Cost per recurrence-free survivor and cost per recurrence-free life-month of adjuvant nivolumab vs pembrolizumab among patients with resected stage IIB/IIC melanoma

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Background

- Both nivolumab (NIVO) and pembrolizumab (PEMBRO) have been approved by the United States (US) Food and Drug Administration (FDA) as adjuvant treatments for adult and pediatric patients (ie, ≥ 12 years of age) with stage IIB/IIC melanoma following complete resection, based on results from the CheckMate 76K and KEYNOTE-716 trials, respectively
- The respective CheckMate 76K and KEYNOTE-716 trials have each demonstrated that adjuvant NIVO and adjuvant PEMBRO significantly improved recurrence-free survival (RFS), with observed benefit in distant metastasis-free survival compared with placebo (PBO)[1-3]
- With the absence of a head-to-head trial, there is limited evidence comparing the clinical and economic outcomes associated with these 2 treatments in patients with completely resected stage IIB/IIC melanoma
- Such evidence is important for optimizing treatments and informing decisions for payers and other healthcare stakeholders

Objective

- This study aimed to compare the cost per recurrence-free survivor (CPRS) and the cost per recurrence-free life-month (CPRLM) of adjuvant NIVO vs adjuvant PEMBRO in patients with completely resected stage IIB/IIC melanoma from a US payer perspective

Methods

Data source

- Patient-level data from the CheckMate 76K trial (data cutoff: April 2023; median follow-up 23.5 months for NIVO and 23.0 months for PBO) and published aggregate data from the KEYNOTE-716 trial (data cutoff: January 2022; median follow-up 27.4 months for PEMBRO and 27.3 months for PBO)[3] were used to ensure similar median follow-up between these 2 trials
- Rates for all-cause grade 3/4 adverse events (AEs), of which the rates of corresponding any-grade AEs were ≥ 10%, were obtained from the CheckMate 76K trial and the KEYNOTE-716 trial
- The unit drug acquisition costs and administration costs for the use of NIVO, PEMBRO, and PBO were obtained from the wholesale acquisition cost in Merative Micromedex RED BOOK (2023)[4] and the Centers for Medicare & Medicaid Services Physician Fee Schedule (2023),[5] respectively
- The unit AE costs were obtained from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project database (2020)[6]

Estimation of cost per outcome

- RFS rates at 12 and 24 months were derived from a matching-adjusted indirect comparison (MAIC) of adjuvant NIVO vs adjuvant PEMBRO, using PBO as the anchor
- Recurrence-free life-month (RFLM) at 12 and 24 months was calculated as the area under a weighted Kaplan-Meier curve for RFS between 12 and 24 months from the MAIC of adjuvant NIVO vs adjuvant PEMBRO using PBO as an anchor
- The MAIC was matched on age, sex, region, tumor (T) stage, and Eastern Cooperative Oncology Group (ECOG) performance status
- Total costs (presented in 2023 US dollars [USD]) included drug acquisition, drug administration, and AE costs; these were estimated over 12 and 24 months, based on the number of doses and mean treatment durations reported for each trial (**Table 1**)
  - Costs associated with all-cause grade 3/4 AEs, of which the rates of corresponding any-grade AEs were ≥ 10% over the entire trial period, were included in this analysis

Table 1. Number of doses and mean treatment durations as per clinical trial design[1-3]

	Dosing schedule	Mean number of doses at 12 months[3]	Mean treatment duration at 12 months, months	Mean treatment duration at 24 months, months
NIVO	480 mg Q4W	10.5	9.66	9.66
PBO (CheckMate 76K)	Q4W	11.8	10.86	10.86
PEMBRO	200 mg Q3W	14	9.66	9.66
PBO (KEYNOTE-716)	Q3W	15	10.35	10.35

Q3W, every 3 weeks; Q4W, every 4 weeks.

- The monthly incremental CPRS and the incremental CPRLM for adjuvant NIVO or adjuvant PEMBRO relative to PBO were calculated at 12 and 24 months using the following formulas:
  - Monthly incremental CPRS of treatment vs PBO = $\frac{\text{Monthly cost of treatment} - \text{Monthly cost of PBO}}{\text{RFS rate of treatment} - \text{RFS rate of PBO}}$
  - Incremental CPRLM of treatment vs PBO = $\frac{\text{Total cost of treatment} - \text{Total cost of PBO}}{\text{RFLM of treatment} - \text{RFLM of PBO}}$
- When the incremental cost per outcome is negative, the treatment is more expensive with inferior efficacy if the total cost difference is > 0 and the treatment is less expensive with superior efficacy if the total cost difference is < 0
- When the incremental cost per outcome is positive, the treatment is expensive yet has superior efficacy when the total cost difference > 0 and PBO is expensive yet has superior efficacy when the total cost difference < 0
- Cost per outcome analyses, such as incremental CPRS and CPRLM, have been widely used in oncology research to evaluate the incremental cost required to achieve an incremental outcome between 2 treatments[7-9]
- In the primary analysis of each trial, RFS was defined as follows:
  - CheckMate 76K: the time from randomization to the date of first recurrence (local, regional, or distant metastasis), new primary melanoma (including melanoma *in situ*), or death (whatever the cause), whichever occurred first
  - KEYNOTE-716: the time from randomization to the date of recurrence of melanoma at any site (local, in-transit or regional lymph nodes, or distant recurrence), or death due to any cause, whichever occurred first
- A sensitivity analysis was conducted, excluding new primary melanomas (including melanoma *in situ*) as RFS events from both trials

Results

MAIC

- After matching, patient characteristics were balanced between CheckMate 76K and KEYNOTE-716 and the following was observed:
  - NIVO had numerically better RFS when compared with PEMBRO
  - Both PBO arms showed statistically significant differences, indicating potential unobserved and nonadjustable variations between the 2 trials

Total costs, RFS rates, and RFLM for adjuvant NIVO, adjuvant PEMBRO, and PBO

- Total costs were $152,055 for adjuvant NIVO, $153,953 for adjuvant PEMBRO, $178 for PBO in CheckMate 76K, and $119 for PBO in KEYNOTE-716 (**Table 2**)
- The absolute difference in landmark RFS rates at 12 and 24 months were 7.48% and 15.59% for adjuvant NIVO vs PBO and 7.37% and 8.43% for adjuvant PEMBRO vs PBO (**Table 2**)
- The RFLM differences at 12 and 24 months were 0.62 and 2.08 for adjuvant NIVO vs PBO and 0.26 and 1.27 for adjuvant PEMBRO vs PBO (**Table 2**)

Table 2. Total costs, RFS rates, and RFLM for adjuvant NIVO, PEMBRO, and PBO[a]

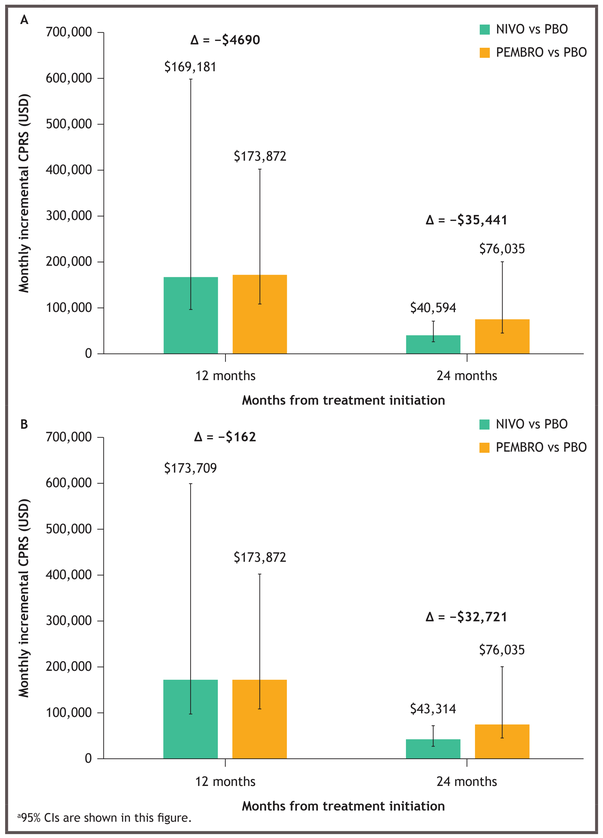
	CheckMate 76K		KEYNOTE-716	
	NIVO	PBO	PEMBRO	PBO
Total cost	$152,055	$178	$153,953	$119
RFS rates, % (95% CI)				
Main analysis				
12 months	89.34 (86.67-92.01)	81.86 (77.19-86.53)	90.56 (87.96-93.15)	83.18 (79.87-86.50)
24 months	77.04 (73.40-80.68)	61.45 (55.56-67.35)	81.02 (77.54-84.50)	72.59 (68.64-76.54)
Sensitivity analysis				
12 months	90.62 (88.10-93.14)	83.34 (78.82-87.85)	90.56 (87.96-93.15)	83.18 (79.87-86.50)
24 months	79.93 (76.47-83.40)	65.32 (59.56-71.09)	81.02 (77.54-84.50)	72.59 (68.64-76.54)
RFLM (95% CI)				
Main analysis				
12 months	11.44 (11.26-11.61)	10.81 (10.48-11.15)	11.48 (11.30-11.65)	11.22 (11.01-11.42)
24 months	21.52 (21.01-22.03)	19.44 (18.51-20.36)	21.85 (21.34-22.36)	20.58 (19.99-21.17)
Sensitivity analysis				
12 months	11.56 (11.41-11.71)	10.95 (10.64-11.27)	11.48 (11.30-11.65)	11.22 (11.01-11.42)
24 months	21.88 (21.42-22.35)	19.91 (19.01-20.81)	21.85 (21.34-22.36)	20.58 (19.99-21.17)

[a]RFS rates and RFLM were estimated from the MAIC of adjuvant NIVO vs adjuvant PEMBRO using PBO as the anchor. The MAIC was matched on age, sex, region, T stage, and ECOG performance status.

Monthly incremental CPRS and incremental CPRLM for adjuvant NIVO and adjuvant PEMBRO relative to PBO

- The monthly incremental CPRS relative to PBO for adjuvant NIVO was consistently lower than that for adjuvant PEMBRO (12 months: $169,181 vs $173,872; 24 months: $40,594 vs $76,035; **Figure 1A**)
  - The notable difference at 24 months (Δ = −$35,441) was primarily due to the large variation in the 24-month difference in landmark RFS rates between the experimental arm and the PBO arm within each trial (15.59% for adjuvant NIVO vs 8.43% for adjuvant PEMBRO)
- Similarly, adjuvant NIVO had consistently lower incremental CPRLM (relative to PBO) compared with adjuvant PEMBRO, with a difference in incremental CPRLM of −$346,708 ($244,964 vs $591,671) over 12 months, and −$48,112 ($73,018 vs $121,130) over 24 months **Figure 2A**)
  - The large difference in the incremental CPRLM at 12 months was mainly driven by the fact that the difference in RFLM between adjuvant NIVO and PBO was 2.38 times greater than the difference between adjuvant PEMBRO and PBO
- Similar trends were observed in the sensitivity analyses (**Table 2**; **Figures 1B** and **2B**)

Figure 1. Monthly incremental CPRS for adjuvant NIVO and adjuvant PEMBRO relative to PBO for the main analysis (A) and sensitivity analysis (B)[a]

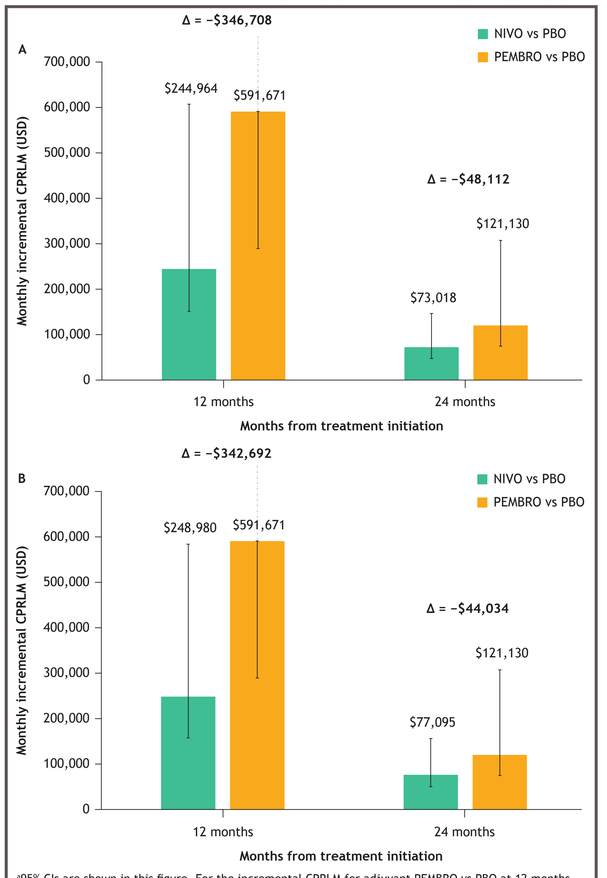


[a]95% CIs are shown in this figure.

Limitations

- Individual patient-level data from KEYNOTE-716 was not used for the MAIC
- The definitions of RFS were slightly different between the 2 trials; however, the sensitivity analysis has demonstrated that these differences had minimal to no impact on the comparative results of this study
- The treatment costs and AE costs were estimated based on mean treatment duration and average AE profile in the clinical trial population, which may not reflect costs incurred in clinical practice and may result in underestimation or overestimation of the actual costs
- The study focused on treatment costs (ie, drug acquisition costs and drug administration costs) and AE costs, which are the major cost drivers associated with the 2 treatment arms; other costs, such as medical costs, were not considered due to lack of data
- Differing dosing schedules led to a higher number of mean doses for PEMBRO vs NIVO

Figure 2. Incremental CPRLM for adjuvant NIVO and adjuvant PEMBRO relative to PBO for the main analysis (A) and sensitivity analysis (B)[a]



[a]95% CIs are shown in this figure. For the incremental CPRLM for adjuvant PEMBRO vs PBO at 12 months, the upper bound of the 95% CI is infinite, and thus is displayed as a dotted line in the figure.

Conclusions

- Adjuvant NIVO had lower incremental CPRS and CPRLM (relative to PBO) compared with adjuvant PEMBRO at 12 months and 24 months after treatment initiation

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Acknowledgments

- The patients and families who have made this study possible
- This study was funded by Bristol Myers Squibb
- Analytical support and editorial assistance were provided by Analysis Group, Inc., and funded by Bristol Myers Squibb
- All authors contributed to and approved the presentation; medical writing and editorial assistance were provided by Samantha L. Dwyer, PhD, and Michele Salernitano of Ashfield MedComms, an Inizio company, funded by Bristol Myers Squibb

Presented at ISPOR 2024; May 5-8, 2024; Atlanta, GA, USA

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