



## Survival and Grades vs. Costs and Values of Nivolumab in Cancer; The Impact of PD-L1 Positivity

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### Background

Nivolumab (Nivo) is a programmed death receptor-1 immune check point antibody widely used in cancer.

**Objectives:** Propose a strategy to grade survival and weigh costs vs. values of Nivolumab in 2<sup>nd</sup>-line cancer.

**Methodology:** Median Overall Survival Gains Over Control in Days (OS), Hazard Ratios (HR) and prices posted by the parent company were quoted. Costs were assessed at 4-week and one-year. The 4-week values were calculated as (4-week cost × HR). The Cost/Life-Year Gain (C/LYG) was calculated as year-costs/OS gain over control in days × 360. Relative Values (RV) of the ICPI were computed as \$100,000/C/LYG as OS gain. Relative Values (RV) were computed as \$100,000/LYG. A sliding scale was designed to grade OS from A to D.

**Results:** Nivo 4-week cost was estimated at \$10,021-\$11,914. In 1<sup>st</sup>-line melanoma, OS was not reached and 4-week value \$4,209. In 2<sup>nd</sup>-line renal cell, OS and Grade (OS/Gr) were 162/A, 4-week value \$7,315, C/LYG \$289,496 and RV 0.35. In 2<sup>nd</sup>-non-squamous Non-Small-Cell Lung Cancer (NSCLC), the OS/gr were 84/C, 4w-week value \$7,315, C/LYG \$558,326 and RV 0.18. The results improved in > 10% PD-L1 to 264/A, \$2,706, \$177,650 and RV 0.56. respectively. In Squamous Cell Head and Neck Carcinoma (SCCHN), the OS/gr were 72/C, 4-week value \$7,015, C/LYG \$651,430 and RV 0.15. The results improved in PD-L1 > 1.0% to 123/B, \$5,512, \$381,287 and 0.26 respectively.

**Conclusions:** A strategy to grade survival was proposed. Hazard ratios were utilized as complementary or substitute tools to survival. In non-squamous NSCLC and SCCHN, the OS and values of Nivo were relatively limited. The PD-L1 enrichment resulted in unprecedented survival with values that would tend to justify costs. The consistency of the results would give credence to our conclusions.

### Abbreviations

AEs: Adverse Events; ASCO: American Society of Clinical Oncology; ACER: Average Cost-Effectiveness Ratios; CI: Confidence Interval; C/LYG: Cost/Life-Year Gain; ESMO: European Society of Clinical Oncology; HR: Hazard Ratio; gr: Grade; ICPA: Immune Check Point Antibody; OS: Median Overall Survival Gain Over Control in Days; m: Metastatic; mg: Milligram; NSCLC: Non-Small-Cell Lung Cancer; PD1: Programmed Death Receptor-1; PD-L1: Programmed Death Receptor-Ligand1; QALY: Quality Adjusted Life-Year; QoL: Quality of Life; RV: Relative Values; SCCHN: Squamous Cell Cancer of the Head and Neck; TPS: Tumor Proportion Score

### Introduction

Nivolumab (Nivo) is a fully human IgG4 Immune Checkpoint Antibody (ICPA) which disrupts the PD-1 signaling and may restore antitumor immunity [1]. It is widely used throughout the United States (US) to treat various types of cancer. Nivolumab, in view of its safety has essentially replaced docetaxel in 2<sup>nd</sup>-line treatment of Non-Small-Cell Lung Cancer (NSCLC). The American (ASCO) and European Societies of Clinical Oncology (ESMO) emphasized the role of value [2,3] over cost in the drug economy. In the US, the Average Cost-Effectiveness Ratios (ACER) ranged from \$50,000 to \$150,000 per Qual-

ity Adjusted Life-Year (QALY). The National Institute for Health and Care Excellence in the United Kingdom is still negotiating the cost of Nivo in 2<sup>nd</sup>-line NSCLC. The Euro-

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pean Medicines Agency has promptly approved the drug for the same indication. We previously proposed simplified methodology to weigh drug costs and values in metastatic castrate-resistant prostate cancer using \$100,000 as a reference [4]. Values of Nivo between the various approved indications have not been compared. Our objectives were to compare and grade the overall survival and values of Nivo in 1<sup>st</sup>-line melanoma, 2<sup>nd</sup>-line renal carcinoma, squamous-NSCLC, non-squamous-NSCLC and Squamous-Cell Cancer of the Head and Neck (SCCHN).

## Methods

Nivo Median Overall Survival Gain Over Control in Days (OS), Hazard Ratios (HR), doses, frequency and protocols were extracted from the previously published clinical trials. Prescribing information and prices posted by the parent company were utilized. Costs were computed at 4-week and at one-year. The 4-week values were calculated as (4-week cost × HR). The year-cost/life-year gain was expressed as (C/LYG). Relative Values (RV) were computed as \$100,000/LYG. The OS was graded: D up to 45, C > 45-90, B > 90-135 and A > 135.

## Results

In early 2016, the 4-week cost of Nivo was estimated at \$10,021 at one-year cost of \$130,273. The recommended dose has recently been changed to a 240 mg at 4-week cost of \$11,914. Table 1 shows the proposed grading system of OS gains over the corresponding controls. Table 2 summarizes the OS gains [1,5-8], grade, HR, 4-week values, \$C/LYG and RV.

**Table 1:** Grading of OS.

Grade (gr)	OS gain over control in days
A	> 135
B	> 90-135
C	> 45-90
D	Up to 45

**Table 2:** Overall Survival, Grade (OS/gr) and values of Nivo in 1<sup>st</sup> and 2<sup>nd</sup>-line.

Nivo in 1 <sup>st</sup> - and 2 <sup>nd</sup> -line	OS gains in days, grade (OS/gr) & HR	\$4-week value (4-week cost × HR)	\$C/LYG	Relative Value (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/A & 0.73 P = 0.002	7,315	289,496	0.35
Nivo vs. docetaxel, squamous-NSCLC	96/B & 0.59 P = 0.00025	5,912	488,524	0.20
Nivo vs. docetaxel, non-squamous-NSCLC, CheckMate 057	84/C & 0.73 P = 0.0016	7,315	558,326	0.18
Subset analysis in >10% PD-L1	264/A & 0.27	2,706	177,650	0.56
Nivo vs. investigator's choice, SCCHN	72/C & 0.70 P = 0.0101	7,015	651,430	0.15
Subset analysis in >1.0 PD-L1, SCCHN	123/B & 0.55	5,512	381,287	0.26

1. In 1<sup>st</sup>-line melanoma, OS was not reached at the closure of the study [5]. The reported HR was 0.42 at an estimated 4-week value of \$4,209.
2. In 2<sup>nd</sup>-line renal cancer, the OS and Grade (OS/gr) was 96/B, 4-week value \$7,305, C/LYG \$289,496 and RV 0.35.
3. In the squamous NSCLC, the OS/gr was 96/B, 4-week value \$5,912, C/LYG \$488,234 and RV 0.20.
4. In the non-squamous histology, the OS/gr were 84/C, 4-week value \$7,315, C/LYG \$558,326 and RV 0.18. In > 10% PD-L1, the OS/gr improved to 264/A, 4-week value \$2,706, C/LYG \$177,650 and RV 0.56.
5. In the SCCHN, the OS/gr were 72/C, 4-week value \$7,015, C/LYG \$651,430 and RV 0.15. The results improved in PD-L1 > 1.0% to 123/B, \$5,512, \$381,287 and RV 0.26 respectively.

## Discussion

The present investigation was prompted by the rising C, diminishing V and decreasing affordability of anticancer drugs [9,10]. Our objectives were to propose a strategy to grade survival and assess V of Nivo in various types of cancer. Nivo, a prototype of PD-1 Immune Checkpoint Antibody (ICPA), was chosen since it prolonged the OS in 1<sup>st</sup>-line melanoma [5], 2<sup>nd</sup>-line squamous-NSCLC, CheckMate 017 [6], non-squamous-NSCLC, CheckMate 057 [1], renal cell carcinoma, CheckMate 025 [7] and SCCHN [8]. It was not the plan to compare Nivo cost and values with the cheaper and probably more toxic generic drugs. The standard cost effectiveness ratio methodology measuring cost/outcome differences were not utilized since the dose, schedule and cost of Nivo were similar in all the approved indications. The incremental cost per day and year gain in OS was adopted as the basis of our comparison. The 4-week-cost (4 wC) of \$10,021-

\$11,914 was within the current estimated average range of the newly approved patent drugs of \$10,000-\$12,000.

In the present study, a \$100,000 reference was proposed for drugs with documented safety records, lack of the Federal Drug Administration (FDA) black box warnings and documented preservation of Quality of Life (QoL). Docetaxel gr  $\frac{3}{4}$  Adverse Events (AEs) were > 20% in metastatic castrate prostate cancer and NSCLC [4,11]. In addition, docetaxel carries a black box warning. In comparison, the AEs of Nivo were rarely above 10% [1,5,8].

### PD-L1 enrichment

The results demonstrated that at the same amount of the dollar spent, relatively fair values were noted in 1<sup>st</sup>-line melanoma and 2<sup>nd</sup>-line renal cell. In 2<sup>nd</sup>-line squamous-NSCLC, values were borderline. In non-squamous-NSCLC and SCCHN, values were low. However, the PD-L1 enrichment significantly enhanced OS and values in both these malignancies to levels seem to justify costs.

### HR vs. OS

At the closure of some clinical studies OS are not reached. Hazard ratio was used in 1<sup>st</sup>-line melanoma due to lack of available OS [5]. In contrast to HR, survival is more subject to variation along the time curve. Parallel use of both OS and HR was therefore adopted whenever possible throughout our investigation. The HR-based strategy of using 4-week-value could offer a snapshot approach to measure V in the absence of mature OS data.

### Merits

Overall survival was used throughout the present investigation. Progression-free survival and other endpoints could be used if appropriate adjustments in the \$100,000 reference were made. Drug costs and values were calculated in a few minutes once the data were collected. The proposed OS grading system could facilitate clear transmission of economic issues between physicians and patients [12]. Patients as consumers would like to know how much they pay for the value in return. Upfront costs and values could be promptly disclosed in advance.

### Limitations

The scanty available data on cost and value comparison could limit the significance of our findings. The methodology failed to account for the AEs treatment cost [13]. The latter could be costly and “toxic” [14]. Venkatachalam, et al. [11] reported that the average Nivo treatment cost of adverse events per patient in CheckMate 017 (squamous-NSCLC) in US\$ were \$439 vs. docetaxel of \$7,024.

### PD-L1 testing, positivity and enrichment

Some of the early studies on the ICPA were reported at different level of positivity and Tumor Proportion Score (TPS). In our study, we used the terminology of PD-L1 positivity and enrichment. Uniformity and standardization of the PD-L1 tests have evolved and settled. The PD-L1 might not be the perfect predictive test of ICPA outcome. However, our study is the first to demonstrate improved values by PD-L1 enrichment in 2<sup>nd</sup>-line non-squamous NSCLC and SCCHN. From an economic point of view, it would be prudent to pay few hundred dollars upfront for a PD-L1 test, use the drug in the enriched-setting, secure enhanced OS and improve value. Such approach would spare the non-responders the cost and toxicity of ineffective therapy.

### Duration of treatment

In the Checkmate-057 study of non-sq-NSCLC [1], the median duration of response was > 17 months. In our study, values of Nivo were calculated at one year. Currently the optimal duration of therapy has not been clearly defined. Continued treatment for 1-2 years or till disease progression or intolerance has generally been employed.

### Conclusions

A strategy to grade survival was proposed. The HR-based 4-week value served as an early measure offering a snapshot value estimate in the absence of mature survival data. In view of Nivo well-documented safety, the results were expressed relative to the average acceptable C/LYG in the USA of \$100,000. In 1<sup>st</sup>-line melanoma, 2<sup>nd</sup>-line renal cell cancer, Nivo significantly enhanced OS and offered equitable values for the dollars spent. In squamous NSCLC, OS and values were borderline. In non-squamous NSCLC and SCCHN, the OS, gr and values were relatively low. The PD-L1 enrichment resulted in unprecedented survival and values that would justify costs. The consistency of the results could give credence to our conclusions.

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