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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Bevacizumab in combination with taxanes for the treatment of HER2-negative 1st line metastatic breast cancer

New evidence based on two subgroups: prior-taxane treated patients and triple negative patients

Roche new evidence submission to the
National Institute for Health and Clinical Excellence
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1 Executive Summary

At the NICE Appraisal Committee meeting on 17 June 2010 members of the Committee and the nominated Clinical Expert raised the question of the efficacy of bevacizumab in sub-groups of metastatic breast cancer patients. Currently there is not yet a defined biomarker to predict which particular patients may gain greater or lesser benefit from bevacizumab therapy, the available clinical data for bevacizumab in metastatic breast cancer do however suggest that certain subgroups of patients might gain greater benefit with this therapy than the ITT population. These particular subgroups of patients, namely those with triple negative disease and patients with previous adjuvant exposure to taxane therapy, are also groups of patients who have a great unmet clinical need for improved therapy. Patients in these groups tend to have a very poor prognosis, with rapid relapse and short progression-free and overall survival despite aggressive therapy.

Based on exploratory analyses, the clinical effectiveness and cost-effectiveness of bevacizumab in combination with taxanes in triple negative patients and those given prior adjuvant taxane therapy are presented. Alongside the previously reported clinical benefits of bevacizumab in these subgroups in E2100, supporting data from Phase III bevacizumab RCTs AVADO and RIBBON-1 demonstrate the consistently increased clinical benefits observed in these subgroups. For prior taxane treated patients in particular, the large benefit in median OS gain in E2100 (8.7 months) was reinforced in AVADO (9.3 months), where prior-taxane treatment status was a stratification variable. The particularly strong benefit in prior-taxane treated patients was confirmed once again in an individual patient meta-analysis in 1st line taxane treated patients across all three RCTs demonstrating a statistically significant overall survival benefit (OS HR 0.73, 95% CI 0.55-0.97, p=0.030). Although out of scope as an intervention in this appraisal, further confirmation of the predictive effect of prior taxane patients was observed in the bevacizumab in combination with capectabine data in RIBBON 1.

[redacted]. In the context of the management of metastatic breast cancer, this enables a subgroup of HER2 negative breast cancer patients to realize the same incremental survival gains as observed following the introduction of trastuzumab in HER2+ positive metastatic breast cancer patients (Slamon 2001; Marty 2005).

An economic analysis was conducted to determine the cost-effectiveness of bevacizumab in combination with paclitaxel for prior-taxane treated and triple negative patients. The Committee's considerations of the original ITT model were taken into account when updating the economic model. As a result, we utilized an alternative method of modeling overall survival, specifically, parametric extrapolations were fitted directly to the observed E2100 overall survival curves for these subgroups, thereby producing results with greater face validity in relation to the RCT outcomes. When considering real-world paclitaxel prices and ignoring the bevacizumab 10 gram cap patient access scheme, the ICER for prior-taxane treated patients and triple negative patients is £57,416 and £64,092, respectively, when comparing bevacizumab in combination with paclitaxel to the NICE recommended therapy, docetaxel. If the Department of Health accepts the proposed bevacizumab 10 gram cap patient access scheme, the ICER for the prior taxane treated and triple negative subgroups falls to £36,213 and £41,416 when comparing bevacizumab in combination with paclitaxel to docetaxel respectively.

These additional data demonstrate a considerable improvement in both the clinical and cost-effectiveness of bevacizumab when treating these clinically recognized subgroups. Considering the high unmet need within the prior-taxane treated and triple negative subgroups and corresponding ICERs, it would appear that bevacizumab in combination with paclitaxel is a cost effective option for the treatment of HER2 negative breast cancer patients.

2 Background: Unmet clinical need

As shown in the Roche submission of 8 March 2010, in spite of many significant advances in therapy over recent years, there is still a subset of the breast cancer patient population who have a very poor prognosis and a high unmet clinical need for new therapies. These patients do not have a durable response to therapy; they relapse rapidly and as a consequence tend to have a short overall survival duration. Although a number of different patient types may be assigned to this 'poor prognosis' or 'high risk' group, the majority are patients with triple negative (ER-/PgR-/HER2-) disease, or Grade 3 tumours, or positive lymph nodes at diagnosis.

The current NICE Guidelines for the treatment of both metastatic and early breast cancer (CG 81 and CG 80) recommend anthracycline therapy as the first treatment option for invasive breast cancer. In general, all those patients treated with adjuvant chemotherapy would receive an anthracycline, unless contraindicated. For patients with early breast cancer, NICE Guideline CG80 goes on to recommend "Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen". This Guideline has now been taken up by the majority of UK breast cancer clinicians.

NICE CG81 recommends that for patients with metastatic breast cancer not suitable for anthracycline therapy (e.g. due to prior anthracycline exposure or contraindication), "systemic chemotherapy should be offered in the following sequence:- single-agent docetaxel, followed by single-agent vinorelbine or capecitabine". This recommendation reflects the general recognition that anthracyclines and taxanes are the most effective chemotherapies in the treatment of invasive breast cancer. However, CG81 does not make any specific recommendation for the treatment of patients with metastatic breast cancer who have received both an anthracycline and a taxane as prior adjuvant therapy. Such patients have already been treated with the two most effective classes of chemotherapy and yet they have recurrent disease which requires treatment. This can often be rapidly-growing aggressive disease, as indicated by the primary tumour characteristics which mandated adjuvant taxane therapy.

It is well recognized that such patients, when they relapse after taxane adjuvant therapy, may have a very poor outcome with taxane re-treatment in the metastatic setting. This

may be due to either constitutional or acquired tumour resistance to taxane therapy. Some clinicians prefer not to rechallenge such patients with a taxane in the metastatic setting, preferring to use capecitabine instead. However, even with this agent, the outcome for prior taxane treated patients is worse than in the ITT population (see RIBBON-1 below).Thus the clinician has a very limited armoury of therapies with which to treat the aggressive disease in patients who have received prior adjuvant taxane and their outlook is often very poor.

3 Clinical effectiveness

3.1 E2100

The submission of 8 March 2010 demonstrated that in the E2100 advanced breast cancer study, the Overall Survival (OS) of the ITT population of patients given paclitaxel plus bevacizumab (median 26.5 months) was not significantly different from that of patients given paclitaxel alone (median 24.8 months) (HR=0.869, 95% CI 0.722-1.046, p=0.1374). However a post-hoc analysis showed that at 1 year there was a significant (p=0.017) improvement in OS for the ITT population given paclitaxel plus bevacizumab (1 year OS 81.4%) versus those given paclitaxel alone (1 year OS 74.0%). This 7.4% absolute improvement at 1 year (a 10% relative improvement in OS) reflects a possible survival benefit amongst the patients with the poorest prognosis, who had the shortest survival outlook and the least opportunity to receive second and third-line therapies, or to crossover to bevacizumab from the paclitaxel arm of the study.

This view is reinforced by subgroup data from the E2100 study for the patient groups which may have the poorest prognosis. These show that the median OS for triple-negative patients of only 16.3 months in the paclitaxel arm, was increased to 20.5 months in the paclitaxel plus bevacizumab arm (HR 0.89, 95% CI 0.66-1.19) associated with a 4.2 month improvement in median survival. Amongst patients previously treated with an adjuvant taxane, the low median OS with paclitaxel alone (17.6 months), was increased to 26.3 months with paclitaxel plus bevacizumab (HR 0.67, 95% CI 0.45-0.99) associated with an 8.7 month improvement in median survival. These data support the view that patients who received adjuvant taxane have a poor outcome when treated with taxane monotherapy in the metastatic setting. However, the statistically significant, 8.7 month improvement in median OS for prior adjuvant taxane patients given paclitaxel plus bevacizumab, raises their survival to the level found in the ITT population.

In the E2100 study, for the ITT population the unstratified HR for PFS was 0.54 (95% CI 0.44-0.67), with an improvement in median PFS from 5.8 to 11.3 months. In the subgroups which might be expected to include patients of poor prognosis, the addition of bevacizumab to paclitaxel appeared to give greater benefit; for the 232 triple-negative patients the HR for PFS was 0.49 (95% CI 0.34-0.70), with an improvement in median

PFS from 5.3 to 10.6 months. The 142 patients given prior adjuvant taxane therapy had a HR of 0.33 (95% CI 0.20-0.54) with an improvement in median PFS from 5.8 to 13.1 months (a 125% increase in median PFS).

3.2 AVADO

We now present additional data, not provided in the 8 March 2010 submission, which show that in a second study (AVADO; Miles et al JCO 2010) of bevacizumab added to first-line taxane therapy for metastatic breast cancer there was also a significant increase in 1 year OS, which was a pre-specified outcome. The AVADO study also showed that in the subgroups which may represent patients with the worst prognosis, i.e. those with triple negative disease or given prior adjuvant taxane therapy, the addition of bevacizumab gave a greater benefit than in the ITT population. This increase in benefit meant that among the patients given prior adjuvant taxane therapy, who had a worse outcome with taxane plus placebo than the ITT population, the addition of bevacizumab increased their OS and PFS to the level seen in the ITT population given bevacizumab.

The randomized, double-blind, phase III study Avastin And Docetaxel (AVADO), investigated the combination of bevacizumab with docetaxel in women with HER2 - negative metastatic breast cancer who had not previously received chemotherapy for metastatic disease. The E2100 Phase III trial of bevacizumab in breast cancer used 10mg/kg bevacizumab 2-weekly, or a dose equivalent of 5 mg/kg/per week. As this is higher than the dose initially licensed for use in colorectal cancer, which is the equivalent of 2.5 mg/kg/week, the AVADO trial combined the 3-weekly equivalent of each dose (7.5 or 15 mg/kg every 3 weeks) with docetaxel and compared this with placebo plus docetaxel.

Methods

Patients were randomly assigned on a 1:1:1 basis to either docetaxel with bevacizumab at a dose of 7.5 (bevacizumab7.5) or 15 mg/kg (bevacizumab15) q3w or docetaxel with placebo q3w. At random assignment, patients were stratified according to geographic region, presence of measurable disease, hormone receptor status, and prior taxane treatment. Patients who had not previously received taxanes underwent an additional stratification that included the following variables: no previous adjuvant/neoadjuvant

chemotherapy; or relapse >12 months or less than 12 months since the last dose of chemotherapy.

The planned dose and schedule of docetaxel was 100 mg/m2 on day 1 of each 3-week cycle for a maximum of nine cycles, although earlier discontinuation was allowed for drug intolerability. Docetaxel dose reduction and interruption were performed according to the prescribing information. Bevacizumab or placebo was also administered on day 1 of each 3-week cycle and was continued until disease progression or unacceptable toxicity occurred. No dose reductions of bevacizumab or placebo were permitted. Treatment was withheld at the first occurrence of protocol-specified grades 3 to 4 events attributed to bevacizumab use and treatment was permanently discontinued at the second occurrence of such events. After progression, all patients were given the option to receive bevacizumab in combination with their second-line chemotherapy regimens.

Tumour assessments were performed by investigators every 9 weeks until week 36 and every 12 weeks thereafter until disease progression, according to RECIST criteria. In patients without measurable disease at baseline, progression was determined by assessment of non-target lesions, appearance of new lesions, or symptomatic deterioration. Adverse events were graded according to the NCI CTCAE version 3.0. Adverse event data were collected up to 28 days after the last dose of study medication or up to 6 months after the end of treatment for adverse events of special interest. Data on treatment-related serious adverse events were collected indefinitely.

Participants

Patients had histologically or cytologically confirmed, HER2-negative locally recurrent (LR) or metastatic breast cancer (MBC). Women age >18 years with good performance status (ECOG 0 to 1) and left ventricular ejection fraction greater than the institutional lower limit of normal were eligible. The presence of measurable disease was not required. Previous chemotherapy for LR or MBC was not permitted. Chemotherapy in the neoadjuvant and/or adjuvant settings had to be completed greater than 6 months before random assignment, except for taxane-based therapy, for which 12 months had to have elapsed. Patients with controlled hypertension were included, and concurrent use of anticoagulation was allowed.

Exclusion criteria included the following: evidence of spinal cord compression or brain metastases; non-breast primary tumours (except for basal cell or squamous carcinoma of the skin or carcinoma in situ of the cervix) within 5 years before random assignment; and major surgery in the previous 28 days or minor surgery in the previous 24 hours. The baseline characteristics of the patients in the study are shown in Table 1, below and are generally well balanced between the three study arms.

Table 1. Baseline characteristics in the AVADO study

Table 1. Patient Demographic and Baseline Disease Characteristics in the Intent-to-Treat Population

Characteristic	Placebo + Docetaxel (n = 241)		Bevacizumab 7.5 mg/kg + Docetaxel (n = 248)		Bevacizumab 15 mg/kg + Docetaxel (n = 247)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	55		54		55	
Range	29-83		26-83		27-76	
< 65	203	84	207	83	199	81
≥ 65	38	16	41	17	48	19
ECOG performance status						
0	147	62	149	61	150	61
1	91	38	94	39	94	39
ER- and PgR-positive	189	78	193	78	187	76
Disease-free interval ≥ 12 months*	195	81	187	75	202	82
≥ 3 metastatic sites	99	41	122	49	122	49
Sites of disease						
Liver	120	50	98	40	112	46
Lung	91	38	102	42	117	48
Bone	142	59	146	60	135	55
Bone only	9	4	21	9	7	3
Measurable disease	207	86	201	81	206	83
Prior adjuvant chemotherapy						
Any	156	65	162	65	167	68
Taxane	35	15	38	15	42	17
Anthracycline	133	55	131	53	136	55
Prior hormone therapy						
(Neo)adjuvant	135	56	137	55	120	49
Metastatic	76	32	74	30	69	28

NOTE. Dosing was every 3 weeks in placebo and each bevacizumab group.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.
*Disease-free interval was defined as the time from histologic diagnosis of primary breast cancer to diagnosis of locally recurrent or metastatic disease, whichever occurred first.

Outcomes

The primary end point was PFS, the time from random assignment to first documented disease progression or death. Patients without a disease related event were censored at the last tumour assessment or last follow-up for disease progression at which they were known to be progression free. Patients without any post-baseline tumour assessments were censored at random assignment. Secondary end points included best overall response, duration of response, time to treatment failure, overall survival (OS), and safety. Quality of life was also a secondary end point; however, these data are as yet unavailable.

Statistical analysis

The analysis population for the primary efficacy analysis was the intent-to-treat (ITT) population, which included all patients randomly assigned onto the study.

In total, 669 patients were required to provide the 430 events necessary to yield 80% power for the detection of an HR for PFS of 0.7, by using a two-sided log-rank test at an α level of 5%. A closed test procedure was employed to adjust for the multiplicity of testing. Allowing for a drop-out rate of 5%, recruitment of 705 patients was planned. There was no hypothesis that the treatment effect would differ between the two bevacizumab doses; therefore, the trial was not designed to detect a statistically significant difference between the two bevacizumab containing arms. The main analysis of PFS was an unstratified comparison (log-rank test). In addition, a preplanned stratified analysis was performed of PFS, adjusting for baseline risk factors that were used at random assignment. This analysis also censored, at the time of their last tumour assessment, patients who received non-protocol therapy before disease progression.

Comparison of response rates was performed by using the X2 test with Schouten correction. For TTF, duration of response, and OS, Kaplan-Meier curves were constructed and compared by using a log-rank test.

The primary analysis of this study, triggered by a pre-specified number of PFS events (which occurred after a median follow-up of 10.2 months) was presented at the ASCO annual meeting in 2008. An additional pre-specified, exploratory analysis of all efficacy endpoints was performed at the time of the final planned analysis of overall survival, at a median follow-up of 25 months and these data are presented below (Miles et al J.Clin Oncol. 2010; 28: 3239-3247)

Results; treatment exposure

More patients received the protocol-specified nine cycles of docetaxel in the bevacizumab-containing treatment arms than the placebo arm: 98 patients (42%) in the placebo arm and 120 patients (48%) and 125 patients (51%) in the bevacizumab7.5 and bevacizumab15 arms, respectively.

Efficacy

In the unstratified analysis, the combination of bevacizumab15 with docetaxel showed superior PFS compared with placebo plus docetaxel (HR, 0.77; P= 0.006); the benefit in the bevacizumab7.5 arm was less pronounced and non-significant (HR, 0.86; P =0.12). No further results for this arm of the study will be presented; the results for the placebo and bevacizumab15 arms are summarized in Table 2.

Median PFS for the ITT population was 8.2 months in the placebo arm, and 10.1 months in the bevacizumab15 arm. In this analysis, data from 22 patients (9%) in the placebo arm and 27 patients (11%) in the bevacizumab15 arm who were still on treatment were censored. In the stratified analysis of PFS, that also censored for non-protocol therapy before disease progression (8% of patients in the placebo arm and 7% of patients in the bevacizumab15 arm), the HR for bevacizumab15 versus placebo was 0.67 (P = 0.001). Median PFS times were 8.1 months in the placebo arm and 10.0 months in the bevacizumab15 arm.

Response was analyzed in the subset of the ITT population with measurable disease at baseline (numbers shown in Table 2). The response rate in the bevacizumab15 arm of 64.1% was superior to that in the placebo arm of 46.4%, p<0.001 . The median duration of response was numerically longer in the bevacizumab15 arm (8.3 months) than in the placebo arm (6.6 months). TTF was longer with bevacizumab15 than placebo (unstratified HR, 0.80; P =0.02), while OS was similar in the treatment arms, with median values of approximately 31 months (HR, 1.03 for bevacizumab15). One-year overall survival was statistically significantly higher in the bevacizumab15 arm (84%) than in the placebo arm (76%) (p=0.02).

Table 2 AVADO study; overview of efficacy endpoints, ITT population

	Placebo + Docetaxel (n = 241)	Bevacizumab 15 mg/kg + Docetaxel (n = 247)
PFS, unstratified		
Patients with PFS event	219	220
%	90.9	89.1
HR vs placebo		0.77
95% CI		0.64 - 0.93
p vs placebo		0.006
Median, months	8.2	10.1
PFS, stratified		
Patients with PFS event	201	199
%	83.4	80.6
HR vs placebo		0.67
95% CI		0.54 - 0.83
p vs placebo		< 0.001
Median, months	8.1	10.0
Overall Survival (OS)		
Patients alive	108	116
%	44.8	47.0
HR vs placebo		1.03
95% CI		0.7 - 1.33
p vs placebo		0.85
Median, months	31.9	30.2
1-year survival, %	76	84
Patients still at risk	178	201
p vs placebo		0.02
Response (n)*	207	206
Overall response rate, %	46.4	64.1
p vs placebo		<0.001
Duration of response		
HR vs placebo		0.82
95% CI		0.62 - 1.08
Median, months	6.6	8.3

*Patients with measurable disease at baseline

Subgroup analyses

The data for patient subgroups were generally consistent with the results for the overall study population. However, in the subgroups which might indicate patients with poor prognosis disease, there were some interesting findings. For the 111 patients with triple

negative (ER-/PgR-/HER2-) disease, the HR for PFS was 0.67 (95% CI 0.46 – 0.99), compared with the unstratified HR for PFS in the 488 patients of the ITT population of 0.77 (95% CI 0.64 to 0.93). The triple negative patients also had a lower HR for OS (0.82, 95% CI 0.51 – 1.31) than the ITT population (1.03, 95% CI 0.70-1.33).

Amongst the 78 patients who had received prior adjuvant taxane therapy, docetaxel plus placebo gave shorter median PFS (6.7 months) and OS (22.3 months) that in the ITT population. However, with the addition of bevacizumab15, the median PFS for this population increased to 10.3 months (HR 0.53, 95% CI 0.33-0.85). Median OS increased by 9.3 months in this subgroup with the addition of bevacizumab15, to 31.6 months (HR 0.58, 95% CI 0.31-1.08). The outcomes for prior adjuvant taxane patients given docetaxel plus bevacizumab15 were very similar to those in the ITT population.

Safety

The combination of bevacizumab with docetaxel had no major impact on the toxicity profile of docetaxel. Most patients in the safety population (99.6% to 100%) experienced at least one adverse event; most were known docetaxel toxicities. A similar number of patients in each study arm discontinued docetaxel for toxicity. Placebo was discontinued by 12% of patients and bevacizumab15 was discontinued in 14% of patients because of adverse events thought by investigators to be related to bevacizumab. Adverse events of special interest were more frequent with bevacizumab; the highest increases were in all-grade bleeding (primarily epistaxis; placebo, 19.5%; bevacizumab15, 49.4%) and hypertension (placebo, 10.0%; bevacizumab15, 21.9%).

Grades 3 to 4 adverse events of special interest were more common in the bevacizumab arms than the placebo group and most of the difference was attributable to hypertension, neutropenia and febrile neutropenia. Grades 3 to 4 gastrointestinal perforation, arterial and venous thromboembolic events and bleeding occurred at similar incidences in the trial arms. A numerically higher incidence of grade 3 or greater events was seen in the bevacizumab15 (75%) than the placebo arm (67%). However, there was no difference in the incidence of adverse events leading to death during the study period (2% in the bevacizumab15 arm v 3% in the placebo arm). Although the incidence of grades 3 to 4 neutropenia and febrile neutropenia was slightly increased in the bevacizumab15 arm

(20 and 16%) versus the placebo arm (17 and 11%), that of grades 3 to 4 peripheral oedema and infection was higher in the control arm.

Summary of Efficacy; AVADO study

This randomized, double-blind study confirmed the clinical benefit of combining bevacizumab with a taxane, as previously reported in the E2100 study. Statistically significant improvements in both the primary end point of PFS and secondary efficacy end points were achieved with bevacizumab15, with little associated increase in toxicity. For the ITT population, the addition of bevacizumab15 to 100mg/kg docetaxel q3w significantly improved both the PFS and the objective response rate, over and above the high values found in the placebo arm of the study. The ORR of 64.1% for bevacizumab plus docetaxel exceeds any value previously reported for HER2-negative breast cancer and is matched only by the response rate with trastuzumab plus docetaxel in HER2-positive mBC patients.

The trial was neither powered nor designed to detect a survival difference,as patients in the placebo arm were allowed to cross over to bevacizumab treatment after progression, any effect on this end point may have been confounded. Indeed, 14 patients from the placebo arm received open-label bevacizumab before disease progression and a total of 83 patients from this arm were given bevacizumab with their second-line chemotherapy. However, amongst the patients with the most rapid disease progression and death, ie those not given the chance of second line treatment, the highly significant 8% absolute (10% relative) improvement in 1 year OS when bevacizumab15 was added to docetaxel, demonstrates that for patients with a poor prognosis, bevacizumab15 significantly reduced the risk of death.

There are few subgroup data available from the AVADO study to suggest which patients were most likely to contribute to this significant survival benefit at 1 year. However, as in the E2100 study, the AVADO subgroup data for PFS suggest that the patient groups likely to have a poor prognosis, i.e. those with triple-negative disease or given prior adjuvant taxane therapy, gained considerable benefit from the addition of bevacizumab to their therapy. This benefit appeared particularly marked in the patients given prior adjuvant taxane therapy, where with docetaxel plus placebo median PFS (6.7 months) and OS (22.3 months) were considerably shorter than in the ITT population. However,

with the addition of bevacizumab15, these medians for the prior taxane treated patients were raised to PFS 10.3 months and OS 31.6 months, very similar to the values for the ITT population.

Three-weekly docetaxel, when given at a dose of 100mg/m2, is one of the most active agents available for the treatment of MBC, but is associated with relatively high toxicity. This is shown by the nearly 100% of patients in each arm of this trial who experienced at least one adverse event. Incidence of grade 3 or greater adverse events was numerically higher in both bevacizumab arms than the placebo arm, predominantly because of an increase in neutropenia, febrile neutropenia and hypertension, events that are manageable in today's clinical practice. In contrast, incidence of other grade 3 or greater events previously observed in clinical trials of bevacizumab, such as gastrointestinal perforations, arterial or venous thromboembolic events, CHF, fistula/abscess, bleeding events, proteinuria, or wound-healing complications, was similar in all study arms. The reasons for the considerably lower frequencies of grades 3 to 4 hypertension in this study than in E2100 are unknown, but a contributing factor could be the blinded nature of the AVADO study, reducing reporting bias.

3.3 Meta-analysis

Multiple Phase III RCTs are now completed for bevacizumab for the treatment of 1st line metastatic breast cancer resulting in the opportunity to synthesize the data from these trials and consider with greater power the potential treatment effect in specific subgroups. Two individual patient meta-analyses have been conducted which provides further information on the triple negative and prior-taxane treated populations. Prior to presenting the results of these meta-analyses, we will summarise the results of the E2100 and AVADO studies and present very briefly details of the clinical trial design for the RIBBON 1 study.

3.3.1 Summary: E2100 & AVADO

The two Phase III RCTs, E2100 and AVADO, show a consistent picture for the effect of the addition of bevacizumab to taxane therapy in the first-line treatment of patients with metastatic breast cancer. In the ITT population in both studies the addition of bevacizumab, at a dose equivalent of 5mg/kg per week, to taxane therapy significantly

increased the PFS and the objective response rate. Median overall survival was not increased in either study, but one year OS was significantly increased in both studies by the addition of bevacizumab. The AVADO data also reinforce the conclusions drawn from the E2100 study, that bevacizumab gives very considerable improvement in both OS and PFS in the patient subgroups which have a poor outcome with taxane therapy alone, i.e. patients with triple negative disease and those given prior adjuvant taxane therapy.

As shown in Table 3 and 4, there is a remarkable consistency in the effect of bevacizumab across the two RCTs with taxanes. In particular, there is an almost identical effect on 1-year OS, with a significant benefit equivalent to a 10% relative increase in OS, in both studies when bevacizumab is added to taxane therapy. Such an increase in OS represents a significant extension of lives amongst the patients with the worst disease prognosis. Examination of the subgroup data from the E2100 study suggests that patients with triple-negative disease and those given prior adjuvant taxane therapy had much shorter median OS than the ITT population given taxane alone. Table 3 shows that both these patient subgroups showed a large benefit in median OS. The gains in OS for these subgroups, were also reinforced by a lower HR for PFS than in the ITT population.

Table 3 E2100 outcome data for ITT population and particular subgroups

	ITT		Triple negative		Prior taxane therapy	
	Paclitaxel n=354	Paclitaxel + bev n=368	Paclitaxel n=110	Paclitaxel + bev n=122	Paclitaxel n=69	Paclitaxel + bev n=71
PFS, median (mo)	5.8	11.3	5.3	10.6	5.8	13.1
unstratified PFS HR, 95% CI		0.54 0.44-0.67		0.49 0.34-0.70		0.33 0.20-0.54
OS median (mo)	24.8	26.5	16.3	20.5	17.6	26.3
OS HR		0.87 0.72-1.05		0.89 0.66-1.19		0.67 0.45-0.99
1 year OS (%)	74.0	81.4				
p		0.017				

Table 4 AVADO outcomes for ITT and subgroups

	ITT		Triple negative (n=111)		Prior taxane (n=78)	
	Placebo + Docetax (n = 241)	Bev15 + Docetaxel (n = 247)	Placebo + Docetax	Bev15 + Docetaxel	Placebo + Docetax	Bev15 + Docetaxel
PFS, median (mo)	8.2	10.1	N/A	N/A	6.7	10.3
unstratified PFS HR, 95% CI		0.77 0.64-0.93		0.68 0.46-0.99		0.53 0.33-0.85
OS median (mo)	31.9	30.2	N/A	N/A	22.3	31.6
OS HR 95% CI		1.03 0.7-1.33		0.82 0.51-1.32		0.58 0.31-1.08
1 year OS (%)	76	84	N/A	N/A	N/A	N/A
p		0.02				

N/A = not available

Table 4 shows the more limited subgroup data from the AVADO study, which demonstrate that with docetaxel plus placebo there was also a much shorter median OS amongst the prior adjuvant taxane patients than in the ITT population. However, with the addition of bevacizumab15 the median OS for these patients also increased to the level seen in the ITT population. The triple negative patients in AVADO also showed lower HR values for both PFS and OS, indicating that these patients, as in the E2100 study, gained a greater benefit with bevacizumab than the ITT population.

As discussed above, in the clinical management of metastatic breast cancer, patients given prior adjuvant taxane therapy have a very great unmet need for effective therapy; they cannot be retreated with, or are unsuitable for, anthracyclines, and they have poor outcomes with taxane therapy alone (as confirmed in both the E2100 and AVADO studies). For such patients, the addition of bevacizumab to taxane therapy offers very considerable clinical benefit, including a large increase in overall survival, particularly with the prior-taxane treated subgroup with observed gains of 8.7 month and 9.3 months in median survival when bevacizumab in added to a taxane in E2100 and AVADO respectively. This brings the outcomes of first-line therapy for the poor prognosis, prior adjuvant taxane treated patients up to the level seen for the overall ITT population, meeting their clinical need for effective, life-prolonging therapy for their metastatic breast cancer.

3.3.2 RIBBON 1

RIBBON-1 was a randomized, double-blind, placebo-controlled, phase III trial of standard chemotherapy with or without bevacizumab for first-line treatment of patients with HER2-negative locally recurrent or metastatic breast cancer (Robert et al 2009).

Patients were randomized in a 2:1 ratio to receive bevacizumab + chemotherapy or placebo + chemotherapy. Prior to randomization, investigators chose to use capecitabine, taxane (nab-paclitaxel or docetaxel) or anthracycline-based chemotherapy. Bevacizumab was administered at 15 mg/kg q3wk. The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival, objective response rate and safety. At progression, all patients were eligible for bevacizumab with 2nd line chemotherapy. The capecitabine cohort and the pooled taxane or anthracycline cohort were independently powered and analysed in parallel, using two-sided stratified log-rank test.

The study enrolled 1237 patients (capecitabine, 615; taxane 307; anthracycline 315), with a median follow-up of 15.6 months in the capecitabine cohort and 19.2 months in the taxane + anthracycline cohort. PFS was significantly improved in both patient cohorts; for the 622 patients receiving taxane or anthracycline therapy, median PFS increased from 8.0 to 9.2 months with the addition of bevacizumab (HR 0.66, 95% CI 0.54-0.81). For the 615 patients receiving capecitabine, median PFS increased from 5.7 to 8.6 months with the addition of bevacizumab (HR 0.67, 95% CI 0.55-0.82). It is of interest that, in the capecitabine cohort 245 patients had received prior adjuvant taxane therapy.

The safety profile in RIBBON-1 was comparable to the earlier Phase III studies of bevacizumab.

3.3.3 Bevacizumab in combination with chemotherapy (triple negative patients)

The three randomized trials in patients with metastatic breast cancer evaluating bevacizumab plus first-line chemotherapy regimens, E2100, AVADO, and RIBBON-1, each demonstrated improvement in the primary endpoint of progression-free survival (PFS). Although the trials were not designed to show an overall survival (OS) benefit, it was a secondary endpoint in all trials.

A meta-analysis of PFS and OS in all 2,447 patients from these trials was undertaken, using complete survival data for each study (O'Shaughnessy et al. 2010). Kaplan-Meier methodology was used to estimate the median duration of PFS and OS. Stratified log-rank test was used to assess the difference in PFS and OS between treatment arms (control vs. bevacizumab +chemo). The stratified hazard ratio (HR) was estimated using the Cox regression model. Each individual study was included as a stratification factor in the stratified analysis. 1-year survival rate was compared using a normal approximation method. All p-values were two-sided and tested at the type I error rate of 0.05.

2,447 patients were included in the meta-analysis (1,008 control; 1,439 bevacizumab +chemo). Patient characteristics were well-balanced between the arms (overall median age, 56; hormone receptor-positive, 73%; prior adjuvant chemo, 62%; $\geq$3 metastatic sites, 40%). Duration of follow-up ranged from 29 (AVADO) to 36 (E2100) months. In the pooled ITT analysis, median PFS improved from 6.7 to 9.2 mo (HR=0.64, p<0.0001) in the bevacizumab arm. Pooled results for OS showed no statistically significant difference between the arms (median OS control 26.4 mo, bevacizumab +chemo 26.7 mo; HR=0.97, (95% CI, 0.86 – 1.08, p=0.56). The one-year overall survival rate was greater in the bevacizumab +chemo arms (control, 76.5%; bevacizumab +chemo, 81.6% p=0.003).

The results were consistent across key patient subgroups. HR for PFS in the 621 patients with triple negative disease was 0.63 (95% CI 0.52-0.76) and the HR for OS was 0.96 (95% CI 0.79-1.16). This study did not analyse separately the patients given prior adjuvant taxane therapy.

Table 5 All-patient meta-analysis; outcomes for ITT and subgroups

	ITT (n=2447)		Triple negative (n=621)	
	Chemo alone	Bev15 + chemo	Chemo alone	Bev15 + chemo
PFS, median (mo)	6.7	9.2	N/A	N/A
PFS HR, 95% CI		0.64 0.58-0.71		0.63 0.52-0.76
OS median (mo)	26.4	26.7	N/A	N/A
OS HR 95% CI		0.97 0.86-1.08		0.96 0.79-1.16
1 year OS (%)	76.5	81.6		
p		0.003		

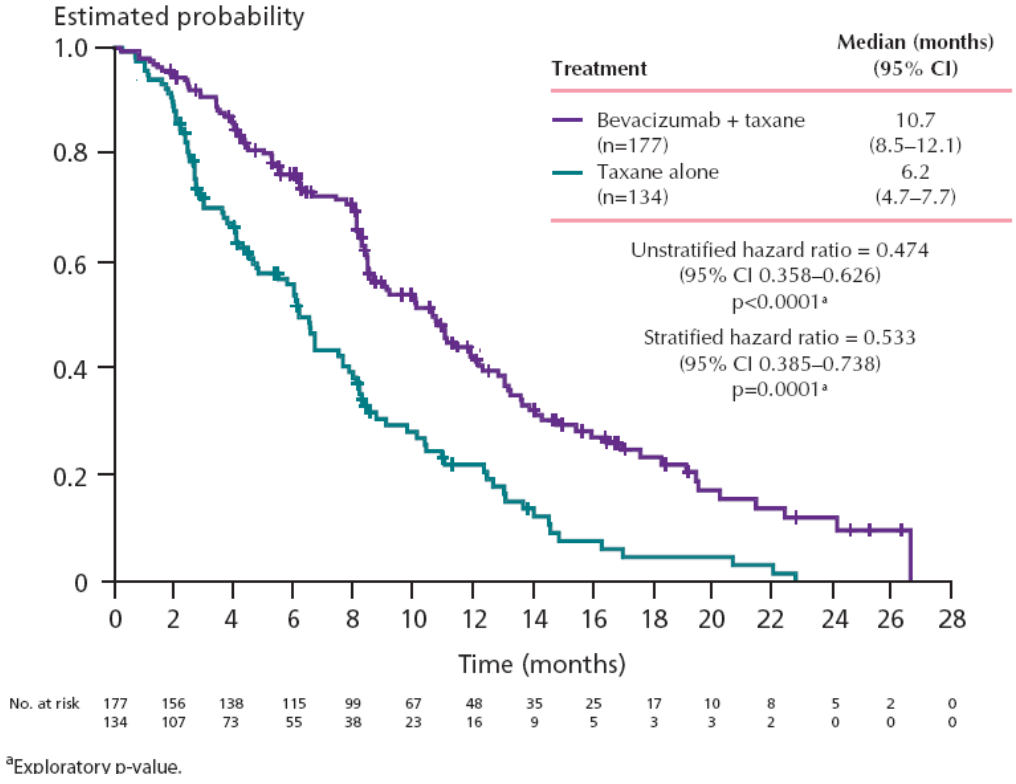
N/A = not available

3.3.4 Bevacizumab in combination with a taxane (prior taxane treated patients)

A further, exploratory meta-analysis addressed the issue of re-treatment with a taxane, in the patients given prior adjuvant taxane therapy (Miles et al ESMO 2010, Roche data on file; to be presented on 11 October 2010). This analysis was restricted to the 1765 patients treated with taxanes plus or minus bevacizumab in the E2100, AVADO and RIBBON-1 study, and a total of 311 of these patients had received prior adjuvant taxane therapy. In this patient population, the median PFS was 6.2 months with taxane alone (134 patients) and this increased to 10.7 months for the 177 patients given taxane plus bevacizumab (HR 0.47, 95% CI 0.35-0.62, p<0.0001). The objective response rate (ORR) for pre-taxane treated patients increased from 27% with taxane alone to 49% with taxane plus bevacizumab (p<0.005). In this group of taxane re-treated patients, median overall survival was also significantly increased with the addition of bevacizumab, from 21.3 months with taxane alone to 26.9 months with taxane plus bevacizumab (HR 0.73, 95% CI 0.55-0.97, p=0.030). Although these differences appear to be statistically significant, it should be noted that this analysis is exploratory only.

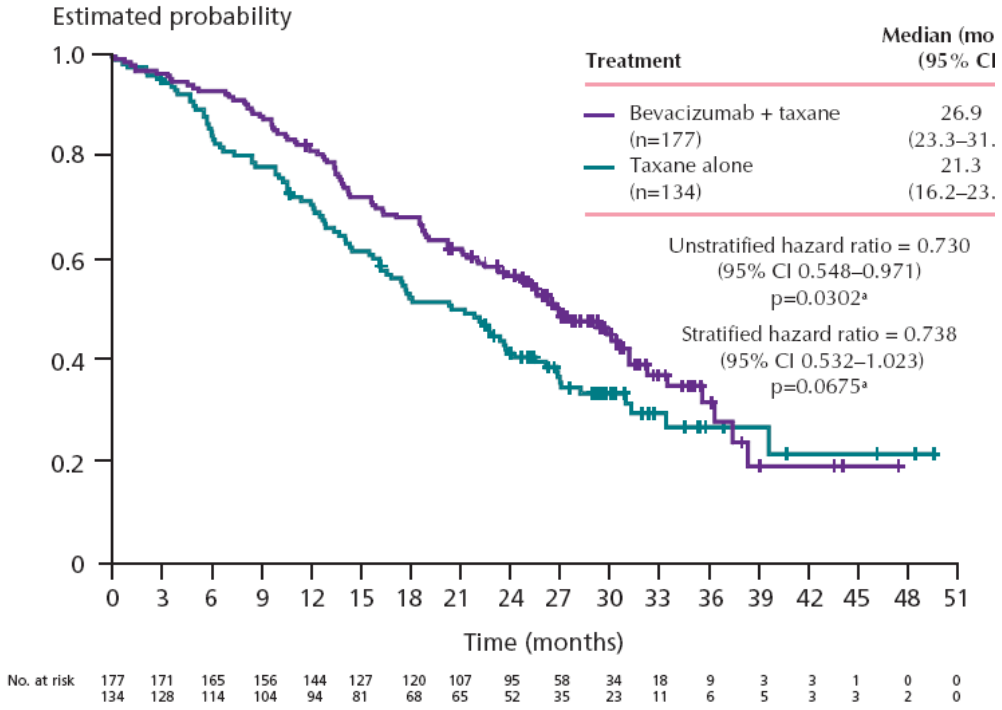
Results from these meta-analyses of pooled data from the Phase III studies show that bevacizumab when combined with first-line chemotherapy not only results in clinically meaningful and statistically significant improvements in PFS, but also gives a significant improvement in OS in the prior-taxane treated patient subgroup.

Figure 1. Kaplan Meier estimates for PFS in prior-taxane treated patients based on an individual patient meta-analysis



[a]Exploratory p-value.

Figure 2. Kaplan Meier estimates for OS in prior-taxane treated patients based on an individual patient meta-analysis



[a]Exploratory p-value.

4 Cost-effectiveness

4.1 Overview

The existing economic model based in the intent-to-treat (ITT) population has been adapted to provide cost-effectiveness estimates for two subgroups of interest: prior-taxane treated patients and triple negative patients. The adapted model differs from the ITT model in the following ways:

- Clinical data updated to reflect the new populations:
    - Progression-free survival (PFS)
    - Overall survival (OS)
    - Time to off treatment
    - Adverse event (AE) rates
- Structural changes to the model:
    - Overall survival has not been modelled as a standard post-progression probability of death. Instead, the overall survival curves from E2100 for the relevant subgroups have been fitted with parametric functions. This was considered preferable by the Committee to add precision to the cost-effectiveness estimates (ACD Section 4.13)
    - Results are presented as they were presented in the original submission, that is, as pair wise ICERs due to the Committee's conclusion that these were appropriate to consider in this instance (ACD Section 4.11).

Following the ACD, the decision problem was also refined based on the Committee's considerations. The following models will be based on these adjustments to the scope:

- **Intervention(s)**: ***bevacizumab in combination with paclitaxel***: "The Committee… considered that the ICER for bevacizumab plus docetaxel would be higher than the ICER for bevacizumab plus paclitaxel compared with weekly paclitaxel and 3-weekly docetaxel. (ACD Section 4.14)" Therefore, we have once again focused strictly on a cost-effectiveness analysis for bevacizumab in combination with paclitaxel.
- **Comparators**: ***weekly paclitaxel and 3-weekly docetaxel***: "The Committee concluded that the relevant comparators for bevacizumab in combination with a

taxane for the first-line treatment of metastatic breast cancer are weekly paclitaxel and 3-weekly docetaxel" (ACD Section 4.2). Therefore, the comparator of gemcitabine in combination of paclitaxel will no longer be considered.

- Furthermore, "The Committee concluded that the cost-effectiveness estimates derived from assuming comparators had equivalent effectiveness to weekly paclitaxel were acceptable." (ACD Section 4.12). Therefore our new models correspond to our original ITT base case which assumes a class effect for these two taxanes.

As noted in our original ACD response, we believe it is inconsistent for the Committee to conclude "that the analyses which incorporated the NHS list prices for all drug treatments were the most appropriate for consideration" (ACD Section 4.10) when gemcitabine was approved in combination with paclitaxel based on the acknowledgment and taking full account of the fact that paclitaxel PASA price is significantly lower than list price. We have therefore retained both PASA prices and list prices when reporting our base case results.

4.2 PFS & OS extrapolation updated to reflect subgroups

The clinical results reported on OS and PFS were non-parametrically (Kaplan-Meier) generated and were under the assumption of proportional hazards. Martingale and Deviance residuals were assessed to confirm that the assumption of proportional hazards was reasonable. The following KM curves are based on the E2100 latest data cut-off of 21 October 2006.

Figure 3. PFS of Bev-Pac vs Pac for Prior taxane treated subgroup

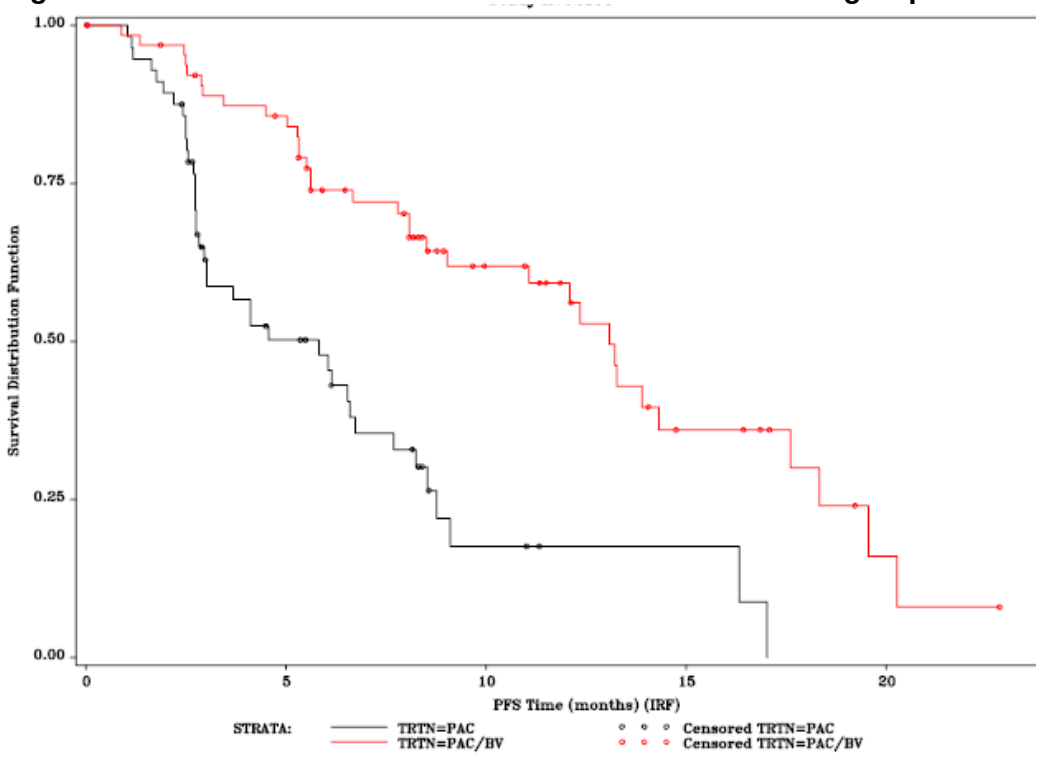


Figure 4. PFS of Bev-Pac vs Pac for Triple negative subgroup

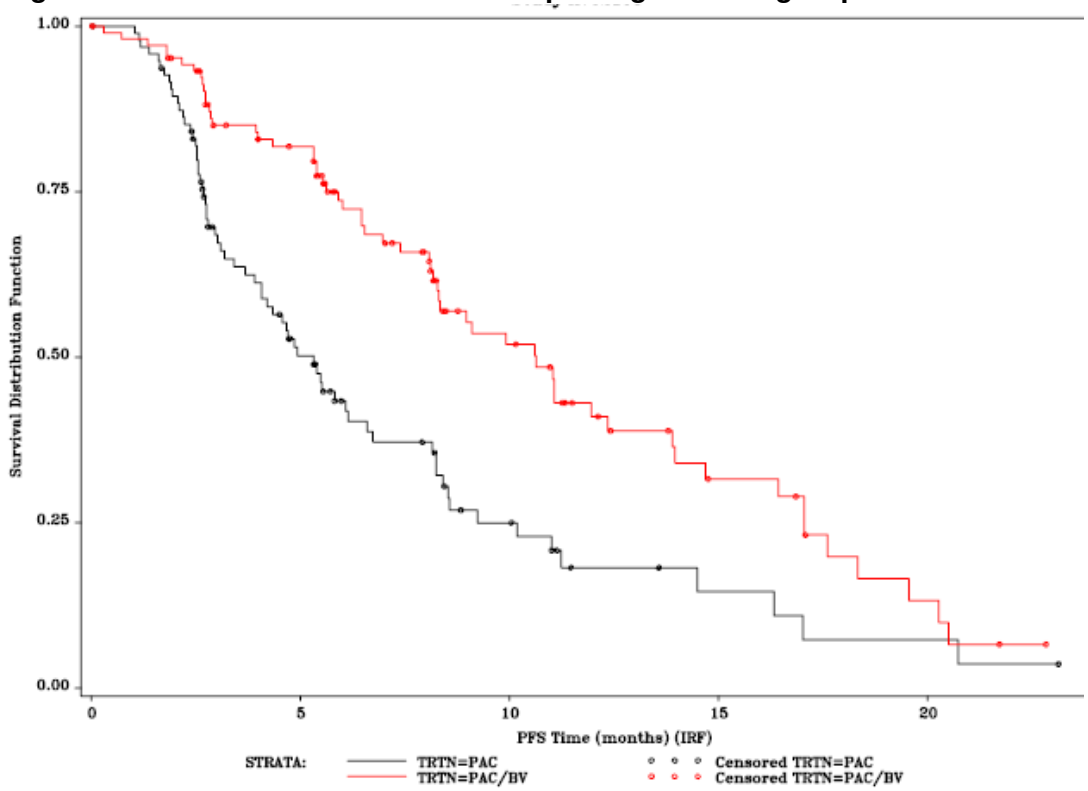


Figure 5. Overall Survival of Bev-Pac vs Pac for prior taxane treated patients

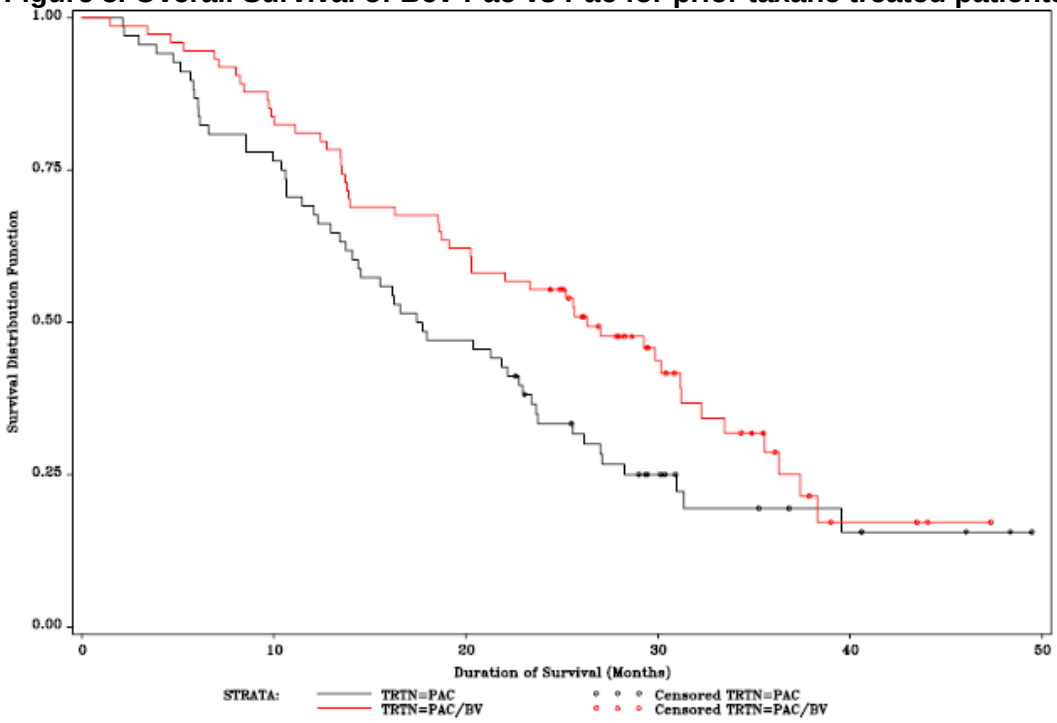
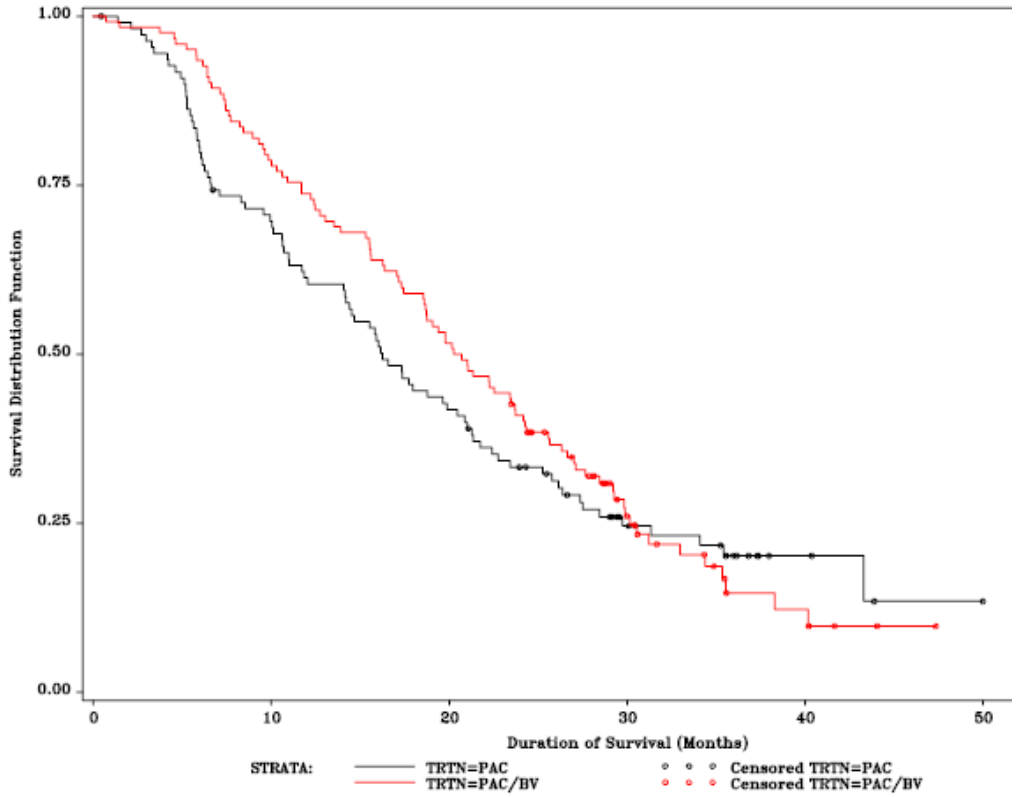


Figure 6. Overall Survival of Bev-Pac vs Pac for triple negative patients



Extrapolation beyond the clinical follow up period can only be performed if one assumes that the data originated from a parametric distribution. The use of a parametric function requires that its unknown parameters (e.g. λ, γ parameters of a Weibull survival function) can be estimated. Various parametric functions were available and each function was assessed for its goodness of fit to the data using Akaike (AIC) and Bayesian Information Criteria (BIC), the mean squared deviance and graphical inspection of fit (e.g., Martingale residuals) to the data before deciding on the final functional form. The parametric model structures assessed for goodness of fit to the data were: Log Logistic, Weibull, Log Normal, Gompertz, Exponential and the Generalised Gamma. The AIC/BIC information for the OS/PFS parametric functions for the prior taxane model is provided below. The corresponding information for the triple negative model can be made available on request.

Table 6: Summary of Parametric Functions' Goodness of Fit for OS/PFS for the prior taxane subgroup model

Model Type	Parameter	BIC	AIC
llogistic	**OS**	**174.4199995**	**169.8118693**
gamma	OS	177.4019765	170.4897813
weibull	OS	177.4791527	170.5669574
lnormal	OS	175.7559761	171.1478459
exponential	OS	181.541816	179.237751
Gompertz	OS	455.904783	447.0373019
gamma	PFS	137.7787519	130.8665566
weibull	PFS	137.9970085	131.0848132
llogistic	**PFS**	**135.8846395**	**131.2765093**
lnormal	PFS	136.3641622	131.756032
exponential	PFS	138.1474524	135.8433873
Gompertz	PFS	257.1350091	248.2675279

The parameters were estimated using patient level clinical data from the E2100 study (21 October 2006 data cut). A proportional hazards log-logistic function was found to be the best fit to the OS data based on the AIC / BIC for OS and graphical inspection of the fit. A relaxation of proportional hazards are indicated whenever there is evidence that the shape of the treatment arms differ. There was no indication of differences in the shapes of the treatments and no violation of the underlying assumption of proportional hazards was noted in the diagnostics (e.g. Martingales) plots. Thus a proportional hazards (same shape parameter) log-logistic model was selected as the best fit parametric function to

model the OS data. For PFS, the gamma function was found to be the best fit according to AIC however the difference between log logistic and gamma for PFS is only one unit (130.86655 and 131.2765). Additionally the BIC which adjusts for a number of parameters in the model is actually best for the log logistic suggesting that this parameter is a better fit to the PFS data when adjusting for a number of parameters estimated in the function. Thus log logistic was selected as best fit for both overall survival and progression-free survival.

The parametric estimates for OS and PFS in prior-taxane treated patients are provided in Table 7 for Bev/Pac and Pac arms under the assumption of proportional hazards for each of the six parametric functions considered. The ‘bevacizumab’ parameter below defines the additional treatment benefit of patients in the bevacizumab+paclitaxel arm above the paclitaxel arm whereas a ‘paclitaxel’ parameter defined the additional treatment benefit of patients in the paclitaxel arm relative to the bevacizumab+paclitaxel (notably negative). The SAS procedure for the gompertz function has been reparameterised to reflect the new therapy instead of the comparator, explaining why a ‘bevacizumab’ term is present instead of a ‘paclitaxel’ term.

Table 7. Parameter estimates for progression-free survival from E2100 for prior taxane treated patients

Log logistic (best fit)	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	2.45201113	0.12271465	0.015059	-0.014776	0.00092
Paclitaxel	-0.85302546	0.17237549	-0.014776	0.029713	-0.000214
Scale	0.50105321	0.04788431	0.00092	-0.000214	0.002293
Weibull	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	2.72111508	0.11588847	0.01343	-0.01352	0.001207
Paclitaxel	-0.75717548	0.1581029	-0.01352	0.024997	-0.001483
Scale	0.66581608	0.06100823	0.001207	-0.001483	0.003722

Gamma	Estimate	Standard Error	Estimated Covariance Matrix			
			Intercept	Paclitaxel	Scale	Shape
Intercept	2.51208908	0.17484256	0.03057	-0.015259	-0.00672	0.046161
Paclitaxel	-0.79771973	0.1693266	-0.015259	0.028671	-0.000699	-0.001623
Scale	0.81488969	0.09940033	-0.00672	-0.000699	0.00988	-0.025857
Shape	0.27653632	0.37094709	0.046161	-0.001623	-0.025857	0.137602

Log normal	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	2.41441676	0.12540146	0.015726	-0.015107	0.002386
Paclitaxel	-0.78725585	0.17295802	-0.015107	0.029914	-0.00097
Scale	0.86407199	0.0739329	0.002386	-0.00097	0.005466

Gompertz	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Bevacizumab	Shape
Intercept	-2.350404958	0.200948395	0.040380257	-0.015328733	-0.003034247
Bevaci-zumab	-1.119399643	0.249535137	-0.015328733	0.062267784	-0.00212291
Shape	0.085867833	0.024992725	-0.003034247	-0.00212291	0.000624636

Expo-nential	Estimate	Standard Error	Estimated Covariance Matrix	
			Intercept	Paclitaxel
Intercept	2.85829404	0.17149858	0.029412	-0.029412
Paclitaxel	-0.87298709	0.23463331	-0.029412	0.055053

Table 8. Parameter estimates for overall survival from E2100 for prior taxane treated patients

Log logistic (best fit)	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	3.20924767	0.10540774	0.011111	-0.011078	0.000404
Paclitaxel	-0.34510963	0.15106827	-0.011078	0.022822	-0.000259
Scale	0.50933302	0.04252858	0.000404	-0.000259	0.001809
Weibull	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	3.47230972	0.09684529	0.009379	-0.009432	0.00062
Paclitaxel	-0.26204213	0.13441858	-0.009432	0.018068	-0.000892
Scale	0.67354499	0.05641514	0.00062	-0.000892	0.003183

Gamma	Estimate	Standard Error	Estimated Covariance Matrix			
			Intercept	Paclitaxel	Scale	Shape
Intercept	3.31296605	0.14116707	0.019928	-0.008913	-0.005573	0.030134
Paclitaxel	-0.31884507	0.15002895	-0.008913	0.022509	-0.002331	0.007617
Scale	0.81438765	0.09404839	-0.005573	-0.002331	0.008845	-0.022503
Shape	0.38253568	0.32232716	0.030134	0.007617	-0.022503	0.103895

Log normal	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	3.19380089	0.11133116	0.012395	-0.012168	0.001293
Paclitaxel	-0.3408934	0.15629941	-0.012168	0.02443	-0.000529
Scale	0.8920512	0.06597179	0.001293	-0.000529	0.004352

Gompertz	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Bevacizumab	Shape
Intercept	-3.654902366	0.20271831	0.041094713	-0.018071801	-0.001337192
Bevaci-zumab	-0.367886487	0.198253885	-0.018071801	0.039304603	-0.000047896
Shape	0.030029396	0.008969234	-0.001337192	-0.000047896	8.04471E-05

Expo-nential	Estimate	Standard Error	Estimated Covariance Matrix	
			Intercept	Paclitaxel
Intercept	3.55355888	0.14285714	0.020408	-0.020408
Paclitaxel	-0.34274147	0.19818196	-0.020408	0.039276

For the triple negative model, the log logistic model was also deemed to be the best fit. Goodness of fit information as well as parameter estimates for the alternative parametric functions can be made available on request.

Table 9. Parameter estimates for progression-free survival from E2100 for triple negative patients

Log logistic (best fit)	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	2.28856554	0.0968129	0.009373	-0.009227	0.000479
Paclitaxel	-0.64046029	0.13475289	-0.009227	0.018158	-0.000072495
Scale	0.50307366	0.03657607	0.000479	-0.000072495	0.001338

Table 10. Parameter estimates for overall survival from E2100 for triple negative patients

Log logistic (best fit)	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	2.9817086	0.07896058	0.006235	-0.006228	0.000083747
Paclitaxel	-0.21450054	0.11883378	-0.006228	0.014121	0.000001898
Scale	0.51121215	0.03177943	0.000083747	0.000001898	0.00101

4.3 Time to off treatment extrapolation updated to reflect subgroups

New time to off treatment curves were calculated from the E2100 study regimens (Bev-Pac and Pac) to reflect the data on the subgroups. The original assumptions for docetaxel remains, that is, treatment until disease progression or a maximum of 6 months (or approximately 8.7 cycles) of treatment.

Dosing was modelled in a similar manner as efficacy (overall & progression free survival) using Kaplan-Meier methods and parametric extrapolation based upon the dosing curves from the trial. The algorithm used to either censor patients or to code patients as having had an event has been previously described in the original Roche submission Section 7.2.1.2. For both subgroups, the Weibull function for both treatments was used in the economic model to reflect time to off treatment (bevacizumab and/or paclitaxel) for each treatment arm.

Table 11. Parameter estimates for bevacizumab time to off treatment calculations for the prior taxane subgroup

Weibull	Estimate	Standard Error	Estimated Covariance Matrix	
			Intercept	Scale
Intercept	2.2380981	0.08351365	0.006975	-0.001377
Scale	0.62598593	0.06538505	-0.001377	0.004275

Table 12. Parameter estimates for bevacizumab time to off treatment calculations for the triple negative subgroup

Weibull	Estimate	Standard Error	Estimated Covariance Matrix	
			Intercept	Scale
Intercept	2.00263435	0.07435523	0.005529	-0.001212
Scale	0.72737843	0.05766586	-0.001212	0.003325

Similarly to the original ITT model, the assumption of proportional hazards was assumed for paclitaxel time to off treatment parametric estimates being that it was administered in both arms. The 'paclitaxel' parameter below defines the additional treatment required of patients in the paclitaxel monotherapy arm (notably always negative). For the prior taxane and triple negative subgroup models, the best fit to the paclitaxel time to off treatment data was a weibull and gompertz function, respectively.

Table 13. Parameter estimates for paclitaxel time to off treatment calculations (for both the bev/pac and pac arms of E2100) – prior taxane subgroup

Weibull	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	2.12725202	0.09405149	0.008846	-0.008479	-0.000701
Paclitaxel	-0.56388323	0.13469383	-0.008479	0.018142	-0.000725
Scale	0.72105678	0.05222847	-0.000701	-0.000725	0.002728

Table 14. Parameter estimates for paclitaxel time to off treatment calculations (for both the bev/pac and pac arms of E2100) – triple negative subgroup

Gompertz	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	-1.745412473	0.128832598	0.016597838	-0.00988567	-0.00122712
Paclitaxel	-0.388406158	0.140612151	-0.00988567	0.019771777	-0.000082661
Scale	0.060640363	0.01547432	-0.00122712	-0.000082661	0.000239455

4.4 Adverse Event rates updated to reflect subgroups

Adverse events rates were updated to reflect those relevant for the E2100 subgroups of interest. Grade 3-4 AEs which were costed in the original submission (febrile neutropenia, hypersensitivity, hypertension, and infection) were the only adverse events for which costs were applied in these subgroups. Disutilities were applied only to febrile neutropenia and peripheral sensory neuropathy. These costs and disutility inputs were described in the original Roche submission. Docetaxel assumptions on AE rates remain the same.

For the prior taxane subgroup, no patients in the paclitaxel arm experienced any of the above five adverse events. In the Bev-Pac arm, 1 patient experienced febrile neutropenia, 2 patients experienced hypersensitivity, 1 patient experienced hypertension, 4 patients experienced infection, and 5 patients experienced peripheral sensory neuropathy.

For the triple negative subgroup, 2 patients experienced hypersensitivity and 1 patient experience peripheral sensory neuropathy in the paclitaxel arm. In the bev-pac triple negative subgroup arm, 1 patient experience febrile neutropenia, 2 patients experienced hypersensitivity, 4 patient experience hypertension, 2 patients experienced infection, and 4 patients experience peripheral sensory neuropathy

4.5 Results

Results for the two models are provided below. Unlike the original Roche submission, the base case in these models do not include the bevacizumab 10 gram capping scheme, however the inclusion of this scheme is incorporated into the sensitivity analysis. The base case does still include two scenarios depending on the generic paclitaxel price used: (1) PASA prices and (2) NHS list prices. We felt this was important as the PASA prices, which do not reflect the NICE reference case, are still significantly more reflective of prices paid in the NHS and is also consistent with the considerations of gemcitabine during technology appraisal 116. Illustrating the impact of this PASA price was explicitly requested during the decision problem meeting for this appraisal. Sensitivity analysis is only conducted on the scenario utilising PASA prices. It should be

noted that aside from the changes noted above, no further changes have been made to the model inputs or assumptions.

4.5.1 Base case results – Prior Taxanes

Costs

Based on paclitaxel PASA prices, Table 15 indicates that bevacizumab given in combination with paclitaxel is associated with an additional average per-patient cost of £33,892 and £28,824 over the analysed patients' lifetime period (a maximum of 10 years) when compared to paclitaxel and docetaxel, respectively.

Table 15: Total average per-patient cost for prior taxane treated patients over a lifetime period of 10 years (deterministic analysis) – PASA prices

Cost component (£)	Bev-Pac	Pac	Doc
Mean cost of PFS	**£40,404**	**£5,587**	**£10,656**
Costs of bevacizumab	£29,738	£0	£0
Administration costs of bevacizumab	£126	£0	£0
Cost of paclitaxel	£746	£428	£0
Administration costs of paclitaxel	£6,647	£3,812	£0
Costs of docetaxel	£0		£7,197
Administration costs of docetaxel	£0		£1,776
Adverse event costs	£112	£0	£326
Cost of supportive care in PFS	£3,035	£1,348	£1,356
Mean cost of Progression	**£11,045**	**£11,970**	**£11,970**
Cost of supportive care in Progression	£7,700	£8,483	£8,483
End of life costs	£3,344	£3,486	£3,486
Mean Total Cost	**£51,449**	**£17,557**	**£22,625**
Incremental Cost		**£33,892**	**£28,824**

Based on paclitaxel NHS list prices, Table 16 indicates that bevacizumab given in combination with paclitaxel is associated with an additional average per-patient cost of £37,358 and £36,951 over the analysed patients' lifetime period (a maximum of 10 years) when compared to paclitaxel and docetaxel, respectively.

Table 16: Total average per-patient cost for prior taxane treated patients over a lifetime period of 10 years (deterministic analysis) – NHS List price

Cost component (£)	Bev-Pac	Pac	Doc
Mean cost of PFS	**£48,531**	**£10,248**	**£10,656**
Costs of bevacizumab	£29,738	£0	£0
Administration costs of bevacizumab	£126	£0	£0
Cost of paclitaxel	£8,873	£5,089	£0
Administration costs of paclitaxel	£6,647	£3,812	£0
Costs of docetaxel			£7,197
Administration costs of docetaxel			£1,776
Adverse event costs	£112	£0	£326
Cost of supportive care in PFS	£3,035	£1,348	£1,356
Mean cost of Progression	**£11,045**	**£11,970**	**£11,970**
Cost of supportive care in Progression	£7,700	£8,483	£8,483
End of life costs	£3,344	£3,486	£3,486
Mean Total Cost	**£59,576**	**£22,218**	**£22,625**
Incremental Cost		**£37,358**	**£36,951**

Life Years and Quality-Adjusted Life Years

Table 17 shows that the combination of Bev-Pac results in a mean gain of 0.654 life years when compared to both regimens and 0.501 and 0.502 quality-adjusted life years (QALYs) when compared paclitaxel and docetaxel over the analysed lifetime period of 10 years. The minor difference in QALY values are attributed to the different adverse event profiles associated with the comparators (specifically the role of febrile neutropenia in patients receiving docetaxel).

Table 17: Total mean QALYs per patient for prior taxane treated patients over a lifetime period of 10 years (deterministic analysis)

Outcome measure	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.624	1.969	1.969
Mean Life Years in PFS (yrs)	1.359	0.615	0.615
Mean life Years in Progression (yrs)	1.264	1.355	1.355
Incremental Life Years		**0.654**	**0.654**
Mean QALYs	1.559	1.058	1.057
Mean QALY in PFS	0.990	0.449	0.447
Mean QALY in Progression	0.569	0.610	0.610
Incremental QALYs		**0.501**	**0.502**

Incremental Cost-Utility Ratio

On the basis of PASA price for paclitaxel, cost per QALY of £67,714 and £57,416 for Bev-Pac therapy relative to paclitaxel and docetaxel, respectively for the prior taxane treated subgroup (Table 18).

Table 18: Cost per life year/cost per QALY gained over a lifetime period of 10 years (deterministic analysis) for prior taxane treated patients – PASA price

Cost-utility results	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.624	1.969	1.969
Mean QALYs	1.559	1.058	1.057
Mean Total Cost	£51,449	£17,557	£22,625
Incremental Life Years		*0.654*	*0.654*
Incremental QALYs		*0.501*	*0.502*
Incremental Cost		*£33,892*	*£28,824*
Cost per Life Year Gained		**£51,816**	**£44,067**
Cost per QALY Gained		**£67,714**	**£57,416**

On the basis of NHS list price for paclitaxel, cost per QALY of £74,640 and £73,605 for Bev-Pac therapy relative to paclitaxel and docetaxel, respectively for the prior taxane treated subgroup (Table 18).

Table 19: Cost per life year/cost per QALY gained over a lifetime period of 10 years (deterministic analysis) for prior taxane treated patients – List price

Cost-utility results	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.624	1.969	1.969
Mean QALYs	1.559	1.058	1.057
Mean Total Cost	£59,576	£22,218	£22,625
Incremental Life Years		*0.654*	*0.654*
Incremental QALYs		*0.501*	*0.502*
Incremental Cost		*£37,358*	*£36,951*
Cost per Life Year Gained		**£57,116**	**£56,492**
Cost per QALY Gained		**£74,640**	**£73,605**

4.5.2 Base case results – Triple Negatives

Costs

Based on paclitaxel PASA prices, Table 20 indicates that bevacizumab given in combination with paclitaxel is associated with an additional average per-patient cost of £25,705 and £20,073 over the analysed patients' lifetime period (a maximum of 10 years) when compared to paclitaxel and docetaxel, respectively for the triple negative subgroup.

Table 20: Total average per-patient cost for triple negative patients over a lifetime period of 10 years (deterministic analysis) – PASA prices

Cost component (£)	Bev-Pac	Pac	Doc
Mean cost of PFS	**£32,713**	**£5,785**	**£11,417**
Costs of bevacizumab	£24,011	£0	£0
Administration costs of bevacizumab	£102	£0	£0
Cost of paclitaxel	£594	£439	£0
Administration costs of paclitaxel	£5,289	£3,913	£0
Costs of docetaxel			£7,747
Administration costs of docetaxel			£1,912
Adverse event costs	£75	£11	£337
Cost of supportive care in PFS	£2,643	£1,421	£1,421
Mean cost of Progression	**£9,629**	**£10,852**	**£10,852**
Cost of supportive care in Progression	£6,186	£7,336	£7,336
End of life costs	£3,443	£3,516	£3,516
Mean Total Cost	**£42,342**	**£16,637**	**£22,269**
Incremental Cost		**£25,705**	**£20,073**

Based on paclitaxel list prices, Table 21 indicates that bevacizumab given in combination with paclitaxel is associated with an additional average per-patient cost of £27,387 and £26,540 over the analysed patients' lifetime period (a maximum of 10 years) when compared to paclitaxel and docetaxel, respectively for the triple negative subgroup.

Table 21: Total average per-patient cost for triple negative patients over a lifetime period of 10 years (deterministic analysis) – NHS List price

Cost component (£)	Bev-Pac	Pac	Doc
Mean cost of PFS	**£39,180**	**£10,570**	**£11,417**
Costs of bevacizumab	£24,011	£0	£0
Administration costs of bevacizumab	£102	£0	£0
Cost of paclitaxel	£7,061	£5,224	£0
Administration costs of paclitaxel	£5,289	£3,913	£0
Costs of docetaxel			£7,747
Administration costs of docetaxel			£1,912
Adverse event costs	£75	£11	£337
Cost of supportive care in PFS	£2,643	£1,421	£1,421
Mean cost of Progression	**£9,629**	**£10,852**	**£10,852**
Cost of supportive care in Progression	£6,186	£7,336	£7,336
End of life costs	£3,443	£3,516	£3,516
Mean Total Cost	**£48,809**	**£21,422**	**£22,269**
Incremental Cost		**£27,387**	**£26,540**

Life Years and Quality-Adjusted Life Years

Table 22 shows that the combination of Bev-Pac results in a mean gain of 0.364 life years when compared to both regimens and 0.312 and 0.313 quality-adjusted life years (QALYs) when compared paclitaxel and docetaxel over the analysed lifetime period of 10 years for the triple negative subgroup. The minor difference in QALY values are attributed to the different adverse event profiles associated with each comparator (specifically the role of febrile neutropenia in patients receiving docetaxel).

Table 22: Total mean QALYs per patient for triple negative patients over a lifetime period of 10 years (deterministic analysis)

Outcome measure	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.179	1.815	1.815
Mean Life Years in PFS (yrs)	1.175	0.646	0.646
Mean life Years in Progression (yrs)	1.004	1.169	1.169
Incremental Life Years		**0.364**	**0.364**
Mean QALYs	1.308	0.996	0.995
Mean QALY in PFS	0.856	0.470	0.469
Mean QALY in Progression	0.452	0.526	0.526
Incremental QALYs		**0.312**	**0.313**

Incremental Cost-Utility Ratio

On the basis of PASA price for paclitaxel, cost per QALY of £67,714 and £57,416 for Bev-Pac therapy relative to paclitaxel and docetaxel, respectively for the triple negative subgroup (Table 23).

Table 23: Cost per life year/cost per QALY gained for triple negative patients over a lifetime period of 10 years (deterministic analysis) – PASA price

Cost-utility results	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.179	1.815	1.815
Mean QALYs	1.308	0.996	0.995
Mean Total Cost	£42,342	£16,637	£22,269
Incremental Life Years		*0.364*	*0.364*
Incremental QALYs		*0.312*	*0.313*
Incremental Cost		*£25,705*	*£20,073*
Cost per Life Year Gained		**£70,636**	**£55,160**
Cost per QALY Gained		**£82,469**	**£64,092**

On the basis of NHS list price for paclitaxel, cost per QALY of £87,865 and £84,740 for Bev-Pac therapy relative to paclitaxel and docetaxel, respectively for the triple negative subgroup (Table 24).

Table 24: Cost per life year/cost per QALY gained for triple negative patients over a lifetime period of 10 years (deterministic analysis)– List price

Cost-utility results	Bev-Pac	Pac	Doc
Mean Life Years (yrs)	2.179	1.815	1.815
Mean QALYs	1.308	0.996	0.995
Mean Total Cost	£48,809	£21,422	£22,269
Incremental Life Years		*0.364*	*0.364*
Incremental QALYs		*0.312*	*0.313*
Incremental Cost		*£27,387*	*£26,540*
Cost per Life Year Gained		**£75,258**	**£72,930**
Cost per QALY Gained		**£87,865**	**£84,740**

4.5.3 Deterministic sensitivity analysis – Prior Taxane treated subgroup

The following sensitivity analysis has been conducted on the prior taxane subgroup only. It can be considered that adjusting model assumptions in the triple negative subgroup

model will result in a similar magnitude of change to those ICERs as well. The following table provides the incremental cost-effectiveness results for a selection of one-way sensitivity analyses. The following tornado diagram ranks these scenarios in terms of impact on the ICER. Sensitivity analysis was performed only on the second base case scenario where the PASA price of paclitaxel are incorporated.

Table 25. One-way sensitivity analyses for prior taxane subgroup

Sensitivity analyses: Bev/Pac compared to	Paclitaxel	Docetaxel
Base case	£67,714	£57,416
10gram capping scheme	£46,447	£36,213
Exponential function	£117,587	£103,143
Log normal function	£70,180	£59,452
Weibull function	£86,854	£72,743
Gompertz function	£100,375	£84,954
Generalized Gamma function	£73,524	£62,148
Utilities: Weighted by response rates (Cooper 2003)	£63,047	£53,090
Utilities: Weighted by response rates (Lloyd 2006)	£59,035	£49,990
First line treatment administered until progression	£136,376	£117,767
Patient weight = 60kg; 1.6 m2	£58,883	£50,062
Patient weight = 80kg; 1.8 m2	£74,777	£64,458
Administration cost: lower quartile	£64,752	£52,176
Administration cost: upper quartile	£69,234	£60,106
Monthy supportive care cost: alternative values (Remak 2004)	£64,278	£54,007
Monthly supportive care cost decrease by 50%	£66,811	£56,524
Monthly supportive care cost increase by 50%	£68,618	£58,308

Figure 7: Tornado diagram for prior taxane subgroup (paclitaxel comparison)

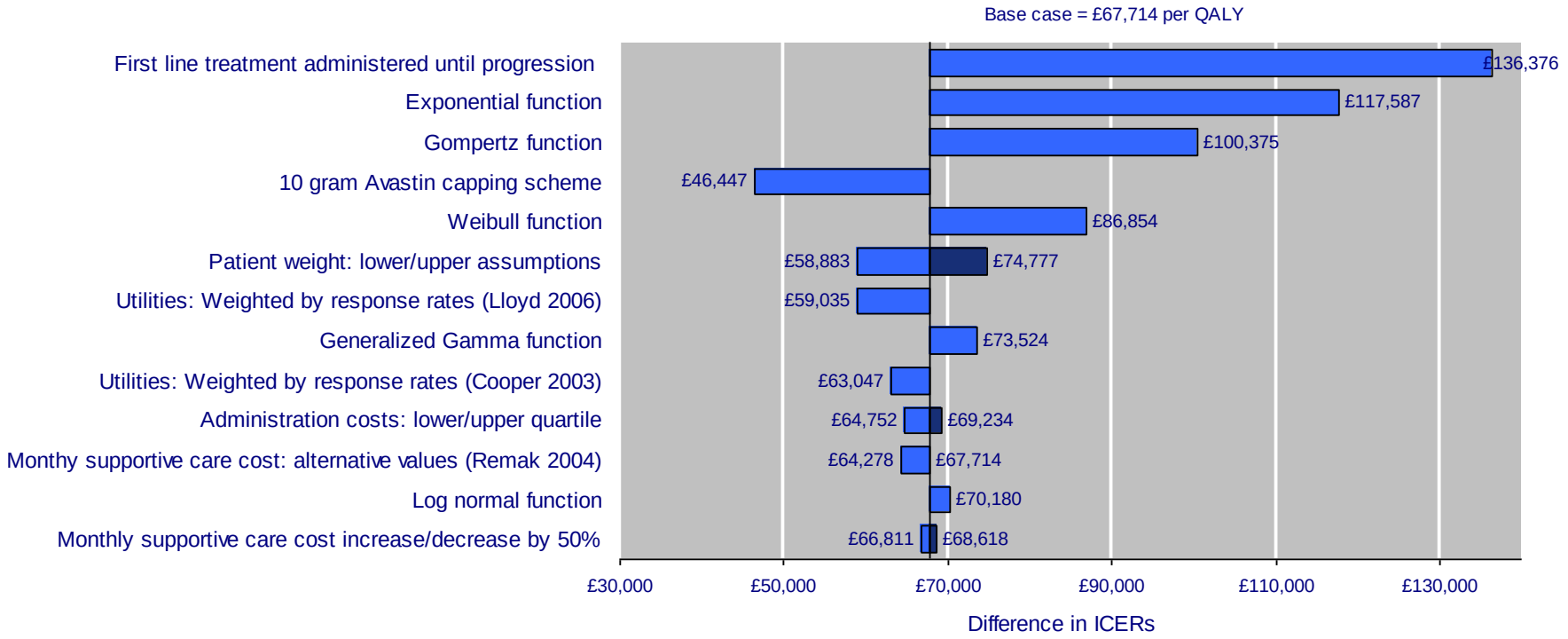
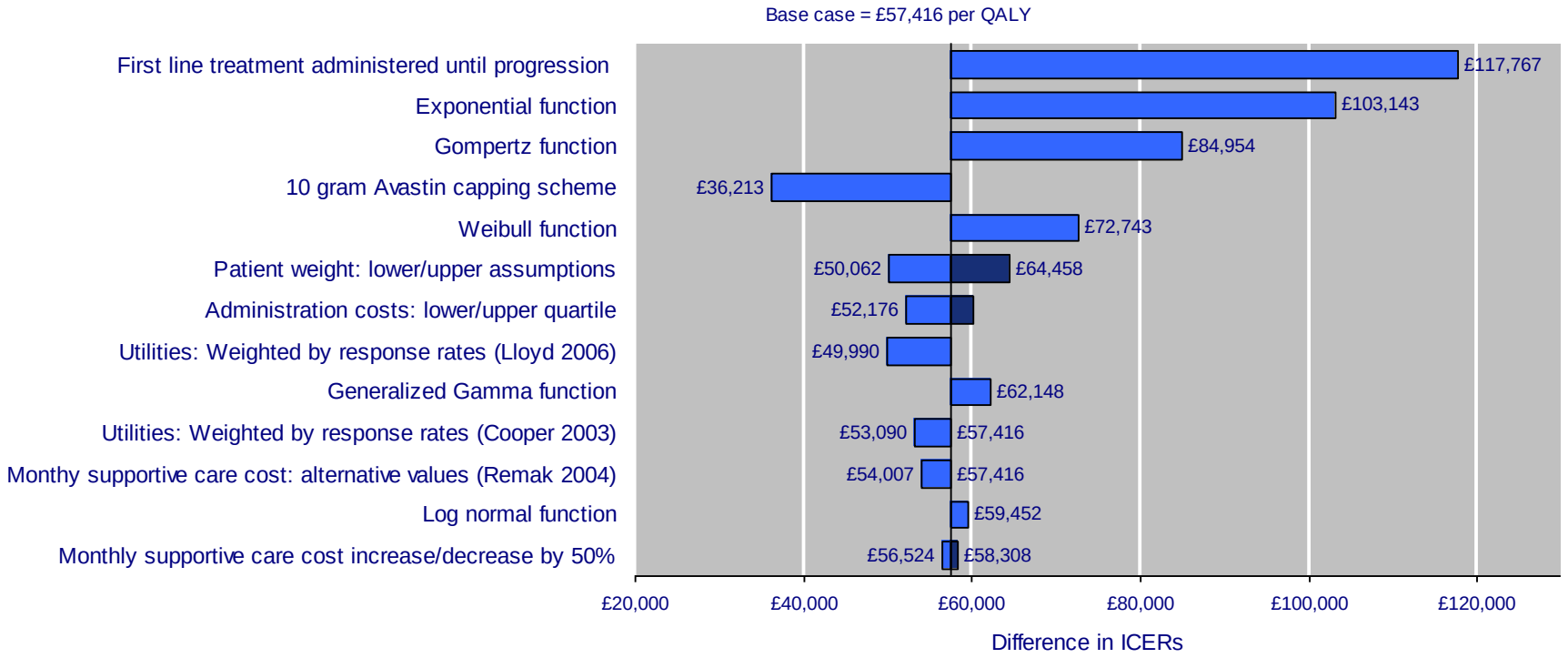


Figure 8: Tornado diagram for prior taxane subgroup (docetaxel comparison)



4.5.4 Probabilistic sensitivity analysis – Prior Taxane treated subgroup

When using a sufficiently high number of Monte Carlo simulations - as example 1,000 iterations - the model produces probabilistic health and economic outcomes that are comparable to that obtained from the deterministic analysis. Below are the mean cost and outcome results from 1,000 runs.

Table 26. Mean Cost Effectiveness results (1000 runs) – Base Case

Bev/Pac compared to paclitaxel	**Base case**	**PSA mean**
Mean incremental costs	£33,892	£34,128
Mean incremental QALYs	0.501	0.508
Cost per QALY Gained	£67,714	£67,148
Bev/Pac compared to docetaxel	**Base case**	**PSA mean**
Mean incremental costs	£28,824	£28,747
Mean incremental QALYs	0.502	0.497
Cost per QALY Gained	£57,416	£57,796

Scatter plots

The cost-effectiveness plane in the example presented below (assumption: 1,000 patients running individually through the model) shows the distribution of incremental cost per QALY ratios in relation to an assumed willingness to pay (WTP) ceiling ratio of £30,000 per QALY.

Figure 9: Scatter plot of ICERs for prior taxane subgroup (paclitaxel comparison)

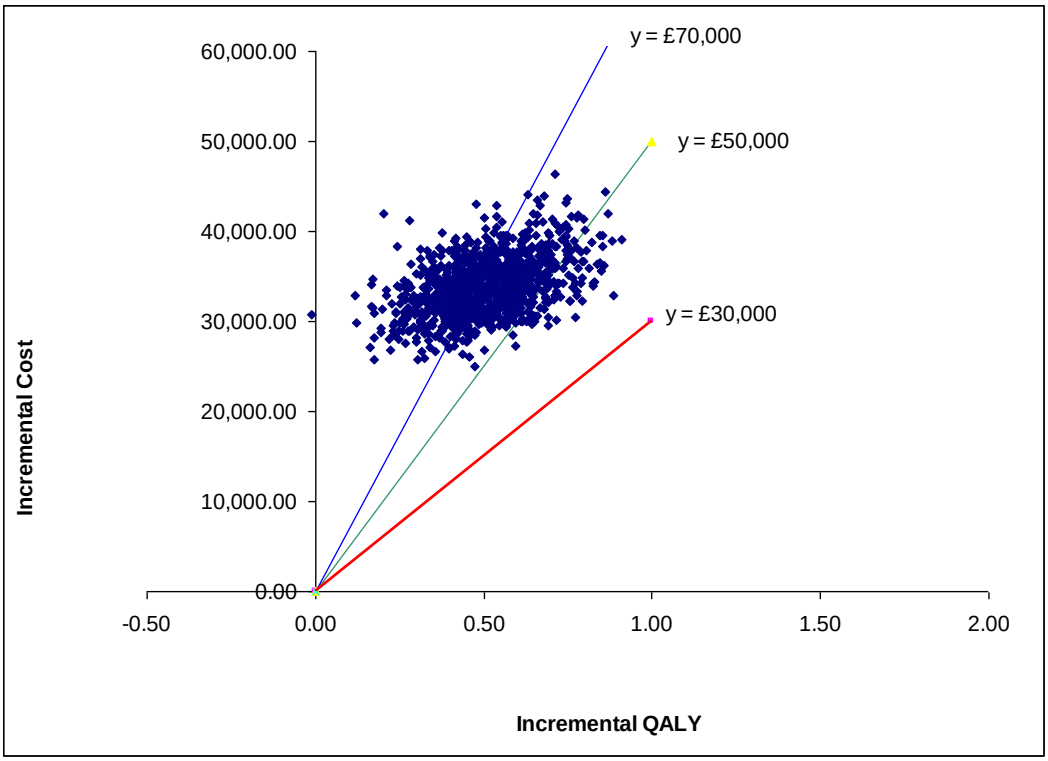
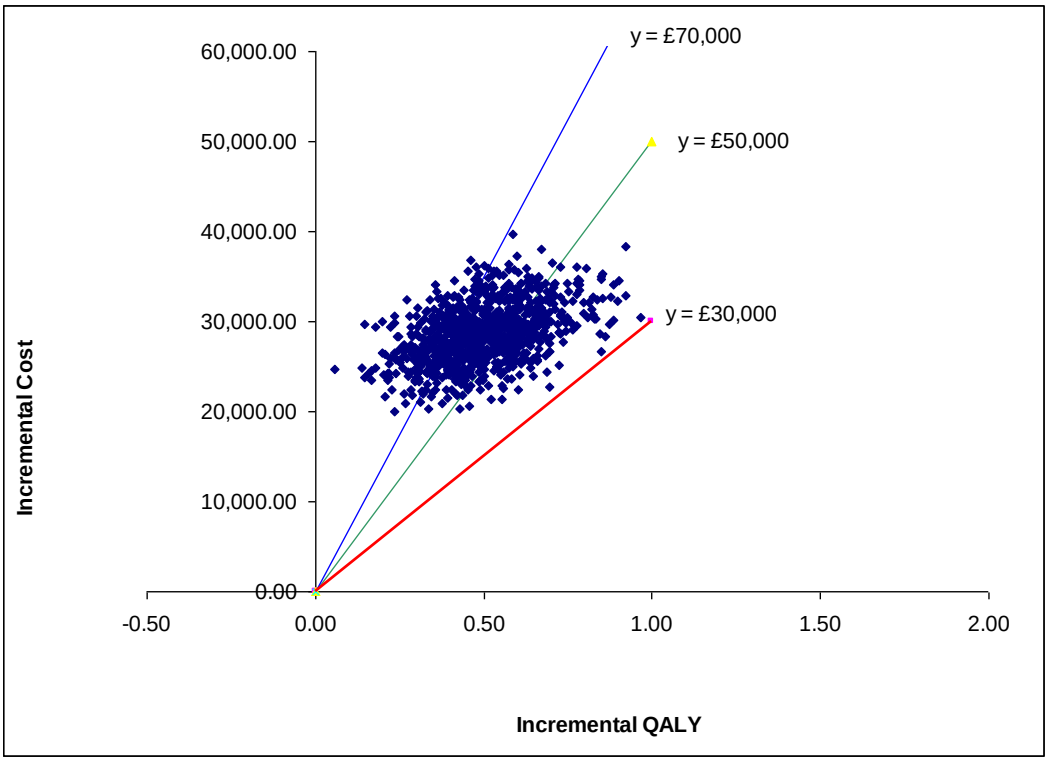


Figure 10: Scatter plot of ICERs for prior taxane subgroup (docetaxel comparison)



Cost-effectiveness acceptability curve (CEAC)

The CEAC graph shows the likelihood of the Bev-Pac treatment being cost-effective at different WTP per QALY thresholds. The probability of not surpassing the £30,000 threshold is 0% against both comparators.

Figure 11: Cost-effectiveness acceptability curve for prior taxane subgroup (paclitaxel comparison)

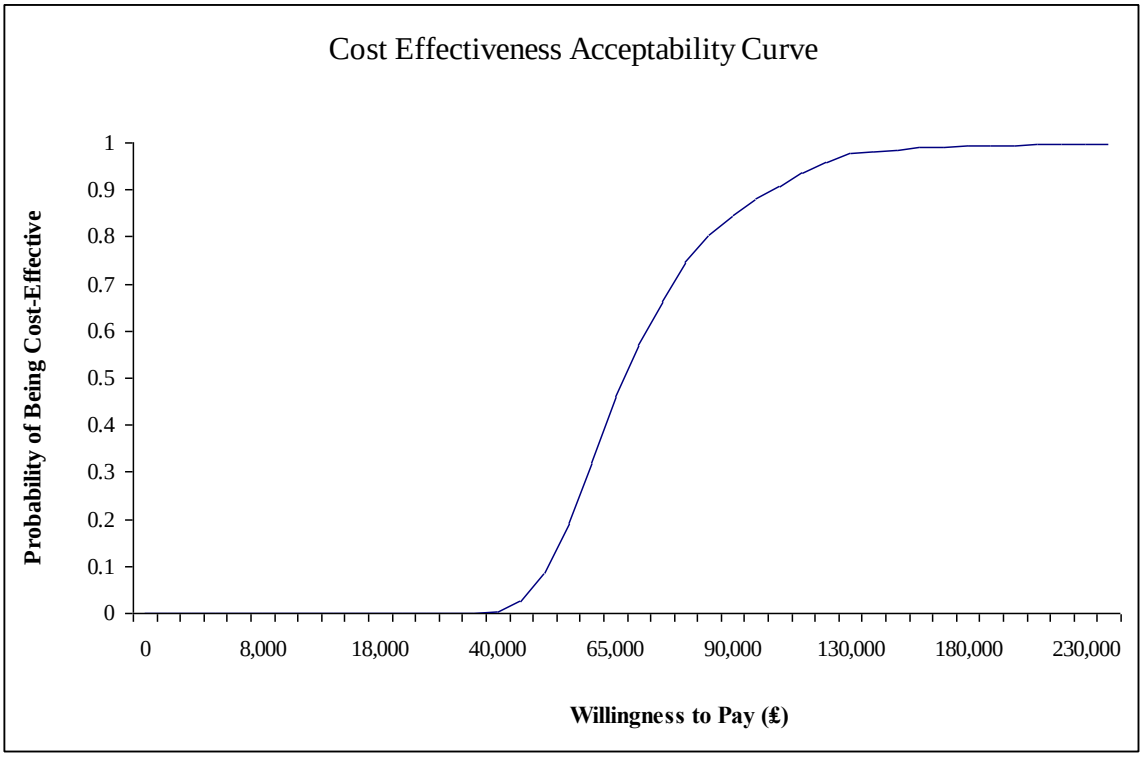
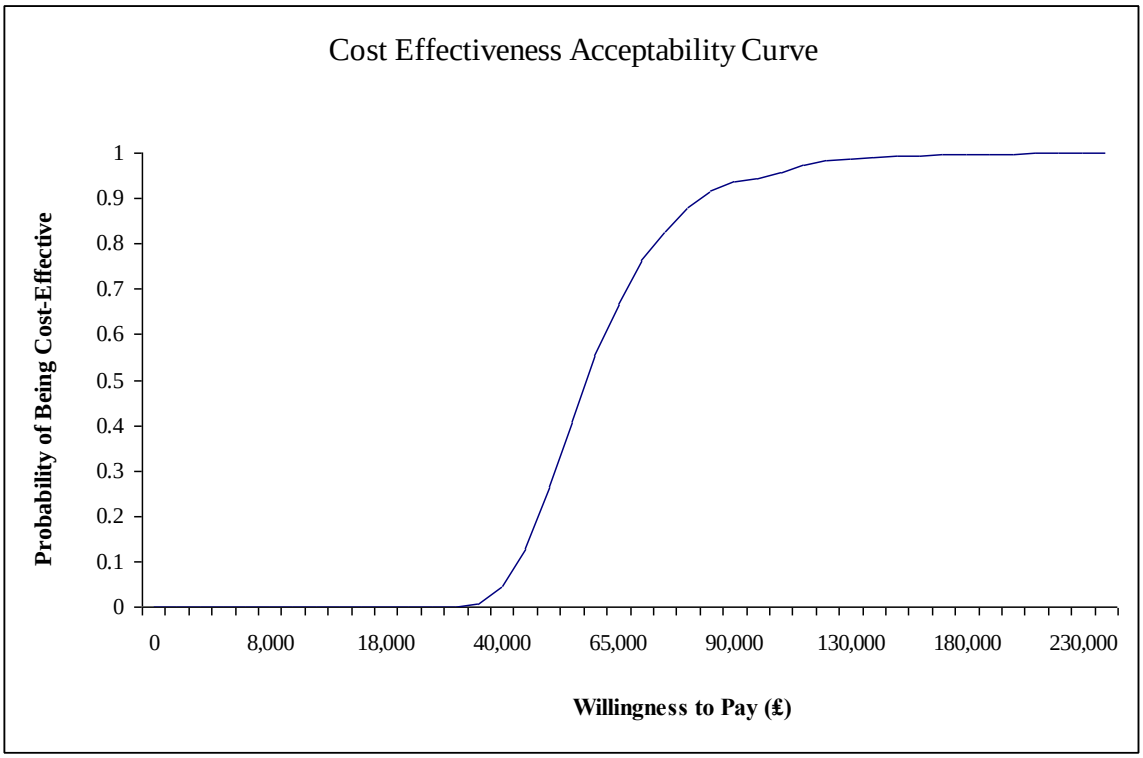


Figure 12: Cost-effectiveness acceptability curve for prior taxane subgroup (docetaxel comparison)



Probabilistic Sensitivity Analysis including the Avastin 10 gram capping program)

One additional set of simulations have been run based on the docetaxel comparison, utilizing the proposed 10 gram capping programme. The PASLU, who assessed the 10g capping programme, has advised the Department of Health that the scheme should not be approved in its current format because the adoption of this scheme would "lead to unduly complex monitoring, disproportionate additional costs and bureaucracy."

However, this decision was not made with consideration of the smaller proposed population (i.e. the prior-taxane subgroup) which may represent the strongest cost-effective case and also a far smaller administration burden on the NHS. The Department of Health has not yet made their final decision on this matter. In this instance that this scheme was made available, the following PSA results would replace those presented above. The probability of not surpassing the £30,000 or £50,000 threshold is 18.2% and 87.9% respectively.

Table 27. Mean Cost Effectiveness results (1000 runs) – including 10g cap

Bev/Pac compared to docetaxel	Base case	PSA mean
Mean incremental costs	£18,179	£18,087
Mean incremental QALYs	0.502	0.501
Cost per QALY Gained	£36,213	£36,138

Figure 13: Scatter plot of ICERs for prior taxane subgroup (docetaxel comparison) – including 10g cap

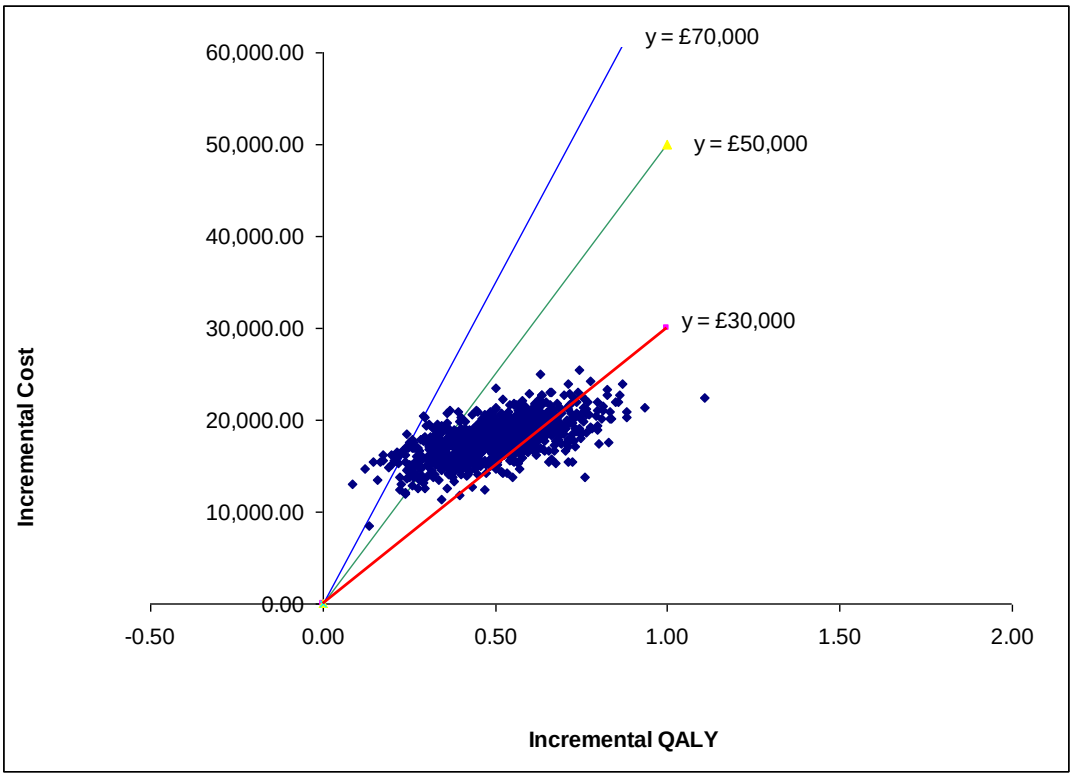
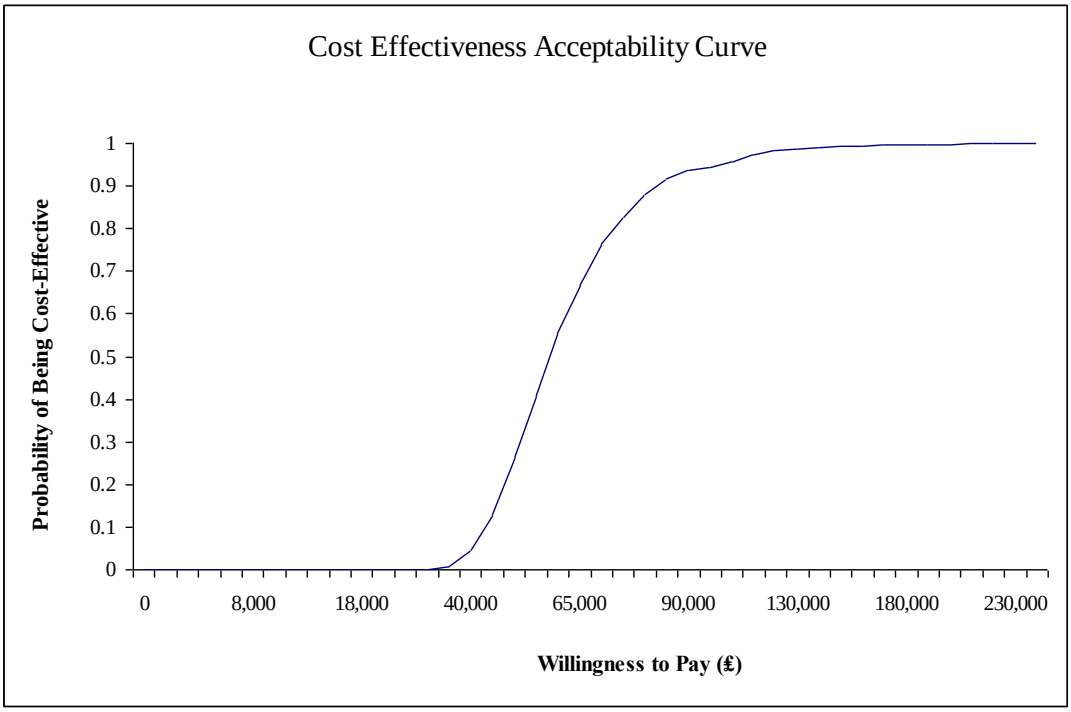


Figure 14: Cost-effectiveness acceptability curve for prior taxane subgroup (docetaxel comparison) – including 10g cap



4.6 Discussion

The results for the updated economic analyses for the prior-taxane and triple negative subgroups reveals that the cost-effectiveness of bevacizumab improves when we consider these sub-populations associated with the improved observed clinical benefit.

Because the updated models attempted to fit the overall survival curves rather than assuming that post-progression mortality rates were identical across arms (as per the original Roche ITT model), these analyses provide a more robust economic case by increasing the face validity of the associated results. Specifically when comparing the median overall survival advantage in the E2100 subgroups to the mean life years gained estimated by the economic model, we can see that the subgroup results are more reflective of the clinical trial than the ITT analysis.

Table 28. Incremental OS gain: comparison of RCT to economic model results

Population	Incremental OS months gained	
	Economic Model means	E2100 RCT medians
ITT	4.2	1.9
Prior Taxane	7.9	8.7
Triple Negative	4.4	4.2

Given that post-progression treatments were not collected in this trial, it is important to remember that cross-over may still factor into the low overall survival gain observed in the E2100 ITT population. This issue may also result in an underestimation of the overall survival gain in our subgroups of interest.

A limitation of this analysis is that the clinical data used to inform the economic models are based on post-hoc exploratory subgroup analyses from a single RCT (E2100). This was necessary as only the E2100 study contained the intervention of interest relative to the scope of this appraisal: bevacizumab in combination with *paclitaxel*. Despite this limitation, we believe that the clinical plausibility of the treatment effects which are utilised in this economic analysis are strongly supported and validated by the additional RCT evidence demonstrating an improved treatment effect in these sub-groups of patients..

It is worth noting that the ICER for prior-taxane treated patients (£57,416 compared to docetaxel) is lower than the ICER for triple negatives (£64,092 compared to docetaxel) despite a higher average patient cost for bevacizumab in the prior taxane subgroup (£29,738 compared to £24,011 for the average triple negative patient). This higher cost is incurred because the prior taxane treated patients remain in PFS longer, thereby completing a longer duration of bevacizumab treatment. However, this higher cost is offset by improved clinical outcomes (i.e. larger QALY gained).

When considering the 10g cap in the sensitivity analysis, it is notable that the ICER drops dramatically for the prior taxane treated and triple negative subgroups to £36,213 and £41,416, respectively, when compared to docetaxel. This highlights one of the benefits of this proposed patient access scheme; where patients who benefit the most from bevacizumab would not incur exceptionally high or greater costs.

5 References

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