



Survival and Values of the Immune Check Point Inhibitors in Non-Small-Cell Lung Cancer

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Abstract

The efficacy and safety of the Immune Check Point Inhibitors (ICPI) have been well documented. Their costs and values have received lesser attention.

Objectives: Design a grading system to measure survival and weigh values of the ICPI in 2nd-line Non-Small-Cell Lung Cancer (NSCLC).

Methodology: Median overall survival, Hazard Ratios (HR) and prices posted by parent company were quoted. Survival gains were Graded (gr) from A to D. The C/LYG was calculated as year-costs/OS gain over control in days × 360. Relative Values (RV) were computed as \$100,000/C/LYG.

Results: Nivolumab (Nivo) in non-squamous NSCLC demonstrated OS/gr 84/C and C/LYG \$558,326. In >10% Programmed Death Receptor-Ligand1 (PD-L1), the OS/gr improved to 264/A and C/LYG \$177,645. Using Atezolizumab (Atezo), irrespective of PD-L1, the OS/gr were 87/C and C/LYG \$618,244. The results improved in enriched PD-L1 to 162/A and \$332,020 respectively. Pembrolizumab (Pembro) in PD-L1 > 1.0%, the OS/gr were 57/C and C/LYG \$659,059. The results improved in > 50% PD-L1 to 201/A and \$186,897. Enrichment of PD-L1 increased the relative values of Nivo from 0.19 to 0.56, Atezo from 0.16 to 0.30 and Pembro from 0.15 to 0.53.

Conclusions: Simplified methodology to grade survival and weigh values of the ICPI was proposed. In 2nd-line non-squamous NSCLC, irrespective of PD-L1 positivity, the OS/gr and values of Nivo, Atezo and Pembro were marginal. The unprecedented OS and the enhanced values with PD-L1 enrichment tend to justify their costs. The consistency of the results could give credence to our conclusions. The available cost comparative data precluded favoring one ICPI over another.

Abbreviations

AEs: Adverse Events; Atezo: Atezolizumab; ACER: Average Cost-Effectiveness Ratios; C/LYG: Cost/Life-Year Gain; CI: Confidence Interval; gr: Grade; FDA: Federal Drug Administration; HR: Hazard Ratio; LYG: Life-Year Gain; ICPI: Immune Check Point Inhibitors; OS: Median Overall Survival Gain in Days; Nivo: Nivolumab; NSCLC: Non-Small-Cell Lung Cancer; Pembro: Pembrolizumab; PD-L1: Programmed Death Receptor-Ligand1; Ramu: Ramucirumab; RV: Relative Values; TPS: Tumor Proportion Score

Introduction

Docetaxel (Doc) has been widely used since 2000 in the 2nd-line treatment of patients with metastatic Non-Small-Cell-Lung Cancer (NSCLC). The median Overall Survival Gain (OS) over best supportive care was 87 days [1]. In 2006, Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor demonstrated a median OS gain of 60 days in 1st-line non-squamous NSCLC [2]. In a landmark study in 2009, the tyrosine kinase inhibitor gefitinib significantly improved the progression-free-survival in epidermal growth factor receptor mutations [3]. The introduction of the Immune Check Point Inhibitors (ICPI) changed the course of NS-

CLC treatment. Nivolumab (Nivo) [4,5] and Pembrolizumab (Pembro) [6,7] both directed against the Program Death Potein1 (PD-1) and Azetolizumab (Atezo) [8-10] targeting the ligand PD-Ligand 1 (PD-L1) were approved by the Federal Drug Administration (FDA) in

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2nd-line. These inhibitors block the PD1 pathway, upregulate the T cell immunity and allow the immune system to attack tumor cells. The approval of Pembro was further expanded to 1st-line in positive PD-L1 NSCLC [11]. Results of Nivo monotherapy and its combinations with chemotherapy have also been reported in 1st-line [12,13]. The efficacy and safety of the entire ICPI class have been well documented [4-10,12,13]. Their cost-effectiveness however has received less attention. In the United States (US), an Average Cost-Effectiveness Ratio (ACER) of 100,000 is generally considered acceptable. Simplified methodology to weigh drug costs and values was previously reported in metastatic castrate-resistant prostate cancer using a \$100,000 reference [14]. The cost/life-year gain of Nivo was recently reported in various types of cancer [15]. There is a need for simplified methodology to facilitate transmission of anti-cancer drug outcome and values between medical professionals, patients and non-medical personnel. Our objectives were to design a grading system to measure survival and weigh values of the ICPI in 2nd-line Non-Small-Cell Lung Cancer (NSCLC).

Methodology

Doses, frequency, OS gain over control in days and Hazard Ratios (HR) were quoted from previously published clinical studies. Prices and protocols were utilized as posted by the parent companies. Docetaxel (Doc) [1] and Ramucirumab (Ramu) [16] were used as comparators. Costs of Nivo 3.0 mg/Kg intravenously (iv) q 2 weeks, Doc 75 mg/m² and Ramu 10 mg/Kg q 3 weeks were calculated for 70 Kg patients. Atezolizumab 1,200

mg and Pembro 2.0, 10 mg/Kg and 200 mg were used q 3 w. The OS gains were graded on a sliding scale as A: OS > 135 days, B: 90-135, C: 45 - < 90 and D: < 45. Costs were estimated at 4 weeks and one year. The C/LYG were calculated as year-costs/OS gain over control in days × 360. Relative Values (RV) were computed as \$100,000/C/LYG.

Results

The initial plan in the early phase of our study was to compare the efficacy, safety, costs and values of drugs used in the 2nd-line treatment of NSCLC. The wide differences observed between the ICPI, Doc and Ramu prompted the change of plan and focus on the ICPI.

Docetaxel and ramucirumab (Table 1)

Without accounting for cost of treatment of Adverse Events (AEs), docetaxel [6] OS gain and grade (OS/gr) in 2nd-line NSCLC were 87/C at an estimated \$26,897 C/LYG. Ramucirumab (Ramu) approved for both squamous- and non-squamous histology [16] demonstrated 42/D OS gains at \$1,039,963 C/LYG (Table 1). Both drugs were reported to demonstrate AEs > 20% and carry black box warnings by the Federal Drug Administration (FDA).

The AEs of ICPI

The reported gr ³/₄ AEs of Nivo, Atezo and Pembro were < 20% [4-10]. They maintained and/or improved the QoL and carried no black box warnings by the FDA. Their C/LYG was measured in RV to \$100,000, the acceptable ACER in the US.

Table 1: Overall survival and values of Docetaxel and Ramucirumab in 2nd-line.

Nivo in 2 nd -line	OS gains in days/Grade (OS/gr) & HR	\$4-week Costs	\$C/LYG
*Generic docetaxel (Doc) 75 mg/m ² vs. supportive care [1]	87/C HR not reported P = 0.01	\$500	\$26,897
*Ramucirumab (Ramu) + Doc vs. Doc, squamous and non-squamous, (REVEL) [16]	42/D HR 0.86 P = 0.0235	\$9,333	\$1,039,963

The C/LYG = year-cost/OS gain × 360 days. *Doc and Ramu demonstrated AEs gr > 20% and had black box warnings. The C/LYG of Doc and Ramu were not calculated relative to \$100,000.

Table 2: Overall survival and values of nivolumab.

Nivo in 2 nd -line	OS gains in days/grade (OS/gr) & HR	\$C/LYG	Relative values (RV) (100,000/LYG)
Nivo vs. Doc, squamous-NSCLC [4]	96/B & 0.59 P = 0.00025	\$488,524	0.20
Nivo vs. Doc, non-squamous- NSCLC, CheckMate 057 [5]	84/C & 0.73 P = 0.0016	\$558,326	0.18
Subset analysis in >10% positive PD-L1	264/A & 0.27	\$177,645	0.56

Nivo, Atezo and Pembro demonstrated AEs gr ³/₄ of < 20%, maintained and/or improved the QoL and carried no black box warnings. The \$C/LYG were weighed vs. \$100,000, the acceptable Average Cost Effectiveness Ratio (ACER) in the US. Relative Values (RV) were computed as \$100,000/C/LYG.

Costs of the ICPI

The estimated median 4-week costs of the ICPI in our study were \$10,077. The 4-week costs of Nivo 3.0 mg/Kg q 2 weeks was \$10,021 and the 240 mg \$11,914. Administered q 3 weeks, costs of Atezo 1,200 mg was \$11,493, Pembro 2.0 mg/Kg \$8,027 and 200 mg \$11,509. At 10 mg/Kg, Pembro the 4-week costs were \$40,135 and Nivo \$33,063.

Nivolumab in squamous vs. non-squamous NSCLC (Table 2)

Nivolumab OS/gr in the squamous histology were 96/B, HR 0.59, C/LYG \$488,524 and RV 0.20. In non-squamous, the OS/gr was slightly lower at 84/C at a higher HR of 0.73. The C/LYG was \$558,326 and RV 0.18.

Summary of the impact of PD-L1 on OS/gr and values:

1. In subset analyses of non-squamous, PD-L1 > 10% enrichment markedly improved Nivo OS/gr from 84/C to 264/A and RV from 0.18 to 0.56 (Table 2).
2. Atezo OS/gr in squamous and non-squamous was 87/C and RV 0.16. The results improved in PD-L1 > 1.0 or tumor infiltrating immune cells to 162/A and RV 0.30 (Table 3).
3. Enrichment of PD-L1 improved Pembro 2.0 mg/Kg OS/gr from 57/C to 201/A and RV from 0.15 to 0.53 (Table 3).

Discussion

The American Society of Clinical Oncology (ASCO) reported frameworks to assess the value of anticancer treatment in 2013 [17]. The Magnitude of Clinical Benefit Scale was also put forward by the European Society of Clinical Oncology (ESMO) [18]. The benefits were given a score, numerical weights and points to reflect the impact of treatment on survival and response rates. Both societies used similar sets of level one data to develop their models [19]. The progress in the development of anticancer drugs came, not surprisingly, at high costs.

The continued rise of drug costs, diminishing or stagnant values and widening gap in communication of cost issues between physicians and patients [20-21] prompted the present investigation. Our focus was to highlight the survival data and values of the ICPI class of drugs using Doc and Ramu as comparators.

The grading of overall survival

There is growing recognition that OS gains by anti-cancer drugs of < 2 months is of questionable clinical significance. Grade D was therefore assigned to < 45 days and A to > 135 days. Based on subset analysis of major clinical studies, the PD-L1 enrichment resulted in an increase of the OS to > 260 days, an unprecedented survival in an incurable 2nd-line NSCLC. If such trend continues to improve, the grading range of OS needs to change.

Rationale behind the C/LYG

The cost-effectiveness methodology [22,23] are widely used to measure differences in cost vs. differences in outcome between 2 entities. However, the costs and values between the ICPI members, Doc and Ramu varied widely. In addition, cost and values differences between Nivo, Atezo and Pembro were non-significant. The costs of the incremental OS gains over control at the one-year milestone were therefore adopted as the basis of our calculation. Regardless of the method used, the results and conclusions would be the same.

Adverse Events (AEs)

The safety of the ICPI have been well documented [4-10]. In contrast, docetaxel and Ramu AEs gr 3/4 were usually > 20% and carried a black box warning. In a recent phase III trial in previously treated NSCLC, all-grade treatment-related AEs were less frequent with Nivo than with docetaxel. The average Nivo AEs treatment costs per patient in CheckMate 017, squamous-NSCLC, were \$439 vs. docetaxel of \$7,024 in \$US. In the CheckMate 057 non-squamous NSCLC, the AEs treatment costs of Nivo were \$518, vs. Doc \$5,940 [24]. The finan-

Table 3: Overall survival and values of Atezolizumab and Pembrolizomab.

Drug and setting	OS gains in days/Grade (OS/gr) & HR	\$C/LYG	RV
Atezo vs. Docetaxel (Doc), irrespective of PD-L1, vs. Docetaxel (phase II, Poplar) [8]	87/C HR 0.73 P = 0.040	\$618,244	0.16
Atezo, squamous and non-squamous, regardless of PD-L1 vs. Doc (OAK) [9]	128/B HR 0.74 P = 0.0004	\$420,213	0.24
Atezo, low or undetectable PD-L1 vs. Doc, Phase III OAK [10]	111/B HR 0.75	\$484,570	0.21
Atezo, PD-L1 > 1.0% or tumor-infiltrating immune cells vs. Doc [10]	162/A HR 0.74 P = 0.0102	\$332,020	0.30
Pembro PD-L1 > 1.0% positive vs. Doc Keynote-010 [7] Subset analysis	57/C HR 0.71 P = 0.0008	\$659,059	0.15
Pembro 10 mg/Kg, PD-L1 1.0% positive, Keynote-010	126/A HR 0.61	\$1,490,729	0.07
Pembro 2.0 mg/Kg, > 50% positive Keynote-010	201/A HR 0.54	\$186,897	0.53

cial burden of AEs treatment of Doc with its potential febrile neutropenia and other non-hematological could be “toxic” [25]. There has been wide spread awareness of potential hazards with continued gain in experience and management of AEs since the introduction of bevacizumab [26]. Nonetheless, costs of generic docetaxel with the precautions taken to minimize its AEs, could still support its value specially in countries with limited financial resources. It is doubtful whether Ramu with 42-day OS gain, 0.86 HR [16] and high C/LYG could justify its value. The drug is currently reserved for later lines of treatments.

Limitations

In the present study, cost-effectiveness was not compared with the commonly used standard treatment of care [22,23]. The cost of inhibitors was calculated with accounting of costs of AEs treatment. Another major limitation was the failure of the C/LYG to measure the quality adjusted life-year [22,23]. The scanty economic data available for analysis and the inherent problems of comparing subset analyses of one clinical study with another might diminish the significance of our conclusions.

Merits

Overall survival, the ultimate and most reliable endpoint in cancer therapy was used throughout the present investigation. Values were calculated in few minutes once the data were collected. The simplicity of the A to D grading system could bridge the communication gap between drug authorities and companies on one hand and media and non-medical personnel on the other. The system might also facilitate full disclosure and transparency of outcome and cost issues between physicians and patients [20,21].

Cost vs. Value

The balance between costs and values has been elusive. The pendulum however has recently tipped in favor of value since ASCO and ESMO issued their initiatives in 2013 [17-18]. Nonetheless, the debate has continued [27]. Based on the unprecedented OS gain observed in our study, the values of ICPI tend to justify their costs. Drug values seemed to be the major determining factor in the economic formulary. Nonetheless, the role of costs ought to be emphasized. The high costs of 10 mg/Kg of Nivo or Pembro would dampen their use. With the expanding role of combination therapy, costs could limit their utilization and restrict access. Both values and costs were important in securing a fair and equitable economic balance.

PD-L1 Biomarker

Early clinical studies on the ICPI used various PD-L1 positivity levels and Tumor Proportion Scores (TPS). At

present, conformity and standardization of the PD-L1 tests seemed to have been achieved. Of interest, there is no documentation yet of benefit of PD-L1 enrichment in the squamous NSCLC. The non-squamous histology is generally considered less homogenous with more incidence in women and non-smokers than the squamous type. Our study is the first to demonstrate enhanced value with PD-L1 enrichment by Nivo. Atezo and Pembro in the non-squamous NSCLC. From an economic point of view, it would be prudent to pay upfront few hundred dollars, on a predictive test and spare the non- or poor responders the cost and toxicity of ineffective therapy. The search for more predictive marker than PD-L1 is presently pursued.

Duration of treatment

The duration of treatment comes down to a choice with cost vs. outcome. The costs as well as the AEs would increase with extended use. The current recommendations are to continue the ICPA treatment till occurrence of AEs or disease progression. Whether to continue treatment to 1-2 years or discontinue after 4-6 months is still unclear. The optimal duration of treatment is worthy of further investigation.

Future directions

Points and scores rather than grades would be assigned to survival. Progression-disease free, disease control rates and other endpoints would be employed after adjustments with appropriate correction factors (Guirgis, in preparation). The use of Nivo and Pembro at 10 mg/Kg as single agents or in combinations with other patent drugs ought to be reconsidered in view of potential prohibitive costs. The superiority of ICPI over chemotherapy has generally been acknowledged in 2nd-line NSCLC. The results of the ICPI in 1st-line as single agents or in chemotherapy have also been rewarding [11-13]. The responses in percent, duration and depth of Pembro in combination with chemotherapy have been recently reported [28]. However, the enthusiasm of the ICPI use in 1st-line needs to be tempered by the economic pressures of countries and patients with limited resources, access and affordability. Costs of Nivo and Pembro were estimated at thousands of times the cost of gold [29]. With upcoming waves of generic drugs including pemetrexed, the role of Doc and many others is not yet dead but just diminished [30].

Conclusions

Methodology to grade OS and weigh drug values was proposed. In 2nd-line non-squamous NSCLC, values of Nivo, Atezo and Pembro without of PD-L1 enrichment, were marginal. The marked enhancement OS and values by PD-L1 enrichment tend to justify their costs. The re-

sults would be the same, regardless of the method used to assess value. The consistency of the results would give credence to our conclusions. The available cost comparative data precluded favoring one ICPI over another.

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