NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
June 2022

Ribociclib with endocrine therapy for HR+/HER2- early breast cancer – adjuvant treatment

Company/Developer	Novartis Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24019	NICE ID: 10738	UKPS ID: 662049

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Ribociclib with endocrine therapy (ET) is currently in clinical development for patients with early breast cancer with hormone receptor positive (HR+)/human epidermal receptor 2 negative (HER2-) subtype. Early breast cancer is where the disease is limited to the breast region and has not spread to other parts of the body. Symptoms include swelling of breast regions, breast or nipple pain, nipple retraction, change in texture of skin covering the breast, nipple discharge and swollen lymph nodes. Despite the use of adjuvant ET, the risk of recurrence remains high in patients with HR+ early breast cancer.

Ribociclib blocks the activity of enzymes known as cyclin-dependent kinases (CDK) 4 and 6, which are important for regulating the way cells grow and divide. By blocking CDK4 and CDK6, ribociclib slows the growth of HR+ breast cancer cells. Ribociclib is administered orally. Evidence suggests that some patients with high-risk, early stage, HR+/HER2- breast cancer could achieve molecular downstaging (i.e. reduced risk of relapse) of their disease with CDK4/6 inhibitor and ET. Therefore, if licensed, ribociclib with ET will offer an additional treatment option for patients with early breast cancer with HR+/ HER2- subtype.

Proposed Indication

Adjuvant treatment for HR+/HER2- early breast cancer.[1]

Technology

Description

Ribociclib (Kisqali, LEE011) is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation.[2] Ribociclib blocks the activity CDK 4 and 6. By blocking CDK4 and CDK6, ribociclib slows the growth of HR+ breast cancer cells.[3]

Ribociclib with endocrine therapy (ET) is currently in phase III trials (NCT04055493, NCT03701334) for patients with early breast cancer with HR+/HER- subtype. In the phase III clinical trial (NCT03701334), participants received ribociclib 400mg once daily on days 1-21 of a 28-day cycle followed by 7 days off. Participants also received ET once daily continuously.[1,4]

Key Innovation

Despite the use of adjuvant ET, the risk of recurrence remains high in patients with HR+ early breast cancer.[5] Evidence suggests that some patients with high-risk, early stage, HR+/HER2- breast cancer could achieve molecular downstaging (i.e. reduced risk of relapse) of their disease with CDK4/6 inhibitor and ET.[6] Therefore, if licensed, ribociclib with ET will offer an additional treatment option for patients with early breast cancer with HR+/HER- subtype.

Regulatory & Development Status

Ribociclib is already licensed in the UK for the treatment of women with HR+/HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.[2]

Ribociclib is in phase II/III clinical development for:[7]

- Liposarcoma
- Soft tissue sarcoma
- Serous carcinoma
- Endometrial carcinoma
- Prostate cancer
- Pancreatic adenocarcinoma
- Melanoma

Patient Group

Disease Area and Clinical Need

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can also have the condition. It usually starts in the cells that line the ducts of the breast.[8] Early stage breast cancer is defined as disease that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers.[9] There are different immune/pathological subtypes of breast cancer, among which is human epidermal growth receptor 2 (HER2). HER2 is a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation. Those with cancer cells with HER2 are HER2+ diagnosed, whereas those

without are diagnosed HER2-.[10,11] Breast cancers can also be hormone receptor positive (HR+), which means that hormones such as oestrogen or progesterone can bind to the cancer cells and promote cell growth. Approximately 70% of breast cancers are oestrogen receptor positive (ER+).[11] The exact aetiology is unknown, but family history is a strong risk factor (hereditary factors).[12] Other risk factors for breast cancer include increased age, reproductive history and hormone exposure, lifestyle factors, medical history and radiation exposure.[13] One of the first noticeable symptom of breast cancer amongst women is a lump or an area of thickened tissue in their breast. Other common signs and symptoms include a change in the size or shape of one or both breasts, nipple discharge, dimpling on the skin of your breasts, and a rash on or around the nipple.[14,15]

In the UK in 2017, breast cancer was the most common cancer accounting for 15% of all new cancer cases.[16] In England, in 2017 there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the direct age-standardised rate per 100,000 population was 166.7 among females and 1.3 among males.[17] Incidence rates among females are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[18] In England, in 2020-21 there were 202,340 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 199,226 hospital admissions resulting in 47,613 bed days and 172,062 day cases.[19] In England, in 2017, the direct age-standardised death rate per 100,000 population was 0.3 and 33.3 among males and females respectively.[17] The latest published survival statistics for breast cancer for women in England (patients diagnoses 2013-2017) reported a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[20]

Recommended Treatment Options

The following are recommended in the treatment of early breast cancer:

- Chemotherapy[21]
  - Anti-cancer drugs that destroy cancer cells. These can be used on their own or in combination with two or three other chemotherapy drugs. Examples of chemotherapy for early breast cancer include docetaxel – cyclophosphamide, epiribicin - cyclophosphamide (EC), doxorubicin - cyclophosphamide (AC), paclitaxel, and cyclophosphamide - methotrexate - fluorouracil (CMF)
- Bisphosphonate therapy[22]
  - Zoledronic acid or sodium clodronate as adjuvant therapy for postmenopausal women to reduce the risk of cancer spreading to other areas of the body
- Hormone therapy[22]
  - Tamoxifen as a treatment for ER-positive breast cancer
  - Aromatase inhibitors, such as anastrozole, exemestane and letrozole for postmenopausal women with ER-positive breast cancer

Clinical Trial Information

Trial	**ADAPTcycle; NCT04055493;** Adjuvant Dynamic Marker - Adjusted Personalized Therapy Comparing Endocrine Therapy Plus Ribociclib Versus Chemotherapy in Intermediate Risk, HR+/HER2- Early Breast Cancer **Phase III –** Recruiting **Location(s):** one EU country **Primary completion date:** July 2027
Trial Design	Randomised, parallel assignment, open-label

Population	N=1670 (estimated); pre- and postmenopausal women 18 years or older
Intervention(s)	Oral tablet ribociclib (3 × 200mg = 600mg/day) plus endocrine treatment of physician´s choice
Comparator(s)	Standard of care
Outcome(s)	Primary outcome measures: ○ Invasive disease-free survival [time frame: at end of study, on average 5 years after start of treatment] ○ Distant disease-free survival [time frame: at end of study, on average 5 years after start of treatment] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**NATALEE;** NCT03701334; EdraCT 2018-002998-21**;** A Phase III Multi-center, Randomized, Open-label Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as an Adjuvant Treatment in Patients With Hormone Receptor-positive, HER2-negative Early Breast Cancer (New Adjuvant TriAl With Ribociclib **Phase III –** Active, not recruiting **Location(s):** 10 EU countries, UK, USA, Canada and other countries **Primary completion date:** May 2026
Trial Design	Randomised, parallel assignment, open-label
Population	N=5101; adults 18 years or older; female patients need to be with known menopausal status at the time of randomisation or initiation of adjuvant ET (whichever occurs earlier)
Intervention(s)	Oral ribociclib 400 mg once daily on days 1-21 of a 28-day cycle followed by 7 days off and ET once daily continuously
Comparator(s)	ET once daily continuously
Outcome(s)	Primary outcome measure: invasive disease-free survival [time frame: 44 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**EarLEE-2; NCT03081234;** A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as an Adjuvant Treatment in Patients With Hormone Receptor-positive, HER2-negative, Intermediate Risk Early Breast Cancer **Phase III** –Withdrawn (withdrawn due to change in plan for this study and not due to safety reasons) **Location(s):** not provided **Primary completion date:** November 2025
Trial Design	Randomised, parallel assignment, triple-blinded, placebo-controlled
Population	N=0 (actual); adults 18 years or older who have histologically confirmed unilateral primary invasive adenocarcinoma of the breast
Intervention(s)	Oral ribociclib (600mg/day) plus ET (tamoxifen, letrozole, anastrozole or exemestane)
Comparator(s)	Matched placebo (600mg/day) with standard adjuvant ET
Outcome(s)	Primary outcome measure: invasive disease-free survival using STEEP criteria [time frame: up to 90 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ribociclib is already in marketed in the UK for the treatment of women with HR+/HER2- locally advanced or metastatic breast cancer. The NHS indicative price for ribociclib tablets are as follows:[23]

- Ribociclib 200mg; 21 tablets cost £983.33
- Ribociclib 200mg; 42 tablets cost £1966.67
- Ribociclib 200mg; 63 tablets cost £2950.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Pertuzumab with trastuzumab emtansine for adjuvant treatment of early HER2-positive breast cancer (ID2711). Publication date: TBC.
- NICE technology appraisal guidance. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (TA632). June 2020.
- NICE technology appraisal guidance. Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer (TA569). March 2019.
- NICE technology appraisal guidance. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer (TA501). January 2018.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE quality standard. Breast cancer (QS12). June 2016.

- NICE diagnostics guidance. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34). December 2018.

NHS England (Policy/Commissioning) 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

- European Society for Medical Oncology. Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. October 2019.[24]
- American Society of Clinical Oncology. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. August 2018.[25]
- Healthcare Improvement Scotland. SIGN 134 – Treatment of primary breast cancer – A national clinical guideline. September 2013.[26]

Additional Information

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