Editorial

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

Helmy M. Guirgis*

The Cancer Free Foundation, Dana Point, CA, USA

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 × 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 (PDL-1), 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.[4] 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 - 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] Pembro + chemo demonstrated $264,422 value,[11,12] 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/Ipililumab is a promising combination which significantly improved the response rates and progression-free survival in chemotherapy-naïve, 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-

Abbreviations: Atezo, Atezolizumab; Doc, Docetaxel; gr, graded; ICPI, immune check point inhibitor; Nivo, Nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death receptor ligand-1; Pembro, Pembrolizumab; QoL, quality-of-life; TMB, tumor mutation burden.

Received: July 08, 2018; Accepted: September 18, 2018

***Correspondence to:** Helmy M. Guirgis, The Cancer Free Foundation, 24806 Sea Crest Dr. Dana Point, CA 92629. E-mail: cancerguir@gmail.com

How to cite this article: Guirgis HM. The Role of Predictive Markers in Outcome and Value of Anticancer Drugs in Non-small Cell Lung Cancer. *J Explor Res Pharmacol* 2018;3(4):93–95. doi: 10.14218/JERP.2018.00020.

Table 1. Docetaxel and the ICPI in 2nd-line NSCLC

Drug	OS gains in days & HR	Cost per year (US$)	$Cost/LYG	Relative value = $100,000/cost/LYG
Doc 75 mg/m^2 q 3 weeks *vs*. supportive care[4]	87, grade C p = 0.01	$63,648	$263,371	0.37 corrected for QoL: 0.18–0.27
Pembro, PD-L1 >1.0% TPS *vs*. Doc	57, grade D HR 0.71 p = 0.0008	$153,365	$968,621	0.10
In >50% positive subset analysis	201, grade B		$274,684 (2.5-fold increase)	0.36
KEYNOTE-010[7,8]	HR 0.54			

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; Pembro, Pembrolizumab; QoL, quality of life; TPS, tumor proportion score.

Table 2. Drugs in 1st-line treatment in NSCLC

Drug	OS gains in Days, HR & PoS	Cost per year (US$)	Cost/PoS
Peme** 500 mg/m^2 q3 w × 1 year ± carboplatin, non-squamous III/IV, Performance status II[11]	120 days 0.63, 0.37	$97,947	$264,722
Pembro 200 mg q 3 w × 1 year *vs*. chemo, TPS > 50%, KEYNOTE-024[9,10]	OS not reached 0.60, 0.40	$153,365	$383,413
Pembro q 3 × 1 year ± Peme and carboplatin q 3 weeks, Irrespective of PD-L1	OS not reached	$153,365	
<1% TPS	0.49		$300
1–49% TPS	0.59		$374
>50%	0.55		$348
non-squamous, KEYNOTE-18912	0.42		$264

Peme* demonstrated OS gains over control and was used as a comparator. Abbreviations: Doc, Docetaxel; HR, hazard ratio; LYG, life-year gain; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death receptor ligand-1; Pembro, Pembrolizumab; Peme, Pemetrexed; PoSm probability of survival; TPS, tumor proportion score.

ment. 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,[14,15] 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

[1] Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. Panel on cost-effectiveness in health and medicine. The role of cost-effectiveness analysis in health and medicine. JAMA 1996;276(14):1172–1177. doi:10.1001/jama.276.14.1172.

[2] Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on cost-effectiveness in health and medicine. JAMA 1996;276(16):1339–1341. doi:10.1001/jama.276.16.1339.

[3] Guirgis HM. The impact of PD-L1 on survival and value of the immune check point inhibitors in non-small-cell lung cancer; proposal, policies and perspective. J Immunother Cancer 2018;6(1):15. doi:10.1186/s40425-018-0320-3.

[4] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, *et al*. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-base chemotherapy. J Clin Oncol 2000;18:2095–2103. doi:10.1016/s0169-5002(00)80193-2.

[5] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al*. Nivolumab versus docetaxel in advanced non-small-cell lung cancer. N Engl J Med 2015;373:1627–1639. doi:10.1056/NEJMoa1507643.

[6] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicentre randomized controlled trial. Lancet 2017;389(10066):255–265. doi:10.1016/S01-40-6736(16)32517-X.

[7] Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han JY, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540–1550. doi:10.3410/f.726044364.793539633.

[8] Herbst RS, Sznol M. Diminished but not dead: chemotherapy for the treatment of NSCLC. Lancet Oncol 2016;17:1464–1465. doi:10.1016/S1470-2045(16)30524-1.

[9] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–2028. doi:10.1056/NEJMoa1501824.
[10] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, *et al*. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:823–1833. doi:10.1056/nejmoa1606774.
[11] Zukin M, Barrios CH, Pereira JR, Ribeiro Rde A, Beato CA, do Nascimento YN, *et al*. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non–small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 2013;31(23):2849–2853. doi:10.1200/JCO.2012.48.1911.
[12] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378(22):2078–2092. doi:10.1056/NEJMoa1801005.
[13] Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, *et al*. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378(22):2093–2104. doi:10.1056/NEJMoa1801946.
[14] Rizvi N. In patients with non-small cell lung cancer, tumor mutation load emerging as biomarker for immunotherapy. The ASCO Post 2017;8(21):11.
[15] Garon EB, Borghaei H, Stevenson JP. The role of immunotherapy in NSCLC. CME/ABIM MOC Released: 2/27/18.