

2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Prostate Cancer

Following coverage by *The ASCO Post*, **Jennifer L. Glass, PA-C, MS**, of the Mayo Clinic dives into the major findings in prostate cancer from the 2019 ASCO Annual Meeting in Chicago and their implications for advanced practitioners.

Abstract LBA2

ENZAMET: Addition of Enzalutamide to Standard of Care in Metastatic Hormone-Sensitive Prostate Cancer

By *The ASCO Post*

Visit <https://meetinglibrary.asco.org/record/174531/abstract> to read the full abstract and view disclosures.

An interim analysis of the international, randomized phase III ENZAMET trial found that 80% of men with metastatic hormone-sensitive prostate cancer who received the nonsteroidal antiandrogen agent enzalutamide along with standard-of-care treatment were alive after 3 years, compared with 72% of men who received other nonsteroidal antiandrogens along with standard treatment. These findings were presented during the 2019 ASCO Annual Meeting Plenary Session by Sweeney et al. (Abstract LBA2).

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“Physicians and patients with prostate cancer now have a new treatment option with enzalutamide, and this is especially relevant for men who cannot tolerate chemotherapy and have a lower burden of disease seen on scans,” said study Co-Chair Christopher Sweeney, MBBS, a medical oncologist at the Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston.

“In men with metastatic prostate cancer starting testosterone suppression, enzalutamide and docetaxel are both active and are reasonable alternatives, but they have different side effects, costs, risks, and benefits,” added study Co-Chair Ian D. Davis, PhD, of Monash University Eastern Health Clinical School, Victoria, Australia.

The study found that enzalutamide is a more effective inhibitor of the androgen receptor than bicalutamide, nilutamide, or flutamide, the comparison standard nonsteroidal antiandrogens used in the trial. However, enzalutamide can lead to different side effects.

Methods

Men with metastatic hormone-sensitive prostate cancer were randomly assigned between March 2014 and March 2017 to receive an injection of a testosterone-suppressing medicine (such as goserelin, leuprolide, or degarelix) with either a 160-mg dose of enzalutamide daily or one of three standard nonsteroidal antiandrogens: bicalutamide, nilutamide, or flutamide. Of the 1,125 men enrolled in the trial, 503 men received early doses of docetaxel, and 602 did not.

Key Points

- Of 596 men with a higher amount of disease on imaging scans, 71% taking enzalutamide were alive compared with 64% taking another nonsteroidal antiandrogen.
- Of 529 men with a low amount of disease on imaging scans, 90% taking enzalutamide were alive compared with 82% taking another nonsteroidal antiandrogen.
- Among patients who received enzalutamide without docetaxel, 83% were alive, compared with 70% taking another nonsteroidal antiandrogen.
- At the time of the first analysis of the data, 64% of men were still taking enzalutamide, compared with 36% of men taking another nonsteroidal antiandrogen.

Results

Men were followed for a median of 34 months. After 3 years, 80% of men with metastatic hormone-sensitive prostate cancer who received enzalutamide along with testosterone suppression, with or without early docetaxel, were alive, compared with 72% of men who received one of the other three nonsteroidal antiandrogens in the trial. Overall, there was a 33% decrease in the risk of death in men receiving enzalutamide compared to those who took another nonsteroidal antiandrogen.

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The Advanced Practitioner Perspective

Jennifer L. Glass, PA-C, MS, Mayo Clinic

Currently, enzalutamide is recommended by the National Comprehensive Cancer Network as an option for secondary hormone therapy at the time of progression/recurrence in metastatic hormone-resistant prostate cancer. Early interim analysis of the ENZAMET trial showed that there was significant improvement in overall survival, clinical progression-free survival, and prostate-specific antigen progression-free survival with the addition of enzalutamide in metastatic hormone-sensitive prostate cancer. These findings support the hypothesis of clinical benefit to incorporate enzalutamide earlier in therapy when the disease is still hormone sensitive.

Among patients who received enzalutamide without docetaxel, 83% were alive, compared with 70% taking another nonsteroidal antiandrogen. At the time of the first analysis of the data, 64% of men were still taking enzalutamide, compared with 36% of men taking another nonsteroidal antiandrogen. Serious adverse events occurred in 42% of men taking enzalutamide compared with 34% of the men taking one of the other nonsteroidal antiandrogens.

Dr. Sweeney noted that a survival benefit is not seen with docetaxel in men with a low volume of disease, but that enzalutamide does improve survival in these men.

Next Steps

The results from this trial are being compiled with results from similar trials so that researchers have a data set that includes over 10,000 men. With that large data set at hand, researchers hope to be able to make extensive comparisons between medicines and determine which might benefit specific groups of men the most, according to Dr. Sweeney. ●

Reference

Sweeney, C., Martin, A. J., Zielinski, R. R., Thomson, A., Tan, T. H., Sandhu, S. K.,...Davis, I. D. (2019). Overall survival results of a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer: ENZAMET (ANZUP 1304), an ANZUP-led international cooperative group trial [Abstract LBA2]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 37(18_suppl). https://doi.org/10.1200/JCO.2019.37.18_suppl.LBA2

Enzalutamide does come with a potential for increased toxicities. Seven seizures (1%) were reported in the treatment group vs. no seizures in the standard-of-care arm. Although the relative risk is minimal, it is important to consider the impact of a seizure event on the patient's quality of life in discussing treatment options as a part of the shared decision-making process. Therefore, if your patient has a history of seizures, enzalutamide may not be the best choice based on its toxicity profile. The concurrent administration of enzalutamide with early docetaxel also proved to be more toxic. There were increased rates of peripheral neuropathy and, notably, without overall survival benefit seen in this subgroup.

ENZAMET indicated that patients with both low- and high-volume disease (as previously outlined by the CHAARTED trial) received overall survival benefit. Enzalutamide is likely to become another treatment option in metastatic

hormone-sensitive prostate cancer, but further follow-up is necessary to determine which subgroup of patients would most likely benefit.

Disclosure: Ms. Glass has no conflicts of interest to disclose.

Abstract 5006

Apalutamide Improves Survival Outcomes in Castration-Sensitive Metastatic Prostate Cancer in TITAN Trial

By *The ASCO Post*

Visit <https://meetinglibrary.asco.org/record/172902/abstract> to read the full abstract and view disclosures.

Adding apalutamide to ADT significantly improved survival in men with metastatic castration-sensitive (also termed hormone-sensitive) prostate cancer, according to the results of the phase III TITAN trial, which were presented at the 2019 ASCO Annual Meeting and simultaneously published in *The New England Journal of Medicine* (Chi et al., 2019a, 2019b). Treatment with apalutamide was tolerable and comparable to other next-generation nonsteroidal antiandrogens.

For the dual primary endpoints of radiographic progression-free survival and overall survival, apalutamide significantly reduced the risk of progression by 52% and reduced the risk of death by 33% compared with placebo.

The TITAN trial joins the ENZAMET trial, another phase III study presented at the ASCO meeting, in demonstrating the benefits of earlier, more aggressive treatment with apalutamide or enzalutamide, respectively, when prostate cancer is still hormone-sensitive (Sweeney et al., 2019). Previous phase III trials have also shown longer survival with both abiraterone acetate plus prednisone and with docetaxel in metastatic hormone-sensitive prostate cancer, particularly patients with high-volume or high-risk disease, so clinicians now have expanded options for treatment beyond ADT.

“These results support the addition of apalutamide to ADT for a broad range of patients with metastatic castration-sensitive prostate cancer, such as those included in the TITAN study (pa-

tients with high-volume and low-volume disease, who had prior docetaxel treatment, who had metastatic disease at diagnosis or relapsed metastatic disease, and who had received prior treatment for localized disease),” said lead author Kim N. Chi, MD, of the BC Cancer Agency, Vancouver, Canada.

Dr. Chi presented the final analysis of radiographic progression-free survival and the first planned interim analysis of overall survival. Based on these results, the study’s independent review committee recommended unblinding and allowing patients receiving placebo to cross over to apalutamide.

Study Details

The TITAN trial was designed to evaluate the addition of the androgen receptor inhibitor apalutamide vs placebo in a broad population of men with metastatic castration-sensitive prostate cancer regardless of disease burden who were treated with continuous ADT. The hypothesis was that more complete suppression of androgen signaling would improve outcomes.

A total number of 1,052 patients with documented metastatic castration-sensitive prostate cancer were randomly assigned 1:1 to apalutamide at 240 mg/d orally (n = 525) or matched placebo (n = 527) in 28-day cycles. Patients were stratified by Gleason score, geographic region, and prior treatment with docetaxel.

The median age of study patients was 68 years. A total of 16.4% had prostatectomy or radiation therapy for localized disease; 10.7% received previous docetaxel; 62.7% had high-volume disease, and 37.3% had low-volume disease. At a median follow-up of 22 months, 66% of patients in the apalutamide group and 46% of those on placebo were still on treatment.

Improvement in Survival Outcomes

Apalutamide reduced the risk of radiographic disease progression by 52% compared with pla-

cebo. The rate of 2-year radiographic progression-free survival was 68% for the apalutamide-treated group vs 48% for the placebo group—an absolute difference of 20% ($P < .0001$). Apalutamide reduced the risk of death by 33%. The 2-year overall survival was 82% in the apalutamide arm vs 74% in the placebo arm ($P = .005$). For both the radiographic progression-free survival and the overall survival analyses, the benefits of apalutamide over placebo were evident across all subgroups.

For the exploratory endpoint of second progression-free survival (defined as the time from randomization to disease progression on the next subsequent treatment), apalutamide reduced the risk by 34% compared with placebo ($P = .0026$). The 2-year rate of second progression-free survival was 75% with apalutamide and 36% with placebo. “This further supports the earlier use of apalutamide,” Dr. Chi told listeners.

Toxicity

The occurrence of side effects was not substantially different between the two treatment arms. Grade 3 or 4 adverse events were reported in 42.2% of the apalutamide group and 40.8% of the placebo group. Rash was more common in patients treated with apalutamide (27%, mostly grades 1 and 2).

However, there were numerically more treatment discontinuations with apalutamide: 8% vs 5.3%, respectively. “The difference in treatment discontinuation for adverse events between the arms was mostly due to rash in 2% of patients,” Dr. Chi explained. “Health-related quality of life according to the FACT-P (Functional Assessment

of Cancer Therapy–Prostate) subscale was preserved on both arms,” he added.

Additional Commentary

Formal study discussant Michael Carducci, MD, of the Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, questioned the survival benefit of apalutamide across all subgroups, including those with visceral disease and low-volume disease. “We need to put these data together with other study data to decide who should get what drug. There is a clear benefit in overall survival with apalutamide in patients with high-volume disease, but there may be subpopulations that may not derive benefit,” Dr. Carducci indicated.

“This disease state of metastatic hormone-sensitive prostate cancer is broadly heterogeneous. The treatment benefit is not consistent in all subsets, and we need to do a better job with molecular taxonomy and we need better predictors for which drug to use in which patient,” Dr. Carducci stated. ●

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The Advanced Practitioner Perspective

Jennifer L. Glass, PA-C, MS, Mayo Clinic

There have been several recent trials that have questioned whether androgen deprivation therapy (ADT) alone as standard of care therapy may not be sufficient in the early treatment of metastatic castration-sensitive prostate cancer (mCSPC). Based upon the clinically significant improvement in overall survival and radiographic progression-free survival seen in the TITAN trial, the manufacturer of apalutamide requested FDA approval for the indication of use in the treatment of

metastatic castration-sensitive prostate cancer in April 2019.

The overall tolerability of apalutamide was confirmed as all of the patients included in this trial had a good performance status (ECOG 0/1), and there was not a significant difference in health-related quality of life between the treatment arms. The overall toxicity profile of apalutamide was also similar to that of the placebo arm. However, the most common grade 3 or greater toxicity was a 6.3% incidence of treatment-related rash in the apalutamide arm compared to 0.6% with placebo. The rash was

most commonly treated with topical corticosteroids, oral antihistamines, dose reduction, or treatment break.

Apalutamide is likely to become another treatment option for patients with metastatic castration-sensitive prostate cancer. However, as echoed in the ENZAMET trial, fur-

ther research will need to be performed to determine which subgroups of mCSPC will benefit most from ADT plus another agent such as docetaxel, enzalutamide, abiraterone, or apalutamide.

Disclosure: Ms. Glass has no conflicts of interest to disclose.

Abstracts 5046 and 5049

Two Studies Question the Role of Continuous LHRH Antagonists in Metastatic Castration-Resistant Prostate Cancer

By The ASCO Post

Visit <https://meetinglibrary.asco.org/record/175867/abstract> and <https://meetinglibrary.asco.org/record/175722/abstract> to read the full abstracts and view disclosures.

In the field of prostate cancer, the use of androgen-deprivation therapy (ADT) in men with metastatic castration-resistant prostate cancer is received wisdom. When experts are asked why ADT is continued once the disease has figured out how to evade hormone suppression, the answer invariably is based on an older meta-analysis, and all the trials of newer agents in metastatic castration-resistant prostate cancer have been conducted with patients on a background ADT in the form of a luteinizing hormone-releasing hormone (LHRH) antagonist. Thus, men with this type of cancer are currently consigned to life-long ADT if they are treated according to the standard of care.

However, two new (albeit small) studies presented at the 2019 ASCO Annual Meeting challenge this assumption (Jha & Engle, 2019; Ohlmann et al., 2019). In both studies, men with metastatic castration-resistant prostate cancer on more potent suppression with abiraterone acetate plus prednisone were studied without the background LHRH antagonists. Taken together, both studies suggest that withholding ADT (in these studies, LHRH antagonists) in this setting does not compromise outcomes. Further, experts interviewed for this article agree that this approach should be studied with the newer hormonal

agents, such as enzalutamide, apalutamide, and darolutamide, not just with abiraterone acetate.

Prospective Study

The first study was a prospective, exploratory phase II trial that enrolled 67 patients with asymptomatic or mildly symptomatic treatment-naïve metastatic castration-resistant prostate cancer (Ohlmann et al., 2019). These patients were randomly assigned 1:1 to receive abiraterone acetate and prednisone plus ADT with luteinizing hormone-releasing hormone (LHRH) therapy vs abiraterone acetate plus prednisone with no ADT.

“Abiraterone acetate is a more potent suppressor of testosterone than ADT. We have had several patients who did not want to continue ADT while on abiraterone, and we found that abiraterone acetate plus prednisone was equally effective. Unfortunately, the labeling requires us to continue ADT,” said lead author Carsten H. Ohlmann, MD, of Malteser Hospital, Bonn/Rhein-Sieg, Germany. “We wanted to explore whether you could stop ADT without compromising outcomes. And to my mind, our study challenges the practice of using continuous ADT. It is a small trial not powered for the endpoints, but we have seen no difference in efficacy between the two treatment arms.”

At a median follow-up of 14.9 months, decline in prostate-specific antigen (PSA) level of 50% or more was achieved in 23 of 34 patients (67%) on the ADT-continuing arm vs 24 of 33 patients (72.7%) on the experimental arm. The median serum testosterone level at the end of treatment was exactly the same on both arms: 0.029 ng/mL. The median treatment duration was 266 days on the ADT-continuing arm vs 420 days on the experimental arm. The time to PSA progression was numerically longer on the experimental arm: median of 288 days vs 336 days, respectively. At month 12, the rate of radiographic progression-free survival

did not significantly differ between the arms: 0.90 in the ADT-containing arm vs 0.78 in the experimental arm.

Almost all patients had at least one adverse event. Adverse events did not significantly differ between the two treatment arms.

“The main advantages of withholding ADT include less treatment, lower cost, and the ability to control the effects of abiraterone plus prednisone better,” Dr. Ohlmann explained.

“Expected survival in this group of patients is 30 to 36 months. We will follow these patients to determine their outcomes. We are also thinking about studying this approach with enzalutamide, apalutamide, and darolutamide,” he added.

Retrospective Review

“Most studies of newer agents, including abiraterone acetate, have been done with ADT. The thinking is that as testosterone levels rise, they promote the growth of prostate cancer, so the goal is suppression of testosterone. Abiraterone acetate plus prednisone blocks the synthesis of testosterone, so there is no reason to give ADT along with this treatment,” proposed lead author of the second study, Gautam Jha, MD, of the University of Minnesota.

“In the 5 to 7 years I have been practicing medicine, I have seen only one treatment failure on abiraterone acetate alone. I am defining treatment failure as a rise in testosterone level above 30 ng/mL,” he said.

Abiraterone acetate and prednisone plus ADT is standard therapy. “In the past several years, I have stopped ADT in patients on abiraterone and followed testosterone levels. Abiraterone alone lowers testosterone to castrate levels,” he continued.

In the retrospective study, testosterone levels were followed in 57 consecutive patients treated at Dr. Jha’s institution with either abiraterone acetate, prednisone, and ADT or abiraterone plus prednisone with no ADT (Jha & Engle, 2019). Of

these patients, 36 received abiraterone acetate plus ADT; 10 received abiraterone acetate without ADT; and 11 started treatment with abiraterone acetate plus ADT but transitioned to ADT alone. Testosterone levels were drawn every 3 months. The mean duration of therapy with abiraterone acetate was 1 year.

“In the overwhelming majority of patients in both arms (88% and 87%, respectively), the testosterone level was undetectable (ie, < 2 ng/dL),” Dr. Jha said. Only one patient had a detectable testosterone level of more than 30 ng/dL, and that patient was in the arm that received abiraterone acetate alone.

The investigators performed a cost analysis of this study by determining the dollar amount in savings if leuprolide injections were avoided while patients were treated with abiraterone acetate. The sobering finding was that for a total duration of therapy of approximately 61 patient-years, withholding ADT eliminated 244 leuprolide administrations and led to a cost savings of approximately \$1.29 million.

“In fact, withholding ADT would translate to an avoidable expense of \$55.5 million for 960 patients in the STAMPEDE trial and \$34.5 million in the LATITUDE study in the combination therapy arm,” Dr. Jha stated. “By conservative estimates, holding leuprolide during abiraterone therapy could save as much as \$332 million annually.” ●

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The Advanced Practitioner Perspective **Jennifer L. Glass, PA-C, MS, Mayo Clinic**

Two small trials (prospective and retrospective) recently disputed the current rationale of combined androgen blockade for metastatic castration-resistant prostate cancer. They evaluated whether luteinizing hormone-releasing hormone (LHRH) therapy could be successfully removed from this treatment regimen in the setting of the novel androgen synthesis inhibitor, abiraterone.

The SPARE phase II prospective randomized trial did not show a difference in radiographic progression-free survival between the treatment arms. However, no statistically significant conclusions can be made based upon those results ($p = .4368$). It is also important to recognize that Dr. Jha's retrospective analysis (Abstract 5049) is based upon single-institution, nonrandomized data and should be in-

terpreted cautiously. If future studies confirm the basic premise of these study hypotheses, it could have dramatic health-care cost savings. It would also be interesting to assess whether the potential cost reduction translated to improved quality-of-life measures for patients. As abiraterone + ADT have already been proven beneficial in castration-sensitive prostate cancer per the LATITUDE and STAMPEDE trials, these results also bring the question of whether it could be possible to omit LHRH therapy earlier in this population as well. Before these results can become practice changing, there will need to be larger randomized controlled studies performed in order to ensure that abiraterone alone is as safe and efficacious as abiraterone + ADT in the treatment of metastatic castration-resistant prostate cancer.

Disclosure: Ms. Glass has no conflicts of interest to disclose.