[News * Analysis * Commentary * Controversy]

March 25, 2012 * Vol. 34 * No. 6

oncology-times.com

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ONCOLOGY TIMES

The Independent Hem/Onc News Source

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ASCO: Make Palliative Care Standard for Metastatic NSCLC Patients, Starting at Diagnosis

BY LOLA BUTCHER

The Society's new "provisional clinical opinion" recommendation was triggered by research showing longer survival, improved quality of life, and other measurable positive results compared with patients receiving only standard care. And although the PCO is specifically for NSCLC, the document states that concurrent palliative care should be considered for other patients as well.

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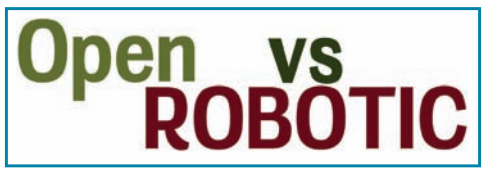
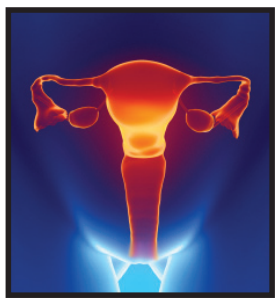


Complications No Less with Robotic vs Open Prostatectomy p.12



Thomas Herzog, MD, Picks the Year's Best Ovarian Cancer Research p.15

Pro-Con: Maintenance Rituximab for Patients with Follicular Lymphoma p.36

[ALSO]

PERIODICALS

Castrate-Resistant Prostate Cancer: MDV3100 and Radium-223 Each Prolong Survival in Phase III Trials

Predictions of 'Major Survival Bump'

BY RABIYA S. TUMA, PHD

SAN FRANCISCO—Two novel agents—MDV3100 and radium-223 chloride—each prolonged overall survival in castrate-resistant prostate cancer (CRPC) patients who had previously had disease progression on docetaxel or were unfit for docetaxel, researchers reported here at the Genitourinary Cancer Symposium. Experts say they expect that new agents will have a substantial impact on patient care in the coming years.

"I think these drugs are both going to be used in sequence in patients; in a simple additive way we would expect the survivals to be fairly dramatically pushed forward," said Nicholas J. Vogelzang, MD, Chair and Medical Director of the Developmental Therapeutics Committee of US Oncology, who moderated a conference call about the findings just before the meeting and who was an investigator on the radium-223 trial (***Abstract 9***).

"It is impossible to know [how big a benefit we will see] because neither of these drugs have yet been given in sequence. Understanding that the mechanisms [of action] are quite different suggests to me that there will be a major bump up in the overall survival in this patient population within the next two to three years."

That view was reiterated by Howard Scher, MD, Chief of the Genitourinary Oncology Service and the D. Wayne Calloway Chair in Urologic Oncology at Memorial Sloan-Kettering Cancer Center, who led the MDV3100 trial (***Abstract LBA1***). "The important thing here is that both drugs are mechanistically different, both drugs have very favorable safety profiles, and both drugs have shown a survival benefit," he said.

"The ALSYMPCA trial [of radium-223 chloride] essentially focused on patients with pain, showing a reduction in one of the most feared complications of the disease, which is the morbidity from bone metastases. Seeing these effects and the effects on survival with drugs that seem like they can be given in sequence or even together, I think they will clearly benefit patients going forward."

When Howard Scher completed his presentation of the data during the news conference call, Nicholas Vogelzang, the moderator, said, "I have only one comment: Wow.... An 18.4-month median survival with 25% of patients having a 90% decline in PSA—that is unprecedented. This is going to definitely change how we take care of patients every day in the office."

MDV3100 Prolongs Survival by 5 Months

To test the value of MDV3100, an oral drug that binds to the androgen receptor and blocks its entry into the cancer cell nuclei, researchers enrolled 1,199 patients with castrate-resistant prostate cancer that had progressed on docetaxel on a randomized placebo-controlled trial. At a planned interim analysis, the median overall survival for the 800 patients in the MDV3100 arm was 18.4 months compared with 13.6 months for the 399 patients in the placebo arm. The hazard ratio was 0.631, which was statistically significant.

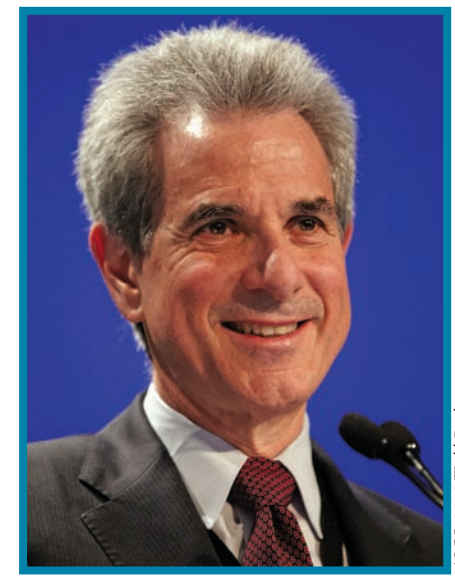
Patients in the MDV3100 arm also had a greater response in terms of PSA level and CT or MRI imaging. Specifically 54.0% of patients on MDV3100 had a 50% or greater decline in PSA and 24.8% had a 90% or greater decline, compared with 1.5% and 0.9% of patients in the control arm, respectively. The median time to confirmed PSA progression was also significantly longer in the patients treated with MDV3100 at 8.3 months compared with those on placebo at 3.0 months.

In the MDV3100 arm, 28.9% of patients showed a radiographic response compared with 3.8% of patients in the placebo arm, and the duration of radiographic progression-free survival was longer in the active drug arm compared with the control (8.3 months versus 2.9 months).

The overall rate for any-grade adverse events was similar in the two arms (98.1% in the MDV3100 arm and 97.7% in the placebo arm), as were the rates for Grade 3 or higher side effects (45.3% and 53.1%), and Grade 3 or higher serious adverse events (28.4% and 33.6%).

The rates of discontinuations due to adverse events (4.6% versus 7.0%) and adverse events leading to death (2.9% versus 3.5%) were numerically lower in the active drug arm. Scher noted that none of these differences reached statistical significance, however.

In terms of specific adverse events, the data presented were limited. However, the authors said in an accompanying news release that the most common adverse events, occurring in more than 2% of patients on MDV3100, were fatigue, diarrhea, and hot flushes. Most adverse events did not require dose reductions. In response to a specific question, Scher noted that there were five patients (0.6%) in the MDV3100 arm who had seizures, but there were no reports of seizures in the control arm.



ASCO 2012/Todd Buchanan

HOWARD SCHER, MD: "The important thing here is that both drugs are mechanistically different, both drugs have very favorable safety profiles, and both have shown a survival benefit.

When Scher completed his presentation of the data during the news briefing call, Vogelzang said, "I have only one comment: Wow."

"That is very impressive," he continued. "An 18.4-month median survival with 25% of patients having a 90% decline in PSA—that is unprecedented. This is going to definitely change how we take care of patients every day in the office."

Radium-223 Reduces Skeletal Related Events

Researchers had reported at the European Society for Medical Oncology meeting in September that advanced castrate-resistant prostate cancer patients who had disease progression on docetaxel or were unfit for docetaxel had prolonged overall survival with radium-223 (Ra-223) treatment compared with placebo, with a median survival of 14.0 months versus 11.2 months. The

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Meeting Co-Sponsors

The symposium is co-sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Urologic Oncology.

→MDV3100, RADIUM 223

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hazard ratio was 0.695, which was statistically significant.

Moreover, they reported that the time to first reported skeletal event was prolonged in patients treated with the drug compared with placebo (13.6 months vs. 8.4 months).

In the new data reported at the GU Cancers Symposium, the team provided details on the skeletal-related events in the randomized phase III trial. The rate of pathologic bone fracture was reduced in the 541 patients who received radium-223 compared with the 268 patients who received placebo (3.6% vs. 6.7%) and the time to the event was prolonged, with a statistically significant hazard ratio of 0.45.

Similarly, the rate of spinal cord compression was nearly halved with the active drug (3.1% vs. 6.0%), with a hazard ratio of 0.44.

Given the promising data from both trials, questions immediately arise about how best to use the new agents in a clinic setting. Although everyone was clear to point out that there are no data on sequencing or combining MDV3100 and radium-223, the investigators emphasized that the distinct mechanisms of action may lead to combinations.

The use of external-beam radiation was also lower at 22.6% in the radium-223 arm compared with 26.9% in the control arm (hazard ratio 0.65). There was no statistically significant difference in the rate of surgical intervention between the two arms, however: The rate was low in both arms and numerically favored the experimental agent (1.7% vs. 1.9%, hazard ratio 0.8).

The drug was well tolerated, said A. Oliver Sartor, MD, the Laborde Professor of Cancer Research at Tulane University School of Medicine and Medical Director of the Tulane Cancer Center, who presented the new analyses.

Perhaps most important, the investigators did not see any cases of leukemia or secondary malignancies associated with the use of the radiological agent. However, the drug, which concentrates in the marrow near bone metastases, was associated with an increase in Grade 3 or 4 hematologic adverse events, including 2% neutropenia and 4% thrombocytopenia, compared with 1% and 2% in the placebo arm, respectively.

The rate of high-grade anemia was similar in the two arms, at 11% in the experimental arm and 12% in the control arm. In terms of non-hematologic adverse events, the only difference in rates was seen in bone pain, favoring the radium-223 arm compared with the control arm (18% vs. 23%).

"We believe this novel alpha-pharmaceutical—the very first one to be tested in phase III in all of medicine—may provide a new standard of care for the treatment of patients with bone metastases and advanced prostate cancer," Sartor concluded.

Vogelzang noted that as a coauthor on the trial he is not entirely unbiased, but he lauded the outcomes nonetheless. "The data speak for themselves, both in terms of survival and in terms of patient benefit," he said. "Hopefully this drug will soon be available in the United States and we will be able to deliver it, literally, to our patients this year."

Combination Trials Predicted

Given the promising data from both trials, questions immediately arise about how best to use them in a clinic setting. Although everyone was clear to point out that there are no data on sequencing or combining these two novel therapies, the investigators emphasized that the distinct mechanisms of action may lead to combinations.

To explain how radium-223 works, Sartor noted that bone metastases not only lead to a deposition of cancer cells, but also alter bone stroma, leading to an increase in osteoblastic reactions and increased concentration of calcium in the immediate area. "Radium-223 behaves like calcium and localizes to these areas of altered bone matrix adjacent to tumor," he said.

As an alpha emitter it destroys cells by causing double-strand breaks in the DNA, but only in a small area. "It irradiates the tumor and surrounding area, but only in a very local range of just two to 10 cell diameters. Within that range it is like a little bomb going off. But it doesn't affect the surrounding tissues much at all."

A. OLIVER SARTOR, MD: "We believe this novel alpha-pharmaceutical—the very first one to be tested in phase III in all of medicine—may provide a new standard of care for the treatment of patients with bone metastases and advanced prostate cancer," Dr. Sartor concluded.

By contrast, MDV3100 works on the androgen receptor signaling pathway and does not affect the marrow.

"These mechanistically distinct therapies will probably be combined, and their additive benefit—or potentially even synergistic benefit—is something that, I think, will have to be demonstrated in clinical trials," Sartor said. "But it is very plausible for us to hypothesize that combinations or sequences of these agents may add even more value than what we see here. So these are important steps forward. But I think we will have even more important steps forward in the future."

The MDV3100 trial was supported by Medivation, Inc., which makes the drug. Scher has served as a consultant or advisor to Medivation and has received research funding from the company. Several coauthors on the study are employees of the company.

The radium-223 study was supported by Algeta ASA, which makes the drug, and Bayer. Sartor has served as a consultant or advisor for Algeta. Vogelzang has served as an advisor for Bayer and received research funding from Algeta. Other coauthors on the study report a leadership or employee position with Algeta and honoraria from Bayer.

NIH Office of Medical Applications of Research Reorganizes

The Office of Medical Applications of Research (OMAR), home of the NIH Consensus Development Program, has combined resources, staff, and key activities with the Office of Disease Prevention (ODP).

The new structure is designed to strengthen ODP leadership and its potential to coordinate NIH disease prevention research, according to a statement from the NIH. The hope is that the move increases collaborations on high-priority issues that come through both offices, and allows more effective research, especially in disease-prevention.

The statement sites OMAR staff expertise in designing research and reporting findings, as well as their network of contacts to involve key stakeholders to work on priority topics, as the reasons this merger will best support improved research efforts.

Both OMAR's "Medicine in the Media" course and the "Medicine: Mind the Gap" seminar series will continue under the restructure. NIH Consensus Development Conferences will be held less frequently, but will focus on the most relevant public health topics, according to the office. The "State-of-the-Science" conferences, though, will be discontinued.