FDA approves Lynparza for metastatic breast cancer

12 January 2018 16:10 GMT

LYNPARZA APPROVED BY US FDA IN GERMLINE *BRCA*-MUTATED METASTATIC BREAST CANCER

Lynparza is the first and only PARP inhibitor approved for use beyond ovarian cancer

Lynparza reduced the risk of disease progression or death by 42%

compared to standard of care chemotherapy

AstraZeneca and Merck & Co., Inc., Kenilworth, N.J., US (Merck: known as MSD outside the US and Canada) today announced that the US Food and Drug Administration (FDA) has approved *Lynparza* (olaparib), for use in patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor positive (HR+) breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Patients are selected for therapy based on an FDA-approved companion diagnostic from Myriad Genetics.

Dave Fredrickson, Executive Vice President, Head of the Oncology Business Unit, AstraZeneca, said: "This new approval for *Lynparza* makes it the first and only PARP inhibitor approved in metastatic breast cancer, and the only PARP inhibitor approved beyond ovarian cancer. This is significant for breast cancer patients, as the identification of *BRCA* status, in addition to hormone receptor and HER2 status, becomes a potentially critical step in the management of their disease."

Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, Merck Research Laboratories said: "This additional approval for *Lynparza* represents an important advance for women with HER2-negative metastatic breast cancer with a germline *BRCA* mutation, which is a difficult-to-treat cancer. Moreover, this approval adds further impetus to our important collaboration with AstraZeneca in developing cancer therapies."

The approval was based on data from the randomised, open-label, Phase III OlympiAD trial which investigated *Lynparza* versus physician's choice of chemotherapy (capecitabine, eribulin, or vinorelbine). In the trial, *Lynparza* significantly prolonged progression-free survival (PFS) compared with chemotherapy, and reduced the risk of disease progression or death by 42% (HR 0.58; 95% CI 0.43-0.80; P=0.0009 median 7.0 vs 4.2 months). Patients with measurable disease taking *Lynparza* (n=167) experienced an objective response rate of 52% (95% CI 44-60), double the response rate for those in the chemotherapy arm (n=66) which was 23% (95% CI 13-35). Additionally, patients experienced a confirmed complete response rate of 7.8% for *Lynparza* compared to 1.5% for the chemotherapy arm. The data from the OlympiAD trial can be found in the June 2017 issue of the *New England Journal of Medicine*.

Susan M. Domchek, Executive Director of the Basser Center for *BRCA* at the Abramson Cancer Center of the University of Pennsylvania, and a national leader on the OlympiAD trials, said: "Patients diagnosed with *BRCA*-related metastatic breast cancer are often younger than other breast cancer patients, and their disease is often much more aggressive and difficult to treat. While there is currently no cure for metastatic breast cancer, today's approval offers a new, targeted option that may help to delay disease progression for these patients."

The most common adverse reactions (≥20%) in the OlympiAD trial of patients who received *Lynparza* were nausea (58%), anaemia (40%), fatigue (including asthenia) (37%), vomiting (30%), neutropenia (27%), respiratory tract infection (27%), leukopenia (25%), diarrhoea (21%), and headache (20%). The percentage of patients who discontinued treatment in the *Lynparza* arm was 5% compared to the chemotherapy arm which was 8%.

This is the third indication approved for *Lynparza* in the US, where it has been used to treat nearly 4,000 advanced ovarian cancer patients. *Lynparza* has the broadest clinical development programme of any PARP inhibitor, and AstraZeneca and MSD are working together to deliver *Lynparza* as quickly as possible to more patients across multiple settings, including breast, ovarian, prostate and pancreatic cancers.

Sustainable and Ongoing Externalisation Revenue

Under the oncology collaboration with Merck, announced in July 2017, AstraZeneca is potentially eligible for more than $6 billion of future Sustainable and Ongoing Externalisation Revenue in the form of sales-related and approval-related payments in addition to option payments until 2019. Following this new approval for *Lynparza*, AstraZeneca will receive $70 million in Sustainable and Ongoing Externalisation Revenue.

About OlympiAD

OlympiAD is a randomised, open-label, multicentre Phase III trial assessing the efficacy and safety of *Lynparza* tablets (300 mg twice daily) compared to physician's choice of chemotherapy in 302 patients with HER2-negative metastatic breast cancer with germline *BRCA*1 or *BRCA*2 mutations, which are confirmed or suspected to be deleterious. The international trial was conducted in 19 countries across Europe, Asia, North America and South America.

Patients in the OlympiAD trial had HER2-negative g*BRCA*1- or g*BRCA*2-mutated breast cancer, which was HR+ or triple negative, and received *Lynparza* for metastatic disease. Approximately half of the patients in the *Lynparza* and chemotherapy arm of the trial were HR+ (n=152), and approximately half were triple negative (n=150). Among the 205 patients treated with *Lynparza*, the median age was 44 years (range: 22 to 76). Before enrolment, patients had prior treatment with an anthracycline (unless contraindicated) and a taxane chemotherapy either in the neoadjuvant, adjuvant or metastatic setting and no more than two prior lines of chemotherapy for metastatic disease. Hormone receptor-positive patients had received at least one endocrine medicine or were not eligible for endocrine medicines. Prior treatments with endocrine medicines were not counted as prior lines of chemotherapy.

The primary endpoint of the trial was PFS as measured by a Blinded Independent Central Review. Secondary endpoints included overall survival, time to second progression or death, objective response rate, and effect on health-related quality of life.

About Metastatic Breast Cancer (MBC)

Three main receptors drive tumour growth in breast cancer: progesterone receptors (PR), estrogen receptors (ER) and HER2 receptors. A patient's breast cancer will test either negative or positive for these three receptors. If a tumour tests positive for PR and/or ER, it is considered HR+. If a tumour tests negative for all three receptors, it is considered triple negative.

MBC is the most advanced stage of breast cancer (Stage IV), and occurs when cancer cells have spread beyond the initial tumour site to other parts of the body outside of the breast.

Despite the increase in treatment options during the past three decades, there is currently no cure for patients diagnosed with MBC and only 26.9% of patients survive five years after diagnosis. Thus, the primary aim of treatment is to slow progression of the disease for as long as possible, improving, or at least maintaining, a patient's quality of life.

It is estimated that in 2018, there will be approximately 155,000 women in the US living with MBC, and this number is projected to increase to approximately 160,000 by the year 2020.

About Germline *BRCA* Mutations

*BRCA*1 and *BRCA*2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role maintaining the genetic stability of cells. When either of these genes is mutated, or altered, such that its protein product either is not made or does not function correctly, DNA damage may not be repaired properly and cells become unstable. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer.

About *Lynparza* (olaparib) *Lynparza* is the first FDA-approved oral poly ADP-ribose polymerase (PARP) inhibitor and the first targeted treatment to potentially exploit DNA damage response (DDR) pathway deficiencies, such as *BRCA* mutations, to preferentially kill cancer cells. Specifically, *in vitro* studies have shown that *Lynparza*-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

Lynparza is being investigated in a range of DDR-deficient tumour types and is the foundation of AstraZeneca's industry-leading portfolio of compounds targeting DDR mechanisms in cancer cells.

About the AstraZeneca and MSD Strategic Oncology Collaboration

In July 2017, AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, US, known as MSD outside the United States and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialise *Lynparza*, the world's first PARP inhibitor, and potential new medicine selumetinib, a MEK inhibitor, for multiple cancer types. The collaboration is based on increasing evidence that PARP and MEK inhibitors can be combined with PD-L1/PD-1 inhibitors for a range of tumour types. Working together, the companies will develop *Lynparza* and selumetinib in combination with other potential new medicines and as a monotherapy. Independently, the companies will develop *Lynparza* and selumetinib in combination with their respective PD-L1 and PD-1 medicines.

About AstraZeneca in Oncology AstraZeneca has a deep-rooted heritage in Oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With at least six new medicines to be launched between 2014 and 2020 and a broad pipeline of small molecules and biologics in development, we are committed to advance New Oncology as one of AstraZeneca's five Growth Platforms focused on lung, ovarian, breast and blood cancers. In addition to our core capabilities, we actively pursue innovative partnerships and investments that accelerate the delivery of our strategy as illustrated by our investment in Acerta Pharma in haematology.

By harnessing the power of four scientific platforms - Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response and Antibody Drug Conjugates - and by championing the development of personalized combinations, AstraZeneca has the vision to redefine cancer treatment and one day eliminate cancer as a cause of death.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular & Metabolic Diseases and Respiratory. The Company also is selectively active in the areas of autoimmunity, neuroscience and infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

For more information, please visit www.astrazeneca.com and follow us on Twitter @AstraZeneca.

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