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ORIGINAL RESEARCH

Cost-Effectiveness of PD-L1 Testing in Non-Small Cell Lung Cancer (NSCLC) Using In Vitro Diagnostic (IVD) Versus Laboratory-Developed Test (LDT)

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ABSTRACT

Introduction: Accurate PD-L1 testing for non-small cell lung cancer (NSCLC) maximizes the benefits of immune checkpoint inhibitor (ICI) drugs like pembrolizumab. False negative test results deny ICI treatments to eligible patients, worsening clinical and economic outcomes, while false positives increase costs by using ICI treatments without their benefits. This study evaluates the cost-effectiveness of PD-L1 testing with an in vitro diagnostic (IVD) compared to a laboratory-developed test (LDT) for allocating patients with NSCLC to treatment with either pembrolizumab or chemotherapy using the German healthcare system as a model.

Methods: We developed a decision analytical model to evaluate the cost-effectiveness of PD-L1 testing with a regulatory body approved IVD compared to an LDT from the national German healthcare payer (statutory health insurance system) perspective. Accuracy of PD-L1 testing was based on data from two independent proficiency testing programs. The 1-year model was based on outcomes data from the KEYNOTE-024 clinical trial and treatment patterns reflecting current German practices.

Results: IVDs produced accurate PD-L1 testing results in 93% (752/811) of tested cases compared to 73% (492/672) with LDTs. Most misclassifications concerned false negatives, occurring in 21% of LDTs vs 7% of IVDs. Total costs of the IVD

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group (48,878 €) were 196 € higher than the LDT group (48,682 €). These costs incorporate testing, first- and second-line therapy, managing treatment-related grade 3+ adverse events (AEs), and end-of-life costs for those who died within the year. Total effectiveness (percentage of patients successfully diagnosed and prescribed the correct therapy per German treatment guidelines) was 19 percentage points higher for the IVD group (88%) compared to the LDT group (69%). These differences in costs and effects lead to an incremental cost-effectiveness ratio (ICER) of 1057 €.
Conclusion: Compared to LDT technology, on-label IVD use for PD-L1 testing is only slightly more costly and substantially more effective for aligning patients with PD-L1-positive NSCLC with ICI therapy according to German practice guidelines. Given these findings, changes to testing and reimbursement policies may be considered to maximize patient outcomes in NSCLC.

Keywords: Advanced NSCLC; Cost-effectiveness; Diagnostic; Germany; PD-L1; Pembrolizumab

Key Summary Points

Why carry out this study?

In many countries, allocating non-small cell lung cancer (NSCLC) patients to treatment with either pembrolizumab or chemotherapy relies on PD-L1 testing using either in vitro diagnostic (IVD) or a laboratory-developed test (LDT).

Accurate testing is essential to personalize therapy and maximize the benefit of immune checkpoint inhibitor (ICI) drugs such as pembrolizumab, since eligible patients have been shown to have improved survival and side effect profiles compared to chemotherapy.

What was learned from the study?

PD-L1 testing accuracy was 93% in the IVD group compared to 73% in the LDT group, with most misclassifications being false negatives (7% of IVDs and 21% of LDTs).

Total per patient costs of the IVD group (48,878 €) were 196 € higher than the LDT group (48,682 €), with total effectiveness 19 percentage points higher for IVD (88%) compared to LDT (69%).

Accurate PD-L1 testing with IVD is only slightly more expensive than LDT, ensures optimal treatment for those eligible for drugs like pembrolizumab, improves survival, and limits adverse event exposure.

INTRODUCTION

Recent advances in therapies for non-small cell lung cancer (NSCLC) have improved the prognosis in patients with late-stage disease. New treatments involve biomarkers that target various receptors, proteins, and pathways. One such protein, the programmed cell death 1 (PD-1), is expressed on the surface of activated T cells [1, 2]. When PD-1 binds to one of its ligands (PD-L1) the cytotoxic T cell response is inhibited [3, 4], allowing tumors to escape recognition and elimination by the immune system [5]. NSCLC tumor samples having a PD-L1 expression of 50% or greater show improved survival and side effect profiles with immune checkpoint inhibitor (ICI) drugs that block the PD-L1 pathway compared to chemotherapy [6–16]. Pembrolizumab (Keytruda®, Merck) was approved by the European Medicines Agency (EMA) in 2015 for first-line treatment of advanced NSCLC in patients whose tumors have PD-L1 expression of 50% or greater [17].

Approximately 18–28% of patients with NSCLC have PD-L1 expression of 50% or greater [6, 10, 18–20]. International guidelines, as well as those specific to Europe and Germany—the latter serving in this study as a model to analyze cost-effectiveness of PD-L1 testing—recommend testing for PD-L1 expression in all patients with advanced NSCLC [21–25].

In Germany, two companion diagnostic assays are Conformitè Européenne in vitro diagnostic (CE-IVD) marked (demonstrating the IVD complies with the European Union's

regulations) and available for use in PD-L1 testing to determine eligibility for pembrolizumab treatment in patients with advanced NSCLC: Roche's VENTANA PD-L1 (SP263) Assay (SP263 hereafter) and Agilent's PD-L1 IHC 22C3 pharmDx (22C3 hereafter). German laboratories, like those in other European countries, may instead choose to use a laboratory-developed test (LDT) and receive the same reimbursement. For this analysis, an assay is considered an IVD when a CE-IVD approved immunohistochemical (IHC) assay or kit is used within its intended use, vendor-recommended protocol settings, and scoring guidelines. Any deviation from these methods changes the status to LDT. Furthermore, all concentrated primary antibodies or kits without predictive claims are also LDTs.

While laboratories in many European countries (e.g., Belgium, Denmark, France, Germany, Holland, Portugal) use a mix of LDT and IVD assays for PD-L1 testing for NSCLC, the tests need to be validated. Validating test quality is the responsibility of the performing laboratory, and no de facto guidelines exist on how to validate, which raises challenges to providing safe, high-quality, effective diagnostic tests [26]. In addition, laboratories may develop their own tests for analyzing PD-L1 expression. There is limited published evidence comparing the effectiveness of IVDs to LDTs in measuring PD-L1 expression in patients with NSCLC.

A systematic review of 35 studies testing PD-L1 expression in patients with NSCLC found that IHC methods varied greatly, using different antibodies, antibody detection systems, staining cutoff points, and scoring methods to classify patients [27]. The authors concluded the need for standardized assays to accurately detect PD-L1 expression for selecting patients with the greatest chance to benefit from anti-PD-L1 therapies.

There is some evidence that IVD assays produce consistent results [28–30]. A study evaluating 500 NSCLC tissue samples for PD-L1 expression determined that three commercially available assays (Roche's SP263, Agilent's 22C3, and Agilent's 28-8) had high concordance and could potentially be used interchangeably [29]. However, a recent study showed that 22C3 IHC had significantly higher PD-L1 expression than SP263 IHC ($p < 0.001$), as discrepant scores crossed the clinically relevant thresholds of 1% and 50% PD-L1 expression [31]. While these assessments used comparatively small numbers of participants and may not refute interchangeability, the results suggest caution.

Accurate testing is essential to personalize therapy and maximize the benefit of ICI drugs such as pembrolizumab. The KEYNOTE-024 trial found patients on pembrolizumab had significantly fewer grade 3+ treatment-related adverse events (AEs) than those on chemotherapy (26% vs 53%), and longer progression-free survival (median 10.3 months vs 6.0 months) during the first year of treatment [8]. In Germany and many European countries, false negative PD-L1 results (i.e., a patient actually has PD-L1 expression of 50% or greater, but the test reports expression less than 50%) would deny pembrolizumab to eligible patients. This could increase healthcare costs as chemotherapy patients experience more AEs, less progression-free and overall survival, and likely a decrease in quality of life. False positive results (i.e., a patient actually has PD-L1 expression less than 50%, but the test reports expression of 50% or greater) increase healthcare costs by using pembrolizumab without its clinical benefits. The goals of this study were to compare the cost-effectiveness of PD-L1 testing accuracy using IVD vs LDT for patients with NSCLC, and to evaluate the clinical and economic impact of inaccurate test results from a German payer perspective.

METHODS

Design

We developed a decision analytical model to evaluate the cost-effectiveness of PD-L1 testing with IVD compared to LDT for allocating patients with NSCLC to treatment with either pembrolizumab or chemotherapy. We used Germany as a model based on evaluation of data access and granularity, and healthcare system construction and transparency. The 1-year model was based on outcomes data from

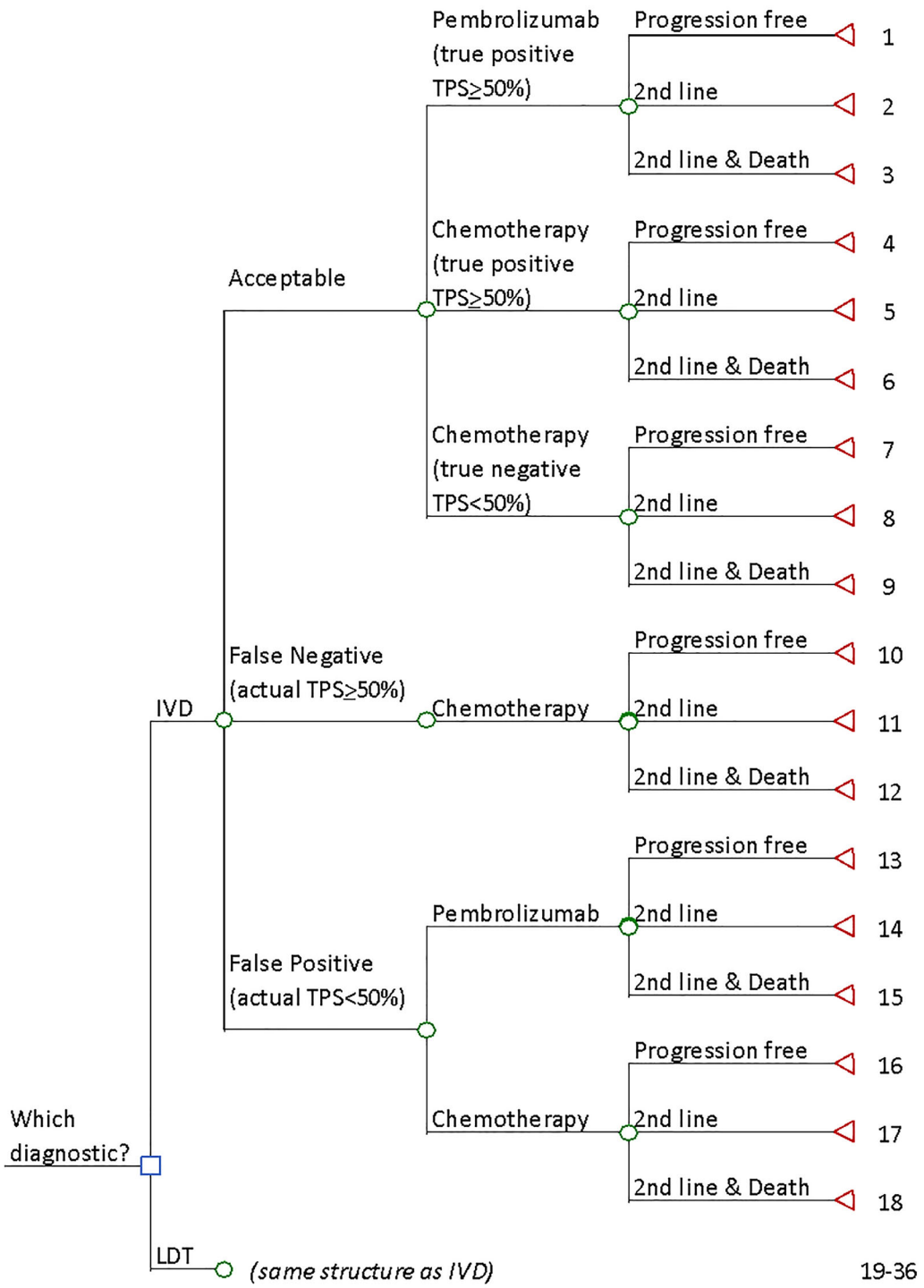

Fig. 1 Decision tree model structure. *IVD* in vitro diagnostic, *LDT* laboratory-developed test, *TPS* total proportion score, *2nd line* second-line treatment

the KEYNOTE-024 clinical trial [8]. The clinical trial was international and the treatment patterns in this model reflect current practices in many European countries, where patients have access to treatment via public healthcare systems, insurance, or a mixture. Focusing on Germany as a model, patients may opt into statutory insurance provided by nearly 100 nonprofit "sickness funds" or may be eligible to purchase private health insurance [32, 33]. Between 86% and 88% of Germans are funded by the statutory health insurance [33]; therefore, the perspective of this study is that of a national German healthcare payer. This study received institutional review board approval from the University of Arizona and complied with all ethical guidelines.

Model Structure and Outcomes

The decision tree model simulated possible outcomes using IVD and LDT, comprising 36 pathways (Fig. 1; pathway descriptions in Table S1 in the electronic supplementary material). Analysis was conducted using Microsoft Excel (2016) and TreeAge Pro (2021).

A true positive was considered PD-L1 expression of 50% or greater (when actually 50% or greater) indicating a patient in Germany was eligible to receive pembrolizumab. A true negative was PD-L1 expression less than 50% (when actually less than 50%) indicating a patient was not eligible to receive pembrolizumab, but instead would receive chemotherapy. A false positive was PD-L1 expression of 50% or greater (when actually less than 50%) indicating a patient was eligible to receive pembrolizumab, but they should have received chemotherapy. A false negative was PD-L1 expression of less than 50% (when actually 50% or greater) indicating a patient was ineligible to receive pembrolizumab, so they received chemotherapy but should have received pembrolizumab.

The primary outcome in this model was a successfully diagnosed patient, defined as having an accurate PD-L1 test result (true positive or true negative) and receiving the correct treatment, as recommended in the German treatment guidelines (IVD pathways 1–3, 7–9 and LDT pathways 19–21, 25–27 in Fig. 1) [34].

The decision tree structure was based on the KEYNOTE-024 trial study design [8, 35] as well as German-specific treatment patterns identified in the CRISP registry [21]. KEYNOTE-024 was a multicenter trial sponsored by Merck for patients with advanced NSCLC who were treatment naïve. Patients with a PD-L1 expression of 50% or greater were randomized to receive pembrolizumab or the investigator's choice of one of five chemotherapy combinations [8, 35]. Our 1-year model incorporated 12-month outcomes from the trial.

The CRISP registry has collected real-world treatment and outcomes data on 3717 patients with advanced NSCLC in Germany [21]. Patients were recruited between 2015 and 2019 from 150 German sites. The registry assesses whether German guidelines are being followed, including biomarker testing frequency, methods utilized, and testing results. Despite the national guidelines recommending pembrolizumab as a first-line treatment for patients with NSCLC with PD-L1 expression of 50% or greater, CRISP data revealed that only about 77% of these patients received pembrolizumab, while 23% received chemotherapy [19]. These data were incorporated into the model structure to reflect real-world German treatment practices rather than the recommended guidelines.

The primary outcome of this analysis is to calculate and interpret the incremental cost-effectiveness ratio (ICER) indicating the cost per additional successfully diagnosed and correctly treated patient using PD-L1 IVD versus LDT. The ICER value equals the difference in total costs between IVD and LDT divided by the difference in probabilities of diagnostic success.

Resource Use

IVDs and LDTs

PD-L1 assessments were conducted for each patient using either an IVD or LDT.

NSCLC First-Line Treatment

On the basis of German treatment guidelines and KEYNOTE-024 data, patients with a PD-L1

Table 1 External quality assessment (EQA) findings for in vitro diagnostic (IVD) and laboratory-developed testing (LDT) for PD-L1 expression

	Acceptable		False negative		False positive		Total	
	n	%	*n*	%	*n*	%	*n*	%
UK NEQAS[a]								
IVD	507	92	40	7	6	1	553	69
LDT	161	66	66	27	16	7	243	31
NordiQC[b]								
IVD	245	95	13	5	0	0	258	38
LDT	331	77	78	18	20	5	429	62
Total								
IVD	752	93	53	7	6	1	811	55
LDT	492	73	144	21	36	5	672	45

Sources: 1. NordiQC data. Received July 16, 2020; 2. UK NEQAS data. Received June 30, 2020
UK NEQAS United Kingdom National External Quality Assessment Service, *NordiQC* Nordic Immunohistochemical Quality Control, *IVD* in vitro diagnostic, *LDT* laboratory-developed test
[a]Data based on eight runs assessed from April 2018 to January 2020: (1) April 1, 2018, (2) July 1, 2018, (3) October 1, 2018, (4) January 1, 2019, (5) April 1, 2019, (6) July 1, 2019, (7) October 1, 2019, (8) January 1, 2020. IVD assay data (based on 22C3 and SP263 antibody clones) and LDT non-assay data are assumed to be tested for pembrolizumab
[b]Data based on five runs from January 2017 to July 2019: (1) January to April 2017, (2) September to December 2017, (3) January to April 2018, (4) September to December 2018, (5) March to July 2019. IVD assay data (based on SP263 and 22C3 and LDT non-assay data (including off-label use of IVD assays, SP142, 28-8 assays and any other LDTs) are assumed to be tested for pembrolizumab

expression of 50% or greater received pembrolizumab IV 200 mg every 3 weeks until disease progression, death, or 1 year was reached [8, 34]. For patients with expression less than 50% investigators chose one of five platinum-based chemotherapy combinations (carboplatin combined with either pemetrexed, gemcitabine, or paclitaxel; or cisplatin combined with either pemetrexed or gemcitabine). Chemotherapy patients received 4–6 three-week cycles followed by optional pemetrexed maintenance therapy for combinations that included pemetrexed. For costing purposes, we used the median of five cycles with optional maintenance therapy until disease progression, death, or 1 year was reached. Chemotherapy treatments in the model (70% carboplatin containing and 30% cisplatin containing) were based on the actual combinations selected by investigators in KEYNOTE-024, which was consistent with German treatment patterns reported in the CRISP registry [19–21]. The CRISP registry does not further specify therapy types beyond containing either carboplatin or cisplatin.

NSCLC Second-Line Treatment

German treatment guidelines recommend platinum-containing chemotherapy as a second-line treatment for pembrolizumab patients who have disease progression [34]. Based on treatment patterns reported by the KEYNOTE-024 trial, CRISP registry, and German treatment guidelines, the model assumed second-line monotherapy with either carboplatin (70%) or cisplatin (30%) [8, 19–21, 34].

German treatment guidelines allow patients who progress on first-line chemotherapy to receive either pembrolizumab or docetaxel, regardless of PD-L1 expression [19–21, 34]. Because treatment utilization data were

Table 2 German treatment patterns for first-line therapies

	PD-L1 TPS ≥ 50%		PD-L1 TPS < 50%		Sources
Total CRISP sample (*N*)[a]	320		1115		[19, 20]
1st line drug therapy, *n* (%)					
Pembrolizumab	247	77.2%	0	0.0%	[19, 20]
Chemotherapy[b]	73	22.8%	1115	100.0%	[19, 20]
Carboplatin-based	–	–	704	63.1%	[20]
Cisplatin-based	–	–	307	27.5%	[20]
Carboplatin/cisplatin-based	–	–	46	4.1%	[20]
Other chemotherapy[c]	–	–	58	5.2%	[20]

CRISP Clinical Research Platform into Molecular Testing, Treatment and Outcomes of (Non-)Small Cell Lung Carcinoma Patients in Germany, *PD-L1* programmed death ligand 1, *TPS* total proportion score

[a]CRISP also reports additional patients that are excluded from this analysis because of insufficient information about the therapies used. These include "another/targeted therapy" for 31 more patients in the TPS > 50% group and 164 more patients in the TPS < 50% group; "carboplatin/cisplatin" therapy for 46 more patients in the TPS < 50% group; "other chemotherapy" for 58 more patients in the TPS < 50%

[b]CRISP does not specify the types of chemotherapy received by patients in the TPS ≥ 50% group, so this information is assumed on the basis of the types and proportions listed for the TPS < 50% group

[c]"Other, not specified therapies, e.g., study medication". However, it was unclear which "other" the poster table notes refers to, or if it refers to both. If one, then probably refers to "Other CT" because the next table note concerned "Targeted therapy"

unavailable for such patients, the model assumed 50% use for each treatment. The model also assumed that all patients who progressed and lived would remain on these second-line treatments until the end of the 1-year model period.

Treatment-Related Adverse Events (AEs)

This analysis included grade 3+ treatment-related AEs from among all treatment-related AEs that occurred in 10% or more patients from the KEYNOTE-024 trial [8].

Death

Overall survival curves were used to estimate numbers of deaths at months 3, 6, 9, and 12 [8, 35]. Those who died during each quarter were assumed to live until the end of the period (e.g., those who died between months 1 and 3 were assumed to die at the end of month 3 and received 3 months of treatment costs). Because median time to progression was 6 months in the chemotherapy group, only deaths occurring after 6 months included second-line treatment costs. Similarly, because those on pembrolizumab had a median progression of 10.3 months, second-line treatments were only included for those dying in the quarter ending in month 12. Additional cost was included to account for end-of-life expenses over the last 30 days based on estimates for German patients with lung cancer [36].

Patients with false positive test results received pembrolizumab. Because these patients had less than 50% PD-L1 expression, we assumed their progression-free survival and overall survival were equivalent to those reported for the chemotherapy group [8], while their probabilities and costs associated with grade 3+ AEs were based on pembrolizumab data.

Event Probabilities

Table 1 summarizes the probabilities of IVD/LDT testing accuracy obtained from quality assurance data provided by Nordic immunohistochemical Quality Control (NordiQC) based in Denmark and the United Kingdom's National External Quality Assessment Service (UK NEQAS) [37, 38]. Pathology laboratories participate in testing schemes designed by external quality agencies to examine agreement between laboratories in IHC quality, wherein differences in performance between IVDs and LDTs can also be explored. Participating laboratories benefit from receiving guidance on achieving optimal results. Inconclusive test results do not impact the model, as laboratories would simply analyze additional material from the original tissue sample without additional costs or consequences to payers or patients.

CRISP registry data were used to estimate probabilities of patients in Germany receiving either pembrolizumab or chemotherapy depending on PD-L1 expression (Table 2) [19–21]. Clinical trial data provided probabilities of patients receiving specific types of platinum-based chemotherapies, as well as model inputs for the number of patients and time to progression, death, and the number and types of treatment-related AEs (Table 3) [8].

Direct Medical Costs and Sources

The model included the following direct medical costs: IVD/LDT diagnostic tests; pembrolizumab and chemotherapy; treatment-related grade 3+ AEs; and end-of-life expenses for those who died (Table 4). All costs were adjusted for inflation to 2020 euros using the German Consumer Price Index for Health (CC13-06) [39].

IVDs and LDTs

German costs were used for IVD/LDT diagnostics. Various IVDs and LDTs are used in Germany for PD-L1 testing, and because reimbursement is the same regardless of test used, a single cost (27 €) was used for these resources [40].

NSCLC First- and Second-Line Treatments

Medication costs were based on annual costs listed in German reimbursement reports [41]. We divided the total annual costs by the number of cycles over 1 year to obtain per cycle estimates of drug costs. For example, the per cycle cost for pembrolizumab was 6222 € (annual cost of 105,768 € divided by 17 cycles). Duration and costs of second-line treatment were based on median progression-free survival for each treatment group. For example, patients who progressed on chemotherapy received five cycles of first-line chemotherapy until progression at 6 months followed by second-line treatment with either pembrolizumab (50%) or docetaxel (50%) for the remaining 6 months.

Treatment-Related Adverse Events (AEs)

Costs of grade 3+ treatment-related AEs were based on German estimates from published literature [42–44].

Death

To account for end-of-life care, 4313 € (SD = 7481 €) was included for patients who died [36].

Sensitivity Analyses

To address uncertainty in model parameters, a probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations was conducted. All event probabilities were included and based on beta distributions. End-of-life costs were included and used a gamma distribution, while all other cost parameters were excluded from the probabilistic analysis, either because they were fixed costs or the cost sources lacked additional information needed.

A series of one-way analyses using upper- and lower-bound estimates examined the impact of every parameter in the model upon overall results. These deterministic analyses used the published ranges; for fixed values, estimates were varied by ± 20%.

Table 3 Treatment outcomes and probability estimates

	Pembrolizumab (*n* = 154)	**Chemotherapy (*n* = 150)**
Progression-free survival (PFS)[a]		
Median PFS (months)[b]	10.3	6.0
PFS at 6 months (%)[c]	0.621	0.503
PFS at 12 months (%)[d]	0.475	0.150
2nd line therapy at 12 months (%)[a]	0.228	0.398
Deaths (cumulative %)[a]		
3 months[d]	0.100	0.180
6 months[e]	0.198	0.276
9 months[d]	0.250	0.400
12 months[f]	0.297	0.452
Adverse events (grade 3+)[g]		
Anemia	0.019	0.193
Colitis	0.013	–
Decreased appetite	–	0.027
Decreased neutrophil count	–	0.040
Decreased platelet count	–	0.060
Decreased white cell count	–	0.020
Diarrhea	0.039	0.013
Fatigue	0.013	0.033
Hypophysitis	0.006	–
Nausea	–	0.020
Neutropenia	–	0.133
Pneumonitis	0.026	0.007
Severe skin reaction	0.039	–
Stomatitis	–	0.013
Thrombocytopenia	–	0.053
Type 1 diabetes mellitus	0.006	–
Vomiting	0.006	0.007
Chemotherapy treatment mix		
Carboplatin–gemcitabine	–	0.133
Carboplatin–paclitaxel	–	0.113
Carboplatin–pemetrexed	–	0.253
Carboplatin–pemetrexed with pemetrexed maintenance	–	0.187

Table 3 continued

	Pembrolizumab (n = 154)	Chemotherapy (n = 150)
Cisplatin–gemcitabine	–	0.073
Cisplatin–pemetrexed	–	0.120
Cisplatin–pemetrexed with pemetrexed maintenance	–	0.120

Costs were excluded for 1 case of nephritis and 1 case of pancreatitis in the pembrolizumab group, and 1 case of increased blood creatinine in the chemotherapy group because published cost estimates were not available. All values come from the following source unless otherwise noted: Reck et al. [8]

PFS progression-free survival

[a]Chemotherapy percentage based on intention-to-treat population (n = 151). All other chemotherapy percentages are based on the as-treated population (n = 150)

[b]95% confidence intervals ranged from 6.7 months to not reached in the pembrolizumab group, and from 4.2 to 6.2 months in the chemotherapy group

[c]95% confidence intervals ranged from 0.538 to 0.694 in the pembrolizumab group, and 0.419 to 0.582 in the chemotherapy group

[d]Interpolated from published Kaplan–Meier curves

[e]95% confidence intervals ranged from 0.143 to 0.271 in the pembrolizumab group, and 0.211 to 0.355 in the chemotherapy group

[f]95% confidence intervals ranged from 0.231 to 0.377 in the pembrolizumab group, and 0.376 to 0.536 in the chemotherapy group. Source: Reck et al. [35]

[g]Grade 3–5 adverse events of any grade events that occurred in > 10% of patients in either group. Additional reported events—increased blood creatinine level (1 chemotherapy patient), nephritis (1 pembrolizumab patient), and pancreatitis (1 pembrolizumab patient)—are excluded from this list and analysis as published German treatment costs were unavailable at the time of this study

RESULTS

The external quality assurance (EQA) data in Table 1 summarize the probabilities of IVD/LDT testing accuracy for PD-L1 expression. IVDs produced accurate PD-L1 testing results in 93% (752/811) of tested cases compared to 73% (492/672) with LDTs. The most frequent misclassifications were false negatives, occurring 21% with LDTs and 7% of the time with IVDs. False positives were less prevalent, occurring in 5% of tests with LDTs and 1% with IVDs.

Overall per patient cost to manage grade 3+ treatment-related AEs was greater for chemotherapy patients (704 €) compared to those on pembrolizumab (641 €) (Tables 3, 4). Supplementary Table S2 summarizes the overall model costs, effects, and ICER. The average total costs of the IVD group at 48,878 € were higher than the LDT group at 48,682 €. These costs incorporated testing, first- and second-line therapy, management of treatment-related grade 3+ AEs, as well as end-of-life costs for those who died. Average total effectiveness (percentage of patients successfully diagnosed) was higher in the IVD group at 88% compared to 69% in the LDT group. These findings show that using IVD testing increased costs by 196 € and was 19 percentage points more effective than using LDTs. The ICER for using IVD instead of LDT was 1057 € per additional patient accurately diagnosed and treated per recommended guidelines. At a willingness to pay of 0 € (i.e., a payer is not willing to pay any additional cost for the added benefit with IVD), the ICER scatterplot (Fig. S1 in the supplementary materials) indicates that IVD dominates LDT in 30% of simulations in the probabilistic sensitivity analysis, meaning IVD is less costly and more effective than LDT. The remaining 70% of simulations indicate a trade-off scenario, wherein IVD costs more (on average 196 €) while providing more benefit. As willingness to pay increases, the probability of IVD being a

Table 4 Resource use costs

	Reported			Source
	Base case	Low	High	
Diagnostic test (IVD or LDT)	27 €	–	–	[55]
Therapy cost per cycle[a]				
Pembrolizumab	6222 €	–	–	[56]
Carboplatin–pemetrexed (median, range)	4652 €	4651 €	4654 €	[56]
Carboplatin–gemcitabine	1224 €	–	–	[56]
Carboplatin–paclitaxel	1883 €	–	–	[56]
Cisplatin–pemetrexed (median, range)	4286 €	4282 €	4562 €	[56]
Cisplatin–gemcitabine (median, range)	871 €	854 €	887 €	[56]
Pemetrexed maintenance (median, range)	4066 €	4065 €	4068 €	[56]
Docetaxel	1311 €	–	–	[56]
Treatment-related adverse events (grade 3+)[b]				
Anemia (mean, 95% CI)	1009 €	911 €	1108 €	[43]
Colitis (median, grade 3, grade 4)	19,004 €	11,016 €	26,993 €	[44]
Decreased appetite (mean, 95% CI)	2092 €	1887 €	2297 €	[43]
Decreased neutrophil count (mean, 95% CI)	867 €	781 €	953 €	[43]
Decreased platelet count (mean, 95% CI)	867 €	781 €	953 €	[43]
Decreased white cell count (mean, 95% CI)	867 €	781 €	953 €	[43]
Diarrhea (mean, 95% CI)	1499 €	1352 €	1645 €	[43]
Fatigue (mean, 95% CI)	1721 €	1551 €	1891 €	[43]
Hypophysitis (median, grade 3, grade 4)	10,256 €	4491 €	16,022 €	[44]
Nausea (grade 3)	714 €	–	–	[44]
Neutropenia (mean, 95% CI)	867 €	781 €	953 €	[43]
Pneumonitis (mean)	2221 €	NA	NA	[42]
Severe skin reaction (mean, 95% CI)	654 €	589 €	719 €	[43]
Stomatitis (mean)	806 €	NA	NA	[42]
Thrombocytopenia (mean, 95% CI)	867 €	781 €	953 €	[43]
Type 1 diabetes mellitus (median, grade 3, grade 4)	11,717 €	6005 €	17,429 €	[44]
Vomiting (median, grade 3, grade 4)	10,509 €	1127 €	19,891 €	[44]

Table 4 continued

	Reported			Source
	Base case	Low	High	
End of life (mean, SD)[c]	4313 €	7481 €	–	[36]

All costs adjusted for inflation to 2020 euros using the German Consumer Price Index—Health (CC13-06). See: Federal Statistical Office. Consumer price index—Germany, years, individual consumption by purpose (61111-0004). Destatis Statistisches Bundesamt: Genesis Online. Published June 5, 2021. https://www-genesis.destatis.de/genesis/online?operation=statistic&levelindex=0&levelid=1627680794066&code=61111#abreadcrumb

IVD in vitro diagnostic, *LDT* laboratory-developed test, *SD* standard deviation

[a]Includes costs of additionally required statutory health insurance (SHI) services, and other services covered by SHI funds, and drug costs after deduction of statutory rebates (LAUER-TAXE)

[b]German costs were unavailable for nephritis, pancreatitis, and increased blood creatinine, and therefore excluded from this list

[c]German health care utilization and hospital expenditures per capita during the last 30 days of life for patients > 65 years old who died from lung cancer in 2010 (type and stage of lung cancer not specified). Total expenditures include "all costs for procedures, pharmaceuticals, staff (physician, nursing, and other personnel), pharmacy, laboratory and diagnostic imaging during the hospital stay." Excluded are outpatient, hospice, patients' co-payments, and other indirect medical expenditures

cost-effective strategy compared to LDT also increases (Supplementary Fig. S2).

A series of one-way sensitivity analyses identified parameters that individually have the most impact upon model results. Of the 72 model parameters included, seven accounted for 98% of variation in the ICER value, while the remaining 65 variables had little to no impact (less than 1%; Supplementary Fig. S3). The most influential parameter was the probability of a false positive LDT result, accounting for 62% of the variability. Compared to the base case estimate of 5.4%, using the high range estimate (7.2%) in the model decreased the ICER from a positive value of 1057 € to a negative value of − 2165 € (meaning IVD is less costly and more effective, dominating the LDT group in this scenario). The higher the false positive rate in the LDT arm, the more expensive LDT becomes as more patients receive costly pembrolizumab treatment without the corresponding clinical benefits. Holding the IVD costs constant, raising the LDT costs further increases differences between the groups, making the ICER more favorable towards IVD. Conversely, a lower probability of LDT false positives (3.8%) decreases the costs of the LDT group because this improves the effectiveness of LDT relative to IVD and therefore increases the ICER to 3828 € (less favorable for IVD). Similarly, using lower estimates for the probability of acceptable LDT results increased LDT costs making the ICER more favorable at − 589 € (IVD dominant over LDT) while the higher value increased the ICER to 2273 €. For other parameters, like the probability of receiving pembrolizumab with a true positive test result, probability of false positive IVD result, and probability of acceptable IVD result, low range values favored IVD and lowered the ICER, while high range values favored LDT and increased the ICER.

DISCUSSION

From the German payer perspective, findings suggest using IVD PD-L1 tests for patients with NSCLC costs 196 € more than LDT but provides 19% more successfully diagnosed patients. The ICER of 1057 € indicates the cost to get one additional patient correctly diagnosed and treated according to German guidelines. Using more accurate testing maximizes the benefits of personalized medicine.

Similar studies show personalized medicine technologies to be cost-effective [45, 46]. A review of 83 studies (43% in cancer) mainly

conducted in Europe and the USA between 2014 and 2018 concluded that most studies (71%) found personalized medicine interventions were at least as cost-effective as usual care [47]. Cost-effectiveness was most influenced by the prevalence of the genetic condition, costs of testing and subsequent treatment, and the probability of complications or mortality.

Like our current study, differences in accuracy have been identified between IVDs and LDTs. A US study evaluated the consequences of inaccurate epidermal growth factor receptor (EGFR) tests between LDTs and IVDs in patients with newly diagnosed metastatic NSCLC [48]. LDTs resulted in misclassifications in 2.4% (n = 1422) of 60,502 patients compared to 1.0% (n = 577) with IVDs. This difference (less than 2%) is relatively small compared to the 20% difference identified in the current study (nearly 27% of LDT patients misclassified compared to approximately 7% in the IVD group). And like the current study, misclassified results led to decreased progression-free survival, higher AE costs, and greater chance of death.

Similarly, for human epidermal growth factor receptor 2 (HER2; also known as ERBB2) assessment in patients with breast cancer [46], LDTs resulted in higher rates of false negatives (25% vs 11%) and false positives (5% vs 0%) compared to IVDs. These findings are consistent with the LDT and IVD false negative rates (21% and 7%) and false positive rates (5% and 1%) identified in the current study. Modeling direct costs associated with inaccurate test results suggested that IVD tests would improve patient survival and reduce health care costs compared to LDTs [46].

Implications

On the basis of our findings, if laboratories in Germany use LDTs for testing PD-L1 expression for treatment decisions in NSCLC, then 19% of patients will be denied optimal treatment. Most of these patients will get a false negative test result, indicating they are not eligible for pembrolizumab, when in reality they are. These patients will be denied the best treatment option, placed on chemotherapy, have more treatment-related grade 3+ AEs, less progression-free survival, and a higher chance of death in the first 12 months of treatment. False positive results will be expected 5% of the time with LDTs (compared to 1% with IVDs), meaning patients will receive pembrolizumab (or another ICI therapy) when they are not eligible, increasing the drug costs while likely having no improvement in progression-free survival or death rate.

Our findings beg the question: who is ultimately responsible for ensuring patients get an accurate PD-L1 test result? From a policy standpoint, several opportunities exist to encourage adopting IVD tests as standard practice. In Germany and other European countries, unless oncologists specify on-label use of a PD-L1 test, pathologists determine the use of IVD or LDT in the laboratory. However, despite an on-label request, laboratories without the necessary instrumentation will perform the PD-L1 test as an LDT. Both providers (oncologists and pathologists) should be aware of the benefits derived from using an IVD to allocate treatments for patients with NSCLC. National treatment guidelines could recommend use of IVD testing to maximize patient benefit as well. Currently, reimbursement is the same for either IVD or LDT. Primary payers in Europe, like the German statutory health insurance system, could mandate use of IVD over LDT for reimbursement, or modify reimbursements to incentivize laboratories to use IVDs. Patient-directed campaigns to educate patients with NSCLC on the survival benefits associated with accurate testing could encourage them to request IVD tests from their oncologists. Any or all these actions could lead to policy change, but until then, it is incumbent upon oncologists to insist on use of IVD assays per manufacturer's recommendations to ensure their patients receive the most accurate PD-L1 diagnostic test currently available.

Limitations

Incomplete data resulted in several limitations. The testing accuracy data from external quality organizations were collated from multiple

countries and may not be representative of testing in Germany. Anecdotal evidence suggests use of LDTs is higher in Germany; therefore, these EQA data likely underestimate the false positives and negatives seen in Germany. In addition, chemotherapy combinations and rates of use were drawn from KEYNOTE-024 as there were no analogous data available from CRISP for the percentages of patients receiving first- and second-line chemotherapy combinations in Germany [8].

There is also a paucity of data on clinical outcomes for ICI treatments in patients with less than 50% PD-L1 expression. The KEYNOTE-042 trial found no significant difference in overall survival between pembrolizumab and chemotherapy among patients with a PD-L1 expression of 1–49%, but the study did not evaluate progression-free survival among these patients [7]. Our assumption that false positive patients on pembrolizumab experienced the same progression-free and overall survival as chemotherapy patients was based on limited data suggesting higher PD-L1 expression is associated with more benefit [49–51]. Although this assumption affected a small number of patients in the model (4% more in the LDT vs IVD group), more data are required to test the validity of this assumption. Should European treatment guidelines change to allow first-line treatment with ICIs for patients with less than 50% PD-L1 expression, this model would need to be updated.

This model used a 12-month timeframe while the KEYNOTE-024 study reported interim outcomes at 11.2 months, with median treatment durations and survival times also under 1 year for this cohort of patients with stage IV metastatic NSCLC [8]. The 1-year model captures the likely costs and outcomes associated with PD-L1 testing accuracy among these patients. The model is not designed to extrapolate these data over a lifetime horizon to evaluate the long-term cost-effectiveness of therapies. Further, quality-adjusted life years and indirect costs were not appropriate to include in this analysis given the 1-year timeframe and patient population who are unlikely to be employed.

Although many inputs for cost-effectiveness analyses use mean values, our model used median progression-free survival as reported in the KEYNOTE-024 trial and is a typical measure reported in oncology trials. Therefore, using a median may underestimate the costs and benefits.

Finally, KEYNOTE-024 reports the leading treatment-related AEs and identifies those that were grade 3–5, but does not report those AEs that occurred in less than 10% of patients [8]. Thus, treatment-related AE occurrences and costs are likely an underestimate. Rare but expensive AEs could impact the model results.

Future Directions

In 2022, Europe is expected to fully enact the EU IVD Regulation (IVDR) which, among other specifications, requires performance evaluations for diagnostics including significant evidence of clinical performance [52]. The ramifications of these regulatory changes cannot be fully known at present; however, the commercial landscape could be altered to such a degree that this analysis would need to be updated to account for changes in cost and probability parameters.

The clinical and economic implications of testing accuracy may require further evaluation as more evidence for ICI/chemotherapy combination treatment becomes available. Under current guidelines, PD-L1 testing remains best-practice for prescribing ICI therapies. However, Dafni et al. found increased progression-free survival regardless of PD-L1 status when ICI/chemotherapy combinations were used as first-line treatment for NSCLC [53]. In the USA, guidelines for first-line treatment of stage IV PD-L1-positive NSCLC include ICI/chemotherapy combination therapies [54]. If combination treatment replaces pembrolizumab then changes in costs and outcomes would need to be determined in order to update the current model. Further investigations of the outcomes associated with IVD testing would strengthen these study findings and inform potential changes to testing and reimbursement policies.

CONCLUSION

Our findings from international EQA data indicate that IVDs produced accurate PD-L1 testing results in 93% of tested cases compared to 73% with LDTs. Compared to LDT technology, use of an IVD for PD-L1 testing costs only slightly more and is substantially more effective for aligning patients with PD-L1-positive NSCLC with ICI therapy according to German practice guidelines. If the correct therapy increases survival, and patients receive the correct therapy, then patient survival increases. On the basis of this 1-year model, accurate PD-L1 diagnostic tests would prevent 19% of patients with NSCLC from receiving incorrect treatment (88% average total effectiveness for IVDs versus 69% for LDTs), increase patient survival, and reduce costly treatment-related AEs. Changes to testing and reimbursement policies should be explored to shift diagnostic testing practices to maximize patient benefits.

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