National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Breast Cancer Now	Yes.	Comment noted.
	Novartis	It is appropriate to refer this topic to NICE.	Comment noted.
	Pfizer	We consider it appropriate for this topic to be referred to NICE for appraisal.	Comment noted.
Wording	Breast Cancer Now	Yes.	Comment noted.
	Novartis	Yes.	Comment noted.
	Pfizer	We consider the wording of the remit of this appraisal to be appropriate. [redacted]	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]	
Timing Issues	Breast Cancer Now	Early indications from two different studies suggest that this drug used in combination with others can improve progression free survival in advanced/metastatic cancer. Patients with metastatic disease have very limited options for treatment and a poor prognosis. It is therefore important that any new treatments, which extend progression free survival to be made available to this group of patients as soon as possible to help them to have a good quality of life for as long as possible.	Comment noted.
	Novartis	There is an urgency to appraise all treatment options in this setting.	Comment noted.
	Pfizer	Pfizer agrees that the two populations which form part of the anticipated marketing authorisation should be referred to NICE for evaluation. Pfizer would like to make NICE aware that, as the trials are event-driven, there is currently limited information in terms of the overall survival results observed in the PALOMA 2 (palbociclib plus letrozole) and PALOMA 3 (palbociclib plus fulvestrant) clinical trials. [redacted]	Comment noted.

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Additional comments on the draft remit	Breast Cancer Now	None.	No action required.
	Novartis	None.	No action required.
	Pfizer	No comments.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Breast Cancer Now	The statistic that 17% of women with invasive breast cancers have locally advanced or metastatic disease on diagnosis is no longer cited on the CRUK website, provided in the reference. Breast Cancer Now has several alternative options of estimates of secondary breast cancer on its website: http://breastcancernow.org/about-breast-cancer/what-is-breast-cancer/secondary-breast-cancer/what-is-secondary-breast-cancer/how-common-is-secondary-breast-cancer	Comment noted. The background section of the scope has been amended.
	Novartis	The following is from the background section of the draft scope - "Everolimus in combination with exemestane is currently available on the Cancer Drugs Fund for people with hormone receptor positive, HER2-negative breast cancer who have not had previous treatment with exemestane". However the marketing authorisation for everolimus in combination with exemestane is for people with hormone receptor positive, HER2-negative breast cancer who have progessed on a non-steroidal aromatase inhibitor. Please consider amending.	Comment noted. The background section of the scope has now been amended to only describe first line treatment options for metastatic breast cancer.

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	Pfizer	- The figure quoted for overall number of people diagnosed with breast cancer in the UK includes men. The total number of women diagnosed with breast cancer in the UK in 2013 was 44,540 (1) - The figure quoted for overall number of deaths from breast cancer in the UK includes men. The total number of breast cancer deaths in women in the UK in 2012 was 9,698 (2) - Cancer Research UK estimates that in 5 in 100 women (5%) the cancer has already spread to another part of their body when they are first diagnosed (3). This population is commonly known as “de novo” patients. - Data suggest that 35% of all those with a primary diagnosis of metastatic breast cancer will develop metastases in the 10 years following diagnosis (it is therefore not an annual rate) (4) - Early stage breast cancer is generally asymptomatic, whilst the symptoms of metastatic breast cancer are dependent upon the site of metastasis. Besides controlling the disease for a s long as possible, managing symptoms to maintain an optimal quality of life (QOL) is one of the major goals of care in the metastatic setting (5)	Comments noted. The background section of the scope has been amended.
The technology/ intervention	Breast Cancer Now	Yes.	Comment noted.
	Novartis	Yes.	Comment noted.
	Pfizer	No comments.	Comment noted.
Population	Breast Cancer Now	Yes.	Comment noted. The scope population has been amended to only

Section	Consultee/ Commentator	Comments [sic]	Action
			include the population who have not previously received treatment for their metastatic disease. The population who have previously received treatment for their metastatic disease will be considered in another appraisal.
	Novartis	Yes - Twenty percent of those enrolled in each arm of the Paloma-3 trial were premenopausal or perimenopausal and received goserelin to suppress ovarian function. How will these patients be considered if at all? A key consideration that the Paloma studies have not addressed is the use of palbociclib with fulvestrant after it has already been given as a first-line treatment in combination with letrozole. As part of this appraisal, it would be important to advise on this within the context of the metastatic treatment pathway.	Comments noted. The scope population has been amended to only include the population who have not previously received treatment for their metastatic disease. The population who have previously received treatment for their metastatic disease will be considered in another appraisal.
	Pfizer	Assuming that the label remains as originally submitted to the EMA, Pfizer suggests the wording should be updated as follows: - Post-menopausal women with previously untreated, metastatic, hormone receptor-positive, HER2-negative breast cancer	Comment noted. The scope population has been amended to only include the population who have not previously

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		- Women with metastatic, hormone receptor- positive, HER2-negative breast cancer that has progressed after endocrine therapy who are either post-menopausal or pre-/peri-menopausal with ovarian suppression. Pfizer believes it would be more appropriate to appraise the two indications separately. Patients who have previously progressed after endocrine therapy constitute a clinically distinct population from the previously untreated population in the metastatic setting. They differ in clinical characteristics and have different treatment choices available, and as such constitute separate decision problems for NICE to consider.	received treatment for their metastatic disease. The population who have previously received treatment for their metastatic disease will be considered in another appraisal.
Comparators	Breast Cancer Now	The comparators seem appropriate, as palbociclib was tested on two different patient populations - those with previously untreated metastatic and metastatic or locally advanced disease that has progressed after endocrine therapy.	Comments noted. The scope population has been amended to only include the population who have not previously received treatment for their metastatic disease. Scoping workshop attendees agreed that chemotherapy would only be a treatment option for a population with imminently life-threatening disease, whereas palbociclib would only be used to treat people who were expected to respond well to treatment.

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			Therefore chemotherapy was not a relevant comparator for this population and it has been removed from the scope.
	Novartis	Single agent hormone therapy is the most likely "best alternative care" We also believe that capacitabine and vinorelbine should be the chemotherapy options specified for this patient group. In TA 295 section 4.5, the Committee concluded that, of the chemotherapies, in acccordance with NICE guidance,capecitabine and vinorelbine were the most relevant for this patient population. We therefore believe that the scope should be specific on the chemotherapies unless if clinical practice has suddenly changed since the publication of TA 295 two years ago - a highly unlikely scenario. We also suggest including a scenario where palbociclib and everolimus are compared with each other as two interventions (please refer to the 'other considerations and questions for consultation sections for more context on this).	Comments noted. The scope population has been amended to only include the population who have not previously received treatment for their metastatic disease. Scoping workshop attendees agreed that chemotherapy would only be a treatment option for a population with imminently life-threatening disease, whereas palbociclib would only be used to treat people who were expected to respond well to treatment. Therefore chemotherapy was not a relevant comparator

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			for this population and it has been removed from the scope.
	Pfizer	For postmenopausal people with untreated metastatic, hormone receptor-positive, HER2-negative breast cancer: - Pfizer believes aromatase inhibitors (such as letrozole and anastrazole) should be considered the standard of care as first-line treatment for women with hormone receptor-positive metastatic breast cancer, in line with NICE Clinical Guideline 81. Palbociclib has not been studied in the following patients (based on the exclusion criteria as included in PALOMA 2 (palbociclib plus letrozole): • Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement). • Patients with known active uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. The exclusion of these populations is consistent with CG81, which stipulates that use of chemotherapy as a first-line treatment should be restricted to women with hormone-receptor positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement. For this population, a comparison between chemotherapy and palbociclib combination would not be appropriate. However, market research data (IPSOS, 2015) suggest that	Comments noted. The scope population has been amended to only include the population who have not previously received treatment for their metastatic disease. Scoping workshop attendees agreed that chemotherapy would only be treatment option for a population with imminently life-threatening disease, whereas palbociclib would only be used to treat people who were expected to respond well to treatment. Therefore chemotherapy was not a relevant comparator for this population and it has been removed from the scope.

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		chemotherapy as a first-line treatment is currently being used for patients beyond this group, and there are patients who could more appropriately benefit from treatment with endocrine therapy. Pfizer has validated this information with a number of leading UK clinicians, who have suggested that except for patients with imminently life-threatening disease (as per the PALOMA 2 exclusion criteria, and in line with CG81), a large proportion of patients currently receiving chemotherapy could benefit from treatment with endocrine therapy. For these patients, a comparison with palbociclib plus letrozole would be appropriate. Pfizer notes that the evidence base informing a comparison between chemotherapy alone versus endocrine therapy alone for metastatic breast cancer contains significant clinical heterogeneity and relies on studies which are frequently small or more than a decade old (6)(7)(8). Pfizer is aware that the limitations in the existing data available may severely impact any comparisons against chemotherapy and notes that the poor quality of the existing evidence base indicates that a large proportion of the current chemotherapy use in the UK may not be supported by evidence. The validity of any comparison with chemotherapy would therefore be subject to high levels of uncertainty due to the limitations of the evidence base. For people with metastatic, hormone receptor-positive, HER2-negative breast cancer that has progressed after endocrine therapy: - Pfizer agrees that the following are relevant comparators in this population: - Exemestane - Everolimus and exemestane (not recommended by NICE, available through the CDF) - Tamoxifen	

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		- Fulvestrant - Chemotherapy (According to CG81 and clinical practice)	
Outcomes	Breast Cancer Now	Yes.	Comments noted. No changes to the scope required.
	Novartis	Overall survival is the key endpoint to capture the benefit of this technology however the data may not be mature enough to deliver this. At present Phase 2 data is available to support use of palbociclib in combination with letrozole. Result of the confirmatory Phase 3 study would be optimal for this appraisal	Comments noted. No changes to the scope required.
	Pfizer	Pfizer agrees with the outcomes proposed.	Comments noted. No changes to the scope required.
Economic analysis	Breast Cancer Now	No time horizon is provided for comment.	Comments noted. The company will specify this in its submission. No changes to the scope required.
	Novartis	No comment.	No changes to the scope required.
	Pfizer	None.	No changes to the scope required.

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Equality and Diversity	Breast Cancer Now	Not as far as we are aware.	No changes to the scope required.
	Novartis	No comment.	No changes to the scope required.
	Pfizer	Not to our knowledge	No changes to the scope required.
Innovation	Breast Cancer Now	The studies done to date suggest that progression free survival is increased by this drug. It may therefore offer another effective option for patients whose disease has progressed or recurred.	Comments noted. No changes to the scope required.
	Novartis	No comment.	No changes to the scope required.
	Pfizer	Cyclin-dependent kinases (CDKs) are considered a potential target for anticancer medications. The aim is to selectively interrupt cell-cycle regulation in cancer cells by interfering with CDK action. Palbociclib is a first-in-class CDK4/6 inhibitor with a novel mechanism of action that blocks cell proliferation and cellular DNA synthesis by preventing cell-cycle progression from G1 to S phase by preventing RB phosphorylation The unprecedented efficacy observed in patients treated with palbociclib, together with its tolerable toxicity profile, represents a step-change in the management of women with metastatic breast cancer.	Comments noted. The company have the opportunity to make the case for innovation in its submission. No changes to the scope required.
Other considerations	Breast Cancer Now	No suggestions.	Comments noted. No changes to the scope

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			required.
	Novartis	For people with metastatic, hormone receptor-positive, HER2-negative breast cancer that have progressed after endocrine therapy, we believe that everolimus should be an intervention in this appraisal not as a comparator. In August 2015, NICE confirmed that everolimus will reviewed and placed into the work programme and note that everolimus is currently in the NICE work programme. The arrival of palbociclib is timely in that everolimus can now be included in this appraisal avoiding two separate STAs (please refer to the questions for consultation section for further details on this).	Comments noted. In order to produce timely guidance, palbociclib will be evaluated under the STA process. No changes to the scope required.
	Pfizer	None.	No changes to the scope required.
Questions for consultation	Breast Cancer Now	No further comments.	No changes to the scope required.
	Novartis	We believe that this appraisal should follow the MTA process with the inclusion of everolimus as one of the interventions. As mentioned earlier, everolimus is currently undergoing a NICE review. It therefore makes sense to appraise both products in an MTA. This approach has several advantages: NICE will be able to use their resources efficiently as they will avoid undertaking two separate technology appraisals answering a similar decision problem. An MTA will ensure that there is one TAG with all the recommendations that are relevant for this particular patient population minimising the potential for confusion within the NHS on what can or cannot be used in this setting. From a technical standpoint, an MTA will bring a level playing field for the	In order to produce timely guidance, palbociclib will be evaluated under the STA process. No changes to the scope required.

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		indirect analysis comparing palbociclib with everolimus. As it stands, the palbociclib STA will commence first and the manufacturer of palbociclib will be in a position to conduct an indirect analysis vs everolimus with limited involvement from Novartis. However an MTA will enable both manufacturers to present their indirect analyses that will then be reviewed independently by an Assessment Group. In addition both manufacturers will be in a position to present and support their health economics analyses in the same appraisal. However we reiterate that the biggest positive with an MTA is the provision of guidance to the NHS in one single TAG and the efficient use of limited NICE resources (avoiding two separate STAs that are answering the same decision problem).	
	Pfizer	Regarding NICE's additional question "Where do you consider palbociclib will fit into the existing NICE pathways (Early and locally advanced breast cancer [2014] and Advanced breast cancer [2015])?" we believe that palbociclib in combination with endocrine therapy should be offered to patients, as early as possible in the treatment pathway to maximise the benefit associated with treatment, in line with its marketing authorisation: - with letrozole as initial endocrine-based therapy in postmenopausal women - with fulvestrant in women who have received prior therapy	Comments noted. The scope population has been amended to only include the population who have not previously received treatment for their metastatic disease.
Additional comments on the draft scope	Breast Cancer Now	None.	No changes to the scope required.
	Novartis	None.	No changes to the scope required.
	Pfizer	Any additional comments on the draft scope	References noted. No

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		References (1) Office for National Statistics (2015) Cancer registration statistics, England, 2013. Accessed December 2015. Available at http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--44--2013/index.html (2) Cancer Research UK. Breast cancer mortality statistics 2012. Accessed December 2015. Available at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality (3) Cancer Research UK. Statistics and outlook for breast cancer. Outlook by stage. Accessed December 2015. Available at http://www.cancerresearchuk.org/about-cancer/type/breast-cancer/treatment/statistics-and-outlook-for-breast-cancer#stage (4) NICE Clinical Guideline 81. Breast Cancer: diagnosis and treatment – needs assessment. Accessed December 2015. Available at http://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-costing-report2 (5) Irvin W, Muss HB, Mayer DK. Symptom management in breast cancer. Oncologist. 2011;16(9):1203-14. (6) Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747 (7) Cope S, Zhang J, Saletan S, Smiechowski B, Jansen JP, Schmid P. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for	changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		advanced breast cancer. BMC Med. 2014 Jun 5;12:93. (8) Generali D, Venturini S, Rognoni C, Ciani O, Pusztai L, Loi S, Jerusalem G, Bottini A, Tarricone R. A network meta-analysis of everolimus plus exemestane versus chemotherapy in the first- and second-line treatment of estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat. 2015 Jul;152(1):95-117.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Roche Products
Royal College of Nursing