AN ECONOMIC ANALYSIS OF THE ADDITION OF BEVACIZUMAB TO STANDARD CHEMOTHERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Abstract

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Objectives

A recent Phase III trial, MAPS (Mesothelioma Avastin Cisplatin Pemetrexed Study), investigated the addition of bevacizumab to cisplatin plus pemetrexed (PCB) as compared to pemetrexed plus cisplatin (PC) alone in malignant pleural mesothelioma (MPM) patients. The trial results indicate that patients taking bevacizumab had improved progression free survival (PFS) and overall survival (OS) compared with the control group. Our objective was to evaluate the cost-effectiveness of adding bevacizumab to cisplatin and pemetrexed from a Medicare perspective.

Methods

A partition-survival model with 3 health states: Pre-progressive, Progressive and Death, was developed to perform the cost-utility analysis. Survival data were derived from the MAPS study. We used the method described by Hoyle & Henley to derive appropriate parametric survival functions for the PFS and OS curves, using Kaplan-Meier curves extrapolated to lifetime as the base case. The treatment of adverse events (grade 3+ and with frequencies of at least 5% in one of the arms) were included in the evaluation. Utility data were derived from the literature on patient quality of life in non-small cell lung cancer. Costs included treatment, administration, adverse events, and supportive care and were calculated based on average sales price, diagnosis-related group payments, current procedural terminology codes and publications in the literature. The model used monthly cycles, a 3% discount rate and costs were reported in 2015 US$. One-way, scenarios and probabilistic sensitivity analyses (PSA) to evaluate the impact of parameter uncertainty were undertaken. A value of information analysis was performed to determine the value of perfect information and value of perfect parameter information.

Results

Compared to standard chemotherapy, patients receiving bevacizumab plus pemetrexed and cisplatin had 0.285 more life years (LYs), 0.20 more quality adjusted life years (QALYs), and an additional cost of

$146,851 per individual. The incremental cost effectiveness ratios (ICER) were estimated to be $515,850 per life year gained and $726,110 per QALY gained. A one-way sensitivity analysis showed that the parameters with the most impact on the results were the survival distributions, pre-progressive utility scores and bevacizumab drug cost. The PSA indicated that PCB has a 0% probability of being cost effective at a Willingness-To-Pay threshold of $ 150,000 per QALY gained.

Conclusion

The addition of bevacizumab to the current standard of care may not be considered cost-effective from a Medicare perspective according to commonly used willingness-to-pay thresholds.

Introduction

Malignant pleural mesothelioma (MPM) is a rare disease, characterized by aggressive tumors that develop on the pleura. With approximately 3300 cases per year in the United States, MPM is estimated to be the most common type of mesothelioma, accounting for 80% of annual incidence of mesothelioma [1]. The standard of care for mesothelioma has not changed for a decade and the prognosis for patients remains poor. However, new drugs are being developed and evaluated for use in MPM, which may improve outcomes for this difficult- to-treat cancer.

In the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), a phase 3, open-label, multicenter study, patients were randomized (1:1) to receive pemetrexed and cisplatin (PC) (control arm: n = 225) or triplet therapy with bevacizumab, pemetrexed, and cisplatin (PCB) (experimental arm: n = 223). Eligible patients were diagnosed with advanced (stage III/IV) disease, demonstrated good performance status from 0 to 2, had no cardiovascular comorbidities and were chemotherapy naive. No crossover after disease progression was allowed in the study. The results, presented by the French Cooperative Thoracic Intergroup (IFCT) in 2015, demonstrated that the addition of bevacizumab to standard chemotherapy led to improvement in patient's overall survival (hazard ratio 0·77 [0·62–0·95]; p=0·0167) [2]. Bevacizumab toxicities were similar to those seen in other disease settings where bevacizumab has been used, with the most common being hypertension and arterial and venous thrombo-embolic events. Quality of life was similar between the two treatment groups [3].

Following this evidence, the National Comprehensive Cancer Network (NCCN), an alliance of the world's leading cancer centers, issued new guidelines recommending this new regimen as a possible first-line chemotherapy combination for MPM patients eligible for bevacizumab not amenable to curative surgery [4]. The MAPS trial demonstrated that the addition of bevacizumab to a standard chemotherapy doublet is likely to improve outcomes for MPM patients, however the impact on medical costs and the value of

this intervention have yet to be assessed. Our objective was to evaluate the cost-effectiveness of adding bevacizumab to cisplatin and pemetrexed from a Medicare perspective.

Methods

Model structure

A partition-survival model with 3 health states: Pre-progressive, Progressive and Death (Figure 1), was developed to perform a cost-utility analysis. The model was constructed in Microsoft Excel v16. The interventions considered were bevacizumab plus pemetrexed plus cisplatin (PCB), versus pemetrexed plus cisplatin (PC) in a cohort of chemotherapy-naive patients diagnosed with malignant pleural mesothelioma (MPM) similar to patients in the MAPS clinical trial.

Patients received 500 mg/m² of intravenous pemetrexed with 75 mg/m2 of cisplatin every 21 days for six cycles or the same regimen with the addition of 15 mg/kg of intravenous bevacizumab. After six cycles, patients undergoing PCB therapy continued to receive bevacizumab alone until disease progression, while patients in the control arm underwent a surveillance strategy. After progression, we assumed patients were managed similarly to lung cancer patients in their last year of life in terms of both utilities and costs.

Clinical and Cost data

Clinical data, utilities, and costs were derived from publicly available literature, clinical trials and center for Medicare and Medicaid Services data (Table 1).

Survival data

We applied the method developed by Hoyle and Henley et al. to derive parametric survival functions from the survival data. [5] Specifically, we used the DigitizeIt® digitizer software v2.1.4 to extract data values from the MAPS progression-free survival (PFS) and overall survival (OS) Kaplan-Meyer curves. The statistical distributions generated using the Hoyle and Henley method include the Weibull, exponential, log-normal and log-logistic distributions [6] (Table 2). We selected the Log-logistic distribution based on the Akaike's Information Criteria, visual fit to the Kaplan-Meier data, and clinical plausibility [7]. (Figure 2).

Utility data

There were no utility estimates available for MPM. We therefore used data from lung cancer, a similar pulmonary disease with similar survival. This approach has been used in previous cost utility analyses in MPM [8, 9]. Specifically, we used data from the ACTION study which estimated EQ-5D utilities from 967 patients with non-small cell lung cancer (NSCLC) receiving chemotherapy. This study estimated a utility 0.70 until progression, which drops by 0.19 after progression. [10, 11]

Adverse events

To estimate the costs of adverse events, we included events of grade 3/ 4, defined as serious adverse events, and representing more than 5% on at least one of the arms. The serious adverse events reported statistically significantly higher with PCB therapy were hypertension (23% vs 0%) and arterial and venous thromboembolic events (5.8% vs 0.9%). Severe anemia was described to be statistically significantly higher in the PC therapy (7.2% vs 13.4%). The serious adverse events nausea or vomiting (8.1% vs 8%), asthenia or fatigue (13.5% vs 12.5%), neutropenia (44.1% vs 44.6%) and thrombocytopenia (9.9% vs

9.4%) were also considered in the model even if no significance were reported between the arms (Table 3).

Resources use and cost

The unit costs for the drugs in the model were based on US average sale price, obtained from the Medicare part B list [12]. The cost calculation took into account the dose and dose intensity for drugs in both study arms, assuming no vial sharing between patients [2]. Patient height and weight reported from the MAPS study were used to calculate the average drug dose per administration. These data coupled with the dosing schedule and the drug unit costs were used to estimate a per cycle drug cost for each intervention.

Drugs administration costs were calculated using estimates of infusion time based on prescribing information and data from the CMS physician fee schedule [12].

Medical procedure fees and drug cost were attributed based on their CPT code from the 2015 American Medical Association. Monitoring costs were calculated assuming one outpatient visit for every patient each month and a CT scan every other month.

Adverse event costs were estimated based on 2015 Center for Medicaid and Medicare Services (CMS) DRG Payments, assuming the grade 3/4 adverse events result in a hospitalization.

We were not able to find published evidence on cost of care for progressive MPM patients, and survival data from the MAPS study demonstrate that patients will die quickly after progression. We therefore assumed that the cost of care post progression was similar to that of lung cancer patients in the last year of life. We estimated the per cycle cost using a study with data on the cost of lung cancer care in the United States, adjusted by the gender ratio of patients enrolled in the MAPS [13].

Analysis

The model calculated the per-regimen and incremental life-years, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratio (ICER), defined as the ratio of the difference in cost and the difference in effects (cost per QALY). The base case model adopted the Medicare perspective and lifetime horizon. Costs and QALYs were discounted at an annual rate of 3%. All costs are presented in 2015 US $.

Sensitivity Analysis

We performed a one-way sensitivity analysis to assess the effect of different parameter estimates on the incremental cost-effectiveness ratio. Each input parameter was varied separately to examine the impact of its uncertainty on the ICER. When available from the literature, we used the bounds of the 95% confidence intervals (CIs) as high and low estimates in the sensitivity analysis. When the bounds of the 95% CIs were unavailable, we used a range of ±10% for probabilities and for costs.

We also performed a probabilistic sensitivity analysis with 10,000 Monte Carlo simulations with random draws from parameter distributions using the sensitivity ranges. Cost inputs were assumed to follow the normal distribution; utilities and frequencies were assumed to follow the beta distribution; and all other input types were assumed to follow the normal distribution. For survival data, we extracted information about uncertainty and correlation between the statistical parameters with a covariance matrix, also called Cholesky matrix (Table 4), which allows us to generate probabilistic estimates.

We performed a scenario analysis with different statistical distributions for survival data. As the base case scenario was built using the log logistic function, we also explored alternate survival functions, Kaplan Meyer with a log logistic tail, Weibull, and Kaplan Meyer with a Weibull tail, in scenario analyses.

We also performed a scenario analysis to measure the impact of potential bevacizumab price discounts on the ICER that might be available with the introduction of biosimilars, expected in 2019. We evaluated discounts ranging from 10 to 50 percent of the bevacizumab injection cost, based on previous biosimilar price discounts [14]. A threshold analysis was performed to estimate the price reduction needed to reach $150,000/QALY and $300,000/QALY willingness-to-pay thresholds.

Value of Information Analysis

We performed a value of information analysis following commonly accepted methods [15]. The affected population used to calculate the population expected value of perfect information (EVPI) was estimated from a study of US mesothelioma patterns from 1973 to 2002 [16]. The addition of bevacizumab to standard PC was expected to be an option for 20% of MPM patients in year 1, 40% in year 2, and increasing each year until the target of 80% of first line therapy in MPM patients in year 4 and would remain at 80% for future years. An expected value of perfect parameter information (EVPPI) analysis was conducted to estimate the value of reducing individual parameter uncertainty.

Results

Base Case results

In the base case, the use of PCB on average resulted in 0.28 more life years lived (2.00 versus 1.72 years), 0.20 more QALYs (1.24 versus 1.04 QALYs), and an additional cost of $146,851 ($272,662 versus $125,812) compared to PC (Table 5). The corresponding ICER's were $515,850/LY and $726,110/QALY, respectively.

Sensitivity analysis results

In one-way sensitivity analysis, the survival distributions, pre-progressive utility score and bevacizumab drug cost had the largest impact on the ICER (See figure 3). The results of the probabilistic sensitivity analysis are provided in Table 6 and via a scatterplot (Figure 4) and a cost effectiveness acceptability curve (CEAC) (Figure 5). The CEAC demonstrates that the BPC regimen has a 0% probability of being cost-effective at a willingness to pay value of $150,000 per QALY.

In the scenario using Kaplan-Meyer curve from the trials with a log-logistic tail, we obtained an ICER of $807,963/QALY. In the scenario using the Weibull distribution, the ICER was $727,947/QALY. In the scenario using Kaplan-Meyer curve from the trials with a Weibull tail, we obtain an ICER of $807,963/QALY.

With a 10% discount on bevacizumab drug cost, the ICER was $464,855/LY and $654,329/QALY. At a 50% discount, the ICER is estimated to be $260,874/LY and $367,206/QALY. We observe a linear relation between percentage price discount and ICER (Figure 6). To reach an ICER below a $300k threshold, the discount on bevacizumab needs to be at 60 % ($295,425/QALY). To meet a $150k threshold, the discount will need to be 81% ($144,686).

VOI analysis

The values of reducing uncertainty in all model parameters were $0 per person assuming a US population willingness-to-pay of $150,000/QALY and $300,000/QALY. Consequently, the expected value of perfect information (EVPI) and the expected value of perfect parameter information (EVPPI) were $0. This result is not surprising because PCB was found not to be cost-effective and at all ranges of uncertainty over a $300,000/QALY willingness-to-pay threshold. There is no predicted economic value in reducing uncertainty of the efficacy parameter because it is not predicted to change the decision if based on cost-effectiveness alone.

Discussion

The demonstration of improved overall survival for the combination of bevacizumab, pemetrexed and cisplatin led the National Comprehensive Cancer Network (NCCN), to issue new guidelines recommending this regimen as a possible first-line chemotherapy combination. We evaluated the clinical and economic impact of BPC vs. PC and found that the addition of bevacizumab is a more effective and costlier strategy compared to the combination of pemetrexed and cisplatin alone. The projected ICER of $726,110/QALY is well above commonly used ranges for being called cost-effective from a Medicare or a US payer perspective [17].

Examining the median PFS and OS furnished by the French Cooperative Thoracic Intergroup at ASCO 2015 meeting, we can infer validity of our model based on the similar survival difference between the two groups. In the MAPS study, the improvement observed in median OS was 2.7 months between PCB (median 18·8 months [95% CI 15·9–22·6]) and PC (16·1 months [14·0–17·9]) groups. This value is consistent with the 3.4 incremental life-months (0.28 Lys) obtained in the model. The observed increase of 0.7 months in survival may be due to mean versus median estimates in this positively skewed distribution.

The high ICER is driven by the high cost of treatment. However, commonly accepted cost-effectiveness thresholds may be less relevant to decision making in diseases with unsatisfactory available treatment options such as mesothelioma. Whether the benefits are worth the costs depends on the stakeholder we examine, and patients with advanced cancer may perceive greater value than healthy patients, policymakers, insurers, and physicians [18]. Although MPM is a rare disease, bevacizumab has not received an orphan drug designation for this indication, contrary to renal cell carcinoma, glioblastoma, epithelial ovarian, fallopian tube, or primary peritoneal cancer [19]. Therefore, the orphan drug status should not justify an increase in the willingness-to-pay threshold in this indication.

The rationale for a scenario discounting the price of bevacizumab is due to its patent, which is set to expire in the US in July 2019 [20]. This will likely to result in market entry of biosimilars. Bevacizumab is given to pre-progressive patients and their proportion in our cohort after 3 years of treatment is estimated to be less than 7%, therefore this would not have a substantial impact on the value for the current patient population. However, the threshold analysis indicated that there would need to be a discount of 81% off the current average sales price (ASP), for biosimilars to meet a 150,000/QALY threshold. Given that biosimilars to date have not entered the market with that level of price reduction, it is unlikely that biosimilars will be cost-effective as well.

There were no other known US cost effectiveness analyses in mesothelioma performed at the time we made the economic analysis. The only available cost effectiveness analyses were performed in the UK setting and not considered comparable in terms of the ICER or funding implications [8, 9]

There are a few limitations in our work which warrant discussion. The utility scores are not specific to patients with stable or progressive malignant pleural mesothelioma, but correspond to a condition we assumed to be comparable in terms of utility. The rationale for the choice of these utility value is the validation of the NICE agency of these measures in others economic evaluations in MPM [8, 9].

Cost of care for post-progression patients with MPM was assumed to be the same as those lung cancer patients in their last year of life. This can be an underestimate or an overestimate of the real cost. However, one-way sensitivity analysis shows that the impact of this parameter is very low on the ICER.

Finally, we assumed that both the PCB and PC patients received the same average cost of care per month after progression. However this might not reflect the reality, because the treatment regimens and available therapeutic options could vary after receiving different first line treatments. However, this input was not a major driver of model results.

In conclusion, although adding bevacizumab to current standard of care in first line therapy corresponds to an increase in patient survival, the minimal improvement does not appear to be cost-effective. The possible entry of biosimilars, in parallel to the development of other therapeutic agents, is likely to modify the treatment patterns of malignant pleural mesothelioma in the upcoming years.

Table 1: Probability of clinical events and costs

Base Case Input	Mean	Standard Error	Distribution	Reference
Age of onset (years)	65	7.2	Normal	[2]
Cycle time (month)	1	N/A	N/A	N/A
Time Horizon (years)	100	N/A	N/A	N/A
Sex ratio (Male)	0.754	0.0754	Normal	[2]
Patient Weight (kg)	72.8	7.28	Normal	[2]
Patient Height (m)	170	17	Normal	[2]
Discount rate	0.03	N/A	N/A	N/A
Distribution parameters				
PCB OS lambda	0.005	We used cholesky covariance matrices to account for the uncertainty around these log-logistic distribution parameters		[2,5]
PCB OS gamma	1.79			[2,5]
PCB PFS lambda	0.008			[2,5]
PCB PFS gamma	2.10			[2,5]
PC OS lambda	0.004			[2,5]
PC OS gamma	2.04			[2,5]
PC PFS lambda	0.007			[2,5]
PC PFS gamma	2.50			[2,5]
Utilities				
Pre-progressive patient utility	0.7	0.036	Beta	[9]
Progressive patient utility	0.51	0.026	Beta	[9]
Dead	0	0	Beta	N/A
Costs ($)				
Bevacizumab injection	68	7	Normal	[12]
Pemetrexed injection	61	6	Normal	
Cisplatin injection	2.0	0.2	Normal	
Management of progressive patients	7767	777	Normal	[13]
Management of Nausea / Vomiting AE (Grade 3+)	3861	386	Normal	[12]
Management of Asthenia / Fatigue AE (Grade 3+)	4188	419	Normal	[12]
Management of Hypertension AE (Grade 3+)	3683	368	Normal	[12]
Management of Neutropenia AE (Grade 3+)	9710	971	Normal	[12]
Management of Thrombocytopenia AE (Grade 3+)	9710	971	Normal	[12]
Management of Anemia AE (Grade 3+)	7534	753	Normal	[12]
Management of arterial and venous thrombo-embolic AE (Grade 3+)	5679	568	Normal	[12]

One hour chemotherapy infusion	136	14	Normal	[12]
One hour physician visit	146	15	Normal	[12]
CT scan for Mesothelioma patient	180	18	Normal	[12]
Frequencies				
Bevacizumab Dose Intensity	0.986	0.05031	Beta	[2]
Pemetrexed intensity dose (PCB arm)	0.956	0.04878	Beta	[2]
Pemetrexed intensity dose (PC arm)	0.97	0.04949	Beta	[2]
Cisplatin intensity dose (PCB arm)	0.918	0.04684	Beta	[2]
Cisplatin intensity dose (PC arm)	0.932	0.04755	Beta	[2]
Nausea / Vomiting AE (PCB arm)	0.081	0.00413	Beta	[2]
Nausea / Vomiting AE (PC arm)	0.08	0.00408	Beta	[2]
Asthenia / Fatigue AE (PCB arm)	0.135	0.00689	Beta	[2]
Asthenia / Fatigue AE (PC arm)	0.125	0.00638	Beta	[2]
Hypertension AE (PCB arm)	0.23	0.01173	Beta	[2]
Hypertension AE (PC arm)	0	0	Beta	[2]
A&V thrombo-embolic AE (PCB arm)	0.058	0.00296	Beta	[2]
A&V thrombo-embolic AE (PC arm)	0.009	0.00046	Beta	[2]
Neutropenia freq AE (PCB arm)	0.441	0.0225	Beta	[2]
Neutropenia AE (PC arm)	0.446	0.02276	Beta	[2]
Thrombocytopenia AE (PCB arm)	0.099	0.00505	Beta	[2]
Thrombocytopenia AE (PC arm)	0.094	0.0048	Beta	[2]
Anemia AE (PCB arm)	0.072	0.00367	Beta	[2]
Anemia AE (PC arm)	0.134	0.00684	Beta	[2]

Table 2: Distribution parameters for each outcome curves of the MAPS

DATA	ARM	STATISTIC	AIC	INTERCEPT	LOG SCALE	SE intercept	SE log scale	LAMBDA	GAMMA	Mean (Weibull)
OS	PCB	Exponential	1140.29	3.304	N/A	0.077	N/A	0.037	N/A	N/A
		Weibull	1131.88	3.301	-0.216	0.062	0.063	0.017	1.242	25.328
		Log-normal	1128.52	2.918	-0.017	0.069	0.060	0.051	1.018	18.382
		Log-logistic	1121.93	2.931	-0.582	0.066	0.067	0.005	1.79	16.668
	PC	Exponential	1166.49	3.115	N/A	0.074	N/A	0.044	N/A	N/A
		Weibull	1150.17	3.140	-0.265	0.057	0.058	0.017	1.304	21.332
		Log-normal	1132.63	2.765	-0.155	0.059	0.056	0.040	1.168	15.041
		Log-logistic	1128.30	2.765	-0.715	0.058	0.063	0.003	2.044	14.063
PFS	PCB	Exponential	1066.07	2.629	N/A	0.071	N/A	0.072	N/A	N/A
		Weibull	1056.82	2.669	-0.200	0.060	0.056	0.038	1.221	13.511
		Log-normal	1025.19	2.285	-0.176	0.058	0.055	0.066	1.192	9.257
		Log-logistic	1017.57	2.268	-0.743	0.055	0.063	0.008	2.102	8.555
	PC	Exponential	1021.91	2.221	N/A	0.067	N/A	0.108	N/A	N/A
		Weibull	980.17	2.312	-0.393	0.048	0.053	0.0325	1.481	9.129
		Log-normal	972.36	1.986	-0.348	0.048	0.053	0.060	1.416	6.628
		Log-logistic	966.79	2.003	-0.916	0.046	0.061	0.007	2.499	6.573

Table 3: Adverse events frequencies included in the analysis

Grade 3+ adverse event	PCB therapy (%)	PC therapy (%)
hypertension	23 *	0
arterial and venous thromboembolic events	5.8 *	0.9
Anemia	7.2	13.4 *
nausea or vomiting	8.1	8.0
asthenia or fatigue	13.5	12.5
neutropenia	44.1	44.6
thrombocytopenia	9.9	9.4

* Difference between arm significantly greater than zero based on MAPS publication

Table 4: Cholesky matrix of the Log-logistic distribution for each outcome curves of the MAPS

OS	**PCB**		(Intercept)	Log(scale)
		(Intercept)	0.06575043	0.00000000
		Log(scale)	0.00521526	0.06692659
	PC		(Intercept)	Log(scale)
		(Intercept)	0.05768582	0.00000000
		Log(scale)	0.00354109	0.06333500
PFS	**PCB**		(Intercept)	Log(scale)
		(Intercept)	0.05548108	0.00000000
		Log(scale)	0.00153217	0.06297922
	PC		(Intercept)	Log(scale)
		(Intercept)	0.04607153	0.00000000
		Log(scale)	-0.00227344	0.06077220

Table 5: Base case incremental cost, LY and QALYs

	Pre-progressive	Progressive	Total	LY	QALYs
PC	$ 42,859	$ 82,953	$ 125,812	1.72	1.04
PCB	$ 191,166	$ 81,497	$ 272,662	2.01	1.24
Incremental	$ 148,307	$ - 1,457	$ 146,851	0.28	0.20
ICER			**$ 515,850 / LY**	**$ 726,110 / QALY**	

Table 6: Probabilistic sensitivity results with 10,000 Monte Carlo simulations

	PC		PCB		Incremental	
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
Mean	1.04	125,868	1.24	272,657	0.20	146,790
SD	0.06	12,422	0.07	19,313	0.07	19,486
Lower 95%	0.92	101,521	1.11	234,804	0.07	108,597
Upper 95%	1.15	150,215	1.37	310,510	0.33	184,983

Figure 1: Partition-survival model with 3 health states

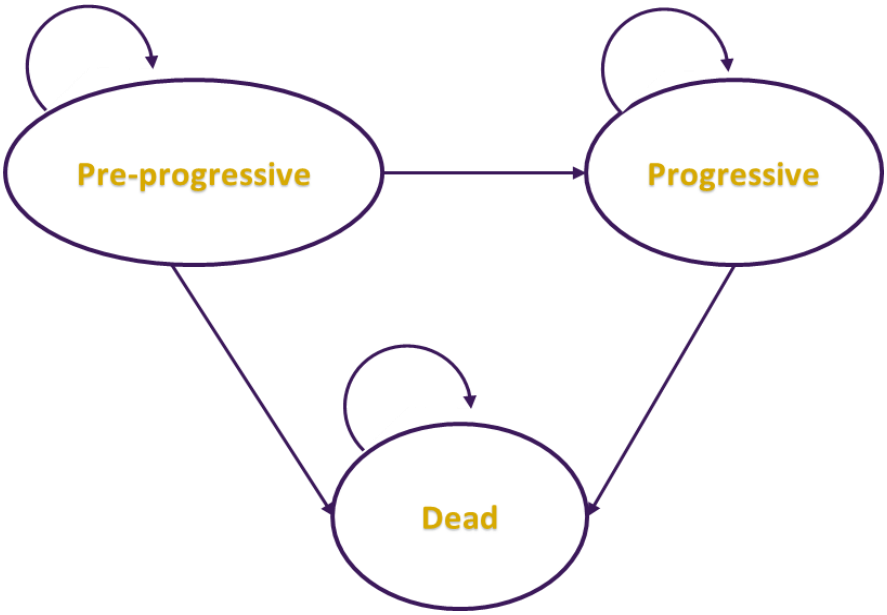


Figure 2: Visual representation of the distribution for each outcome curves of the MAPS

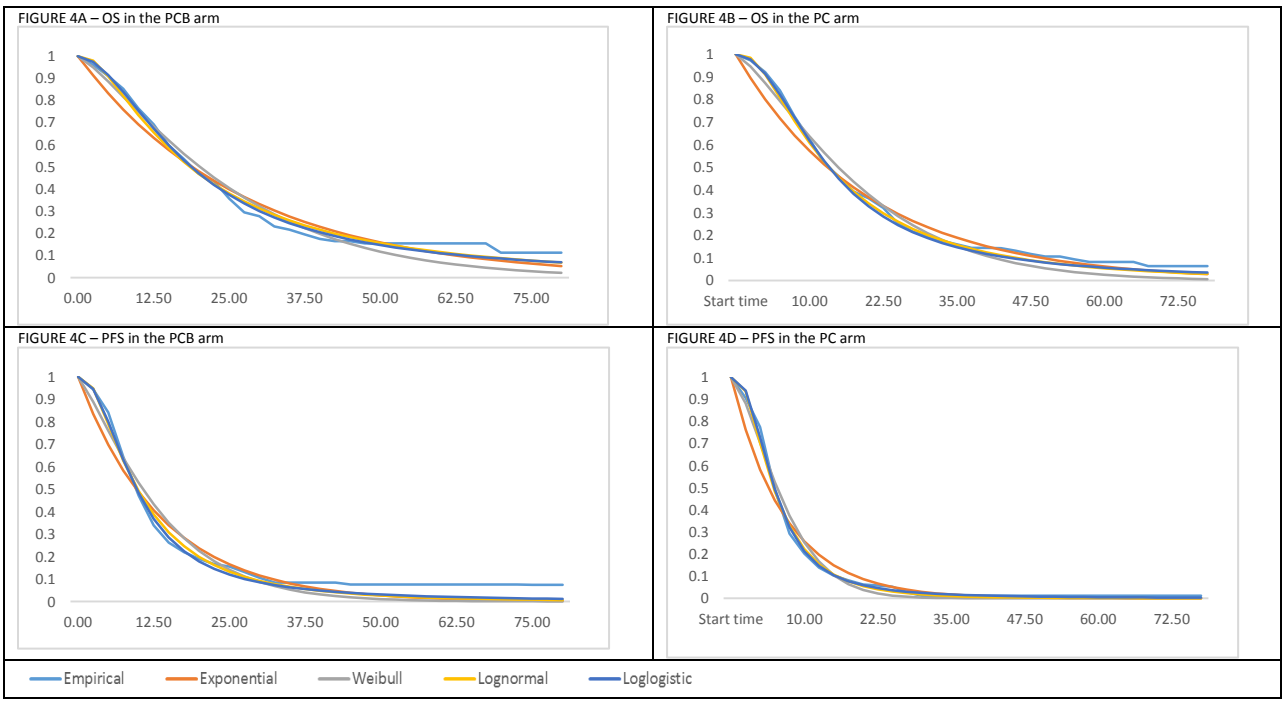


Figure 3: One-way Sensitivity Analysis Tornado Diagram of parameter ranges influencing ICER

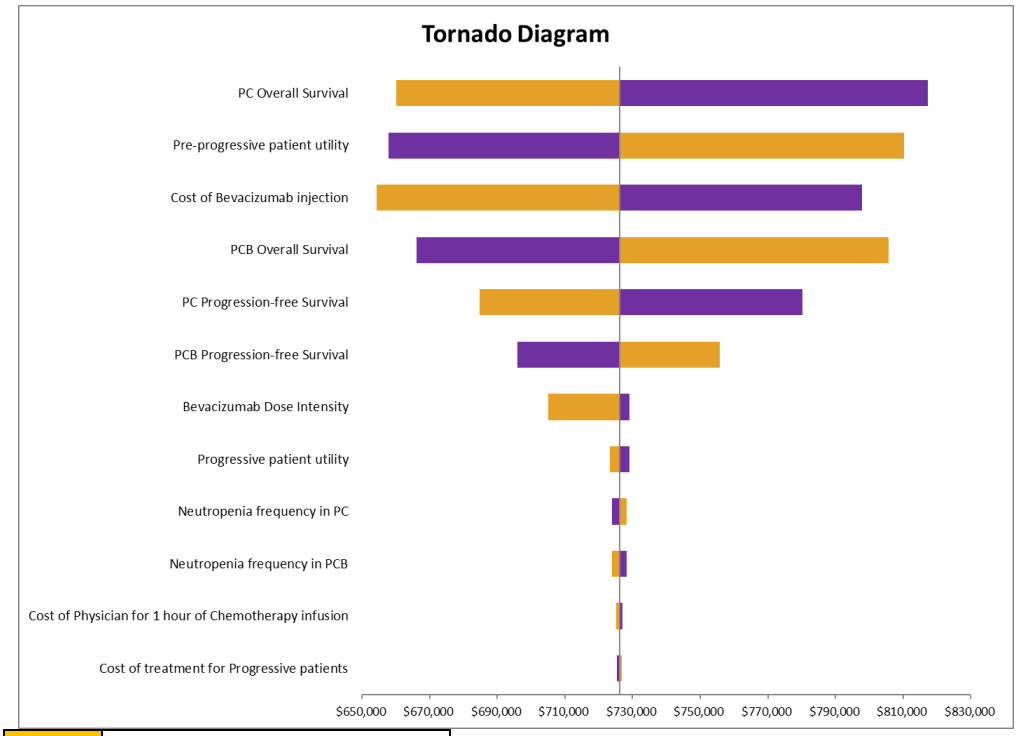


Figure 4: Incremental cost effectiveness plane plotting incremental cost against incremental QALYS. Each point represents the ICER for one iteration (10,000 plotted)

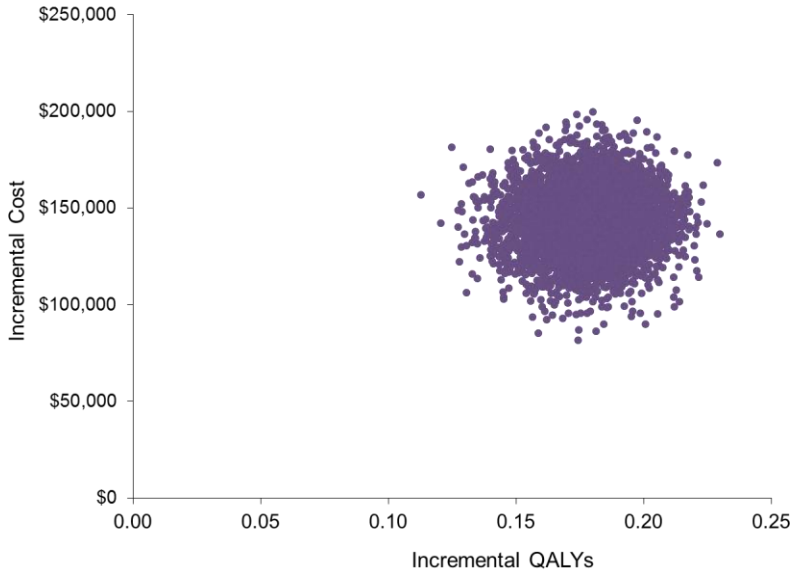


Figure 5: Cost effectiveness acceptability curve showing percentage of 10,000 iterations, where each strategy is cost effective over a range of Willingness-To-Pay thresholds.

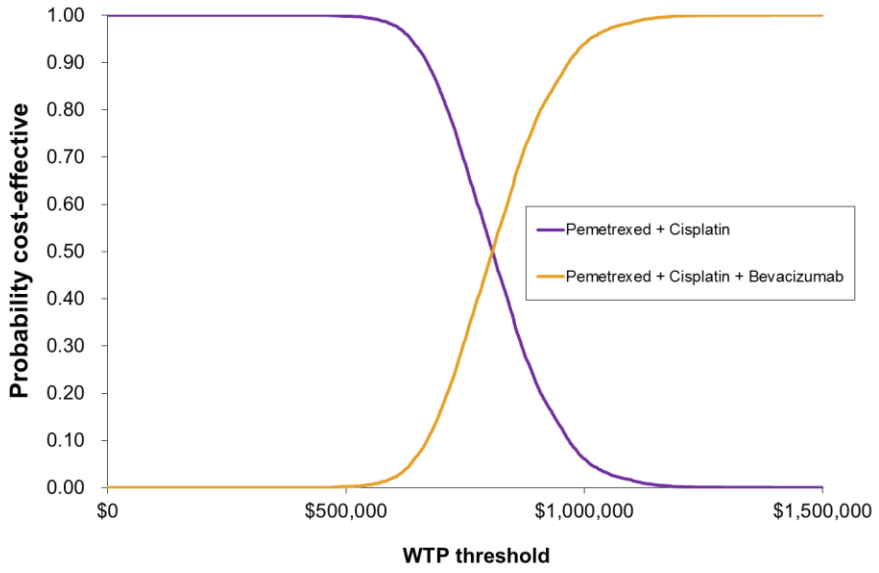
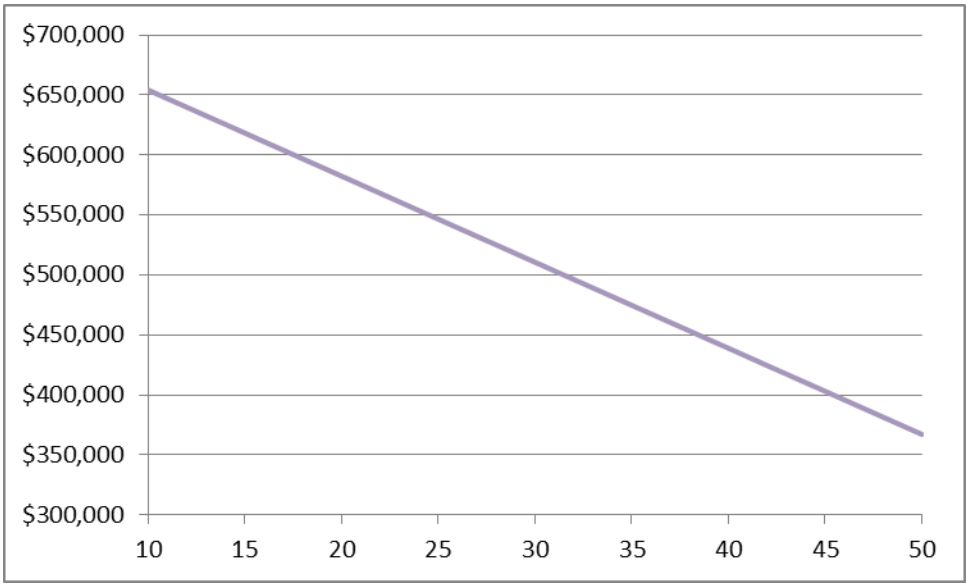


Figure 6: Effect of bevacizumab price discount on the ICER ($/QALY)



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