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Abemaciclib in combination with fulvestrant for advanced or metastatic breast cancer after prior endocrine therapy

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LAY SUMMARY

Breast cancer, a cancer that develops from the tissues of the breast, is the most common cancer in the UK. There are many types of breast cancer and they are often grouped based on the presence or absence of some specific types of proteins ('receptors') in the cells of the patient. The most common type of breast cancer are those that are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-). The advanced form of the HR+ and HER2- breast cancer occurs when the cancer has spread to other parts of the body such as the bones, brain and liver.

Abemaciclib is a new drug that is being developed for patients with the HR+/HER2- type of advanced breast cancer. The drug is being developed to be given in combination with fulvestrant, a drug that is already in use for the treatment of advanced breast cancer. Abemaciclib works differently from other drugs by targeting a very specific type of enzyme produced by cancer cells in patients with HR+/HER2- breast cancer. Abemaciclib is taken orally while fulvestrant is given by injection. If approved, the combination of both drugs will offer additional treatment options for patients with advanced HR+/HER2- breast cancer that have not responded well to other drugs.

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TARGET GROUP

Women with locally advanced or metastatic breast cancer [hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-)] in combination with fulvestrant after prior endocrine therapy.

TECHNOLOGY

DESCRIPTION

Abemaciclib is under development for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer in combination with fulvestrant.[1] Abemaciclib is intended to be used in patients, who have relapsed on, or soon after the completion of prior endocrine therapy.[2]

Abemaciclib is a small molecule, selective Adenosine TriPhosphate (ATP)-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and 6) that are enzymes crucial for the normal cell cycle. Overexpression of CDK4 and 6 occurs in certain types of cancer and causes cell cycle deregulation. Specifically, the blocking of CDK4 and 6 inhibits the phosphorylation of the retinoblastoma (Rb) protein in early G1 phase of the cell cycle. The inhibition of Rb phosphorylation prevents the G1-S phase transition, hence arresting the cell cycle in the G1 phase. It also suppresses DNA synthesis and inhibits cancer cell growth.[2]

Fulvestrant (Faslodex) is a medication (hydroxysteroid derivative) that acts as an anti-oestrogen agent. Specifically, it binds to the oestrogen receptor with affinity comparable to that of oestradiol and down regulates the oestrogen receptor protein in human breast cancer cells (selective oestrogen receptor degrader).[3]

The development of abemaciclib in combination with fulvestrant is intended as a treatment of women with HR+, HER2- locally advanced or metastatic breast cancer (MBC) whose cancer has relapsed or progressed after receiving endocrine therapy.[1]

In a Phase III clinical trial (MONARCH 2), participants in the experimental arm received abemaciclib at 150mg (or 200 mg prior to amendment) given orally once every 12 hours in 28 day cycles, and 500 mg fulvestrant administered as two 250-mg injections intramuscularly (IM) on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.[1, 4]

The combination of abemaciclib with fulvestrant does not currently have marketing authorisation in the EU for any indication. Abemaciclib also does not have a marketing authorisation in the EU for any indication.

Abemaciclib is currently under development in phase II and III studies for the treatment of:[5]

- Metastatic breast cancer (monotherapy and in combination)
- Non-Small Cell Lung Cancer (including Squamous Non-Small Cell Lung Cancer)
- Pancreatic Ductal Adenocarcinoma
- Metastatic Melanoma
- Dedifferentiated Liposarcoma
- Mantle Cell Lymphoma

- Primary CNS Lymphoma
- Astrocytoma
- Ependymoma
- Meningioma
- Oligodendroglioma
- Recurrent Glioblastoma Multiforme (GBM)

Fulvestrant is a marketed drug in the UK/EU, indicated for the treatment of HR+, locally advanced or metastatic breast cancer in post-menopausal women not previously treated with endocrine therapy, or with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy.[6] Fulvestrant is formulated as injection solution for intramuscular route of administration. Fulvestrant is associated with adverse effects that include; urinary tract infections, reduced platelet count, hypersensitivity reactions, anorexia, headache, hot flushes, venous thromboembolism, nausea, vomiting, diarrhoea, elevated hepatic enzymes (ALT, AST, ALP), elevated bilirubin, rash, joint and musculoskeletal pain, back pain, vaginal haemorrhage, asthenia, injection site reactions, neuropathy peripheral, sciatica.[6]

INNOVATION and/or ADVANTAGES

If licensed, abemaciclib in combination with fulvestrant will offer an additional treatment option for women with HR+, HER2- locally advanced or metastatic breast cancer whose cancer has relapsed on, or progressed after receiving endocrine therapy.

Abemaciclib has the potential to have a more improved safety profile when compared to other treatments in its class through its limiting gastro-intestinal toxicities.[7]

DEVELOPER

Eli Lilly and Company Limited.

AVAILABILITY, LAUNCH or MARKETING

Abemaciclib was designated a breakthrough therapy for advanced breast cancer by the US FDA in October 2015[8] and was granted a Priority Review in July 2017 for the treatment of advanced breast cancer.[9]

PATIENT GROUP

BACKGROUND

Breast cancer is cancer that develops from breast tissue. Breast cancer is not a single disease, but rather a group of several different tumour subtypes. Early breast cancer typically manifests as a localized lump within the breast. As the disease progresses, increasing involvement of the lymph nodes is observed, followed by distant metastasis. Metastatic breast cancer is also classified as Stage IV breast cancer. Frequent sites of metastasis observed in breast cancer include the bones, brain, liver, and lungs.[10]

Although many subtypes of breast cancer exist, they are generally categorized by the presence or absence of hormonal receptors (HRs) and human epidermal growth factor receptor type 2 (HER2). HRs

are proteins — found in and on breast cells — that pick up hormone signals telling the cells to grow. HR+ breast cancer includes disease in which tumours express either oestrogen receptors (ER+) or progesterone receptors (PR+). Approximately 80% of breast cancers in postmenopausal women are HR+.[11] HER2 is a protein that can affect the growth of some cancer cells. It is found on the surface of normal breast cells. When there are higher levels of the HER2 protein in a breast cancer, it is called HER2+ breast cancer. HER2+ breast cancers tend to be more aggressive than HER2- breast cancers.[12] HR+/HER2- breast cancer is the most common form of breast cancer. This type accounts for more than 70% of all breast cancers.[13]

The causes of breast cancer are not completely understood. However, a number of factors are known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, being taller, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors.[14] The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes e.g. BRCA2, BRCA1 and TP53. Breast cancer in adults can occur at any age, with an increased risk in postmenopausal women, and in those with a previous benign breast lump, or a prior diagnosis of early breast cancer further increases the risk.[15]

Patients diagnosed with early stage breast cancer can live for many years without their quality of life being dramatically impacted by the disease. This is particularly evident for patients diagnosed with Stage 0 carcinomas in situ, who have up to a 100% five-year survival rate, and often live a normal lifespan. Advanced breast cancers that require complete removal of the breast, known as a mastectomy, can be very distressing for a woman, affecting sexuality and body image. In metastatic breast cancer, the bone is one of the most common sites of tumour infiltration, occurring in up to 70% of breast cancer patients, resulting in bone pain that can vary from a single site of severe pain to scattered pain throughout the skeleton.[16]

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers.[17] There were around 55,200 new cases of breast cancer in the UK in 2014, that's 150 cases diagnosed every day. Breast cancer risk is strongly related to age, with almost half (48%) of breast cancer cases in the UK each year are diagnosed in people aged 65 and over (2012-2014).[18]

An estimated 27% of female breast cancers in the UK are linked to lifestyle factors including overweight and obesity (9%), alcohol (6%), and certain occupational exposures (5%). The lifetime risk of developing breast cancer is 1 in 8 for women in 2012 in the UK. Incidence rates for breast cancer are projected to rise by 2% in the UK between 2014 and 2035, to 210 cases per 100,000 females by 2035.[18]

More than 1 in 10 breast cancer cases are diagnosed at an advanced or metastatic stage in the UK. Approximately 5% of patients present with metastatic breast cancer, and around 30% of people who present with localised disease will later develop metastases. Approximately 70–80% of people with metastatic breast cancer have HER2-negative tumours, of which about 50% will also be HR+.[16, 18]

There were around 11,400 breast cancer deaths in the UK in 2014, that's 31 deaths every day. Breast cancer is the third most common cause of cancer death in the UK, accounting for 7% of all cancer deaths in 2014. Breast cancer deaths in England are more common in females living in the most deprived areas.[18]

Breast cancer survival is improving and has doubled in the last 40 years in the UK. Breast cancer survival in England is highest for women diagnosed aged 60-69, probably because of screening, and less favourable tumour characteristics in younger women (2009-2013). Five year net survival in women aged 15-99 years in England and Wales during 2010-2011 was 87%.[18]

According to the 2015/2016 hospital episode statistics for England, breast cancer (ICD-10 Code – C50) accounted for 205,329 finished consultant episodes (FCEs), 201, 863 hospital admissions and 93,757 FCE bed days.[19]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Breast cancer (early) – intrabeam radiotherapy system [ID618] (GID-TAG353). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Breast cancer (hormone-receptor positive, HER2-negative) - palbociclib [ID915] (GID-TA10068). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523] (GID-TAG322). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2 negative, HR positive) – everolimus (with Exemestane, after endocrine therapy) (ID965). (GID-TA10028). Expected date of issue to be confirmed
- NICE technology appraisal in development. Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072] (GID-TA10094). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer [ID916] (GID-TA10095). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ribociclib for breast cancer [ID1026] (GID-TA10141). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951] (GID-TA10106) Expected publication date: 28 February 2018
- NICE technology appraisal in development. Breast cancer (brain metastases) - etirinotecan pegol [ID881] (GID-TA10066). Expected publication date: 27 December 2017
- NICE technology appraisal in development. Breast cancer (locally advanced, metastatic) - eribulin (after chemotherapy) [ID964] (GID-TA10030) Expected publication date: 21 December 2016
- NICE technology appraisal. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). July 2017
- NICE technology appraisal. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016
- NICE technology appraisal. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA 424). December 2016
- NICE technology appraisal. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (TA107). March 2014
- NICE technology appraisal. Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (TA295). August 2013.

- NICE technology appraisal. Bevacizumab in combination with capecitabine for the firstline treatment of metastatic breast cancer (TA263). August 2012.
- NICE technology appraisal. Eribulin for the treatment of locally advanced or metastatic breast cancer (TA250). April 2012.
- NICE technology appraisal. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA239). December 2011.
- NICE technology appraisal. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (TA214). February 2011.
- NICE technology appraisal. Gemcitabine for the treatment of metastatic breast cancer (TA116). January 2007.
- NICE clinical guideline. Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (CG164). June 2013.
- NICE Clinical Guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009. Last Updated July 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer*. Version 2.2017 – April 2017.[20]
- Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *The Breast* 23(5), Oct 2014. P 489-502.[21]

CURRENT TREATMENT OPTIONS

The aim of treatment for locally advanced or metastatic breast cancer is to control and slow down the spread of the cancer, relieve symptoms and give the patient the best quality of life for as long as possible. A number of treatment options exist. The most appropriate treatment will depend on factors such as where the breast cancer is in the body, how extensive it is (how many sites and how large), symptoms, previous treatments, the characteristics of the cancer (such as oestrogen receptors) and general health (and any other medical conditions) of the patient.[22]

Treatment options of HR+/HER- advanced or metastatic breast cancer according to NICE include:[23]

<u>Endocrine therapy or chemotherapy – first line</u>

- Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive (HR+) advanced breast cancer.
- Offer chemotherapy as first-line treatment for patients with ER-positive (HR+) advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.
- For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy.

Endocrine therapy

- Offer an aromatase inhibitor (either non-steroidal or steroidal) to:
    - Post-menopausal women with ER-positive breast cancer and no prior history of endocrine therapy
    - Post-menopausal women with ER-positive breast cancer previously treated with tamoxifen.
- Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and peri-menopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
- Offer ovarian suppression to premenopausal and peri-menopausal women who have previously been treated with tamoxifen and then experience disease progression.

Chemotherapy

- On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.
- Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.
- For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:
    - first line: single-agent docetaxel
    - second line: single-agent vinorelbine or capecitabine
    - third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

<u>Other second-line treatments</u>

- Everolimus
    - Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced human epidermal growth factor receptor 2 negative (HER2-), hormone receptor positive (HR+) breast cancer in post-menopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor. Everolimus is recommended only if the company provides it with the discount agreed in the patient access scheme.

- Fulvestrant
    - Fulvestrant is not recommended within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy.
    - Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-

oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Other third-line treatment

- Eribulin
  - Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
    - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)
    - the company provides eribulin with the discount agreed in the patient access scheme.
  - This guidance is not intended to affect the position of patients whose treatment with eribulin was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

EFFICACY and SAFETY	
Trial	MONARCH 2, NCT02107703; Women with advanced/metastatic, HR+/HER2- Breast Cancer; Abemaciclib vs placebo, both in combination with fulvestrant.
Sponsor	Eli Lilly and Company
Status	Ongoing, but not recruiting participants.
Source of Information	Publication,[24] abstract,[1] trial registry[4, 25]
Location	EU (not UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double-blinded, parallel assignment
Participants	n=669; aged ≥ 18 years; females; breast cancer; HR+/HER2-; advanced and/or metastatic; progression despite receiving (neo) adjuvant or adjuvant endocrine therapy.
Schedule	Randomized 2:1 to receive abemaciclib at 150 mg (or 200 mg prior to amendment) or placebo capsules, orally every 12 hours on a continuous dosing schedule in 28 day cycles; both in combination with 500 mg fulvestrant as two 250 mg injections intramuscularly (IM) on days 1 and 15 of cycle 1, then on day 1 of cycle 2 and beyond.
Follow-up	Treatment continued until progressive disease (PD), death, or patient withdrawal.
Primary Outcomes	Progression-Free Survival (PFS) [Time Frame: Baseline up to Approximately 31 Months].
Secondary Outcomes	• Overall Survival (OS) [Time Frame: Baseline up to Approximately 80 Months]

	• Objective Response Rate (ORR) [Time Frame: Baseline up to Approximately 31 Months] • Duration of Response (DoR) [Time Frame: Baseline up to Approximately 31 Months] • Disease Control Rate (DCR) [Time Frame: Baseline up to Approximately 31 Months] • Clinical Benefit Rate (CBR) [Time Frame: Baseline up to Approximately 31 Months] • Change from Baseline in Pain and Symptom Burden Assessment Using the Brief Pain Inventory (BPI) [Time Frame: Baseline, End of Study (up to approximately 31 months)] • Pharmacokinetics (PK): Area Under the Concentration Curve (AUC) of Abemaciclib, Its Metabolites, and Fulvestrant [Time Frame: Baseline up to Approximately 31 Months] • Change from Baseline in Health Status Using the EuroQol 5-Dimension 5 Level (EQ-5D 5L) [Time Frame: Baseline, End of Study (up to approximately 31 months)] • Change from Baseline in Quality of Life Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [Time Frame: Baseline, End of Study (up to approximately 31 months)] • Change from Baseline in Quality of Life Using the EORTC QLQ-BR23 (breast) Questionnaire [Time Frame: Baseline, End of Study (up to approximately 31 months)]
Key Results	In the Intention-To-Treat (ITT) population 379 PFS events were observed with a median PFS of 16.4 m for abemaciclib + Fulvestrant and 9.3 m for placebo + Fulvestrant (HR: 0.553; 95% CI: 0.449, 0.681, P<.0000001 by log-rank test).[1] In pts with measurable disease, the ORR was 48.1% (3.5% complete response [CR]) for abemaciclib + fulvestrant and 21.3% (0% CR) for placebo + fulvestrant.[1] The conclusion reached was that abemaciclib + fulvestrant was an effective treatment in patients with HR+/HER2- advanced breast cancer who progressed on endocrine therapy with significantly improved PFS and ORR.
Adverse effects (AEs)	The most frequent treatment emergent adverse events for abemaciclib + Fulvestrant vs Placebo + Fulvestrant were diarrhoea (86.4% vs 24.7%), neutropenia (46.0% vs 4.0%), nausea (45.1% vs 22.9%), and fatigue (39.9% vs 26.9%).[1]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of abemaciclib in combination with fulvestrant is not yet known.

Fulvestrant (Falsodex) is marketed in the UK for the treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy.

The NHS indicative price for 2 pre-filled disposable injection of fulvestrant (Faslodex) 250mg/5ml solution is £522.41.[26]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

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