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Abiraterone Plus Olaparib Improves Outcomes in Metastatic Castration-Resistant Prostate Cancer

A combination of abiraterone and olaparib (Lynparza, AstraZeneca) led to longer progression-free survival (PFS) and a better response rate than the use of olaparib or abiraterone alone in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) mutations in *BRCA1/2* or *ATM*, according to results from the phase 2 BRCAAway trial.

In the trial, which was presented by Dr Maha Hussain, 61 patients with mCRPC and HRR mutations were randomly assigned in a 1:1:1 ratio to first-line treatment with abiraterone (plus prednisone; n=19), olaparib (n=21), or olaparib plus abiraterone (plus prednisone; n=21).

The median PFS was 8.4 months (95% CI, 2.9-17) in the abiraterone group, 14 months (95% CI, 8.4-20) in the olaparib group, and 39 months (95% CI, 22 to not reached) in the olaparib/abiraterone group. The objective response rate (ORR) was 22% (95% CI, 6.4-48), 14% (95% CI, 3-36), and 33% (95% CI, 15-57), respectively. The prostate-specific antigen (PSA) response rate was 61% (95% CI, 36-83), 67% (95% CI, 43-85), and 95% (95% CI, 76-100), respectively. The overall survival (OS) data were not yet mature.

At progression, 8 of 19 patients in the abiraterone group crossed over to olaparib and 8 of 21 patients in the olaparib group crossed over to abiraterone. The median PFS from randomization was shorter among patients who crossed over than those who received combination therapy, at 16 vs 39 months, respectively.

Grade 1 to 3 adverse events (AEs) occurred in 58%, 90%, and 95% of patients in the 3 groups, respectively, and grade 3 AEs occurred in 21%, 14%, and 19%, respectively. The most common grade 3 AEs in the combination group were fatigue and anemia. There were no grade 4 treatment-related AEs (TRAEs).

The authors concluded that in mCRPC patients with *BRCA1/2* or *ATM* alterations, abiraterone plus olaparib was well-tolerated and resulted in a longer PFS vs either agent alone or sequentially.

The results of this study were consistent with those of the PROpel trial, which led to the US Food and Drug Administration's approval of abiraterone plus olaparib for adults with *BRCA*-mutated mCRPC in 2023.

The combination of poly(ADP-ribose) polymerase inhibition and androgen receptor (AR) inhibition has a synergistic effect and provides a new standard of care for patients with metastatic castration resistant prostate cancer harboring a *BRCA1/2* mutation.

Hussain MH, Kocherginsky M, Agarwal N, et al. BRCAAway: a randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm) [ASCO GU abstract 19]. *J Clin Oncol*. 2024;42(4)(suppl).

Cabozantinib Plus Atezolizumab Improves PFS in Patients With mCRPC

A combination of cabozantinib (Cabometyx, Exelixis) and atezolizumab (Tecentriq, Genentech) improved PFS compared with the use of a second novel hormonal therapy (NHT) in patients with mCRPC who had a very poor prognosis, according to the results of the CONTACT-02 study.

The phase 3 study, by Dr Neeraj Agarwal and colleagues, enrolled 507 patients with mCRPC whose disease had progressed on 1 prior NHT and who had extrapelvic nodal or visceral metastasis. Patients were randomly assigned in a 1:1 ratio to cabozantinib plus atezolizumab or control treatment with abiraterone or enzalutamide.

After a median follow-up of 14.3 months in the PFS intention-to-treat (ITT) population, the median PFS by blinded independent central review was significantly longer with cabozantinib plus atezolizumab vs control treatment, at 6.3 vs 4.2 months, which translated into a 35% reduction in the risk of progression or death. The reduction in the risk of progression or death was even more pronounced in 2 prespecified subgroups: those with liver metastasis (57% reduction) and those with prior docetaxel treatment for mCSPC (43% reduction). The ORR, median duration of response, and disease control rate were all better in the cabozantinib/atezolizumab patients than in the control patients. The OS data were immature and did not show a significant difference between the arms in

median OS, which was 16.7 months in the cabozantinib/atezolizumab arm and 14.6 months in the second NHT arm (HR, 0.79; 95% CI, 0.58-1.07; *P*=.13).

Treatment-emergent AEs (TEAEs) occurred in 97% of the cabozantinib/atezolizumab patients vs 87% of the control patients, including grade 3/4 TEAEs in 48% vs 23% of patients, respectively. Grade 5 TEAEs occurred in 8% vs 12% of patients, respectively, and no grade 5 TRAEs occurred in either arm. TRAEs led to the discontinuation of any treatment components in 13% of patients in the cabozantinib/atezolizumab arm and 2% of those in the control arm.

The authors concluded that cabozantinib/atezolizumab significantly improved PFS vs the use of a second NHT in these patients, who have a high unmet medical need. The benefits were especially notable in patients with liver and bone metastasis, and those who previously received docetaxel for mCSPC. Follow-up for OS is ongoing.

Agarwal N, Azad A, Carles J, et al. CONTACT-2: phase 3 study of cabozantinib (C) plus atezolizumab (A) vs second novel hormonal therapy (NHT) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract 18]. *J Clin Oncol*. 2024;42(4)(suppl).

HPN328 Demonstrates Promising Clinical Activity in Neuroendocrine Carcinoma

The novel delta-like ligand 3 (DLL3)-targeting T-cell engager HPN328 is well-tolerated and demonstrates promising clinical activity across neuroendocrine carcinomas, including genitourinary (GU) neuroendocrine cancers, according to interim results of a phase 1/2 study.

The study, which was presented by Dr Himisha Beltran, enrolled 85 patients with relapsed or refractory metastatic neuroendocrine PC, small cell lung cancer, or other neuroendocrine neoplasms associated with DLL3 expression. Out of the 85 patients, 61 received a 1-mg priming dose of HPN328, after which the dose was escalated to 6 mg per week, 12 mg per week or every 2 weeks, or 24 mg per week or every 2 weeks.

Among the 50 patients evaluable for a response, the ORR was 56%, the confirmed response rate (cRR) was 31%, and the disease control rate (DCR) was 68%. Among the 12 patients who had GU neuroendocrine cancer and were evaluable for a response, the ORR was 58%, the cRR was 25%, and the DCR was 83%.

Among the full group of 85 patients, 100% experienced an all-grade TEAE and 51.8% experienced a grade 3 or higher TEAE. A total of 92.9% of patients experienced an all-grade TRAE and 24.7% experienced a grade 3 or higher TRAE. TRAEs included cytokine release syndrome (58.8% all grade, 3.5% ≥ grade 3) and immune effector cell–associated neurotoxicity syndrome (7.1% grade 1, 2.4% grade 2, none ≥ grade 3). The most common grade 3 or higher TRAE was neutropenia (4.7%).

Dr Beltran concluded that "HPN328 is a novel DLL3-targeted T-cell engager that is well tolerated and demonstrates promising clinical activity in neuroendocrine carcinomas, including GU neuroendocrine cancers."

Beltran H, Dowlati A, Jain P, et al. Interim results from a phase 1/2 study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T-cell engager, in patients (pts) with neuroendocrine prostate cancer (NEPC) and other neuroendocrine neoplasms (NEN) [ASCO GU abstract 121]. *J Clin Oncol*. 2024;42(4)(suppl).

BMS-986365 Shows Promising Clinical Activity in Heavily Pretreated mCRPC

The AR ligand–directed degrader BMS-986365 shows promising clinical activity in patients with heavily pretreated mCRPC, according to initial results from a phase 1 study that Dr Dana Rathkopf presented as a poster. The agent was also well-tolerated, with a manageable safety profile.

The open-label, multicenter, dose-finding study enrolled 95 patients with mCRPC that had progressed on androgen deprivation therapy, at least 1 second-generation hormonal therapy, and taxane chemotherapy. The study evaluated escalation doses of 100 to 1200 mg per day and 600 to 900 mg twice a day, and expansion doses of 600 mg per day and 400, 600, and 900 mg twice a day..

Treatment was well-tolerated, with no grade 4 or higher TRAEs or discontinuations due to TRAEs. Of the 27 patients treated in escalation, treatment was well-tolerated, with 2 patients experiencing nonserious grade 3 TRAEs at doses of at least 800 mg a day that were manageable with dose modifications. One dose-limiting toxicity of asymptomatic QTc prolongation occurred at a dose of 900 mg twice a day and resolved with dose interruption. The maximum tolerated dose was not reached.

Nearly half (46%) of the 68 evaluable patients across all dose levels in the expansion phase achieved a 30% or greater decline in PSA from baseline (PSA30). The rate of patients with PSA30 increased dose-dependently from 400 to 900 mg twice a day. Among the 20 patients who received a dose of 900 mg twice a day, 13 (65%) achieved PSA30, 9 (45%) achieved PSA50, and 2 (10%) achieved PSA90. PSA responses and radiographic tumor shrinkage occurred across all dose levels, including in patients with and without mutations or amplification in the AR. The median duration of treatment at 900 mg twice a day was 182 days.

Dr Rathkopf concluded that BMS-986365 is well-tolerated and shows promising and prolonged clinical activity. The investigators are in the process of selecting a recommended dose for phase 2 of the trial.

Rathkopf DE, Patel MR, Choudhury AD, et al. First-in-human phase 1 study of CC-94676, a first-in-class androgen receptor (AR) ligand-directed degrader (LDD), in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract 134]. *J Clin Oncol*. 2024;42(4)(suppl).