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Olaparib for metastatic pancreatic cancer with gBRCA mutation

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LAY SUMMARY

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas – a large gland that is a part of the digestive system. It can be localized (limited to the pancreas) or metastatic. Metastatic cancer is when the disease has spread to other organs in the body. Several causes have been associated with pancreatic cancer. Mutations in BRCA1 and BRCA2, most commonly linked with breast and ovarian cancers, are now gaining wider recognition for being associated with pancreatic cancer as well. People with these mutations face a 5 percent risk of getting pancreatic cancer in their lifetime.

Olaparib is an inhibitor of an enzyme called human poly (ADP-ribose) polymerase enzymes (PARP), and has been shown to reduce the growth of tumour cells. It is already approved as a maintenance therapy for some other types of cancers and is currently being developed as an orally administered treatment for gBRCA mutated metastatic pancreatic cancer in patients that have been treated with standard chemotherapies. If licensed olaparib will offer an additional maintenance treatment option for these patients whose disease has not progressed following treatment with first line chemotherapies.

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TARGET GROUP

Pancreatic cancer (gBRCA mutated, metastatic)

TECHNOLOGY

DESCRIPTION

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.[1]

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as breast cancer 1 and 2 (BRCA1 or 2), DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells.[1]

Olaparib is being studied in patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy. In the phase III trial (POLO; NCT02184195), patients will be randomised within 6 weeks after their last dose of chemotherapy to receive olaparib 300mg oral tablets twice daily until disease progression.[2]

Olaparib is licensed in the UK for ovarian, fallopian and peritoneal cancers.[3]

Olaparib has been associated with adverse reactions generally of mild or moderate severity and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.[4]

Besides pancreatic cancer olaparib is in phase III trials for the following indications:[5]

- Ovarian cancer
- Breast cancer
- Prostate cancer
- Gastric cancer
- Fallopian cancer
- Primary peritoneal cancer

It is in phase II trials for the following indications:[6]

- Bladder cancer

- Ovarian cancer
- Lung cancer
- Gastric cancer
- Breast cancer
- Gliomas
- Prostate cancer
- Squamous cell carcinoma of the head and neck

INNOVATION and/or ADVANTAGES

BRCA-associated cancers have increased sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPis).[1] If licensed, olaparib will offer a maintenance treatment option for patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy.

DEVELOPER

AstraZeneca Pharmaceuticals Ltd.

PATIENT GROUP

BACKGROUND

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas – a large gland that is a part of the digestive system.[7] Pancreatic cancers are grouped into two main types: exocrine and endocrine tumours. Exocrine tumours, which occur in the exocrine cells of the pancreas, are the most common form of pancreatic cancer. These tumours account for well over 95% of all pancreatic cancers. Pancreatic ductal adenocarcinoma (PDAC) is the most common type, making up about 90% of all exocrine tumours.[8]

Pancreatic cancer may be localized (limited to the pancreas) or metastatic. Metastatic cancer is when the cancer has spread through the bloodstream, or the lymphatic system, to other organs in the body. The most common place for it to spread to is the liver. Other sites include the peritoneum, lungs and bones.[9]

Several factors have been associated with pancreatic cancer. Mutations in BRCA1 and BRCA2, most commonly linked with breast and ovarian cancers, are now gaining wider recognition for being associated with pancreatic cancer as well. People with BRCA1 or BRCA2 mutations face a 5 percent risk of getting pancreatic cancer in their lifetime.[10]

In the early stages, a tumour in the pancreas does not usually cause any symptoms, which can make it difficult to diagnose. The first noticeable symptoms of pancreatic cancer are often pain in the back or stomach area, unexpected weight loss and jaundice. Other possible symptoms of pancreatic cancer include nausea and vomiting, bowel changes, fever and shivering, indigestion and blood clots.[7]

The cause of pancreatic cancer is not fully understood but a number of risk factors for developing the condition have been identified which include age, smoking and having a history of certain health

conditions such as diabetes, chronic pancreatitis (long-term inflammation of the pancreas), stomach ulcer and Helicobacter pylori infection (a stomach infection).[7]

Pancreatic cancer is characterized by aggressiveness and high mortality rates that nearly parallel its incidence. While there have been some advances in the treatment options of pancreatic cancer, there has only been a dismal increase from 2% to 6% in 5-year pancreatic cancer survival rates from 1975-2008. Since success of treatment options and their impact on traditional outcomes such as progression free survival (PFS) or overall survival (OS) is so limited, the focus of treatment has been said to shift towards better quality-of-life (QoL).[11]

CLINICAL NEED and BURDEN OF DISEASE

According to the Office for National Statistics, in 2016, there were 8,455 per 100,000 patients registered as newly diagnosed cases of malignant neoplasm of pancreas (ICD-10 code:C25) in the UK.[12]

In England and Wales, 8,315 deaths were registered due to pancreatic cancer in 2016 in 2016.[13]

Between 2011 and 2015 the age-standardized one-year net survival and five-year survival for malignant neoplasm of pancreas for adults aged 15 to 99 years in England has been calculated to be 23.7% and 6.9% respectively. [14]

According to the 2016/17 Hospital Episodes Statistics (HES) data, 28,204 patients were admitted due to malignant neoplasm of pancreas which led to 91,409 FCE bed days.[15]

These estimates do not differentiate between localized or metastatic pancreatic cancer. Estimates regarding patients with gBRCA mutation could not be made from the current literature therefore the population likely to be eligible to receive olaparib could not be estimated.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidelines. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Pancreatic (Adult). A02/S/b.

OTHER GUIDANCE

- Pancreatic Adenocarcinoma. NCCN Clinical Practice Guidelines in Oncology. 2016.[16]
- Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[17]

CURRENT TREATMENT OPTIONS

Pancreatic cancer is often symptomless until advanced stages of the disease, meaning curative surgery is often not possible by the time the condition has been diagnosed. Consequently, patients with locally advanced or metastatic disease may be offered chemotherapy, radiotherapy or palliative surgery to

help control tumour growth and symptoms. These may be given alone or in combination with each other.[18]

According to NICE guidance, patients with metastatic pancreatic cancer should be offered;

- A combination of folic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) as a first-line treatment.
- Gemcitabine should be offered to patients who are not well enough to tolerate FOLFIRINOX.
- Oxaliplatin-based chemotherapy as second-line treatment should be considered for people who have not had first-line oxaliplatin.
- Gemcitabine-based chemotherapy as second-line treatment should be considered for people whose cancer has progressed after first-line FOLFIRINOX.[19]
- Surveillance should be offered for pancreatic cancer with BRCA mutations.[19]

EFFICACY and SAFETY	
Trial	POLO, NCT02184195, D081FC00001; adults aged 18 to 99 years; olaparib vs placebo, phase III
Sponsor	AstraZeneca Pharmaceuticals Ltd.
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl UK), USA, Canada, Australia, Israel and Republic of Korea
Design	Randomised, placebo-controlled, double blind
Participants	n=144 (planned); aged 18-99 years; pancreatic cancer; gBRCA1 or gBRCA2 positive; metastatic; disease not progressed on first line platinum based chemotherapy
Schedule	Randomised to olaparib 300mg orally twice daily until disease progression
Follow-up	Up to 4 years
Primary Outcomes	Progression free survival (PFS) by central review of modified RECIST 1.1 [Time frame: up to 4 years]
Secondary Outcomes	• Overall survival (OS) • Time from randomisation to second progression or death (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST) • Time from randomisation to study treatment discontinuation or death (TDT) • Objective response rate by BICR using modified RECIST 1.1 • Disease control rate by BICR using modified RECIST 1.1 • Adjusted mean change from baseline in global quality of life (QoL) score from the EORTC-QLQ-C30 questionnaire • Safety and tolerability of olaparib • Improvement rate of global quality of life (QoL) Time frame for all secondary outcomes is up to 4 years.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as November 2018.

ESTIMATED COST and IMPACT

COST

Olaparib is already marketed in the UK for the treatment of ovarian, fallopian tube and peritoneal cancers; a pack of 448 50mg capsules costs £3550.[20] This means 14 days of treatment costs £2318.

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: Testing for BRCA mutations
- ☐ None identified

OTHER ISSUES

- ☐ Clinical uncertainty or other research question identified:
- ☒ None identified

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