# Lead team presentation

# Pertuzumab for the adjuvant treatment of HER2-positive breast cancer

For committee, projector and the public

1st Appraisal Committee meeting

**Background and clinical effectiveness**

Committee A

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Assessment Group: Warwick Evidence

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22 May 2018

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## Key decision points

1. If recommended, would pertuzumab in combination with trastuzumab and chemotherapy as an adjuvant treatment only be available to patients who had not already received this treatment in the neoadjuvant setting?
2. The APHINITY trial did not include people who had prior neoadjuvant therapy (biologic or chemo). How generalizable are the results of the trial?
3. Is invasive disease-free survival (IDFS) a reliable surrogate outcome?
4. Does adding pertuzumab to trastuzumab and chemotherapy result in a meaningful clinical benefit in the ITT population?
5. Which of the APHINITY subgroups were pre-specified? Is the presentation of statistical analyses of these subgroups appropriate?
6. Are lymph-node positive patients and hormone receptor negative patients clinically relevant subgroups?
7. Does the committee accept that pertuzumab has a greater treatment effect in the lymph-node positive population compared to the overall HER2+ population and other subgroups?
8. Are there any other subgroups who fall within marketing authorisation that are clinically relevant/might be expected to experience greater treatment benefit (the exclusion of other subgroups was not justified)?

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# Early or locally advanced breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast.
  - Approximately 46,500 people diagnosed with breast cancer in England in 2014
  - Third most common cause of cancer death in 2014.
- Terminology and clinical staging:
  - 'Early' breast cancer describes tumours that are restricted to the breast, or the breast and nearby lymph nodes and have not spread to other parts of the body (clinical stages 1 and 2)
  - 'Locally advanced' breast cancer describes tumours larger than 5 cm that may have grown into the skin or muscle of the chest or nearby lymph nodes but have not spread to other parts of the body (clinical stage 3)
  - Around 35% of those with early or locally advanced disease will progress to metastatic breast cancer. 5 year survival rate for metastatic breast cancer in England is 15%

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# Human epidermal growth factor receptor 2 (HER2)

- Human epidermal growth factor is a naturally occurring protein in the body that attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cancer cells to divide and grow.
- Some breast cancer cells overexpress HER2 receptors and are described as HER2-positive.
- It is estimated that approximately 15-25% of women with breast cancer will have HER2-positive tumours (men are less likely to have HER-2 positive breast cancers).
- HER2-positive tumours:
  - are associated with aggressive disease and poor prognosis, and,
  - patients are ~5 years younger than the average breast cancer population

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# Patient perspective

"All treatments have side effects. Treatment with chemotherapy usually has a number of unpleasant side effects which can have a significant impact on everyday activities, ability to work, social life and relationships. Hormone therapy can also have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy. Targeted therapies for HER2 breast cancer tend to be better tolerated"

"A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking and in the longer-term, the fear of breast cancer returning or spreading […] can cause considerable stress for both the patients and their loved ones"

"Any treatment that improves outcomes is a welcome step forward"

"One potential disadvantage [of pertuzumab is] its method of administration […] Patients may need to spend longer in hospital to receive this treatment as pertuzumab and trastuzumab will be delivered intravenously where given together. However, the reduced risk of recurrence may outweigh the potential inconvenience to patients of spending longer in hospital"

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# Pertuzumab (Perjeta)

| | |
|---|---|
| **Mechanism of action** | Pertuzumab is a recombinant monoclonal antibody which targets HER2-positive breast tumours. The antibody binds to HER2 receptor proteins on breast cancer cells. In doing so it prevents the HER2 receptors from binding to growth factor proteins which can cause the cancer cells to divide and grow |
| **Positive CHMP opinion received on 26th April 2018** | In combination with trastuzumab and docetaxel as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of disease recurrence |
| **Administration** | Intravenous (IV) in combination with trastuzumab and docetaxel for a total of one year (maximum of 18 cycles) regardless of the timing of surgery. |
| **Dose** | 840 mg loading dose, then 420 mg every three weeks |
| **Cost (list price)** | £2,395 per 420 mg vial |
| **Patient access scheme** | Commercial access agreement approved by Department of Health which provides a simple discount to list price |

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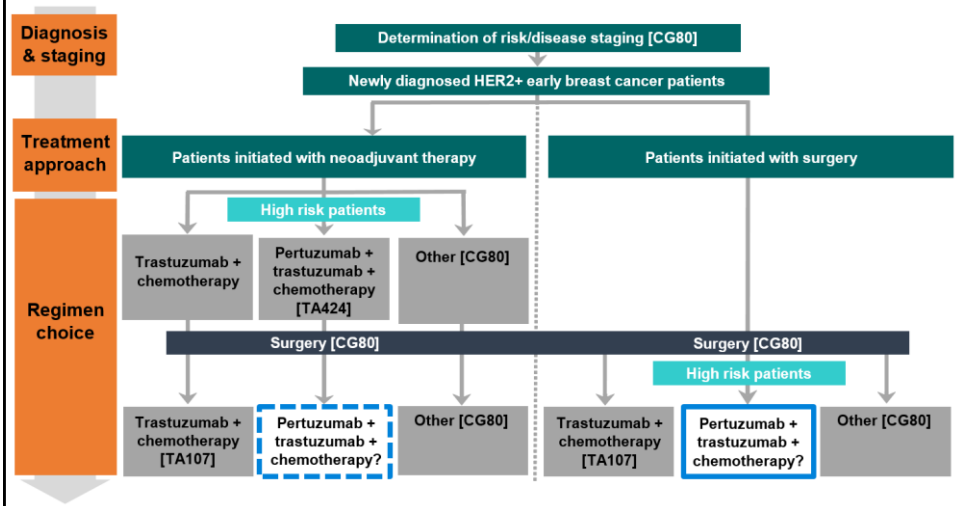
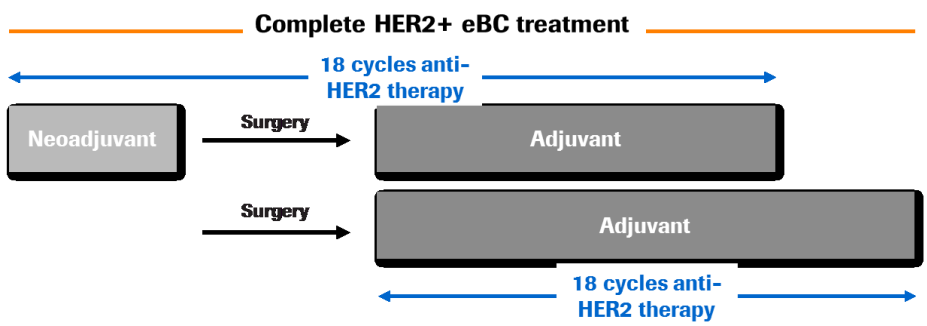
# How is HER2-positive breast cancer treated?




NICE clinical guideline 80 states patients with early invasive breast cancer, irrespective of age, should be treated with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. Radiotherapy is only recommended by NICE in the adjuvant (post-surgical) setting. 7

# Neoadjuvant and adjuvant treatment




- The goal of systemic neoadjuvant treatment is to reduce the tumor size to render it operable and de-escalate surgery
- The goal of systemic adjuvant treatment is to reduce the risk of micrometastases

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# Decision problem – NICE vs. Company

## Population in company's decision problem is in line with marketing authorisation

| Population | |
|---|---|
| NICE scope | Company submission |
| People with early or locally advanced HER2-positive breast cancer who have undergone surgery | People with early or locally advanced HER2-positive breast cancer who have undergone surgery *and are at **high risk of recurrence*** |

Company submission notes that lymph node-positive and hormone (oestrogen or progesterone) receptor-negative patients are at higher risk of recurrence

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# Decision problem – NICE vs. Company

## Company's decision problem reflects APHINITY trial outcomes

| Outcomes | |
|---|---|
| NICE scope | Company submission |
| • Overall survival (OS)<br>• Disease-free survival (DFS)<br>• Recurrence-free interval (RFI)<br>• Adverse effects of treatment<br>• Health-related quality of life (HRQoL) | • OS<br>• Disease Free Survival<br>• Recurrence-free interval (RFI)<br>• Adverse effects of treatment<br>• HRQoL<br>• Invasive Disease-Free Survival (IDFS) *excluding* second primary non-breast cancer events *[this was the primary endpoint in the APHINITY trial and company submission]*<br>• IDFS (including second primary non-breast cancer events [STEEP definition])<br>• Distant recurrence-free interval (DRFI) |

The company's primary IDFS endpoint was defined as *"time from randomization until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause"*

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# Key trial: APHINITY study

| | |
|---|---|
| Design | Phase III, randomised, double-blind placebo-controlled trial |
| Population | Patients **newly diagnosed** with primary invasive HER2-positive breast cancer (N=4,805) |
| Intervention | Pertuzumab + trastuzumab + standard chemotherapy |
| Comparator | Placebo + trastuzumab + standard chemotherapy |
| Primary outcomes | IDFS excluding second primary non-breast cancer events |
| Secondary outcomes | IDFS including second primary non-breast cancer (STEEP definition); DFS; OS; RFI; DRFI; cardiac safety; overall safety; HRQoL |
| Follow-up | 3-years |
| Stratification groups | **Nodal status**, chemotherapy regimen, **hormone receptor status**, geographic region, and **protocol version (A or B)** |

The company's submission includes clinical evidence for the ITT population but the main economic model is specific patients with lymph node-positive disease. They also present cost effectiveness data for patients with hormone (oestrogen or progesterone) receptor-negative disease:

- These subgroups were named in the NICE scope
- The APHINITY study was not powered for subgroups
- The company stated that after 3,655 patients, the protocol was amended to prevent further enrolment of patients with node-negative disease; an additional 1,000 node-positive patients were then included

Differences in baseline characteristics across ITT treatment groups were not tested for statistical significance but appeared well balanced

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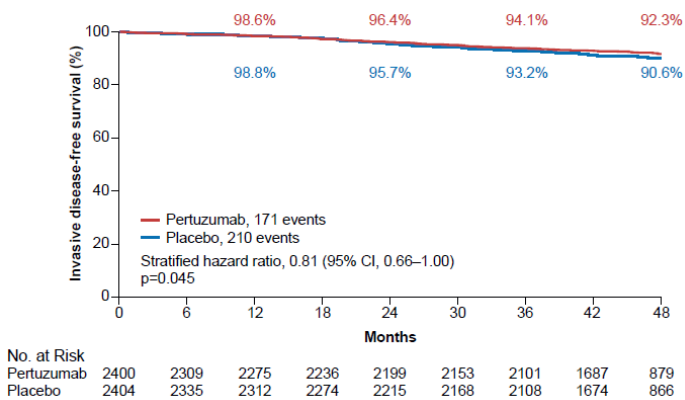
# Primary outcome: IDFS excluding second primary non-breast cancer events

## Marginal benefit in ITT population




The pre-specified primary analysis was conducted after 379 IDFS events (19th December 2016) in the ITT population. The 3-year event-free rates were derived from Kaplan-Meier estimates. Hazard ratio (95% CIs) was estimated by Cox-regression.

- Treatment benefit but borderline statistical significance - ERG note company assumption that effect was maintained until year 7 not well substantiated (shorter treatment duration assessed by the ERG)
- ERG noted that curves only begin to diverge around 20 months – treatment effect appears delayed

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# IDFS in ITT population cont.

## Results for primary and secondary IDFS outcomes are similar

| Outcome definition | Pertuzumab (n=2,400) | Placebo (n=2,404) | HR (95% CI; P value) |
|---|---|---|---|
| **Primary outcome: IDFS excluding second primary non-breast cancer events** | 94.1 | 93.2 | 0.81 (0.66, 1.00; 0.045) |
| **Secondary outcome: IDFS including second primary non-breast cancer events** | 93.5 | 92.5 | 0.82 (0.68, 0.99; 0.043) |

- **In the ITT population findings are very similar for both IDFS definitions**
- Primary outcome was associated with the more conservative of the two estimates of effect. The use of this IDFS *excluding* second primary non-breast cancer events is unlikely to result in overestimation of treatment benefit compared to the secondary outcome definition
- However, the treatment effect is of borderline statistical significance and the **ITT population data were not used in the company's economic analysis**

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# Secondary efficacy outcomes for ITT population

## Marginal benefit in DFS and RFS

| Outcome | Pertuzumab (n=2,400) | Placebo (n=2,404) | HR (95% CI); P value |
|---|---|---|---|
| **Overall survival (OS)** | 97.7 | 97.7 | 0.89 (0.66, 1.21; 0.467) |
| **Disease-free survival (DFS)** | 93.4 | 92.3 | 0.81 (0.67, 0.98; 0.033) |
| **Recurrence-free interval (RFS)** | 95.2 | 94.3 | 0.79 (0.63, 0.99; 0.043) |
| **Distant recurrence-free interval (DRFI)** | 95.7 | 95.1 | 0.82 (0.64, 1.04; 0.101) |

- DFS and RFI show borderline statistically significant treatment benefit
- No survival benefit –data are immature (only 26% events required for the final analysis of OS having occurred [i.e. 169 /640 deaths planned final OS analysis])
- ERG noted that Kaplan-Meier plots were not presented for the secondary outcomes

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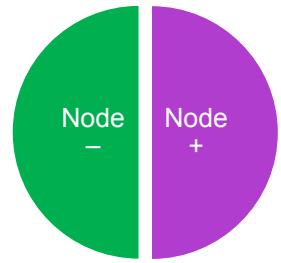
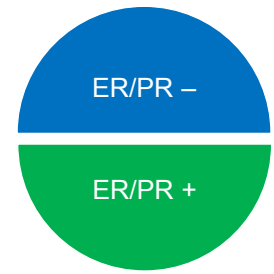
# Subgroups prioritised by company


**ITT population HER2+ N=4,805; Pertuzumab n=2,400 vs. Placebo n=2,404**
*(Safety population N=4,769; Pertuzumab n=2,364 vs. Placebo n=2,405)*




**Prioritised Node-positive subgroup n=3,005; Pertuzumab n=1,503 vs. Placebo n=1,502**



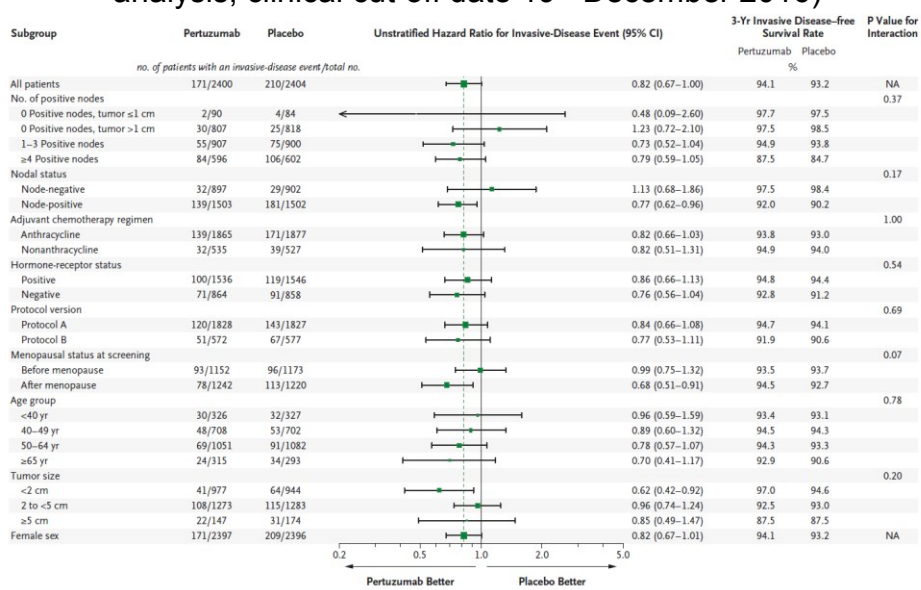

**Also considered Hormone receptor-negative subgroup n=1722; pertuzumab n=864 vs. placebo n=858**

*The ERG noted that baseline characteristics were well balanced across the treatment arms of the nodal status and hormone-receptor subgroups*

Patients with node-negative tumours between 0.5 and 1.0 cm were initially eligible if they met one of three additional criteria: tumour grade 3, age <35 years, or hormone-receptor (ER/PgR) positive. However, enrollment of patients with node-negative tumors ≤1 cm was limited to <10% of the total number of randomised patients and **following the protocol amendment patients with node-negative disease were excluded completely**

# Subgroup results – IDFS

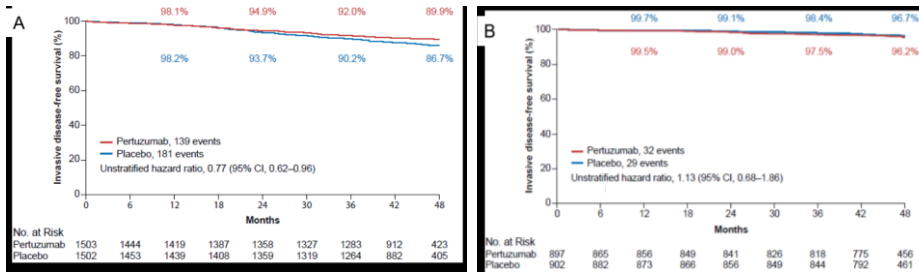
## Forest plot for different subgroups in the ITT population (primary analysis, clinical cut-off date 19th December 2016)



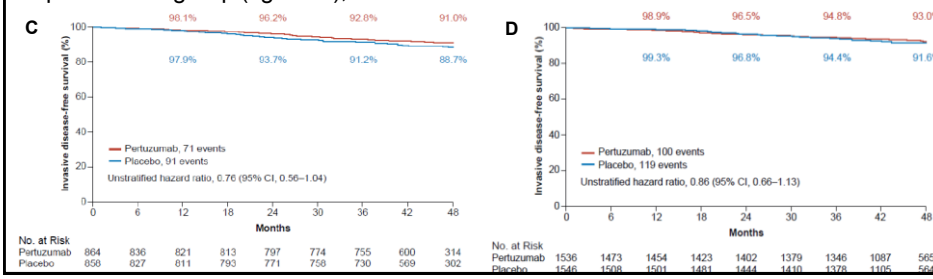
| Subgroup | Pertuzumab | Placebo | Unstratified Hazard Ratio for Invasive-Disease Event (95% CI) | 3-Yr Invasive Disease–free Survival Rate | | P Value for Interaction |
|---|---|---|---|---|---|---|
| | | | | Pertuzumab | Placebo | |
| | *no. of patients with an invasive-disease event/total no.* | | | % | | |
| All patients | 171/2400 | 210/2404 | 0.82 (0.67–1.00) | 94.1 | 93.2 | NA |
| No. of positive nodes | | | | | | 0.37 |
| 0 Positive nodes, tumor ≤1 cm | 2/90 | 4/84 | 0.48 (0.09–2.60) | 97.7 | 97.5 | |
| 0 Positive nodes, tumor >1 cm | 30/807 | 25/818 | 1.23 (0.72–2.10) | 97.5 | 98.5 | |
| 1–3 Positive nodes | 55/907 | 75/900 | 0.73 (0.52–1.04) | 94.9 | 93.8 | |
| ≥4 Positive nodes | 84/596 | 106/602 | 0.79 (0.59–1.05) | 87.5 | 84.7 | |
| Nodal status | | | | | | 0.17 |
| Node-negative | 32/897 | 29/902 | 1.13 (0.68–1.86) | 97.5 | 98.4 | |
| Node-positive | 139/1503 | 181/1502 | 0.77 (0.62–0.96) | 92.0 | 90.2 | |
| Adjuvant chemotherapy regimen | | | | | | 1.00 |
| Anthracycline | 139/1865 | 171/1877 | 0.82 (0.66–1.03) | 93.8 | 93.0 | |
| Nonanthracycline | 32/535 | 39/527 | 0.82 (0.51–1.31) | 94.9 | 94.0 | |
| Hormone-receptor status | | | | | | 0.54 |
| Positive | 100/1536 | 119/1546 | 0.86 (0.66–1.13) | 94.8 | 94.4 | |
| Negative | 71/864 | 91/858 | 0.76 (0.56–1.04) | 92.8 | 91.2 | |
| Protocol version | | | | | | 0.69 |
| Protocol A | 120/1828 | 143/1827 | 0.84 (0.66–1.08) | 94.7 | 94.1 | |
| Protocol B | 51/572 | 67/577 | 0.77 (0.53–1.11) | 91.9 | 90.6 | |
| Menopausal status at screening | | | | | | 0.07 |
| Before menopause | 93/1152 | 96/1173 | 0.99 (0.75–1.32) | 93.5 | 93.7 | |
| After menopause | 78/1242 | 113/1220 | 0.68 (0.51–0.91) | 94.5 | 92.7 | |
| Age group | | | | | | 0.78 |
| <40 yr | 30/326 | 32/327 | 0.96 (0.59–1.59) | 93.4 | 93.1 | |
| 40–49 yr | 48/708 | 53/702 | 0.89 (0.60–1.32) | 94.5 | 94.3 | |
| 50–64 yr | 69/1051 | 91/1082 | 0.78 (0.57–1.07) | 94.3 | 93.3 | |
| ≥65 yr | 24/315 | 34/293 | 0.70 (0.41–1.17) | 92.9 | 90.6 | |
| Tumor size | | | | | | 0.20 |
| <2 cm | 41/977 | 64/944 | 0.62 (0.42–0.92) | 97.0 | 94.6 | |
| 2 to <5 cm | 108/1273 | 115/1283 | 0.96 (0.74–1.24) | 92.5 | 93.0 | |
| ≥5 cm | 22/147 | 31/174 | 0.85 (0.49–1.47) | 87.5 | 87.5 | |
| Female sex | 171/2397 | 209/2396 | 0.82 (0.67–1.01) | 94.1 | 93.2 | NA |

# IDFS in subgroups prioritised by company

IDFS in lymph node-positive subgroup (figure A) and in lymph node-negative subgroup (figure B); P value for interaction: 0.17




IDFS in hormone receptor-negative subgroup (figure C) or hormone receptor positive subgroup (figure D); P value for interaction: 0.54




# IDFS in ITT vs. lymph node subgroups

| Population | F/U | Pertuzumab | Placebo | HR (95% CI) |
|---|---|---|---|---|
| **ITT population (N=4,804)** | | n=2,400 | n=2,404 | |
| **Median f/u: 45.4 mo** | 3 years | 94.1 | 93.2 | 0.81 (0.66, 1.00) |
| | 4 years | 93.2 | 90.6 | |
| **Lymph node-positive patients (n=3,005)** | | n=1,503 | n=1,502 | |
| | 3 years | 92.0 | 90.2 | 0.77 (0.62, 0.96) |
| **Median f/u: 44.5 mo** | 4 years | 89.9 | 86.7 | |
| **Lymph node-negative patients (n=1,799)** | | n=897 | n=902 | |
| | 3 years | 97.5 | 98.4 | 1.13 (0.68-1.86) |
| **Median f/u: 48.3 mo** | 4 years | 96.2 | 96.2 | |

- **IDFS is only efficacy outcome reported for both ITT and subgroups**
  - Node positive population – company suggest clearer evidence of benefit compared to ITT
  - Trend in event rates continues at 4 years
- Committee to consider
  - Uncertainty regarding true effect size; upper bound of confidence interval in node-positive population = 0.96
  - Does the evidence show meaningful benefit in the population outlined in the MA (patients at high risk of recurrence)?

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# IDFS in ITT vs. hormone receptor subgroups

| Population | F/U | Pertuzumab | Placebo | HR (95% CI) |
|---|---|---|---|---|
| ITT population (N=4,804) | | n=2,400 | n=2,404 | |
| Median f/u: 45.4 mo | 3 years | 94.1 | 93.2 | 0.81 (0.66, 1.00) |
| | 4 years | 93.2 | 90.6 | |
| Hormone receptor-negative patients (n=1,722) | | n=864 | n=856 | |
| Median f/u: NR | 3 years | 92.8 | 91.2 | 0.76 (0.56, 1.04) |
| | 4 years | 91.0 | 88.7 | |
| Hormone receptor-positive patients (n=3,082) | | n=1,536 | n=1,546 | |
| Median f/u: | 3 years | 94.8 | 94.4 | 0.86 (0.66, 1.13) |
| | 4 years | 93.0 | 91.6 | |

- **IDFS is only efficacy outcome reported for both ITT and subgroups**
  - Hormone receptor negative – lower point estimate than ITT but results are not statistically significant
  - Trend in event rates continues at 4 years
- Committee to consider
  - Does the evidence show meaningful benefit in the population outlined in the MA (patients at high risk of recurrence)?

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# Adverse events – Safety population

- Over 99% of patients in both arms experienced at least one adverse event during the treatment period (pertuzumab: 99.9%; placebo: 99.5%)
- Statistical significance of differences between treatment arms was not reported in company submission but was investigated by ERG – see below

| Most frequently reported AEs for pertuzumab | Pertuzumab (N=2,364) | Placebo (N=2,405) | ERG P values |
|---|---|---|---|
| Nausea | 69.0% | 65.5% | 0.009 |
| Diarrhoea | 71.2% | 45.2% | <0.0001 |
| Fatigue | 48.8% | 44.3% | 0.002 |
| Stomatitis | 28.4% | 23.8% | 0.0003 |
| Anaemia | 27.7% | 23.2% | 0.0003 |
| Dysgeusia | 26.0% | 21.5% | 0.0003 |
| Rash | 25.8% | 20.3% | <0.0001 |
| Decreased appetite | 23.9% | 19.9% | 0.0008 |
| Mucosal inflammation | 23.4% | 18.6% | <0.0001 |
| Epistaxis | 18.2% | 13.6% | <0.0001 |

15 other adverse events also reported with ≥15% incidence in at least one arm but differences were not statistically significant: alopecia, arthralgia, constipation, myalgia, vomiting, neutropenia, headache, asthenia, hot flush, pyrexia, oedema peripheral, peripheral sensory neuropathy, insomnia, neuropathy peripheral, cough

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# Adverse events in safety population cont.

**Fatal and serious adverse events**

- Higher incidence of grade ≥3 AEs in the pertuzumab arm – company note mainly driven by diarrhoea but ERG found anaemia was also statistically worse

**Cardiac safety events**

- Almost double the number of patients in the pertuzumab arm had primary cardiac event (n=17 versus n=8 in the placebo arm) but overall percentage of patients in either arm experiencing this type of event was very low (0.7% and 0.3% respectively). Secondary cardiac event rates similar across groups: pertuzumab group n=64 (2.7%); placebo group n=67 (2.8%)
- NYHA class III or IV heart failure and substantial decrease in LVEF only cardiac event to be found statistically significant by ERG

| Event | Pertuzumab N=2,364 | Placebo N=2,405 | ERG Relative risk (95% CI) | ERG P value |
|---|---|---|---|---|
| Deaths (total) | 73 (3.1%) | 95 (4.0%) | - | - |
| Fatal AE | 18 (0.8%) | 20 (0.8%) | 0.92 (0.49 to 1.73) | 0.787 |
| Grade ≥3 AE | 1,518 (64.2%) | 1,379 (57.3%) | 1.12 (1.07 to 1.17) | <0.0001 |
| Diarrhoea | 232 (9.8%) | 90 (3.7%) | 2.62 (2.07 to 3.32) | <0.0001 |
| Anaemia | 163 (6.9%) | 113 (4.7%) | 1.47 (1.16 to 1.85) | 0.001 |
| NYHA class III/IV heart failure and substantial decrease in LVEF | 15 (0.6) | 6 (0.2) | 2.54 (1.00 to 6.54) | 0.044 |

# Health-related quality of life (HRQoL) – ITT population

- HRQoL was measured in APHINITY ITT population using three validated tools (see below)
- The ERG noted
  - patients completed questionnaires at baseline, end of anthracycline treatment period (if applicable), end of taxane therapy, week 25, at the end of study treatment and at 18, 24 and 36 months post randomisation
  - completion rates were satisfactory (consistently above 85%)
- **Only the evidence from the EQ-5D was incorporated into the company's economic analyses - ERG note that the EQ-5D administration schedule was not designed to identify differences between treatment arms**

| | |
|---|---|
| EuroQol 5-Dimension (EQ-5D): | Generic, non-disease specific QoL questionnaire |
| European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) | General cancer QoL measure |
| EORTC QLQ-BR23 | Breast cancer-specific QoL measure |

# HRQoL in ITT population cont.

## EQ-5D results vs. other PRO measures

| | |
|---|---|
| **EQ-5D** | • No differences (≥5%) between treatment arms in the EQ-5D domains |
| **EORTC QLQ-C30** | ERG note:<br>• Whilst no MCID was observed between the treatments, average scores consistently lower (worse) for pertuzumab arm<br>• Changes from baseline at week 13 greater than MCID were observed for physical functioning scale in both arms, but not for other functional scales (role, emotional, cognitive and social)<br>• Changes in physical function from baseline were similar between arms (-10.7 vs -10.6, pertuzumab vs placebo)<br>• Mean (SD) change from baseline at 1 year for diarrhoea symptoms exceeded MCID in the pertuzumab arm (22.3 (29.8) vs. 9.2 (23.9)) |
| **EORTC QLQ-BR23** | ERG note:<br>• Decrease (exceeding the MCID) in scores from baseline to end of taxane treatment for both body image and sexual enjoyment in both arms<br>• Decrease in sexual enjoyment sustained until HER2 treatment end in pertuzumab arm but not placebo arm<br>• Other findings not clearly reported |

**EORTC QLQ-C30 / QLQ-BR23 more sensitive to the impact of AEs – statistical differences NR**

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# ERG's critique – clinical evidence

## Evidence of treatment efficacy is not robust

1. The ERG considered the outcomes of the trial to be appropriate
2. **Treatment effect measured by IDFS in the ITT population was marginal**
   - in contrast to stratified HR of 0.81 (95% CI: 0.66, 1.00; p=0.045), unstratified log-rank test yielded a HR of 0.82 (p=0.0549) which was not statistically significant at 0.05 threshold
3. The **results of the trial may not be a reliable estimate of the true treatment effect**
   - hazard ratios produced from the comparison of KM data using stratified Cox models unlikely to be reliable because test assumes proportional hazards were maintained throughout treatment
   - the 0.05 significance threshold for p values may not be appropriate. **None of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity**
4. Although there was a small statistically significant benefit in IDFS in the ITT population there was no consistent difference in effect until roughly 20 months

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# ERG's critique – clinical evidence

## Evidence of HRQoL unlikely to have captured real impact of adverse events.

5. The **patient reported outcome measures (PROMs) data reported in the APHINITY trial may underrepresent the true HRQoL impact of the treatments** due to the methods and timings of data capture in this study
   - the infrequency of the collection of the PROMs during the APHINITY trial means that they potentially failed to capture the effects of adverse events
   - the evidence of increased frequency of adverse events provides some evidence that pertuzumab may be associated with a slightly worse HRQoL
     - this is not represented in the summaries of the PROMs
     - it can be seen in the difference in mean diarrhoea score from the QLQ-C30

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# ERG's critique – clinical evidence

## Adverse events

6. Only **events that occurred in at least 15% of patients in either arm were reported. The ERG considers this threshold to be rather high**, but were unable to compare it against pre-existing thresholds due to the lack of previous technology appraisals evaluating adjuvant early breast cancer treatments
7. Evidence suggests **pertuzumab has a worse safety profile** than placebo
   - **Incidence** grade ≥3 adverse events higher in pertuzumab arm p<0.0001
   - **6% higher rate of grade 3/4 diarrhoea in the pertuzumab arm**
     - in line with data from other trials (CLEOPATRA/PHEREXA)
     - recurrence of episodes were not reported (may be an underestimate)
   - Significantly higher rates of grade ≥3 anaemia in the pertuzumab arm (p=0.001)
   - Incidence of **NYHA class III of IV heart failure with a substantial decrease in LVEF**) **statistically worse in pertuzumab arm (0.6% vs. 0.2%, p=0.04)**
   - Association between pertuzumab and heart disease (clinical adviser)

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# ERG's critique – clinical evidence cont.

## Company's consideration of clinically relevant subgroups

8. The APHINITY trial was not powered to detect subgroup differences; lack of clarity in the supporting documentation regarding the point at which nodal status was prioritised for subgroup analysis
9. ERG unconvinced of pertuzumab efficacy for the hormone receptor-negative population
10. ERG concerned lack of evidence of efficacy in the node-negative population is being treated as evidence that the drug is ineffective in this subgroup

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# Key decision points

1. If recommended, would pertuzumab in combination with trastuzumab and chemotherapy as an adjuvant treatment only be available to patients who had not already received this treatment in the neoadjuvant setting?
2. The APHINITY trial did not include people who had prior neoadjuvant therapy (biologic or chemo). How generalizable are the results of the trial?
3. Is invasive disease-free survival (IDFS) a reliable surrogate outcome?
4. Does adding pertuzumab to trastuzumab and chemotherapy result in a meaningful clinical benefit in the ITT population?
5. Which of the APHINITY subgroups were pre-specified? Is the presentation of statistical analyses of these subgroups appropriate?
6. Are lymph-node positive patients and hormone receptor negative patients clinically relevant subgroups?
7. Does the committee accept that pertuzumab has a greater treatment effect in the lymph-node positive population compared to the overall HER2+ population and other subgroups?
8. Are there any other subgroups who fall within marketing authorisation that are clinically relevant/might be expected to experience greater treatment benefit (the exclusion of other subgroups was not justified)?

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## Back up slides

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## Patient characteristics – ITT population

| Characteristic | Pertuzumab | Placebo |
|---|---|---|
| Age, median, range (years) | 51.0 (22–86) | 51.0 (18–85) |
| <65 years<br>≥65 years | 86.9%<br>13.1% | 87.8%<br>12.2% |
| Race, white / Asian / Other | 71.2 / 24.7 / 4.1% | 70.5 / 24.9 / 4.6% |
| USA | 12.3% | 12.2% |
| Canada/Western Europe/ Australia-New Zealand/South Africa | 53.9% | 53.6% |
| Eastern Europe | 8.3% | 8.3% |
| Asia-Pacific / Latin America | 22.9 / 2.5% | 23.2 / 2.7% |
| Type of primary surgery | | |
| Mastectomy / Breast conserving surgery | 53.3 / 46.7% | 55.2 / 44.8% |
| Adjuvant radiotherapy | | |
| Yes / no | 72.2 / 27.8 | 72.8 / 27.2 |

Differences across ITT treatment groups were not tested for statistical significance but appeared well balanced

**Question for committee: is this evidence generalizable to English population?**

# Treatment discontinuation in ITT population vs. lymph-node positive subgroup

| | Pertuzumab N=2,400 | Placebo N=2,404 |
|---|---|---|
| **ITT population** | | |
| Discontinued treatment | 15.5% | 12.6% |
| Discontinued for safety reasons | 7.8% | 6.4% |
| Adverse events | 7.3% | 6.2% |
| Death | 0.4% | 0.2% |
| Pregnancy | <0.1% | 0.0% |
| **Lymph-node positive subgroup** | | |
| Discontinued treatment | 15.6% | 13.3% |
| Discontinued for safety reasons | 8.0% | 6.8% |
| Adverse events | 7.5% | 6.5% |
| Death | 0.4% | 0.3% |
| Pregnancy | <0.1% | 0.0% |

ERG found difference in discontinuations between pertuzumab and placebo to be statistically significant (p=0.005)

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