Pfizer Logo

European Commission Approves TALZENNA® (talazoparib) for Patients with Inherited (Germline) BRCA-Mutated Locally Advanced or Metastatic Breast Cancer

Friday, June 21, 2019 - 06:45am

Only once-daily PARP inhibitor approved in Europe for hereditary breast cancer

Pfizer Inc. (NYSE:PFE) today announced that the European Commission approved TALZENNA® (talazoparib), an oral poly (ADP-ribose) polymerase (PARP) inhibitor, as monotherapy for the treatment of adult patients with germline breast cancer susceptibility gene (g*BRCA*)1/2-mutations, who have human epidermal growth factor receptor 2-negative (HER2-) locally advanced (LA) or metastatic breast cancer (MBC). Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive (HR+) breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.[1] This approval follows the medicine's approval by the U.S. Food and Drug Administration (FDA) in October 2018.

"Today's approval of TALZENNA for certain patients with advanced-stage breast cancer and an inherited *BRCA* mutation is the latest example of our successful precision medicine approach to drug development," said Andreas Penk, M.D., Regional President, Oncology International Developed Markets at Pfizer. "This important milestone builds on Pfizer's decades-long legacy of developing therapies that improve outcomes for patients with breast cancer. We are thrilled that we can now offer these patients in Europe, who are often diagnosed at a younger age and have limited treatment options, an effective, once-daily, alternative treatment to chemotherapy."

The European Commission's approval of TALZENNA, which was acquired as part of Pfizer's acquisition of Medivation, is based on results from the EMBRACA trial - the largest Phase 3 study of a PARP inhibitor in g*BRCA*-mutated, HER2- LA or MBC. The global trial evaluated once-daily TALZENNA compared to physician's choice standard chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine) in patients with an inherited *BRCA*1/2 mutation in triple-negative or HR+/HER2- LA or MBC who may have received up to three prior cytotoxic chemotherapy regimens for their advanced disease. The primary endpoint was progression-free survival (PFS), as assessed by blinded independent central review (BICR).[1,2]

"In the EMBRACA trial, TALZENNA reduced the risk of disease progression by 46 percent and more than doubled the overall response rate compared to chemotherapy," said Johannes Ettl, M.D., Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technical University of Munich in Germany and an investigator in the EMBRACA trial. "This improvement in outcomes for patients treated with TALZENNA reinforces the increasingly key role of genetic testing in treatment decision-making for patients with locally advanced or metastatic breast cancer."

In the EMBRACA trial, TALZENNA significantly outperformed chemotherapy, extending median PFS to 8.6 months compared to 5.6 months for those treated with standard chemotherapy [95% CI: 7.2-9.3 vs. 4.2-6.7, respectively]. The superior PFS benefit with TALZENNA was observed across prespecified patient populations, including patients with triple-negative breast cancer, HR+/HER2- disease, with or without a history of CNS metastasis, and those who received prior cytotoxic chemotherapy regimens. Secondary endpoints from the EMBRACA trial included objective response rate (ORR), overall survival (OS) and safety. TALZENNA demonstrated an ORR of 62.6% (95% CI: 55.8-69.0), more than double that in the standard chemotherapy arm (27.2%) (95% CI: 19.3-36.3). OS is an event-driven endpoint and the data are not yet mature.[1]

Based on pooled data from patients who received 1 mg TALZENNA in clinical studies for solid tumors, the most common adverse reactions (? 25%) of patients receiving TALZENNA were fatigue (57.1%), anemia (49.6%), nausea (44.3%), neutropenia (30.2%), thrombocytopenia (29.6%) and headache (26.5%). Grade 3 or higher adverse reactions (? 10%) in patients treated with TALZENNA were anemia (35.2%), neutropenia (17.4%) and thrombocytopenia (16.8%).[1]

About EMBRACA

The pivotal, Phase 3, open-label, 2:1 randomized EMBRACA trial is the largest Phase 3 trial of a PARP inhibitor in g*BRCA*-mutated, HER2- LA or MBC. The trial evaluated TALZENNA (1 mg once daily) compared to physician's choice chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine) in 431 patients with an inherited *BRCA*1/2 mutation and locally advanced or metastatic triple-negative or HR+/HER2- breast cancer who may have received up to three prior cytotoxic chemotherapy regimens. Of the patients enrolled, 190 were from European countries, such as Belgium, France, Germany, Ireland, Italy, Poland, Spain and the United Kingdom. The primary endpoint was PFS, as assessed by BICR. Safety, ORR and OS were key secondary endpoints.[1,2]

Primary results from the EMBRACA trial were published in the *New England Journal of Medicine*, simultaneous to the online publication of patient-reported outcomes data in *Annals of Oncology* in August 2018.[2,3]

For more information on the EMBRACA trial, go to www.clinicaltrials.gov.

About Germline (Inherited) *BRCA*-Mutated Breast Cancer

*BRCA*1 and *BRCA*2 are human genes that produce proteins involved in DNA repair. When either of these genes is altered or mutated, DNA repair may not progress correctly. This can lead to the development of certain types of cancer such as breast cancer.[4] *BRCA* mutations can be hereditary (germline) or occur spontaneously (somatic).[5] Together, germline *BRCA*1 and *BRCA*2 mutations account for about 25 to 30% of hereditary breast cancers and approximately 3 to 6% of all breast cancers.[5,6,7,8,9]

Epidemiologic studies indicate that individuals with g*BRCA*-mutated breast cancer are diagnosed in their 30s-40s, which is approximately 20 years younger than the overall breast cancer population.[10,11]

BRCA-mutated breast cancer is metastatic if the disease has spread beyond the breast or to other parts of the body, including the bones, liver, lung or brain.[12] There is currently no cure for MBC, the most advanced stage (stage IV) of the disease. The goal of treatment is to delay or slow disease progression while maintaining quality of life.[13,14]

Current European and U.S. clinical guidelines recommend g*BRCA* testing to inform therapeutic considerations for HER2- LA or MBC patients.[15,16]

About talazoparib

Talazoparib is an inhibitor of PARP enzymes, which play a role in DNA repair. Preclinical studies suggest that talazoparib may work by blocking PARP enzyme activity and trapping PARP at the site of DNA damage, leading to decreased cancer cell growth and cancer cell death. Talazoparib anti-tumor activity also was observed in human patient-derived xenograft breast cancer tumor models that expressed mutated or wild-type *BRCA*1/2.[1]

In addition to g*BRCA*-mutated LA or MBC, talazoparib is being evaluated in several ongoing clinical trials in breast and other cancers, including early triple-negative breast cancer and prostate cancer, as well as other novel combinations with targeted therapies and studies with immunotherapy in various solid tumors.

Indication in the U.S.

TALZENNA® (talazoparib) is approved in the U.S. for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (g*BRCA*)?mutated (*gBRCAm*) human epidermal growth factor receptor 2?negative (HER2-), locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.[17]

TALZENNA® (talazoparib) Important Safety Information from the U.S. Prescribing Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received TALZENNA. Overall, MDS/AML have been reported in 2 out of 584 (0.3%) solid tumor patients treated with TALZENNA in clinical studies. The duration of TALZENNA treatment in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively. Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia have been reported in patients treated with TALZENNA. Grade ?3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 39%, 21%, and 15% of patients receiving TALZENNA. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 0.7%, 0.3%, and 0.3% of patients.

Monitor complete blood counts for cytopenia at baseline and monthly thereafter. Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous therapy. If hematological toxicity occurs, dose modifications (dosing interruption with or without dose reduction) are recommended. **With respect to MDS/AML**, for prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If the levels have not recovered after 4 weeks, refer the patient to a hematologist for further investigations. If MDS/AML is confirmed, discontinue TALZENNA.

TALZENNA can cause **fetal harm** when administered to pregnant women. Advise women of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose. A pregnancy test is recommended for females of reproductive potential prior to initiating TALZENNA treatment. Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment with TALZENNA and for at least 4 months after receiving the last dose. Based on animal studies, TALZENNA may impair fertility in males of reproductive potential. Advise women not to breastfeed while taking TALZENNA and for at least 1 month after receiving the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions (?20%)** of any grade for TALZENNA vs chemotherapy were fatigue (62% vs 50%), anemia (53% vs 18%), nausea (49% vs 47%), neutropenia (35% vs 43%), headache (33% vs 22%), thrombocytopenia (27% vs 7%), vomiting (25% vs 23%), alopecia (25% vs 28%), diarrhea (22% vs 26%),

and decreased appetite (21% vs 22%).

The **most frequently reported Grade ?3 adverse reactions (?5%)** for TALZENNA vs chemotherapy were anemia (39% vs 5%), neutropenia (21% vs 36%), and thrombocytopenia (15% vs 2%).

The **most common lab abnormalities (?25%)** for TALZENNA vs chemotherapy were decreases in hemoglobin (90% vs 77%), leukocytes (84% vs 73%), lymphocytes (76% vs 53%), neutrophils (68% vs 70%), platelets (55% vs 29%), and calcium (28% vs 16%) and increases in glucose (54% vs 51%), aspartate aminotransferase (37% vs 48%), alkaline phosphatase (36% vs 34%), and alanine aminotransferase (33% vs 37%).

Coadministration with P-gp inhibitors or **BCRP inhibitors** may increase TALZENNA exposure. If coadministering with the P-gp inhibitors amiodarone, carvedilol, clarithromycin, itraconazole, or verapamil is unavoidable, reduce the TALZENNA dose to 0.75 mg once daily. When the P-gp inhibitor is discontinued, increase the TALZENNA dose (after 3–5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the P-gp inhibitor. When co-administering TALZENNA with other known P-gp inhibitors or BCRP inhibitors, monitor patients for potential increased adverse reactions.

For patients with moderate **renal impairment**, the recommended dose of TALZENNA is 0.75 mg once daily. No dose adjustment is required for patients with mild renal impairment. TALZENNA has not been studied in patients with severe renal impairment or in patients requiring hemodialysis.

TALZENNA has not been studied in patients with moderate or severe **hepatic impairment**. No dose adjustment is required for patients with mild hepatic impairment.

Please see full U.S. Prescribing Information and Patient Information for TALZENNA® (talazoparib) at www.TALZENNA.com.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of patients. Today, Pfizer Oncology has an industry-leading portfolio of 18 approved innovative cancer medicines and biosimilars across more than 20 indications, including breast, prostate, kidney, lung and hematology. Pfizer Oncology is striving to change the trajectory of cancer.

Pfizer Inc: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube, and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this release is as of June 21, 2019. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or

future events or developments.

This release contains forward-looking information about TALZENNA® (talazoparib) and an approval by the European Commission, including its potential benefits, that involve substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when applications for TALZENNA may be filed in other jurisdictions or for any other indications; whether and when any such other applications for TALZENNA that may be pending or filed may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether TALZENNA will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of TALZENNA; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

---

[1] TALZENNA® (talazoparib). Summary of Product Characteristics.
[2] Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379(8):753-763.
[3] Ettl J, Quek R G W, Lee K-H, et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 *mutation*: patient-reported outcomes from the EMBRACA phase III trial. *Ann Oncol.* 2018: mdy257. doi:10.1093/annonc/mdy257.
[4] National Cancer Institute. BRCA mutations: Cancer risk and genetic testing. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed September 10, 2018.
[5] Kleibl Z, Kristensen VN. Women at high risk of breast cancer: molecular characteristics, clinical presentation and management. *The Breast*. 2016;28:136-144.
[6] Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. *J Clin Oncol.* 2016;34(13):1460-1468.
[7] Nelson HD, Fu R, Goddard K et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Dec. Report No.: 12-05164-EF-1.
[8] Meynard G, Villanueva C, Thiery-Vuillemin A, et al. Real-life study of BRCA genetic screening in metastatic breast cancer. *Annals of Oncology*. 2017; Volume 28, Issue suppl_5, mdx365.047.
[9] Fasching PA, Hu C, Hart SN, et al. Cancer predisposition genes in metastatic breast cancer - association with metastatic pattern, prognosis, patient and tumor characteristics. Paper presented at: San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, TX.

[10] Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402–2416. doi:10.1001/jama.2017.7112.
[11] Mavaddat N, Barrowdale D, Andrulis IL et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012;21(1):134.
[12] American Cancer Society. Treatment of invasive breast cancer, by stage. http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-treating-by-stage. Accessed September 20, 2018.
[13] O'Shaughnessy J. Extending Survival with Chemotherapy in Metastatic Breast Cancer. *The Oncologist*. 2005;10:20-29.
[14] Smith I. Goals of treatment for patients with metastatic breast cancer. *Semin Oncol.* 2006 Feb; 33(1 Suppl 2): S2-5.
[15] Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol.* 2018;29(8):1634-1657. doi:10.1093/annonc/mdy192.
[16] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed May 8, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
[17] TALZENNA® (talazoparib) Prescribing Information. New York. NY: Pfizer Inc: 2018.

Pfizer Media Contacts: Lisa O'Neill (EU) (44) 7929 339 560 Lisa.O'Neill@pfizer.com Jessica Smith (U.S.) (212) 733-6213 Jessica.M.Smith@pfizer.com Pfizer Investor Contact: Ryan Crowe (212) 733-8160 Ryan.Crowe@pfizer.com