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Addition of Olaparib to Abiraterone Improves Progression-Free Survival in First-Line Metastatic Castration-Resistant Prostate Cancer

The addition of olaparib (Lynparza, AstraZeneca) to first-line treatment with abiraterone significantly improves radiographic progression-free survival (rPFS) in patients with metastatic castration-resistant prostate cancer (mCRPC), according to an interim analysis of the phase 3 PROpel study. The regimen benefited patients regardless of homologous recombination repair (HRR) mutation status.

In PROpel, Dr Fred Saad and colleagues studied 796 men with mCRPC that was not responding to primary androgen therapy. The men were randomly assigned in a 1:1 ratio to receive either the poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib (300 mg twice daily) or placebo, in addition to abiraterone (1000 mg once daily) and prednisone or prednisolone. Patients were allowed to have undergone prior docetaxel chemotherapy for metastatic hormone-sensitive prostate cancer (mHSPC), but no prior androgen receptor (AR) inhibition in any setting was permitted. All patients underwent tissue and plasma molecular profiling at baseline to determine HRR mutation status, but such testing was not required for eligibility.

The planned interim analysis revealed that median rPFS by investigator assessment was significantly longer in the olaparib group than in the control group, at 24.8 vs 16.6 months (hazard ratio [HR], 0.66; 95% CI, 0.54-0.81; *P*<.0001). The improvement in rPFS occurred across all prespecified subgroups, including patients with (HR, 0.50; 95% CI, 0.34-0.73) and patients without (HR, 0.76; 95% CI, 0.60-0.97) HRR mutations. The improvement in rPFS was confirmed by independent radiographic review (27.6 vs 16.4 months; HR, 0.61; *P*<.0001). Although overall survival (OS) data were not mature, the trend favored the olaparib group (HR, 0.86).

Grade 3 or higher adverse events (AEs) occurred in 47.2% of patients in the olaparib group vs 38.4% of those in the control group; these included grade 3 or higher anemia in 15.1% and 3.0% of the patients, respectively. Pulmonary emboli occurred in 6.5% of those in the olaparib group vs 1.8% of those in the control group. AEs led to treatment discontinuation in 13.8% of those in the olaparib group and 7.8% of those in the control group. Quality of life was comparable in the 2 groups.

The researchers concluded that the addition of olaparib to abiraterone and prednisone as first-line treatment improves rPFS in patients with mCRPC, regardless of HRR status. The safety and tolerability of hte olaparib combination were consistent with those of hte individual drugs. Patient follow-up is continuing for the planned analysis of OS.

Saad F, Armstrong AJ, Thiery-Vuillemin A, et al. PROpel: Phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract 11]. *J Clin Oncol*. 2022;40(6)(suppl).

Niraparib Improves PFS in Patients With Prostate Cancer and Alterations in Homologous Recombination Repair Genes

The addition of niraparib (Zejula, GlaxoSmithKline/Janssen) to abiraterone improves rPFS among men with mCRPC who have alterations in HRR-associated genes, according to first results of the phase 3 MAGNITUDE study. The study found no evidence of benefit from the addition of niraparib among patients with mCRPC who were negative for HRR gene alterations, and the agent increased toxicity. Patients who are negative for HRR gene alterations comprise approximately 70% to 80% of patients with mCRPC.

For the study, Dr Kim Chi and colleagues prospectively identified 423 patients with HRR gene alterations and 233 without HRR gene alterations who had mCRPC and had not received more than 4 months of abiraterone treatment. Patients in both groups were randomly assigned in a 1:1 ratio to receive niraparib (200 mg once daily) or placebo, in addition to abiraterone and prednisone.

After a median follow-up of 18.6 months, the researchers found that rPFS by central review was significantly longer in the niraparib group than in the control group among the patients with HRR gene alterations, at 16.5 vs 13.7 months (HR for progression or death, 0.73; 95% CI, 0.56-0.96; *P*=.02). After a median follow-up of 16.7 months, rPFS by central review also was significantly longer in the niraparib group than in the control group in a subgroup of patients with *BRCA1/2* mutations, at 16.6 vs 10.9 months (HR for progression or death, 0.53; 95% CI, 0.36-0.79; *P*<.001). In contrast, niraparib showed no benefit among the patients without HRR gene alterations. OS data were immature.

Among the patients with HRR gene alterations, grade 3/4 AEs occurred in 67.0% of those in the niraparib group and 46.4% of those in the control group. Grade 3/4 AEs that were more common with niraparib

included anemia, thrombocytopenia, and hypertension. The treatment discontinuation rate was 9.0% in the niraparib group and 3.8% in the control group. Quality of life was comparable in the 2 groups.

Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations [ASCO GU abstract 12]. *J Clin Oncol*. 2022;40(6)(suppl).

Darolutamide Improves Overall Survival in Men With De Novo Metastatic Hormone-Sensitive Prostate Cancer

The addition of the structurally distinct AR inhibitor darolutamide (Nubeqa, Bayer HealthCare) to standard androgen deprivation therapy (ADT) and docetaxel improves OS among men with mHSPC, according to a new study. Darolutamide had previously been shown to improve OS in nonmetastatic CRPC.

In the phase 3 ARASENS study, Dr Matthew Smith and colleagues randomly assigned 1306 men with mHSPC in a 1:1 ratio to darolutamide (600 mg twice daily) or placebo, in addition to ADT and docetaxel. In the randomization, patients were stratified according to extent of disease. Approximately 86% of the men had M1 disease at diagnosis, and only a small number had had prior local therapy.

The researchers found that the risk for death was significantly lower in the darolutamide group than in the control group (HR, 0.68; 95% CI, 0.57-0.80; *P*<.001), even though fewer patients in the darolutamide group subsequently received antineoplastic therapy (56.8% vs 75.6%). Darolutamide also significantly delayed the time to development of CRPC, time to pain progression, time to first symptomatic skeletal event, and time to subsequent initiation of systemic antineoplastic therapy.

The rates of treatment-emergent AEs (TEAEs) were similar in the 2 treatment arms, with grade 3/4 TEAEs occurring in 66.1% of patients in the darolutamide group and 63.5% of those in the control group; the most common of the TEAEs was neutropenia. TEAEs led to the discontinuation of darolutamide or placebo in 13.5% of patients in the darolutamide arm and 10.6% of patients in the control arm.

Dr Smith concluded that early treatment of mHSPC with darolutamide added to ADT and docetaxel significantly improved OS and key secondary endpoints.

Smith MR, Hussain MH, Saad F, et al. Overall survival with darolutamide versus placebo in combination with androgen-deprivation therapy and docetaxel for metastatic hormone-sensitive prostate cancer in the phase 3 ARASENS trial [ASCO GU abstract 13]. *J Clin Oncol*. 2022;40(6)(suppl).

Neoadjuvant Regimen Leads to Tumor Response in Nonmetastatic, High-Risk Renal Cell Carcinoma

A neoadjuvant regimen consisting of the immune checkpoint inhibitor avelumab (Bavencio, EMD Serono/Pfizer) and the vascular endothelial growth factor inhibitor axitinib (Inlyta, Pfizer) was shown to induce a partial response in more than one-quarter of patients with nonmetastatic, high-risk renal cell carcinoma (RCC). This regimen is already approved for use as a first-line treatment in metastatic RCC.

In the single-arm, phase 2 NeoAvAx study, Dr Axel Bex and coinvestigators administered avelumab and axitinib for 12 weeks to 40 patients with nonmetastatic, high-risk clear cell RCC before they underwent nephrectomy.

A partial response of the primary tumor was observed in 30% (n=12) of the patients, with a median decrease in tumor size of 20%. At a median follow-up of 23.5 months, 32% of the patients (n=13) had had a recurrence, which occurred after a median of 8 months and caused death in 3 patients. Of the 12 patients with a partial response of the primary tumor, 83% (n=10) were disease-free. Median disease-free survival (DFS) and OS were not reached.

Postoperative grade 3/4 AEs occurred in 5 patients, with 1 surgical delay related to treatment. A comparison of tumor biopsy samples taken after neoadjuvant therapy with samples taken before treatment showed upregulation of programmed death ligand 1 (PD-L1) expression and total CD8+ cell densities. No clear differences in immune markers were observed between the patients with a partial response of the primary tumor and those without a partial response. Post-treatment samples taken from the patients with a recurrence were characterized by lower densities of total, intra-epithelial, and stromal CD8+ cells; intra-epithelial CD8+/CD39+ cells; and total CD8+/GZMB+ cells.

The investigators concluded that treatment with neoadjuvant avelumab/axitinib for nonmetastatic high-risk RCC can induce a partial response of the primary tumor that correlates with DFS.

Bex A, Abu-Ghanem Y, van Thienen JV, et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx) [ASCO GU abstract 289]. *J Clin Oncol*. 2022;40(6)(suppl).

Adjuvant Pembrolizumab Continues to Benefit DFS in High-Risk Patients With RCC

Adjuvant pembrolizumab (Keytruda, Merck) vs placebo continues to improve DFS in patients with RCC who are at high risk for recurrence, according to 30-month results from the phase 3 KEYNOTE-564 trial. The trial did not

reveal any new safety signals with the programmed death 1 (PD-1) inhibitor.

KEYNOTE-564 enrolled patients who had clear cell RCC and were at intermediate or high risk for recurrence after nephrectomy with or without resection of metastatic lesions. Dr Toni K. Choueiri and colleagues randomly assigned 994 patients in a 1:1 ratio to adjuvant pembrolizumab or placebo. At 24 months of follow-up, DFS by investigator assessment was significantly better in the patients who had received pembrolizumab than in those who had received placebo (HR, 0.68; 95% CI, 0.53-0.87; *P*=.0010 [one-sided]).

In this updated analysis at 30 months of follow-up, DFS continued to be significantly better with pembrolizumab than with placebo (HR, 0.63; 95% CI, 0.50-0.80; nominal *P*<.0001). The improvement in DFS with pembrolizumab was consistent across subgroups, including patients with nonmetastatic disease and at intermediate or high risk for recurrence (HR, 0.68; 95% CI, 0.52-0.89). The OS data were immature, although the trend favored the pembrolizumab group.

No increase in any-grade or grade 3/4 AEs occurred from 24 to 30 months. No deaths related to pembrolizumab occurred.

Dr Choueiri and colleagues concluded that improvement in DFS continued at 30 months of follow-up in the patients with high-risk RCC who took adjuvant pembrolizumab rather than placebo.

Choueiri T, Tomczak P, Park SH, et al. Pembrolizumab as post nephrectomy adjuvant therapy for patients with renal cell carcinoma: results from 30-month follow-up of KEYNOTE-564 [ASCO GU abstract 290]. *J Clin Oncol.* 2022;40(6)(suppl).

Sacituzumab Govitecan Plus Pembrolizumab Can Benefit Patients With Metastatic Urothelial Carcinoma

A combination of the antibody-drug conjugate sacituzumab govitecan (Trodelvy, Gilead) and the checkpoint inhibitor pembrolizumab can benefit pretreated, checkpoint inhibitor–naive patients with metastatic urothelial carcinoma (mUC), according to interim results from cohort 3 of the phase 2 TROPHY-U-01 trial. Checkpoint inhibitors are standard therapy for patients with mUC that has progressed on platinum-based chemotherapy, but response rates and long-term disease control are limited.

Cohort 3 of this trial enrolled patients with mUC whose UC had progressed on or after platinum-based chemotherapy and who had never received a checkpoint inhibitor. Dr Petros Grivas and colleagues presented interim results from 41 patients who had received sacituzumab govitecan at least once at the recommended phase 2 dose of 10 mg/kg.

At a median follow-up of 5.8 months, the investigator-assessed objective response rate (ORR) was 34% (95% CI, 20.1-50.6), the clinical benefit rate was 61% (95% CI, 44.5-75.8), and the median PFS was 5.5 months. The median time to response was 2.0 months (95% CI, 1.3-2.8), and the median response duration and OS were not reached.

Grade 3/4 treatment-related AEs (TRAEs) occurred in 59% of patients; the most common any-grade TRAEs were diarrhea (71%), nausea (54%), neutropenia (44%), and anemia (41%). TEAEs of any cause led to treatment discontinuation in 1 patient. No treatment-related deaths occurred.

Although this was a small, nonrandomized trial with limited follow-up, Dr Grivas and colleagues concluded that their data support further evaluation of sacituzumab govitecan plus pembrolizumab in mUC.

Grivas P, Pouessel D, Park CH, et al. TROPHY-U-01 Cohort 3: sacituzumab govitecan (SG) in combination with pembrolizumab (pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens [ASCO GU abstract 434]. *J Clin Oncol.* 2022;40(6)(suppl).

Neoadjuvant Enfortumab Vedotin Produces Promising Activity in Patients With Muscle-Invasive Bladder Cancer

The antibody-drug conjugate enfortumab vedotin (Padcev, Astellas/Seagen) improves the pathologic complete response (pCR) rate in patients with muscle-invasive bladder cancer (MIBC) who are ineligible for treatment with cisplatin, according to a new study. Previous research has shown that neoadjuvant chemotherapy improves OS in patients who are eligible for cisplatin treatment.

Cohort H of the EV-103 phase 1b/2 trial enrolled 22 patients with MISC who were eligible for radical cystectomy and pelvic lymph node dissection and ineligible for treatment with cisplatin. Dr Dan Petrylak and coinvestigators administered 3 cycles of neoadjuvant enfortumab vedotin (1.25 mg/kg) before surgery.

More than one-third of the patients (36.4%) had a pCR, and pathologic downstaging occurred in 50.0%, with central pathology review pending in 1 case.

The most common AEs related to enfortumab vedotin were fatigue (45.5%), alopecia (36.4%), and dysgeusia (36.4%). Grade 3/4 TEAEs occurred in 18.2% of patients. No surgeries were delayed because of administration of the antibody-drug conjugate.

The investigators concluded that enfortumab vedotin showed promising activity in patients with MIBC who were ineligible for cisplatin, and that ongoing phase 2 and 3 trials of enfortumab vedotin in MIBC should continue.

Petrylak DP, Flaig TW, Mar N, et al. Study EV-103 Cohort H: antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients (pts) with muscle invasive bladder cancer (MIBC) who are cisplatin-ineligible [ASCO GU abstract 435]. *J Clin Oncol.* 2022;40(6)(suppl).