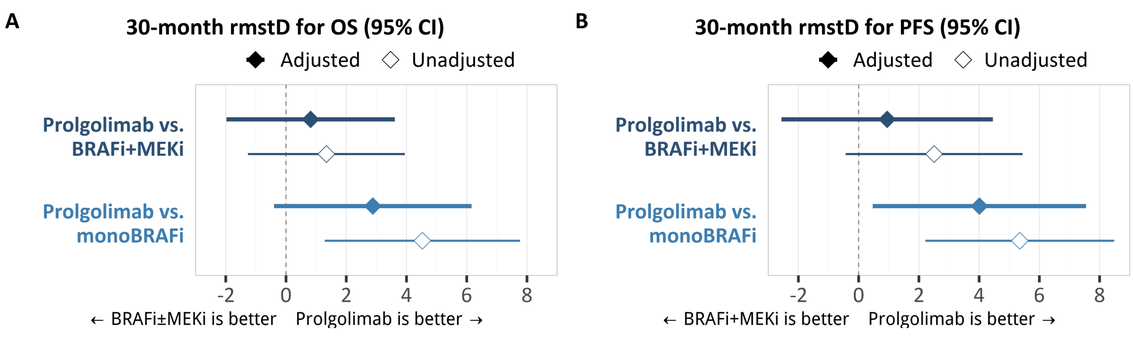

Figure 4. Difference in the restricted mean survival time over 30 months for OS (A) and PFS (B) on prolgolimab in comparison to targeted therapies