ORIGINAL ARTICLE

A Cost-Effectiveness Analysis of Nivolumab versus Docetaxel for Advanced Nonsquamous NSCLC Including PD-L1 Testing

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ABSTRACT

Introduction: Nivolumab (NIV) was recently approved in several countries for patients with pretreated advanced NSCLC. NIV is not cost-effective compared with docetaxel (DOC) for the treatment of squamous NSCLC. However, its cost-effectiveness for nonsquamous NSCLC and the consequences of programmed death ligand 1 (PD-L1) testing are unknown.

Methods: This literature-based health economic study used CheckMate-057 trial data to model the incremental cost-effectiveness ratio (ICER) of NIV versus DOC in the Swiss health care setting. The effect of PD-L1 positivity for patient selection was assessed.

Results: In the base case model, NIV (mean cost CHF66,208; mean effect 0.69 quality-adjusted life-years [QALYs]) compared with DOC (mean cost CHF37,618; mean effect 0.53 QALYs) resulted in an ICER of CHF177,478/QALY gained. Treating only patients with PD-L1–positive tumors (threshold $\geq$10%) with NIV compared with treating all patients with DOC produced a base case ICER of CHF124,891/QALY gained. Reduced drug price, dose, or treatment duration decreased the ICER partly below a willingness-to-pay threshold of CHF100,000/QALY. Health state utilities strongly influenced cost-effectiveness.

Conclusions: Compared with DOC, NIV is not cost-effective for the treatment of nonsquamous NSCLC at current prices in the Swiss health care setting. Price reduction or PD-L1 testing and selection of patients for NIV on the basis of test positivity improves cost-effectiveness compared with DOC.

Keywords: Lung cancer; Nivolumab; Docetaxel; Cost-effectiveness; QALY; ICER

Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide.[1] Lung cancer is diagnosed in approximately 1.5 million people—mostly smokers—each year. NSCLC is the most common histological subtype, with 70% to 80% of patients presenting with metastatic disease at diagnosis. Despite significant progress in molecular diagnostics and targeted therapy over the past decade, the prognosis for patients with advanced NSCLC remains poor.

Chemotherapy is the mainstay of palliation. Platinum-based combination therapies are the standard of first-line

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care, with docetaxel (DOC), pemetrexed, and erlotinib for further-line options.[2,3] Survival has been shown to be significantly better with DOC than with best supportive care in patients previously treated with platinum-based therapy,[4] and although pemetrexed and erlotinib are better tolerated, they do not improve survival compared with DOC.[5–7] In a U.K. study, docetaxel was cost-effective compared with best supportive care[8] and pemetrexed, which has been studied mainly as first-line treatment,[9] was not cost-effective as maintenance in our previous Swiss study.[10] With respect to erlotinib and other EGFR inhibitors, patient selection by EGFR mutation status is recommended.[11–13]

Immune checkpoint inhibitors are gaining interest in oncology, including in lung cancer.[14] Pembrolizumab and nivolumab (NIV), two antibodies targeting programmed cell death protein 1 (PD-1), are new treatment options for patients with advanced NSCLC on the basis of the results of large clinical trials. For example, in the KEYNOTE-001 trial, 495 patients were treated with either 2 mg or 10 mg of pembrolizumab per kg body weight every 3 weeks or 10 mg/kg every 2 weeks.[15] Tumor expression of programmed death ligand 1 (PD-L1) was prospectively assessed by immunohistochemical (IHC) testing. In the entire patient population, the response rate was 19.4%, progression-free survival (PFS) was 3.7 months, and median survival was 12.0 months. In patients with PD-L1-positive tumors, the response rate was 45.2% and PFS was 6.3 months, with median survival not yet reached at the time of publication. As a result, the U.S. Food and Drug Administration (FDA) approved pembrolizumab (Keytruda [Merck Sharp and Dohme, Hiddesdon, UK]) in 2015 for second-line therapy of PD-L1–positive NSCLC, together with a companion diagnostic test (22C3 pharmDx [Dako, Glostrup, Denmark]).

With respect to nivolumab, in the CheckMate-017 (squamous NSCLC) and CheckMate-057 (non-squamous NSCLC) randomized phase III trials, pre-treated patients received NIV at a dose of 3 mg/kg every 2 weeks or DOC, 75 mg/m^{2,} every 3 weeks.[16,17] Both trials demonstrated clinically relevant survival differences of approximately 3 months in favor of NIV. CheckMate-057 included a retrospective biomarker analysis: tumor material was available from 78% of patients, and NIV activity was greatest in the 46% of patients with PD-L1–positive tumors (defined as at least 1% tumor cell positivity). This finding was consistent with a meta-analysis of other PD-1 and PD-L1 checkpoint inhibitors in NSCLC and other indications.[18] In 2015, the FDA approved NIV (Opdivo [Bristol-Myers Squibb, Lawrenceville, NJ]) for pre-treated patients with advanced squamous or non-squamous NSCLC irrespective of PD-L1 expression but also approved a companion test (28-8 pharmDx, Dako) to identify patients who might benefit most from NIV. In November 2015, the Swissmedic (the Swiss agency for therapeutic agents) approved NIV for the same indication, and on April 1, 2016, the Swiss Federal Office of Public Health included NIV in the list of pharmaceutical specialities,[19] allowing reimbursement under compulsory health insurance at a defined public price. The European Medicines Agency approved NIV for patients with squamous NSCLC in 2015, and in 2016, the European Committee for Medicinal Products for Human Use recommended NIV for nonsquamous NSCLC.

The cost of cancer care is of growing concern.[20] The American Society of Clinical Oncology recently published a framework to assess the value of cancer treatments, and the European Society of Medical Oncology developed a tool to stratify the magnitude of clinical benefit of cancer therapies.[21,22] Although these initiatives are important and useful, complementary cost-effectiveness models remain indispensable for estimating the economic implications of cancer treatments at the national level. In December 2015, the U.K. National Institute for Health and Care Excellence (NICE) reported that NIV for squamous NSCLC was not cost-effective, with an estimated £109,000 to £129,000 ($151,120–$178,849) per quality-adjusted life year (QALY) gained.[23] In a Canadian model, NIV cost an additional $151,560 per QALY gained.[24] Statements on nonsquamous NSCLC from NICE and the Canadian Agency for Drugs and Technologies in Health are pending.

In view of these data, we hypothesized that NIV is not cost-effective for the treatment of nonsquamous NSCLC in Switzerland under current conditions. We used a literature-based Markov modeling approach to test several strategies, including a reduction in price, dose, and treatment duration for NIV and limiting NIV use to patients with PD-L1–positive cancers. We modeled clinical data from the Checkmate-057 registration trial,[16] public drug prices, and the real cost of care of patients treated with NIV or DOC. The aim of our work was to calculate incremental cost-effectiveness ratios (ICERs) for NIV compared with DOC from the perspective of the Swiss health care system.

Materials and Methods

A Markov model was constructed on the basis of clinical data from the CheckMate-057 study.[16] The model compared three main strategies: (1) all patients treated with docetaxel (DOC), (2) all patients treated with nivolumab (NIV), and (3) patients treated according to their PD-L1 status. In the latter case, patients with PD-L1–positive tumors (a positivity threshold of $\geq$1% or

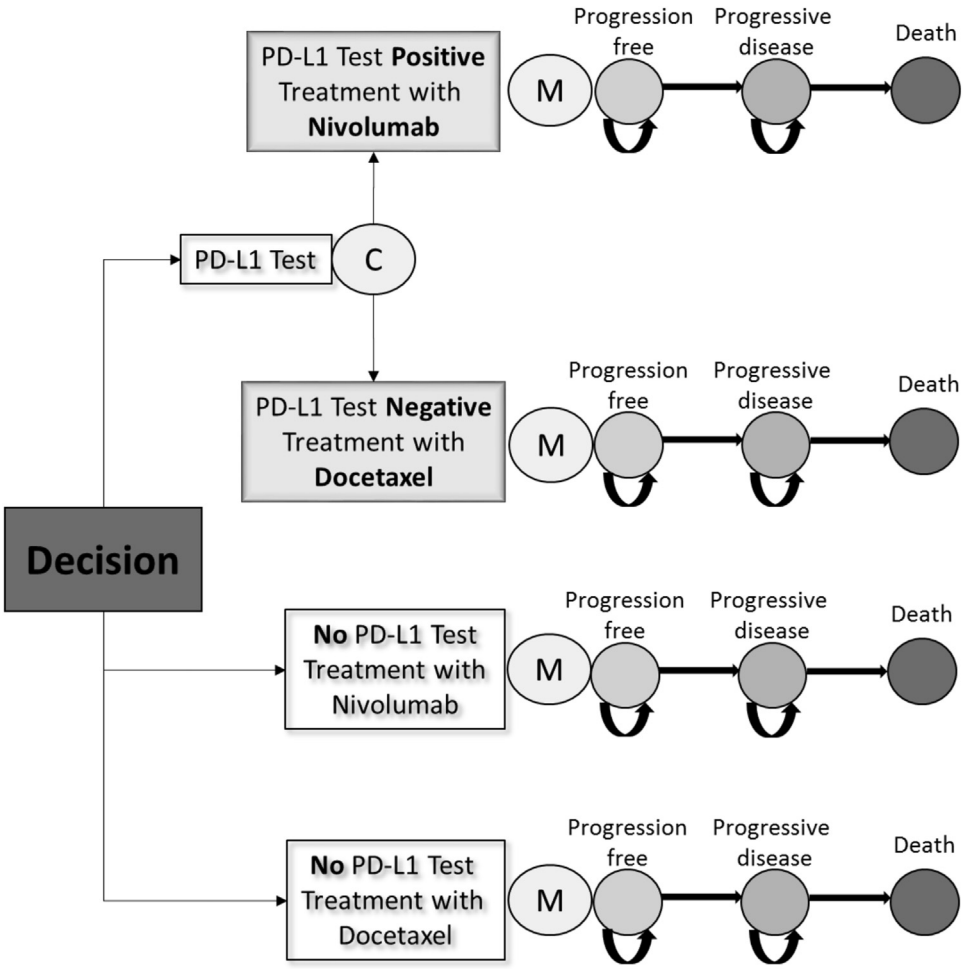

Figure 1. Model structure. PD-L1, programmed death ligand 1; C, chance node; M, Markov node.

≥10%) were treated with NIV, and patients with PL-L1–negative tumors (below the positivity threshold) were treated with DOC (Fig. 1). Because IHC positivity can be influenced by many factors, we applied minimal and maximal thresholds for PD-L1 positivity as used in the Checkmate-057 trial.[25] In the primary analyses, NIV was compared with DOC, PD-L1 testing was compared with DOC, and PD-L1 testing was compared with NIV. Irrespective of established rational choice rules (which exclude inferior strategies), we calculated ICERs for all these comparisons because NIV has been available since 2015 for pretreated patients with advanced NSCLC as part of an early access program in Switzerland without a requirement for PD-L1 testing.

All analyses were performed from the perspective of the Swiss health care system, and a lifelong time horizon was adopted to capture related costs and outcomes. Drug therapies, major adverse events, and treatments during progression were considered direct medical costs. Drug prices were based on Swiss prices and tariff lists. For NIV, we used the public price (CHF18.05/mg) released by Bristol-Myers Squibb on March 31, 2016. The health state utilities used in the model were obtained from the literature.[11]

In the original randomized, open-label, international phase III study, patients with nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy were eligible to receive NIV (n = 292, 3 mg/kg body weight every 2 weeks) or DOC (n = 290, 75 mg/m^2 every 3 weeks) until progression. Grade 3 or 4 treatment-related adverse events were reported in 10% of patients in the NIV group compared with in 54% of those in the DOC group. Febrile neutropenia and alopecia (mainly in the DOC group) were considered to have a relevant impact on costs and quality of life (QoL).

Our primary end point was the ICER expressed as cost per QALY gained by using NIV compared with DOC in patients with NSCLC. Secondary end points were the ICERs for comparing PD-L1 testing (1% or 10% positivity thresholds) with either DOC or NIV. In the PD-L1 testing arm, only patients with PD-L1–positive tumors (1% or 10% positivity thresholds) received NIV,

whereas the remaining patients received DOC (see Fig. 1). ICERs were compared with a possible willingness-to-pay (WTP) threshold of CHF100,000 per QALY gained.[10,26,27]

One-way and probabilistic sensitivity analyses were performed to test the robustness of the results. Sensitivity analyses for a NIV dose or reduced number of treatment cycles were performed. The effect of a NIV price reduction on the ICERs was also assessed.

Model Structure

In each treatment strategy in the Markov model, patients transitioned through three mutually exclusive health states (see Fig. 1): stable/responsive (progression-free) disease, progressive disease, and death. A cycle length of 1 month was chosen by taking the life expectancy of the study population into account. The medication schemes (NIV every 2 weeks, DOC every 3 weeks) were adapted to fit a monthly cycle. All patients started with stable, progression-free disease and either remained at that stage or transitioned to progressive disease. Once in the progressive stage, patients could remain in that stage or transition to death.

Clinical Effectiveness and QoL

Effectiveness data were inferred from the PFS and overall survival (OS) outcomes reported in the original trial publication and supplementary materials.[16] PFS and OS hazards were assumed to be constant over time, and the median time spent in each state was used to estimate hazard rates for the DOC or NIV strategy by using the formula Hazard Rate = −ln(0.5)/Median Time in state before conversion into Markov state transition probabilities. Median times from progression to death in the relevant treatment arms were estimated to fit the reported median OS times because this information was not provided in the original publication. Data from the supplementary materials in the original publication were used for the PD-L1 test results and corresponding PFS and OS.

Quality-adjusted progression-free time and time in progression were calculated according to published utilities.[11,28] Utilities for DOC[28] were based on a utility study using the EuroQuol EQ-5D instrument.[29] Because no NIV utility scores were available for patients with nonsquamous NSCLC, we assumed possible increases in utility (owing to fewer adverse events) of 0.05 to 0.15 (see Supplementary Table 1) while patients were in the progression-free state. Utilities for progressive disease were assumed to be equal in all treatment arms and were based on utilities for progressive disease after DOC treatment.[11,28]

All values for the base case input parameters are listed in Supplementary Table 1 (mean or median values and 95% confidence intervals where appropriate).

Use of Medical Resources and Unit Costs

Only drug use and adverse event information were provided in Checkmate-057. No data on other medical resource use such as hospitalizations or supportive care were available. For the progressive disease (follow-up) phase, many different treatments were listed in the supplementary material of the original trial but without any details on duration, treatment scheme, or doses. Because these subsequent therapies were highly variable and some are not available or approved for NSCLC in Switzerland, we calculated an average monthly treatment price (using a wide distribution to account for uncertainty in the sensitivity analysis) on the basis of representative patients from the Cantonal Hospital Lucerne.

Swiss public health care prices were used where available. The public price of DOC was CHF5.79/mg,[19] and the public price of NIV was CHF 18.05/mg for a 100-mg vial (including value-added tax). Treatment costs for adverse events were provided by the Cantonal Hospital Lucerne using representative patients with advanced NSCLC treated with DOC or NIV, Swiss medical tarif code for outpatient care,[30] and Swiss diagnosis-related groups for inpatient care (see Supplementary Table 2).[31] Reimbursement for one diagnostic (PD-L1) IHC test was CHF136, including CHF73 for technical work and CHF63 for interpretation. Costs and benefits were not discounted given the short life expectancy of study population.

Sensitivity Analyses and Dosing and Price Scenarios

A series of one-way sensitivity analyses were performed to assess the influence of uncertainty in individual input parameters on the ICER. All parameters subject to uncertainty were varied across 95% confidence intervals or plausible ranges (if no confidence intervals were available), as shown in Supplementary Tables 1 and 2 (for follow-up costs). Furthermore, all parameters subject to uncertainty were simultaneously varied in a probabilistic sensitivity analysis (a second-order Monte Carlo simulation) based on corresponding distributions (see Supplementary Tables 1 and 2). The probability of reaching cost-effectiveness on the basis of a WTP threshold of CHF100,000 per QALY gained was analyzed. Although there is no official WTP threshold in Switzerland, the selected WTP is analogous (but increased owing to inflation) to an analysis for the Swiss setting in 2009[32] and WTPs used in other countries.[33]

Three additional scenarios were also tested. The first included a dose reduction of NIV to 1mg/kg, presuming similar activity to the registered dose of 3mg/kg.[34] The second scenario contained the number of NIV cycles to a maximum treatment duration of 3 months (i.e., six NIV

applications), again presuming similar activity. The third scenario analyzed the effect of NIV price reductions on the ICER. For all three scenarios, ICERs for NIV versus DOC (primary end point) and PDL-L1 positivity (1% and 10% thresholds) versus DOC and versus NIV (secondary end points) were analyzed.

Model Validation

Trackers for PFS and OS were included as a basis for analyzing correct data fit. The model was calibrated to match the PFS and OS data in the original publication. All outputs were reviewed for plausibility. Key input parameters were subjected to extreme variation to assess model plausibility.

Results

The clinical effectiveness data from the original Checkmate-057 trial[16] were modeled as follows: median PFS for NIV and DOC were 2.3 and 4.2 months in the trial and 2.30 (NIV) and 4.23 (DOC) months in the calibrated model. The model-based median OS was 9.5 months for DOC (9.4 in the clinical trial) and 12.25 months for NIV (12.2 in the clinical trial). Therefore, the modeled PFS and OS for DOC and NIV satisfactorily matched the clinical trial results. The modeled PFS and OS for DOC and NIV after PD-L1 testing (1 and 10% positivity thresholds) also matched the clinical trial results (Supplementary Table 1).

In the base case model, NIV (mean cost CHF66,208; mean effect 0.69 QALYs) compared with DOC (mean cost CHF37,618; mean effect 0.53 QALYs) resulted in an ICER of CHF177,478/QALY gained (Table 1). When NIV was given only to patients with 1% or greater PD-L1 tumor positivity (and DOC to those not reaching ≥1% PD-L1 tumor positivity), the resulting ICER was CHF 133,267/QALY compared with DOC for all. NIV only for patients with 10% or greater PD-L1 tumor positivity (and DOC to those not reaching ≥10% PD-L1 tumor positivity) compared with DOC for all resulted in an ICER of CHF124,891/QALY. Although NIV for all patients was weakly dominated by the test-based strategies, we also compared PD-L1 testing to NIV, because NIV has been available in an early access program since 2015 in Switzerland for all pretreated patients with advanced NSCLC, irrespective of PD-L1 testing. PD-L1 testing with a 1% positivity threshold, treating only patients with positive tests with NIV and all others with DOC, compared with NIV for all resulted in an ICER of CHF65,774/QALY (see Table 1 and Fig. 2) and an ICER of CHF37,860/QALY with a 10% positivity threshold (see Table 1). Both test threshold levels resulted in ICERs below a WTP threshold of CHF100,000/QALY.

The univariate sensitivity analyses for NIV versus DOC (Fig. 3) showed that the utility scores for PFS and progressive disease had the strongest influence on the ICER. However, neither parameter reduced the ICER to below the WTP threshold. Costs for best supportive care in the

Table 1. Base Case and Scenario Analyses

Treatment Arm	Mean Cost (CHF)	Effect Month (Mean)	Effect QALY (Mean)	Compared with	Incremental Cost (CHF)	Incremental Effect	ICER (CHF)	Probability Cost-Effective
Base case								
DOC	37,618	10.99	0.53					
NIV	66,208	15.42	0.69	DOC	28,589	0.16	**177,478**	14.1%
PD-L1 ≥1%[a]	74,968	17.26	0.79	DOC	35,530	0.27	**133,267**	19.7%
				NIV	6941	0.11	*65,774*	85.2%
PD-L1 ≥10%[a]	69,893	16.83	0.78	DOC	32,274	0.26	**124,891**	22.1%
				NIV	3685	0.10	*37,860*	86.7%
NIV dose reduction to 1 mg								
NIV	47,410	15.42	0.69	DOC	9792	0.16	*60,787*	74.4%
PD-L1 ≥1%[a]	55,205	17.26	0.79	DOC	17,587	0.27	*65,964*	85.1%
				NIV	7795	0.11	*73,866*	82.3%
PD-L1 ≥10%[a]	54,990	16.83	0.78	DOC	17,372	0.26	*67,223*	88.2%
				NIV	9792	0.10	*77,874*	67.8%
Max 3-mo NIV								
NIV	55,394	15.42	0.69	DOC	17,776	0.16	**110,349**	46.6%
PD-L1 ≥1%[a]	56,539	17.26	0.79	DOC	18,920	0.27	*70,966*	81.8%
				NIV	1144	0.11	*10,845*	96.8%
PD-L1 ≥10%[a]	54,747	16.83	0.78	DOC	17,129	0.26	*66,283*	87.5%
				NIV	-647	0.10	*-6647*	94.8%

Note: Boldface means not cost-effective; italics mean cost-effective.
[a]Patients with positive test results receive nivolumab, patients with negative test results receive docetaxel.
DOC, docetaxel arm; NIV, nivolumab arm; PD-L1 ≥1%, PD-L1 test with cutoff of 1% positive tumor cells; PD-L1 ≥10%, PD-L1 test with cutoff of 10% positive tumor cells; QALY, quality adjusted life years; ICER, incremental cost effectiveness ratio.

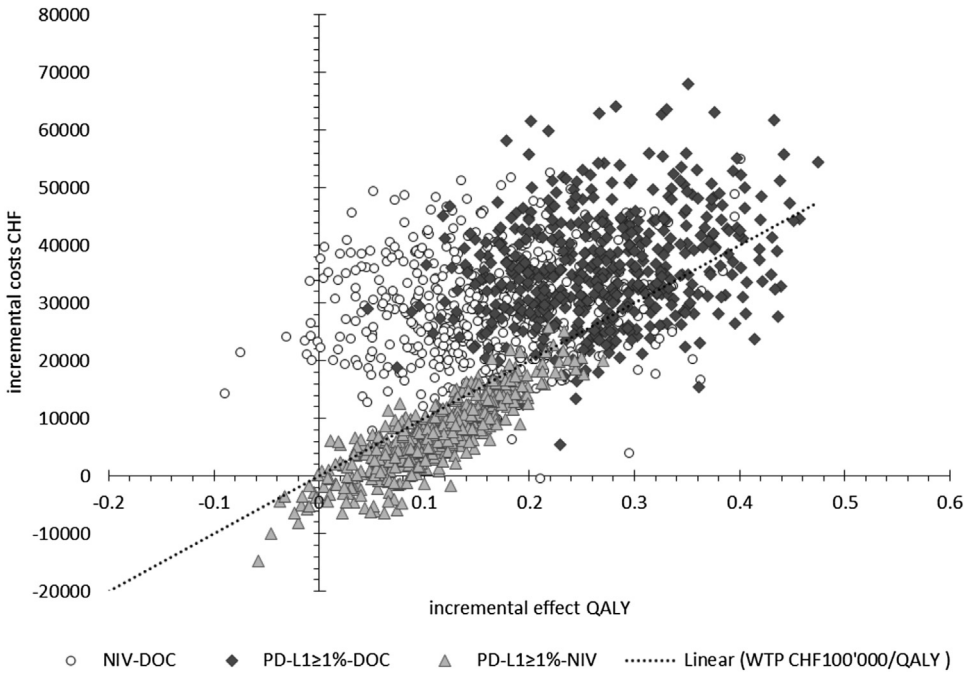

Figure 2. Probabilistic sensitivity analyses for nivolumab (NIV) versus docetaxel (DOC) and by programmed death ligand 1 (PD-L1) testing with a cutoff of 1% or more positive cells (PD-L1 $\geq$1%). PD-L1 $\geq$1% testing versus docetaxel (patients with positive test results receive nivolumab, patients with negative test results receive docetaxel) and PD-L1 $\geq$1% test versus nivolumab. QALY, quality-adjusted life-year; WTP, willingness-to-pay threshold.

progressive disease state and body weight (affecting the given amount of NIV) had a strong influence. The results of univariate sensitivity analyses for PD-L1 testing compared with DOC or NIV are shown in Supplementary Figure 1. For 1% and 10% PD-L1 positivity thresholds, treating only patients with positive test results with NIV and negative patients with DOC compared with DOC for all, the utility scores, best supportive care costs, and body weight again influenced the ICERs the most. In contrast, treating patients with positive test results with NIV and all others with DOC (both for the 1% and 10% PD-L1 positivity thresholds) compared with all patients receiving NIV, the PFS for NIV (all patients), the percentage of patients reaching a positive PD-L1 threshold,

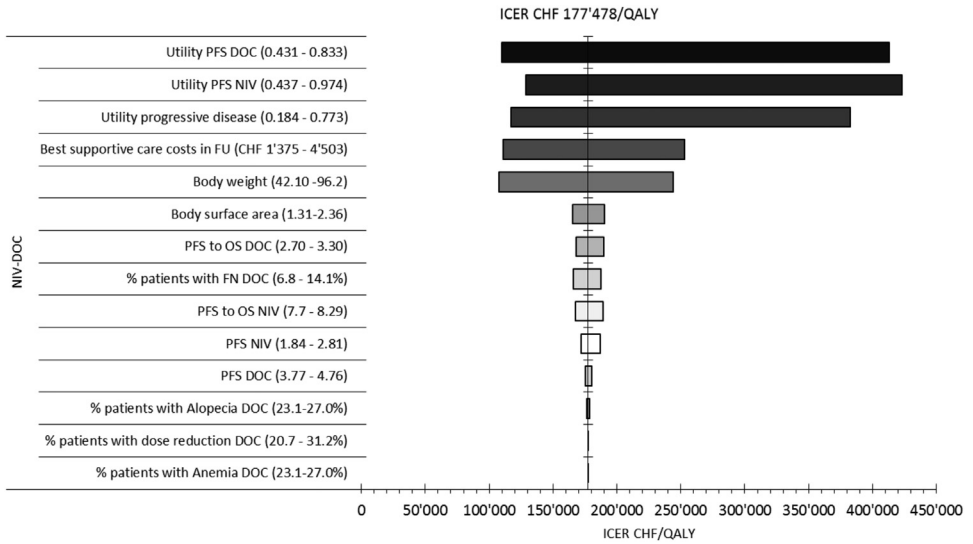

Figure 3. Tornado plot of the univariate sensitivity analyses for nivolumab (NIV) versus docetaxel (DOC). ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PFS, progression-free survival; OS, overall survival; FU, follow-up phase; FN, febrile neutropenia.

the PFS in NIV patients with positive PD-L1 tumors, and utility scores during PFS for the DOC-treated patients had the greatest effect on the ICER.

Reducing NIV doses to 1 mg/kg compared with DOC decreased the ICER to CHF60,787/QALY (probability of being cost-effective 74.4%). Restricting the duration of NIV treatment to a maximum of 3 months reduced the ICER of NIV compared with DOC to CHF110,349/QALY (probability of being cost-effective 46.6%). In both scenarios, PD-L1 testing (1% and 10% positivity thresholds, NIV for patients with positive test results, DOC for all others) compared with all patients receiving DOC or NIV resulted in ICERs below the WTP threshold (see Table 1). Price reduction analyses showed that for NIV compared with DOC, a reduction in the NIV price by least 45% would be needed to reach a WTP of CHF100,000/QALY (Fig. 4). In the case of PD-L1 testing compared with DOC, a price reduction of 27% to 33% could achieve a WTP threshold-range ICER.

Probabilistic sensitivity analyses confirmed the aforementioned results (see Fig. 2). For NIV versus DOC and NIV given only to PD-L1–positive patients (1% and 10% positivity thresholds) versus DOC, the NIV-based strategies had a small probability of being cost-effective (14%–22% [see Table 1 and Fig. 2]). NIV only for patients with positive PD-L1 test results compared with NIV for all patients, however, showed a high probability (85%–87%) of being cost-effective. In the additional scenarios assuming reductions in dose, duration, or NIV price, the probabilistic sensitivity analyses mainly resulted in high probabilities (see Table 1) of reaching cost-effectiveness, the only exception being testing NIV versus DOC when NIV was given for a maximum of 3 months (see Table 1).

Discussion

Immune checkpoint inhibitors represent a significant advance in the treatment of patients with advanced NSCLC. They are active against chemotherapy-resistant tumors, can induce long-lasting remission, and are relatively well tolerated. NIV was approved in Switzerland in November 2015 and has been reimbursed by compulsory health insurance since April 2016. Publicly available cost efficacy studies from the United Kingdom and Canada are currently limited to squamous NSCLC. To the best of our knowledge, the cost efficacy of NIV for nonsquamous NSCLC has yet to be reported for Switzerland or indeed any other country. Therefore, we conducted the present study to address this knowledge gap because prices for recently approved cancer drugs are rising and immune checkpoint inhibitors are in the spotlight with respect to drug pricing in oncology, including in Switzerland.[35–37]

We estimated the cost-effectiveness of NIV compared with DOC for the treatment of advanced nonsquamous NSCLC in Switzerland. There is no official cost-effectiveness threshold in Switzerland, so we used a WTP of CHF100,000/QALY as a tentative reference point.[32,33] In the base case analysis of NIV for all patients compared with DOC for all patients, the probability of NIV being cost-effective was low (14.1%), and the ICER was clearly above the WTP threshold of CHF100,000/QALY (CHF 177,478/QALY). These findings are comparable to those of previous U.K. and Canadian studies of patients with squamous NSCLC treated with NIV.[23,24]

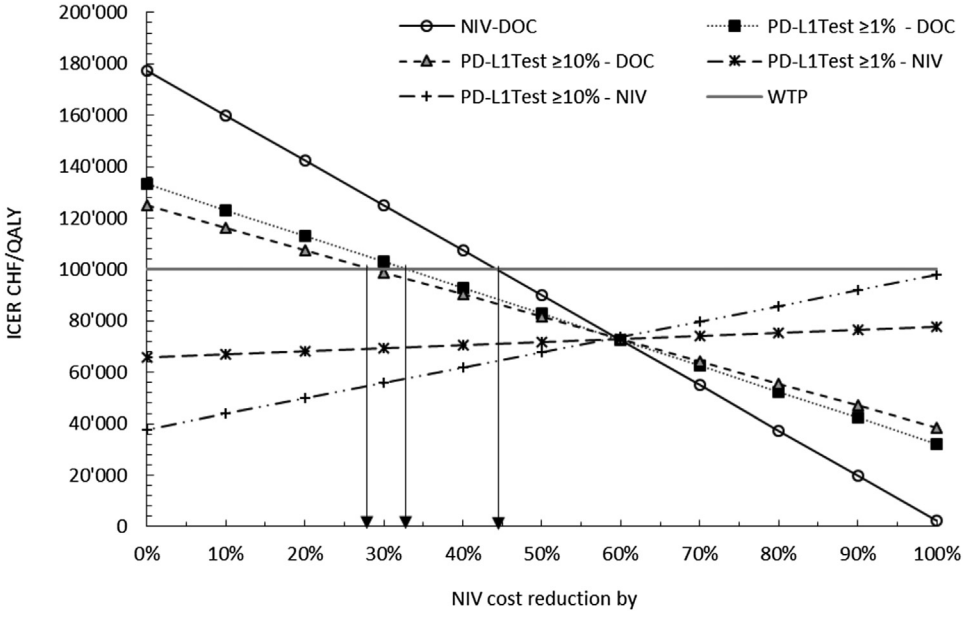

Figure 4. Results of the nivolumab (NIV) cost reduction analyses. DOC, docetaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; WTP, willingness-to-pay threshold.

A simple way to improve cost-effectiveness is to lower drug prices. Depending on the setting, a cost reduction of NIV by at least 33% (NIV given to patients with PD-L1–positive tumors versus DOC) or 45% (NIV given to all patients versus DOC) resulted in ICERs below or near the WTP threshold. It will be interesting to see whether NICE reaches similar conclusions for nonsquamous NSCLC and whether it can negotiate a lower price for NIV in the United Kingdom.

Reducing the NIV dose or treatment duration (assuming equal effectiveness) reduced the ICER below the WTP independent of PD-L1 testing. In a previous phase I trial of patients with solid tumors including NSCLC, tumor responses were seen with doses of 1, 3, and 10 mg/kg NIV.[34] Since the response rate in patients with NSCLC was greatest at 3 mg/kg, which is now the approved dose, it is unlikely that a lower dose will be registered in the future. Ipilimumab (Yervoy [Bristol-Myers Squibb]), another immune checkpoint inhibitor, is approved for patients with advanced melanoma, in whom it is given every 3 weeks (a total of four administrations).[38] We tested a similar treatment period of 3 months (corresponding to six NIV infusions), an approach that resulted in a reduction in the ICER for NIV versus DOC to near the WTP threshold (CHF110,349/QALY). New trials using a fixed NIV treatment duration are needed.

NIV's molecular target is PD-L1, a receptor expressed at the tumor cell surface that can be tested by IHC analysis. PD-L1 positivity by IHC analysis was predictive of clinical response and survival in Checkmate-057.[16] IHC analysis is fast, relatively inexpensive, and widely available compared with other molecular diagnostic tests used for nonsquamous NSCLC (e.g., fluorescence in situ hybridization or next-generation sequencing). Although the FDA has approved an IHC test to select patients for NIV therapy, current registrations do not mandate previous testing, mainly because PD-L1 positivity was not a stratification factor in the registration trial.[39] IHC staining and interpretation can be influenced by many factors, so we applied different PD-L1 positivity thresholds to our mode.[25] Treating only patients with PD-L1–positive tumors with NIV increased the probability of NIV compared with DOC being cost-effective to 19.7% (1% test positivity threshold) or 22.1% (10% test positivity threshold), but the ICERs were still greater than a CHF100,000/QALY WTP threshold. Comparing test-based strategies to "NIV for all" would, for both positivity thresholds, result in ICERs far below the WTP. However, NIV for all patients is itself weakly dominated; that is, the cost-effectiveness is worse than that of the test-based strategies when DOC is used as a common reference point.

In our analyses, both PD-L1 test strategies (NIV only for those patients reaching the 1% or 10% positive test thresholds) resulted in higher mean costs but also in better effectiveness than treating all patients with NIV. This can be explained by the unusual lower PFS for NIV compared with DOC for all patients, which is reversed (higher PFS for NIV compared with DOC) in both diagnostic test settings. Together with the crossing of the Kaplan-Meier curves for PFS and OS observed in Checkmate-057, this suggests the existence of two populations with different responses to NIV. In addition, the global median OS in the testing setting was higher than for NIV alone, and patients incurred more costs for treatments in the progressive disease phase.

The parameters that most affected the ICER in all settings were the utility scores (QoL weights) for progression-free and progressive disease, highlighting the impact of QoL on cost-effectiveness. The Checkmate-057 publication did not report utility scores, so we relied on utility scores from the literature for DOC[11] and an oral presentation of Checkmate-017 for NIV.[3] We believe that early reporting of utility scores should be a requirement for new palliative therapies entering the registration process[40,41]

The strengths of our study are its timeliness, independence from the pharmaceutical industry, and implementation of a biomarker. However, there are some limitations. Any conclusion about cost efficacy depends largely on the WTP, which ranges between $50,000 and $160,000 in the literature and was approximately $100,000 in our study, a number comparable to those in other Swiss health economic analyses.[27,32,33] We did not have access to information about the supportive care used in Checkmate-057; therefore, we could not model these costs. Subsequent therapies did not significantly differ in the two arms of Checkmate-05, although minor differences were observed; how patients will be treated after NIV in Switzerland is currently unknown. We did not have exact information on the median time for which patients were in the progressive disease state in Checkmate-057, so this was estimated from the OS. In the trial the median PFS for NIV versus DOC was 2.3 versus 4.2; however, the rate of PFS at 1 year was higher in NIV (19%) versus in DOC (8%). In the model we could not compensate for this particular situation. As a consequence, the costs for the NIV arm would increase because of more patients still receiving NIV during PFS and hence increase the ICER, making NIV less cost-effective. Finally, although our results are not directly generalizable to other countries, the Swiss system is comparable to the U.S. system and to those of many European countries in terms of patient care and cost.[42]

We focused entirely on nonsquamous NSCLC because this is the predominant histological subtype in Switzerland[43] and because PD-L1 expression predicted

clinical outcomes in Checkmate-057.[16] The International Association for the Study of Lung Cancer recently started a project to harmonize PD-L1 IHC testing, which will facilitate its routine application.[40] Unless PD-L1 testing becomes mandatory for reimbursement, many clinicians may prefer NIV over DOC because of the favorable toxicity profile. In patients with PD-L1–negative tumors (expression <1%), the response rates were clearly in favor of DOC in Checkmate-057. Although NIV is generally well tolerated, it can induce serious adverse effects in some patients.[44] The clinical development of other PD-1– and PD-L1–targeting antibodies, including pembrolizumab and atezolizumab, strongly focuses on PD-L1–positive NSCLC.[45] Although the current NIV label is understandable, it is questionable from a socioeconomic viewpoint and will need reconsideration when checkpoint inhibitors are used as first-line therapy or in combination with other drugs.[46]

We conclude that compared with DOC, NIV is not cost-effective for the treatment of nonsquamous NSCLC in the Swiss health care system and that a price well below the current public price appears to be justified. PD-L1 testing should be considered in patients with nonsquamous NSCLC who are candidates for PD-1 and PD-L1 checkpoint inhibitor therapy.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.05.032.

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