PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

More Highlights in Prostate Cancer From the 2023 American Society of Clinical Oncology Annual Meeting

June 2-6, 2023 • Chicago, Illinois and Virtual

Last month, Clinical Advances in Hematology & Oncology *highlighted the PEACE-1 trial, the TALAPRO-2 study, and research on an artificial intelligence–derived pathology biomarker. This month, we highlight the ICECaP study, research on BRCA status, and the LuPARP study.*

PSA Level After Radiation Therapy Linked to Survival Outcomes in Localized Prostate Cancer

Patients with localized prostate cancer whose lowest prostate-specific antigen (PSA) level is 0.1 ng/mL or greater within 6 months of completing radiation therapy (RT) have worse prostate cancer–specific survival (PCSS), metastasis-free survival (MFS), and overall survival (OS) than those with lower PSA levels, according to an analysis of randomized trials from the ICECaP collaborative. This finding "aids in counseling patients treated in routine practice," said presenter Dr Praful Ravi.

The analysis looked at data on 10,415 patients from 16 randomized clinical trials of RT, with or without androgen deprivation therapy (ADT), who had evaluable PSA follow-up. All the clinical trials were in the ICECaP repository. A total of 2629 (25%) patients had been allocated to RT alone, 6033 (58%) to RT plus short-term ADT (3-6 months), and 1753 (17%) to RT plus long-term ADT (24-36 months). The median follow-up was 10.1 years.

The researchers found that within 6 months after completing RT, 98% of patients in the RT group, 84% in the RT/short-term ADT group, and 77% in the RT/long-term ADT group had a PSA nadir of 0.1 ng/mL or higher. After adjusting for age, Eastern Cooperative Oncology Group (ECOG) performance status, clinical tumor stage, Gleason score, and PSA at randomization, having a PSA of this level was associated with poorer PCSS (hazard ratio [HR], 1.97 for both groups), MFS (HR, 1.27 and 1.58), and OS (HR, 1.26 and 1.59) in patients allocated to RT/short-term ADT and RT/long-term ADT, respectively. The association was weaker in patients allocated to RT, with an HR of 1.82 for PCSS, 2.23 for MFS, and 1.72 for OS.

Dr Ravi concluded that the prognostic value of PSA nadir after RT "confirms what we know when we see patients in the clinic." He added that this finding has implications for the design of adjuvant trials that look at the addition of novel systemic therapies to treatment with RT and ADT, along with intensification and de-intensification approaches.

Ravi P, Kwak L, Armstrong J, et al. Prognostic impact of PSA nadir (n) ≥0.1 ng/mL within 6 months (m) after completion of radiotherapy (RT) for localized prostate cancer (PCa): an individual patient-data (IPD) analysis of randomized trials from the ICECAP collaborative [ASCO abstract 5002]. *J Clin Oncol.* 2023;41(16) (suppl).

Germline and Somatic *BRCA1/2* Mutations Linked to Worse Outcomes in Metastatic Castration-Resistant Prostate Cancer

Both germline and somatic *BRCA1/2* mutations are linked to worse outcomes in metastatic castration-resistant prostate cancer (mCRPC), according to data from cohort 1 of the CAPTURE trial.

For the study, Dr David Olmos and colleagues used a custom next-generation sequencing panel to examine the DNA of 729 patients enrolled in a study of first-line treatment for mCRPC with novel hormonal therapy or a taxane. Eligible patients had an ECOG performance status of 0 to 2 and had not received prior poly(ADP-ribose) polymerase (PARP) inhibition or alkylating agents. The median age at baseline was 72 years.

The investigators found that 96 (13.2%) of the patients had a *BRCA1/2* mutation, 127 (17.4%) had a non-*BRCA* homologous recombination repair (HRR) alteration such as *ATM*, and 406 (69.4%) did not have

an HRR alteration. Radiographic progression-free survival (PFS), time to second objective disease progression (PFS2), and OS were all significantly worse in the *BRCA* group than in the non-*BRCA* groups. In addition, PFS2 and OS were significantly worse in the *BRCA* group than in the non-*BRCA* HRR group. Outcomes were not significantly different between patients with somatic vs germline *BRCA* alterations.

Dr Olmos concluded that "these results further support the importance of a screening for germline and somatic *BRCA1/2* alterations" to deliver more precise care to patients. He added that these findings are especially important in light of recent phase 3 trials suggesting that PARP inhibition can improve the poor outcomes seen in patients with *BRCA* mutations, and perhaps in patients with other HRR mutations.

Olmos D, Lorente D, Alameda D, et al. Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving first-line (1L) treatment stratified by BRCA status [ASCO abstract 5003]. *J Clin Oncol.* 2023;41(16)(suppl).

^{177}Lu-PSMA-617 Plus Olaparib Shows Promising Activity in mCRPC

A combination of ^{177}Lu-PSMA-617 (Pluvicto, Novartis) and olaparib (Lynparza, AstraZeneca) shows promising activity and is well tolerated in mCRPC, according to results from the dose-escalation stage of the phase 1 LuPARP study. The study investigators had hypothesized that olaparib would promote radiosensitization of ^{177}Lu-PSMA-617, leading to heightened DNA damage and improved efficacy.

The study, by Dr Shahneen Sandhu and colleagues, enrolled patients with mCRPC that had progressed on an androgen receptor pathway inhibitor and docetaxel, and who had an ECOG performance status of 0 or 1. Patients were required to have high prostate-specific membrane antigen (PSMA) expression and no evidence of discordance between fluorodeoxyglucose positron emission tomography (PET) and PSMA PET/computed tomography. In the dose-escalation stage of the trial, which had a standard 3 + 3 design, 32 patients (median age, 70 years) received ^{177}Lu-PSMA-617 at 7.4 GBq intravenously every 6 weeks for up to 6 cycles in conjunction with 9 prespecified dose schedules of olaparib, starting at 50 mg twice a day and increased in 50-mg increments to 300 mg twice a day for up to 6 cycles. The dose-limiting toxicity (DLT) period was 6 weeks. The primary objectives were to determine DLTs and the recommended phase 2 dose for the next phase of the study.

No DLTs were seen, and no patients discontinued treatment because of toxicity. Common grade 1/2 treatment-related adverse events (TRAEs) included xerostomia (78%), nausea (59%), fatigue (47%), constipation (28%), anorexia (19%), vomiting (13%) and diarrhea (9%). Hematologic grade 3 TRAEs included anemia (6%), neutropenia (6%), and thrombocytopenia (3%), which were transient and without clinical sequelae. A total of 66% of patients experienced a PSA response rate of at least 50%, and 44% experienced a PSA response rate of at least 90%. The overall response rate was 78%.

Dr Sandhu concluded that the combination of ^{177}Lu-PSMA-617 and olaparib was "well tolerated" and had "promising activity." Based on the results of this dose-finding study, the recommended dose for the phase 2 of LuPARP is ^{177}Lu-PSMA-617 at 7.4 GBq plus olaparib at 300 mg twice a day administered from days –4 to 18 for 6 weekly cycles.

Sandhu S, Joshua AM, Emmett L, et al. LuPARP: phase 1 trial of 177Lu-PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 5005]. *J Clin Oncol.* 2023;41(16)(suppl).