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AstraZeneca's OlympiAD Trial Kick-Starts PARP In Breast Cancer

by Emily Hayes

The OlympiAD monotherapy study paves the way for AstraZeneca's Lynparza in breast cancer, as well as other PARP inhibitors down the line, but the ASCO presentation raises questions about trial design and whether combinations are needed to boost efficacy.

AstraZeneca PLC's *Lynparza* has set an important, if modest, precedent for PARP inhibitors with positive progression-free survival results from the Phase III OlympiAD study opening the door for a new indication for use in women with BRCA-mutated breast cancer.

The company released results from the study of about 300 women with metastatic HER2-negative (hormone receptor-positive or triple negative) breast cancer on June 4 during a plenary session at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago. Based on OlympiAD, AstraZeneca plans to seek US FDA approval for the drug in breast cancer during the second half of this year and file for approval in the EU in 2018.

OlympiAD tested Lynparza as a monotherapy against physician's choice of three kinds of chemotherapy (eribulin, capecitabine or vinorelbine) in patients who previously had up to two prior lines of chemotherapy. Platinum-based chemotherapy (e.g. carboplatin and cisplatin) is standard in this patient population and participants could have had this treatment, but were not allowed into OlympiAD if they had progressed.

Lynparza demonstrated a significant progression-free survival benefit compared to chemotherapy alone with a median of seven months versus 4.2 months for chemotherapy, a 42% reduction in risk. An overall survival benefit has not been demonstrated yet. Furthermore, the objective response rate was 60% for Lynparza versus 29% for chemotherapy.

The ASCO data release followed a top-line disclosure in February of a positive outcome in the study (Also see "*Lynparza's Wider Prospects Boosted By Late-Stage Breast Cancer Study*" - Scrip, 17

Feb, 2017.)

The first PARP inhibitor on the market, Lynparza (olaparib) is currently approved for fourth-line ovarian cancer with germline BRCA mutations and in this indication AstraZeneca is looking to move earlier into the maintenance setting and for tumors regardless of mutation status. (Also see "*AstraZeneca Mulls Broad Ovarian Cancer Maintenance Approval For Lynparza*" - Pink Sheet, 14 Mar, 2017.) Lynparza had sales of $218m in 2016 and a breast cancer indication has the potential to improve its financial outlook.

While only about 8% of patients with HER2-negative breast cancer have BRCA mutations, given the prevalence of breast cancer that translates into tens of thousands of women who could be candidates for treatment, commented Erica Mayer, assistant professor of medicine at Harvard Medical School, during an interview at the conference.

Lynparza dosing for ovarian cancer is 400 mg twice daily in capsule form, but it was given at 300mg twice daily by tablet for the OlympiAD breast cancer study. AstraZeneca explains that this new dosing regimen is more convenient for patients, because far fewer pills need to be taken, but notes that the formulations are equivalent in terms of efficacy. The new tablet formulation will be priced at parity with the capsules, execs explained during a June 4 media briefing at the ASCO meeting.

"It is not a commercial advantage – it's more a practicality advantage for the patients," said Klaus Edvardsen, head of oncology, global medicines development at AstraZeneca.

In addition to demonstrating better efficacy, Lynparza was also better tolerated, with a lower rate of grade 3 or higher adverse events (36.6% versus 50.5%) and fewer discontinuations due to toxicity (4.9% versus 7.7%).

Lynparza also is being evaluated in Phase III trials testing the drug in various breast cancer settings (*see table below*).

Daniel Hayes, president of ASCO and a breast cancer specialist at the University of Michigan Health System Comprehensive Cancer Center, commented during an ASCO press briefing that the results represented a "major step forward in breast cancer."

Plenary discussant Allison Kurian concluded that the data were "practice-changing."

Kurian noted the long development history of PARP inhibitors in breast cancer and a major misstep in breast cancer in particular that shows why Lynparza's efficacy now is a step forward for the field.

Sanofi's iniparib looked promising as an add-on to platinum-based chemotherapy in a Phase II trial of triple negative breast cancer released in 2011, but went on to fail progression-free survival and overall survival endpoints in Phase III, putting a damper on development for PARP inhibitors in breast cancer. (Also see "*Surprise! It's A Phase III Failure*" - Scrip, 12 Aug, 2016.)

OlympiAD represents the "end of the beginning of a long road for the development of PARP inhibitors for breast cancer therapy," said Kurian, director of the Women's Clinical Cancer Genetics Program at Stanford University Medical Center in Palo Alto, Calif.

Asked to explain the iniparib failure in contrast with the olaparib success, OlympiAD lead investigator Mark Robson, medical oncologist at *Memorial Sloan Kettering Cancer Center*, said during the press briefing that iniparib structurally is not actually a PARP inhibitor, as originally thought.

Questions About Trial Design

The OlympiAD trial was positive and ground-breaking, but drew scrutiny.

ASCO acknowledged in a press release about the data: "More research is needed to determine how well olaparib works in cancers that worsen despite platinum-based chemotherapy, a standard regimen not included in this study, and whether platinum-based chemotherapy would be useful after cancers worsen despite olaparib."

Platinum-based chemotherapy is very active in BRCA-mutated breast cancer, but has a similar mechanism of action on DNA repair as PARP inhibitors. Consequently, PARP inhibitors are less effective in women who have progressed on prior platinum-based chemotherapy and many trials for drugs with this mechanism of action are not evaluating the therapies in this population, Jennifer Keating Litton, associate professor in breast oncology at the *MD Anderson Cancer Center*, commented in an interview at the meeting.

Litton also noted, however, that there are advantages in terms of less toxicity for PARP inhibitors over platinum-based chemotherapy and PARP inhibitors also have more convenient oral administration, rather than intravenous delivery.

Harvard's Mayer noted that platinum-based chemotherapy has a variety of unpleasant side effects, including weakening of the immune system, nausea and fatigue.

"Our goals of care in treating metastatic breast cancer are not only prolonging survival, but also maintaining and preserving quality of life, and a therapy that can better allow us to help patients feel as good as possible while also prolonging survival is a wonderful step forward," Mayer commented.

There were non-significant improvements in performance for olaparib in patients who were triple-negative and naïve to platinum-based chemotherapy, Kurian noted during her presentation. It's "certainly plausible" that the drug would work better in these patients, but the study was underpowered to draw a conclusion on that question.

"We do need further study of subgroups to understand who really benefits from this therapy," Kurian said.

Biomedtracker analysts said in a note from the ASCO meeting that subgroup analyses showing lower efficacy in estrogen receptor-positive (ER+) and/or hormone receptor-positive (PR+) patients, or in patients who received prior platinum chemotherapy, "suggest that the trial success may have been driven primarily by triple negative breast cancer patients."

"Thus, regulators may want further study to better define the appropriate treatment population," the analysts commented.

AstraZeneca's Edvardsen cautioned during the company's media briefing that OlympiAD was not designed to assess performance in subgroups and advised caution in interpreting these results.

Among other questions about the trial's design, Kurian wondered why the comparator in OlympiAD was not anthracycline and taxane chemotherapy as opposed to the three types used in the study – eribulin, vinorelbine and capecitabine.

Edvardsen explained that many high-risk patients, such as the ones included in the study, would typically have already been treated with anthracycline and taxanes in the adjuvant setting and that the choices in the trial represented the standard of care.

"I disagree with that comment that the comparator in that setting should have been anthracycline and taxane," Edvardsen said.

The PFS benefit of only about three months compared to chemotherapy also raised some questions, as it was viewed as a short-lived, rather modest benefit. Researchers are exploring use of PARP inhibitors in earlier stage settings, including combination regimens, to improve efficacy and durability.

"Combinations will be even more powerful," Litton said.

Lynparza Leads PARPs In Breast Cancer

In addition to Lynparza, two other PARP inhibitors are FDA-approved and could play a role in breast cancer – *Clovis Oncology Inc.*'s *Rubraca* (rucaparib) and *Tesaro Inc.*'s *Zejula* (niraparib). (Also see "*Broad Label Gives Tesaro's Niraparib A Head Start In Ovarian Cancer*" - Scrip, 28 Mar,

2017.) All three are approved for ovarian cancer, but with differences in approved populations. Rubraca is cleared for third-line ovarian cancer with BRCA mutations and Zejula has the broadest labeling as a maintenance treatment in ovarian cancer regardless of mutation status.

Zejula and various investigational PARP inhibitors are in Phase III for breast cancer, and Rubraca is in Phase II. Clovis noted that several investigator-initiated and/or cooperative group studies are under way examining Rubraca in breast cancer, including a trial sponsored by *Roche* investigating the drug in combination with *Tecentriq* (atezolizumab).

Pfizer Inc. announced results from a Phase II study of its investigational PARP inhibitor talazoparib in heavily pretreated BRCA1/2 positive advanced breast cancer on June 3 at the ASCO meeting.

The company reported a 21% objective response rate in 49 patients who progressed after responding to platinum-based chemotherapy and a 37% ORR in a cohort of 35 patients who had progressed after at least three lines of non-platinum-based therapy. The most common adverse events included anemia (51.8%), thrombocytopenia (32.5%) neutropenia (26.5%) and diarrhea (32.5%). The treatment-related dropout rate was 4%.

Pfizer is now testing the drug in the Phase III EMBRACA study, which is fully enrolled and has a primary completion date of June 2017; the company plans to report results in the first quarter of 2018.

Phase III Studies Of PARP Inhibitors In Breast Cancer

Study/Description	Patient Number/Completion Date
AstraZeneca's Lynparza	
OlympiAD: Efficacy and safety of olaparib monotherapy vs. physicians' choice chemotherapy in HER2-negative metastatic breast cancer with germline BRCA1/2 mutations. Prior platinum-based chemo allowed, as long as no breast cancer progression occurred on treatment or if given in adjuvant/neoadjuvant setting at least 12 months from last dose to study entry elapsed.	N=302. Primary completion date: December 2016
OlympiA: Olaparib vs. placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.	N=1,500. Primary completion: March 2020

PARTNER: Neoadjuvant trial for patients with triple negative breast cancer and/or gBRCA breast cancer, safety and efficacy (improvement in pathological complete response at surgery) with platinum-based chemotherapy (paclitaxel and carboplatin) vs. paclitaxel/carboplatin alone. Sponsored by Cambridge University Hospitals with AstraZeneca.	N=527. Primary completion date: January 2022.
Tesaro's Zejula	
BRAVO: Zejula vs. physician's choice of four therapies in HER2-negative gBRCA-positive breast cancer. Patients with platinum-resistant cancer excluded.	N=306. Primary completion: September 2017
AbbVie Inc.'s Veliparib	
NCT02163694: Placebo-controlled trial of carboplatin/paclitaxel with or without veliparib in HER2-negative metastatic or locally advanced unresectable BRCA-associated breast cancer.	N=500. Primary completion: May 2018
NCT02032277A: Veliparib with carboplatin vs. addition of carboplatin to standard chemotherapy vs. standard chemotherapy in early-stage triple negative breast cancer.	N=624. Primary completion: March 2016
Pfizer's Talazoparib	
EMBRACA: Talazoparib vs. protocol-specific physician’s choice of chemotherapy in patients with advanced and/or metastatic gBRCA-positive breast cancer who have received zero to three prior chemotherapy regimens for advanced disease.	N=431. Primary completion: June 2017

Source: ClinicalTrials.gov