NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (CDF review TA579) [ID2727]

Committee Papers

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CANCER DRUGS FUND REVIEW

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (CDF review TA579) [ID2727]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1		Breast Cancer Now	Breast Cancer Now welcomes the opportunity to comment on this NICE ACD. We are incredibly disappointed that NICE has provisionally been unable to recommend abemaciclib with fulvestrant for routine use on the NHS following its time on the Cancer Drugs Fund (CDF). This treatment combination provides an extremely valuable option for patients with hormone receptor positive, HER2 negative, secondary breast cancer after prior endocrine (hormone) therapy. It will be deeply concerning and a step backwards in the treatment options available for this group of patients if the issues identified in the ACD cannot be resolved sufficiently during the consultation period to ultimately result in a positive recommendation in the FAD. We are also concerned about the disparity of access across the UK that will result if this provisional decision is not reversed, with the treatment being routinely available in Scotland and therefore an option available to clinicians and patients but not across the rest of the UK. With reference to 3.10 and the committee concluding that all the ICERs were higher than what NICE considers a cost-effective use of NHS resources, we urge Lilly UK, NICE and NHS England to work together to see if the cost-effectiveness of abemaciclib with fulvestrant could be improved so that it can be made routinely available on the NHS.	Thank you for your comments. The recommendation has changed since the ACD was issued, following a second committee discussion and abemaciclib plus fulvestant is now recommended as a treatment option. The committee considered the value of abemaciclib to patients in its decision-making. See sections 3.1, 3.2 and 3.12 of the FAD.
2		Breast Cancer Now	*Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* We believe that it remains clear that there is a group of patients living with incurable secondary breast cancer that could benefit from this treatment option. We welcome the confirmation in the ACD that the Committee concluded that there is a population that could benefit from abemaciclib with fulvestrant being routinely available. We want to reiterate that there will continue to be a group of	Thank you for your comment. The committee considered the population that could benefit from abemaciclib plus fulvestrant treatment. The committee also discussed exemestane plus everolimus as the comparator. See sections 3.1 and 3.2 of the FAD.

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			patients whose disease progresses on or within 12 months of neoadjuvant or adjuvant hormone therapy who are not eligible for CDK 4/6 inhibitors with aromatase inhibitors in the NHS. Furthermore, there is a group of patients who may start on hormone therapy alone as their first line treatment and their disease may progress slowly but their next option could be abemaciclib with fulvestrant. It is crucial this remains a treatment option for patients in the future. Whilst several areas of uncertainty have been identified by the committee, it would be very concerning if collectively these issues could not be resolved sufficiently to enable a positive recommendation for routine commissioning on the NHS. Abemaciclib with fulvestrant has correctly been compared to exemestane with everolimus, however, we would like to reiterate that in some cases this can be sub-optimal for patients given the toxicities and needing to reduce the dose or stop everolimus. In the first appraisal of this treatment, clinical experts suggested its use may therefore be limited in clinical practice. The introduction of CDK 4/6 inhibitors into NHS practice has been hugely welcomed and we urgently need to ensure there is a choice of clinically-effective treatments routinely available on the NHS, at a price the NHS can afford.	Section 3.10 of the FAD discusses that people may spend a shorter time taking exemestane plus everolimus than the people in BOLERO-2 did. The decreasing use of exemestane plus everolimus is described in section 3.12 of the FAD.
3		Breast Cancer Now	Since this provisional decision was announced, another CDK 4/6 inhibitor– ribociclib in combination with fulvestrant – has been approved for routine use on the NHS following its time on the CDF. Whilst this is welcome news, we reiterate our comments made in earlier submissions and the committee meeting regarding the different side effect profiles and that one CDK 4/6 inhibitor may suit a patient better than another one – which is crucial both for quality of life but also compliance with taking the medication. For example, whilst a less common side effect, ribociclib can cause a change in the way a person's heart beats. Both before and during treatment, a patient will have an ECG and sometimes treatment may be delayed or the dose reduced if tests show any problems with a patient's heart. Ribociclib with fulvestrant may not be a suitable option for patients with an existing heart condition. Therefore, having a range of treatments options is key. We are pleased that the ACD references that the Committee concluded that "having a choice of treatments….is valued by people…". We would reiterate the point that we highlighted as patient expert, alongside the clinical expert - the	Thank you for your comment. The committee considered the different side effect profiles of CDK 4/6 inhibitors and having a choice of treatment options, see sections 3.1 – 3.3, 3.12 of the FAD. Thank you for providing statements from patients. The importance of having a choice of CDK 4/6 inhibitors to patients has been emphasised in section 3.3 of the FAD.

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			importance of having a choice of CDK 4/6 inhibitors because they have different-side effect profiles and people can change to a different option if needed (within the framework of the criteria set out in the BlueTeq form). We are concerned that this provisional decision would limit the options available for clinicians to discuss with their patients and we are concerned the importance of this and the impact on quality of life may not have been given enough weighting in the decision-making process. We would ask for reassurances that the assessment has taken into account the full value that this treatment option can provide? One patient told us: "I have been on this combo since October 2019 and have been stable currently with no evidence of active cancer. My oncologist said people can stay on this for several years. I previously tried ribociclib for a month and this made me ill with vomiting and low white cells. It is a great shame that abemaciclib is not considered cost effective as I think it is gentler than both ribociclib and palbociclib. I feel I am very lucky to be on abemaciclib and am concerned that it will be stopped altogether in the future. Self funding is not an option for most people."	
4		Breast Cancer Now	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* In regards to 3.3, we would like the Committee to explore whether there is a more flexible approach to the uncertainty identified between the pre-amendment and post-amendment groups, given there is still improvement in efficacy which is crucial for this patient group. We understand the Committee has an important role in looking at what is used in clinical practice and that whether the pre or post amendment group is used can impact on the cost-effectiveness estimates. However, we would suggest it is not uncommon to see dose reductions across all CDK 4/6 inhibitors, yet we still hear from patients the benefits they are receiving from the treatments. In particular, we would like to see the clinical community's views explored and considered further. For example, the clinical expert explained that they would not expect the efficacy of abemaciclib to differ between the 150mg and 200mg doses and that in clinical practice, outcomes with the 2 doses would be similar. The clinical expert also went on to explain that a higher dose for a short time at the start of treatment was not likely to confer a long-term advantage, because CDK4/6 inhibitors work through long-term suppression of tumour growth. What further consideration will the Committee	Thank you for your comment. Please note that some of the section numbering was updated from the ACD to the FAD. The committee considered the doses associated with the pre- and post-amendment populations, as well as the effects on overall survival and progression-free survival, see sections 3.4, 3.5, 3.7 and 3.8 of the FAD. Although the post amendment data remained the preferred, the committee took into account the uncertainty around the reasons for different results in the two datasets in its decision making. See section 3.12 of the FAD.

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			give to this advice? In response to 3.4, we are pleased that further data collection has confirmed the previous progression-free survival results and that updated data from MONARCH 2 showed that abemaciclib with fulvestrant statistically significantly improved overall survival compared with placebo plus fulvestrant in the full trial population. Whilst the Committee's preferred assumption is that the improvement in overall survival was less certain in the post-amendment group data, from a patient perspective we would like to reiterate that any improvement in overall survival is significant for this group of patients. Clinical experts during the appraisal highlighted that in their clinical practice they have seen the direct impact of this treatment combination, including delaying chemotherapy use and longer periods of disease control and overall survival. The supporting patient quotes we have included at the end of this consultation also highlight the impact this treatment combination is having on the lives of patients. Whilst we understand that the Committee's preferred assumption is impacting on the cost-effectiveness estimates, we would like to emphasise that for patients living with incurable secondary breast cancer, any improvement in progression free survival and overall survival is highly valued. It can mean more quality time to spend with their relatives and friends. One patient told us: "I am grateful all the time for the 14 months so far of brilliant quality life that I have been given by this combination of drugs." Another patient told us: "I've been on abemaciclib with fulvestrant for 6 months, having previously received hormone treatment. I feel this treatment is effective and in fact from scans I know that the tumours are reducing. It is an easy treatment, I pitch up at hospital every 4 weeks to get the injection and a new prescription of abemaciclib. I find the side effects are minimal and I have a good quality of life." Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. Any improvement in PFS or OS can also have a positive impact on patients' emotional wellbeing and mental health as well as that of their friends and family. This treatment combination can also delay the use of chemotherapy and the debilitating side effects that this can be associated	

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			with. We are pleased that the Committee concluded that “having a choice of treatments that extend how long people live before their disease progresses and delay chemotherapy is valued by people.”	
5		Breast Cancer Now	Please note, the ACD does not fully reflect what I said about exemestane with everolimus and instead focuses on a comment regarding chemotherapy. In particular, some patients may not tolerate this treatment and there may be a discussion about changing the dose or stopping the everolimus part of this treatment combination and therefore its use being limited in some circumstances in clinical practice.	Thank you for your comment. The committee discussed the effects of exemestane and everolimus as a treatment, see sections 3.2 and 3.10 of the FAD.
6		Breast Cancer Now	We would welcome the opportunity to return to the next Committee meeting for this appraisal and would urge the Committee to consider this. Can you please confirm whether the patient and clinical expert will be invited to the second Committee meeting?	Thank you for your comment. Patient and clinical experts were invited to the second committee meeting.
7		Breast Cancer Now	Since this draft decision was announced, we have been contacted by over 60 people concerned about this, with a number patients wanting to share their experience of this treatment. Whilst they understand this provisional decision will not impact on their own treatment, they feel extremely strongly about what this could mean for this group of patients with secondary breast cancer in the future. Please see comments from patients below that we would like to see considered by the Committee:	Thank you for providing statements from patients. The committee considered all patient perspectives on side effects/benefits of abemaciclib plus fulvestrant compared with other treatment options when making its recommendations.
8		Breast Cancer Now	“I am currently receiving abemaciclib with fulvestrant, (I commenced this in March 2020) and I understand it has been provisionally rejected for routine use on the NHS. I am appalled at this decision as it has worked very well for me and I would like future patients to receive this combination of drugs to help them combat the disease. Since last March I have had some significant shrinkage as a direct result of being on this treatment and I am so grateful to be having it. It is bad enough to receive a diagnosis of INCURABLE but to know that there are treatments like this to help is such a relief. This treatment is a lifeline to being able to live with this devastating disease and it offers a good quality of life. Please do all you can to ensure that this regime of treatment is available to future patients. I, along with many other patients depend on this treatment which gives hope for the future."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the benefits of abemaciclib plus fulvestrant when making its recommendations.
9		Breast Cancer Now	“I have been on this treatment for 18 months. There are side effects but can be managed by diet. I have kept well and it was my last option before chemotherapy. I felt very lucky to have been able to have this treatment.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.

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10		Breast Cancer Now	“I’m currently on abemaciclib and fulvestrant, First line treatment for 15 months for lung nodule secondaries. Few side effects, on 100 mg.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
11		Breast Cancer Now	"I've been on abemaciclib with fulvestrant for 6 months, having previously received hormone treatment. I feel this treatment is effective and in fact from scans I know that the tumours are reducing. It is an easy treatment, I pitch up at hospital every 4 weeks to get the injection and a new prescription of abemaciclib. I find the side effects are minimal and I have a good quality of life. At the beginning, following blood test results I did have a dose reduction. I do feel that this treatment appears to be a very effective treatment for many people, it results in minimal disruption to life and the frequency of appointments is less than other alternatives. Having previously received chemotherapy, this option delays having to receive that again and having to spend much more time at hospital and the associated hair loss.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
12		Breast Cancer Now	“I've been on this treatment, for secondary breast cancer, since 2019 and have been stable all that time. I received abemaciclib due to it being offered, for free, by the drug manufacturer directly to my hospital. It could be given to secondary breast cancer patients on compassionate grounds. The offer from Lilly came at exactly the right time for me, as I needed a new treatment right away. So I was given fulvestrant first for 2 cycles then the abemaciclib was added as soon as it became available to the hospital. It is a drug with some unpleasant side effects, namely the diarrhoea and stomach problems it causes, which were debilitating at first. However, following two dose reductions over the 22 months I've been taking it, I have learnt to live with the side effects. I am grateful for the reasonable quality time this drug combination has given me. My tumour markers are now rising so there may have to be a rethink for me. But I would hate for other people not to be allowed to give this treatment a go.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/ benefits of abemaciclib plus fulvestrant when making its recommendations.
13		Breast Cancer Now	“I would like to just say I've been on this combination now since April 2020. Up to now my cancer has shrunk considerably on my last two CT scans. For me, up to now this treatment is working and I hope it will continue working for me. I'm so grateful to be on this treatment and I feel that people should be offered it as a treatment for them. It does say it won't affect people who are already on it which I am so very very grateful. Please give people the chance to be able to go on this wonderful drugs if they are suitable to them.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the benefits of abemaciclib when making its recommendations.
14		Breast Cancer Now	“I have been on this combination for just over a year and it’s working wonders at keeping me stable. I am able to function sufficiently on a day to day basis and continue to be mum to my two children on my own.”	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side

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				effects/benefits of abemaciclib plus fulvestrant and the need for multiple CDK 4/6 treatment options when making its recommendations.
15		Breast Cancer Now	"I was diagnosed with breast cancer back in 2004 and did very well on Letrozole for many years, controlling bone mets too. Mets to liver found in 2019. Had chemo in October 2019. Rapid spread soon after and my oncologist was at a loss as to what treatment options I had left as I had liver damage. I've been on abemaciclib and Faslodex (fulvestrant) since June last year and my liver mets and CA15-3 levels are reducing nicely and I feel very well. It truly has been a life saver for me".	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
16		Breast Cancer Now	"I have been on it since Sept 19 and have found it to be very doable. I have extensive bone mets which have been kept stable and pleural mets which have gone thanks to this treatment. I am still on the max 150mg dose. I have found the side effects to be minimal and work full time as a teaching assistant in a primary school. This should continue to be available on the NHS. Everyone deserves the best treatments available."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
17		Breast Cancer Now	"I did receive this treatment from May 2019 to June 2020. My cancer had progressed to my liver and so I was moved onto this. At the time palbociclib was not available to secondary patients for second line treatment but not long afterwards it was. I must admit I struggled a bit on this treatment whereas the ones on palbociclib seemed to do better. The abemaciclib had to be taken everyday without a break whereas palbociclib patients get a break. I also had pretty bad tummy problems with bad diarrhoea and an extremely sore mouth. It did keep things stable (no reduction) for 9-12 months but then my CT scan show a rapid progression in my liver. The only benefit I could really see to this drug over palbociclib was that I didn't get a low blood count whereas many palbociclib patients do. However, I have been at this over 6 years and never had a low blood count even on chemotherapy. I think we should have as many treatment options as possible as what suits one person will not suit another. I have been very lucky so far".	Thank you for sharing your experience of abemaciclib plus fulvestrant and of palbociclib. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations. It also took into account the importance to patients of having multiple treatment options.
18		Breast Cancer Now	"I was fortunate to be prescribed it under CDF in August 2019. My tumour markers have fallen every month since, fungating ulcerating wound dried up and effusions not visible on last scan August 2020. This regime has been a game changer for me, given me a quality of life I had not expected and I urge NICE to review their decision".	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the benefits of abemaciclib plus fulvestrant when making its recommendations.
19		Breast Cancer Now	"I have had breast cancer on and off for 23 years, two primary cancers (including the loss of use of my right hand and arm) and was finally diagnosed with secondary breast cancer in my right lung in 2018. I was prescribed Tamoxifen and then Capecitabine, both of which my cancer eventually became resistant to.	Thank you for sharing your experience of abemaciclib plus fulvestrant and deciding between treatment options. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its

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			Then Vinorelbine which didn't work at all, meaning more spread of my cancer. At this point my cancer markers had shot up to 350. I was given the choice of Abemaciclib and Fulvestrant or IV Chemotherapy. I didn't want to lose my hair again and chose the Abemaciclib/Fulvestrant treatment. I celebrate every day now that I made that choice. Even on the reduced dose of 100mg the spread of my cancer and symptoms have been reduced or made stable and the cancer markers have reduced each cycle, down to 67 (and still falling). Also, I feel 'normal' and I am able to live life to the full with my husband and children. I haven't needed any hospital admissions and my fingers on my right hand are no longer blistering and infected, cutting costs to the NHS. I am devastated that other women could potentially not be offered a treatment I know works so well".	recommendations.
20		Breast Cancer Now	"Getting the diagnosis was very hard, on myself and my family, but the situation was helped somewhat by the speed of diagnosis, and the start of my treatment, Fulvestrant and Abemaciclib. The treatment is not without side effects, but the overriding knowledge that what could be done was being done, was life affirming, and helped me make tentative plans for after lockdown. We hear all the time that great progress is being made in the treatment of breast cancer - we need to be making the most of these developments".	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
21		Breast Cancer Now	"Treatment with abemacicib and fulvestant was started in September 2019 . The first CT scan in December 2019 showed " reduction in size of mediastinal lymph node mass and stable liver and bone lesions ". Every 3 monthly scan to date shows stable disease. I have been on this treatment for 1 year and 5 months with minimal side effects , I have an active and enjoyable life. It has been fantastic for my husband and children to see me so well . To be able to see my 4 small grandchildren grow gives me immeasurable quality of life."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
22		Breast Cancer Now	"I have been on this treatment for over a year now of which it had replaced the previous treatment I was on. It has allowed me to carry on with my life living it to the best of my ability. And to continue working for my company of which I have been there for 33 years. I do have side effects but these I can cope with to be able to just live. The thought of taking this treatment away and not having life prolonged would be devastating."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
23		Breast Cancer Now	"I have been on this combo since October 2019 and have been stable currently with no evidence of active cancer. My oncologist said people can stay on this for several years. I previously tried Ribociclib for a month and this made me ill with vomiting and low white cells. It is a great shame that Abemaciclib is not considered cost effective as it is gentler than both Ribociclib and palbociclib. I feel I am very lucky to be on abemaciclib and am concerned that it will be stopped altogether in the future. Self funding is not an option for most people."	Thank you for sharing your experience of abemaciclib plus fulvestrant and of ribociclib. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations. It also took into account the importance to patients of having multiple treatment options.
24		Breast	"I have been having treatment with abemaciclib and fulvestrant for 15 months	Thank you for sharing your experience of

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		Cancer Now	now. It has been a lifeline and freed me from having blood transfusions and intravenous chemotherapy. I have stage 4 breast cancer which metastasised on my bones and since August 2019 has spread to my bone marrow. This treatment has given me another year and counting to spend time enjoying my family and even though lockdown has prevented me from participating in a lot of things, my cancer treatment has not."	abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
25		Breast Cancer Now	"As a current user of this treatment myself I find this news very disappointing and distressing. This treatment is working very well on me. I have only been on it for 6 months but already it has reduced the lesions in my liver significantly to the point of no longer being visual by scan and stabilised the cancer in my bones with no further growth detected. The side effects of this drug are minimal giving full quality of life and my immune system has not been compromised which is saving money in the long run as I do not need any other medication for any other symptoms. I do not understand how a cost can be put on a person's life at all and I feel that if this drug is working and can significantly help reduce the growth of cancer in cancer patients then surely this will save money as these patients will not require other treatments. This drug has been a god send to me, I feel normal and not like a cancer sufferer, I can get on with my life with hardly any disruption, just a couple of injections once per month which is nothing compared to the other treatments out there. Taking a pill every day and injections once per month is a breeze compared to how disabling other treatments can be and gives me my life back, which is priceless. Please do not discontinue this drug on the NHS as so many other cancer sufferers can benefit from this drug and in the long run, I believe, save money for the NHS."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
26		Breast Cancer Now	"I have never taken abemaciclib however it could potentially be an option for me in the future. The fact that this treatment may not be available to me or other people with SBC could be devastating. When you are diagnosed with SBC you cling on to every positive story you can - you even try and 'read' your radiographer's face when you have finished a scan to see if they're looking positive. The good results I have read about this drug gives people hope and if that's a line of treatment that's taken away from us then hope is gone.	Thank you for sharing your experience. The committee took into account the benefits of abemaciclib plus fulvestrant and the importance to patients of having multiple treatment options when making its recommendation.

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			To add, if this drug is available privately and not on the NHS then that's a further kick in the teeth to those that couldn't afford it. Imagine knowing that those who can access this drug privately and potentially thriving while you are going through progression and possibly approaching end of life because you can't afford it?"	
27		Breast Cancer Now	"I've been on this treatment since November 2019 when it became apparent that other drugs were no longer working to keep my cancer stable. I was diagnosed with metastatic breast cancer in April 2018 and after chemotherapy was prescribed tamoxifen. I was on it for just over a year and endured the side effects because we thought it was working. Once my consultant changed my treatment to include abemaciclib it improved my quality of life. To date the side effects are negligible."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
28		Breast Cancer Now	"In 2019 I had a further recurrence which has been treated since August 2019 with Abemaciclib and Fulvestrant. My breast tumour began to shrink within weeks of beginning this treatment and this was confirmed by CT scans and surgery in July 2020 which showed only slight trace remains of the tumour. Throughout this treatment I have remained very well, with only slight side effects which have had very little affect on my day to day life. I was dismayed to read of the provisional recommendation by NICE not to recommend Abemaciclib and Fulvestrant for routine use. I do understand that the treatment I am receiving is very expensive but in my experience it is effective and provides a very good quality of life for patients who are receiving it. I feel very lucky to be receiving these drugs and to hear that in future women may be denied them feels wrong and extremely upsetting."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
29		Breast Cancer Now	"I commenced Fulvestrant and Abemaciclib in Feb 2019 (continuing with Zoladex and Denosumab). I feel really well and to date have had no particular side effects from this treatment. I know I am very lucky to be on these drugs which are a compassionate supply. It is very disappointing and distressing to think of others who may be missing out on this incredibly positive treatment and I would urge NICE to rethink their decision."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
30		Breast Cancer Now	"I was very sad to read that this combination of drugs has not been authorised for use. I was diagnosed with secondary breast cancer in March 2019 with mets in liver & numerous bones at 47 years (My primary diagnosis & treatment was just a year before) Abemaciclib & Fulvestrant were my first drugs & I continued on them for 19 months. The side effects very manageable & I was able to carry on with all my normal activities. My liver mets were healing at my first scan & I had no active cancer in my liver after 6 months. That has remained the same. My bone mets had a partial response & healed in places but in October 2020 I had a couple of new spots on my spine so I am now on Capecitabine with good	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.

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			results so far. I am shocked that this treatment will not be offered."	
31		Breast Cancer Now	"I was diagnosed in 2012 with secondary breast cancer, having had breast cancer in 1998 and 2000. I was put on exemestane but in 2019 it was discovered it was no longer effective. In September 2019, I was offered fulvestrant with abemeciclib and I felt, and still do, that it is my lifeline. It has, to date, worked very well, my scans show everything stable. I would be devastated if the medication was withdrawn - I have such confidence in its ability to keep my cancer stable. I did have a few side effects but once a dose that suited me was found everything was great. I was told by oncology that the best treatment was to have the abemeciclib along with fulvestrant as results were really good. I do feel very strongly that such a brilliant treatment should be offered to everyone that meets the criteria for it - it's an important life line and should not be denied - it's risking people's lives!"	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
32		Breast Cancer Now	"I received my diagnosis in May 2019 and was advised I had incurable metastatic breast cancer. Following a multi-disciplinary meeting with my medical team, it was decided that the most effective treatment would be abemaciclib with Fulvestrant. I have secondary breast cancer and have been on the combination of Abemaciclib with Fulvestrant 19 months, with no progression. I strongly believe this should be an option for all women with secondary breast cancer. In the 19 months I have been on it, I have had a good quality of life and I have been living with dignity. As the treatment is not invasive, it is very doable and it needs to be made available on the NHS, so it is an option for everyone."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
33		Breast Cancer Now	"I've been on this treatment for 3 months now. I tried Ribociclib and Palbociclib but my liver reacted badly to these. It's early days for me on the Abema but I am very happy to say that so far all is going well and my 3 month scan showed significant tumour reduction."	Thank you for sharing your experience of ribociclib, palbociclib and abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant and the importance to patients of having multiple treatment options when making its recommendation.
34		Breast Cancer Now	"I was put on Abemaciclib and Fulvestrant in July 2019. In addition to this I swapped from Zometa to Denosumab in the Autumn of 2019. This is my second line of treatment and follows a Letrozole/Zometa combo that I had been on since diagnosis of breast cancer in December 2016. I find the drug to be much kinder to me than the Letrozole was, and even attended a gym 4 days a week before lockdown. This was nothing short of amazing, considering the fatigue and joint pain I had had with Letrozole which stopped me from walking more than very short distances. The only side effect I have had is stomach acid which we control using Lansoprazole and Kolanticon Gel. I have never had to miss a dose because of poor blood results. I understand that the aim of treatment of Stage 4 Breast Cancer patients is to optimise quality of life. These drugs have certainly	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			achieved this for me."	
35		Breast Cancer Now	"I've been taking the combo of Abemaciclib tablets & Fulvestrant injections since October 2019. I have found the combination of these drugs along with pain killers I take (pregablin & paracetamol) has helped a lot with pain management & quality of life. Prior to taking these drugs it felt like someone was constantly stood on my spine in heels. These days it's more just a dull background pain, which for me is amazing. I initially had side effects taking the 150mg of Abemaciclib, it set my IBS off & ended up in hospital a few times (apparently diarrhoea is quite common- it just also flared my IBS off) Once they reduced the dose to 100mg I've been a lot better. I think it'll be devastating if other patients aren't allowed access to these drugs, as it'll mean more premature deaths unnecessarily. Even if it can extend the lives of a handful of patients, surely that is worth it!'	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
36		Breast Cancer Now	"I have secondary breast cancer and have had Fulvestrant and Abemaciclib since May 2019. This combination has stopped my cancer from progressing and enabled me to live an active life so far."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
37		Breast Cancer Now	"I am on hormone treatment - letrozole and 4 weekly denosamub injections since being diagnosed 4 and a half years ago. I heard with dismay that NICE have provisionally rejected the use of abemaciclib with fulvestrant for treatment of secondary breast cancer as it is deemed not a cost effective use of NHS money. For someone who's been on first line treatment for 4 and half years, this combination was likely to be my next option. So what next?"	Thank you for sharing your experience and consideration of treatment options. The committee took into account the importance to patients of having multiple treatment options when making its recommendations.
38		Breast Cancer Now	"I have been on this treatment regime for 2.5 years and I'm in really good shape! Completely independent and active. Side effects are very manageable."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
39		Breast Cancer Now	"My mother started this drug in January 2020 after the first line treatment of hormone therapy and radiotherapy hadn't worked and the cancer spread from the lymph nodes to the spine. For the last year there has been some shrinkage and no further progression and apart from tiredness and a little diarrhoea initially which was almost instantly cured by having a week break from the 150 mg tablets of Abemaciclib and then resuming on 100mg. The side effects are now minimal and include tiredness and a lack of energy and she is able to enjoy life to the full and spending time with her 6 young grandchildren who love her dearly. This drug has given us so much hope that the cancer can be managed and surpassing the terrifying 5 year survival statistic is possible."	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
40		Breast	"I was prescribed Albemaciclib and Faslodex in October. My oncologist said I	Thank you for sharing your experience of

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
		Cancer Now	had to start on the full dose - this was the rule. I managed 10 days and then I was really ill managing to eat one piece of toast in three days and suffering from diarrhoea etc. After a consult with my oncologist the dose was lowered to 100mg. Although I didn't suffer from diarrhoea and sickness my appetite disappeared altogether. I couldn't cope with this either as I was underweight to begin with. The dose was lowered to 50mg and I have now taken the drug for a month without trouble. I had a scan on the 26 January and only just got the results which say the disease is stable. My previous scan in October showed some progression so this feels OK."	abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.
41		Breast Cancer Now	"In October 19 when I was told that the tamoxifen treatment was no longer working and there had been further spread of the mets; I was frightened and concerned about what the next treatment would be. I was so relieved and pleased to hear that the abemaciclib / fulvestrant treatment had been approved as a second line treatment for women like me. Despite the long list of side effects I have been able to carry on my normal life almost without alteration, I am working, I can be physically active and I feel really well. I don't look or feel like a cancer patient, I feel like myself and that is worth everything. I know it is expensive treatment, but I have been grateful every day that it has been made available to me. I have three daughters, the youngest of whom was only 17 when I was diagnosed with secondaries. She was full of fear that she was going to lose her Mum; and while she has come to terms with things pretty well – it has been a huge comfort to me to still be her normal Mum, and not a very ill woman. It means that the time I have had, and continue to have, is such good quality life – it doesn't feel like a slow slide to my death; it's a proper 100% life. While I look and actually am really well, those around me, particularly my youngest girl and my elderly parents, are comforted. They are able to treat me normally (mostly) and that's fantastic all round. Any stage 4 person will tell you that having to manage other people's distress, however much they try to hide it, is just about the worst thing. I am grateful all the time for the 14 months so far of brilliant quality life that I have been given by this combination of drugs. I am enormously grateful to the NHS for everything they do for me. I am sad that my life will be shorter than I had always imagined, but the months and years I have is 'proper-time', well-time. It's real life. I have had side effects at various times, but I haven't ever been ill – I haven't had one day where I've needed to be in bed. For the first couple of weeks I got very tired and had to go bed early. Sometimes I still suddenly feel tired, but most days I don't experience that. When I'd been on the	Thank you for sharing your experience of abemaciclib plus fulvestrant and its side effects. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			treatment for 3 months, I started experiencing diarrhoea which obviously isn't lovely; but weirdly it didn't feel like a tummy upset and I didn't feel ill. I just didn't want to be far from a loo! The acute phase of that lasted a few weeks and I took the meds I'd been given (like immodium) if it ever got a bit much. Anyway after that we were in lockdown for the first time and I never have been far from my own bathroom… Occasionally that will return for a day or 2, but it has been fine not debilitating. In the last few months I have lost most of my hair – it was a slow process, and of course I did struggle with that when I realised it was happening. On the other hand, I could appreciate the drug was building up in my system and there were bound to be some toxic side effects. I wear a wig now, and mainly that's fine. That by far has been the most difficult thing; but it's still a brilliant trade off – my good life for my hair. Before they slightly reduced the abemaciclib there had been a couple of blood tests where the liver function thing was too high, and the white blood cells were too low. I missed one month's worth of injections, and had 2 weeks holiday from all the medicines. Since then and the lower dose I have felt fine and my bloods have been fine. When I got the email from Breast Cancer Now about the provisional NICE decision, I was so upset. I understand that it won't effect me; but I am so sad for the women coming after me. I know how difficult it is to accept that your life is going to be shorter and to face an uncertain future. This treatment option has given me more than a year so far of just fantastically well life. It honestly makes me so sad to think that other women might not have that. I feel immense empathy for the people at NICE who have to make impossible decisions; but I really hope there is a way to overturn this decision perhaps with the help of the drugs company who manufacture the drugs."	
42		Breast Cancer Now	"Having begun my current regime on Abemaciclib and Fulvestrant five months back after treatment with palbociclib both my oncologist and I are pleased with progress. Within three months the primary tumour had begun to shrink and cancer activity in my body had reduced. Now, five months in, the initial tumour is barely palpable and my tumour markers are down. Without abemaciclib, together with Fulvestrant, I suspect that I would have been treated with potentially less successful and possibly more invasive drugs and would have missed out on what, from my perspective, has been a valuable medication for delaying the spread of my secondary breast cancer. It would be very disappointing indeed if other women in my position in the future	Thank you for sharing your experience of abemaciclib plus fulvestrant. The committee considered all patient perspectives on the side effects/benefits of abemaciclib plus fulvestrant when making its recommendations. The committee also took into account the importance to patients of having multiple treatment options when making its recommendations.

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			were deprived of treatment with Abemaciclib, since it is a useful alternative to Palbociclib which I understand NICE has approved for use by the NHS - why limit the use of this alternative? It makes no sense and seems extremely unjust."	
43		Eli Lilly & Company Ltd	**EXECUTIVE SUMMARY** Lilly is disappointed with the draft decision to not recommend abemaciclib in combination with fulvestrant which, if maintained, would mean that this regimen would no longer be available to patients. Abemaciclib in combination with fulvestrant would represent a valuable addition to the treatment armamentarium, providing patients and clinicians with a greater choice of treatment options that can be used in place of exemestane in combination with everolimus. Lilly have provided a response which focusses on areas of uncertainty that were identified by the appraisal committee, and provides further comments with regard to clinical and cost-effectiveness. Specifically: • The use of only the subgroup data from MONARCH 2 • The most appropriate method to model time to discontinuation for abemaciclib in combination with fulvestrant • The most appropriate method to model time to discontinuation for exemestane in combination with everolimus Lilly have also proposed a revised patient access scheme price for abemaciclib of [redacted] (a discount of [redacted] from list price) per 28-day treatment cycle.	Thank you for your comment. The committee considered abemaciclib in combination with fulvestrant as an additional treatment option, see sections 3.2 and 3.3 of the FAD. Thank you for responding to the areas of uncertainty described in the ACD. The response is given to each as they are raised below.
44		Eli Lilly & Company Ltd	**Use of the post-amendment data in MONARCH 2 to assess the clinical and cost-effectiveness of abemaciclib with fulvestrant** The committee noted that data from the post-amendment subgroup of patients from MONARCH 2 should be used to estimate the clinical and cost-effectiveness of abemaciclib plus fulvestrant. Lilly accepts this decision for the purposes of this appraisal and have used the committee's preference in the revised cost-effectiveness analyses presented throughout this response. However, Lilly would like to clarify a misunderstanding of the MONARCH 2 trial design. Despite increasing the number of enrolled patients, the calculation of required number of PFS events (n=378) determining the power for the primary analysis was based on ITT population. There was no additional requirement for	Thank you for your comment and for providing analyses applying the committee's preferred modelling assumptions. Section 3.4 of the FAD has been updated to state that the sample size calculations for the postamendment population were based on safety outcomes rather than progression-free survival

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			PFS events in a subgroup, as evident from the Statistical Analysis Plan.[1] In contrast to the ERG's suggestion, the protocol was updated to increase the number of enrolled patients in order to describe the safety of abemaciclib in this subgroup. [redacted] and clinical expert opinion sought by Lilly stated that it was not appropriate to analyse these subgroups separately. Disregarding the intention-to-treat population does not reflect the intention of the MONARCH 2 trial or the totality of the available evidence. Therefore, Lilly does not agree that it is appropriate to disregard the ITT population when considering the efficacy of abemaciclib in combination with fulvestrant.	The unresolved uncertainty around the differences in clinical effectiveness estimates from the post amendment and ITT populations were taken into account in decision making (see section 3.12 of the FAD)
45		Eli Lilly & Company Ltd	**<u>Time to treatment discontinuation for abemaciclib plus fulvestrant</u>** The appraisal committee noted that the most appropriate modelling approach to estimate time to treatment discontinuation for abemaciclib plus fulvestrant was uncertain. Lilly believes that a hazard ratio of [redacted] represents the most plausible assumption, because it relies on the intention-to-treat population and is consistent with the Evidence Review Group's preferred approach that was used to calculate a hazard ratio of 1.58 for everolimus. However, Lilly acknowledges the committee's preferred assumptions, as well as the Evidence Review Group's concern with visual fit between clinical data and modelled time-on-treatment. To address this concern, Lilly considered a range of alternatives between post-amendment progression free survival and time to discontinuation. Using a lognormal extrapolation, in line with the Evidence Review Group's preferred assumptions, Lilly conducted a range of scenario analyses of hazard ratios between progression-free survival and time to discontinuation using a restricted mean survival time analysis. • 54 months – hazard ratio: [redacted] • 70 months – hazard ratio: [redacted] • 90 months – hazard ratio: [redacted] • 110 months – hazard ratio: [redacted]	Thank you for your comment. The committee considered the different estimates of time to treatment discontinuation for abemaciclib plus fulvestrant, see section 3.9 of the FAD.

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			• 120 months – hazard ratio: [redacted] The hazard ratio only varies slightly, gradually moving from [redacted] to [redacted] as the time horizon increases from the follow-up length of MONARCH-2 (54 months) up towards an extended duration of 120 months (10 years). Of note, a lifetime extrapolation approach results in a hazard ratio of [redacted] between progression-free survival and time to discontinuation, as reported in the technical engagement response. Lilly proposes that there is sufficient certainty to say that the most reasonable hazard ratio to estimate time to discontinuation for abemaciclib with fulvestrant lies between a range of [redacted] and [redacted]. A hazard ratio of [redacted] is considered in the company's revised base case analysis, while a conservative scenario analysis is considered using the hazard ratio of [redacted] that was observed when restricting the mean survival time to 54 months, the duration of the Kaplan-Meier data available for the post-amendment population. A scenario analysis using the lifetime extrapolation hazard ratio of [redacted] has also been considered.	
46		Eli Lilly & Company Ltd	**<u>Time to treatment discontinuation for exemestane plus everolimus</u>** The appraisal committee noted that the appropriate modelling approach for time to treatment discontinuation for exemestane plus everolimus was uncertain. Lilly notes that in the recently published final appraisal document for ribociclib in combination with fulvestrant [ID1318][2], the appraisal committee considered two different methods for estimating time to treatment discontinuation, which were also proposed in Lilly's technical engagement response: • Using summary data from BOLERO-2 to estimate the hazard ratios for stopping exemestane plus everolimus (equal to a hazard ratio of 1.58) • A scenario based on clinical expert opinion, where 20% of patients stop everolimus at Month 6. Of the patients continuing everolimus, 70% reduce their dose at Month 6 from 10 mg daily to 5 mg daily (Lilly has calculated that that scenario for total discounted costs is equivalent to a hazard ratio of approximately [redacted]) Lilly notes that in the aforementioned recently published final appraisal, the appraisal committee "agreed that the time to stopping everolimus is likely to be between clinical opinion, and the Evidence Review Group's model using BOLERO-2 data".	Thank you for your comment. The committee considered the different estimates of time to treatment discontinuation for exemestane plus everolimus, see section 3.10 of the FAD.

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			Consequently, Lilly estimates that the hazard ratio for the time to treatment discontinuation for everolimus lies between the two hazard ratios of [redacted] and 1.58. This assumption aligns with the appraisal committee's preference in the recently published final appraisal document for ribociclib in combination with fulvestrant [ID1318].[2] In addition, Lilly proposes an approach to determine the relationship between progression-free survival and time to treatment discontinuation for everolimus based on the properties of the exponential distribution. **Restricted mean survival time analysis** • Restricted mean survival time analysis can be used to estimate a relationship between progression-free survival and exposure to everolimus in BOLERO-2. • Lilly calculated the monthly rate for progression-free survival and exposure and implemented this as an extrapolation. • As can be seen in [Figure 1, based on visual inspection alone, this choice seems reasonable. • Using restricted mean survival time analysis at 30 months following the initiation of treatment (in line with the duration of the Kaplan-Meier data available from BOLERO-2), the hazard ratio between progression free survival and time to discontinuation of everolimus is approximately [redacted]. • Sensitivity analyses where the time is restricted at earlier months in the KM curve result in ratios that tend towards [redacted] at month 6. • Sensitivity analysis where the time is restricted at later months in the KM curve result in ratios that tend towards [redacted] **[Figure 1 has been removed from this table – see the ACD response for more info]** • Lilly believes that a hazard ratio of [redacted] between progression free-survival and time to discontinuation of everolimus represents an appropriate approach for the revised base case cost-effectiveness analysis • Lilly notes that this hazard ratio of [redacted] appears to align with the appraisal committee's preference in the ribociclib in combination with	

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			fulvestrant final appraisal document, lying between the clinical expert opinion scenario ([redacted]) and the Evidence Review Group's model using data from BOLERO-2 (1.58). It is also aligned with expert opinion sought by the Evidence Review Group stating that patients discontinue everolimus at a greater rate compared to abemaciclib	
47		Eli Lilly & Company Ltd	**<u>Updated Cost-Effectiveness Analyses</u>** Lilly presents a revised company base case, accommodating the committee's preferred assumptions: • A hazard ratio of [redacted] between progression free survival and time to discontinuation for abemaciclib with fulvestrant has been adopted as in the base case analysis. A scenario considering a conservative hazard ratio of [redacted] has also been considered • A hazard ratio of [redacted] between progression-free survival and time to discontinuation of everolimus • A revised patient access scheme price for abemaciclib of [redacted] (a discount of [redacted] from list price) per 28-day treatment cycle. • The fulvestrant list price has been used in the revised base case cost-effectiveness analysis. A range of scenarios considering discounted fulvestrant rebate prices have also been considered (**Error! Reference source not found.**) • Removed half-cycle correction (in line with the committee's preferred assumption) The revised base-case deterministic and probabilistic cost-effectiveness analyses are presented in Appendix 1. Lilly have conducted scenarios varying the rebate price of fulvestrant due to the loss of exclusivity of fulvestrant; the availability of generics means that the price of fulvestrant is likely to decrease further in the future. Additionally, Lilly have conducted a scenario considering the administration cost associated with fulvestrant injections, assuming a lower cost as fulvestrant becomes more routinely used within the National Health Service and injections move towards a more efficient method of administration by community nurse specialists, rather than in hospitals. These scenarios are presented in Appendix 1. In conclusion, Lilly believes the plausible scenarios demonstrate that	Thank you for your comment. The committee considered the updated cost-effectiveness analyses presented by the company. The cost-effectiveness results are discussed in 3.12 of the FAD. The scenario analysis on fulvestrant administration costs have also been considered by the committee and discussed in section 3.11 of the FAD.

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			abemaciclib with fulvestrant is a cost-effective use of NHS resources as compared to exemestane with everolimus and is therefore suitable to be recommended for routine commissioning.	
48		United Kingdom Breast Cancer Group (UKBCK)	The NICE Appraisal Consultation Document (ACD) for Abemaciclib with Fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy was discussed at the executive committee of the United Kingdom Breast Cancer Group (UKBCK) on February 12th. UKBCG were concerned that the preliminary recommendation was based on an unplanned subgroup analysis of the trial population in the Monarch 2 clinical trial which tested the combination based on patients enrolled after a protocol amendment which reduced the Abemaciclib dose from 200 mg twice daily to 150 mg twice daily. This protocol amendment was made to reduce the toxicity of the treatment, in particular with respect to diarrhoea. Although the change in dose could lead to some uncertainty about how well the drug might work in clinical practice, there is clear supporting evidence for the lower dose from the Monarch 3 trial which tested the use of Abemaciclib at a dose of 150 mg bd in combination with an aromatase inhibitor. The Hazard ratio in favour of Abemaciclib vs. placebo of 0.54 in this trial was entirely consistent with the effect seen in the intention to treat population in the Monarch 2 trial with Abemaciclib with fulvestrant and validates 150 mg bd as an effective dose of the drug.	Thank you for your comment. The committee considered the effects of doses in the trial populations but concluded the reason for the different estimates of clinical effectiveness was unclear. See section 3.4, 3.5 and 3.8 of the FAD.
49		UKBCG	UKBCG noted that Fulvestrant with Ribociclib has been approved by NICE. In the Ribociclib plus Fulvestrant FAD it is stated that “There are no trials directly comparing ribociclib plus fulvestrant against exemestane plus everolimus. But an indirect comparison suggests that ribociclib plus fulvestrant may be the more effective option for people who have already had hormone therapy”. This use of an indirect comparator does not appear to be a barrier to the positive recommendation for ribociclib plus fulvestrant, but is inconsistent with the interpretation in the Abemaciclib ACD which states that “There is also uncertainty because there is no evidence directly comparing abemaciclib plus fulvestrant with exemestane plus everolimus. An indirect comparison suggests that people having abemaciclib plus fulvestrant have longer before their disease progresses and live longer than people having exemestane plus everolimus”. The view of the UKBCG is that there is a class effect and the three CDK 4/6 inhibitors appear to perform in a similar way in endocrine sensitive and resistant	Thank you for your comment. The text in the “why the committee made these recommendations” section has been updated in the FAD and the text “there is also uncertainty because there is no evidence directly comparing abemaciclib plus fulvestrant with exemestane plus everolimus” has been deleted.

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			disease as evidenced by the remarkable consistency of hazard ratios in favour of the drugs in all of the scenarios that have been tested. This opinion is independently corroborated by the latest iteration of the ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5, Cardoso et al. Ann Oncol: 31;12, 1623-1649, 2020) which gave the same ESMO-MCBS (Magnitude of Clinical Benefit Scale) scores for all 3 of the CDK 4/6 inhibitors in the endocrine resistant setting. On that basis, UKBCG felt that it would be desirable to be able to use Abemaciclib in combination with Fulvestrant as an alternative to the other CDK4/6 inhibitors as this allows more flexible management of side effects. There is no budget impact to the NHS if clinicians are able to choose what they believe to be the most appropriate CDK4/6 inhibitor in combination with Fulvestrant for each patient, giving the ability to offer individualised treatment recommendations and optimise side effect management.	The committee considered the use of abemaciclib plus fulvestrant as an alternative treatment in order to allow flexible management of side effects, see sections 3.2, 3.3 and 3.12 of the FAD.
50		Sanofi UK	We have no comments to add to this appraisal consultation document.	Noted.
51		Pfizer	No comments.	Noted.
52	Web comment		There is a population who could benefit from abemaciclib plus fulvestrant Secondary breast cancer can be treated but it cannot be cured. Treatments aim to control and slow down the disease to enable patients to have the best possible quality of life for as long as possible. We will be undertaking two studies that look at quality of life. Make 2nds Count is funding the largest study of secondary breast cancer patients and clinical trials in the UK with Warwick University. We aim to survey over 3,000 secondary breast cancer patients with a focus on clinical trials and quality of life. The study is vital to understand patients own experience so we can address gaps in information and participation in trials and treatment. The needs of every patient with secondary breast cancer are unique – no treatment works the same. It's essential there is more research funded, to extend trials and improve personalised treatment. And also, to better understand and increase the quality of life for those affected by the disease. We will be happy to share the findings with NICE in 12 months time. Three years before a further review is too long and treatment and trials have already been severely delayed by Covid-19. The average life expectancy of a patient with secondary breast cancer is 3 to 5 years, so this delay will have a	Thank you for your comment and for highlighting the studies that you will be undertaking. The committee considered the view that there is a population that can benefit from abemaciclib plus fulvestrant treatment and took into account the need for multiple treatment options, see sections 3.1 to 3.3 of the FAD.

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			direct impact on patients, which the consultations refers to, who could benefit from abemaciclib plus fulvestrant.	
53	Web comment		I am a SBC patient who is ER+ HER2- and these drugs could extend my life to see my daughter grow up. Our lives matter and we deserve all treatment lines as an option. Your research stated: An indirect comparison suggests that people having abemaciclib plus fulvestrant have longer before their disease progresses and live longer than people having exemestane plus everolimus. Are we not worth this extra time. I was misdiagnosed for 2 years and as a result I have extensive secondary mets.	Thank you for your comment. The committee considered patient perspectives on the benefits of abemaciclib plus fulvestrant compared with exemestane plus everolimus and the value of having multiple treatment options available. The recommendations were updated following the second committee discussion.
54	Web comment		My friend in the USA was on Ibrance & fulvestrant for 2 years, when this stopped working she was then on Xeloda for a year. She is now on verzenio/Albemaciclib with no fulvestrant for a year and is keeping things under control. I have MBC with widespread mets to bones, liver and lungs. I was diagnosed in May 2018, I've been on Ibrance & letrozole for 2 years, an oral SERD trial for 3 months & now on Xeloda. I've been extremely grateful to be on these meds and I've never had IV chemo in my life, nor do I want it. I'm so hoping the next treatment I can try is Verzenio/Abemaciclib before any IV chemo. I've worked very hard all my life & paid tax & nhs contributions for over 40 years. I'm now 58 and hoping for a few years extra quality of life. Why should the nhs deem me not cost effective.... I really want to remain under the nhs for their excellent care but may now have to pay privately to try this drug or ask Lilly for help. Please, please reconsider - imagine it was you who needed to try this drug.	The committee considered patient perspectives on the benefits of abemaciclib plus fulvestrant compared with exemestane plus everolimus and the value of having multiple treatment options available. The recommendations were updated following the second committee discussion

NICE National Institute for Health and Care Excellence

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 5 March 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly & Company Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

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Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**EXECUTIVE SUMMARY** Lilly is disappointed with the draft decision to not recommend abemaciclib in combination with fulvestrant which, if maintained, would mean that this regimen would no longer be available to patients. Abemaciclib in combination with fulvestrant would represent a valuable addition to the treatment armamentarium, providing patients and clinicians with a greater choice of treatment options that can be used in place of exemestane in combination with everolimus. Lilly have provided a response which focusses on areas of uncertainty that were identified by the appraisal committee, and provides further comments with regard to clinical and cost-effectiveness. Specifically: • The use of only the subgroup data from MONARCH 2 • The most appropriate method to model time to discontinuation for abemaciclib in combination with fulvestrant • The most appropriate method to model time to discontinuation for exemestane in combination with everolimus Lilly have also proposed a revised patient access scheme price for abemaciclib of £[redacted] (a discount of [redacted] from list price) per 28-day treatment cycle.
2	**Use of the post-amendment data in MONARCH 2 to assess the clinical and cost-effectiveness of abemaciclib with fulvestrant** The committee noted that data from the post-amendment subgroup of patients from MONARCH 2 should be used to estimate the clinical and cost-effectiveness of abemaciclib plus fulvestrant. Lilly accepts this decision for the purposes of this appraisal and have used the committee's preference in the revised cost-effectiveness analyses presented throughout this response. However, Lilly would like to clarify a misunderstanding of the MONARCH 2 trial design. Despite increasing the number of enrolled patients, the calculation of required number of PFS events (n=378) determining the power for the primary analysis was based on ITT population. There was no additional requirement for PFS events in a subgroup, as evident from the Statistical Analysis Plan.[1] In contrast to the ERG's suggestion, the protocol was updated to increase the number of enrolled patients in order to describe the safety of abemaciclib in this subgroup. [redacted] and clinical expert opinion sought by Lilly stated that it was not appropriate to analyse these subgroups separately.

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	Disregarding the intention-to-treat population does not reflect the intention of the MONARCH 2 trial or the totality of the available evidence. Therefore, Lilly does not agree that it is appropriate to disregard the ITT population when considering the efficacy of abemaciclib in combination with fulvestrant.
3	**Time to treatment discontinuation for abemaciclib plus fulvestrant** The appraisal committee noted that the most appropriate modelling approach to estimate time to treatment discontinuation for abemaciclib plus fulvestrant was uncertain. Lilly believes that a hazard ratio of [redacted] represents the most plausible assumption, because it relies on the intention-to-treat population and is consistent with the Evidence Review Group's preferred approach that was used to calculate a hazard ratio of 1.58 for everolimus. However, Lilly acknowledges the committee's preferred assumptions, as well as the Evidence Review Group's concern with visual fit between clinical data and modelled time-on-treatment. To address this concern, Lilly considered a range of alternatives between post-amendment progression free survival and time to discontinuation. Using a lognormal extrapolation, in line with the Evidence Review Group's preferred assumptions, Lilly conducted a range of scenario analyses of hazard ratios between progression-free survival and time to discontinuation using a restricted mean survival time analysis. • 54 months – hazard ratio: [redacted] • 70 months – hazard ratio: [redacted] • 90 months – hazard ratio: [redacted] • 110 months – hazard ratio: [redacted] • 120 months – hazard ratio: [redacted] The hazard ratio only varies slightly, gradually moving from [redacted] to [redacted] as the time horizon increases from the follow-up length of MONARCH-2 (54 months) up towards an extended duration of 120 months (10 years). Of note, a lifetime extrapolation approach results in a hazard ratio of [redacted] between progression-free survival and time to discontinuation, as reported in the technical engagement response. Lilly proposes that there is sufficient certainty to say that the most reasonable hazard ratio to estimate time to discontinuation for abemaciclib with fulvestrant lies between a range of [redacted] and [redacted]. A hazard ratio of [redacted] is considered in the company's revised base case analysis, while a conservative scenario analysis is considered using the hazard ratio of [redacted] that was observed when restricting the mean survival time to 54 months, the duration of the Kaplan-Meier data available for the post-amendment population. A scenario analysis using the lifetime extrapolation hazard ratio of [redacted] has also been considered.
4	**Time to treatment discontinuation for exemestane plus everolimus** The appraisal committee noted that the appropriate modelling approach for time to treatment discontinuation for exemestane plus everolimus was uncertain. Lilly notes that in the recently published final appraisal document for ribociclib in combination with fulvestrant [ID1318][2], the appraisal committee considered two different methods for estimating time to treatment discontinuation, which were also proposed in Lilly's technical engagement response: • Using summary data from BOLERO-2 to estimate the hazard ratios for stopping exemestane plus everolimus (equal to a hazard ratio of 1.58) • A scenario based on clinical expert opinion, where 20% of patients stop everolimus at Month 6. Of the patients continuing everolimus, 70% reduce their dose at Month 6 from 10 mg daily to 5 mg daily (Lilly has calculated that that scenario for total discounted costs is equivalent to a hazard ratio of approximately [redacted])

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Lilly notes that in the aforementioned recently published final appraisal, the appraisal committee "agreed that the time to stopping everolimus is likely to be between clinical opinion, and the Evidence Review Group's model using BOLERO-2 data".

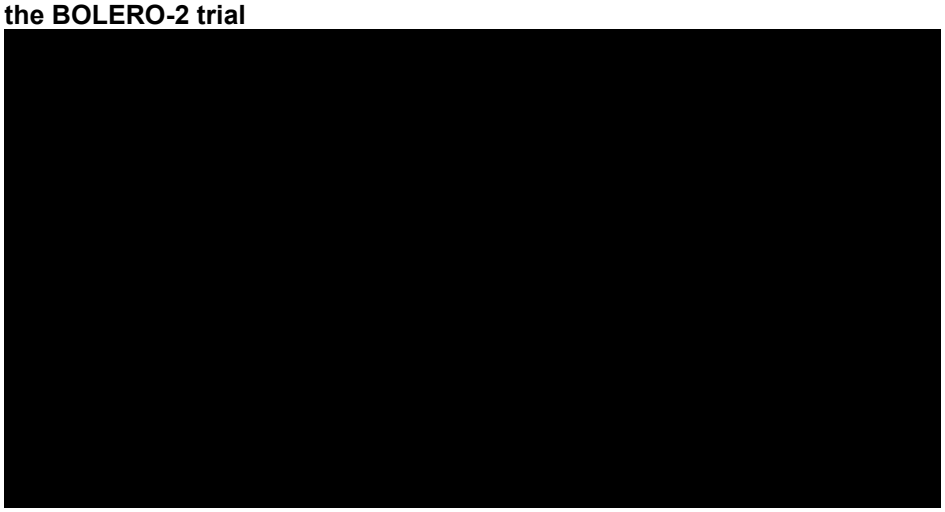
Consequently, Lilly estimates that the hazard ratio for the time to treatment discontinuation for everolimus lies between the two hazard ratios of [redacted] and 1.58. This assumption aligns with the appraisal committee's preference in the recently published final appraisal document for ribociclib in combination with fulvestrant [ID1318].[2]

In addition, Lilly proposes an approach to determine the relationship between progression-free survival and time to treatment discontinuation for everolimus based on the properties of the exponential distribution.

Restricted mean survival time analysis

- Restricted mean survival time analysis can be used to estimate a relationship between progression-free survival and exposure to everolimus in BOLERO-2.
- Lilly calculated the monthly rate for progression-free survival and exposure and implemented this as an extrapolation.
- As can be seen in Figure 1, based on visual inspection alone, this choice seems reasonable.
- Using restricted mean survival time analysis at 30 months following the initiation of treatment (in line with the duration of the Kaplan-Meier data available from BOLERO-2), the hazard ratio between progression free survival and time to discontinuation of everolimus is approximately [redacted].
- Sensitivity analyses where the time is restricted at earlier months in the KM curve result in ratios that tend towards [redacted] at month 6.
- Sensitivity analysis where the time is restricted at later months in the KM curve result in ratios that tend towards [redacted]

Figure 1: Exponential extrapolations for progression-free survival and exposure to everolimus in the BOLERO-2 trial



Abbreviations: EXE: exemestane; EVE: everolimus; PFS: progression-free survival.
Source: Lilly Data on File

- Lilly believes that a hazard ratio of [redacted] between progression free-survival and time to discontinuation of everolimus represents an appropriate approach for the revised base case cost-effectiveness analysis

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	• Lilly notes that this hazard ratio of [redacted] appears to align with the appraisal committee's preference in the ribociclib in combination with fulvestrant final appraisal document, lying between the clinical expert opinion scenario ([redacted]) and the Evidence Review Group's model using data from BOLERO-2 (1.58). It is also aligned with expert opinion sought by the Evidence Review Group stating that patients discontinue everolimus at a greater rate compared to abemaciclib
5	**Updated Cost-Effectiveness Analyses** Lilly presents a revised company base case, accommodating the committee's preferred assumptions: • A hazard ratio of [redacted] between progression free survival and time to discontinuation for abemaciclib with fulvestrant has been adopted as in the base case analysis. A scenario considering a conservative hazard ratio of [redacted] has also been considered • A hazard ratio of [redacted] between progression-free survival and time to discontinuation of everolimus • A revised patient access scheme price for abemaciclib of [redacted] (a discount of [redacted] from list price) per 28-day treatment cycle. • The fulvestrant list price has been used in the revised base case cost-effectiveness analysis. A range of scenarios considering discounted fulvestrant rebate prices have also been considered (**Error! Reference source not found.**) • Removed half-cycle correction (in line with the committee's preferred assumption) The revised base-case deterministic and probabilistic cost-effectiveness analyses are presented in Appendix 1. Lilly have conducted scenarios varying the rebate price of fulvestrant due to the loss of exclusivity of fulvestrant; the availability of generics means that the price of fulvestrant is likely to decrease further in the future. Additionally, Lilly have conducted a scenario considering the administration cost associated with fulvestrant injections, assuming a lower cost as fulvestrant becomes more routinely used within the National Health Service and injections move towards a more efficient method of administration by community nurse specialists, rather than in hospitals. These scenarios are presented in Appendix 1. In conclusion, Lilly believes the plausible scenarios demonstrate that abemaciclib with fulvestrant is a cost-effective use of NHS resources as compared to exemestane with everolimus and is therefore suitable to be recommended for routine commissioning.
	References 1. Eli Lilly. I3Y-MC-JPBL Statistical Analysis Plan Version 4. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without LY2835219, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer. Available at https://clinicaltrials.gov/ProvidedDocs/03/NCT02107703/SAP_005.pdf [accessed 05 March 2021], 2016. 2. National Institute for Health and Care Excellence (NICE). Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (CDF review of TA593) [ID3755]. Available at (https://www.nice.org.uk/guidance/indevelopment/gid-ta10675/documents) [accessed 02 March 2021]. 3. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2019. Available at https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ [accessed 26 February 2021].

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix 1: Revised Cost-Effectiveness Analyses

Base Case Cost-Effectiveness Results

Table 1: Updated company base case cost-effectiveness results (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Abemaciclib with fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Exemestane with everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

The probabilistic sensitivity analysis within the economic model has been corrected to properly account for variation in the restricted mean survival time. The results of the probabilistic analysis include 5,000 iterations of random combinations of beta1 and beta2 values for overall survival FP NMA, quantifying any uncertainty around the survival benefit of abemaciclib with fulvestrant versus everolimus in combination with exemestane in terms of total life years gained.

Lilly thanks the ERG for discovering an error in the values used in the PSA presented in the previous version of this response. The results from the updated PSA are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 2: Updated company base case cost-effectiveness results (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Exemestane with everolimus	[redacted]	[redacted]	[redacted]				
Abemaciclib with fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,038

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; NA: not applicable; QALY: quality-adjusted life year.

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Figure 2: Scatterplot of the probabilistic results for the company's updated base case analysis

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE; exemestane; FUL: fulvestrant; QALY: quality-adjusted life year.

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Scenario Analyses

Table 3: A summary of cost-effectiveness scenario analyses to evaluate the uncertainty around the time to discontinuation assumptions for abemaciclib with fulvestrant and everolimus with exemestane

		Approach to modelling time to discontinuation for abemaciclib with fulvestrant		
		Hazard ratio of [redacted]	**Hazard ratio of** [redacted]	**Hazard ratio of** [redacted]
Approach to modelling time to discontinuation for everolimus with exemestane	20% of patients discontinue everolimus at six months, 70% of patients remaining on treatment have a dose reduction (equivalent to a hazard ratio of [redacted])	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant
	Hazard ratio of [redacted] applied to progression-free curve for everolimus time to discontinuation, while exemestane is costed to disease progression	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant	**Revised Company Base Case** Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant
	Hazard ratio of 1.58 applied to the progression free survival curve, costing exemestane to disease progression	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: £35,639	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: £26,112	Incremental costs: Change from base case: [redacted] Incremental QALYs: Change from base case: [redacted] ICER: Dominant

Footnote: All incremental costs, QALYs and ICERs are presented for abemaciclib with fulvestrant versus exemestane with everolimus.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

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Table 4: A summary of additional cost-effective scenario analyses presented as part of this response

Scenario and cross reference	Scenario detail	ICER for abemaciclib with fulvestrant versus exemestane with everolimus
Base case	Not applicable	Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant
Fulvestrant discount price scenarios (all other assumptions are the same as the base case)		
Fulvestrant 50% discount	A 50% discount is applied to the drug acquisition cost of fulvestrant, resulting in a price of £262.21 per 28-day cycle.	Incremental costs: [redacted] Change from base case: Incremental QALYs: [redacted] Change from base case: ICER: Dominant
Fulvestrant 70% discount	A 70% discount is applied to the drug acquisition cost of fulvestrant, resulting in a price of £156.72 per 28-day cycle.	Incremental costs: [redacted] Change from base case: Incremental QALYs: [redacted] Change from base case: ICER: Dominant
Fulvestrant 80% discount	An 80% discount is applied to the drug acquisition cost of fulvestrant, resulting in a price of £104.48 per 28-day cycle.	Incremental costs: [redacted] Change from base case: Incremental QALYs: [redacted] Change from base case: ICER: Dominant

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Fulvestrant 85% discount	An 85% discount is applied to the drug acquisition cost of fulvestrant, resulting in a price of £78.36 per 28-day cycle.	Incremental costs: [redacted] Change from base case: Incremental QALYs: [redacted] Change from base case: ICER: Dominant
Fulvestrant administration cost price scenario (all other assumptions are the same as the base case)		
Community administration of fulvestrant injections	All fulvestrant injections are assumed to take place in the community, except for the initial loading dose. The cost associated with administration is assumed to equal to the cost of 15 minutes of Band 6 community nurse specialist time, of £11.50 per 28-day cycle.[3] This replaces the current prices for fulvestrant injections, which are based on TA496, which was published in 2018. Since that time, fulvestrant has become part of routine practice in the National Health Service. Consequently, it is reasonable to assume that this will result in increased efficiency and reduced costs associated with fulvestrant injections over time. It is unreasonable to suggest that a large proportion of patients will continue to attend a hospital appointment in order to receive fulvestrant. Consequently, Lilly believes it is reasonable to consider a scenario analysis where all fulvestrant injections are assumed to take place in the community, with the exception of the initial loading dose.	Incremental costs: [redacted] Change from base case: Incremental QALYs: [redacted] Change from base case: ICER: Dominant

Footnote: All incremental costs, QALYs and ICERs are presented for abemaciclib with fulvestrant versus exemestane with everolimus.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Breast Cancer Now welcomes the opportunity to comment on this NICE ACD. We are incredibly disappointed that NICE has provisionally been unable to recommend abemaciclib with fulvestrant for routine use on the NHS following its time on the Cancer Drugs Fund (CDF). This treatment combination provides an extremely valuable option for patients with hormone receptor positive, HER2 negative, secondary breast cancer after prior endocrine (hormone) therapy. It will be deeply concerning and a step backwards in the treatment options available for this group of patients if the issues identified in the ACD cannot be resolved sufficiently during the consultation period to ultimately result in a positive recommendation in the FAD. We are also concerned about the disparity of access across the UK that will result if this provisional decision is not reversed, with the treatment being routinely available in Scotland and therefore an option available to clinicians and patients but not across the rest of the UK. With reference to 3.10 and the committee concluding that all the ICERs were higher than what NICE considers a cost-effective use of NHS resources, we urge Lilly UK, NICE and NHS England to work together to see if the cost-effectiveness of abemaciclib with fulvestrant could be improved so that it can be made routinely available on the NHS.
2	*Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* We believe that it remains clear that there is a group of patients living with incurable secondary breast cancer that could benefit from this treatment option. We welcome the confirmation in the ACD that the Committee concluded that there is a population that could benefit from abemaciclib with fulvestrant being routinely available. We want to reiterate that there will continue to be a group of patients whose disease progresses on or within 12 months of neoadjuvant or adjuvant hormone therapy who are not eligible for CDK 4/6 inhibitors with aromatase inhibitors in the NHS. Furthermore, there is a group of patients who may start on hormone therapy alone as their first line treatment and their disease may progress slowly but their next option could be abemaciclib with fulvestrant. It is crucial this remains a treatment option for patients in the future. Whilst several areas of uncertainty have been identified by the committee, it would be very concerning if collectively these issues could not be resolved sufficiently to enable a positive recommendation for routine commissioning on the NHS. Abemaciclib with fulvestrant has correctly been compared to exemestane with everolimus, however, we would like to reiterate that in some cases this can be sub-optimal for patients given the toxicities and needing to reduce the dose or stop everolimus. In the first appraisal of this treatment, clinical experts suggested its use may therefore be limited in clinical practice. The introduction of CDK 4/6 inhibitors into NHS practice has been hugely welcomed and we urgently need to ensure there is a choice of clinically-effective treatments routinely available on the NHS, at a price the NHS can afford.
3	Since this provisional decision was announced, another CDK 4/6 inhibitor– ribociclib in combination with fulvestrant – has been approved for routine use on the NHS following its time on the CDF. Whilst this is welcome news, we reiterate our comments made in earlier submissions and the committee meeting regarding the different side effect profiles and that one CDK 4/6 inhibitor may suit a patient better than another one – which is crucial both for quality of life but also compliance with taking the medication. For example, whilst a less common side effect, ribociclib can cause a change in the way a person's

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	heart beats. Both before and during treatment, a patient will have an ECG and sometimes treatment may be delayed or the dose reduced if tests show any problems with a patient's heart. Ribociclib with fulvestrant may not be a suitable option for patients with an existing heart condition. Therefore, having a range of treatments options is key. We are pleased that the ACD references that the Committee concluded that "having a choice of treatments….is valued by people…". We would reiterate the point that we highlighted as patient expert, alongside the clinical expert - the importance of having a choice of CDK 4/6 inhibitors because they have different-side effect profiles and people can change to a different option if needed (within the framework of the criteria set out in the BlueTeq form). We are concerned that this provisional decision would limit the options available for clinicians to discuss with their patients and we are concerned the importance of this and the impact on quality of life may not have been given enough weighting in the decision-making process. We would ask for reassurances that the assessment has taken into account the full value that this treatment option can provide? One patient told us: "I have been on this combo since October 2019 and have been stable currently with no evidence of active cancer. My oncologist said people can stay on this for several years. I previously tried ribociclib for a month and this made me ill with vomiting and low white cells. It is a great shame that abemaciclib is not considered cost effective as I think it is gentler than both ribociclib and palbociclib. I feel I am very lucky to be on abemaciclib and am concerned that it will be stopped altogether in the future. Self funding is not an option for most people."
4	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* In regards to 3.3, we would like the Committee to explore whether there is a more flexible approach to the uncertainty identified between the pre-amendment and post-amendment groups, given there is still improvement in efficacy which is crucial for this patient group. We understand the Committee has an important role in looking at what is used in clinical practice and that whether the pre or post amendment group is used can impact on the cost-effectiveness estimates. However, we would suggest it is not uncommon to see dose reductions across all CDK 4/6 inhibitors, yet we still hear from patients the benefits they are receiving from the treatments. In particular, we would like to see the clinical community's views explored and considered further. For example, the clinical expert explained that they would not expect the efficacy of abemaciclib to differ between the 150mg and 200mg doses and that in clinical practice, outcomes with the 2 doses would be similar. The clinical expert also went on to explain that a higher dose for a short time at the start of treatment was not likely to confer a long-term advantage, because CDK4/6 inhibitors work through long-term suppression of tumour growth. What further consideration will the Committee give to this advice? In response to 3.4, we are pleased that further data collection has confirmed the previous progression-free survival results and that updated data from MONARCH 2 showed that abemaciclib with fulvestrant statistically significantly improved overall survival compared with placebo plus fulvestrant in the full trial population. Whilst the Committee's preferred assumption is that the improvement in overall survival was less certain in the post-amendment group data, from a patient perspective we would like to reiterate that any improvement in overall survival is significant for this group of patients. Clinical experts during the appraisal highlighted that in their clinical practice they have seen the direct impact of this treatment combination, including delaying chemotherapy use and longer periods of disease control and overall survival. The supporting patient quotes we have included at the end of this consultation also highlight the impact this treatment combination is having on the lives of patients. Whilst we understand that the Committee's preferred assumption is impacting on the cost-effectiveness estimates, we would like to emphasise that for patients living with incurable secondary

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	breast cancer, any improvement in progression free survival and overall survival is highly valued. It can mean more quality time to spend with their relatives and friends. One patient told us: “I am grateful all the time for the 14 months so far of brilliant quality life that I have been given by this combination of drugs.” Another patient told us: “I've been on abemaciclib with fulvestrant for 6 months, having previously received hormone treatment. I feel this treatment is effective and in fact from scans I know that the tumours are reducing. It is an easy treatment, I pitch up at hospital every 4 weeks to get the injection and a new prescription of abemaciclib. I find the side effects are minimal and I have a good quality of life.” Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. Any improvement in PFS or OS can also have a positive impact on patients’ emotional wellbeing and mental health as well as that of their friends and family. This treatment combination can also delay the use of chemotherapy and the debilitating side effects that this can be associated with. We are pleased that the Committee concluded that “having a choice of treatments that extend how long people live before their disease progresses and delay chemotherapy is valued by people.”
5	Please note, the ACD does not fully reflect what I said about exemestane with everolimus and instead focuses on a comment regarding chemotherapy. In particular, some patients may not tolerate this treatment and there may be a discussion about changing the dose or stopping the everolimus part of this treatment combination and therefore its use being limited in some circumstances in clinical practice.
6	We would welcome the opportunity to return to the next Committee meeting for this appraisal and would urge the Committee to consider this. Can you please confirm whether the patient and clinical expert will be invited to the second Committee meeting?
7	Since this draft decision was announced, we have been contacted by over 60 people concerned about this, with a number patients wanting to share their experience of this treatment. Whilst they understand this provisional decision will not impact on their own treatment, they feel extremely strongly about what this could mean for this group of patients with secondary breast cancer in the future. Please see comments from patients below that we would like to see considered by the Committee:
8	“I am currently receiving abemaciclib with fulvestrant, (I commenced this in March 2020) and I understand it has been provisionally rejected for routine use on the NHS. I am appalled at this decision as it has worked very well for me and I would like future patients to receive this combination of drugs to help them combat the disease. Since last March I have had some significant shrinkage as a direct result of being on this treatment and I am so grateful to be having it. It is bad enough to receive a diagnosis of INCURABLE but to know that there are treatments like this to help is such a relief. This treatment is a lifeline to being able to live with this devastating disease and it offers a good quality of life. Please do all you can to ensure that this regime of treatment is available to future patients. I, along with many other patients depend on this treatment which gives hope for the future."
9	“I have been on this treatment for 18 months. There are side effects but can be managed by diet. I have kept well and it was my last option before chemotherapy. I felt very lucky to have been able to have this treatment.”
10	“I’m currently on abemaciclib and fulvestrant, First line treatment for 15 months for lung nodule secondaries. Few side effects, on 100 mg.”
11	"I've been on abemaciclib with fulvestrant for 6 months, having previously received hormone treatment. I feel this treatment is effective and in fact from scans I know that the tumours are reducing. It is an easy treatment, I pitch up at hospital every 4 weeks to get the injection and a new prescription of abemaciclib. I find the side effects are minimal and I have a good quality of life.

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	At the beginning, following blood test results I did have a dose reduction. I do feel that this treatment appears to be a very effective treatment for many people, it results in minimal disruption to life and the frequency of appointments is less than other alternatives. Having previously received chemotherapy, this option delays having to receive that again and having to spend much more time at hospital and the associated hair loss."
12	"I've been on this treatment, for secondary breast cancer, since 2019 and have been stable all that time. I received abemaciclib due to it being offered, for free, by the drug manufacturer directly to my hospital. It could be given to secondary breast cancer patients on compassionate grounds. The offer from Lilly came at exactly the right time for me, as I needed a new treatment right away. So I was given fulvestrant first for 2 cycles then the abemaciclib was added as soon as it became available to the hospital. It is a drug with some unpleasant side effects, namely the diarrhoea and stomach problems it causes, which were debilitating at first. However, following two dose reductions over the 22 months I've been taking it, I have learnt to live with the side effects. I am grateful for the reasonable quality time this drug combination has given me. My tumour markers are now rising so there may have to be a rethink for me. But I would hate for other people not to be allowed to give this treatment a go."
13	"I would like to just say I've been on this combination now since April 2020. Up to now my cancer has shrunk considerably on my last two CT scans. For me, up to now this treatment is working and I hope it will continue working for me. I'm so grateful to be on this treatment and I feel that people should be offered it as a treatment for them. It does say it won't affect people who are already on it which I am so very very grateful. Please give people the chance to be able to go on this wonderful drugs if they are suitable to them."
14	"I have been on this combination for just over a year and it's working wonders at keeping me stable. I am able to function sufficiently on a day to day basis and continue to be mum to my two children on my own."
15	"I was diagnosed with breast cancer back in 2004 and did very well on Letrozole for many years, controlling bone mets too. Mets to liver found in 2019. Had chemo in October 2019. Rapid spread soon after and my oncologist was at a loss as to what treatment options I had left as I had liver damage. I've been on abemaciclib and Faslodex (fulvestrant) since June last year and my liver mets and CA15-3 levels are reducing nicely and I feel very well. It truly has been a life saver for me".
16	"I have been on it since Sept 19 and have found it to be very doable. I have extensive bone mets which have been kept stable and pleural mets which have gone thanks to this treatment. I am still on the max 150mg dose. I have found the side effects to be minimal and work full time as a teaching assistant in a primary school. This should continue to be available on the NHS. Everyone deserves the best treatments available."
17	"I did receive this treatment from May 2019 to June 2020. My cancer had progressed to my liver and so I was moved onto this. At the time palbociclib was not available to secondary patients for second line treatment but not long afterwards it was. I must admit I struggled a bit on this treatment whereas the ones on palbociclib seemed to do better. The abemaciclib had to be taken everyday without a break whereas palbociclib patients get a break. I also had pretty bad tummy problems with bad diarrhoea and an extremely sore mouth. It did keep things stable (no reduction) for 9-12 months but then my CT scan show a rapid progression in my liver. The only benefit I could really see to this drug over palbociclib was that I didn't get a low blood count whereas many palbociclib patients do. However, I have been at this over 6 years and never had a low blood count even on chemotherapy. I think we should have as many treatment options as possible as what suits one person will not suit another. I have been very lucky so far".
18	"I was fortunate to be prescribed it under CDF in August 2019. My tumour markers have fallen every month since, fungating ulcerating wound dried up and effusions not visible on last scan August 2020. This regime has been a game changer for me, given me a quality of life I had not expected and I urge NICE to review their decision".
19	"I have had breast cancer on and off for 23 years, two primary cancers (including the loss of use of my right hand and arm) and was finally diagnosed with secondary breast cancer in my right lung in 2018. I was prescribed Tamoxifen and then Capecitabine, both of which my cancer eventually became resistant to. Then Vinorelbine which didn't work at all, meaning more spread of my cancer.

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	At this point my cancer markers had shot up to 350. I was given the choice of Abemaciclib and Fulvestrant or IV Chemotherapy. I didn't want to lose my hair again and chose the Abemaciclib/Fulvestrant treatment. I celebrate every day now that I made that choice. Even on the reduced dose of 100mg the spread of my cancer and symptoms have been reduced or made stable and the cancer markers have reduced each cycle, down to 67 (and still falling). Also, I feel 'normal' and I am able to live life to the full with my husband and children. I haven't needed any hospital admissions and my fingers on my right hand are no longer blistering and infected, cutting costs to the NHS. I am devastated that other women could potentially not be offered a treatment I know works so well".
20	"Getting the diagnosis was very hard, on myself and my family, but the situation was helped somewhat by the speed of diagnosis, and the start of my treatment, Fulvestrant and Abemaciclib. The treatment is not without side effects, but the overriding knowledge that what could be done was being done, was life affirming, and helped me make tentative plans for after lockdown. We hear all the time that great progress is being made in the treatment of breast cancer - we need to be making the most of these developments".
21	"Treatment with abemacicib and fulvestant was started in September 2019 . The first CT scan in December 2019 showed " reduction in size of mediastinal lymph node mass and stable liver and bone lesions ". Every 3 monthly scan to date shows stable disease. I have been on this treatment for 1 year and 5 months with minimal side effects , I have an active and enjoyable life. It has been fantastic for my husband and children to see me so well . To be able to see my 4 small grandchildren grow gives me immeasurable quality of life."
22	"I have been on this treatment for over a year now of which it had replaced the previous treatment I was on. It has allowed me to carry on with my life living it to the best of my ability. And to continue working for my company of which I have been there for 33 years. I do have side effects but these I can cope with to be able to just live. The thought of taking this treatment away and not having life prolonged would be devastating."
23	"I have been on this combo since October 2019 and have been stable currently with no evidence of active cancer. My oncologist said people can stay on this for several years. I previously tried Ribociclib for a month and this made me ill with vomiting and low white cells. It is a great shame that Abemaciclib is not considered cost effective as it is gentler than both Ribociclib and palbociclib. I feel I am very lucky to be on abemaciclib and am concerned that it will be stopped altogether in the future. Self funding is not an option for most people."
24	"I have been having treatment with abemaciclib and fulvestrant for 15 months now. It has been a lifeline and freed me from having blood transfusions and intravenous chemotherapy. I have stage 4 breast cancer which metastasised on my bones and since August 2019 has spread to my bone marrow. This treatment has given me another year and counting to spend time enjoying my family and even though lockdown has prevented me from participating in a lot of things, my cancer treatment has not."
25	"As a current user of this treatment myself I find this news very disappointing and distressing. This treatment is working very well on me. I have only been on it for 6 months but already it has reduced the lesions in my liver significantly to the point of no longer being visual by scan and stabilised the cancer in my bones with no further growth detected. The side effects of this drug are minimal giving full quality of life and my immune system has not been compromised which is saving money in the long run as I do not need any other medication for any other symptoms. I do not understand how a cost can be put on a person's life at all and I feel that if this drug is working and can significantly help reduce the growth of cancer in cancer patients then surely this will save money as these patients will not require other treatments. This drug has been a god send to me, I feel normal and not like a cancer sufferer, I can get on with my life with hardly any disruption, just a couple of injections once per month which is nothing compared to the other treatments out there.

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	Taking a pill every day and injections once per month is a breeze compared to how disabling other treatments can be and gives me my life back, which is priceless. Please do not discontinue this drug on the NHS as so many other cancer sufferers can benefit from this drug and in the long run, I believe, save money for the NHS."
26	"I have never taken abemaciclib however it could potentially be an option for me in the future. The fact that this treatment may not be available to me or other people with SBC could be devastating. When you are diagnosed with SBC you cling on to every positive story you can - you even try and 'read' your radiographer's face when you have finished a scan to see if they're looking positive. The good results I have read about this drug gives people hope and if that's a line of treatment that's taken away from us then hope is gone. To add, if this drug is available privately and not on the NHS then that's a further kick in the teeth to those that couldn't afford it. Imagine knowing that those who can access this drug privately and potentially thriving while you are going through progression and possibly approaching end of life because you can't afford it?"
27	"I've been on this treatment since November 2019 when it became apparent that other drugs were no longer working to keep my cancer stable. I was diagnosed with metastatic breast cancer in April 2018 and after chemotherapy was prescribed tamoxifen. I was on it for just over a year and endured the side effects because we thought it was working. Once my consultant changed my treatment to include abemaciclib it improved my quality of life. To date the side effects are negligible."
28	"In 2019 I had a further recurrence which has been treated since August 2019 with Abemaciclib and Fulvestrant. My breast tumour began to shrink within weeks of beginning this treatment and this was confirmed by CT scans and surgery in July 2020 which showed only slight trace remains of the tumour. Throughout this treatment I have remained very well, with only slight side effects which have had very little affect on my day to day life. I was dismayed to read of the provisional recommendation by NICE not to recommend Abemaciclib and Fulvestrant for routine use. I do understand that the treatment I am receiving is very expensive but in my experience it is effective and provides a very good quality of life for patients who are receiving it. I feel very lucky to be receiving these drugs and to hear that in future women may be denied them feels wrong and extremely upsetting."
29	"I commenced Fulvestrant and Abemaciclib in Feb 2019 (continuing with Zoladex and Denosumab). I feel really well and to date have had no particular side effects from this treatment. I know I am very lucky to be on these drugs which are a compassionate supply. It is very disappointing and distressing to think of others who may be missing out on this incredibly positive treatment and I would urge NICE to rethink their decision."
30	"I was very sad to read that this combination of drugs has not been authorised for use. I was diagnosed with secondary breast cancer in March 2019 with mets in liver & numerous bones at 47 years (My primary diagnosis & treatment was just a year before) Abemaciclib & Fulvestrant were my first drugs & I continued on them for 19 months. The side effects very manageable & I was able to carry on with all my normal activities. My liver mets were healing at my first scan & I had no active cancer in my liver after 6 months. That has remained the same. My bone mets had a partial response & healed in places but in October 2020 I had a couple of new spots on my spine so I am now on Capecitabine with good results so far. I am shocked that this treatment will not be offered."
31	"I was diagnosed in 2012 with secondary breast cancer, having had breast cancer in 1998 and 2000. I was put on exemestane but in 2019 it was discovered it was no longer effective. In September 2019, I was offered fulvestrant with abemeciclib and I felt, and still do, that it is my lifeline. It has, to date, worked very well, my scans show everything stable. I would be devastated if the medication was withdrawn - I have such confidence in its ability to keep my cancer stable. I did have a few side effects but once a dose that suited me was found everything was great. I was told by oncology that the best treatment was to have the abemeciclib along with fulvestrant as results were really good. I do feel very strongly that such a brilliant treatment should be offered to everyone that meets the criteria for it - it's an important life line and should not be denied - it's risking people's lives!"
32	"I received my diagnosis in May 2019 and was advised I had incurable metastatic breast cancer. Following a multi-disciplinary meeting with my medical team, it was decided that the most effective

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	treatment would be abemaciclib with Fulvestrant. I have secondary breast cancer and have been on the combination of Abemaciclib with Fulvestrant 19 months, with no progression. I strongly believe this should be an option for all women with secondary breast cancer. In the 19 months I have been on it, I have had a good quality of life and I have been living with dignity. As the treatment is not invasive, it is very doable and it needs to be made available on the NHS, so it is an option for everyone."
33	"I've been on this treatment for 3 months now. I tried Ribociclib and Palbociclib but my liver reacted badly to these. It's early days for me on the Abema but I am very happy to say that so far all is going well and my 3 month scan showed significant tumour reduction."
34	"I was put on Abemaciclib and Fulvestrant in July 2019. In addition to this I swapped from Zometa to Denosumab in the Autumn of 2019. This is my second line of treatment and follows a Letrozole/Zometa combo that I had been on since diagnosis of breast cancer in December 2016. I find the drug to be much kinder to me than the Letrozole was, and even attended a gym 4 days a week before lockdown. This was nothing short of amazing, considering the fatigue and joint pain I had had with Letrozole which stopped me from walking more than very short distances. The only side effect I have had is stomach acid which we control using Lansoprazole and Kolanticon Gel. I have never had to miss a dose because of poor blood results. I understand that the aim of treatment of Stage 4 Breast Cancer patients is to optimise quality of life. These drugs have certainly achieved this for me."
35	"I've been taking the combo of Abemaciclib tablets & Fulvestrant injections since October 2019. I have found the combination of these drugs along with pain killers I take (pregablin & paracetamol) has helped a lot with pain management & quality of life. Prior to taking these drugs it felt like someone was constantly stood on my spine in heels. These days it's more just a dull background pain, which for me is amazing. I initially had side effects taking the 150mg of Abemaciclib, it set my IBS off & ended up in hospital a few times (apparently diarrhoea is quite common- it just also flared my IBS off) Once they reduced the dose to 100mg I've been a lot better. I think it'll be devastating if other patients aren't allowed access to these drugs, as it'll mean more premature deaths unnecessarily. Even if it can extend the lives of a handful of patients, surely that is worth it!'
36	"I have secondary breast cancer and have had Fulvestrant and Abemaciclib since May 2019. This combination has stopped my cancer from progressing and enabled me to live an active life so far."
37	"I am on hormone treatment - letrozole and 4 weekly denosamub injections since being diagnosed 4 and a half years ago. I heard with dismay that NICE have provisionally rejected the use of abemaciclib with fulvestrant for treatment of secondary breast cancer as it is deemed not a cost effective use of NHS money. For someone who's been on first line treatment for 4 and half years, this combination was likely to be my next option. So what next?"
38	"I have been on this treatment regime for 2.5 years and I'm in really good shape! Completely independent and active. Side effects are very manageable."
39	"My mother started this drug in January 2020 after the first line treatment of hormone therapy and radiotherapy hadn't worked and the cancer spread from the lymph nodes to the spine. For the last year there has been some shrinkage and no further progression and apart from tiredness and a little diarrhoea initially which was almost instantly cured by having a week break from the 150 mg tablets of Abemaciclib and then resuming on 100mg. The side effects are now minimal and include tiredness and a lack of energy and she is able to enjoy life to the full and spending time with her 6 young grandchildren who love her dearly. This drug has given us so much hope that the cancer can be managed and surpassing the terrifying 5 year survival statistic is possible."
40	"I was prescribed Albemaciclib and Faslodex in October. My oncologist said I had to start on the full dose - this was the rule. I managed 10 days and then I was really ill managing to eat one piece of toast in three days and suffering from diarrhoea etc. After a consult with my oncologist the dose was lowered to 100mg. Although I didn't suffer from diarrhoea and sickness my appetite disappeared altogether. I couldn't cope with this either as I was underweight to begin with. The dose was lowered to 50mg and I have now taken the drug for a month without trouble. I had a scan on the 26 January and only just got the results which say the disease is stable. My previous scan in October showed some progression so this feels OK."
41	"In October 19 when I was told that the tamoxifen treatment was no longer working and there had

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	been further spread of the mets; I was frightened and concerned about what the next treatment would be. I was so relieved and pleased to hear that the abemaciclib / fulvestrant treatment had been approved as a second line treatment for women like me. Despite the long list of side effects I have been able to carry on my normal life almost without alteration, I am working, I can be physically active and I feel really well. I don't look or feel like a cancer patient, I feel like myself and that is worth everything. I know it is expensive treatment, but I have been grateful every day that it has been made available to me. I have three daughters, the youngest of whom was only 17 when I was diagnosed with secondaries. She was full of fear that she was going to lose her Mum; and while she has come to terms with things pretty well – it has been a huge comfort to me to still be her normal Mum, and not a very ill woman. It means that the time I have had, and continue to have, is such good quality life – it doesn't feel like a slow slide to my death; it's a proper 100% life. While I look and actually am really well, those around me, particularly my youngest girl and my elderly parents, are comforted. They are able to treat me normally (mostly) and that's fantastic all round. Any stage 4 person will tell you that having to manage other people's distress, however much they try to hide it, is just about the worst thing. I am grateful all the time for the 14 months so far of brilliant quality life that I have been given by this combination of drugs. I am enormously grateful to the NHS for everything they do for me. I am sad that my life will be shorter than I had always imagined, but the months and years I have is 'proper-time', well-time. It's real life. I have had side effects at various times, but I haven't ever been ill – I haven't had one day where I've needed to be in bed. For the first couple of weeks I got very tired and had to go bed early. Sometimes I still suddenly feel tired, but most days I don't experience that. When I'd been on the treatment for 3 months, I started experiencing diarrhoea which obviously isn't lovely; but weirdly it didn't feel like a tummy upset and I didn't feel ill. I just didn't want to be far from a loo! The acute phase of that lasted a few weeks and I took the meds I'd been given (like immodium) if it ever got a bit much. Anyway after that we were in lockdown for the first time and I never have been far from my own bathroom… Occasionally that will return for a day or 2, but it has been fine not debilitating. In the last few months I have lost most of my hair – it was a slow process, and of course I did struggle with that when I realised it was happening. On the other hand, I could appreciate the drug was building up in my system and there were bound to be some toxic side effects. I wear a wig now, and mainly that's fine. That by far has been the most difficult thing; but it's still a brilliant trade off – my good life for my hair. Before they slightly reduced the abemaciclib there had been a couple of blood tests where the liver function thing was too high, and the white blood cells were too low. I missed one month's worth of injections, and had 2 weeks holiday from all the medicines. Since then and the lower dose I have felt fine and my bloods have been fine. When I got the email from Breast Cancer Now about the provisional NICE decision, I was so upset. I understand that it won't effect me; but I am so sad for the women coming after me. I know how difficult it is to accept that your life is going to be shorter and to face an uncertain future. This treatment option has given me more than a year so far of just fantastically well life. It honestly makes me so sad to think that other women might not have that. I feel immense empathy for the people at NICE who have to make impossible decisions; but I really hope there is a way to overturn this decision perhaps with the help of the drugs company who manufacture the drugs."
42	"Having begun my current regime on Abemaciclib and Fulvestrant five months back after treatment with palbociclib both my oncologist and I are pleased with progress. Within three months the primary tumour had begun to shrink and cancer activity in my body had reduced. Now, five months in, the initial tumour is barely palpable and my tumour markers are down. Without abemaciclib, together with Fulvestrant, I suspect that I would have been treated with potentially less successful and possibly more invasive drugs and would have missed out on what, from my perspective, has been a valuable medication for delaying the spread of my secondary breast cancer.

NICE National Institute for Health and Care Excellence

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	It would be very disappointing indeed if other women in my position in the future were deprived of treatment with Abemaciclib, since it is a useful alternative to Palbociclib which I understand NICE has approved for use by the NHS - why limit the use of this alternative? It makes no sense and seems extremely unjust."

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

The NICE Appraisal Consultation Document (ACD) for Abemaciclib with Fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy was discussed at the executive committee of the United Kingdom Breast Cancer Group (UKBCK) on February 12th. UKBCG were concerned that the preliminary recommendation was based on an unplanned subgroup analysis of the trial population in the Monarch 2 clinical trial which tested the combination based on patients enrolled after a protocol amendment which reduced the Abemaciclib dose from 200 mg twice daily to 150 mg twice daily. This protocol amendment was made to reduce the toxicity of the treatment, in particular with respect to diarrhoea.

Although the change in dose could lead to some uncertainty about how well the drug might work in clinical practice, there is clear supporting evidence for the lower dose from the Monarch 3 trial which tested the use of Abemaciclib at a dose of 150 mg bd in combination with an aromatase inhibitor. The Hazard ratio in favour of Abemaciclib vs. placebo of 0.54 in this trial was entirely consistent with the effect seen in the intention to treat population in the Monarch 2 trial with Abemaciclib with fulvestrant and validates 150 mg bd as an effective dose of the drug.

UKBCG noted that Fulvestrant with Ribociclib has been approved by NICE. In the Ribociclib plus Fulvestrant FAD it is stated that "There are no trials directly comparing ribociclib plus fulvestrant against exemestane plus everolimus. But an indirect comparison suggests that ribociclib plus fulvestrant may be the more effective option for people who have already had hormone therapy".

This use of an indirect comparator does not appear to be a barrier to the positive recommendation for ribociclib plus fulvestrant, but is inconsistent with the interpretation in the Abemaciclib ACD which states that "There is also uncertainty because there is no evidence directly comparing abemaciclib plus fulvestrant with exemestane plus everolimus. An indirect comparison suggests that people having abemaciclib plus fulvestrant have longer before their disease progresses and live longer than people having exemestane plus everolimus".

The view of the UKBCG is that there is a class effect and the three CDK 4/6 inhibitors appear to perform in a similar way in endocrine sensitive and resistant disease as evidenced by the remarkable consistency of hazard ratios in favour of the drugs in all of the scenarios that have been tested. This opinion is independently corroborated by the latest iteration of the ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5, Cardoso et al. Ann Oncol: 31;12, 1623-1649, 2020) which gave the same ESMO-MCBS (Magnitude of Clinical Benefit Scale) scores for all 3 of the CDK 4/6 inhibitors in the endocrine resistant setting. On that basis, UKBCG felt that it would be desirable to be able to use Abemaciclib in combination with Fulvestrant as an alternative to the other CDK4/6 inhibitors as this allows more flexible management of side effects.

There is no budget impact to the NHS if clinicians are able to choose what they believe to be the most appropriate CDK4/6 inhibitor in combination with Fulvestrant for each patient, giving the ability to offer individualised treatment recommendations and optimise side effect management.

[redacted] on behalf of the UKBCG. 4th March 2021.

Comments on the ACD received from the public through the NICE Website

Name	
Comments on the ACD:	

There is a population who could benefit from abemaciclib plus fulvestrant

Secondary breast cancer can be treated but it cannot be cured. Treatments aim to control and slow down the disease to enable patients to have the best possible quality of life for as long as possible.

We will be undertaking two studies that look at quality of life. Make 2nds Count is funding the largest study of secondary breast cancer patients and clinical trials in the UK with Warwick University. We aim to survey over 3,000 secondary breast cancer patients with a focus on clinical trials and quality of life.

The study is vital to understand patients own experience so we can address gaps in information and participation in trials and treatment. The needs of every patient with secondary breast cancer are unique – no treatment works the same. It's essential there is more research funded, to extend trials and improve personalised treatment. And also, to better understand and increase the quality of life for those affected by the disease. We will be happy to share the findings with NICE in 12 months time.

Three years before a further review is too long and treatment and trials have already been severely delayed by Covid-19. The average life expectancy of a patient with secondary breast cancer is 3 to 5 years, so this delay will have a direct impact on patients, which the consultations refers to, who could benefit from abemaciclib plus fulvestrant.

Name	
Comments on the ACD:	
I am a SBC patient who is ER+ HER2- and these drugs could extend my life to see my daughter grow up. Our lives matter and we deserve all treatment lines as an option. Your research stated: An indirect comparison suggests that people having abemaciclib plus fulvestrant have longer before their disease progresses and live longer than people having exemestane plus everolimus. Are we not worth this extra time. I was misdiagnosed for 2 years and as a result I have extensive secondary	

Name	
Comments on the ACD:	
My friend in the USA was on Ibrance & fulvestrant for 2 years, when this stopped working she was then on Xeloda for a year. She is now on verzenio/Albemaciclib with no fulvestrant for a year and is keeping things under control. I have MBC with widespread mets to bones, liver and lungs. I was diagnosed in May 2018, I've been on Ibrance & letrozole for 2 years, an oral SERD trial for 3 months & now on Xeloda. I've been extremely grateful to be on these meds and I've never had IV chemo in my life, nor do I want it. I'm so hoping the next treatment I can try is Verzenio/Abemaciclib before any IV chemo. I've worked very hard all my life & paid tax & nhs contributions for over 40 years. I'm now 58 and hoping for a few years extra quality of life. Why should the nhs deem me not cost effective.... I really want to remain under the nhs for their excellent care but may now have to pay privately to try this drug or ask Lilly for help. Please, please reconsider - imagine it was you who needed to try this drug.	

BMJ TAG

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (CDF review of TA579)

ERG review of company's response to the ACD

May 2021

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1 Introduction

This document provides the ERG's response in relation to the company's comments and additional data presented as a response to the appraisal consultation document (ACD).

2 ERG review of comments

2.1 Comment 1: Executive summary

The company provided further comments around the clinical and cost-effectiveness of abemaciclib in combination with fulvestrant (ABE-FUL) compared to everolimus and exemestane (EVE-EXE). These are discussed in the following sections in detail and consist on the following:

1. The use of the post-amendment data from MONARCH 2;
2. The method to model time to treatment discontinuation (TTD) for ABE-FUL;
3. The method to model TTD for EVE-EXE;
4. The use of a revised patient access scheme (PAS) price for abemaciclib.

2.2 Comment 2: Use of the post-amendment data in MONARCH 2 to assess the clinical and cost-effectiveness of abemaciclib with fulvestrant

The ERG acknowledges that sample size calculations for the post-amendment population were not directly based on PFS events, but rather on safety outcomes as highlighted by the company in Comment 2. Nonetheless, the ERG maintains its position that the post-amendment subgroup is methodologically robust and provides the most appropriate results to inform this appraisal. The post-amendment subgroup had a sample size of over 450, which, as the company states, was powered to detect differences between treatment arms for safety outcomes. In addition, the ERG reiterates that MONARCH-2 initially planned to enrol 450 patients, in order to provide more than 90% statistical power to detect superiority of ABE+FUL over FUL in the ITT population (assuming a HR 0.703). Given that the sample size of the post-amendment subgroup exceeded this (N=491), and the early data-cut hazard ratio (HR) was 0.588, the ERG considers that the post-amendment subgroup was appropriately powered to detect superiority of ABE+FUL over FUL for PFS based on the same assumptions as used in the original protocol's power calculation.

Taking this into account, coupled with the fact that the post-amendment subgroup matches the dose of the marketing authorisation for abemaciclib, the ERG maintains that the post-amendment subgroup is the most appropriate to inform this appraisal.

The company further state in their comment that,

[redacted]

The ERG does not agree with this statement. While the ERG appreciates that

[redacted]

Figure 1 and Figure 2 show a change in [redacted] The estimates derived from the FP NMA gave a median PFS of [redacted] for ABE-FUL for the PA population compared to a median PFS of [redacted] for the ITT population. Similarly, median OS was [redacted] for ABE-FUL for the post-amendment population, compared to [redacted] for the ITT population.

Figure 1. PFS KM curves for ABE-FUL and PBO-FUL in the post amendment population and the ITT population (latest data cut)

Figure 2. OS KM curves for ABE-FUL and PBO-FUL in the post amendment population and the ITT population (latest data cut)

2.3 Comment 3: Time to treatment discontinuation for abemaciclib plus fulvestrant

The ACD reported that the most appropriate modelling approach to estimate TTD for ABE-FUL is uncertain. To address the concerns raised by the ERG, the company considered an additional range of HRs between PFS and TTD in the post amendment population. Using a lognormal extrapolation, and using a restricted mean survival time analysis, the company estimated HRs for different points in time:

- 54 months – HR of [redacted];
- 70 months – HR of [redacted];
- 90 months – HR of [redacted];
- 110 months – HR of [redacted];
- 120 months – HR of [redacted].

The company concluded that the variation in the HRs was small as the time horizon increased from the follow-up length of MONARCH 2 (54 months) up towards an extended duration of 120 months (10 years) in the lognormal extrapolated curve. The company chose the HR of [redacted] for the company's revised base case analysis.

The ERG maintains its original view that the HR of [redacted] is likely to be the most appropriate value to estimate the treatment costs with ABE-FUL in the model; however, the ERG acknowledges that a HR of [redacted] is also a potentially valid estimate. As discussed in the ERG's critique of the company's response to technical engagement (TE), the relative positioning of the TTD and PFS modelled curves with a HR of [redacted] seems to be aligned to the relative positioning of the observed TTD and PFS KM curves in the post-amendment population in the MONARCH 2 data and also results from comparing the areas under the PFS and TTD curves for the period of time where KM data were available. For completeness, the ERG included a scenario using a HR of [redacted] in its results, discussed in Section 2.5.1.

2.4 Comment 4: Time to treatment discontinuation for exemestane plus everolimus

The company noted that in the recently published final appraisal document (FAD) for ribociclib in combination with fulvestrant [ID1318](1), the committee considered two different methods for estimating time to treatment discontinuation:

1. Using summary data from BOLERO 2 to estimate a HR by diving the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the KM PFS curve from BOLERO 2 at the time of median TTD in the same trial (5.5 months), resulting in a HR of 1.58;
2. A scenario based on clinical expert opinion, where the company assumed that 20% of patients will discontinue everolimus 6 months after the initiation of treatment, and that 70% of the of the patients remaining on everolimus will have their dose reduced from 10 mg daily to 5 mg daily at month six. Patients on exemestane were assumed to stay on treatment until progression.

The company added that in the published FAD for ribociclib in combination with fulvestrant, the appraisal committee, "*agreed that the time to stopping everolimus is likely to be between clinical opinion, and the ERG's model using BOLERO-2 data*".

The company also estimated that the scenario based on clinical expert opinion is the equivalent of assuming a HR of [redacted] between the PFS and TTD curves for everolimus. The company, therefore, concluded that that PFS/TTD HR for everolimus lies between the two HRs of [redacted] and 1.58.

The company explored an alternative method to determine the relationship between PFS and TTD for everolimus based on a restricted mean survival analysis of the data from BOLERO 2. To undertake the analysis, the company assumed that the PFS and TTD outcomes for EXE-EVE from BOLERO 2 could be fitted with an exponential model. Subsequently, using the properties of the exponential model, the company derived the hazard function for PFS and TTD as -ln (0.5) divided by median PFS and median TTD, respectively. Using the hazard function, the company calculated the area under the curve for PFS and TTD exponential curves at month 30 (maximum follow-up for PFS outcomes in BOLERO 2). The company then divided the estimated area under the PFS curve by the area under the TTD curve to estimate the HR of [redacted].

The company concluded that the HR of [redacted] aligns with the appraisal committee's stated preference in the ribociclib in combination with fulvestrant FAD, as it lies between the clinical expert opinion scenario ([redacted]) and the ERG's proposed HR of 1.58.

The company, therefore used the HR of [redacted] to estimate the treatment costs with everolimus in the model, and produced Figure 3 to justify that based on visual inspection alone, using an exponential model in the analysis was a reasonable approach.

Figure 3. Exponential extrapolations for progression-free survival and exposure to everolimus in the BOLERO-2 trial

Source: Lilly Data on File

The ERG disagrees with the use of the HR of [redacted] to estimate treatment costs with everolimus. Firstly, the company's approach relies on the assumption that both the PFS and the TTD data in BOLERO 2 can be fitted with an exponential curve. The ERG notes that BOLERO 2 did not report TTD data other than median estimates, therefore it is not possible to validate the company's assumption that an exponential curve would provide a good fit to these data. Furthermore, while the exponential curve might provide a reasonable fit to the KM PFS curve for EXE-EVE from month 7 (see Figure 3) the ERG notes that the initial 7 months in the model underestimate PFS for EXE-EVE. Given that the HR of [redacted] derived by the company was estimated by dividing the area under the PFS curve by the area under the TTD curve, having a smaller area under the PFS curve leads to a smaller (potentially underestimated) HR.

Importantly, the ACD for ABE-FUL reported the following: "*The clinical experts noted that the change* [i.e. stopping everolimus treatment] *at 6 months seemed implausible because people would be more likely to stop gradually throughout the first 6 months. The committee said that BOLERO 2 data, even if not based on individual patient data from the trial, were preferable to the opinion of 1 clinician. The committee was aware that the results of the economic model were highly sensitive to the assumption used to estimate the time to treatment discontinuation for exemestane plus everolimus. It concluded that there was uncertainty about the most appropriate method to estimate time to treatment discontinuation for exemestane plus everolimus.*"

The ERG considers that the HR relying on the fewest assumptions is the HR of 1.58, which is based on the observed median PFS and observed median TTD in BOLERO 2 for everolimus. As concluded by the committee, using trial data is preferrable to basing the costs of everolimus on clinical assumptions (the equivalent of assuming a HR of [redacted]). Even though the company's newly proposed HR of [redacted] lies within these two HRs (see Figure 4), the ERG considers this is likely to be underestimated (given the underestimation of the area under the PFS exponential curve for EXE-EVE). The ERG notes that the choice between any of these three HRs is one of the key model drivers.

Figure 4. PFS curves for EXE-EVE and alternative TTD curves for estimating treatment costs with everolimus

2.5 Comment 5: Updated cost-effectiveness analysis

The company's updated base case is based on the following assumptions:

1. Using the post amendment population from MONARCH 2 in the clinical and economic analysis (see Section 2.2);
2. Using a HR of [redacted] to estimate the costs of ABE-FUL (see Section 2.3);
3. Using a HR of [redacted] to estimate the costs of everolimus (see Section 2.4);
4. Updating the patient access scheme (PAS) price for abemaciclib, with the discount increasing from [redacted] to [redacted];
5. Using the fulvestrant list price and including a range of discounts in scenario analyses;
6. Removing the half-cycle correction from the model.

The company's updated deterministic base case ICER is provided in Table 1 and shows that ABE-FUL dominates EXE-EVE. Table 2 reports the company's probabilistic ICER of £2,020 per QALY gained. From investigating the company's model, the ERG concluded that the company's probabilistic analysis does not allow for the ABE-FUL HR of [redacted] to be varied in the analysis.

Compared to the company's base case ICER pre-ACD (and post TE) of £6,674 the company's results became more favourable for ABE-FUL. This is due to the change in the HR used to estimate TTD for EXE-EVE (HR changed from 1.58 to [redacted]). Decreasing this HR led to an increase in the total costs associated with EXE-EVE of approximately £8,000. The other key driver of the economic results remains the HR used to estimate TTD for ABE-FUL. The company's updated analysis uses a HR of [redacted] ([redacted] in the company's previous base case), which led to an increase in the costs for abemaciclib of approximately [redacted]. Overall, there was a decrease in the incremental costs for ABE-FUL when compared to EXE-EVE, causing the ICER to become dominant in favour of ABE-FUL.

Table 1. Company's base case deterministic results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Updated base case results							
ABE-FUL	[redacted]	[redacted]	[redacted]	-	-	-	-
EVE-EXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 2. Company's base case probabilistic results (5,000 simulations)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Updated base case results							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,020

2.5.1 ERG's analysis

The ERG's preferred assumptions remain unchanged pre and post ACD. These consist on the following:

1. Using the updated NMA with the post amendment data;
2. Removal of the half-cycle correction from the model;
3. Removal of fulvestrant discount from the analysis;

In addition to assumptions 1 to 3, the ERG combined the latter with two alternative scenarios to model TTD for ABE-FUL:

a) Using the HR of [redacted] to estimate TTD for ABE-FUL in the model;
b) Using the HR of [redacted] to estimate TTD for ABE-FUL in the model.

And an additional two scenarios to model TTD with EXE-EVE:

c) Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE in order to cost treatment with everolimus, and assuming that exemestane was given until disease progression;
d) Assuming that 20% of progression-free patients receiving EVE-EXE will discontinue everolimus at six months after the initiation of treatment, and that 70% of the of the patients remaining on everolimus will have their dose reduced from 10 mg to 5 mg daily at month six. Patients were also assumed to receive exemestane until disease progression in this scenario.

Given the committee's preference for the use of trial data instead of clinical expert opinion, the ERG's preferred ICER is one including a HR of 1.58. For completeness, the ERG also presented the results incorporating scenario d (i.e. clinical expert opinion) in the ICER.

Results of the ERG's analysis are reported in

Table 3 for the comparison of ABE-FUL with EXE-EVE. The key drivers of the economic results remain the assumptions made to cost treatment with ABE-FUL and with EXE-EVE.

Depending on the assumption used to cost treatment with everolimus, the ERG combined deterministic ICER ranges from £36,431 to dominant (in favour of ABE-FUL). The ERG notes that due to time constraints, it was not possible to produce probabilistic ICERs; however, given the similarity between the company's probabilistic and deterministic results, the ERG is confident that the ERG's probabilistic results would be aligned with the deterministic ones.

The ERG also notes that the results provided in this document include the updated PAS for abemaciclib but do not include the PASs available for everolimus and fulvestrant. Results of the ERG's combined analysis with all PASs included are reported in a confidential appendix.

In conclusion, the key drivers of the model remain the HRs used to estimate TTD for EXE-EVE and ABE-FUL, in particular the HR chosen to model the costs associated with everolimus.

Table 3. ERG's combined analysis with updated abemaciclib PAS

Scenario		Incremental costs	Incremental QALYs	ICER
1+2+3	Company base case	[redacted]	[redacted]	Dominant
1+2+3+a	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	Dominant
1+2+3+a+c	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve + Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£36,431
1+2+3+a+d	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve + Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	Dominant
1+2+3+b+c	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve + Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£26,112
1+2+3+b+d	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve + Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

3 References

1. National Institute for Health and Care Excellence (NICE). Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (CDF review of TA593) [ID3755]. Available at (https://www.nice.org.uk/guidance/indevelopment/gid-ta10675/documents) [accessed 02 March 2021].