Slides for public – ACIC information redacted

NICE National Institute for Health and Care Excellence

Abemaciclib with an aromatase inhibitor for untreated advanced HR-positive, HER2-negative breast cancer

Chair's presentation

2nd appraisal committee meeting

Committee A

Lead team: Brian Shine, Pamela Rees, and Paul Robinson

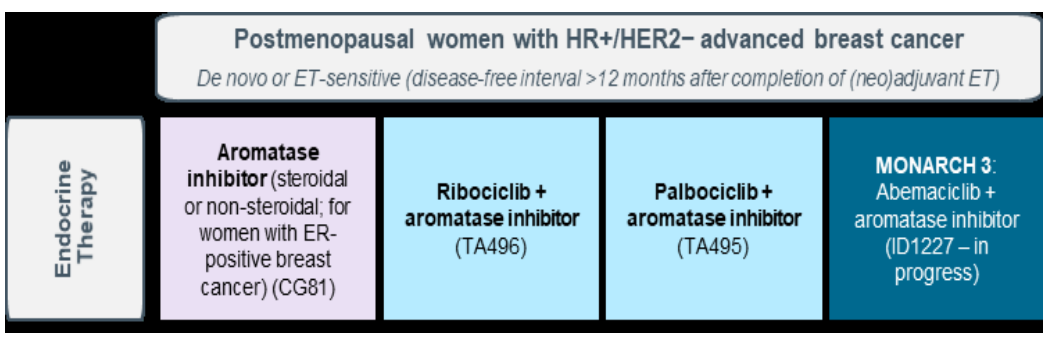
ERG: Southampton Health Technology Assessments Centre

NICE technical team: Marcela Haasova and Joanna Richardson

Company: Eli Lilly

15th November 2018

Company: treatment pathway 1st line



- Sequential chemotherapy for imminently life-threatening disease or if early relief of symptoms is required (CG81)

[redacted]

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Decision problem

	Final scope	Company
Population	People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease
Intervention	Abemaciclib in combination with an aromatase inhibitor	Abemaciclib + non-steroidal aromatase inhibitor [i.e. anastrozole or letrozole]
Comparators	• Palbociclib with an aromatase inhibitor • Ribociclib with an aromatase inhibitor	• Palbociclib + aromatase inhibitor (letrozole) • Ribociclib + aromatase inhibitor (letrozole)

[redacted]

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Abemaciclib (Verzenios, Eli Lilly)

Marketing authorization received on 26th September 2018	The treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer **in combination with an aromatase inhibitor**… **as initial endocrine-based therapy…** In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
Mechanism of action	Selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK 4/6).
Administration	• 150 mg oral tablet twice daily for 28-days, in combination with aromatase inhibitor. • Women must be in a postmenopausal state prior to therapy.
Acquisition cost	List price of abemaciclib: [redacted] per 28-day cycle. • Cost per mean Time on Treatment: [redacted] • A revised PAS has been approved by the Department of Health and Social Care

[redacted]

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ACD: preliminary recommendation

1.1 Abemaciclib with an aromatase inhibitor is not recommended, within its anticipated marketing authorisation, as an option for treating locally advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer as first endocrine-based therapy in adults.

[redacted]

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Clinical evidence: MONARCH 3

Design	Phase III, multi-centre, placebo-controlled, randomised, double-blinded.
Location	International: 158 sites & 22 countries; 4 sites in UK ([redacted]).
Intervention and comparator	• Abemaciclib (N=328) 300mg/day for 28day cycle with a NSAI (either anastrozole or letrozole). • Placebo (N=165) with a NSAI (as above).
Outcomes	• Investigator-assessed PFS (primary), OS, OS rate, RRs (ORR, DCR, CBR, DoR), TEAE, EORTC QLQ-C30, EQ-5D-5L, also independent review PFS.

[redacted]

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MONARCH 3: Survival at final PFS analysis

	Abemaciclib + NSAI (n=328)	Placebo + NSAI (n=165)	Treatment Effect /p-value
Progression-free survival			
Median PFS, months Investigator assessed	[redacted]	[redacted]	[redacted]
Median PFS, months Independent Review	[redacted]	[redacted]	[redacted]
Overall survival			
Median OS, months	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]	-

[redacted]

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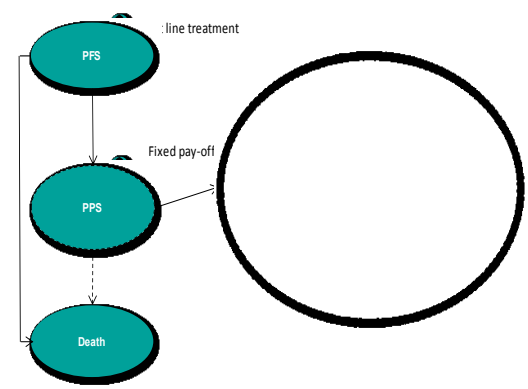
Company: model structure

- **Cohort state-transition model** with 2 health states (PFS1 & PPS1) and death, with **'fixed pay-off' sub-model**.
- A new approach that explicitly models second-line treatments to reduce uncertainty around overall survival. This approach has similarities to that used in TA496.



- Calibration is used to adjust the time spent in the pay-off sub-model to reflect PFS/OS relationship:
  - 27.5% PFS/OS gain 'partial surrogacy' assumed.

[redacted]

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Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

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NMA: 1st line clinical inputs (PFS & OS)

- **Treatment effects relative to placebo+NSAI:**

Outcome, HR (95% CrI)	Network	Abemaciclib + NSAI	Palbociclib + NSAI	Ribociclib + NSAI
PFS	8 studies: tamoxifen and fulvestrant also included	[redacted]	[redacted]	[redacted]
OS	15 studies: megestrol acetate, toremifene, tamoxifen (different doses) and fulvestrant also included	[redacted]	[redacted]	[redacted]

- Proportional hazards assumption did not hold for all analyses.
- Clinical heterogeneity due to differences in site of disease and degree of visceral involvement. Full assessment of heterogeneity not possible.
- Results are uncertain.

[redacted]

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Key: N, **number of studies in NMA;** FE, fixed effects model; RE, random effects model.

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Model: Time on treatment differences (ERG updated)

- Small differences in modelled PFS and OS between company's base case and ERG's preferred analyses, and between the treatments.
- Treatment with abemaciclib was shorter compared to treatments with palbociclib and ribociclib:

Treatment	Median ToT (months)		
	Modelled		Reported (Trial/document)
	CS	ERG	
ABE-NSAI	[redacted]	[redacted]	[redacted] (MONARCH 3)
PAL-NSAI	[redacted]	[redacted]	13.81 (PALOMA-1) 19.82 (PALOMA-2) 19.00 (SmPC)
RIBO-NSAI	[redacted]	[redacted]	13.00 (MONALEESA-2) 15.10 (MONALEESA-7) 20.30 (EMA)

[redacted]

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Committee's considerations

- No trials directly compare abemaciclib with palbociclib and ribociclib.
- Abemaciclib with an aromatase inhibitor improves progression-free survival compared with letrozole or anastrozole alone
- There is a high level of uncertainty in the company's network meta-analysis, but there is no evidence of a difference between abemaciclib with palbociclib and ribociclib.
- Difference in treatment duration between the 3 CDK 4/6 inhibitors is not plausible.
- It is appropriate to consider a class effect for the CDK 4/6 inhibitors.
- The cost-effectiveness results are uncertain and not suitable for decision making.
- Assuming the clinical effectiveness of abemaciclib, palbociclib and ribociclib is comparable, a cost-comparison approach is preferred.

[redacted]

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ACD consultation responses

- Consultee comments from:
  - Company
  - UK Breast Cancer Group
  - Breast Cancer Now
- Commentator comments from:
  - Pfizer
- No web comments were received

[redacted]

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Commentator ACD comments

- *Pfizer is not aware of evidence that would support an assumed efficacy advantage for abemaciclib versus either palbociclib or ribociclib combined with an aromatase inhibitor. Indeed, the committee concluded that an assumption of comparability is preferred between the inhibitors (ACD 3.13).*
- *…the company's economic model appears contradictory as it produced a QALY advantage for abemaciclib over palbociclib and ribociclib; the robustness of economic model results that favour abemaciclib thus appear questionable. Any incremental cost difference modelled for abemaciclib (outside of the acquisition cost of drug) is similarly questionable.*

[redacted]

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Consultee ACD comments

UK Breast Cancer Group

- *Abemaciclib is a CDK4/6 inhibitor which when combined with an aromatase inhibitor results in prolonged progression-free survival with acceptable toxicity. It has similar efficacy but different toxicity to two other CDK4/6 inhibitors, palbociclib and ribociclib, that have already been approved for use in the NHS by NICE.*
- *We hope that the Committee will reconsider their decision.*

Breast Cancer Now

- *It is disappointing that NICE has not been able to recommend abemaciclib with an aromatase inhibitor …*
- *With a slightly different side effect profile, abemaciclib with an aromatase inhibitor could provide an alternative treatment option that may be preferred by some patients. The side effect profile of drugs is an important factor for many patients in their treatment decisions and if abemaciclib was recommended for use it would expand the options available for clinicians to discuss with their patients.*
- *We would urge Eli Lilly to work with NICE and NHS England to see if the cost-effectiveness of abemaciclib with an aromatase inhibitor could be improved in order to enable NICE to recommend it for use.*

[redacted]

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Company's ACD comments

- *…disappointed that NICE has not recommended abemaciclib with an aromatase inhibitor (AI), within its anticipated marketing authorisation*
- *…agree that the three cyclin-dependent kinase 4 and 6 (CDK4 & 6) inhibitors (abemaciclib, palbociclib, ribociclib) have similar clinical effectiveness, with some differences noted in their respective safety profiles.*
- *… agree that a cost-comparison approach is appropriate for abemaciclib, palbociclib and ribociclib.*
- *Given there are no differences to model following the committee's ACD conclusions on the cost-effectiveness estimates, we propose that a simple comparison of the patient access scheme (PAS) prices of the three CDK4 & 6 inhibitors should be conducted.*
- Revised PAS price for abemaciclib was submitted.

[redacted]

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Results

- Results with confidential patient access scheme discounts and commercial access agreements for the intervention, comparators and subsequent treatments are confidential and cannot be presented here.

- The results are presented in a separate confidential appendix [cPAS] which to committee will discuss in the confidential part 2b of this meeting.

[redacted]

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Key issues for consideration

- What effect does the revised PAS have on the cost effectiveness of abemaciclib?

[redacted]

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