

CLINICAL UPDATE

Current Developments in the Management of Prostate Cancer

Combination Therapy With Radium-223 and Enzalutamide in Castration-Resistant Prostate Cancer



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H&O What question was your recent study in *The Oncologist* designed to answer?

BLM We recently published the final results of our phase 2 study, which was designed to identify any signal of efficacy for the combination of radium-223 (Xofigo, Bayer) and enzalutamide (Xtandi, Astellas) vs enzalutamide alone in men with metastatic castration-resistant prostate cancer (mCRPC).

Over the past 10 or so years, effort has been increasing to find new drug combinations that are more effective—either additively or synergistically—than single-drug sequential therapy, which was the standard approach for many years. The development of combination therapy started in the hormone-sensitive setting—that is, as first-line treatment for patients with metastatic prostate cancer. Trials included GETUG-AFU 15, STAMPEDE, and CHAARTED.

Now we are starting to explore drug combinations in later lines of therapy—that is, when disease is castration-resistant. We undertook our trial to see if we could identify a combination that was particularly effective.

H&O Can you describe the design of the trial?

BLM First, a small group of 8 patients received radium-223 plus enzalutamide as part of a safety cohort. Such a safety cohort would not be necessary today because many studies have looked at combinations of abiraterone or enzalutamide plus radium-223, but this was a novel approach when we first designed our trial. After the safety evaluation period, 39 additional patients were randomly assigned in a 2:1 ratio to radium-223 plus enzalutamide (n=23) or enzalutamide alone (n=12). Patients received

up to 6 cycles of radium-223 so long as they were tolerating and benefiting from the treatment. Enzalutamide was also administered so long as patients continued to benefit. The primary endpoints were efficacy, which was based on a decline in the bone metabolism marker serum N-telopeptide and the number of adverse events. The secondary endpoints were prostate-specific antigen progression-free survival (PSA-PFS), radiographic PFS, time to next subsequent therapy, overall survival (OS), and PSA-PFS2. PSA-PFS2 is an emerging endpoint in which we look at the time from the start of protocol therapy to PSA progression during subsequent therapy.

H&O Why was serum N-telopeptide selected as a primary endpoint?

BLM Because radium-223 targets the bone, we thought it made sense biologically to pick a bone marker as the pharmacodynamic response endpoint. The men in this study had to meet all the standard US Food and Drug Administration (FDA) criteria for receiving radium-223 therapy, meaning that they had to have bone metastases but not have visceral metastases. This population is difficult to study because we do not have any markers of response to radium-223 in routine use in clinical practice. The use of response evaluation criteria in solid tumors (RECIST) is not possible because the metastases are not in soft tissue, where they could potentially regress. Bone metastases never regress; they are either present or absent, and once they are present, they remain present. Furthermore, radium-223 rarely leads to a decline in PSA. Conversely, alkaline phosphatase nearly always declines with radium-223. Therefore, we chose serum N-telopeptide as a marker of pharmacodynamic response.

The SWOG 0421 trial, which looked at the experimental endothelin A receptor antagonist atrasentan plus docetaxel or docetaxel alone, found that serum bone metabolism markers have statistically significant independent prognostic value in CRPC. These bone metabolism markers included markers for bone resorption (N-telopeptide and pyridinoline) and markers for bone formation (C-terminal collagen propeptide and bone alkaline phosphatase). Additional, smaller studies have also found serum bone metabolism markers to be of prognostic value. We chose N-telopeptide because it is associated with the breakdown of bone and because it is the best-developed and best-established of the serum bone metabolism markers.

H&O What are the results of your trial, including the secondary endpoint results that you recently published?

BLM In the initial publication, of which Dr Neeraj Agarwal was the first author, we concluded that the combination of radium-223 and enzalutamide was safe and feasible after 6 months of follow-up. We saw a significantly greater reduction of N-telopeptide levels in the combination arm than in the enzalutamide-alone arm, suggesting a good response in the bones. We also saw a better PSA response rate in the combination group than in the enzalutamide arm. This response correlated with the decline in N-telopeptide levels.

In the more recent publication, which had a median follow-up of 22 months, we saw a significant improvement in PSA-PFS2 in the combination arm vs the enzalutamide-only arm. Numerical improvements in PSA-PFS, radiographic PFS, time to next subsequent therapy, and OS were seen with the combination vs single-agent therapy, but none of the differences were statistically significant.

H&O Can you explain why you did not see a statistically significant increase in OS with radium-223?

BLM It would be very difficult to identify an improvement in OS with such a small number of patients unless the difference was incredibly profound. The fact that we saw a trend toward benefit for OS in all other secondary endpoints with combination therapy suggests that a true benefit may exist, but a larger, subsequent trial will be required to prove this. We hope to get the answers we need from PEACE III, which is an ongoing phase 3 randomized trial that is looking at the combination of radium-223 and enzalutamide. This is the type of confirmatory trial that we need to fully understand the results

of our small phase 2 trial.

The other notable study that looked at radium-223 plus novel hormonal therapy was ERA 223, which was published by Smith and colleagues in 2019. This study did not show any improvement with radium-223 plus abiraterone vs abiraterone alone. It is important to remember, however, that even though abiraterone and enzalutamide are similar agents that are grouped together as novel hormonal therapies, they have different adverse effect profiles, the potential to cause the development of different types of resistance mechanisms, and different efficacy rates. Therefore, the fact that ERA 223 did not show a benefit with radium-223 plus abiraterone does not inherently mean that radium-223 plus enzalutamide will also be ineffective.

Our results are encouraging, which is why we are so eager to see the results of PEACE III.

H&O Could you discuss the risk for fracture seen with radium-223?

BLM One of the important results of ERA 223 was that it helped oncologists awaken to the idea of bone fractures as a substantial problem for men with metastatic prostate cancer. The fracture rate in ERA 223 was high in the monotherapy arm, and even higher in the combination treatment arm. The reason is that androgen deprivation therapy increases the risk for fractures, and radium-223 further increases that risk. Now that treatments are getting better and patients are living longer, the risk for fractures is increasingly important.

We have already seen some safety data from the PEACE III trial that echo the findings from ERA 223. In results that Dr Silke Gillessen presented at the 2021 American Society of Clinical Oncology Annual Meeting, the bone fracture rates at 12 and 18 months among men who did not receive a bone-protecting agent were very high in the combination arm (37% and 46%, respectively); they were also high in the enzalutamide arm (16% and 22%, respectively). Among the men who received a bone-protecting agent, however, the rates were just 3% in the combination arm and 4% in the enzalutamide arm at 12 and 18 months, respectively. This study looked only at

osteoporotic fractures that were not related to the growth of prostate cancer in the location of the fracture. The difference with bone-protecting agents was so striking that the use of these agents became mandatory within the trial for patients without a specific contraindication, and that changed the practice across the field.

Nearly all the patients in our study were on bone-protective therapy; just one patient in each arm had a contraindication. As a result, we saw very few fractures in our trial. These findings highlight the need to take care of our patients' overall health, including bone health.

H&O Would you say that your study has changed anything regarding the use of radium-223 with enzalutamide?

BLM I would caution physicians against the use of radium-223 with enzalutamide outside clinical trials at this point, especially given the increase in toxicity with no increase in efficacy seen with radium-223 plus abiraterone in ERA 223. I think that our results are encouraging, however, which is why we are so eager to see the results of PEACE III. We may well see a difference between the combination used in ERA 223 and the combination used in our study and in PEACE III.

H&O What other questions remain to be answered regarding radium-223 and prostate cancer?

BLM Several questions about how best to use radium-223 are ongoing. For instance, a lot of interest is being shown in exploring more potent, effective immunotherapy approaches for metastatic prostate cancer. One burning question is, Does the use of radium-223 as radiation treatment increase antigen expression and therefore synergize with checkpoint inhibitors? A phase 1b study by Fong and colleagues looked at radium-223 plus atezolizumab (Tecentriq, Genentech) in mCRPC. Unfortunately, this study found that the combination was more toxic than either drug alone, with no clear evidence of additional clinical benefit. A phase 2 trial from Dana-Farber Cancer Institute is looking at radium-223 plus pembrolizumab (Keytruda, Merck) as a possible treatment for mCRPC (NCT03093428). In addition, our institution is enrolling patients in Rad2Nivo, a phase 1/2 single-arm trial that is looking at radium-223 plus nivolumab (Opdivo, Bristol Myers Squibb) in men with mCRPC who have

metastases to bone only (NCT04109729).

Another unanswered question is whether the investigational radioligand therapy lutetium Lu 177 prostate-specific membrane antigen-617 (¹⁷⁷Lu-PSMA-617) might be sequenced with radium-223 because these radiopharmaceuticals have different targets. We expect ¹⁷⁷Lu-PSMA-617 to receive FDA approval soon, on the basis of results of the phase 3 VISION trial. After that happens, we may begin to see studies of radium-223 and ¹⁷⁷Lu-PSMA-617 in combination.

Disclosure

Dr Maughan has received financial compensation as a paid consultant/advisor to AVEO Oncology, Janssen, Astellas, Bristol Myers Squibb, Clovis Oncology, Tempus, Merck, Exelixis, Bayer Oncology, and Peloton Therapeutics. He has also received institutional research funding from Exelixis, Bavarian Nordic, Clovis Oncology, and Bristol Myers Squibb.

Suggested Readings

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