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NICE National Institute for Health and Care Excellence

Neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

2nd Appraisal Committee meeting

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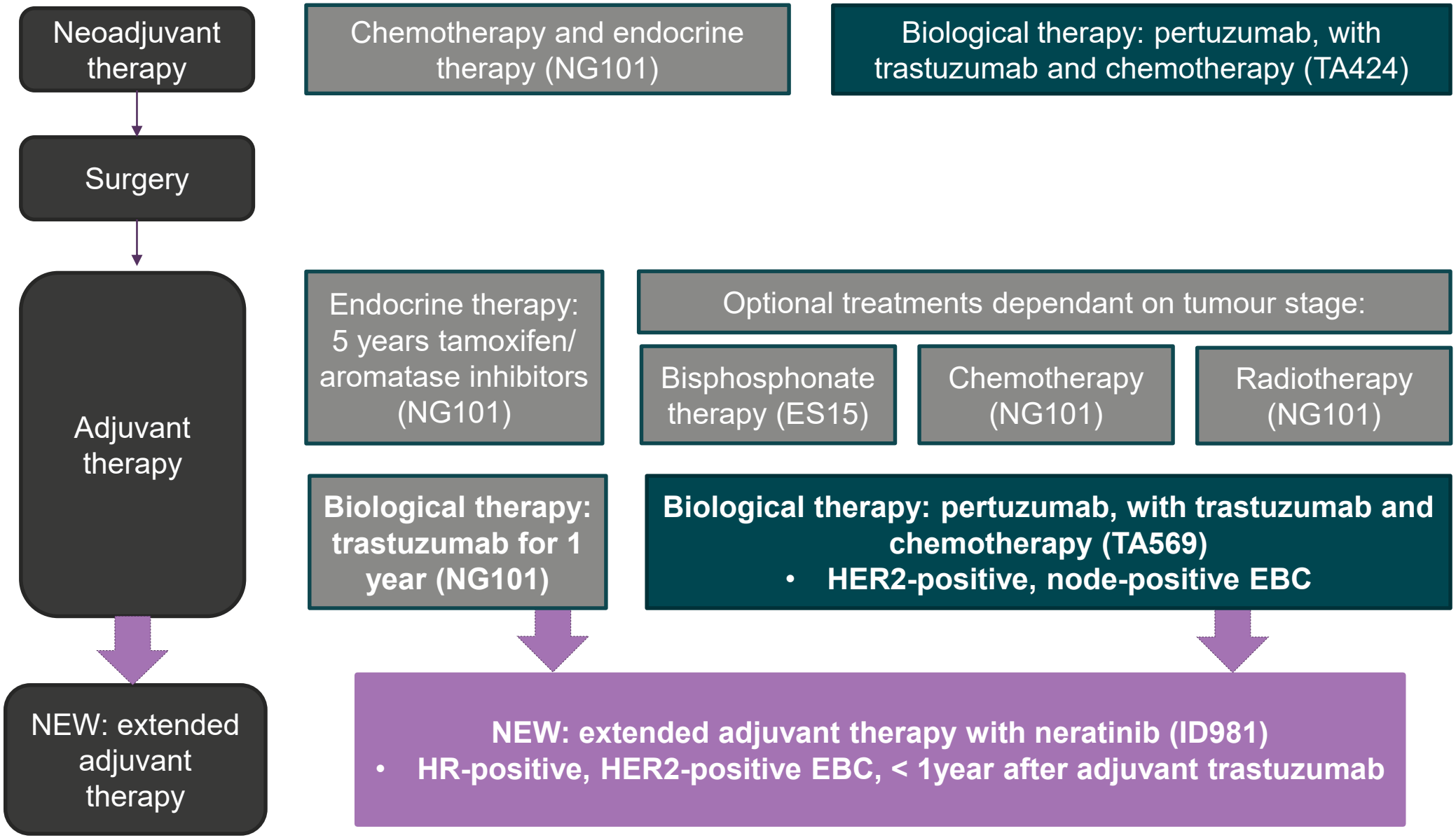
Neratinib (Nerlynx, Pierre Fabre)

- Tyrosine kinase inhibitor that blocks signal transduction through epidermal growth factor receptors (ErbB1/HER1, ErbB2/HER2 & ErbB4).

Marketing authorisation (August 2018)	Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.
Administration	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year.

Treatment Pathway: HR+ HER2+ EBC



ACD recommendation

1 Recommendations

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 (see section 2).

[redacted]

ACD committee considerations

- Neratinib is an oral treatment in a new place in the pathway.
- Treatment pathway has changed. Pertuzumab alongside trastuzumab is recommended for adjuvant treatment in HER2-positive early stage breast cancer with lymph node positive disease.
- Some people who did not receive adjuvant pertuzumab would benefit from extended adjuvant treatment with neratinib. However, it is unclear which people would receive neratinib in clinical practice.
- OS data are immature. Final ITT analysis after 248 events (~[redacted]). Final label population analysis in [redacted] as more events will be needed and these are likely to happen later.
- It is unclear how to model iDFS. Both ERG's and company's approach could be plausible.
- ERG's approach to modelling neratinib treatment effect and duration is appropriate
- The cost-effectiveness estimates are uncertain, but within the range NICE normally considers an acceptable use of NHS resources
- **There is no evidence for neratinib in people with a pathological complete response after neoadjuvant treatment**
- **There is no evidence for neratinib in people who have had pertuzumab treatment**

[redacted]

ACD cost-effectiveness results - including neratinib PAS

Alteration	Notes	PAS ICER
Company post TE base-case	**age-adjusted utilities added post TE (same as ERG)**	[redacted]
1. Lidgren et al. 2007 utility for distant recurrence state instead of Lloyd et al. 2006	Issue 6 – Utilities used in the model	[redacted]
2. Stratified generalised gamma to model iDFS instead of flexible-spline Weibull with 1 knot	Issue 3 – Invasive disease-free survival modelling	[redacted]
3. Declining treatment effect at 140 months (11.67 years) instead of 166.8 months (13.9 years).	Issue 4 – Duration and type of treatment effect	[redacted]
ERG's post TE base case (cumulative assumptions 1-3)	**ExteNET dose ([redacted]) post TE (same as company)**	[redacted]

[redacted]

ACD consultation responses

- Consultee comments from:
  - Company
  - Breast Cancer Care and Breast Cancer Now

- No commentator or web comments were received

[redacted]

Consultee ACD comments

- **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.

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.

[redacted]

Company's ACD comments

- Proposed changes to ACD draft recommendation wording to clarify:
  - **neratinib use after trastuzumab adjuvant therapy.**

  Clarity regarding adjuvant and extended adjuvant treatment planning.

  Ensure, that the wording does not limit the use of neratinib if trastuzumab is replaced in the future with alternative treatments, such as biosimilars.

  - **neratinib use after neoadjuvant therapy**.

  ExteNET inclusion criteria: *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.

[redacted]

Company's proposed wording:

1 Recommendations

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**-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'

- if they had neoadjuvant **chemotherapy-based regimens** ~~treatment~~, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and

[redacted]

Company's ACD comments continued

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*….

- **Company:** decision about the most suitable treatment would be based on both clinical judgement and patient preferences.

  Company's proposed text:*…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.*

[redacted]

Company's ACD comments continued

Section 3.9:…*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.*

- **Company**: wording around the discussion of survival extrapolation should be updated to accurately reflect the company's approach.

  Company's proposed text:…*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.*

[redacted]

Neratinib Blueteq criteria for use

…

6. The patient has completed adjuvant therapy with trastuzumab as HER2-targeted monotherapy and is within 1 year of completing such trastuzumab monotherapy.

Note: NICE has not recommended use of neratinib if the patient received any pertuzumab as part of adjuvant therapy. ***Patients treated with neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab are only eligible for neratinib therapy if the pertuzumab was solely used as part of neoadjuvant treatment and no pertuzumab was used as part of adjuvant therapy.***

…

[redacted]

Key issues

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***
  - NICE biosimilar position statement: …*all relevant published guidance that includes the originator molecule will apply to the biosimilar medicinal product at the time it is made available for use in the NHS…*
- ***if they had neoadjuvant treatment, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and ...***
  - does not exclude people with prior neoadjuvant pertuzumab therapy
  - excludes people without residual disease after all types of neoadjuvant therapy

Does the current wording make it clear who neratinib is recommended for?

[redacted]