The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study

Hannah E. Carter[1], *Diana Zannino*[1], *R. John Simes*[1], *Deborah J. Schofield*[1], *Kirsten Howard*[2], *John R. Zalcberg*[3], *Timothy J. Price*[4], *Niall C. Tebbutt*[5]

1. NHMRC Clinical Trials Centre, University of Sydney

2. School of Public Health, University of Sydney

3. Peter MacCallum Cancer Centre, and Department of Medicine, University of Melbourne

4. The Queen Elizabeth Hospital, Woodville, and The University of Adelaide

5. Austin Health, Heidelberg

Corresponding author: Hannah Carter, NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, NSW 2050, Australia.
hannah.verry@ctc.usyd.edu.au

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Running head: Cost effectiveness of bevacizumab plus capecitabine in colorectal cancer

Abstract

Purpose

The purpose of this study was to evaluate the cost effectiveness of adding bevacizumab to capecitabine monotherapy in patients with metastatic colorectal cancer.

Methods

Individual patient level data on resource use and progression free survival were prospectively collected in the Phase III MAX trial. Resource use data were collected for the period between randomisation and disease progression, and unit costs were assigned from the perspective of the Australian health care funder. Effectiveness was measured in quality adjusted progression free survival years, with utility scores obtained from both the community valued EQ-5D questionnaire and the patient valued UBQ-C questionnaire. Progression free survival was used as a secondary effectiveness measure.

Results

The addition of bevacizumab to capecitabine monotherapy cost approximately $192,156 (95% confidence interval [CI], $135,619 to $326,894) per quality adjusted progression free survival year gained when using publicly listed pharmaceutical prices and utility values from the EQ-5D questionnaire. This decreased to $149,455 (95% CI, $100,356 to $245,910) when values from the UBQ-C questionnaire were applied. The incremental cost per progression free survival year was $145,059 (95% CI, $106,703 to $233,225).

Conclusions

Bevacizumab was not found to be cost effective at its listed price, based on results from the MAX trial.

Introduction

Colorectal cancer is the second most common cause of cancer death in Australia behind lung cancer, accounting for 2,856 deaths in 2010.[1,2] Although there have been advances in the treatment of metastatic colorectal cancer, most patients continue to have incurable disease. Accordingly there has been an imperative to develop and evaluate promising new treatments that may provide improved health outcomes over standard chemotherapy. The introduction of a new medical treatment for cancer is often costly and it is important to ensure that where public funds are limited, those treatments which represent the best value for money are identified.[3]

The MAX trial evaluated the effect of adding bevacizumab, with or without mitomycin C, to capecitabine as initial treatment for patients with metastatic colorectal cancer.[4] Consistent with the results of other randomised studies of bevacizumab in the 1st and 2nd line setting of advanced colorectal cancer,[5-7] the MAX study demonstrated an improvement in progression free survival (PFS), the trial's primary outcome. However, the treatment was not found to have a significant impact on the response rate (RR) or overall survival (OS).

Based on the clinical data, bevacizumab has been approved in Australia and globally for the treatment of advanced colorectal cancer.[8] However, there have been no prospective analyses of its cost-effectiveness. A number of small retrospective studies assessing the cost-effectiveness of bevacizumab in different treatment contexts have generally concluded that the treatment is not likely to be cost-effective.[9-12]

The aim of this study was to determine the cost effectiveness of adding bevacizumab to capecitabine monotherapy in patients with untreated metastatic colorectal cancer, using data from the prospective economic evaluation conducted alongside the MAX trial.

Methods

An economic evaluation from the perspective of the Australian health care funder was performed using individual patient level data from the previously reported MAX trial.[4]

Study parameters:

The MAX trial was an open label, multicentre, phase III randomised study sponsored by the Australasian Gastro-Intestinal Trials Group (AGITG), conducted at 43 institutions in Australia, New Zealand and the United Kingdom.

A total of 471 patients with previously untreated, unresectable metastatic colorectal cancer were randomly assigned to three groups: capecitabine; capecitabine plus bevacizumab; or capecitabine, bevacizumab and mitomycin C. Treatment was planned to continue until confirmed disease progression. Capecitabine plus bevacizumab, with or without mitomycin C, was compared with capecitabine alone for progression free survival after a median follow up of 31 months.

Economic methods:

As the MAX trial found no significant treatment difference with the addition of mitomycin C to bevacizumab and capecitabine, the cost of mitomycin was excluded from this study and the primary analysis focused on the cost effectiveness of bevacizumab in addition to capecitabine compared with capecitabine alone. To maximise the available data for this study, the two bevacizumab arms of the trial were combined and are henceforth referred to as capecitabine plus bevacizumab.

The primary outcome measure used in this study was quality adjusted progression free survival (QAPFS); with progression free survival (PFS) also reported. We used a similar approach to Cohn et al by using QAPFS time in place of the traditional quality

adjusted life year (QALY) as the measure of effectiveness in our analysis, as the MAX trial was not powered to assess effects on overall survival and estimates of this outcome were unreliable.[13] We acknowledge that the use of PFS limits our ability to draw reasonable inferences regarding the incremental cost per QALY; however the inclusion of overall survival in a sensitivity analysis based on a set of plausible assumptions was intended to address this limitation. ~~PFS was the primary endpoint of the MAX trial.[13] Further, the MAX trial was not powered to reliably assess the effects of treatment on overall survival.~~

The time horizon of the analysis was the duration of the clinical trial, truncated at 18 months, as more than 95% of patients had experienced the primary outcome (progression) by the end of the data collection period. Due to the relatively short time frame of the analysis, discounting of costs and health outcomes was not necessary.

Patients:

The cost effectiveness analysis included data from all patients who had completed a baseline and at least one on-study utility assessment. This resulted in 401 patients being included in the EuroQoL-5D (EQ-5D) analysis and 386 patients included in the Utility Based Quality of Life Questionnaire–Cancer (UBQ-C) analysis. Data was analysed on an intention-to-treat basis. There were 27 patients that did not complete any utility assessments (mostly due to inadequate English comprehension) who were excluded from the cost-effectiveness analysis. The impact of imputing missing utility values for the additional 42 patients that had completed an inadequate number of utility questionnaires was considered in a sensitivity analysis.

Resource usage and costs:

Resource use was derived from individual patient data recorded in the MAX trial and costs are presented in 2011 Australian dollars. The specific resource use categories and sources are outlined in Table 1. Broadly, costs were obtained from standard Australian sources: the Pharmaceutical Benefits Schedule for drug costs[8] and the Medicare Benefits Schedule[14] for outpatient health services. Details of all hospital admissions throughout the trial were collected and costed based on Version 5.1 of the Australian Refined-Diagnosis Related Group (AR-DRG) cost weights[15] using 3M Core Grouping Software.

Both chemotherapy regimens were micro-costed using individual patient data and accounting for the total number of cycles required and the drug dosage per cycle. Because of the varying dosage quantities available for purchase, any drug wastage costs were negligible. The cost of administering intravenous chemotherapy in an outpatient clinic was also included. Routine follow up evaluations during treatment were costed per protocol until progression for each patient, which was assumed to be consistent with the level of resource use in standard practice.

Unit costs were multiplied by resources used on a per patient basis. All costs were censored after disease progression.

Utility scores and outcome measurement:

The self reported EQ5D and UBQ-C questionnaires were prospectively collected to assess preference based measures of health status in the form of a utility score. Utility scores range from 0 (death) to 1 (full health). Responses from the EQ5D questionnaire produce utility values based on community preferences for health states,[16] while utilities derived from the UBQ-C questionnaire are based on patient preferences.[17]

Both instruments were completed by patients at baseline, every 3 weeks for the first 12 weeks, and then every 6 weeks until disease progression occurred. A median of 6 of each of the questionnaires were completed per patient up to 18 months, with average completion rates above 87% for both questionnaires.

A QAPFS time over 18 months was calculated for each patient based on the methods described by Glasziou, Simes and Gelber[18] and used in a similar study by Cohn et al.[13] For patients with missing utility scores, the last utility observation was carried forward.

Sensitivity analysis:

Bootstrap sampling with 1000 replications of individual cost and effect pairs was used to determine confidence intervals and the impact of uncertainty on the incremental cost-effectiveness ratios.

Results

Base case:

Table 2 displays the disaggregated cost components as measured in the study. Patients treated with capecitabine plus bevacizumab accumulated an average cost of $44,169 per patient from the beginning of treatment to time of progression, compared with an average of $14,577 for patients treated with capecitabine alone. The price of bevacizumab as listed in the Pharamceutical Benefits Schedule (PBS) was the main cost driver, comprising over 90% of the total cost difference between the two treatment arms. The cost of routine follow up and hospitalisations were also lower in the capecitabine alone arm.

An analysis of all hospitalisation episodes over the course of the trial (table 3) revealed that patients receiving capecitabine plus bevacizumab had a higher overall rate of

admissions than those receiving capecitabine alone. Patients in the bevacizumab arms had a lower proportion admissions directly related to their cancer, but a higher proportion related to treatment toxicity. The cost per hospital admission was approximately $2,646 higher in patients receiving capecitabine alone. However, the mean cost of hospitalisations per patient over the trial period was similar in both treatment groups.

Table 4 displays the estimated utility scores for each arm, calculated using both the community valued EQ-5D questionnaire and the patient rated UBQ-C questionnaire. As expected, in both treatment groups, health states valued by patients were higher than those valued by the community. Utility scores were estimated to be marginally higher for the capecitabine alone group in both questionnaires.

Results of the cost effectiveness analysis are displayed in Table 5. Patients receiving capecitabine plus bevacizumab gained an additional 0.204 years (2.44 months) of PFS compared with patients receiving capecitabine alone, which translated to an additional 0.154 years (1.85 months) of QAPFS when using community preferences, and 0.198 years (2.37 months) of QAPFS when using patient preferences. QAPFS was higher in both arms when using the UBQ-C compared with the EQ-5D, with a statistically significant difference in QAPFS seen between the two arms when using the UBQ-C measure.

In the base case analysis, the cost per progression free life year gained was $145,059. The cost per QAPFS year gained when using utility values obtained from the UBQ-C instrument was $149,455, which increased to $192,156 when using values from the EQ-5D instrument.

Sensitivity analysis

A simple decision analysis was conducted using a set of plausible assumptions to examine the likely impact of the treatment on cost-effectiveness in terms of overall survival. When making the assumptions that either 1) the survival time post progression was the same in both treatment groups or 2) survival time post progression was less for capecitabine plus bevacizumab (whereby post progression survival was offset by 50% of the total PFS gain) and 3) monthly costs post progression were the same for both treatment groups, capecitabine plus bevacizumab did not represent a cost effective treatment and our conclusions remained unchanged. This result was robust to a relatively wide range of post progression cost estimates.

The impact of extending the analysis to include the 443 patients that had completed an inadequate number of quality of life assessments (i.e. either no baseline or no on-study assessments) is presented in Table 6. The ICER for capecitabine plus bevacizumab was slightly more favourable in the larger group due to both lower incremental mean costs and an increased incremental QAPFS time. Nonetheless, the ICER remained above $100,000 per each additional year of PFS gained. In addition, the hazard ratio of the treatment effect for the subset of patients included in the analysis was not statistically different to the hazard ratio for the overall study.

The impact of pooling data from the two bevacizumab arms of the trial was also examined in a sensitivity analysis. The cost effectiveness outcomes were not found to be significantly different when comparing capecitabine alone with either of the bevacizumab arms separately. While mitomycin C was associated with some additional costs related to toxicity, these costs were modest and the cost of mitomycin C itself was low.

Figure 1 displays the bootstrapped distribution of incremental cost effectiveness ratios. The cost effectiveness acceptability curves are presented in Figure 2, which depict the probability that each intervention will be cost effective given a range of cost effectiveness thresholds. The probability of the ICER falling below $100,000 per year of PFS or QAPFS gained was close to zero, demonstrating the robust nature of our conclusions.

Discussion:

In Australia, bevacizumab has received approval for government re-imbursement following a positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) which examines both the clinical effectiveness and cost-effectiveness of new pharmaceutical treatments. However, this is the first prospective study to evaluate the cost effectiveness of bevacizumab in metastatic colorectal cancer. Our results indicate that adding bevacizumab, with or without mitomycin C, to capecitabine monotherapy in patients with metastatic colorectal cancer exceeds AU$100,000 per quality adjusted PFS year gained (when applying the publicly listed price for bevacizumab in Australia) and is therefore unlikely to represent a cost effective use of health care resources in this context. Our results were estimated using individual level patient data and were robust to the effects of uncertainty.

Our findings were consistent with retrospective studies that have estimated the cost effectiveness of bevacizumab in advanced colorectal cancer, either alone or in combination with other therapies.[9,10,12] A 2008 meta analysis concluded that while bevacizumab has a significant effect on time to progression, there was no consensus on its cost-effectiveness in first-line therapy.[11]

Our study has a number of strengths. It is the first study to compare the cost-effectiveness of bevacizumab in combination with capecitabine for colorectal cancer, and the first to collect data as part of a prospectively designed health economics study built into a phase III randomised controlled trial. Data were captured on all hospital admissions and their causes, an area of resource use which previous cost effectiveness studies of bevacizumab have not reported on. A sensitivity analysis demonstrated that our results were highly robust to the effects of uncertainty in both the costs and effects of treatment.

~~A limitation~~The main limitation of our study ~~is~~ was that it did not produce an ICER in terms of overall survival or quality adjusted overall survival (QALYs) as are commonly ~~used~~ required by decision makers. The PFS analysis presented here was planned in advance of the MAX trial results as ~~The~~ the~~MAX~~ trial was not powered to reliably assess the effects of treatment on overall survival~~. and estimates of this outcome were unreliable~~. In addition, the effectiveness measures presented here (PFS and QAPFS) reflect the fact that survival following progression on first line therapy is generally affected by individualisation of treatment and cross over effects. We acknowledge that, as reported in our sensitivity analysis, the use of PFS ~~may~~ is likely to produce a more favourable cost effectiveness ratio than an ICER based on overall survival. However, given that the treatment was not found to be cost-effective we assume that the use of an OS endpoint would not alter our conclusions. A further limitation of this study is that no data were collected on health care utilisation outside of hospitalisations and routine follow up procedures, for example unscheduled outpatient visits, off-study pharmaceutical use or patient out of pocket costs.

While there is no explicit threshold for an ICER at which a treatment is considered to be cost effective for funding purposes in Australia, a retrospective study found that PBAC

have historically been unlikely to recommend a drug for reimbursement if the ICER exceeded $100,000 per life year gained.[19] The UK has a similar funding model to Australia, and preliminary NICE findings were recently reported as not supporting the use of bevacizumab in combination with oxaliplatin for the treatment of metastatic colorectal cancer,[20] despite the fact that NICE has allowed for a higher cost-effective threshold when appraising end-of-life treatments.[21] However, bevacizumab has been approved for the treatment of advanced colorectal cancer in Australia, Europe and the United States, based on its clinical effectiveness as demonstrated in prospective randomised studies. The results of this study, along with other studies evaluating the cost-effectiveness of bevacizumab, highlight that in making funding decisions, governments may consider factors beyond the incremental cost-effectiveness ratios.

Our analysis found that the main driver of the cost effectiveness outcome was the drug acquisition cost of bevacizumab. However, a key factor that remains unknown in these analyses is the extent of government negotiation of pharmaceutical pricing. The initial PBAC submission for the public reimbursement of bevacizumab was rejected on the grounds of an unacceptably high cost effectiveness ratio of between $105,000 and $200,000 per QALY gained[1].[22] A second submission following changes to the economic model (including a price decrease among other matters of concern) resulted in a new base case ICER of between $45,000 and $75,000 per QALY.[23] Based on this result the PBAC recommended that a risk share arrangement be developed, which was accepted by the manufacturer. As details of the agreement remain confidential, the only option available in costing analyses is to use the publicly listed price. The capacity of a

[1] Key differences between the analysis in the PBAC submissions and that presented here include the use of different combinations of drugs with bevacizumab (either 5-fluorouracil (FU)/leucovorin (LV) or irinotecan plus 5-FU/LV (IFL)), a different comparator group (patients treated with bolus irinotecan/5-fluorouracil/leucovorin (IFL)) and the use of QALYs as the outcome measure.

pharmaceutical company to negotiate on price is unknown and likely to be influenced, at least in Australia, by currency fluctuations.

An additional factor that may influence the cost effectiveness of chemotherapy treatments such as bevacizumab is the possibility of generic products coming onto the market once a pharmaceutical's patent has expired. While this will not influence initial funding decisions of patented pharmaceuticals, the potential for the cost effectiveness ratio to improve over time is an important consideration when undertaking analyses of potentially effective but expensive drugs. In Australia, there is currently a mandatory 16% price reduction on originator products with the introduction of a second brand.

The use of both the EQ-5D and the UBQ-C utility instruments in this study allows comparisons to be made between community and patient preferences for health states. The patient valued UBQ-C instrument produced significantly higher utility values than the community valued EQ-5D, which is consistent with studies comparing patient versus community preferences and may reflect the human ability to 'adapt' over time to inferior health states.[24] While the EQ5D produced a lower absolute utility value, this instrument reported a larger relative treatment effect (Table 5). Despite this, the UBQ-C analysis produced an ICER that was more than $40,000 less per QAPFS year than the EQ-5D analysis. While both ICERs remained beyond a reasonable threshold of cost effectiveness in this instance, this nonetheless highlights the influence that the choice of utility instrument can have over the cost effectiveness ratio.

Although we have demonstrated that the use of bevacizumab was not cost effective in advanced colorectal cancer in the context of the MAX trial, the ICER could be significantly improved if a biomarker selecting a patient population who derive greater benefit with bevacizumab could be identified. Efforts to identify such a biomarker for

bevacizumab have not been successful to date. However, with other targeted therapies such as cetuximab, the use of a predictive biomarker had a significant impact on cost effectiveness. Data from the CO17 trial showed that the ICER of cetuximab in metastatic colorectal cancer was reduced by almost half, from $299,613 per QALY in the entire study population to $186,761 per QALY gained in patients with wild type K-Ras gene status.[25]

In conclusion, given the high costs in relation to its clinical benefits, the addition of bevacizumab to capecitabine for the first-line treatment of metastatic colorectal was not found to be cost-effective in the MAX trial when using publicly listed pharmaceutical prices. As new information becomes available in relation to the cost of the treatment or a biomarker discovery this result may change and should be considered in future studies. Given the escalating cost of cancer care globally, it is important that future studies of new agents incorporate prospective cost effectiveness analyses in order to more effectively inform governments and other bodies making decisions in relation to drug re-imbursement.

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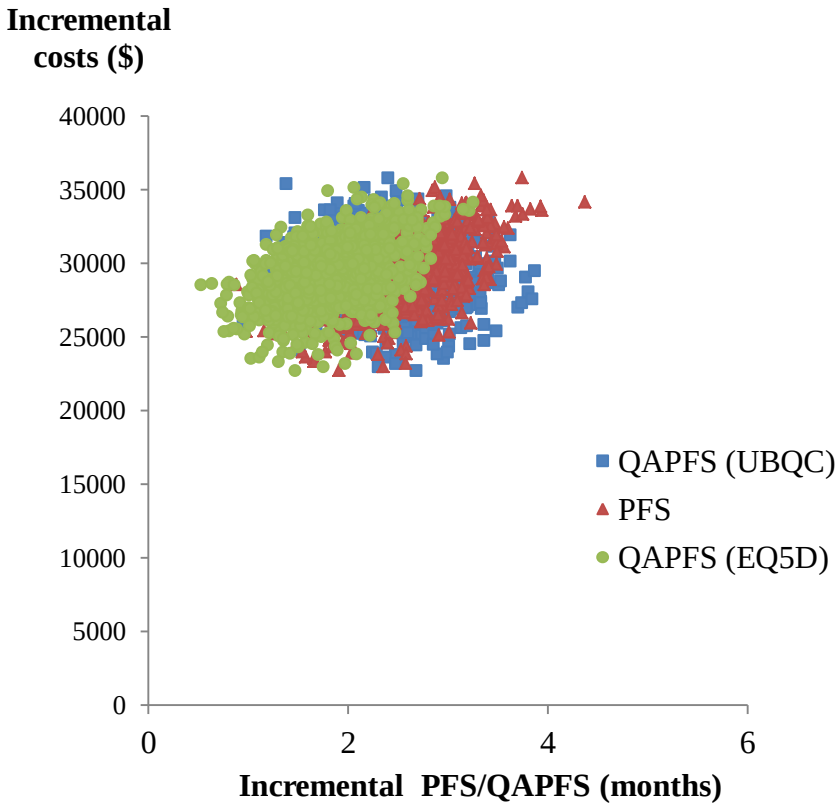
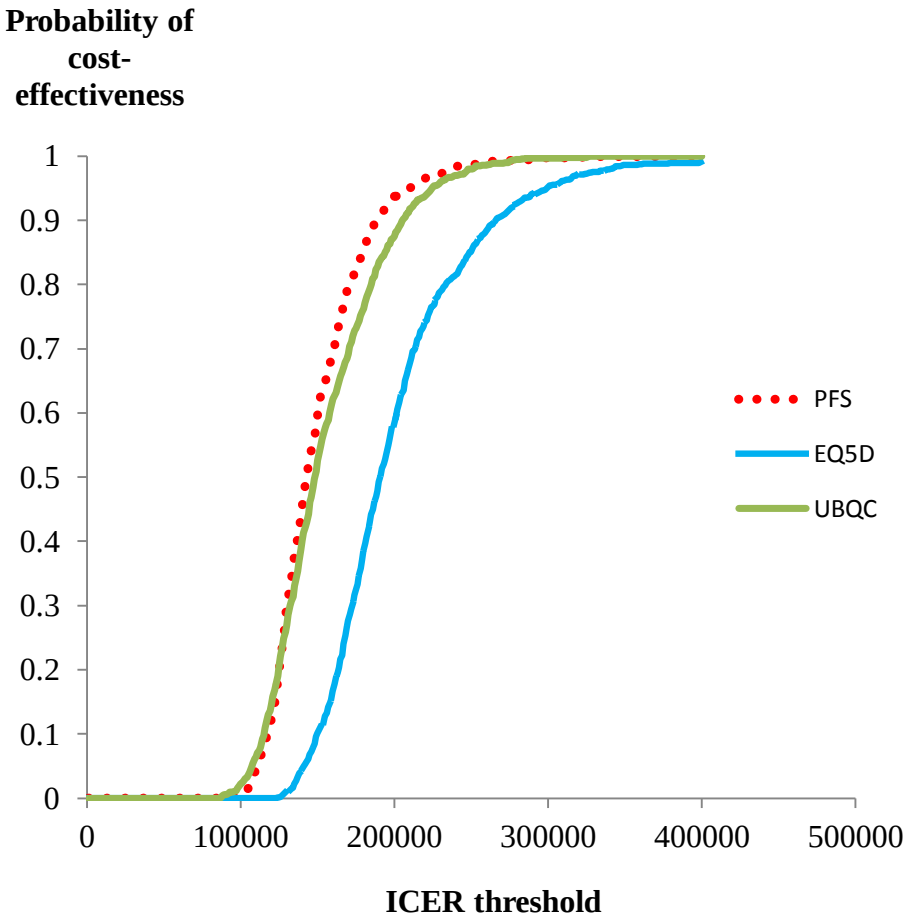
Figure legends:

Figure 1: Incremental cost effectiveness: PFS vs QAPFS (EQ5D and UBQC)



Scatter plot depicting the bootstrapped incremental cost-effectiveness ratios (ICERs). Each point represents one of the 1000 iterations of the bootstrap and depicts the mean incremental cost and effectiveness of bevacizumab plus capecitabine compared with capecitabine alone. Red points represent ICERs calculated using progression free survival (PFS) as the effectiveness outcome, green points using quality adjusted progression free survival (QAPFS) based on responses to the EQ-5D utility instrument and blue points using QAPFS based on responses to the UBQ-C utility instrument.

Figure 2: Cost effectiveness acceptability curves



Cost-effectiveness acceptability curves for the bootstrapped ICERs plotted in Figure 1. Each curve represents the probability that bevacizumab plus capecitabine is cost-effective compared with capecitabine alone based on a given threshold for the incremental cost-effectiveness ratio. The red curve represents the probability for ICERs calculated using progression free survival (PFS) as the effectiveness outcome, the green curve using quality adjusted progression free survival (QAPFS) based on responses to the EQ-5D utility instrument and blue curve using QAPFS based on responses to the UBQ-C utility instrument.

Tables

Please note: Tables 4 and 6 are to be online only

Table 1: Unit costs and sources

Cost category	Unit cost ($)	Source	Item number
Capecitabine			
Dosage: 1.25 g/m2 bd on day 1–14 every 3 weeks	1.39/mg	PBS[8]	8362D
Bevacizumab			
Dosage: 7.5 mg/kg starting day 1, every 3 weeks	4.30/mg	CPAP[26]	5850X
Intravenous administration: 30-90 mins	61.50	MBS[14]	13915
Mitomycin C			
Dosage: 7 mg/m2 on day 1 and every 6 weeks, with a maximum dose of 14 mg and for only four treatments	5.24/mg	Austin Pharmacy	
Intravenous administration: 15 mins	61.50	MBS	13915
Routine follow up/imaging			
History and physical exam	72.65	MBS	116
Haematology	17.05	MBS	65070
Biochemistry	17.80	MBS	66512
Tumour markers	24.50	MBS	66650
CT scan	560.00	MBS	56807
In patient hospital admissions		AR-DRG [15]	Version 5.1

PBS = Pharmaceutical Benefits Scheme, CPAP = Chemotherapy Pharmaceutical Access Program, MBS = Medicare Benefits Schedule, AR-DRG = Australian Refined Diagnosis Related Groups

Table 2: Disaggregated costs

Cost category	Mean cost per patient in capecitabine alone	Mean cost per patient in capecitabine + bevacizumab	Difference
Treatment drug cost	$5,182	$32,443	$27,262
Drug administration cost	$0	$672	$672
Routine follow up procedures	$3,778	$5,345	$1,567
Hospitalisations	$5,617	$5,709	$92
Total	$14,577	$44,169	$29,592

Table 3 Inpatient hospitalisation costs

Hospitalisations	Capecitabine alone	Capecitabine + bevacizumab	Difference
Mean number of admissions per patient on study	0.62	0.88	0.26
Proportion of patients with at least one admission	39%	51%	12%
Type of admissions:			
Cancer related admissions	47%	30%	-17%
Treatment related admissions	26%	38%	12%
Other admissions	27%	32%	5%
Mean length of stay per admission (days)	10.4	7.2	-3.22
Mean cost per admission	$9,153	$6,507	-$2,646
Mean cost of hospitalisations per patient on study	$5,617	$5,709	$92

Table 4 Utility scores for capecitabine alone versus capecitabine plus bevacizumab [Online only]

	Capecitabine	Capecitabine + Bevacizumab	Difference
EQ-5D*	0.7939	0.7839	-0.01
UBQ-C*	0.9389	0.9379	-0.001

*With adjustment for baseline EQ5D utility

Table 5: Results of the cost effectiveness analysis

	Capecitabine alone	Capecitabine + bevacizumab	Difference	ICER ($)
Cost	14,577	44,169	29,592	
95% CI	*12,041 - 18,129*	*41,209 - 46,979*	*25,089 - 33,388*	
PFS years	0.562	0.766	0.204	145,059
95% CI	*0. 496 - 0.625*	*0. 714 - 0.812*	*0. 120 - 0.283*	*106,703 - 233,225*
QAPFS years (EQ-5D)	0.446	0.600	0.154	192,156
95% CI	*0. 391 - 0.498*	*0. 553 - 0.640*	*0.085 - 0.223*	*135,619 - 326,894*
QAPFS years (UBQ-C)	0.531	0.729	0.198	149,455
95% CI	*0.467 - 0.592*	*0.681 - 0.773*	*0.122- 0.276*	*100,356 – 245,910*

PFS = progression free survival, QAPFS = quality adjusted progression free survival, ICER = incremental cost effectiveness ratio

Table 6 Comparison of results when including patients with only one EQ-5D utility assessment

[Online only]

	401 patients		443 patients	
Incremental differences	Mean	95% CI	Mean	95% CI
Cost ($)	29,592	25,089 - 33,388	26,569	22,879 - 30,116
PFS years	0.204	0. 120 - 0.283	0.221	0.130 - 0.302
ICER: PFS ($)	145,059	106,703 - 233,225	120,159	89,872 - 189,778
QAPFS years (EQ5D)	0.154	0.085 - 0.223	0.158	0.087 - 0.240
ICER: QAPFS ($)	192,156	135,619 - 326,894	167,901	115,691 - 283,709

PFS = progression free survival, ICER = incremental cost effectiveness ratio, QAPFS = quality adjusted progression free survival