The Role of Predictive Markers in Outcome and Value of Anticancer Drugs in Non-small Cell Lung Cancer

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Rising costs and stagnant value of anticancer drugs are of serious concerns to authorities and patients worldwide. The widely used methodology of comparing value of one intervention with another has been the foundation of various additions and modifications.\(^1,2\) Quality-of-life (QoL) measures were later introduced and incorporated. At present, the methodology is mainly utilized by medical economists and specialized oncologists.

Over the last 10 years, we have developed simplified platforms for use by the practicing physicians, oncologists, pharmacists and nurses.\(^3\) The main objective was to facilitate communication of outcome, cost and value of anticancer drugs between oncologists and patients with clarity, transparency and full disclosure. The proposed platforms have been applied successfully in multiple types of cancer, including prostate cancer, and used in the present communication to assess drugs in non-small cell cancer (NSCLC).

Methods

The platforms have the capacity of comparing multiple drugs simultaneously. Costs and value could be weighed in any currency units, making the methodology universally applicable. The methodology could potentially bridge the communication gap between physicians and patients. Calculations were carried out in a few minutes, once the data were entered. The methodology has two main components:

1. Similar to the cancer staging system, the overall survival (OS) gains in days over control were graded (gr) on a sliding scale with days assigned to OS, as D: <60 days, C: 60 to 150, B: >150 to 240 and A: >240. By using grades rather than days of survival, oncologists, pharmacists and nurses could explain in simple terminology to their patients the impact of treatment on outcome and value.

2. Drug value was calculated as the yearly-drug cost over the incremental gain in days over control \(\times 360\) days (cost/life-year gain). Value was based on cost of the evaluated drug, with other drugs in the combination being excluded. Relative values were computed as \$100,000/cost/life-year gain. The adverse events-treatment costs were observed to be \(<5.0\%\) of the yearly-trade name drug costs and were calculated separately.

Results

Docetaxel (Doc) was compared with Nivolumab (Nivo),\(^4,5\) Atezolizumab (Atezo),\(^6\) and Pembrolizumab (Pembro) in 2nd-line NSCLC.\(^7,8\) In cases with nonactionable EGFR mutations and negativity for low programmed death receptor ligand-1 (PD-L1), the average OS gain by Atezo was 111 days with gr C. Doc, Nivo and Pembro demonstrated OS gains of \(<100\) days with grade D to C. Enrichment of PD-L1 increased the OS to an unparalleled \(>200\) days with grade B to A. There was a corresponding marked enhancement of value. PD-L1 enrichment enhanced the OS and value of Nivo by 4.1-fold and Atezo by 3.1.

In the present work, Pembro improved the OS and value by 3.6 without any negative impact on QoL. The limited comparative data available and subset analysis precluded favoring one tyrosine kinase inhibitor over another. In contrast to the immune check point inhibitor (ICPI), Doc was reported to have a negative impact of QoL.\(^9\) Since the perception and significance of quantity to QoL usually vary from one patient to another, a correction factor ranging from 25% to 50% was applied to adjust for the drug impact on QoL. Using a 25% correction factor, Doc value dropped from $263,371 to $329,214 (Table 1).\(^4,7,8\)

OS has not been reached at the closure of some clinical studies. For drugs with unavailable OS, \((1.0 - \text{hazard ratio})\) was used and expressed as probability of survival. The rationale behind using the hazard ratio was based on the widely recognized observations that hazard ratio is less subject to variation along the time curve than survival. At the 1-year milestone, value was computed as cost/probability of survival. The results demonstrated the feasibility of using probability of survival to weigh drug outcome and value. In 1st-line NSCLC, Pembro in >50% Tumor progression score (KEYNOTE-025) had $383,413 value at $153,365 cost.\(^9,10\) Pembrolizumab demonstrated $264,422 value.\(^11,12\) Pembrolizumab is noninferior to Pemetrexed with $264,722 value (Table 2).\(^9,11\) The trade name Pemetrexed, however, could lose its exclusivity in a few years and become generic. In view of costs and value, Doc and Pemetrexed would remain economically viable and universally useful.

Effort, time and investments have been spent to improve the outcome of the ICPI class of drugs. Nivo/Iplilimumab is a promising combination which significantly improved the response rates and progression-free survival in chemotherapy-naive, stage IV or recurrent NSCLC.\(^13\) However, its value could not be ascertained until the closure of the study in 2019. The ICPI combined with a brand name drug could be costly in dollar amount and AEs treat-
In addition, the logistics of labor, time, preparation and administration of multiple drugs need to be factored in. Strategies to improve the ICPI outcome and value are presently focused on combination therapy and development of markers. It seemed reasonable to suggest that a winning strategy ought to emphasize marker development while maintaining the search for safe and not so costly drug combinations. Precise markers, including PD-L1, tumor mutation burden and others still emerging, could spare the nonresponders the AEs and financial toxicity while enhancing the outcome of responders.

Conflict of interest

The author has no conflict of interest to declare.

Author contributions

Helmy M. Guirgis is the sole author.

References


[6] Pembro q 3 × 1 year ± Peme and carboplatin q 3 weeks, Irrespective of PD-L1

<table>
<thead>
<tr>
<th>Drug</th>
<th>OS gains in Days, HR &amp; PoS</th>
<th>Cost per year (US$)</th>
<th>Cost/LYG</th>
<th>Relative value = $100,000/cost/LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc 75 mg/m² q 3 weeks vs. supportive care</td>
<td>87, grade C</td>
<td>$63,648</td>
<td>$263,371</td>
<td>0.37 corrected for QoL: 0.18–0.27</td>
</tr>
<tr>
<td>Pembro, PD-L1 &gt;1.0% TPS vs. Doc</td>
<td>57, grade D HR 0.71</td>
<td>$153,365</td>
<td>$968,621</td>
<td>0.10</td>
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<tr>
<td>In &gt;50% positive subset analysis</td>
<td>201, grade B</td>
<td>$274,684 (2.5-fold increase)</td>
<td>0.36</td>
<td></td>
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<td>KEYNOTE-010</td>
<td>HR 0.54</td>
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Abbreviations: Doc, Docetaxel; HR, hazard ratio; ICPI, immune check point inhibitor; LYG, life-year gain; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death receptor ligand-1; Pembrolizumab; PoSm probability of survival; TPS, tumor proportion score.


