National Institute for Health Research

NIHR Innovation Observatory
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Entinostat for Hormone Refractory, HR+ Breast Cancer in Men and Postmenopausal Women

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LAY SUMMARY

Breast cancer is the most common cancer in the UK with 140 people diagnosed every day. It can affect males and females, although the overwhelming majority of cases occur in females. Some breast cancers have receptors (or proteins) which hormones, such as oestrogen or progesterone, can attach to and stimulate the cancer to grow. These 'hormone receptor positive' (HR+) breast cancers are more common in women following the menopause and in men. HR+ breast cancer can be treated using drugs that lower the levels of hormones in the body or blocking hormones from reaching the cancer cells. However, in some cases the breast cancer will continue to grow and spread despite hormone treatment and chemotherapy. In these cases, new treatment options are needed to help treat reoccurring HR+ breast cancer.

Entinostat is a new drug for the treatment of reoccurring HR+ breast cancer in postmenopausal women and men. Studies on entinostat have suggested when combined with regular hormone therapy, it may lengthen survival time and slow the progression of the breast cancer.

If entinostat is licenced in the UK, it could provide a new treatment option for patients with reoccurring HR+ breast cancer, which may extend patients' survival time.

TARGET GROUP

Breast Cancer: Hormone Refractory, Hormone Receptor positive (HR+), Human Epidermal growth factor receptor negative (HER2-); men and women

TECHNOLOGY

DESCRIPTION

Entinostat (KHK-2375; KHK2375; MS-275; MS-275; NSC 706995; NSC-706995; SNDX-275; SNDX275) is a second generation histone deacetylase Class 1 (HDAC1) inhibitor of the benzamide chemical class which inhibits the activity of HDACs that control tumour cell proliferation, cell cycle control and DNA damage repair.[1] Entinostat is intended for the treatment of advanced Human Epidermal growth factor receptor negative (HER2-) and estrogen receptor positive (ER+) metastatic breast cancer in men, postmenopausal women, and premenopausal women with ovarian suppression.[2] In an ongoing phase III clinical trial, participants received 25mg Exemestane (orally, once a day) and 5mg Entinostat or placebo (orally, once a day) on days 1, 8, 15 and 22 of 28 day treatment cycles until disease progression or unacceptable toxicity occurred.[3]

Entinostat does not currently have Marketing Authorisation in the EU for any indication. Entinostat is currently in Phase II clinical trials for:

- Melanoma
- Prostate Cancer
- Non-small cell Lung Cancer
- Acute Myelogenous Leukaemia
- Chronic Myelomonocytic Leukaemia
- Myelodysplastic Syndrome
- Hodgkin's Lymphoma
- Colorectal Cancer
- Triple-negative Breast Cancer
- Ovarian Cancer

INNOVATION and/or ADVANTAGES

If licensed, entinostat will offer an additional treatment option for postmenopausal women, premenopausal women with ovarian suppression, and men with HR+ refractory breast cancer. Results from phase II trials of entinostat suggest treatment with entinostat in combination with a steroidal aromatase inhibitor (Exemestane) may improve overall survival and lengthen progression free survival compared to placebo.[4]

DEVELOPER

Bayer and Syndax

AVAILABILITY, LAUNCH or MARKETING

Entinostat was designated Breakthrough Therapy by FDA.

PATIENT GROUP

BACKGROUND

Breast cancer is the most common cancer and cause of cancer death worldwide.[5] The primary symptoms of breast cancer are breast lumps and changes to the size and appearance of the nipple and breast.[6] Breast cancer is a multifactorial disease with many risk factors including; genetic mutations (e.g. BRACA, BRACB and p53), prolonged exposure to endogenous estrogen, early menarche, late menopause, late age at first childbirth, exposure to exogenous hormones (as part of oral contraceptive or hormone replacement therapy), alcohol use, obesity and physical inactivity.[7] Although breast cancer is more common in women, it does also occur in men and the symptoms, risk factors and treatments remain similar.[8]

More than 80% of breast cancers are classed as hormone receptor positive (HR+), either estrogen receptor positive (ER+) or progesterone receptor positive (PR+). Breast cancers can also be classified by the amplification of protein receptors such as Human Epidermal Receptor Growth Factor 2 (HER2), which can be detected in approximately 15% early breast cancer cases.[9] The incidence of HR+ breast cancers strongly correlates with menopausal status, with 75% of breast cancers classed as HR+ in postmenopausal women, compared to 50% in premenopausal women.[5] HR+ breast cancers are usually treated using hormone (or endocrine) therapy given alongside more general treatment such as surgery and chemotherapy.[10]

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.[11] The prevalence of breast cancer (females) in the UK is 691,000 in 2015 and mortality due to breast cancer was 11,732 people in 2012. 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.[12]

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.[13]

The hormone receptor status of the breast cancer affects prognosis. HR+ breast cancers have higher rates of survival compared to HR- breast cancers (breast cancer cells which do not overexpress estrogen or progesterone receptors) at 5 years after diagnosis (1989 to 2004) at 85% vs. 69% respectively.[14] 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

- NHS Technology appraisal guidance. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer (ID951). In development.
- NHS Technology appraisal guidance. Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer (ID916). In development.
- NHS Technology appraisal guidance. Breast cancer (HER2 negative, HR positive) – everolimus (with Exemestane, after endocrine therapy) (ID965). In development.
- NHS Technology appraisal guidance. Breast cancer (hormone-receptor positive, HER2-negative) – palbociclib (ID915). In development
- NHS Technology appraisal guidance. Everolimus in combination with Exemestane for treating advanced HER2- negative hormone-receptor-positive breast cancer after endocrine therapy (TA295). August 2013. Withdrawn.
- NHS Technology appraisal guidance. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA 239). December 2011.
- NHS Clinical Guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009. Last Updated July 2014.

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 estrogen and progesterone). The type of hormonal therapy offered depends on the stage and grade of cancer, age, menopausal status and other treatments.[10, 15]

Current first line treatments for HR+ breast cancer include:[10, 15]

- Surgery
    - Breast conserving surgery (removal of the tumour only)
    - Mastectomy (removal of whole breast)
- 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,[15] which include:

- Everolimus – second line treatment recommended for HR+, HER2- recurrent breast cancer in postmenopausal women after non-steroidal aromatase inhibitors
- Fulvestrant - second line treatment for oestrogen receptor + ,advanced/metastatic, anti oestrogen 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		
Trial	NCT02115282, NCTNE2112; NCI-2014-00746; TrialTroveID-151546; AAAP3707; CTSU/E2112; E2112; E2112-CIRB; ECOG 2112; ECOG E2112; ECOG-ACRIN 2112; ECOG-ACRIN E2112; ECOG-E2112; NCG 257114, ER+ HER2 Negative relapsed/refractory advanced breast cancer ;Entinostat vs placebo, both in combination with Exemestane; phase III.	NCT00676663; SNDX-275-0301; TrialTroveID-090131; BRE 144; BRE 144 IST; ENCORE 301; ENCORE-301; EudraCT Number: 2009-012623-28; GCC 0818; HRPP #080483, ER+ second line or greater/refractory/ relapsed Stage III, Stage IV; Entinostat vs placebo, both in combination with Exemestane; ENCORE 301; phase II.
Sponsor	Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH)	Syndax
Status	Ongoing	Complete and published
Source of Information	poster [16], trial registry [3].	Publication [4], abstract [17], poster [18], trial registry [19]
Location	South Africa, USA	USA, Canada and Russia, Hungary and Czech Republic
Design	Randomised, placebo-controlled	Randomised, placebo-controlled
Participants	N= 600 planned; over 18 years old; breast cancer; ER+, HER2 negative, second line or greater/refractory/relapsed, advanced or metastasised; postmenopausal women and men who have previously progressed on nonsteroidal aromatase inhibitors, pre/peri- and postmenopausal women with metastatic ER+ breast cancer who have progressed on hormonal therapy.	N= 130; over 18 years old; Female; breast cancer; locally recurrent or metastatic ER+ second line or greater/refractory/relapsed stage III and stage IV; postmenopausal women progressing on treatment with non-steroidal aromatase inhibitors, anastrozole or letrozole who previously received hormonal therapy (1 prior line 42%; .1 prior line 58%) and may have received prior chemotherapy.

Schedule	Randomised to 5mg Entinostat OR 5mg placebo on days 1, 8, 15 and 22 of a 28 day treatment cycle; both in combination with 25mg oral Exemestane (once per day) and for pre-menopausal women, goserelin acetate (subcutaneous) on day 1	Randomised to 5mg Entinostat OR 5mg placebo once a week; both in combination with 25mg oral Exemestane (once per day)
Follow-up	Active treatment in 28 day cycles repeated until disease progression or unacceptable toxicity, follow-up every 3mths for 2yrs, every 6mths for 3yrs, then annually for 5 yrs.	Active treatment until disease progression or intolerable Adverse Event (AE)
Primary Outcomes	Progression-free survival (PFS) and Overall survival (OS).	Progression-free survival (PFS)
Secondary Outcomes	Treatment toxicity, symptom burden (including health related quality of life (HRQL), pharmacokinetic profile	Adverse Events (AEs), Overall Survival (OS), pharmacodynamics, tumour markers, bone turnover, objective response rate (ORR), clinical benefit rate (CBR)
Key Results	-	Progression free survival (PFS) was significantly longer (defined as p= <0.10) in the Exemestane + Entinostat group compared to the Exemestane + Placebo group (4.28 vs. 2.27 mths, hazard ratio (HR) =0.73, P=0.06), CI 0.49, 1.09. Median OS improved in the Exemestane + Entinostat group compared to the Exemestane + Placebo group at 28.1 and 19.8 mths respectively (HR, 0.59; 95% CI 0.36 to 0.97, p=0.036).[4]
Adverse effects (AEs)	-	Exemestane + Entinostat was generally well tolerated. Most frequent AEs with higher incidence (>20%) in the Exemestane + Entinostat group compared to the Exemestane + Placebo group included fatigue (46% vs26% respectively) and uncomplicated neutropenia (25% vs 0% respectively).[18] Treatment discontinuation was higher in the Exemestane + Entinostat group vs the Exemestane + Placebo group (11% vs 2%).[4]
Expected reporting date	Study completion date for OS outcome measure reported as March – November 2022	-

ESTIMATED COST and IMPACT

COST

The cost of Entinostat is not yet known.

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
- ☒ None identified

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