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Ribociclib + fulvestrant + PI3K inhibitor (buparlisib or alpelisib) for HR positive, HER2 negative postmenopausal breast cancer – second or third line

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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 types of breast cancer are those that are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 (HER2)-negative. 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.

The combination of ribociclib, fulvestrant, and buparlisib or alpelisib is being developed for the treatment of HR+ and HER2- locally recurrent or advanced metastatic breast cancer. Ribociclib is given by mouth (capsules). It acts by helping to slow the progression of cancer by inhibiting two certain types of proteins that play a role in ensuring that cancer cells do not grow uncontrollably. Buparlisib and alpelisib are other types of drugs that act by reducing tumour cell growth and survival. Both are also given by mouth. Fulvestrant is a drug that is given by injection and is already in use for the treatment of advanced breast cancer. If licensed, the combination of ribociclib, fulvestrant, and buparlisib or alpelisib will offer an additional treatment option for postmenopausal women with HR+, HER2- negative locally recurrent or advanced metastatic breast cancer.

TARGET GROUP

Breast cancer (postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2) – negative, locally recurrent or advanced metastatic breast cancer) – second or third line; in combination with fulvestrant and PI3K inhibitor (buparlisib or alpelisib).

TECHNOLOGY

DESCRIPTION

Ribociclib (Kisqali, LEE011) is a selective cyclin dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated in a cell, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not grow uncontrollably.[1]

Buparlisib (BKM120) is an inhibitor of all 4 isoforms (alpha, beta, gamma, delta) of class I phosphatidylinositol 3-kinase (PI3K). PI3K signalling pathway is integral to diverse cellular functions, including cellular proliferation, differentiation and survival. PI3Ks are a family of lipid kinases whose primary biochemical function is to phosphorylate the 3-hydroxyl group of phosphoinositides. Phosphorylation results in activation of second messenger molecules with consequent signal transduction that sets in motion a variety of physiological cellular metabolic and survival functions. Buparlisib simultaneously inhibits the proliferation and growth of tumour cells. It also sensitizes them toward programmed cell death.[2]

Alpelisib (BYL719) is a PI3K alpha inhibitor with potential antineoplastic activity. The drug specifically inhibits PI3K alpha isoform of PI3K. Its biological activity correlates with inhibition of various downstream signalling components of the PI3K/AKT (protein kinase B) signalling pathway. This may result in inhibition of tumour cell growth and survival in breast cancer cell lines harbouring phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations.[3,4,5]

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).[6]

In the phase II clinical trial (NCT02088684), ribociclib was given as capsules of dosage strength of 50 mg or 200 mg in 28 day cycles (21 days followed by a 7 day break - dose escalating). It was given in combination with; daily alpelisib tablets of dosage strength of 10 mg, 50 mg or 200 mg (dose escalating) or daily buparlisib of dosage strength of 10 mg or 50 mg capsules (dose escalating); and fulvestrant Intramuscular (i.m) injection - 500 mg given on day 1 and day 15 of cycle 1, then on day 1 of each subsequent cycle.[7]

The combination of ribociclib, fulvestrant and a PI3K inhibitor (buparlisib or alpelisib) does not currently have marketing authorisation in the EU for any indication.

Ribociclib is licenced in the EU for the treatment of advanced or metastatic breast cancer (cancer that has spread to other parts of the body) in postmenopausal women. It can only be used when the cancer cells have receptors for certain hormones on their surface (HR+) and do not have large quantities of another receptor called HER2 (HER2-negative). It is used with an aromatase inhibitor (a cancer medicine that reduces oestrogen). The most common side effects associated with ribociclib (which

may affect more than 1 in 5 people) are low levels of white blood cells, headache, back pain, nausea, vomiting, diarrhoea, constipation, tiredness, hair loss and rash. The most common severe side effects with ribociclib (which may affect more than 1 in 50 people) are low levels of white blood cells, nausea, vomiting, tiredness, back pain, abnormal blood tests for liver function and low levels of phosphate in the blood (hypophosphatemia). [8]

Buparlisib does not currently have Marketing Authorisation in the EU for any indication.

Buparlisib is in phase II stage of development for the treatment of the following conditions:[2]

- Prostate Cancer;
- Glioblastoma Multiforme (GBM);
- Thyroid Cancer;
- Myelofibrosis;
- Follicular Lymphoma;
- Relapsed Chronic Lymphocytic Leukaemia (CLL);
- Refractory Chronic Lymphocytic Leukaemia (CLL);
- Pancreatic Cancer;
- Endometrial Cancer;
- Head and Neck Cancer Squamous Cell Carcinoma;
- Hepatocellular Carcinoma;
- Mantle Cell Lymphoma;
- Metastatic Colorectal Cancer
- Metastatic Transitional (Urothelial) Tract Cancer;
- Post-Polycythaemia Vera Myelofibrosis (PPV-MF)
- Recurrent Glioblastoma Multiforme (GBM);
- Refractory Acute Myeloid Leukaemia;
- Thrombocythemia Myelofibrosis;
- Thymoma (Thymic Epithelial Tumour).

Alpelisib does not currently have Marketing Authorisation in the EU for any indication.

Alpelisib is currently in phase III stage of development for the treatment of metastatic breast cancer and it is in II stage of development for the treatment of the Acute Myelocytic Leukaemia and Refractory Multiple Myeloma.[3]

Fulvestrant is a marketed drug in the UK/EU, indicated for the treatment of HR+, metastatic breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy. It is indicated for the treatment of advanced breast cancer, with a distinct and different mode of action. Fulvestrant is also indicated in combination with palbociclib for the treatment of women with HR+, HER2- advanced or metastatic breast cancer whose cancer has progressed after endocrine therapy, as monotherapy for expanded use in women with HR+, HER2-negative advanced breast cancer, who have gone through menopause and have not received previous endocrine therapy. Fulvestrant is formulated as injection solution for intramuscular route of administration.[6] 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.[9]

INNOVATION and/or ADVANTAGES

Ribociclib belongs to a class of drugs (CDK4/6 inhibitors) that has been indicated to have had an impact on the length of time that advanced or metastatic breast cancer is controlled.[10] Furthermore, it is indicated that PI3K–AKT–Mechanistic Target of Rapamycin (mTOR) is the most frequently activated pathway in breast cancer. Early clinical studies with PI3K inhibitors have demonstrated preliminary antitumor activity and acceptable safety profiles. Alpelisib is a PI3K alpha-selective inhibitor; targeting a single PI3K isoform may allow administration at therapeutic doses without being limited by toxicities associated with inhibiting multiple isoforms. Also, preclinical data have demonstrated that buparlisib in combination with fulvestrant can reverse resistance to mTOR inhibitors and/or fulvestrant.[11]

Therefore, if licensed, the combination of ribociclib, fulvestrant and PI3K inhibitor (buparlisib or alpelisib) will offer an additional treatment option for postmenopausal women with HR+, HER2-negative locally recurrent or advanced metastatic breast cancer.

DEVELOPER

Novartis Pharmaceuticals UK Ltd

PATIENT GROUP

BACKGROUND

Breast cancer arises from the tissues of the breast and most commonly originates in the cells that line the ducts. There are several types of breast cancer described according to the receptors expressed on the surface of tumour cells, stage of diagnosis, and rate of growth.[12] HR+ breast cancer includes disease in which tumour cells express either oestrogen receptors (ER+) or progesterone receptors (PR+).[13] Approximately 80% of breast cancers in postmenopausal women are HR+ and around two-thirds of breast cancers are ER+.[14] Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. HER2 are overexpressed in around 15-30% of women with invasive breast cancer, which has both prognostic and predictive implications.[15] HER2-negative breast cancer refers to disease that does not overexpress HER2.[13]

Advanced or metastatic (stage IV) breast cancer refers to disease that has spread to other parts of the body. Common sites for metastases include the bones, liver, lung and brain. 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. The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).[16]

Breast cancer in adults can occur at any age, though there is an increased risk in postmenopausal women, and a previous benign breast lump or diagnosis of early breast cancer further increases the risk. Breast cancer is normally characterised by a lump or thickened tissue in the breast area, however not all lumps will be cancerous. Other features include a change in breast size or shape, discharge from the nipple (which may include blood), lumps/swelling in armpits, dimples on the skin of the breast and a rash around the nipple area. Symptoms include pain in the breast or axilla and signs and symptoms can occur in one or both breasts.[17]

Breast cancer patients experience physical symptoms and psychosocial distress that adversely affect their quality of life (QOL). Treatment, including chemotherapy, can cause physical and psychological

problems that adversely affect patient QOL, and cancer can have other effects including anger, grief, suffering and pain.[18]

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers.[19] Breast cancer risk is strongly related to age, with almost half (48%) of breast cancer cases in the UK each year being diagnosed in people aged 65 and over (2012-2014). 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.[20]

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+.[20, 21]

The hormone receptor status of the breast cancer affects prognosis. HR+ breast cancers have higher rates of survival compared to HR-negative breast cancers (breast cancer cells which do not overexpress oestrogen or progesterone receptors) at 5 years after diagnosis (1989 to 2004) at 85% vs. 69% respectively.[22]

In England in 2015 there were 46,083 registrations of newly diagnosed cancer of the breast (ICD-10 code C50), and the directly age-standardised rate per 100,000 population was 170.2 for females. There were 9,626 registrations of death from neoplasm of the breast, and the directly age-standardised rate per 100,000 population was 34.3 for females.[23]

In England in 2016/17 there were 207,043 finished consultant episodes (FCEs) and 85,801 FCE bed days with primary diagnosis of ICD-10 code C50 (malignant neoplasm of breast). There were 203,454 hospital admissions, of which 169,800 were day cases.[24]

The population likely to be eligible to receive ribociclib in combination with fulvestrant and PI3K inhibitor (buparlisib or alpelisib) could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072] (GID-TA10094). Expected publication date to be confirmed.
- NICE technology appraisal in development. Ribociclib for breast cancer [ID1026] (GID-TA10141). Expected publication date to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2 negative, HR positive) - Everolimus (with exemestane, after endocrine therapy) [ID965] (GID-TA10028). Expected publication date to be confirmed.
- NICE technology appraisal in development. Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer [ID916] (GID-TA10095). Expected publication date to be confirmed.
- NICE technology appraisal in development. Breast cancer (hormone-receptor positive, HER2-negative) - palbociclib [ID915] (GID-TA10068). Expected publication date to be confirmed.

- NICE technology appraisal in development. Breast cancer (brain metastases) - etirinotecan pegol [ID881] (GID-TA10066). Expected publication date to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523] (GID-TAG322). Expected publication date to be confirmed.
- NICE technology appraisal in development. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951] (GID-TA10106). Expected publication date: January 2018.
- NICE technology appraisal. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016.
- NICE technology appraisal. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423). December 2016.
- NICE technology appraisal. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016.
- NICE technology appraisal. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). August 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.
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- 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.[25]
- 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.[26]

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.[27]

NICE guidelines for managing HR+, HER2-negative advanced breast cancer recommend the following treatments: [28]

- Endocrine therapy or chemotherapy: for patients with HR+ 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:
        - postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
        - postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.
    - Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
    - Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.
    - Offer tamoxifen as first-line treatment to men with HR+ advanced breast cancer.

- 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).

- Other second-line treatments:
    - Everolimus: Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced HR+, HER2-negative breast cancer in postmenopausal 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 treatments:
    - 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	**NCT02088684, CLEE011X2108; Ribociclib + fulvestrant + buparlisib vs ribociclib + fulvestrant + alpelisib vs ribociclib + fulvestrant; phase II.**
Sponsor	Novartis Pharmaceuticals.
Status	Ongoing, not recruiting.
Source of Information	Trial registry,[7] Global data.[29]
Location	EU (incl UK), USA, Korea, Republic of Singapore, Taiwan.
Design	Non-randomised, parallel assignment, open label.
Participants	n=70; aged 18 and older; females; breast cancer; postmenopausal, HR+, HER2-negative; locally advanced or metastatic; unlimited number of lines of endocrine therapy and one line of cytotoxic chemotherapy in the metastatic setting
Schedule	Randomised to ribociclib capsules of dosage strength of 50 mg or 200 mg in 28 day cycles (21 days followed by a 7 day break - dose escalating) + daily alpelisib tablets of dosage strength of 10 mg, 50 mg or 200 mg (dose escalating) + fulvestrant IM injection - 500 mg given on day 1 and day 15 of cycle 1, then on day 1 of each subsequent cycle; or ribociclib capsules of dosage strength of 50 mg or 200 mg in 28 day cycles (21 days followed by a 7 day break - dose escalating) + daily buparlisib of dosage strength of 10 mg or 50 mg capsules (dose escalating), + fulvestrant IM injection - 500 mg given on day 1 and day 15 of cycle 1, then on day 1 of each subsequent cycle; or ribociclib capsules of dosage strength of 50 mg or 200 mg in 28 day cycles + fulvestrant IM injection - 500 mg given on day 1 and day 15 of cycle 1, then on day 1 of each subsequent cycle.
Follow-up	Active treatment for 28 day cycles, follow-up 36 months.
Primary Outcomes	• Incidence of dose limiting toxicities (DLTs) - phase lb only [Time Frame: 28 days] • Progression free survival (PFS) - Phase ll only [Time Frame: 36 months]
Secondary Outcomes	Time Frame: 36 months • Safety and Tolerability of the combinations of LEE011 with fulvestrant, LEE011 + BKM120 with fulvestrant and LEE011 + BYL719 with fulvestrant • Plasma concentration-time profiles of LEE011, BKM120, BYL719 and fulvestrant. • Overall Response Rate (ORR) • Duration of Response (DOR)

	• Overall Survival (OS)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as September 2018.

ESTIMATED COST and IMPACT

COST

The costs of ribociclib, buparlisib, and alpelisib, as monotherapy and in combination, are 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.[30]

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

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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