ADJUSTING TO NON-OVERLAPPING VARIABLES IN THE UNANCHORED MATCHING-ADJUSTED INDIRECT COMPARISONS OF SURVIVAL OUTCOMES: APPLICATION OF MONTE-CARLO SIMULATIONS

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INTRODUCTION

Prolgolimab (PROLGO) + nurulimab (NURU) is a fixed 3:1 dose combination of PD-1 and CTLA4 inhibitors, respectively, approved in 2023 in the Russian Federation for the treatment of patients (pts) with advanced melanoma. In phase II (OBERTON) and III (OCTAVA) randomized clinical trials (RCTs) it demonstrated superiority to PROLGO monotherapy with respect to progression-free survival (PFS). We conducted a systematic literature review to compare overall survival (OS) and PFS for PROLGO+NURU versus 3:1 and 1:3 combinations of nivolumab (NIVO) and ipilimumab (IPI) using unanchored matching-adjusted indirect comparisons (MAICs). Populations in OCTAVA and the selected RCTs of NIVO+IPI (CheckMate 067 (CM067) and CheckMate 511 (CM511)) were non-overlapping, because the latter included pts with mucosal melanoma (mM) and inactive brain metastases (mts), both considered unfavorable prognostic factors for survival. This lack of overlap compromises the feasibility of MAIC.

OBJECTIVE

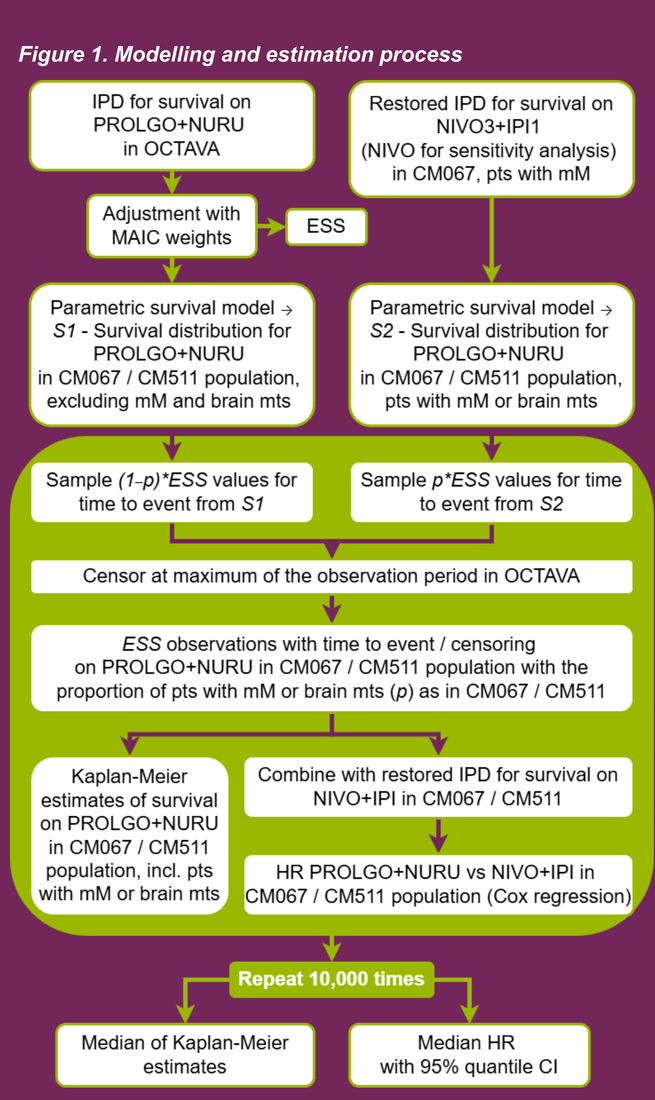
To compare OS and PFS between PROLGO+NURU and NIVO3+IPI1 or NIVO1+IPI3 in the first line therapy of pts with advanced melanoma in populations of CM067 and CM511 with adjustment to non-overlapping variables.

METHODS

The main steps of the modelling and estimation process are shown in Fig.1.

- **For OCTAVA, individual patient data (IPD) were available** with cut-off on April 11, 2025; **for the comparator arms, IPD on OS and PFS were restored** from the most recent Kaplan-Meier curves [1,2,3] using a Guyot's algorithm [4] and aggregated data on baseline characteristics [5,6] were employed.
- **Survival on PROLGO+NURU in pts without mM and brain mts (*S1*)** within CM067 and CM511 populations was assumed equivalent to the matching-adjusted survival of pts who received PROLGO+NURU in OCTAVA. MAIC weights were derived to balance the following characteristics (* in CM067 only, ** in CM511 only): mean(*) or median(**) age, median SLD (*), proportions of pts with EGOG 1, BRAF mutation, m1c stage, LDH >2×ULN, PD-L1 expression <5%, prior adjuvant therapy (**), >3 organs with distant mts (*). Effective sample size (ESS) was estimated.
- **Survival on PROLGO+NURU for pts with mM and brain mts (*S2*)** in both target populations was assumed similar to that observed in pts with mM who received NIVO3+IPI1 in CM067.
- **Optimal parametric models** for survival on PROLGO+NURU for both subgroups (*S1* and *S2*) were selected following NICE TSD 14, based on information criteria, visual assessment, and expert opinion regarding the plausible range of survival probabilities beyond OCTAVA follow-up.
- **To adjust MAIC results to the presence of pts with mM and brain mts in target populations, we performed 10,000 Monte-Carlo simulations (MCS) comparing OS and PFS on PROLGO+NURU versus NIVO3+IPI1 in CM067, NIVO3+IPI1 and NIVO1+IPI3 in CM511**. In each simulation, a sample of size equal to the ESS was drawn for PROLGO+NURU: *p*% of ESS from *S2* and *(1-p)%* of ESS from *S1*, where *p* denotes the proportion of pts with mM or brain mts in the corresponding target population (12.4% in CM067, 10.6% in CM511). These data were combined with the restored IPD for comparators, and Cox proportional hazards regressions were evaluated within each target population to estimate hazard ratios (HRs) for PROLGO+NURU versus the corresponding NIVO+IPI combination. In addition, survival in the entire PROLGO+NURU group was estimated using Kaplan-Meier (KM) method. Finally, medians and 95% quantile confidence intervals (CIs) for the KM and HR estimates across all simulations were calculated.

Figure 1. Modelling and estimation process



RESULTS

We used data for 135 pts who received PROLGO+NURU in OCTAVA. After weighting, ESS was 75 (56% of the original sample size) in CM067 and 80 (59%) in CM511 populations. *S1* models for OS were fitted to data censored at 18 months to yeild more conservative estimates beyond that time point. A Weibull distribution with Royston-Parmar splines was selected as the optimal model for OS (with 1 internal knot for both *S1* and *S2*) and PFS (with 3 and 1 internal knots for *S1* and *S2*, respectively). 10/75 (13.3%) and 9/80 (11.3%) pts were modelled as having mM or brain mts in CM067 and CM511 populations, respectively.

KM curves for PROLGO+NURU and HRs with 95% CIs comparing it to NIVO+IPI combinations in the CM067 and CM511 populations, obtained in MAIC and MSC before and after replacing *p*% of ESS with pts having mM or brain mts, are shown in Figs.2-3. Adjustment to non-overlapping groups had minimal impact on PFS but produced more conservative OS estimates.

Figure 2. *OS and PFS estimates for PROLGO+NURU and NIVO+IPI combinations in CM067 and CM511 populations*

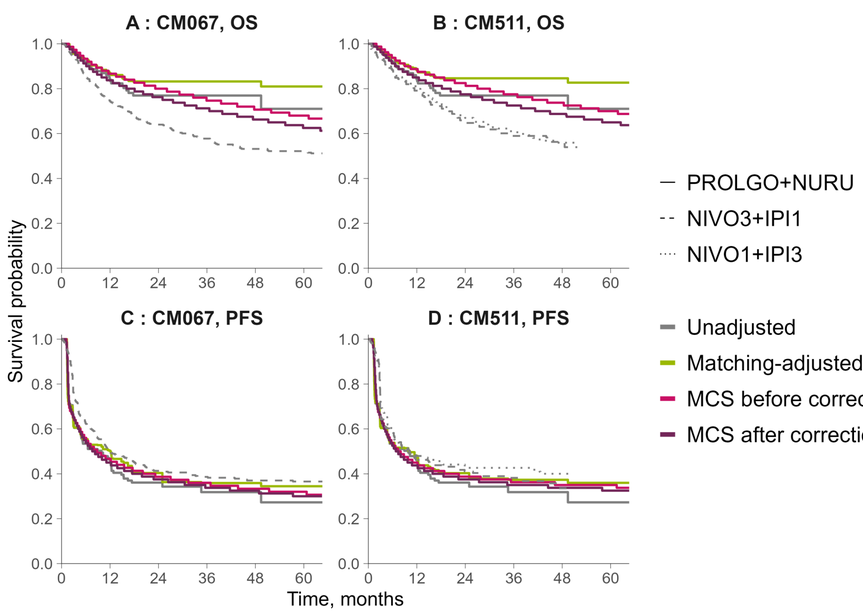
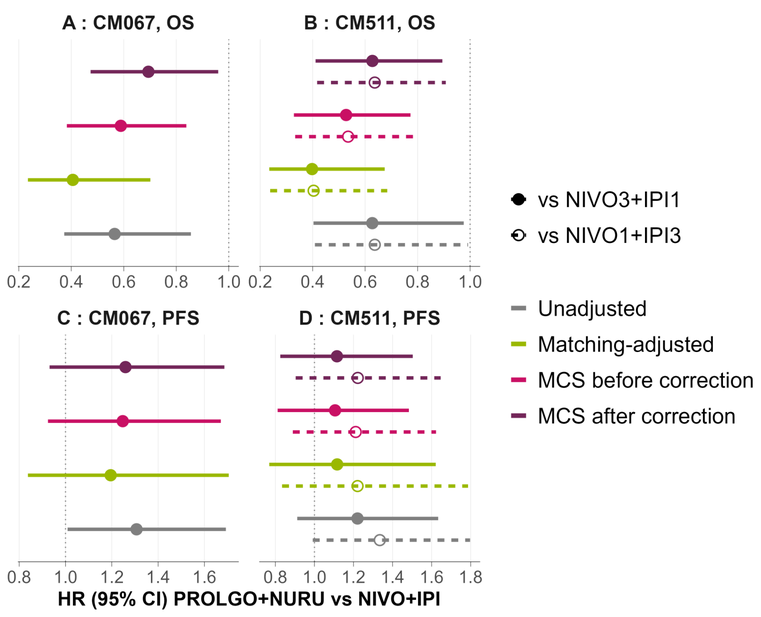


Figure 3. *HRs with 95% CIs for PROLGO+NURU vs NIVO+IPI combinations in CM067 and CM511 populations*



CONCLUSIONS

Monte-Carlo simulations are applicable for adjustment to non-overlapping groups in MAICs, although they require additional assumptions about survival distribution on the study treatment in unstudied populations, which are subject to further validation.

CONTACT INFORMATION

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