Prostate Cancer: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner

Morgane C. Diven, PharmD, BCOP, of Phoenix VA Health Care System, evaluates research on an investigational radiolabeled small molecule, combination therapy in the treatment of de novo metastatic prostate cancer, and a CYP17-lyase inhibitor in metastatic hormone-sensitive prostate cancer. Coverage provided by *The ASCO Post*.

Abstract LBA4

VISION Trial: Novel PSMA-Targeted Radiotherapy Improves Outcomes in Metastatic Prostate Cancer

By Alice Goodman

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Lutetium-177–PSMA-617 (LuPSMA)—an investigational radiolabeled small molecule—significantly improved radiographic progression-free survival and overall survival when added to the standard of care compared with the standard of care alone for men with metastatic castration-resistant prostate cancer who had experienced disease progression on other lines of treatment. These findings were from the phase III VISION trial presented during the 2021 ASCO Annual Meeting.[1]

LuPSMA plus the standard of care achieved a median of 8.7 months of radiographic progression-free survival vs 3.4 months with the standard of care alone—more than doubled in this pretreated population with advanced disease. Overall survival was also extended to 15.3 months with LuPSMA plus the standard of care vs 11.3 months with the standard of care alone.

"In patients with metastatic castration-resistant prostate cancer whose cancer had progressed after chemotherapy and androgen receptor pathway inhibitors, LuPSMA prolonged life and delayed the time to progression of cancer on scans. It was well tolerated, with no new safety signals of concern. These findings warrant LuPSMA as a new treatment option for metastatic castration-resistant prostate cancer, pending FDA review," stated presenting author Michael J. Morris, MD, Head of the Prostate Section at Memorial Sloan Kettering Cancer Center, New York.

"This trial is clearly important. These men had disease progression even with very low levels of testosterone. LuPSMA is an alternative therapy delivered directly to the prostate cancer cells, and survival was significantly improved. The use of LuPSMA, if it gets regulatory approval, could become an important new treatment option for patients with metastatic castration-resistant prostate cancer," said Immediate Past President of ASCO Lori J. Pierce, MD, FASTRO, FASCO, at a press conference where the findings were discussed.

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Background

Prostate cancer is the most common cancer in men and the second leading cause of male cancer-related deaths in the United States. Although a number of treatment options are available for metastatic castration-resistant prostate cancer, most patients experience disease progression and need several lines of therapy; durable remissions are uncommon with each new line of therapy.

PSMA (prostate-specific membrane antigen) is highly expressed on prostate cells across the disease spectrum and disease sites and is an excellent target for treatment and imaging. PSMA positron-emission tomography (PET) scans are FDA approved to detect occult cancers in patients with high-risk localized disease and also biochemically relapsed disease. In VISION, PSMA PET imaging was used to establish PSMA expression in men with metastatic disease as a companion diagnostic to the therapeutic PSMA-directed treatment. Targeting PSMA with a radioligand such as LuPSMA is a novel treatment approach, and hopes were high in the prostate cancer community that it would be successful.

"LuPSMA targets PSMA with high affinity. It releases its payload of beta radiation into the prostate cancer cell, which is exposed to lethal radiation and dies," Dr. Morris explained.

Study Details

VISION enrolled patients with metastatic castration-resistant prostate cancer and a PSMA-positive PET scan who had experienced disease progression on previous treatment with an androgen receptor pathway inhibitor and one to two taxane chemotherapy regimens. Patients (n = 831) were randomly assigned 2:1 to receive the standard of care (determined by the treating physician) plus LuPSMA or the standard of care alone. The experimental radioligand pharmaceutical was given for four cycles every 6 weeks; responders with residual disease could have an extra two cycles.

"The standard of care excluded chemotherapy, immunotherapy, radium-223, and investigational drugs because the toxicity of these treatments in combination with LuPSMA was unknown," Dr. Morris explained.

There were two primary endpoints: overall survival and radiographic progression-free survival. If either or both were positive, the trial would be considered a success.

Baseline characteristics were as expected for this population, and previous exposure to androgen receptor inhibitors and taxanes was evenly distributed in both arms of the study. The analysis of radiographic progression-free survival was performed on 531 patients; the overall survival analysis was based on 831 patients.

"Nine months after enrollment, a high dropout rate was observed in the standard-of-care arm [56%], but enhanced study site education and communication reduced the dropout rate in both arms," Dr. Morris said.

Key Results

Median follow-up was 20.9 months at the time of data cutoff. LuPSMA plus the standard of care significantly improved radiographic progression-free survival by 60% vs the standard of care alone: median radiographic progression-free survival was 8.7 months vs 3.4 months, respectively ($P < .001$). Overall survival was also significantly improved by 38% with LuPSMA plus the standard of care vs the standard of care alone: median overall survival was 15.3 months vs 11.3 months ($P < .001$). All key secondary endpoints were also statistically improved for the experimental arm vs the control arm.

"These benefits were maintained in the entire population of randomly assigned patients," Dr. Morris said.

"Dramatic differences were observed between treatment arms favoring LuPSMA for prostate-specific antigen (PSA) reductions of more than 50% and more than 80%," he added. PSA reductions of 50% or more were observed in 46% of the experimental arm and 7.1% of the standard-of-care-alone arm; PSA reductions of 80% or more were seen in 33% and 2%, respectively.

A slightly higher percentage of patients in the control arm received post-protocol chemotherapy and radiotherapy.

Toxicity

"Side effects of all grades and higher grades were more common with LuPSMA, but none were unexpected," Dr. Morris said.

Fatigue, bone marrow suppression, dry mouth, and nausea/vomiting of all grades were

the most commonly reported side effects (about 40% to 50% of patients in the experimental arm). More treatment-emergent adverse events were observed in the experimental arm: 52.7% vs 38% with the standard of care alone.

Among patients receiving LuPSMA, high-grade bone marrow suppression was observed in 23.4%; high-grade anemia, in 13%; low platelet count, in 8%; and dry mouth (not high grade), in 39%. High-grade renal side effects were observed in 3.5% of the experimental arm and 2.9% of the control arm.

"LuPSMA is currently being studied in earlier stages of prostate cancer," Dr. Morris noted.

Clarifying the Dropout Rate

During the question-and-answer session following his presentation, Dr. Morris cited two reasons for the high dropout rate initially: First, in sites where the partnership between nuclear medicine and medical oncology was not strong, there was a breakdown in communication. These patients had very advanced disease and required medical oncology as well as nuclear medicine. Second, this therapy was available internationally, and a small number of patients randomly assigned to the standard of care arm dropped out.

"Our measures helped reduce the dropout rate and rebalance the equipoise, so patients understood the intent and design of the trial," Dr. Morris explained.

Reference

1. Morris MJ, De Bono JS, Chi KN, et al: Phase III study of lutetium-177–PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). 2021 ASCO Annual Meeting. Abstract LBA4. Presented June 6, 2021.

The Advanced Practitioner Perspective

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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–PSMA-617 (LuPSMA) was previously evaluated in the phase II TheraP trial that compared LuPSMA to cabazitaxel in patients who had progressed on docetaxel. This study showed a significant difference in favor of LuPSMA in regard to the PSA decline. The VISION trial was a phase III study evaluating LuPSMA plus standard of care compared to standard of care alone in patients with metastatic castration-resistant prostate cancer who had progressed on other lines of treatment. Of note, the prior therapies included were androgen receptor pathway inhibitors and one to two prior taxane therapies. The standard of care could not include chemotherapy, immunotherapy, radium-223, or investigational drugs. With a median follow-up of 20.9 months, the primary endpoints of overall survival (OS) and radiographic-progression free survival (PFS) showed a significant difference in favor of LuPSMA for both.

Overall, side effects of all grades and higher grades were more common in the LuPSMA arm. The most common side effects in the LuPSMA arm were fatigue, bone marrow suppression, dry mouth, and nausea/vomiting. High-grade adverse drug events included bone marrow suppression, anemia, decreased platelet count, and renal side effects. These are consistent with prior studies with LuPSMA. In evaluating the current study and applying it to patients, the choice for standard of care will be of interest. It is also important to consider the importance of coordination of care where needed between nuclear medicine and medical oncology when considering the use of LuPSMA.

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

Abstract 5000

Prostate Cancer: Abiraterone Acetate, Prednisone, and Radiotherapy in Metastatic Disease

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/196406/abstract to read the full abstract and view author disclosures.

Karim Fizazi, MD, PhD, of Institut Gustave Roussy, discusses first results from the phase III PEACE-1 trial, which showed that abiraterone plus androgen-deprivation therapy and docetaxel improves radiographic progression-free survival in men with de novo metastatic prostate cancer. A transcript of his interview with *The ASCO Post* follows.

PEACE-1 is a phase III trial that enrolled patients with metastatic prostate cancer. It had a 2 × 2 factorial design; one is whether we should add abiraterone on top of standard of care for these men with metastatic prostate cancer, and the second is whether we should use radiation therapy on top of standard of care.

As you're well aware of, we've made major progresses in the past 5 years or so for men with de novo metastatic prostate cancer. Indeed, we've been able to demonstrate that adding docetaxel or abiraterone or other androgen receptor inhibitors, and/or radiation therapy to the prostate are all associated with clinical improvements in men, including overall survival benefit.

What we don't know as clinicians at this point, is whether and how we should combine these various treatments on top of androgen deprivation therapy. This is exactly what PEACE-1 is asking.

We were able to enroll almost 1,200 men in the trial in Europe. These patients all received standard of care, so in the beginning of the trial, that was androgen deprivation therapy and at the end of the trial it was more androgen deprivation therapy and docetaxel. All of these men were randomized to receive either standard of care alone, standard of care combined with abiraterone acetate and prednisone, standard of care combined with radiation therapy to the prostate, or standard of care with abiraterone and radiation therapy to the prostate. The standard of care included docetaxel, then abiraterone was started during docetaxel, while radiation therapy was started when docetaxel was finished.

What we report at ASCO 2021 is the first coprimary endpoint of radiographic progression-free survival (PFS) for the abiraterone group, and that's because the number of events has been reached for this population. The trial is positive for the finding that radiographic PFS significantly improved in men receiving abiraterone on top of androgen deprivation therapy and docetaxel, with or without radiation therapy. Actually, there is no interaction between abiraterone and radiation.

Looking at the data, the median time to radiographic PFS in the control arm of androgen deprivation therapy and docetaxel is only 2 years, and it's 4.5 years in men receiving abiraterone on top of standard of care. In other words, there was a benefit of 2.5 more years without radiographic progression or death for these patients, which is enormous. The hazard ratio is 0.50, and the *P* value was significant.

There was no additional toxicity of abiraterone on top of docetaxel; for example, 5% febrile neutropenia was reported, and the abiraterone toxicity was as expected, with more hypertension and hypokalemia.

We're glad to have these data from PEACE-1, and we believe that these data have the potential to change practice.

The Advanced Practitioner Perspective

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The PEACE-1 trial is a phase III study designed to evaluate the addition of abiraterone or radiation therapy to the standard of care treatment for men with de novo metastatic prostate cancer. The trial included almost 1,200 men in Europe, and standard of care changed over the duration of the study from androgen deprivation therapy (ADT) to ADT plus docetaxel. The randomization arms were standard of care alone, standard of care plus abiraterone and prednisone, standard of care with radiation therapy, or standard of care with abiraterone and radiation therapy. The data presented at ASCO 2021 reported on the co-primary endpoint of radiographic progression-free survival (PFS) for the abiraterone group.

These data showed that the radiographic PFS was significantly improved in patients receiving abiraterone in addition to ADT and docetaxel, with or without radiation. Additionally, there was no interaction between abiraterone and radiation. The median time to radiographic PFS in the control arm (ADT + docetaxel) compared to abiraterone + standard of care was 2 years compared to 4.5 years. No additional toxicities were noted for the addition of abiraterone to docetaxel. It is important to note the order that treatment was initiated in patients who received ADT + doxetaxel + abiraterone with radiation therapy. Abiraterone was started during docetaxel therapy and radiation was started after docetaxel therapy was completed.

This study will provide important information about combination therapy in the treatment of de novo metastatic prostate cancer. The patient characteristics will be important for evaluating the applicability of this study to the wider patient population. Additionally, it will be of interest to see what subsequent treatment options are for patients who progress on the ADT + docetaxel + abiraterone combination therapy.

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

Abstract 5001

Prostate Cancer: Androgen-Deprivation Therapy With Orteronel or Bicalutamide

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/196407/abstract to read the full abstract and view author disclosures.

Neeraj Agarwal, MD, of Huntsman Cancer Institute at the University of Utah, discusses phase III data from the SWOG S1216 trial, which evaluated the clinical benefit of using androgen-deprivation therapy with either orteronel (or TAK-700, a CYP17 inhibitor) or bicalutamide in patients with newly diagnosed metastatic hormone-sensitive prostate cancer. A transcript of his interview with *The ASCO Post* follows.

The SWOG S1216 trial was a federally funded trial in men with metastatic hormone-sensitive prostate cancer. In this trial, the experimental agent was TAK-700, which is a drug with a similar mechanism of action as abiraterone, but doesn't require concurrent prednisone in the doses it was used in the trial because of its high specificity for CYP17-lyase enzyme inside the prostate tumor.

The primary endpoint of the trial was overall survival, and the secondary endpoint was progression-free survival. Other secondary endpoints also included PSA at 7 months, which is a known intermediate validated surrogate for overall survival, and safety of the combination.

Results

After median follow-up of 57 months, which is a long follow-up, the median overall survival in the TAK-700 arm was 81 months, and in the control arm, with ADT + bicalutamide, was 70 months. So there was an 11-month improvement in median overall survival with TAK-700, with a hazard ratio of 0.86, and a *P* value of .04, favoring TAK-700.

However, despite this magnitude of improvement in the absolute overall survival, the predefined criteria for statistical significance were not met. The secondary endpoint of PFS was sig-

nificantly improved with TAK-700, with a 42% reduction in risk of death. PSA at 7 months was also significantly improved with TAK-700. This was obviously intriguing to see why and how median overall survival in the TAK-700 arm was 81 months and 11 months higher than the control arm, but the trial was still not able to meet the prespecified criteria for statistical significance. And that likely happened because of a much better overall survival in the control arm of 70 months, which was 16 months longer than the control arm survival estimates at the time that we conceived the trial. When we conceptualized the trial, we assumed the median overall survival of the control arm to be 54 months.

So we look back at the SWOG-9346 trial, which was reported in 2013, where the median overall survival of patients with newly diagnosed metastatic hormone-sensitive prostate cancer was 46 months. And the risk stratification or proportion of patients with extensive risk disease was exactly the same, at 48% to 49%. And in that trial, the median overall survival was 46 months.

The message here is that the median overall survival in patients who receive standard ADT has actually improved from 46 months to 70 months likely due to the advancements in drugs approved in the setting of castrate-resistant prostate cancer, and this is great news for patients. The second takeaway is that TAK-700 improved the median overall survival by 11 months. We already have multiple drugs approved in the setting of metastatic hormone-sensitive prostate cancer. Now, we call them ADT intensification, and they include docetaxel, apalutamide, enzalutamide, abiraterone, and so on. So, if we can have our patients access ADT intensification therapy in the setting of metastatic hormone-sensitive prostate cancer, and those life-prolonging therapies that are approved in the castrate-resistant prostate cancer setting, I think that will lead to optimal improvement in overall survival of our patients.

The Advanced Practitioner Perspective

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The phase III SWOG S1216 trial evaluated orteronel (TAK-700) or bicalutamide in patients with newly diagnosed metastatic hormone-sensitive prostate cancer. Orteronel is a CYP17-lyase inhibitor, similar in mechanism of action to abiraterone without the need for concurrent prednisone due to high specificity for the CYP17-lyase enzyme. Median follow-up was 57 months. The median OS in patients receiving TAK-700 was 81 months compared with 70 months in the patients receiving bicalutamide. These results did not meet the predefined criteria for statistical significance. This lack of statistical significance could be related to a longer-than-estimated OS in the control arm. The secondary endpoint of PFS was significantly improved with TAK-700 as was the PSA at 7 months. There were more grade 3/4 adverse drug events (hypertension, fatigue) in the TAK-700 arm compared to the bicalutamide arm.

The SWOG-9346 trial was published in 2013 and showed the median OS of patients with newly diagnosed metastatic hormone-sensitive prostate cancer was 46 months. In the time since that study was published, OS has improved in this patient population, and there are a number of drugs approved in this setting. The long-term role of TAK-700 in the treatment of metastatic hormone-sensitive prostate cancer will need to be clarified with further studies.

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