

Prostate Cancer in Focus • Section Editor: Andrew J. Armstrong, MD

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⁶⁸Ga-PSMA-11 PET Has Poor Sensitivity, Good Specificity for Pelvic Nodal Metastases

⁶⁸Ga-PSMA-11 positron emission tomography (PET) has poor sensitivity and good specificity for detecting pelvic nodal metastases compared with histopathology at the time of radical prostatectomy, according to a new trial.

For the prospective, multicenter, single-arm, open-label phase 3 trial, Dr Thomas A. Hope and coinvestigators enrolled 633 patients with intermediate- to high-risk prostate cancer for whom radical prostatectomy with pelvic lymph node dissection was being considered. All patients underwent a single ⁶⁸Ga-PSMA-11 PET scan that was read by 3 blinded independent central readers.

Of the 633 enrolled patients, 277 (44%) underwent radical prostatectomy and pelvic lymph node dissection. The sensitivity of ⁶⁸Ga-PSMA-11 PET for pelvic nodal metastases was 40%, the specificity was 95%, the positive predictive value was 75%, and the negative predictive value was 81%. Sensitivity was higher in patients with larger nodes, higher preoperative prostate-specific antigen (PSA) levels, and higher Gleason scores.

The investigators cautioned that 87% of the patients in whom lymph node metastases were identified after radical prostatectomy had an immediate biochemical recurrence following the surgery. “Further work needs to be done” to determine the optimal management of patients based on prostate-specific membrane antigen (PSMA) PET results, said Dr Hope.

Hope TA, Armstrong WR, Murthy V, et al. Accuracy of ⁶⁸Ga-PSMA-11 for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase III imaging study [ASCO abstract 5502]. *J Clin Oncol*. 2020;38(15)(suppl).

PET/CT Imaging With Novel Agent Superior to Standard Imaging in Prostate Cancer

The use of ¹⁸F-DCFPyL (PyL) in PET/computed tomography (CT) is superior to standard diagnostic imaging in men with biochemically relapsed prostate cancer, according to results from the CONDOR study. PyL is a novel PET imaging agent that binds with high affinity to PSMA.

For the prospective, phase 3 study, Dr Michael J. Morris and colleagues enrolled 208 men with rising levels

of prostate-specific antigen (PSA) after definitive therapy. All patients had negative or equivocal results on standard-of-care imaging, such as CT/magnetic resonance imaging or bone scintigraphy.

Three blinded, independent reviewers identified a correct localization rate of 84.8% to 87.0% among the patients, and the lower bound of the 95% CI for the correct localization rate was greater than 77%. A total of 69.3% (142/205) of patients had PSMA-avid lesions, and 63.9% (131/205) had a change in intended management after PyL-PET/CT. Of these changes, 78.6% (103/131) were attributable to positive PyL findings and 21.4% (28/131) were attributable to negative PyL scans. Changes included the following: salvage local therapy to systemic therapy (n=58), observation before initiation of therapy (n=49), noncurative systemic therapy to salvage local therapy (n=43), and planned treatment to observation (n=9).

CONDOR found PyL to be well tolerated. The most common adverse event was headache (n=4), and 1 drug-related serious adverse event of hypersensitivity occurred.

The results of this trial, in combination with those of the OSPREY study, establish the benefits of PyL in localized, biochemically relapsed, and metastatic prostate cancer, according to the investigators.

Morris MJ, Carroll PR, Saperstein L, et al. Impact of PSMA-targeted imaging with ¹⁸F-DCFPyL-PET/CT on clinical management of patients with biochemically recurrent prostate cancer: results from a phase III, prospective, multicenter study (CONDOR) [ASCO abstract 5501]. *J Clin Oncol*. 2020;38(15)(suppl).

¹⁷⁷Lu-PSMA-617 More Active Than Cabazitaxel in Pretreated Metastatic CRPC

¹⁷⁷Lu-PSMA-617 (LuPSMA) is more active than cabazitaxel (Jevtana, Sanofi-Aventis) in men with disease progression after docetaxel treatment for metastatic castration-resistant prostate cancer (mCRPC), according to initial results from the TheraP study. LuPSMA is a radioactively labeled small molecule that binds with high affinity to PSMA.

The phase 2 study enrolled men who had mCRPC with a high level of expression of PSMA and no sites of fluorodeoxyglucose-positive/PSMA-negative disease. Dr Michael S. Hofman and colleagues randomly assigned 200

men across 11 sites in Australia in a 1:1 ratio to LuPSMA (6-8 GBq every 6 weeks for ≤ 6 cycles) or cabazitaxel (20 mg/m² every 3 weeks for ≤ 10 cycles). Patients were stratified by disease burden, prior novel anti-androgen (abiraterone or enzalutamide [Xtandi, Astellas]) therapy, and study site.

After a median follow-up of 13 months, patients in the LuPSMA group were significantly more likely than those in the cabazitaxel group to have experienced at least a 50% decrease in PSA level: 66% vs 37%, respectively. A preliminary analysis also found that PSA–progression-free survival (PFS) was significantly longer with LuPSMA than with cabazitaxel (hazard ratio, 0.69; $P=.02$). Data on overall survival and radiologic PFS were not mature.

An analysis of 183 patients who received treatment found that the incidence of grade 3 or 4 toxicities was 54% among men receiving cabazitaxel vs 35% among those receiving LuPSMA. Grade 3 or 4 neutropenia and grade 1 or 2 diarrhea, dysgeusia, and neuropathy were more common with cabazitaxel than with LuPSMA, whereas grade 3 or 4 thrombocytopenia, grade 1 or 2 dry mouth, and grade 1 or 2 dry eye were more common with LuPSMA than with cabazitaxel.

Hofman MS, Emmett L, Sandhu SK, et al. TheraP: a randomised phase II trial of ¹⁷⁷Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer progressing after docetaxel: initial results (ANZUP protocol 1603) [ASCO abstract 5500]. *J Clin Oncol*. 2020;38(15)(suppl).

Health-Related Quality of Life Better With Olaparib Than With Hormonal Agents

Health-related quality-of-life (HRQoL) scores are higher with olaparib (Lynparza, AstraZeneca) than with novel anti-androgens in men who have mCRPC and homologous recombination repair (HRR) gene alterations, according to updated results from the PROfound trial. Previous results from this trial had shown improved radiographic PFS with olaparib compared with novel anti-androgens, and also improved time to progression of pain, in a subset of men with mutations in *BRC1A1*, *BRC1A2*, or *ATM*.

The open-label phase 3 trial looked at men with mCRPC and HRR gene alterations whose disease had progressed on a prior novel anti-androgen, specifically enzalutamide or abiraterone. Dr Antoine Thiery-Vuillemin and coinvestigators randomly assigned 387 men in a 2:1 ratio to olaparib or physician's choice of novel anti-androgen.

The researchers found that olaparib delayed deterioration in HRQoL scores compared with novel anti-androgens and was associated with better HRQoL functioning over time. HRQoL was assessed in the overall study population with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, which includes 5 subscales: physical well-being (PWB), functional well-being (FWB), emotional well-being, social well-being, and

prostate cancer subscale (PCS). The Trial Outcome Index (PWB+FWB+PCS) and FACT Advanced Prostate Symptom Index (FAPSI-6) were also calculated.

The FACT-P total and subscale scores during treatment were all higher for olaparib than for novel anti-androgens, with clinically meaningful differences noted between treatment arms in mean changes from baseline for all but FWB and FAPSI-6.

Thiery-Vuillemin A, De Bono JS, Saad F, et al. Health-related quality of life (HRQoL) for olaparib versus enzalutamide or abiraterone in metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations: PROfound [ASCO abstract 5539]. *J Clin Oncol*. 2020;38(15)(suppl).

ARV-110 Shows Clinical Activity in Heavily Pretreated mCRPC in Phase 1 Trial

ARV-110 showed “promising” clinical activity in heavily pretreated patients with mCRPC, according to results from a first-in-human, phase 1 trial. ARV-110 is a proteolysis targeting chimera (PROTAC) protein degrader that targets the androgen receptor.

For the trial, Dr Daniel P. Petrylak and colleagues enrolled 22 men who had received at least 2 prior therapies for mCRPC, including enzalutamide and/or abiraterone. Patients received ARV-110 orally once daily in a standard 3-plus-3 dose-escalated fashion, beginning with 35 mg.

A confirmed PSA response occurred in 2 patients with known mutations for resistance to both abiraterone and enzalutamide. A confirmed Response Evaluation Criteria in Solid Tumors (RECIST) response occurred in another patient in combination with a PSA response; this was one of the 2 patients with a PSA decline.

Treatment-related adverse events of any grade that occurred in more than 10% of patients included nausea, diarrhea, fatigue, increased alanine aminotransferase (ALT), increased aspartate transaminase (AST), decreased lymphocyte count, and vomiting. One patient had dose-limiting grade 3/4 elevated ALT/AST levels followed by acute renal failure while taking rosuvastatin. Another patient had grade 3 elevated ALT/AST levels while taking rosuvastatin that resolved when the agent was discontinued, permitting re-treatment with ARV-110. As a result, rosuvastatin administration during treatment with ARV-110 is no longer permitted per protocol.

Of the 15 patients who were evaluable for PSA response, 2 patients had confirmed PSA declines of greater than 50%. One of these patients also had an unconfirmed partial response by RECIST. Both responses were ongoing at data cutoff after 8 and 21 weeks of treatment.

Petrylak DP, Gao X, Vogelzang NJ, et al. First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI) [ASCO abstract 3500]. *J Clin Oncol*. 2020;38(15)(suppl).