ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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A MEMBER OF THE RUSSELL GROUP

The manufacturer identified 11 issues in relation to factual errors in the original ERG report. This resulted in some changes to the ERG report. The pages of the report affected are presented here. Text that remains unaltered is greyed out and/or omitted altogether.

Please note, as a result of these changes, two extra references have been inserted as has an extra table, resulting in an extra page to section 5.3.3.

In this erratum, therefore, all sections from section 5.3.3 onwards have been included, excluding the appendices. From section 5.3.3 onwards, the table numbers differ to those in the original ERG report.

Only the references that apply to the erratum have been included in this document. As a result, the reference numbers also differ to those in the original ERG report.

Abbreviations

AE (s)	Adverse event (s)
AUC	Area under the curve
AVADO	*Avastin Plus Docetaxel*
BEV	Bevacizumab
BNF	British National Formulary
BSC	Best supportive care
CAPE	Capecitabine (in the context of the RIBBON-1 trial, CAPE refers to patients who received capecitabine in addition to placebo)
CHD	Coronary heart disease
CI	Confidence interval
CSR	Clinical study report
CVD	Cardiovascular disease
DFI	Disease-free interval
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ER+ve	Oestrogen receptor-positive
ER-ve	Oestrogen receptor-negative
ERG	Evidence Review Group
EORTC	*European Organisation for Research and Treatment of Cancer*
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
HER2+ve	Human epidermal growth factor receptor 2 positive
HER2-ve	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse Probability of Censoring Weights
IRC	Independent review committee
ITT	Intention to treat
KM	Kaplan-Meier
LYG	Life year gained
mBC	Metastatic breast cancer
MS	Manufacturer's submission
NCI-CTC	National Cancer Institute Common Terminology Criteria
NICE	National Institute for Health and Clinical Excellence
NPTs	Non-protocol specified antineoplastic therapies
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PgR+ve	Progesterone receptor positive
PgR-ve	Progesterone receptor negative
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RIBBON	Regimens in *Bevacizumab* for Breast Oncology
RPSFT	Rank Preserving Structural Failure Time
SA	Sensitivity analysis
SD	Stable disease
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
VEGF	Vascular endothelial growth factor
VIN	Vinorelbine
vs	Versus

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from Roche Ltd in support of the use of bevacizumab (BEV) (Avastin) in combination with capecitabine (CAPE) (Xeloda) as a first-line treatment for patients with metastatic breast cancer (mBC).

BEV+CAPE has a marketing authorisation in Europe. It is licensed for the first-line treatment of patients with mBC in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with BEV+CAPE for mBC.

The ERG believes that the patient population for whom the manufacturer presents its clinical evidence is the same patient population that is stipulated in the decision problem in the scope issued by the National Institute for Health and Clinical Excellence (NICE) and for whom BEV+CAPE is licensed. The manufacturer has based the economic evidence on a subgroup of patients that have previously been treated with a taxane in the adjuvant setting. Based on current clinical practice, it is assumed that all patients within this subgroup have also received prior adjuvant treatment with an anthracycline. According to the manufacturer, this more stringent patient population is representative of the population of patients for whom CAPE is licensed, i.e. patients requiring treatment for mBC after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Other than the population utilised in the economic model, the only other deviation from the decision problem as issued in the scope by NICE is the exclusion of vinorelbine (VIN) as a comparator in the clinical section; VIN is only used as a comparator for a scenario analysis in the economic model. Given CAPE is usually preferred to VIN in clinical practice and in the absence of any studies comparing BEV+CAPE to VIN and of evidence to suggest that VIN is superior to CAPE, the ERG is satisfied that CAPE is considered the main comparator.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness section of the manufacturer's submission (MS) is derived from a single manufacturer supported randomised controlled trial (RCT) known as RIBBON-1. RIBBON-1 was a superiority trial using placebo controlled parallel groups of patients in which patients were considered suitable for treatment with CAPE (or in the other cohort of the trial, a taxane/anthracycline) and then randomised in a 2:1 ratio to receive BEV+CAPE or CAPE in combination with a placebo, hereafter simply referred to as CAPE (or BEV+taxane/anthracycline or a taxane/anthracycline in the other cohort of the trial). The primary endpoint was investigator assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary outcomes included independent review committee (IRC) assessed PFS and overall survival (OS). An additional PFS and OS benefit of around 3 months for patients in the BEV+CAPE arm over the CAPE arm was reported (investigator assessed median PFS: 8.6 vs 5.7 months; IRC assessed median PFS: 9.8 vs 6.2 months; median OS: 25.7 vs 22.8 months). However, despite significant improvements also in overall response rate (ORR) for the BEV+CAPE arm (35.4% compared to 23.6%), only the PFS and not the OS findings were statistically significant. The lack of a statistically significant difference in OS between the groups may be explained by differences in the nature and frequency of subsequent treatments received in both arms of the trial following disease progression.

The manufacturer also presents both *a priori* and *post-hoc* exploratory subgroup analyses for PFS and OS. All subgroup analyses suggested improvements in terms of PFS for the BEV+CAPE arm compared with the CAPE arm. A similar pattern was reported for OS. While the majority of subgroups reported statistically significant differences in PFS (all in favour of BEV+CAPE), the only subgroups that reported significant differences in OS (all in favour of BEV+CAPE) were those aged <50 years and those previously treated with a taxane, anthracycline or neoadjuvant/adjuvant chemotherapy.

The subgroup of patients previously treated with a taxane is the population of patients used by the manufacturer in the economic model. For this subgroup, the differences in PFS (4.5 months) and OS (7.9 months) between the BEV+CAPE and CAPE arms appeared to be greater (median PFS: 8.7 vs 4.2 months; median OS: 28.4 vs 20.5 months) than in the Intention To Treat (ITT) population.

A greater proportion of BEV+CAPE patients than CAPE patients in RIBBON-1 reported any adverse event (AE) (40% vs 27%), serious adverse events (SAEs) (25% vs 20%) and National Cancer Institute Common Terminology Criteria (NCI-CTC) grade 3-5 AEs (37% vs 23%). While a greater number of patients in the BEV+CAPE arm reported AEs than in the CAPE arm, no new safety concerns were identified.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Overall, the range of databases selected and search strategies employed to identify RIBBON-1 appear to be appropriate. The ERG does not believe there are any relevant RCTs omitted. With regard to the clinical evidence submitted, the main issues are:

- RIBBON-1 appears to be a well conducted trial, the results of which are likely to be generaliseable to patients in the UK. Generally, baseline characteristics within RIBBON-1 appeared to be balanced across the treatment groups.
- The CAPE dose was not given to patients at the licensed dose of 1250mg/m^2 but rather at a dose of 1000mg/m^2. However, this is a dose that is commonly used in clinical practice.
- For CAPE vs BEV+CAPE, since the hazard ratios (HRs) for investigator and IRC assessed PFS were almost identical (HR=0.69 [95% CI: 0.56 to 0.84] and HR=0.68 [95% CI: 0.54 to 0.86] respectively), the evidence suggesting a benefit in terms of PFS does appear to be robust.
- Interpreting differences in OS is difficult because patients were able to 'cross-over' from the CAPE arm to receive subsequent BEV and those in the BEV+CAPE arm were also able to receive subsequent BEV. Other anti-cancer therapies were also available on progression and, in a minority of instances, prior to progression.
- The ERG urges caution in interpreting subgroup results for all outcomes (adjusted and unadjusted) because no statistical adjustments were performed to control for multiple testing in all subgroups and of all outcomes, thus increasing the likelihood of significant results emerging by chance.
- The ERG agrees that there were a greater proportion of AEs in the BEV+CAPE arm, including AEs 'of special interest' but that no new safety concerns were identified. The ERG believes the difference between the two arms can largely be attributed to differences in grade 3 AEs (27% vs 14%).

Because, as noted above in section 1.1, the economic model is based on the subgroup of patients who received a prior taxane, and as this was not the population for whom evidence was presented by the manufacturer in the clinical section of the MS (with the exception of the PFS and OS findings), the ERG attempted to extract as much data as possible on this subgroup from relevant Microsoft Excel worksheets submitted as part of the economic model. There appear to be baseline differences between this subgroup and the entire ITT population, in particular, the subgroup appears to be a younger and healthier population than the entire ITT population.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

In the absence of any relevant published economic evaluations the manufacturer developed a *de novo* economic model. The model, which has been constructed in Microsoft Excel, is made up of three health states (PFS, progressive disease (PD) and death). The modelled population comprises a subgroup of patients treated in the RIBBON-1 trial, namely those who have previously been treated

with a taxane, rather than the whole population licensed to receive BEV+CAPE. The economic evaluation adopts a time horizon of 15 years, and the perspective is that of the UK NHS. Resource use, costs and utilities have been estimated based on information from trial data and published sources.

The manufacturer's reported base case incremental cost-effectiveness ratio (ICER) is £77,318 per quality adjusted life year (QALY) gained. The manufacturer showed this ICER to be generally robust when subjected to deterministic and probabilistic sensitivity analysis (PSA) (ICERs ranging from £71,662 to £110,092 per QALY gained).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Overall, the ERG found the manufacturer's model to be clearly set out with adequate labelling of tables and parameters. The main areas that give cause for concern are:

- The modelled population is a subgroup of the RIBBON-1 Trial. Baseline characteristics indicate that this subgroup appears to be younger and healthier than the licensed (ITT) population. The model results are therefore unlikely to be generalisable to the licensed population.

- The manufacturer has used the Rank Preserving Structural Failure Time (RPSFT) model *post-hoc* to ameliorate any effect that might arise from patients in both treatment arms receiving the study drug (i.e. BEV) after progression. This approach is recognised as having serious limitations when the proportions of patients receiving the study drug are high and when other therapies are permitted. Model subgroup data from the RIBBON-1 trial show that 44.7% of patients in the BEV+CAPE arm and 52.4% of patients in the CAPE arm received BEV post progression. The ERG is unable to ascertain whether the RPSFT model results in bias towards any particular treatment arm.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The clinical evidence is derived from a well conducted RCT (RIBBON-1) that compares the intervention of interest (BEV+CAPE) to one of the comparators of interest (CAPE). This comparator is considered by the manufacturer and the ERG as the most significant of the comparators (CAPE and VIN) listed in the decision problem. The population of patients included in RIBBON-1 is the same group of patients who are specified in the decision problem and for whom BEV+CAPE has received a marketing licence from the European Union.

1.6.2 Weaknesses and areas of uncertainty

Evidence for cost effectiveness is derived from a subgroup of patients in the RIBBON-1 trial. Because no statistical adjustments were performed to control for multiple testing in all subgroups and of all outcomes, the results must be treated with caution. Furthermore, this is a more stringent patient population than that which is licensed to receive BEV+CAPE. From data extracted by the ERG from relevant spreadsheets of the economic model, it would appear this population differs to the overall population of RIBBON-1 in that it is a younger and healthier population.

The ERG's main concern relates to the reliance on the RPSFT model to ameliorate any effect arising from patients in both treatment arms receiving the study drug (BEV). Three other, relatively minor, areas of uncertainty relating to the model are the estimation of drug costs, the absence of any cost of terminal care and the calculation of utility values.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The manufacturer's ICER is £77,318 per QALY gained. The ERG made three relatively minor alterations/corrections to the model, namely:

- Recalculation of drug costs based on the distribution of patient body weight and body surface area of a UK specific cohort of patients, rather than a simple average based on trial data.
- Addition of the cost of terminal care.
- Correction to the calculation of utility values.

Implementing these three changes increased the ICER to £82,162 per QALY gained. Because of concerns regarding the use of the RPSFT model to adjust for OS, the ERG suggested two alternative approaches to modelling PD. The first model assumed that survival for both patient groups was equivalent during the PD phase and resulted in an ICER of £171,411 per QALY gained. The second

divided patients into two groups, those who had, and those who had not, received BEV. Survival projections for these two groups were generated for the BEV+CAPE and CAPE arms respectively and resulted in an ICER of £92,060 per QALY gained. When all of the ERG's changes are incorporated together into the submitted model, the ICER is estimated to be between £97,963 and £181,648 per QALY gained.

It should be noted that any ICER estimate based on the modelled patient population may be optimistic as the modelled population is a subgroup of RIBBON-1 who, at baseline, appear to be younger and healthier than the licensed (ITT) population.

For illustrative purposes only, assuming the proportion of patients not to be contraindicated to BEV to be 87%, the ERG estimates around 100 fewer patients may be eligible for BEV+CAPE (Table 1).

Table 1 Modified estimate of number of patients eligible for treatment with BEV+CAPE

Assumption	N
Annual incidence of mBC in England and Wales [a]	10,913
32% of these mBC patients receive taxanes in an adjuvant setting [b]	3,492
76% of these are HER2-ve [b]	2,654
72% are treated with chemotherapy [b]	1,911
92% of these are not enrolled in a clinical trial [b]	1,758
55% are treated with CAPE (monotherapy or in combination with another agent) [b]	967
87% are not contraindicated for BEV [c]	803
83% of these have relapsed more than 12 months after initial anthracycline and taxane treatment [d]	666

[a] Calculated from the total population for England and Wales (mid-2010 population estimates)[1] and the age-standardised incidence rate of breast cancer [2]
[b] Roche Data on File
[c] Calculated from the proportion of women in England who do not have CVD[3]
[d] Using data on relapse rates for patients with triple negative breast cancer[4] as a proxy for "poor prognostic patients who receive both anthracycline and taxane therapy in the adjuvant setting" (see Box 2)

taxane and that this subgroup is therefore broadly representative of patients who meet the licence for treatment with CAPE (see section 3.2).

The ERG agrees that the majority of patients in this subgroup would most likely have previously received an anthracycline in addition to a taxane. However the ERG questions whether they would be considered to have 'failed' on these treatments since the RIBBON-1[5] trial excluded patients who had received an adjuvant taxane or anthracycline within the last 12 months. Given most clinicians would consider a DFI>12 months as long enough to consider a re-challenge with either an anthracycline or a taxane, it is debatable whether such patients should be considered to have 'failed' on these treatments. Furthermore, the ERG notes that in clinical practice, while CAPE is only licensed for patients who have 'failed' an anthracycline or a taxane, in clinical practice it is given to patients in off label usage who are not considered appropriate for an anthracycline or taxane, regardless of whether they have 'failed' on these treatment regimens in the past.

Most crucially, however, this subgroup is clearly a more stringent population than is licensed for treatment with BEV+CAPE (see section 3.2). Therefore the ERG believes the ITT population from the RIBBON-1[5] trial to be most appropriate. The ERG requested, from the manufacturer, an appropriate economic model based on the ITT/safety populations of the RIBBON-1[5] trial addressed in the clinical section of the MS rather than on the subgroup of people who have had a prior taxane. In their response, the manufacturer stated that:

> *Since the submitted health economic analysis calculated an ICER of approximately £77,000 per QALY for the "failed anthracycline and taxane therapy" subgroup, analysis of the ITT population would result in a larger ICER and therefore clearly not considered to be a cost-effective use of NHS resources.*

Finally, the ERG notes that the number of estimated patients who have received a prior anthracycline and taxane in the adjuvant setting would result in a much lower estimated number of patients eligible for BEV+CAPE than presented in section 2.2. In RIBBON-1,[5] it is noted that 40% of the ITT population were represented in the subgroup of patients who had received a prior taxane.

3.3 Comparators

The comparators listed in the NICE scope are CAPE and VIN. The marketing indication for CAPE is discussed above. VIN (Navelbine) has the following indication for mBC:[6]

> *Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.*

In the MS, it is stated that compared to CAPE, VIN is rarely used for the treatment of patients with HER2-ve mBC previously treated with anthracyclines and taxanes. It is therefore only included as a comparator in the economic evaluation and only as a scenario analysis. To support its statement that CAPE is more commonly used than VIN, the manufacturer cites market research data from interviews with 43 clinical oncologists and 27 medical oncologists conducted in April 2010 which found that 55.4% of patients received first-line CAPE (48% as monotherapy, 7.4% with another agent) and 12.3% of patients received first-line VIN (10% as monotherapy, 2.3% with another agent).

As p23 of the MS clearly states, identical outcomes from the use of CAPE and VIN is only an assumption. However, no research evidence is presented to support this in the clinical section of the MS where it is stated (p61):

> *An indirect comparison of bevacizumab in combination with capecitabine compared with vinorelbine was not necessary in this setting given the findings of the recent clinical guideline, NICE CG81 which assumed no significant difference in survival outcomes for vinorelbine compared to capecitabine based on a single under-powered study in women who had been heavily pre-treated.*[7, 8]

The ERG notes that the cited study was a phase II trial (EORTC 10001[7]) in which all patients had been pre-treated with an anthracycline and taxane but were not necessarily receiving their treatment as first-line for mBC. EORTC 10001[7] was prematurely closed due to low accrual and planned expansion to a phase III trial was not undertaken. Nevertheless, the outcomes were similar between the two arms in terms of OS and PFS (median 9.3 and 2.8 months respectively for CAPE and 11.0 and 2.6 months for VIN). The safety profiles differed however, grade 3/4 AEs being more common in the VIN arm, particularly neutropenia (46% VIN vs 4% CAPE).

More recently, the ERG also notes the publication of a recent systematic review of phase II or phase III studies of palliative chemotherapy by Oostendorp et al 2011.[9] To be eligible, included studies were required to have at least 80% of patients with advanced breast cancer pre-treated with anthracyclines and taxanes. From ten studies of CAPE monotherapy, weighted mean values were reported to be 13.5 months for median OS and 4.2 months for median PFS. From nine studies of VIN monotherapy, weighted mean values were reported to be 12.6 months for median OS and 3.8 months for median PFS. Caution must be taken in attempting to compare the findings across treatment arms because apart from the study of Pajk et al 2008,[7] all reports provided information from only one study group

and, therefore, as the authors stated (p1058): "***no differences could be assessed or ratios calculated, and standard meta-analytical techniques were not applicable.***"[9]

Clinical advisors to the ERG agreed that CAPE is usually preferred to VIN because it is believed to have a more favourable safety profile (e.g. in addition to neutropenia, occurrences of alopecia are much greater for patients on VIN[10]) and requires fewer out-patient visits. Thus in the absence of any studies comparing BEV+CAPE to VIN and in the absence of evidence to suggest that VIN is superior to CAPE, the ERG is satisfied that CAPE is considered the main comparator and that it is appropriate for VIN to be only used as a comparator in a scenario analysis.

In the MS, patients in the CAPE arm of the included trial (RIBBON-1[5]) also received a placebo (instead of BEV) every 3 weeks (hereafter simply referred to as CAPE in relation to this trial).

Because the only data presented in the MS for this subgroup in the clinical section were the findings for PFS and OS, the ERG requested additional data on baseline characteristics, post-progression treatment and for all other outcomes, including AEs. The manufacturer did not supply further data, indicating in their response that PFS and OS findings were presented in the MS and that data on baseline characteristics, post-progression treatment and AEs were presented in Microsoft Excel worksheets submitted as part of the economic model. These data were extracted, interpreted and critiqued by the ERG.

As can be seen from Table 16, the population of patients who received a prior taxane appears to be different to the entire ITT population. In particular, the ERG notes from differences in the mean/median age and ECOG performance status that the subgroup population appears to be younger and healthier than the entire ITT population.

Table 16 Comparison of selected baseline characteristics presented in the model for the prior taxane subgroup and the ITT population of RIBBON-1

Demographic variable		Prior taxane subgroup		ITT population	
		CAPE (n=84)	BEV+CAPE (n=161)	CAPE (n=206)	BEV+CAPE (n=409)
Age (years)	Mean (SD)	53.4 (11.5)	53.4 (10.2)	57.1 (12.1)	56.6 (11.5)
	Median (range)	52 (23 to 78)	52 (30 to 84)	57 (23 to 88)	56 (28 to 91)
Age category	<40 years	9 (10.7%)	12 (7.4%)	15 (7.3%)	21 (5.1%)
	40-64 years	61 (72.6%)	126 (78.3%)	137 (66.5%)	289 (70.7%)
	>=65 years	14 (16.7%)	23 (14.3%)	54 (26.2%)	99 (24.2%)
Age group	<50 years	33 (39.3%)	59 (36.6%)	54 (26.2%)	119 (29.1%)
	>=50 years	51 (60.7%)	102 (63.4%)	152 (73.8%)	290 (70.9%)
Menopausal Status	Premenopausal	35 (41.6%)	60 (37.3%)	60 (29.1%)	120 (29.3%)
	Perimenopausal	4 (4.8%)	10 (6.2%)	11 (5.3%)	26 (6.4%)
	Postmenopausal	40 (47.6%)	85 (52.8%)	125 (60.7%)	245 (59.9%)
	Not Applicable	1 (0.1%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Unknown	5 (5.9%)	6 (3.7%)	9 (4.4%)	17 (4.2%)
Sex	Female	83 (98.8%)	161 (100%)	204 (99.0%)	408 (99.8%)
Race/ ethnicity	White	58 (69.0%)	115 (71.4%)	157 (76.2%)	308 (75.3%)
	Black	7 (8.3%)	14 (8.7%)	10 (4.9%)	21 (5.1%)
	Other	19 (22.6%)	28 (17.3%)	39 (19.0%)	80 (19.5%)
Geographical region	North America	52 (61.9%)	118 (73.3%)	104 (50.5%)	226 (55.3%)
	Latin America	9 (10.7%)	10 (6.2%)	24 (11.7%)	42 (10.3%)
	Eastern Europe	2 (2.4%)	6 (3.7%)	32 (15.5%)	53 (13.0%)
	Western Europe	7 (8.3%)	11 (6.8%)	28 (13.6%)	57 (13.9%)
	Asia	14 (16.7%)	16 (9.9%)	18 (8.7%)	31 (7.6%)
ECOG performance status	0	48 (57.2%)	94 (58.8%)	110 (53.4%)	214 (52.7%)
	1	36 (42.8%)	66 (41.2%)	96 (46.6%)	192 (47.3%)

[a] All subgroup data is taken from the economic model (Microsoft Excel worksheet)
[b] All ITT data is taken CSR (Table 9 and Table14.1/34)
[c] For data on ECOG performance status, for the prior taxane group, n=84 in the CAPE arm and n=160 in the BEV+CAPE arm, for the ITT population, n=206 in the CAPE arm and n=406 n=615 (n=206 CAPE, n=406 BEV+CAPE)

Table 18 Subsequent anti-cancer therapy for the prior taxane subgroup and for the ITT population in RIBBON-1

Subsequent therapy received	Prior taxane subgroup		ITT population	
	CAPE (n=84)	BEV+CAPE (n=161)	CAPE (n=206)	BEV+CAPE (n=409)
Patients who 'crossed over' to receive additional BEV [a]	44 (52.4%)	72 (44.7%)	120 (59.7%)	184 (45.5%)
Patients who received subsequent therapy [b]	-	-	142 (68.9%)	251 (61.4%)
Type of therapy:				
• BEV [b]	43 (51.2%)	67 (41.6%)	112 (54.4%)	160 (39.1%)
• Chemotherapy [b]	-	-	135 (65.5%)	226 (55.3%)
• Hormonal therapy [b]	-	-	28 (13.6%)	51 (12.5%)
• Radiotherapy [b]	-	-	12 (5.8%)	35 (8.6%)
• Surgery [b]	-	-	4 (1.9%)	3 (0.7%)
• Other [b]	-	-	8 (3.9%)	12 (2.9%)

[a] Data taken from Table 14 of the MS
[b] Data taken from Table 3 of the published paper[5] for the ITT population – data not provided for subsequent therapy for the prior taxane subgroup; although data on subsequent therapy is provided in the economic model (Microsoft Office worksheet), the treatments are not mutually exclusive and the number of patients cannot therefore be determined other than for BEV

Regarding the safety of BEV+CAPE compared to CAPE in the prior taxane subgroup, it was not possible to compare the proportion of patients who experienced any AE, any grade 3–5 AE, any SAE or any AE leading to discontinuation of BEV or placebo because the manufacturer did not present these data. Nor did the manufacturer present data for all deaths (including disease progression) and deaths unrelated to disease progression. However, from the data extracted from the economic model, it is known there was one (0.62%) sudden death in the BEV+CAPE arm.

From the same data source, it was also possible to extract data on AEs 'of special interest' which on the whole appeared to be similar in frequency as in the safety population (Table 19). In addition to AEs 'of special interest', according to the economic model the proportion of patients reporting a cardiac disorder of grade 3 or higher was greater in the BEV+CAPE arm (4.4%) than the CAPE arm (no events reported). Cardiac disorders reported were: cardiac arrest (two [1.2%] patients), cardiac failure, cardio-respiratory arrest, cardiogenic shock, myocardial infarction and pericardial effusion (all one patient [0.6%]). All were grade 4 or grade 5 AEs. For the BEV+CAPE arm, the overall proportion of grade 3 or higher cardiac disorders is a slightly greater proportion than reported in the safety population for cardiac disorders (2.1%). However, the ERG urges caution in interpreting the findings because of the small numbers of patients (and therefore smaller number of AEs) in this subgroup.

Table 19 Patients experiencing at least one AE 'of special interest' [a] (NCI-CTC grade ≥3) in blinded treatment phase for the prior taxane group [b] and safety population [c]

AE 'of special interest'	Prior taxane subgroup		Safety population	
	CAPE (n=84)	BEV+CAPE (n=161)	CAPE (n = 201)	BEV+CAPE (n = 404)
Arterial thromboembolic event [b, c]	0 (0.0%)	0 (0.0%)	3 (1.5%)	6 (1.5%)
Bleeding [b, c]	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
Febrile neutropenia [b, c]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fistula [b, c]	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
Gastrointestinal perforations [b, c]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension [b, c]	0 (0.0%)	14 (8.7%)	2 (1.0%)	38 (9.4%)
Left ventricular systolic dysfunction [b, c]	0 (0.0%)	0 (0.0%)	1 (0.5%)	4 (1.0%)
Neutropenia [b, c]	1 (1.2%).	2 (1.2%)	2 (1.0%)	5 (1.2%)
Proteinuria [b, c]	0 (0.0%)	6 (3.7%)	0 (0.0%)	9 (2.2%)
Reversible posterior leukoencephalopathy syndrome [b, c]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensory neuropathy	0 (0.0%)	4 (4.3%)	1 (0.5%)	12 (3.0%)
Venous thromboembolic event [b, c]	0 (0.0%)	0 (0.0%)	7 (3.5%)	19 (4.8%)
Wound dehiscence [b, c]	0 (0.0%)	1 (0.6%)	0 (0.0%)	3 (0.7%)
Diarrhoea [b,d]	2 (2.5%)	2 (1.2%)	4 (2.0%)	6 (1.5%)
Fatigue [b,d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea [b,d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Palmar-plantar erythrodysesthesia [b,d]	0 (0.0%)	4 (2.5%)	3 (1.5%)	4 (1.0%)
Vomiting [b,d]	1 (1.2%)	0 (0.0%)	2 (1.0%)	2 (0.5%)

[a] AEs identified through clinical review in the MS and collected as per study protocol (AEs 'of special interest', AEs resulting in treatment discontinuation, SAEs) based on the later clinical cut off date of 23 February 2009 (taken from Table 7 of the MS) or AEs identified as commonly experienced by CAPE patients in other studies, highlighted by clinical advisors to the ERG and taken from Table 14.3/23 of the CSR

[b] AEs taken from economic model (Microsoft Excel worksheet) and Table 28 of MS for prior taxane subgroup

[c] AEs taken from Table 60 of the MS and [d] AEs taken from Table 14.3/23 of the CSR for ITT population

4.4 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence is derived from a single, relatively large, well conducted, manufacturer supported, placebo controlled RCT (RIBBON-1[5]) which compares BEV+CAPE to CAPE. The trial reported an additional PFS and OS benefit of around 3 months for patients in the BEV+CAPE arm over the CAPE arm (investigator assessed median PFS: 8.6 vs 5.7 months; IRC assessed median PFS: 9.8 vs 6.2 months; median OS: 25.7 vs 22.8 months). Since the HRs for investigator and IRC assessed PFS were almost identical (HR=0.69 [95% CI: 0.56 to 0.84] and HR=0.68 [95% CI: 0.54 to 0.86] respectively), the evidence suggesting a benefit in terms of PFS does appear to be robust. However, despite significant improvements also in ORR for the BEV+CAPE arm (35.4% compared to 23.6%), only the PFS and not the OS findings were statistically significant. The lack of a statistically significant difference in OS between the groups may be explained by differences in the nature and frequency of subsequent treatments received in both arms of the trial following disease progression.

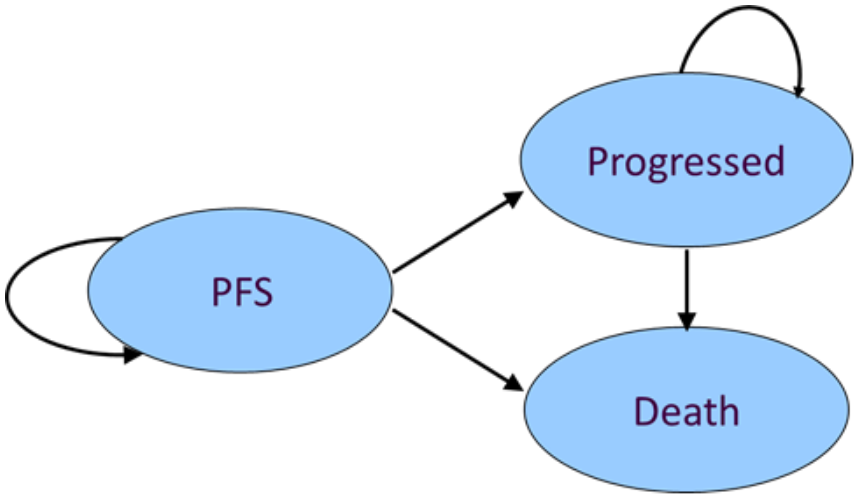

Figure 1 Schema of manufacturer's model

Parameters and values

Key population parameters used in the cost-effectiveness analysis are presented in Table 23.

Table 23 Key parameters in the cost-effectiveness analysis

Patient variables	Value	Source
Patient age	53.0years	RIBBON-1[5] study prior taxane subgroup
Patient weight	72.1kg	RIBBON-1[5] study prior taxane subgroup
Patient height	160.89cm	RIBBON-1[5] study prior taxane subgroup
Body surface area	1.7609m^2	RIBBON-1[5] study prior taxane subgroup

Note: Where there are discrepancies, the values in the table are those used in the model rather than those reported in the MS

5.2.3 Population

The modelled population is a subgroup of the RIBBON-1[5] trial population. The ERG has concerns that this subgroup may not be representative of the population licensed to receive BEV+CAPE. A full discussion of the issues may be found in section 4.3 of this report; the key points are that:

- Patients in the modelled subgroup appear to be younger and healthier than the ITT population;
- Detailed trial data are not available on the treatments received post progression for this subgroup.

5.2.11 Model validation and face validity check

It is reported that no clinical experts were consulted in the development of this economic model. The manufacturer felt that having recently held two advisory boards to obtain validation of the assumptions and inputs utilised in other mBC economic models (BEV in combination with a taxane and trastuzumab in combination with an aromatase inhibitor) rendered further validation of resource use inputs unwarranted.

5.3 Detailed critique of manufacturer's economic model

Table 35 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[11]

Table 35 Critical appraisal checklist for the cost-effectiveness analysis

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	ERG agrees that with the manufacturer that VIN is not a valid comparator
Was the effectiveness of the programme or services established?	No	The modelled population is a subgroup of the licensed population. RIBBON-1[5] trial data indicate that, at baseline, this subgroup appears to be younger and healthier than the licensed population. Therefore, model results may be optimistic.
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The ERG notes that the economic model does not include terminal care costs. Additionally, social care costs are not considered.
Were costs and consequences measured accurately in appropriate physical units?	Not always	Sources of resource use and cost data were appropriate (e.g. NHS Reference Costs 09-10[12] PSSRU 2010[13] and NICE guidelines CG81[8]) ERG prefers to incorporate distribution of body surface area/weight and UK patient characteristics into cost calculations where appropriate
Were the cost and consequences valued credibly?	Not always	The ERG identified an error in the calculation of utility values. The approach used by the manufacturer to model survival in PD may not accurately reflect the effectiveness of BEV.
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Plenty of detail is presented by the manufacturer as per the NICE template
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	SA and PSA were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Mostly	It would have been informative if the costs and benefits of subsequent lines of treatment had been explicitly included in the economic model

5.3.1 Model structure and design

The manufacturer has adopted a simple three-state model design, adapting a model structure previously used in several submissions to NICE appraisals of cancer drugs. The model is driven by survival models governing PFS and PD, calibrated against data from the RIBBON-1[5] clinical trial.

An important limitation of the approach taken is that although the model covers a period of 15 years, no further chemotherapy is considered within the model following disease progression after treatment with either BEV+CAPE or CAPE. This could lead to substantial bias as, if there is better PFS in one arm than the other, the discounted costs and benefits of subsequent treatments will differ. Furthermore, if the proportion of patients able to receive subsequent lines of therapy differs between the arms then the costs and outcomes will also differ. Additionally, the omission of subsequent lines of treatment from the model is contrary to the expectations in the NICE Methods Guide to Technology Appraisal[14] that models will encompass all likely consequences of an innovative treatment over a whole lifetime.

5.3.2 Model implementation

The manufacturer's model is implemented as a series of Microsoft Excel worksheets. The layout of the model is generally clear and tables are adequately labelled; however, the inclusion of superfluous sheets and formulae relating to parametric models which were considered during the model development process but not actually implemented in the final version of the model can make navigation confusing.

5.3.3 Estimation of patient outcomes

PFS

The modelling approach used by the manufacturer to estimate PFS involves the direct use of KM data from the RIBBON-1[5] trial for the first 12 months and a fitted exponential curve thereafter. This approach appears credible.

PD

Although a similar approach, in terms of using trial data for the first 12 months and a parametric curve thereafter, was used to model PD, the ERG is concerned that the design of the RIBBON-1[5] trial allowed patients to receive BEV (subject to the consulting physician's discretion) post progression. The manufacturer felt that this may have introduced bias in estimation of treatment effects, as patients randomised to the control arm may have had their survival prolonged due to receiving the study drug after disease progression. The manufacturer has therefore used the RPSFT model to 'uncross' data prior to modelling survival in PD. However, as highlighted in section 4.3, this approach is unsuitable when a large proportion of patients cross-over from the control arm, and when those in the

intervention arm also 'cross-over'. For the modelled population 44.7% of the BEV+CAPE arm and 52.4% of the CAPE arm received BEV after progression. Furthermore, although exact proportions are unclear, patients in the modelled subgroup also received other therapies after progression.

The ERG carried out analysis of the original PD trial data to explore survival during this phase. A comparison of survival times during this phase (Table 36) shows that although survival is similar in each group and overall the four groups do not show strong evidence of heterogeneity (Log Rank test p=0.081), one group (CAPE with no crossover) appears to differ when tested pairwise against the other 3 groups.

Table 36: Mean and median survival times following disease progression

	Mean				Median			
Arm	**Estimate**	**Std error**	**95% Confidence interval**		**Estimate**	**Std error**	**95% Confidence interval**	
			Lower bound	**Upper bound**			**Lower bound**	**Upper bound**
BC	470.6	30.8	410.4	530.9	418.8	36.3	347.7	490.0
BC	525.6	38.6	449.8	601.3	554.0	52.1	451.8	656.2
PC	497.3	43.3	412.5	582.1	507.1	51.4	406.4	607.8
PN	324.1	40.3	245.2	403.0	350.0	36.7	278.2	421.9
Overall	485.7	21.3	444.0	527.4	448.0	36.7	376.2	519.9

BC = BEV+CAPE (cross over); BN=BEV+CAPE (no cross over); PC = CAPE (cross-over); PN= CAPE (no cross-over)

As a result the ERG developed two different models. The first groups all patients together and models a scenario where survival post-progression is equivalent irrespective of first line therapy or crossover. The second groups together all the BEV patients and the CAPE patients who crossed , and looks at the CAPE patients who did not cross separately. This second model allows a clear comparison between patients who did and did not receive BEV during the trial and gives a representation of the effect of cross over. Each model portrays an extreme, allowing consideration of a best and worst case scenario for the effect of crossover on post progression survival.

Model 1: Equivalent survival post-progression

The KM plot using data from the whole population is shown in Figure 4. Examination of the KM survival estimates at each event time identified one extreme data point (at about 800 days) with sufficient uncertainty that the 95% confidence interval included zero survival. This was excluded from the analysis to avoid unpredictable bias in modelling long-term survival. This outlier data point is shown in grey in Figure 4 and Figure 5.

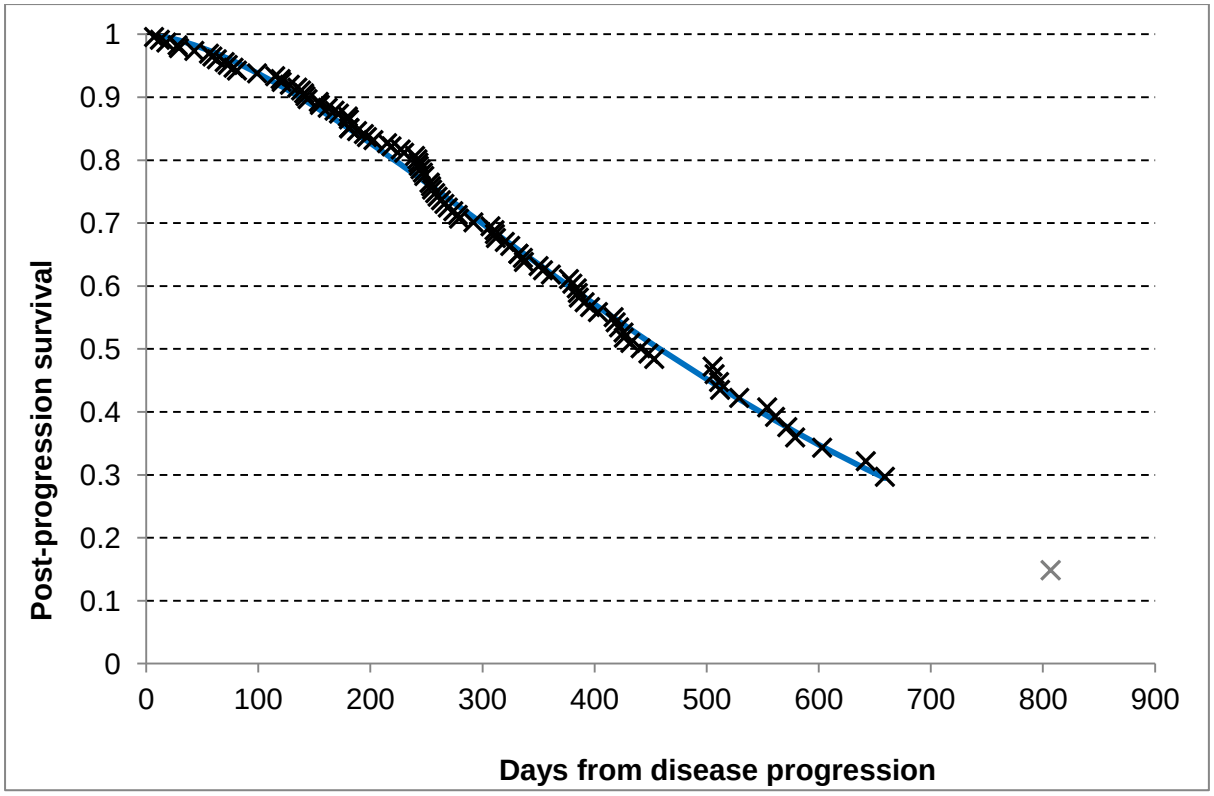

Figure 4 Kaplan-Meier analysis of PD from RIBBON-1 clinical trial for all modelled patients, with Weibull projective model – post-progression

A Weibull function was found to provide a very good representation of the trial data (solid line in Figure 4 and Figure 5), and indicated that the mean survival following disease progression could be estimated as 521 days (17.11 months).

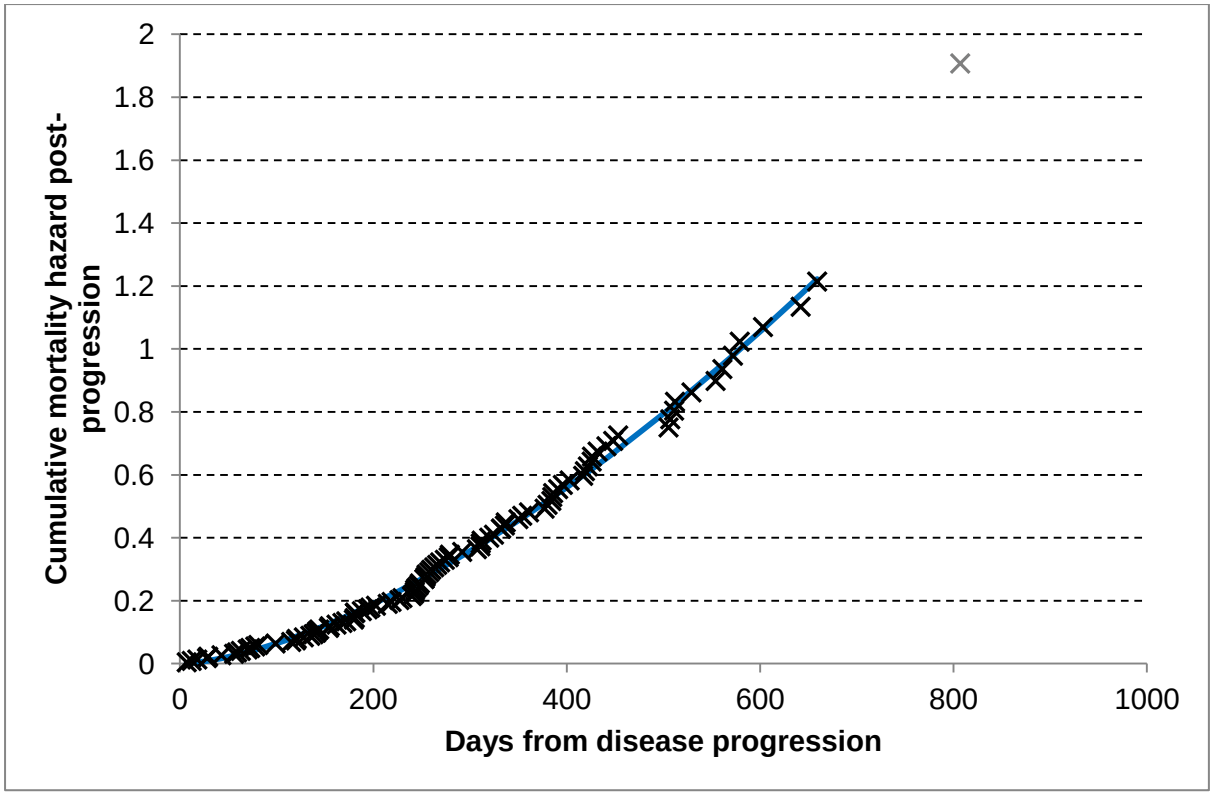

Figure 5: Kaplan-Meier analysis of PPS from RIBBON-1 clinical trial for all patients, with Weibull projective model – cumulative mortality hazard post-progression

Using the PD survival model based on data from the whole population for both trial arms decreases the incremental life year gain by 0.628 and decreases the QALY gain by 0.312 compared with the manufacturer's base case, resulting in an ICER of £171,411 per QALY gained (£94,093 greater per QALY gained than the base case).

Model 2: Differentiating between the populations that did and did not receive BEV

The KM plots using data from all patients who received BEV at any time are shown in Figure 6, together with a separate analysis of the small group who received no BEV at any time. Further examination of the data suggest that two data points from the CAPE only arm and one in the combined BEV group are outliers subject to wide uncertainty (shown faintly in Figure 6) and could not be considered to be significantly different from zero; these have therefore been excluded from further analysis as before.

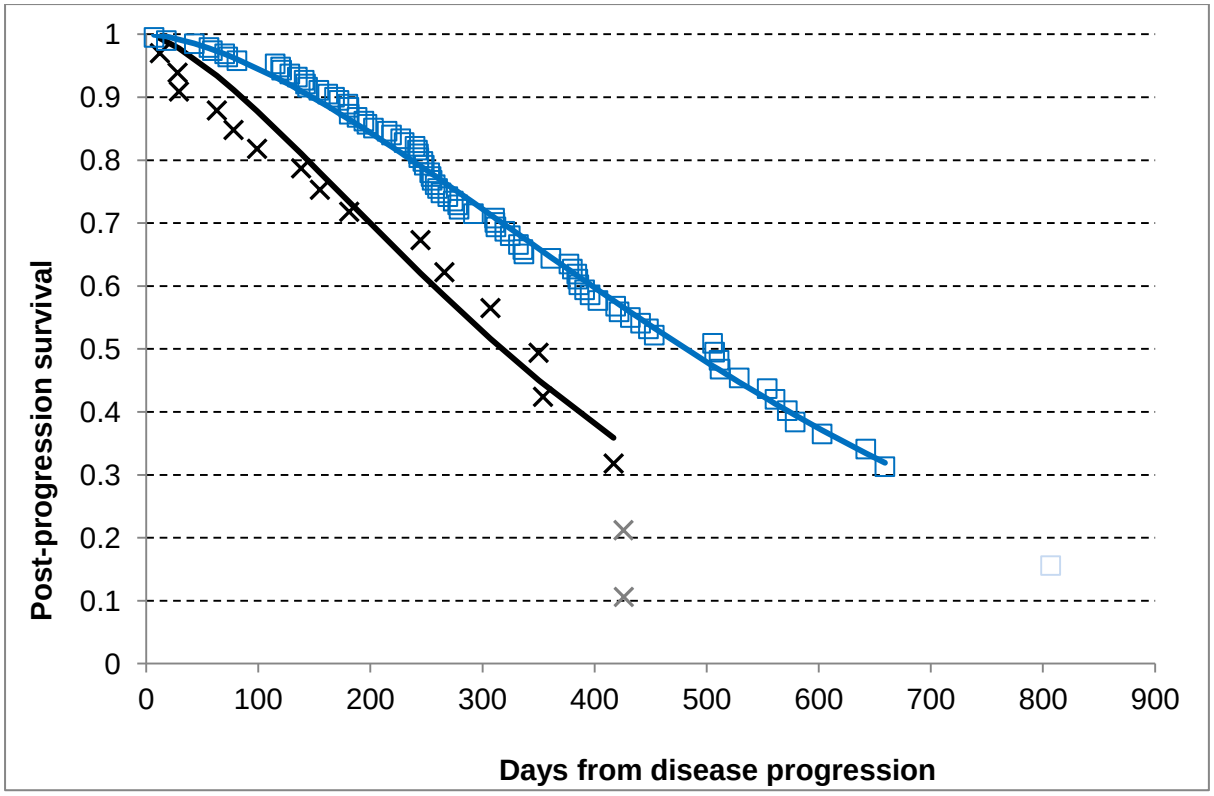

Figure 6 Kaplan-Meier analysis of PD from RIBBON-1 clinical trial distinguishing between those patients who did (X) and did not (□) receive BEV, with Weibull projective models – post-progression

Weibull functions were found to provide a very good representation of the BEV trial data, and an acceptable fit for the small group who had not received BEV at any time (Figure 6 and Figure 7). The estimated long-term mean post-progression survival is estimated as 372 days (12.22 months) and 544 days (17.86 months) for the CAPE only group and the group receiving BEV respectively. The difference between these estimates provides a simple indication of the maximum likely adjustment that might be made to the trial results for CAPE patients who crossed over to BEV after disease progression, amounting to 172 days (5.64 months). Some caution should be taken when considering these results due to the small size of the population who did not receive BEV at any time (15 events in 31 patients included in the analysis).

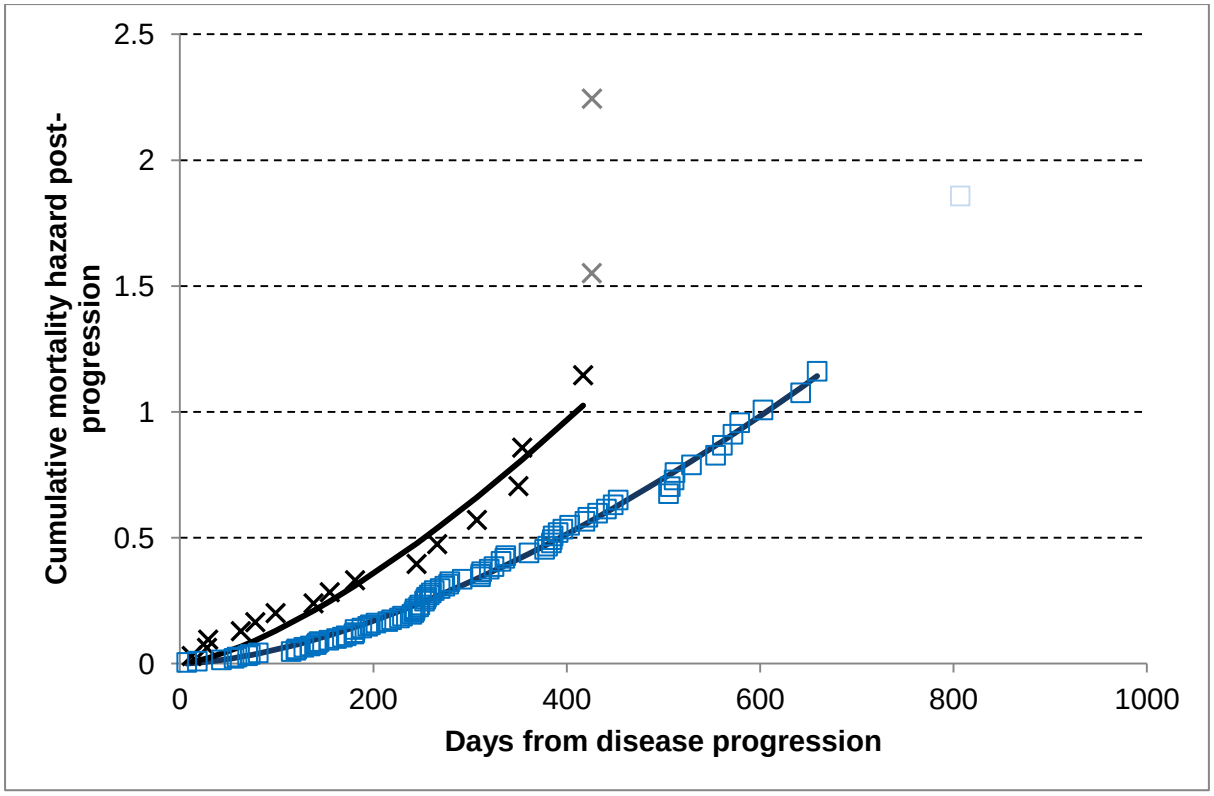

Figure 7 Kaplan-Meier analysis of PPS from RIBBON-1 clinical trial, distinguishing between those patients who did and did not receive BEV, with Weibull projective models – cumulative mortality hazard post-progression

The PD survival models generated by differentiating between those who did and did not receive BEV were used to represent the BEV arm and the CAPE arm of the trial respectively. The result, compared with the manufacturer's base case, was a decrease in the incremental life year gain of 0.206 and a decrease in the QALY gain of 0.102, resulting in an ICER of £92,060 per QALY gained (£14,742 greater per QALY gained than the base case).

5.3.4 Cost estimation and parameter values

Active treatment costs

The ERG has re-estimated the costs of therapy based on the distribution of patient body weight and body surface area of a UK specific cohort of patients using data from Sacco et al,[15] rather than the use of simple average based on trial data. Overall these changes increase the drug costs in the BEV+CAPE arm by £2,966 per patient and the drug costs in the CAPE arm by £50 per patient. These adjustments result in a revised ICER that is £5,793 higher per QALY gained than the manufacturer's base case ICER.

Adverse event costs

In the submitted model, the costing of AEs seems to have been implemented without justification of assumptions. Some alternative choices could have been made by the authors of the manufacturer's model, but the ERG is of the opinion that such changes would have only a very minor impact on the incremental cost and the estimated ICER, and so can be ignored.

Terminal care costs

The manufacturer's model does not include the costs of terminal care during the last 2 weeks of life, as specified in NICE guidelines[14]. This cost was estimated by uplifting costs reported by Remak et al[16] to 2009/10 prices using the Hospital & Community Health Services (HCHS) pay and prices index published by PSSRU. To test its impact, this cost was added into the submitted model and, as a result of the modest improvement in OS attributable to BEV, this modification produced a small discounted cost difference which reduces the incremental cost per patient by £53, and reduces the ICER by £105 per QALY gained.

5.3.5 Utility estimation and parameter values

The utility values used in the submitted model have been estimated using the statistical model detailed in a study by Lloyd et al.[17] This model features several factors including the rate of response to chemotherapy, and the exposure to a set of important AEs. It has been used in previous NICE appraisals and probably represents the best source currently available.

There is a lack of consensus amongst economists in relation to the most appropriate value for the age parameter in the Lloyd et al[17] model, i.e. whether it should be that of the population surveyed by Lloyd et al[17] or that relating to the age of the population taking part in the original health state valuation exercise carried out by Kind et al.[18] The manufacturer has used 47 years, the mean age of the population taking part in the original Kind et al study.[18] This approach has the advantage that it is consistent with standard UK EQ-5D tariff scores and facilitates easy comparisons across NICE appraisals. The lack of consensus relating to the most appropriate age value to use in the Lloyd et al[17] model does, however, highlight the degree of uncertainty that should be attached to the value of the utility scores used in the model.

When using the Lloyd et al[17] model to estimate utility values the manufacturer has not included AE rates for the modelled subgroup. However, examination of the reported frequency of AEs indicates very low rates for the key events and the ERG is, therefore, satisfied that no adjustments for AE disutility are necessary.

The ERG found a formula error in the model, relating to months 0-13 in the CAPE arm. Correcting this error results in a decrease in the manufacturer's base case ICER of £786.08 per QALY gained.

5.3.6 Sensitivity analysis - licensed dose of CAPE

The manufacturer reports that in the RIBBON-1[5] trial CAPE was administered at a dose of 1,000mg/m^2. The manufacturer points out that this differs slightly from the SPC[19] specified dose in which it is recommended that CAPE be given at a dose of 1,250mg/m^2. The ERG expert advisors have suggested that in practice CAPE tends to be administered at the lower dose due to the higher incidence of AEs observed at the higher dose. Comparing AE rates at the lower and higher doses is not straightforward and although a request was made for this information in the first clarification letter the manufacturer was not able to provide it.

The ERG notes that:

- At a dose of 1000mg/m^2 the impact of AEs on overall costs is negligible;
- Assuming that increasing the dose to 1250mg/m^2 has equal impact, in terms of increased incidence of AEs, on both treatment arms, then the modelled effect (in terms of cost rather than patient well being) should cancel itself out.

Bearing in mind these two factors the ERG found that changing the dose of CAPE to 1,250mg/m^2 results in a monthly cost of £398.55, an overall incremental increase in drug costs of £3,782 and an accompanying increase of £7,512 to the ICER estimate.

5.4 Conclusions of the cost-effectiveness section

The manufacturer's review of the published cost-effectiveness literature describing BEV+CAPE vs CAPE for previously untreated advanced breast cancer patients did not identify any relevant cost-effectiveness studies. The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

The manufacturer's reported base case ICER is £77,318 per QALY gained. It should be noted, however, that the modelled population is a subgroup of the population licensed to receive BEV+CAPE, namely those who have previously received a taxane in the adjuvant setting. The baseline characteristics of this subgroup indicate that they appear to be younger and healthier than the whole licensed population; suggesting that the ICER per QALY gained for the whole licensed population may be somewhat higher than the value generated by the manufacturer's model.

The ERG made three relatively minor amendments/corrections to the manufacturer's model, the impact of which was to change the manufacturer's ICER by between -£786 and £5,793 per QALY gained. However, the ERG's re-estimation of PD survival, and as a consequence OS, suggests that the manufacturer's ICER may be optimistic.

6 IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE ERG

The alterations to the submitted economic model described above were implemented by the ERG to assess their influence on the incremental cost-effectiveness ratio for BEV+CAPE vs CAPE. In most cases the required amendments were relatively minor, but the introduction of the ERG's approach to the estimation of survival in PD proved to be more substantial. This involved considering two extreme examples. In both cases the differing timings of entry into, and deaths whilst in, PD were maintained. In the first model the ERG assumed that survival during PD was equivalent irrespective of previous treatment and developed a common projection for both regimens. In the second model the ERG considered the survival of patients who had received BEV at any point during the trial (BEV+CAPE arm) and compared this with patients who had not received BEV (CAPE arm).

Table 37 shows the results of applying the sensitivity analysis related to using the licensed rather than the trial dose of CAPE and each of the ERG model amendments. Three of these lead to relatively minor alterations to the estimated ICER; with revised ICERs ranging between £76,532 and £83,111 per QALY gained. The two new methods of estimating survival during PD are more important and result in ICER per QALY gained estimates of £171,411 for model 1 (common projection) and £92,060 for model 2 (different projections for the two intervention arms). When all the relatively minor amendments are applied simultaneously, the final ERG ICER estimate increases to £82,162 per QALY gained. Incorporating these changes with the two alternative approaches to modelling PD suggested by the ERG results in ICER estimates of £181,648 per QALY gained for model 1 and £97,963 per QALY gained for model 2.

The manufacturer's reported base case ICER is £77,318 per QALY gained. The manufacturer's choice to base their model on a subgroup of patients licensed to receive BEV+CAPE suggests that, as acknowledged by the manufacturer (see section 3.1), the ICER for the whole licensed population is likely to be somewhat higher than the reported base case.

Table 37 Cost-effectiveness results following application of ERG model amendments

Scenario / model change	BEV +CAPE					CAPE					Incremental			
	Life-years	QALYs	Drug costs	Support-ive care costs	All costs	Life-years	QALYs	Drug costs	Support-ive care costs	All costs	Life-years	QALYs	Costs	ICER
SA: Use of CAPE at licensed dose	2.228	1.338	£39,568	£16,264	£55,900	1.365	0.835	£3,588	£9,606	£13,194	0.864	0.503	£42,706	£84,830
Manufacturer's base case	**2.228**	**1.338**	**£35,313**	**£16,264**	**£51,645**	**1.365**	**0.835**	**£3,115**	**£9,606**	**£12,721**	**0.864**	**0.503**	**£38,924**	**£77,318**
ERG drug costs	2.228	1.338	£38,280	£16,264	£54,612	1.365	0.835	£3,165	£9,606	£12,771	0.864	0.503	£41,841	£83,111
Add terminal care costs	2.228	1.338	£35,313	£16,264	£53,351	1.365	0.835	£3,115	£9,606	£14,479	0.864	0.503	£38,871	£77,213
ERG revised utility values	2.228	1.338	£35,313	£16,264	£51,645	1.365	0.829	£3,115	£9,606	£12,721	0.864	0.509	£38,924	£76,532
ERG PD survival estimate – model 1 (common projection))	2.059	1.254	£35,313	£14,631	£50,013	1.824	1.062	£3,115	£14,035	£17,150	0.235	0.192	£32,862	£171,411
ERG PD survival estimate – model 2 (different projections)	2.114	1.281	£35,313	£15,160	£50,542	1.456	0.880	£3,115	£10,490	£13,605	0.658	0.401	£36,937	£92,060
ERG Changes to Drug cost, Terminal care & Utility values	2.228	1.338	£38,280	£16,264	£56,317	1.365	0.829	£3,165	£9,606	£14,529	0.864	0.509	£41,788	£82,162
All ERG changes														
Model 1	2.059	1.254	£38,280	£14,631	£54,695	1.824	1.057	£3,165	£14,035	£18,931	0.235	0.197	£35,764	£181,648
Model 2	2.114	1.281	£38,280	£15,160	£55,221	1.456	0.875	£3,165	£10,490	£15,409	0.658	0.406	£39,812	£97,963

Base-case: manufacturer

- The manufacturer reports an ICER of £77,318 per QALY gained for the comparison of BEV+CAPE vs CAPE as a first-line therapy for patients with untreated HER2-ve mBC who have previously received a taxane in the adjuvant setting (and have most likely also received an anthracycline in the adjuvant setting).

- Results of the PSA conducted by the manufacturer suggest that, based on the assumptions made and the evidence available, BEV+CAPE is not a cost-effective treatment compared with CAPE at a willingness to pay of £30,000 or £50,000 per QALY gained in any circumstances (0% probability).

Base case: ERG

- The ERG made three comparatively minor amendments/corrections to the manufacturer's model and these included modifications to drug costs, the addition of terminal care costs, and use of ERG revised utility values. Individually, these resulted in only relatively small changes to the manufacturer's base-case ICER per QALY gained (range: £76,532-£83,111). The ERG's two alternative approaches to modelling survival in PD, one assuming common, and the other different, survival projections for the intervention arms, resulted in ICER estimates of £171,411 and £92,060 per QALY gained respectively.

- When all of the ERG's changes are incorporated together into the submitted model the ICER is estimated to be between £97,963 and £181,648 per QALY gained.

7 OVERALL CONCLUSIONS

The clinical effectiveness evidence is derived from a single, manufacturer supported, placebo controlled RCT (RIBBON-1[5]). This trial, which was well conducted, compared BEV+CAPE to CAPE. Given anthracyclines or taxanes were a possible treatment options prior to randomisation, it seems reasonable to assume these patients would therefore be considered unsuitable for an anthracycline or a taxane. For all these patients (the ITT population), it can be assumed that a taxane or anthracycline were not considered appropriate. Thus this population can be considered to be a group of patients for whom BEV+CAPE is licensed. Compared with the CAPE arm, a statistically significant increase in PFS (2.9 months) but not OS was reported for BEV+CAPE. Despite there being a greater proportion of AEs reported for patients in the BEV+CAPE arm, no new safety concerns were identified.

The cost-effectiveness analysis is based on a subgroup of patients from RIBBON-1,[5] namely a group of patient who had previously received a taxane (and by implication, it is assumed an anthracycline) for adjuvant treatment. In this subgroup, significant improvements in PFS of 4.5 months and OS of 7.9 months were reported for patients who received BEV+CAPE compared with CAPE. However, this was just one of a number of subgroups for which analyses of PFS and OS were conducted. No statistical adjustments were performed to control for multiple significance testing and so these findings must be treated with caution. In addition, baseline characteristics suggest that this appears to be a younger and healthier group of patients than the ITT population.

The manufacturer's reported base case ICER is £77,318 per QALY gained. Implementing all three of the ERG's relatively minor changes increases the manufacturer's base case ICER to £82,162 per QALY gained. The ERG's two alternative approaches to modelling PD survival, one using common, and the other using different, survival projections for the intervention arms, results in ICER estimates of £171,411 and £92,060 per QALY gained respectively. When all of the ERG's changes are incorporated together into the submitted model the ICER is estimated to be between £97,963 and £181,648 per QALY gained.

The manufacturer's base case ICER per QALY gained cannot be considered to be generalisable to the whole licensed population. This is because analyses of the RIBBON-1[5] trial data show that the subgroup on which this ICER is based is a selected population who, at baseline, appear younger and healthier than the ITT population. Further, there are caveats around the subgroup PFS and OS findings. Both the manufacturer and the ERG believe that the ICER per QALY gained for the licensed population would be higher than that for the modelled subgroup.

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