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

1st Appraisal Committee meeting

Committee A

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ERG: Liverpool Reviews & Implementation Group (LRiG)

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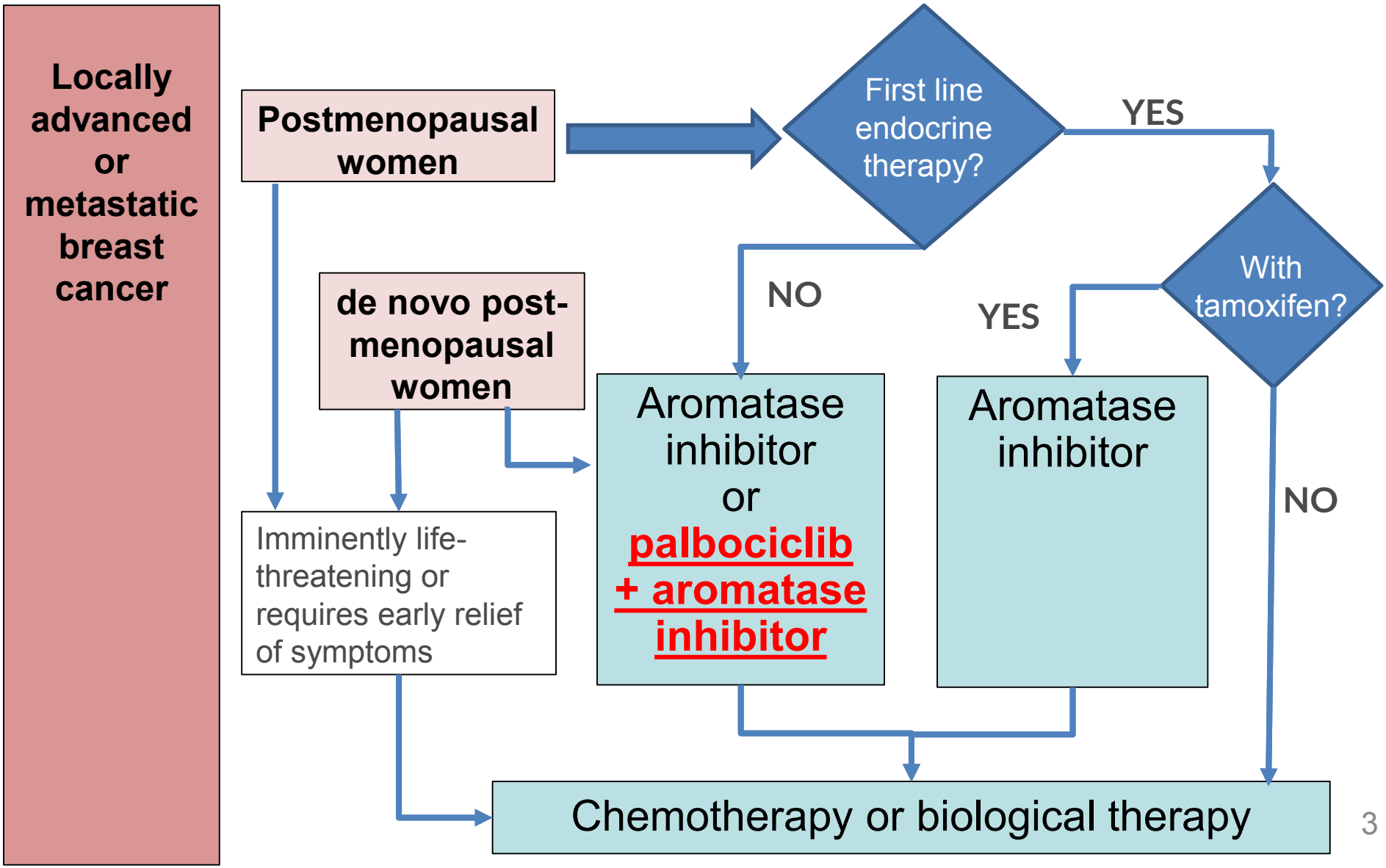
ER+/HER2- advanced breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast. Advanced breast cancer has been defined as “Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (that is, with known metastatic disease)” (CG81)
- Locally advanced breast cancer (stage 3) is where the cancer has spread to lymph nodes and/or other tissue in the breast. Metastatic breast cancer (stage 4) is where the cancer has spread to other sites in the body.
- Over 46,417 people were diagnosed with breast cancer in England in 2014, and there were approximately 9,554 deaths from breast cancer in 2014.
- Approximately 5% of people with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer
- Oestrogen receptor (ER) positive and human epidermal growth factor receptor (HER) negative is the most common type of UK metastatic breast cancer, accounting for 56.3% of cases.
- The estimated number of people who are post-menopausal with metastatic ER+/HER2- breast cancer previously untreated in the metastatic setting is estimated to be 5,435 (see table 8 of company submission)

Treatment pathway ER+/HER- breast cancer (CG81)



Palbociclib (Ibrance, Pfizer)

- Marketing authorisation (granted November 2016)
  - for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer ***in combination with an aromatase inhibitor*** or in combination with fulvestrant in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist
- Administration:
  - Oral treatment in combination with an aromatase inhibitor; 125mg once daily for 21 consecutive days, followed by 7 days off treatment
  - Requires full blood count prior to the start of therapy, at the beginning of each cycle, on Day 14 of the first 2 cycles, and as clinically indicated
- Cost:
  - List price: £2,950 per pack of 21 capsules

Decision Problem

	Final scope issued by NICE	Decision problem
Intervention	Palbociclib in combination with an aromatase inhibitor	
Population	Post-menopausal people with metastatic, hormone receptor-positive, HER2-negative breast cancer previously untreated in the metastatic setting.	Evidence submitted is in post-menopausal women
Comparator(s)	Aromatase inhibitors (such as letrozole or anastrazole)	
Outcomes	• overall survival (OS) • progression free survival (PFS) • response rate (RR) • adverse effects of treatment • health-related quality of life (HRQL)	In addition to the outcomes listed in the final scope issued by NICE the decision problem addressed also includes clinical benefit rate (CBR)
Subgroups	None	Those treated in the adjuvant setting compared with those who are presenting for the first time with metastatic disease

Patient and professional feedback

- No new treatments have been approved by NICE for this group of patients since the introduction of aromatase inhibitors.
- Those on aromatase inhibitor alone may be seen only every 8 – 12 weeks in clinic. With the addition of palbociclib patients need to be seen monthly. However, many patients have bone metastases and are quite often already seen monthly.
- Living with MBC is difficult to come to terms with. As time is limited and treatments usually have side effects (often severe), patients say that QoL is as important as length of life.
- Palbociclib has increased risk of side-effects, but for individual patients a longer progression-free survival can be more important. As delaying progression will delay the need for patients to move on to non-targeted chemotherapies, many patients will be able to lead a more 'normal' life and experience improved mental health and wellbeing.
- "Lack of progression of a metastatic cancer may bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness."
- Both palbociclib and letrozole are taken orally, therefore minimising the length and frequency of hospital visits needed whilst on this medication.
- Experience of this drug is increasing with studies in both the neoadjuvant setting (PALLET study) and the adjuvant (PALLAS study).
- Drugs with a similar mode of action (CDK4/6 inhibitors) are under investigation.

Clinical-effectiveness evidence

Company submission section 4

Clinical trial evidence – PALOMA-1

Design	Phase I/II, open label, multicentre (50 sites), RCT
Population	N=165, postmenopausal women with ER+/HER- locally advanced or metastatic breast cancer
Intervention	n=84; palbociclib plus letrozole 125mg, oral, 28-day cycle - once-daily for 21 days then 7 days off; letrozole 2.5mg, oral, once-daily continuous daily dosing.
Comparator	n=81; letrozole monotherapy 2.5mg, oral, once-daily continuous daily dosing
Outcomes	Primary outcome: Investigator-assessed PFS, as defined by RECIST 1.0
	Secondary outcomes: OR, CBR, OS, pain (mBPI-sf), DOR, TTP, Safety
Subgroups	Disease free interval (DFI) (≤12 months, ≤12 months + de novo, >12 months; ≤5 years, >5 years)
Other	All PALOMA-1 data correspond to the data cut-off date of 29 November 2013. [redacted]

PFS - progression-free survival; OR - objective response; CBR - clinical benefit rate; OS - overall survival; mBPI-SF - Modified Brief Pain Inventory-short form; DOR - duration of response; TTP - time to progression

Source: table 11, page 40-42 of company submission

Clinical trial evidence – PALOMA-2

Design	Phase III, double-blind, multicentre (186 sites [7 UK]), RCT
Population	N=666, postmenopausal women with ER+/HER- locally advanced or metastatic breast cancer
Intervention	n=444; palbociclib plus letrozole. Palbociclib - 125mg, oral, 28-day cycle - once-daily for 21 days then 7 days off; letrozole - 2.5mg, oral, once-daily continuous daily dosing.
Comparator	n=222; placebo plus letrozole Placebo - oral, 28-day cycle - once-daily for 21 days then 7 days off; letrozole - 2.5mg, oral, once-daily continuous daily dosing
Outcomes	Primary outcome: Investigator-assessed PFS, as defined by RECIST 1.1
	Secondary outcomes: OR, CBR, OS, HRQL (EQ-5D and FACT-B), DOR, Safety, biomarker expression vs PFS
Subgroups	Disease free interval (DFI) (≤12 months, >12 months, de novo)
Other	All PALOMA-2 data presented in this submission correspond to the data cut-off date of 26 February 2016
PFS - progression-free survival; OR - objective response; CBR - clinical benefit rate; OS - overall survival; HRQL - Health related quality of life; FACT - Functional Assessment of Cancer Therapy-Breast; DOR - duration of response; TTP - time to progression	
Source: table 14, page 47-51 of company submission	

Clinical results – PALOMA-1 OS and PFS

Outcome	Palbociclib-letrozole (n = 84)	Letrozole (n = 81)
Progression-free survival (95%CI) - Investigator-assessed		
Median months	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)
HR progression / death	0.488 (0.319 to 0.748, one-sided p = 0.0004)	
Progression-free survival (95%CI) – BICR**		
Median months	25.7 (17.7 to NE)	14.8 (9.3 to 20.4)
HR progression / death	0.621 (0.378 to 1.019, one-sided p = 0.0286)	
Overall survival (95%CI) - Investigator-assessed		
Median OS, months	37.5 (28.4-not reached)	33.3 (26.4-not reached)
HR (95%CI) death	0.813 (0.492 to 1.345, stratified 1-sided p = 0.2105)	

BICR - blinded independent central review; HR - hazard ratio; NE - not estimable; **BICR was conducted on 97% of the intention-to-treat population.

Source: table 22, page 70 of the company submission

PALOMA-1 Kaplan-Meier – Progression-free survival

- PFS data from PALOMA-1 were not used to inform the company's economic model, as data from PALOMA-2 were available

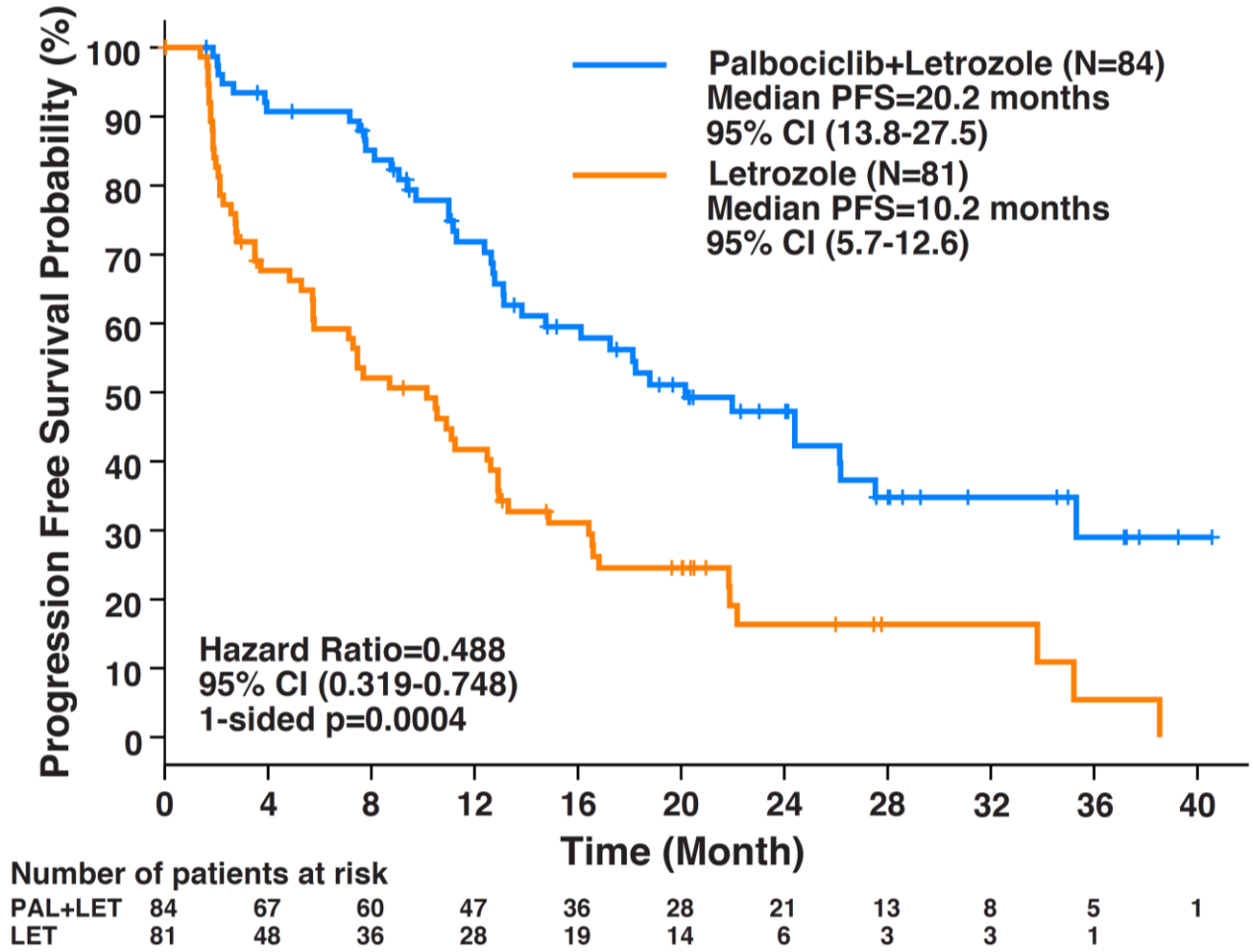


Figure 9, page 71 of the company submission

PALOMA-1 Kaplan-Meier – Overall Survival

- OS data from PALOMA-1 (2013 data cut) are used to inform the company's economic model, as data from PALOMA-2 are not currently available.

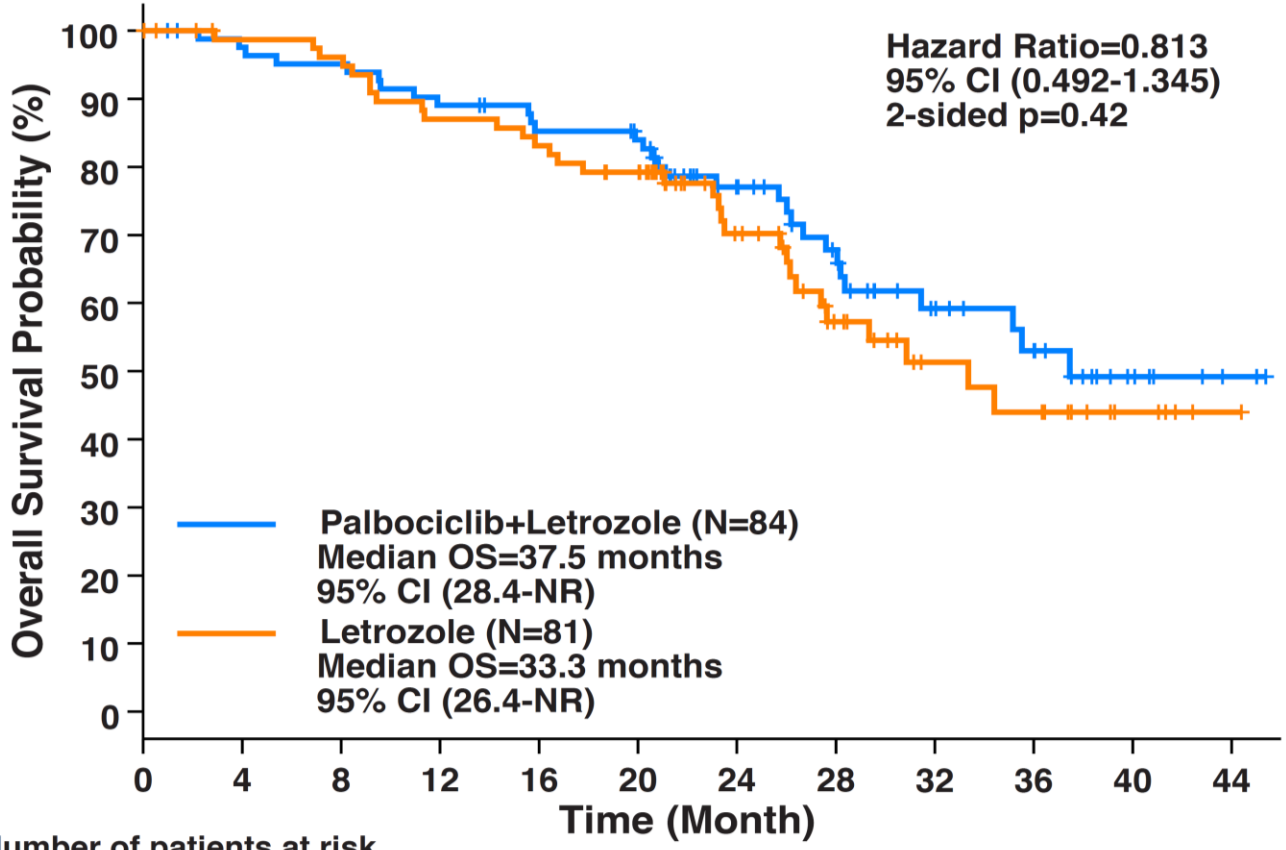


Figure 11, page 74 of the company submission

PALOMA-1 – Secondary outcomes

Outcome	Palbociclib-letrozole (n = 83)			Letrozole (n = 77)		
Adverse events						
Grade	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Patients (%)	83 (100)	49 (59.0)	14 (16.9)	65 (84.4)	16 (20.8)	0 (0)
Source: table 39, page 101 of the company submission						

Drug	Palbociclib-letrozole (n = 83)		Letrozole (n = 77)
	Palbociclib	Letrozole	Letrozole
Duration of treatment			
Median, days	420.0	428.0	231.0
Number (%) of patients with at least one:			
Cycle delay	70 (84.3)	--	--
Dose reduction	33 (39.8)	--	--
Dose interruption	47 (56.6)	32 (38.6)	23 (29.9)
Relative dose intensity*, %			
Mean (SD)	94.1 (26.2)	99.5 (1.1)	99.5 (2.2)
Median	95.4	100.0	100.0
Source: table 40, page 102 company submission			

Clinical results – PALOMA-2 OS and PFS

Outcome	Palbociclib-letrozole (n = 84)	Placebo-letrozole (n = 81)
Progression-free survival (95%CI) - Investigator-assessed		
Median PFS, months	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)
HR progression / death	0.576 (0.463 to 0.718, one-sided p < 0.000001)	
Progression-free survival (95%CI) – BICR		
Median PFS, months	30.5 (27.4-NE)	19.3 (16.4 to 30.6)
HR progression / death	0.653 (0.505 to 0.844, stratified log-rank one-sided p = 0.000532)	
Overall survival (OS)		
Not yet analysed. Investigators, patients, and Pfizer remain blinded to the OS data. As of 26 February 2016 there have been only [redacted] of the required 390 total deaths needed for the final OS analysis[+]		

BICR - blinded independent central review; HR - hazard ratio; NE - not estimable

Source: table 24, page 75 of the company submission;
[+]page 2 of the company clarification response

Kaplan-Meier – Progression-free survival

- Kaplan-Meier analysis of progression-free survival in the intention-to-treat population of PALOMA-2

Figure 12, page 77 of the company submission

PALOMA-2 – Secondary outcomes

	Palbociclib-letrozole (n=444)			Placebo-letrozole (n=222)		
Adverse events						
Grade	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Patients (%)	439 (98.9)	276 (62.2)	60 (13.5)	212 (95.5)	49 (22.1)	5 (2.3)
Pre-progression health-related quality of life, final score (95% CI)						
FACT-B	[redacted]			[redacted]		
EQ-5D	[redacted]			[redacted]		
Source: section 4.7.2.3, page 78-80, and table 41, page 104 of the company submission						

	Palbociclib-letrozole (n=444)		Placebo-letrozole (n=222)	
	Palbociclib	Letrozole	Placebo	Letrozole
Duration of treatment				
Median, days	603	617	413	420
Number (%) of patients with at least one:				
Cycle delay	303 (68.2)	--	60 (27.0)	--
Dose reduction	160 (36.0)	--	3 (1.4)	--
Dose interruption	310 (69.8)	237 (53.4)	94 (42.3)	99 (44.6)
Relative dose intensity*, %				
Median	93.0 (40.3-109.5)	99.9 (73.4-100.2)	99.6 (56.1-104.5)	100.0 (79.0-100.0)
Source: table 42, page 104 of the company submission				

ERG Critique – PALOMA-1

- It is not clear why there was no gain in OS in PALOMA-1 given there was such a large gain in PFS although it should be noted, the OS data were immature
- The ERG notes that the findings from a final analysis of PFS reported by the EMA shows large differences between investigator and BICR assessed PFS for cohort 1

	Cohort 1		Cohort 2	
	PAL+LET (n=34)	LET (n=32)	PAL+LET (n=50)	LET (n=49)
Progression-free survival (95%CI) - Investigator-assessed				
Median months	26.1 (11.2 to NE)	5.7 (2.6 to 10.5)	18.1 (13.1 to 27.5)	11.1 (7.1 to 16.4)
Hazard ratio	0.299 (0.156 to 0.572)		0.508 (0.303 to 0.853)	
p-value	p=0.0001		p=0.0046	
Progression-free survival (95%CI) - BICR				
Median months	31.6 (11.2 to NE)	38.6 (7.5 to 38.6)	20.3 (12.2 to NE)	14.6 (8.1 to 20.0)
Hazard ratio	0.731 (0.300 to 1.779)		0.576 (0.316 to 1.050)	
p-value	p=0.2442		p=0.0342	
Source: table 13, page 56 of the ERG report				

ERG Critique – PALOMA-1 proportional hazards

- The ERG considered that the proportional hazards (PH) assumption was valid for PFS data, but not for OS data. Therefore, the use of HRs for OS is not appropriate.

Figure 25 (OS log-log plot), page 128 of the ERG report

ERG Critique – Overview

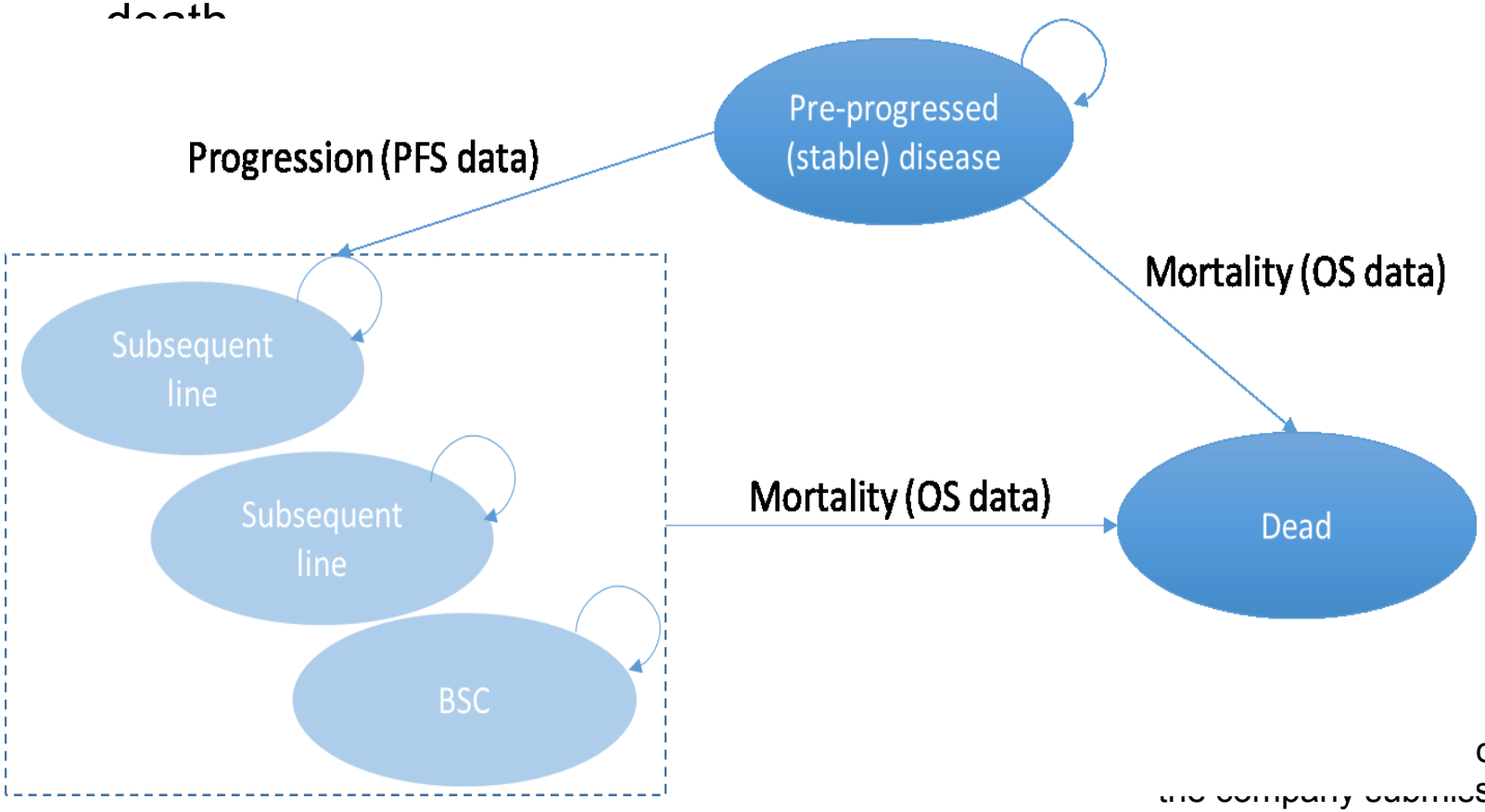
- The ERG is satisfied that the analysis method for each of the outcomes was pre-specified, and that all results were reported fully
- Both trials were international multi-centre RCTs
  - PALOMA-1 shows large differences between investigator assessed PFS and BICR assessed PFS for cohort 1 (data submitted to EMA)
  - PALOMA-2 trial was much larger, and double-blinded. The findings of the therefore appear to be more robust than those from the PALOMA-1 trial
- PAL+LET treatment led to higher rates of neutropenia
  - The company noted that managing palbociclib-associated neutropenia is relatively uncomplicated and reversible
  - The ERG concurs that the data appear to support this assertion
- While the PALOMA trials have a high proportion of patients presenting with de novo disease the ERG agrees the patient populations in both trials are representative of the patients who would be treated in clinical practice
- All OS data are from a data cut-off of 29 November 2013 of PALOMA-1. It is surprising a more recent data-cut have not been made available

Cost-effectiveness evidence

Company submission section 5

Model structure

- Partitioned survival model, with all patients entering in the pre-progressed health state
- It is assumed that 25% of post-progression patients would not switch to a subsequent line, and would instead receive BSC until death



of the company submission

Company key inputs and assumptions

	Source / assumption	Company rationale
PFS	PALOMA-2 + Weibull extrapolation	PALOMA-2 is the larger more recent trial, whilst Weibull was both conservative and the best fit
OS	PALOMA-1 + Weibull and adjusted OS to reflect median PFS gain in PALOMA 2	PALOMA-1 trial only OS available. Adjustment as literature identifies a correlation between PFS and OS in advanced breast cancer
Treatment duration	Until progression (PALOMA-2)	No restriction to a pre-defined number of cycles
Safety	Grade 3 and 4 of >5% incidence only (PALOMA-2)	Other appraisals do not consider grade 1, 2 As low incidence, grade 5 events not considered
Safety costs	Equal to those of neutropenia grade 3 or grade 4	neutropenia was the most prevalent adverse event
Utilities	PALOMA-2* then Lloyd 2006 multiplier for post-progression	Only PALOMA-2 contained EQ-5D data, and only up to disease progression
Administration cost	None	Both regimens are orally self-administered by patients at home
Sequence	25% patients progress to BSC at each transition	clinical expert opinion that (either choice or health reasons) people would not want treatment
***The ERG were unable to replicate the results presented by the company**		
Source: adapted from table 72 and 73; page 149-156 of the company submission		

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

Company scenario analyses (I)

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
Base case deterministic ICER		£150,869	
27	Only PFS gain for PAL+LET (10.3 months) No OS gain for PAL+LET (0 months)	£312,635	**+ £161,766**
28a	Increase median OS gain for PAL+LET to 5 years	£61,822	**- £89,047**
28b	Increase median OS gain for PAL+LET to 5 years, but removing post-progression costs	£42,794	**- £108,075**
29	Increase in utility of +0.1 for patients in the PFS state	£134,134	**- £16,735**
30	A comparator with the same monthly acquisition costs (i.e. fixed cost of £2,951.52 per month, but only for respective treatment durations)	£53,074	**- £97,795**
31	Reduced treatment duration by 12 months in each arm (PFS reduced from 15.7 to 3.7 months for LET, and from 24.9 to 12.9 months for PAL+LET)	£86,419	**- £64,450**
32	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) No change to base case OS assumption	£47,187	**-£103,682**
33	• Comparative monthly acquisition costs (#30) • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months	£43,819	**-£107,050**

Company scenario analyses (II)

Scenario # in CS	Assumptions varied	ICER/QALY gained	ICER change
Base case deterministic ICER		£150,869	-
34	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 12 months • Removal of post-progression costs	£40,482	**-£110,387**
35	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months	£36,194	**-£114,675**
36	• Comparative monthly acquisition costs • Value of PFS utility increase (+0.1) • Incremental median OS gain of 24 months • Removal of post-progression costs	£26,996	**-£123,873**
From scenarios 33 and 34	Incremental OS gain of 12 months	£134,294	**-£16,575**
From scenarios 35 and 36	Incremental OS gain of 24 months	£95,656	**-£55,213**
From scenarios 28b, 34, 35 & 36	Remove all post-progression costs	£150,303	**-£566**

Source: table 43, page 137 of the ERG report and section 5.8.3, page 169-172 of the company submission

ERG critique – Progression-free survival (I)

- ERG identified two key issues with the company's estimates of PFS
  - Data from the PALOMA-2 trial are inconsistent with the data from the PALOMA-1 trial used to model OS
  - Weibull model used in the base case produces implausible results
- ERG prefers that the PFS data from the PALOMA-1 trial are used
- The Weibull models used by the company to model PFS in both arms of the PALOMA-1 trial have monotonically increasing hazards
  - This means that, the longer a patient remains progression free, the more likely they are to progress or die than they were previously
  - ERG considers this to be implausible over the 40 year time horizon used in the model
  - Re-censored K-M data reveals clear exponential trends

ERG critique – Progression-free survival (II)

- The ERG used the full K-M data for the LET arm
- The ERG used K-M data until 16.6 months, then an exponential extrapolation
  - Switching point identified using the smallest of the weighted squared residuals
- Mean PFS gain was [redacted] months (ERG) versus [redacted] months (Company)

Figure 14 (ERG PALOMA-1 PFS projections), page 97 of the ERG report

ERG critique – Overall and post-progression survival (I)

- Modelling of OS in the base case is informed by the assumption that 100% of PFS gain will translate into OS gain. The ERG does not agree that this assumption is justified
- Company has attempted to reconcile OS data from the PALOMA-1 trial and PFS data from the PALOMA-2 trial – which is not methodologically sound
- Company has adjusted the fitted OS curve from the PALOMA-1 trial for treatment with PAL+LET so that median OS gain in the model equals median (modelled) PFS gain from the PALOMA-2 trial.
  - This does not result in equality between mean OS gain and mean PFS gain
  - Adjusting the scale parameter has a proportionately greater effect on mean OS and therefore on mean OS gain
- The ERG does not agree that OS data from the PALOMA-1 trial are insufficiently reliable to provide a basis for modelling, and considers using the OS data from the PALOMA-1 trial, alongside other time-to-event data from the same trial, to be preferable to the method used by the company

ERG critique – Overall and post-progression survival (II)

- No evidence for the assumption of zero post-progression survival (PPS) gain:
  - Evidence from the PALOMA-1 trial indicates a restricted mean PPS loss for treatment with PAL+LET of [redacted] months (left-hand figure)
- ERG fit a two-part exponential curve to re-censored OS K-M data (right-hand figure)
  - Restricted mean OS gain of [redacted] months for ERG analysis versus 11.2 months for the company base case for treatment with PAL+LET
  - ERG notes that this projected OS gain is based on data whose restricted means are not statistically different, therefore there is considerable uncertainty in the estimate

Source: Figure 6 (PPS), page 89 and Figure 10 (OS projections), page 93 of the ERG report

ERG critique – Time to treatment discontinuation

- The company assumes all patients in the model are treated to progression
- ERG use K-M data, and extrapolate using exponential for PAL+LET
- Mean time to treatment discontinuation in the model was
  - For PAL+LET: [redacted] months (ERG) versus 30.9 months (Company)
  - For LET: [redacted] months (ERG) versus 20.2 months (Company)

Figure 18 (TTD and PFS projections for PALOMA-1), page 100 of the ERG report

Impact of ERG changes to the ICER

Model scenario 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	[redacted]	[redacted]	£189,310	***+£38,441***
ERG PFS estimates based on data from PALOMA-1	[redacted]	[redacted]	£121,408	***-£29,461***
ERG TTD estimates based on data from PALOMA-1	[redacted]	[redacted]	£102,928	***-£47,941***
ERG recalculated pre-progression utility values from PALOMA-2 trial	[redacted]	[redacted]	£167,727	***+£16,858***
ERG recalculated post-progression utility values	[redacted]	[redacted]	£151,146	***+£277***
Use mid-cycle correction	[redacted]	[redacted]	£148,687	***-£2,182***
Use full reference costs for AEs	[redacted]	[redacted]	£152,472	***+£1,603***
Correct AE incidence calculation	[redacted]	[redacted]	£150,015	***-£854***
Change discounting to annual	[redacted]	[redacted]	£150,710	***-£159***
Use 365.25 days per year	[redacted]	[redacted]	£150,871	***+£2***
B. ERG revised base case	[redacted]	[redacted]	*£132,872*	***-£17,997***

Table 34; page 111 of the ERG report

ERG critique – Company scenario analyses

- Scenarios which explore OS gain for PAL+LET
  - the ERG considers the magnitude of the gains modelled to be implausible given the preliminary data from PALOMA-1 and PALOMA-2
- Acquisition costs of letrozole
  - methodologically flawed as, rather than changing the price of letrozole to equal that of palbociclib and thus double the cost of the combined therapy, only the price of letrozole when used as monotherapy is amended.
- Pre-progression utility values
  - Company argues that PFS is undervalued, ERG considers adequately reflected in the utility values used to represent the health states within the model
  - The data used to value PFS in this model are the best available and consistent with the NICE reference case, which is used to benchmark all appraisals
- Post-progression costs
  - As the only post-progression costs that are included within the company model are the costs of monitoring patients undergoing further therapy, the impact of removing these costs is minimal

ERG scenario analyses – PALOMA-2 data

- Company, ERG, and EMA consider PALOMA-2 trial to be of lower risk of bias
- ERG considered mixing PALOMA-1/2 to introduce methodological flaws
  - ERG have presented a scenario analyses of the company's preferred method of including PALOMA-2 PFS, incorporating the ERG's changes to methodology

Figure 20 (ERG revised PFS model), page 105 of the ERG report

ERG scenario analyses – PALOMA-2 data

	Company base-case	ERG base-case	ERG scenario
PFS gain (months)	10.7	[redacted]	[redacted]
Time on treatment PAL+LET (months)	30.9	[redacted]	[redacted]
Time on treatment LET (months)	20.2	[redacted]	[redacted]

Source: section 5.6.13, page 97, 100, and 105 of the ERG report; * ERG model

ERG revision	Incremental		ICER	ICER
	Cost (£)	QALYs	£/QALY	Change
A. Company original base case	***£94,853***	***0.629***	***£150,869***	-
ERG PFS estimates based on data from PALOMA-2	[redacted]	[redacted]	£156,984	+£6,115
ERG time on treatment estimates based on data from PALOMA-2	[redacted]	[redacted]	£146,238	-£4,631
ERG scenario (incorporating all other ERG base-case changes)	[redacted]	[redacted]	***£213,206***	***+£62,337***

Source: table 34, page 111 of the ERG report

Innovation, Equality, and End-of-Life

Innovation

- The company considers palbociclib innovative because it is:
  - A novel therapy, which addresses current clinical unmet need: increasing PFS and delaying the need for chemotherapy
  - An innovative therapy recognised at the regulatory level
  - A first-in-class targeted therapy with a new mechanism of action
- For full details see section 2.5 of the company submission

Equality

- Company: no equality issues were raised
- Consultees: no equality issues were raised

End-of-life criteria

- The company has not proposed this drug meets the end-of-life criteria

Key issues for consideration

Clinical

- Where would treatment with palbociclib be used in clinical practice?
- Is the comparison with letrozole generalisable for other aromatase inhibitors?
- What is the benefit of improved PFS to patients, and has this been captured?
- Can improved OS be assumed from evidence of improved PFS?

Cost

- Does the committee consider the company base-case robust?
  - What is the committee's view of the changes made by the ERG?
- Does the committee consider it more appropriate to use PALOMA-1 or PALOMA-2 PFS data for the cost-effectiveness analysis?
- What is the committee's view on the company scenarios which explored:
  - The OS gain of treatment with palbociclib
  - Acquisition costs of the comparator treatment
  - Health-related quality of life of the pre-progression state
- What is the committee's view on the most plausible ICER?