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January 10, 2013 * Vol. 35 * No. 1

oncology-times.com

ONCOLOGY TIMES

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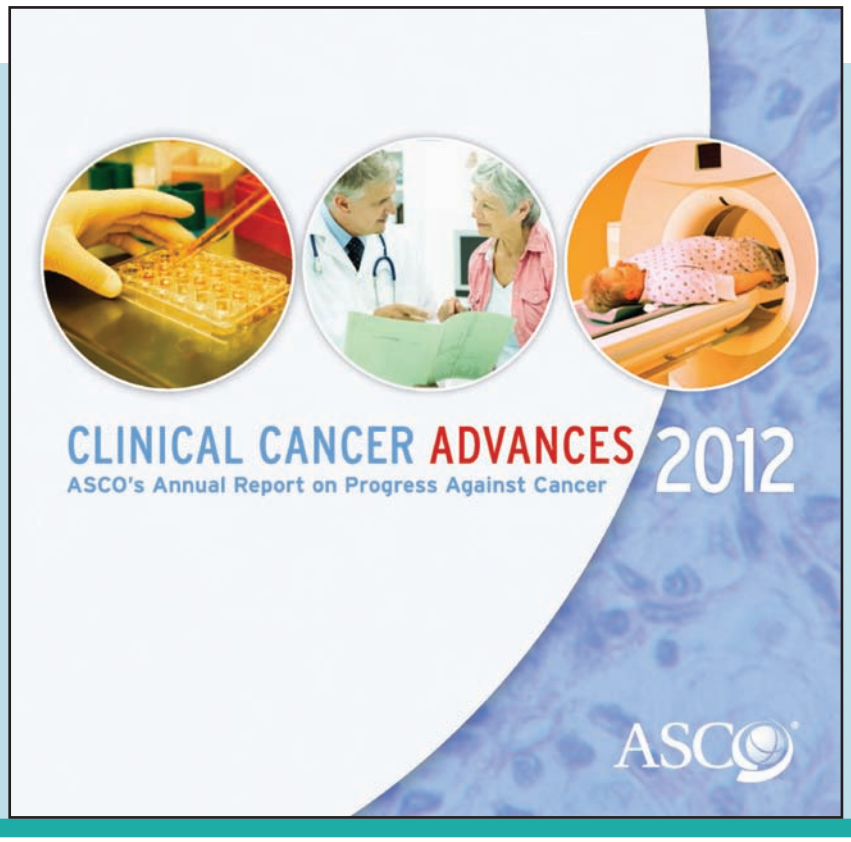

ASCO Year-End Report on Clinical Cancer Advances Stresses Precision Medicine

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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JEFF BRADLEY's Key Lung Cancer Takeaways p. 13

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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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→PROSTATE CANCER

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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.

→PAZOPANIB vs SUNITINIB

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With pazopanib, the percent of patients who develop a very high value is higher than with the other agents—12 percent. But, generally, that doesn't cause symptoms with the patients.

"With pazopanib we monitor LFT in the first two months," he continued. "Usually, if it is going to happen, it is in the first three or four months. It is important to monitor pazopanib patients. If we find [an ALT elevation], we stop the drug and hold the patients. About half the patients with high LFTs, when the drug is held, recover and can go back on it. In virtually all of the patients, when drug is held, liver function tests return to normal."

ROBIN WILTSHIRE, MD, of Pfizer, which makes sunitinib (Sutent): "The trial showed non-inferiority, and that is not the same as equivalence. We have a difference of more than one month of progression-free survival in favor of Sutent. … Both drugs cause the expected level of toxicity, similar in some ways and different in others. What we know is Sutent has been around for six years and has been used in more than 150,000 patients, and physicians are experienced in handling the side effects."

Patient Preference

Still, in the end, the decision of which drug to take comes down to patient preference, he said. "In an era of personalized medicine, patients should be given the option of either pazopanib or sunitinib."

The COMPARZ results are unlikely to change treatment guidelines, Motzer added. Speaking about the National Comprehensive Cancer Network guidelines, he said: "For the most part, [both drugs] are listed as options. And I think they will remain options—along with bevacizumab plus interferon."

A member of the audience asked, "If Votrient [pazopanib] is better tolerated, wouldn't better adherence be expected and thus better efficacy?" Motzer replied, "No, the efficacy is the same. PFS is the same, overall survival is the same, and response rate is the same. It is just that pazopanib has a different safety profile."

Pfizer Response

Not surprisingly, Pfizer offered a different interpretation of the data. Said Robin Wiltshire, MD, the company's Global Medical Lead for Sutent (sunitinib): "The trial showed non-inferiority, and that is not the same as equivalence. We have a difference of more than one month of progression-free survival in favor of Sutent."

Asked, though, if that one month is clinically meaningful, he said, "Efficacy is the most important driver, but that has to be balanced with tolerability. Both drugs cause the expected level of toxicity. The toxicity was similar in some ways and different in others. What we know is that Sutent has been around for six years and has been used in more than 150,000 patients, and physicians are experienced in handling the side effects."

Study Discussant

The Discussant for the study, Professor Tim Eisen of the Department of Oncology at the University of Cambridge, said that two factors should be considered when comparing the drugs: (1) efficacy; and (2) if efficacy is comparable, "which is softer on the patient."

On efficacy, he said, "there is no significant difference between the two. I wouldn't put too much store on a 1.1 month survival difference. That is due to the timing of the study assessment."

Regarding safety, though, he continued, "I would say pazopanib does have fewer side effects that matter to patients. These are maintenance agents taken for as long as they are controlling disease, and even low-grade adverse events can be problematic for patients. ALT and AST elevations don't usually trouble patients, but they would if doctors didn't manage them properly. So, pazopanib is probably ahead at this point."

However, there are some factors that confound the interpretation of the results, he said: "For example, pazopanib is given continuously and sunitinib is given on and off, so the disease-assessment intervals would tend to favor pazopanib."

Eisen also said he would not be so "generous" about the results of the quality-of-life assessments because they were administered during the first six months of treatment, which is when patients on sunitinib generally feel the worst.

He said he believes there is a SNP—single nucleotide polymorphism—that could help predict patients at risk for liver problems, but that he doesn't think it is validated.

Final survival data for the study are expected to be reported next year.