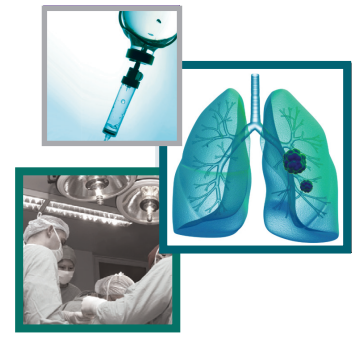
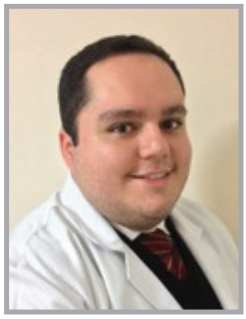
Lung Cancer Management



COMMENTARY

Cost–effectiveness of immune checkpoint inhibitors in NSCLC according to PD-L1 expression



"...the use of PD-L1 expression as a biomarker for treatment with immunotherapy may optimize the cost–effectiveness of the treatment with immune checkpoint inhibitors, decrease the overall economic impact and the cost per life-year saved."

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• cost–effectiveness • health technology assessment
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Historically, cancer had few therapeutic options and an almost universal poor outcome. Population aging and environmental factors led to an increase in cancer incidence and consequently in mortality around the world [1]. In 2008, the economic impact of premature mortality and morbidity of cancer patients was estimated at US$895 billion worldwide [2]. The global scientific community responded and the field of cancer drug discovery and development burgeoned. In the 2000s, almost 25 new drugs were approved for the treatment of cancer; an impressive figure totaling more than half the number of new drugs approved in the preceding four decades [3]. Between 2010 and 2013 the number of new agents approved for the treatment of cancer superseded the value observed in the past 10 years [3]. If this rate of growth continues, the 2010s may see up to 67 new cancer drugs enter the market [3]. To complicate matters, novel cancer drugs typically cost more and are taken for longer periods of time than the older alternatives [3].

These data account for the significant increase in the cost of treating cancer. Data from the Brazilian Court of Auditors reported that the cost of treating cancer doubled between the years 2002 and 2008, from US$250 to US$500 million [4]. The acceleration of cancer's economic burden is disproportionately high and out of keeping with trends in median household income and rates of inflation [5]. Consequently, this places strain on global and regional health systems, and may hypothetically lead to system failures. This risk obligates clinical practitioners and policy makers to provide the best treatment possible at an affordable cost.

The immune checkpoint inhibitors are monoclonal antibodies targeted to tumor or lymphocyte receptors to stimulate the immune system against cancer. The most studied pathway in lung cancer is the PD-1/PD-L1. In this mechanism of immune evasion, the PD-1 receptor on the lymphocyte surface binds to PD-L1 expressed by tumor cells, resulting in lymphocyte inactivation [6].

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Tumor PD-L1 expression is the biomarker most evaluated for the treatment of NSCLC with immune checkpoint inhibitors. Tumor expression is assessed through an immunohistochemistry assay and the surface expression can range from 0 to 100%. To date, there is not a standard cutoff value that indicates a significant degree of expression. Moreover, there are three antibody clones developed to perform measure PD-L1 expression, but the US FDA approved only the Dako 22C3 as a companion test for pembrolizumab.

Three meta-analyses have shown that PD-L1-positive tumors are two- to three-times more likely to respond as well as achieve increased progression-free survival and overall survival (OS) [7–9]. One of these studies showed that tumor response was greater with higher PD-L1 expression [9]. In the 2-year follow-up study, PD-L1 status was not linked to survival in CheckMate-017; however, in CheckMate-057, stronger OS outcomes were again observed in PD-L1-positive patients, including a 57% reduction in the risk of death at 2 years for those with the highest PD-L1 levels [10]. Although these studies have shown that PD-L1 expression may be a predictive biomarker, the assessment of PD-L1 expression is yet to become part of routine clinical practice.

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Currently, there are two FDA-approved anti-PD1 agents for the second-line treatment of NSCLC: nivolumab and pembrolizumab. Nivolumab is a fully humanized IgG4 monoclonal antibody against PD-1. The first Phase III study (CheckMate 017) included only patients with squamous histology and showed a statistically significant increase in OS when compared with docetaxel (median OS: 9.2 vs 6.0 months; hazard ratio [HR]: 0.59; 95% CI: 0.44–0.79) [11]. In a retrospective analysis, PD-L1 expression did not appear to be a good predictor of treatment benefit (among patients with PD-L1 <1%, the OS HR of nivolumab vs docetaxel was 0.58; 95% CI: 0.37–0.92) [11]. A second Phase III study (CheckMate 057) included only patients with nonsquamous histology and showed a statistically significant increase in OS when compared with docetaxel (median OS: 12.2 vs 9.4 months; HR: 0.73; 95% CI: 0.59–0.89) [12]. Conversely, in a retrospective analysis similar to the one conducted for CheckMate 017, PD-L1 expression appeared to be a good predictor of response (interaction p-value was 0.0646 for 1% threshold, 0.0004 for 5% threshold and 0.0002 for 10% threshold) [12].

Pembrolizumab is a humanized IgG4 monoclonal antibody also targeted against PD-1. The first Phase III study (KEYNOTE-010) included only patients with tumor PD-L1 expression of at least 1% based on previous findings of Phase I/II trials [13]. In KEYNOTE-010, there was a statistically significant benefit in OS compared with docetaxel (median OS: 10.4 vs 8.5 months; HR: 0.71; 95% CI: 0.58–0.88) [14]. In a preplanned analysis, patients with PD-L1 ≥50% had even a higher benefit (median OS: 14.9 vs 8.2 months; HR: 0.54; 95% CI: 0.38–0.77) [14].

Although the results from these trials were encouraging, only a fraction of patients will have a long-term benefit nivolumab or pembrolizumab. Data from a 2-year follow-up of the previously cited studies showed that the 2-year survival rate was 23% among patients with squamous tumors treated with nivolumab vs 8% among patients treated with docetaxel [10]. The values among patients with nonsquamous tumors were 29 and 16%, respectively [10].

In general, the immune checkpoints inhibitors are better tolerated than second-line cytotoxic chemotherapy. In CheckMate 017 study, grade 3 or 4 adverse events were observed in 7% of patients treated with nivolumab and in 57% of patients treated with docetaxel [11]. The discontinuation rates due to toxicity were 5 and 17%, respectively [11]. There were three deaths in the docetaxel arm related to the treatment [11]. No deaths related to the treatment with nivolumab were observed [11].

Data from a Phase IV study that included >800 patients confirmed nivolumab previous safety data: 27% of patients had grade 3 or 4 adverse events and 4% of patients had serious adverse events that interrupted treatment due to toxicity [15]. Although tolerability profile appears to be better than chemotherapy, some immune-related adverse events can cause serious morbidity and even mortality if not detected and treated early. In the Phase IV study cited above, there were five deaths because of adverse immune-related events [15].

A major concern for immunotherapy in NSCLC is the high cost of treatment. Nivolumab cost per milligram was US$24.69, the cost per cycle was around US$5184 and the cost per year of treatment can reach up to US$134,807. Pembrolizumab costs US$43.80 per milligram, US$6132 US$ per cycle and up to 104,244 per year of treatment. Contrastingly, docetaxel costs are US$18.26 per milligram, US$2465 per cycle

and approximately US$41,906 per year of treatment. Therefore, a biomarker is crucial in the view of limited portion of patients with long-term benefit, the high cost of these new agents and potentially harms adverse events.

In a recent study presented as a poster at the American Society of Clinical Oncology (ASCO) Annual Meeting 2016 and at the Presidential Session of Latin American Lung Cancer Conference (LALCA) 2016 our group evaluated the role of PD-L1 as cost–effectiveness of biomarker in the treatment of second-line NSCLC [16]. We also evaluated the economic impact of immunotherapy with or without the use of this biomarker.

Among all patients with squamous histology, the incremental quality-adjusted life years (QALY) of nivolumab was 0.23. The incremental cost–effectiveness ratio (ICER) was US$128,000. PD-L1 expression improved incremental QALY only for patients with PD-L1 expression of ≥5 and ≥10% (by 15 and 18%, respectively). Among all patients with nonsquamous histology, the incremental QALY of nivolumab was 0.12. The ICER was US$121,000. PD-L1 expression improved incremental QALY for patients with PD-L1 ≥1, ≥5 and ≥10% (by 67, 157 and 137%, respectively). All patients treated with pembrolizumab had at least 1% of PD-L1 expression; the incremental QALY was 0.13. The ICER was US$116,000. PD-L1 expression above 50% improved QALY by 18%.

In addition, the estimated cost of treating all American patients with nivolumab in the second-line was US$1.57 billion yearly. The estimate of expenses for only treating patients with PD-L1 ≥1% with pembrolizumab was US$0.97 billion yearly.

As noted above, the PD-L1 cutoff point of 50% further optimized the cost–effectiveness of treatment; however, it seems overly restrictive (with this strategy, we treat only 28% of patients and save only 32.2% of potential years of life to be saved by the treatment).

Our findings are consistent with a recent Swiss study that evaluated just the CheckMate 057 study data and showed a reduction in the ICER of nivolumab among patients with PD-L1-positive tumors [17]. The Swiss study and our study found that immunotherapy was not cost effective (ICER higher than US$100,000) even with patient selection through PD-L1 expression [16,17].

To corroborate this, NICE issued an opinion that nivolumab was not cost-effective for the second-line treatment of squamous NSCLC [18]. They estimated an ICER per QALY between GB£109,000 and GB£129,000 when the limit accepted by the institute is GB£30,000 [18].

Although our study is the largest and considers both monoclonal antibodies and both tumor NSCLC histologies, we acknowledge some limitations, such as the absence of an extended model for a lifetime horizon and the failure to include utilities of the evaluated treatments or utilities of the population intended to treat. Nevertheless, we consider our findings sufficient to answer the main question of the study.

It is an oversimplified view to state that biomarker-driven treatment individualization may deny therapy for some patients; the main objective is to ensure that effective treatment becomes broadly available for those patients who will benefit most given economic constraints.

Many societal discussions should be conducted to define the most sustainable strategy to deliver immune checkpoint inhibitors in the treatment of NSCLC. The definition of value is impossible to generalize because it depends on social, cultural and spiritual features; a high value placed on a specific treatment for a severe disease with few other therapeutic options by one culture may be considered of a low value by another.

In conclusion, the use of PD-L1 expression as a biomarker for treatment with immunotherapy may optimize the cost–effectiveness of the treatment with immune checkpoint inhibitors, decrease the overall economic impact and the cost per life-year saved. Nevertheless, the cost–effectiveness of anti-PD1 for the second-line treatment of NSCLC remains unfavorable.

Biomarker-driven treatment selection might be more important in the first-line setting of treatment when the economic impact can be higher. Moreover findings from new studies support patient selection: CheckMate 026 (NCT02041533) is a Phase III trial of nivolumab versus chemotherapy for patients with at least 5% of PD-L1 expression that fails to improve patients' outcomes, while KEYNOTE-024 (NCT02142738), another Phase III trial of pembrolizumab versus chemotherapy for patients with PD-L1 expression of 50% or more, met its primary end point [19,20]. We predict these results will generate further economic and value-based investigation to find the optimal strategy for patient selection and treatment sequencing.

"Many societal discussions should be conducted to define the most sustainable strategy to deliver immune checkpoint inhibitors in the treatment of NSCLC."

Financial & competing interests disclosure

P Aguiar Jr has received honoraria from BMS and AstraZeneca. He has received research honoraria from Roche and is speaker for MSD and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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