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Taselisib in combination with fulvestrant for advanced ER positive, HER2-negative breast cancer – second line after aromatase inhibitor therapy

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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 cancers including one referred to as oestrogen-receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer.

Taselisib is investigated as a new oral treatment for ER+, HER2- type of breast cancer. It is being investigated as a medicine to work on a pathway regulating cell growth and cell survival. If taken in combination with an intramuscular injection of fulvestrant, which stops the effect of hormones altering the breast cells, taselisib has the potential to prolong survival. If licenced, this combination of treatments will offer an additional therapy option for those who have already had hormonal therapy but their cancer has relapsed.

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TARGET GROUP

Breast cancer; postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative, PIK3CA-mutant, unresectable, locally advanced or metastatic breast cancer – second line after recurrence or progression during or after an aromatase inhibitor (AI) therapy; in combination with fulvestrant.

TECHNOLOGY

DESCRIPTION

Taselisib (GDC0032, RG7604), a new molecular entity (NME), is under development for the treatment of advanced or metastatic solid tumours including metastatic hormone receptor-positive and negative breast cancer.[1] Taselisib is a phosphoinositide 3-kinase (PI3K) enzymes inhibitor and acts by selectively inhibiting PIK3CA and its mutant forms in the PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR pathway is an intracellular signalling pathway important in regulating the cell cycle, which results in tumour cell apoptosis and growth inhibition in PIK3CA-expressing tumour cells. By specifically targeting PI3KCA, taselisib selectivity inhibits PI3K over other kinases and inhibited activation of downstream signalling components in the PI3K pathway. This leads to cell cycle arrest and apoptosis.[2]

In the phase III clinical trial, taselisib is administered orally at a dose of 4 mg once a day beginning at Cycle 1, Day 1 and fulvestrant 500 mg intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination.[3]

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

Taselisib is currently in phase III for metastatic breast cancer and phase II/III for the treatment of squamous non-small cell lung cancer.[4]

INNOVATION and/or ADVANTAGES

If approved, taselisib in combination with fulvestrant will offer an additional treatment option for patients with unresectable, locally advanced or metastatic breast cancer after recurrence or progression during or after an aromatase inhibitor (AI) therapy.

DEVELOPER

F. Hoffmann-La Roche 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.[5] Breast cancers with receptors for the hormone oestrogen are called oestrogen-receptor positive or ER positive breast cancer. About 70% of breast cancers are ER positive.[6] Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity.[7] HER2 are

overexpressed in around 15-25% of women with breast cancer and promote tumour growth.[8] HER2-negative breast cancer refers to disease that does not overexpress HER2.[5]

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.[9] The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).[10]

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. [8] 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. [8]

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 in females in the UK in 2015 was 691,000.[12] 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.[13]

From 2016 to 2017, there were 203,454 admissions (205,821 female, 1,222 male) for malignant neoplasm of the breast (ICD-10: C50) in England, resulting in 85,801 bed days and 207,043 finished consultant episodes.[14]

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.[15] 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 in development. Breast cancer (hormone receptor positive, HER2 negative) – palbociclib (GID-TA10068). Expected date of issue to be confirmed: TBC

- NICE technology appraisal in development. Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimens (GID-TA10094). Expected date of issue to be confirmed: TBC
- NICE technology appraisal in development. Abemaciclib monotherapy for treating advanced hormone-receptor positive, HER2- negative breast cancer after endocrine therapy and chemotherapy (GID-TA10264). Expected date of issue to be confirmed: TBC
- NICE technology appraisal in development. Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2- negative breast cancer after endocrine therapy (GID-TA10263). Expected date of issue to be confirmed: TBC
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- NICE technology appraisal. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). 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. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA239). December 2011.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and treatment (CG80). February 2009.
- Improving outcomes in breast cancer. Cancer service guideline (CSG1) Published August 2002
- NICE quality standard. Breast cancer (QS12). September 2011. Updated June 2016

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.[16]
- 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.[17]

CURRENT TREATMENT OPTIONS

If HR+ and HER- breast cancer recurs or progresses after hormonal therapy, a variety of second and third line treatments are also currently recommended by NICE, which include:[18]

- 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 oestrogen 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.[19]
- Eribulin – third line treatment recommended for advance/metastatic breast cancer which has progressed after at least 2 chemotherapy regimens

EFFICACY and SAFETY

Trial	SANDPIPER, GO29058, NCT02340221, EudraCT Number: 2014-003185-25;; phase III
Sponsor	F. Hoffmann-La Roche Ltd
Status	Ongoing, recruiting
Source of Information	Trial registry[20]
Location	USA and 14 EU countries (incl UK)
Design	Randomized, double-blind, placebo-controlled, parallel assignment, multi-centred
Participants	n=600 (planned); 18 Years and Older; females; breast cancer; Oestrogen Receptor (ER) positive; Human Epidermal Growth Factor Receptor 2 (HER2) negative; locally advanced; phosphatidylinositol-4,5-bisphosphate 3-kinase; catalytic subunit alpha (PIK3CA) gene mutant positive; postmenopausal women; progressive and recurrent disease despite an aromatase inhibitor (AI) therapy
Schedule	Randomised to taselisib 4mg orally once daily beginning at Cycle 1, Day 1; or placebo beginning at Cycle 1, Day 1; both in combination with fulvestrant 500 mg intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination.
Follow-up	Not reported
Primary Outcomes	Progression-free survival (PFS) To compare the efficacy between taselisib plus fulvestrant versus placebo plus fulvestrant
Secondary Outcomes	• Overall survival • Percentage of participants with objective response (Partial Response [PR] Plus Complete Response [CR] • Percentage of participants with clinical benefit • Clinical benefit is defined as objective response (PR+CR), or no disease progression lasting for more than or equal to (>/=) 24 weeks since randomization. • Duration of objective response • PFS • Percentage of participants with adverse events • Maximum observed plasma concentration (Cmax) of taselisib • Minimum observed plasma concentration (Cmin) of taselisib • European organisation for research and treatment of cancer (EORTC) quality of life questionnaire score 30 (QLQ-C30) Score • Modified EORTC quality of life questionnaire breast cancer module 23 (QLQ-BR23) score • Patient-reported outcomes • To evaluate the safety of taselisib plus fulvestrant versus placebo plus fulvestrant
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

The cost of taselisib is not yet known.

Drug	Dose	Unit cost
Everolimus (Afinitor)[21]	10 mg once daily	£89.1
Fulvestrant (Faslodex 250mg/5ml)[22]	500 mg every 2 weeks for the first 3 doses, then 500 mg every month, to be administered into the buttock.	£261.2
Eribulin (Halaven)[23]	0.88mg/2ml solution for injection vials 1.32mg/3ml solution for injection vials	£361.00 £541.50

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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