Talazoparib Improves Radiographic Progression-Free Survival in Patients With Metastatic Castration-Resistant Prostate Cancer

The addition of talazoparib (Talzenna, Pfizer) to enzalutamide (Xtandi, Astellas) improves radiographic progression-free survival (rPFS) when used as first-line treatment in men with metastatic castration-resistant prostate cancer (mCRPC) unselected for DNA repair deficiencies, according to results from the TALAPRO-2 study. This was the first phase 3 study to combine the poly(ADP-ribose) polymerase (PARP) inhibitor talazoparib with enzalutamide.

For the double-blind study, Dr Neeraj Agarwal and colleagues randomly assigned 805 men with mCRPC to receive talazoparib at 0.5 mg daily plus enzalutamide or placebo plus enzalutamide as first-line therapy. Prior exposure to docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC; 21%-23% of patients) and prior abiraterone exposure in the mHSPC setting (5%-6% of patients) was permitted. Approximately 21% of patients were found to have homologous recombination repair (HRR) mutations by tumor tissue testing, but approximately one-third of patients were not evaluable for testing owing to insufficient tissue samples or DNA quality.

After a follow-up of nearly 25 months, median rPFS by blinded independent central review (BICR) was not reached in the talazoparib arm vs 21.9 months in the placebo arm (hazard ratio [HR], 0.63; 95% CI, 0.51-0.78; P<.001). The rPFS by BICR continued to favor the talazoparib over placebo in prespecified subgroups, including those with genes associated with HRR (HR, 0.48) or without these genes or with unknown gene status (HR, 0.69). The addition of talazoparib reduced the risk of progression or death by 37% compared with enzalutamide alone. An exploratory analysis of patients without HRR gene alterations based on prospective tumor tissue testing showed a 34% reduced risk of progression or death with talazoparib vs placebo (HR, 0.66).

The overall survival (OS) data were immature but favored talazoparib over placebo (HR, 0.89; 95% CI, 0.69-1.14; P=.35). Objective responses by imaging and prostate-specific antigen PFS favored the combination as well, with fewer patients progressing through therapy (5.8%) in the talazoparib group than in the placebo group (23%).

The rate of grade 3 or 4 treatment-related adverse events (AEs) was 72% in the talazoparib arm and 41% in the placebo arm. Severe anemia requiring intervention such as transfusion was seen in 43% of men in the talazoparib arm vs 4.2% of those in the placebo arm. Patients in the talazoparib arm were significantly more likely than those in the placebo arm to experience dose interruptions (75% vs 23%, respectively) and dose reductions (56% vs 7.2%, respectively). Myelodysplastic syndrome (MDS) occurred in 1 patient and acute myeloid leukemia (AML) occurred in 1 patient, both in the talazoparib arm. The most common AEs leading to dose reduction of talazoparib were anemia, neutropenia, and nausea. In addition, talazoparib plus enzalutamide significantly prolonged time to confirmed deterioration in global health status and quality of life.

“Results from the primary analysis of the TALAPRO-2 trial support the use of talazoparib plus enzalutamide as a first-line treatment in men with mCRPC, regardless of HRR alteration status,” Dr Agarwal concluded.

Agarwal N, Arad A, Carles J, et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract LBA17]. J Clin Oncol. 2023;41(6)(suppl).

Rucaparib Improves PFS Over Docetaxel or Abiraterone/Enzalutamide in mCRPC

The use of rucaparib (Rubraca, Clovis Oncology) improves rPFS compared with physician’s choice of therapy in patients with BRCA1/2-altered mCRPC, according to results of the TRITON-3 study. Rucaparib has received accelerated approval in the United States for the treatment of BRCA1/2-altered mCRPC in patients previously treated with taxane-based chemotherapy and second-generation androgen receptor pathway inhibition (ARPI).

The phase 3 study, by Dr Alan H. Bryce and colleagues, enrolled 405 patients with chemotherapy-naive mCRPC and a BRCA1/2 or ATM alteration. Patients had prior treatment with 1 prior potent androgen receptor inhibitor and approximately 23% had received prior docetaxel for mHSPC. Patients were randomly...
assigned in a 2:1 ratio to rucaparib at 600 mg twice a day or physician’s choice of therapy, which consisted of either docetaxel (n=71) or second-generation ARPI with abiraterone/enzalutamide (n=59).

The researchers found that rucaparib halved the risk of radiographic progression or death in patients with BRCA alterations. Rucaparib also improved median rPFS more than physician’s choice of therapy in both the intention-to-treat (ITT) population (10.2 vs 6.4 months; HR, 0.61; P=.0003) and the BRCA subgroup (11.2 vs 6.4 months; HR, 0.50; P<.0001). Three-quarters of patients in the physician’s choice arm who had progressive disease crossed over to rucaparib upon progression. The interim OS results were immature and showed no improvement in OS with rucaparib vs placebo in the BRCA1/2-mutated population (HR, 0.81; P=.21) nor the overall ITT population (HR, 0.94; P=.67).

The most frequent treatment-emergent AEs in all treatment groups were asthenia and fatigue, and 24% of patients required transfusion for severe anemia. No cases of MDS or AML occurred.

The results of TRITON-3 were also published in the New England Journal of Medicine on February 23. This publication included the observation that rucaparib did not improve median rPFS over physician’s choice of therapy in patients with ATM mutations; these benefits were largely observed in carriers of the BRCA1/2 mutation.


Addition of Olaparib to Abiraterone Improves Radiographic PFS and OS in mCRPC

The addition of olaparib to abiraterone improves rPFS in patients with mCRPC, according to the results of the PROpel trial. The trial also showed a strong trend toward improved OS with olaparib overall, and significant improvements in OS with olaparib among certain subgroups defined by HRR/BRCA status, according to presenter Dr Noel Clarke.

The phase 3 PROpel trial enrolled 776 patients with mCRPC who had not received prior abiraterone. Patients were randomly assigned to first-line treatment with either olaparib plus abiraterone or placebo plus abiraterone. The results were published in NEJM Evidence on June 3, 2022, after the reporting of rPFS following the second planned data cut-off. These results showed that median rPFS in the ITT population was significantly longer in the olaparib group than in the placebo group, at 27.6 vs 16.4 months, respectively, when measured by independent central reporting (HR, 0.61; 95% CI, 0.49-0.74; P<.0001) and 24.8 vs 16.6 months when measured by investigator assessment (HR, 0.66; 95% CI, 0.54-0.81; P<.0001). OS results from the third prespecified data cutoff presented at the ASCO GU symposium in 2023 were based on 47.9% of patients experiencing a mortality event. This showed a trend toward longer OS in the olaparib group than in the placebo group (42.1 vs 34.7 months), a difference of more than 7 months (HR, 0.81; 95% CI, 0.67-1.00; P=.0544; prespecified alpha error of 0.0377 for significance). Improvements in rPFS and OS with the addition of olaparib were observed across the subgroups regardless of HRR alteration status, but greater benefits were observed in patients with HRR and BRCA4 mutations. For example, the HR for improved rPFS with olaparib was 0.23 in BRCA-mutated patients, 0.50 in HRR-mutated patients, and 0.76 in patients without an HRR mutation. The HR for improved OS with olaparib was 0.29 in BRCA-mutated patients, 0.66 in HRR-mutated patients, and 0.89 in patients without an HRR mutation.

Side effects in the olaparib group included grade 3 or higher anemia in 16.1% of patients, all-grade fatigue or asthenia in 38.7% of patients, and all-grade nausea in 30.7% of patients. Most of these side effects occurred early, and with the exception of fatigue, most of them decreased within 6 months.

Dr Clarke concluded that the overall results “support combination treatment with abiraterone and olaparib as an important new first-line treatment option in patients with mCRPC.”

Clarke NW, Armstrong AJ, Thiery-Vailllemir A, et al. Final overall survival (OS) in PROpel: abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract LBA16]. J Clin Oncol. 2023;41(6)(suppl).

Addition of Niraparib to Abiraterone/Prednisone Continues to Improve Outcomes in mCRPC

The addition of niraparib (Zejula, GSK) to abiraterone/ prednisone continues to improve outcomes in patients with mCRPC who have HRR alterations, according to a second interim analysis of the MAGNITUDE trial by Dr Eleni Efstathiou and colleagues.

The HRR-positive cohort of the phase 3 MAGNITUDE trial enrolled 423 patients with mCRPC and HRR alterations. Patients were randomly assigned in a 1:1 ratio to receive niraparib plus abiraterone/prednisone or placebo plus abiraterone/prednisone.

At the prespecified second interim analysis at a median follow-up of 26.8 months, the primary endpoint of median rPFS continued to be longer in the niraparib group than in the placebo group, at 19.5 vs 10.9 months, respectively, in the BRCA4-mutated subgroup (HR, 0.55; 95% CI, 0.39-0.78; P=.0007). Regarding secondary endpoints, the time
to symptomatic progression was significantly longer with niraparib than with placebo in the overall group, with consistent benefit in the BRCA-mutated subgroup (HR, 0.54). In addition, the time to initiation of cytotoxic chemotherapy was significantly longer with niraparib than with placebo in the overall group and in the BRCA-mutated subgroup (HR, 0.56). However, OS was similar in both treatment groups within the BRCA-mutated population (HR, 0.88; 95% CI, 0.58-1.34; P=.55). The median OS with niraparib vs placebo in the BRCA-mutated subgroup in the primary stratified analysis was 29.3 vs 28.6 months, respectively.

The most common AEs in the niraparib vs placebo group were anemia (50% vs 22.7%), hypertension (33.0% vs 22.3%), and constipation (33.0% vs 15.6%).

The investigators concluded that these data continue to support the addition of niraparib to abiraterone/prednisone in patients with mCRPC who have BRCA alterations or certain other HRR gene alterations.

Efstathiou E, Smith MR, Sandhu S, et al. Niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations: second interim analysis (IA2) of MAGNITUDE [ASCO GU abstract 170]. J Clin Oncol. 2023;41(6)(suppl).

Phase 3 Trial of Rucaparib Plus Enzalutamide in mCRPC Enrolling Patients

The phase 3 CASPAR trial, which will examine the addition of rucaparib to enzalutamide as first-line treatment in patients with mCRPC, is currently enrolling patients. A total of 984 patients will be randomly assigned in a 1:1 ratio to receive rucaparib plus enzalutamide or placebo plus enzalutamide. Unlike previous studies, patients who have previously received docetaxel and/or ARPIs are eligible if they were given in the hormone-sensitive setting or in the nonmetastatic castration-resistant setting, allowing for testing of the benefits of PARP inhibition plus enzalutamide in patients whose disease has failed to respond to 1 prior ARPI.

All patients will undergo next-generation targeted exome sequencing using archival tumor tissue, with a new biopsy required only if no archival tissue is available. Treatment will continue until progression of disease, with no crossover allowed.

Eligible patients must be 18 years or older and have an Eastern Cooperative Oncology Group performance status of 0 to 2 and no prior treatment for mCRPC. An HRR gene aberration is not required for enrollment.

The co-primary endpoints are OS and rPFS, with the OS analysis undertaken as a primary endpoint only if the rPFS endpoint is met. Key secondary endpoints are rPFS and OS in patients with and without BRCA1, BRCA2, or PALB2 alterations. The study will also measure differences in AEs and quality of life outcomes between the treatment arms.

Enrollment in this trial began in July 2021, and the study is available to participants at all National Clinical Trials Network sites in the United States (NCT04455750). Dr Arpit Rao is the study chair.