NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence

1 Recommendations

1.1 Abemaciclib with endocrine therapy is recommended, within its marketing authorisation, as an option for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence, defined as pathological tumour involvement in:

- at least 4 positive axillary lymph nodes, or
- 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
  - grade 3 disease (defined as at least 8 points on the modified Bloom-Richardson grading system or equivalent), or
  - primary tumour size of at least 5 cm.

It is recommended only if the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Adjuvant treatment aims to reduce the risk of cancer returning after surgery. Chemotherapy or endocrine therapy is standard care for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high

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risk of recurrence. Abemaciclib plus endocrine therapy is another adjuvant treatment option.

Clinical trial evidence shows that adjuvant treatment with abemaciclib plus endocrine therapy increases how long people are free of disease compared with endocrine therapy alone. This is for people whose condition is at high risk of recurrence because the cancer has spread into:

- at least 4 axillary (armpit) lymph nodes on the same side of the body, or
- 1 to 3 axillary lymph nodes, and there is either grade 3 disease or the primary tumour is at least 5 cm.

It is uncertain how long the benefit of abemaciclib with endocrine therapy lasts because data is still being collected.

The cost-effectiveness estimates are also uncertain, but the most likely estimates are within the range NICE considers an acceptable use of NHS resources. Therefore, abemaciclib is recommended.

2 Information about abemaciclib

Marketing authorisation indication

2.1 Abemaciclib (Verzenios, Eli Lilly) 'in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for abemaciclib.

Price

2.3 The list price for abemaciclib is £2,950 per 28-day cycle of 150 mg tablets (£1,475 per 28 tablet pack or £2,950 per 56 tablet pack; excluding VAT; BNF online, accessed May 2022).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes abemaciclib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Eli Lilly, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

New treatment option and treatment pathway

People with early breast cancer and their families would welcome a new effective treatment option that reduces the risk of recurrence

3.1 Breast cancer is the most common cancer in the UK. Hormone receptor-positive, HER2-negative breast cancer is the most common subtype, accounting for about 70% of all breast cancers. The patient experts explained that hormone receptor-positive, HER2-negative, node-positive early-stage breast cancer at high risk of recurrence has a considerable impact on quality of life. Initial diagnosis is distressing and the fear of the cancer returning is a common cause of stress and anxiety for patients and their families. This is because of the need to have further treatment or the possibility of progression to non-curable metastatic disease. For people with HER2-negative disease, treatment options are limited and are associated with unpleasant side effects that make completing the recommended course of therapy difficult. The clinical

expert noted that early breast cancer relapses after initial treatment in 30% of people. They noted that the risk of recurrence is higher with certain clinical and pathological risk factors such as a high number of positive lymph nodes, large tumour size, or high cellular proliferation measured by tumour grade or biomarkers. People whose disease is at high risk of recurrence after surgery have significant unmet need. Patients and clinicians would greatly value targeted therapies to reduce the risk of recurrence. The committee concluded that people with hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, and their families, would welcome a new effective treatment option that reduces the risk of recurrence.

Abemaciclib plus endocrine therapy is an important step-change for managing the condition

3.2 Adjuvant treatment with cytotoxic chemotherapy or endocrine therapy, or both, has remained the standard of care for many years. After surgery, adjuvant treatment is prescribed based on prognostic and predictive factors. The clinical experts explained that most people whose cancer is at high risk of recurrence are first offered adjuvant chemotherapy. Extended adjuvant endocrine therapy is then offered for 5 years to 10 years. They noted that the risk of recurrence does not decrease with time for people with hormone receptor-positive, HER2-negative, node-positive early breast cancer. But, people whose disease is identified as being at high risk of recurrence have the highest risk during the first 3 years after surgery. Abemaciclib plus endocrine therapy offers a targeted adjuvant treatment option earlier in the treatment pathway, thereby increasing the chance of curing the disease and reducing the likelihood of developing incurable advanced disease. The clinical expert also noted that although abemaciclib can cause diarrhoea and other side effects, these can usually be managed and are preferable to having chemotherapy. The committee concluded that abemaciclib plus endocrine therapy is an important step-change in the treatment of hormone receptor-

positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.

Clinical evidence

Cohort 1 from monarchE is the relevant population for consideration and is generalisable to NHS clinical practice

3.3 The evidence for abemaciclib with endocrine therapy came from monarchE. This is an ongoing multicentre, open-label, randomised, double-blind trial in 5,637 people with hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. The committee noted that abemaciclib should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs. Within MonarchE, abemaciclib (taken for up to 2 years) plus endocrine therapy (taken for 5 years to 10 years) was compared with endocrine therapy alone (taken for 5 years to 10 years). Over 60% of people in the trial had prior adjuvant chemotherapy but no more than 12 weeks of endocrine therapy before enrolment. The trial included 199 people from the UK and included 2 cohorts that used different inclusion criteria to define high risk of recurrence. The ERG raised concerns about whether the overall trial population reflected people with high-risk disease that could easily be identified in clinical practice. It considered that results from cohort 1 of monarchE would be more relevant to the NHS. Cohort 1 enrolled people at high risk of recurrence based on the following clinical and pathological features:

- pathological tumour involvement in at least 4 positive axillary lymph nodes, or
- pathological tumour involvement in 1 to 3 positive axillary lymph nodes, and:
  - grade 3 disease (defined as at least 8 points on the Bloom-Richardson grading system), or

- primary tumour size of at least 5 cm.

Cohort 2 was a smaller group that enrolled people at high risk of recurrence based on a Ki-67 index value of at least 20%. The company noted that this biomarker is not routinely tested in the NHS and it was not proposing introducing Ki-67 testing. The clinical experts explained that people whose disease is at high risk of recurrence, based on clinical and pathological risk factors, represented a small population in clinical practice (see section 3.1). They considered that cohort 1 was an adequate representation of this population and results from analyses using cohort 1 data were suitable for decision making. The committee noted that the marketing authorisation was grated only for cohort 1 from monarchE and concluded it is generalisable to NHS clinical practice.

Abemaciclib with endocrine therapy improves invasive disease-free survival compared with endocrine therapy

3.4 The primary outcome for monarchE was invasive disease-free survival. In cohort 1, people having abemaciclib with endocrine therapy had improved invasive disease-free survival compared with people having endocrine therapy alone (hazard ratio 0.680; 95% confidence interval 0.572 to 0.808). Median overall survival has not been reached in either treatment arm of monarchE (results are confidential and cannot be reported here). The clinical experts noted that although disease-free survival is a widely accepted surrogate for overall survival, studies have successfully used invasive disease-free survival as a compound surrogate outcome for overall survival. The Cancer Drugs Fund clinical lead considered that improved invasive disease-free survival with abemaciclib may take up to 10 years to show a clinically worthwhile overall survival benefit. The clinical experts considered overall survival benefit may be seen earlier, from 5 years onwards for people whose disease is at high risk of recurrence. The committee acknowledged the difficulty of obtaining

mature overall survival data for adjuvant treatments which are used at early stages when there is no known residual disease after surgery. It concluded that, in the absence of mature overall survival data, invasive disease-free survival is a suitable surrogate for decision making. However, it recognised that the extent to which invasive disease-free survival translates into long-term overall survival benefit is not known.

Differences in treatment effect based on menopausal status and type of endocrine therapy used are minimal

3.5 The type of endocrine therapy used in clinical practice depends on menopausal status. The ERG noted that bias may be introduced because of differences in comparators for pre- and postmenopausal people. It further noted that outcomes for invasive disease-free survival and disease relapse-free survival are better for premenopausal people, therefore results for pre- and postmenopausal subgroups should be considered separately. The clinical expert explained that many people in clinical practice cannot tolerate one endocrine treatment and switch to another. A key challenge for clinicians is finding a treatment combination that balances treatment benefit and side effects and helps treatment adherence. Often clinicians will try different endocrine therapies to find the optimal treatment combination for the person's individual needs. The company also highlighted that in monarchE cohort 1, there were no statistically significant differences for menopausal status at diagnosis for invasive disease-free survival and distant relapse free survival. It also highlighted that previous NICE technology appraisals for hormone receptor-positive, HER2-negative breast cancer had not considered subgroups by menopausal status. The clinical experts explained that abemaciclib had a treatment benefit irrespective of the endocrine therapy option taken alongside abemaciclib. Despite an initial difference in treatment effect between pre- and post-menopausal subgroups at 12 months and 24 months, the treatment effect at 36 months was similar between the 2 groups. The committee concluded that differences in

treatment effect based on menopausal status and type of endocrine therapy used are minimal and that the whole monarchE cohort 1 population is suitable for decision making.

Adverse effects

The safety profile of abemaciclib with endocrine therapy is acceptable

3.6 The committee noted that treatment discontinuations because of adverse events were more common with abemaciclib plus endocrine therapy than endocrine therapy alone. The patient experts explained that adverse events reported in monarchE were consistent with the known safety profile for abemaciclib, which is used in the NHS to treat advanced breast cancer. The most common side effect of abemaciclib is diarrhoea, which can disrupt day-to-day activities in the worst cases, but can generally be managed through medication or treatment breaks. For many patients, the potential benefit of abemaciclib with endocrine therapy outweighs the risk of side effects. The clinical experts agreed that abemaciclib's adverse effects are generally well tolerated. But, they noted that treatment delays because of toxicities and subsequent burden of increased appointments with GPs and oncologists are a potential disadvantage of the treatment. The committee concluded that the safety profile of abemaciclib with endocrine therapy is acceptable to patients.

The company's economic model

Extrapolation of invasive disease-free survival using the log-logistic curve is a source of uncertainty but is suitable for decision making

3.7 The company presented a cohort state transition model with 5 health states: invasive disease-free survival, non-metastatic recurrence, remission, metastatic recurrence and death. The non-metastatic recurrence state was split into 2 substates, second primary neoplasm and locoregional or contralateral. The company model included subsequent treatments after metastatic recurrence of the disease, occurring either

during endocrine therapy (endocrine resistant) or 12 months after endocrine therapy (endocrine sensitive). Because there is limited trial data available, the company used parametric curves to extrapolate invasive disease-free survival data over a lifetime time horizon. This results in considerable uncertainty in the long-term effectiveness of abemaciclib with endocrine therapy compared with endocrine therapy alone. The company and ERG both used the log-logistic curve to extrapolate invasive disease-free survival data in their base-case analyses because it provided the best statistical fit. However, the ERG noted that the choice of curve is a source of substantial uncertainty because of the very limited trial data available. A scenario analysis using an alternative curve (lognormal) to extrapolate invasive disease-free survival data increased the cost-effectiveness estimate. The company noted that the lognormal curve provided the worst statistical fit to the first 3 years of Kaplan–Meier data from monarchE and was not clinically plausible. The clinical experts considered invasive disease-free survival predicted by extrapolation of data using the log-logistic curve for the endocrine therapy arm was clinically plausible for a population whose disease was at high risk of recurrence. The committee concluded that extrapolation of long-term invasive disease-free survival using the log-logistic curve is a source of uncertainty, but in the absence of an alternative option, is suitable for decision making.

The assumed duration of treatment effect and treatment waning assumptions for abemaciclib are very uncertain

3.8 The company's base-case analysis assumed a full treatment effect for abemaciclib with endocrine therapy that is maintained for 8 years and then a treatment waning effect lasting 19 years until year 27. This was based on NICE's technology appraisal guidance on neratinib. The committee recalled that abemaciclib should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs The ERG considered that there was no evidence to support the treatment

effect for abemaciclib lasting 8 years and for the treatment waning assumptions used by the company. In the ERG's base-case, the abemaciclib treatment effect is maintained for 3 years based on monarchE follow-up data, then gradually decreases to no treatment effect at 8 years. The company considered the ERG's approach to be more conservative than previously accepted in NICE technology appraisals for early breast cancer where the full treatment effect was assumed to last for a minimum of 4 years. It noted that monarchE demonstrates a treatment effect of abemaciclib with endocrine therapy beyond discontinuation. Furthermore, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial reporting up to 10 years of data for anastrazole and tamoxifen showed a lasting treatment benefit up to 8 years for 1 endocrine therapy over the other. This was used as a proxy to inform plausible duration of treatment effect for abemaciclib. The ERG acknowledged that its base-case analysis could be potentially conservative. It explored different waning assumptions in scenario analyses, noting that this was one of the key drivers for the cost-effectiveness analyses. The committee noted that the ERG scenario analyses with varied assumptions about the duration of treatment effect using the patient access scheme price for abemaciclib without other confidential discounts, still resulted in cost-effectiveness estimates within the acceptable range. This was except the very conservative scenario when treatment was assumed to stop completely at 3 years, which was not supported by the Kaplan–Meier trial data. The committee concluded that the duration of treatment effect and treatment effect waning for abemaciclib with endocrine therapy that would be seen in clinical practice is highly uncertain. It took into consideration a range of potentially plausible estimates.

Adherence to adjuvant endocrine therapy has not been included in the economic model but is not critical for decision making

3.9 Non-adherence to adjuvant endocrine therapy in clinical practice was considered a concern by the ERG, who noted that its impact was not

modelled in the company model. The company explained that the pattern of non-adherence seen in monarchE is representative of clinical practice in the NHS. Also, any reduction in endocrine therapy cost is likely to have a small impact on the cost-effectiveness estimates because the overall costs for endocrine therapy are relatively low. The clinical expert considered that people whose condition is at high risk of recurrence are highly motivated to continue treatment to prevent their cancer returning and tend to adhere to treatment. Furthermore, medication adherence rate is likely to be the same for those taking it with and after abemaciclib, and those taking it as monotherapy. There is no evidence to suggest a larger impact on the abemaciclib with endocrine therapy arm. The committee concluded that adherence to adjuvant endocrine therapy is not critical for decision making.

Cost-effectiveness estimates

The most plausible ICER is uncertain but unlikely to be cost ineffective

3.10 The company's base-case incremental cost-effectiveness ratio (ICER) for abemaciclib with endocrine therapy compared with endocrine therapy alone was £9,164 per quality-adjusted life year (QALY) gained. This includes the confidential patient access scheme discount for abemaciclib but list prices for endocrine therapy in both arms and subsequent treatments in response to a metastatic recurrence of the disease. The company's base-case:

- used the log-logistic curve to extrapolate invasive disease-free survival data beyond the trial period (section 3.7)
- assumed a constant treatment effect for 8 years
- assumed a treatment waning effect for 19 years until year 27 (see section 3.8)

The ERG also used the log-logistic curve to extrapolate invasive disease-free survival data beyond the trial period but made the following

changes to the duration of treatment effect and treatment waning assumptions:

- assumed a constant treatment effect for 3 years
- assumed treatment waning for 5 years with no treatment effect beyond year 8 (see section 3.8).

The ERG's preferred base case ICER for abemaciclib with endocrine therapy compared with endocrine therapy alone, including the patient access scheme discount for abemaciclib but list prices for all other treatments, was £17,810 per QALY gained. The committee recalled that there is substantial uncertainty in the predicted benefit of adjuvant abemaciclib over a long time-horizon and the actual duration of treatment effect and treatment effect waning for abemaciclib with endocrine therapy. However, with a range of scenarios considered, the cost-effectiveness estimates remained within the range considered a cost-effective use of NHS resources. The committee concluded that the most plausible ICER for abemaciclib with endocrine therapy compared with endocrine therapy alone is uncertain but unlikely to be cost ineffective.

Some people who develop metastatic disease after having abemaciclib may have another CDK4/6 inhibitor, but the proportion is unknown

3.11 Abemaciclib is a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. The company assumed that people who had abemaciclib as adjuvant therapy would not have another CDK4/6 inhibitor later in the treatment pathway if they developed metastatic disease. The ERG carried out a scenario analysis which assumed that someone who developed metastatic disease after abemaciclib would be just as likely to have another CDK4/6 inhibitor as someone who had not had abemaciclib. The clinical experts and Cancer Drugs Fund clinical lead explained that people whose disease had an early recurrence after abemaciclib would not likely be treated with another CDK4/6 inhibitor. However, if they had a later recurrence, clinicians would consider treating with another CDK4/6 inhibitor. The

committee considered that the ERG scenario analysis assuming all people would receive a CDK4/6 inhibitor again after metastatic disease was very conservative and unlikely in clinical practice. The committee concluded that subsequent treatments after metastatic disease may include a proportion of people who have another CDK4/6 treatment, but the proportion is unknown.

The cost-effectiveness estimates are uncertain but within the range that NICE considers an acceptable use of NHS resources

3.12 The confidential discounts for abemaciclib, the treatment distribution assumed for endocrine therapy and subsequent treatments in response to a metastatic recurrence of the disease were considered. Both the company's and the ERG's preferred ICERs are within the range NICE normally considers an acceptable use of NHS resources. The exact ICERs are commercial in confidence and cannot be reported here. The committee was aware of the uncertainty associated with the extrapolation of invasive disease-free survival data over a lifetime time horizon (section 3.7), treatment effect duration (section 3.8), and treatment waning assumptions (section 3.8). It considered that the most plausible ICER is uncertain. However, it agreed that the most plausible ICER is unlikely to be above what NICE normally considers an acceptable use of NHS resources. It therefore recommended abemaciclib with endocrine therapy as an option for the adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions,

local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence and the doctor responsible for their care thinks that abemaciclib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
June 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sana Khan
Technical lead

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