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

3rd Appraisal Committee meeting

Committee A

Chair Jane Adam

ERG: Liverpool Reviews & Implementation Group

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

Company: Pfizer

4th October 2017

Palbociclib

MA received November 2016	For hormone receptor (HR)-positive (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor (subject of this appraisal)
Administration	125 mg palbociclib orally, once daily for 21 days followed by 7 days off. Treatment continued as long as the patient has clinical benefit or until unacceptable toxicity
Acquisition cost	£2,950 for a 21-capsule pack of 125-mg capsules (LIST PRICE excluding VAT; MIMS online, accessed January 2017).

Key: AE, adverse events; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive
Note: *, using the original PAS.

History of the appraisal

- First committee meeting: 11 January 2017
  - ACD issued: not recommended
- Second committee meeting scheduled for 6 April 2017 cancelled on request of the company
  - Company submitted a confidential patient access scheme
  - Updated OS data from PALOMA-1
  - Company advocated adopting a ‘flexible’ approach in methodology regarding
    - utility of progression free disease
    - alternative comparator costs
- Second committee meeting: 8 June 2017
  - FAD release was withheld on request of company
  - Company submitted a new patient access scheme and a revised economic case (to be discussed today)

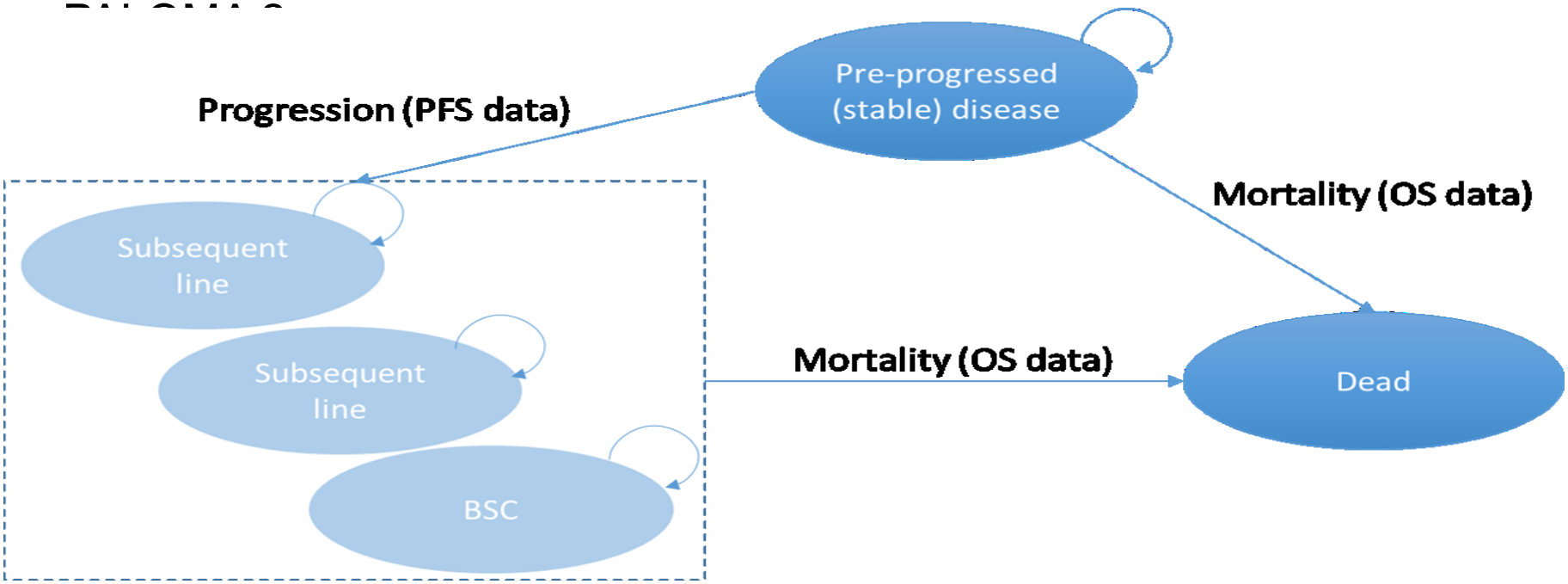
Clinical evidence

Outcome	Palbociclib-letrozole	Letrozole	Difference	HR (95%CI)
PALOMA-1, Phase I/II open label study, N=165				
PFS (median months)*	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)
OS (median months)** final analysis	37.5	34.5	**3.0**	0.897 (0.623 to 1.294)
PALOMA-2, Phase III, double-blinded, RCT, N=666				
PFS (median months)*	30.5	19.7	**10.8**	0.653 (0.505 to 0.844)

* Assessed by blind independent review committee
** Submitted at ACD consultation stage

Company's original model

- Partitioned survival model
- PFS from PALOMA-2+ **Weibull** extrapolation
- Time to treatment discontinuation (TTD) was not modelled separately, company assumed that all patients in pre-progressed state will continue having treatment until progression
- OS from PALOMA-1+ Weibull; adjusted to maintain median PFS gain in



Company's approach and ERG's key amendments

	Company	ERG
Modelling of trial data		
PFS	Fitted 2 separate Weibull curves to both arms of PALOMA-2	K-M data from PALOMA-1. Palbociclib arm appended by exponential curve K-M data was complete for letrozole arm (decreased company's ICER by 19.5%)
TTD	All patients would have treatment until progression, used PFS data	K-M data on TTD from PALOMA-1. Palbociclib arm appended by exponential curve K-M data was complete for letrozole arm (decreased company's ICER by 31.8%)
OS	Fitted separate Weibull curves to both arms of PALOMA-1. Adjusted curve of palbociclib arm so that OS gain matched to PFS gain from PALOMA-2.	K-M data from PALOMA-1. Appended by exponential curves fitted to pooled OS data from PALOMA-1 No adjustment of OS data (increased company's ICER by 25.5%)

All percentage changes based on the list price ICER

Progression-free survival (ERG's view)

- Company used 2 separate Weibull curves for the two arms of PALOMA-2
- ERG preferred PALOMA-1 because OS was modelled using same trial, used K-M data from PALOMA-1 for palbociclib arm appended by exponential curve
- K-M data was complete for letrozole arm
- Mean modelled PFS gain was 13.3 months (ERG) versus 10.7 months (Company)

Company and ERG progression-free survival estimates

Mean PFS (months)	Company Weibull to PFS from PALOMA-2	ERG KM data from PALOMA-1 + exponential projection for PAL+LET
PAL+LET	[redacted]	[redacted]
LET	[redacted]	[redacted]
PFS gain	[redacted]	[redacted]

Time to treatment discontinuation (and relation to PFS): company and ERG view

- The company assumed all patients in the model are treated to progression: TTD=PFS and used PALOMA-2 data
- Company: modelled mean TTD difference was 10.7, same as modelled PFS
- ERG modelled TTD separately from PFS (used PALOMA-1 trial TTD data, and extrapolated using exponential for PAL+LET as TTD data for the LET arm was complete)
- ERG chose exponential extrapolation because it considered that exponential trends established from ~ 9 months in the PAL+LET arm and ~ 5 months in the LET arm
- ERG: modelled mean TTD difference was 7.9 months i.e. less than modelled PFS (13.3 months)
- ERG said that the difference between TTD and PFS was justified by patients stopping due to adverse events

Utility values: Company's approach and ERG's key amendments

	Company	ERG
Utility values		
PFS	Higher value for palbociclib arm (0.74) vs. letrozole arm (0.71) derived from PALOMA-2	Average of pooled values for European patients from both arms of PALOMA-2 (0.721) (increased company's ICER by 11.2%)
PPS	Derived a multiplier from Lloyds study and applied on PFS utility values (0.4492)	Recalculated using same source (0.5052) (increased company's ICER by 0.2%)

All percentage changes based on the list price ICER

Cost-effectiveness results (considered earlier)

S. No.	Model scenario	ICER £/QALY
1	Company original base case (OS=PFS)	£150,869
2	ERG revised base case (OS based on PALOMA-1 and other changes)	£132,872
3	Company's revised base-case with PAS (assuming full surrogacy, that is, median OS gain= median PFS gain)	[redacted]
4	Company's revised base-case with PAS (OS based on PALOMA-1, that is partial surrogacy, median OS gain= 27.5% of PFS gain)	[redacted]

Company's additional analyses (submitted before 2nd meeting)

- Scenarios using alternative utility values
  - assuming utility value for progression-free state as 1.0 (base-case 0.72) and 0.51 in progressed state or
  - utility value for progression-free state 0.72 and 0.36 (base case 0.51) in progressed state
- Scenarios using alternative comparators
  - average list price of therapies for metastatic breast cancer
  - cost of a blended comparator (30% chemotherapy 50% aromatase inhibitor and 20% best supportive care)
  - cost of capecitabine
- A combination of alternative utility values and alternative comparators suggested

Key Committee Conclusions

Comparator	aromatase inhibitors such as letrozole are the right comparator
PFS	Significant improvement in progression-free survival
Overall survival	• PALOMA-1: numerically better in palbociclib arm, however difference was not statistically significant • PALOMA-2: no data on OS are available • PFS benefit likely to result in some OS benefit. However, the size of the benefit remains uncertain
Modelling of trial data	No evidence to support an assumption of OS gain equal to the PFS gain
Utility values	The base-case utility values were derived from data collected in PALOMA-2 or the medical literature, which is in accordance with NICE methods guide, and were in line with those used in other appraisals.
Cost of comparator	Not appropriate to compare with a hypothetical (expensive) comparator than current NHS practice.
ICER	Both ICERs, calculated either using OS data from PALOMA-1 only or adjusting OS so that OS gain=PFS gained, remained higher than the cost-effectiveness threshold

Company comments (submitted after 2nd meeting)

- The company reiterated that palbociclib deserves special consideration because
  - No NICE recommended treatment for people with previously untreated hormone-positive, HER2 negative metastatic breast cancer; the most common metastatic breast cancer
  - current treatment has been the same for ~ 20 years
  - Palbociclib is first-in-class CDK 4/6 inhibitor, first ever therapy to be associated with over two years progression-free survival
  - delays the burden of advanced disease, helping patients stay healthy, benefit of delaying chemotherapy not captured in the health-economic analysis
  - awarded a Promising Innovative Medicines designation by the MHRA

‘*the committee should be flexible in its application of the cost-effectiveness threshold*’.

Company's revised economic case (submitted after 2nd meeting)

- The company's revised economic case included
  - An updated patient access scheme
  - ERG's amendment regarding use of PALOMA-1 data AND
    - Modelling of PFS (KM data appended by exponential curve)
    - Modelling of TTD (KM data appended by exponential curve)
  - 2 further amendments in the model
    - Higher costs for post-progression state (£2000/£1395/£1140 per cycle vs. £573 per cycle in original model)
    - Higher utility values for progression-free state (0.772/0.75 vs. ERG's preferred 0.72)
- Results were presented assuming partial surrogacy (median OS gain=27.5% PFS gain), full surrogacy (median OS gain=median PFS gain) and
  - a midpoint ICER, using average of incremental costs and QALYs resulting from full surrogacy and partial surrogacy assumptions

Post-progression costs

Post-progression costs

- Company categorised it in to 2 types
  - disease related (management, monitoring, CT scans, etc)
  - subsequent-treatment (drug acquisition costs, administration costs, adverse event management costs, etc)

Disease related cost

- Company considered its original estimate £573 conservative because
  - NICE accepted a disease related cost of £1,140 per cycle in TA421

Subsequent-treatment cost

- Company had not included any subsequent-treatment cost in the original model
  - reported that average cost of NICE approved subsequent line medicines is £2,139 per cycle
  - suggested that total subsequent treatment costs would be higher if administration and adverse event management costs are included
- Company presented 3 scenarios amending the post progression costs to
  - £2,000 per cycle in the revised base-case
  - £1,396 per cycle, calculated from the ERG's preferred source Kurosky et al (2015)
  - £1,140 per cycle as a scenario

Company's revised analysis (all incorporate updated PAS)

S. No.	Scenario	Modelling of OS		
		OS=PFS (full surrogacy)	OS from PALOMA-1 (partial surrogacy)	**Midpoint ICER***
1	Previous base-case** with updated PAS	[redacted]	[redacted]	[redacted]
2	Post-progression cost (£1,140)	[redacted]	[redacted]	[redacted]
3	Post-progression cost (£1,395)	[redacted]	[redacted]	[redacted]
4	Post-progression cost (£2,000)	[redacted]	[redacted]	[redacted]

* ICERs calculated using arithmetic mean of incremental costs and incremental QALYs resulted from full surrogacy and partial surrogacy assumptions
** Post-progression cost of £573 per cycle in the previous base-case
Utility value for progression-free state maintained as 0.72

ERG critique of company's revised analysis – **disease-related cost**

Company's new estimates for disease-related costs are not verifiable

- Company states that cost of progressive disease based on NICE TA421 inflated to 2017 prices.
  - NICE TA421 (2016) is a review of NICE TA295 (2013).
  - The cost for progressed disease in TA295, was £802 per month at 2011 prices. Unclear how it was inflated to £1,140
- ERG considers company's original estimate (average £573.86 per cycle) more robust because
  - It was based on the same source as TA295 (Package 2 from NICE Clinical Guideline 81 on advanced and metastatic breast cancer), updated with clinical input in 2016
  - Company did not explain why its new estimate is better

ERG critique of company's revised analysis – **subsequent treatment cost**

- ERG agrees with the company that subsequent therapy costs should be included
- ERG did not agree with company's
  - estimate (£2,000 per cycle)
  - approach that applied subsequent treatment cost in best supportive care state
- ERG estimated average subsequent treatment (drug + administration) cost per cycle (£760),
  - based on a retrospective medical record review of post-menopausal patients with HR+/HER2- metastatic breast cancer in UK by Kurosky et al (2015) and clinical advice
  - assumed that the cost of drugs in all therapy lines was the same and did not include any drug related cost for best supportive care
- By combining subsequent treatment costs with company's original disease related costs; the ERG estimated an average post-progression cost as £1,200 per cycle (and £975 for BSC)

ERG's estimate for post-progression cost

Line of therapy	Treatment cost	Disease-related cost (company original model)	Total cost
Second	£759.86	£245.22	£1,005.08
Third	£759.86	£437.88	£1,197.74
Fourth	£759.86	£636.98	£1,396.84
Average for treatment lines			£1,199.89
BSC	N/A	£975.38	£975.38

Utility for progression-free state

- Company restated that utility value for progression-free state favoured by the ERG (0.72) does not capture true benefit of remaining progression free
  - people with progression-free disease have a near-normal life
  - many benefits (e.g. delaying chemotherapy) remained unaccounted
  - utility value for palbociclib arm derived from PALOMA-2 was higher (0.74)
  - In TA421, NICE have accepted a utility value of 0.772 for people with the same disease (under consideration) that has recurred or progressed after an aromatase inhibitor,
    - the company argued that people with untreated disease should be assumed to have a better quality of life
  - Company presented scenarios using values 0.772 and 0.75 for progression-free state in the revised-analysis

Company's revised analysis (all incorporate updated PAS)

S. No.	Scenario	Modelling of OS: OS=PFS (full surrogacy)	Modelling of OS: OS from PALOMA-1 (partial surrogacy)	Midpoint ICER*
utility value of 0.75 for PFS state				
5	Post-progression cost (£1,140)	[redacted]	[redacted]	[redacted]
6	Post-progression cost (£1,395)	[redacted]	[redacted]	[redacted]
7	Post-progression cost (£2,000)	[redacted]	[redacted]	[redacted]
utility value of 0.772 for PFS state				
8	Post-progression cost (£1,140)	[redacted]	[redacted]	[redacted]
9	Post-progression cost (£1,395)	[redacted]	[redacted]	[redacted]
10	Post-progression cost (£2,000) Company's revised base-case	[redacted]	[redacted]	[redacted]

* ICERs calculated using arithmetic mean of incremental costs and incremental QALYs resulted from full surrogacy and partial surrogacy assumptions

ERG critique of revised analysis – utility value for progression-free state

- ERG does not consider updated utility value (0.772) to be appropriate
  - 0.72 was derived from the relevant clinical trial (PALOMA-2)
  - ERG thinks that the company's argument that
  - people receiving first-line treatment could be assumed to have at least the same quality of life as accepted for those receiving second-line treatment after progression
  - is not robust to justify rejecting utility value derived from the trial and preferring literature based values

ERG's preferred assumptions

- ERG preferred assumptions included
  - OS from PALOMA-1 (partial surrogacy in OS modelling [median OS gain= 27.5% of median PFS gain])
  - post progression cost (disease related and subsequent therapy) £1200 per cycle for all post-progression state except best supportive care state
  - only disease-related cost for best supportive care state £975 per cycle
  - progression-free health state utility 0.72
- Taking into account the updated PAS, the ERG's revised base case ICER is [redacted] per QALY
- Using company's updated PFS utility value (0.772) + ERG's estimated post-progression costs (£1200 for subsequent treatment line and £975 for BSC) the ICERs are
  - [redacted] per QALY for partial surrogacy assumption (OS from PALOMA-1).
  - [redacted] per for full surrogacy assumption (OS gain=PFS gain)

CDF clinical lead's view: Modelling

- KM plots indicates approx. 6 month difference between TTD and PFS in MONALEESA and PALOMA trials:
  - Partly due to: additional toxicity, trial protocol and to clinician unfamiliarity with ribociclib/palbociclib and the substantial neutropenia they cause. Also letrozole continued after ribociclib/ palbociclib discontinuation without evidence of disease progression.
- PFS: exponential extrapolation is clinically reasonable.
- TTD: is not only determined by the rate of developing resistance but also other factors: toxicities, management of toxicities, clinician familiarity with the management and treatment protocols. There is some justification to use Weibull extrapolation.

CDF clinical lead's view: subsequent treatment cost

Disease-related cost

- agrees that disease-related cost will progressively increase with each line of therapy
  - there is escalating need for diagnostic tests, blood tests, palliative radiotherapy, palliative care, out patients visits etc

Subsequent treatment cost

- NHS England with experts in the Chemotherapy Clinical Reference Group estimated the proportions of patients proceeding to various therapies in the 2nd and 3rd line settings and calculated average treatment costs (including confidential discounts and administration cost) per patient per month
- Please see NHS England submission page 4 and 6 for estimated average monthly cost for 2nd, 3rd, and 4th lines of treatments.

Key issues for consideration

1. What does the committee consider to be the appropriate utility value or range of values to use for the progression-free state, and on what basis?
2. What is the most realistic estimate for average (per month) post-progression cost?
   - £573, £1140, £1395 or £2000 and assuming same cost for BSC state
   - £1,200 (for all post-progression states except BSC state) and £975 for BSC state (disease-related costs only)
3. What does the committee consider to be the correct approach for modelling overall survival: the overall survival data from PALOMA 1 (partial surrogacy), or the OS data adjusted to match the PFS gain (full surrogacy)?
4. Is the committee concerned about the difference between PFS and TTD? Does the committee need to revisit the extrapolation of PFS and TTD?

Additional slides

Time to treatment discontinuation (ERG's amendment)

Mean TTD (months)	Company (PFS from PALOMA-2)	ERG (TTD from PALOMA-1	Difference between company's and ERG' estimate
PAL+LET	[redacted]	[redacted]	[redacted]
LET	[redacted]	[redacted]	[redacted]
TTD gain	[redacted]	[redacted]	[redacted]

Time to treatment discontinuation and relation to PFS (ERG approach)