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# Ribociclib (Kisqali) and fulvestrant for advanced HR positive, HER2-negative breast cancer in postmenopausal women, first or second line

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## LAY SUMMARY

Breast cancer is the most common cancer in the UK. Most women who get breast cancer are over 50 years of age. However, younger women, and in rare cases, men, may also get it. Survival beyond five years from diagnosis is relatively high but it depends on cancer stage at diagnosis, with less chance of survival at advanced stages.

There are many types of breast cancer. Ribociclib is a new treatment for a type of breast cancer that is called hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2) negative. Ribociclib it is taken orally and works by stopping cancer cells multiplying. If taken in combination with an intramuscular injection of fulvestrant, which stops the effect of hormones altering the breast cells, ribociclib has the potential to prolong survival free progression. If licenced, this combination of treatments will offer an additional therapy choice for those patients newly diagnosed with HR+/HER2 –ve, or a second-line option for those who have already had hormonal therapy but their cancer has relapsed.

## TARGET GROUP

Advanced breast cancer in postmenopausal women (hormone receptor +, HER2-negative) – first or second line.

## TECHNOLOGY

### DESCRIPTION

Ribociclib (Kisqali, Ribociclib succinate, LEE-011,) is an antineoplastic agent. It is formulated as tablet for oral route of administration. Ribociclib succinate in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor -positive (HR+), human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer.[1]

Ribociclib inhibits the activity of an enzyme CDK4/6. CDK4/6 is involved in the process that allows both normal and cancer cells to divide and multiply. Ribociclib decreases the ability of the bone marrow to make white blood cells, platelets, and red blood cells. Although these effects are expected to be reversible, they can increase the risk of infection, bleeding and fatigue.[1]

The most common side effects of ribociclib are neutropenia, leukopenia, nausea, diarrhoea and vomiting.[6]

Fulvestrant (Faslodex) is an oestrogen receptor antagonist. It binds to the oestrogen receptor alpha (ESR1) and oestrogen receptor beta (ESR2) in a competitive manner with affinity comparable to that of estradiol, the predominant form of oestrogen,[2] and down regulates the oestrogen receptors protein in human breast cancer cells. It is formulated as injection, solution for intramuscular route of administration. It is 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 for 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-negative advanced or metastatic breast cancer (MBC) whose cancer has progressed after endocrine therapy.[3]

Fulvestrant is under development for the treatment of HR+ locally advanced or metastatic breast cancer. It was also under development for the treatment of recurrent or metastatic endometrial carcinoma, systemic lupus erythematosus, non-small cell lung cancer, hormone refractory (castration resistant, androgen-independent) prostate cancer and precocious puberty with McCune-Albright syndrome.[3]

In the phase III trial (NCT02422615), ribociclib 600mg is administered daily orally (days 1 to 21 in a 28-day Cycle) in combination with fulvestrant 500mg intra muscular (IM) injections every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1.[4]

In March 2017, the FDA approved ribociclib for use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer.[5]

In June 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Kisqali in combination with an aromatase inhibitor, intended for the treatment of postmenopausal women with HR+, HER2-negative locally advanced or metastatic breast cancer as initial endocrine based therapy.[6]

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

Ribociclib is currently in phase II trials for the following indications:

- Liposarcoma, Dedifferentiated; Liposarcoma - Well Differentiated; Liposarcoma; Mixed Type; Soft-Tissue Sarcoma (NCT03096912)
- Malignant Neoplasms of Female Genital Organs, Endometrial Carcinoma (NCT03008408)
- Soft Tissue Sarcoma (NCT03114527)
- Estrogen Receptor Positive; Postmenopausal; Recurrent Fallopian Tube Carcinoma; Recurrent Ovarian Carcinoma; Recurrent Primary Peritoneal Carcinoma; Recurrent Uterine Corpus Carcinoma (NCT02657928)
- Gastrointestinal Cancer (NCT02420691)
- Neuroendocrine Tumours (NCT03070301)
- Teratoma (NCT02300987)
- Hormone-Resistant Prostate Cancer; Metastatic Prostate Carcinoma; Prostate Carcinoma Metastatic in the Bone; Stage IV Prostate Cancer (NCT02555189)
- High Grade Glioma; Diffuse Intrinsic Pontine Glioma; Bithalamic High Grade Glioma (NCT02607124)
- Locally Advanced Metastatic BRAF Mutant Melanoma (NCT01777776)
- Non-small Cell Lung Cancer (NCT02292550)
- Hepatocellular Carcinoma (NCT02524119)
- Solid Tumours; Pancreatic Cancer; Colorectal Cancer (NCT02703571)
- Metastatic Pancreatic Adenocarcinoma (NCT02985125)

## INNOVATION and/or ADVANTAGES

If licensed, ribociclib in combination with fulvestrant will offer an additional treatment option for men and postmenopausal women in the first line setting. withthe potential to increase progression-free survival (PFS).[7] In the second line setting, ribociclib in combination with fulvestrant will provide an alternative treatment that has the potential to prolong PFS, although MONALEESA-3 trial results are yet to be analysed. To date, a combination therapy including endocrine therapy (ET) with CDK4/6 inhibitors (palbociclib and fulvestrant) has been trialled in PALOMA3 trial in ET pre-treated premenopausal and perimenopausal women with positive results.[7]

## DEVELOPER

Novartis Pharmaceuticals

## AVAILABILITY, LAUNCH or MARKETING

Ribociclib was designated Breakthrough therapy by the FDA in August 2016.[8]

Ribociclib was received Priority Review by the FDA in November 2016.[8]

Ribociclib is approved for use in both USA and EU.[5]

# 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.[9] HR+ breast cancer includes disease in which tumour cells express either oestrogen receptors (ER+) or progesterone receptors (PR+).[10] Approximately 80% of breast cancers in postmenopausal women are HR+ and around two-thirds of breast cancers are ER+. Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity.[11] HER2 are overexpressed in around 15-25% of women with breast cancer and promote tumour growth.[12] HER2-negative breast cancer refers to disease that does not overexpress HER2.[10]

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.[13] The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).[13]

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.[7] 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.[7]

## CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, with an incidence of 172.1 per 100,000 population in 2014 in females and an incidence of 1.5 per 100,000 population in 2014 in men.[14] The prevalence of breast cancer in females in the UK in 2015 was 691,000.[15] In 2014, there were 11,433 breast cancer deaths in the UK: 11,360 (99%) in females and 73 (1%) in males, giving a female:male ratio of around 1,556:10. The crude mortality rate shows that there are around 35 breast cancer deaths for every 100,000 females in the UK and less than 1 for every 100,000 males. The survival rate for breast cancer 2007 to 2011 in the UK was 92.1% and 85% for men and women respectively. Breast cancer survival rates are mainly impacted by cancer stage at diagnosis, e.g. >5 years survival in those diagnosed 2002 to 2006 is 90%, 70%, 50% and 13% for diagnosis at Stage 1, Stage 2, Stage 3 and Stage 4 respectively.[15]

In 2015 to 2016, there were 201,863 admissions (204,086 female, 1,240 male) for malignant neoplasm of the breast (ICD-10: C50) in England, resulting in 93,757 bed days and 205,329 finished consultant episodes.[16]

The hormone receptor status of the breast cancer affects prognosis. HR+ breast cancers have higher rates of survival compared to HR-ve 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.[17] However, no independent data on breast cancer by HR status could be obtained from available published sources apart from survival rates.

# PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Ribociclib for breast cancer (ID1026). In development. Expected date of publication: TBC
- NICE technology appraisal guidance. Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer (ID916). In development. Expected publication date: TBC.
- NICE technology appraisal guidance. Breast cancer (hormone-receptor positive, HER2- negative) – palbociclib (ID915). In development. Expected publication date: TBC.
- NICE technology appraisal guidance. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer (ID951). In development. Expected publication date: 28 February 2018
- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). July 2017
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016
- NICE technology appraisal guidance. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016
- NICE technology appraisal guidance. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (TA107). March 2014
- NICE technology appraisal guidance. Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (TA295). August 2013
- NICE technology appraisal guidance. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). August 2012
- NICE technology appraisal guidance. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA 239). December 2011.
- 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.[18]
- 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.[19]

## CURRENT TREATMENT OPTIONS

Current treatment pathways have been determined for the treatment of HR+ breast cancers, and are the same in men and women. NICE and NHS England recommend (as first-line treatments) traditional breast cancer treatments, including surgery to remove masses and chemotherapy, usually followed by hormonal (or endocrine) therapies. Hormonal/endocrine therapies aim to prevent the stimulation of HR+ breast cancer growth by lowering the levels of or preventing the effects of hormones (such as oestrogen and progesterone). The type of hormonal therapy offered depends on the stage and grade of cancer, age, menopausal status and other treatments.[20,21]

Current first line treatments for HR+ breast cancer include:

- Surgery
  - Breast conserving surgery (removal of the tumour only)
  - Mastectomy (removal of whole breast) Ref
- Chemotherapy (in advanced cancer: offer systemic therapy)
  - First line – single agent docetaxel
  - Second line – single agent vinorelbine or capecitabine
  - Third line – single agent capecitabine or vinorelbine (whichever not used in second line)
- Hormonal therapies
  - Tamoxifen - first line treatment for men and women (orally once per day)
  - Non-steroidal Aromatase inhibitors - (e.g. anastrozole, and letrozole) and steroidal aromatase inhibitor (e.g. exemestane) (orally once per day) especially for post-menopause
  - Ovarian ablation or suppression – recommended for premenopausal women (e.g. goserelin) (subcutaneous injection once per month)

If HR+ breast cancer recurs or progresses after hormonal therapy, a variety of second and third line treatments are also currently recommended for use by NICE pathways recently updated in August 2017[22], which include:

- Everolimus – second line treatment recommended for HR+, HER2-negative recurrent breast cancer in postmenopausal women after non-steroidal aromatase inhibitors
- Fulvestrant - second line treatment for ooestrogen receptor + , advanced/metastatic, anti-ooestrogen therapy resistant breast cancer in postmenopausal women. Use of this drug in this indication is licenced but NICE do not approve the use of this drug
- Eribulin – third line treatment recommended for advance/metastatic breast cancer which has progressed after at least 2 chemotherapy regimens

## EFFICACY and SAFETY

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|---|---|
| **Trial** | NCT02422615; MONALEESA-3; CLEE011F2301 |
| **Sponsor** | Novartis Pharmaceuticals |
| **Status** | ongoing |
| **Source of Information** | Trial registry[4] |
| **Location** | USA and Canada, EU (incl UK), Russia, Norway, Mexico, Colombia, Argentina, Malaysia, Australia, Lebanon, Jordan and Korea. |
| **Design** | Randomised, placebo/controlled |
| **Participants** | n= 660; aged 18-65 years; male and females; HR+ and HER2-negative breast cancer; advanced and/or metastatic; progression despite first line endocrine treatment. |
| **Schedule** | Randomised to ribociclib 600mg daily oral (days 1 to 21 in a 28-day Cycle) in combination with fulvestrant 500mg IM injections every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1; or ribociclib placebo 600mg |

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| | daily oral (days 1 to 21 in a 28-day Cycle) in combination with fulvestrant 500mg IM injections every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1 |
| **Follow-up** | Follow up for up to 26 months (for primary outcome) |
| **Primary Outcomes** | Progression Free Survival (PFS) |
| **Secondary Outcomes** | • Overall Survival (OS) at 58 months<br>• Overall Response Rate (ORR)<br>• Time to definitive deterioration of Eastern Cooperative Oncology Group (ECOG) performance status in one category of the score<br>• Safety<br>• Time to definitive 10% deterioration in the global health status/quality of life (QOL) scale score of the European Organization for Research and<br>• Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30<br>• Change from baseline in the global health status/QoL scale score of the EORTC QLQ-C30<br>• Clinical benefit ratio (CBR)<br>• Time to response (TTR)<br>• Duration of response (DOR) |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Estimated primary completion date February 2020 |

## ESTIMATED COST and IMPACT

### COST

The cost of ribociclib is not available.

### 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: *uncertain unit cost compared to existing treatments*

☐ None identified

## OTHER ISSUES

☒ Clinical uncertainty or other research question identified: uncertainty on second line setting for this population group.

☐ None identified

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