[redacted]

Friday 16th April 2010

[redacted]
Midcity Place
71 High Holborn
London
WC1V 6NA

BY E-MAIL

Re: Single Technology Appraisal – Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer

Dear [redacted]

Please find below our responses to the ERG clarification questions.

It has not been possible to provide a response for question B14 within the timescales to date, but will be supplied during the week commencing April 19th. Apologies for any inconvenience this may cause.

We hope this feedback helps clarify the issues raised by the ERG. If you require any further clarification or information then please do not hesitate to contact us.

Yours sincerely,

[redacted]

[redacted]

Section A: Clarification on effectiveness data (all priority questions)

Background

A1. Please provide additional background information regarding which regimens are currently used in UK clinical practice (and how widely these are used) for first line treatment, for example using descriptive data from IMS Oncology registry. Comment on whether there may be situations where particular treatments (or regimens) may not be considered to be relevant comparators (for example frailer patients or those intolerant of particular regimens).

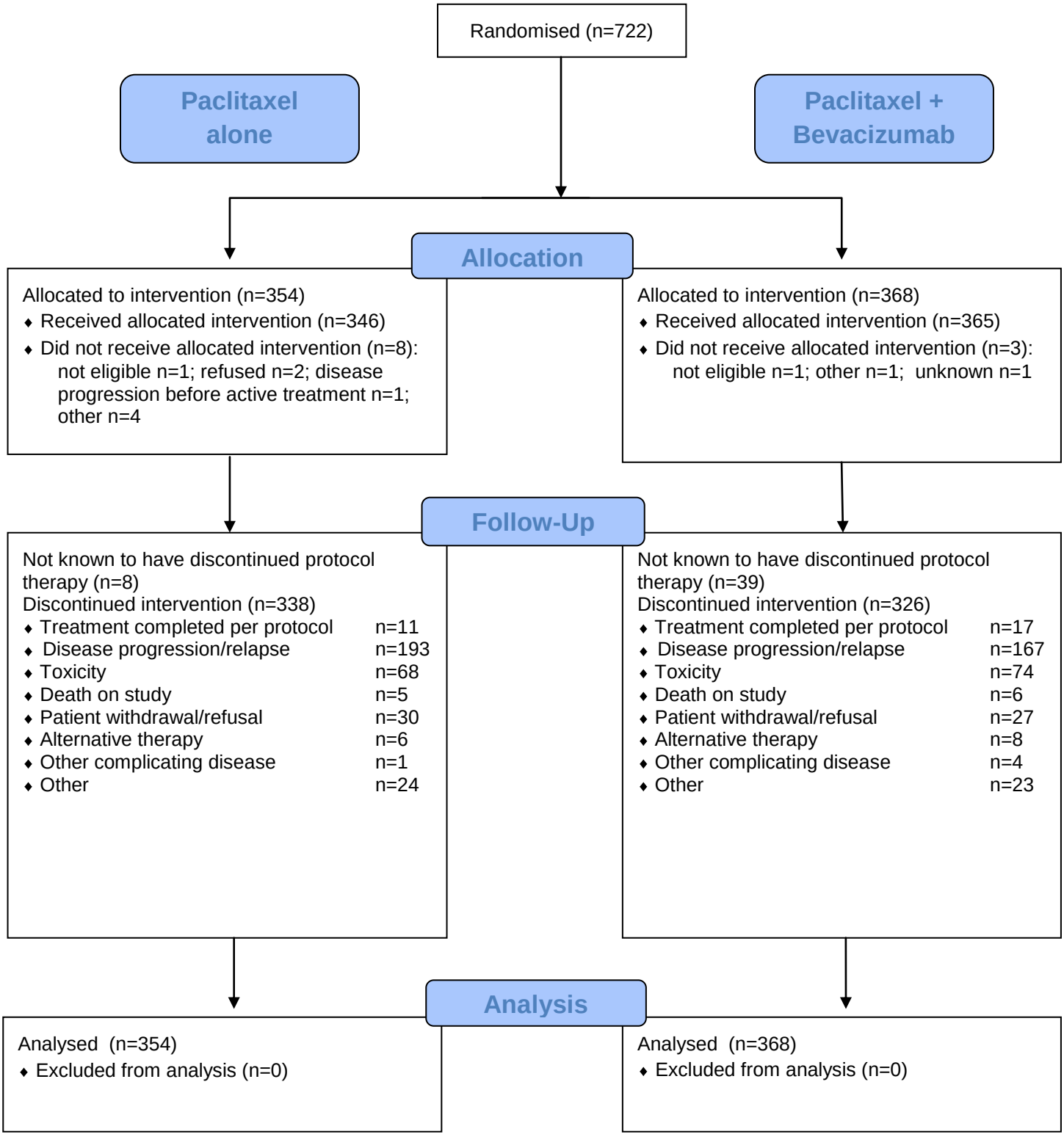
The 2009 NICE Clinical Guideline 81 recommends that for patients with advanced breast cancer who are not suitable for anthracyclines, systemic chemotherapy should be offered in the following sequence:- single-agent docetaxel first-line, followed by single-agent vinorelbine or capecitabine, followed by the alternative single-agent, capecitabine or vinorelbine. The IMS patient record study for the NHS shows that 6% of first-line chemotherapy prescribed for metastatic breast cancer is single-agent epirubicin and combination anthracycline regimens (FEC, EC, AC) are given to an additional 22% of patients. Single-agent taxane is given to 36% of patients (29% docetaxel and 7% paclitaxel), while 32% of first-line patients receive capecitabine and 2% receive vinorelbine. The 34% of patients who do not receive either an anthracycline or a taxane first-line are characterized either by early relapse (within 12 months) after adjuvant taxane therapy or they are patients considered by their clinician to be unable to tolerate the level of toxicity associated with taxane therapy.

Participants

A2. [P82] Consort flow chart for study E2100: The status of 11 patients in the paclitaxel monotherapy arm and 38 patients in the paclitaxel/bevacizumab group was not stated. For example, the total number of patients who received paclitaxel monotherapy is stated as 344, but the total accounted for at follow-up (including those lost) is stated as 333. Please provide information on these patients.

More complete follow-up has provided additional information on the disposition of patients within the study. An updated Consort flow diagram is shown below.

Figure 1. Consort flow diagram of patients in study E2100



A3. [P105] Please provide further justification for including studies with >50% HER2-negative patients in the indirect comparison, given that this criterion is >90% in the direct comparison.

The search for the direct comparison was designed to highlight studies of bevacizumab in line with the scope issued by NICE, i.e. in HER2-negative metastatic breast cancer. Thus the inclusion/exclusion criteria were set for a threshold of >90% HER2-negative patients. Bevacizumab studies in breast cancer commenced after HER2 status was routinely assessed in patients. However, the search for the indirect treatment comparison included studies which commenced before the significance of HER2 status was recognised and some of these studies did not report the proportion of HER2 positive patients or did not select according to HER2 status. For this search a lower proportion of HER2-negative patients was more appropriate. Applying the lower threshold of >50% to the search outputs for both the direct and indirect comparisons does not alter the final list of included studies.

A4. [P106] Selection criteria for the indirect comparison state that trials with ≥60% of patients receiving second or later line treatment were excluded. Please provide justification for setting this threshold at 60%.

The inclusion/exclusion criteria for the indirect comparison were designed to highlight studies in line with the scope issued by NICE, i.e. in first-line metastatic breast cancer. A threshold of 60% was chosen to ensure that studies in which a majority of patients were not treated in the first-line setting were excluded. However, all the trials identified through the search and then excluded on the basis of a majority (≥60%) of patients not being first-line would also be excluded because they do not include two arms relevant to the scope issued by NICE and would not inform the indirect treatment comparison. Therefore, even in the absence of this exclusion criterion the final list of studies for the indirect treatment comparison would remain the same

A5. [P124] Please provide justification for combining the included trials in the indirect comparison, given the observed variation in baseline characteristics presented in Table 19.

The absolute efficacy values shown in the network of studies which provide the indirect treatment comparison are at no point compared directly with one another. Instead each study is used to show the relative efficacy of one therapy versus another, with the assumption that this relative efficacy holds true throughout the patient populations recruited to the various studies. It is therefore important that the baseline characteristics of patients randomised to different arms within the **same** study are very similar, in order to give a true view of the relative efficacy of the therapies compared in that study. However, it is of less importance that the baseline characteristics of patients in the **different** studies are comparable, as there is no direct comparison of the absolute efficacy values for different therapies across the studies.

A6. [P124] The selection criteria state that >50% of study participants must be HER-2 negative for inclusion in the indirect comparison. However, Table 19 states that the proportion of HER-2 negative patients was not reported in

the Albain, CALGB, or Jones studies. Please clarify why these studies were included in the indirect comparison.

The importance of HER2 testing was not recognised until the value of trastuzumab therapy for HER2+ breast cancer was demonstrated. As a consequence, many clinical studies that commenced recruitment prior to the widespread use of trastuzumab did not require HER2 testing and so cannot report the proportion of HER2+ patients recruited. As shown in Section 4.1, some 15-24% of the overall population of breast cancer patients have HER2+ disease. It is therefore reasonable to assume that in clinical studies which did not select patients according to HER2 status (e.g. Albain, Jones), fewer than 50% of the patients had HER2 positive disease. In the CALGB study, some of the patients were HER2 tested, but as there was no enrichment of the population for HER2+ patients, these are very unlikely to make up more than 50% of the total.

Interventions

A7. Please provide full intervention details for the E2100 study, including the (A) dosage and (B) number of treatment cycles received in each study arm, (C) number of patients in each arm who discontinued any of the treatments, (D) details of any co-interventions and (E) the number of patients crossing over between treatment arms.

Part A.

Table 1. Dosage of paclitaxel (PAC) and bevacizumab (BV) in E2100 study

	PAC (n = 342)*	PAC/BV (n = 358)*	
		PAC	BV
Estimated overall dose intensity (mg/kg/cycle for BV and mg/m^2/cycle for PAC)			
n	342	358	358
Mean (SE)	240.9 (2.3)	216.8 (2.9)	17.9 (0.1)
Median	257.3	231.0	18.6
Range	90.0–356.0	32.7–285.0	7.7–29.0
25th−75th percentile	225.0–270.0	189.7–264.2	16.7–20.0
Estimated cumulative dose intensity by Cycle 3 (mg/kg/cycle BV & mg/m^2/cycle PAC)			
n	288	330	330
Mean (SE)	258.7 (1.3)	253.6 (1.5)	19.2 (0.1)
Median	270.0	270.0	20.0
Range	138.3–282.0	145.0–279.0	10.0–23.3
Estimated cumulative dose intensity by Cycle 6 (mg/kg/cycle BV & mg/m^2/cycle PAC)			
n	184	256	267
Mean (SE)	257.7 (1.6)	249.0 (1.7)	19.1 (0.1)
Median	270.0	261.4	20.0
Range	178.5–290.5	138.3–279.0	8.3–21.7
Estimated cumulative dose intensity by Cycle 9 (mg/kg/cycle BV & mg/m^2/cycle PAC)			
n	108	175	196
Mean (SE)	256.6 (2.3)	245.0 (2.3)	19.3 (0.1)
Median	268.4	260.0	19.9
Range	170.0–295.0	133.3–277.0	14.9–21.6

* non- Expanded Participation Project (EPP) patients receiving drug

Part B.

Table 2. Number of treatment cycles received in each study arm of E2100

Doses received per patient	PAC (n=342)*	PAC/BV (n=358)*	
		PAC	BV
Mean (SE)	19.6 (0.8)	27.4 (0.9)	20.1 (0.7)
Median	17	24	18
Range	1 − 74	1 − 97	1 − 76
25th−75th ile	9 − 27	14 − 40	10 − 30
Proportion receiving the following cycles			
1–3	117 (34.2%)	57 (15.9%)	
4–6	89 (26.0%)	70 (19.6%)	
7–9	66 (19.3%)	48 (13.4%)	
10+	70 (20.5%)	183 (51.1%)	
Duration of protocol therapy (months)			
Mean (SE)	5.9 (0.3)	9.7 (0.3)	
Median	5	9	
Range	0–25	0–35	
25th–75th percentile	2–8	5–14	

* non- Expanded Participation Project (EPP) patients receiving drug

Part C. Number of patients in each arm who discontinued any of the treatments; please see Consort diagram.

Part D.

Table 3. Details of co-interventions

Non-Protocol Therapies Administered prior to Progressive Disease

	PAC (n = 354)	PAC/BV (n = 368)	Total (n = 722)
No. of patients who had non-protocol therapy prior to PD per IRF	58 (16.4%)	55 (14.9%)	113 (15.7%)
Chemotherapy	33 (9.3%)	27 (7.3%)	60 (8.3%)
Hormonal therapy	25 (7.1%)	22 (6.0%)	47 (6.5%)
Immunotherapy/biological response modifiers	0 (0.0%)	1 (0.3%)	1 (0.1%)
High-dose chemotherapy/stem cell transplant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Surgery	2 (0.6%)	0 (0.0%)	2 (0.3%)
Radiation	5 (1.4%)	10 (2.7%)	15 (2.1%)
Other non-protocol therapy	1 (0.3%)	2 (0.5%)	3 (0.4%)
Non-protocol therapy given for the disease of protocol			
Yes	55 (15.5%)	54 (14.7%)	109 (15.1%)
No	2 (0.6%)	1 (0.3%)	3 (0.4%)
Unknown	1 (0.3%)	0 (0.0%)	1 (0.1%)

Part E. Number of patients crossing over between treatment arms; apart from the details shown in the CONSORT diagram, these data were not recorded in the E2100 study

A8. [P77] Please provide complete data for the subgroup of relevant patients from the RIBBON-1 trial.

Please see the response to question A.9

Comparators

A9. The ERG has been advised that 100mg/m^2 of docetaxel is used in UK clinical practice. Please provide comprehensive details and data for the AVADO study.

Although 100mg/m^2 docetaxel is routinely used in the adjuvant therapy of early breast cancer, in the therapy of metastatic breast cancer this dosage is only used by a minority of UK clinicians and not for all their docetaxel patients. It is not routine clinical practice across the UK to use the AVADO regimen of 100mg/m^2 docetaxel for 9 cycles. IMS sales data (Section 6.2.3 of Roche Submission) illustrated that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles q3w, at an average planned dose of 150mg (or 79mg/m^2 for an average 1.9m^2 patient). Although the AVADO regimen is in line with the docetaxel licensed indication, it has little relevance for the vast majority of routine NHS clinical practice.

In addition bevacizumab in combination with docetaxel is almost certain to be less cost-effective than bevacizumab in combination with paclitaxel (see page 210 of Roche Submission). Therefore the role of bevacizumab in combination with docetaxel as either an intervention or a comparator of interest for this appraisal is limited as it can be quickly eliminated from a cost effective perspective without the requirement for a complex cost utility model.

Outcomes

A10. [P83] Please clarify if more recent follow-up data are available from the E2100 study than those presented in the submission. If more recent analyses are available, please provide these in full.

The data in this submission are those from the most recent analyses. The most recent data from the E2100 study (overall survival update) were approved by the EMEA and included in the Summary of Product Characteristics on 26 Feb 2008.

A11. [P92] Based on the E2100 trial, please report the median progression-free survival (PFS) for Bev-Pac and Pac alone for each of the subgroups reported in Figure 4.

Figure 4 of the original submission provides the results of median PFS in subgroups from the Investigator-determined dataset. Results for PFS subgroups from the Independently reviewed (IRF) dataset are shown below.

Median overall survival subgroup data are provided on Page 94 of the submission.

Baseline Risk Factor		Total n	PAC (n=354) n	PAC (n=354) Median (mo)	PAC/BV (n=368) n	PAC/BV (n=368) Median (mo)	Hazard Ratio	(95% CI)
All Patients		722	354	5.8	368	11.3	0.54	(0.44 - 0.67)
Age (yrs)								
	<40	59	32	4.8	27	8.3	0.54	(0.26 - 1.09)
	40-64	496	239	6.1	257	12.1	0.51	(0.39 - 0.66)
	>=65	167	83	6.1	84	10.4	0.67	(0.42 - 1.05)
Disease-free interval(months)								
	<=24 months	296	146	4.9	150	10.6	0.58	(0.42 - 0.79)
	>24 months	426	208	8.3	218	12.1	0.50	(0.38 - 0.67)
ER status								
	Positive	446	223	7.7	223	11.9	0.59	(0.44 - 0.78)
	Negative	265	127	4.9	138	11.1	0.44	(0.31 - 0.61)
	Unknown	11	4	21.3	7	*	1.70	(0.15 - 19.07)
ER/PR/HER2 combined								
	Negative	232	110	5.3	122	10.6	0.49	(0.34 - 0.70)
	All others	490	244	7.4	246	12.5	0.57	(0.44 - 0.75)
Number of metastatic sites								
	< 3	514	252	6.6	262	13.3	0.53	(0.41 - 0.69)
	>=3	208	102	4.8	106	8.3	0.56	(0.38 - 0.81)
Measurable Disease at baseline†								
	Yes	472	243	6.7	229	10.7	0.66	(0.51 - 0.85)
	No	250	111	4.1	139	16.6	0.37	(0.25 - 0.54)
Prior adjuvant hormone therapy								
	Yes	343	175	6.1	168	12.4	0.56	(0.41 - 0.77)
	No	379	179	5.5	200	11.1	0.52	(0.39 - 0.70)
Metastatic/Recurrence hormone therapy								
	Yes	262	128	6.0	134	11.9	0.53	(0.37 - 0.77)
	No	460	226	5.8	234	11.1	0.55	(0.43 - 0.72)
Prior adjuvant chemotherapy								
	Yes	475	231	5.8	244	12.4	0.47	(0.36 - 0.61)
	No	247	123	6.1	124	11.2	0.70	(0.49 - 1.01)
Prior taxane therapy								
	Yes	142	68	5.8	74	13.1	0.33	(0.20 - 0.54)
	No	580	286	6.0	294	11.0	0.60	(0.47 - 0.76)
Prior anthracycline therapy								
	Yes	364	180	6.0	184	12.8	0.46	(0.34 - 0.62)
	No	358	174	5.7	184	10.6	0.64	(0.47 - 0.86)

* no median estimate.

A12. Please provide tabulated data on treatment efficacy for each arm in all trials included in the indirect comparison.

Phase III study	**Median PFS/TTP/TTF**		**Objective response rate (ORR)**		**Median overall survival (OS)**	
	Paclitaxel qw	*Paclitaxel qw + Bev*	*Paclitaxel qw*	*Paclitaxel qw + Bev*	*Paclitaxel qw*	*Paclitaxel qw + Bev*
Cameron 2008; Gray 2009 (E2100) Paclitaxel qw (n=354) vs paclitaxel qw + Bev (n=368)	5.8 months	11.3 months	22.2%	49.8%	24.8 months	26.5 months
	Paclitaxel q3w	*Paclitaxel qw*	*Paclitaxel q3w*	*Paclitaxel qw*	*Paclitaxel q3w*	*Paclitaxel qw*
Seidman 2008 Paclitaxel q3w (n=385) vs weekly (n=350)	5.0 months	9.0 months	29%	42%	12 months	24 months
	Paclitaxel q3w	*GemPac*	*Paclitaxel q3w*	*GemPac*	*Paclitaxel q3w*	*GemPac*
Albain 2008 GemPac (n=266) vs Paclitaxel (n=263)	3.98 months	6.14 months	26.2%	41.4%	15.8 months	18.6 months
	Paclitaxel q3w	*Docetaxel q3w*	*Paclitaxel q3w*	*Docetaxel q3w*	*Paclitaxel q3w*	*Docetaxel q3w*
Jones 2005 Docetaxel (n=225) vs paclitaxel (n=224)	3.6 months	5.7 months	25.0%	32.0%	12.7 months	15.4 months

Bev: Bevacizumab; GemPac: Gemcitabine + paclitaxel; PFS: Progression-free survival; q3w: Every 3 weeks; qw: Weekly; TTF: Time to treatment failure; TTP: Time to progression.

A13. [P87] Please provide further justification for imputing FACT-B values of zero for patients who had disease progression.

Two imputation rules were used, one that assumes that missing values are not at random and are likely to be in patients who feel worse (given a zero score) and another assuming that missing values are at random because progression does not worsen patients' status.

The imputation rule of zero for patients with disease progression was agreed with the FDA, at the time of study approval. It is widely accepted that patients are less likely to fill in questionnaires when their disease is worsening. This means that there is the possibility the missing QoL data are not random, potentially introducing a bias against the arm with better outcomes. This is a reason to use the imputation rule of zero for missing values, whether or not the patient has progressed. It may also be argued that all patients with missing values have progressed and that these patients feel worse than those who have not progressed. As the QoL score for these patients is not known, an extreme value of zero is assumed. Utilities scores for responders, stable and progressed patients are reflected in the 2009 NHS Breast Cancer Treatment guidelines.

A14. Please provide safety data reported in the AVADO trial and also for patients receiving bevacizumab and docetaxel in the RIBBON-1 trial.

Please see answer to question A9. In addition, the 2251 patients in the ATHENA study (including 61 patients from 9 UK centres), with its primary endpoint of safety, provide a much larger database for the safety of bevacizumab than the patients in the AVADO and RIBBON-1 studies. The size of the ATHENA study allowed the recognition of Adverse Events which occurred at a frequency of 0.5% and ATHENA patients were treated according to physician's routine clinical practice. Thus the ATHENA study (Section 6.8) provides the most comprehensive and robust safety database for the use of bevacizumab in metastatic breast cancer.

A15. [P101] Please confirm that Table 18 shows the means of the 'raw data' for FACT-B, as collected within the E2100 trial, without any adjustments for missing data. Please confirm whether a negative value of the statistic used (change from baseline) indicates a 'better' or 'worse' result. Please provide the baseline scores (TOI-B and TOT-B) of the FACT-B measure.

Yes, Table 18 shows 'raw' data with no adjustments for missing data. Higher scores were better and lower scores were worse, so a smaller negative change from baseline is "less worse" than a larger negative change from baseline.

Unfortunately it has not been possible to locate the original TOT-B Baseline data, but TOI-B baseline data are shown below.

Table 4. TOI-B Baseline data

	PAC (n=354)	PAC/BV (n=368)
N	327	347
Mean (SD)	63.8 (14.5)	65.1 (13.8)
Median	65	67
Range	14 - 90	22 - 91
25th-75th percentile	54 - 76	56 - 75

A16. [P101] (A) Please clarify the number of patients completing the QoL questionnaire at each stage of the E2100 study (baseline, 17 weeks, 33 weeks) and (B) how these numbers correspond to those reported in Figure 2 (p.82). (C) Please give reasons for censoring/missing data at various time points in the QoL data. (D) Can it be shown that there was no informative censoring/missing data? (E) If available, please provide summary characteristics for those patients who did not complete QoL questionnaires at each time point.

A. please see Table below, Quality of Life Assessment Compliance

B. The numbers in the top row of this Table show the number of patients within the clinical study at baseline and weeks 17 and 33. The patients completing the Quality of Life assessments do not correspond with the numbers shown in Figure 2 on Page 82. C. Reasons for missing data are death, progression of disease or patient declining to fill out the Quality of Life instrument.

D. Please see A13 above and the various imputation rules.

E. Unfortunately these data are not available.

Table 5. Quality of Life Assessment Compliance; Randomized Patients with Baseline FACT−B Assessment

	Baseline		Week 17		Week 33	
	PAC (n=353)	PAC/BV (n=365)	PAC (n=335)	PAC/BV (n=360)	PAC (n=321)	PAC/BV (n=339)
No. of patients with compliance form at visit	321	340	217	276	168	212
No. of patients who self-administered	296 (92.2%)	325 (95.6%)	205 (94.5%)	263 (95.3%)	157 (93.5%)	198 (93.4%)
No. of patients who were assisted	20 (6.2%)	13 (3.8%)	10 (4.6%)	9 (3.3%)	11 (6.5%)	10 (4.7%)
Type of assistance						
Questions were read aloud	15 (75.0%)	7 (53.8%)	9 (90.0%)	6 (66.7%)	9 (81.8%)	8 (80.0%)
Clarification of questions or instructions	3 (15.0%)	5 (38.5%)	0 (0.0%)	2 (22.2%)	1 (9.1%)	0 (0.0%)
Other assistance	2 (10.0%)	1 (7.7%)	1 (10.0%)	1 (11.1%)	1 (9.1%)	1 (10.0%)
Completed independently by another person	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
Reason for assistance						
Language difficulty	5 (25.0%)	4 (30.8%)	1 (10.0%)	2 (22.2%)	2 (18.2%)	0 (0.0%)
Literacy difficulty	4 (20.0%)	3 (23.1%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	1 (10.0%)
Disablity	4 (20.0%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)
Telephone interview	4 (20.0%)	1 (7.7%)	2 (20.0%)	2 (22.2%)	6 (54.5%)	6 (60.0%)
Other	3 (15.0%)	5 (38.5%)	5 (50.0%)	3 (33.3%)	2 (18.2%)	3 (30.0%)

Additional Issues

A17. Please provide details of the intention to treat (ITT) approach used in the analysis of the E2100 trial (e.g. last observation carried forward, imputation), and whether the approach differed for different outcomes.

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients who were randomized to study treatment, irrespective of whether or not the assigned treatment was actually received.

PFS is defined as the time from randomization until the first date that recurrent or progressive disease was objectively documented by the Independent Review Facility (IRF) or death within 84 days of the last study treatment. For patients who did not have disease progression or death by 9 February 2005, PFS was censored at the date of their last tumor assessment in the IRF reviewed database (or if no tumor assessments were performed after the baseline visit, at the time of randomization plus 1 day). Data for patients who died after the data cutoff date of 9 February 2005 without progressive disease (PD) were censored at the last tumor evaluation date before the cutoff date. Data for patients who died before the cutoff date but after 84 days following the last treatment date were censored at the last tumor evaluation date. Data for patients who receive non–protocol-specified cancer therapy prior to experiencing documented disease progression were also be censored at the time of the last tumor assessment

prior to receiving non–protocol-specified cancer therapy. Data for patients with no scans or pertinent medical information submitted to the IRF were censored at the randomization date.

Objective response as determined by the IRF was defined as the occurrence of a complete or partial best overall response (per RECIST), confirmed by repeat assessment performed $\geq$ 4 weeks after the criteria for response were first met. Randomized patients who did not meet this criterion, including patients for whom a post-baseline tumor assessment was not performed, are considered non-responders in the analysis of objective response.

OS is defined as the time from randomization to death from any cause. OS for patients who had not died (or were not known to have died, or were lost to follow-up) at the time of analysis were censored at the date the patient was last known to be alive.

A18. Please provide further methodological and technical details for the indirect comparison analysis (including formulas used and any software packages used to calculate the pooled estimates).

As described in Section 6.6 of the original submission, an indirect comparison was carried out according to the method suggested by Bucher (Bucher et al. 1997) and Song (Song et al. 2003) to compare alternative therapies in which no head-to-head RCT has been conducted. Where standard errors for the hazard ratios were missing, an estimate of this standard error was calculated by the method proposed by Tuder (Tuder et al. 2001). The analysis was performed in Excel. Full details and formulas are provided in the spreadsheet attached.

A18 ITC Calculations.xls

A19. Please clarify how the studies were initially selected for inclusion in section 6.2, prior to the full inclusion criteria listed in 6.2.2 being applied.

Studies were initially selected by running the searches detailed in section 6.1 of the submission using the databases recommended by NICE, as well as other relevant databases. The full results of these searches are provided in appendix 2, section 10.2 of the submission. At this stage, only RCT records were retained for further analysis. Full details of the excluded RCTs are provided in the response to A20 below. Details of the RCTs excluded at first pass and the reason for their exclusion are presented in the table in appendix 2, section 10.2 of the original submission. RCTs retained for further investigation are detailed in section 6.2.1 of the submission.

A20. [P77] Please provide details of the reasons for exclusion of the 266 non-RCT studies in Figure 1.

Details of the 266 excluded non-RCT records are presented in the table below. Most were either review articles or single-arm studies investigating a combination not relevant to the scope of the submission (i.e., combinations other than bevacizumab + paclitaxel or bevacizumab + docetaxel) or in a non-relevant disease setting (e.g., colorectal cancer, neoadjuvant breast cancer, second-line metastatic breast cancer).

The 266 non-RCT records included:

- 120 Non-relevant single-arm studies
    - 82 investigating an agent or combination not relevant to the scope of the submission
    - 21 investigating bevacizumab in a non-relevant disease
    - 17 investigating a non-relevant agent/combination in a non-relevant disease
- 88 Review articles
    - 12 on biological/targeted therapy or anti-angiogenesis in oncology
    - 16 on biological/targeted therapy or anti-angiogenesis in breast cancer
    - 18 on breast cancer treatment in general
    - 22 on bevacizumab in breast cancer
    - 7 on bevacizumab in general
    - 13 other (including biomarkers, imaging, agents other than bevacizumab, non-relevant disease, e.g., HER2-positive)
- 16 Editorials/Opinion pieces
- 14 Case reports/case series
- 11 Biomarker studies
- 9 Small safety studies
- 2 Preclinical studies
- 1 Imaging study
- 5 Other (record deleted by publisher n=2, duplicate record n=2, safety data published in full elsewhere n=1)

AE: Adverse event; BC: Breast cancer; Bev: Bevacizumab: Bio: Biomarker study; CR: Case report or case series; CTCs: Circulating tumour cells; Edit: Editorial; mBC: Metastatic breast cancer; Preclin: Preclinical study; pts: Patients; RA: Not relevant agent; RD: Not relevant disease; Retrosp: Retrospective study; Rev: Not relevant agent.

All studies listed are single-arm, non-randomized studies and therefore do not provide any comparative data.

Search Database	Non-RCT no.	Publication Author	Publication Year	RCT Y/N	Reason for exclusion	Further information
BIOSIS	1.	Bidard	2009	N	Bio	Small biomarker subgroup study (n=67) of ATHENA. No new efficacy or safety data presented
BIOSIS	2.	Ramaswamy	2009	N	RA	Bev + vorinostat
BIOSIS	3.	Jansen	2009	N	RD	Ocular opinion piece
BIOSIS	4.	Kerbel	2009	N	Rev	Anti-angiogenesis in BC
BIOSIS	5.	Grandis	2009	N	Rev	Anti-angiogenesis in oncology
BIOSIS	6.	Jackish	2009	N	Rev	Targeted therapy in oncology
BIOSIS	7.	Traina	2009	N	RA	Bev + capecitabine
BIOSIS	8.	Makhoul	2009	N	RA/RD	Bev + cyclophosphamide/docetaxel, neoadjuvant
BIOSIS	9.	Yardley	2009	N	RA	Bev + anastrazole or fulvestrant
BIOSIS	10.	Rugo	2009	N	RA	Bev + lapatanib
BIOSIS	11.	Dickler	2009	N	RA	Bev + lapatanib
BIOSIS	12.	Volk	2009	N	RA/Preclin	Bev + nab-paclitaxel, preclinical study
BIOSIS	13.	Trinh	2009	N	CR	Biomarker study of 2 pts in AVADO study
BIOSIS	14.	Mayer	2009	N	RA	Vandetanib + chemotherapy
BIOSIS	15.	Ramaswamy	2009	N	RA	Vorinostat + paclitaxel
BIOSIS	16.	Mathews	2008	N	CR	Neuroimaging of 1 pt treated with Bev
BIOSIS	17.	Daniele	2008	N	Rev	Bev in BC
BIOSIS	18.	Barni	2008	N	Rev	General BC treatment
BIOSIS	19.	Saenz	2008	N	RA	Bev + methotrexate + cyclophosphamide
BIOSIS	20.	Bogusz	2008	N	Rev	Bev all indications
BIOSIS	21.	Yu	2008	N	CR	AE in Bev pt
BIOSIS	22.	Gokmen	2008	N	Editorial	Targeted therapy
BIOSIS	23.	Widakowich	2008	N	Rev	HER2-targeted therapy
BIOSIS	24.	Volk	2008	N	RA	Bev + nab-paclitaxel
BIOSIS	25.	Hayes	2008	N	Rev	Angiogenesis in BC
BIOSIS	26.	Heinemann	2008	N	Rev	Bev in BC

BIOSIS	27.	Hurvitz	2008	N	Small safety	Small single-arm study (n=76) of Bev + docetaxel in mBC. Primary outcome safety – unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
BIOSIS	28.	Danso	2008	N	RA	Bev + nab-paclitaxel
BIOSIS	29.	Heinemann	2008	N	Rev	Bev in BC
BIOSIS	30.	Cameron	2008	N	Rev	Bev in BC
BIOSIS	31.	Miles	2008	N	Rev	Bev safety in BC – no new data presented
BIOSIS	32.	Harbeck	2008	N	Rev	Anti-angiogenesis in BC
BIOSIS	33.	Bell	2008	N	Rev	Bev in BC
BIOSIS	34.	Volk	2008	N	RA/Preclin	Bev + nab-paclitaxel, preclinical study
BIOSIS	35.	Baeuerle	2008	N	Preclin	Bone metastases model
BIOSIS	36.	Schroeder	2008	N	Rev	Molecular imaging in BC
BIOSIS	37.	Petrelli	2008	N	Rev	Targeted therapy in oncology
BIOSIS	38.	Hurvitz	2007	N	Small safety	Small single-arm study (n=76) of Bev + docetaxel in mBC. Primary outcome safety – unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
BIOSIS	39.	Schneider	2007	N	Bio	VEGF polymorphism in E2100 – does not provide any new efficacy or safety data
BIOSIS	40.	Ron	2007	N	RA/Preclin	Bev + nab-paclitaxel, preclinical study
BIOSIS	41.	Fumoleau	2007	N	Rev	Anti-angiogenesis in BC
BIOSIS	42.	Mizukami	2007	N	RD/Preclin	Preclinical study in lung cancer
BIOSIS	43.	Lobo	2007	N	RA	Bev + nab-paclitaxel + gemcitabine
BIOSIS	44.	Pivot	2007	N	Rev	Bev in BC
BIOSIS	45.	Miles	2007	N	Rev	Bev in BC
BIOSIS	46.	British Microcirculation Society abstracts	2007	N	RD	Ocular
BIOSIS	47.	Conte	2007	N	Rev	Targeted therapy in BC
BIOSIS	48.	Perez	2006	N	RA	Bev + capecitabine + docetaxel
BIOSIS	49.	Miller	2006	N	RA	Bev + capecitabine
BIOSIS	50.	Link	2006	N	RA	Bev + nab-paclitaxel

BIOSIS	51.	Nicolini	2006	N	Rev	General BC treatment
BIOSIS	52.	Shamseddine	2006	N	RA	Cisplatin + vinorelbine and docetaxel
BIOSIS	53.	Lyseng	2006	N	Rev	Bev all indications
BIOSIS	54.	Winer	2006	N	Opin	General BC treatment – mBC guidelines
BIOSIS	55.	Rugo	2006	N	RA/Bio	Bevacizumab + letrozole
BIOSIS	56.	Di Leo	2006	N	Rev	Biological therapy in oncology
BIOSIS	57.	Fumoleau	2006	N	Opin	General BC treatment – new agents
BIOSIS	58.	Hudis	2006	N	Opin	General BC treatment – first-line therapy mBC
BIOSIS	59.	Nicolini	2006	N	Rev	Biomarkers in BC
BIOSIS	60.	Traina	2005	N	RA	Bev + letrozole
BIOSIS	61.	Rugo	2004	N	RA/Bio	Bev + erlotinib preclinical study
BIOSIS	62.	Garber	2004	N	Opin	Biomarkers – CTCs in oncology trials
BIOSIS	63.	Ramaswamy	2003	N	Small safety	Small single-arm study (n=27) of Bev + docetaxel in mBC. Unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
BIOSIS	64.	Cobleigh	2001	N	RA/RD	Bev monotherapy – dose-finding study previously treated mBC
BIOSIS	65.	Han	2010	N	Rev	Anti-angiogenesis in oncology
BIOSIS	66.	Aggarwal	2009	N	Opin	Biological therapy in oncology
BIOSIS	67.	Record deleted by publisher		n/a	n/a	
BIOSIS	68.	Aapro	2009	N	Rev	General BC treatment - elderly
BIOSIS	69.	Giordano	2009	N	Rev	Targeted therapy in BC
EMYY/ MEYY	70.	Alexander	2009	N	RA	Ipilumumab
EMYY/ MEYY	71.	Balduzzi	2009	N	RA	FEC → Bev + pacli
EMYY/ MEYY	72.	Dickler	2008	N	RA	Bev + erlotinib
EMYY/ MEYY	73.	Burstein	2008	N	RA/Bio	Bev + vinorelbine
EMYY/ MEYY	74.	Toth	2008	N	Rev	Anti-angiogenesis in BC
EMYY/ MEYY	75.	Dales	2008	N	Rev/RA/RD	Bev + lapatinib HER2-positive disease
EMYY/	76.	Prescrire	2008	N	Rev	Bev safety – no new data presented

MEYY		International				
EMYY/ MEYY	77.	Garcia	2008	N	RA	Bev + cyclophosphamide + methotrexate
EMYY/ MEYY	78.	Dellapasqua	2008	N	RA	Bev + cyclophosphamide + capecitabine
EMYY/ MEYY	79.	Daniele	2008	N	Rev	Bev in BC
EMYY/ MEYY	80.	Barni	2008	N	Rev	General BC treatment – chemo/hormonal therapy
EMYY/ MEYY	81.	Roukos	2008	N	Edit	Bev in BC
EMYY/ MEYY	82.	Sirohi	2008	N	Rev	Bev in BC
EMYY/ MEYY	83.	O'Shaugh-nessy	2008	N	Opin	RIBBON-1 and -2 trial overview, description of study designs and aims – published prior to any data being available
EMYY/ MEYY	84.	Heinemann	2008	N	Rev	Bev in BC
EMYY/ MEYY	85.	Krome	2008	N	Opin	Bev in BC and renal cell carcinoma
EMYY/ MEYY	86.	Sledge	2007	N	Edit	General BC treatment
EMYY/ MEYY	87.	Eniu	2007	N	Rev	Biological therapy in BC
EMYY/ MEYY	88.	Lobo	2007	N	RA	Bev + nab-paclitaxel
EMYY/ MEYY	89.	Thukral	2007	N	Imaging/ Retrosp	Retrospective study of 19 patients treated with Bev + paclitaxel – analysis of three imaging methods
EMYY/ MEYY	90.	Pivot	2007	N	Opin	Bev in BC
EMYY/ MEYY	91.	Miles	2007	N	Opin	Bev in BC
EMYY/ MEYY	92.	Klem	2007	N	RA	SABCS 2006 meeting highlights – two non-RCTs summarized (both not RA): Bev + docetaxel + capecitabine; Bev + capecitabine
EMYY/ MEYY	93.	Muss	2006	N	Rev	Targeted therapy in BC

EMYY/ MEYY	94.	Cinieri	2006	N	Opin	General BC treatment
EMYY/ MEYY	95.	Ramaswamy	2006	N	Small safety	Small single-arm study (n=27) of Bev + docetaxel in mBC. Unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
EMYY/ MEYY	96.	Gradishar	2005	N	Opin	General oncology – CTCs and angiogenesis
EMYY/ MEYY	97.	Rugo	2005	N	Opin	Comment on E2100 study – no new data presented
EMYY/ MEYY	98.	Tyagi	2005	N	Rev	Bev in BC
EMYY/ MEYY	99.	Pharmaceut-ical Journal	2005	N	Rev/RA	Bev in BC and lung cancer
EMYY/ MEYY	100.	Rugo	2004	N	Rev	Bev in BC
EMYY/ MEYY	101.	Ramaswamy	2003	N	Small safety	Small single-arm study (n=27) of Bev + docetaxel in mBC. Unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
EMYY/ MEYY	102.	Cobleigh	2003	N	RA/RD	Bev monotherapy – dose-finding study, previously treated mBC
EMYY/ MEYY	103.	Orazio	2001	N	Rev	Bev in BC
EMYY/ MEYY	104.	No author listed	2008	N	Rev	Bev in BC
EMYY/ MEYY	105.	Kassam	2009	N	Retrosp/RA	Triple-negative breast cancer – any treatment
EMYY/ MEYY	106.	Record deleted by publisher	2009	n/a	n/a	
EMBA/ MEIP	107.	Jansen	2009	N	RD	Ocular opinion piece
EMBA/ MEIP	108.	Hsu	2009	N	Rev	Anti-angiogenesis in oncology
EMBA/ MEIP	109.	Greil	2009	N	RA/RD	Bev + capecitabine + docetaxel, neoadjuvant BC

EMBA/ MEIP	110.	Pinto-Marin	2009	N	CR	AE in Bev pt
EMBA/ MEIP	111.	Mychaluk	2009	N	CR	AE in Bev pt
EMBA/ MEIP	112.	Shih	2009	N	Rev	Biological therapy in oncology
EMBA/ MEIP	113.	Miles	2009	N	Rev	General BC treatment
EMBA/ MEIP	114.	Kerbel	2007	N	Rev	Anti-angiogenesis in oncology
EMBA/ MEIP	115.	Sanchez	2009	N	Rev	Biological therapy in BC
EMBA/ MEIP	116.	Mychaluk	2009	N	CR	AE in Bev pt
EMBA/ MEIP	117.	Khosravi	2009	N	Bev	Anti-angiogenesis in BC
EMBA/ MEIP	118.	Petrelli	2009	N	Rev	General BC treatment – triple-negative disease
EMBA/ MEIP	119.	Roland	2009	N	Preclin	Mechanisms of VEGF inhibition in BC
EMBA/ MEIP	120.	Labidi	2009	N	CR	Four patients with brain metastases treated with Bev + paclitaxel
EMBA/ MEIP	121.	Milano	2007	N	Rev	Bev in BC
EMBA/ MEIP	122.	Normanno	2009	N	Rev	Targeted therapy in BC
EMBA/ MEIP	123.	Lorusso	2009	N	Rev	Bev in BC
EMBA/ MEIP	124.	Telli	2009	N	Rev	General BC treatment
EMBA/ MEIP	125.	Brufsky	2009	N	Rev/RA	Trastuzumab in BC
EMBA/ MEIP	126.	Coltelli	2009	N	CR/Biom	VEGF expression in one patient treated with Bev + paclitaxel
EMBA/ MEIP	127.	Pal	2009	N	Rev	General BC treatment – triple-negative disease

EMBA/ MEIP	128.	Collignon	2009	N	Rev	Biological therapy in BC
EMBA/ MEIP	129.	Chekhun	2009	N	Retrosp/RA	Triple-negative breast cancer – any treatment
EMBA/ MEIP	130.	Jassem	2009	N	Rev	General BC treatment
EMBA/ MEIP	131.	Higa	2009	N	Rev	Bev safety – no new data presented
EMBA/ MEIP	132.	Yamauchi	2009	N	Rev	General BC treatment
EMBA/ MEIP	133.	Besse	2010	N	Retrosp/RD	Patients with brain metastases treated with Bev – all licensed indications included
EMBA/ MEIP	134.	Traina	2010	N	RA	Bev + letrozole
EMBA/ MEIP	135.	Perez	2010	N	RA	Bev + capecitabine + docetaxel
EMBA/ MEIP	136.	Wong	2009	N	Rev	General BC treatment
EMBA/ MEIP	137.	Tkackzuk	2009	N	Rev	General BC treatment
EMBA/ MEIP	138.	Schwartz	2009	N	Rev	General BC treatment
EMBA/ MEIP	139.	Goldfarb	2010	N	Rev	Bev in BC
EMBA/ MEIP	140.	Calleri	2009	N	RA	Bev + capecitabine + cyclophosphamide
EMBA/ MEIP	141.	Valachis	2010	N	RA/RD	Meta-analysis of Bev studies in BC – included studies in second-line mBC (RD) and with combinations not relevant (RA) (Bev + capecitabine; Bev + cyclophosphamide + methotrexate)
EMBA/ MEIP	142.	Harris	2010	N	Opin	BC trial design
EMBA/ MEIP	143.	Cortes	2010	N	Rev/RA	Nab-paclitaxel
EMBA/ MEIP	144.	Chekhun	2009	N	Retrosp/RA	Triple-negative breast cancer – any treatment
EMBA/	145.	Meriggi	2009	N	Rev	Biological therapy in BC

MEIP						
EMBA/ MEIP	146.	Toppmeyer	2009	N	Rev/RA	Ixabepilone in BC
EMBA/ MEIP	147.	Bossung	2010	N	Rev	Anti-angiogenesis in BC
EMBA/ MEIP	148.	Kerbel	2009	N	Opin	Anti-angiogenesis in BC
EMBA/ MEIP	149.	Kessler	2010	N	Rev	General oncology treatment
EMBA/ MEIP	150.	Munnink	2009	N	Rev	Imaging methods in BC
EMBA/ MEIP	151.	Montero	2009	N	Rev/RA	Gemcitabine + nab-paclitaxel
EMBA/ MEIP	152.	Endo	2010	N	RA/Preclin	Captothecin analogue
EMBA/ MEIP	153.	Morris	2009	N	RA/RD	Doxorubicin + cyclophosphamide, adjuvant BC
EMBA/ MEIP	154.	Yang	2009	N	Rev	Bev in BC
EMBA/ MEIP	155.	Barnett	2009	N	Opin	General BC treatment
EMBA/ MEIP	156.	Spector	2009	N	Rev/RA	Trastuzumab
EMBA/ MEIP	157.	Sanchez	2009	N	Rev	Targeted therapy in BC
EMBA/ MEIP	158.	Marin	2009	N	CR	AE in Bev pt
EMBA/ MEIP	159.	Jassem	2009	N	Rev	General BC treatment
EMBA/ MEIP	160.	Moreno	2009	N	Rev	General BC treatment
EMBA/ MEIP	161.	Marrs	2009	N	Rev	Bev all indications
EMBA/ MEIP	162.	Ardavanis	2009	N	Retrosp/RD	Retrospective study of 42 patients with previously treated BC treated with Bev + paclitaxel
EMBA/	163.	Kerbel	2007	N	Rev	Anti-angiogenesis in oncology

MEIP						
EMBA/ MEIP	164.	Miles	2009	N	Rev	General BC treatment
EMBA/ MEIP	165.	Petrelli	2009	N	Rev	General BC treatment – triple-negative disease
EMBA/ MEIP	166.	Lorusso	2008	N	Rev	Bev in BC
EMBA/ MEIP	167.	Milano	2009	N	Rev	Bev in BC
EMBA/ MEIP	168.	Coltelli	2009	N	CR/Biom	VEGF expression in one patient treated with Bev + paclitaxel
EMBA/ MEIP	169.	Kumar	2009	N	Rev	Targeted therapy in oncology
EMBA/ MEIP	170.	Franco	2008	N	CR	AE in two Bev pts
EMBA/ MEIP	171.	Drucker	2008	N	Rev	Biological therapy in oncology – economic impact
Cochrane	172.	Guardino	2007	N	RA	Bev + gemcitabine + paclitaxel
ASCO	173.	Rochlitz	2009	N	RA	Bev + liposomal doxorubicin
ASCO	174.	Falkson	2009	N	RA	Bev + hormonal therapy
ASCO	175.	Vanneuville	2009	N	RD	Bev + taxane second- or later line
ASCO	176.	Rastogi	2009	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	177.	Waintraub	2009	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	178.	Ryan	2009	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	179.	Miller	2009	N	RA	Bev monotherapy, case-control study
ASCO	180.	Yardley	2009	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	181.	Yeh	2009	N	Retrosp/RD	Retrospective study of safety in Bev-treated pts – all indications
ASCO	182.	Boasberg	2009	N	RD	Melanoma single-arm study
ASCO	183.	Rohr	2009	N	Retrosp/RD	Retrospective study of safety in Bev-treated pts with brain metastases – BC and lung cancer
ASCO	184.	Espinos	2008	N	RA	Bev + irinotecan
ASCO	185.	Waintraub	2008	N	CR/RA/RD	Five patients treated with Bev + any chemotherapy, any line of treatment
ASCO	186.	Falkson	2008	N	RA	Bev + hormonal therapy
ASCO	187.	Danso	2008	N	RA	Bev + nab-paclitaxel
ASCO	188.	Traina	2008	N	RA	Bev + capecitabine

ASCO	189.	Enzinger	2008	N	RD	Esophagogastric cancer single-arm study
ASCO	190.	Greil	2008	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	191.	Rugo	2008	N	RA	Bev + lapatinib
ASCO	192.	Gluck	2008	N	RA	Bev + gemcitabine + nab-paclitaxel
ASCO	193.	Richardson	2008	N	CR/Retrosp	Elderly pts treated with Bev at a single centre
ASCO	194.	Chu	2008	N	Rev	Bev safety – no new data presented
ASCO	195.	Sierecki	2008	N	RA/RD	Bev + AC + nab-paclitaxel, adjuvant therapy
ASCO	196.	Fiebig	2008	N	RA/Bio	Bev + sunitinib
ASCO	197.	Fu	2008	N	RD	Liver metastases in colorrectal cancer
ASCO	198.	Link	2007	N	RA	Bev + nab-paclitaxel
ASCO	199.	Sledge	2007	N	RA	Bev + capecitabine
ASCO	200.	Rocca	2007	N	RA	Bev + capecitabine + cyclophosphamide
ASCO	201.	Hsu	2007	N	RD	Hepatocellular carcinoma
ASCO	202.	Ramies	2007	N	RD	Colorectal and lung cancer
ASCO	203.	Schmidt	2007	N	RD	Bev safety and G-CSF use – all indications
ASCO	204.	Hart	2007	N	RD/Retrosp	Retrospective analysis of 26 Bev pts, all indications
ASCO	205.	Rugo	2006	N	RA	Bev + letrozole
ASCO	206.	Traina	2006	N	RA	Bev + letrozole
ASCO	207.	Bernstein	2006	N	RA	Bev + carboplatin + nab-paclitaxel
ASCO	208.	Lobo	2006	N	RA	Bev + gemcitabine + nab-paclitaxel
ASCO	209.	Drucker	2006	N	Rev	Biological therapy in oncology
ASCO	210.	Traina	2005	N	RA	Bev + letrozole
ASCO	211.	Rugo	2005	N	RA	Bev + erlotinib
ASCO	212.	Ebrahimi	2005	N	CR/RD	Safety in 31 Bev pts – all indications
ASCO	213.	Skillings	2005	N	RD	Pooled analysis of Bev safety – all indications
ASCO	214.	Dickler	2004	N	RA	Bev + erlotinib
ASCO	215.	Swain	2007	N	Bio	Biomarker study in BC
ASCO	216.	Denduluri	2005	N	Bio	Biomarker study in BC
ASCO	217.	Locatelli	2008	N	RA	Bev + vinorelbine + capecitabine
ASCO	218.	Ordonez	2006	N	RA	Bev + trastuzumab
ASCO	219.	Smith	2009	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	220.	Raefsky	2008	N	RA/RD	Bev + standard neoadjuvant therapy
ASCO	221.	Walshe	2006	N	Bio	CTCs in BC
SABCS	222.	Tan	2009	N	RA	Bev + fulvestrant
SABCS	223.	Guardino	2009	N	RA	Bev + gemcitabine + paclitaxel

SABCS	224.	Bidard	2009	N	Bio	Small biomarker subgroup study (n=67) of ATHENA. No new efficacy or safety data presented
SABCS	225.	Geberth	2009	N	Small safety	Small single-arm study of Bev + paclitaxel in mBC (n=307). Primary outcome safety – unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
SABCS	226.	Mego	2009	N	Bio	CTCs in BC
SABCS	227.	Hurvitz	2009	N	RA	Bev + trastuzumab
SABCS	228.	Rugo	2009	N	RA	Lapatinib
SABCS	229.	Guarneri	2009	N	Safety data presented in full elsewhere	Pooled safety analysis of incidence of osteonecrosis of the jaw (ONJ) in AVADO and ATHENA – no new data presented
SABCS	230.	Hancock	2009	N	Bio	VEGF polymorphisms
SABCS	231.	Hilsenbeck	2009	N	Rev	Clinical trial summary/meeting highlights
SABCS	232.	Ramaswamy	2008	N	RA	Bev + paclitaxel + vorinostat
SABCS	233.	Traina	2008	N	RA	Bev + capecitabine
SABCS	234.	Yardley	2008	N	RA	Bev + hormonal therapy
SABCS	235.	Trinh	2008	N	Bio	Biomarker study of two patients from AVADO study
SABCS	236.	Dickler	2008	N	RA	Bev + lapatinib
SABCS	237.	Smith	2008	N	n/a	Duplicate record
SABCS	238.	Rugo	2008	N	RA	Bev + lapatinib
SABCS	239.	Makhoul	2008	N	RA	Bev + any chemotherapy
SABCS	240.	Lyandres	2008	N	RA	Sunitinib
SABCS	241.	Hurvitz	2007	N	Small safety	Small single-arm study (n=76) of Bev + docetaxel in mBC. Primary outcome safety – unlike the ATHENA study (n>2000) not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
SABCS	242.	McArthur	2007	N	RA/RD	Bev + AC → Bev + nab-paclitaxel, adjuvant BC
SABCS	243.	Greil	2007	N	RA/RD	Bev + standard neoadjuvant therapy
SABCS	244.	de Boer	2007	N	RA/RD	AC + paclitaxel, adjuvant BC
SABCS	245.	Kozloff	2007	N	RA	Sunitinib + paclitaxel
SABCS	246.	Khan	2007	N	RA	Aromatase inhibitor
SABCS	247.	Miller	2006	N	RA	Bev + capecitabine
SABCS	248.	Link	2006	N	RA	Bev + nab-paclitaxel
SABCS	249.	Higgins	2006	N	RA	Bev + capecitabine

SABCS	250.	Perez	2006	N	RA	Bev + capecitabine + docetaxel
SABCS	251.	Sledge	2006	N	RA	Bev + capecitabine
ECCO/ ESMO	252.	Wildiers	2009	N	Rev	General BC treatment - elderly
ECCO/ ESMO	253.	Lorigan	2009	N	RD	Melanoma
ECCO/ ESMO	254.	Pajares	2009	N	Bio/RD/RA	Biomarkers and anti-angiogenesis agents, all indications
ECCO/ ESMO	255.	Foerster	2009	2009	Small safety	Small single-arm study of Bev + paclitaxel in mBC (n=307, data from n=165 available). Primary outcome safety – unlike the ATHENA study (n>2000), safety population not large enough to inform about safety of Bev. Does not inform about efficacy of Bev because no comparator arm.
ECCO/ ESMO	256.	Campagnoli	2009	N	RA	Bev + cyclophosphamide + capecitabine
ECCO/ ESMO	257.	Rochlitz	2009	N	RA	Bev + liposomal doxorubicin
ECCO/ ESMO	258.	Dickler	2008	N	RA	Bev + lapatinib
ECCO/ ESMO	259.	Dellapasqua	2008	N	RA	Bev + cyclophosphamide + capecitabine
ECCO/ ESMO	260.	Gluck	2008	N	RA	Bev + gemcitabine + nab-paclitaxel
ECCO/ ESMO	261.	Ran	2008	N	RA/Preclin	Preclinical study of Bev + nab-paclitaxel
ECCO/ ESMO	262.	Papazisis	2008	N	RA	Bev + vinorelbine + carboplatin
ECCO/ ESMO	263.	Bencardino	2007	N	RD	Colorectal cancer
ECCO/ ESMO	264.	Leong	2007	N	RD	Colorectal cancer
ECCO/ ESMO	265.	Smith	2007		n/a	Duplicate record
ECCO/ ESMO	266.	Kozloff	2007	N	RD	Colorectal cancer

A21. [**P106] The submission states that 'trials with <100 patients receiving a relevant study treatment were excluded' from the indirect comparison. Please provide details of the 12 records excluded on this basis.**

The full citations and abstracts for each of the 12 records are listed below.

1. Meier CR et al. Weekly vinorelbine (VIN) vs weekly docetaxel (DOC) for metastatic breast cancer failing anthracyclines. Planned interim analysis of a randomized trial. J Clin Oncol 2004; 22 (14 Suppl), Abstract 744.

Abstract

Background: Optimal therapy is controversial for metastatic breast cancer no longer eligible for anthracyclines. VIN and DOC are known active regimens. **Methods:** Randomized patients (pts) received VIN 30 mg vs DOC 35 mg/m^2 weekly x 6 for ≤4 cyles of 8 weeks duration. Upon progression, crossing of treatment arms (CTA) was offered. Primary endpoint is time to progression (TTP), others are survival (OS), response, toxicity, and quality of life (not reported here). Analysis at 120 of 240 pts accrued was planned for evaluation of trends. **Results:** Of 121 pts randomized from 11/98 til 07/03, 112 are currently evaluable, VIN (n=57) vs DOC (n=55). Common risk factors are well balanced. 65 CTA pts had VIN (n=31) or DOC (n=34) as 2nd therapy. Overall median follow-up is 230 days (5–1588). Before or without CTA, VIN pts had a median of 7 doses (1–28) for a TTP of 81 days (CI: 67–99), while DOC pts had a median of 11 doses (2–24) for a slightly longer TTP of 103 days (CI: 98–119), (p= 0.1178, log-rank-test). OS for initial VIN vs DOC was 253 (CI: 173–331) vs 288 days (CI: 231–424), (p= 0.1895, log-rank-test). One year survival was 31% for VIN (CI: 20–46%) vs 44% for DOC (CI: 30–60%). More VIN pts (42%) than DOC pts (18%) had disease progression as best response (p=0.00751, Fisher's exact test, double sided); other responses slightly favored initial DOC (not significant). After CTA, DOC produced more responses (35% vs 3%, p≤ 0.0014, Fisher's exact test, double sided), but again without significant benefit in terms of TTP and OS, respectively. Generally, VIN vs DOC resulted in more treatment delays (76% vs 46%), more leukopenia (61% vs 10%) or neutropenia (43% vs 7%) grade 3/4, but less mucositis/stomatitis (1% vs 8%)-(all p<0.05, Fisher's exact test, double sided). 2/5 VIN pts with severe adverse event (SAE) died of neutropenic sepsis, or pulmonary embolism, respectively. 1/10 DOC pts with SAE died of DIC and multiorgan failure. **Conclusion:** DOC was more efficient at response and less toxic than VIN, both before and after crossing of treatment arms, but so far with marginal or no benefit at TTP or OS. TTP benefit may become apparent once accrual is complete.

2. Boccia RV et al. Gemcitabine plus paclitaxel and gemcitabine plus docetaxel in first- or second-line metastatic breast cancer: A phase II randomized trial. J Clin Oncol 2007; 25 (18 Suppl), Abstract 1046.

Abstract

Background: The combination of gemcitabine (G) with paclitaxel (P) has proven efficacy in the first-line treatment of metastatic breast cancer (MBC). In addition, the combination of G with docetaxel (D) has shown activity in several nonrandomized, Phase II, MBC trials. This randomized Phase II trial was conducted to assess the

efficacy and safety of G plus P and G plus D combination regimens in previously treated patients with MBC. **Methods:** Patients with locally advanced or metastatic breast cancer were randomized equally into two groups to receive either GP (G 1,250 mg/m^2 IV on Days 1 and 8 plus P 175 mg/m^2 IV on Day 1) or GD (G 1,000 mg/m^2 IV on Days 1 and 8 plus D 75 mg/m^2 IV on Day 1). Treatment was administered every 21 days and continued until disease progression or undue toxicity. Planned enrollment was 112 patients (56 per group). The primary study objective was tumor response assessed using RECIST criteria. Toxicities were assessed using the NCI Common Toxicity Criteria, Version 2.0. **Results:** Twenty-five patients were enrolled in each treatment group and accrual was stopped due to slow enrollment. In the GP group, only 23 patients were evaluable for response and 24 patients were monitored for safety. One patient did not receive study medication and was not assessed for efficacy or safety. A second patient was determined to have nonmeasurable disease at baseline and was not assessed for response. Overall response rate was 39% (95% CI 20, 61) for the GP group and 40% (95% CI 21, 61) for the GD group. The median number of cycles administered was 6.5 in the GP group and 6.0 in the GD group. Detailed study results are summarized in the table below. **Conclusions:** These results show that GP and GD combination regimens are both efficacious in the treatment of MBC, with similar response rates and manageable toxicity profiles.

Characteristics/Results	GP (N=25)	GD (N=25)
Median age, years	52.4	58.1
Karnofsky performance status, n (%) 70 80 90 100	 3 (12) 7 (28) 6 (24) 9 (36)	 0 (0) 3 (12) 11 (44) 11 (44)
Prior chemotherapy regimens, n (%) 0 1 2	 7 (28) 15 (60) 3 (12)	 9 (36) 13 (52) 3 (12)
Prior adjuvant taxane therapy, n (%) Yes No	 10 (40) 15 (60)	 9 (36) 16 (64)
Efficacy (evaluable patients)	GP (n=23)	GD (n=25)
Complete response (CR), n (%)	0 (0)	2 (8)
Partial response (PR), n (%)	9 (39)	8 (32)
Stable disease (SD), n (%)	6 (26)	6 (24)
Progressive disease (PD), n (%)	2 (9)	2 (8)
Overall response rate (CR+PR), n (%) (95% CI)	9 (39) (20, 61)	10 (40) (21, 61)
Disease control rate (CR+PR+SD), n (%) (95% CI)	15 (65) (43, 84)	16 (64) (43, 82)
Safety	GP (n=24)	GD (n=25)
Grade 3/4 neutropenia, n (%)	8 (33)	11 (44)

Grade 3/4 anemia, n (%)	1 (4)	3 (12)
Grade 3/4 febrile neutropenia, n (%)	0 (0)	4 (16)
Grade 3/4 thrombocytopenia, n (%)	2 (8)	2 (8)
Grade 3/4 abnormal liver function test, n (%)	1 (4)	0 (0)
Grade 3/4 neuropathy, n (%)	2 (8)	0 (0)

3. Wasemann C et al. Docetaxel versus epirubicin/cyclophosphamide (EC) as first-line therapy in metastatic breast cancer (MBC): Results from the randomized phase II TIPP study. J Clin Oncol 2004; 22 (14 Suppl), Abstract 823.

Abstract

Background: Docetaxel is one of the most active single-agent therapies for MBC and may produce higher response rates than current standard regimens. This two-centre randomized, phase II study of docetaxel vs EC was initiated to investigate the therapeutic potential of single-agent docetaxel as first-line therapy for MBC. **Methods:** Patients (pts) with MBC (no prior chemotherapy for metastatic disease) and WHO performance status 0–1 are eligible for the study. Accrual of 60 patients is planned. Pts are randomized to either docetaxel 100mg/m^2 as a 1-hour intravenous infusion (with standard oral dexamethasone premedication) or epirubicin 90mg/m^2 followed by cyclophosphamide 600mg/m^2, each administered as an intravenous bolus. Both regimens are repeated every 3 weeks for a maximum of 6 cycles. **Results:** To date, interim data are available for 34 patients (docetaxel 14, EC 20) who have completed 6 cycles of therapy. In total, 24, 31, and 34 pts are evaluable for tumor response, efficacy, and toxicity, respectively. Two pts died after the first cycle of treatment and 1 pt had only received 1 cycle of treatment at the time of evaluation. Overall response rates were 70% and 64% for docetaxel and EC, respectively (p=ns). Median time to response was significantly shorter for docetaxel compared with EC (3.0 vs 5.7 weeks, p=0.044) and median time to progression was similar for both groups (35.9 vs 39.9 weeks, respectively). To facilitate the comparison of toxicity between treatments, we calculated the mean incidence per cycle of WHO grade toxicities. Grade 1–3 neurotoxicity was reported by significantly more pts receiving docetaxel compared with EC (p=0.028). There were no reports of clinical grade 4 toxicity for either regimen. **Conclusions:** These preliminary phase II data suggest that docetaxel is as effective and well tolerated as EC when used as first-line treatment for MBC. More mature data for 42 pts, including hematotoxity results, will be available by ASCO.

4. Beslija S et al. Randomized trial of sequence vs. combination of capecitabine (X) and docetaxel (T): XT vs. T followed by X after progression as first-line therapy for patients (pts) with metastatic breast cancer (MBC)**.** J Clin Oncol 2006; 24 (18 Suppl), Abstract 571.

Abstract

Background: Capecitabine (Xeloda [X]) and docetaxel (Taxotere [T]) are highly active single agents in MBC. The XT combination leads to superior overall survival (OS), time to progression (TTP) and response rate (RR) vs. T alone in anthracycline-preatreated MBC [O'Shaughnessy et al. J Clin Oncol 2002], although only one third of pts in the T group received X after progression. We designed this study to

determine whether XT is better than sequential T→X in first-line MBC. **Methods:** 100 pts with measurable MBC, prior adjuvant anthracyclines (100%) but no prior chemotherapy for MBC and KPS ≥70 received 3-weekly cycles of either XT (X 1250mg/m^2 bid d1-14 + T 75mg/m^2 d1) or T→X (T 100mg/m^2 d1 followed after progression by X 1250mg/m^2 bid d1-14). X monotherapy data were not considered in the RR or TTP analyses but were included for OS and safety. **Results:** The XT and T→X arms were well balanced for prognostic factors: median age 48 (29-59) vs. 51 (31-64) years; median KPS 100 (70-100) in both arms; hormone-responsive disease 20 vs. 16%; dominant metastatic sites (liver 42 vs. 44%, lymph nodes 34 vs. 36%, lung 28 vs 24%, bone 20 vs 18%); number of involved organs (1 = 58 vs. 52%, >1 = 42 vs. 48%); median interval since prior adjuvant anthracyclines (18.5 vs. 17.0 months). Efficacy findings are shown in the table. 74% of the pts in the T→X arm crossed-over to X on progression. The post-study treatment rate was similar in both arms. The most common grade 3/4 adverse events (>5% of pts) with XT vs. T→X were: hand-foot syndrome 18 vs. 4%; stomatitis 16 vs. 8%; neutropenia 12 vs. 14%; neutropenic fever 12 vs. 14%; diarrhea 12 vs. 8%; fatigue 8 vs. 12%; alopecia 6 vs. 8%; edema 4 vs. 8%. Dose reductions were necessary for 52% of pts on XT and 36% of pts on T→X. **Conclusions:** XT provides significant RR, TTP and OS advantages over T→X. XT should be the standard therapy in fit poor-prognosis pts with aggressive disease.

	XT combination (n=50)	**Sequential T→X (n=50)**	**p value**
Overall response, %	68	40	0.004
Complete response **Partial response**	14 54	6 34	
Median TTP, months (95% CI)	9.3 (8.5-10.2)	7.7 (6.3-9.0)	0.001
	HR = 0.547 (0.312-0.756)		
Median OS, months (95% CI)	22.0 (20.8-23.2)	19.0 (17.9-20.1)	0.006
	HR = 0.528 (0.283-0.811)		

5. Xu B et al. Randomized phase II study of biweekly gemcitabine (gem)-paclitaxel (pac), gem-carboplatin (carb) and gem-cisplatin (cis) as first-line treatments in metastatic breast cancer (MBC) after anthracycline failure. J Clin Oncol 2007; 25 (18 Suplp), Abstract 1099.

Abstract
Background: Biweekly gem-pac and gem-cis regimens have shown promising activity and safety in different tumor types. In MBC biweekly gem-pac is active and well tolerated. The aim of this multi-country study is to evaluate the efficacy and safety of gem in combination with pac, carb or cis on a biweekly schedule in patients (pts) with MBC. **Methods:** Major eligibility criteria included: tissue diagnosis of stage IV breast carcinoma; prior anthracycline therapy; ECOG performance status (PS) of 0 or 1; and written informed consent. Pts were randomized to receive gem 2500 mg/m^2 in combination with pac 150 mg/m^2 (Arm A), carb AUC 2.5 (Arm B) or cis 50 mg/m^2 (Arm C) on day 1 of 2-week cycles. The primary endpoint was response rate, with safety a secondary endpoint. **Results:** This interim analysis was planned to occur when patient enrollment had reached 50% (75/150 pts), at which point there

were 26 pts in Arm A, 25 in Arm B and 24 in Arm C, with 12 pts still on treatment. The baseline characteristics were similar in the three arms, including mean age (Arm A 50.2 yr, Arm B 46.1, Arm C 47.3); ECOG PS (PS 0: 50.0%, 64.0%, 54.2%); mean number of sites of tumor involvement (2.9, 2.6, 2.7); dominant type of metastasis (visceral: 73.1%, 80.0%, 79.2%); and disease-free interval (<24 mo: 53.8%, 60.0%, 41.7%). The mean number of cycles was 6.4, 6.0 and 5.8. There was a partial response in 5/26 efficacy qualified pts (19.2%), 5/25 pts (20.0%) and 2/23 pts (8.7%) in Arms A, B and C, respectively, stable disease in 10 pts (38.5%), 9 pts (36.0%) and 9 pts (39.1%), and progressive disease in 5 pts (19.2%), 6 pts (24.0%) and 6 pts (26.1%). There were no treatment-related deaths. **Conclusions:** The three regimens appear to show activity and have manageable toxicity when given on a biweekly schedule.

Grade 3/4 Toxicity	Arm A (n=167 cycles* or 26 pts**)	Arm B (n=151 cycles* or 25 pts**)	Arm C (n=139 cycles* or 24 pts**)
Neutropenia*	16 (9.6%)	5 (3.3%)	9 (6.5%)
Thrombocytopenia*	1 (0.6%)	0	1 (0.7%)
Anemia*	0	9 (6.0%)	2 (1.4%)
Infection + grade 3/4 neutropenia*	1 (0.6%)	0	0
Nausea**	0	1 (4.0%)	7 (29.2%)
Vomiting**	0	0	8 (33.3%)
ALT**	2 (7.7%)	0	0
AST**	1 (3.8%)	1 (4.0%)	0
Neuropathy - motor/sensory**	0	0	0

6. Bensalem A & Bouzid K. Gemcitabine/paclitaxel compared to gemcitabine/vinorelbine in metastatic breast cancer: An interim analysis. J Clin Oncol 2007; 25 (18 Suppl), Abstract 1097.

Abstract

Background: New combinations and strategies have been developed over the past 10 years including new drugs such as taxanes and gemcitabine. It is not clear whether the activity of the gemcitabine-paclitaxel (GP) combination regimen would translate into better progression-free or overall survival (OS) when compared with gemcitabine-vinorelbine (GV) especially in metastatic breast cancer. This study was conducted to evaluate the overall response rate (RR) of GP Vs GV. Secondary objectives included individual responses of GP and GV, time to progression (TTP), time to treatment failure (TTF), OS, and toxicities. **Methods:** Patients(pts) with histological diagnosis of stage IV or recurrent breast cancer who had PS =2 and measurable disease were randomized to receive GP (Gemcitabine: 1,250mg/m^2 D1 & D8- paclitaxel: 175 mg/m^2 D1, D1=D28) or GV (Gemcitabine: 1,250mg/m^2 D1 & D8 - vinorelbine: 25mg/m^2 D1 & D8, D1=D21). Pts received anthracycline and/or capecitabine chemotherapy in adjuvant and/or metastatic setting. **Results:** Of 47 patients enrolled, 24 patients were randomized to GP arm and 23 to GV arm. 72% of patients were stage IV and 28% recurrent disease. To date, all patients were qualified for safety, TTF, TTP and OS analysis. Hematologic toxicities were: Neutropenia in 23% in GP Vs 17% in GV, Anemia in 12% in GP Vs 9% in GV. Non

hematologic toxicities were essentially nausea and vomiting grad 2-3 in 27% in GP Vs 31% in GV. Anti-emetic agents were administrated to decrease them. The Complete Response (CR) was 27% in GP Vs 30% in GV, the Partial Response (PR) was 23% in GP Vs 17% in GV; with an Overall Response Rate (ORR) of 50% in GP Vs 47% in GV. Median TTF in weeks was 12 in GP Vs 14 in GV. Median TTP (weeks) was 14 in GP Vs 19 in GV. Median OS (weeks) was 32 in GP Vs 50 in GV. **Conclusions:** In our experience, schedules incriminating gemcitabine are efficient and produce clinical benefit and there activities are very interesting. The analysis of the useful of paclitaxel or vinorelbine associated to gemcitabine demonstrates that these associations are active with no significant differences in toxicities. Therefore, the questions are what regimens, for what patients to what high responses in pre-treated metastatic breast cancer.

7. Talbot DC et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. Br J Cancer 2002; 86(9): 1367-72.

Abstract
Capecitabine, an oral fluoropyrimidine carbamate, was designed to generate 5-fluorouracil preferentially at the tumour site. This randomised, phase II trial evaluated the efficacy and safety of capecitabine or paclitaxel in patients with anthracycline-pretreated metastatic breast cancer. Outpatients with locally advanced and/or metastatic breast cancer whose disease was unresponsive or resistant to anthracycline therapy were randomised to 3-week cycles of intermittent oral capecitabine (1255 mg m(-2) twice daily, days 1-14, (22 patients)) or a reference arm of i.v. paclitaxel (175 mg m(-2), (20 patients)). Two additional patients were initially randomised to continuous capecitabine 666 mg m(-2) twice daily, but this arm was closed following selection of the intermittent schedule for further development. Overall response rate was 36% (95% CI 17-59%) with capecitabine (including three complete responses) and 26% (95% CI 9-51%) with paclitaxel (no complete responses). Median time to disease progression was similar in the two treatment groups (3.0 months with capecitabine, 3.1 months with paclitaxel), as was overall survival (7.6 and 9.4 months, respectively). Paclitaxel was associated with more alopecia, peripheral neuropathy, myalgia and neutropenia, whereas typical capecitabine-related adverse events were diarrhoea, vomiting and hand-foot syndrome. Twenty-three per cent of capecitabine-treated patients and 16% of paclitaxel-treated patients achieved a > or =10% improvement in Karnofsky Performance Status. Oral capecitabine is active in anthracycline-pretreated advanced/metastatic breast cancer and has a favourable safety profile. Furthermore, capecitabine provides a convenient, patient-orientated therapy.

8. Tabernero J et al. A multicentre, randomised phase II study of weekly or 3−weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 2004; 15(9): 1358-65.

Abstract
BACKGROUND: A phase II randomised trial was conducted to evaluate the tolerability and activity of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. PATIENTS AND METHODS: Eighty-three patients with histologically proven metastatic breast cancer were randomised to receive either docetaxel 40 mg/m2 weekly for 6 consecutive weeks followed by 2 weeks without treatment (n = 41), or docetaxel 100 mg/m2 on day 1 every 3 weeks (n = 42). RESULTS: The

incidence of all grade 3-4 adverse events was higher in the 3-weekly group than in the weekly group (96 versus 44), and the number of patients with grade 3-4 adverse events was also greater in the 3-weekly group (31 versus 20). Analysis of individual adverse events tended to favour the weekly regimen. Intent-to-treat overall response rate was 34% and 33% in the weekly and 3-weekly groups, respectively. Median time to progression was 5.7 and 5.3 months after weekly and 3-weekly docetaxel, respectively, and median time to treatment failure was 4.1 and 4.9 months, respectively. CONCLUSION: Weekly docetaxel is an active regimen in metastatic breast cancer with comparable efficacy to 3 weekly docetaxel. Although both schedules were well tolerated, weekly docetaxel appears to have a more favourable toxicity profile.

9. Robert N et al. A randomized, phase II trial of weekly paclitaxel versus weekly paclitaxel+carboplatin for first−line metastatic breast cancer. Breast Cancer Res Treat 2003; 82 (Suppl 1), Abstract 534.

Abstract

Background: We have previously reported a phase II study evaluating weekly paclitaxel and carboplatin in first-line metastatic breast cancer (Loesch et al, J Clin Oncol, 20:3857-3864, 2002). In that study there was a response rate of 62%. In this randomized phase II study, we evaluated single-agent weekly Paclitaxel (P) and the combination of weekly paclitaxel and carboplatin (P+C) in patients with previously untreated metastatic breast cancer. **Patients and Methods**: One hundred forty-one patients were registered and randomized to receive, on a weekly basis, either P alone, 100 mg/m^2, or with carboplatin with an AUC = 2 (P+C). Chemotherapy was given on days 1, 8, and 15 of a 28-day cycle. The majority of the patients were Caucasian (82%), ECOG performance status 0/1/2 was 50%/44%/6% and the median age was 59 years (range 33-85). About half of the patients (55%) had received prior adjuvant chemotherapy for breast cancer, and 56% of the patients were ER positive. Patients who were Her-2 *neu* 3+ or FISH positive were excluded. **Results:** For this analysis 84 patients were evaluable for response and time to progression (TTP). The response rate (CR+PR) was 35.0% with P vs. 42.5% with P+C (p=0.64). Median TTP was 5 months with P vs. 7.7 months with P+C (p=0.054). Forty-one (29%) patients died, 1 due to cardiopulmonary arrest, 1 due to unknown causes, and the rest primarily due to progressive disease. In terms of grade 3-4 toxicities, P+C was associated with more neutropenia (38% vs. 14%, p = 0.002). There was no statistically significant difference in neuropathy, neutropenic fever, or fatigue. **Discussion:** Preliminary results of this randomized phase II trial show a trend but no statistically significant improved response rate or time to progression for P+C versus P. This improved trend was not associated with increased toxicity, except for increased neutropenia.

10. Moiseenko VM et al. A comparative randomized phase−II study of Xeloda (capecitabine) and paclitaxel in patients with breast cancer progressing after anthracycline antibiotics. Vopr Onkol 2000; 46(3): 285-89.

Abstract

A randomized study of the effectiveness of treatment with capecitabine (Xeloda) (22) and paclitaxel (taxol) (19) was carried out in breast cancer patients resistant to anthracycline antibiotic drugs. Capecitabine and paclitaxel showed comparable effectiveness, although the former appeared less toxic, particularly, in hematologic complication situations. Therefore, it may be administered to out-patients who previously received several courses of chemotherapy.

11. Wasemann C et al. Randomized phase II study of docetaxel vs. epirubicin/cyclophosphamide to optimize first−line therapy of metastatic breast cancer (MBC): Preliminary results of the TIPP study. Breast Cancer Res Treat 2002; 76 (Suppl 1), Abstract 330.

Abstract

Background: Docetaxel is the most active single agent in the treatment of MBC and may produce higher response rates than current standard regimens. To define the therapeutic role of docetaxel more clearly, we initiated a single-center randomized phase II study of docetaxel versus epirubicin and cyclophosphamide (EC). **Methods:** Patients (pts) with MBC, no prior chemotherapy for metastatic disease, and WHO performance status 0-1 are eligible for the study. Accrual of 40-60 pts is planned. Docetaxel is given at 100 mg/m^2 along with standard oral dexamethasone premedication. Patients in the EC arm receive epirubicin 90 mg/m^2 as an intravenous bolus followed by an intravenous infusion of cyclophosphamide 600 mg/m^2 . In both arms, cycles are repeated every 3 weeks to a maximum of 6 cycles. **Results:** To date, 26 pts have been randomized (docetaxel 11; EC 15), and 12 pts (docetaxel 6; EC 6) have completed chemotherapy. Two EC pts died of progressive disease and another 2 EC pts showed progression under therapy. EC was given at full doses, whereas the dose of docetaxel was reduced to 75 mg/m^2 in one elderly frail pt. No dose delays were required. G-CSF for neutropenia prophylaxis was used in 9 patients (docetaxel 5; EC 4). A total of 32 cycles of docetaxel (mean=4.57) and 55 cycles of EC (mean=4.23) in 20 patients are currently evaluable for toxicity. Toxicity was mild to moderate except for alopecia. To facilitate comparison of toxicity between treatments, we calculated mean WHO grades per cycle. No significant differences for any specific toxicity were seen except for grade I cardiac toxicity in 6 pts (docetaxel 1; EC 5; P=0.036) and grade 1-3 neurotoxicity (docetaxel 6; P=0.028). Mean grade for all toxicities was <1 except nausea/vomiting in the EC arm (1.2) and alopecia in both arms (docetaxel 2.6; EC 2.7). **Conclusion:** Preliminary results indicate that both docetaxel and EC regimens are well-tolerated. More mature data, including response rates, will be available by October 2002.

12. Dieras V et al. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. Semin Oncol 1995; 22(4): 33-39.

Abstract

Paclitaxel (Taxol; Bristol–Myers Squibb Company, Princeton, NJ) has been shown to be an effective agent in the treatment of **metastatic breast** carcinoma. This multicenter **randomized** study compared **paclitaxel** 175 mg/m2 given as a 3–hour infusion every 3 weeks with mitomycin 12 mg/m2 given as an intravenous infusion every 6 weeks. Eighty–one patients have been **randomized,** and preliminary results of a planned analysis of the first 36 evaluable patients per arm are reported. Pretreatment characteristics were well balanced between the two groups. All patients previously have received chemotherapy for **metastatic** disease, and half had both adjuvant therapy and chemotherapy for **metastatic** disease. All but one patient previously had received anthracyclines. Of the first 81 **randomized** patients, 72 were evaluable for response and toxicity (four never treated, five concomitant hormonotherapy). Partial responses were seen in 17% of patients in the **paclitaxel** arm and 6% in the mitomycin arm (P = .14). Crossover to **paclitaxel** therapy following progression on mitomycin achieved an objective response rate of 24% (five of 21 patients). Responses to **paclitaxel** therapy lasted for a median duration of 9.1 months (range, 6.2 to 12+ months). Median time to progression was significantly longer in the **paclitaxel** arm (3.5 months v 1.6 months; P = .026). The quality–of–life–adjusted analysis confirmed the advantage of **paclitaxel** therapy, even when the delay of disease progression was adjusted for important adverse events. Adverse events, most importantly neutropenia and neuropathy, were more frequently observed in the **paclitaxel** arm. However, patients remained on **paclitaxel** therapy for many more courses than did those treated in the mitomycin arm. In conclusion, **paclitaxel** 175 mg/m2 given as a 3–hour intravenous infusion has been demonstrated to be an active agent in the treatment of chemotherapy–refractory advanced **breast cancer,** even after therapy with mitomycin has failed.

Section B: Clarification on cost-effectiveness data

Comparators in the evidence synthesis and economic analysis

B1. Priority question: Please consider approaches to formally incorporate the following comparators into the existing economic analysis and present the results of these analyses:

- **3-weekly paclitaxel monotherapy**
- **Bevacizumab + docetaxel**

If information derived from clinical trials other than the E2100 is used, please provide detailed input data sources and assumptions.

For the comparison against 3-weekly paclitaxel, the economic model for the comparison against gemcitabine + 3-weekly paclitaxel was used, with the following adjustments

1. The treatment benefit of bevacizumab+weekly paclitaxel relative to 3-weekly paclitaxel was derived using the network available from Section 6.6. This consisted of a simple indirect comparison of bevacizumab + weekly paclitaxel versus weekly paclitaxel (from E2100) and weekly paclitaxel versus 3-weekly paclitaxel (from Jones 2005, Seidman 2008). The calculated PFS hazard ratio is 0.338 (95% CI 0.26 to 0.44) as presented in Table 6 below. The calculation is available in the spreadsheet presented in response to clarification question A18.

Table 6. Indirect treatment comparison between bevacizumab+weekly paclitaxel & 3-weekly paclitaxel

Progression Free Survival		HR	LCL	UCL	Reference
A vs. B	HR(BV/Pac q1w vs Pac q1w)	0.484	0.386	0.484	E2100
C vs. B	HR(Pac q3w vs Pac q1w)	1.430	1.23	1.430	Jones 2005Seidman 2008
A vs. C	HR(BV/Pac q1w vs Pac q3w)	0.338	0.26	0.338	ITC
C vs. A	HR(Pac q3w vs. BV/Pac q1w)	2.955	2.248	2.955	ITC

2. The drug and administration cost of gemcitabine was removed from the model inputs

The results, presented in Table 7, suggest that the cost-effectiveness ratio for this comparison against 3-weekly paclitaxel (£59,339 per QALY) is very similar for the comparison against gemcitabine+3-weekly paclitaxel (£60,101 per QALY). This was due to the offset of improved incremental QALYs (0.376 versus 0.259 QALYs gained, respectively) against higher incremental cost (£22,310 versus £15,545 additional cost, respectively). These results are provided according to the assumptions of the second base case (using the paclitaxel PASA price and the 10g cap for bevacizumab.

Table 7. Cost-effectiveness results for bevacizumab+weekly paclitaxel compared to 3-weekly paclitaxel (comparison against gemcitabine+3-weekly paclitaxel presented also)

Cost-utility results	Bev-Pac	Pac 3-weekly	Gem-Pac
Mean Life Years (yrs)	2.682	2.195	2.330
Mean QALYs	1.498	1.122	1.239
Mean Total Cost	£40,826	£18,516	£25,281
Incremental Life Years		*0.487*	*0.352*
Incremental QALYs		*0.376*	*0.259*
Incremental Cost		*£22,310*	*£15,545*
Cost per Life Year Gained (£)		**£45,812**	**£44,168**
Cost per QALY Gained (£)		**£59,339**	**£60,101**

A comparison against bevacizumab + docetaxel is not practical for two reasons:

1. Bevacizumab + docetaxel is not a relevant comparator for several reasons

    - Bevacizumab in combination with docetaxel can be quickly eliminated from a cost effective perspective without the requirement for a complex cost utility model (page 210 of the original submission)

    - This intervention is not recommended by NICE

    - It is not used in standard UK practice

2. The Bucher method used to perform the indirect comparison is only intended to compare two trials via a common comparator. The original analyses presented in Section 6.6 of the submission are already limited by the linking of 3 trials via the Bucher method.

    - The network required to link bevacizumab+paclitaxel with bevacizumab+docetaxel would require 4 linking trials in order to make the requested comparison (Bev/Pac q1w **to** Pac q1w **to** Pac q3w **to** Doc q3w **to** Bev/Doc q3w) and would therefore results in a great level of uncertainty in the point estimates produced. Furthermore, the evidence base for these links are also considerably limited as previously described in Section 6.6 of the original submission.

B2. Priority question: The base-case model assumes that the regimens paclitaxel, docetaxel, and gemcitabine + paclitaxel are equally effective. As an alternative scenario, please re-run the cost effectiveness analysis using the results of the evidence synthesis (disregarding issues of statistical significance).

1. Bevacizumab + weekly paclitaxel compared to 3-weekly docetaxel

Using the hazard ratios calculated in Table 20 of the original submission, the results of the bevacizumab + weekly paclitaxel to docetaxel comparison using the indirect treatment comparison results (HR 0.555 95%CI: 0.39 to 0.78) are presented alongside the original base case results assuming an identical treatment benefit for weekly paclitaxel and docetaxel (due to non-significant HR 1.147 95%CI: 0.89 to 1.48). These results are provided according to the assumptions of the second base case (using the paclitaxel PASA price and the 10g cap for bevacizumab). From Table 8, using the indirect treatment comparison to determine relative treatment benefit for bevacizumab+weekly paclitaxel over docetaxel results in a cost per QALY of £59,310 compared to the base case of £57,753 per QALY where a class effect of weekly paclitaxel and 3-weekly docetaxel was assumed.

Table 8. Cost effectiveness results for bevacizumab+weekly paclitaxel compared to docetaxel using ITC (comparison against docetaxel base case assumption of class effect presented also)

Cost-utility results	**Bev-Pac**	**Doc using ITC**	**Doc base case**
Mean Life Years (yrs)	2.682	2.340	2.330
Mean QALYs	1.498	1.233	1.225
Mean Total Cost	£40,826	£25,111	£25,057
Incremental Life Years		*0.343*	*0.352*
Incremental QALYs		*0.265*	*0.273*
Incremental Cost		*£15,715*	*£15,769*
Cost per Life Year Gained (£)		**£45,865**	**£44,805**
Cost per QALY Gained (£)		**£59,310**	**£57,753**

2. Bevacizumab + weekly paclitaxel compared to gemcitabine + 3-weekly paclitaxel

Using the hazard ratios calculated in Table 21 of the original submission, the results of the bevacizumab + weekly paclitaxel to gemcitabine + 3-weekly paclitaxel comparison using the indirect treatment comparison results (HR 0.464 95%CI: 0.34 to 0.64) are presented alongside the original base case results assuming an identical treatment benefits for weekly paclitaxel and gemcitabine + 3-weekly paclitaxel (due to non-significant HR 0.958 95%CI: 0.76 to 1.21). These results are provided according to the assumptions of the second base case (using the paclitaxel PASA price and the 10g cap for bevacizumab). From Table 9, using the indirect treatment comparison to determine relative treatment benefit for bevacizumab+weekly paclitaxel over gemcitabine + 3-weekly paclitaxel results in a cost per QALY of £51,795 compared to the base case of £60,101 per QALY.

Table 9. Cost effectiveness results for bevacizumab+weekly paclitaxel compared to gemcitabine+3-weekly paclitaxel using ITC (base case comparison against gemcitabine+3-weekly paclitaxel presented also)

Cost-utility results	Bev-Pac	Gem-Pac using ITC	Gem-Pac base case
Mean Life Years (yrs)	2.682	2.282	2.330
Mean QALYs	1.498	1.197	1.239
Mean Total Cost	£40,826	£25,271	£25,281
Incremental Life Years		*0.400*	*0.352*
Incremental QALYs		*0.300*	*0.259*
Incremental Cost		*£15,555*	*£15,545*
Cost per Life Year Gained (£)		**£38,899**	**£44,168**
Cost per QALY Gained (£)		**£51,795**	**£60,101**

Time on treatment

B3. Priority question: [P156-157] Please provide estimated coefficients, standard errors (SE) and variance-covariance matrices for all parametric functions used in fitting these data (as reported in Tables 29 and 30).

The requested parameter estimates are provided below. In order to see how these figures apply to the economic model, please see the sheet entitled 'Doseparm' in the Excel model which includes the Weibull parameters (best fit).

The bevacizumab time to off treatment parametric estimates are provided in Table 10. The Gompertz function did not converge and therefore no parameters could be estimated for this function.

Table 10. Parameter estimates for bevacizumab time to off treatment calculations

Weibull	Estimate	Standard Error	Estimated Covariance Matrix	
			Intercept	Scale
Intercept	2.07839341	0.04325378	0.001871	-0.000404
Scale	0.73801585	0.03330793	-0.000404	0.001109
Gamma	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**	
			Intercept	**Scale**
Intercept	2.21405144	0.06371901	0.004060	-0.001616
Scale	0.66595514	0.03846902	-0.001616	0.001480
Log normal	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**	
			Intercept	**Scale**
Intercept	1.62765896	0.06492503	0.004215	0.000020322
Scale	1.15956907	0.04619626	0.000020322	0.002134
Log logistic	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**	
			Intercept	**Scale**
Intercept	1.77121052	0.05154471	0.002657	-0.000084870
Scale	0.54322380	0.02584931	-0.000084870	0.000668
Exponential	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**	
			Intercept	**Scale**
Intercept	2.00303762	0.05625440	NA	NA
Scale	NA	NA	NA	NA

The paclitaxel time to off treatment parametric estimates are provided in Table 11. The assumption of proportional hazards was assumed for paclitaxel given 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).

Table 11. Parameter estimates for paclitaxel time to off treatment calculations (for both the bev/pac and pac arms of E2100)

Weibull	Estimate	Standard Error	Estimated Covariance Matrix		
			Intercept	Paclitaxel	Scale
Intercept	1.97680365	0.04330155	0.001875	-0.001790	-0.000196
Paclitaxel	-0.31664433	0.06087851	-0.001790	0.003706	-0.000056135
Scale	0.75962512	0.02411607	-0.000196	-0.000056135	0.000582
Gompertz	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Shape**
Intercept	-1.936832385	0.0734272662	0.0053915634	-0.002778951	-0.000412082
Paclitaxel	-0.423474447	0.0808188331	-0.002778951	0.0065316838	-0.000097466
Shape	0.0806459784	0.0089649308	-0.000412082	-0.000097466	0.00008037
Gamma	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**			
			Intercept	**Paclitaxel**	**Scale**	**Shape**
Intercept	2.07080962	0.05221269	0.002726	-0.001227	-0.000787	0.003493
Paclitaxel	-0.29150382	0.05761910	-0.001227	0.003320	-0.000245	0.001041
Scale	0.70732905	0.02878486	-0.000787	-0.000245	0.000829	-0.001879
Shape	1.29483181	0.10717742	0.003493	0.001041	-0.001879	0.011487
Log normal	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	1.53559397	0.06387495	0.004080	-0.004080	0.000009842
Paclitaxel	-0.35078265	0.09158600	-0.004080	0.008388	-0.000009842
Scale	1.14627050	0.03247577	0.000009842	-0.000009842	0.001055
Log logistic	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	1.68318788	0.05098692	0.002600	-0.002597	-0.000039583
Paclitaxel	-0.38534998	0.07332155	-0.002597	0.005376	0.000021173
Scale	0.54165521	0.01830288	-0.000039583	0.000021173	0.000335
Expo-nential	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	1.91104357	0.05598925	0.003135	-0.003135	0
Paclitaxel	-0.33450366	0.08008424	-0.003135	0.006413	0
Scale	NA	NA	0	0	0

B4. [P156-157] Please report the mean [and SE or 95% confidence interval (CI)] of the time to off drug for bevacizumab and paclitaxel (for the Bev-Pac arm and the Pac alone arm of the E2100 trial) based on both the Kaplan Meier curves [e.g. by using the area under the curve (AUC) method] and the parametric functions fitted to the data.

The requested information is provided in Table 12 below. Kaplan Meier data is based on last observed time based on 21 October 2006 cutoff, representing a median follow up of 35.2854 months (95% CI: 34.2669, 36.0411), whilst the economic model data is based on the parametric extrapolation of lifetime treatment.

Table 12. Mean time to off treatment

Time to off treatment (months)	Kaplan Meier (mean/SE based on last observed time)	Model (mean/95%CI from PSA with 10,000 runs using Weibull best fit)
Bevacizumab	7.3765 (SE 0.2910)	7.83 (95% CI: 7.20 to 8.42)
Paclitaxel (Bev/Pac arm)	6.7226 (SE 0.2571)	7.16 (95% CI: 6.57 to 7.71)
Paclitaxel (Pac arm)	4.8382 (SE 0.2168)	5.35 (95% CI: 4.98 to 5.77)

Progression-free survival (PFS)

B5. [P169, Figure 13] Based on the E2100 trial, please provide the following from the Kaplan Meier analysis (and thus for every time point a failure has occurred or at regular time points, for example monthly) for each arm of the trial.

- **Number at risk over time**
- **Proportion of 'survivors' over time**
- **Confidence intervals for each of these proportions**

Attached below is the Kaplan Meier output for PFS from E2100. Standard errors, instead of confidence intervals, are available for each time point a failure has occurred.

B5 KM_PFS.xls

B6. Priority question: [P171, Table 34 and Figure 13] Please provide estimated coefficients, standard errors and variance-covariance matrices for all parametric functions reported in Table 34. Please provide a figure showing the predicted PFS estimates for all parametric functions superimposed with the Kaplan Meier estimates.

The progression-free survival parametric estimates are provided in Table 13 for Bev/Pac and Pac arms under the assumption of proportional hazards. 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. In order to see how these figures apply to the economic model, please see the sheet entitled 'Gompertz' in the Excel model which includes the PFS parameters for the best fit.

Figures showing the predicted PFS estimates for all parametric functions superimposed with the KM estimates was provided in the original submission (Figures 18 through 22).

Table 13. Parameter estimates for progression-free survival from E2100

Gompertz (best fit)	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Bevacizumab**	**Shape**
Intercept	-2.519162728	0.091091132	0.008297594	-0.004130136	-0.000543326
Bevaci-zumab	-0.616736972	0.108672413	-0.004130136	0.011809693	-0.000247607
Shape	0.0533628	0.010154641	-0.000543326	-0.000247607	0.000103117
Weibull	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	2.67541305	0.05647175	0.003189	-0.003158	0.000268
Paclitaxel	-0.46804655	0.07788783	-0.003158	0.006067	-0.00016
Scale	0.73381046	0.03063155	0.000268	-0.00016	0.000938
Gamma	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**			
			Intercept	**Paclitaxel**	**Scale**	**Shape**
Intercept	2.50183824	0.07876471	0.006204	-0.003534	-0.001491	0.007436
Paclitaxel	-0.49926663	0.08358376	-0.003534	0.006986	-0.000143	0.000153
Scale	0.88432738	0.05251886	-0.001491	-0.000143	0.002758	-0.005763
Shape	0.42287118	0.14879276	0.007436	0.000153	-0.005763	0.022139
Log normal	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	2.3475997	0.06451263	0.004162	-0.003938	0.000637
Paclitaxel	-0.4842809	0.08805375	-0.003938	0.007753	-0.000113
Scale	0.99447172	0.03858535	0.000637	-0.000113	0.001489
Log logistic	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	2.38354618	0.06103193	0.003725	-0.003631	0.000234

Paclitaxel	-0.561584	0.0852646	-0.003631	0.00727	0.000004574
Scale	0.56178607	0.02435971	0.000234	0.000004574	0.000593
Expo-nential	**Estimate**	**Standard Error**	**Estimated Covariance Matrix**		
			Intercept	**Paclitaxel**	**Scale**
Intercept	2.77137045	0.07602859	0.00578	-0.00578	0
Paclitaxel	-0.50802912	0.10590151	-0.00578	0.011215	0
Scale	NA	NA	0	0	0

B7. Priority question: Please report the mean (and SE or 95% CI) time to PFS for the regimens Bev-Pac and Pac alone based on both the Kaplan Meier curves (e.g. using AUC calculations) and the parametric functions considered.

The requested information is provided in Table 14 below. Kaplan Meier data is based on last observed time based on 21 October 2006 cutoff, representing a median follow up of 35.2854 months (95% CI: 34.2669, 36.0411), whilst the economic model data is based on the parametric extrapolation of lifetime progression-free survival (10 year time horizon).

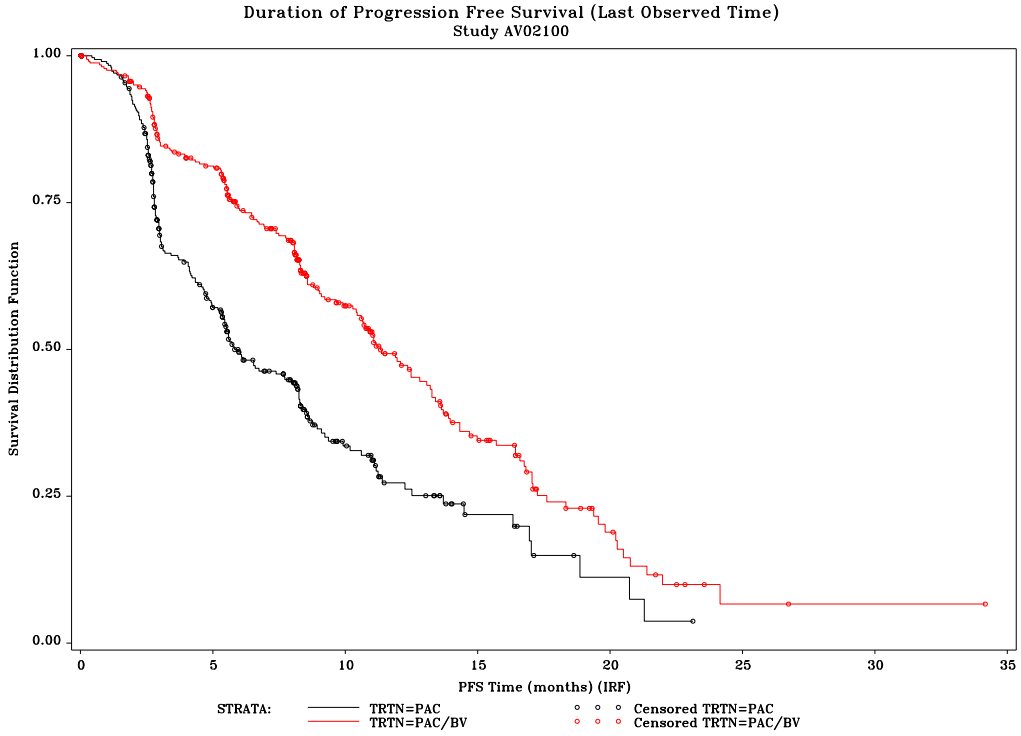
Table 14. Mean time in progression-free survival

Progression-free survival (months)	Kaplan Meier (mean/SE based on last observed time)	Model (mean/95%CI from PSA with 10,000 runs using Gompertzl best fit)
Bevacizumab/Paclitaxel	12.7547 (SE 0.4977)	12.47 (95% CI: 11.16 to 13.68)
Paclitaxel	8.6411 (SE 0.6867)	8.21 (95% CI: 7.32 to 9.12)

B8. Please provide the results of statistical tests (or graphs) to justify the assumption of proportional hazards when analysing PFS.

From the KM plot of PFS (reproduced in Figure 2 below), because the curves do not cross there is no reason to suspect that the underlying assumption of proportional hazards has been violated. Furthermore, no violation of the underlying assumption of proportional hazards was noted in the diagnostic plots (deviance and martingales plots plots provided in Figure 3 and Figure 4). The negative log of survival across time (Figure 5) and the log of the negative log of survival across log time (Figure 6) are provided as well.

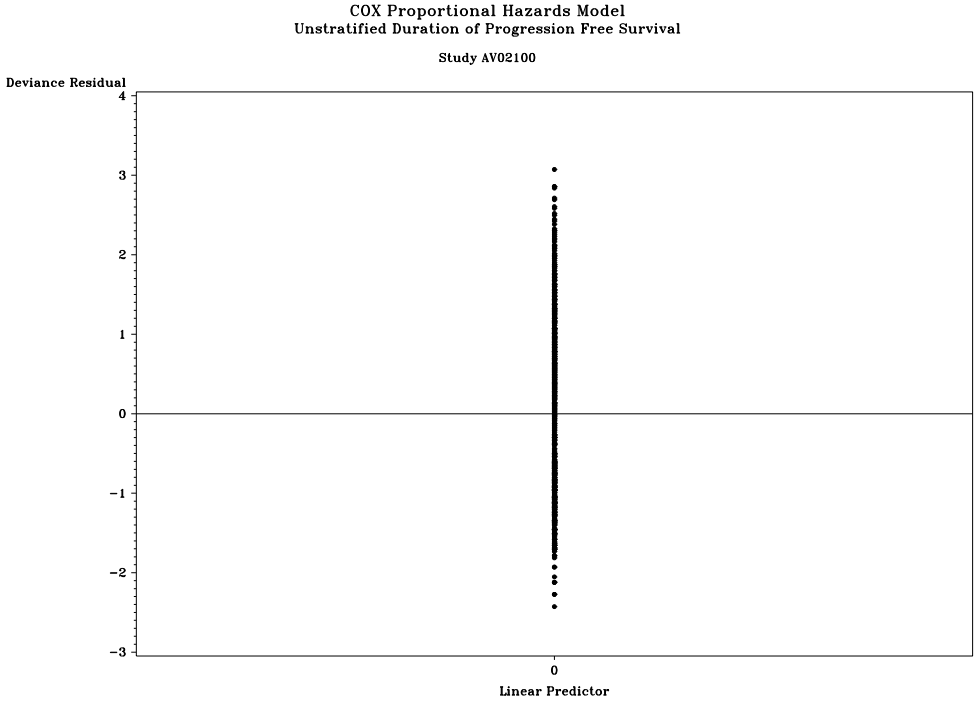
Figure 2. KM curves for progression-free survival from E2100



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 09APR2010 09:54

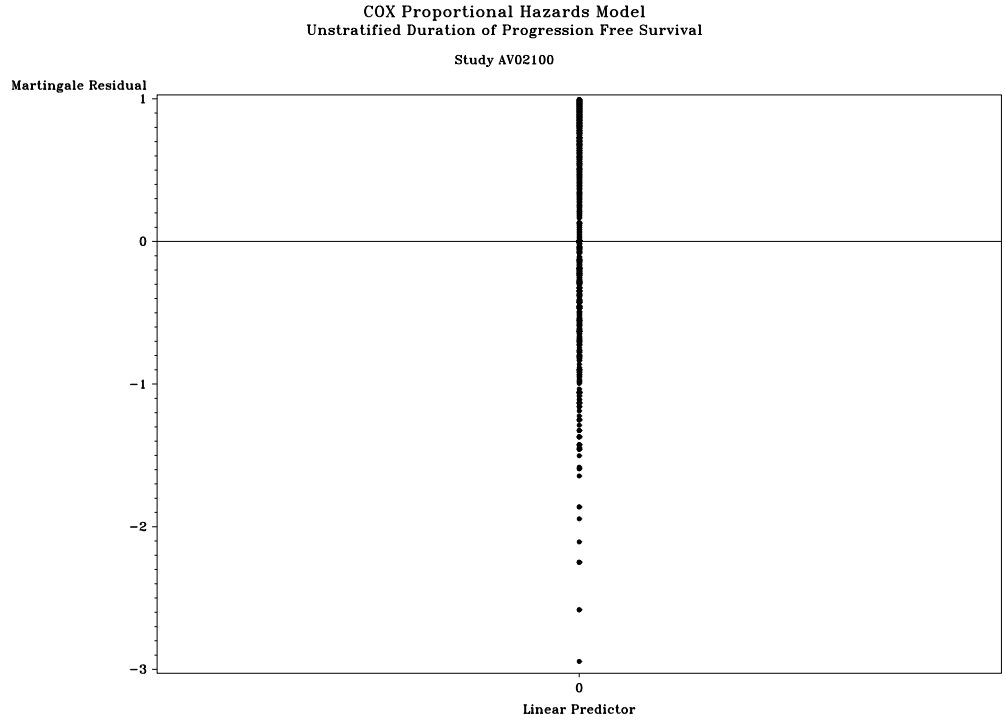
Figure 3. Deviance residual plots for progression-free survival from E2100



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 09APR2010 09:54

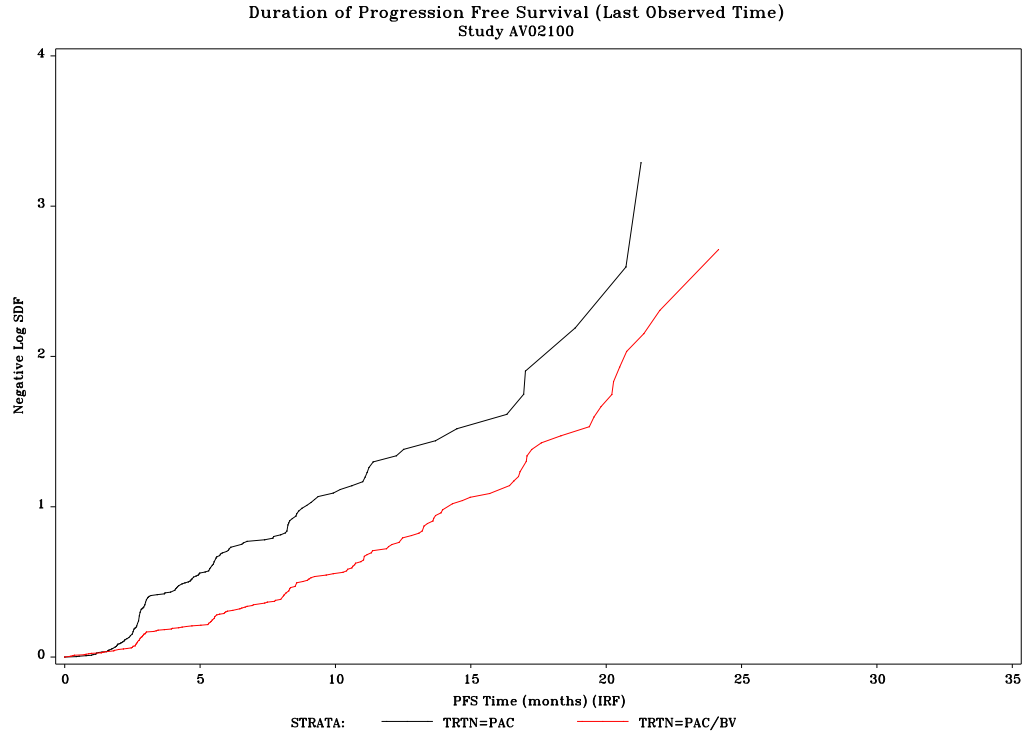
Figure 4. Martingale residual plots for Progression-free survival from E2100



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 09APR2010 09:54

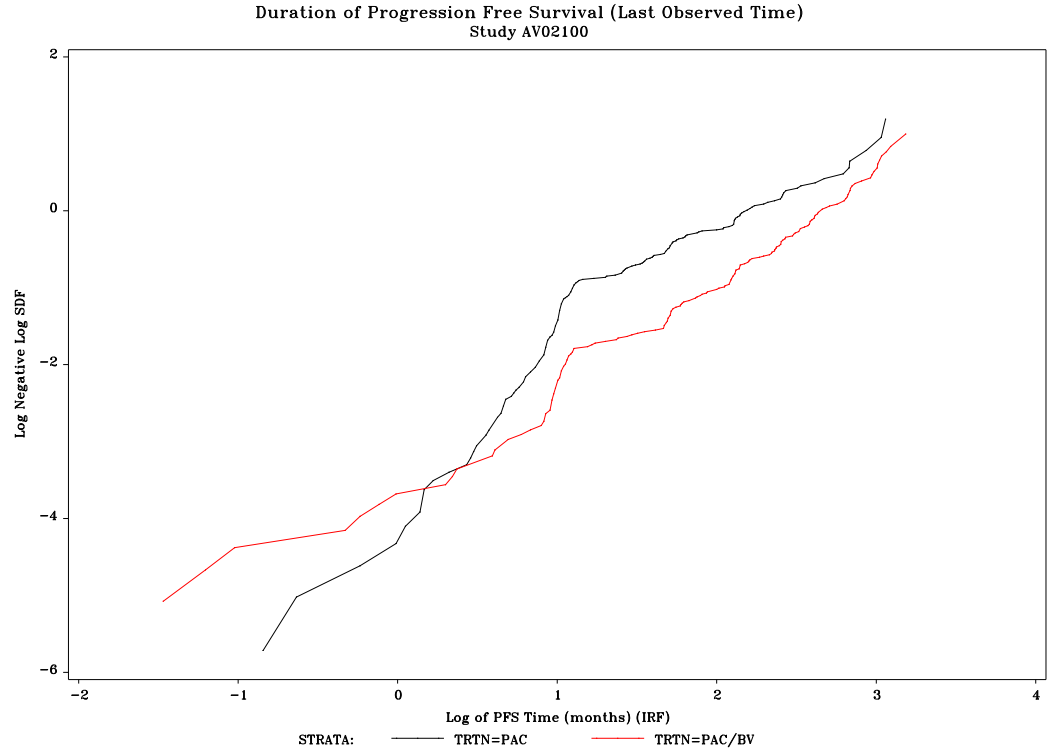
Figure 5. Negative log of survival modeled across time for PFS



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 09APR2010 09:54

Figure 6. Log of the negative log of survival modeled across the log of time for PFS



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 09APR2010 09:54

Overall survival (OS)

B9. [P170, Figure 14] Please provide the equivalent information requested in B5 for overall survival.

Attached below is the Kaplan Meier output for OS from E2100. Standard errors, instead of confidence intervals, are available for each time point a failure has occurred.

B9 KM_OS.xls

B10. Priority question: Please model OS using a similar approach to PFS (i.e. not combining the individual trial arms). If the assumption of proportional hazards does not hold, please fit independent survival curves to each arm separately. For all models and parametric functions fitted, please provide

point estimates, standard errors and variance-covariance matrices for the regression coefficients and/or parameters of the distributions.

Roche acknowledge that the overall survival curves within the study generate a smaller overall survival advantage compared to the economic model. A rationale for this observation has been provided in response to question B17 below. Directly utilising the OS curves from the trial within the model would increase the ICER. Therefore given the base case ICER value, this analysis was not considered necessary to further inform the decision.

B11. Priority question: Please report the mean (and SE or 95% CI) OS assumed for the regimens Bev-Pac and Pac alone based on the following approaches:

- **The OS estimates for Bev-Pac and Pac alone derived from the economic model.**

- **The OS estimates for Bev-Pac and Pac alone derived from the separate Kaplan Meier curves reported in Figure 14 (e.g. using AUC estimates)**

- **The OS estimates for Bev-Pac and Pac alone based on the alternative parametric functions (either assuming proportional hazards or based on fitting individual survival curves, i.e. derived from B10)**

The requested information is provided in Table 14 below. Kaplan Meier data is based on last observed time based on 21 October 2006 cutoff, representing a median follow up of 35.2854 months (95% CI: 34.2669, 36.0411), whilst the economic model data is based on the parametric extrapolation of lifetime survival (time horizon = 10 years). As the analysis from B10 was not completed, the corresponding OS mean values are not provided below.

Table 15. Mean time of overall survival

Overall survival (months)	Kaplan Meier (mean/SE based on last observed time)	Model (mean/95%CI from PSA with 10,000 runs)
Bevacizumab/Paclitaxel	28.0049 (SE 0.9214)	32.17 (95% CI: 31.08 to 33.12)
Paclitaxel	26.3232 (SE 0.9477)	27.95 (95% CI: 27.36 to 28.56)

Time from progression to death

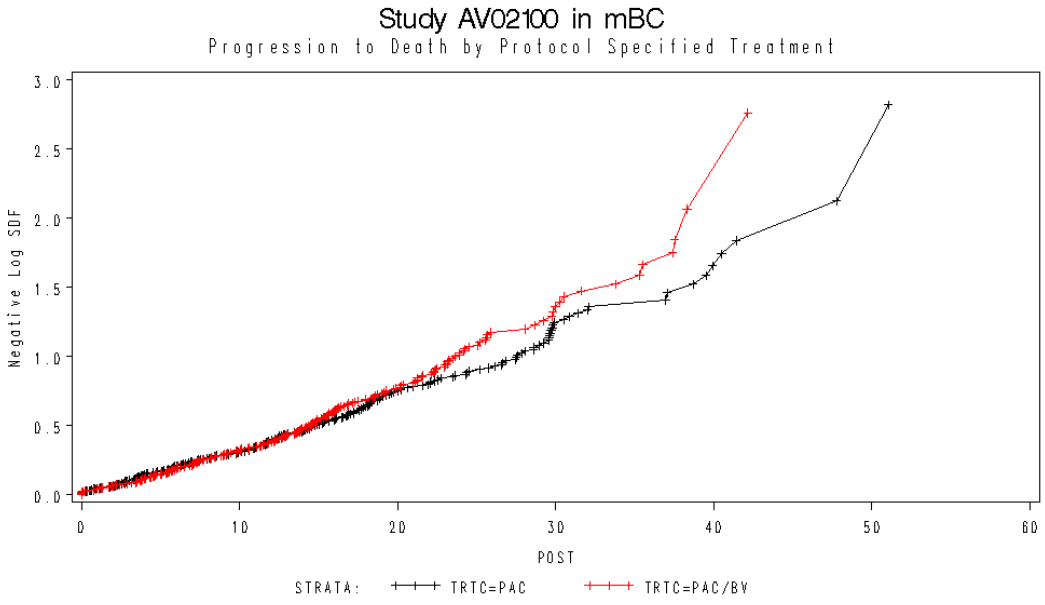
B12. Priority question: [Figure 16, P174] Please model time from progression to death separately for each arm. Please conduct an additional scenario of the cost effectiveness model using this approach.

The log-rank suggests that survival post-progression is not different between the two E2100 arms. Furthermore, modelling time from progression to death separately would suggest that there are different post-progression treatments impacting on survival outcomes in different ways, however, in UK clinical practice, we would not expect any difference in the treatment strategy post-progression (please see response to question B15) and therefore no difference in the risk of death post-progression. Therefore we have not conducted this analysis.

B13. [Figure 16, P174] Please provide additional justification to support the assumption of a constant hazard of death (over time). Please consider fitting alternative parametric functions to these data and provide the results (point estimates, SE and variance-covariance matrices for the coefficients and other relevant parameters).

The justification for constant hazard of death over time is due in part to the underlying assumption of the KM that the data comes from an exponential distribution. If the log of survival across time is parallel, this also suggests that the distribution is exponential. The negative log of post-progression surivival across time has been provided in Figure 7. It is reasonably linear with the exception of the tail which is not unexpected as this is where one would expect to deviate from linearity due to few patients and the impact one event has on the location of the graph (an event can make the curve drop substantially from its previous location).

Figure 7. Negative log of Post-progression survival across post-progression time



Due to the assumption of the same rate of death post-progression across the two arms of E2100, it can be inferred that alternative parametric fits (also following this assumption) would not significantly impact on the incremental life years or costs.

Resource use

B14. Please report the following:

- **The mean number of chemotherapy cycles (and SE) in the E2100 study for each treatment in each arm**

- **Descriptive statistics from the E2100 study reporting the proportion of patients receiving 0,1,2,3,4,5,… chemotherapy cycles for each treatment in each arm**

- **The mean number of cycles assumed in the economic model for each treatment of each regimen**

To be provided week commencing April 19th.

B15. Please provide further justification for the costs of second-line therapies following progression. Please detail relevant protocols followed in UK clinical practice and comment on the impact on cost effectiveness of considering higher costs after progression.

The second-line therapies generally used in the NHS for metastatic breast cancer are as recommended in NICE CG81. Thus patients with disease recurrent after first-line therapy will receive a taxane if eligible, or capecitabine or vinorelbine, or in some cases gemcitabine**.** Patients are rarely re-challenged with the same therapy because of the belief that their tumour has developed resistance.

The choice of treatment post progression will be governed by the previous cytotoxic therapies administered and the patient's performance status. There is no reason to believe that in the NHS either of these factors will be different in patients given bevacizumab+paclitaxel versus paclitaxel alone (or for any of the other relevant comparators). It was therefore considered reasonable to assume the same post progression death rate and treatment costs in each arm.

Standard treatments post-progression were excluded from the monthly post-progression costs as post progression treatment strategies are assumed to be identical in the model. Therefore as the duration of time spent in the post progression health state is equivalent across each arm, inclusion of these costs would not affect the ICER.

As illustrated in our original submission, variation in the assumed post progression treatment costs did not modify the ICER with any significance.

QoL

B16. [P101] Please state whether a mapping algorithm was searched for and considered to estimate EQ-5D from the FACT QoL instrument, in order to estimate utility at baseline and each follow-up in each treatment group.

A systematic search was not performed however Roche is not aware of any mapping function between FACT-B and EQ-5D. It is worth noting that Roche is currently conducting a UK trial of bevacizumab + taxanes in 1st line triple negative metastatic breast cancer, with routine 6-weekly collections of FACT-B and EQ-5D data in order to create just such a mapping function. Data from this study are expected within the next 18-24 months.

Subgroup and sensitivity analyses for the survival regressions and economic model

B17. The economic model finds that the difference in overall life expectancy between Bev + Pac compared with Pac is about 4 months (Table 55). This is considerably greater than the results of the E2100 RCT, which shows a much lower, non-significant difference in overall life expectancy (Figure 5). Please provide further explanation for this difference between the model and the RCT, and consider providing a sensitivity analysis where the parameters are estimated or calibrated to fit more closely with the trial data.

We assume the purpose of a decision analysis model for NICE is to model expected UK clinical practice and not necessarily replicate the outcomes observed within the respective clinical trials. As outlined in question B15 above, in UK practice there is no reason to believe that the post-progression treatment strategy would be different across the two arms within the model. Therefore the assumption of an equivalent risk of death across both arms post progression was considered a more appropriate assumption than relying upon the observed trial treatment arms post progression. The key justification for this being that following progression there is no randomisation for treatment and therefore, as is often the case in oncology studies, significant crossover and confounding can occur.

A further perspective is that the greater than 2 years' median OS for both arms of the E2100 study exceeds the OS found in virtually all Phase III studies of metastatic patients treated with chemotherapy, even in first-line studies, suggesting the possibility that patients in both arms of the study may have received the benefit of bevacizumab therapy. Unfortunately the number of patients from the paclitaxel arm of this open label study who crossed-over to receive bevacizumab after progression was not recorded in the E2100 study. However, the publication of initial data showing a significant PFS benefit for bevacizumab in E2100, while the majority of patients were still alive, will have increased the likelihood of crossover in the USA where the drug was already available for colorectal cancer. In studies of trastuzumab in the same setting (1st line metastatic breast cancer), 57% and 70% of placebo patients cross over have occurred to the new agent (trastuzumab) (Marty *et al* 2005*,* J Clin Oncol 23:4265-4274, Kaufman *et al* 2009, J Clin Oncol 27:5529-5537.)

Amongst the patient subgroups with the shortest OS in E2100, where the opportunity to crossover to bevacizumab was least, there was at least a 4 months' benefit in OS, median OS for ER negative patients was only 16.0 months with paclitaxel alone, compared with 20.3 months with paclitaxel plus bevacizumab (HR 0.86, 95% CI 0.65–1.13) and for triple-negative patients OS was 16.3 months in the paclitaxel arm, compared with 20.5 months in the paclitaxel plus bevacizumab arm (HR 0.89, 95% CI 0.66–1.19).

For the patients previously treated with adjuvant taxane, median OS increased from 17.6 months with paclitaxel alone to 26.3 months with paclitaxel plus bevacizumab (HR 0.67, 95% CI 0.45–0.99).

Relevance of other economic evaluations

B18. [P151, Table 27] The submission found other cost-effectiveness analyses, but stated that they were not relevant as they were all conducted outside the UK. The ERG considers that as there are very few published economic evaluations these may be of interest to the Committee. Please briefly review the main methods and results of the full economic evaluations (i.e., that compare both costs and outcomes of two or more relevant interventions) and compare these to the results of the current study.

Only one publication from the literature review analysed the cost-effectiveness of bevacizumab in metastatic breast cancer (Dedes 2009). The analysis is based on the E2100 study in which Avastin plus paclitaxel is compared to paclitaxel alone. The analysis was conducted from the Swiss system perspective and results are reported in 2008 Euros. A Markov model simulating non-progressed, progressed and death states was built. The authors used data from published literature and analysis conducted by the E2100 principal investigator (K. Miller). In the base case analysis, the model reports an ICER of € 189,427 per QALY gained. This is equivalent to £140,316 per QALY gained (01/01/2008 exchange rate for 1.35883 EUR = GBP).

The results were based on a comparison with paclitaxel monotherapy and did not incorporate any existing capping schemes. Therefore the results presented in the Dedes 2009 study are most comparable to the results provided in our original submission of £117,803 per QALY gained (bev-pac versus pac using the NICE reference case – no 10g capping scheme).

Whilst the model structure in Dedes 2009 is quite similar to the model structure presented to NICE, one major difference in the model inputs is the measure of treatment benefit. The economic model provided to NICE by Roche uses data on the ITT population where the hazard ratios were (0.48) whereas Dedes 2009 used the "per protocol analysis" excluding patients from the analysis after they were randomized to participate in the trial with a HR of 0.6. If the author had used the ITT data, this would have resulted in a lower cost per QALY than the equivalent to £140,316 reported in this article.

With this further adjustment, it is apparent that the cost per QALYs presented in Dedes 2009 and the ones presented in this submission are reasonably similar.

Section C: Textual clarifications and additional points

C1. [Figure 16, P174] The labelling at the foot of Figure 16 is difficult to understand. The Pac + Bev label seems to be missing. Please clarify which curve represents which treatment.

The black curve represents the paclitaxel monotherapy arm whilst the red curve represents the bevacizumab + paclitaxel arm.