NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Pierre-Fabre**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Breast Cancer Care and Breast Cancer Now

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

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

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 Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Breast Cancer Care and Breast Cancer Now	NICE has provisionally recommended neratinib where trastuzumab is the only HER2 directed treatment that patients have received in the adjuvant setting; and where patients that have had neoadjuvant treatment still have residual disease. This reflects the profile of patients in the main clinical trial for neratinib. It is clear from the document that patients receiving pertuzumab alongside trastuzumab in the adjuvant setting would not be eligible for neratinib. However, it would be helpful if NICE could clarify whether patients that receive pertuzumab in the neoadjuvant setting and still have residual disease would be eligible for neratinib. Our reading of the document is that they would be. If this is not the intention, then the final document should perhaps be amended to say that neratinib is recommended where trastuzumab is the only HER2 directed treatment that patients have received in either the neoadjuvant or adjuvant setting.	Thank you for your comment. No action is needed.
2	Consultee	Breast Cancer Care and Breast Cancer Now	The document states that both subcutaneous trastuzumab and neratinib could both be given at home. Just to note that it is unclear how many hospitals will be providing subcutaneous trastuzumab as a home treatment.	Thank you for your comment. No action is needed.
3	Company	Pierre Fabre Ltd	**Draft recommendation wording bullet 1:** *Neratinib is recommended as an option for the extended adjuvant treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults who completed adjuvant trastuzumab-based therapy less than 1 year ago only if:* *trastuzumab is the only HER2-directed treatment in the adjuvant setting they have had, and* *if they had neoadjuvant treatment, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and* *the company provides neratinib according to the commercial arrangement*	Thank you for your comment. No action is needed.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			(see section 2). Within this recommendation, the statement "trastuzumab is the only HER2-directed treatment in the adjuvant setting they have had, and" requires clarification regarding the current treatment pathway and the evolution of the treatment pathway to avoid any confusion going forward. As stated in Section 3.2 of the ACD, the treatment pathway has changed and now includes the option of pertuzumab in the adjuvant setting. We suggest alternative wording that better reflects the current treatments available, provides clarity for clinicians regarding adjuvant and extended adjuvant treatment planning, and will not limit the use of neratinib if trastuzumab is replaced in the future with alternative treatments, such as biosimilars, which are out of scope of NICE appraisals. Two suggested alternative wordings that would add clarification are provided below (see underlined text): Neratinib is recommended….only if: "Trastuzumab-based monotherapy is the only HER2-directed treatment in the adjuvant setting they have had, and'' Or "patients have not previously received more than one HER2-directed therapy in the adjuvant setting, and''	
4	Company	Pierre Fabre Ltd	**Draft recommendation wording bullet 2:** *if they had neoadjuvant treatment, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and* We believe that the current text does not fully reflect the inclusion criteria of the ExteNET trial on which the recommendation was based. The ExteNET inclusion criteria were: if patients had prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab, regardless of nodal status at initial diagnosis), they were eligible, provided they had residual invasive cancer in the breast and/or axilla after completing neoadjuvant therapy. The current wording has the potential to incorrectly exclude any women who had received neoadjuvant endocrine therapy and who may derive benefit from neratinib. Neoadjuvant endocrine therapy is recommended in NICE clinical guideline NG101 for postmenopausal women with ER+	Thank you for your comment. The wording has been updated as suggested. See FAD section 1 for more details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			disease who receive neoadjuvant endocrine therapy if there is no definite indication for chemotherapy. Suggested revised wording that would add clarification is as follows (see underlined text): "if they had neoadjuvant chemotherapy-based regimens, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and"	
5	Company	Pierre Fabre Ltd	**ACD Section 3.2:** *The clinical experts stated that the decision about the most suitable treatment for patients with node positive disease would be based on the patient's preferences.* We would like to highlight that the wording in this section does not fully reflect the views the clinical experts expressed at the appraisal committee meeting. In light of the fact that the treatment pathway for HER2+/HR+/node positive now includes adjuvant pertuzumab, the experts stated that the decision about the most suitable treatment would be based on **both** clinical judgement and patient preferences. As the wording currently stands, it implies that the decision would be based solely on patient preference between an oral extended adjuvant treatment with neratinib later in the treatment pathway, or intravenous adjuvant pertuzumab at the same time as trastuzumab. At the committee meeting, there was discussion on the differing efficacies of neratinib and pertuzumab in HR+ patients. Clinical experts stated that pertuzumab had lower efficacy in HR+ patients, and there was a suggestion that ER+ patients do not respond well to dual antibody therapy and that ER+/HER2+ patients would benefit from neratinib because of cross talk between ER and HER2 signalling pathways. Suggested alternative wording to fully reflect the appraisal committee discussion is as follows: "The clinical experts stated that the decision about the most suitable treatment for patients with node positive disease would be based on clinical judgement, based on the efficacy of the appropriate treatment in patients with HER2+/HR+ cancer and the patient's preferences."	Thank you for your comments. The wording has been updated. See FAD section 3.2 for more details.
6	Company	Pierre Fabre Ltd	**ACD Section 3.9:** *It is unclear which approach to iDFS modelling is the most appropriate: The clinical experts considered both extrapolations plausible, however they noted that the extrapolations are difficult to judge because 5-year follow-up data from ExteNET is extrapolated for the next 50 years. The committee agreed that the proportional hazards assumption was met for the duration of the trial but not for the extrapolation put*	Thank you for your comments. The wording has been updated. See FAD section 3.9 for more details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			forward by the company. The committee concluded that it is unclear which approach to iDFS is the most appropriate and that both approaches could be plausible. We would like to request that the wording in this section is clarified, as we believe that it does not fully reflect the views expressed at the open session of the committee meeting. An expert committee member made clear that the proportional hazards assumption of the company could be deemed the most appropriate. Assessment of the proportional hazard assumption, in line with DSU guidance (Technical Support Document 14), can only be done within the trial time horizon given that no data beyond this time point are currently available. Thus, in line with the DSU guidance, the assumption of proportional hazards beyond the trial time horizon should be addressed with the duration of treatment effect (as was done in the company model). Unless the current wording is based on further discussions during the closed session, we suggest that the wording is changed to reflect the view that the proportional hazards assumption was considered the most appropriate.	

NICE National Institute for Health and Care Excellence

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 August 2019 **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):	Pierre Fabre Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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2	**Draft recommendation wording bullet 2:** *if they had neoadjuvant treatment, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and* We believe that the current text does not fully reflect the inclusion criteria of the ExteNET trial on which the recommendation was based. The ExteNET inclusion criteria were: if patients had prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab, regardless of nodal status at initial diagnosis), they were eligible, provided they had residual invasive cancer in the breast and/or axilla after completing neoadjuvant therapy. The current wording has the potential to incorrectly exclude any women who had received neoadjuvant endocrine therapy and who may derive benefit from neratinib. Neoadjuvant endocrine therapy is recommended in NICE clinical guideline NG101 for postmenopausal women with ER+

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	disease who receive neoadjuvant endocrine therapy if there is no definite indication for chemotherapy. Suggested revised wording that would add clarification is as follows (see underlined text): "if they had neoadjuvant chemotherapy-based regimens, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and"
3	**ACD Section 3.2:** *The clinical experts stated that the decision about the most suitable treatment for patients with node positive disease would be based on the patient's preferences.* We would like to highlight that the wording in this section does not fully reflect the views the clinical experts expressed at the appraisal committee meeting. In light of the fact that the treatment pathway for HER2+/HR+/node positive now includes adjuvant pertuzumab, the experts stated that the decision about the most suitable treatment would be based on **both** clinical judgement and patient preferences. As the wording currently stands, it implies that the decision would be based solely on patient preference between an oral extended adjuvant treatment with neratinib later in the treatment pathway, or intravenous adjuvant pertuzumab at the same time as trastuzumab. At the committee meeting, there was discussion on the differing efficacies of neratinib and pertuzumab in HR+ patients. Clinical experts stated that pertuzumab had lower efficacy in HR+ patients, and there was a suggestion that ER+ patients do not respond well to dual antibody therapy and that ER+/HER2+ patients would benefit from neratinib because of cross talk between ER and HER2 signalling pathways. Suggested alternative wording to fully reflect the appraisal committee discussion is as follows: "The clinical experts stated that the decision about the most suitable treatment for patients with node positive disease would be based on clinical judgement, based on the efficacy of the appropriate treatment in patients with HER2+/HR+ cancer and the patient's preferences."
4	**ACD Section 3.9:** *It is unclear which approach to iDFS modelling is the most appropriate: The clinical experts considered both extrapolations plausible, however they noted that the extrapolations are difficult to judge because 5-year follow-up data from ExteNET is extrapolated for the next 50 years. The committee agreed that the proportional hazards assumption was met for the duration of the trial but not for the extrapolation put forward by the company. The committee concluded that it is unclear which approach to iDFS is the most appropriate and that both approaches could be plausible.* We would like to request that the wording in this section is clarified, as we believe that it does not fully reflect the views expressed at the open session of the committee meeting. An expert committee member made clear that the proportional hazards assumption of the company could be deemed the most appropriate. Assessment of the proportional hazard assumption, in line with DSU guidance (Technical Support Document 14), can only be done within the trial time horizon given that no data beyond this time point are currently available. Thus, in line with the DSU guidance, the assumption of proportional hazards beyond the trial time horizon should be addressed with the duration of treatment effect (as was done in the company model). Unless the current wording is based on further discussions during the closed session, we suggest that the wording is changed to reflect the view that the proportional hazards assumption was considered the most appropriate.

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	We also wish to clarify that the wording in this section is not factually accurate regarding the time horizon of the company extrapolations. As discussed at the appraisal committee meeting, the 5-year follow-up data in the company model are not extrapolated for the next 50 years as currently stated; they are only extrapolated until the trial data cross the survival curve representing the general population mortality, which is at approximately 10 years. We suggest that the wording around the discussion of survival extrapolation is updated to accurately reflect the company approach. Suggested alternative wording to replace the current text in Section 3.9: "The clinical experts considered both extrapolations plausible. The committee agreed that the proportional hazards assumption was met for the duration of the trial but considered both approaches to invasive disease-free survival modelling as possibly plausible."

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.
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