PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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The Addition of PARP Inhibition to Androgen Receptor Pathway Inhibition in Metastatic Hormone-Sensitive Prostate Cancer

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H&O What was the rationale for conducting the AMPLITUDE trial?[1]

GA We were trying to solve 2 problems. First, although 30% of patients who are started on treatment with androgen deprivation therapy (ADT) and an androgen receptor pathway inhibitor (ARPI) are in remission at 10 years, another 30% experience rapid progression and have a short survival.[2] Enriched among this group of people with poor outcomes are those whose cancers have a *BRCA* alteration.

Second, poly(ADP-ribose) polymerase (PARP) inhibitors have been established for end-stage prostate cancer for several years; they are typically used after patients have received an ARPI and often chemotherapy. Even though PARP inhibitors are effective and *BRCA*-mutant cancers are sensitive to this treatment, resistance to PARP inhibitors develops rapidly when they are started late in the disease pathway. The seminal trials in this disease setting have shown that although the response rate is high—up to 50%—the duration of the response is short, and resistant disease develops in all patients within 18 months.[3]

The AMPLITUDE trial was designed to address 2 challenges. The first challenge was to identify patients who have cancers with a mutation in *BRCA* or in other genes in the homologous recombination repair (HRR) pathway; these patients have a poor prognosis and therefore require treatment beyond ADT and an ARPI. The second challenge was to see whether using a PARP inhibitor when the disease volume was lowest could ensure maximum efficacy and reduce the risk of rapid resistance.

H&O Could you describe the design of AMPLITUDE?

GA AMPLITUDE was a placebo-controlled, double-blind, randomized phase 3 global trial that enrolled patients with HRR-deficient metastatic hormone-sensitive prostate cancer (mHSPC). HRR alterations consisted of alterations in *BRCA2*, *BRCA1*, *BRIP1*, *CHEK2*, *CDK12*, *FANCA*, *PALB2*, *RAD51B,* or *RAD54L*. Non-*BRCA* HRR mutations are far less common than *BRCA* mutations.

The backbone of first-line treatment for metastatic prostate cancer is ADT plus one of the ARPIs: abiraterone, apalutamide (Erleada, Janssen), darolutamide (Nubeqa, Bayer HealthCare), or enzalutamide (Xtandi, Astellas). We chose to use abiraterone for this trial because pharmacokinetic interactions with PARP inhibitors do not occur with this drug, so all patients received ADT and abiraterone.

We enrolled patients who were within 6 months of starting ADT, and previous use of an ARPI was not permitted except prior use of abiraterone for no more than 28 days. Previous use of docetaxel and palliative radiotherapy were permitted so long as they were completed before randomization. A total of 16% of the patients in AMPLITUDE received docetaxel.

A total of 696 patients from 204 centers across 32 countries were randomly assigned to either abiraterone

plus placebo or abiraterone plus niraparib (Zejula, GSK). Patients received regular follow-up that included computed tomography or magnetic resonance imaging and bone scans to detect disease progression. The primary endpoint was radiographic progression-free survival (rPFS).

H&O What were the key efficacy and safety results?

GA The trial met its primary endpoint; abiraterone plus niraparib significantly prolonged the duration of rPFS in comparison with abiraterone alone. The statistical analysis used a hierarchical test for efficacy. Among patients with *BRCA* aberrations, rPFS was significantly better in the niraparib group, with a hazard ratio (HR) of 0.52. In addition, rPFS was significantly better in the niraparib group among patients in a slightly expanded group called the HRR effector subgroup, which included patients with mutations in *BRCA* (55% of patients) plus several other genes (45% of patients), with an HR of 0.57, and in the intention-to-treat group, with an HR of 0.63. An exploratory analysis showed a trend toward improved rPFS with niraparib in patients with non-*BRCA* HRR gene alterations, but the difference was not statistically significant.

The 2 key secondary endpoints were time to symptomatic progression and overall survival (OS), both of which were also analyzed in a hierarchical test. The time to symptomatic progression was significantly longer in the abiraterone-plus-niraparib group than in the abiraterone-alone group, with an HR of 0.44 in the *BRCA*-mutant group and of 0.50 in the intention-to-treat group. The OS data were not mature, with trends toward improved OS with niraparib that were not statistically significant. We should see more data regarding OS over the next couple of years.

H&O What are the key safety considerations or tolerability challenges associated with adding niraparib to the treatment?

GA The rate of grade 3 or 4 toxicity was 75% in the niraparib group vs 59% in the placebo group, so an increase of 16 percentage points. In addition, the rate of serious adverse events was higher in the niraparib group than in the placebo group, at 39% vs 28%, as was the discontinuation rate, at 15% in the niraparib group vs 10% in the placebo group.

The most common toxicity related to myelosuppression was caused by the effect of niraparib on blood hematinics (eg, iron, vitamin B_{12}, and folic acid). In the niraparib group, the rate of any-grade anemia was 52%, the rate of grade 3 or 4 anemia was 30%, and 25% of the patients required a blood transfusion. The rate of hypertension was also higher with niraparib than with placebo, at 43% vs 32%.

One longer-term concern worth flagging is that prior trials of PARP inhibitors in other types of cancer have described potential long-term risks of myelodysplasia or acute myeloid lymphoma, primarily in patients who have received a platinum agent. We are uncertain what the effect of the earlier use of PARP inhibitors might be, but at the time of reporting, a blood disorder had occurred in 1 patient in the niraparib group and no patients in the placebo group.

> The results of the AMPLITUDE study apply only to patients whose disease is metastatic on conventional imaging.

H&O Was AMPLITUDE a practice-changing trial, even though the OS data are not mature?

GA AMPLITUDE has been practice-changing, with a clear benefit in duration of rPFS. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have extended the indications for niraparib plus abiraterone (Akeega, Janssen Biotech) to include *BRCA2*-mutant mHSPC and *BRCA1/2*-mutant mHSPC, respectively, on the basis of this study. The extension of the indication is similar to what we have seen in other tumor types, such as ovarian cancer and breast cancer, in which the earlier use of PARP inhibitors was introduced on the basis of intermediate endpoints. We await the OS data for mHSPC as we did for ovarian cancer and breast cancer. Equipoise remains for patients with non-*BRCA* HRR genes, partly because the subgroups are small and partly because the treatment effect is heterogeneous across different gene alterations, so I understand the decision of the FDA and the EMA not to include these patients in the license extension.

We should remember that approximately one-third of patients in the control arm in this primary analysis received a PARP inhibitor after progression, so this is not purely an experiment of early vs late treatment. We will need to think about some level of subsequent PARP inhibitor use when interpreting the OS data, however.

H&O How do you approach patient selection in your clinical practice?

GA The results of the AMPLITUDE study apply only to patients whose disease is metastatic on conventional imaging. A common question I am asked is what to do about patients with metastases on prostate-specific membrane antigen positron emission tomography (PSMA PET) but not on conventional imaging. We need to be careful with these patients because the balance of long-term benefit vs risk must still be ascertained.

My current approach is to start patients who have mHSPC on ADT and an ARPI and order a tissue analysis. Here in the United Kingdom, we are preparing to offer PARP inhibition to all patients who have mHSPC with a *BRCA* mutation. I would not use PARP inhibition for patients who have a non-*BRCA* HRR gene alteration.

H&O What other trials are evaluating combinations of PARP inhibition plus an ARPI?

GA Two other large, randomized phase 3 trials are ongoing: EvoPAR-Prostate01 (NCT06120491) and TALAPRO-3 (NCT04821622).

In EvoPAR-Prostate01, patients who have mHSPC—both with and without HRR gene mutations—are being randomly assigned to either the experimental PARP inhibitor saruparib plus an ARPI or placebo plus an ARPI. We expect the balance between harm and benefit starts to shift when the sensitivity is less, so that will be an important factor to consider when these results are interpreted.

In TALAPRO-3, patients with mHSPC and HRR gene mutations are being randomly assigned to either talazoparib (Talzenna, Pfizer) plus enzalutamide or placebo plus enzalutamide. Pharmacokinetic interactions between these agents are possible, so it will be valuable to see the extent of toxicity with this combination.

H&O What are the key unanswered questions in this field?

GA I am looking forward to seeing 2 big questions answered. The first question is, how do we determine which treatments to give and which treatments should be combined? Six months after I presented the results of AMPLITUDE, 2 trials with positive results in mHSPC were reported. The CAPItello-281 trial looked at use of the AKT inhibitor capivasertib (Truqap, AstraZeneca) plus abiraterone vs placebo plus abiraterone in patients with *PTEN* (phosphatase and tensin homolog) gene loss and mHSPC.[4] The PSMAddition trial looked at the addition of the radioligand therapeutic lutetium 177 (^{177}Lu)-PSMA-617 to standard therapy with ADT plus an ARPI in patients with PSMA-positive mHSPC.[5] What we do not know is whether capivasertib or ^{177}Lu-PSMA-617 could be combined with an agent such as niraparib, and what the best way to select patients for one treatment over another would be.

The second burning question is, why does resistance still develop? We know that resistance is common in end-stage disease. When we reported our first analysis of AMPLITUDE, fewer than half of the patients on niraparib had experienced progression, but a significant proportion still did. Understanding what drives that resistance is a key question for the field.

H&O Is there anything you would like to add?

GA I expect that the results of AMPLITUDE will lead to a shift in molecular testing to earlier in metastatic prostate cancer, when the disease is still hormone-sensitive. *BRCA* testing not only is important for treatment selection but also can lead to the testing of family members for *BRCA* alterations if the patient has a germline mutation. Such testing could allow relatives of the carrier of a *BRCA* mutation to be eligible for additional cancer screenings, especially screenings for ovarian and breast cancer if relevant.

Disclosures

Dr Attard has received grants or contracts from Astellas Pharma, Blue Earth Therapeutics, Janssen, Veracyte, and Novartis; advisory board consultancy fees from Amgen, AstraZeneca, Astellas Pharma, Bayer, Blue Earth Therapeutics, Janssen-Cilag, Merck & Co, Merck Serono Ltd, Novartis, Pfizer, and Veracyte; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Astellas Pharma, Janssen, AstraZeneca, Sanofi, and Sandoz; support for attending meetings and/or travel from Amgen, Astellas Pharma, Bayer, Janssen, Merck Serono, and Pfizer; receipt of equipment, materials, drugs, medical writing, gifts, or other services from Agilent Technologies; and commercial agreements with Artera and Veracyte. On The Institute of Cancer Research discoveries' list of abiraterone acetate, Dr Attard personally receives a share of revenue received by The Institute of Cancer Research. He is listed as an inventor of a docetaxel predictive biomarker (Veracyte).

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