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Tuesday, 24 January 2012

Kate Moore
Level 1A, City Tower

Piccadilly Plaza

Manchester

M1 4BD

BY E-MAIL

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

Dear Kate,

Please find below our responses to the ERG clarification questions received 10th January 2012. Our response to the second clarification letter of 20th January 2012 will be sent separately.

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

Issues relating to the RIBBON-1 trial

A.1 Please provide a breakdown of the reasons for the patients who withdrew from the blinded follow-up phase in the "other" category in figure 3 (page 49) of the manufacturer's submission.

Table 1 outlines the reasons why patients on the bevacizumab/placebo arm discontinued treatment, as listed in the CSR report, table 14.1/8, page 215.

Table 1: Reasons for study treatment discontinuation (ref: RIBBON1 Clinical Study Report)

Discontinued bevacizumab /placebo therapy	Capecitabine and placebo (N=206) Number of patients (%)	Capecitabine and bevacizumab (N=409) Number of patients (%)
Death	6 (2.9%)	11 (2.7%)
Disease progression	145 (70.4%)	245 (59.9%)
Adverse event	11 (5.3%)	37 (9%)
Physician's decision to withdraw	6 (2.9%)	17 (4.2%)
Patient's/guardian's decision to withdraw	5 (2.4%)	25 (6.1%)
Treatment completion	**0**	**1 (0.2%)**
>60 days since last administration of bevacizumab/placebo	**1 (0.5%)**	**8 (2.0%)**
Other*	**5 (2.4%)**	**5 (1.2%)**

Note: * In the Clinical Study Report, the "Other" category was not defined further.

A.2 On page 45 of the manufacturer's submission, it is stated that "One-year survival rate would be compared only when a statistically significant result is observed in overall survival between two treatment arms." A significant result in overall survival was not observed between the treatment arms and yet one-year survival estimates were still presented. Please explain why one-year survival estimates were presented.

Page 45 makes reference to formal statistical testing of the overall survival (OS) data from the RIBBON-1 study and the test procedures which were used to maintain a type I error rate of α=0.05 (two-sided). The data presented on Page 65 which show the OS at one year provide descriptive information about the OS curves, which is of importance to the submission because it may indicate that some of the patients in the study gained a greater benefit from bevacizumab. Two other large Phase III studies of bevacizumab in breast cancer (E2100 and AVADO) show a significant OS benefit at 1 year and the RIBBON-1 study may continue this trend.

Section B: Clarification on cost-effectiveness data

B.1 Priority Request: Modelled survival in progressive disease (PD)

Please provide the following:

a. Details of the models used to represent survival in PD (displayed in Figure 15, page 88 of the manufacturer's submission);

Survival in PD was modeled using Kaplan-Meier survival data from RIBBON-1 directly until patients had spent a total of 12 months with progressed disease (determined as the inflexion point in the cumulative hazard for the placebo arm), after which the survival curve was extrapolated using treatment-specific exponential functions (derived from the tails of the cumulative hazard plots).

Bevacizumab arm:

Probability of remaining in PD after 12 months = exp (-(0.0553 x months – 0.0754))

Capecitabine arm:

Probability of remaining in PD after 12 months = exp (-(0.1908 x months – 1.3411))

b. The estimated area under the curve for PD, including projections;

The area under the curve for PD used in the model (i.e. observed Kaplan-Meier survival for months 0-11 and the exponential curves described in **B.1 a** above from 12 months onwards) is 20.163 months for the bevacizumab arm and 11.489 months for the placebo arm. This is estimated by taking the sum of the monthly survival probabilities in column I of sheet 'Bevacizumab-PPD' and column F of sheet 'Placebo-PPD'.

c. Percentage of patients who died at progression (i.e. those who didn't enter the post-progression survival [PPS] phase)

The data in table 13 of the submission contains this information and is reproduced here.

Table 2: Reproduction of Table 13 in the submission

	BEV + CAP (N=161)	CAP (N=84)
Number of PFS Deaths	7	3
PFS Person-Months	1324.76	467.36
Monthly Rate of PFS Deaths	0.00528	0.00642
Monthly probability of Death	0.00527	0.00640

Therefore the percentage of patients who died at progression in each treatment arm is 4.35% for patients randomized to receive bevacizumab and 3.70% to control patients.

B.2 Priority Request: Observed survival analyses

Clinical results in the submission do not allow for exploration of issues related to time to events. Please provide the following clinical result analyses (a sample table structure for responses is included at the end of this question):

a. Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the RIBBON-1 trial data for time from progression to time of death (PPS)

By Observed survival analyses, we understand using survival time actually observed in the study, i.e. not the uncrossed survival data using RPSFT methodology. Therefore these data are not the ones used in the model.

Table 3: Product Limit Survival Estimates for Stratum 1, Bevacizumab crossover

Stratum 1: TRTCROSSC = BEVACIZUMAB CROSSOVE						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	72
80.964		0.9861	0.0139	0.0138	1	71
119.924		0.9722	0.0278	0.0194	2	70
120.837		0.9583	0.0417	0.0235	3	69
148.231	*				3	68
161.928		0.9442	0.0558	0.0271	4	67
168.015		0.9301	0.0699	0.0301	5	66
171.972		0.9161	0.0839	0.0328	6	65
181.103		0.9020	0.0980	0.0352	7	64
193.887	*				7	63
194.191		0.8876	0.1124	0.0374	8	62
199.061	*				8	61
207.888	*				8	60
217.019	*				8	59
218.846		0.8726	0.1274	0.0397	9	58
227.064		0.8576	0.1424	0.0418	10	57
229.803	*				10	56
239.848	*				10	55
241.978		0.8420	0.1580	0.0438	11	54
243.196		0.8264	0.1736	0.0457	12	53
246.848		0.8108	0.1892	0.0474	13	52
248.066	*				13	51
248.979	*				13	50
252.936					14	49
252.936		0.7783	0.2217	0.0508	15	48
255.066		0.7621	0.2379	0.0522	16	47
255.979	*				16	46
256.284	*				16	45

Stratum 1: TRTCROSSC = BEVACIZUMAB CROSSOVE						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
257.197	*				16	44
257.806	*				16	43
259.023	*				16	42
259.936		0.7440	0.2560	0.0541	17	41
269.067	*				17	40
269.068		0.7254	0.2746	0.0558	18	39
271.198	*				18	38
273.938		0.7063	0.2937	0.0575	19	37
299.809	*				19	36
303.766	*				19	35
305.897	*				19	34
311.984		0.6855	0.3145	0.0595	20	33
322.029	*				20	32
332.073					21	31
332.073		0.6427	0.3573	0.0630	22	30
336.030		0.6213	0.3787	0.0644	23	29
336.943		0.5998	0.4002	0.0657	24	28
350.031	*				24	27
357.032	*				24	26
357.032	*				24	25
362.815	*				24	24
384.121		0.5748	0.4252	0.0675	25	23
391.122		0.5498	0.4502	0.0691	26	22
395.079	*				26	21
395.992		0.5237	0.4763	0.0706	27	20
398.123	*				27	19
418.820		0.4961	0.5039	0.0720	28	18
422.777	*				28	17
431.908		0.4669	0.5331	0.0735	29	16
453.214		0.4377	0.5623	0.0744	30	15
454.128	*				30	14
479.999	*				30	13

Stratum 1: TRTCROSSC = BEVACIZUMAB CROSSOVE						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
485.174	*				30	12
490.044	*				30	11
490.044	*				30	10
497.044	*				30	9
578.921		0.3891	0.6109	0.0805	31	8
609.054	*				31	7
641.927		0.3335	0.6665	0.0861	32	6
658.972		0.2779	0.7221	0.0879	33	5
690.931	*				33	4
704.933	*				33	3
706.759	*				33	2
707.063	*				33	1
739.936	*				33	0

Table 4: Product Limit Survival Estimates for Stratum 2, Bevacizumab-no crossover

Stratum 2: TRTCROSSC = BEVACIZUMAB NO CROSS						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	82
4.870	*				0	81
16.132	*				0	80
17.958		0.9875	0.0125	0.0124	1	79
21.915	*				1	78
22.219	*				1	77
22.828	*				1	76
24.046	*				1	75
42.917		0.9743	0.0257	0.0179	2	74
56.005		0.9612	0.0388	0.0220	3	73
59.049		0.9480	0.0520	0.0253	4	72
64.223	*				4	71

Stratum 2: TRTCROSSC = BEVACIZUMAB NO CROSS						
Product-Limit Survival Estimates						
POST		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
70.006		0.9346	0.0654	0.0283	5	70
72.746		0.9213	0.0787	0.0309	6	69
101.053	*				6	68
142.143		0.9077	0.0923	0.0332	7	67
159.188	*				7	66
179.886		0.8940	0.1060	0.0355	8	65
180.799		0.8802	0.1198	0.0375	9	64
181.103		0.8665	0.1335	0.0394	10	63
185.060	*				10	62
185.060	*				10	61
190.843	*				10	60
196.931		0.8520	0.1480	0.0413	11	59
199.974	*				11	58
202.105	*				11	57
202.714		0.8371	0.1629	0.0432	12	56
206.975	*				12	55
214.889		0.8219	0.1781	0.0450	13	54
219.759	*				13	53
228.890	*				13	52
230.108		0.8061	0.1939	0.0468	14	51
237.717	*				14	50
239.848		0.7899	0.2101	0.0486	15	49
243.196	*				15	48
254.153		0.7735	0.2265	0.0503	16	47
257.806		0.7570	0.2430	0.0518	17	46
262.067	*				17	45
262.980		0.7402	0.2598	0.0533	18	44
279.112		0.7234	0.2766	0.0547	19	43
280.025	*				19	42
281.851	*				19	41
299.809	*				19	40
310.767		0.7053	0.2947	0.0563	20	39

Stratum 2: TRTCROSSC = BEVACIZUMAB NO CROSS						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
315.028	*				20	38
319.898		0.6867	0.3133	0.0578	21	37
324.768		0.6682	0.3318	0.0591	22	36
333.899	*				22	35
336.030	*				22	34
368.903	*				22	33
372.859	*				22	32
375.903	*				22	31
376.816	*				22	30
377.729	*				22	29
380.164		0.6451	0.3549	0.0614	23	28
385.034		0.6221	0.3779	0.0634	24	27
393.861	*				24	26
398.123	*				24	25
421.864		0.5972	0.4028	0.0655	25	24
434.039	*				25	23
437.083	*				25	22
461.128	*				25	21
465.998	*				25	20
473.912	*				25	19
476.043	*				25	18
482.739	*				25	17
503.132	*				25	16
505.263		0.5599	0.4401	0.0713	26	15
510.133	*				26	14
511.959		0.5199	0.4801	0.0766	27	13
518.046	*				27	12
544.831	*				27	11
546.049	*				27	10
553.963		0.4679	0.5321	0.0848	28	9
563.703	*				28	8
567.051	*				28	7

Stratum 2: TRTCROSSC = BEVACIZUMAB NO CROSS						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
602.967		0.4011	0.5989	0.0954	29	6
604.793	*				29	5
630.969	*				29	4
635.231	*				29	3
664.146	*				29	2
778.896	*				29	1
806.898		0	1.0000	0	30	0

Table 5: Product Limit Survival Estimates for Stratum 3, Placebo-crossover

Stratum 3: TRTCROSSC = PLACEBO CROSSOVER						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	44
7.001		0.9773	0.0227	0.0225	1	43
84.921	*				1	42
115.054		0.9540	0.0460	0.0318	2	41
128.142		0.9307	0.0693	0.0386	3	40
134.838		0.9075	0.0925	0.0441	4	39
140.926		0.8842	0.1158	0.0487	5	38
143.969		0.8609	0.1391	0.0527	6	37
154.014		0.8377	0.1623	0.0562	7	36
188.104		0.8144	0.1856	0.0592	8	35
231.934	*				8	34
233.151	*				8	33
242.891		0.7897	0.2103	0.0624	9	32
248.066		0.7650	0.2350	0.0651	10	31
259.023	*				10	30
277.894		0.7395	0.2605	0.0678	11	29
291.896		0.7140	0.2860	0.0701	12	28
311.071		0.6885	0.3115	0.0720	13	27

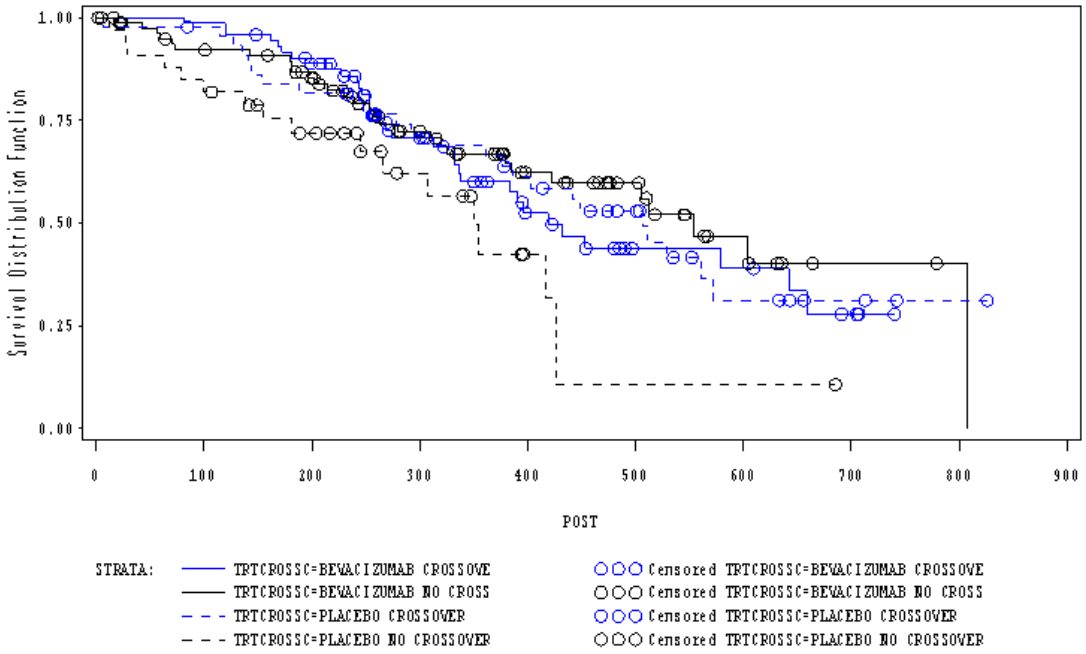
Stratum 3: TRTCROSSC = PLACEBO CROSSOVER						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
360.989		0.6630	0.3370	0.0738	14	26
377.121		0.6375	0.3625	0.0752	15	25
378.034	*				15	24
385.948		0.6110	0.3890	0.0766	16	23
402.993		0.5844	0.4156	0.0777	17	22
413.950	*				17	21
441.039		0.5566	0.4434	0.0789	18	20
448.040		0.5287	0.4713	0.0797	19	19
458.084	*				19	18
474.216	*				19	17
483.043	*				19	16
501.001	*				19	15
503.741	*				19	14
507.089		0.4910	0.5090	0.0825	20	13
511.046		0.4532	0.5468	0.0843	21	12
529.004		0.4154	0.5846	0.0853	22	11
535.091	*				22	10
535.091	*				22	9
552.136	*				22	8
560.963		0.3635	0.6365	0.0891	23	7
571.921		0.3116	0.6884	0.0902	24	6
633.100	*				24	5
643.144	*				24	4
655.928	*				24	3
712.846	*				24	2
742.066	*				24	1
826.074	*				24	0

Table 6: Product Limit Survival Estimates for Stratum 4, Placebo-no crossover

Stratum 4: TRTCROSSC = PLACEBO NO CROSSOVER						
Product-Limit Survival Estimates						
POST		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	34
1.826	*				0	33
12.175		0.9697	0.0303	0.0298	1	32
28.003		0.9394	0.0606	0.0415	2	31
29.220		0.9091	0.0909	0.0500	3	30
63.006		0.8788	0.1212	0.0568	4	29
77.920		0.8485	0.1515	0.0624	5	28
98.922		0.8182	0.1818	0.0671	6	27
107.140	*				6	26
138.186		0.7867	0.2133	0.0716	7	25
141.839	*				7	24
149.144	*				7	23
154.927		0.7525	0.2475	0.0762	8	22
181.103		0.7183	0.2817	0.0800	9	21
189.017	*				9	20
203.931	*				9	19
217.019	*				9	18
229.803	*				9	17
241.978	*				9	16
244.718		0.6734	0.3266	0.0867	10	15
245.022	*				10	14
263.893	*				10	13
266.024		0.6216	0.3784	0.0943	11	12
278.808	*				11	11
307.114		0.5651	0.4349	0.1012	12	10
339.987	*				12	9
347.292	*				12	8
350.031		0.4945	0.5055	0.1105	13	7
353.988		0.4238	0.5762	0.1151	14	6
394.166	*				14	5
395.992	*				14	4
416.994		0.3179	0.6821	0.1260	15	3

Stratum 4: TRTCROSSC = PLACEBO NO CROSSOVER						
Product-Limit Survival Estimates						
POST		Survival	Failure	Survival Standard Error	Number Failed	Number Left
425.821		0.2119	0.7881	0.1206	16	2
426.125		0.1060	0.8940	0.0962	17	1
685.148	*				17	0

Figure 1: Kaplan Meier estimates of Post-progression survival



For information, we also provide below charts showing the survival of patients with progressed disease in the placebo (Figure 2) and bevacizumab (Figure 3) arms for the cohorts above, compared to survival of these cohorts after adjustment for cross-over using the RPSFT method.

Figure 2: The survival of post-progression patients randomised to the placebo arm before (blue and red lines) and after adjustment for crossover (black line)

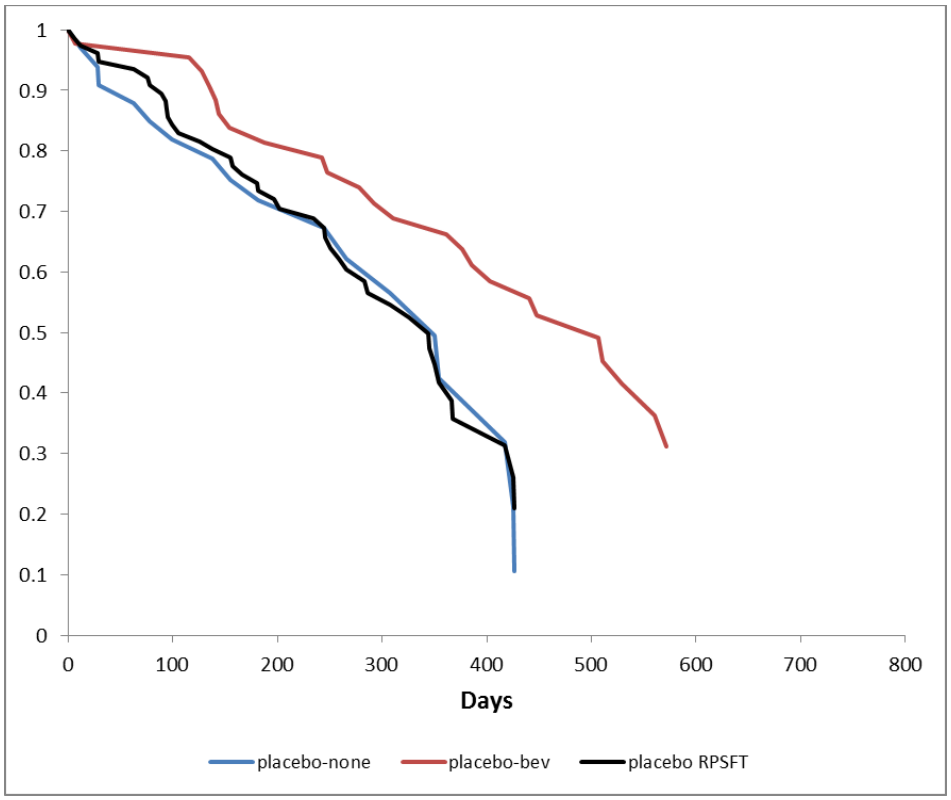


Figure 3: The survival of post-progression patients randomised to the bevacizumab arm before (blue and red lines) and after adjustment for crossover (black line)

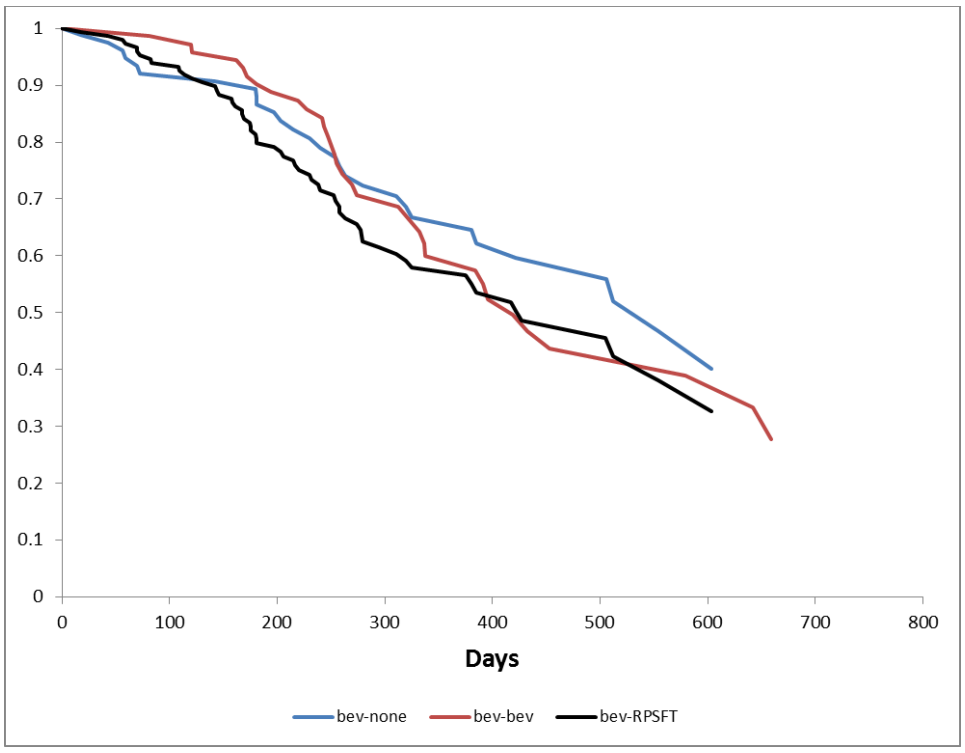


Figure 2 clearly demonstrates an increased survival advantage for patients randomized to the control arm of the trial who received bevacizumab after progression (red line) compared to patients who did not (blue line). This over-estimation of survival of patients with progressed disease is adjusted for by RPSFT and results in a survival curve that more accurately illustrates survival of this cohort (black line). In contrast, the survival advantage of continuing to administer bevacizumab to patients beyond progression is much less certain (red and blue lines in Figure 3) and adjustment using the RPSFT method appears to result in a slight under-estimation of survival in this cohort (black line).

b. In addition, please provide for each set of outputs the estimated mean survival time from baseline up to the time of last event, together with the standard error of the mean estimate.

Table 7: Summary statistics for the outputs of the Product Limit Survival Estimates (Table 3-Table 6)

Randomised arm	Post-progression treatment	Median (days)	95% CI (days)	Mean (days)	Standard Error (days)
BEVACIZUMAB	BEVACIZUMAB	418.820	(336.03, 658.972)	448.145	26.608
	-	553.963	(385.034, 806.898)	525.553	38.642
PLACEBO	BEVACIZUMAB	507.089	(377.121, 571.921)	418.109	27.368
	-	350.031	(266.024, 425.821)	296.667	27.255

B.5 The manufacturer's submission refers to a paper by Zielinski et al 2009 which suggests that for capecitabine 1250mg/m^2 and capecitabine 1050mg/m^2, efficacy is similar but adverse events are reduced at the lower dose. Figure 1 of this paper appears to support the adverse event data by plotting adverse event rates from different studies. If available, please provide pooled data on the incidence of these same adverse events and any other relevant adverse events (such as those listed in Table 28) for capecitabine at a 1250mg/m^2 dose and how these compare with adverse events at the 1000mg/m^2 dose (and if data allows by grade) .

The data requested for adverse events from patients who received capecitabine at 1250mg/m^2 versus 1000mg/m^2 do not exist in a pooled format and so we are unable to provide this information.

B4. Priority Request: Table 14 (page 82 of the manufacturer's submission) shows patients who received bevacizumab post-progression. For each treatment arm, please provide the number (and %) of patients who received any post-progression therapy and details of the therapies received (including type of treatment and the number of lines of treatment if data is available).

The subsequent anti-cancer therapy patients received after discontinuation of assigned study treatment was assessed in the RIBBON-1 study. As expected for patients relapsing after first-line treatment of metastatic breast cancer, the majority of patients received additional lines of systemic treatment, either with hormonal agents or with chemotherapy and

for some patients this second-line chemotherapy was combined with bevacizumab. In total, 69% and 61% of patients in the PL-Cap and BV-Cap groups, respectively, received subsequent therapy. Table 8 below summarises the subsequent anticancer therapy patients received (Robert et al. 2011).

Table 8: Subsequent anticancer therapy ITT population (Robert 2011)

	Capecitabine and placebo Number of patients (%)	Capecitabine and bevacizumab Number of patients (%)
Patients who received subsequent therapy	142 (68.9%)	251 (61.4%)
Type of therapy:		
Chemotherapy	135 (65.5%)	226 (55.3%)
Bevacizumab or open-label bevacizumab	112 (54.4%)	160 (39.1%)
Hormonal therapy	28 (13.6%)	51 (12.5%)
Radiotherapy	12 (5.8%)	35 (8.6%)
Surgery	4 (1.9%)	3 (0.7%)
Other	8 (3.9%)	12 (2.9%)
Missing	0	0

In addition, the spreadsheet labeled “Post-Prog treatment” in the Excel model contains full details of the treatments received by the prior-taxane sub-group of patients in each arm of the trial.

B.5 To adjust for crossover, the Rank Preserving Structural Failure Time (RPSFT) Model is used to estimate overall survival in the economic model (page 83 of the manufacturer’s submission).

a. Please justify the use of the RPSFT over other methods that may be used for adjusting for cross-over, such as the Inverse Probability of Censoring Weights (IPCW).

The most appropriate method for accounting for cross-over in clinical trials is the subject of an ongoing academic debate. It was nevertheless perceived that the IPCW method involved more subjective choices than the RPSFT method, in that the calculation of the stabilized weights used in the weighted Cox proportional hazard regression model in IPCW may depend on the choice of the baseline covariates and the time-dependent covariates.
In addition, the IPCW method requires that patients not crossing over are weighted more strongly to compensate for censoring of those who receive treatment following progression. In situations where such a large proportion of patients cross-over, the number of patients not crossing over is reduced and therefore their weighting is increased, potentially magnifying consequences of small errors. Taking all of these factors into consideration, it was determined that the RPSFT was most appropriate for this submission.

b. Please present overall survival estimates using both the RPSFT and IPCW methods

Roche does not have the resource capacity to provide this analysis within the timeframe required and have doubts that such an analysis would result in a significant enough change in incremental cost effectiveness to affect the final decision.

Section C: Textual clarifications and additional points

Issues relating to the number of patients eligible for bevacizumab in combination with capecitabine (page 18 of the manufacturer's submission)

C.1 Please can you highlight/explain from where in Scarborough et al 2010 the assumption that 96% of patients are not contraindicated for bevacizumab is derived?

The publication by Scarborough et al 2010 states that the percentage of patients who have coronary heart disease (CHD) in the UK is 4%. The assumption made in the manufacturer's submission is that these patients are contraindicated to bevacizumab, leaving the remaining 96% of patients not contraindicated.

Patients with the following conditions were excluded from recruitment to the RIBBON-1 study:

- Blood pressure >150/100 mmHg
- Unstable angina
- New York Heart Association (NYHA) Grade II or greater congestive heart failure
- History of myocardial infarction (within last 6 months)
- History of stroke or transient ischemic attack (within last 6 months)
- Clinically significant peripheral vascular disease

These are all symptoms associated with CHD and they all indicate patients for whom therapy with bevacizumab is not advisable. We have taken the UK incidence of CHD, as shown in Scarborough 2010, to demonstrate the percentage of patients within the population for whom it would be inadvisable to prescribe bevacizumab for the above reasons and have assumed that the distribution of CHD in the metastatic breast cancer population would be similar to that in the general population.

In addition, the contraindications for bevacizumab are as follows:- hypersensitivity to the active substance or to any of the excipients, hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies and pregnancy (Avastin SPC). However, there are few statistics for the number of patients who are hypersensitive to excipients/CHOs, or for the number of patients who are pregnant whilst receiving treatment for metastatic breast cancer. The figure of 96% of patients not contraindicated for bevacizumab may therefore be a slight overestimate of the eligible patient population, but the percentage of the population with CHD is the only good estimate to be found for at least one group of patients who will be unable to receive the drug.

C.2 Please can you highlight/explain from where in Dent et al 2007 the assumption that 83% of patients have relapsed more than 12 months after initial anthracycline and taxane treatment is derived?

In the absence of a publication on the relapse rate for patients who have received both anthracycline and taxane in the adjuvant setting, this assumption in the manufacturer's submission was made from the relapse rates from triple negative (Her2-/ER-/PgR-) patients. Triple negative breast cancer patients typify the poor prognostic patients who receive both anthracycline and taxane therapy in the adjuvant setting. In addition, PFS data from several large phase III trials demonstrate that triple negative patients and adjuvant taxane treated patients with metastatic breast cancer have similar short PFS and OS duration (Robert et al

2011, Miles et al 2010, Gray et al 2009). The data from Dent et al 2007 was thus taken to give an example of the relapse rate seen for poor prognosis breast cancer patients treated with both adjuvant anthracycline and taxane.

Dent et al. 2007 examined the clinical features and patterns of recurrence in a large cohort of patients with breast cancer; 180 of the 1601 patients in the study had triple negative breast cancer. The assumption that 83% of patients relapse more than 12 months after anthracycline and taxane treatment has been derived from Figure 1 of Dent et al 2007, as shown in Figure 4.

Figure 4: The calculation of the rate of recurrence (Dent et al 2007)

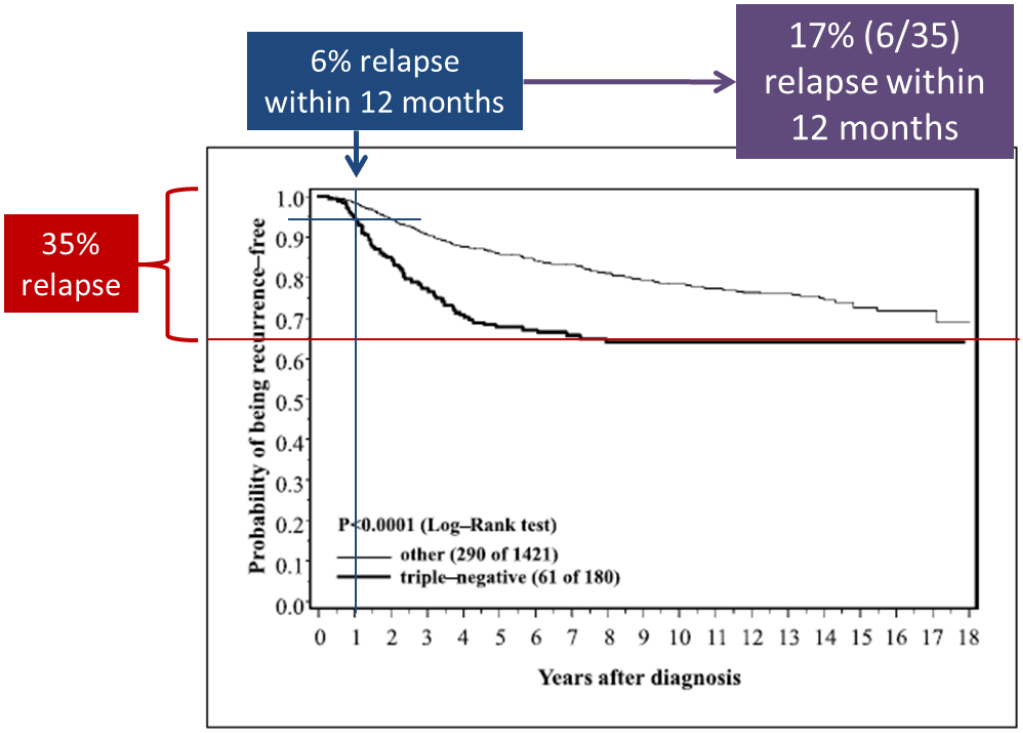


Fig. 1. Rates of distant recurrences in triple-negative and other breast cancers.

6% of triple negative patients relapsed within one year, with a total of 35% of patients relapsing within 18 years. 6%/35% = 17% risk of relapse in patients with triple negative breast cancer within one year after treatment, thus 83% of a patients who relapse, will do so after one year.

References:

Dent et al. Triple-negative breast cancer: clinical features and patterns of recurrence *Clin Can Res* 2007 13(15):4429-4434.

Gray et al Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2009 20(30):4966-72

Miles et al. 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. 2010 10(20):3239-47

Robert et al. 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 2011 29(10):1252-60

Scarborough et al 2010 *Coronary heart disease statistics: 2010 edition*, Department of Public Health, University of Oxford, Oxford, UK. Accessed: www.bhf.org.uk/idoc.ashx?docid=9ef69170-3edf...version=-1