



# Cost-effectiveness of pembrolizumab plus chemotherapy as first-line treatment in PD-L1-positive metastatic triple-negative breast cancer

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**Objective:** This study evaluated the cost-effectiveness of pembrolizumab/chemotherapy combinations for previously untreated metastatic triple-negative breast cancer patients in the USA with PD-L1 combined positive score  $\geq 10$ . **Methods:** A partitioned-survival model was developed to project health outcomes and direct medical costs over a 20-year time horizon. Efficacy and safety data were from randomized clinical trials. Comparative effectiveness of indirect comparators was assessed using network meta-analyses. A series of sensitivity analyses were performed to test the robustness of the results. **Results:** Pembrolizumab/chemotherapy resulted in total quality-adjusted life-year (QALY) gains of 0.70 years and incremental cost-effectiveness ratio of US\$182,732/QALY compared with chemotherapy alone. The incremental cost-effectiveness ratio for pembrolizumab/nab-paclitaxel versus atezolizumab/nab-paclitaxel was US\$44,157/QALY. Sensitivity analyses showed the results were robust over plausible values of model inputs. **Conclusion:** Pembrolizumab/chemotherapy is cost effective compared with chemotherapy as well as atezolizumab/nab-paclitaxel as first-line treatment for PD-L1-positive metastatic triple-negative breast cancer from a US payer perspective.

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Breast cancer is the most common malignancy in women globally, accounting for 30% of female cancers with 281,550 new diagnoses and 43,600 deaths expected among women in the US in 2021 [1]. Triple-negative breast cancer (TNBC), which accounts for 10–20% of breast cancer diagnoses [2], is characterized by the absence of estrogen and progesterone receptor and *HER2* expression [3]. The molecular profile of TNBC makes these tumors insensitive to hormone therapy and agents targeting *HER2* such as trastuzumab [4], the first-line treatment for advanced *HER2*-positive breast cancer [5]. Consequently, TNBC has a high risk of relapse and its prognosis is poor compared with other types of breast cancer [6]. TNBC also imposes a considerable economic burden on healthcare payers: the cumulative cost of treatment with three or more chemotherapy regimens is estimated at \$143,150 from the US Medicare perspective [7].

Treatment options for TNBC patients were previously limited, and chemotherapy including taxanes, gemcitabine and platinum-based agents has been the standard of care for metastatic TNBC (mTNBC) [8,9]. However, chemotherapies have limited efficacy, with a median survival of 13.3 months [10]. The development of immunotherapies targeting immune checkpoint components such as PD-1 or its ligand (PD-L1) that suppress the T cell-mediated antitumor response have expanded the treatment options for TNBC [11]; their efficacy is also enhanced when they

are used in combination with standard chemotherapy drugs [12]. The anti-PD-L1 antibody atezolizumab combined with nab-paclitaxel was granted accelerated approval by the US FDA in March 2019 [13] and by the EMA in June 2019 [14] for the treatment of locally advanced or mTNBC expressing PD-L1 (tumor-infiltrating immune cells  $\geq 1\%$ ) based on the results of the phase III IMpassion130 trial (NCT02425891), which showed that the regimen prolonged progression-free survival (PFS) compared with placebo plus nab-paclitaxel in treatment-naïve patients with PD-L1-expressing tumors (tumor-infiltrating immune cells  $\geq 1\%$ ) [15,16]. However, the application for full approval of atezolizumab plus nab-paclitaxel was withdrawn in the US as no statistically significant difference in overall survival (OS) was observed between trial arms in this population [17].

Pembrolizumab is a monoclonal antibody targeting PD-1 that was granted accelerated approval by the FDA in November 2020 [18] and regular approval in July 2021 [19] in combination with chemotherapy for the treatment of locally recurrent inoperable or mTNBC that expresses PD-L1 (combined positive score [CPS]  $\geq 10$ ), as determined by an FDA-approved test using Dako 22C3 PD-L1 immunohistochemistry assay. The approvals were based on data from the randomized, double-blind, phase III KEYNOTE-355 trial (NCT02819518) of pembrolizumab (200 mg every 3 weeks) plus chemotherapy (taxane [paclitaxel or nab-paclitaxel] or gemcitabine plus carboplatin) versus placebo plus chemotherapy in previously untreated patients with locally recurrent inoperable or mTNBC [20,21]. Compared with chemotherapy alone, the combination of pembrolizumab and chemotherapy significantly prolonged PFS (median PFS: 9.7 vs 5.6 months; hazard ratio: 0.66; 95% CI: 0.50–0.88) and OS (median OS: 23.0 vs 16.1 months; hazard ratio: 0.73; 95% CI: 0.55–0.95) and was well tolerated in patients with PD-L1-positive (CPS  $\geq 10$ ) tumors [21].

There have been no analyses of the economic value of pembrolizumab in mTNBC patients. The main objective of the present study was to evaluate the cost–effectiveness of pembrolizumab plus chemotherapy versus chemotherapy as first-line treatment for patients with PD-L1-positive (CPS  $\geq 10$ ) mTNBC from a US third-party public healthcare payer perspective.

Although atezolizumab regimens did not obtain full approval by the FDA in first-line mTNBC, atezolizumab in combination with nab-paclitaxel is being used and is believed to yield clinical benefits in the PD-L1-positive population by medical decision-makers in Europe and other parts of the world [14,22]. Therefore we also evaluated the economic value of pembrolizumab plus nab-paclitaxel versus atezolizumab plus nab-paclitaxel in this indication.

## Patients & methods

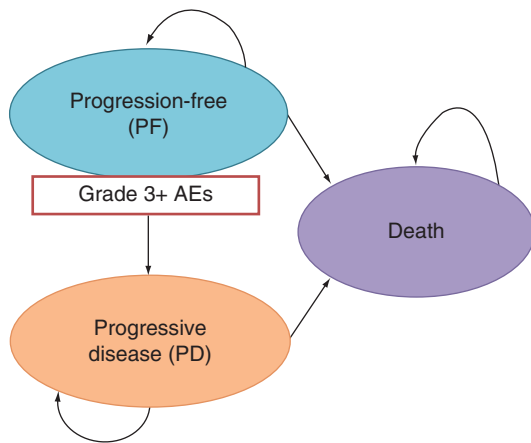
### Overview

The analytical methods used in this cost–effectiveness analysis (CEA) were similar to those of previously published economic analyses in breast cancer [23] and of pembrolizumab economic evaluations in other solid tumors such as non-small-cell lung cancer [24,25]. A partitioned-survival model was developed to evaluate the economic implications of treating patients with mTNBC whose tumors expressed PD-L1 with pembrolizumab combined with chemotherapy in the first-line setting. The model estimated expected costs and clinical effectiveness (including life years [LYs] and quality-adjusted life-years [QALYs]) along with incremental cost–effectiveness ratios as the incremental cost per LY and QALY gained with pembrolizumab plus chemotherapy versus with chemotherapy alone. The efficacy, safety and utility data used in the model were derived from the KEYNOTE-355 trial (data cutoff date: 15 June 2021) [20,21]. The cost–effectiveness of pembrolizumab plus nab-paclitaxel versus atezolizumab plus nab-paclitaxel was evaluated based on a network meta-analysis (NMA) [26] using data from the subgroup of mTNBC patients with CPS  $\geq 10$  in the IMpassion130 trial [16,24].

### Population & interventions

The target population from KEYNOTE-355 that formed the basis for the CEA consisted of adult patients with mTNBC whose tumors expressed PD-L1 (CPS  $\geq 10$ ) and who had not received treatments in the metastatic setting.

KEYNOTE-355 included three chemotherapy regimens: paclitaxel, nab-paclitaxel, and gemcitabine plus carboplatin. Treatment allocation was according to subject inclusion criteria and at the physician's discretion. The model evaluated the treatments included in KEYNOTE-355 (pembrolizumab plus chemotherapy vs chemotherapy). The distribution of patients among the three chemotherapy options was assumed to be the same as the distribution in the trial. Subgroup analyses were performed by on-study chemotherapy: pembrolizumab plus taxane (paclitaxel or nab-paclitaxel) versus taxane; pembrolizumab plus nab-paclitaxel versus nab-paclitaxel; pembrolizumab plus paclitaxel versus paclitaxel; and pembrolizumab plus gemcitabine plus carboplatin versus gemcitabine plus carboplatin.



**Figure 1. Schematic of the cost-effectiveness analysis evaluating first-line treatments in PD-L1-positive (combined positive score  $\geq 10$ ) metastatic triple-negative breast cancer. AE: adverse event.**

The model also evaluated indirect comparator atezolizumab plus nab-paclitaxel for comparison with pembrolizumab plus nab-paclitaxel.

### Model structure

The model comprised three mutually exclusive health states: progression-free disease, progressive disease and death (Figure 1). State membership was modeled based on patient-level PFS and OS data from KEYNOTE-355. For the comparator not included in the trial (i.e., atezolizumab plus nab-paclitaxel), state membership was modeled by applying a hazard ratio (HR) estimated from the NMA [26] to the relevant reference arm. For each health state, a specific cost and quality of life adjustment weight (i.e., utility) was assigned within each model cycle to estimate the cumulative costs and cumulative QALYs over the modeled time horizon.

### Perspective, time horizon, cycle length & discount rate

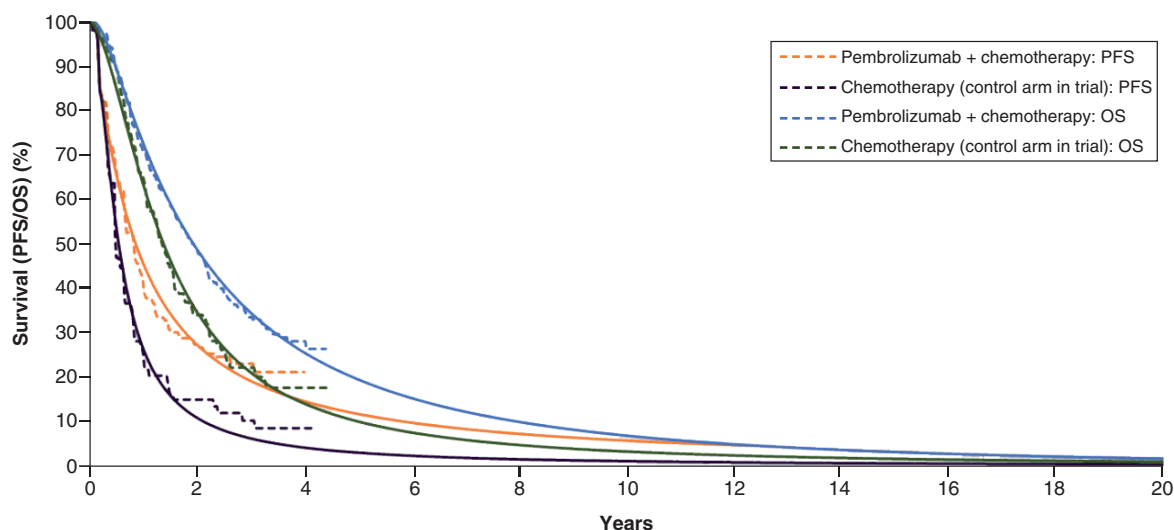
The analysis was conducted from a US third-party payer perspective. The model used a weekly cycle length. A 20-year time horizon was selected for the model base case to accommodate patients' life expectancy and to ensure that important differences in costs and outcomes between the interventions were captured. A 10-year time horizon was also tested as an alternative scenario. Costs and outcomes were discounted at 3% per year as recommended by the Institute for Clinical and Economic Reviews [27]; additionally, discount rates of 0 and 6% were explored in scenario analyses.

### Clinical parameters from KEYNOTE-355

The model effectiveness parameters for the pembrolizumab plus chemotherapy and chemotherapy arms were derived from the patient-level PFS and OS data from KEYNOTE-355. Time on treatment (ToT) data were also analyzed to facilitate the calculation of drug costs. Survival curve fitting was carried out in line with the NICE Decision Support Unit guidelines [28]. Standard and two-piece models were explored using exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalized gamma distributions. Statistical tests based on the Akaike information criterion and Bayesian information criterion combined with visual inspection were used to select the best-fit parametric distributions for the base case. Finally, the clinical plausibility of the long-term extrapolations was evaluated for the selected distributions. Alternative parametric functions were tested in scenario analyses.

In KEYNOTE-355, PFS was assessed according to the Response Evaluation Criteria in Solid Tumors (v. 1.1) [29] by means of blinded, independent, central radiologic review. For PFS extrapolations, Kaplan–Meier curves from KEYNOTE-355 were used directly up to week 9 and parametric functions were fitted thereafter. This was because the first radiologic tumor response assessment was conducted at Week  $8 \pm 7$  days, resulting in a protocol-driven drop in PFS around this time point. Log-logistic function was selected as the best fit for both treatment arms (Figure 2). The Akaike information criterion and Bayesian information criterion for each distribution are shown in Supplementary Table 1.

For OS, a standard parametric model with log-normal and log-logistic distribution was considered as the best fit for the pembrolizumab plus chemotherapy and chemotherapy arms, respectively (Figure 2). Within each weekly



**Figure 2. Observed and modeled progression-free and overall survival curves for pembrolizumab plus chemotherapy versus chemotherapy.**

OS: Overall survival; PFS: Progression-free survival.

cycle of the model, the probability of death was constrained by background mortality according to the age of the model cohort in that cycle.

In the KEYNOTE-355 trial, treatment was continued for the specified number of cycles or until disease progression, intolerable toxicity, patient withdrawal or investigator decision. Clinically stable patients considered by the investigator to be deriving clinical benefit were eligible to continue pembrolizumab regimens beyond progression.

The proportion of patients remaining on treatment in each cycle was modeled using parametric curves fitted to observed patient-level ToT data from KEYNOTE-355. Gamma and log-logistic distribution were selected as the best fit for the pembrolizumab plus chemotherapy and chemotherapy arms, respectively. Patients were assumed to receive pembrolizumab for a maximum of 35 cycles (2 years) as per trial protocol and US FDA-approved label. No treatment cap was assumed for chemotherapies (either used alone or in combination with pembrolizumab).

### Clinical inputs for atezolizumab plus nab-paclitaxel

The IMpassion 130 trial is a phase III trial evaluating atezolizumab plus nab-paclitaxel compared with nab-paclitaxel as a first-line treatment for mTNBC. The two primary efficacy end points, investigator-assessed PFS and OS, were evaluated in both the intention-to-treat population and the subgroup of patients with PD-L1-positive tumors, which was defined as tumor-infiltrating immune cells  $\geq 1\%$  using the SP142 immunohistochemistry assay.

A *post hoc*, exploratory substudy of IMpassion130 was conducted to investigate analytical concordance between the SP142 and Dako 22C3 PD-L1 immunohistochemistry assays. PFS and OS were evaluated for subgroups identified by each assay. The HR for the comparison between atezolizumab plus nab-paclitaxel and nab-paclitaxel in patients with CPS  $\geq 10$  (by 22C3 [30]) was 0.71 (95% CI: 0.54–0.94) for PFS and 0.77 (95% CI: 0.57–1.03) for OS.

An NMA was conducted [26] to assess the comparative efficacy of pembrolizumab plus chemotherapy versus atezolizumab plus nab-paclitaxel based on the PFS and OS outcomes reported in KEYNOTE-355 and IMpassion130 for PD-L1 CPS  $\geq 10$  mTNBC patients. Relative treatment effects were synthesized with proportional HRs in a Bayesian framework with non-informative priors.

PFS and OS of atezolizumab plus nab-paclitaxel were derived by applying HRs (HR vs pembrolizumab plus nab-paclitaxel for OS: 1.22; HR for PFS: 1.25) estimated from the NMA [26] to survival curves of pembrolizumab plus nab-paclitaxel (Table 1).

In the absence of detailed ToT data for atezolizumab plus nab-paclitaxel, the ToT was set equal to the ToT for pembrolizumab plus nab-paclitaxel in the model. Alternative scenarios allowed for atezolizumab plus chemotherapy ToT to be set equal to PFS. As a conservative assumption, the same treatment cap as for pembrolizumab (a maximum

Table 1. Base-case model inputs.

	OS	PFS	ToT	Ref.
Pembrolizumab plus chemotherapy	Log-normal distribution	KM curve up to week 9 followed by log-logistic tail	Gamma distribution	
Chemotherapy	Log-logistic distribution	KM curve up to week 9 followed by log-logistic tail	Log-logistic distribution	
HR	OS	PFS	Source	
Atezolizumab plus nab-paclitaxel (reference arm: pembrolizumab plus nab-paclitaxel)	1.22	1.25	NMA	[26]
Utility values (by time-to-death category, pooled treatment arms)		Mean utility	Source	
≥360		0.833	KEYNOTE-355	[20]
180–360		0.778		
90–180		0.712		
30–90		0.634		
<30		0.540		
Costs (healthcare payer's portion)		Costs (in 2021 US\$)	Source	
PD-L1 testing cost				
Cost per test		175.87	Centers for Medicare and Medicaid Services	[31]
Prevalence of PD-L1-positive CPS ≥ 10		38%	KEYNOTE-355	[20]
Disease management costs per cycle (time to death)				
≥360		780	Sieluk <i>et al.</i>	[32]
180–360		797		
90–180		942		
30–90		1290		
<30		2224		
Subsequent therapy costs				
Pembrolizumab plus chemotherapy		12,744	KEYNOTE-355 Analysource.com	[20,33]
Chemotherapy		23,989		
AE management costs per cycle				
Pembrolizumab plus chemotherapy		2268	KEYNOTE-355 Centers for Medicare and Medicaid Services	[2031]
Chemotherapy		1837		
Drug administration costs				
			Centers for Medicare and Medicaid Services (CPT code)	
Intravenous infusion, first hour		118.64	96413	
Intravenous infusion, additional hour		25.12	96415	
Intravenous infusion, each additional sequence		90.72	96417	
Intravenous, push		57.50	96409	

AE: Adverse event; CPS: Combined positive score; CPT: Current Procedural Terminology; HR: Hazard ratio; KM: Kaplan–Meier; NMA: Network meta-analysis; OS: Overall survival; PFS: Progression-free survival; ToT: Time on treatment.

treatment duration of 2 years) was assumed for atezolizumab. To be consistent with the IMpassion130 trial, an assumption of no atezolizumab treatment duration cap was also explored in a scenario analysis.

## Adverse events

All-cause grade 3+ adverse events (AEs) with an incidence rate ≥5% for at least one comparator were included in the model. Incidence rate, mean duration and hospitalization rate for each AE were obtained for the pembrolizumab plus chemotherapy and chemotherapy comparator arms from KEYNOTE-355 [20]. AE rates for atezolizumab plus nab-paclitaxel were obtained from the IMpassion130 trial [16].

### Utility inputs

Health state utility inputs were derived from EuroQol-5 Dimensions, 3 Levels (EQ-5D-3L) data collected in KEYNOTE-355 [20]. The EQ-5D-3L questionnaire was administered at treatment cycles 1, 2 and 3 and at every third cycle thereafter during the first year and every fourth cycle thereafter in year 2 when patients were on treatment; it was also administered at the discontinuation visit and 30-day safety follow-up visit. Generic health status assessed with the EQ-5D-3L questionnaire was converted to a population-based utility value using a US scoring algorithm based on time trade-off techniques [34].

Utilities were analyzed by time-to-death categories to reflect the deterioration of patients' quality of life as they approach death [35]. The model examined four categories ( $\geq 360$ , 180–360, 30–180 and  $< 30$  days until death) in the base case. Pooled data were used as there were no significant differences between treatment arms (Table 1) [36].

### Resource utilization & cost inputs

The cost inputs included in the CEA were regimen-related (drug acquisition and administration), disease management, subsequent treatment and AE management costs. It was assumed that 80% of healthcare costs would be paid by healthcare payers [37,38]. All costs were adjusted to 2021 US\$ using the Medical Care Consumer Price Index [39].

#### *Regimen-related costs*

Pembrolizumab is available as single-use vials of 100 mg and is administered at a fixed dose of 200 mg every 3 weeks [40]. The list price for pembrolizumab was \$5134 per 100-mg vial at the time of the analysis [33]; therefore the cost per dose is \$10,269. The list price for a single-use 840 mg vial of atezolizumab is \$6629.89 [33] and the drug is administered at a dose of 840 mg every 2 weeks [41]. The average number of vials per administration for the majority of chemotherapy regimens was calculated using the body surface area distribution (mean  $\pm$  standard deviation,  $1.75 \pm 0.21 \text{ m}^2$ ) of patients in KEYNOTE-355 and an optimal vial mix algorithm for minimizing vial wastage assuming no vial sharing occurs [20]. The cost of platinum-based chemotherapy was calculated based on the area under the curve as specified in the product label [40]. A total of 80% of the drug cost was assumed to be paid by healthcare payers. The cost of intravenous drug administration was obtained from the 2021 Centers for Medicare and Medicaid Services Physician Fee Schedule [31]. The number of treatment cycles in the model was based on the estimated ToT and was adjusted using the relative dose intensity observed in the clinical trial to account for any delays or interruptions in administration (e.g., due to AEs or noncompliance).

#### *PD-L1 testing costs*

The cost of PD-L1 testing (i.e., to detect a PD-L1-positive [CPS  $\geq 10$ ] patient) was included in the model as a function of PD-L1-positive (CPS  $\geq 10$ ) prevalence rates and cost per PD-L1 test (Table 1).

#### *Disease management costs*

Weekly costs of disease management were applied based on the time-to-death approach ( $\geq 360$ , 180–360, 90–180, 30–90 and  $< 30$  days) in the model base case (Table 1). These costs were based on a Surveillance, Epidemiology and End Results (SEER) Medicare study among patients with TNBC [42]. Cost elements included inpatient, emergency care, outpatient, skilled nursing facility and hospice visits.

#### *Subsequent therapy costs*

About 58% of patients in the pembrolizumab plus chemotherapy arm and 64% in the chemotherapy arm received subsequent therapy following study treatments in KEYNOTE-355. A much higher proportion of patients in the chemotherapy arm received anti-PD-1/PD-L1 therapy in the subsequent lines of treatment. The distribution and duration of subsequent treatments from the trial were used in the model.

Any PD-1/PD-L1 therapies as well as the five most commonly used second-, third- and later-line chemotherapy regimens were included in the model. The percentages of patients receiving any other chemotherapies were redistributed among the top chemotherapy regimens to ensure that the total proportion receiving subsequent therapy in either arm was aligned with the trial data. The subsequent treatment costs were calculated using unit costs for drug acquisition and administration, mean treatment duration for each individual regimen used in each subsequent line and the proportion of patients using each subsequent treatment. The estimated subsequent treatment costs for each treatment arm are shown in Table 1. The costs were incorporated in the model as one-off costs upon patients' entry into the progressive disease state.



### *AE management costs*

Costs associated with the management of grade 3–5 AEs in the inpatient [43] and outpatient [31] settings were obtained from 2021 Centers for Medicare and Medicaid Services payment rates and applied as one-time costs at model entry. The unit cost of one outpatient hospital visit for any AE was \$146.55. Unit costs for AE-related hospitalizations as well as proportions hospitalized are presented in [Supplementary Table 2](#). The total average cost per patient for managing AEs for each treatment arm was calculated based on AE incidence rates, unit costs of medical management for each AE episode in the inpatient or outpatient setting, and the hospitalization rate for each AE event ([Table 1](#)).

### **Sensitivity analyses**

One-way deterministic sensitivity analysis and probabilistic sensitivity analysis were carried out to assess the sensitivity of the model outcomes to the uncertainty in model parameters.

Scenario analyses were conducted to assess uncertainty in the model related to key model assumptions and specifications. Scenarios tested included different model time horizons and discounting of costs and effectiveness. Alternative plausible scenarios for OS, PFS and ToT were explored. There was also an option to apply a constant hazard rate of death for long-term OS extrapolations (from year 4) based on an observed real-world long-term survival rate. The constant hazard assumption and the estimate of the hazard rate was based on the observed OS of patients with stage IV TNBC in the SEER database in the US [44].

Subgroup analyses were conducted to evaluate the cost-effectiveness of pembrolizumab chemotherapy combinations by on-study chemotherapy (taxane, nab-paclitaxel, paclitaxel, gemcitabine plus carboplatin).

Parameters tested in the sensitivity analyses and scenarios tested in the scenario analyses are shown in [Table 2](#).

## **Results**

### **Comparison of pembrolizumab plus chemotherapy versus chemotherapy**

#### *Base-case analysis*

The base-case analysis projected longer PFS (1.04 years) and LYs (0.84) and greater QALYs (0.70) in patients receiving pembrolizumab plus chemotherapy compared with those who received chemotherapy alone. Pembrolizumab was also projected to be associated with higher overall medical costs (\$127,706), mainly driven by drug acquisition costs. The incremental cost per QALY gained was \$182,732 and the incremental cost per LY was \$152,289 ([Table 3](#)).

#### *One-way deterministic sensitivity analysis & probabilistic sensitivity analysis*

The impact of parameter variation on ICERs derived by the one-way deterministic sensitivity analysis is shown in the tornado diagram in [Figure 3](#). ICERs for pembrolizumab plus chemotherapy versus chemotherapy ranged from \$138,572 to \$288,651 per QALY gained. The ICERs were most sensitive to variations in parameter estimates for OS and ToT, disease management costs and utility values in the time-to-death category of longer than 360 days.

The probabilistic sensitivity analysis yielded an average ICER of \$183,014/QALY for pembrolizumab plus chemotherapy versus chemotherapy ([Figure 4](#)), with a 65% probability that the ICER would be below \$200,000 per QALY gained.

#### *Scenario analyses*

Over a 10-year time horizon, the ICER was \$204,065/QALY. Changes in the discount rate had little effect on the ICER. The results were not greatly affected when alternative assumptions and parametric functions were applied to the extrapolation of OS, PFS and ToT from trial data to the 20-year time horizon, with ICER ranging from \$154,764 to \$204,150/QALY ([Supplementary Table 3](#)).

#### *Subgroup analyses*

The results for subgroup analyses by on-study chemotherapy are summarized in [Supplementary Table 4](#). The ICER was similar for the nab-paclitaxel (\$122,866) and paclitaxel (\$112,399) subgroups. For pembrolizumab plus taxane (nab-paclitaxel or paclitaxel) versus taxane, the incremental LY and QALY gains were 1.66 and 1.38, respectively, with an incremental cost of \$169,609. This yielded an ICER of \$122,768/QALY. For pembrolizumab plus gemcitabine plus carboplatin versus gemcitabine plus carboplatin, the incremental LY and QALY gains were 0.26 and 0.22, respectively; the difference in cost was \$110,305 and yielded an ICER of \$511,640.

**Table 2. One-way deterministic sensitivity analysis and probabilistic sensitivity analysis parameters.**

Model parameter	Base-case value	OWSA range	PSA distribution model	Notes
PFS: pembrolizumab plus chemotherapy	KM9 + log-logistic onwards	95% CI limits of the parameter estimates in the log-logistic function	Random numbers generated from multivariate normal distribution model	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
PFS: chemotherapy	KM9 +log-logistic onwards	95% CI limits of the parameter estimates in the log-logistic function	Random numbers generated from multivariate normal distribution model	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
OS: pembrolizumab plus chemotherapy	Log-normal model	95% CI limits of the parameter estimate in the log-normal function	Random numbers generated from the upper and lower bounds of the KM curve	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
OS: chemotherapy	Log-logistic model	95% CI limits of the parameter estimate in the log-logistic function	Random numbers generated from the upper and lower bounds of the KM curve	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
ToT: pembrolizumab plus chemotherapy	Gamma model	95% CI limits of the parameter estimate in the gamma function	Random numbers generated from multivariate normal distribution model	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
ToT: chemotherapy	Log-logistic model	95% CI limits of the parameter estimate in the log-logistic function	Random numbers generated from multivariate normal distribution model	Uncertainty in the parametric model is represented by the variance–covariance matrix of the parameter estimates.
Time-constant HRs of PFS vs reference arm	Based on NMA	95% CI limits of the parameter estimate from NMA	Log-normal distribution	HRs and corresponding standard errors were obtained from a NMA
Time-constant HRs of OS vs reference arm	Based on NMA	95% CI limits of the parameter estimate from NMA	Log-normal distribution	HRs and corresponding standard errors were obtained from a NMA
Utilities	Based on KEYNOTE-355 trial data	95% CI limits estimated from the KEYNOTE-355 trial	Beta distributions using the mean and SE estimated from the KEYNOTE-355 trial	The mean and SE estimated from the KEYNOTE-355 trial
Cost of PD-L1 test	\$175.87	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
Disease management costs	Based on SEER Medicare	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
Terminal care costs	Based on SEER Medicare	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
Subsequent therapy costs: pembrolizumab plus chemotherapy	\$12,744	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
Subsequent therapy costs: pembrolizumab plus chemotherapy	\$23,989	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
AE management cost: pembrolizumab	\$2268	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value
AE management cost: chemotherapy	\$1837	95% CI limits estimated from the gamma distribution	Gamma distribution	SE assumed to be equal to 20% of the base-case value

AE: Adverse event; HR: Hazard ratio; ITC: Indirect treatment comparison; NMA: Network meta-analysis; OS: Overall survival; OWSA: One-way deterministic sensitivity analysis; PFS: Progression-free survival; PSA: Probabilistic sensitivity analysis; SE: Standard error; SEER: Surveillance, Epidemiology and End Results; ToT: Time on treatment.

Based on the results of the subgroup analyses, we derived the outcomes for the pembrolizumab plus chemotherapy and the chemotherapy arms using the weighted average approach based on the distribution of each on-study chemotherapy in KEYNOTE-355. The resultant total QALY and total LY gains resulting from pembrolizumab plus chemotherapy versus chemotherapy alone were 0.74 and 0.88, respectively. This led to an incremental cost per QALY gained of \$181,383 (Supplementary Table 5), which was consistent with the base-case results.

### Comparison of pembrolizumab plus nab-paclitaxel versus atezolizumab plus nab-paclitaxel

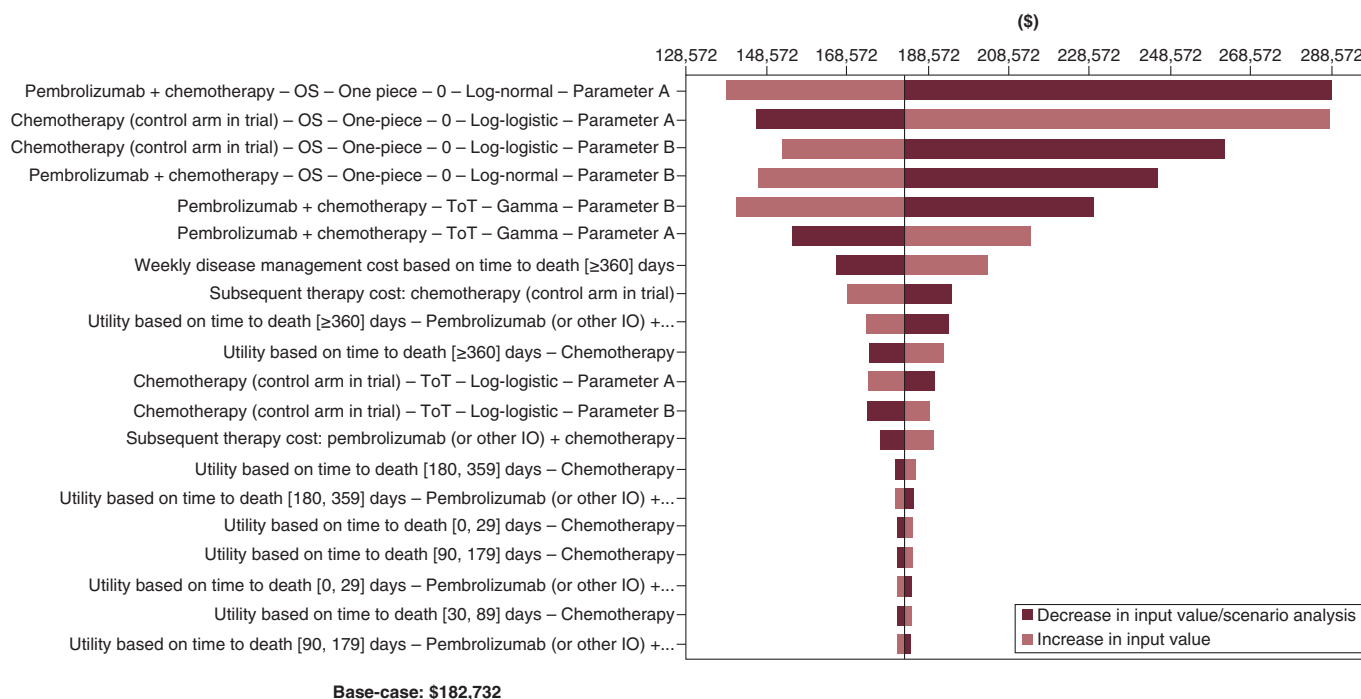
Compared with atezolizumab plus nab-paclitaxel, pembrolizumab plus nab-paclitaxel was associated with total LY and total QALY gains of 0.73 and 0.61, respectively (Table 4). This resulted in an incremental cost per LY gained



**Table 3. Base-case results for the cost-effectiveness of pembrolizumab plus chemotherapy versus chemotherapy.**

Outcome	Pembrolizumab plus chemotherapy	Chemotherapy <sup>†</sup>	Pembrolizumab plus chemotherapy vs chemotherapy
<b>Cost (\$)</b>			
Total costs	\$284,122	\$156,416	\$127,706
Regimen-related costs	\$137,186	\$32,454	\$104,732
Drug acquisition costs	\$130,920	\$27,961	\$102,959
Drug administration costs	\$5804	\$4493	\$1311
Testing costs	\$461	\$0	\$416
Subsequent therapy costs	\$11,844	\$23,204	-\$11,361
AE management costs	\$2268	\$1837	\$431
Disease management costs	\$132,824	\$98,919	\$33,904
<b>Effectiveness</b>			
Total QALY	2.40	1.70	0.70
Total LY	2.99	2.16	0.84
– Progression-free	2.04	1.00	1.04
– Progressive disease	0.96	1.15	-0.20
<b>Incremental cost-effectiveness ratio (\$)</b>			
Incremental cost per QALY gained			\$182,732
Incremental cost per LY gained			\$152,289

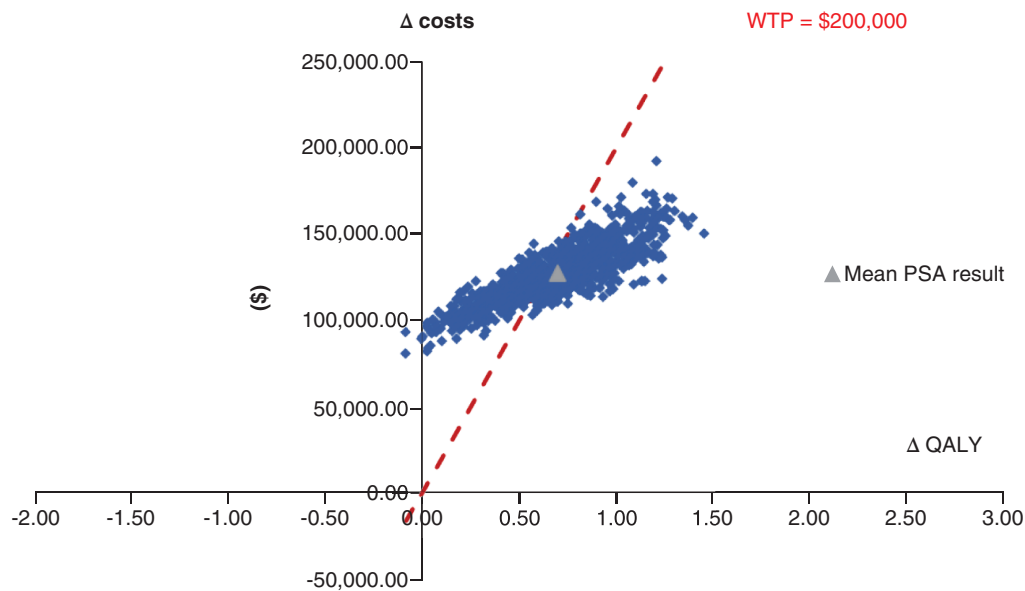
<sup>†</sup> Control arm in the KEYNOTE-355 trial.  
 AE: Adverse event; LY: Life year; QALY: Quality-adjusted life year.



**Figure 3. One-way sensitivity analysis tornado diagram of the incremental cost-effectiveness ratio (cost per quality-adjusted life-year gained) of pembrolizumab plus chemotherapy versus chemotherapy.**  
 IO: Immuno-oncology; OS: Overall survival; ToT: Time on treatment.

of \$36,917 and an incremental cost per QALY gained of \$44,157.

The scenario analysis without assuming a treatment cap for atezolizumab yielded an ICER (pembrolizumab plus nab-paclitaxel vs atezolizumab plus nab-paclitaxel) of \$24,864/QALY. When PFS was used as a proxy of ToT for atezolizumab plus nab-paclitaxel, pembrolizumab plus nab-paclitaxel was projected to be associated with greater QALYs and lower total costs.



**Figure 4. Incremental cost–effectiveness plane of pembrolizumab plus chemotherapy versus chemotherapy in the probabilistic sensitivity analysis.** The broken red line indicates the WTP threshold.  
PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life year; WTP: Willingness to pay.

Table 4. Cost–effectiveness results for the indirect treatment comparison of pembrolizumab plus nab-paclitaxel versus atezolizumab plus nab-paclitaxel.			
Outcome	Pembrolizumab plus nab-paclitaxel	Atezolizumab plus nab-paclitaxel	Pembrolizumab plus nab-paclitaxel vs atezolizumab plus nab-paclitaxel
Costs (\$)			
Total costs	\$361,766	\$334,899	\$26,867
Regimen-related costs	\$183,301	\$186,100	-\$2799
– Drug acquisition costs	\$177,762	\$180,398	-\$2636
– Drug administration costs	\$5079	\$5242	-\$163
– Testing costs	\$461	\$461	\$0.00
Subsequent therapy costs	\$11,281	\$11,753	-\$471
Adverse event management costs	\$1353	\$464	\$889
Disease management costs	\$165,830	\$136,581	\$29,248
Effectiveness			
Total QALY	3.10	2.49	0.61
Total LY	3.82	3.09	0.73
– Progression-free	3.05	2.24	0.81
– Progressive disease	0.77	0.85	-0.08
Incremental cost–effectiveness ratio (\$)			
Incremental cost per QALY gained			\$44,157
Incremental cost per LY gained			\$36,917

LY: Life year; QALY: Quality-adjusted life year.

Discussion

With the escalating price of cancer drugs [45] and healthcare expenses [46], the cost of treatment versus the derived benefit is an important consideration in clinical management decisions. mTNBC is often associated with evident unmet need, poor health outcomes and high healthcare costs. Care for TNBC patients has rapidly evolved in recent years, with immunotherapies emerging as a new treatment paradigm. The new therapies delay disease progression and prolong patients’ survival but impose higher treatment costs [45]. As such, research is needed to evaluate the cost impact and cost–effectiveness of the new therapies for the management of TNBC. This is the first study to

evaluate the economic value of pembrolizumab-containing regimens compared with chemotherapies and other immunotherapies for the treatment of mTNBC.

Base-case results of the analysis showed that over the modeled time horizon of 20 years, pembrolizumab combined with chemotherapy was expected to result in an additional 0.84 LYs and 0.70 QALYs and an incremental cost of US\$127,706, yielding an incremental cost of US\$182,732/QALY gained over chemotherapy alone. The main driver of the increased cost with pembrolizumab was drug acquisition cost. A sensitivity analysis indicated that the results were robust to changes in model inputs, and the survival advantage with pembrolizumab was consistent with the efficacy reported in KEYNOTE-355 [20,21]. Results from the analysis of pembrolizumab plus chemotherapy versus chemotherapy using a weighted distribution approach were consistent with those of the base case, confirming the validity of the analysis.

The cost-effectiveness ratio threshold in the US is not clearly defined. US\$50,000/QALY gained [47] is frequently cited, but higher thresholds have been proposed by WHO (i.e., three-times the gross domestic product per capita per disability-adjusted LY gained [48]; ~US\$209,000 in 2021 [49]) and by Neumann *et al.* (US\$100,000–150,000/QALY gained, with allowance for up to US\$200,000/QALY gained [50]). The base-case ICER for pembrolizumab in this study was US\$182,732/QALY, which is within the range of these recommended thresholds.

The KEYNOTE-355 trial investigated combinations of pembrolizumab and different chemotherapies (taxane [nab-paclitaxel or paclitaxel] or gemcitabine plus carboplatin). The subgroup analyses suggested that pembrolizumab was more cost-effective in combination with taxane-containing regimens (\$122,768). However, the ICER for pembrolizumab plus gemcitabine plus carboplatin versus gemcitabine plus carboplatin (\$511,640) was significantly higher than the base-case value (\$182,732). Gemcitabine and carboplatin are among the few available treatment options following cancer relapse after early-stage treatment with taxanes for TNBC [51]; they are also more commonly used in the population with a disease-free interval shorter than 12 months. Thus the gemcitabine plus carboplatin subgroup in KEYNOTE-355 comprised relapsed patients with poorer prognosis, in whom the addition of pembrolizumab showed lesser efficacy. In this case the additional cost of pembrolizumab would not have been mitigated by its survival benefits, resulting in the unfavorable ICER in the comparison with gemcitabine plus carboplatin. Further analysis of the cost-effectiveness of pembrolizumab combined with gemcitabine plus carboplatin would be of interest in a population of patients with *de novo* mTNBC or mTNBC with a disease-free interval of at least 12 months.

Results from the phase III IMpassion130 trial showed PFS benefits with atezolizumab plus nab-paclitaxel in patients with mTNBC [15,16]; however, a statistically significant improvement in OS was not demonstrated for either the intention-to-treat population or the PD-L1-positive subgroup. This PD-L1 inhibitor in addition to paclitaxel also failed to demonstrate superiority over paclitaxel in the phase III IMpassion131 trial [17]. However, atezolizumab plus nab-paclitaxel was approved by the EMA and is still being used as a first-line treatment in PD-L1-positive mTNBC; therefore it is of interest to evaluate the economic value of pembrolizumab compared with atezolizumab in this indication. As there have been no head-to-head studies of pembrolizumab versus atezolizumab in TNBC, we performed an NMA [26] between these two immunotherapies (in combination with nab-paclitaxel) using efficacy and safety data derived from the KEYNOTE-355 and IMpassion130 trials in the PD-L1-positive patient population with combined positive score  $\geq 10$  (based on the *post hoc*, exploratory substudy conducted by Rugo *et al.* [30]). Using the outcomes from the NMA, the results of the cost-effectiveness analysis showed that pembrolizumab plus nab-paclitaxel has greater clinical benefit and economic value compared with atezolizumab plus nab-paclitaxel, with an incremental QALY of 0.61 and incremental cost per QALY gained of \$44,157; this is attributed to the greater improvements in PFS and OS with pembrolizumab compared with atezolizumab for the population with combined positive score  $\geq 10$ . There have been no cost-effectiveness analyses of pembrolizumab in TNBC, but studies conducted in Japan, Singapore, China and the US using IMpassion130 data found that atezolizumab plus nab-paclitaxel was not cost-effective compared with nab-paclitaxel alone for the treatment of PD-L1-positive TNBC [32,52,53]. The ICER of atezolizumab plus nab-paclitaxel versus nab-paclitaxel was estimated to be \$229,359.88 per QALY gained for PD-L1-positive (tumor-infiltrating immune cells  $\geq 1\%$ ) mTNBC populations in the US [32].

### Strengths & limitations

A strength of this study was that it was primarily based on the efficacy and safety data from a randomized clinical trial directly comparing pembrolizumab plus chemotherapy with chemotherapy. In addition, external validation was performed to verify the selected parametric distributions for the PFS and OS extrapolations. The clinical

plausibility of the approach used to model OS and long-term outcomes was verified by an independent clinical expert panel review of the projected treatment effects of pembrolizumab and 5- and 10-year survival percentages, and the projected OS curve of chemotherapy was validated with survival data from three real-world studies of mTNBC [7,48,49].

This study also had certain limitations. First, the median follow-up of KEYNOTE-355 was 44 months at the data cutoff date for this analysis; extrapolation was necessary to model a lifetime time horizon, and uncertainty is inherent in this process. Although multiple scenario analyses were explored to assess the different extrapolations, longer-term follow-up of the clinical trial will be imperative to confirm the model results. Second, as the KEYNOTE-355 trial was not powered to detect statistical significance among treatment subgroups, the results of our subgroup analyses should be interpreted with caution. Third, pembrolizumab and atezolizumab regimens have not been directly compared in a head-to-head clinical trial; therefore the cost-effectiveness analysis comparing these two immunotherapies was based on an indirect comparison by NMA, which introduced additional uncertainty. Finally, the primary end points in the KEYNOTE-355 trial were evaluated based on Response Evaluation Criteria In Solid Tumors (RECIST). However, immune-related RECIST in addition to RECIST criteria are often used to verify disease progression for immunotherapies [54]. To be consistent with the clinical publications and regulatory evaluations of KEYNOTE-355, this study was based on the primary efficacy end points when estimating both effectiveness and costs associated with the treatments. These estimates can be different in the real-world setting where immune-related RECIST is used. However, we have no data to address the limitation at this point.

## Conclusion

Pembrolizumab in combination with chemotherapy has been shown to significantly improve PFS and OS compared with chemotherapy alone in patients with previously untreated mTNBC whose tumors express PD-L1 (combined positive score  $\geq 10$ ). The results of this study suggest that the ICER of pembrolizumab combined with chemotherapy is below the WHO willingness-to-pay threshold of three-times the GDP per capita compared with chemotherapy alone and is below the US\$50,000 per QALY threshold compared with atezolizumab plus nab-paclitaxel. In summary, pembrolizumab plus chemotherapy improves quality-adjusted life expectancy and can be considered as a cost-effective first-line treatment option compared with both comparators for PD-L1-positive mTNBC patients in the US.

### Summary points

- Triple-negative breast cancer is associated with a high risk of relapse and a poor prognosis.
- The immunotherapy agent pembrolizumab combined with chemotherapy has been shown to improve survival compared with chemotherapy alone in patients with previously untreated locally recurrent unresectable or metastatic triple-negative breast cancer (mTNBC) whose tumors express PD-L1 (combined positive score  $\geq 10$ ).
- This is the first study to evaluate the economic value of pembrolizumab in addition to chemotherapy compared with chemotherapy alone or atezolizumab plus nab-paclitaxel in patients with mTNBC.
- A partitioned-survival model was developed to estimate patients' expected costs and clinical effectiveness over a 20-year time horizon. Patient-level data of time on treatment, progression-free survival and overall survival from the KEYNOTE-355 trial were used in the model, with extrapolation based on parametric models and validation with historical trials and real-world studies. Atezolizumab plus nab-paclitaxel was compared with pembrolizumab plus nab-paclitaxel through a network meta-analysis using data from the IMpassion130 trial.
- The base-case analysis projected an expected gain of 0.84 life-years (LYs) and 0.70 quality-adjusted life-years (QALYs) in patients receiving pembrolizumab plus chemotherapy compared with those who received chemotherapy alone; the incremental cost per QALY gained was US\$182,732 and the incremental cost per LY was US\$152,289.
- Compared with atezolizumab plus nab-paclitaxel, pembrolizumab plus nab-paclitaxel was associated with total LY and total QALY gains of 0.73 and 0.61, respectively. This resulted in an incremental cost per LY gained of \$36,917 and an incremental cost per QALY gained of \$44,157.
- Pembrolizumab plus chemotherapy increased QALYs in patients with PD-L1-positive mTNBC and is projected to be cost-effective from a US third-party public healthcare payer perspective compared with chemotherapy or atezolizumab plus nab-paclitaxel at published thresholds of cost-effectiveness.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/imt-2022-0082](http://www.futuremedicine.com/doi/suppl/10.2217/imt-2022-0082)

# Author contributions

All authors contributed to the study design and methodology, interpretation of the results and development and writing of the draft manuscript and approved the final version.

# Financial & competing interests disclosure

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. M Huang, A Haiderali, W Pan and P Hu are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, the sponsor of this study and manuscript. Z Zhou are employees of Analysis Group, Inc., which received consulting fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA in connection with this study. E Gray was an employee of Analysis Group, Inc., at the time this study was conducted. P Fasching reports personal fees from Novartis Pfizer, Daiichi-Sankyo, Astra Zeneca, Eisai, Merck Sharp & Dohme, Lilly Pierre Fabre, SeaGen, Roche, Hexal and Agendia, and grants from Biontech and Cepheid. J O'Shaughnessy receives consulting fees and/or honorarium from AbbVie Inc., Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene Corporation, Clovis Oncology, Daiichi Sankyo, Eisai, G1 Therapeutics, Genentech, Gilead Sciences, GRAIL, Halozyme Therapeutics, Heron Therapeutics, Immunomedics, Ipsen Biopharmaceuticals, Lilly, Merck, Myriad, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Prime Oncology, Roche, Samsung Bioepis, Sanofi, Seagen, Syndax Pharmaceuticals, Synthon, Taiho Oncology and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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# Data sharing statement

Several datasets were used for this analysis: (1) efficacy, safety, patient-reported outcomes and healthcare resource utilization data collected in phase III KEYNOTE-355 trial. The patient-level data are not publicly available, but the results of the trials have been presented in several publications. The trial results supporting the findings of this analysis are available within the article and its supplemental material. (2) Observational data from the SEER databases and other publications, for which references are provided in the article. (3) Cost data used in the model were obtained from CMS or other publications.

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