ORIGINAL ARTICLE

The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC

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Background: Immune checkpoint inhibitors improve outcomes compared with chemotherapy in lung cancer. Tumor PD-L1 receptor expression is being studied as a predictive biomarker. The objective of this study was to assess the cost-effectiveness and economic impact of second-line treatment with nivolumab, pembrolizumab, and atezolizumab with and without the use of PD-L1 testing for patient selection.

Design: We developed a decision-analytic model to determine the cost-effectiveness of PD-L1 assessment and second-line immunotherapy versus docetaxel. The model used outcomes data from randomized clinical trials (RCTs) and drug acquisition costs from the United States. Thereafter, we used epidemiologic data to estimate the economic impact of the treatment.

Results: We included four RCTs (2 with nivolumab, 1 with pembrolizumab, and 1 with atezolizumab). The incremental quality-adjusted life year (QALY) for nivolumab was 0.417 among squamous tumors and 0.287 among non-squamous tumors and the incremental cost-effectiveness ratio (ICER) were $155 605 and $187 685, respectively. The QALY gain in the base case for atezolizumab was 0.354 and the ICER was $215 802. Compared with treating all patients, the selection of patients by PD-L1 expression improved incremental QALY by up to 183% and decreased the ICER by up to 65%. Pembrolizumab was studied only in patients whose tumors expressed PD-L1. The QALY gain was 0.346 and the ICER was $98 421. Patient selection also reduced the budget impact of immunotherapy.

Conclusion: The use of PD-L1 expression as a biomarker increases cost-effectiveness of immunotherapy but also diminishes the number of potential life-years saved.

Key words: immunotherapy, pharmacoeconomics, lung cancer, chemotherapy

Introduction

Lung cancer is the most common cause of cancer-related death in the United States and the world [1, 2]. The incidence and mortality rate of lung cancer in the United States is 57.3 and 46.0 per 100 000, respectively, with 224 390 projected new cases and 158 050 deaths in 2016 [2, 3].

Despite innovative drug development in the past two decades, there are few options for second-line treatment and the most commonly used agent in the United States before the advent of immune checkpoint inhibitors was docetaxel [4].

Evasion of the immune system is a primary feature of cancers [5]. One mechanism by which tumor cells (TC) can evade immune surveillance checkpoints is by triggering apoptosis of T-lymphocytes by binding to Programmed Death-1 (PD-1) receptors [6, 7]. Advancements in our understanding of this mechanism has led to the rational design of three FDA-approved monoclonal antibodies that specifically target and block the PD-L1/PD-1 interaction: nivolumab, pembrolizumab, and atezolizumab [8–11].

As such PD-L1 expression is presumably a logical predictor of outcomes for patients treated with immune checkpoint inhibitors.
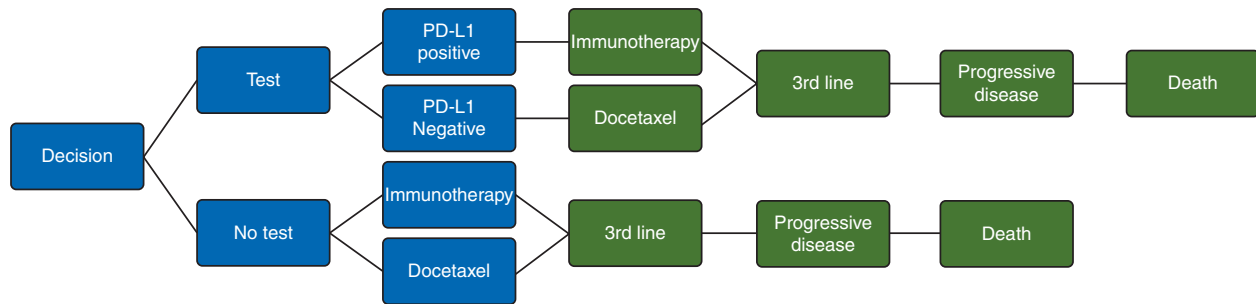
Figure 1. Decision-analytic model used in the study

Two recent meta-analyses have shown response and survival to immunotherapy to increase proportionally with the extent of PD-L1 expression in TC [12, 13]. A targeted approach to treatment using predictive biomarkers has the potential not only to maximize clinical benefit, but also to improve cost-effectiveness and reduce the economic burden of the disease.

As the global impact of non-small-cell lung cancer (NSCLC) continues to grow, the implementation of novel and more effective therapies becomes important but also costly [14]. Analysis of the cost-effectiveness and economic impact of new therapies is imperative to ensure the appropriate and sustainable use of advanced targeted treatments in NSCLC. The current study investigates the cost-effectiveness and economic burden of treatment with checkpoint inhibitors with and without patient selection using PD-L1 expression.

Methods

The authors developed a decision-analytic model using clinical data from the four available phase III studies (CheckMate 017, CheckMate 057, KeyNote 010, and OAK Study) [8–11]. The model compared three main strategies: (i) tumor sample not tested for PD-L1 expression and all patients treated with docetaxel, (ii) tumor sample not tested for PD-L1 expression and all patients treated with immunotherapy, and (iii) patients treated according to their PD-L1 status: immunotherapy for patients with PD-L1 expression of 1% or more and docetaxel for patients without PD-L1 expression (Figure 1).

We analyzed data from the perspective of the US Medicare system. We considered the costs of PD-L1 testing (Dako 22C3 immunohistochemistry assay), drug acquisition, adverse events, as well as agents prescribed after progression. Other direct costs such as administration costs, monitoring costs, and end-of-life costs were also considered [15]. Drug acquisition prices were based on the USA data. For nivolumab, we considered USD 24.69/mg on 10 February 2016. For pembrolizumab, we considered USD 43.80/mg on 10 February 2016. For atezolizumab, we considered USD 10.42/mg on 14 November 2016. The utility of each health state as well as the disutility of each relevant adverse event were obtained from the literature [16, 17].

The primary end point of this study was the incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life year (QALY) gained by using immunotherapy compared with docetaxel for the second-line treatment of NSCLC with or without PD-L1 expression determining treatment selection.

Secondary end points were the economic impact of each strategy expressed by the total amount expended each year, the number of life years saved, and the cost of each life year saved with or without PD-L1 assessment. Deterministic sensitivity analyses were carried out to test the robustness of the results.

Table 1. Deterministic sensitivity analysis parameters

Parameter	Mean deterministic	Lower value	Upper value
General			
Discount rate	10%	NA	NA
	20%	NA	NA
Average body weight	70	58.4	87.6
Body Surface Area	1.8	1.46	2.18
Costs			
Administration costs (per cycle)	$290	$232	$348
Monitoring costs CT (per cycle)	$658	$526	$790
Monitoring costs ICI (per cycle)	$732	$589	$878
End-of-life costs (per case)	$8632	$6906	$10 358
Outcomes			
Progression-free survival utility	0.65	0.63	0.67
Post-progression survival utility	0.43	0.39	0.47
Survival			
HR on PFS (CM 017)	0.62	0.47	0.81
HR on OS (CM 017)	0.59	0.44	0.79
HR on PFS (CM 057)	0.92	0.77	1.11
HR on OS (CM 057)	0.73	0.59	0.89
HR on PFS (KN 010)	0.88	0.74	1.05
HR on OS (KN 010)	0.71	0.58	0.88
HR on PFS (OAK)	0.95	0.82	1.10
HR on OS (OAK)	0.73	0.62	0.87

CT, chemotherapy; ICI, immune checkpoint inhibitors; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Model structure

In the decision-analytic model (Figure 1), patients were classified into three mutually exclusive health states: progression-free disease, post-progression disease, and death.

The PD-L1 positive arm of the model considered 1%, 5%, and 10% thresholds for nivolumab and 1% and 50% thresholds for pembrolizumab based on the data available.

For atezolizumab, we considered as positive all patients with PD-L1 expression score above 1 among TC or infiltrating cells (IC). We also divided the patients whose scores were 3 for TC or IC.

Clinical effectiveness and quality of life

We obtained effectiveness data from the area under curves of progression-free survival (PFS) and overall survival (OS) outcomes

Table 2. Summary of base-case analysis

Parameter	Squamous tumors		Non-squamous tumors		All histology		All histology	
	PD-L1 unselected		PD-L1 unselected		PD-L1 ≥1%		PD-L1 unselected	
	Nivo	Doc	Nivo	Doc	Pembro	Doc	Atezo	Doc
Median No. of cycles	15	5	14	7	9	7	8	7
Drug cost	$77 774	$12 326	$72 589	$17 256	$55 188	$17 256	$100 032	$17 256
AEs costs	$202	$6922	$1738	$7002	$1380	$3513	$749	$4415
PPS costs	$6638	$5925	$6989	$7676	$9599	$12 457	$5947	$9270
EOL costs	$7251	$8287	$7251	$8287	$6776	$8261	$7251	$8287
Adm costs	$4350	$1450	$4060	$2030	$2610	$2030	$2320	$2030
Mon costs	$8238	$3290	$8164	$4606	$6588	$4606	$5856	$4606
Total costs	$104 453	$39 516	$100 791	$46 856	$82 201	$48 182	$122 155	$45 864
Mean PFS	7.28	4.07	6.72	5.33	6.56	5.06	6.03	5.25
Mean PPS	11.80	6.45	14.50	9.60	15.78	8.95	16.05	7.95
Mean OS	19.08	10.52	21.22	14.93	22.34	14.01	22.08	13.20
Utility	0.82	0.45	0.88	0.63	0.92	0.59	0.90	0.57
AEs	0.00	−0.05	−0.01	−0.05	0.00	−0.02	0.00	−0.03
QALY	0.82	0.40	0.87	0.59	0.92	0.57	0.90	0.54
QALY gain	0.417		0.287		0.346		0.354	
ICER	$155 605		$187 685		$98 421		$215 802	
LYG	1.59	0.88	1.77	1.24	1.86	1.17	1.84	1.10
Incremental LYG	0.71		0.53		0.69		0.74	
Cost per Incremental LYG	$91 034		$102 896		$49 007		$103 095	
PD-L1 ≥1% or TC ≥ 1	QALY	0.322	QALY	0.480	QALY	Above	QALY	0.405
	ICER by QALY	$201 461	ICER by QALY	$112 311	ICER by QALY	Above	ICER by QALY	$188 632
PD-L1 ≥5%	QALY	0.481	QALY	0.740	QALY	NA	QALY	NA
	ICER by QALY	$135 080	ICER by QALY	$72 897	ICER by QALY	NA	ICER by QALY	NA
PD-L1 ≥10%	QALY	0.495	QALY	0.683	QALY	NA	QALY	NA
	ICER by QALY	$131 159	ICER by QALY	$78 921	ICER by QALY	NA	ICER by QALY	NA
PD-L1 ≥50% or TC 3	QALY	NA	QALY	NA	QALY	0.409	QALY	0.999
	ICER by QALY	NA	ICER by QALY	NA	ICER by QALY	$80 735	ICER by QALY	$76 459

Nivo, nivolumab; Doc, docetaxel; Pembro, pembrolizumab; Atezo, atezolizumab; No, number; AEs, adverse events; PPS, post-progression survival; EOL, end-of-life; Adm, administering; Mon, monitoring; PFS, progression-free survival; OS, overall survival; TC, tumor cells or infiltrating cells PD-L1 expression score.

reported in the trials' publications and supplementary materials. A lifetime model was carried out after the updates of the included studies [18–21]. We considered a horizon of 5 years.

QALY for the time of progression-free disease and the time after progression were calculated according to published utilities [16, 17]. We were unable to use different scores for each treatment arm because of the paucity of published data regarding quality of life. The disutility of the most frequent adverse events was also considered.

Medical costs

We considered a body weight of 70 kilograms and a body surface area of 1.8 square meters to calculate the costs of each treatment. The costs of adverse events were calculated according to published data corrected by inflation [22–24].

The costs of post-progression therapies were calculated according to the number of patients receiving each post-progression drug listed in the supplementary material of each study.

Deterministic sensitivity analysis

We carried out several one-way deterministic sensitivity analyses (DSA) to evaluate the influence of uncertainty in individual input parameters on the ICER. We considered the 95% confidence intervals or plausible ranges (if no confidence intervals were available) of uncertainty for the most important variables (Table 1). The probability of reaching cost-effectiveness based on a Willingness To Pay (WTP) threshold of USD 100 000 per QALY gained was analyzed with or without PD-L1 testing for each drug assessed by each randomized clinical trial (RCT).

Budget impact analysis

The number of eligible patients for each treatment strategy was approximated using the estimated number of new cases in the United States published by the Surveillance, Epidemiology, and End Results Program (SEER) [2]. The proportion of patients in advanced stage treated at the first- and the second-line setting were calculated using the National Lung Cancer Audit Report 2014 (NLCA) and the European real life study published by Moro-Sibilot et al. respectively [25, 26]. The proportion of patients with PD-L1 expression ≥1% or ≥50% was retrieved from the included RCTs [8–10].

The authors considered a hypothetical market penetration of 100% among each eligible population after the release of immune checkpoints inhibitors for better understanding of the economic impact of each treatment strategy.
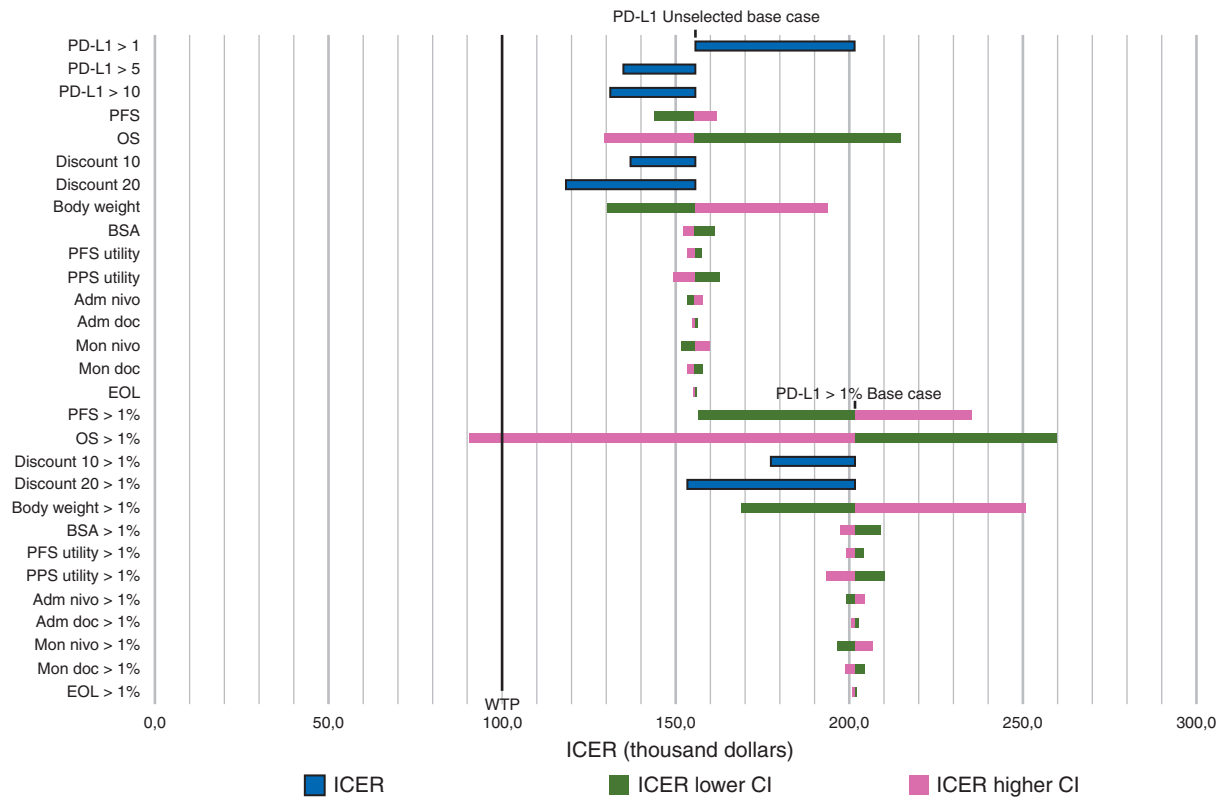
Figure 2. Tornado Diagram for nivolumab vs docetaxel (SQ Tumors). SQ, squamous; PFS, progression-free survival; OS, overall survival; BSA, body surface area; PPS, post-progression survival; Adm, administration costs; Nivo, nivolumab; Doc, docetaxel; Mon, monitoring costs; EOL, end-of-life costs; >1%, PD-L1 expression >1%; ICER, incremental cost-effectiveness ratio; CI, confidence interval; WTP, willingness to pay.

Results

Base-case scenarios

In the base case of patients with squamous histology, the QALY gained with nivolumab was 0.417, and the corresponding ICER was USD 155 605. The incremental life-years gain (LYG) was 0.71 and the cost per incremental LYG was USD 91 034. PD-L1 expression improved incremental QALY only for patients with PD-L1 $\geq$5% and $\geq$10%, by 15% and 18%, respectively. In the base case of patients with non-squamous tumors, the incremental QALY for nivolumab was 0.287, and the corresponding ICER was USD 187 685. The incremental LYG was 0.53 and the cost per incremental LYG was USD 102 896. PD-L1 expression improved incremental QALY for patients with PD-L1 $\geq$1%, $\geq$5%, and $\geq$10%, by 67%, 157%, and 137%, respectively.

All patients treated with pembrolizumab had at least 1% PD-L1 expression. In patients treated with pembrolizumab, the incremental QALY was 0.346, and the ICER was USD 98 421. The incremental LYG was 0.69 and the cost per incremental LYG was USD 49 007. PD-L1 expression above 50% improved QALY by 18% and decreased ICER to USD 80 735.

In the base case of patients treated with atezolizumab, the QALY gain was 0.354, and the corresponding ICER was USD

215 802. The incremental LYG was 0.74 and the cost per incremental LYG was USD 103 095. PD-L1 expression TC or IC $\geq$1, and TC or IC 3 improved incremental QALY by 15% and 183%, respectively. Table 2 summarizes all base-case results.

Deterministic sensitivity analysis

OS 95% confidence intervals (95% CI) had the strongest influence on the incremental QALY (ranging from 0.047 in the lower OS value to 1.202 in the higher OS value). The strongest influence on incremental costs was body weight [ranging from USD 68 171 for the 95% CI lower body weight (58.4 kg) to USD 250 953 for the 95% CI higher body weight value (87.6 kg)].

The second most important factor influencing the cost-effectiveness of immunotherapy were hypothetical discounts in the immune checkpoint inhibitors acquisition costs. With at least a 10% discount, the probability that immunotherapy was cost-effective increased from 21.9% (with no discount) to 23.1% (with 10% of discount), and to 24.3% when a discount of 20% was considered.

All deterministic sensitivity analysis are summarized in Tornado Diagrams for each monoclonal antibody (Figures 2–5).

Giving immunotherapy only for patients with PD-L1 expression $\geq$ 1% or TC $\geq$ 1 improved almost all incremental QALY and
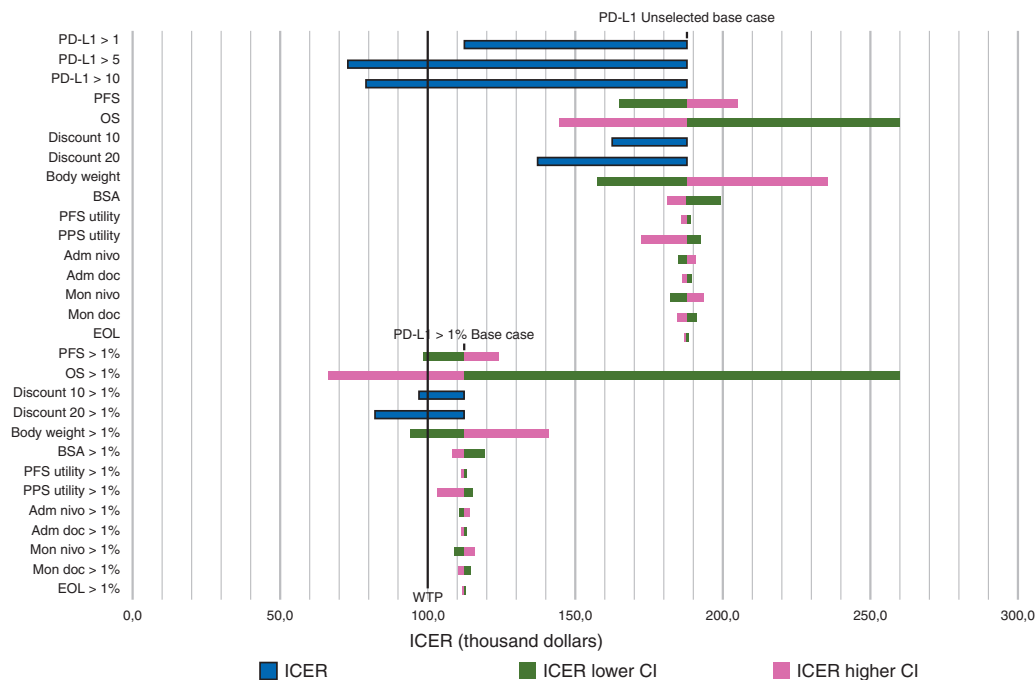
Figure 3. Tornado Diagram for nivolumab vs docetaxel (nSQ Tumors). nSQ, non-squamous; PFS, progression-free survival; OS, overall survival; BSA, body surface area; PPS, post-progression survival; Adm, administration costs; Nivo, nivolumab; Doc, docetaxel; Mon, monitoring costs; EOL, end-of-life costs; >1%: PD-L1 expression >1%; ICER, incremental cost-effectiveness ratio; CI, confidence interval; WTP, willingness to pay.
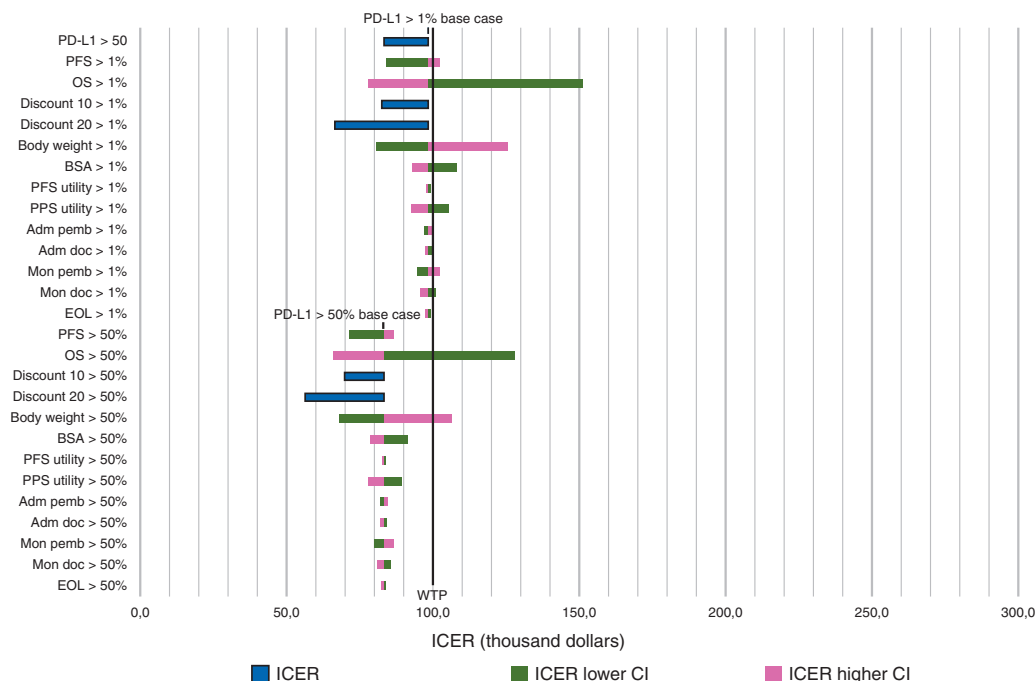

Figure 4. Tornado Diagram for pembrolizumab vs docetaxel. PFS, progression-free survival; OS, overall survival; BSA, body surface area; PPS, post-progression survival; Adm, administration costs; Pemb, pembrolizumab; Doc, docetaxel; Mon, monitoring costs; EOL, end-of-life costs; >1%: PD-L1 expression >1%; ICER, incremental cost-effectiveness ratio; CI, confidence interval; WTP, willingness to pay.

improved cost-effectiveness as a whole. Considering a WTP of USD 100 000, PD-L1 expression ≥1% or TC ≥1 increased the probability that immunotherapy be more cost-effective than docetaxel (from 0% with no testing to 29% with PD-L1 testing; Figure 6A and B).

Budget impact

The estimated number of advanced NSCLC patients eligible for second-line treatment according to the eligibility criteria previously used in the RCTs was 37 638, comprised of 8656 patients
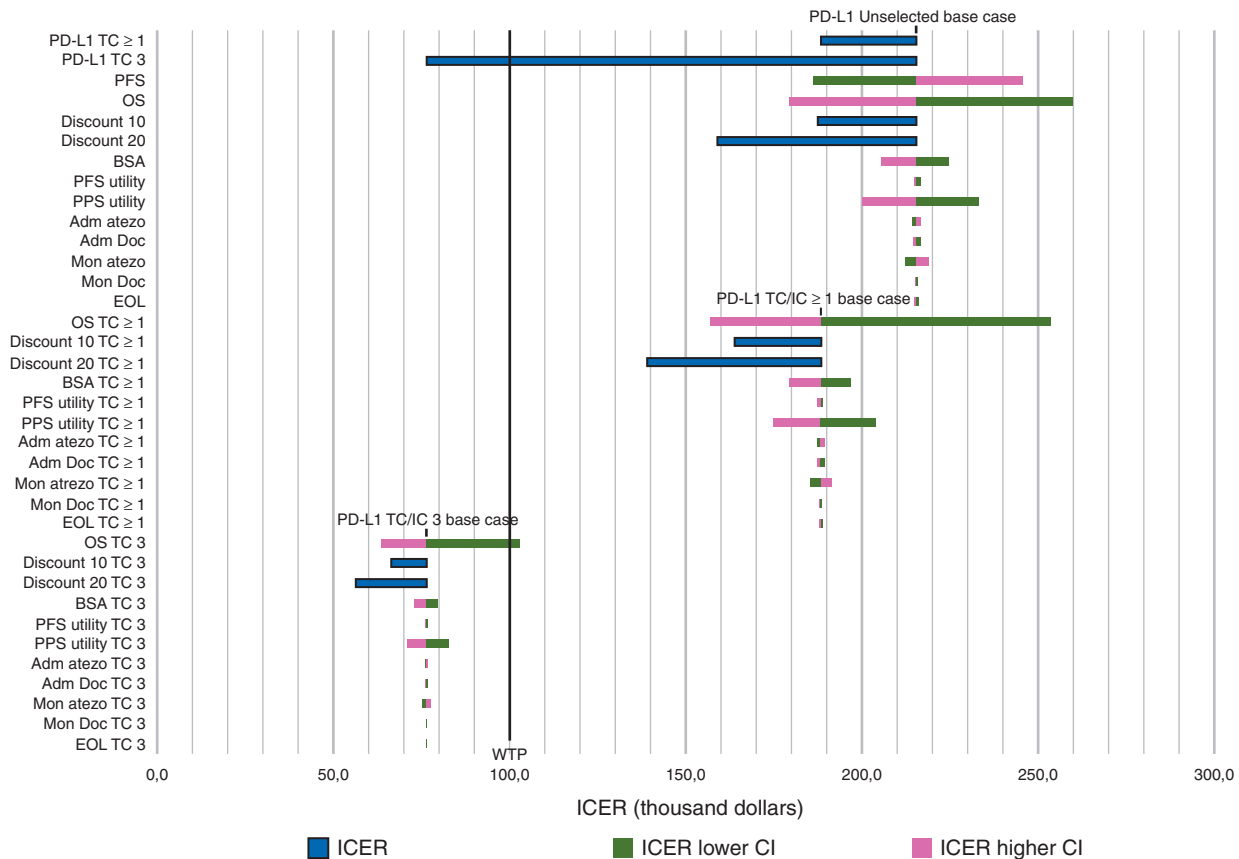
Figure 5. Tornado Diagram for atezolizumab vs docetaxel. TC, tumor cells or infiltrating cells PD-L1 expression score; PFS, progression-free survival; OS, overall survival; BSA, body surface area; PPS, post-progression survival; Adm, administration costs; Atezo, atezolizumab; Doc, doce-taxel; Mon, monitoring costs; EOL, end-of-life costs; ICER, incremental cost-effectiveness ratio; CI, confidence interval; WTP, willingness to pay.

with squamous histology and 28 982 patients with non-squamous histology each year.

Treating this entire cohort with nivolumab could lead to an in-cremental cost of USD 1.6 billion annually. Treating this same co-hort with atezolizumab could lead to an incremental cost of USD 2.4 billion annually.

Treating only patients with at least 1% PD-L1 expression (46% of eligible patients) with nivolumab would represent an annual incremental cost of USD 849 million.

Pembrolizumab treatment was studied (in a phase III trial) only for patients with at least 1% of PD-L1 expression (about two thirds of patients enrolled to participate in KeyNote 010). The annual in-cremental cost of this treatment selection strategy would be USD 971 million. Treating only patients with tumor PD-L1 expression >50% with pembrolizumab (∼28% of the eligible population) represents an annual incremental cost of USD 411 million.

Discussion

Recently published and presented clinical trials continue to con-firm the effectiveness of immune checkpoint inhibitors as se-cond line agents for NSCLC [8–11]. Despite promising results, a minority of patients with NSCLC respond to these immuno-therapy agents, underscoring the need for predictive biomarkers [27]. PD-L1 expression in TCs is such a potential biomarker.

Evidence demonstrates that outcomes are better for patients whose tumors have increasing levels of PD-L1 [12, 13, 28]. Improving cost-effectiveness through patient selection may in-crease uptake of immune checkpoint inhibitors by rationalizing therapy from a clinical standpoint thus making treatment more cost-effective.

In December 2015, the British National Institute for Health and Care Excellence (NICE) issued an opinion that nivolumab was not cost-effective for the second-line treatment of squamous NSCLC [8]. Without biomarker selection, they estimated ICERs between GBP 109 000 and GBP 129 000 (USD 133 895 and USD 154 463) when the limit accepted by the institute is generally around GBP 30 000 (USD 36 852) [29].

Our study found that in most scenarios that did not select pa-tients by PD-L1 expression immunotherapy is not cost-effective in the second-line treatment of NSCLC in the United States. PD-L1 testing may improve cost-effectiveness of immune checkpoint inhibitors. The deterministic sensitivity analysis confirmed that these results are robust.

Although nivolumab and atezolizumab are currently approved for patients with NSCLC who progressed after platinum-doublet chemotherapy regardless of PD-L1 expression, from the payers' point of view, treating only patients whose tumors express PD-L1 could decrease the budget impact by up to 50% and this may im-prove access to these innovative therapies to patients who benefit the most in resource-constrained settings.
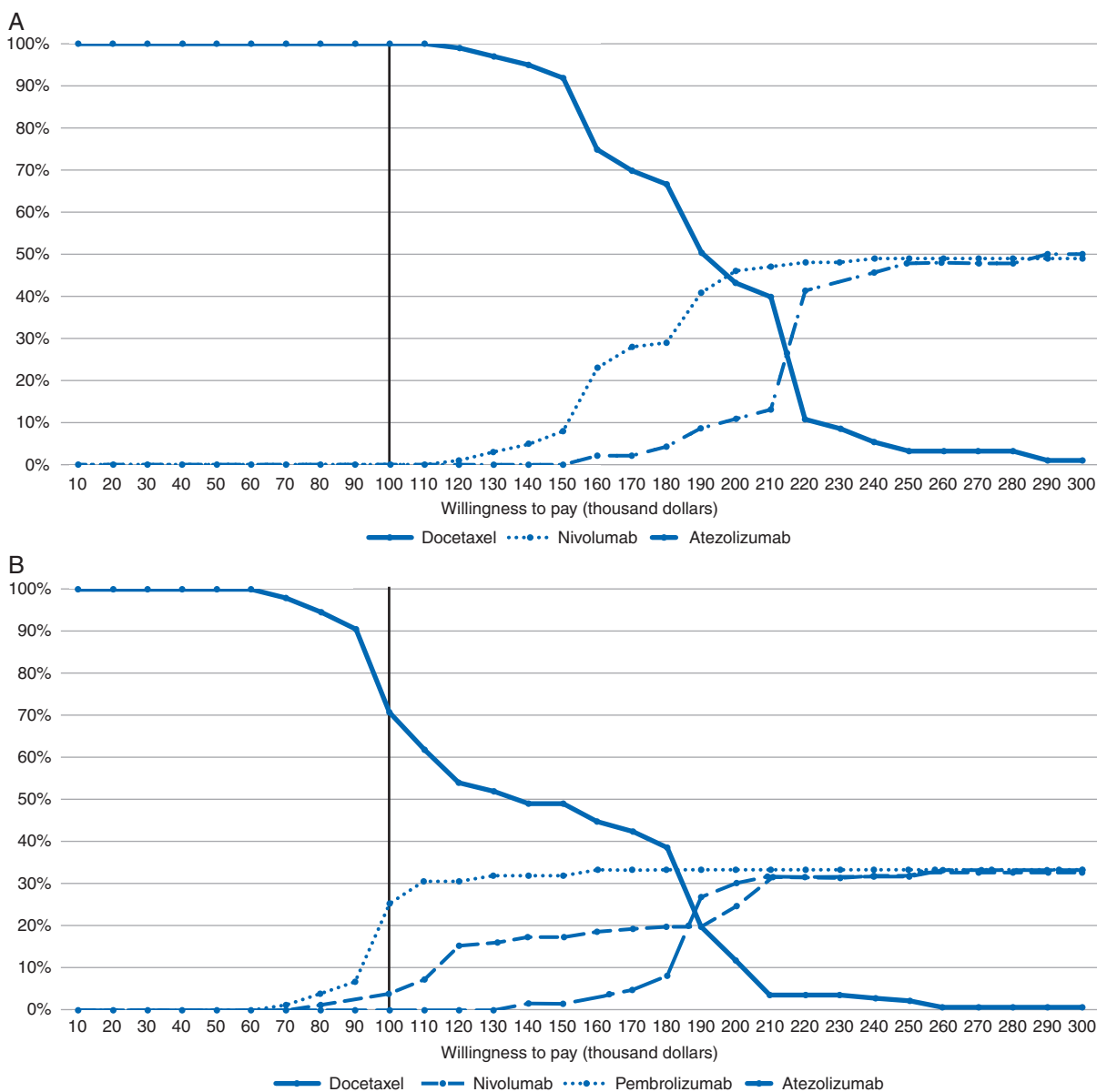
Figure 6. Probability of being cost-effective. 6A: PD-L1 unselected; 6B: PD-L1 positive (PD-L1 ≥ 1% or Tumor Cells or Infiltrating Cells PD-L1 expression score ≥ 1).

Our data are comparable to other previously published health economics analysis [30–32], but other studies were limited by the inclusion of only one clinical trial comparing nivolumab or pembrolizumab versus docetaxel while ours included all published trials on immune checkpoint inhibitors, placing no restriction on tumor histology [30–32].

Interestingly, analyzing the nivolumab data, the selection of patients by PD-L1 expression ≥1% may have a negative impact in the cost-effectiveness among patients with tumors of squamous histology. That notwithstanding, using a higher PD-L1 expression cutoff (≥5% or ≥10%) may improve cost-effectiveness. This analysis by tumor histology was not possible with pembrolizumab nor atezolizumab given the lack of available published data.

Nonetheless, our model has limitations. Utilities were extrapolated from literature and were not related to the treatments of the studies included in the analysis, introducing a further possibility of bias [33]. Another limitation is the difficulty in finding clear data regarding post-progression therapies in the published RCTs.

Finally, our study was not planned to make comparisons between immune checkpoint inhibitors. We designed this study to assess the cost-effectiveness of immunotherapy versus docetaxel with or without patient selection by PD-L1 expression.

Although we demonstrated that therapy selection based on PD-L1 expression increases cost-effectiveness and decreases the overall economic impact of therapy with immune checkpoint inhibitors, our results also show that the total number of life-years

saved by these drugs would decrease with biomarker selection. Further clinical, translational and health economics studies and societal discussion is warranted in order to find the optimal acceptable strategy for patient selection.

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Disclosure

The authors have declared no conflicts of interest.

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