NICE National Institute for Health and Care Excellence

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Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer (CDF review of TA593)

Lead team presentation

1st appraisal committee A meeting

Chair: Jane Adam

Lead team: Justin Daniels, Becky Pennington, Pamela Rees

ERG: BMJ Technology Assessment Group

NICE technical team: Sharlene Ting, Carl Prescott, Henry Edwards

Company: Novartis

5th January 2021

Key clinical issues

- Overall survival (OS) data still immature (key uncertainty in TA593) but pre-planned trial outcome reached, so trial ended
  - Does the committee consider that ribociclib with fulvestrant has been shown to be clinically effective?

Ribociclib (Kisqali, Novartis)

Marketing authorisation	For hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in people who have had prior endocrine therapy. **NB: TA593 recommendation narrower than MA: ONLY in combination with fulvestrant, and *after* prior endocrine therapy**
Mechanism of action	Selective CDK4/6 inhibitor. When these 2 proteins are activated, they can promote cancer cell growth
Administration and dose	**Ribociclib** oral, 600 mg daily for 21 days, then 7 days off treatment (28-day cycle) **Fulvestrant** 500 mg intramuscular injections on days 1, 15 and 29, and once monthly thereafter
List price per 28 day course	**Ribociclib:** 63 x 200 mg £2,950; 42 x 200 mg £1,966.67; 21 x 200 mg £983.33. Simple PAS discount **Fulvestrant:** 2 x 250mg/5ml solution for injection £522.41. Confidential discount

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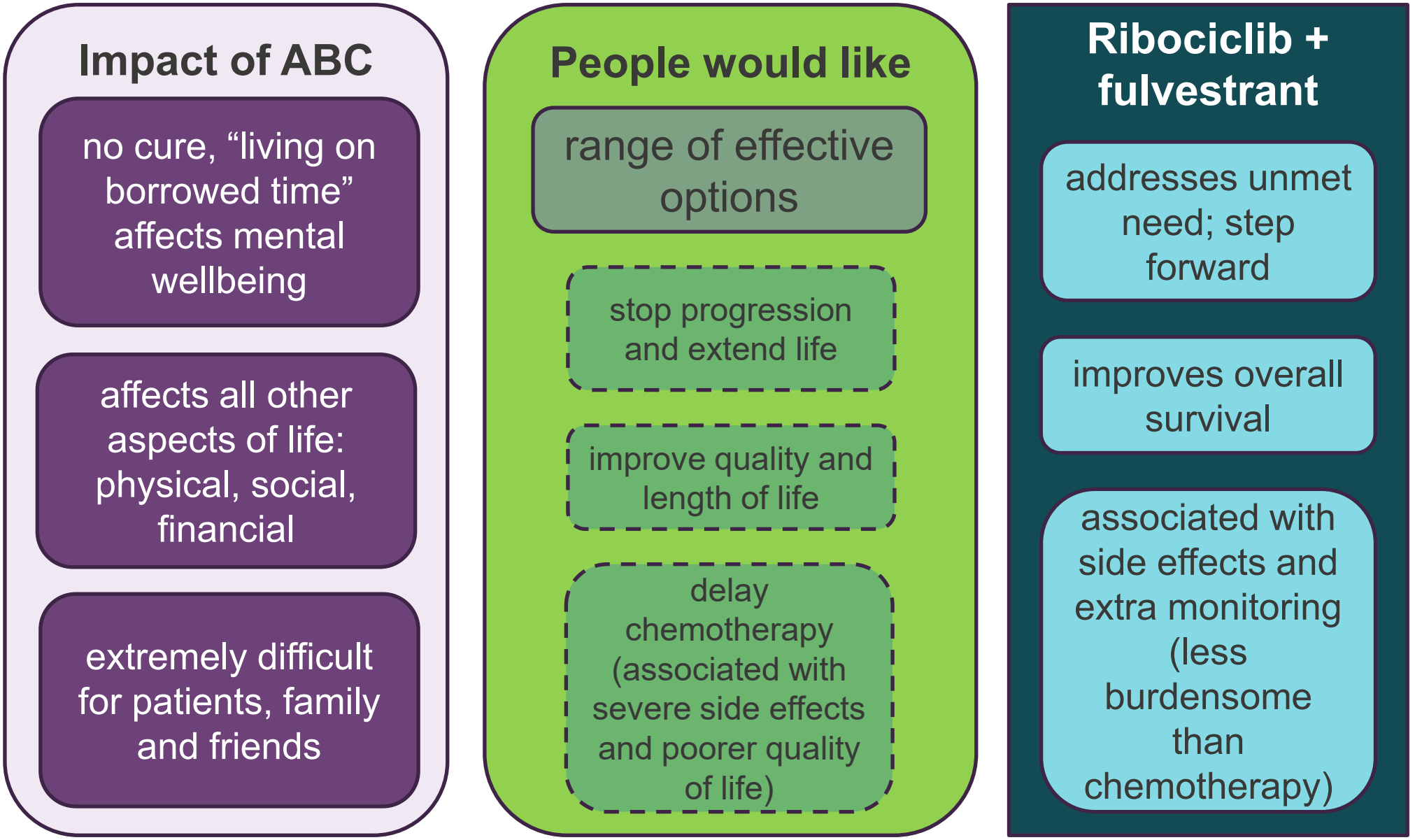
Key: CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; MA, marketing authorisation; mg, milligram; ml, millilitre; PAS, patient access scheme; TA, technology appraisal

Advanced breast cancer

- Breast cancer – most common cancer among women in UK
  - Approx. 55,200 incidence & 11,400 deaths (2015-2017 figures)
- Approx. 13% breast cancer is advanced at diagnosis, i.e. either:
  - Locally advanced: spread to nearby tissue and cannot be completely removed by surgery
  - Metastatic: spread to other parts of body
- Approx. 35% of early or locally advanced disease progresses to metastatic within 10 years
- Approx. 73% breast cancer is hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+, HER2-)

Key: Approx, approximately; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; i.e., that is

Patient perspective: Breast Cancer Now



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Key: ABC, advanced breast cancer

Treatment pathway for HR+, HER2– ABC

	Population	Treatments
First-line ABC	**First-line** • de novo ABC • ABC that progressed >12 months after neo/adjuvant endocrine therapy	• **Palbociclib + AI** (AI; TA495) • **Ribociclib + AI** (TA496) • **Abemaciclib + AI** (TA563) • Tamoxifen • Aromatase inhibitor (AI)
Second-line ABC	**Endocrine-resistant** • ***First-line endocrine resistant***: ABC that progressed on or ≤12 months after neo/adjuvant endocrine therapy • ***Second-line endocrine resistant***: ABC that progressed on/after 1 line of endocrine therapy	• **Exemestane + everolimus** • Exemestane • Tamoxifen • Fulvestrant • Chemotherapy
		CDF review of TA593: Ribociclib + fulvestrant (ID3755) (would not be used after prior CDK4/6 therapy*)
		CDF review of TA579: Abemaciclib + fulvestrant (ID2727)

- ***Is the proportion of people receiving CDK 1st line increasing?**
- **If so, will number of people eligible for treatment with ribociclib be decreasing over time?**

Key: ABC, advanced breast cancer; AI, aromatase inhibitor; CDF, Cancer Drugs Fund; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; TA, technology appraisal

History of appraisal of ribociclib with fulvestrant

ACD April 2019 (not recommended):
Ribociclib with fulvestrant is **not recommended** for whole MA population

TA593 August 2019 (recommended for CDF in subpopulation):
Recommended within the **Cancer Drugs Fund** for treating HR+ve, HER2-negative breast cancer, **only for people who have had previous endocrine therapy and if exemestane plus everolimus is the most appropriate alternative** treatment

ID3755
- **Sept 2020:** Company submission
- **Nov-Dec 2020:** Technical engagement

Further data collection

1) Managed access agreement
2) Additional data from MONALEESA-3
3) Real world data (SACT)

CDF review January 2021

Key: ACD, appraisal consultation document; CDF, Cancer Drugs Fund; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MA, marketing authorisation; SACT, systemic anti-cancer therapy dataset; TA, technology appraisal

Cancer Drugs Fund and CDF Review

Committee's uncertainties in TA593

Uncertainty	Issue addressed?
Immaturity of overall survival	✓ Median OS reached Used in partitioned survival model
Efficacy estimates (based on subgroup, not powered to detect differences)	✘ No change
Progression-free survival (choice of network meta-analysis and extrapolation)	✓ Revised methods For discussion
Time-to-treatment discontinuation	✓ Revised methods For discussion
Post-progression survival	NA - Using overall survival

- Further data collection from MONALEESA-3: overall survival and longer-term progression-free survival for key subpopulation
- Real world data (SACT) will help to support generalisability of MONALEESA-3 data

Key: SACT, systemic anti-cancer therapy dataset

Key issues in ERG report

Technical issue	Notes
1. Overall survival (OS): MONALEESA-3 OS remains immature	✓ Trial reached prespecified endpoint ? But OS immature & no more data due
2. Time to treatment discontinuation (TTD) ribociclib: Company rejected best fitting curve as it suggested patients would never discontinue ribociclib	Company submitted alternative; ERG agree
3. TTD for everolimus plus exemestane: Company originally assumed patients would receive everolimus until disease progression. But people may stop sooner due to tolerability	✓Company changed assumption ? Company used expert opinion (from ERG clinical expert) to inform assumption; ERG question if trial data more appropriate
4. Economic model: Company used semi-Markov model as per TA593, but this does not include trial survival data, whereas partitioned survival model (PSM) would	✓Company now using PSM and trial OS data ? Choice of OS extrapolation to be discussed
5. Progression free survival (PFS) for everolimus + exemestane: Evidence suggests proportional hazards may be violated. Fractional polynomial (FP) network meta-analyses account for varying hazards so should be explored	? Company amended its base case to use FP NMA, but ERG note high levels of uncertainty

Trial data

Trial	MONALEESA-3 (key intervention trial)	BOLERO-2 (trial used for comparator assumptions)
Design	Double blind placebo-controlled phase 3 RCT	
Population	People with HR+, HER2- ABC (note only women recruited): • **Population B**: endocrine resistant disease • progression on/≤12 months after neo/adjuvant endocrine therapy (population Bi) & progression after 1 line of endocrine therapy in advanced setting (population Bii+Biii)	Postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer whose disease is refractory to letrozole or anastrozole
Intervention	Ribociclib + fulvestrant (Population B n=**237**; total population n=484)	Everolimus + exemestane (n=485)
Comparator	Matched placebo + fulvestrant (Population B n=**109**; total population n=242)	Placebo + exemestane (n=239)
Primary outcome	Progression-free survival (PFS) based on local assessment • Blinded independent review: for approximately 40% patients	PFS based on local radiology review of tumour assessments

Key: ABC, advance breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; RCT, randomised control trial;

Key trial: MONALEESA-3

Population	PFS			OS		
	Events		HR (95% CI)	Events		HR (95% CI)
	Ribo+ful	Ful+ pbo		Ribo+ful	Ful+ pbo	
November 2017	131/236 (55.5%)	84/109 (77.1%)	0.565 (0.428 to 0.744)	50/236 (21.2%)	32/109 (29.4%)	0.68 (0.44 to 1.07)

TA593 FAD: OS data immature, MONALEESA-3 ongoing with further OS data.

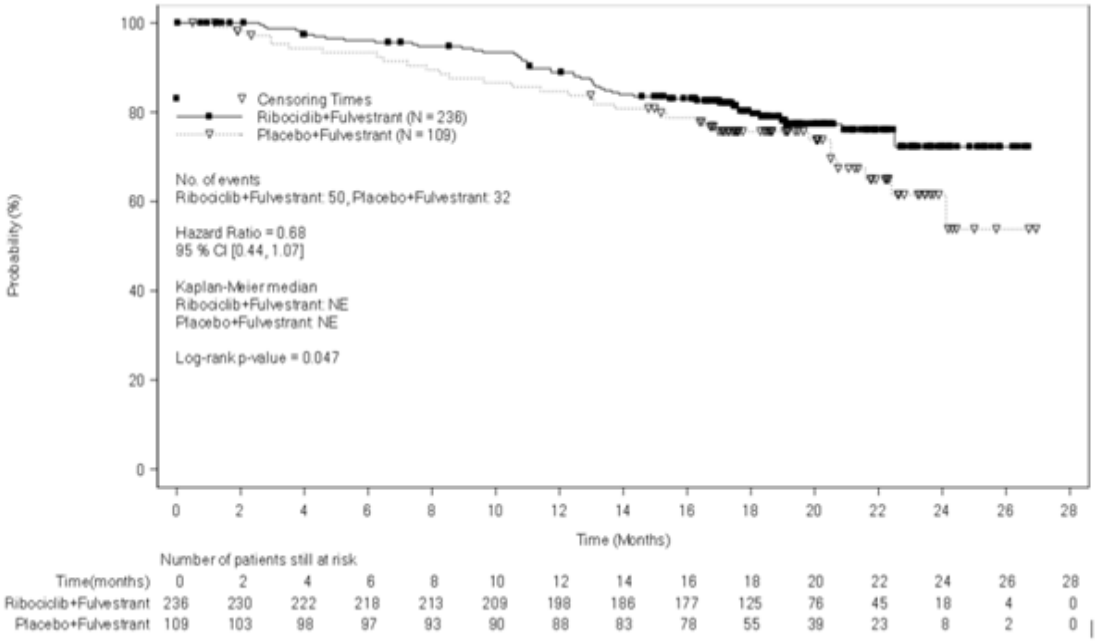
CDF data collection period

Population	PFS			OS		
	Events		HR (95% CI)	Events		HR (95% CI)
	Ribo+ful	Ful+ pbo		Ribo+ful	Ful+ pbo	
June 2019	167/237 (70.5%)	95/109 (87.2%)	0.57 (0.44 to 0.74)	102/237 (43%)	60/109 (55%)	0.73 (0.53 to 1.00)

Key: CI, confidence interval; ful, fulvestrant; HR, hazard ratio; pbo, placebo; PFS, progression-free survival; OS, overall survival; pop; population; ribo, ribociclib.
Note: ribociclib N increases (236 to 237) due to data availability for 1 patient at first data cut

MONALEESA-3: OS subpopulation B

2017 data cut

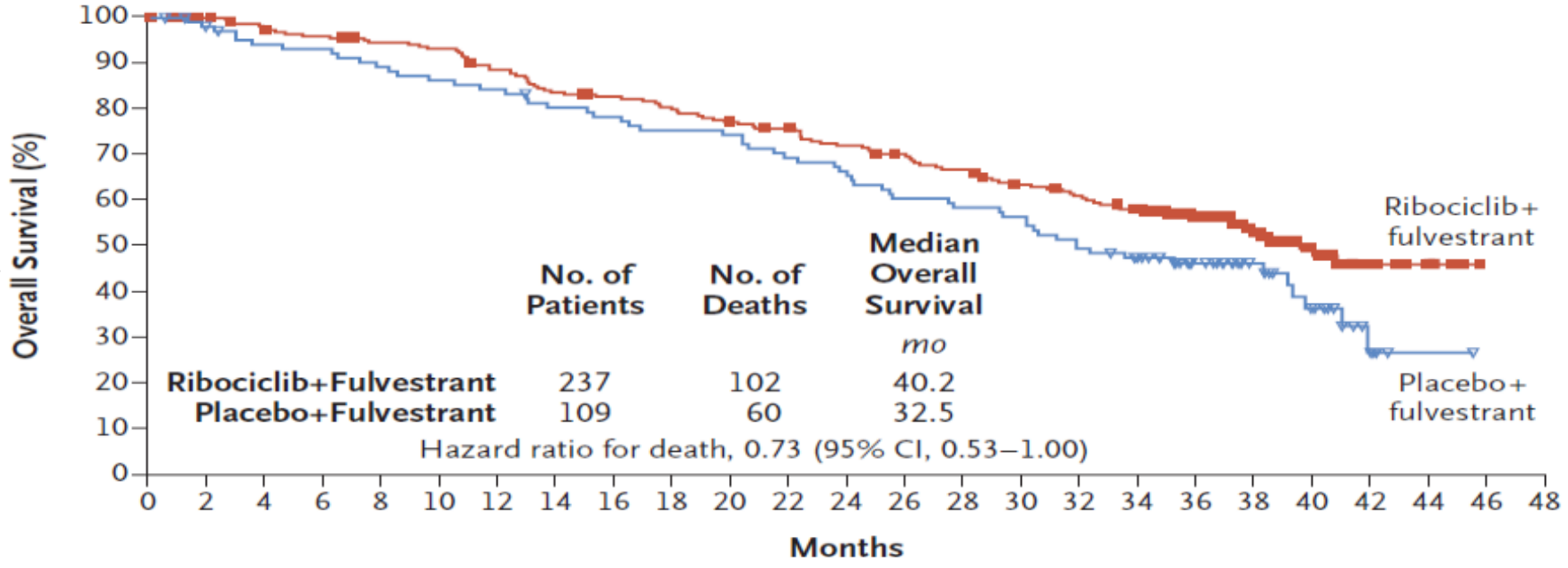


End of 2017 data cut

New data since TA593

End of 2019 data cut

2019 data cut



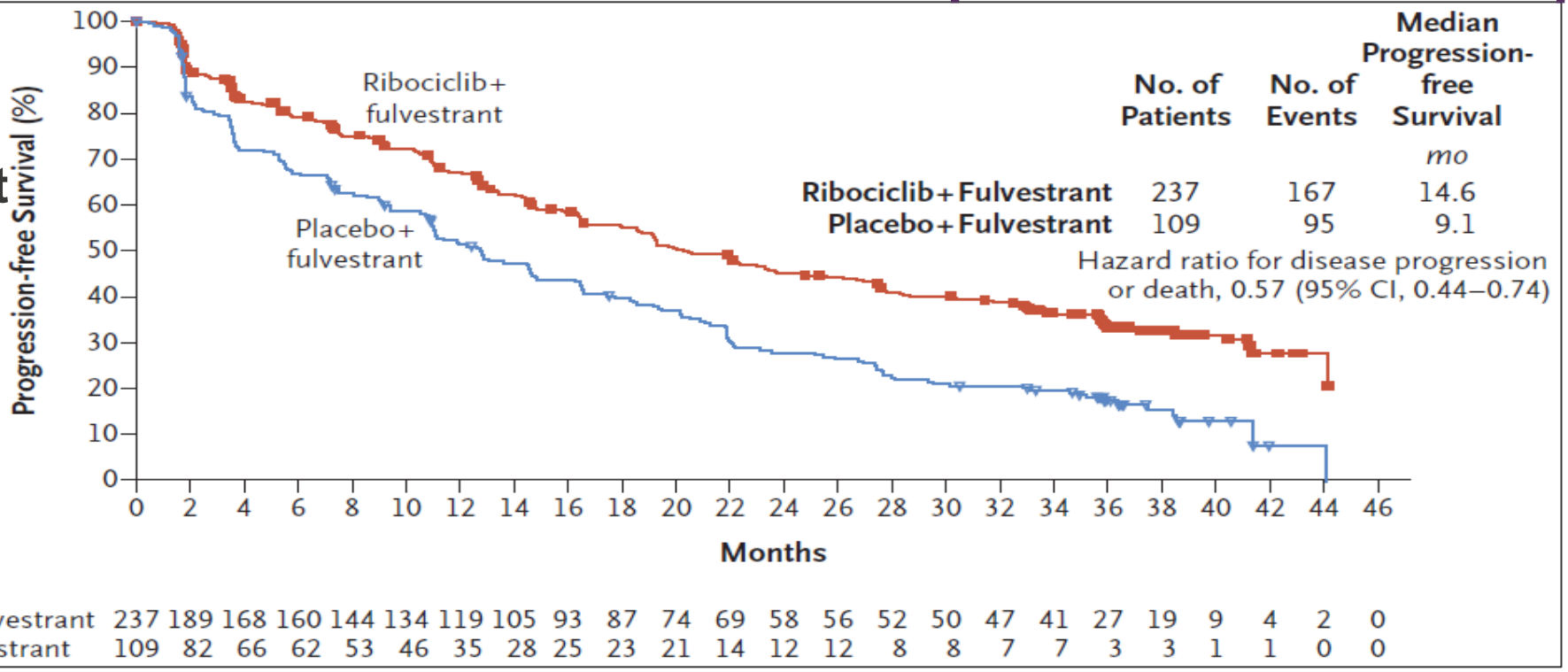
MONALEESA-3: PFS subpopulation B

End of 2017 data cut

End of 2019 data cut

New data since TA593

2019 data cut



OS data reached trial end point but remains immature (ERG Issue 1)

- Immaturity of overall survival (OS) data was key uncertainty in TA593
- MONALEESA-3: in CDF: ongoing data collection
  - Trial stopped early when **in full population** "The one-sided stratified log-rank test p value (0.00455) crossed the prespecified O'Brien-Fleming stopping boundary to claim superior efficacy"
  - Median OS reached and ribociclib statistically significantly better for **full population** (trial not statistically powered for subpop B)
- ERG: OS more mature, but remains somewhat immature
  - median OS only just reached and upper bound confidence intervals not estimable
- Approach to OS data in cost-effectiveness model:
  - Pre-technical engagement – not used (post progression survival used instead)
  - Post-technical engagement – used

- **Has OS uncertainty been addressed?**

SACT data collection

- Public Health England provided SACT (Systemic Anti-Cancer Therapy) dataset report on patients who received ribociclib plus fulvestrant
  - Data collected between 17 July 2019 and 16 January 2020
  - 187 received treatment
  - Mean follow-up time of 3.7 months
  - 75% remained on treatment
- Not used in the model

Cost-effectiveness evidence

Key issues

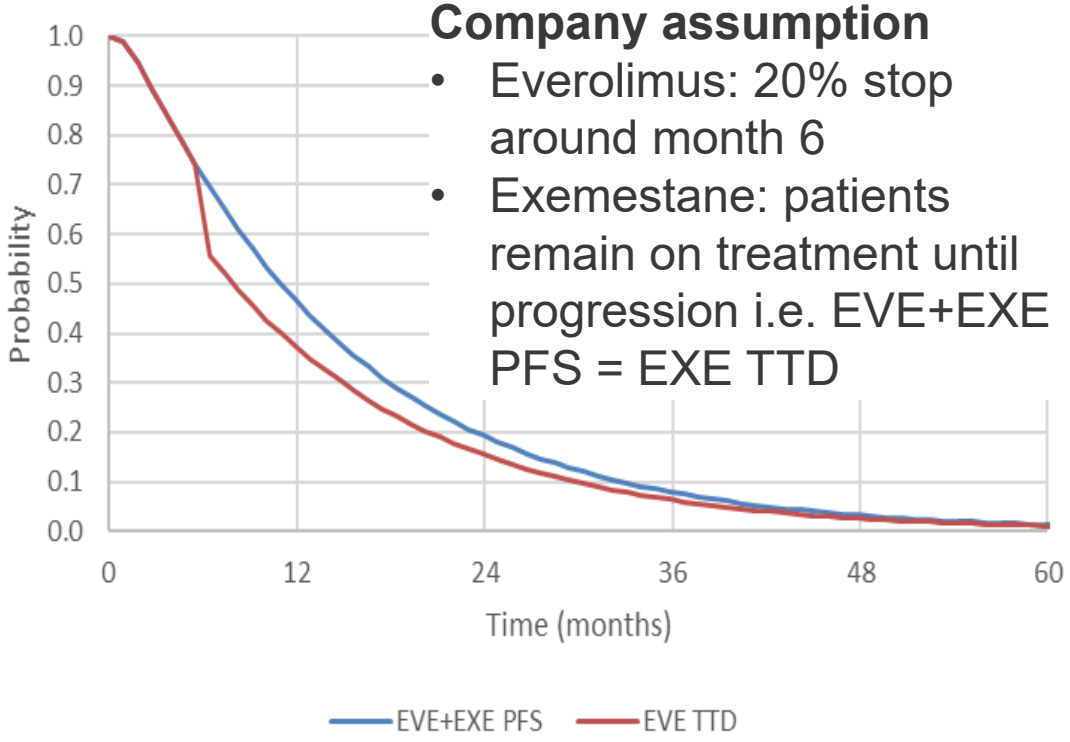
- Time to treatment discontinuation for everolimus
  - Company and ERG agree that patients stop treatment with everolimus before disease progression, because of tolerability. How long do people remain on treatment in clinical practice?
  - Which is most clinically valid source to inform this assumption: expert opinion or BOLERO-2 trial?
- Which curve should be used for OS extrapolation; Weibull, or Gompertz?
- Proportional hazards are violated in BOLERO-2 trial (exemestane vs everolimus trial, used for comparator PFS), therefore alternative approaches explored
  - Which approach generates the most plausible assumptions, Bucher NMA or fractional polynomials? If fractional polynomials are the most appropriate, which approach is the most valid?

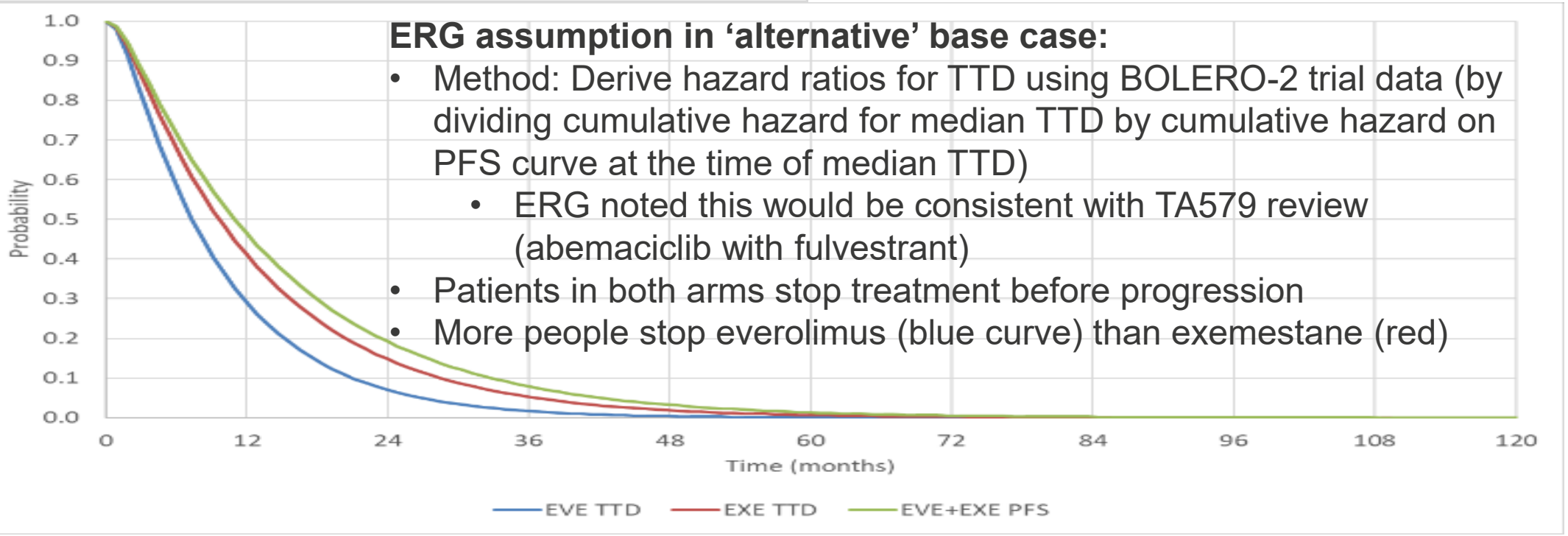
TTD exemestane and everolimus (ERG issue 3)

- Company originally assumed all patients continued everolimus until disease progression
- In clinical practice many patients stop treatment or reduce dose due to tolerability
- Company revised this to assuming some people stop or reduce everolimus, using ERG clinical expert opinion:
  - 20% discontinue everolimus at month 6
  - 70% of those continuing at month 6 reduce dose from 10 mg daily to 5 mg daily
- Company also used an off-treatment utility value
- ERG agreed with the spirit of these changes, but identified a further alternative method using trial data
- See next slide for visual representation of TTD

Should clinical expert opinion or BOLERO-2 data be used to inform TTD?

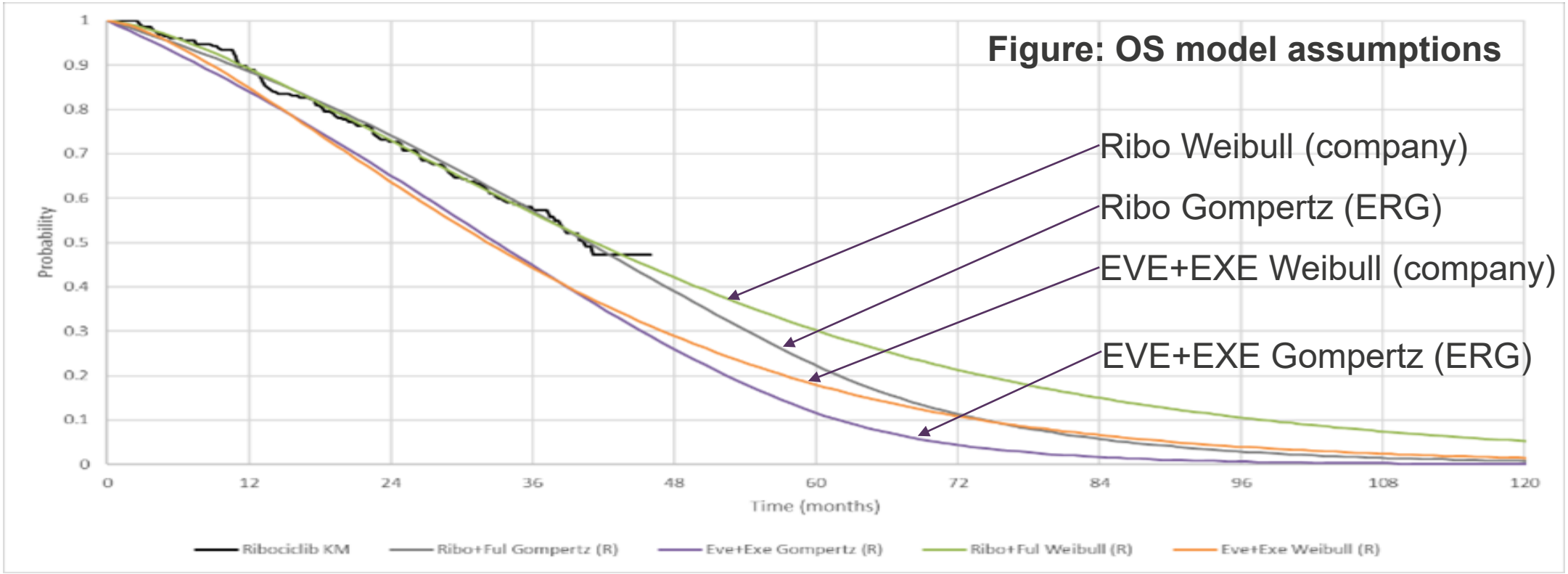
TTD exemestane and everolimus (ERG issue 3)





Including OS in the model (ERG Issue 4)

- Company changed model structure to allow use of trial OS data, as requested by ERG
- Company selected Weibull to extrapolate ribociclib OS (applying a HR to curve to derive comparator)
- ERG preferred Gompertz for both, based on :
  - Clinical expert opinion
  - Heavy censoring present at end of KM curve from MONALEESA-3
  - Gompertz is another PH model with good fit statistics
  - Gompertz is jointly fitted model which has better visual fit to MONALEESA-3 fulvestrant arm



- **Which curve gives the most relevant OS extrapolation assumptions?**

Proportional hazards violated for PFS (ERG Issue 5)

- Modelling of PFS in indirect comparison between ribociclib plus fulvestrant vs exemestane plus everolimus is source of uncertainty
- Committee noted in TA593 that proportional hazards was violated for PFS in NMA (where a Bucher NMA had been used)
- In response, in post-CDF submission, company used alternative approach to Bucher, instead using fractional polynomial (FP) models
- FP models used for continuous covariate models where relationships may be non-linear

Proportional hazards violated for PFS (ERG issue 5)

- Company presented various first order and second order FP NMAs
- Used second order FP in new base case. However ERG state:
  - Company's estimates highly uncertain (95% credible intervals overlap)
  - Company uses informed prior in FP NMA for fulvestrant 500mg derived from MONALEESA-3. Methodologically inappropriate.
- Therefore ERG conducted its own first and second order FP analyses, with informed prior removed. It found:
  - First order models provide broadly similar results to Bucher NMA
  - Best statistical fit for company and ERG analyses are second order models with highly uncertain results
  - ERG prefers second order, where there is more rapid drop in PFS compared with first order, and difference between treatment arms is smaller
- ERG concluded:
  - All NMAs presented (Bucher and FP NMAs) suggest a numerical (but non-statistically significant) benefit in PFS for ribociclib vs comparator
  - Therefore, likely to be some benefit – but magnitude uncertain
  - In light of uncertainty, company should revert back to more conservative NMA used in initial base case (Bucher NMA)
  - Several scenarios varying PFS NMA presented to explore impact of varying this assumption

Which method is most appropriate? Use FP NMA, or revert back to Bucher NMA?

Company and ERG base case assumptions

Base case includes:

- Updated Nov 2019 data cut MONALEESA-3, using partitioned survival model (PSM)
- Updated prices for ribociclib and fulvestrant
- Utility values for PFS now based on whether patient is on or off treatment

Table: Company base case assumption and scenario analyses using ERG alternative

Assumption	Company	ERG
ERG issue 3: TTD everolimus	Expert opinion	BOLERO-2 (as 'alterative' base case)
ERG issue 4: OS extrapolation ribociclib	Weibull	Gompertz
ERG issue 5: PFS source	FP NMA	Bucher NMA