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NEWS & ANALYSIS

New outlook for neuroendocrine cancer

CAROLINE HELWICK

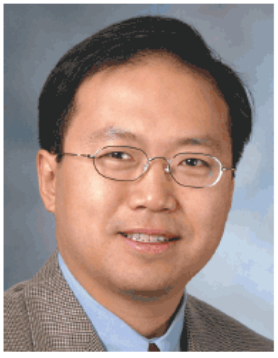
SAN FRANCISCO—Two agents dramatically delayed the time to disease progression in metastatic neuroendocrine tumors, according to reports at the 2009 Gastrointestinal Cancers Symposium.

The PROMID study (Placebo-controlled prospective Randomized study on the antiproliferative efficacy of Octreotide LAR in patients with metastatic neuroendocrine MIDgut tumors) evaluated the antitumor effects of the somatostatin analog octreotide acetate (Sandostatin LAR), which already is used to treat the severe diarrhea and flushing associated with neuroendocrine tumors (NET).

“Th is study demonstrates that octreotide also helps control tumor growth,” said Rudolf Arnold, MD, of Philipps-University Marburg in Germany, who added that the mechanism for its antitumor effects is unclear. “Currently, the only effective therapy for NET is surgery; however, many malignant tumors are metastatic. New regimens with few or minimal side effects, therefore, are highly desired.”

Th e multicenter prospective phase III trial, conducted in Germany, randomized 85 patients with metastatic NET of the midgut to receive first-line treatment with 30 mg of octreotide LAR or placebo every four weeks for 18 months or until tumor progression (abstract 121).

Octreotide LAR reduced the risk of progression of disease by 66%, producing a median time to progression (TTP) of 14.3 months, compared with six months in the placebo arm (P =.000072), Dr. Arnold reported.



For most patients, stable disease was the best response and this was observed in 64% with octreotide and 37% with placebo (P = .0079). One patient per arm had a partial response. The drug worked in patients with both functioning and nonfunctioning tumors.

Low hepatic burden

The most favorable effect was observed among the 70% of patients with a low hepatic tumor load (≤ 10% (P < .0009) and in patients with a resected primary tumor (P < .01). In patients with low hepatic load, the time-to-progression was 27.14 months with octreotide, compared with 7.21 months with placebo, for a reduction in risk of 74%. Patients with higher hepatic tumor loads had a nonsignificant 36% reduction in risk and a TTP of 10.35 months vs 5.45 months.

“Durable responses... were observed among patients with chemo-therapy refractory pancreatic NET.”

—JAMES YAO, MD

While the overall survival estimate is premature, median survival was 73.7 months in the placebo arm but has not been reached in the octreotide arm after 77 months. Octreotide was well tolerated, with no difference in serious adverse events between the arms (abstract 122).

At a symposium press conference, Jennifer Obel, MD, a gastrointestinal oncologist at NorthShore Health Systems in

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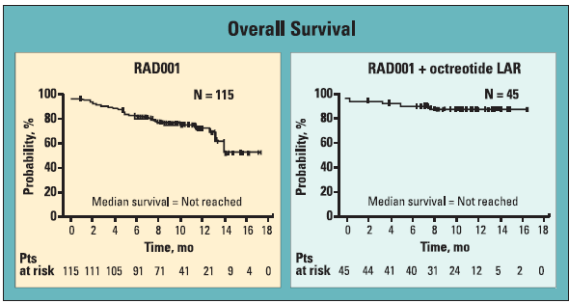
Chicago, commended the researchers for incorporating a control group.

“This allows us to evaluate whether this tumor’s slow growth is due to biology or is affected by the treatment,” Dr. Obel said. “I think this study demonstrates that delay of progression was related to the medication. These findings are practice-changing.”

mTOR inhibitor

Other investigators reported that the mTOR inhibitor everolimus (RAD001) may also be beneficial for pancreatic NET. The phase II trial included 160 patients with metastatic disease who had progressed aft er chemotherapy and were treated with 10 mg of everolimus or everolimus plus octreotide. Most patients responded or achieved stable disease.

Clinical benefit was observed by central review in 76.5% with everolimus monotherapy and in 82.2% with everolimus plus octreotide, and by investigator assessment in 73% and 80%, respectively.



Median response duration with the single agent was 10.8 months by central review and 10.15 months by investigator assessment, but it has not been reached for the combination. Progression-free and overall survival rates were higher with the combination (see Figure on pages 1 and 4).

Approximately half the patients with abnormal baseline levels of the circulating neuroendocrine marker chromogranin achieved significant reductions or normalization of levels with treatment.

Their TTP was significantly longer than that of patients whose levels were not affected.

“Durable responses and stable disease were observed among patients with chemotherapy- refractory pancreatic NET.

The progression-free and overall survival data support the efficacy of RAD001,” said lead author James Yao, MD, of M.D. Anderson Cancer Center in Houston. Th e symposium was jointly sponsored by ASCO, the American Society for Radiation Oncology, the Society for Surgical Oncology, and the American Gastroenterological Association.