NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Ipatasertib in addition to paclitaxel for locally advanced or metastatic triple-negative breast cancer

NIHRIO ID	21691	**NICE ID**	10062
Developer/Company	Roche Products Ltd	**UKPS ID**	648995

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Ipatasertib in addition to paclitaxel is in clinical development for the treatment of adults with locally advanced or metastatic triple-negative breast cancer (TNBC) with PIK3CA/AKT1/PTEN-altered tumour. This type of breast cancer is caused by a combination of genetic abnormalities and loss of some genes in the body. TNBC is an uncommon type of breast cancer whose cells do not have receptors for the hormones oestrogen and progesterone or HER2 protein. This means that many cancer treatments do not work for people with TNBC. Patients with TNBC have worse clinical outcomes and a unique pattern of recurrence compared with the other major subtypes of breast cancer. Patients with TNBC have been shown to have the highest rate of recurrence within the first 5 years after diagnosis.

Ipatasertib is administered orally. It works by blocking the activity of a protein called serine/threonine-protein kinase (AKT) which may prevent cancer cell growth and survival. The combination of ipatasertib and paclitaxel is also well tolerated and demonstrated a better objective response rate in TNBC. If licensed, ipatasertib in addition to paclitaxel may offer an additional treatment option for locally advanced or metastatic TNBC with PIK3CA/AKT1/PTEN-altered tumours with no prior chemotherapy in the advanced setting.

PROPOSED INDICATION

Adults with locally advanced or metastatic triple-negative breast cancer (TNBC) with PIK3CA/AKT1/PTEN-altered tumours with no prior chemotherapy in advanced setting.[a]

TECHNOLOGY

DESCRIPTION

Ipatasertib (GDC-0068) is an inhibitor of the serine/threonine-protein kinase AKT (protein kinase B) with potential antineoplastic activity. Ipatasertib binds to and inhibits the activity of AKT in a non-ATP-competitive manner, which may result in the inhibition of the PI3K/AKT signalling pathway, tumour cell proliferation and the induction of tumour cell apoptosis. Activation of the PI3K/AKT signalling pathway is frequently associated with tumorigenesis and dysregulated PI3K/AKT signalling may contribute to tumour resistance to a variety of antineoplastic agents.[1]

Ipatasertib in addition to paclitaxel is in clinical development for the treatment of locally advanced or metastatic triple-negative breast cancer with PIK3CA/AKT1/PTEN-altered tumour. In the phase II/III clinical trial (NCT03337724), patients received 400 mg ipatasertib orally once a day on days 1-21 of each 28-day cycle and 80 mg/square meter paclitaxel intravenously on days 1, 8, and 15 of each 28-day cycle until disease progression, intolerable toxicity, elective withdrawal from the study or study completion or termination.[2]

INNOVATION AND/OR ADVANTAGES

Ipatasertib is a potent, novel, selective, ATP-competitive small-molecule inhibitor of all three forms of AKT.[3,4] The novel feature of Ipatasertib is that it has a greater than 100-fold selectivity over other relevant kinases, including a greater than 600-fold selectivity over protein kinase A. Ipatasertib is effective for both preclinical cancer cell lines and in xenograft models with activation of AKT, including tumours with complete loss of PTEN, decreased expression of PTEN, or mutations in PIK3CA.[4]

Preclinical studies showed synergy between ipatasertib and paclitaxel. In breast cancer, the combination of ipatasertib and paclitaxel was well tolerated with a safety profile consistent with the single agent.[5]

Further, the initial results from the phase II clinical trial suggest that ipatasertib demonstrated a median overall survival (OS) of 23.1 months compared with 18.4 months in placebo arm.[6] Ipatasertib also demonstrated an improved progression-free survival (PFS) 6.2 months vs 4.9 months in placebo (stratified HR, 0.60; 95% CI, 0.37-0.98). In the subset of patients with PIK3CA/AKT1/PTEN-altered tumours (n=42), the benefit of ipatasertib on median PFS was more pronounced compared with placebo (9.0 months vs. 4.9 months, unstratified HR, 0.44; 95% CI, 0.20-0.99).[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ipatasertib does not currently have Marketing Authorisation in the EU/UK for any indication.

Ipatasertib in addition to paclitaxel is in phase II and III clinical development for several breast cancer indications.[8]

[a] Information provided by Roche Products Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can have the condition. It usually starts in the cells that line the milk ducts of the breast.[9] Locally advanced breast cancer occurs when cancer has spread from the breast to lymph nodes close to breast or to the skin of the breast or to the chest wall. Metastatic breast cancer occurs when cancer has spread to other parts of the body such as the liver or bones.[10]

Triple-negative breast cancer (TNBC) represents a subgroup of breast tumours defined by lack of expression of the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).[11] TNBC, which accounts for an estimated 15-20% of invasive breast cancers has been associated with rapid growth, distant metastasis and shorter overall and relapse-free survival when compared to other breast cancer sub-types across multiple studies.[12] TNBC is more likely to be diagnosed in people younger than age 50 years, unlike other breast cancer types which more commonly occur in people aged 60 years and older.[13]

TNBC tends to be biologically aggressive, and with a lack of commonly utilised targeting agents, it is often associated with a poor prognosis.[11] Patients with TNBC have shown to have the highest rate of recurrence within the first 5 years after diagnosis, with a significant decrease and plateauing of the recurrence rate afterwards. Post-recurrence survival is also decreased compared to HER-positive tumours.[14]

An important number of TNBC cases harbour aberrations in the PI3K pathway, leading to constitutive activation of the downstream signalling pathway. Among mechanisms of PI3K enhancement, PIK3CA mutations are most frequently (~30%) observed, along with protein loss of PTEN and AKT activation by phosphorylation (pAkt).[15]

Symptoms of TNBC are similar to other breast cancer types, and can include a lump or thickening in an area of the breast, changes in the size, shape or feel of the breast or nipple, or a swelling in the armpit.[16] TNBC patients experience physical symptoms and psychosocial distress that adversely affect their quality of life. Treatment, including chemotherapy, can have other effects including anger, grief, suffering and pain.[17]

CLINICAL NEED AND BURDEN OF DISEASE

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.[18] Age standardised Incidence rates among females are projected to rise by 2.24% in the UK between 2014 and 2035.[19] Approximately 20-40% of patients with an early-stage TNBC will develop metastatic disease.[20]

In 2018-19 there were 219,885 finished consultant episodes (FCEs) and 80,435 FCE bed days with a primary diagnosis of malignant neoplasm of breast (ICD-10; C50). There were 215,644 hospital admissions, of which 183,828 were day cases.[21]

In England in 2017, there were 10,219 deaths with malignant neoplasm of breast (ICD-10 code C50) recorded as the underlying cause.[22] The latest published survival statistics for breast cancer for women in England (2018, patients diagnosed 2013-2017) report a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatments for TNBC are surgery and chemotherapy, depending on the location, stage and grade of cancer confirmed by pathology, and the patient's general health. Surgery may be lumpectomy (usually followed by radiotherapy to the rest of the breast tissue) or a mastectomy. Chemotherapy may be given before surgery and is also usually given following surgery.[16]

CURRENT TREATMENT OPTIONS

NICE recommends 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), single-agent docetaxel should be offered as first-line treatment.[24]

NICE recommends gemcitabine in combination with paclitaxel, within its licensed indication, as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[25]

PLACE OF TECHNOLOGY

If licensed, ipatasertib in addition to paclitaxel may offer an additional treatment option for patients with locally advanced or metastatic TNBC with PIK3CA/AKT1/PTEN-altered tumours.

CLINICAL TRIAL INFORMATION

Trial	**IPATunity130,** NCT03337724, EudraCT 2017-001548-36; A double-blind, placebo-controlled, randomized phase III study of ipatasertib in combination with paclitaxel as a treatment for patients with PIK3CA/AKT1/PTEN-Altered, locally advanced or metastatic, triple-negative breast cancer or hormone receptor-positive, her2-negative breast cancer **Trial phase II/III** – Recruiting **Location(s):** EU (including UK), USA, Canada and other countries **Primary completion date:** December 2021
Trial design	Randomised, parallel-assignment, placebo-controlled, triple-blinded
Population	n= 450 (planned); aged 18 years and older; triple-negative breast cancer (TNBC) or HR+/HER2-adenocarcinoma; locally advanced, metastatic and is not amenable to resection with curative intent
Intervention(s)	Experimental arm • Ipatasertib, 400 mg, administered orally once a day on days 1−21 of each 28-day cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination • Paclitaxel, 80 mg/square meter, administered intravenously on days 1, 8, and 15 of each 28-day cycle until disease progression, intolerable toxicity, elective

	withdrawal from the study, or study completion or termination
Comparator(s)	Placebo arm • Paclitaxel, 80 mg/square meter, administered intravenously (IV) on days 1, 8, and 15 of each 28-day cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination • Matching placebo, administered orally once a day on days 1−21 of each 28-day cycle until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination
Outcome(s)	Progression-Free Survival (PFS) (Time frame: from randomization until the first occurrence of disease progression or death from any cause, whichever occurs earlier, up to approximately 53 months) See trial details for other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ipatasertib is not yet known

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer (TA639). July 2020.
- 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. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (TA214). February 2011.
- NICE technology appraisal guidance. Gemcitabine for the treatment of metastatic breast cancer (TA116). January 2007.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

OTHER GUIDANCE

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[26]

ADDITIONAL INFORMATION

REFERENCES

1 National Cancer Institute. *Ipatasertib*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/ipatasertib [Accessed 23 July 2020].

2 Clinicaltrials.gov. *A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer (IPATunity130). Trial ID: NCT03337724*. Available from: https://clinicaltrials.gov/ct2/show/NCT03337724 [Accessed 23 July 2020].

3 Sun L, Huang Y, Liu Y, Zhao Y, He X, Zhang L, et al. Ipatasertib, a novel Akt inhibitor, induces transcription factor FoxO3a and NF-kappaB directly regulates PUMA-dependent apoptosis. *Cell Death Dis*. 2018 Sep 5;9(9):911. Available from: https://doi.org/10.1038/s41419-018-0943-9.

4 Saura C, Roda D, Rosello S, Oliveira M, Macarulla T, Perez-Fidalgo JA, et al. A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. *Cancer Discov*. 2017 Jan;7(1):102-13. Available from: https://doi.org/10.1158/2159-8290.Cd-16-0512.

5 Isakoff S, Infante J, Juric D, Chan W, Jia S, Musib L, et al. Phase Ib dose-escalation study of the Akt inhibitor ipatasertib (Ipat) with paclitaxel (P) in patients (pts) with advanced solid tumors. *Annals of Oncology*. 2014;25:iv148. Available from: https://doi.org/10.1093/annonc/mdu331.6.

6 Dent R, Im S-A, Espie M, Blau S, Tan AR, Isakoff SJ, et al. Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). *Journal of Clinical Oncology*. 2018;36(15_suppl):1008-. Available from: https://doi.org/10.1200/JCO.2018.36.15_suppl.1008.

7 Onclive. *Early OS Data Support Phase III Trial With AKT Inhibitor Ipatasertib for TNBC*. Available from: https://www.onclive.com/conference-coverage/asco-2018/data-support-phase-3-trial-with-akt-inhibitor-in-triple-negative-breast-cancer [Accessed 23 July 2020].

8 Clinicaltrials.gov. *Ipatasertib | Phase 2*. Available from: https://clinicaltrials.gov/ct2/results?term=ipatasertib&age_v=&gndr=&type=&rslt=&phase=1&Search=Apply [Accessed 23 July 2020].

9 Cancer Research UK. *What is breast cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 23 July 2020].

10 Cancer Research UK. *About breast cancer staging and grades*. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/about-breast-cancer-staging-grades [Accessed 23 July 2020].

11 Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. *Medicine*. 2016;95(35). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5008562/.

12 Yeh J, Chun J, Schwartz S, Wang A, Kern E, Guth AA, et al. Clinical characteristics in patients with triple negative breast cancer. *International journal of breast cancer*. 2017;2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5585655/.

13 Breastcancer.org. *Triple-Negative Breast Cancer*. Available from: https://www.breastcancer.org/symptoms/diagnosis/trip_neg [Accessed 23 July 2020].

14 Reddy SM, Barcenas CH, Sinha AK, Hsu L, Moulder SL, Tripathy D, et al. Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and

relationship with low hormone receptor positivity. *Br J Cancer*. 2018 Jan;118(1):17-23. Available from: https://doi.org/10.1038/bjc.2017.379.

15 Jouali F, Marchoudi N, Talbi S, Bilal B, El Khasmi M, Rhaissi H, et al. Detection of PIK3/AKT pathway in Moroccan population with triple negative breast cancer. *BMC cancer*. 2018;18(1):900. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-4811-x.

16 Canceresearch UK. *Triple negative breast cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/types/triple-negative-breast-cancer [Accessed 23 July 2020].

17 Perry S, Kowalski TL, Chang CH. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. *Health Qual Life Outcomes*. 2007 May 2;5:24. Available from: https://doi.org/10.1186/1477-7525-5-24.

18 Office for National Statistics. *Cancer registration statistics, England.* 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 23 July 2020].

19 Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer*. 2016 Oct 25;115(9):1147-55. Available from: https://doi.org/10.1038/bjc.2016.304.

20 Sharma P. Update on the Treatment of Early-Stage Triple-Negative Breast Cancer. *Current Treatment Options in Oncology*. 2018 April 14;19(5):22. Available from: https://doi.org/10.1007/s11864-018-0539-8.

21 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 23 July 2020].

22 Office for National Statistics. *Death registrations summary tables - England and Wales.* 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 23 July 2020].

23 Office for National Statistics. *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 23 July 2020].

24 National Institute for Health and Care Excellence. *Managing advanced breast cancer*. Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-triple-negative-disease [Accessed 23 July 2020].

25 NICE technology appraisal guidance. *Gemcitabine for the treatment of metastatic breast cancer (TA116)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta116/chapter/1-Guidance [Accessed 23 July 2020].

26 Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Annals of Oncology*. 2018;29(8):1634-57. Available from: https://doi.org/10.1093/annonc/mdy192.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.