Slides for Public Handout

# Palbociclib for the treatment of postmenopausal people with metastatic, hormone receptor-positive, human epidermal growth factor receptor 2-negative (HER2-) breast cancer previously untreated in the metastatic setting

2nd Appraisal Committee meeting

Committee A

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ERG: Liverpool Reviews & Implementation Group

NICE technical team: Anwar Jilani, Thomas Strong, Joanna Richardson, Janet Robertson

Company: Pfizer

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# Palbociclib

- ACD: not recommended
- Marketing authorisation (November 2016)

  for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer

  – *in combination with an aromatase inhibitor* **(subject of this appraisal)** or

  – in combination with fulvestrant in women who have received prior endocrine therapy.
- Administration:
  – Orally in combination with an aromatase inhibitor
  – 125mg once daily for 21 consecutive days, followed by 7 days off treatment

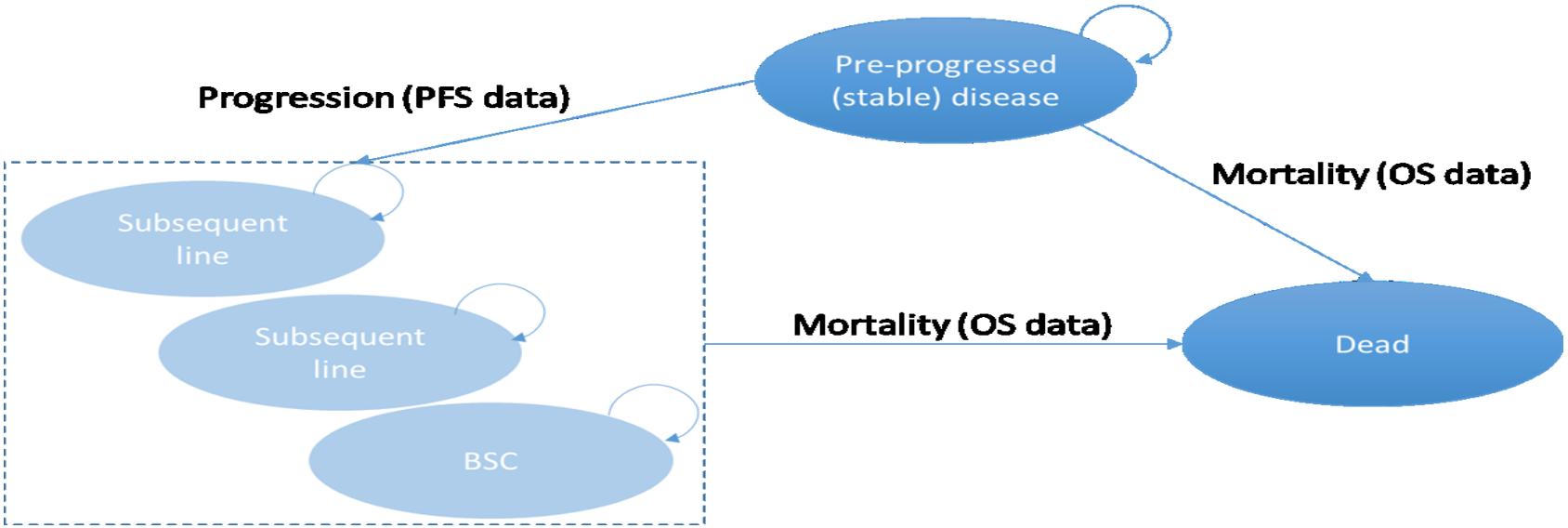
# Clinical evidence

| Outcome | Palbociclib-letrozole | Letrozole | Difference | HR(95%CI) |
|---|---|---|---|---|
| PALOMA-1, Phase I/II open label study, N=165 | | | | |
| PFS (median months) | | | | |
| investigator | 20.2 | 10.2 | **10** | 0.488 (0.319 to 0.748) |
| BICR | 25.7 | 14.8 | **10.9** | 0.621 (0.378 to 1.019) |
| OS (median months) | | | | |
| Interim analysis | 37.5 | 33.3 | **4.2** | 0.813 (0.492 to 1.345) |
| Final analysis* | [redacted] | [redacted] | [redacted] | [redacted] |
| PALOMA-2, Phase III, double-blinded, RCT, N=666 | | | | |
| PFS (median months) | | | | |
| investigator | 24.8 | 14.5 | **10.3** | 0.576 (0.463 to 0.718) |
| BICR | 30.5 | 19.7 | **10.8** | 0.653 (0.505 to 0.844) |

* Submitted at ACD consultation stage

# Company's model

- Partitioned survival model
- PFS from PALOMA-2+ Weibull extrapolation
- OS from PALOMA-1+ Weibull; adjusted to maintain median PFS gain in PALOMA 2



# Company base-case ICERs (deterministic)

| Technologies | Total costs (£) | Total LYs | Total QALYs | Incremental | | | ICER (£ per QALY) |
|---|---|---|---|---|---|---|---|
| | | | | Costs (£) | LYGs | QALYs | |
| **Company base case** | | | | | | | |
| **Letrozole** | £21,843 | 3.02 | 1.77 | | | | |
| **Palbociclib + letrozole** | £116,696 | 3.79 | 2.40 | £94,853 | 0.78 | 0.63 | **£150,869** |

**LY - Life year; QALY - Quality Adjusted Life Year; LYG - Life year gain; ICER - Incremental Cost Effectiveness Ratio**

**source: table 74, page 157 of the company submission**

# ERG's exploratory analyses

| Model scenario<br>ERG revision | Incremental | | ICER | ICER |
|---|---|---|---|---|
| | Cost (£) | QALYs | £/QALY | Change |
| **A. Company original base case** | £94,853 | 0.629 | ***£150,869*** | **-** |
| **ERG OS estimates based on data from PALOMA-1** | £90,977 | 0.481 | £189,310 | ***+£38,441*** |
| **ERG PFS estimates based on data from PALOMA-1** | £81,928 | 0.675 | £121,408 | ***-£29,461*** |
| **ERG TTD estimates based on data from PALOMA-1** | £64,712 | 0.629 | £102,928 | ***-£47,941*** |
| **ERG recalculated pre-progression utility values from PALOMA-2 trial** | £94,853 | 0.566 | £167,727 | ***+£16,858*** |
| **ERG recalculated post-progression utility values** | £94,853 | 0.628 | £151,146 | ***+£277*** |
| **Use mid-cycle correction** | £93,433 | 0.628 | £148,687 | ***-£2,182*** |
| **Use full reference costs for AEs** | £95,861 | 0.629 | £152,472 | ***+£1,603*** |
| **Correct AE incidence calculation** | £94,317 | 0.629 | £150,015 | ***-£854*** |
| **Change discounting to annual** | £96,262 | 0.639 | £150,710 | ***-£159*** |
| **Use 365.25 days per year** | £94,854 | 0.629 | £150,871 | ***+£2*** |
| **B. ERG revised base case** | £59,934 | 0.451 | ***£132,872*** | ***-£17,997*** |

# ACD: Key Committee Conclusions

| | |
|---|---|
| **PFS** | Significant improvement in progression-free survival |
| **Overall survival** | Expected that improved PFS would have some OS benefit<br>Size of benefit uncertain<br>Plausible OS gain lies somewhere between estimates by ERG (OS from PALOMA-1) and the company (OS gain assumed to be equal to PFS gain from PALOMA-2) |
| **Modelling of trial data** | Unable to judge whether it is more appropriate to mix PALOMA-1 PFS data and PALOMA-2 OS data or to use PALOMA-1 throughout |
| **Utility of PFS** | EQ-5D may not fully capture a person's preference to avoid future events (e.g delay in starting chemotherapy).<br>The company's utility values were based on data collected in PALOMA-2, and were in line with those used in other appraisals. |
| **Cost of comparator** | Could not accept cost effectiveness based on a hypothetical (expensive) comparator than current NHS practice. |
| **ICER** | although ERG and company used different modelling inputs assumptions, the resulting ICERs were very similar, ERG's estimate was slightly lower £132,872 than company's £150,869 |

# Comments on ACD consultation

## Consultees

- **Company**
- **Patient and professional:**
  - Breast Cancer Now (including annex of patient testimonials)
  - UK Breast Cancer Group
  - Breast Cancer care

## Clinical & patient experts

- None

## Comparators

- Novartis (letrozole)

## Web comments

- Patient x1; Professional x2; Carer x2

**The committee has received and considered the consultation comments in full**

# Patient, Professional, and Web comments

- Palbociclib is a clinically effective technology – increase in PFS is unprecedented
- Patients value improved PFS
- Unfair to compare with a cheaper generic treatment
- Unfair that PFS gains are undervalued in cost-effectiveness analyses compared with OS gains
- People diagnosed with metastatic breast cancer because of delayed diagnosis should have access to the most effective treatments
- Palbociclib should be considered under end-of-life criteria as metastatic breast cancer is an incurable condition
- Negative recommendation widens the gap in the standard of cancer care between England and other comparable countries
- Renegotiation between the relevant stakeholders should take place

# Company comments and additional analyses

- Company commented on ACD (submitted on 24 February 2017), focused on 3 aspects
  - Expected overall survival benefit
  - 'Undervaluing' of the utility of progression-free survival (compared with post progression survival)
  - Acquisition cost of 'generic' comparator
- Company advocated adopting a 'flexible' approach in methodology
- ERG critiqued the company comments
- Company submitted a revised response with additional analyses on 4th May 2017
- Company's additional analyses included
  - Final OS data from PALOMA-1 (as on slide 3)
  - A confidential patient access scheme
  - Revised ICERs with scenarios exploring effect
    - Different approaches for modelling OS
    - Different utility values for progression-free or post-progression states
    - Alternative comparator costs

# Company comment (1)
## Expected overall survival benefit

- Committee's conclusion; mean OS benefit would be somewhere between 6.6 months (ERG's estimate) to 11.2 months (company's estimate)
- Company justifies its base-case estimate of overall survival gain (11.2 months) – equivalent to mean progression-free survival of PALOMA-2 because
  - clinical expert (at the meeting) clarified that 1-to-1 translation of PFS benefit to OS benefit was a reasonable assumption
  - trial OS data will be confounded due to randomness of response of post-progression *(chemotherapies)*
- Company justifies its approach of modelling overall survival (to maintain PFS gain seen in PALOMA-2 on OS data from PALOMA-1)
  - Similar patient population, same outcomes

# Company comment (2)
## Final OS data from PALOMA-1

- Earlier submission presented OS data from an interim analysis
  - OS (median months) 37.5 vs. 33.3, HR **0.813** (0.492 to 1.345, p=0.2105)
- OS data from final analysis
  - OS (median months) [redacted]
- With updated data, using the ERG's modelled base case the company estimated the mean OS gain (lower bound of the range considered plausible by committee) as [redacted] (previously *6.2* months)

# Kaplan-Meier graphs for updated OS

# Company comment (3)
## Undervaluing PFS

- Utility values for post-progression state is **2.43 times** more than the additional utility of being progression-free
  - utility value for progression-free state **0.72**, post-progression state **0.51** therefore additional utility of being progression-free (0.72-.51=**0.21**) and **0.51/0.21=2.43**
- Patient testimonials demonstrate value of remaining progression-free
- an advisory board of 8 leading UK experts unanimous concluded that improving progression-free time as important to patients as improving overall survival
- NICE appraisal of abiraterone (TA387) has previously taken the benefit of delaying chemotherapy into account

# Company comment (4)
## Undervaluing PFS

- The company suggested that additional utility gain for being in progression-free state should be valued equally to the utility accrued due to the extension of the same length of time in the post-progression state.
- The company implemented these scenarios in 2 ways as follows,
  - assuming utility value for progression-free state as 1.0 (base-case 0.72) and 0.51 in progressed state and
  - assuming utility value for progression-free state as 0.72 and 0.36 (base case 0.51) in progressed state
- Note: The company reported that across NICE appraisal for therapies in metastatic breast cancer average utility value for progression-free state was **0.76** and for post-progression state was **0.50** (see footnote of table 9, page 14 of the company's revised response to the ACD)

# Company comment (5)
## Cost of the comparator

- Palbociclib is an add-on to current treatment - there is no cost offset, making its *entire* treatment cost 'incremental'
- Assessment methods increase inequality by penalizing disease areas where technologies are add-ons
- Company presented different analyses assuming alternative comparator cost
  - average list* price of therapies for metastatic breast cancer
    - 13 therapies NICE have appraised
    - 7 therapies NICE have recommended
  - cost of a blended comparator (30% chemotherapy 50% aromatase inhibitor and 20% best supportive care)
  - Cost of capecitabine
- Company adjusted the effectiveness by a naïve comparison and also presented ICERs assuming equal discount for the comparator price (no access to PAS prices)

*several technologies have confidential patient access schemes in place

# Company's additional analyses-1 (all incorporate updated PAS)

| S. No. | Scenario | Modelling of OS | |
|---|---|---|---|
| | | OS=PFS | OS from PALOMA-1 |
| 1 | Updated OS data from PALOMA-1 | [redacted] | [redacted] |
| 2 | Utility of pre-progression state=1 | [redacted] | [redacted] |
| 3 | Utility of post-progression state=0.36 | [redacted] | [redacted] |
| 4 | Alternative comparator (13 NICE appraised treatment) | [redacted] | [redacted] |
| 5 | 4+2 | [redacted] | [redacted] |
| 6 | 4+3 | [redacted] | [redacted] |
| 7 | Alternative comparator (7 NICE recommended treatment) | [redacted] | [redacted] |
| 8 | 7+2 | [redacted] | [redacted] |
| 9 | 7+3 | [redacted] | [redacted] |
| 10 | Alternative comparator (blended comparator) | [redacted] | [redacted] |
| 11 | 10+2 | [redacted] | [redacted] |
| 12 | 10+3 | [redacted] | [redacted] |

Original base-case; company: £150,869, ERG: £132,872

# Company comment (6) Innovations

- Formal recognition by the MHRA that it is promisingly innovative
- First-in-class medicine allows metastatic breast cancer patients to experience a median PFS in excess of 2 years
- Prolongs progression-free survival and delays the need for chemotherapy
- List price of the medicine is consistent with previous therapies
  - Palbociclib £2,950 for a cycle of 28 days
  - Average cost across all appraised therapies £2,530 per month
  - Average cost across only NICE recommended therapies £2,139 per month
- Monthly cost of letrozole is less than £2, which is too low and causes

  *'an insurmountable barrier to innovation in this disease area'*
- Lack of access to innovative treatments today limits the likelihood of access to future innovations tomorrow.

# End-of-life

- The Company has not made a case for End-of life consideration
- However, note that the EoL criteria give ‘greater weight to QALYs achieved in the later stages of terminal disease, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age’

Company indicated that overall the committee should adopt methodological flexibility in this case as it is the Institute’s responsibility to recognise the potential for long term benefits to the NHS of innovation

# ERG critique of company response

- ERG considers the final OS analysis from the PALOMA-1 trial to be the best available evidence for OS
- No evidence that subsequent treatments or any other confounding factors present in trial would be different than in the UK clinical practice
- ERG estimated mean OS gain by modelling updated PALOMA-1 data
  - Using company's approach (exponential curve throughout) [redacted]
    - Note: Company reported modelled survival benefit as [redacted] months
  - using K-M curves + exponential fitting from the end of the K-M curves [redacted] months
- ERG won't comment upon on proposals (by the company) to deviate from NICE methodology (PFS valuation, comparator cost)
  - Out of the remit of the ERG

# Key issues for consideration

1. What does the committee consider to be the appropriate utility values to use for the pre progression and post progression state, and on what basis?
2. Is it reasonable to use another comparator/s, not in the scope, and if so, on what basis should this/they be selected, and how should the comparison be carried out?
3. Is it  unreasonable to compare with a generic comparator in clinical use?
4. What does the committee consider to be the appropriate data to use for modelling overall survival gain: the overall survival data from PALOMA 1, or  the OS data adjusted to match the PFS gain?

# Additional slides

# Utility values

| | | Company's original submission | | ERG' base-case | | Revised analysis |
|---|---|---|---|---|---|---|
| **Progression free state** | Palbociclib -letrozole | [redacted] | average EQ-5D values from PALOMA-2 for individual treatment arm | 0.721 | Average utility value for European patients in the first 21 cycles in the PALOMA-2 | Same as ERG's base-case |
| | Letrozole | [redacted] | | | | |
| **Post progression state** | Palbociclib -letrozole | [redacted] | A multiplier for disease progression based on Lloyds (2006) was applied to average PFS utility value (both arms) from PALOMA-2 trial | 0.5052 | The ERG recalculated the post-progression utilities using the results of the mixed model analysis given in the Lloyd study | |
| | Letrozole | | | | | |

# Company's additional analyses-2 (all incorporate updated PAS)

| S. No. | Scenario | Modelling of OS | |
|---|---|---|---|
| | | OS=PFS | OS from PALOMA-1 |
| 13 | Alternative comparator capecitabine | [redacted] | [redacted] |
| **Alternative comparator assumed to have same PAS discount** | | | |
| 14 | Alternative comparator (13 NICE appraised treatment) | [redacted] | [redacted] |
| 15 | 14+2 | [redacted] | [redacted] |
| 16 | 14+3 | [redacted] | [redacted] |
| 17 | Alternative comparator (7 NICE recommended treatment) | [redacted] | [redacted] |
| 18 | 17+2 | [redacted] | [redacted] |
| 19 | 17+3 | [redacted] | [redacted] |

Original base-case; company: £150,869, ERG: £132,872

# Methods guide: utility values

5.3.1 For the cost-effectiveness analyses health effects should be expressed in QALYs. For the reference case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults

5.3.8 If not available in the relevant clinical trials, EQ-5D data can be sourced from the literature….. The justification for choosing a particular data set should be clearly explained. When more than 1 plausible set of EQ-5D data is available, sensitivity analyses should be carried out to show the impact of the alternative utility values.

# Methods guide: comparator

6.2.1 The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the clinical and cost-effectiveness evidence.

6.2.2 When selecting the most appropriate comparator(s), the Committee will consider:

- established NHS practice in England
- the natural history of the condition without suitable treatment
- existing NICE guidance
- cost effectiveness
- the licensing status of the comparator.

# Methods guide: comparator

- 6.2.3 The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s).
- When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology.