The Value of Performance-Based Risk Sharing Arrangements in the United States: A Case Study of First-Line Pembrolizumab Therapy in Advanced Non-Small Cell Lung Cancer

Harry Lee

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2017

Committee:

David Veenstra, Chair

Josh Carlson

Program Authorized to Offer Degree:

Pharmacy

University of Washington

Abstract

The Value of Performance-Based Risk Sharing Arrangements in the United States: A Case Study of First-Line Pembrolizumab Therapy in Advanced Non-Small Cell Lung Cancer

Harry Lee

Chair of the Supervisory Committee:
Professor and Associated Director of Pharmaceutical Outcomes Research and Policy Program,
David Veenstra
Department of Pharmacy

OBJECTIVES: The objective of this study was to evaluate the health and financial implications of implementing a PBRSA along with lower patient cost sharing for two distinct PBRSAs in a case study of first-line pembrolizumab (PEMB) therapy in patients with advanced NSCLC.

METHODS: We evaluated two distinct PBRSAs based on surrogate endpoints from the pivotal KEYNOTE-024 trial for a hypothetical treated population of 50 patients. The first PBRSA is an example of a conditional treatment continuation (CTC-PBRSA) arrangement in which a 25% rebate or manufacturer (MFTR) risk share of PEMB costs is applied to all in patients the first four months and subsequently dropped for patients who achieve or maintain an objective response. The second PBRSA is an outcome guarantee arrangement (OG-PBRSA),

where the payer is reimbursed based on the duration of progression free survival realized by each patient relative to an outcome target of ten months. To evaluate the potential health and cost implications of these PBRSAs along with lower patient cost sharing we developed a partitioned survival model composed of three health states: PFS, disease progression, and death. Parametric survival curves were fit using published survival data from pivotal clinical trials and survival was extrapolated for a lifetime time horizon using one-week increments. Model parameters such as survival, drug utilization rates, adverse event rates, utilities, and costs were derived from clinical trials and other published sources. The analysis was performed from a third-party payer perspective.

RESULTS: In our hypothetical treated population of 50 patients, three additional patients were treated with PEMB under our PBRSAs at an additional drug cost of approximately $600,000, excluding drug rebates, compared to the base case. The payer received drug rebate amounts of $460,000 under the CTC-PBRSA and $113,000 under the OG-PBRSA. Average lifetime QALYs were 1.64 for the base case and 1.67 for both of our PBRSAs, which produced an incremental cost per QALY of $85,000 and $321,000 for the CTC-PBRSA and OG-PBRSA compared to traditional reimbursement practices, respectively. From our sensitivity analysis, the initial cost of implementing a pilot PBRSA was found to be the most influential parameter for both of our PBRSAs.

CONCLUSIONS: The results of our decision model showed the CTC-PBRSA was more cost-effective than the OG-PBRSA with similar MFTR risk sharing of drug costs relative to the base case. Our findings suggest the barriers to the use of PBRSAs in the US health care

environment are not insurmountable, and their use along with lower patient cost sharing may lead to cost savings and improved health outcomes. However, the generalizability of our results is limited to the specific terms of our PBRSAs, which reaffirms the need to carefully structure and implement PBRSAs based on the needs and demographics of the patient population of interest.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all the persons who have been helpful towards the successful completion of my graduate thesis. First and foremost, I would like to thank my immediate advisor Dr. David Veenstra whose patience, insight, and steadfast encouragement being instrumental in the successful completion of this project. Without his guidance and persistent help this dissertation would not have been possible.

I would also like to gratefully acknowledge Josh Carlson, John Watkins, and Pete Fullerton who in spite of being extraordinarily busy took the time to listen and guide me to the conclusion of my thesis. Their knowledge, feedback, and advice was influential and essential throughout this entire process.

Lastly, and most of all, I would like to thank Jessica Shih who supported me until the very end of this journey.

DEDICATION

To my parents,

You did your best…

And it was more than enough

Chapter 1. BACKGROUND

1.1 Performance Based Risk Sharing Arrangements (PBRSAs)

There has been growing interest in performance-based risk sharing arrangements (PBRSAs) as a potential solution to address issues of affordability and sustainability due to rising drug costs in the United States. PBRSAs are outcomes-based risk sharing agreements (RSAs) between the payer and manufacturer that predicates coverage and/or reimbursement on the real-world effectiveness or performance of a medication.[i] With outcomes guarantees – a type of PBRSA, the metrics of drug performance typically include observed clinical or surrogate outcomes, which enables a more accurate assessment of indication-specific drug value versus trial based outcomes and can be used to inform decision makers.[ii] If the drug fails to meet a pre-specified outcome target, the payer receives a rebate, refund, or price adjustment from the manufacturer.[i] In exchange, manufacturers typically receive preferred formulary placement or less restrictive coverage criteria to enhance market uptake for their products. Patients benefit from earlier access to medications, lower cost sharing, and the additional clinical evidence generated by these agreements can be used to evaluate and guide the delivery of excellent but affordable care to patients. Despite the potential benefits of PBRSAs to multiple stakeholders, adoption of these agreements in the US private sector has been relatively slow due to a variety of operational challenges and barriers. However, there have been several notable examples in the US that have garnered considerable attention among US payers such as a cardiovascular outcomes-based RSA between Amgen and Harvard Pilgrim for evolocumab (Repatha®).[iii]

1.2 Barriers and challenges to PBRSAs

In a recent survey of key stakeholders by Garrison et al., respondents identified logistical, cost, and legislative concerns as significant barriers to the adoption of PBRSAs in the US.[i] For example, an appropriate health outcome that can be measured readily and reliably may not always be available, and it can be challenging to assess a medications impact on how a patient ultimately feels, functions, and survives. Furthermore, the lack of adequate data infrastructure capable of securely collecting individual patient data (IPD) necessary for a PBRSA poses significant operational challenges to payers. It is also difficult to predict patient behavior in terms

of their willingness to start treatment and remain adherent over the course of therapy, which can have a substantial impact on health outcomes. Finally, government price-reporting obligations, such as Medicaid's best price, impose limitations on pricing concessions manufacturers may be willing to offer purchasers.

1.3 Rationale for case study

Critics have also cited the lack of evidence demonstrating the ability of PBRSAs to lower costs.[iv] The limited body of evidence supporting the use of PBRSAs is due in part to the proprietary nature of PBRSAs, which limits the reporting of the results of known arrangements between the principle parties involved. Thus, the operational challenges, financial consequences, and general inexperience with implementing an outcomes-based RSAs may make US payers and manufacturers wary of entering such arrangements. However, the lack of evidence does not preclude the potential value these arrangements may provide to stakeholders, which warrants a formal evaluation of the financial and clinical implications of implementing PBRSAs in the current US health care environment. There is a need for the development of a decision framework to inform purchasing decisions so payers may consider the use of PBRSAs to address lapses in patient care due to cost barriers.

The objective of this analysis was to evaluate the financial and health implications of utilizing two types of PBRSAs for a specific case example, pembrolizumab as first line treatment in advanced non-small cell lung cancer (NSCLC), and provide a decision framework for purchasers to utilize PBRSAs to lower costs and improve patient health outcomes. Pembrolizumab is a programmed death-1 (PD1) inhibitor that has been shown to prolong survival in patients with tumor programmed death ligand-1 (PD-L1) expression greater than 50%, but among these patients only a small subset may be able to achieve durable and sustained survival. Furthermore, tumor PD-L1 expression has been found to be an unreliable predictor of treatment response, and efforts to identify a biomarker or prognostic indicator that can identify these strong responders is currently ongoing.[v,vi] Pembrolizumab is typically classified as a specialty medication and accompanied by high patient cost sharing, which has been known to compel some patients to forgo or delay care.[vii] Thus, the high cost of pembrolizumab and uncertainty surrounding its effectiveness in a small subset of patients makes it an ideal candidate for a PBRSA.

Chapter 2. METHODS

2.1 PBRSAs

In both of our hypothetical PBRSAs, significant drug rebates are provided to payers for previously untreated patients with advanced NSCLC who experienced disease progression on pembrolizumab (PEMB) in exchange for preferred formulary placement with 25% lower patient cost sharing and continuous coverage beyond the current indicated treatment duration of two years. In our analysis, the assessment of drug performance for both of our PBRSAs was referenced to surrogate outcomes reported in the original KEYNOTE-024 trial, which is the only known randomized controlled trial evaluating our indication of interest. The key distinction between our PRBSAs is the estimation of payer drug rebates based on the achievement of distinct treatment goals under each arrangement. Specifically, we examined the use of two subtypes of PBRSAs, conditional treatment continuation (CTC) and outcomes guarantee (OG) arrangements, compared to traditional reimbursement practices.

2.1.1 *Conditional Treatment Continuation (CTC) Arrangement*

The first PBRSA (CTC-PBRSA) is an example of CTC arrangement in which continuation of drug coverage is predicated upon the achievement of short-term treatment goals.[viii] The use of a CTC arrangement can lower payer uncertainty in the effectiveness of a costly new health technology within a subset of patients by only fully reimbursing the manufacturer (MFTR) for patients who achieve an agreed upon outcome target such as treatment response. There are several known examples of CTC arrangements or other variations implemented in Europe such as sunitinib (Pfizer) and sorafenib (Bayer) for renal cell carcinoma in Italy.[viii] In these two examples, a financial utilization component was integrated into a CTC arrangement in which a hospital drug discount of 50% was applied to the first few months of treatment and subsequently dropped for patients who responded to therapy during the pre-assessment phase.[viii]

Under the terms of our CTC-PBRSA, the payer receives a fixed 25% drug rebate for the first seven treatment cycles among all patients receiving PEMB, which is dropped thereafter for patients who could achieve or maintain an objective response, defined as partial or complete

response per RECIST criterion. Furthermore, the payer will also receive this rebate for patients who experience treatment associated toxicities categorized as Grade 3 or higher. The time point of patient health outcome assessment was determined by doubling the reported median time to response of 2.2 months from the original KEYNOTE-024 trial to 4.4 months, which corresponds to a time point at which the patient would have received at least seven infusion cycles of PEMB. A trial period of 4.4 months provides most patients sufficient time to achieve an objective response, including those who initially experienced paradoxical disease progression or no change in tumor burden. Thus, a trial period of seven treatment cycles would prevent the premature discontinuation of treatment among patients without rapid clinical deterioration that initially appeared to fail PEMB therapy.

The drug rebates provided under the terms of the CTC-PBRSA lower the payer's financial risk of treatment failures in the first four months of therapy, which is shared with patients in the form of 25% lower patient out-of-pocket (OOP) costs. As the preferred first-line treatment option in patients with advanced NSCLC per National Comprehensive Cancer Network (NCCN) guidelines, lower patient cost sharing improves access to PEMB and increases the likelihood of achieving optimal health outcomes by minimizing the consequences of forgone or delayed care. Finally, a larger treated population increases the uptake of the MFTR's product despite the uncertainty of the effectiveness of PEMB in patients with advanced NSCLC.

2.1.2 *Outcomes-Guarantee (OG) Arrangement*

The second PRBSA (OG-PBRSA) is an example of OG arrangement in which the MFTR provides a rebate, refund, or price adjustment *if their product fails to meet an agreed upon outcome target*. In contrast to a CTC arrangement, the payer is reimbursed based on the duration of treatment benefit realized by all patients instead of the achievement of a short-term treatment goal among select patients. Our OG-PBRSA was based on an outcomes-based RSA described by Fox et al., which involved the use of an OG arrangement for bevacizumab as first-line treatment in patients with NSCLC. In this agreement, the outcome target was based on the median PFS observed in a phase III clinical trial evaluating bevacizumab for the indication of interest.[ix] The payer received a drug rebate from the MFTR directly proportional to the magnitude of the difference between the observed PFS and expected PFS using equation [1] presented below:

$$Rebate\ Amount = \frac{Expected\ Benefit - Actual\ Benefit}{Expected\ Benefit} \times Risk\ Share \times Treatment\ duration\ (Months) \times \frac{Drug\ Cost}{Month} \quad (2.1)$$

The risk share variable in equation [1] is the proportion of drug costs the MFTR would reimburse the payer for patients who failed to reach the agreed upon outcome target.

Under the terms of our hypothetical OG-PBRSA case study, the agreed upon outcome target for patients receiving PEMB was ten months of PFS, which was determined by rounding the reported median PFS of 10.3 months from the original KEYNOTE-024 trial. For patients who fail to realize at least ten months of PFS, a rebate amount was estimated using equation [1] published by Fox et al., but treatment duration and drug costs were based on treatment cycles instead of months due to the odd dosing frequency of once every three weeks for PEMB. If a patient remained in the progression free state by the agreed upon rebate threshold, a rebate would not be paid to the payer. The financial and health benefits for payers and patients described under the first PBRSA were also assumed to hold under our second PRBSA. A summary of the contractual terms of each PBRSA are presented in Table 2.1 below;

Table 2.1. Summary of PBRSA contractual terms

Characteristics	**CTC-PBRSA**	**OG-PBRSA**
Type of PBRSA	Conditional Treatment Continuation	Outcome Guarantee
Performance Metric	Objective Response Rate	Median PFS
Reference Clinical Outcome	2.2 Months (KEYNOTE-024)	10.3 Months (KEYNOTE-024)
Target Clinical Outcome	4.4 Months	10 Months
MFTR Risk Sharing	25%	25%
Initial Cost of Implementation	$200,000	$200,000

2.2 Model Structure and Process of Care

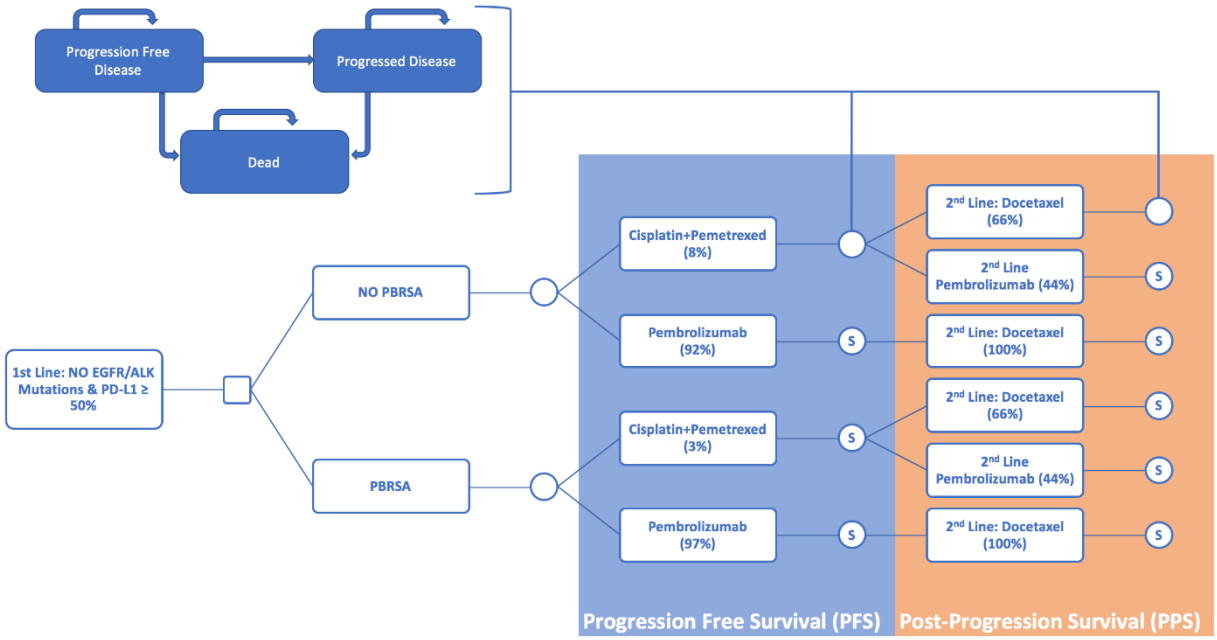

Figure 2.1. Decision model diagram.

To evaluate the economic and health consequences of utilizing PBRSAs for PEMB in previously untreated advanced NSCLC patients compared to not using a PBRSA, a decision model was developed to determine the incremental costs, total costs, payer financial net yields, life-years (LYs), and quality-adjusted life-years (QALYs) gained to produce incremental cost-effectiveness ratios (ICERs) over a lifetime horizon. Our model is composed of a decision tree and partitioned survival model composed of three health states: progression free disease, progressed disease, and death. This modeling approach was selected to account for differential drug utilization based on patient cost sharing and the impact of past treatment history on transitions across health states. The model population was composed of 50 previously untreated patients aged 65 years or older with advanced NSCLC who possess no EGFR mutations or ALK translocations with tumor PD-L1 expression ≥ 50% who were analyzed using a cohort simulation approach.[x] Subjects entered the decision model outlined in Figure 2.1 to receive care provided under a PBRSA or without. First-line treatment options include PEMB 200 mg intravenously (IV) every three weeks or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 (CIS+PEM) IV every three weeks for six cycles followed by pemetrexed maintenance therapy. The modeled chemotherapy regimen was chosen because it was the second most common platinum-based

chemotherapy used in the control population of the KEYNOTE-024 trial that did not require area under the curve dosing. Subjects who respond to first-line treatment remained in the progression free survival (PFS) phase until disease progression, unacceptable toxicity, or death. Following treatment failure, defined as disease progression or unacceptable toxicity, all patients initially treated with PEMB transitioned to the post-progression survival (PPS) phase and receive second-line docetaxel (DOC) 75 mg/m^2 IV every three weeks up to one week before entering the collecting terminal of death. Whereas, patients failing first-line CIS+PEM therapy were eligible to receive either second-line DOC or PEMB until one week before death. Approximately half of subjects failing first-line CIS+PEM would receive second-line PEMB therapy with the remainder receiving DOC, which was modeled to account for the treatment crossover rates observed in the control arm of the KEYNOTE-024 trial. We assumed patients who were not eligible for PEMB received docetaxel based on existing clinical guidelines. To account for differences in expected survival benefits of the modeled treatment regimens, a lifetime horizon was used to capture the entirety of cost and health outcomes over time. Model parameters such as clinical efficacy, adverse event (AEs) rates, drug utilization, patient characteristics, MFTR risk share of drug costs, health state utilities, and costs were derived from clinical trials and other published sources. Model outcomes were discounted at a rate of 3% per annum as per the recommendation of the Second Panel on cost-effectiveness in health and medicine, and costs were analyzed from a third-party US payer perspective.[xi]

2.3 Patient Behavior and Drug Utilization

To model the consequences of high patient out-of-pocket (OOP) costs, we assumed in the absence of a PBRSA approximately 8% of patients would substitute PEMB for CIS+PEM despite being eligible for the former due to higher patient cost sharing. This parameter was based on a cross-sectional study using claims data to assess the abandonment of newly initiated oral oncolytic drugs.[xii] To model the increase in PEMB utilization with lower patient cost sharing provided under both of our PBRSAs, we used an estimate of patients' elasticity of demand from a preference analysis by Goldman et al.[xiii] By exploiting differences in plan generosity, the investigators estimated patients' elasticity of demand or the relationship between how the probability of initiating therapy responds to changes in OOP costs and income for five high-cost specialty medications treating metastatic disease or hematologic malignancies using claims data.

Under the terms of both PBRSAs, PEMB would receive preferred formulary placement along with 25% lower patient OOP costs, which we assumed would lead to approximately 5% higher PEMB utilization relative to the base case. All subjects would continue receiving their respective treatments over the modeled time horizon based on the assumption providers would be hesitant to prematurely discontinue treatments in responding patients. Finally, all subjects were assumed to be completely adherent to assigned treatments.

2.4 Clinical Parameters

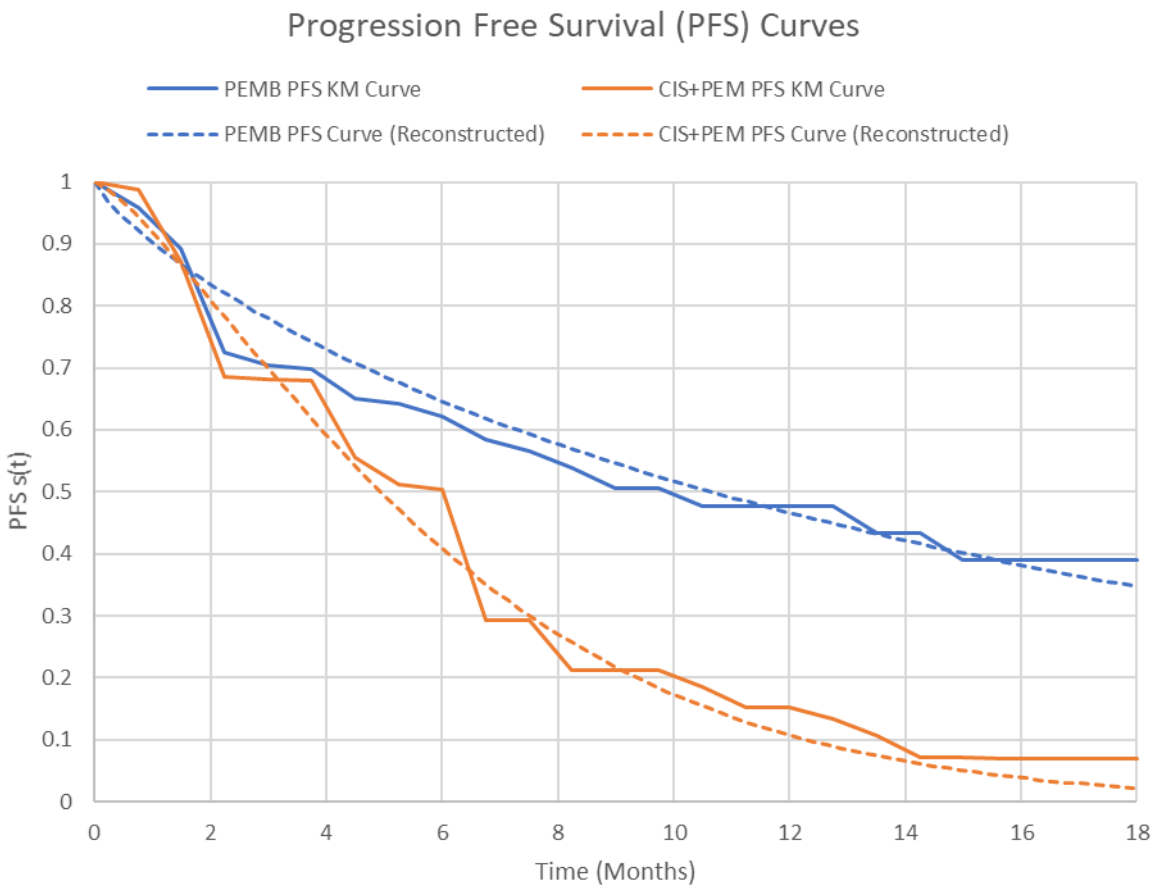

Figure 2.2. Published and reconstructed PFS curves.

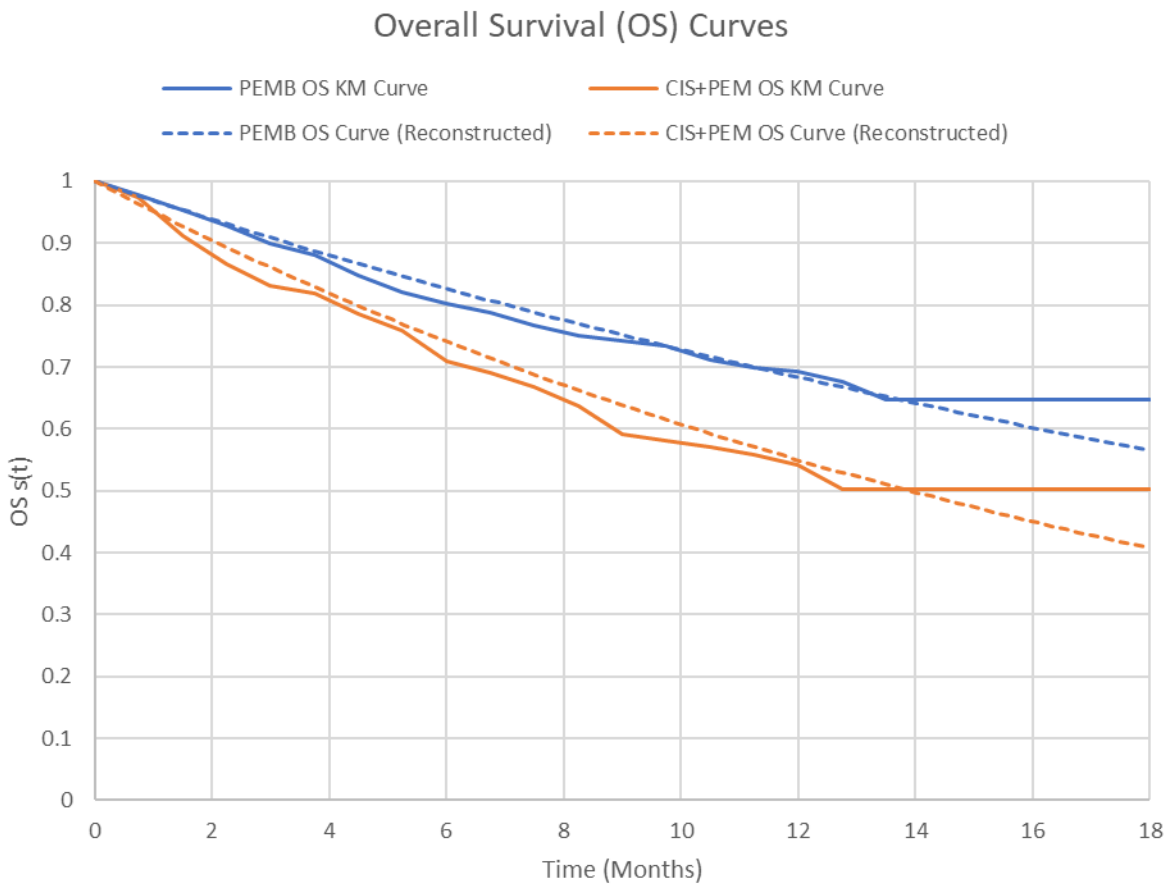

Figure 2.3. Published and reconstructed OS curves.

Parametric survival curves were fit using methods described by Hoyle and Henley using published survival data from the original KEYNOTE-024 trial (Figures 2.2 & 2.3).[xiv] Survival was extrapolated for a lifetime horizon using one-week cycle lengths. Preliminary analysis suggested a violation of proportional hazards assumption, which necessitated the use of separate models for PEMB and CIS+PEM. Based on Akaike Information Criteria and visual inspection, Weibull and exponential parametric functions were determined to be the best fitting models for treatment PFS and overall survival (OS) curves, respectively. Furthermore, to ensure our partition state model could satisfactorily generate survival outcomes that were consistent with the reference clinical data we compared our projected median PFS and rates of PFS and OS at six months along with their corresponding 95% credible intervals to their respective values observed in the KEYNOTE-024 trial.

A mean subject weight and height obtained from the KEYNOTE-001 trial were used to estimate chemotherapy doses based on body surface area. Relevant adverse event rates for each respective treatment were derived from their package inserts and clinical trial safety data, which are presented in the appendix section of this study.

2.5 Quality of Life Parameters

PFS health utility values were obtained from a study of NSCLC health state preferences in a sample of international patients with advanced NSCLC by Chouaid et al. (2013).[xv] Health utility values for PPS and disutilities for grade 3 or higher AEs were based on a community sample from the U.K. by Nafees et al. (2006).[xvi] A summary of model health state utility values is presented in Table 2.2 below, and disutilities for grade 3 or higher AEs are presented in the appendix section of this study.

Table 2.2. Summary of health state utility values by process of care.

Process of Care	PFS (95% CI)	PPS (95% CI)
First Line Therapy	0.71 (0.67 to 0.76)	0.67 (0.59 to 0.75)
Second Line Therapy	0.67 (0.59 to 0.75)	0.47 (0.43 to 0.52)

2.6 Payer Costs

Drug costs and procedure costs were derived from quarterly Medicare average sale prices (ASP) and Medicare fee schedules, respectively. The Medicare ASP for medications is the volume weighted MFTR's drug sales to all purchasers in the US, which accounts for most or all drug price concessions except for medications purchased through the Medicaid drug rebate program. The net acquisition cost of medications or size of drug rebates obtained through the Medicaid drug rebate program are confidential, which introduces uncertainty in the amount of financial risk the MFTR would be willing to accept in our case study. To determine the MFTRs risk share of drug costs under our PBRSAs, we estimated the net cost of PEMB purchased through the Medicaid drug rebate program using a Congressional Budget Office (CBO) report on the relationship between Medicaid costs and the average wholesale price (AWP) amount for brand name medications. This CBO report appears to be the only known public disclosure of Medicaid rebate amounts, which estimated the average cost of brand name drugs obtained

through the Medicaid rebate program to be 64% of the AWP. Accounting for Medicaid drug rebates, we estimated Medicaid's net cost for PEMB to be approximately $7000 per infusion cycle, which is approximately 73% of the Medicare ASP. [xvii] Thus, we assumed drug rebates greater than 27% of the Medicare ASP would trigger a new Medicaid best price for the MFTR.[xviii] In both of our PBRSAs, we evaluated a MFTR risk share equal to 20% of drug costs for PEMB, and uncertainty was assessed using a range of 15% to 25% in our sensitivity analyses. A summary of the PEMB acquisition costs used in our case study is presented in Table 2.3 below.

Table 2.3. Acquisition costs for PEMB 100 mg vial by source

Price Source	PEMB 100 mg Vial Acquisition Cost (USD)
Average Wholesale Price (AWP)	$5,415.84
Medicare Average Sales Price (ASP)	$4,729.70*
Medicaid net cost (Estimated)	$3,466.14

**Decision model acquisition cost of PEMB*

To reflect the substantial costs associated with end-of-life (EOL) care we assumed EOL care would incur a cost of $50,000 during the last week of life.[xix] Average weekly utilization costs for subjects in the PPS receiving second line PEMB and DOC were estimated using survival data from the KEYNOTE-010 trial, and applied to subjects in the PPS health state until one week before death. All costs prior to 2017 were adjusted to August 2017 US dollars (USD) based on the medical care component of the consumer price index.

2.6.1 *Costs of implementing a PBRSA*

The viability of both our PBRSAs is contingent on the ability to accurately and reliably assess patient health outcomes, which entails tracking indication-specific utilization and collecting IPD. The cost of implementing a PBRSA was assumed to be similar to an observational study given the patient data needed to assess drug effectiveness would be generated from routine clinical practice. However, there may be considerable variability across US payers based on their existing data infrastructure and resources. In our analysis, the additional payer cost of implementing both of our hypothetical PBRSAs was assumed to be approximately $200,000, which accounts for the costs of data management, source data validation, staffing requirements, and legal fees (Table 2.4). The individual components of the

operational costs of our PBRSAs were estimated based on the duration of the arrangements, expected patient population size, and expertise necessary for implementing a PBRSA.

Table 2.4. Costs of PBRSA implementation

Component	Cost (USD)
Data management	$50,000
Payer Staffing Requirements	$125,000
Legal fees	$25,000
Total Costs	**$200,000**

The data system requirements to collect and maintain patient data were assumed to cost approximately $50,000 based on a US Department of Health & Human Services (DHHS) report on the costs of clinical research.[xx] Prior to implementation of our PBRSAs, contract negotiations with the MFTR would incur an estimated $25,000 in legal fees for attorneys to review and finalize the terms of our PRBSAs. The payer staffing costs account for the total employee time needed to develop and operationalize our PBRSAs over a period of one year, which would require a 1.0 full time equivalent (FTE) employee and two 0.5 FTE ancillary payer staff. We assumed an existing or additional payer employee with a background in health economics and outcomes research (HEOR) would be needed to participate in negotiating the terms of our PBRSAs with the MFTR. This HEOR specialist would also oversee data collection, validation, and analysis of patient outcomes data with the assistance of existing payer personnel (e.g., pharmacy technicians). We assumed a prior authorization (PA) submission system would be in place for PEMB prior to PBRSA implementation, which would facilitate identification of indication-specific usage by eligible patients. Prior to PA approval, patient PD-L1 expression, EGFR/ALK mutation status, functional status, and indication of use would be reviewed and documented by in-house clinical staff on a case-by-case basis. It was assumed a similar submission system for patient outcomes data would be used. Thus, the overall cost of payer staff needed to implement our PBRSAs was estimated to be $125,000, which accounts for the $100,000 annual salary of the HEOR specialist and $25,000 for the costs of temporarily diverting ancillary payer staff to assist in patient data collection. Given the uncertainty and likely variability in the total cost of PBRSA implementation for US payers, we evaluated a wide range of possible values in our sensitivity analysis.

2.7 Sensitivity and Scenario Analyses

Multiple sensitivity analyses and scenario analyses were performed to assess the impact of uncertainty on the outcomes of our PBRSAs. A one-way sensitivity analysis (OWSA) was conducted to evaluate uncertainty in each model parameter. The range of values considered in OWSA included 95% confidence intervals and ± 25% of the base case values except for the total cost of PBRSA implementation, which was varied over a range of plausible values between $25,000 and $400,000. The results of the OWSA are presented in a tornado diagram. Scenario analyses were also conducted to further assess known PBRSA barriers and key uncertainties identified in the OWSA.

2.7.1 *Probabilistic Scenario Analysis (PSA)*

The overall impact of uncertainty in the model was assessed by performing a probabilistic sensitivity analysis (PSA) with all model parameters varied within their respective distributions. The PSA was performed over 5000 iterations, and results were plotted on the cost-effectiveness plane as scatterplots. Cost-effectiveness acceptability curves (CEAC) and value of information (VOI) were also derived from the PSA results. The CEAC illustrates the likelihood of the PBRSAs being cost-effective across various willingness-to-pay (WTP) thresholds. To assess the uncertainty in the payer's total cost of utilizing PBRSAs for our case study, additional PSAs were performed to estimate the payer's likelihood of recovering the total costs of each PBRSA, which is composed of the initial costs of PBRSA implementation and increase in drug expenditures due to higher PEMB utilization under our PRBSAs. For each value within the range of potential startup costs of implementing a PBRSA we performed a PSA over 5000 iterations.

2.7.2 *Model Validation*

Model validation was performed by comparing extrapolated survival outcomes to the reference clinical data and survival outcomes data among patients with advanced NSCLC from the Surveillance, Epidemiology and End Results (SEER) program to verify our estimates are consistent with the known clinical data.[xxi] Clinical, decision modeling, and payer experts were consulted to judge the validity of key assumptions for the conceptual model, model parameters used, and technical aspects of the computerized model.

Chapter 3. RESULTS

3.1 MODEL VALIDATION

The PFS and OS curves produced survival outcomes that satisfactorily matched the results from the KEYNOTE-024 trial, except for the CIS+PEM PFS curve (Table 3.5). The observed discrepancy at six months between the extrapolated PFS outcomes for CIS+PEM and their reference values was attributed to a precipitous decline in PFS at six months in the control arm of the KEYNOTE-024 trial. Despite the underestimation of PFS at six months, the overall fit of the PFS curve for CIS+PEM matched its corresponding published Kaplan Meier survival curve, which is illustrated in Figure 2.2 above.

Table 3.5. Model validation results summary

Treatment	Study Endpoint	Published (95% CI)	Estimated (95% CI)
PEMB	Median PFS (Months)	10.3 (6.7 to NR)	10.6 (7.8 to 14.0)
	PFS at 6 Months (%)	62.1 (53.8 to 69.4)	64.7 (57.8 to 71.1)
	OS at 6 Months (%)	80.2 (72.9 to 85.7)	82.7 (77.5 to 87.0)
CIS+PEM	Median PFS (Months)	6.0 (4.2 to 6.2)	4.8 (4.1 to 5.5)
	PFS at 6 Months (%)	50.3 (41.9 to 58.2)	41.0 (34.2 to 47.9)
	OS at 6 Months (%)	72.4 (64.5 to 78.9)	74.2 (68.2 to 79.1)

3.2 CLINICAL RESULTS: PEMB VS CIS+PEM

The OS curves in the partition state model projected 5-year OS rates of 15% for 5% and for PEMB and CIS+PEM, respectively. The projected 5-year OS for CIS+PEM was slightly higher than what was reported by Cetin et al., but this could be attributed to differences in patient characteristics in the control arm of the KEYNOTE-024 trial and patient population of the SEER registry data.[x,xxi] Patients treated with PEMB would spend an average of 18.9 months and 12.7 months in the PFS and PPS health states, respectively. Whereas, patients receiving CIS+PEM would remain in the PFS health state on average for 6.0 months and spend an average of 14.0 months in the PPS health state.

3.3 Financial and Health Implications of PBRSAs

Table 3.6. Lifetime PBRSA incremental costs and clinical outcomes by treatment regimen versus base case

Scenario	**Both PBRSAs**	**CTC-PBRSA**		**OG-PBRSA**	
Treatment Regimen (N)	**CIS+PEM (1)**	**PEMB (49)**	**Total (50)**	**PEMB (49)**	**Total (50)**
Total Costs	**$(435,064)**	**$559,885**	**$124,822**	**$907,095**	**$472,031**
Drug Costs	$(140,953)	$130,651	$(10,302)	$477,861	$336,908
PFS Supportive Care Costs	$(22,657)	$66,383	$43,725	$66,383	$43,725
Administration Costs	$(4,012)	$8,474	$4,461	$8,474	$4,461
Progression Costs	$(142,865)	$41,235	$(101,629)	$41,235	$(101,629)
Death Costs	$(112,531)	$109,546	$(2,985)	$109,546	$(2,985)
Adverse Event Costs	$(12,045)	$3,597	$(8,448)	$3,597	$(8,448)
Monitoring Costs	$-	$200,000	$200,000	$200,000	$200,000
Drug Rebate	**$-**	**$459,906**	**$459,906**	**$112,696**	**$112,696**
Total QALYs	**-2.49**	**3.96**	**1.47**	**3.96**	**1.47**
PFS QALYs	-0.84	2.51	1.66	2.51	1.66
PPS QALYs	-1.64	1.45	-0.19	1.45	-0.19
Total LYs (OS)	**-3.79**	**5.78**	**2.00**	**5.78**	**2.00**
PFS LYs	-1.19	3.53	2.34	3.53	2.34
PPS LYs	-2.59	2.25	-0.34	2.25	-0.34
ICER (QALYs)			**$84,990**		**$321,403**
ICER (LYs)			**$62,459**		**$236,197**

In our hypothetical model cohort of 50 patients, each patient treated with PEMB and CIS+PEM gained a total of 1.67 QALYs and 1.06 QALYs, respectively. Over a lifetime horizon, the total cost of each treatment regimen was approximately $347,000 for PEMB and $184,154 for CIS+PEM. Whereas under our PBRSAs, the total cost of PEMB for each patient was $341,650 and $348,799 for the CTC-PBRSA and OG-PBRSA, respectively.

Compared to the base case, a 25% reduction in patient OOP led to approximately three additional patients treated with PEMB for a total of 49 patients out of 50 patients receiving PEMB therapy under both of our PBRSAs. Excluding payer drug rebates provided under our PBRSAs, higher PEMB utilization increased total PEMB-related drug expenditures, defined as drug, patient screening, and infusion costs, by approximately $600,000 over a lifetime horizon relative to the base case. For the entire cohort, the use of our PBRSAs resulted in a total incremental 1.47 QALYs gained at an additional cost of $124,822 and $472,031 under the CTC-PBRSA and OG-PBRSA, respectively.

The use of our CTC arrangement compared to a traditional reimbursement arrangement resulted in an ICER of $84,990 per QALY gained. Under the terms of the CTC-PBRSA, the payer received $459,906 in drug rebates for all 49 patients receiving PEMB therapy during the trial period. Among these patients, thirteen patients failed to PEMB by the end of the trial period while 35 patients remained in the PFS state and continued receiving treatment until disease progression, unacceptable toxicity, or death. Conversely, the use of an OG arrangement compared to the base case produced an ICER of $321,403 per QALY gained. Over the duration of the OG-PBRSA, the payer received $112,696 in drug rebates for 26 patients who failed to realize at least ten months of PFS. Compared to the base case, total payer drug costs associated with higher PEMB utilization increased by $139,125 and $486,335 under the CTC-PBRSA and OG-PBRSA, respectively.

In addition to the drug rebates provided under both of our PBRSAs, the payer realized additional cost savings by treating more patients with PEMB instead of CIS+PEM. The three additional patients treated with PEMB under our PBRSAs led to a reduction in costs associated with disease progression, death, and adverse drug events, which resulted in an overall savings of $113,000. However, the costs of PFS supportive care and drug administration increased by $50,000 under both of our PBRSAs. To summarize, our CTC-PBRSA was found to be significantly more cost-effective than the OG-PBRSA, compared to current reimbursement practices.

3.4 Sensitivity Analyses

3.4.1 *Univariate Sensitivity Analysis*

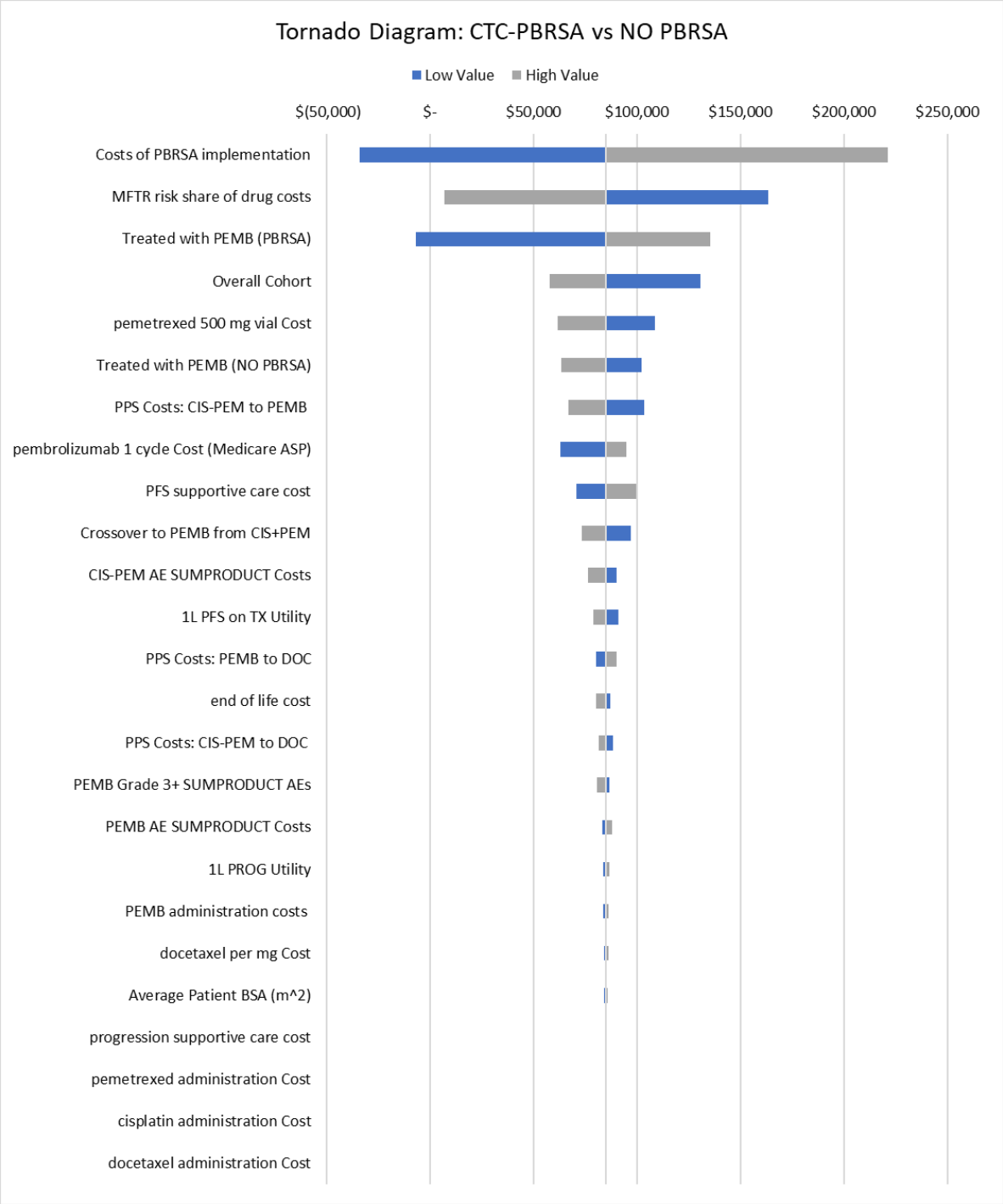

Figure 3.1. CTC-PBRSA one-way sensitivity analysis.

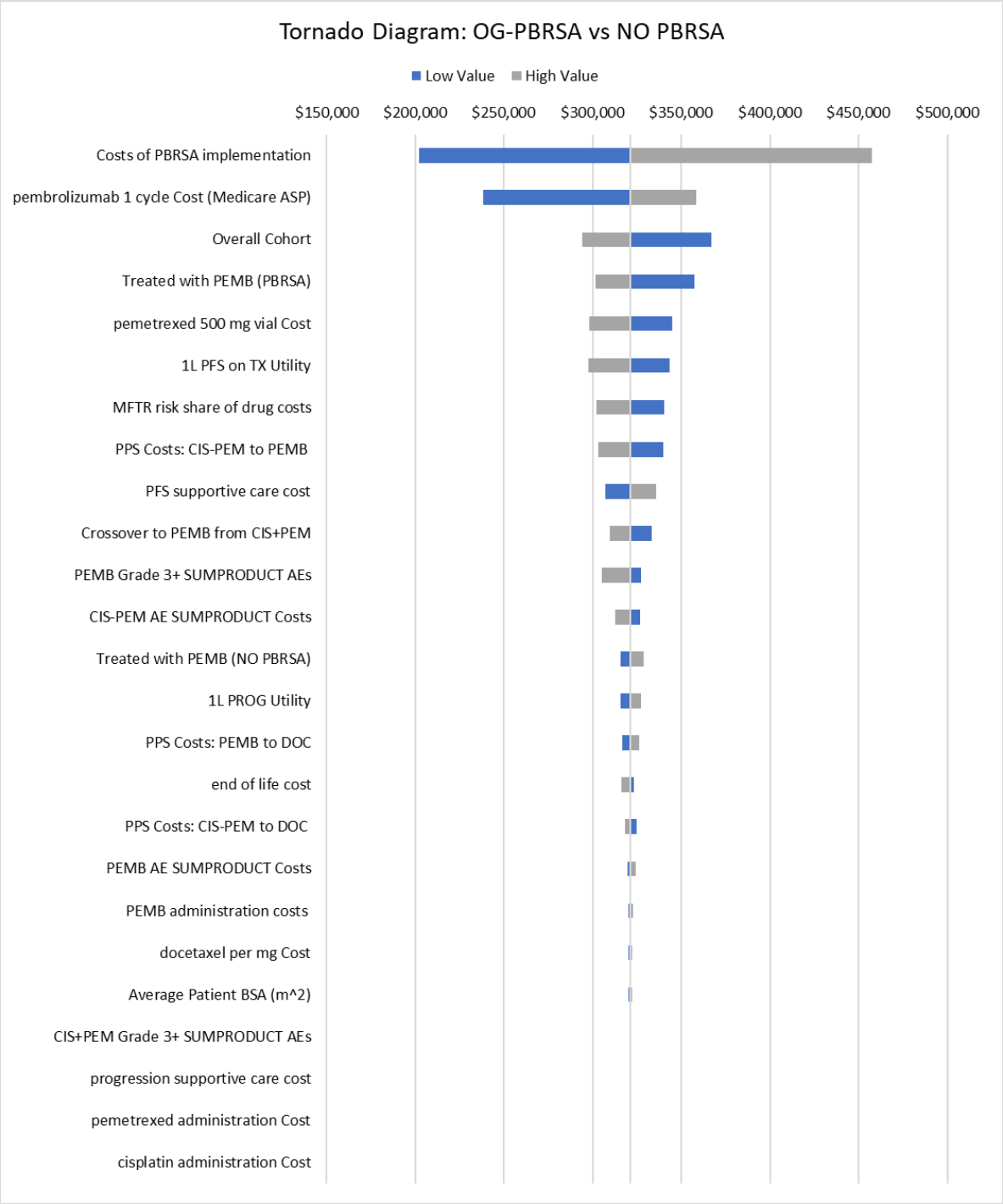

Figure 3.2. OG-PBRSA one-way sensitivity analysis.

The results of our univariate sensitivity analyses were plotted as tornado diagrams in Figures 3.1 and 3.2, which present the top 15 influential parameters for each of our PBRSAs. For both of our PBRSAs, the results were most sensitive to the initial costs of PBRSA

implementation, which produced the largest variation in our ICER estimates. In the CTC-PBRSA model, the subsequent two most influential parameters were the MFTR risk share of drug costs and drug utilization rates of PEMB. In the OG-PBRSA model, the cost of PEMB and size of the treated population were the second and third most influential parameters, respectively. Across all parameters of the OG-PBRSA, none of the values tested produced an ICER lower than a WTP threshold of $200,000 per QALY. Based on the results of our OWSA, we performed several deterministic and probabilistic scenario analyses to explore how varying the number of patients treated, initial costs of PBRSA implementation, and change in PEMB utilization altered our results.

3.4.2 *Probabilistic Sensitivity Analysis*

The results of our PSA were plotted on the cost-effectiveness (CE) plane as scatter plots (Figures 3.3 & 3.5). Almost all PSA simulation results for our OG-PBRSA aggregated in the northeast quadrant of the CE plane. In contrast, approximately 25% of PSA simulations for the CTC-PBRSA aggregated in the southeast quadrant, indicating the CTC-PBRSA may dominate traditional reimbursement practices. From the PSA results, the probabilities of each PBRSA being cost-effective across a range of WTP thresholds are illustrated in Figures 3.4 and 3.6 as CEAC. At a WTP threshold of $150,000 per QALY, the CTC-PBRSA had the highest probability of being cost-effective at 71% while the OG-PBRSA had a probability of less than 1% of being cost-effective. From our VOI analysis, the per subject expected value of perfect information (EVPI) at our chosen WTP threshold was found to be $585 and $1 for the CTC-PBRSA and OG-PBRSA, respectively. The VOI results (Figure 3.7) imply future research into the use of a CTC arrangement for PEMB may produce a higher return on investment compared to an OG arrangement.

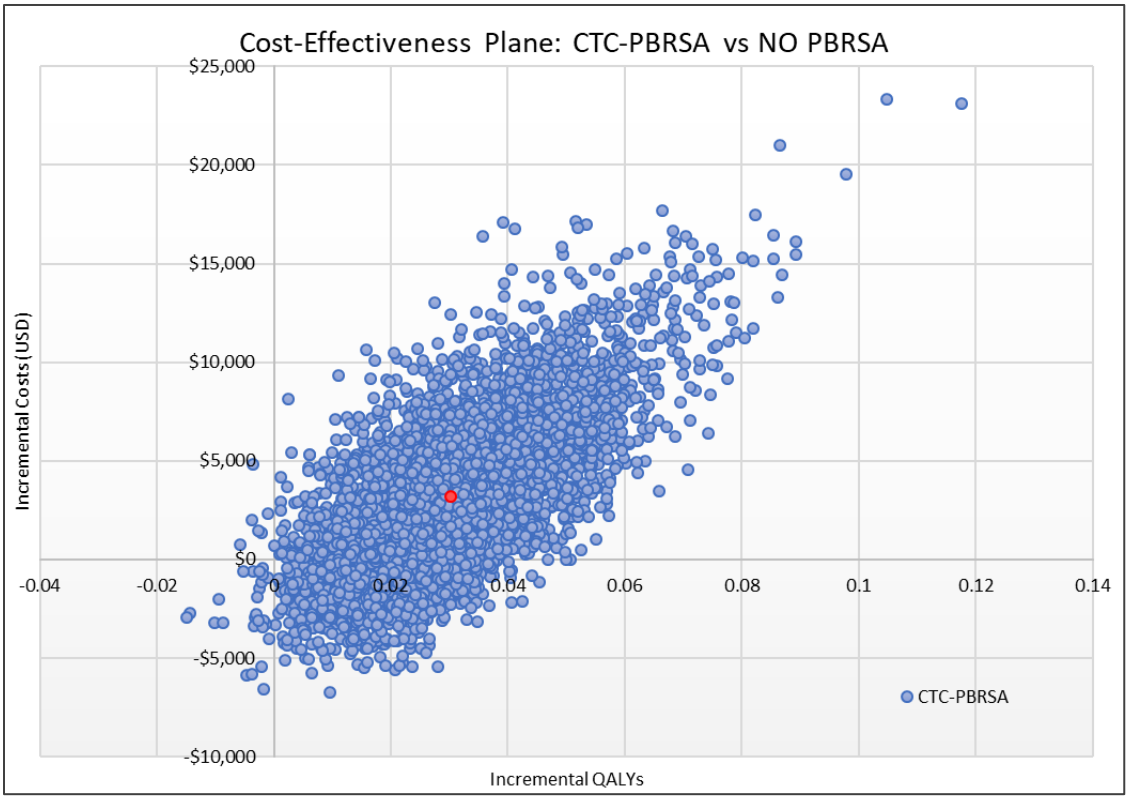

Figure 3.3. CTC-PBRSA probabilistic sensitivity analysis scatter plot.

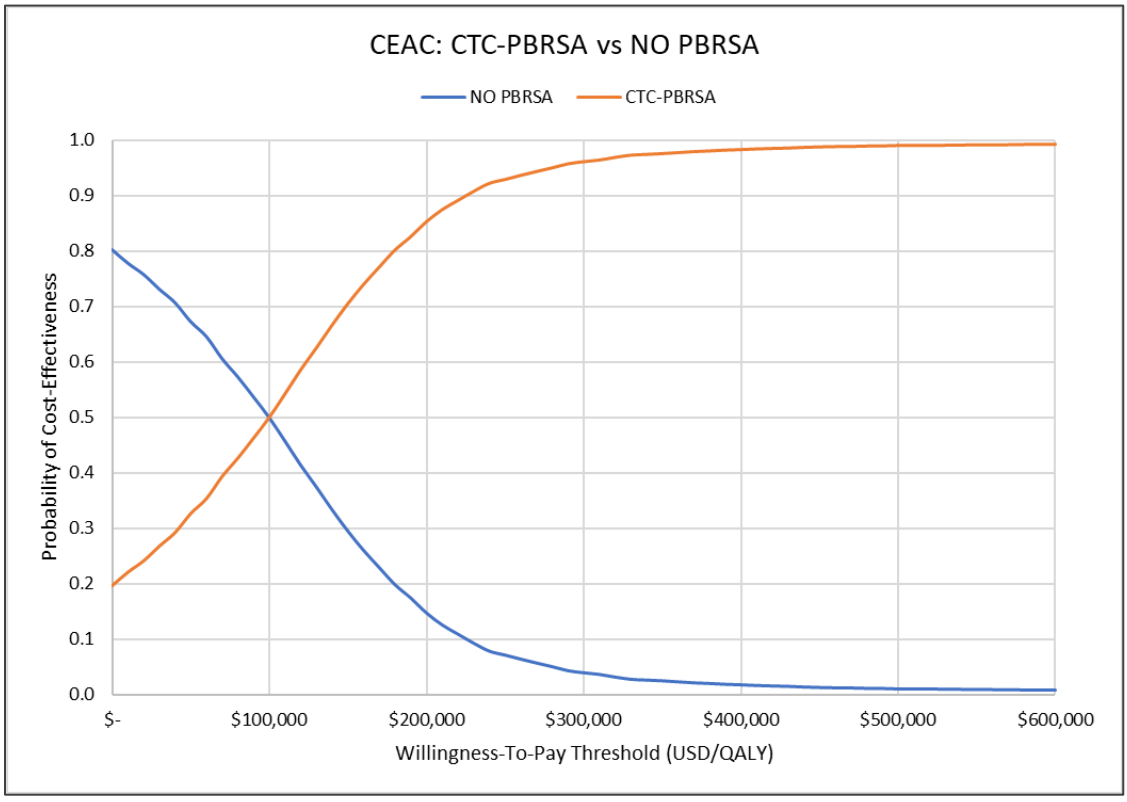

Figure 3.4. CTC-PBRSA cost-effectiveness acceptability curve (CEAC).

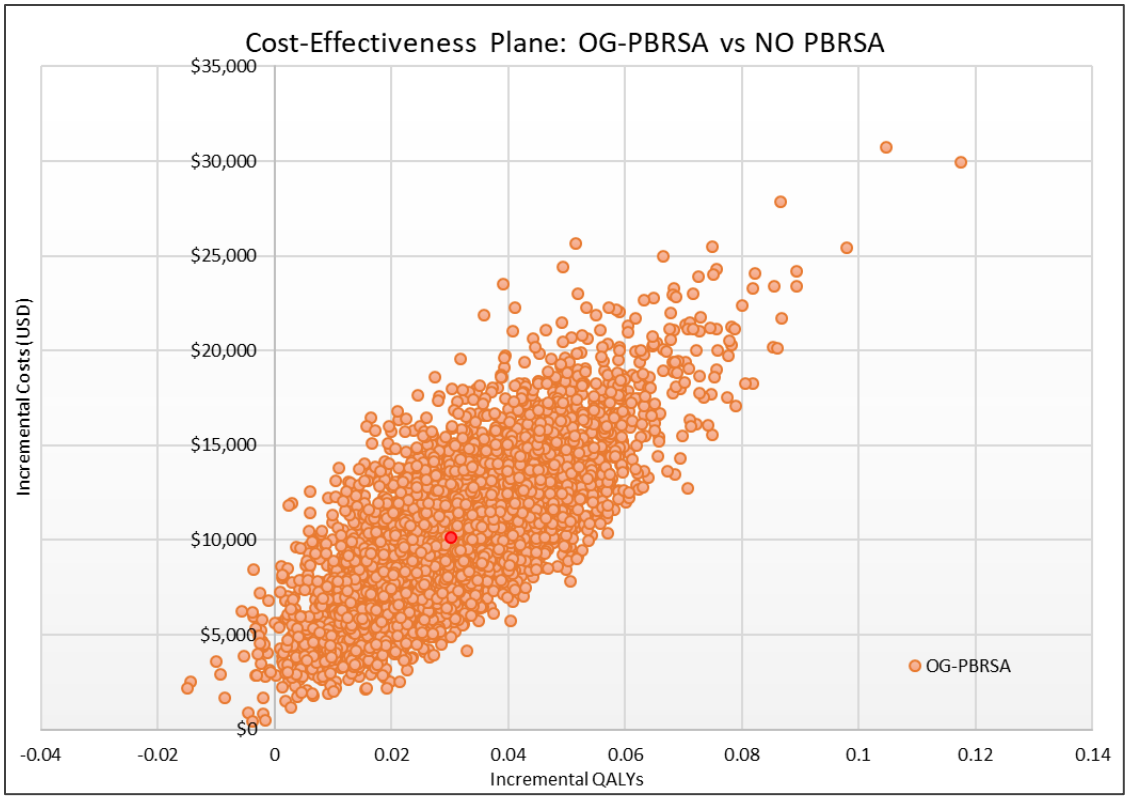

Figure 3.5. OG-PBRSA probabilistic sensitivity analysis scatter plot.

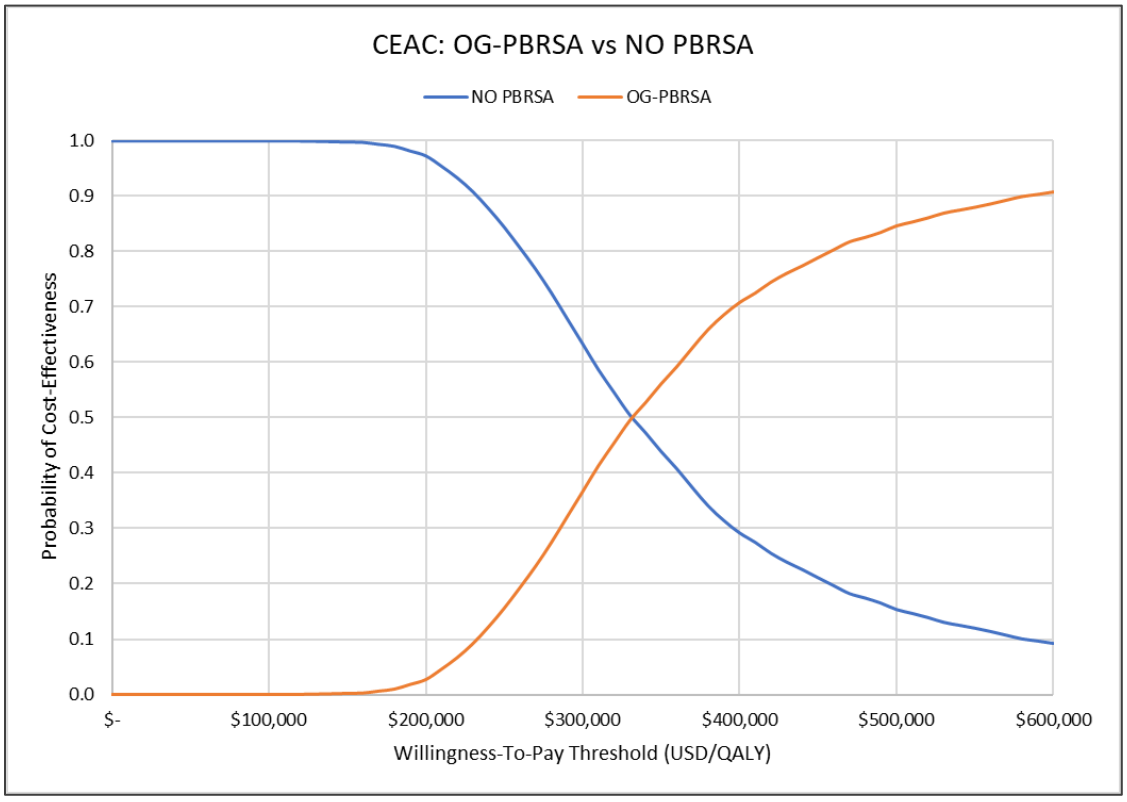

Figure 3.6. OG-PBRSA cost-effectiveness acceptability curve (CEAC).

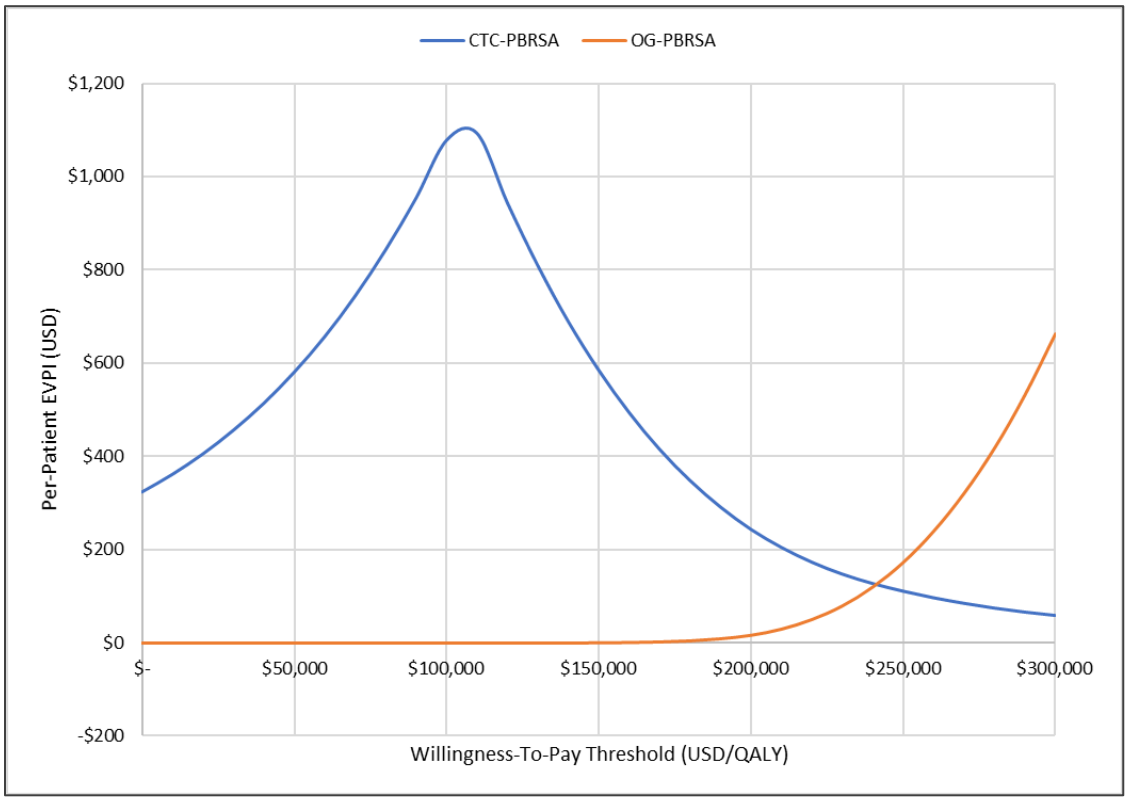

Figure 3.7. Per-patient expected value of perfect information (EVPI).

3.5 Deterministic Scenario Analyses (DSA)

3.5.1 *Pembrolizumab Utilization*

Table 3.7. DSA: incremental results per 1% increase in PEMB utilization among 50 patients versus base case

Incremental Result	**CTC-PBRSA**	**OG-PBRSA**
ΔTotal Costs	$76,689	$80,264
ΔTotal QALYs	0.31	0.31
ΔDrug Spend	$119,067	$125,592
Payer Drug Rebate	$4,735	$1,160

In our first deterministic scenario analysis (DSA), we varied the change in PEMB utilization in our PBRSAs to assess its impact on key financial and health outcomes relative to the base case. The results of this DSA are summarized in Table 3.7, which show a 1% increase in PEMB utilization among 50 patients lead to an additional 0.31 QALYs gained at an additional total cost of approximately $76,700 and $80,260 for the CTC-PBRSA and OG-PBRSA,

respectively. Drug rebates provided under the CTC-PBRSA were approximately four times larger than the OG-PBRSA, but drug costs associated with higher PEMB utilization increased in a commensurate manner under both PBRSAs. Furthermore, we found the relationship between the cost-effectiveness of our PBRSAs and higher PEMB utilization relative to the base case was non-linear, which is illustrated in Figure 3.8 below.

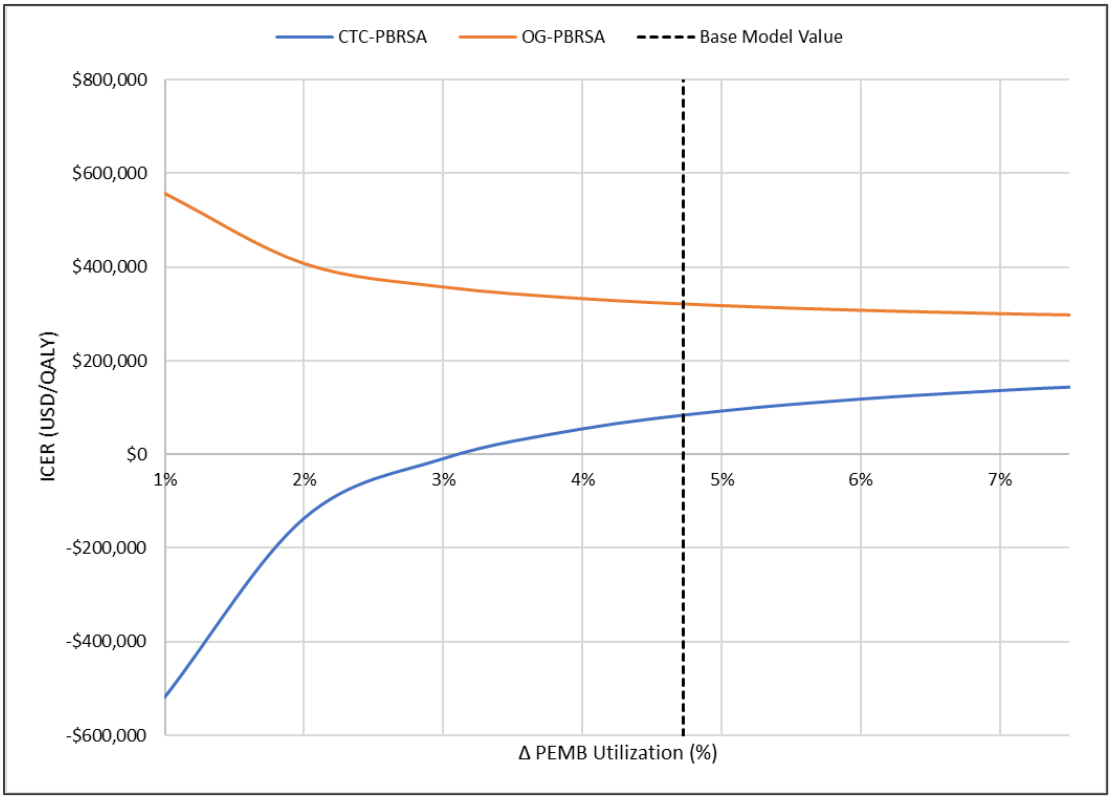

Figure 3.8. DSA: PBRSA ICERs versus ΔPEMB utilization relative to base case.

As PEMB utilization increased under our PBRSAs, we observed the cost-effectiveness of the CTC-PBRSA declined while the OG-PBRSA improved, relative to the base case. If patient PEMB utilization was lower than expected, the CTC-PBRSA was highly cost-effective compared to traditional reimbursement practices given the drug rebate would far exceed the negligible change in PEMB-related drug costs with a fixed PBRSA startup cost. Under the CTC-PBRSA, the payer received drug rebates for all patients treated with PEMB during the trial period, which effectively subsidized the cost of treatment failures and enabled the payer to reallocate more resources for responding patients to reap the cumulative health benefits beyond the duration of the arrangement. In contrast, the cost-effectiveness of our OG-PBRSA declined significantly given a smaller change in PEMB utilization led to a marginal gain of QALYs with

overall higher costs relative to the base case. If all patients were treated with PEMB, the CTC-PBRSA and OG-PBRSA produced ICER estimates of $146,040 per QALY and $297,554 per QALY, respectively. Thus, the CTC-PBRSA would still be considered cost-effective at a WTP threshold of $150,000 per QALY regardless of the change in PEMB utilization. However, the cost-effectiveness of the OG-PBRSA would decline substantially with higher than expected PEMB utilization relative to the base case.

3.5.2 *Treated Population Size*

In our second DSA, we varied the size of the modeled treated NSCLC population from 1 to 200 to determine the optimal number of patients needed to recoup the initial costs of PBRSA implementation and to produce an ICER below a WTP threshold of $150,000 per QALY for each of our PBRSAs (Figure 3.9). The results of our second DSA confirms our initial findings that there needs to be a sufficient patient population to justify the use of a PBRSA. At our chosen WTP threshold of $150,000 per QALY in our case study, the CTC-PBRSA required a minimum of 22 patients to be considered cost-effective relative to the base case, but the OG-PBRSA was not cost-effective across the entire range of treated populations. Furthermore, the results of our deterministic scenario analysis on the impact of the treated population on the cost-effectiveness of our PBRSAs relative to the base case indicate there are diminishing returns as the population of patients with advanced NSCLC increases. Finally, we found the size of the treated patient population needed for the payer to recover just the initial costs of PBRSA implementation were 22 and 90 patients with advanced NSCLC for the CTC-PBRSA and OG-PBRSA, respectively.

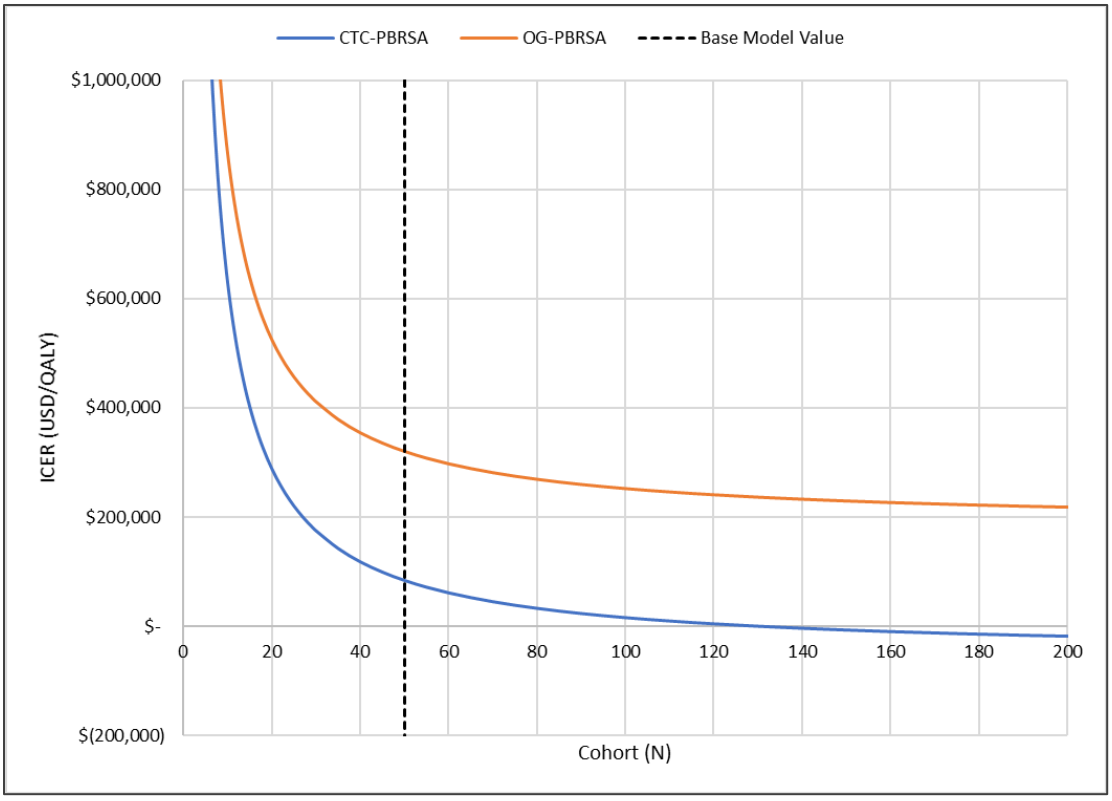

Figure 3.9. DSA: PBRSA ICERs versus total treated population.

3.6 Probabilistic Scenario Analyses

3.6.1 *Payer Return on Investment (ROI)*

In our final scenario analysis, we assessed the impact of the overall uncertainty in our decision model on the likelihood each of our PBRSAs can yield a net gain for the payer with two hypothetical treated populations across a range of potential startup costs for implementing a pilot PBRSA. For our PBRSAs to yield a positive return on investment (ROI) for the payer, a net cost savings must be produced between the drug rebate provided under each PBRSA and the total cost of each respective PBRSA, which is defined in equation [2] below:

$$ROI\ with\ PBRSA = Payer\ rebate\ amount - Total\ payer\ cost\ of\ PBRSA \quad (3.1)$$

In equation [2], the total cost of PBRSA variable was defined as the sum of initial cost of PBRSA implementation and change in drug costs associated with higher PEMB utilization relative to the base case. Given the likely variability in the initial costs of PBRSA implementation, we evaluated a range of startup costs from $0.00 to $400,000 in increments of

$50,000 by performing a series of PSAs varying all other model parameters within their respective distributions for two hypothetical populations of 50 patients and 100 patients at each potential value over 5000 iterations. For each potential cost, we identified the proportion of PSA iterations in which the payer was net positive under each PBRSA at one year (Figure 3.10) and five years (Figure 3.11).

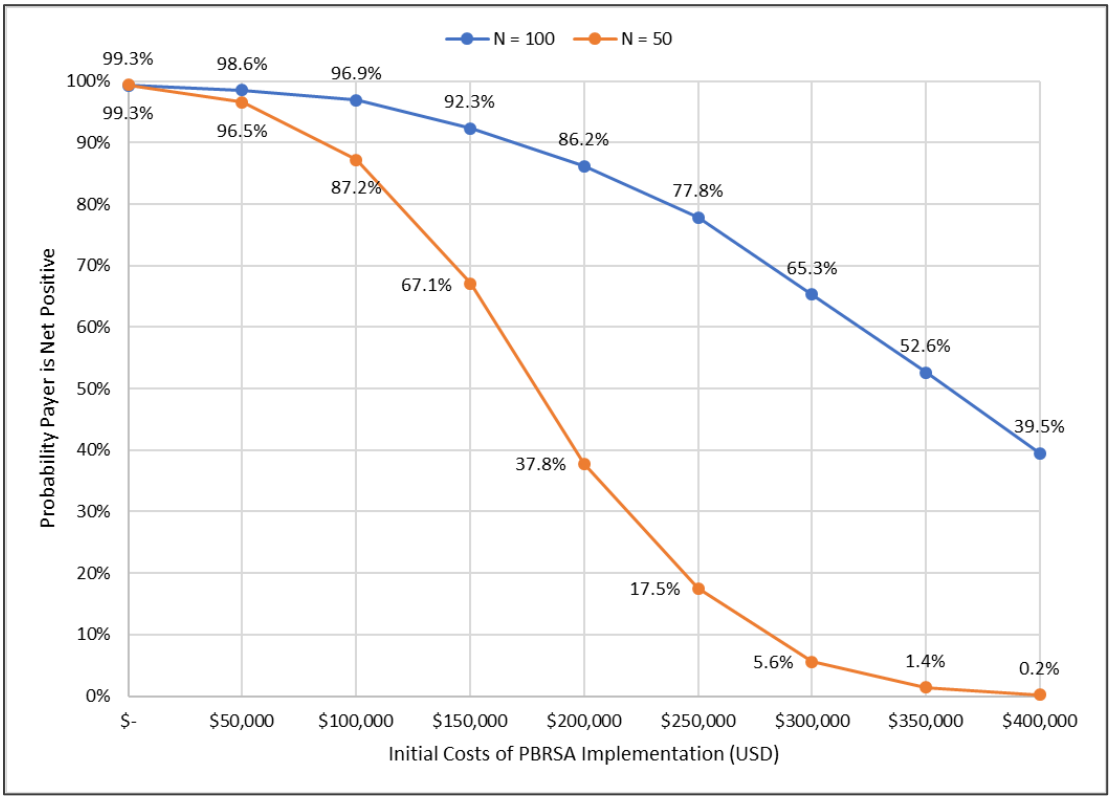

Figure 3.10. PSA (Time = 1 Year): Probability payer is net positive versus Initial costs of PBRSA implementation for 50 and 100 patients.

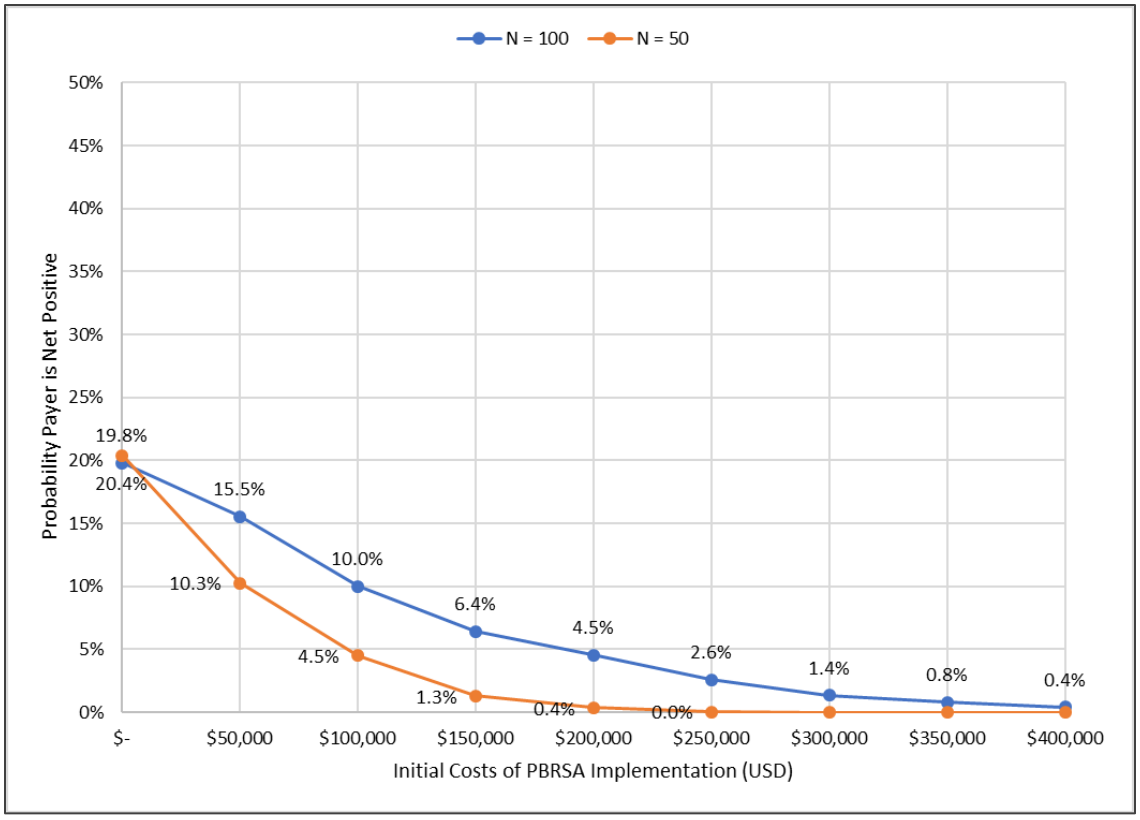

Figure 3.11. PSA (Time = 5 Years): Probability payer is net positive versus Initial costs of PBRSA implementation for 50 and 100 patients.

The results of our probabilistic scenario analysis showed our OG-PBRSA was highly unlikely to produce a net gain for the payer at one year or five years regardless of the startup costs. The OG-PBRSA was subsequently excluded from our plots in Figures 3.10 and 3.11. This observation was not unexpected given the OG-PBRSA rebate amount in our deterministic model was insufficient to subsidize the $276,000 increase in drug costs due to 5% higher PEMB utilization relative to the base case. Conversely, the probabilities our CTC-PBRSA would yield a positive ROI for the payer at our estimated total startup cost of a pilot PBRSA at one year were approximately 86% and 38% for 100 patients and 50 patients, respectively. The observed difference in our probability estimates between 100 patients and 50 patients at one year was also conserved at five years (Figure 3.11). Based on our findings, it appears the likelihood our CTC-PBRSA can yield a net gain for the payer at one and five years rises as the treated population of patients with advanced NSCLC increases. Furthermore, we also found the probability our CTC-PBRSA can produce cost savings for the payer declines sharply from one year to five years. This observation was consistent with results from our deterministic model. Relative to our base case,

PEMB-related drug expenditures effectively doubled from $276,200 at one year to $553,000 at five years under both of our PBRSAs, excluding drug rebates. Finally, the results of our probabilistic scenario analysis indicate there is high probability a CTC-PBRSA can yield a positive net gain for the payer at one year if the initial startup cost of a pilot PBRSA is less than $125,000 in our case study.

Chapter 4. DISCUSSION

4.1 Summary of Methods and Results

To assess the potential outcomes of utilizing PBRSAs from a US payer perspective we developed a decision model for the use of two distinct PBRSAs in a case study of pembrolizumab as a first line treatment in patients with advanced NSCLC. We assumed a 25% reduction in patient cost sharing provided under our PBRSAs led to a total of 49 patients treated with PEMB compared to 46 patients in the base case. Both of our PBRSAs produced an incremental gain of 1.47 QALYs at an additional cost of $599,030 in payer drug expenditures, without accounting for drug rebates. Under the terms of the CTC-PBRSA and OG-PBRSA, the payer received drug rebate amounts for $459,905 and $112,695, respectively. Compared to traditional reimbursement practices, the use of a CTC-PBRSA or OG-PBRSA was associated with an incremental cost per QALY of $84,990 and $321,402, respectively.

From our scenario analyses, smaller cohort sizes were found to dramatically worsen the cost-effectiveness of both of our PBRSAs. If less than five patients with advanced NSCLC were treated, both of our PBRSAs produced ICERs greater than $1,000,000 per QALY, but as the treated population increased, the cost-effectiveness of our PBRSAs dramatically improved. For the payer to subsidize the initial cost of PBRSA implementation with drug rebates provided under our PBRSAs, the OG-PBRSA would require four times the number needed to treat under our CTC-PBRSA. Higher PEMB utilization also had a marked impact on the cost-effectiveness of our PBRSAs. By varying the prescription substitution rate, we observed an inverse relationship between the CTC-PBRSA and OG-PBRSA, where higher PEMB utilization improved the cost-effectiveness of the OG-PBRSA and worsened the CTC-PBRSA. Finally, the results of our probabilistic scenario analysis on the impact of overall uncertainty in the ability of our PBRSAs to yield a positive ROI at one year for the payer showed there is a greater than 75% probability the payer would benefit significantly from the use of a CTC-PBRSA compared to an OG-PBRSA if the initial startup costs are less than $125,000. At a willingness-to-pay threshold of $150,000 per QALY, the probability a CTC-PBRSA would be considered cost-effective in our case study of 50 patients with advanced NSCLC was estimated to be 70% while the OG-PBRSA had a less than 1% probability of being cost-effective. This finding is further supported by the

results of our VOI analysis, which implied there is greater value in further research into the use of a CTC arrangement compared to an OG arrangement for our indication of interest. Based on our findings, it is clear PBRSAs are not a panacea and there are inherent risks and uncertainties associated with their use for payers and MFTRs, which warrants a careful evaluation of several key factors prior to implementing a PBRSA.

4.2 Implications of our Findings

Our model-based analysis suggests the use of PBRSAs to improve patient health outcomes is not entirely impractical for US payers despite the uncertainty in their ability to lower costs and operational challenges. The results of our case study showed the use of a CTC-arrangement along with lower patient cost sharing may reduce costs and improve patient health outcomes by mitigating the costs of delayed or forgone care among patients with advanced NSCLC. It is important to note the ability of a PBRSA to improve patient health outcomes is predicated on lowering cost barriers by sharing cost savings with patients in the form of lower patient cost sharing or less restrictive coverage. The high costs typically associated with a new health technology create barriers to care, which limits its widespread use among patients who could potentially benefit and worsens health outcomes. Thus, a PBRSA should be considered for a disease state associated with high costs of care in which a sufficient patient population may potentially benefit from improved access to care. For example, the health and cost consequences of forgone and delayed care among patients with advanced cancer can be substantial. The high costs of cancer care are known to place a significant emotional and financial strain on patients reliant on state or federal health care programs who are ineligible for MFTR patient assistance programs. A study linking SEER cancer registry records to federal bankruptcy records by Ramsey et al. found financial insolvency may be a significant risk factor for mortality among patients with cancer. Thus, PBRSAs may be used to fill these gaps in care by lowering patient cost barriers to novel treatments and provide patients timely and consistent access to care. This would also serve to avoid possible misunderstanding on the intent of PBRSAs among patients and providers to minimize public enmity based on the perception these arrangements are strictly cost saving measures between payers and MFTRs.

Our findings also reaffirm the operational challenges imposed by government price-reporting obligations, such as Medicaid best price. Compared to our CTC-PBRSA, the OG-

PBRSA was not as cost-effective relative to traditional reimbursement arrangements, which was likely due to the disparity in the size of rebates provided under our PBRSAs. In our case study, the MFTR risk share of drug costs used to estimate payer drug rebates under both of our PBRSAs was based on an estimation of the Medicaid's drug price threshold for triggering a new best price. We assumed the MFTR would be unwilling to offer additional drug rebates greater than 27% of the Medicare ASP. Given drug rebates provided under the OG-PBRSA were based on the duration of benefit realized in each patient, a 20% MFTR risk share of drug costs resulted in rebate amounts ranging from $1900 to $6500 depending on when each patient failed PEMB. Whereas, the CTC-PBRSA applied a temporary 20% drug rebate to the entirety of drug costs during the trial period, which produced rebate amounts ranging from $1900 to $11,100 for all patients regardless of PEMB's effectiveness. Thus, the drug rebates provided under the terms of the CTC-PBRSA were considerably more generous than the OG-PBRSA, which subsequently limited its cost-effectiveness relative to the base case. Our findings do not preclude the viability of our OG-PBRSA, but indicate an OG arrangement would likely require a larger reallocation of risk from the payer to the MFTR compared to a CTC arrangement. However, government price-reporting obligations constrain the size of rebates or discounts MFTRs may be willing to offer US payers under a PBRSA, which limits the use of certain types of PBRSAs such as our OG-PBRSA.

From our scenario analysis, the decision to utilize a PBRSA should be based on the needs and characteristics of the patient population for the indication of interest. The logistical needs of operationalizing a PBRSA represents a significant startup cost for US payers, and there must be a sufficient patient population for the payer to justify this initial investment. In our case study, our results showed the minimum patient population needed to subsidize the initial startup cost of our PBRSAs were 22 patients and 90 patients for the CTC-PBRSA and OG-PBRSA, respectively. It appears the size of the patient population should not only influence the decision to implement a PBRSA but also the structure or type of PBRSA. Furthermore, our findings suggest a larger patient population may justify higher startup costs for a CTC-PBRSA given that a proportionally larger drug rebate relative to a fixed cost increases the likelihood of producing a net monetary gain for the payer at one year and five years.

The current body of evidence on the use and outcomes of PBRSAs in the US health care market is limited given the confidential nature of known examples. Our study appears to be

unique as a formal evaluation of two distinct PBRSAs based on examples from published literature using a decision model while accounting for patient drug utilization behavior and Medicaid best price implications. However, it is important to note the generalizability of our findings is limited to the specific terms of our PBRSAs in this case study, because the operational and financial viability of a PBRSA is highly dependent on the specific terms of each arrangement. This highlights the need for further research into this area to evaluate and identify other types of PBRSAs that may be viable in the current US health care environment.

4.3 Study Limitations

There were several notable limitations addressed in the methods of our study. First, there are inherent limitations with assessing patient health outcomes using PFS, which is an intermediate outcome that is correlated with symptoms and death in cancer patients but the causal association between tumor burden and OS is still unclear.[iv] Despite this limitation, PFS is a surrogate endpoint that is widely accepted by government regulatory bodies, and it is commonly used in clinical practice to ascertain treatment response for select malignancies. It can be consistently measured with defined response criterion within a reasonable amount of time, which makes it an ideal outcome target to estimate payer rebates in our PBRSAs. However, the basis of our partition state model used to extrapolate long term survival outcomes was clinical data from a single phase III trial, and there is considerable uncertainty in the impact of PEMB on long term OS given the absence of long term clinical data. Other studies using similar methods to predict survival beyond known clinical data have produced similar results for pembrolizumab in advanced NSCLC with predicted 5-year OS rates up to 25%.[xxii] To minimize bias, we took a conservative approach in extrapolating long-term survival outcomes, and evaluated uncertainty in our PSA and probabilistic scenario analysis. Furthermore, our predictions of survival outcomes assumed that all patients were completely adherent to their assigned treatments and were treated until disease progression, unacceptable toxicity, or death. Outside a controlled study environment, complete patient adherence and prescribing patterns fully consistent with clinical guidelines are seldom observed in actual practice. However, the consistent application of our assumptions across all modeled treatment regimens should minimize bias in our results.

In the context of patient behavior, the second issue was the current body of evidence on the relationship between plan characteristics and patient health care utilization is conflicting at

best. In the setting of advanced cancer, the assumption that patients are motivated by self-preservation will not always hold, and there will be a proportion of cancer patients who ultimately decide to forgo or delay treatment due to a myriad of reasons beyond cost issues. Furthermore, the patients' elasticity of demand coefficient used in our study were found to not be statistically different from zero, and the investigators also found higher plan generosity reduced the number of claims for specialty oncology drugs among patients with advanced cancer. Thus, we cannot rule out a scenario in which lower patient OOP does not lead to higher PEMB utilization and improved patient health outcomes. To address this issue, we performed multiple scenario analyses to assess the impact of uncertainty in patient behavior on our results, which showed a less than 1% change in PEMB utilization between our PBRSAs and traditional reimbursement practices did not fundamentally alter our conclusions.

Finally, there is likely no single fixed payer cost for implementing a PBRSA, and it was challenging to obtain a reasonable estimate of this cost that may be generalizable to most US payers. To address this limitation, we tried to take a conservative approach by being generous in our estimates of startup costs, and evaluated a wide range of potential costs of PBRSA implementation in our sensitivity and scenario analyses. The results of our univariate sensitivity analysis confirmed the ability of this cost to significantly influence our results, and our probabilistic scenario analysis showed initial startup costs greater than $200,000 for both of our PBRSAs will likely produce a negative ROI for the payer. However, these findings only strengthen our conclusion that payers and MFTRs must perform a thorough evaluation of the operational requirements and associated costs to ascertain if a PBRSA is in their best interests.

4.4 Concluding Thoughts

To assess the financial and health consequences of two distinct PBRSAs from the payer perspective, we used a decision model to evaluate a CTC-PBRSA and OG-PBRSA in a case study of pembrolizumab as first line treatment for advanced NSCLC. Our findings indicate a CTC arrangement may be highly cost-effective compared to traditional reimbursement practices for indications in which there is considerable uncertainty in the effectiveness of a medication among a subset of patients. The reallocation of payer risk for treatment failures during a short trial period can produce sufficient cost savings to lower cost barriers so patients may receive timely and consistent access to appropriate treatments and achieve optimal outcomes. Compared

to our CTC-PBRSA, our OG-PBRSA was not cost-effective at our chosen MFTR risk share of drug costs relative to the base case. Based on our findings, an OG-arrangement may require a larger reallocation of financial risk between the payer and MFTR to produce the necessary financial incentives for the payer to consider its use. However, the MFTR's ability to provide larger rebates may be limited due to government-price reporting obligations, which limits the use of other novel pricing and reimbursement schemes given the potential financial disincentives for the payer. Our model-based analysis suggests the barriers to the adoption of PBRSAs by US payers and MFTRs are not insurmountable, but there is a clear need for further research into this area.

BIBLIOGRAPHY

[1] Garrison LP, Carlson JJ, Preeti SB, et al. Private sector risk-sharing agreements in the United States: Trends, Barriers, and Prospects. *Am J Manag Care*. 2015; 21(9): 632-640

[2] Garrison LP, Towse A, Briggs A, et al. Performance-based risk sharing arrangements-good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value in Health*. 2013; 16: 703-719

[3] Amgen and Harvard Pilgrim agree to first cardiovascular outcomes-based refund contract for Repatha (evolocumab). (2017, May 2). Retrieved from https://www.amgen.com/media/news-releases/2017/05/amgen-and-harvard-pilgrim-agree-to-first-cardiovascular-outcomesbased-refund-contract-for-repatha-evolocumab/

[4] Thomas K, Ornstein C. (2017, July 10). Considering the side effects of drugmakers' money-back guarantees. *The New York Times*. Retrieved from https://www.nytimes.com

[5] Santarpia M, Gonzalez-Cao M, Viteri S, et al. Programmed cell death ligand-1 pathway inhibition and predictive biomarkers: understanding transforming growth factor-beta role. *Transl Lung Cancer Res.* 2015; 4(6): 728-742

[6] Chae YK, Pan A, Davis AA, et al. Biomarkers for PD-1/PD-L1 blockade therapy in non-small cell lung cancer: is PD-L1 expression a good marker for patient selection? *Clinical Lung Cancer*. 2016; 17(5): 350-361

[7] Carlson JJ, Sullivan SD, Garrison LP, et al. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*. 2010, doi: 10.1016/j.healthpol.2010.02.005

[8] Fox J, Watrous M (2017, April 3). Overcoming challenges of outcomes-based contracting for pharmaceuticals: early lessons learned. *Health Affairs Blog*. Retrieved from https://www.healthaffairs.org/blog

[9] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-Positive non-small-cell lung cancer. *The New England Journal of Medicine*. 2016; DOI: 10.1056/NEJMoa1606774

[10] Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-Effectiveness Analyses: Second Panel on Cost Effectiveness in Health and Medicine. *JAMA*. 2016;316(10):1093-1103

[11] Streeter SB, Schwartzberg L, Husain N, et al. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *Journal of Oncology Practice*. 2010; 7(3S): 46-51

[12] Goldman DP, Jena AB, Lakdawalla DN, et al. The value of specialty oncology drugs. *Health Services Research*. 2010; 45(1): 115-132

[13] Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Medical Research Methodology*. 2011; 11: 139

[14] Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer. *J Thorac Oncol.* 2013; 8: 997-1003

[15] Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health and Quality of Life Outcomes.* 2008; 6:84

[16] U.S. Congressional Budget Office (2005) Prices for Brand Name Drugs Under Selected Federal Programs (Washington, D.C., Congress of the United States).

[17] Graham J, Earnshaw S, Lim J, et al. Cost-effectiveness of afatinib versus erlotinib in the first-line treatment of patients with metastatic non-small cell lung cancer with EGFR exon 19 deletion mutations. *Journal of Clinical Pathways*. 2016; 2(4): 31-39

[18] U.S. Department of Health & Human Services. Examination of clinical trial costs and barriers for drug development. HHSP23337007T. https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development. Published July 25, 2014. Accessed March 3, 2017

[19] Cetin K, Ettinger DS, Hei Y, et al. Survival by histologic subtype in stage IV non-small cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clinical Epidemiology.* 2011; 3: 139-148

[20] Hellman MD, Ma J, Garon EB, et al. Estimating long-term survival of PD-L1 expressing, previously treated, non-small cell lung cancer patients who received pembrolizumab in KEYNOTE-001 and -010. Poster session presented at the ASCO-SITC Clinical Immuno-Oncology Symposium, Orlando, FL

APPENDIX A

Table 4.8. Summary of decision model parameters

Model Input Category	Parameters	Base Value	Low Value	High Value	Reference
Patient Parameters	Crossover to 2nd Line PEMB	44%	0.19	0.69	KEYNOTE-024
	Average Patient Height (cm)	178.30	133.73	222.88	KEYNOTE-010
	Average Patient Weight (kg)	74.10	55.58	92.63	KEYNOTE-010
	Average Patient BSA (m^2)	1.92	1.44	2.40	KEYNOTE-010
Health State Utilities	1L PFS on TX	0.71	0.53	0.89	Chouaid et al. (2013)
	1L PROG	0.67	0.50	0.84	Chouaid et al. (2013)
	2L PFS on TX	0.67	0.50	0.84	Nafees et al. (2008)
	2L PROG	0.47	0.35	0.59	Nafees et al. (2008)
Adverse Event Disutilities	Anemia	0.090	0.068	0.113	Nafees et al. (2008)
	Diarrhea	0.047	0.035	0.059	Nafees et al. (2008)
	Dyspnea	0.050	0.038	0.063	Doyle et al. (2008)
	Fatigue	0.073	0.055	0.091	Nafees et al. (2008)
	Hyponatremia	0.090	0.068	0.113	Nafees et al. (2008)
	Infection	0.047	0.035	0.059	Nafees et al. (2008)
	Leukopenia	0.090	0.068	0.113	Nafees et al. (2008)
	Nausea	0.048	0.036	0.060	Nafees et al. (2008)
	Neuromotor	0.069	0.052	0.086	Doyle et al. (2008)
	Neutropenia	0.090	0.068	0.113	Nafees et al. (2008)
	Paronychia/Nail disorders	0.032	0.024	0.040	Nafees et al. (2008)
	Pneumonitis/Pneumonia	0.073	0.055	0.091	Nafees et al. (2008)
	Pulmonary/Respiratory Infx.	0.046	0.035	0.058	Doyle et al. (2008)
	Rash	0.032	0.024	0.040	Nafees et al. (2008)
	Skin reactions	0.032	0.024	0.040	Nafees et al. (2008)
	Stomatitis	0.032	0.024	0.040	Nafees et al. (2008)
PEMB ADR	Anemia	3.80%	2.85%	4.75%	KEYNOTE-010
	Diarrhea	3.90%	2.93%	4.88%	KEYNOTE-024
	Dyspnea	3.70%	2.78%	4.63%	KEYNOTE-010
	Fatigue	1.30%	0.98%	1.63%	KEYNOTE-024
	Hyponatremia	8.00%	6.00%	10.00%	KEYNOTE-010
	Infection	0.00%	0.00%	0.00%	PEMB Package insert
	Leukopenia	0.00%	0.00%	0.00%	PEMB Package insert
	Nausea	1.30%	0.98%	1.63%	KEYNOTE-010
	Neuromotor	0.00%	0.00%	0.00%	PEMB Package insert
	Neutropenia	0.00%	0.00%	0.00%	KEYNOTE-024
	Paronychia/Nail disorders	0.00%	0.00%	0.00%	PEMB Package insert
	Pneumonitis/Pneumonia	2.60%	1.95%	3.25%	KEYNOTE-024
	Pulmonary/Respiratory Infx.	1.00%	0.75%	1.25%	PEMB Package insert
	Rash	0.40%	0.30%	0.50%	KEYNOTE-010
	Skin reactions	3.90%	2.93%	4.88%	KEYNOTE-024
	Stomatitis	0.00%	0.00%	0.00%	KEYNOTE-024
	SUMPRODUCT AEs	1.96%	1.10%	3.06%	Estimated
CIS+PEM ADR	Anemia	19.30%	14.48%	24.13%	KEYNOTE-024
	Diarrhea	1.30%	0.98%	1.63%	KEYNOTE-024

	Dyspnea	0.00%	0.00%	0.00%	KEYNOTE-021
	Fatigue	3.30%	2.48%	4.13%	KEYNOTE-024
	Hyponatremia	3.50%	2.63%	4.38%	KEYNOTE-021
	Infection	0.00%	0.00%	0.00%	KEYNOTE-021
	Leukopenia	2.00%	1.50%	2.50%	KEYNOTE-024
	Nausea	2.00%	1.50%	2.50%	KEYNOTE-024
	Neuromotor	0.00%	0.00%	0.00%	KEYNOTE-024
	Neutropenia	13.30%	9.98%	16.63%	KEYNOTE-024
	Paronychia/Nail disorders	0.00%	0.00%	0.00%	KEYNOTE-024
	Pneumonitis/Pneumonia	0.70%	0.53%	0.88%	KEYNOTE-024
	Pulmonary/Respiratory Infx.	0.00%	0.00%	0.00%	KEYNOTE-024
	Rash	1.60%	1.20%	2.00%	KEYNOTE-021
	Skin reactions	0.00%	0.00%	0.00%	KEYNOTE-024
	Stomatitis	1.30%	0.98%	1.63%	KEYNOTE-024
	SUMPRODUCT AEs	3.97%	2.23%	6.20%	Estimated
DOC ADR	Anemia	9.00%	6.75%	11.25%	DOC Package Insert
	Diarrhea	3.00%	2.25%	3.75%	DOC Package Insert
	Dyspnea	2.60%	1.95%	3.25%	KEYNOTE-010
	Fatigue	18.00%	13.50%	22.50%	DOC Package Insert
	Hyponatremia	2.90%	2.18%	3.63%	KEYNOTE-010
	Infection	10.00%	7.50%	12.50%	DOC Package Insert
	Leukopenia	49.00%	36.75%	61.25%	DOC Package Insert
	Nausea	5.00%	3.75%	6.25%	DOC Package Insert
	Neuromotor	5.00%	3.75%	6.25%	DOC Package Insert
	Neutropenia	65.00%	48.75%	81.25%	DOC Package Insert
	Paronychia/Nail disorders	1.00%	0.75%	1.25%	DOC Package Insert
	Pneumonitis/Pneumonia	1.00%	0.75%	1.25%	KEYNOTE-010
	Pulmonary/Respiratory Infx.	21.00%	15.75%	26.25%	DOC Package Insert
	Rash	0.00%	0.00%	0.00%	KEYNOTE-010
	Skin reactions	1.00%	0.75%	1.25%	KEYNOTE-010
	Stomatitis	2.00%	1.50%	2.50%	DOC Package Insert
	SUMPRODUCT AEs	15.14%	8.52%	23.65%	Estimated
Treatment Costs	Cisplatin per mg	$0.36	$0.27	$0.45	Redbook
	EGFR gene com variants	$340.15	$255.11	$425.19	CMS
	ALK	$260.19	$195.14	$325.24	CMS
	KRAS Gene	$203.56	$152.67	$254.45	CMS
	Immunohisto antb addl slide	$92.23	$69.17	$115.29	CMS
	Microdissection Manual	$123.10	$92.33	$153.88	CMS
	Immunohisto antb 1st stain	$108.38	$81.29	$135.48	CMS
	Lung Cancer Panel with KRAS	$1,127.61	$845.71	$1,409.51	Estimated
	cisplatin administration	$91.72	$68.79	$114.65	Redbook
	pemetrexed 500 mg vial	$3,162.00	$2,371.50	$3,952.50	Redbook
	pemetrexed 100 mg vial	$632.40	$474.30	$790.50	Redbook
	pemetrexed administration	$136.15	$102.11	$170.19	Redbook
	docetaxel per mg	$9.55	$7.16	$11.94	Redbook
	docetaxel administration	$136.15	$102.11	$170.19	Redbook
	pembrolizumab 100 mg vial	$4,380.74	$3,285.56	$5,475.93	Redbook
	PEMB administration costs	$136.15	$102.11	$170.19	Redbook
	PD1 assay cost	$274.00	$205.50	$342.50	CMS
	end of life cost	$50,000.00	$37,500.00	$62,500.00	Graham et al.

	progression supportive care cost	$109.00	$81.75	$136.25	Estimated
	PFS supportive care cost	$360.00	$270.00	$450.00	Graham et al.
AE Costs	Anemia	$12,109.62	$9,082.22	$15,137.03	DRG 808
	Diarrhea	$6,462.33	$4,846.75	$8,077.91	DRG 809
	Dyspnea	$3,951.10	$2,963.33	$4,938.88	DRG 810
	Fatigue	$6,136.10	$4,602.08	$7,670.13	DRG 811
	Hyponatremia	$6,133.39	$4,600.04	$7,666.74	DRG 812
	Infection	$10,314.26	$7,735.70	$12,892.83	DRG 813
	Leukopenia	$12,109.62	$9,082.22	$15,137.03	DRG 814
	Nausea	$6,462.33	$4,846.75	$8,077.91	DRG 815
	Neuromotor	$6,926.21	$5,194.66	$8,657.76	DRG 816
	Neutropenia	$12,109.62	$9,082.22	$15,137.03	DRG 817
	Paronychia/Nail disorders	$7,787.85	$5,840.89	$9,734.81	DRG 818
	Pneumonitis/Pneumonia	$7,728.24	$5,796.18	$9,660.30	DRG 819
	Pulmonary/Respiratory Infx.	$10,314.26	$7,735.70	$12,892.83	DRG 820
	Rash	$7,428.56	$5,571.42	$9,285.70	DRG 821
	Skin reactions	$7,428.56	$5,571.42	$9,285.70	DRG 822
	Stomatitis	$8,101.08	$6,075.81	$10,126.35	DRG 823
SUMPRODUCT Costs	PEMB	$2,136.34	$1,201.69	$3,338.04	Estimated
	CIS-PEM	$5,098.61	$2,867.97	$7,966.58	Estimated
	DOC	$20,732.11	$11,661.81	$32,393.93	Estimated
PPS Costs	CIS-PEM to PEMB	$2,497.13	$1,872.85	$3,121.42	Estimated
	CIS-PEM to DOC	$553.68	$415.26	$692.10	Estimated
	PEMB to DOC	$582.21	$436.66	$727.77	Estimated
Mean Time in PROG (MO)	CIS-PEM to PROG	13.53	10.14	16.91	Estimated
	PEMB to PROG	12.88	9.66	16.09	Estimated

[i] Garrison LP, Carlson JJ, Preeti SB, et al. Private sector risk-sharing agreements in the United States: Trends, Barriers, and Prospects. *Am J Manag Care*. 2015; 21(9): 632-640
[ii] Garrison LP, Towse A, Briggs A, et al. Performance-based risk sharing arrangements-good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value in Health.* 2013; 16: 703-719
[iii] Amgen and Harvard Pilgrim agree to first cardiovascular outcomes-based refund contract for Repatha (evolocumab). (2017, May 2). Retrieved from https://www.amgen.com/media/news-releases/2017/05/amgen-and-harvard-pilgrim-agree-to-first-cardiovascular-outcomesbased-refund-contract-for-repatha-evolocumab/
[iv] Thomas K, Ornstein C. (2017, July 10). Considering the side effects of drugmakers' money-back guarantees. The New York Times. Retrieved from https://www.nytimes.com
[v] Santarpia M, Gonzalez-Cao M, Viteri S, et al. Programmed cell death ligand-1 pathway inhibition and predictive biomarkers: understanding transforming growth factor-beta role. *Transl Lung Cancer Res* 2015; 4(6): 728-742
[vi] Chae YK, Pan A, Davis AA, et al. Biomarkers for PD-1/PD-L1 blockade therapy in non-small cell lung cancer: is PD-L1 expression a good marker for patient selection? *Clinical Lung Cancer*. 2016; 17(5): 350-361
[vii] Weaver KE, Rowland JH, Bellizzi KM, et al. Forgoing medical care because of cost. *Cancer*. 2015; DOI: 10.1002/cncr.25209
[viii] Carlson JJ, Sullivan SD, Garrison LP, et al. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*. 2010; DOI: 10.1016/j.healthpol.2010.02.005
[ix] Fox J, Watrous M (2017, April 3). Overcoming challenges of outcomes-based contracting for pharmaceuticals: early lessons learned. *Health Affairs Blog*. Retrieved from https://www.healthaffairs.org/blog
[x] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-Positive non-small-cell lung cancer. *The New England Journal of Medicine.* 2016; DOI: 10.1056/NEJMoa1606774
[xi] Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-Effectiveness Analyses: Second Panel on Cost Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093-1103
[xii] Streeter SB, Schwartzberg L, Husain N, et al. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *Journal of Oncology Practice*. 2010; 7(3S): 46-51
[xiii] Goldman DP, Jena AB, Lakdawalla DN, et al. The value of specialty oncology drugs. *Health Services Research.* 2010; 45(1): 115-132
[xiv] Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Medical Research Methodology*. 2011; 11: 139
[xv] Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer. *J Thorac Oncol.* 2013; 8: 997-1003
[xvi] Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health and Quality of Life Outcomes*. 2008; 6:84
[xvii] U.S. Congressional Budget Office (2005) Prices for Brand Name Drugs Under Selected Federal Programs (Washington, D.C., Congress of the United States)
[xviii] U.S. Congressional Budget Office (2005) Prices for Brand Name Drugs Under Selected Federal Programs (Washington, D.C., Congress of the United States)
[xix] Graham J, Earnshaw S, Lim J, et al. Cost-effectiveness of afatinib versus erlotinib in the first-line treatment of patients with metastatic non-small cell lung cancer with EGFR exon 19 deletion mutations. *Journal of Clinical Pathways.* 2016; 2(4): 31-39
[xx] U.S. Department of Health & Human Services. Examination of clinical trial costs and barriers for drug development. HHSP23337007T. https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development. Published July 25, 2014. Accessed March 3, 2017
[xxi] Cetin K, Ettinger DS, Hei Y, et al. Survival by histologic subtype in stage IV non-small cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clinical Epidemiology*. 2011; 3: 139-148
[xxii] Hellman MD, Ma J, Garon EB, et al. Estimating long-term survival of PD-L1 expressing, previously treated, non-small cell lung cancer patients who received pembrolizumab in KEYNOTE-001 and -010. Poster session presented at the ASCO-SITC Clinical Immuno-Oncology Symposium, Orlando, FL