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Veliparib in combination with carboplatin and paclitaxel for breast cancer – first to 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 type of breast cancer are those that are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-). The advanced form of the breast cancer occurs when the cancer has spread to other parts of the body such as the bones, brain and liver. Breast cancer in adults can occur at any age, with an increased risk in postmenopausal women. The risk of developing breast cancer can increase with inheritance of certain genes called e.g. BRCA2, BRCA1 and TP53.

Veliparib is a new oral drug that is being developed for patients with HER2- breast cancer that is advanced and cannot be removed completely through surgery. The drug acts by targeting specific enzymes involved in the repair of damaged DNA that helps the body to kill cancer cells while allowing ordinary cells to survive. Veliparib is being developed to be used in combination with the chemotherapy drugs paclitaxel and carboplatin. If licenced, this combination will offer an additional treatment option for patients with HER2- metastatic or locally advanced unresectable BRCA-associated breast cancer.

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TARGET GROUP

Breast cancer (HER2-, metastatic or locally advanced, unresectable, BRCA-associated) – first to third line; in combination with carboplatin and paclitaxel

TECHNOLOGY

DESCRIPTION

Veliparib (ABT-888) is an oral poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor. It acts by blocking PARP-1 and PARP-2 which are enzymes involved in the repair of damaged DNA. By blocking PARP-1 and -2, the medicine prevents cancer cells from repairing their DNA, eventually killing them while allowing ordinary cells to survive. It is expected that the medicine will be able to be used on its own to kill those cancer cells that do not have other ways of repairing DNA damage, such as those with abnormalities in the BRCA-1 or BRCA-2 genes, which are found in some ovarian cancer patients. Veliparib is also expected to be used in combination with other cytotoxic (cell-killing) cancer medicines that cause DNA damage, such as chemotherapy, where it is expected to enhance their activity by preventing DNA repair.[1,2]

Paclitaxel and carboplatin (often referred to as Carbo Taxol) are chemotherapy drugs that destroy quickly dividing cells, such as cancer cells.[3] Paclitaxel is used in the EU for the treatment of metastatic breast cancer, metastatic adenocarcinoma of the pancreas, and non-small cell lung cancer.[4] Carboplatin is indicated in the EU for the treatment of advanced ovarian carcinoma of epithelial origin and small cell carcinoma of the lung.[5]

In the Phase III clinical trial subjects receive 120mg dose of veliparib as an oral tablet twice daily on day 2 through 5 of a 21-day cycle. In addition, carboplatin and 80mg/m^2 dose of paclitaxel intravenous (IV) infusion is administered on day 1, 8, and 15 of a 21-day cycle.[20]

Veliparib does not currently have Marketing Authorisation in the EU for any indication. However, it is in late stage clinical development in the EU or globally for the following indications:[2]

- Fallopian tube cancer
- Epithelial ovarian cancer
- Peritoneal cancer
- Germ cell tumours
- Testicular cancer
- Small-cell lung cancer
- Metastatic adenocarcinoma of the pancreas
- Metastatic colorectal cancer
- Rectal cancer

INNOVATION and/or ADVANTAGES

If licensed, Veliparib in combination with paclitaxel and carboplatin will offer an additional treatment option for patients with HER2- metastatic or locally advanced unresectable BRCA-associated breast cancer.

DEVELOPER

AbbVie Ltd

PATIENT GROUP

BACKGROUND

Breast cancer is cancer that develops from breast tissue. Breast cancer is not a single disease, but rather a group of several different tumour subtypes. Early breast cancer typically manifests as a localized lump within the breast. As the disease progresses, increasing involvement of the lymph nodes is observed, followed by distant metastasis. Metastatic breast cancer is also classified as Stage IV breast cancer. Frequent sites of metastasis observed in breast cancer include the bones, brain, liver, and lungs.[6]

Although many subtypes of breast cancer exist, they are generally categorized by the presence or absence of hormonal receptors (HRs) and human epidermal growth factor receptor type 2 (HER2). HRs are proteins — found in and on breast cells — that pick up hormone signals telling the cells to grow. HR+ breast cancer includes disease in which tumours express either oestrogen receptors (ER+) or progesterone receptors (PR+). Approximately 80% of breast cancers in postmenopausal women are HR+.[7] HER2 is a protein that can affect the growth of some cancer cells. It is found on the surface of normal breast cells. When there are higher levels of the HER2 protein in a breast cancer, it is called HER2+ breast cancer. HER2+ breast cancers tend to be more aggressive than HER2- breast cancers.[8] HR+/HER2- breast cancer is the most common form of breast cancer. This type accounts for more than 70% of all breast cancers.[9]

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.[10] The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes e.g. BRCA2, BRCA1 and TP53. Breast cancer in adults can occur at any age, with an increased risk in postmenopausal women, and in those with a previous benign breast lump, or a prior diagnosis of early breast cancer further increases the risk.[11]

Patients diagnosed with early stage breast cancer can live for many years without their quality of life being dramatically impacted by the disease. This is particularly evident for patients diagnosed with Stage 0 carcinomas in situ, who have up to a 100% five-year survival rate, and often live a normal lifespan. Advanced breast cancers that require complete removal of the breast, known as a mastectomy, can be very distressing for a woman, affecting sexuality and body image. In metastatic breast cancer, the bone is one of the most common sites of tumour infiltration, occurring in up to 70% of breast cancer patients, resulting in bone pain that can vary from a single site of severe pain to scattered pain throughout the skeleton.[12]

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers.[13] There were around 55,200 new cases of breast cancer in the UK in 2014, that's 150 cases

diagnosed every day. 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).[14]

An estimated 27% of female breast cancers in the UK are linked to lifestyle factors including overweight and obesity (9%), alcohol (6%), and certain occupational exposures (5%). The lifetime risk of developing breast cancer is 1 in 8 for women in 2012 in the UK. 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.[14]

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+.[12]

There were around 11,400 breast cancer deaths in the UK in 2014, that's 31 deaths every day. Breast cancer is the third most common cause of cancer death in the UK, accounting for 7% of all cancer deaths in 2014. Breast cancer deaths in England are more common in females living in the most deprived areas.[14]

Breast cancer survival is improving and has doubled in the last 40 years in the UK. Breast cancer survival in England is highest for women diagnosed aged 60-69, probably because of screening, and less favourable tumour characteristics in younger women (2009-2013). Five year net survival in women aged 15-99 years in England and Wales during 2010-2011 was 87%.[14]

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 1.4 for males and 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 0.3 for males and 34.3 for females[15]

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.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Breast cancer (hormone-receptor positive, HER2-negative) - palbociclib [ID915] (GID-TA10068). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523] (GID-TAG322). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Breast cancer (HER2 negative, HR positive) – Everolimus (with exemestane, after endocrine therapy) (ID965) (GID-TA10028). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072] (GID-TA10094). Expected date of issue to be confirmed.

- NICE technology appraisal in development. Palbociclib for treating hormone-receptor positive, HER2-negative breast cancer [ID916] (GID-TA10095). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ribociclib for breast cancer [ID1026] (GID-TA10141). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951] (GID-TA10106). Expected publication date: 31 January 2018.
- NICE technology appraisal in development. Breast cancer (brain metastases) - etirinotecan pegol [ID881] (GID-TA10066). Expected date of issue to be confirmed.
- NICE technology appraisal. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016.
- 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. 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.
- NICE technology appraisal. Guidance on the use of trastuzumab for the treatment of advanced breast cancer (TA34). March 2002.
- 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.
- 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.

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.[17]

Treatment options of HR+ or HR-/HER- advanced or metastatic breast cancer according to NICE include:[18]

<u>Endocrine therapy or chemotherapy – first line</u>

- Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive (HR+) advanced breast cancer.
- Offer chemotherapy as first-line treatment for patients with ER-positive (HR+) advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.
- For patients with ER-positive 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:
    - Post-menopausal women with ER-positive breast cancer and no prior history of endocrine therapy
    - Post-menopausal women with ER-positive breast cancer previously treated with tamoxifen.
- Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and peri-menopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
- Offer ovarian suppression to premenopausal and peri-menopausal women who have previously been treated with tamoxifen and then experience disease progression.

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).
- Gemcitabine
    - Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.
- Bevacizumab in combination with capecitabine
    - Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months. People currently receiving bevacizumab in combination with capecitabine that is not recommended according to above should have the option to continue treatment until they and their clinician consider it appropriate to stop.
- Bevacizumab in combination with a taxane

- Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer. Patients currently receiving bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Other second-line treatments

- Everolimus
  - Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced human epidermal growth factor receptor 2 negative (HER2-), hormone receptor positive (HR+) breast cancer in post-menopausal 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 treatment

- 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	NCT02163694, EudraCT-2014-000345-70; carboplatin and paclitaxel with or without veliparib; Phase III
Sponsor	AbbVie

Status	Ongoing
Source of Information	Trial registry[19], Global Data[20]
Location	20 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	N=500 (planned); >= 18 years old; breast cancer; HER2-; metastatic or locally advanced, unresectable, BRCA-associated; first to third line
Schedule	Participants receive veliparib or placebo on day 2 through 5 of a 21-day cycle. In addition, carboplatin and paclitaxel will be administered on day 1 of a 21-day cycle.
Follow-up	Not reported
Primary Outcomes	Progression-free survival (PFS)
Secondary Outcomes	Overall survival (OS), Clinical benefit rate (CBR), Objective response rate (ORR), Progression-free survival 2, Duration of overall response (DOR)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date May 2018. Estimated study completion date February 2019.

ESTIMATED COST and IMPACT

COST

The cost of veliparib 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

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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