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Cost per Survivor and Cost per Life-month of Nivolumab plus Ipilimumab vs. Pembrolizumab plus Axitinib for Previously Untreated Advanced Renal Cell Carcinoma

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Background

- Nivolumab in combination with ipilimumab (NIVO+IPI), which demonstrated a superior survival benefit compared with sunitinib (SUN) in the CheckMate 214 trial, was the first FDA approved first-line immuno-oncology (IO)-based combination therapy for previously untreated patients with intermediate- or poor-risk advanced renal cell carcinoma (aRCC).[1]
- Pembrolizumab in combination with axitinib (PEMBRO+AXI), which showed a survival benefit vs. SUN in the KEYNOTE-426 trial for previously untreated aRCC, was approved by the FDA in the subsequent year.[2]
- With the absence of a head-to-head trial, the comparative efficacy and cost between NIVO+IPI and PEMBRO+AXI has not been assessed.
- Evidence of cost efficiency of these IO-based combination therapies may help inform treatment decision making.

Objective

- This study aimed to compare the cost per survivor (CPS) and cost per life-month (CPLM) of NIVO+IPI vs. PEMBRO+AXI among patients with previously untreated aRCC, irrespective of prognostic risk score.

Methods

Data sources

- Individual patient data (IPD) of the intention-to-treat population from the CheckMate 214 trial (data cutoff February 2020; minimum follow-up 48 months) and published aggregate results based on the KEYNOTE-426 trial[3] (data cutoff January 2021; minimum follow-up 35.6 months) were used.

Comparative efficacy

- Adjusted overall survival (OS) rates and mean life months at 12, 24, 36, and 48 months were obtained from a matching-adjusted indirect comparison (MAIC) of NIVO+IPI vs. PEMBRO+AXI using SUN as anchor.
- The MAIC adjusted for age, sex, nephrectomy status, International Metastatic Renal Cell Carcinoma Database Consortium risk group, and metastases in adrenal gland, lung, and bone.
- The OS rates for NIVO+IPI and SUN (CheckMate 214) were obtained from the weighted OS curves in the MAIC based on IPD, and the OS rates for PEMBRO+AXI and SUN (KEYNOTE-426) were from the reconstructed OS curves from the trial publication.
- The mean life month was calculated as the restricted mean survival time (i.e., the area under the corresponding OS curve) to each time point.

Treatment costs

- Treatment costs included drug acquisition costs, drug administration costs, and management costs of grade 3/4 adverse events (AE). Total costs were estimated over 12 months, 24 months, 36 months, and 48 months.
- The drug acquisition and administration costs were calculated based on the mean treatment duration (approximated using progression-free survival [PFS] for each treatment for each time point),[4] unit drug price (Wholesale Acquisition Cost), and unit administration costs (from Physician Fee Schedule).
- Costs of all-cause grade 3/4 AEs with any-grade incidence rates ≥ 20% were calculated using AE rates obtained from the CheckMate 214 and KEYNOTE-426 trials. Unit management costs of the corresponding AEs were derived using the data from the Healthcare Cost and Utilization Project (HCUP).
- All costs were inflated to 2020 USD using the Consumer Price Index Medical Care Component.

Incremental cost per survival outcome

- The monthly incremental CPS and the incremental CPLM for NIVO+IPI or PEMBRO+AXI relative to SUN were calculated at 12, 24, 36, and 48 months as follows
  - $\text{Incremental CPS} = \frac{[\text{Total cost for treatment of interest}] - [\text{Total cost for SUN}]}{[\text{OS rate for treatment of interest}] - [\text{OS rate for SUN}]}$
  - $\text{Incremental CPLM} = \frac{[\text{Total cost for treatment of interest}] - [\text{Total cost for SUN}]}{[\text{Life months for treatment of interest}] - [\text{Life months for SUN}]}$
- The incremental CPS and incremental CPLM represent the incremental costs associated with obtaining one additional survivor and life month, respectively, when treating with the treatment of interest instead of SUN.

Results

- In the MAIC, both NIVO+IPI and PEMBRO+AXI had greater OS rates and mean life months compared with SUN throughout a 48-month follow-up. (**Table 1**)

Table 1. Total costs, OS rate, and mean life months from MAIC for NIVO+IPI, PEMBRO+AXI, and SUN*

	CheckMate 214		KEYNOTE-426	
	NIVO+IPI	SUN	PEMBRO+AXI	SUN
Total costs (2020 USD)				
12 months	$173,386	$123,579	$290,738	$119,407
24 months	$246,861	$194,425	$466,594	$178,014
36 months	$303,703	$240,930	$531,988	$212,010
48 months	$347,382	$269,622	$572,318	$228,735
OS rate, % (95% CI)				
12 months	84.11 (80.88, 87.34)	79.50 (75.88, 83.12)	89.54 (86.65, 92.43)	79.00 (75.15, 82.85)
24 months	71.33 (67.34, 75.32)	63.08 (58.75, 67.41)	74.16 (70.03, 78.29)	65.39 (60.89, 69.89)
36 months	59.55 (55.22, 63.88)	52.85 (48.37, 57.33)	62.66 (58.10, 67.22)	53.85 (49.13, 58.57)
48 months	53.34 (48.94, 57.74)	44.76 (40.30, 49.22)	46.28 (41.58, 50.98)	41.03 (36.38, 45.68)
Life months (95% CI)				
12 months	11.08 (10.89, 11.27)	10.87 (10.64, 11.09)	11.39 (11.22, 11.56)	10.72 (10.47, 10.98)
24 months	20.40 (19.87, 20.94)	19.34 (18.69, 19.99)	21.11 (20.60, 21.62)	19.35 (18.68, 20.02)
36 months	28.21 (27.23, 29.20)	26.27 (25.11, 27.43)	29.19 (28.27, 30.10)	26.41 (25.30, 27.52)
48 months	34.99 (33.50, 36.48)	32.14 (30.48, 33.80)	35.92 (34.58, 37.27)	32.14 (30.61, 33.66)

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; NIVO+IPI: nivolumab plus ipilimumab; OS: overall survival; PEMBRO+AXI: pembrolizumab plus axitinib; SUN: sunitinib; USD: United States dollars.

* The OS rates and mean life months were from a matching-adjusted indirect comparison analysis controlling for different patient characteristics. Results for PEMBRO+AXI and SUN (KEYNOTE-426) were based on derived OS curves from publication, and the 48-month OS data were based on a small sample. No OS rates at 48 months were reported in the KEYNOTE-426 publication

- The monthly incremental CPS of NIVO+IPI relative to SUN, which is interpreted as the incremental cost to gain one additional survivor compared with SUN, decreased over time from $90,035 for 12 months to $18,881 for 48 months, while there was no clear pattern regarding the monthly incremental CPS of PEMBRO+AXI relative to SUN, with $135,461 for 12 months and $136,342 for 48 months. (**Figure 1a**)
- The monthly incremental CPS relative to SUN for NIVO+IPI was consistently lower than that for PEMBRO+AXI with the largest difference seen at 48 months (difference in incremental CPS: $117,461).
- A similar trend was seen for incremental CPLM of NIVO+IPI relative to SUN, which represents the incremental costs associated with obtaining one additional life month compared with SUN, with the highest value seen at month 12 ($237,179) and the value decreased to $27,284 at month 48 (**Figure 1b**).
- The incremental CPLM of NIVO+IPI relative to SUN was consistently lower compared with that of PEMBRO+AXI across all time points assessed, with a difference of $18,539 at month 12 and larger differences at subsequent time points ($114,497, $82,743, and $63,611 at months 24, 36, and 48 respectively).

Figure 1a. Monthly incremental cost per survivor for NIVO+IPI and PEMBRO+AXI relative to SUN[a,b]

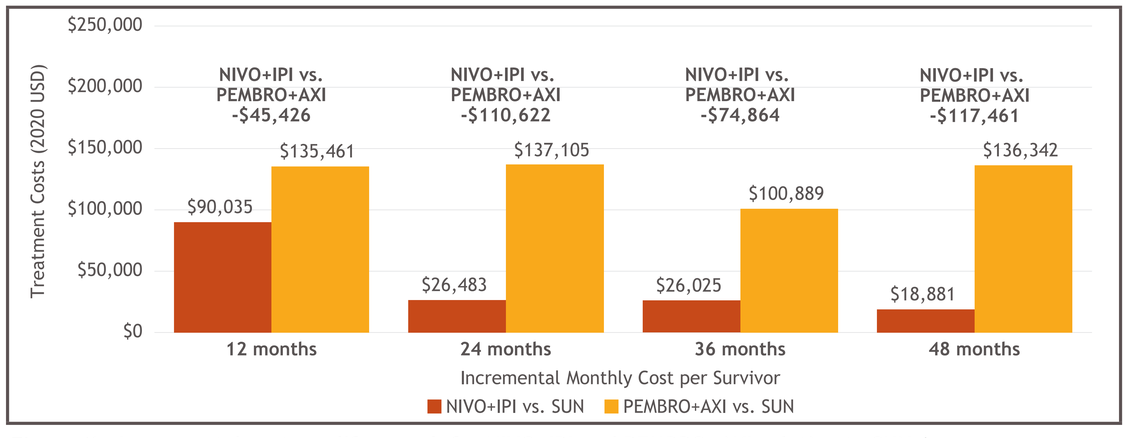
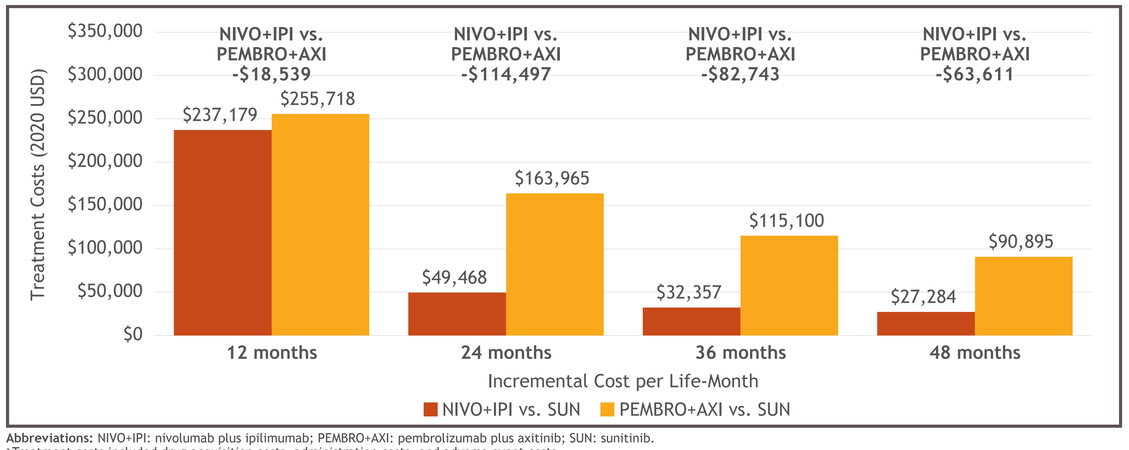


Figure 1b. Incremental cost per life-month for NIVO+IPI and PEMBRO+AXI relative to SUN[a,b]



Abbreviations: NIVO+IPI: nivolumab plus ipilimumab; PEMBRO+AXI: pembrolizumab plus axitinib; SUN: sunitinib.
[a] Treatment costs included drug acquisition costs, administration costs, and adverse event costs
[b] Results for PEMBRO+AXI and SUN (KEYNOTE-426) at 48 months were based on a small sample due to limited follow up for the datacut used

Limitations

- Limitations for the MAIC analyses (e.g., unobserved or unmeasured cross-trial differences) might have persisted and affected the relative efficacy inputs for this study.
- Drug costs and AE costs were calculated based on estimated treatment duration and average AE rates in the clinical trial population, which may not accurately reflect costs incurred in clinical practice.
  - The mean PFS time was used to approximate mean treatment duration due to the lack of the relevant data for the KEYNOTE-426 trial.[4]
  - The costs of grade 3/4 AEs only included hospitalization costs assuming each patient who experienced a grade 3/4 AE had a corresponding hospitalization.
- Other costs, such as subsequent treatment costs, were not considered due to lack of available data, which may have resulted in an underestimation of the total cost.
- The 48-month OS rates for the two arms of the KEYNOTE-426 trial were obtained from the reconstructed OS curves from publication. Very few patients (less than 20 patients for each arm) were at risk at month 48 in both arms.

Conclusions

- In the absence of head-to-head trials, this study compared the CPS and CPLM of NIVO+IPI vs. PEMBRO+AXI in the first-line treatment setting for aRCC.
- NIVO+IPI was associated with consistently lower incremental CPS and CPLM (relative to SUN) compared with PEMBRO+AXI at each time point throughout the treatment course.
- These results indicate greater cost efficiency for NIVO+IPI vs. PEMBRO+AXI as first-line treatment for patients with aRCC, throughout the course of treatment.

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Disclosure Declaration:

- Stephen Huo and Viviana Del Tejo are employees of Bristol Myers Squibb. Keith A. Betts, Andi Chin, Ella X. Du, and Aozhou Wu are employees of Analysis Group Inc., which has received consultancy fees from Bristol Myers Squibb.

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