RIBOCICLIB IN COMBINATION WITH AN AROMATOSE INHIBITOR FOR PREVIOUSLY UNTREATED ADVANCED OR METASTATIC HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER: A REVIEW OF THE MODEL STRUCTURE, INPUTS AND ASSUMPTIONS

REPORT BY THE DECISION SUPPORT UNIT

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1. EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) is appraising ribociclib in combination with an aromatose inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The model submitted by the company (Novartis) uses an approach that the Committee have not seen in advanced breast cancer before and so NICE have requested the Decision Support Unit (DSU) to explore the validity of the structure, data and assumptions.

Novartis' model assumes that after progression on ribociclib or comparator, patients who are still alive follow the progression-free survival (PFS) and overall survival (OS) of the subsequent treatment. Novartis estimate subsequent PFS and OS from a trial of everolimus plus exemestane in patients with hormone receptor-positive, HER2-negative breast cancer who have previously received an aromatose inhibitor. This approach assumes full surrogacy: that survival after progression is identical for ribociclib and the comparator, and therefore any gain in PFS translates into the same gain in OS. The DSU conducted a non-systematic review to establish whether the assumption of full surrogacy is valid in this population and found that the evidence was inconclusive. An alternative to assuming full surrogacy is to conduct analyses assuming partial surrogacy: where OS gain is smaller than PFS gain. Partial surrogacy is implemented by decreasing the time spent in states after first line PFS in the ribociclib arm of the model.

Regardless of whether full or partial surrogacy is assumed, the cost-effectiveness of ribociclib is influenced by the costs of ribociclib treatment, time to discontinuation (TTD), PFS and the utility values in PFS.

Novartis assume the observed dose reduction on ribociclib in the trial decreases drug costs as patients can take fewer than the recommended 3 tablets daily.

The extrapolation of TTD and PFS beyond the trial period relies on parametric distributions fitted in survival analysis – in the base case Novartis use the exponential distribution for both TTD and PFS, but the ERG consider that the Weibull may be equally plausible, which increases the incremental cost-effectiveness ratio (ICER). When the exponential distributions are used for TTD and PFS, the mean TTD for ribociclib is much lower than the mean PFS for ribociclib. When using the Weibull distribution for TTD and PFS, the difference between

mean PFS and mean TTD for ribociclib is less than when using the exponential, and it appears more consistent with rate of discontinuations due to AEs for ribociclib.

Novartis used EQ-5D-5L utilities in the PFS1 state, valued using the 5L value set. The 5L value set is not recommended by NICE, so Novartis have now mapped the scores to 3L, which produces a lower utility. The value Novartis used for PFS2 was not EQ-5D, and [redacted]. An EQ-5D score for second line treatment in this population is available from another source.

Under the assumption of full surrogacy, the treatment pathway, survival, costs and utilities beyond progression on first line treatment are the same for ribociclib and comparator, and therefore do not influence cost-effectiveness results. Under the assumption of partial surrogacy, the costs, life years and quality-adjusted life years (QALYs) accrued beyond first-line progression differ for ribociclib and comparator, and therefore do influence cost-effectiveness results. If later-line treatments are more cost-effective, this favors the comparator as patients in the comparator arm receive them for longer – and so the ICER for ribociclib increases. If later-line treatments are less cost-effective, this favors ribociclib as patients in the ribociclib arm receive them for less time – and so the ICER for ribociclib decreases.

Novartis' model assumes that patients receive that patients receive treatment for all lines post progression on second line therapy with a fixed drug cost of £2,000 after progression on second line treatment. Novartis' assumption that these treatments cost £2,000 per month until death likely overestimates the cost of treatments beyond second line. The ERG provided an alternative cost of £1,140 which appears more reasonable.

Novartis' base case ICER was [redacted]/QALY without the patient access scheme (PAS), and [redacted]/QALY with the PAS. Using the ERG's cost for treatment after progression and EQ-5D-3L utilities for PFS1 (EQ-5D-5L mapped to 3L from the trial) and PFS2 (EQ-5D-3L in second line therapy from Mitra *et al* 2016) [redacted] the ICERs to [redacted](without PAS) and [redacted](with PAS). Varying the assumptions around TTD, PFS, dosing and surrogacy [redacted] the ICERs to a [redacted] of [redacted](without PAS) and [redacted](with PAS).

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ABBREVIATIONS AND DEFINITIONS

3L	Three level (EuroQol Five Dimension)
5L	Five level (EuroQol Five Dimension)
BNF	British National Formulary
BOLERO-2	Breast Cancer Trials of Oral Everolimus-2
CG	Clinical Guideline
DSU	Decision Support Unit
eMIT	Electronic Marketing Information Tool
EQ-5D	EuroQol Five Dimension
ER	(O)estrogen receptor
ERG	Evidence Review Group
HR	Hormone receptor
HER2	Human epidermal growth factor
ICER	Incremental cost-effectiveness ratio
MONALEESA-2	Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety-2
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PALOMA-1	Palbociclib: Ongoing Trials in the Management of Breast Cancer-1
PALOMA-2	Palbociclib: Ongoing Trials in the Management of Breast Cancer-2
PAS	Patient access scheme
PDS	Post-discontinuation survival
PFS	Progression-free survival
QALY	Quality-adjusted life-year
SACT	Systemic Anti-Cancer Therapy
TA	Technology Appraisal
TPC	Treatment of physician's choice
TTD	Time to discontinuation

2. INTRODUCTION

2.1. Background

The National Institute for Health and Care Excellence (NICE) is appraising ribociclib (Novartis) in combination with an aromatose inhibitor for previously untreated advanced or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer (ID1026)[1]. NICE is also appraising palbociclib (Pfizer) in the same indication (ID915)[2]. The companies for the two technologies used different economic models and reported different cost-effectiveness results, whereas the clinical trials report similar findings. Pfizer developed a partitioned survival analysis model for palbociclib, whereas Novartis used a patient level simulation model to model later-line treatments after patients have progressed on ribociclib or comparator. The committee have not seen the approach used by Novartis in this disease area before, and want to have confidence in the approach and data used. The committee questioned some of the assumptions and results in Novartis' model for ribociclib.

The Decision Support Unit (DSU) has been commissioned to help the committee understand Novartis' model, and whether it is a valid approach. The DSU have been asked to:

- review the model assumptions, inputs and structure, and explore the quality of the evidence underpinning these
- describe the assumptions or data that cause the greatest uncertainties and:
    - critique the values used by the company
    - identify plausible alternatives if those used by the company lack validity
    - perform scenario analyses to explore the impact of using plausible alternative values

2.2. Treatment pathway in HER2-negative, Hormone-receptor positive advanced breast cancer

NICE Clinical Guideline (CG)81 on advanced breast cancer recommends endocrine therapy as first-line treatment for the majority of patients with oestrogen receptor (ER)-positive advanced breast cancer[3]. This endocrine therapy should be an aromatose inhibitor for postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy, and for postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. The comparator for ribociclib in the scope for ID1026 is aromatose inhibitors[4], and this will is the positioning for ribociclib in combination with an aromatose inhibitor in the company submission[5]

CG81 recommends that on disease progression, systemic sequential chemotherapy is offered to the majority of patients who have decided to be treated with chemotherapy.

Technology Appraisal (TA)421 recommends everolimus, in combination with exemestane, within its marketing authorisation, as an option for treating advanced HER2-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor[6].

TA423 recommends eribulin for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)[7].

CG81 recommends that for patients not suitable for anthracyclines, the sequence of chemotherapy should be single-agent docetaxel followed by single-agent vinorelbine or capecitabine and then single-agent capecitabine or vinorelbine.

3. MODELLING APPROACH

3.1. Partitioned survival analysis

Many economic models for previous NICE technology appraisals in breast cancer have used a partitioned survival approach, extrapolating PFS and OS curves from the clinical trials (TA214[8], TA263[9], TA116[10], TA257[11], TA458[12], TA421[6], TA423[7], TA239[13]). Partitioned survival models use the "area under the curve" to calculate the proportion of patients in the pre-progression, post-progression and death states at each time point. Typically, survival analysis is performed to fit curves to the Kaplan-Meier data, and extrapolate data beyond the trial period until all patients have died. Time to discontinuation (TTD) may be modelled in the same way as PFS and OS. This approach is shown in **Error! Reference source not found.**. The DSU has published a technical support document (TSD) on partitioned survival analysis, including an explanation, review and critique[14]. This is the approach that Pfizer have taken for palbociclib – although they have adjusted the parametric curve for OS for palbociclib such that the difference between the median OS for palbociclib and median OS for placebo is equal to the difference between median PFS for palbociclib and median PFS for placebo.

3.2. Modelling approach in ID1026

Novartis do not use partitioned survival analysis, and instead use a patient-level state-transition model. Novartis stated that the immaturity of OS data in MONALEESA-2 would make direct estimation of OS challenging and for this reason external data is used to estimate

OS[5]. In this approach, Novartis extrapolate the PFS data from their trial, and then add on survival from the next line of therapy to patients who are still alive. Survival for the next line of therapy is estimated by extrapolating time to discontinuation (TTD) and post-discontinuation survival (PDS) data from the BOLERO-2 study and applying hazard ratios to model different treatments. TTD and PDS on any given second line therapy is the same for patients who received letrozole plus placebo and ribociclib plus letrozole in first line. This broad approach is shown in Figure 2. More detail around second line treatment is presented in Figure 3 – three second line treatments are modelled, and a different proportion of patients on ribociclib and placebo receive each second line treatment.

The approach used by Novartis assumes that PFS gain translates into OS gain (100% surrogacy) and that patients entering the second line BOLERO-2 study are representative of patients progressing on first line therapy. We have reviewed the evidence to support the assumption that PFS gain is a surrogate for OS gain, and tested the validity of this approach in advanced breast cancer.

Figure 1: Partitioned Survival Analysis (all data illustrative)

OS: Overall survival, PFS: progression free survival, TTD: time to discontinuation

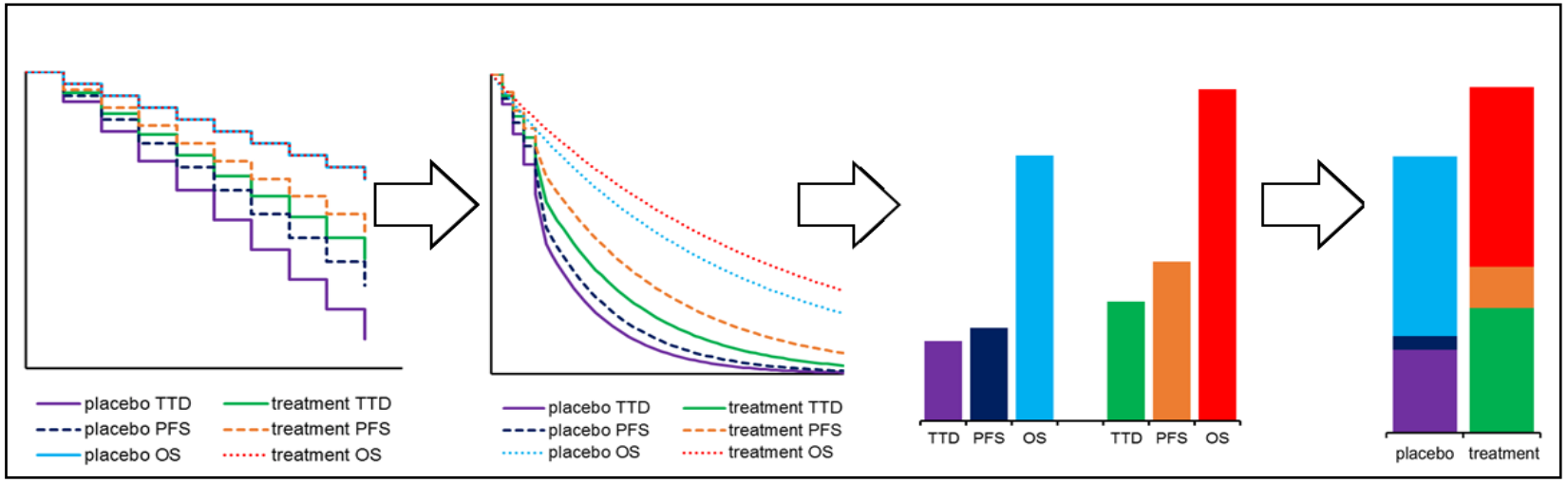


Figure 1: Modelling approach in ID1026 (all data illustrative)

OS: overall survival, PDS: post discontinuation survival, PFS: progression-free survival, TTD: time to discontinuation

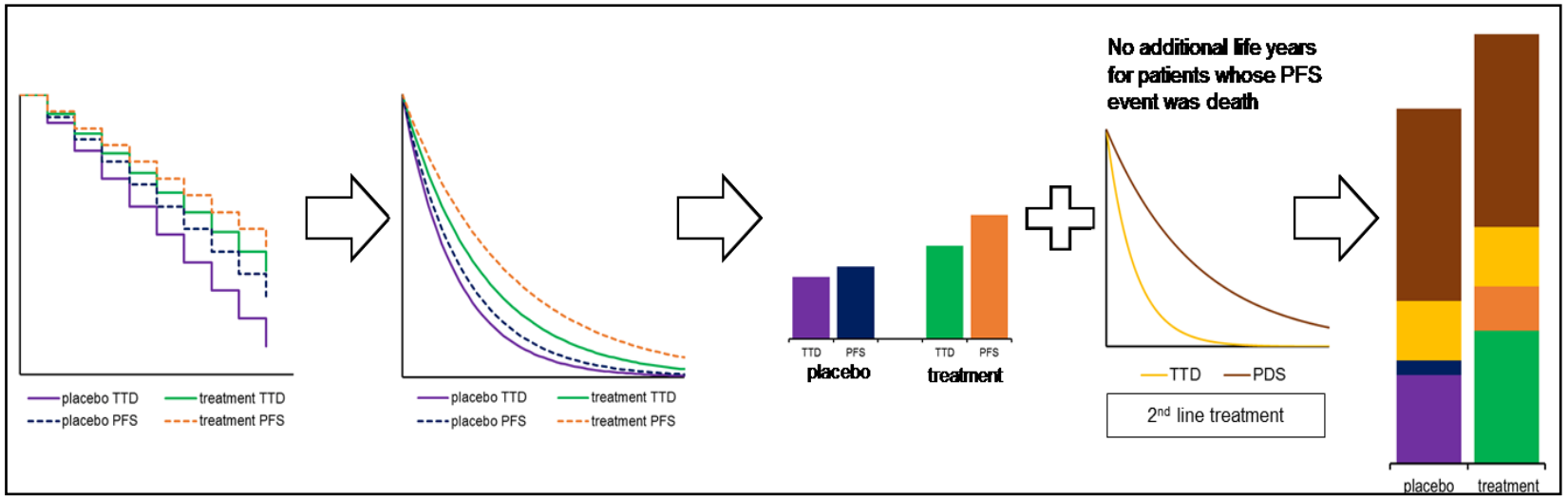
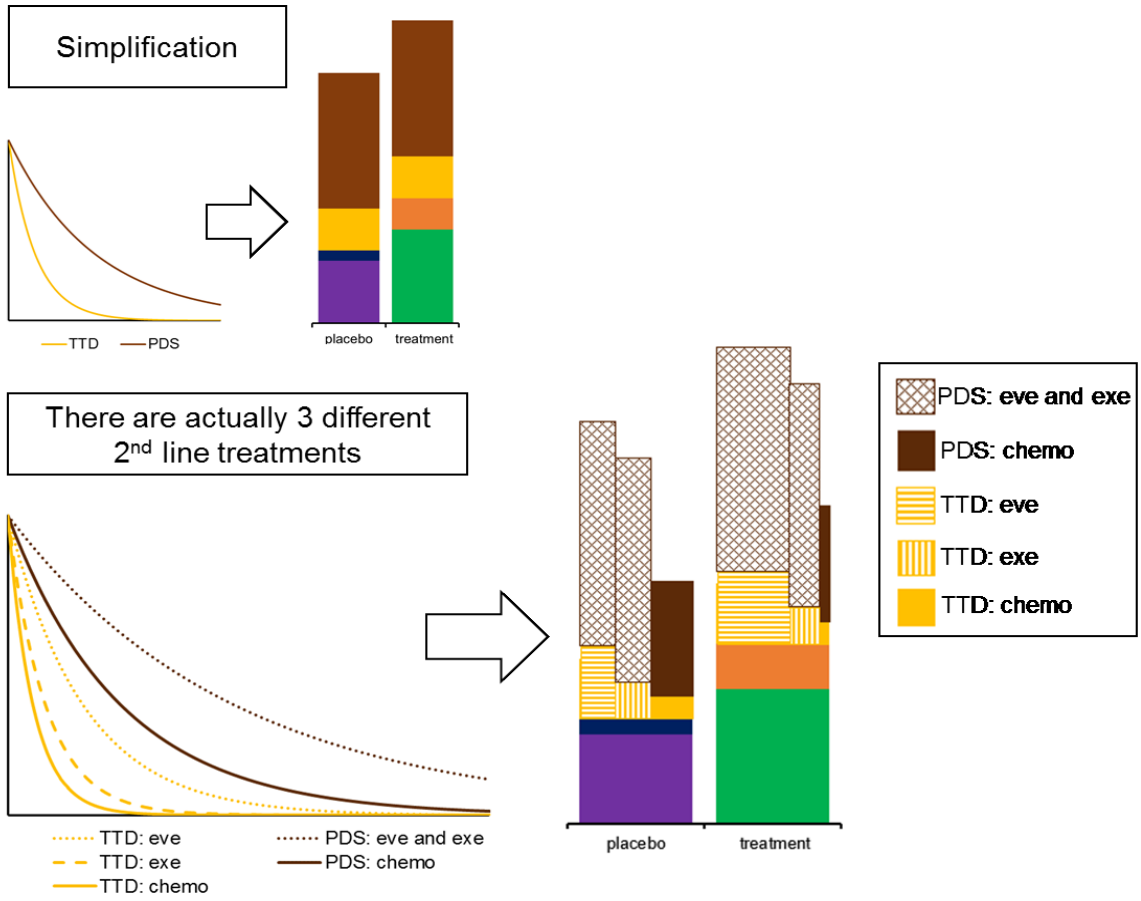


Figure 2: Modelling approach in ID1026: continued

Chemo: chemotherapy, eve: everolimus plus exemestane, exe: exemestane only, PDS: post discontinuation survival, TTD: time to discontinuation



3.2.1. PFS gain as a surrogate for OS gain

We reviewed the relationship between PFS and OS gains in several studies – these studies were identified as those included in the company submissions for ribociclib[5] and palbociclib[15], and those included in the DSU report[16] (and update[17]) reviewing the relationship between PFS and OS. The results, shown in Table 1, suggest that while a PFS gain is likely to result in an OS gain, there is no clear relationship between the size of PFS gain and OS gain.

Table 1: Relationship between PFS gain and OS gain

Study	Line of therapy	Intervention	Comparator	Δ median PFS	Δ median OS	PFS gain greater or less than OS gain?	Difference between Δ median PFS and Δ median OS
PALOMA-1[15]	First line	Palbociclib + letrozole	Letrozole	10.0	4.2	Greater	5.8
Parideans[18]	First line	Exemestane	Tamoxifen	4.2	6.1	Less	-2.0
Martin[19]	First line	Bevacizumab + letrozole/ fulvestrant	Letrozole/ fulvestrant	4.9	0.3	Greater	4.6
Dickler [20]	First line	Bevacizumab + letrozole	Letrozole	4.6	3.3	Greater	1.3
BOLERO-2[21]	Second line	Everolimus + exemestane	Exemestane	4.6	4.4	Greater	0.2
Study301[22]	Third line	Eribulin	Capecitabine	0.2	2.6	Less	-2.4
Study305[22]	Fourth line	Eribulin	TPC	1.5	2.9	Less	-1.4
Beauchemin[23]	Mixed	Various	Various	ΔOS = -0.088 + 1.753 x ΔPFS		Less	Varies
Burzykowski [24]	First line	Anthracycline (alone or in combination)	Taxane (alone in or combination with anthracycline)	A weak and imprecise positive association between treatment effects for PFS and OS			
Miksad[25]	Mixed	Anthracycline or taxane based	Any	Statistically significant association between both direction and magnitude of trial-level treatment effect on PFS and OS			
Petrelli and Barni[26]	First line	Various	Various	Highly significant correlation between HR for PFS and OS in a linear regression			
Michiels[27]	Mixed	Various – but all HER2+	Various – but all HER2+	Treatment effects on PFS correlated moderately with treatment effects on OS			
Sherrill[28]	Mixed	Various	Various	Treatment effect on progression is concordant but not as large for the OS outcome			

HER2+: human epidermal growth factor positive, HR: hazard ratio, PFS: progression-free survival, OS: overall survival

3.2.2. Testing the validity of this approach

To test the validity of the approach used by Novartis, we performed similar analysis using median and mean estimates for PFS and OS in varying lines of treatment. We estimated OS for first, second and third line therapy by adding the OS of the next line of therapy onto the PFS for that line for the proportion of patients still alive. We compared these cumulative estimates of survival to the actual values from the trial. We did this for median values (reported in the literature) and mean values (reported in the literature or calculated from the

parametric distributions in the economic models). The first line estimates are from the PALOMA-1 study[15], the second line estimates are from BOLERO-2[21], and the third line and fourth estimates are from study 301 and study 305 in TA423[22]. The proportion of patients who have died by the median or mean PFS was calculated by reading off the Kaplan-Meier graphs for overall survival from each source.

In each case, we do not know which treatment patients in the trial actually received as their subsequent therapy, so we present estimates using the treatment and comparator arm of the next line trial.

The results, shown in Table 2, demonstrate that this approach appears to overestimate survival in first line, and underestimate survival in second line. In third line, the estimates from the cumulative approach appear closer to the actual values, with the cumulative approach overestimating survival for some treatment sequences and underestimating survival in others. It is unclear whether this approach is valid – and which direction it may be biasing results. We explored this further by considering the proportion of patients receiving subsequent lines of therapy, baseline characteristics, and longer-term validation.

Table 2: Validating the cumulative survival approach

OS: overall survival, PFS: progression-free survival, TPC: treatment of physician's choice

	Line	Treatment	Assumed next line treatment	PFS	% dead by PFS	OS of next line	Cumulative OS	Trial OS	Cumulative greater or smaller than trial?	Difference between cumulative and trial
Median	1L	Palbociclib	Everolimus plus Exemestane	20.2	0.15	31	46.6	37.5	Greater	9.1
		Palbociclib	Exemestane			26.6	42.8		Greater	5.3
		Letrozole	Everolimus plus Exemestane	10.2	0.1	31	38.1	33.3	Greater	4.8
		Letrozole	Exemestane			26.6	34.1		Greater	0.8
	2L	Exemestane	Eribulin	7.8	0.08	16.1	22.6	31	Smaller	-8.4
		Exemestane	Capecitabine			13.5	20.2		Smaller	-10.8
		Everolimus plus Exemestane	Eribulin	3.2	0.03	16.1	18.8	26.6	Smaller	-7.8
		Everolimus plus Exemestane	Capecitabine			13.5	16.3		Smaller	-10.3
	3L	Eribulin	TPC	4.0	0.11	13	13.7	13.5	Smaller	-2.4
		Eribulin	Eribulin			10.1	16.4		Greater	0.3
		Capecitabine	TPC			13	13.0		Smaller	-0.5
		Capecitabine	Eribulin			10.1	15.6		Greater	2.1
Mean	1L	Palbociclib	Everolimus plus Exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Palbociclib	Exemestane							
		Letrozole	Everolimus plus Exemestane							
		Letrozole	Exemestane							
	2L	Exemestane	Eribulin							
		Exemestane	Capecitabine							
		Everolimus plus Exemestane	Eribulin							
		Everolimus plus Exemestane	Capecitabine							
	3L	Eribulin	TPC	4.56	0.07	16.07	16.68	21.75	Smaller	-5.1
		Eribulin	Eribulin			13.03	19.51		Smaller	-2.2
		Capecitabine	TPC	3.99	0.11	16.07	15.59	17.13	Smaller	-1.5
		Capecitabine	Eribulin			13.03	18.29		Greater	1.2

3.2.2.1. Proportion of patients receiving subsequent therapies

We note that not all patients may receive the next line of therapy when they progress. However, in the clarification questions, Novartis stated that [redacted] went on to receive a non-therapeutic therapy after progression in the MONALEESA-2 study[5].

3.2.2.2. Patient characteristics

The baseline characteristics of the MONALEESA-2 study[5] and the BOLERO-2 study[29] are reproduced in Table 3 and Table 4.

Table 3: MONALEESA-2 baseline characteristics

Baseline characteristics	**Ribociclib group (n=334)**	**Placebo group (n=334)**
Median age (years)	62	63
Age range (years)	23-91	29-88
Race, (%)		
White	80.5	60.5
Asian	8.4	6.9
Black	3.0	2.1
Other	8.1	7.2
ECOG performance status, (%)		
0	61.4	60.5
1	38.6	39.5
2	0	0
No. of metastatic sites, (%)		
0	0.6	0.3
1	29.9	35.0
2	35.5	30.8
≥3	34.1	33.8
Previous neoadjuvant or adjuvant chemotherapy (%)	43.7	43.4

Table 4: BOLERO-2 baseline characteristics

Baseline characteristics	**Everolimus and exemestane group (n=334)**	**Placebo and exemestane group (n=334)**
Median age (years)	62	61
Age range (years)	34-93	28-90
Race, (%)		
White	74	78
Asian	3	1
Black	20	19
Other	3	2
ECOG performance status, (%)		
0	60	59
1	36	35
2	2	3
No. of metastatic sites, (%)		
0	0	0
1	32	29
2	31	34
≥3	36	37
Previous neoadjuvant or adjuvant chemotherapy (%)	44	40

The median ages in the two studies are similar, whereas we may expect the patients in BOLERO-2 to be slightly older as it is a later line of therapy– but we would not expect this to make a large difference. The distribution of ECOG status and number of metastatic sites are similar between the studies. The proportion with previous neoadjuvant or adjuvant chemotherapy is similar between the studies. 100% of patients in BOLERO-2 had received previous treatment with letrozole or anastrazole. There does not appear to be anything

obvious to indicate that BOLERO-2 could not represent patients progressing in MONALEESA-2.

3.2.2.1. Long term validation

Novartis compared the predicted OS for letrozole from their model with two more mature studies of first line endocrine therapy in advanced breast cancer: LEA[19] and ALLIANCE[20]. The median OS estimates for endocrine therapy in LEA and ALLIANCE are 51.8 and 43.9 months. Although the LEA and ALLIANCE studies provide slightly different Kaplan-Meier estimates for the OS on endocrine therapy, the modelled OS prediction for letrozole from the Novartis model, which is based on PFS data from the MONALEESA-2 study and OS from BOLERO-2, seems to be [redacted] with the average OS of these two longer-term studies (Figure 3).

Figure 3: Novartis' validation of overall survival (reproduced)

Original figure 45 on page 185 of Novartis' company submission. Reproduced from Novartis' economic model using progression-free survival data from January 2017. Ribociclib data removed for clarity.

[redacted]

In ID915, Pfizer compared their predicted OS for letrozole to Paridaens 2008[18], Bergh 2012[30] and Mouridsen 2003[31] which reported much lower median OS than LEA or ALLIANCE: 37.2, 37.8 and 34.0 months respectively. There is such a large variation in OS estimates for

endocrine therapy that it is difficult to know which estimate is most relevant for validation, and therefore whether Novartis' predicted results are valid.

3.3. Other modelling approaches in (breast) cancer

There are a few NICE technology appraisals in breast cancer that did not use partitioned survival analysis: TA424 used response as a surrogate for survival[32], TA112 used disease-free survival data and relapse to model progression to metastatic disease and modelled survival from metastatic disease using other sources[32], and TA108 used a similar approach to TA112 using recurrence-free progression[33].

Although the approach of "adding on" overall survival from a later line has not been used previously in NICE appraisals for breast cancer, it has been used in the evaluation of bosutinib for chronic myeloid leukaemia in TA401[34]. In this appraisal, the clinical effectiveness data for bosutinib came from a single arm trial and overall survival data was immature. The committee accepted a cumulative approach in which the overall survival from standard care was added on after time on treatment for bosutinib.

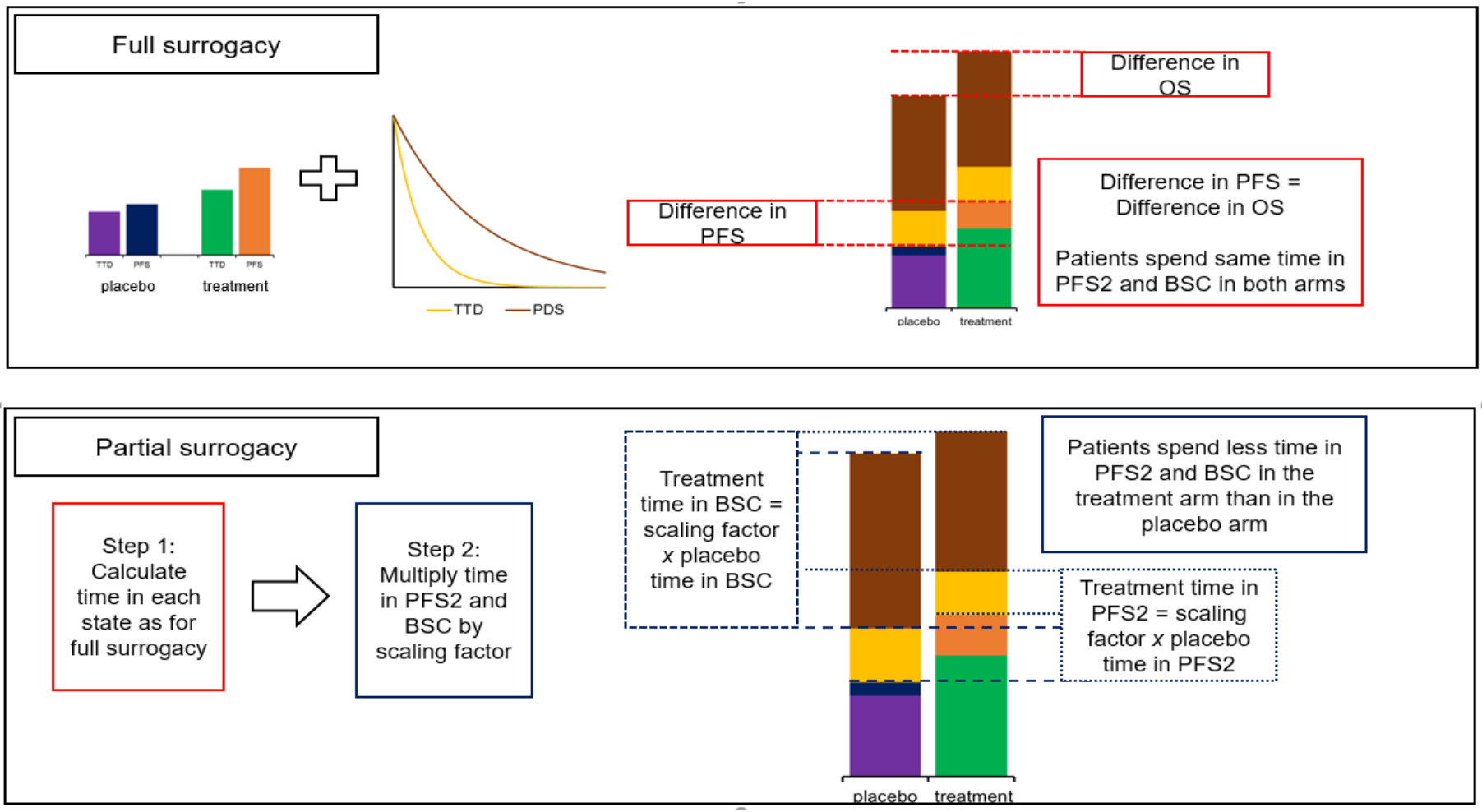
4. FULL OR PARTIAL SURROGACY

4.1. Time in health states

As discussed in Section 3.2, Novartis assumed 100% surrogacy. The evidence review group (ERG) considered this assumption speculative, and referred to the PALOMA-1 trial where the ratio of gain in median OS to gain in median PFS was 38.5% (37.5-33.3)/(25.7-14.8)[5]. (We note an updated analysis indicates that the ratio of median OS gain to median PFS gain may be smaller at 27.5% (37.5-34.5)[35]/(25.7-14.8)[15]). The ERG assumed partial surrogacy using the ratio of 38.5% in their base case analysis. For all analyses in this document using partial surrogacy, we use the ratio of 38.5%. To implement this in the economic model for ribociclib, a scaling factor is applied to reduce the time spend in the health states beyond PFS to adjust the total life years such that the difference in OS between treatment and comparator is reduced. This means that the time in PFS2 and BSC is lower for ribociclib than for placebo. The scaling factor was incorporated by Novartis in response to a request from the ERG. A comparison of full and partial surrogacy is shown in Figure 5.

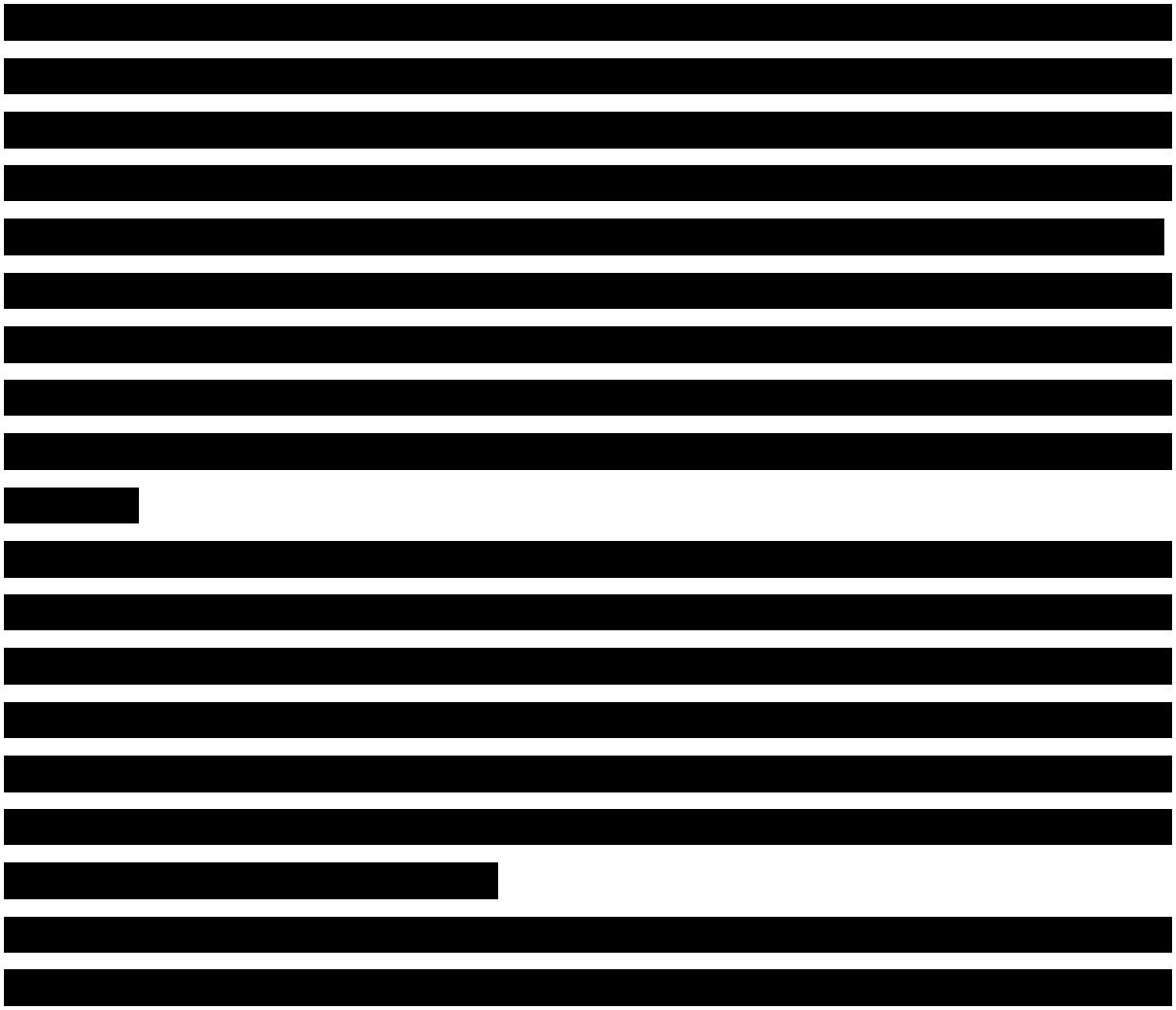
Figure 4: Full and partial surrogacy

BSC: best supportive care, Chemo: chemotherapy, eve: everolimus plus exemestane, exe: exemestane only, PDS: post discontinuation survival, PFS: progression-free survival, TTD: time to discontinuation



4.2. Effect of full or partial surrogacy on cost-effectiveness

The different health states have different costs and different utility values. The cost per quality-adjusted life year (QALY) for each health state therefore differs, shown in Table 5. The overall incremental cost-effectiveness ratio (ICER) for treatment versus comparator depends on the difference in costs and QALYs for PFS1, PFS2 and BSC. The costs and QALYs in PFS1 are the same when full or partial surrogacy are assumed as the time in PFS1 does not change. The costs and QALYS in PFS2 and BSC are similar for treatment and comparator when full surrogacy is assumed, but they differ substantially when partial surrogacy is assumed because patients on treatment spend less time PFS2 and BSC than patients on placebo. Patients spend longer in BSC than PFS2 so the cost effectiveness of the BSC state makes a bigger difference than the PFS2 state. Two costs are available for the BSC state: £2,000 per month used by Novartis, or £1,140 per month preferred by the ERG[5].



[redacted]

Table 5: Health state costs, utilities and cost per QALY

Health state	Health state cost /week	Treatment cost /week	AE cost /week	Monitoring cost /week	Total cost /week	Utility value	Cost per QALY
BSC: CS	£45	£462			£507	0.51	[redacted]
BSC: ERG	£45	£263			£308	0.51	[redacted]
PFS2: eve	£36	[redacted]			[redacted]	0.77	[redacted]
PFS2: exe	£36	£1.39			£37	0.77	[redacted]
PFS2: chemo	£36	£109			£145	0.66	[redacted]
PFS1: off treatment	£36	£0			£36	[redacted]	[redacted]
PFS1: on letrozole	£36	£0.38	£0.65		£37	[redacted]	[redacted]
PFS1: on ribociclib (list price)	£36	[redacted]			[redacted]	[redacted]	[redacted]
PFS1: on ribociclib (PAS)	£36	[redacted]	£2.07	0-4: £44 6-20: £4 24+ £0	[redacted]	[redacted]	[redacted]

AE: adverse event, BSC: best supportive care, Chemo: chemotherapy, CS: company submission, ERG: evidence review group, eve: everolimus plus exemestane, exe: exemestane only, PAS: patient access scheme, PDS: post discontinuation survival, PFS: progression-free survival, QALY: quality-adjusted life-years

5. MODEL VERIFICATION

To determine whether the Novartis model is structurally sound and does not contain hidden errors we used black-box testing and assessed the external validity of the Novartis model using inputs from the palbociclib appraisal, as the decision problems for these two appraisals are similar. Black-box testing is a form of model validation that involves changing the model

inputs and observing whether the model outputs move in the manner expected. In this case, we used the model inputs from the palbociclib appraisal within the ribociclib model. From this we confirmed that the model outputs behaved in the manner expected when alternative values were inputted one at a time. We also assessed the external validity of the Novartis model structure by making several of the key inputs consistent with those used in the palbociclib model. We found that the Novartis model was able to produce outputs reasonably consistent with those reported for palbociclib when using inputs from the palbociclib model, which confirms the external validity of the ribociclib model. These two tests of quality assurance provide some reassurance that the model structure used by Novartis is externally valid and does not contain any hidden errors. However, it should be noted that the DSU did not attempt to exhaustively validate the Novartis model.

The black-box analysis was also useful in exploring the impact on the ICER of varying different inputs under the assumption of both full and partial surrogacy. We identified that the inputs that cause the greatest impact on the ICER are:

1. The drug costs of ribociclib
2. Costs beyond second line, if partial surrogacy is used
3. Utilities
4. Progression-free survival
5. Overall survival

Each of these inputs is discussed in more detail in later sections. Sections 6 - 10 report scenario analyses to demonstrate the impact of using alternative inputs for each of the key model drivers listed above, using Novartis' base case as a starting point. Scenarios for the costs and survival beyond second line are conducted for both full and partial surrogacy as the impact of second line costs varies depending on this assumption, but in the other sections full surrogacy is used as per Novartis' base case. Section 11 reports results of scenario analyses using the inputs we consider most plausible.

6. DRUG COSTS OF RIBOCICLIB

The total drug cost for ribociclib is influenced by the duration of ribociclib treatment and the cost per dose. Both of these are discussed further.

6.1. Duration of ribociclib treatment

Novartis fitted parametric curves to the TTD data from MONALEESA-2 (Figure 5). They chose the exponential curve on the basis that it was also used for PFS, visual inspection and

clinical validation. The exponential had the highest Akaike Information Criterion (AIC) score and Bayesian Information Criterion (BIC) score for ribociclib, indicating the least good statistical fit. The ERG for ID915 also used the exponential distribution for TTD, but used Kaplan-Meier data at the beginning of the curve. Neither Novartis nor the ERG for ID1026 report scenario analysis varying the TTD curve in isolation, and instead vary both the TTD and PFS curves simultaneously. We note that the [redacted] curves in Figure 5 [redacted] the PFS curve, suggesting that patients [redacted]. The economic model contains a constraint in the coding that sets time on treatment to be the minimum of the sampled time on treatment and sampled progression free survival, to ensure that simulated patients do not continue treatment beyond progression.

Figure 5: Novartis' time to discontinuation parametric curves (reproduced)

PFS: progression-free survival. Reproduced from Novartis' company submission, figure 29 page 120.

In their company submission, Novartis state that the expected number of courses of treatment is [redacted] courses ([redacted] months), from the CSR[5]. The mean of the fitted exponential TTD distribution is [redacted] months. The mean of the fitted exponential PFS distribution is [redacted] months. It is unclear why TTD is so much shorter than PFS. We note that in modelling second line treatment, TTD is used as a proxy for PFS, implying the two are similar if not the same. The company submission states that [redacted] of patients had adverse events leading to discontinuation. If [redacted] of patients had discontinued due to adverse events at the beginning of the study, and the remaining [redacted] had discontinued upon progression or death, then the mean TTD using the

[redacted]_distribution for PFS would be [redacted] months ([redacted] * [redacted] months). This is notably higher than the mean of the fitted [redacted] distribution for TTD.

Using the exponential distribution for TTD assumes that the rate of discontinuing is constant over time (patients are equally likely to discontinue at the beginning, middle or end of the study). We may expect that there is a higher rate of discontinuing early in the study if there is a proportion of patients who experience intolerable adverse events, or later in the study if patients are then more likely to progress or die.

Unlike the exponential, the Weibull distribution allows the rate of discontinuation to vary over time. The Weibull curve fitted to the TTD data assumes that the rate of discontinuation decreases over time. The Weibull curve that fitted to the PFS data assumes that the rate of progression or death increase over time. This means that the Weibull PFS and TTD curves converge more quickly than the exponential PFS and TTD curves (Figure 7), and the difference between the mean Weibull PFS and mean Weibull TTD is less than the difference between the mean exponential PFS and mean exponential TTD.

The mean of the fitted [redacted] TTD distribution is [redacted] months. The mean of the fitted PFS [redacted] distribution is [redacted] months. If [redacted] of patients had discontinued due to adverse events at the beginning of the study, and the remaining [redacted] had discontinued upon progression or death, then the mean TTD using the [redacted] distribution for PFS would be [redacted] months ([redacted] * [redacted] months). This is close to the mean of the fitted [redacted] distribution for TTD. This may suggest that the Weibull distribution is a more appropriate extrapolation of TTD and PFS than the exponential distribution.

Additionally, we note that the data for PFS uses analysis from a cut-off in January 2017. The data for TTD uses analysis from a cut-off in January 2016 and is therefore less mature and there is more uncertainty around the extrapolation beyond the cut-off.

Figure 6: Ribociclib PFS and TTD

PFS: progression-free survival, TTD: time to discontinuation

When we used the Weibull curve for TTD (for both ribociclib and letrozole), the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. We also considered a scenario using the log-normal curve as an example with a much longer TTD. We chose the log-normal on the basis that the Gompertz does not look like a good visual fit, and the AIC and BIC are lower (better) for the log-normal than the log-logistic. When we used the log-normal curve, the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. This demonstrates that the ICER is sensitive to the choice of curve. Full results are provided in Table 6.

Table 6: Scenario analysis varying TTD curves

	Total QALYs		Total Costs		ICER
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Without PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull					
log-normal					
With PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull					
log-normal					

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

6.2. Ribociclib cost

The licensed dose for ribociclib is 600mg once daily for 21 days of a 28 day cycle[5]. This dose consists of three 200mg tablets. Ribociclib 200mg is available in packs of 63, 42, and 21 tablets, with a pricing structure such that each 200mg tablet has the same price regardless of the pack size.

A proportion of patients in MONALEESA-2 had their dose reduced to 400mg and 200mg daily. Novartis assumed that patients who reduce their dose do not waste tablets as they can simply take fewer tablets daily, and so a pack lasts longer. Novartis used individual patient data to calculate the total number of days patients received each dose for per cycle to cost the drug per cycle (cycle 10 data is used for cycle 10 onwards due to decreasing patient numbers). Drug acquisition costs per cycle are reproduced from Novartis' submission in Table 7 (without the PAS). Without considering dose reduction, one cycle of ribociclib costs [redacted] (without the PAS).

Table 7: Novartis' ribociclib drug costs (reproduced)

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Reproduced from Novartis' company submission, table 43 page 153.

The ERG noted that wastage at discontinuation should be included, which increased the ICER by less than [redacted] per QALY.

When we assumed that all patients received the full dose of ribociclib each cycle, the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. Full results are provided in Table 8.

Table 8: Scenario analysis varying dose reduction

	Total QALYs		**Total Costs**		**ICER**
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case: dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

7. TREATMENTS BEYOND SECOND LINE

Novartis did not explicitly model treatments beyond second line, but instead applied a monthly drug cost of £2,000 to the progressed health state. Novartis stated this cost was based upon "expert clinical validation and consideration of previous NICE appraisals…in advanced breast cancer"[5]. In their scenario analysis, Novartis found that reducing this cost to £0 increased the ICER by less than [redacted] (without PAS). This is because under the

assumption of full surrogacy, the time in the progressed health state is similar between arms (see Section 4.2). The ERG preferred to use a monthly drug cost of £1,140 in the progressed health state, based on third-line treatment costs in TA239[13]. When the ERG varied this cost under the assumption of partial surrogacy, they found that this cost had a big impact on the ICER: using a cost of £0 [redacted] the ICER by around [redacted] with the PAS, and by around [redacted] without the PAS. Using a cost of [redacted] decreased the ICER by around [redacted] with the PAS and by around [redacted] without the PAS[5]. When we applied the partial surrogacy assumption used by the ERG (38.5% of full surrogacy) to Novartis' base case, we found that using the ERG's 3rd line cost instead of Novartis' [redacted] the ICER by around [redacted] without the PAS, and by around [redacted] with the PAS. Full results are presented in Table 9.

Table 9: Scenario analysis varying 3rd line costs: partial surrogacy

	Total QALYs		Total Costs		ICER
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case: Full surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with ERG 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: Full surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with ERG 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: evidence review group, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

7.1. Treatment pathway beyond second line

In Novartis' model, patients in the progressed health state remain there until death, and thus are assumed to receive the treatments included in the monthly drug cost until death.

The NICE guidance does not appear to specify a number of lines of treatments, and the pathway is not clear. A poster by Kurosky *et al.*[36] reports that the most popular regimens in third line are capecitabine, fulvestrant, tamoxifen, eribulin and anastrazole. Fulvestrant is not recommended by NICE[13], tamoxifen is recommended only for premenopausal and perimenopausal women in CG81[3], and patients in Novartis' model have already received an aromatose inhibitor (letrozole) so it seems unlikely that they would receive another (anastrazole). The Systemic Anti-Cancer Therapy (SACT) chemotherapy dataset Top Regimens reports that the most common palliative regimens in breast cancer include capecitabine, paclitaxel and eribulin, although we note that this dataset is not specific to this particular indication[37].

7.1.1. Costs of treatments beyond second line

7.1.1.1. Capecitabine

Novartis included the cost of capecitabine in their model as a second-line treatment. Novartis costed treatment using the British National Formulary (BNF), giving a drug cost per cycle of £146. We note that a cost for capecitabine is available from the NHS Electronic Marketing Information Tool (eMIT) (£19.55 for 120 500mg tablets and £3.13 for 60 150mg tablets)[38] which reduces the drug costs to £19.71 per cycle. Novartis considered an administration cost of £181 to deliver oral chemotherapy from NHS reference costs. Using Novartis' administration costs and drug costs from eMIT, the cost per 21-day cycle is therefore £201.

7.1.1.1. Paclitaxel

Novartis included the cost of paclitaxel in their model as a potential second-line treatment. Novartis costed treatment using the BNF, giving a drug cost per cycle of £668. We note that a cost for paclitaxel is available from eMIT (£34.33 for 300mg/50ml and £61.92 for 30mg/5ml)[38] which reduces the drug costs to £96 per cycle. Novartis considered an administration cost of £239 in the first cycle and £326 in subsequent cycles, from NHS reference costs[39]. Using Novartis' administration costs and drug costs from eMIT, the cost per 21-day cycle is therefore £347 for the first cycle and £435 for subsequent cycles.

7.1.1.1. Eribulin

TA423 reports that the per cycle drug cost for eribulin is £1,805[22]. There is a confidential PAS scheme in place for eribulin, so we know that the true cost to the NHS is less than this[22], although we do not know what this is. Eribulin is administered intravenously, and there are two doses, so there are two sets of administration costs each cycle. Using the administration costs from Novartis' model, the administration cost is £566 (£239 + £326) in the first cycle

and £653 (£326 + £326) in subsequent cycles. Without a PAS, the cost per 21-day cycle of eribulin is therefore £2,371 in the first cycle and £2,458 in subsequent cycles.

7.1.2. Duration of treatments beyond second line

The poster by Kurosky *et al.*[36] reports mean time on third-line treatments as 6.1 months for chemotherapy only. TA423 reports that the anticipated number of 21-day cycles for eribulin is 6, and the mean PFS for eribulin after one prior chemotherapy is 4.06 months[22]. The mean PFS for capecitabine after one prior chemotherapy in TA423 was 3.99 months[22].

7.1.3. Total costs of treatment beyond second line

7.1.3.1. Total costs of treatment using Novartis's monthly cost

In Novartis' model, patients in the ribociclib arm spend [redacted] years in progression, and patients in the letrozole arm spend [redacted] years in progression.

Using Novartis's cost of £2,000 per month, the total discounted third line drug cost is [redacted] for letrozole, and [redacted] for ribociclib.

Following letrozole, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without eribulin's PAS (longer with eribulin's PAS). Following ribociclib, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without the PAS (longer with eribulin's PAS). These durations of treatment are much longer than those reported in Section 7.1.2, and for capecitabine and paclitaxel are longer than patients are alive in the model for. Applying the monthly cost of £2,000 for the duration of progressed disease therefore clearly overestimates drug costs beyond second line.

7.1.3.2. Total costs of treatment using the ERG's monthly cost

Using the ERG's cost of £1,140 per month, the total discounted third line drug cost is [redacted] for letrozole and [redacted] for ribociclib.

Following letrozole, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without eribulin's PAS (longer with eribulin's PAS). Following ribociclib, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without the PAS (longer with eribulin's PAS). These durations of treatment are still longer than those reported in Section 7.1.2, and for capecitabine and paclitaxel are longer than patients are alive in the model for. Applying the monthly cost of £1,140 for the duration of progressed disease therefore also likely overestimates costs beyond second line, but is closer than the cost of £2,000 per month.

8. UTILITIES

The NICE reference case for measuring and valuing health effects states that the EQ-5D is the preferred measure of health-related quality of life in adults[40]. If not available from trials, EQ-5D values can be obtained from the literature or mapped from other health-related measures in the relevant clinical trials. The methods guide states that the EQ-5D-5L may be used for reference-case analysis, and that the validated mapping function from EQ-5D-5L to EQ-5D(-3L)[41] should be used until an acceptable valuation set is available for EQ-5D-5L. NICE's position statement on the EQ-5D-5L value set states that the 5L valuation set is not recommended for use and that data gathered using EQ-5D-5L should be mapped onto the 3L valuation set using the function developed by van Hout et al (2012)[41,42]

8.1. PFS1

EQ-5D-5L estimates for patients with progression free disease ([redacted]) were based on data collected in the MONALEESA-2 trial. The mean estimate for PFS1 was derived from a mixed effects model in order to reflect the fact that patients contribute repeated observations throughout the trial. Scores were calculated using the value set by Devlin et al 2016[43]. The estimate was [redacted] (standard error = [redacted]). These data were combined for both arms of the trial. There was [redacted].

Upon NICE's request, Novartis mapped their EQ-5D-5L scores to 3L, which produced a score of [redacted] for the PFS1 state.

8.2. PFS2

The utility value for PFS2 was taken from Lloyd et al (2006)[44], with adjustments made for age and the numbers of degree of response to treatment based on rates observed in the BOLERO-2 trial. Lloyd is based on vignettes valued by the general population using standard gamble[44]. The mean estimate was 0.774. This utility value was used in TA421 for the appraisal of everolimus with exemestane after endocrine therapy[6]. For patients receiving chemotherapy, a decrement of 0.113 is applied, which Novartis state is based on a study by Peasgood et al (2010)[45], although the ERG was unable to verify this disutility.

Previous technology appraisals in later-line therapies for advance breast cancer have differentiated utility between pre and post progression (TA421[6], TA423[7]), so it would appear appropriate use a different utility for PFS2 than that used for progressed disease. However, the value used by Novartis (0.774) does not meet NICE's reference case, [redacted]

Additionally, we note that the FAD for TA421 states that the committee concluded it would have been appropriate for Novartis to present estimates for 'stable disease' from BOLERO-2, which included a disease-specific measure of health-related quality of life which could theoretically be mapped to EQ-5D[6].

8.1. Beyond PFS2

For progressed disease, the utility estimate was also taken from Lloyd et al (2006) and was a mean of 0.5052, as has been used in previous technology appraisals in HER2-negative, HR-positive advanced breast cancer[22].

In scenario analysis we consider that the utility value for PFS2 could be the same as for PFS1, or could be 0.69 in line with EQ-5D scores for second line therapy in the same population from a conference poster by Mitra *et al*. (2016)[46]. We also consider a scenario using the same utilities as in ID915: [redacted] for PFS1 and the same as BSC for PFS2 (0.5052).
In scenario analysis, we found that when we used the PFS1 mapped 3L utility value for PFS1 and PFS2, the ICER [redacted] by around [redacted] without the PAS, and by around [redacted] with the PAS. When we used the PFS1 mapped 3L value for PFS1 and 0.69 for PFS2, the ICER [redacted] by around [redacted] without the PAS, and by around [redacted] with the PAS. In a scenario using the PFS1 utility from ID915 and the BSC utility for PFS2 (the same value is used in ID915 and the ribociclib BSC health states), the ICER [redacted] by around [redacted] without the PAS and by around [redacted] with the PAS. Full results are shown in Table 10.

Table 10: Scenario analysis varying PFS1 and PFS2 utility values

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: PFS1: 5L, PFS2: TA421	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L, PFS2: PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L PFS2: 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: ID915, PFS2: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: PFS1: 5L, PFS2: TA421	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L, PFS2: PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L PFS2: 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: ID915, PFS2: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3L: EQ-5D 3Level, 5L: EQ-5D 5L, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality-adjusted life years, TA: technology appraisal

9. PROGRESSION-FREE SURVIVAL

Novartis fitted parametric curves to the PFS data from MONALEESA-2. Extrapolating beyond the trial period introduces uncertainty. Novartis selected the exponential distribution for PFS, on the basis that it had the second-lowest (second-best) AIC and BIC scores, comparison to long-term studies (LEA[19] and ALLIANCE[20]), "validation with clinical experts", and the ERG for ID915 suggesting that the exponential is more appropriate than the Weibull[5].

[redacted]

The ERG considered that the exponential and Weibull curves are equally plausible. We have discussed the exponential and Weibull curves in Section 6.1.

Figure 7: Novartis' time to discontinuation parametric curves (reproduced)

KM: Kaplan-Meier, ML-2: MONALEESA-2. Reproduced from Evidence Review Group report, figure 5.9 on page 80.

With Novartis' base case settings, when we used the Weibull for PFS (but not for TTD), the ICER increased by around [redacted] with the PAS, and by around [redacted] without the PAS. Full results are shown in Table 11.

Table 11: Scenario analysis varying progression-free survival

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

10. OVERALL SURVIVAL

Extrapolating overall survival beyond the trial period introduces uncertainty. As discussed in Section 3.2, overall survival data in MONALEESA-2 is immature and so Novartis did not fit

parametric curves. As an alternative to the approach taken by Novartis, we explored a scenario in which overall survival followed an exponential distribution, with median survival for letrozole and ribociclib assumed to be the same as the median survival for letrozole and palbociclib respectively in the PALOMA-1 trial[15]. In this scenario, we estimated overall survival in the same way that a partitioned survival approach estimates survival. This does not use the assumption of full surrogacy, but nor does it use the scaling factor. However, the difference in median OS estimates is less than the difference in PFS, so in effect it assumes partial surrogacy. The time in the PFS1 and PFS2 states does not change unless the overall survival is less than the time in these states. The time in BSC is the difference between the overall survival and the sum of the time in PFS1 and PFS2. The time in BSC therefore changes when overall survival changes.

Using Novartis' base case assumptions, this [redacted] the ICER by around [redacted] without the PAS and [redacted] the ICER by around [redacted] with the PAS (Table 12). [redacted] Using the ERG's third line drug cost, using median survival from PALOMA-1 [redacted] the ICER by around [redacted] without the PAS and decreased the ICER by less than [redacted] with the PAS.

Table 12: Scenario analysis varying overall survival using partitioned survival approach

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: using second-line OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1 with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: using second-line OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1 with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, QALYs: quality-adjusted life years

The difference in survival between ribociclib and letrozole has a substantial impact on the ICER – this is already discussed in the context of full and partial surrogacy (Section 4). Under the assumption of full surrogacy, the survival after ribociclib and letrozole does not impact results since it is the same between both arms – this is why Novartis found that varying the post-discontinuation survival curve did not impact their ICER[5]. However, under the assumption of partial surrogacy, the relative survival benefit of ribociclib depends on the absolute survival for letrozole. As discussed in Section 4.2, under the assumption of partial surrogacy, ICERs are influenced by the cost-effectiveness of later line treatments. Using Novartis' base case assumptions, under the assumption of partial surrogacy, without the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using Novartis' base case assumptions, under the assumption of partial surrogacy, with the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using the ERG's third line drug cost, under the assumption of partial surrogacy, without the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using the ERG's third line drug cost, under the assumption of partial surrogacy, with the

PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by [redacted]. Full results are shown in Table 13. We note that the log-normal has the highest AIC and BIC, does not appear to be a good visual fit to the data, and reports survival estimates that do not appear valid compared to long-term studies. The log-normal is presented here as a hypothetical example and is not considered further.

Table 13: Scenario analysis varying overall survival: partial surrogacy

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: Full surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS	[redacted]				
Base case: Full surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
With PAS					
Base case: Full surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS	[redacted]				
Base case: Full surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS with ERG 3rd line cost	[redacted]				

ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, PDS: post-discontinuation survival, QALYs: quality-adjusted life years

11. SCENARIO ANALYSES VARYING THE KEY INPUTS

We have performed scenario analyses varying the key inputs, as identified in Section 5. For the utilities and costs beyond second line, we have identified alternative values that the DSU

considers to be more plausible than the values used in the Novartis base case. Here we present analyses demonstrating the impact that changing these have on Novartis' base case ICER. For TTD and PFS, we present all analyses with the Weibull and Exponential curves as the ERG considered them equally plausible. We present all analyses assuming dose reduction for ribociclib in line with the trial data, and assuming full dosing in line with the licence. To address the uncertainty associated with overall survival, we present all analyses under the assumption of both full and partial surrogacy. We do not vary the extrapolation of survival as previous scenario analysis (Section 10) indicated that using the exponential instead of Weibull has minimal impact, and the log-normal does not appear to be a valid choice.

Table 14 presents results with Novartis' base case assumptions and changes made using the DSU's preferred inputs: first using the ERG 3rd line drug cost, and then additionally using EQ-5D 3L utilities for PFS1 (using the MONALEESA-2 5L scores mapped to 3L) and for PFS (using the value of 0.69 for second line treatment from Mitra *et al*[46]). Scenario analyses for the Novartis base case updated with the DSU's preferred values are summarised using ICERs alone in Table 15 without the PAS, and Table 16 with the PAS. Total costs and QALYs and ICERs for each scenario are shown in Table 17 without the PAS and Table 18 with the PAS.

Table 14: Impact of applying the DSU's preferred values for utilities and 3rd line drug costs

	Total QALYs		**Total Costs**		**ICER**
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: ERG 3rd line cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 plus PFS: EQ-5D 3L utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: ERG 3rd line cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 plus PFS: EQ-5D 3L utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG 3rd line cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

ERG: evidence review group, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality-adjusted life years

Table 15: Summary of scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): without PAS

		PFS: Exponential		PFS: Weibull	
		TTD: Exponential	TTD: Weibull	TTD: Exponential	TTD: Weibull
Full surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				
Partial surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

PAS: patient access scheme, PFS: progression-free survival, TTD: time to discontinuation

Table 16: Summary of scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): with PAS

		PFS: Exponential		PFS: Weibull	
		TTD: Exponential	TTD: Weibull	TTD: Exponential	TTD: Weibull
Full surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				
Partial surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

PAS: patient access scheme, PFS: progression-free survival, TTD: time to discontinuation

Table 17: Scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): without PAS

Full/ Partial	Dosage	PFS curve	TTD curve	Total QALYs		Total Costs		ICER
				Ribociclib	Letrozole	Ribociclib	Letrozole	
Full	Reduced	Exp	Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
Partial	Reduced	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

Exp: exponential, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality adjusted life years, TTD: time to discontinuation, Wei: Weibull

Table 18: Scenario analyses: with PAS

Full/ Partial	Dosage	PFS curve	TTD curve	Total QALYs		Total Costs		ICER
				Ribociclib	Letrozole	Ribociclib	Letrozole	
Full	Reduced	Exp	Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
Partial	Reduced	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

Exp: exponential, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality adjusted life years, TTD: time to discontinuation, Wei: Weibull

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