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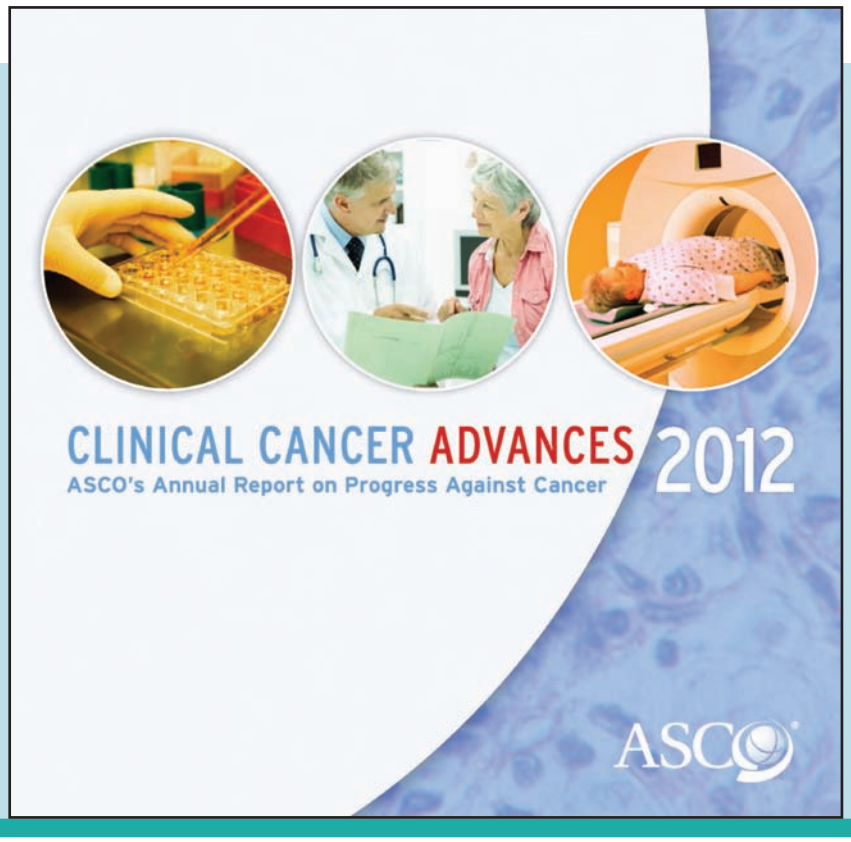

ASCO Year-End Report on Clinical Cancer Advances Stresses Precision Medicine

BY PEGGY EASTMAN

This 8th annual report on progress against cancer includes 17 major advances from clinical trials, many of which are targeted treatments based on data that show increased understanding of molecular biology. And, while the news is good, it comes at a time of grave concerns about funding for cancer research. *Page 10*

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Prostate Cancer: Focused Radiation Achieves Good Disease Control with Minimal Toxicity

BY CHARLENE LAINO

A Phase III study confirms that adding radiation to ADT significantly increased survival in men with local advanced prostate cancer.

BOSTON—In terms of prostate cancer, the American Society for Radiation Oncology Annual Meeting provided a great deal of encouraging news. For example:

- For patients with organ-confined cancer, focused stereotactic body radiotherapy (SBRT) achieved better disease control rates than would be expected with other forms of intensity-modulated radiation therapy (IMRT), according to the results of a large cohort study (*Abstract 365*).
- Additionally, SBRT was associated with minimal genitourinary toxicity and acute gastrointestinal toxicities, according to a second, Phase II study (*Abstract 366*).
- A Phase III study found that adding radiation to androgen-deprivation therapy (ADT) significantly increased survival in men with local advanced prostate cancer (*Abstract 8*).
- And the randomized Phase III Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial (*Abstract 7*) showed that the targeted alpha-emitter radium-223 significantly improved survival time in men with metastatic castration-resistant prostate cancer.

SBRT

"SBRT involves ultra-precise delivery of very high-dose radiation using converging, finely collimated beams," explained Alan J. Katz, MD, JD, a radiation oncologist at Flushing Radiation Oncology in New York City.

"It's a short five-day, non-invasive treatment that can be done on an outpatient basis with no need for a urinary catheter," he explained.

SMRT can be delivered using various modalities. Robotic surgery, which he uses, employs computer-guided robotic technology to deliver stereotactic radiotherapy—"the accuracy and conformity of which are ideal for a highly hypofractionated treatment," he said. Intrafraction tracking of fiducial seeds al-lows for corrections in all dimensions to achieve less than 1 mm accuracy."

ALAN J. KATZ, MD: "The bottom line is that patients now have the option of choosing a one-week course instead of the traditional eight or nine weeks."

There have been several small studies of SBRT in prostate cancer, so Katz and colleagues decided to pool the results to increase their power.

The pooled analysis involved 1,101 patients, 92 percent of whom had Stage T1-2a and eight percent of whom had Stage T2b-3 cancer. Low-, intermediate-, and high-risk patients comprised 59, 30, and 11 percent of the study population, respectively.

All received doses of 35 to 40 Gy in four to five fractions, as opposed to 40 to 45 Gy, which is standard, Katz said, noting that the dose given was equivalent to a range of 90 to 112 Gy in conventional fractionation.

The median follow-up was 36 months, and 465 patients have been followed for at least four years. The actuarial five-year biochemical relapse-free survival rates—the primary endpoint—were 95, 90, and 80 percent in the low-, intermediate-, and high-risk groups, respectively. "We used the Phoenix definition: If PSA drops to nadir and does not go two points above that, it's a success; and if goes up two or more points, it's biochemical failure," Katz said.

When the patients were divided into groups depending on the dose received—35 Gy or less vs. 36 to 37 Gy vs. 38 to 40 Gy—"the low dose seemed to work just as well as the high dose. While not part of the study, there definitely was less toxicity with the lower dose."

Androgen-deprivation therapy was given to 146 patients (14%). "Use of ADT made no difference in terms of outcomes," said Katz, who received an honoraria from Accuray, the manufacturer of the CyberKnife Robotic Radiosurgery System.

"These results are superior to those of standard IMRT treatment of 40 to 45 days in terms of control. Our hypothesis was that prostate cancer has greater sensitivity to dose per fraction and that fewer high doses would give better results. And the data seem to support that.

"Very importantly, this approach results in huge savings in time for the patient and in costs for the payer. Focused stereotactic body radiotherapy is about half the price of other forms of IMRT."

Minimal Toxicity

In another study, Robert M. Meier, MD, a radiation oncologist at the Swedish Cancer Institute, said his group hypothesized that use of SBRT would minimize side effects since it minimizes radiation to the rectum, bladder, urethra, and nerves.

The Phase II, prospective study involved 129 patients with intermediate-risk, organ-confined disease cancer who were treated with SBRT and followed for a median of 36 months.

ROBERT M. MEIER: "SBRT would minimize side effects since it minimizes radiation to the rectum, bladder, urethra, and nerves."

There were no reports of Grade 4 or 5 toxicity. Thirty patients (23%) had acute Grade 2 GU toxicity and 11 (8.5%) had acute GI toxicity. Late Grade 2 GU and GI toxicities occurred in 14 patients (11%) and three patients (2%), respectively. One patient had a Grade 3 bladder neck injury one year after treatment.

Quality of life was also assessed, using the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire for urinary, bowel, and sexual function. Scores showed that patients' urinary and bowel functions dropped one month after treatment, but returned to normal by 24 months. One patient required temporary catheter placement for acute urinary retention.

"These results appear favorable compared with other radiotherapy modalities," Meier reported. There was an initial drop in sexual quality-of-life, which then continued to decline slowly over the three-year study period—a pattern typical of radiotherapy modalities, he said.

At baseline, 52 percent of patients were potent, defined as having erections firm enough for intercourse; by 24 months, this declined to 36 percent.

Patients were treated for one week with the CyberKnife, and MRI was used to guide target localization. Patients received SBRT at 40 Gy in five fractions of 8 Gy to the prostate, and 36.25 Gy was delivered to the seminal vesicles. No patient received androgen-deprivation therapy.

Since all the patients were treated with the CyberKnife, it's not known whether the results can be applied to other SBRT platforms, he said.

Longer Follow-up Needed

ASTRO 2012-2013 President Colleen A. Lawton, MD, Professor and Vice-Chair of

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the Department of Radiation Oncology at the Medical College of Wisconsin Clinical Cancer Center, moderated a news briefing to discuss the findings, calling the approach "cutting-edge, and clearly cost saving."

"The results are impressive, but the follow-up periods [in both studies] were relatively short to be drawing conclusions about disease control or toxicity," she said. "The devil is in the details. We have to make sure we deposit the dose where it needs to be deposited and avoid healthy tissue."

Katz said he agreed about the additional follow-up, but still, "any significant toxicity is [going to be seen] within two years and certainly by three years." The bottom line, he said, is that patients now have the option of choosing a one-week course of treatment instead of the traditional eight or nine weeks.

RT + ADT

In the third study, a one-two punch with radiation and androgen-deprivation therapy significantly increased overall survival by 30 percent and significantly reduced the risk of dying from the disease by 54 percent compared with use of ADT alone, said senior author Padraig Warde, MBChB, Head of Radiation Oncology at the University of Toronto's Princess Margaret Hospital.

The study involved 1,205 men with locally advanced or organ-confined disease randomized to receive lifelong ADT with bilateral orchiectomy or a luteinizing hormone-releasing hormone agonist, with or without radiation. The radiation was given as 65 to 69 Gy to the prostate (plus the seminal vesicles if needed), with or without 45 Gy to the pelvic nodes. The median follow-up time was eight years.

ASTRO/Todd Buchanan

PADRAIG WARDE, MBCHB, said he hopes the results of the study he reported will persuade oncologists and urologists to stop using ADT alone in patients with locally advanced disease. In the U.S., he noted, up to 45 percent, of these men are still given ADT alone.

The addition of radiation had only a small detrimental effect on late gastrointestinal toxicity, he reported: 1.0 percent of patients had Grade II or higher proctitis vs. 0.3 percent on ADT alone.

Warde said he hopes the results will persuade oncologists and urologists to give radiation plus ADT to patients with locally advanced disease. In the U.S., a "huge" percentage—up to 45 percent—of these men are still given ADT alone, he said.

But not all men with locally advanced disease are candidates for radiation, he cautioned. For example, in older men with a life expectancy of less than five or 10 years and significant overall comorbidities, the risks may outweigh the benefits.

The interim results of the study were presented by Warde at the 2010 ASCO Annual Meeting (***OT, 8/10/10***).

Radium-223

In the randomized, placebo-controlled ALSYMPCA trial, radium-223 did more than improve survival times: The time to a first skeletal-related event (SRE) increased significantly, and there was a significant delay in the time to the first use of radiation to treat bone pain in the radium-223 group, reported Howard M. Sandler, MD, Chair of Radiation Oncology at Cedars-Sinai Medical Center.

The median overall survival time increased by 30 percent in men who received radium-223: 14.0 vs. 11.2 months for those given placebo; and the delay to a first SRE was a median of 13.5 months in the treatment group vs. 8.4 months in the placebo group, corresponding to a significant 39 percent reduction.

The time to first use of external-beam radiation therapy was 17.0 months and 10.9 months in the radium-223 and placebo groups, respectively. This represents a significant 35 percent reduction in the treatment arm, he noted.

The study involved 901 patients with confirmed castrate-resistant prostate cancer and two or more bone metastases randomized to receive six

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Renal Cell Cancer: Tolerability of Pazopanib vs. Sunitinib in First-Line Treatment a Plus

BY CHARLENE LAINO

VIENNA—The results of a head-to-head randomized, open-label Phase III trial of pazopanib vs. sunitinib showed that pazopanib was non-inferior to sunitinib in terms of efficacy in first-line advanced renal cell carcinoma (RCC).

Pazopanib may be better tolerated, however, reported the study's principal investigator, Robert J. Motzer, MD, a medical oncologist at Memorial Sloan-Kettering Cancer Center, in reporting the results here at the European Society for Medical Oncology Congress.

The median progression-free survival time in the study (*Abstract LBA8)*, which was funded by GlaxoSmithKline, was 9.5 months for the patients receiving sunitinib compared with 8.4 months for those receiving pazopanib—a nonsignificant difference that fell within the predetermined criteria for showing non-inferiority, he said. "The hazard ratio was 1.047, and one means exactly identical. In laymen's terms, the efficacy for pazopanib is the same as for sunitinib."

The name of the study, COMPARZ, is derived from "COMParing the efficacy, sAfety and toleRability of paZopanib vs. sunitinib."

"In an era of personalized medicine, patients should be given the option of either pazopanib or sunitinib."

ROBERT J. MOTZER, MD: "In general, this trial tips the scale for the preferred treatment for most patients from sunitinib to pazopanib based on the better tolerance for pazopanib. The side effects that are worse with sunitinib are the ones that impact on a patient's day-to-day living."

Sunitinib Standard Rx

Pazopanib and sunitinib are both oral multi-kinase angiogenesis inhibitors that improved progression-free survival rates in Phase III trials. Both drugs already are approved for metastatic RCC, but sunitinib was approved first and has become the standard therapy.

"It changed the paradigm for treating this disease," Motzer said. Indirect analyses comparing the two targeted agents showed comparable progression-free survival rates and a differentiated safety profile with regard to certain side effects, he said.

COMPARZ, which was designed to provide a direct comparison of the two drugs, confirmed each agent's unique side effect profile, he said.

Sunitinib is associated with significantly more fatigue, hand-foot syndrome, taste alteration, and thrombocytopenia. Pazopanib, on the other hand, caused more ALT elevations and whitening of the hair, he said.

Study Design

In the study, a total of 1,110 patients were randomized to receive treatment with pazopanib at 800 mg/daily or sunitinib at 50 mg/daily for four weeks followed by two weeks off treatment. Treatment continued until disease progression, unacceptable toxicity, voluntary withdrawal, or death due to any cause.

As with the primary endpoint of progression-free survival, there was no significant difference in the secondary endpoint of overall response rates between the two arms: 31 percent for pazopanib and 25 percent for sunitinib. An interim analysis also showed a non-significant difference in overall survival times: a median of 28.4 months in the pazopanib arm vs. 29.3 months in the sunitinib arm.

Weighing Side Effects

Motzer made a case that sunitinib's side effects are more bothersome to patients than pazopanib's are. "In general, this trial tips the scale for the preferred treatment, in my opinion, for most patients from sunitinib to pazopanib based on the better tolerance for pazopanib. The side effects that are worse with sunitinib are the ones that impact on a patient's day-to-day living," he said.

The most common adverse events (occurring in 30% or more of patients) that were more common with sunitinib were: fatigue (63% vs. 55%) hand-foot syndrome (50% vs. 29%); taste alteration (36% vs. 26%); and thrombocytopenia (34% vs. 10%).

TIM EISEN, MD, PHD: "Pazopanib can now be considered first-line standard of care alongside sunitinib. For an unselected population, most patients would tolerate pazopanib better."

Side effects that were more common with pazopanib were ALT increase (31% vs. 18%) and hair whitening (30% vs. 10%).

Additionally, 11 of the 14 quality-of-life measures were in favor of pazopanib over sunitinib, he reported. These included measures of fatigue, kidney symptoms, and mouth and throat soreness.

A total of 42 percent of patients in the pazopanib arm and 41 percent in the sunitinib arm had serious adverse events. Serious adverse events occurring in three percent or more of patients in the pazopanib arm were ALT increase and AST increase; and serious adverse events occurring in three percent or more of patients in the sunitinib arm were pyrexia and thrombocytopenia.

Thirteen patients (2%) in the pazopanib arm and 19 patients in the sunitinib arm (3%) had fatal adverse events.

Clinical Relevance of ALT Elevations?

Asked about the clinical relevance of the ALT elevations with pazopanib, Motzer said, "All of these VEGF inhibitors cause elevations of liver function tests [LFTs]—or drug-induced hepatitis—in some patients.

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injections of radium-223 at a dose of 50 kBq/kg IV every four weeks or matching placebo.

The Discussant for the study, Jason A. Efstathiou, MD, DPhil, Assistant Professor of Radiation Oncology at Harvard Medical School and Massachusetts General Hospital, called radium-223 a potential new standard of care for castration-resistant prostate cancer with bone metastases. But first, he pointed out, the FDA needs to approve it.

The agency is now reviewing the agent under its fast track designation. Also, Bayer HealthCare has received FDA approval to proceed with an expanded access program. The study was supported by Bayer and Algeta.