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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Neoadjuvant Pembrolizumab plus Chemotherapy Followed by Adjuvant Pembrolizumab in Patients with High-Risk, Early-Stage, Triple-Negative Breast Cancer in Switzerland

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Abstract

Aim This study assessed the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy plus placebo followed by adjuvant placebo for patients with high-risk, early-stage, triple-negative breast cancer (TNBC) from a Swiss third-party payer perspective over a lifetime horizon (51 years).

Materials and Methods A transition model with four health states (event-free, locoregional recurrence, distant metastasis, and death) was developed to assess the cost-effectiveness of pembrolizumab plus chemotherapy versus chemotherapy alone for the treatment of high-risk, early-stage TNBC. Data were utilized from the KEYNOTE-522 randomized controlled trial (ClinicalTrials.gov, NCT03036488). The incremental cost-effectiveness ratio (ICER) was calculated, which was reported as cost per life year or quality-adjusted life year (QALY) gained. A one-way deterministic sensitivity analysis, a probabilistic sensitivity analysis (PSA) and scenario analyses were conducted to assess the robustness of the model results.

Results Base-case results estimated an ICER of 14,114 Swiss francs (CHF)/QALY for pembrolizumab plus chemotherapy versus chemotherapy alone. Results were most sensitive to changes in the extrapolation of event-free survival (EFS). All sensitivity and scenario analyses generated ICERs below the willingness-to-pay threshold of CHF100,000/QALY, and the PSA showed a 98.8% probability that the ICER would be below this threshold.

Limitations Due to the limited follow-up period in the KEYNOTE-522 trial, EFS data were extrapolated over the lifetime horizon to inform transition probabilities. Extensive validation and scenario analyses ensured the results were robust.

Conclusion The model demonstrated that neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab was cost-effective versus chemotherapy alone in patients with high-risk, early-stage TNBC in Switzerland.

1 Introduction

Breast cancer is the most common type of cancer in women globally, with a total of 2,261,419 new cases and 648,996 deaths due to breast cancer in 2020 [1, 2]. In Switzerland, breast cancer is associated with the highest incidence and the highest number of deaths in women attributable to cancer [3]. In Europe, 531,086 new cases were reported in

Key Points for Decision Makers

Pembrolizumab was projected to be a cost-effective treatment option versus chemotherapy alone for patients with high-risk, early-stage, triple-negative breast cancer, with estimated incremental cost-effectiveness ratios (ICERs) lower than all commonly cited willingness-to-pay thresholds in Switzerland.

Results for the ICER were most sensitive to changes in the event-free survival (EFS) extrapolation from the KEYNOTE-522 trial, performed due to the lack of long-term data. Despite the robustness of the base-case ICER being supported by the sensitivity analysis, further research to obtain long-term EFS data could reduce the uncertainty around the extrapolation.

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2020, with the highest prevalence rates reported in Northern and Western Europe [1]. The National Agency for Cancer Registration reported 38 deaths in men and 7002 deaths in women caused by breast cancer in Switzerland between January 2015 and December 2019 [4]. Furthermore, a total of 141,765 deaths due to breast cancer were recorded in Europe in 2020 [1]. In the same year, a total of 7292 new cases (12.1% of all cancer cases) and 1506 deaths were reported in Switzerland alone [5].

Breast cancer is classified into subtypes based on the expression of specific hormone or protein receptors, which dictate a patient's prognosis and treatment options [6]. Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen receptors (ERs), progesterone receptors (PRs) and human epidermal growth factor receptor 2 (HER2) [7]. Approximately 20% of all breast cancer cases are TNBC, with the highest prevalence rates reported in African, American and Hispanic women aged under 40 years old [8].

TNBC is the most aggressive and difficult to treat breast cancer subtype [8]. Poorer survival and relapse rates have been reported in patients with TNBC in Switzerland compared to patients with other types of breast cancer [9, 10]. A retrospective study of cancer registries in Switzerland reported a survival rate of 60% for patients with TNBC after a median follow-up of 10.9 years compared to 66% for those with luminal A-like disease [9]. A higher relapse rate was also reported in patients with TNBC (27%) versus luminal A-like disease (13%) and luminal B-like disease (23%) [9]. Furthermore, in a prospective study of patients with stage I–III breast cancer ($n = 1118$), patients with TNBC ($n = 255$) had significantly lower 3-year progression-free survival (PFS) when compared to patients with other breast cancer subtypes (63% vs 76%, respectively, $p < 0.0001$) [11]. This study also found that overall survival (OS) rates were significantly lower in patients with TNBC versus hormone receptor–positive patients (64% vs 81% 5-year OS, respectively) [11].

Molecularly targeted treatments aimed at specific therapeutic targets, such as HER2 or hormone receptors (e.g., trastuzumab or endocrine therapy, respectively), are not appropriate for the treatment of patients with TNBC [12]. Therefore, neoadjuvant chemotherapies, such as anthracyclines, taxanes and cyclophosphamide, are the standard of care for patients with high-risk, early-stage TNBC (small, localized tumors that are at high-risk of recurrence) [13–15]. Despite some studies showing that TNBC responds better to chemotherapy than other types of breast cancer, clinical outcomes in TNBC remain poor, with high recurrence rates and low survival rates reported [16]. This highlights the unmet need for an effective therapy in patients with TNBC.

Breast cancer is associated with a substantial economic burden that is largely driven by high treatment costs. A systematic review conducted in 2023 demonstrated substantial variation in the proportion of total cancer care costs attributable to anticancer drugs, from 7.5% (systemic therapies) to 75% (targeted therapy [bevacizumab]) [17–19]. For immune checkpoint inhibitors, a retrospective analysis of United States (US) Medicaid files demonstrated an increase in expenditure from 2.8 million US dollars (USD) (~2.58 million Swiss francs [CHF]) in 2011 to USD4.1 billion (CHF~3.78 billion) in 2021 across all cancer types [20].

These costs have been shown to further increase in patients with advanced stages of breast cancer [21]. In a systematic literature review (SLR), including 20 studies from ten different countries, cumulative treatment costs increased from USD29,724 (currency year, 2015) (CHF~27,369) to USD62,108 (CHF~57,189) in patients with stage I versus stage IV breast cancer, respectively (exchange rate, as of January 2023: USD1 = CHF0.9208) [21]. The previously mentioned SLR published by Huang et al. reported that mean per-patient annual direct medical costs for patients with TNBC ranged from USD20,000 to over USD100,000 (CHF~18,415–92,078) in patients with stage I–III TNBC and from USD100,000 to USD300,000 (CHF~92,078–276,187) in those with stage IV TNBC (exchange rate, as of January 2023: USD1 = CHF0.9208) [17].

Unlike other types of breast cancer (hormone receptor–positive and ERBB2-positive, hormone receptor–negative and ERBB2-positive and hormone receptor–positive and ERBB2-negative), where costs have been shown to decrease over time since diagnosis, overall and anticancer therapy costs for patients with metastatic TNBC have been shown to remain constant with time since diagnosis [22]. This highlights the importance of providing effective treatments in patients with early-stage breast cancer to reduce the risk of progression and subsequently ameliorate the burden of the disease [21]. Prophylactic bilateral mastectomy in combination with salpingo-oophorectomy for women not yet affected by breast cancer who test positive for a BRCA1/2 mutation is also recommended to reduce healthcare system costs and improve patient outcomes [23].

Programmed cell death protein 1 (PD-1), a protein expressed on T and B cell surfaces, inhibits T cell inflammatory activity in order to downregulate the immune response [24]. In the last decade, immunotherapies targeting PD-1 and programmed death-ligand (PD-L1) have been recommended for the treatment of various types of cancers [24, 25]. In patients with TNBC, a study assessing PD-L1 expression demonstrated the promising potential of novel immunotherapies in targeting this tumor type [26].

Pembrolizumab (Keytruda®) is a high-affinity monoclonal antibody that binds to the PD-1 receptor, blocking its interaction with PD-L1 to activate an immune response targeting cancer cells [27]. The phase III randomized controlled trial KEYNOTE-522 (NCT03036488) investigated the efficacy and safety of pembrolizumab in the treatment of early TNBC [28]. The primary endpoint of KEYNOTE-522 showed a statistically significant difference in event-free survival (EFS) at 36 months for patients treated with pembrolizumab plus chemotherapy versus chemotherapy alone (EFS 84.5% vs 76.8%, respectively; hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.43–0.82; $p < 0.001$) [28]. The trial also demonstrated that the treatment was well-tolerated, with no new safety concerns [28].

Based on the KEYNOTE-522 results, pembrolizumab has been approved by the Food and Drug Administration (FDA) (in July 2021) and the European Medicines Agency (EMA) (in April 2022) in combination with chemotherapy as a neoadjuvant treatment and then continued as a single agent adjuvant treatment for high-risk, early-stage TNBC [27, 29]. Pembrolizumab is also approved for use in combination with chemotherapy for the treatment of unresectable or metastatic TNBC [27, 29]. In Switzerland, the use of pembrolizumab for the treatment of metastatic TNBC was approved in January 2022; however, it is not yet approved for use as a neoadjuvant and adjuvant treatment for patients with TNBC [30].

The aim of this study was to assess the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy plus placebo followed by adjuvant placebo, for patients with high-risk, early-stage TNBC in Switzerland from a third-party payer perspective over a lifetime horizon.

2 Materials and Methods

2.1 Population

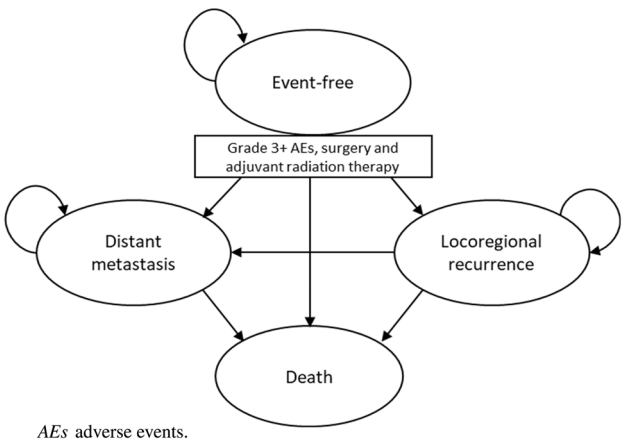
The model population consisted of adult patients with high-risk, early-stage TNBC [31]. Population eligibility and baseline characteristics of patients were aligned with the KEYNOTE-522 trial (ClinicalTrials.gov, NCT03036488; participants were from 22 countries; however, no patients from Switzerland were included) (e.g., patients with newly diagnosed, previously untreated and nonmetastatic disease) [28]. The model assumed that all patients were female and the starting age at model entry was 49 years old [32, 33].

2.2 Model Structure

A Markov state cohort transition model with four health states (event-free [EF]; locoregional recurrence [LR]; distant metastasis [DM], and death) was developed (Fig. 1) to estimate the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy plus placebo followed by adjuvant placebo (referred to as pembrolizumab plus chemotherapy versus chemotherapy alone hereafter). The model considered clinical events, including grade 3+ adverse events (AEs) from neoadjuvant and adjuvant treatment, surgery following neoadjuvant treatment, and radiation therapy in the adjuvant treatment phase, for which specific cost inputs were applied. A 1-week model cycle length was used for a granular estimation of treatment-related costs, and a half-cycle correction was applied in the base-case analysis. An annual discount rate of 3% was applied to both costs and effectiveness in the base-case analysis, in line with recently published cost-effectiveness analyses in Switzerland [34–36]. A lifetime horizon of up to 51 years (maximum 100 years of age) was used to comprehensively capture differences in costs, effectiveness and outcomes between treatment arms, aligning with standard practice guidelines [37]. All analyses were conducted from a third-party payer perspective in Switzerland, representing the obligatory health insurance system, which has 100% coverage in the country. The model was developed in Microsoft Excel® 2016, and VBA was utilized to perform sensitivity analyses.

2.3 Intervention and Comparator

The intervention in the model was neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab and the comparator was neoadjuvant chemotherapy followed by adjuvant placebo, reflecting the treatment arms in the KEYNOTE-522 trial [28]. Patients received neoadjuvant pembrolizumab plus chemotherapy, administered as four cycles of pembrolizumab (200 mg every 3 weeks) plus paclitaxel (80 mg/m^2 weekly) and carboplatin (area under



AEs adverse events.

Fig. 1 Model schematic

the curve [AUC] 5 every 3 weeks). This was followed by four cycles of pembrolizumab plus doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2 every 3 weeks in the subsequent 12 weeks). Following definitive surgery, patients received adjuvant radiation therapy plus pembrolizumab once every 3 weeks for up to nine cycles. The comparator arm was modeled to reflect the placebo arm in the KEYNOTE-522 trial, following the same schedule as the chemotherapy in the intervention arm.

2.4 Transition Probabilities

Transition probabilities were estimated using data from the KEYNOTE-522 trial and natural mortality data from the Federal Statistical Office (2013–2020) [33, 37]. EFS was estimated using patient-level data from the KEYNOTE-522 trial and extrapolated over the modeled time horizon [33]. Survival curve fitting was carried out in line with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines [37]. The base-case parametric survival models were chosen based on statistical tests, visual assessment of fit and clinical plausibility of the long-term extrapolated model. Separate survival models were fitted for each therapy arm and standard (one-piece) parametric models were fitted, including exponential, Weibull, log-normal, log logistic, Gompertz, gamma and generalized gamma. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection, were used to select the best-fit parametric distributions.

As standard parametric models did not provide a good fit to the observed data, piecewise parametric models were explored. For both arms, a 50-week cut-off point was used. This ensured the Kaplan-Meier (KM) data were robust enough to generate short-term transition probabilities for the first 50 weeks, and that enough data remained to extrapolate transition probabilities after week 50. For the pembrolizumab plus chemotherapy arm, a generalized gamma distribution provided the best fit, based on both AIC and BIC and confirmed by visual inspection. For the chemotherapy arm, AIC indicated a best fit using a generalized gamma distribution; however, BIC indicated a log-normal distribution as the best fit. Although the visual inspection suggested generalized gamma is more plausible, neither distribution fitted the observed EFS data well. As the standard parametric models did not provide a good fit, piecewise parametric models were explored. A log-normal distribution was found to be the best fit and was used in the base case for the chemotherapy arm. Scenario analysis tested a generalized gamma distribution for both therapy arms and a log-normal distribution for both therapy arms (results are presented in the Supplementary materials_1: Table S9; see the electronic supplementary material).

Transition probabilities from LR to DM or death were estimated using data from the KEYNOTE-522 trial [33]. Parametric models were fitted to the time from LR to DM or death, and an exponential distribution was used in the base case as it had the best fit.

The transition probabilities from DM to death were estimated based on the survival time for patients who had documented DM from the KEYNOTE-522 trial. Parametric models were fitted to the data. Exponential distribution was selected as the best fit, and time-constant transition probabilities for DM to death were estimated based on the fitted exponential distributions [33]. All-cause natural mortality was incorporated for all individuals in the model, and therefore, the probability of death was at least as high as the all-cause natural mortality.

2.5 Adverse Event Rates and Durations

The model included grade 3+ all-cause AEs with an incidence of at least 5% for combined neoadjuvant and adjuvant phase in either treatment arm. AEs included neutropenia, febrile neutropenia, neutrophil count decrease, anemia, decrease in white blood cells and increase in alanine aminotransferase. AE rates and mean durations were obtained from the KEYNOTE-522 trial [33] and were considered separately for each treatment arm (Supplementary materials_1: Table S1; see the electronic supplementary material). A mean duration of 12.5 weeks was applied to all grade 3+ AEs based on pooled data from the KEYNOTE-522 trial [33]. AE-related disutility and costs were applied in the model (Supplementary materials_1: Table S2).

2.6 Utility Inputs

Health state utility values used in the base case were derived from EQ-5D-5L data collected in the KEYNOTE-522 trial [33] and converted to population-based utility values using a published algorithm [38]. There is no EQ-5D value set for Switzerland; therefore, the model used the German value set in the base-case analysis [39, 40]. The German value set for the EQ-5D-5L was developed through interviews with a representative sample of the general population in Germany (n = 1158) as part of a time trade-off and discrete choice experiment [39]. Utility inputs used for the base-case model can be found in Supplementary materials_1: Table S2 (see the electronic supplementary material). A one-time AE utility decrement of − 0.022 was applied for grade 3+ AEs in both arms based on pooled data from the KEYNOTE-522 trial [33]. A disutility related to patient age (years) was applied per year of increasing age in the base-case analysis based on

a model of mean health state utility values from the general population [41].

2.7 Cost and Resource Use Inputs

Cost data were reported in CHF (2022) and estimated from a Swiss third-party payer perspective. The consumer price index was sourced from the Swiss Federal Office for Statistics and used to inflate costs as needed to 2022 values [42]. The following cost components were considered in the model: neoadjuvant treatment costs, adjuvant treatment costs, surgery costs, radiation costs, disease management costs, terminal care costs, AE management costs and distant metastatic treatment costs. Details of each cost input and the associated sources are outlined below and presented in Supplementary materials_1: Table S2 (see the electronic supplementary material).

Neoadjuvant and adjuvant treatment costs included drug acquisition costs (unit acquisition cost, number of units per administration, dose intensity and proportion of treatment allocation) and drug administration costs, for each cycle for the duration of treatment.

Surgery and radiation costs were calculated based on the unit costs and the proportion of patients receiving surgery or radiation in each treatment arm. Recurring disease management costs included consultations, mammograms and ultrasounds, which were applied weekly (Supplementary materials_1: Table S2). Disease management costs for patients who remained in the EF state for more than 10 years were assumed to be zero. A one-off terminal care cost was applied before death. AE costs were calculated as a function of the AE rates, the proportion hospitalized for each AE event and the unit costs of medical management for each AE in the inpatient or outpatient setting. A one-off cost was applied upon entry to the DM state, which included drug acquisition and administration costs associated with metastatic TNBC therapies. Treatment rate, distribution and duration of metastatic treatments were derived from the KEYNOTE-522 trial.

2.8 Time on Treatment

The time on neoadjuvant and adjuvant treatment for both therapy arms was estimated using the observed KM curve from the KEYNOTE-522 trial. For scenario analyses, the lower and upper 95% CIs of the KM curve were considered.

2.9 Sensitivity Analyses

A one-way deterministic sensitivity analysis (DSA), a probabilistic sensitivity analysis (PSA) and scenario analyses were performed to analyze the robustness of the base-case results. The DSA was performed to test the robustness of the model to parameter uncertainty, by varying one model input or assumption at a time by their 95% CI derived from the standard error. In the PSA, model inputs were varied simultaneously for each parameter over 1000 iterations to assess uncertainty in the cost-effectiveness model results (Supplementary materials_1: Table S3; see the electronic supplementary material). Scenario analyses were conducted to assess the impact of different assumptions for the time horizons, discount rates, efficacy, EFS parametric functions, half-cycle correction, vial sharing, relative dose intensity, utilities (including removing the age disutility), time on treatment, remission rates, AE costs, treatment waning and subsequent treatment cost being equal in both arms (with the highest cost applied [CHF53,716.19]) (Supplementary materials_1: Table S4). Furthermore, scenario analyses investigating a generalized gamma distribution and a log-normal distribution for both therapy arms were also performed.

2.10 Model Validation

Validation of the modeled EFS curves was performed with internal and external sources. The modeled EFS was found to be comparable to the observed EFS in the KEYNOTE-522 trial, a retrospective study of patients with TNBC (median follow-up: 30 months) and a randomized, open-label, phase II trial of patients with stage II or III TNBC ($n = 443$) for both therapy arms (Supplementary materials_1: Table S5 and Fig. S1; see the electronic supplementary material) [33, 43]. The EFS results from these studies were shown to be similar to the base-case chemotherapy EFS, which confirms the plausibility of the EFS projections. As there are no long-term EFS data for patients with TNBC who received pembrolizumab, long-term EFS of the pembrolizumab plus chemotherapy arm was validated through discussions with a panel of key opinion leaders (KOLs), consisting of eight medical oncologists and two health economists from Europe. KOLs validated the intervention extrapolation in terms of the clinical plausibility and in comparison with the comparator extrapolation in terms of the expected improvement with immuno-oncology therapies.

Predicted cumulative incidence rates of EF to LR, DM or death were validated with the observed cumulative incidence rates from the KEYNOTE-522 trial [33]. This analysis demonstrated that the modeled cumulative incidence rates were comparable to the observed data (Supplementary materials_1: Fig. S1). Furthermore, the predicted OS data were validated using internal and external sources, including the KEYNOTE-522 trial, the CALGB 40603 (Alliance) trial and the study by Walsh et al. (2019; a retrospective study) [43, 44]. Modeled OS was comparable to observed OS in the KEYNOTE-522 trial and the two external studies

(Supplementary materials_1: Figure S2). These analyses were performed using short-term data (up to 3 years), as there were no long-term OS data for patients with early-stage TNBC receiving pembrolizumab.

3 Results

3.1 Base-Case Results

Over the life-time horizon, total costs for the pembrolizumab plus chemotherapy therapy were CHF128,692 versus CHF85,245 for chemotherapy. Total quality-adjusted life years (QALYs) for pembrolizumab plus chemotherapy were 15.17 compared to 12.10 for chemotherapy, and total life years (LYs) were estimated to be 18.47 for pembrolizumab plus chemotherapy versus 14.67 for the chemotherapy arm. The calculated incremental cost-effectiveness ratio (ICER) for pembrolizumab plus chemotherapy versus chemotherapy alone was CHF14,114/QALY gained, and CHF11,449/LY gained (Table 1). The disaggregated results are presented in the Supplementary materials_1: Tables S6 and S7 (see the electronic supplementary material).

3.2 One-way Deterministic Sensitivity Analyses

To assess the robustness of the model base-case results to parameter uncertainty, a DSA was conducted. Results of the 20 most influential parameters are presented in the tornado diagram in Fig. 2. The ICER for pembrolizumab plus chemotherapy versus chemotherapy alone ranged from CHF7517/QALY (46.7% decrease from the base-case ICER) to CHF40,308/QALY (185.6% increase from base-case ICER). The ICER was most sensitive to parameters determining EFS extrapolations for both therapy arms, and the results were moderately sensitive to variations in the costs of pembrolizumab, the exponential rate of transition from DM to death and total metastatic disease cost (detailed scenario analyses results are presented in Supplementary materials_1: Table S8; see the electronic supplementary material).

3.3 Probabilistic Sensitivity Analysis

Across the 1000 iterations of the PSA, the average incremental cost was CHF43,282 and the average incremental QALY gain was 2.95. The average probabilistic ICER for pembrolizumab plus chemotherapy versus chemotherapy alone was CHF14,660/QALY, which was similar to the result obtained in the base-case (CHF14,114/QALY).

The incremental cost and effectiveness plane is shown in Fig. 3 for pembrolizumab plus chemotherapy versus chemotherapy alone, with a willingness-to-pay (WTP) threshold of CHF100,000/QALY gained (the threshold typically used for cost-effectiveness analyses in Switzerland) [45, 46]. The majority of the plotted points are to the right of the WTP threshold, showing that pembrolizumab was cost-effective in those scenarios. In addition, the cost-effectiveness acceptability curve (Fig. 4) shows the probability of pembrolizumab plus chemotherapy being cost-effective versus chemotherapy alone at different WTP thresholds. Overall, there was a 98.8% probability of pembrolizumab plus chemotherapy being cost-effective at a WTP threshold of CHF100,000/QALY gained.

3.4 Scenario Analyses

The ICER ranged from CHF7577/QALY (0% discount rate for effectiveness) to CHF80,462/QALY (time horizon of 10 years) in the scenario analyses. Compared to the base case, the ICER increased when a 20-year time horizon (CHF25,532) and a 30-year time horizon (CHF16,653) were applied to the model. Further, the ICER increased from the base-case value when a 6% annual discount rate was applied (CHF23,654) versus the 0% discount rate for effectiveness. Detailed scenario analyses results are presented in the Supplementary materials_1: Table S9 (see the electronic supplementary material).

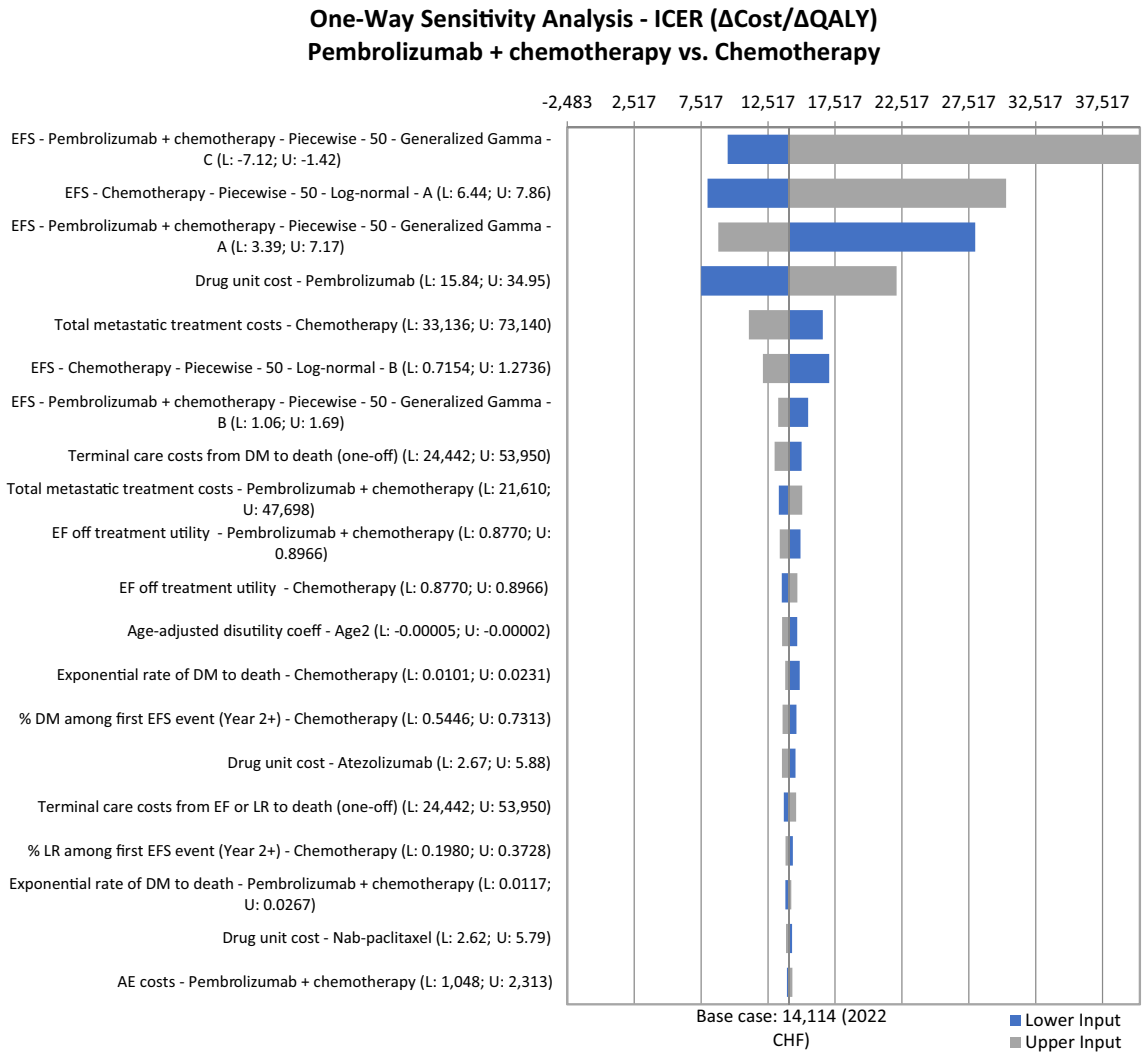
4 Discussion

The phase III, randomized KEYNOTE-522 trial demonstrated statistically significant improvements in EFS at 36 months for patients with high-risk, early-stage TNBC

Table 1 Base-case analysis results for pembrolizumab plus chemotherapy vs chemotherapy

Therapy arm	Total costs (CHF)	Total QALYs	Total LYs	ICER vs comparator (CHF/QALY gained)	ICER vs comparator (CHF/LY gained)
Pembrolizumab plus chemotherapy	128,692	15.17	18.47	–	–
Chemotherapy	85,245	12.10	14.67	–	–
Pembrolizumab plus chemotherapy vs chemotherapy	43,446	3.08	3.79	14,114	11,449

CHF Swiss francs, *ICER* incremental cost-effectiveness ratio, *LY* life year, *QALY* quality-adjusted life year



AE adverse event; *CHF* Swiss Francs; *DM* distant metastasis; *DSA* deterministic sensitivity analysis; *EFS* event-free survival; *ICER* incremental cost-effectiveness ratio; *LR* locoregional recurrence; *QALY* quality adjusted life year. *L* lower; *U* upper; *Nab-paclitaxel* Nanoparticle albumin-bound paclitaxel

Fig. 2 Tornado diagram of the most influential factors in the DSA—ICER (CHF/QALY)

treated with pembrolizumab plus chemotherapy versus chemotherapy alone (EFS 84.5% vs 76.8%, respectively; HR 0.63 [95% CI 0.43–0.82]; $p < 0.001$) [28]. Pembrolizumab was shown to be well-tolerated with a manageable safety profile [28]. The objective of this study was to evaluate the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus chemotherapy alone for patients with high-risk, early-stage TNBC from a Swiss third-party payer perspective.

The results of the model demonstrate that pembrolizumab plus chemotherapy is cost-effective when compared to chemotherapy alone, with an ICER of CHF14,114/QALY gained, which is below the WTP threshold of CHF100,000/QALY [45, 46]. The total costs associated with pembrolizumab plus chemotherapy were higher compared to chemotherapy (incremental cost CHF43,447 per patient). The increased costs associated with pembrolizumab were largely attributable to the drug acquisition costs in the neoadjuvant and adjuvant phases. However, these costs were partially offset by the reduction in metastatic treatment costs, disease management costs and terminal care costs.

TNBC has a substantial impact on patients' health-related quality of life (HRQoL). An SLR of 19 studies published between 2016 and 2021 reported significant reductions in Functional Assessment of Cancer Therapy—Breast scores

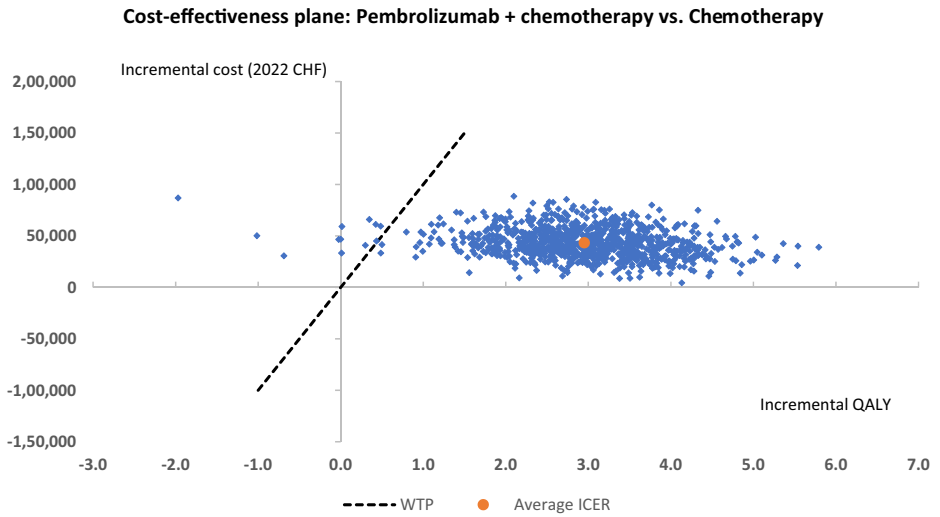
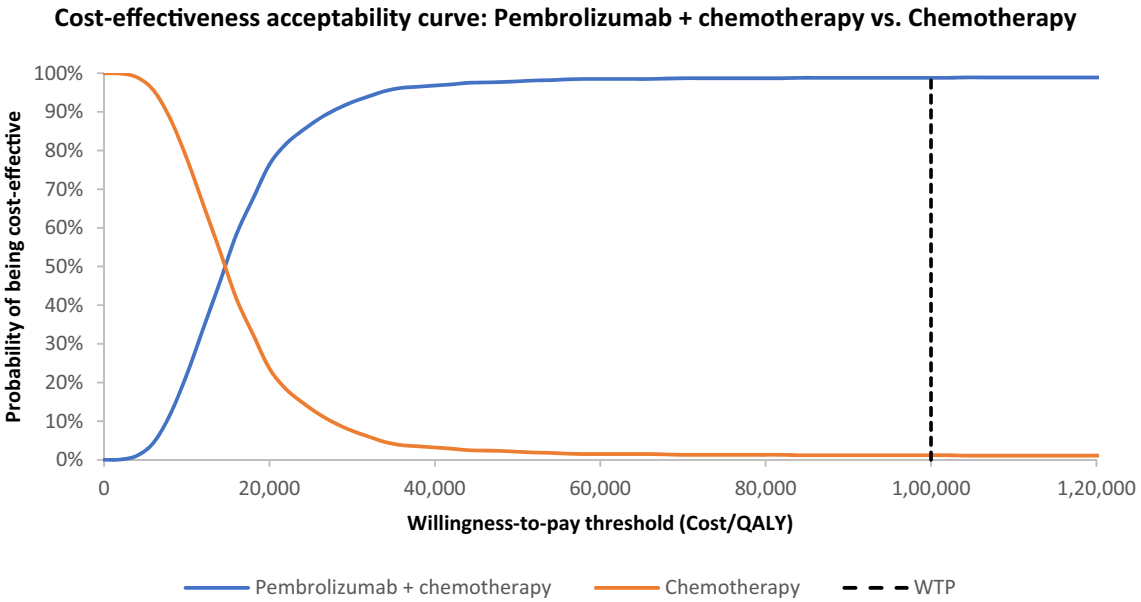


Fig. 3 Incremental cost and effectiveness plane: pembrolizumab plus chemotherapy vs chemotherapy alone

CHF Swiss Franc; *QALY* quality-adjusted life years; *WTP* willi ngness-to-pay.



QALY quality-adjusted life years; *WTP* willingness-to-pay.

Fig. 4 Cost-effectiveness acceptability curve: pembrolizumab plus chemotherapy vs chemotherapy alone

in patients with TNBC compared to those with non-TNBC [17]. Furthermore, a clinically meaningful decrease in mean utility values was reported in patients experiencing a progressed disease state (EQ-5D-3L index 0.601) compared to those in a progression-free state (EQ-5D-3L index 0.715) [17]. Pembrolizumab was found to improve HRQoL relative to chemotherapy in PD-L1–positive patients with metastatic TNBC [17]. Moreover, this review reported substantial indirect costs associated with TNBC due to lost work productivity and absenteeism [17]. This demonstrates the need for an effective treatment in patients with TNBC to improve HRQoL and reduce the impact of the disease on a patient's ability to work.

The economic impact of cancer, including on a patient's employment and income, was reported in a study assessing the socio-economic consequences of cancer from a patients' perspective in Europe. Employment levels were shown to fall by 41% when patients were diagnosed with cancer versus before their diagnosis [47]. Furthermore, 57% of patients with cancer in Switzerland experienced a loss of income

due to their disease [47]. Moreover, these patients incurred additional out-of-pocket expenses during diagnosis and treatment such as increased travel expenses, unreimbursed treatments and indirect costs (to cover household tasks or childcare) [47]. This is exacerbated in patients with TNBC as overall and anticancer therapy costs have been continuing to increase over time, especially for patients with more advanced disease [17, 22]. Cancer has a detrimental impact on patients and their families, and therefore, there is a need for effective treatments to reduce the risk of progression and alleviate these socio-economic consequences [17].

A key strength of this study was that data were derived from the KEYNOTE-522 randomized controlled trial, which directly compared pembrolizumab plus chemotherapy to chemotherapy alone [28]. Data from KEYNOTE-522 trial facilitated the extrapolation of EFS beyond the trial period, which was conducted in accordance with the NICE DSU guidelines [37]. EFS and OS predictions were validated against two external sources that evaluated efficacy outcomes in patients with early-stage TNBC, and these analyses showed a good fit of the modeled data to the external data sources [43, 44]. Furthermore, utility and AE disutility inputs were derived from the KEYNOTE-522 trial, which assessed HRQoL using the EQ-5D-5L (the recommended measure for eliciting utility values by NICE and a widely used and accepted HRQoL measure for clinical trials in oncology). Finally, the Markov cohort model used in this analysis is a well-established modeling approach, which has been used extensively in health technology assessment submissions for treatments of breast cancer and other oncology indications.

Limitations of this model included the uncertainty around the extrapolation of EFS from the KEYNOTE-522 trial, due to the lack of long-term data. Multiple scenario analyses evaluated alternative extrapolation approaches for EFS and the results from the sensitivity analyses supported the robustness of the base-case ICER. Furthermore, EFS curves from the published literature were digitized and fitted against the model so that the predicted EFS at specific time points could be compared against external data [43, 44]. Additional research to obtain longer-term EFS data would be important to ensure the model outcomes are representative of clinical practice.

There was also uncertainty regarding the transition probabilities from the DM to death state. These data were derived from the OS reported in the KEYNOTE-522 trial, which reflected the treatment pattern in the clinical trial follow-up period. Therefore, the estimated mean OS may not reflect current real-world data due to additional treatments that may be available in clinical practice. To assess the uncertainty in mortality data, the model incorporated a scenario analysis using data from the KEYNOTE-355 trial where the mean OS of each first-line treatment for metastatic TNBC was estimated based on the predicted OS curves in a cost-effectiveness model in 1L metastatic TNBC [48]. An additional limitation of the model is the use of a German value set for the utility inputs [39]. However, the use of non-Swiss EQ-5D values is an unavoidable limitation due to no country-specific data being available.

The results of this model align with similar previously published studies. A partitioned-survival model published in 2022 estimated that pembrolizumab plus chemotherapy was cost-effective compared with chemotherapy as a first-line treatment for metastatic TNBC in the US [49]. A recent cost-effectiveness analysis, from a US third-party payer perspective, showed that pembrolizumab plus chemotherapy as a neoadjuvant treatment and continued as a single-agent adjuvant treatment is a cost-effective option to treat high-risk, early-stage TNBC when compared to chemotherapy alone [50]. In the US analysis, the ICER for pembrolizumab plus chemotherapy was USD27,285 per QALY gained [50]. The current model conducted from a Swiss perspective is an adaptation of the US model and assumed the same transition probability inputs [50]. Two authors of this article were also authors for the US model publication [50]. The current study is the first published economic model evaluating the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab alone for patients with TNBC in Switzerland. Further research to understand the socioeconomic consequences and impact on indirect costs of adjuvant cancer treatments for patients and families would be important to provide a broader perspective.

The structure and results of this model align with the NICE appraisal published in November 2022, which recommended the use of pembrolizumab for the neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer [51]. The Evidence Review Committee deemed the economic model suitable for decision making and the base-case ICER was below the range considered a cost-effective use of National Health Service (NHS) resources (ICERs not reported due to confidential commercial agreements) [51].

5 Conclusion

In patients with high-risk, early-stage TNBC, there is a substantial unmet need for an effective treatment option to reduce recurrence rates and improve survival. Results from this analysis show that neoadjuvant pembrolizumab in combination with chemotherapy followed by adjuvant pembrolizumab is a cost-effective treatment option for patients with high-risk, early-stage TNBC compared to chemotherapy, from a Swiss third-party payer perspective. Moreover, cost

offsets may be achieved through the reduction of subsequent treatment costs.

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Declarations

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Declaration of Financial/Other Interests Andrea Favre-Bulle is employed by MSD. Min Huang and Amin Haiderali are employed by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA (MSD). Arjun Bhadhuri received financial support via employment institution from MSD.

Data Availability All data generated or analyzed during this study are included in this published article and its supplementary information.

Code Availability (software application or custom code) The model was developed in Microsoft Excel and is not publicly available, but is available from the authors upon request with permission of Merck & Co., Inc., and receipt of a signed confidentiality agreement.

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Consent to Participate Not applicable.

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