

# Costs and Values of Nivolumab in Advanced/ Metastatic Cancer

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## Abstract

**Background:** Nivolumab (Nivo) is a programmed death immune checkpoint antibody widely used to treat cancer. Accepted average incremental cost effectiveness ratio in the United States is 100,000.

**Objectives:** Compare values (V) of Nivo in advanced/metastatic melanoma, squamous (sq-) and non-sq-non-small-cell lung cancer (NSCLC), renal cell and sq-cell cancer of head and neck (SCCHN).

**Methods:** Median overall survival gain over control in days (OS), hazard ratios (HR) and prices posted by the parent company were quoted. Values were computed at 4-week as  $C \times HR$  (4wV) and one-year as C/life-year gain (LYG). Relative values (RV) were calculated as  $\$100,000/C/LYG$ .

**Results:** Estimated Nivo 4wC was \$10,021. In 1st-line melanoma, OS was not reached, HR 0.42 and 4wV 4,209. In 2nd-line renal cell, OS was 162, 4wV 7,315, C/LYG 289,496 and RV 0.35. In sq-NSCLC, OS 96, 4wV was 5,912, C/LYG 488,524 and RV 0.20. In non-sq-NSCLC, OS was 84, 4wV 7,315, C/LYG 558,326 improving in > 10% PD-L1 to 264, 5,512 and 177,650 respectively. In SCCHN, OS was 72, 4wV 7,015 and C/LYG 651,430 improving in PD-L1 >1.0% to 123, 5,512 and 381, 287. PD-L1 enrichment significantly increased RV from 0.18 to 0.56 in non-sq- NSCLC and from 0.15 to 0.26 in SCCHN.

**Conclusions:** The results suggested that HR could serve as adjunct or substitute tools to survival in V-based model. Nivo in 1st-line melanoma, 2nd renal and sq-NSCLC were fair and worth the C. Enrichment of PD-L1 significantly improved V of Nivo in non-sq-NSCLC and SCCHN.

**Abbreviations:** Adverse events (AEs); Average cost-effectiveness ratios (ACER); Confidence Interval (CI); Cost/Life-year gain (C/LYG); 4-week costs (4wC); 4-week values (4wV); Day (d); Hazard Ratio (HR); Immune check point antibody (ICPA); Incremental cost effectiveness ratio (ICER); Median overall survival gain over control in days (OS); Metastatic (m); Milligram (mg); Non-small-cell-lung cancer (NSCLC); Non-squamous (non-sq-); Quality of life (QoL); Quality-adjusted life-year (QALY); Relative values (RV); Squamous (sq-); Squamous cell carcinoma of the head and neck (SCCHN); Week (w);

## Introduction

Nivolumab (Nivo) is a fully human IgG4 immune checkpoint antibody (ICPA) which disrupts the protein death 1 (PD-1) signaling and restores the antitumor immunity [1]. It is widely used throughout the United States (US) to treat various types of cancer.

The American (ASCO) and European (ESMO) Societies of Clinical Oncology emphasized the importance of values (V) in the drug economy [2,3]. In the US, the incremental cost-effectiveness ratio (ICER) ranging from \$ 50,000 to \$ 150,000 per quality adjusted life-year (QALY) is considered acceptable. The National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) rejected Nivo in 2-nd line non-small-cell lung cancer (NSCLC) while the European Medicines Agency (EMA) approved the drug for the same indication. We previously proposed simplified methodology to weigh drug costs (C) and V in metastatic (m) castrate-resistant prostate cancer (CRPC) using \$ 100,000 as

a point of reference [4]. Values of Nivo have not been compared between the various approved indications. Our objectives were to compare the V of Nivo in 1st-line melanoma, and 2nd-line renal cell carcinoma, Squamous (sq)- NSCLC, and non-sq-NSCLC and Squamous cell cancer of the head and neck (SCCHN).

## Methods

The median overall survival gain of Nivo over control in days (OS), hazard ratios (HR), doses, frequency and protocols were extracted from previously published clinical trials. Prescribing information and prices posted by the parent company were utilized. Costs of Nivo at 2.0 mg/Kg q 2 weeks were assessed. Values were computed at 4-week as  $C \times HR$  (4wV) and one-year as C/life-year gain (LYG). Relative values (RV) were calculated as  $\$100,000/C/LYG$ .

**Results**

In early 2016, the 4wC of Nivo2.0 mg/Kg q 2 w were estimated at \$ 10,021 at a yearly C of \$ 130,273. The recommended total dose of 2.0 mg/Kg has since been changed to a total of 240 mg q 2 weeks and the C has increased by about 7.0%. In 1st-line melanoma, OS was not reached at the closure of the study. The HR was 0.42 and the 4wV 4,209. The OS gain; HR, V and RV of Nivo in 1st- and 2nd-lines [1, 5-8] were shown in Table. The RV in 2nd-line renal cancer were 0.35 and in sq-NSCLC 0.20. The PD-L1 enrichment significantly increased the RV from 0.18 to 0.56 in non-sq- NSCLC and 0.15 to 0.26 in SCCHN.

**Discussion**

The present investigation was prompted by the rising C, diminishing V and decreasing affordability of anticancer drugs [9,10]. Our objective was to compare V of Nivo in various cancer using the same doses, frequency, protocols and C. Nivo, a prototype of PD-1 immune checkpoint antibody(ICPA), was chosen since it prolonged the OS in 1st-line melanoma [5], 2nd-line sq-

NSCLC, CheckMate 017 [6], non-sq- NSCLC, CheckMate 057 [1] and renal cell carcinoma, CheckMate 025 [7] and SCCHN [8]. The standard ICER formula based on differences in C per differences in outcome could not be applied in our study since C of Nivo was the same in all the cited indications. Nivo4wCwas within the current estimated average range of the newly approved patent drugs of \$ 10,000 - \$ 12,000 in the US. The available data on comparative V issues were limited. Nonetheless, the results clearly suggested that Nivo V were fair and worth the dollars spent in 1st-line melanoma and 2nd-line renal and to a lesser extent in sq-NSCLC. Values in 2nd-line non-sq-NSCLC and SCCHN were marginal but significantly improved byPD-L1 enrichment.

**HR vs. OS**

At the closure of the Nivo study in 1st-line melanoma, OS was not reached and HR was therefore used [5]. Parallel use of both OS and HR was adopted whenever possible throughout our investigation. The HR-based strategy could offer a snapshot approach to measure V in the absence of mature OS data.

**Table:** Nivo Values in 1<sup>st</sup> and 2<sup>nd</sup> lines cancer

Nivo in 1 <sup>st</sup> - and 2 <sup>nd</sup> -line	OS in days (d) & HR	4wV (4wC x HR)	C/LYG	RV (\$100,000/LYG)
1 <sup>st</sup> - line: Nivo vs. dacarbazine, Melanoma	OS not reached HR 0.42	4,209	-----	-----
2 <sup>nd</sup> - line: Nivo vs. everolimus, Renal cell	162 HR 0.73 P = 0.002	7,315	289,496	0.35
Nivo vs. docetaxel, sq-NSCLC	96 HR 0.59 P = 0.00025	5,912	488,524	0.20
Nivo vs. docetaxel, non-sq-NSCLC-CheckMate 057	84 HR 0.73 P = 0.0016	7,315	558,326	0.18
----- Subset analysis in >10% PD-L1	264 HR 0.27	5,512	177,650	0.56
Nivo vs. investigator's choice, SCCHN	72 HR 0.70 P = 0.0101	7,015	651,430	0.15
----- Subset analysis in >1.0 PD-L1	123 HR 0.55	5,512	381,287	0.26

**Merits**

Overall survival generally considered the ultimate measure of clinical benefit was used throughout the present investigation; The C/LYG was measured relative to 100,000, an accepted average cost-effectiveness ratio (ACER) in the US. The safety of patients treated by Nivo have been well documented [1, 5 -7]. The reported Nivo gr ¾ adverse events (AEs) were in general less than 5.0% in all the cited clinical studies. Costs and values were

calculated in a few minutes once the data was collected. The RV approach could facilitate clear transmission of economic issues between physicians and patients [11]. Patients as consumers would like to know in advance the C incurred to better manage their budgets. Using this simplified model, upfront costs and values could be promptly disclosed to patients.

## Limitations

A correction factor would be needed to adjust for the C of AEs treatment of drugs as Doc and dacarbazine. Cost treatment of AEs [12] could be costly and “toxic” [13]. In a recent phase III trial in previously treated NSCLC, all-grade treatment-related AEs were less frequent with Nivo than with docetaxel [14].

## Duration of Treatment

The costs and values of Nivo were calculated for one year. In the Checkmate-057 study of non-sq- NSCLC [1], the median duration of response was >17 months. Currently the optimal duration of therapy has not been defined. Continued treatment until disease progression or intolerance has been recommended.

## Conclusion

A simplified survival and HR- based model was presented to evaluate V of Nivo in various cancers. Values were defined as C x HR and as C per the incremental increase in OS gain over control in days. The 4wV served as an early screening measure of V. In view of Nivo well-documented safety and favorable impact on quality of life, the results were expressed relative to \$ 100,000, the average acceptable C/QALY in the US. Values of Nivo in 1st-line melanoma, 2nd-line renal cell and to a lesser extent sq-NSCLC were fair and worth the dollars spent. The marginal V in non-sq-NSCLC and SCCHN significantly improved by PD-L1 enrichment.

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