Prostate Cancer: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner

Morgane C. Diven, PharmD, BCOP, of Phoenix VA Health Care System, breaks down abstract summaries published in *The ASCO Post* on a novel target, imaging agent, and androgen-deprivation therapy for prostate cancer, along with their implications for advanced practitioners.

Abstract 5500

Lutetium-177–Labeled PSMA-617 Improves PSA Response in First Analysis From TheraP Trial in Metastatic Prostate Cancer

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/187000/abstract to read the full abstract and view author disclosures.

Initial results of the randomized phase II TheraP trial show that therapy directed to prostate-specific membrane antigen (PSMA) with lutetium-177–labeled PSMA-617 (LuPSMA) significantly improved prostate-specific antigen (PSA) response compared with cabazitaxel in men with metastatic castration-resistant prostate cancer that had progressed on docetaxel.[1] LuPSMA had an improved toxicity profile as well.

"This is the first randomized trial to compare LuPSMA with a standard of care in men with docetaxel-progressing metastatic castration-resistant prostate cancer," stated lead author Michael S. Hofman, FRACP, MBBS, of Peter MacCallum Cancer Centre, Melbourne. "Cabazitaxel, the comparator, is a relevant comparator that has been shown to improve overall survival in men who have disease progression on docetaxel," he added.

TheraP Overview

At the ASCO20 Virtual Scientific Program, Dr. Hofman presented initial results of TheraP for the primary endpoint of PSA response and secondary endpoint of safety. Other key secondary endpoints, such as radiographic progression-free survival, overall survival, and patient-reported quality of life, will be presented in the future.

"My clinical interpretation of these results is that LuPSMA represents a novel class of radiopharmaceutical with high activity and relatively low toxicity in [metastatic castration-resistant prostate cancer] progressing on docetaxel. These results are consistent with prior single-center phase II data, and LuPSMA may represent a favorable treatment option compared with cabazitaxel in a selected population with high PSMA expression," Dr. Hofman stated.

"Improvement in overall survival [with LuPSMA] is not yet defined. We eagerly await results of the upcoming phase III VISION trial, which will tell us more," he continued. VISION is comparing

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standard of care with or without LuPSMA for patients with metastatic castration-resistant prostate cancer who have disease progression on docetaxel and enzalutamide or abiraterone acetate.

"Study results thus far warrant further exploration of LuPSMA earlier in the course of disease and in combinations," Dr. Hofman said.

"Results of TheraP are a positive step in the development of LuPSMA for post–androgen receptor inhibitor, post-docetaxel, [metastatic castration-resistant prostate cancer]," noted David R. Wise, MD, PhD, of Perlmutter Cancer Center at NYU Langone Health, New York. TheraP was one of three prostate cancer abstracts that Dr. Wise discussed during the Genitourinary Cancer Highlights Session at the ASCO20 meeting. "We await the results of VISION," he added.

Background

Metastatic castration-resistant prostate cancer is a lethal disease. Several life-prolonging treatments are available, including docetaxel, sipuleucel-T, cabazitaxel, abiraterone acetate, enzalutamide, radium-223, and olaparib, but the vast majority of patients still succumb to the disease. Novel treatments are needed, and one fertile avenue of research is PSMA-directed therapy.

PSMA is a unique antigen expressed on the surface of prostate cancer cells. LuPSMA is a radiolabeled small molecule that binds with high affinity to PSMA and delivers therapeutic beta-emitting radiation to tumor sites.

Lu-177–PSMA-617 is the furthest along in development of PSMA-targeted agents being studied. Several nonrandomized trials have shown encouraging efficacy and safety of LuPSMA in metastatic castration-resistant prostate cancer. One phase II trial, of which Dr. Hofman was lead author, found that LuPSMA reduced the PSA level by 50% or more in 64% of men, with low toxicity.[2,3]

Study Details

TheraP is the first randomized trial to compare LuPSMA in men with docetaxel-progressing metastatic castration-resistant prostate cancer defined by rising PSA and PSA > 20 ng/mL. The study was conducted at 11 sites in Australia. Participants were screened with a PSMA-directed positron-emission tomography (PET) scan and fluorodeoxyglucose (FDG)–PET/computed tomography (CT).

A total of 200 patients were randomly assigned 1:1 to LuPSMA for 6-week cycles for up to 6 cycles or cabazitaxel 20 mg/m2 every 3 weeks for up to 10 cycles. If an exceptional response was observed in the LuPSMA arm, treatment was paused and restarted upon progression.

Patients were stratified by disease burden, prior enzalutamide or abiraterone acetate therapy, and study site. Of the 200 randomly assigned patients, 98 were treated in the LuPSMA arm and 85 were treated in the cabazitaxel arm.

The primary analysis was an intention-to-treat analysis, and sensitivity analysis per protocol was performed as well. The primary endpoint was PSA response, defined as ≥ 50% reduction in PSA from baseline. Secondary endpoints, including PSA progression-free survival, overall survival, and quality of life, will be reported in the future.

At baseline, treatment arms were well balanced. About 91% had received prior enzalutamide or abiraterone acetate, 78% had a high disease burden (> 20 metastatic sites on PSMA-PET), and 92% were Eastern Cooperative Oncology Group performance status 0 or 1. Median PSA was 110 ng/mL in the LuPSMA arm and 94 in the cabazitaxel arm. More than 50% of patients had Gleason scores of 8 or higher at diagnosis, and about 30% had Gleason 7 disease. As of data cutoff on March 31, 2020, the median follow-up was 13.3 months, Dr. Hofman reported.

For the primary endpoint, the intention-to-treat analysis showed that LuPSMA led to a significantly greater percentage of patients with a PSA decline ≥ 50%: 66% in the LuPSMA arm vs 37% in the cabazitaxel arm, representing a 29% absolute greater PSA response in the experimental arm compared to cabazitaxel ($P < .0001$). The sensitivity analysis adjusting for the many more patients that dropped out before treatment in the cabazitaxel cohort showed a 23% difference in PSA response rate favoring LuPSMA ($P = .0016$).

A preliminary analysis of PSA progression–free survival found that LuPSMA delayed disease progression by 31% compared with cabazitaxel. Progression-free survival data are not yet mature.

Safety

Grade 3/4 neutropenia was more common with cabazitaxel: 8% vs 40%, respectively. Febrile neutropenia occurred in 8% of men with cabazitaxel compared to none with LuPSMA. Cabazitaxel was associated with more diarrhea, change in taste, and neuropathy than LuPSMA, whereas more thrombocytopenia, dry mouth, and dry eye occurred in LuPSMA-treated patients. Grade 3/4 adverse events were more frequent with cabazitaxel: 54% compared with 35% in those receiving LuPSMA. There was one treatment discontinuation due to toxicity in the LuPSMA arm and three in the cabazitaxel arm. ●

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The Advanced Practitioner Perspective

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Treatment options for advanced prostate cancer include oral agents, such as enzalutamide and abiraterone, intravenous agents, such as docetaxel and cabazitaxel, and radiopharmaceuticals, including radium-223. A novel target for treatment is the prostate-specific membrane antigen (PSMA), which is unique to prostate cancer cells. The agent used in this study is one of the agents being evaluated for use against this target. Lutetium-177–labeled PSMA-617 (LuPSMA) allows for targeted treatment to the PSMA.

This phase II TheraP trial compared LuPSMA to cabazitaxel in patients with metastatic prostate cancer who had progressed on docetaxel. The primary endpoint in this trial was PSA decline, and there was a significant difference in favor of LuPSMA compared with cabazitaxel. The PSA progression-free preliminary analysis showed benefit in favor of LuPSMA as well.

In regards to side effects, LuPSMA was well tolerated. LuPSMA was associated with thrombocytopenia, dry mouth, and dry eye side effects. This study was a randomized trial with a clinically appropriate comparator arm, which is of benefit when evaluating treatment options in these patients. Side effects with LuPSMA in this phase II study are somewhat different compared with other agents used to treat advanced prostate cancer, and there were fewer grade 3 or 4 side effects overall with this agent. Longer follow-up will be important in further evaluating the role of this novel agent in the treatment of advanced prostate cancer.

Disclosure: Dr. Diven has no conflicts of interests to disclose.

Abstract 5501

PSMA-Targeted PET/CT Imaging May Be Useful in Biochemically Recurrent Prostate Cancer

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/187017/abstract to read the full abstract and view author disclosures.

Positron-emission tomography/computed tomography (PET/CT) imaging with the prostate-specific membrane antigen (PSMA)-targeted radiotracer fluorine F-18 DCFPyL (PyL) successfully identified areas of occult metastasis in men with biochemically recurrent metastatic castration-resistant prostate cancer. This type of imaging led to management changes in about two-thirds of participants in the CONDOR trial. These results were presented during the ASCO20 Virtual Scientific Program.[1]

CONDOR is the second trial to confirm the diagnostic superiority of PyL–PET/CT to conventional imaging. OSPREY was the first to do so, in the setting of high-risk localized disease and radiographically recurrent disease.[2] CONDOR's focus was on men who had biochemically relapsed after undergoing definitive local therapy, but who had uninformative or equivocal standard imaging studies. Both trials were initiated to support the regulatory approval of PSMA-directed PET in the United States.

"CONDOR met and even well exceeded its primary endpoint, showing that PyL–PET/CT has excellent diagnostic performance in men with biochemically relapsed prostate cancer, even at low levels of PSA [prostate-specific antigen]. The study shows that PyL–PET/CT is superior to standard imaging in men with biochemically recurrent prostate cancer and that the results yielded actionable information that is clinically significant," stated Michael J. Morris, MD, of Memorial Sloan Kettering Cancer Center, New York.

"Optimized treatment patterns need to be further defined. This trial, coupled with the OSPREY study, have now established the performance characteristics of PyL–PET/CT in localized biochemically recurrent and metastatic prostate cancer," Dr. Morris stated.

Originally, the data from CONDOR were planned as two separate presentations—one for the primary endpoint of diagnostic performance, and the second for the impact of imaging results on management of patients in the trial. Both abstracts were pooled as one presentation once the ASCO20 virtual meeting was planned.

Background

Current imaging modalities are inadequate for localizing and characterizing occult disease in men with biochemically recurrent prostate cancer, particularly in patients with low PSA levels (< 2 ng/mL). There is a need for improved diagnostic imaging to better inform treatment planning.

Several types of PSMA-targeted imaging are under study in hopes of improving diagnostic accuracy. CONDOR focused on PyL-PET-CT in men with metastatic castration-resistant prostate cancer.

PyL is a lysine-linked, urea-based small molecule and novel PET imaging agent that binds selectively with high affinity to PSMA, which is overexpressed in prostate cancer cells. PyL-PET imaging is conducted 1 to 2 hours following administration of a single dose of PyL.

Study Details

CONDOR enrolled 208 men aged 18 years or older with a rising PSA level after definitive therapy and negative or equivocal standard-of-care imaging (eg, CT, magnetic resonance imaging [MRI], bone scintigraphy). A PSA level of 0.2 ng/mL was required for those who had undergone radical prostatectomy and a PSA level > 2 ng/mL for those treated with prior systemic therapy. All patients had biochemically recurrent metastatic castration-resistant prostate cancer. All patients had no previous radiologic findings. The objective of the first part of the study was to detect occult disease.

Diagnostic performance was assessed using correct localization rate, "a term proposed by [the U.S. Food and Drug Administration] for positive predictive value with the added requirement of anatomic location matching," Dr. Morris said. "An anatomic atlas was created prior to the study to provide a consistent reference for anatomical location matching across imaging modalities."

Correct localization rate was defined as the percentage of patients with a 1:1 correspondence between at least one lesion identified by PyL–PET/CT and the composite "standard of truth": pathology, correlative imaging, or PSA response. The trial was considered successful if the lower bound of the 95% confidence interval for correct localization rate exceeded 20% for two of three independent, blinded central PyL–PET/CT reviewers.

After meeting eligibility requirements, clinicians completed questionnaires both preimaging and postimaging about intended management of each patient. PyL scans were read by three blinded independent readers.

CONDOR was conducted at 14 sites in the United States and Canada. Eighty-five percent of the study population underwent radical prostatectomy alone or with radiation. "The PSA values were representative of this population, and median PSA was quite low, at 0.8 ng/mL, although there were some outliers," Dr. Morris said. About half the patients had a PSA level < 1 ng/mL, and 70% had a PSA level < 2 ng/mL, "which are PSA ranges

in which most decisions about subsequent salvage focal or systemic therapies are made," he noted.

The correct localization rate or positive predictive value was excellent—89%, 87%, and 84% for the three readers, respectively. "This was well in excess of the 20% benchmark we had set," Dr. Morris said.

"The robust performance of [correct localization rate] was maintained regardless of PSA values. PyL detected disease even at the lowest of PSA values," he stated.

Changes in Management

For the secondary endpoint of impact on treatment, 64% of patients had a change in management due to PSMA-PET findings. Of them, 78% were attributable to positive findings, and 21.4% to negative PyL scans.

Specific changes included the following:

- 21% had their goal changed from noncurative to curative salvage local therapy.
- 28% changed from salvage local therapy to systemic therapy.
- 23.9% changed from observation to initiation of therapy.
- 4.4% downgraded from planned treatment to observation.

PyL was associated with no significant safety issues. The radiotracer was well tolerated, with one drug-related serious adverse event (hypersensitivity); the most common adverse event was headache, reported in four patients (1.9%).

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The Advanced Practitioner Perspective

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Current NCCN Guidelines refer to next-generation imaging for staging of small-volume recurrence of prostate cancer as a rapidly developing field and that the newer tracers are not currently FDA-approved. The CONDOR and OSPREY trials were designed to achieve FDA-approval of a PSMA-targeted imaging with 18F-DCFPyL. This agent is a novel imaging agent that preferentially binds to the PSMA.

The CONDOR study evaluated patients with biochemical relapse after definitive local treatment without correlation on imaging. Imaging to detect recurrence is difficult in patients with low PSA (< 2 ng/mL). Improving diagnostic accuracy could allow for earlier treatment in patients with progression. The improved ability to detect progression will provide clinicians with an opportunity to impact patient care, especially in this subset of patients. However, it will be important to have long-term data to show that the ability to diagnose progression and initiate treatment earlier leads to improved oncologic outcomes to further support the use of this imaging modality.

Disclosure: Dr. Diven has no conflicts of interests to disclose.

Abstract 5602

Novel Androgen-Deprivation Therapy With Relugolix Causes Fewer Cardiac Events Than Leuprolide in Advanced Prostate Cancer

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/191602/abstract to read the full abstract and view author disclosures.

Men with prostate cancer on androgen-deprivation therapy are usually treated with leuprolide, a long-acting injectable luteinizing hormone-releasing hormone (LHRH) agonist requiring an every-3-month injection, but it may be possible for ADT to be delivered by a daily oral treatment, pending regulatory approval. In the phase III HERO study, oral relugolix, given daily, was superior to leuprolide for achieving testos-

terone suppression in men with advanced prostate cancer who required androgen-deprivation therapy, as reported during the ASCO20 Virtual Scientific Program by Neal D. Shore, MD, FACS, of Carolina Urologic Research Center, Myrtle Beach, South Carolina, and published online in *The New England Journal of Medicine* to coincide with the presentation.[1,2]

The study met the primary endpoint of sustained castration levels of testosterone at 48 weeks. Almost all men treated with relugolix (96.7%) maintained castration levels of testosterone through 48 weeks vs 88% of men treated with leuprolide ($P < .001$ for superiority). In addition, the risk of developing a major adverse cardiovascular event was 54% lower with relugolix.

"Prescribing information for leuprolide and other LHRH agonists already contains warnings about increased risk of myocardial infarction, sudden cardiac death, and stroke. In the HERO trial, the oral GnRH antagonist relugolix showed sustained testosterone suppression superior to that of leuprolide [an LHRH agonist]," stated Dr. Shore.

"Relugolix is a novel, oral GnRH antagonist that has the potential to become a new standard for androgen-deprivation therapy in advanced prostate cancer," he added.

Practice-Changing Results?

This abstract was one of three prostate cancer abstracts selected for the Genitourinary Highlights session at this year's ASCO meeting. David Wise, MD, of Perlmutter Cancer Center at NYU Langone Health in New York, who discussed the highlights, agreed that relugolix is a new standard of care. "Is this practice-changing? Yes, for a subset of patients with a history of significant cardiovascular disease and without gastrointestinal malabsorption problems," Dr. Wise stated. "I will use this drug to avoid injection-site reactions commonly experienced with degarelix [another GnRH antagonist]. The concern for noncompliance with an oral drug will necessitate more frequent serum testosterone checks, particularly for monotherapy," he added.

Dr. Shore explained that the reduced incidence of major adverse cardiovascular events with relugolix is noteworthy, because men with prostate cancer have an increased risk of cardiovascular events. "Cardiovascular events are the leading cause of death in men with prostate cancer, now accounting for up to one-third of deaths. Approximately 30% of men with prostate cancer have known cardiovascular disease, and many more have risk factors such as obesity, diabetes, hypertension, and hyperlipidemia. In the HERO trial, more than 90% of men had cardiovascular risk factors."

Study Details

The global trial randomly assigned 930 men with advanced prostate cancer in a 2:1 ratio to receive oral relugolix at 120 mg/d (n = 622) or leuprolide injections (n = 308) every 3 months, for a total of 48 weeks. To be eligible for the trial, men had to be 18 years or older, have histologically confirmed adenocarcinoma of the prostate, and be candidates for at least 1 year of continuous androgen-deprivation therapy. Eligible patients had to have one of the following: evidence of biochemical or clinical relapse after primary therapy with curative intent, newly diagnosed hormone-sensitive metastatic disease, or advanced localized disease unlikely to be cured. Patients who experienced major adverse cardiovascular events within 6 months of enrollment were excluded.

Key Points

The phase III HERO trial found that oral relugolix was superior to leuprolide, the current standard of care for androgen-deprivation therapy, in achieving castration testosterone levels in men with advanced prostate cancer.

Moreover, the risk of major adverse cardiovascular events was 54% lower with relugolix than with leuprolide.

At baseline, the median patient age was 71 years, and 28.6% were older than age 75. About 31% had metastatic disease, 43% had Gleason 8 to 10 disease, 11.9% had previous androgen-deprivation therapy, and 30.3% had previous radiotherapy. The median prostate-specific antigen (PSA) level at baseline was 10.8 ng/mL. The mean testosterone level at baseline was 427.5 ng/dL. More than 90% of men had at least one cardiovascular risk factor, and the percentage of men with risk factors was well balanced in the two arms. Treatment adherence was more than

99% in both groups. The median time to follow-up, including safety, was 52 weeks.

Key Results

In addition to superiority for the primary endpoint of maintained castration levels of testosterone over 48 weeks, relugolix was superior to leuprolide for all key secondary endpoints ($P < .001$). These endpoints included the cumulative probability of castrate levels on day 4 (56% vs 0%) and on day 15 (98.7% vs 12%) and of testosterone suppression to profound levels (ie, < 20 ng/dL). The percentage of patients with a confirmed PSA response at day 15 was 79.4% with relugolix and 19.8% with leuprolide ($P < .001$).

Men treated with relugolix achieved castration levels of testosterone more rapidly than leuprolide, and this response was maintained throughout treatment. On the other hand, patients who discontinued relugolix treatment had faster testosterone recovery to normal levels.

"Another clinical advantage of oral relugolix over leuprolide is a higher percentage of men achieved testosterone recovery to normal levels within 90 days after treatment discontinuation (54% vs 3%)," Dr. Shore noted. "This should be particularly relevant for men receiving intermittent androgen-deprivation therapy, short-course androgen-deprivation therapy, or stopping treatment to recover from serious and debilitating testosterone suppression adverse effects," he explained.

Safety

The overall incidence of adverse events was consistent across the two treatment arms. Hot flash was the most common adverse event in both arms: 54.3% for relugolix and 51.6% for leuprolide. Moderate or mild diarrhea was reported in more patients in the relugolix group (12.2%) than in the leuprolide group (6.8%). There were no treatment withdrawals due to diarrhea.

Fatal events occurred in 1.1% of the relugolix group and 2.9% of the leuprolide group. A prespecified analysis after 48 weeks of treatment found the incidence of major adverse cardiovascular events was 2.9% with relugolix compared with 6.2% with leuprolide—a rate 54% lower with the oral androgen-deprivation therapy.

In a subgroup of patients with a reported history of major adverse cardiovascular events, the incidence of such events during treatment was 3.6% for relugolix and 17.8% for leuprolide. "The odds ratio was 5.8 times higher with leuprolide in comparison to relugolix in men with a history of major adverse cardiovascular events," Dr. Shore stated.

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The Advanced Practitioner Perspective

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Relugolix is a new oral GnRH agonist that was compared to leuprolide in this phase III study. Patients were eligible for randomization to relugolix 120 mg daily or leuprolide every 3 months. In this study, the authors found that significantly more men achieved and sustained castration levels for the study duration of 48 weeks. Relugolix achieved castration as early as day 4 in the clinical trial, which is of interest, as degarelix has a rapid decrease in testosterone levels within 3 days.

In a prespecified analysis, the authors showed a lower incidence of cardiovascular events with relugolix. The other side effects were similar between the two arms. It is important to remember that patients with major adverse cardiac events within 6 months of randomization were excluded from this trial.

Based on these results, relugolix could provide an alternative to leuprolide injections in appropriately selected patients. The patient's ability to adhere to the daily regimen is important to consider, as well as the potential pill burden with the addition of an oral daily medication. Additionally, clinicians should incorporate patients receiving this agent into the monitoring follow-up available for patients receiving oral medications for their cancer treatment, and potentially consider closer follow-up in patients who are receiving relugolix, especially as monotherapy.

Disclosure: Dr. Diven has no conflicts of interests to disclose.