Robert Fernley
Technology Appraisal Administrator
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY EMAIL

10 May 2012

RE: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer

Dear Robert,

Please find below our comments on the appraisal consultation document received 11th April 2012 for the above appraisal. If you require any further clarification or information then please do not hesitate to contact us.

Yours sincerely,

[redacted]

[redacted]

[redacted]

Roche Products Limited

Comments on the ACD

1. Has all of the relevant evidence been taken into account?

1.1. The relevance of capecitabine dose to UK clinical practice

In Section 4.3 of the ACD it states:

> *"The Committee noted that the dose of capecitabine in the trial was 1000 mg/m^2 rather than the licensed dose of 1250 mg/m^2. The Committee was aware that the dose of capecitabine used in UK practice was often lower in older patients and those with poor performance status, but observed that all patients in the RIBBON-1 trial were of ECOG performance status 0 or 1 and the median age was 56 years. It therefore considered the licensed dose of 1250 mg/m^2 capecitabine would be more appropriate. The Committee concluded that the trial may have limited relevance to clinical practice in the UK."*

COMMENT:

More than 40 UK patients entered the capecitabine arm of the RIBBON-1 study, at 4 sites in England and Wales, to be randomised between placebo or bevacizumab. The full study protocol was submitted to both main and local ethics committees and was approved by all 5 committees. This approval would never have been granted unless the ethics committees were convinced by their local clinicians that all the patients randomised to 1000mg/m^2 capecitabine plus placebo would receive the UK standard of care therapy for their disease. This further reinforces the acceptability of the 1000 mg/m^2 bd dose in UK clinical practice.

1.2. The presentation of probabilistic sensitivity analysis results

In Section 4.8 of the ACD it states:

> *"The Committee noted that an ICER based on probabilistic sensitivity analysis had not been reported and so the deterministic ICERs presented should be treated with caution."*

COMMENT:

Our submission included the results of a PSA in the form of a cost-effectiveness plane and cost-effectiveness acceptability curve in Section 6.6.8 (Figures 21 and 22 on pages 134 and 135). For information, the mean ICER of 1000 iterations of the PSA was £80,073 (mean incremental costs = £40,161 (95% CI, £36,703- £45,079), mean incremental QALYs = 0.502 (95% CI, 0.33-0.66)). This is compared to the deterministic base case ICER of £77,318 per QALY (incremental costs = £38,856, incremental QALYs = 0.5034).

1.3. The calculation of overall survival in the economic model

In Section 4.10 of the ACD it states:

> *"The Committee noted the ERG's concerns around the rank preserving structural failure time method used by the manufacturer to remove the effect of crossover to open-label bevacizumab in the modelling of survival in the progressed disease state. The Committee noted that the rank preserving structural failure time method could be considered to be appropriate in situations when large numbers of patients crossed over as occurred in the RIBBON-1 trial. However, the Committee noted that the subsequent treatments had not been modelled, which in combination with the impact of crossover, could have led to confounding of the overall survival results. The ERG confirmed that it had not been possible to estimate the effect of these factors on overall survival. The Committee concluded that the manufacturer's modelled overall survival results could not be considered to be robust."*

COMMENT:

The decision problem under assessment is for bevacizumab in combination with capecitabine in HER2-negative metastatic breast cancer patients previously untreated in the metastatic setting – thereby covering only the use of bevacizumab in the first-line setting. In the only relevant RCT, there was no control over the therapies available to patients following progression of the disease and since a large number of these patients received bevacizumab in this setting (for which it is unlicensed), we feel it is appropriate to make an adjustment to account for this. However, whilst we remain unconvinced of the arguments put forward concerning the limitations of the method used in the base case model compared to alternatives, we have used the unadjusted survival data from the trial in an alternative scenario analysis provided below. We believe that this alternative economic model provides a robust estimate of the cost-effectiveness of the addition of bevacizumab to capecitabine in mBC as observed in the RIBBON-1 trial.

Our original model included information on the therapies received by patients (as well as the treatment durations) in the trial after progression (Table 1), although this information was not used to extrapolate post-progression therapy costs in either treatment arm as they were considered likely to cancel each other out. This assumption is justified somewhat by the observation that the expected difference in costs of therapies received in the PD state is between approximately £130 and £490 per patient in the 2 arms of the trial (Table 2).

However, we accept the Committee's concern that the costs of these treatments had not been modelled and provide estimates of the cost-effectiveness of a number of scenarios using survival curves adjusted and un-adjusted for post-progression bevacizumab where the cost of these treatments are included according to observations in RIBBON-1 and likely use in clinical practice in the NHS (Table 3). These changes have been implemented in a revised model which incorporates both the correction to the calculation of utility in the CAPE arm identified by the ERG and the inclusion of terminal care costs as described on p64 of ERG Report Erratum. Although the ERG also described one further alteration to the model, concerning the use of UK-specific patient characteristics to calculate drug costs, this is the subject of a separate comment (2.2 below) and was not included in the revised model.

Table 1: Frequency, dose, duration and costs of treatments recieved by patients after progression in RIBBON-1

							Usual dose (mg)	frequency (days between doses)	IV?	Number of Administrations		Ave total dose (mg) received by patients		Unit costs	Total cost of drug in PD cohort		Cost of administration**		TOTAL COST OF PD TREATMENT	
			Cumulative days		Ave days/pt										£200,745	£372,584	£83,190	£112,523	£3,505	£3,013
Post progression treatment	PLA	BEV	PLA	BEV	PLA	BEV				PLA	BEV	PLA	BEV	price per mg	PLA	BEV	PLA	BEV	PLA	BEV
BISPHOSPHONATE	35	72	2597	2916	74.2	40.5	50	1				3710	2025	£0.131	£17,037	£19,130	£0	£0	£210	£119
BEVACIZUMAB#	43	67	900	1023	20.93	15.27	1081	21	IV	1.00	0.73	1078	786	£2.427	£112,472	£127,855	£5,475	£6,224	£1,456	£833
PACLITAXEL	10	25	395	2033	39.5	81.32	158	7	IV	5.64	11.62	890	1831	£2.003	£17,823	£91,731	£7,209	£37,106	£309	£800
VINORELBINE	15	20	1488	1536	99.2	76.8	44	7	IV	14.17	10.97	621	480	£0.511	£4,757	£4,910	£27,158	£28,035	£394	£205
GEMCITABINE	8	16	702	1002	87.75	62.63	2190	10.5	IV	8.36	5.96	18299	13061	£0.023	£3,306	£4,719	£8,542	£12,193	£146	£105
ABRAXANE	12	15	178	226	14.83	15.07	455	21	IV	0.71	0.72	322	327	£2.460	£9,494	£12,060	£1,083	£1,375	£131	£83
GEMCITABINE	10	15	521	858	52.1	57.2	2190	10.5	IV	4.96	5.45	10865	11928	£0.023	£2,453	£4,040	£6,339	£10,440	£109	£90
CARBOPLATIN	7	12	240	826	34.29	68.83	570	21	IV	1.63	3.28	931	1868	£0.030	£195	£673	£1,460	£5,025	£20	£35
DOCETAXEL	6	10	157	344	26.17	34.4	131	21	IV	1.25	1.64	164	215	£4.510	£4,430	£9,706	£955	£2,093	£66	£73
CAPECITABINE	5	10	85	134	17	13.4	1752	*				49048	49048	£0.004	£1,085	£2,171	£0	£0	£13	£13
IXABEPILONE#	2	9	64	199	32	22.11	70	21	IV	1.52	1.05	107	74	£41.152	£8,788	£27,322	£389	£1,211	£113	£177
ZOLEDRONIC ACID	2	7	64	226	32	32.29	4	21	IV	1.52	1.54	6	6	£43.535	£531	£1,874	£389	£1,375	£11	£20
FULVESTRANT	5	6	200	164	40	27.33	500	28	IV	1.43	0.98	1929	1500	£1.045	£10,075	£9,403	£913	£748	£136	£63
EXEMESTANE	4	6	135	235	33.75	39.17	25	1				844	979	£0.118	£400	£696	£0	£0	£5	£4
RADIOTHERAPY~	2	3													£5,160	£7,740	£0	£0	£64	£48
LETROZOLE	2	3	55	56	27.5	18.67	2.5	1				69	47	£1.212	£167	£170	£0	£0	£2	£1
DOXORUBICIN	2	3	6	88	3	29.33	88	21	IV	0.14	1.40	13	122	£0.404	£10	£148	£37	£535	£1	£4
TAMOXIFEN	1	3	23	148	23	49.33	20	1				460	987	£0.005	£2	£15	£0	£0	£0	£0
MITOMYCIN	2	2	134	121	67	60.5	18	42	IV	1.60	1.44	28	25	£1.928	£108	£97	£408	£368	£6	£3
ANASTROZOLE	2	2	29	192	14.5	96	1	1				15	96	£1.778	£52	£341	£0	£0	£1	£2
MEGESTROL	1	2	0	15	0	7.5	160	1				160	1200	£0.004	£1	£10	£0	£0	£0	£0
TRASTUZUMAB	1	2	0	73	0	36.5	577	21	IV	1.00	1.74	577	1003	£2.716	£1,567	£5,446	£128	£444	£21	£37
RADIOTHERAPY TO BRAIN~	0	2													£0	£5,160	£0	£0	£0	£32
IRINOTECAN	0	2	0	92	0	46	613	21	IV		2.19	0	1343	£0.147	£0	£394	£0	£560	£0	£6
TRABECTEDIN#	0	2	0	214	0	107	3	21	IV	0.00	5.10		13	£1,366.000	£0	£36,576	£0	£1,302	£0	£235
METHOTREXATE	4	1	406	120	101.5	120	70	7	IV	14.50	17.14	1016	1201	£0.022	£88	£26	£7,410	£2,190	£93	£14
DICLOXACILLIN/DOXORUBICIN	3	1	58	29	19.33	29	88	21	IV	0.92	1.38	81	121	£0.404	£98	£49	£353	£176	£6	£1
OXALIPLATIN	1	1	0	43	0	43	149	14	IV	1.00	3.07	149	457	£0.147	£22	£67	£128	£392	£2	£3
MITOXANTRONE	1	1	133	120	133	120	14	21	IV	6.33	5.71	89	80	£0.674	£60	£54	£809	£730	£11	£5
CYCLOPHOSPHAMIDE	3	0	276	0	92	0	288	3	IV	30.67	0.00	8844	0	£0.011	£279	£0	£11,754	£0	£149	£0
GOSERELIN	2	0	1	0	0.5	0	1	28	IV	0.02	0.00	0	0	£18.025	£1	£0	£5	£0	£0	£0
EPIRUBICIN	2	0	90	0	45	0	210	21	IV	2.14	0.00	450	0	£0.306	£275	£0	£548	£0	£10	£0
FLUOROURACIL	2	0	93	0	46.5	0	1082	7	IV	6.64	0.00	4326	0	£0.001	£11	£0	£1,697	£0	£21	£0

***, capecitabine is administered every day for the first 14 days of a 21-day cycle.**

#, unlicensed for use in metastatic breast cancer as a second-line treatment option

~, radiotherapy is assumed to comprise of 20 doses of radiation (every day, 5 days a week for 4 weeks)

****, IV infusion cost = £128 (Department of Health 2011)**

Table 2: Average costs of treatments received by patients in RIBBON-1 trial following progression under different conditions

	BEV+CAPE	PLA+CAPE	Incremental cost
All treatments	£3,013	£3,505	-£492
All (Excluding bevacizumab)	£2,180	£2,049	£131
Licensed treatments only	£1,768	£1,936	-£168

Table 3: Cost-effectiveness results following incorporation of executable amendments suggested by the ERG

Scenario			BEV+CAPE			PLA+CAPE			Incremental			
			Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER
	Base case		2.228	1.338	£51,645	1.365	0.835	£12,721	0.864	0.503	£38,924	£77,318
	Revised base case	Inclusion of terminal care costs and correction of utility calculation	2.228	1.338	£53,353	1.365	0.829	£14,482	0.864	0.509	£38,872	£76,428
	Survival estimate	**PD therapy costs**										
1	Base case (RPSFT)	None	2.228	1.338	£53,353	1.365	0.829	£14,482	0.864	0.509	£38,872	£76,428
2		all (excluding bevacizumab)			£55,385			£16,423			£38,962	£76,605
3		licensed therapies only			£55,001			£16,318			£38,685	£76,061
4		vinorelbine			£58,015			£17,157			£40,858	£80,333
5	unadjusted survival estimates	none	2.306	1.376	£54,094	1.683	0.987	£17,533	0.623	0.389	£36,560	£93,979
6		all (including bevacizumab)			£56,902			£20,855			£36,047	£92,658
7		licensed therapies only			£55,741			£19,368			£36,373	£93,498
8		vinorelbine			£59,010			£21,254			£37,756	£97,052

We believe these results are more robust than those proposed by the ERG and more representative of the cost-effectiveness of the RIBBON-1 trial as observed (Scenario 6, ICER = £92,658), as well as for patients receiving bevacizumab in addition to capecitabine in 1L treatment of mBC in the NHS (Scenario 3, ICER = £76,061). In addition, we provide supplementary cost-effectiveness estimates based on the assumption that all patients in the model receive vinorelbine as a second-line therapy until death in agreement with recent clinical guidelines (NICE CG81 2009). This assumption has the effect of increasing monthly supportive care costs in PD from £804 to £1077.38 (£804 + [monthly cost of generic vinorelbine (£77.29) + IV administration (196.09)] from Table 29 on p118 of original submission) and results in an increase in the ICER of approximately £3000 - £4000 for the 2 scenarios considered here (Scenario 4 and 8 in Table 3).

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

2.1. The robustness of the results from the prior taxane subgroup

In Section 4.7 of the ACD it states:

> *"*… However, the Committee noted that previous taxane therapy was not a stratification factor at randomisation and that this subgroup was specified after the trial had begun but before the analysis was completed. The Committee also noted that the overall survival results were based on very small numbers of events: 70 patients in the bevacizumab plus capecitabine arm and 44 patients in the capecitabine plus placebo arm. In addition, the Committee was aware that no statistical adjustments were made to control for multiple testing, thus increasing the risk of chance findings. The Committee noted the ERG's statement that the patients in this subgroup appeared to be younger and healthier than the ITT population. The Committee concluded that the results from the subgroup of patients who were previously treated with a taxane were not robust.*"*

COMMENT:

Data from RIBBON-1 demonstrates that patients who had received a prior taxane have extended progression free and overall survival with capecitabine in combination with bevacizumab. The addition of bevacizumab to capecitabine in this large subgroup of patients (n=245) raised their overall survival and PFS above a level found in the ITT population with bevacizumab and capecitabine, thus counteracting the poor prognosis of these patients (Table 4). Whilst the ERG correctly identified that the age and prognostic factors of the prior-taxane subgroup would suggest that they should have a better prognosis than the ITT population, median PFS and OS figures in the control arm of RIBBON-1 highlight that these patients actually experienced worse outcomes.

Whilst the prior-taxane subgroup was not pre-stratified, thereby suggesting the possibility that the results are a consequence of data dredging, two additional phase III studies (Gray et al. 2009;Miles et al. 2010; Miller et al. 2007) have demonstrated a similar PFS increase in prior taxane treated

patients who have received bevacizumab and chemotherapy compared to chemotherapy alone thereby supporting the convergent validity of a treatment effect of bevacizumab specifically in prior-taxane treatment patients.

The AVADO study (Miles et al. 2010) compared placebo plus docetaxel (DOC) against bevacizumab plus docetaxel (BEV+DOC) in first-line therapy of metastatic breast cancer and prior-taxane use was a stratification factor for randomisation. In contrast, the E2100 study (Gray et al. 2009) compared placebo plus paclitaxel (PAC) against bevacizumab plus paclitaxel (BEV+PAC) in first-line therapy of metastatic breast cancer and prior-adjuvant therapy was pre-stratified, as in the RIBBON-1 (Robert et al. 2011) trial. However, despite the lack of this specific stratification for prior-taxane use, the patients previously treated with taxanes in the latter 2 studies were well balanced between the placebo- and bevacizumab-containing arms.

The results (Table 4) demonstrate that incremental PFS and OS in prior taxane treated patients are notably and consistently increased across all three trials, compared to the ITT population, strongly suggesting that these patients, with a particularly poor prognosis and few treatment options, benefit especially from bevacizumab treatment. For example, median OS in prior taxane treated patients not given bevacizumab is between 2 and 9 months worse than the ITT population, whilst survival in prior taxane treated patients receiving bevacizumab is at least as good as that in the ITT.

Table 4: ITT and sub group data from 3 trials of bevacizumab in mBC

		PFS					
		ITT			Prior Taxane		
		N	Median	Benefit	N	Median	Benefit
E2100	PAC vs BEV+PAC	354/368	5.8 vs 11.3	5.5	68/74	5.8 vs 13.1	7.3
AVADO	DOC vs BEV+DOC	247/241	8.2 vs 10.1	1.9	42/35	6.7 vs 10.3	3.6
RIBBON-1	CAPE vs BEV+CAPE	206/409	5.7 vs 8.6	2.9	84/161	4.2 vs 8.7	4.5

		OS					
		ITT			Prior Taxane		
		N	Median	Benefit	N	Median	Benefit
E2100	PAC vs BEV+PAC	354/368	24.8 vs 26.5	1.7	68/74	17.6 vs 26.3	8.7
AVADO	DOC vs BEV+DOC	247/241	31.9 vs 30.2	-1.7	42/35	22.3 vs 31.6	9.3
RIBBON-1	CAPE vs BEV+CAPE	206/409	22.8 vs 25.7	2.9	84/161	20.5 vs 28.4	7.9

Furthermore, meta-analyses of the hazard ratios for PFS and OS from the 3 studies above are shown in Figure 1 and Figure 2, respectively. These clearly demonstrate the significant improvement in both PFS and OS seen with bevacizumab in such patients, while the improvement in outcomes for patients in the ITT population is considerably less and is non-significant for OS.

Figure 1: Meta-analysis of PFS hazard ratios from 3 trials of bevacizumab in mBC

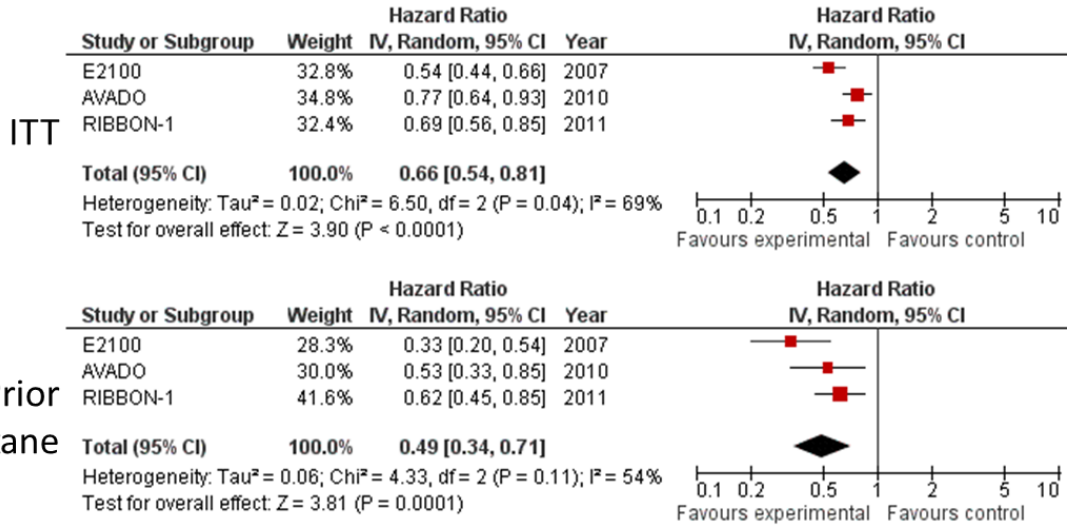
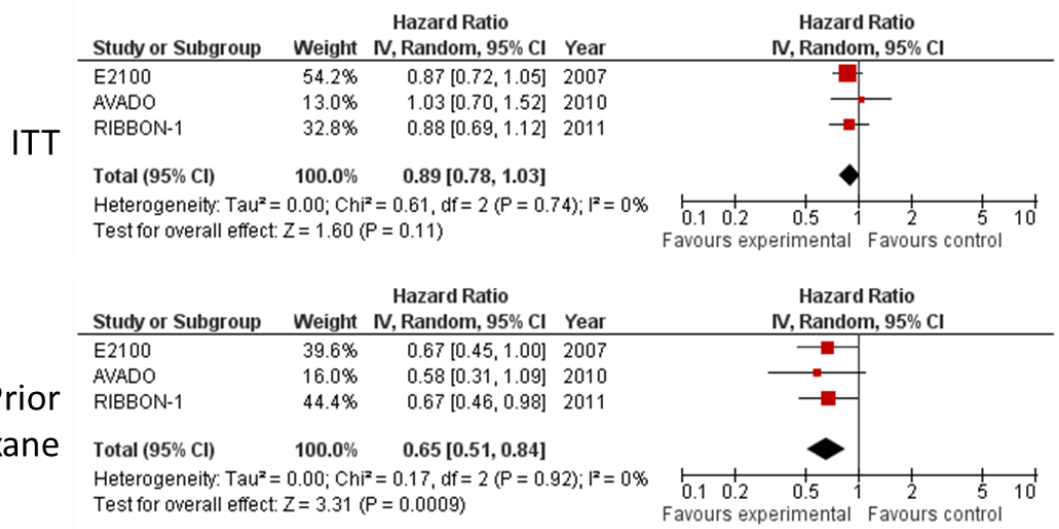


Figure 2: Meta-analysis of OS hazard ratios from 3 trials of bevacizumab in mBC



An article in the Lancet in 2005 which explored the importance, indications and interpretation of subgroup analysis in randomised controlled trials (Rothwell 2005), states that the best test of the validity of subgroup analyses is not significance, but replication. For example, although an early RCT of coronary artery bypass grafting, suggesting that survival benefit was mainly confined to patients with left main coronary artery disease or three-vessel disease, had only a few hundred patients (Takaro et al. 1976), the observation was biologically plausible and was reproduced in a subsequent trial (European Coronary Surgery Study Group 1982). However, it was not until 20 years later that a pooled analysis of seven RCTs had sufficient power to demonstrate a significant interaction (Yusuf et al. 1994). Similarly, in the metastatic breast cancer indication three phase III RCTs have all demonstrated that patients who have received a taxane in the adjuvant setting gain greater benefit from bevacizumab in combination with chemotherapy for 1st line metastatic treatment than the ITT population. There are a number of possible biological explanations for this observation, including adaptive resistance to earlier taxane therapy and the increased level of angiogenesis which is seen in more aggressive breast tumours. Importantly, in the context of the management of metastatic

breast cancer, this greater efficacy of bevacizumab in prior-taxane treated patients enables a subgroup of HER2 negative breast cancer patients to realize the same incremental survival gains as observed following the introduction of trastuzumab in HER2+ positive metastatic breast cancer patients (Marty et al. 2005;Slamon et al. 2001).

2.2. The re-calculation of drug costs in the economic model

In Section 4.9 of the ACD it states:

> *"The Committee noted the adjustments made by the ERG to the economic model:*
>
> - *basing costs on the distribution of patient body weight and body surface area in a UK-specific cohort of patients rather than using a simple average based on trial data*
>
> *The Committee concluded that these adjustments were appropriate."*

COMMENT:

We wish to draw the Committee's attention to the fact that the reference supplied by the ERG in relation to the "UK-specific cohort of patients" used in this calculation (Sacco et al. 2010) only provides data on the body surface area of cancer patients and can therefore only be used to recalculate the estimated capecitabine dose. This lack of data means that it has not been possible to verify the increase in drug costs in patients receiving bevacizumab (which required information on weight in kg) in combination with capecitabine (reported to be £2,966). The relevant data from that paper and our submission (based on the RIBBON-1 trial) are summarised in Table 5 .

Table 5: Comparison of patient body mass index and weight in manufacturer submission and ERG report

	RIBBON-1	**(Sacco et al. 2010)**
Mean BSA	**1.761mg/m^2 (calculated)**	**1.75mg/m^2**
Mean body weight	**72.1kg**	***Not reported***

It is clear that, with respect to the mean BSA of breast cancer patients, the original patient cohort in our model is actually slightly larger than the UK average. Furthermore, we have been unable to reproduce the increase in drug costs reported by the ERG for the capecitabine plus placebo arm (£50 total drug costs) and cannot confirm the validity or appropriateness of these updated calculations (our attempt to incorporate Sacco et al 2010 data in the calculation of drug cost is provided on Sheet "BSA Calculations" of the revised economic model). We would strongly recommend that the Committee treat these adjusted calculations with great caution until more details concerning the methodology and the assumptions used are available.

2.3. Section 3.6

"The overall survival results were based on 70 patients in the bevacizumab plus capecitabine arm and 44 patients in the capecitabine plus placebo arm."

COMMENT:

The use of "patients" in this sentence should be changed to "events" as the data refer to the number of deaths in a large cohort of 245 patients.

2.4. Section 4.10

"The Committee noted that the rank preserving structural failure time method could be considered to be appropriate in situations when large numbers of patients crossed over as occurred in the RIBBON-1 trial."

COMMENT:

We believe the current wording of this sentence is confusing and should be reconsidered to avoid possible ambiguity and doubt concerning the Committee's position on RPSFT in this situation.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We are disappointed that the Committee did not accept the prior taxane cohort as a legitimate subgroup of patients (who have a worse prognosis and fewer treatment options than other patients with metastatic disease) despite the evidence we have provided and we hope further analysis presented here, as well as independent clinical advice, may be more compelling.

References

Department of Health 2011, *NHS reference costs 2009-2010*, Department of Health.

European Coronary Surgery Study Group 1982, "Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris.", *The Lancet*, vol. 2, no. 8309, pp. 1173-1180.

Gray, R., Bhattacharya, S., Bowden, C., Miller, K., & Comis, R. L. 2009, "Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, vol. 27, pp. 4966-4972.

Marty, M., Cognetti, F., Maraninchi, D., Snyder, R., Mauriac, L., Tubiana-Hulin, M., Chan, S., Grimes, D., Anton, A., Lluch, A., Kennedy, J., O'Byrne, K., Conte, P., Green, M., Ward, C., Mayne, K., & Extra, J. M. 2005, "Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group", *J Clin.Oncol.*, vol. 23, no. 19, pp. 4265-4274.

Miles, D. W., Chan, A., Dirix, L. Y., Cortes, J., Pivot, X., Tomczak, P., Delozier, T., Sohn, J. H., Provencher, L., Puglisi, F., Harbeck, N., Steger, G. G., Schneeweiss, A., Wardley, A. M., Chlistalla, A., & Romieu, G. 2010, "Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer", *J Clin.Oncol.*, vol. 28, no. 20, pp. 3239-3247.

Miller, K., Wang, M., Gralow, J., Dickler, M., Cobleigh, M., Perez, E. A., Shenkier, T., Cella, D., & Davidson, N. E. 2007, "Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer", *New England Journal of Medicine*, vol. 357, no. 26, pp. 2666-2676.

NICE CG81 2009, "National Institute for Health and Clinical Excellence (NICE); Winstanley J & Murray N. (2009) Advanced breast cancer: diagnosis and treatment, Clinical Guideline 81 (CG81). February 2009.", *Accessed online 21/09/10 at: http://guidance.nice.org.uk/CG81*.

Robert, N. J., Dieras, V., Glaspy, J., Brufsky, A. M., Bondarenko, I., Lipatov, O. N., Perez, E. A., Yardley, D. A., Chan, S. Y., Zhou, X., Phan, S. C., & O'Shaughnessy, J. 2011, "RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer", *J Clin.Oncol.*, vol. 29, no. 10, pp. 1252-1260.

Roche Data on File. RXUKDONF00200: Xeloda in mBC Market Research Study conducted by First Line Research Ltd. 2012.
Ref Type: Data File

Rothwell, P. M. 2005, "Subgroup analysis in randomised controlled trials: importance, indications, and interpretation", *The Lancet*, vol. 365, no. 9454, pp. 176-186.

Sacco, J. J., Botten, J., Macbeth, F., Bagust, A., & Clark, P. 2010, "The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study", *PLoS ONE*, vol. 5, no. 1, p. e8933.

Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., Fleming, T., Eiermann, W., Wolter, J., Pegram, M., Baselga, J., & Norton, L. 2001, "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2", *New England Journal of Medicine*, vol. 344, no. 11, pp. 783-792.

Takaro, T., Hultgren, H. N., Lipton, M. J., & Detre, K. M. 1976, "The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions", *Circulation*, vol. 54, no. 6 Suppl, p. III107-III117.

Yusuf, S., Zucker, D., Peduzzi, P., Fisher, L. D., Takaro, T., Kennedy, J. W., Davis, K., Killip, T., Passamani, E., Norris, R., & . 1994, "Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration", *The Lancet*, vol. 344, no. 8922, pp. 563-570.