Still Early, but MET-Inhibitor Is Showing Promise in Gastric Cancer

BY ED SUSMAN

SAN FRANCISCO—A small subset of gastric cancer patients appear to benefit from treatment with the investigative MET tyrosine kinase inhibitor AMG 337, researchers reported here at the Gastrointestinal Cancers Symposium (***Abstract 1***).

The meeting is co-sponsored by the American Gastroenterological Association Institute, American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology.

In eight of 13 patients whose tumors exhibited amplification of the MET gene, "dramatic responses" were observed, said Eunice L. Kwak, MD, PhD, Assistant Professor of Medicine at Dana-Farber Cancer Institute/Massachusetts General Hospital/Harvard Medical School, who presented data from an ongoing Phase I trial.

"The responses have been rapid," she said, "with initial responses observed in four weeks with patients achieving tumor shrinkage and symptomatic improvement quickly, Several patients have been on the study for two or more years."

In the case of one 63-year-old man with multiple metastatic gastroesophageal junction cancers, virtually all the lesions vanished from appearance on imaging scans within 33 weeks of treatment; he has remained cancer-free on imaging studies out to 105 weeks, Kwak said in her oral presentation at the opening packed plenary session of the symposium. The patient's tumor was tested while he was undergoing first-line chemotherapy.

When the cancer progressed on chemotherapy, the patient was moved to treatment in the dose-escalation phase of the AMG 337 trial, she reported. "He experienced a rapid response to the widespread tumors both radiographically and symptomatically by five weeks; by week 33, upon central review, this patient had achieved a complete response that is ongoing. The patient continues on treatment for 155 weeks.

"This study demonstrates that MET-amplification is an oncogenic driver in some of these cancers," she said.

Ed Susman

EUNICE KWAK, MD: "The responses have been rapid, with initial responses observed in four weeks with patients achieving tumor shrinkage and symptomatic improvement quickly. Several patients have been on the study for two years or longer."

'Impressive Cytotoxic or Cytoreductive Activity'

The study discussant, Jaffer Ajani, MD, Professor of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center, said: "AMG 337 showed impressive cytotoxic or cytoreductive activity. Granted this is only seen in 13 patients, but in 13 patients, eight is a big number. Here we can say that the biomarker—MET-amplification—is good and the drug is good. And this drug should really be pursued further."

Kwak noted that the MET gene promotes cancer cell proliferation, motility, survival, and migration/invasion. The gene can impact these conditions through ligand binding, overexpression activation, activating mutations and through crosstalk with other molecules to block the impact of targeted agents such as epithelial growth factor receptor (EGFR) inhibitors, she explained.

"Therefore MET inhibition is an attractive strategy for drug development," she said. "AMG 37, being developed by Amgen, is a potent and highly selective small molecule inhibitor of wild-type and some mutant forms of MET. In a competitive binding assay conducted with 402 human kinases, AMG 337 bound only to MET."

Experiments with AMG 337 analogs indicated that the compounds bound to stomach cancer cell lines at low nanomolar levels, she said.

Building upon that background, researchers took AMG 337 to the clinic in an attempt to determine the maximum tolerated dose among adult patients diagnosed with solid tumors who were in ECOG performance status 2 or less. To be eligible for the trial, patients had to still maintain adequate organ functioning.

Ed Susman

JAFFER AJANI, MD: "Here we can say that the biomarker—MET-amplification—is good and the drug is good. And this drug should really be pursued further."

The maximum tolerated dose of AMG 337 was found to be an oral dose of 300 mg once daily, Kwak said, adding that the dose-limiting toxicity was headache.

The primary endpoint of the Phase I study was to scrutinize the pharmacokinetics of AMG 337, to determine its safety and efficacy, and to set a dose that would be taken forward into Phase II trials—in this case, the 300 mg once daily dosage.

> "This study demonstrates that MET-amplification is an oncogenic driver in some of these cancers."

Secondary endpoints sought to see if treatment with AMG 337 produced objective responses based on Response Evaluation Criteria in Solid Tumors. The researchers also conducted an exploratory analysis of how tumors exhibiting MET-amplification correlated with response.

"This exploratory cohort was expanded once the 300 mg maximum tolerated dose was established," Kwak said.

"For patients who came to the trial with evidence of MET abnormalities in

continued on page 57

AMG 337

Continued from page 56

their tumors, the determination of MET status analysis was performed either by central laboratories or by experienced local laboratories. For MET amplification, analysis was performed by fluorescence in situ hybridization [FISH] or by next-generation sequencing; MET overexpression was determined through immunohistochemistry."

The 90 patients in the Phase I trial were about 59 years old; about 61 percent were men; 845 were white; 95 percent were in ECOG performance status 0 or 1; the median number of former therapies for gastric cancer was two; 19 of the patients had tumors that exhibited MET-amplification.

The patients were being treated for a variety of solid tumors—the largest group of 21 patients had gastric-esophageal junction/gastric/esophageal cancers. The last patients were enrolled in July 2014.

Adverse Events

Nausea, vomiting, and fatigue were most often seen as Grade 1 to 2 adverse events. The dose-limiting toxicity of headache was experienced by 47 of the patients—more than 50 percent, and seven of those patients experienced Grade 3 or higher headaches.

"Headache is an interesting dose-limiting side effect," she said, "It is thought to be caused by AMG 337's binding to the adenosine transporter. Caffeine appears to ameliorate that adverse effect among patients on the trial."

In the secondary efficacy analysis, Kwak illustrated that all the patients who achieved an objective response to therapy with AMG 337 had some form of MET abnormality—either amplification or over-expression—in their tumors.

When the researchers scrutinized outcomes among the patients who had MET-amplified gastric cancers, "we see that there were 13 patients treated who had MET-amplification in gastric/esophageal cancers—all of which were adenocarcinomas. Four of the patients remain on treatment. Eight of the patients achieved a partial response. Therefore the overall response rate in this small group of patients is 62 percent," she said.

Of note, she said, is that of the nine patients in the study with esophagogastric cancers that did not exhibit MET-amplification, none achieved a partial response.

Ed Susman

PAUL ENZINGER, MD: "The concern is that the group of patients who respond may be very small. This is a rare cancer in the United States, so the question is how do we move forward."

'Clearly Shows a Responding Subgroup'

Also commenting on the study results, session moderator Paul Enzinger, MD, Clinical Director of the Gastrointestinal Malignancy Program at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School, said the study "clearly shows that there is a subgroup of patients who respond to the MET inhibitor but we don't fully understand who they are.

"The concern is this group may be a very small number of patients. It is a rare cancer in the United States, so the question is how do we move forward."

The study was sponsored by Amgen, which is enrolling patients with MET-amplification into a Phase II clinical trial using AMG 337 at the 300 mg once-daily dose.

> Amgen is now enrolling patients with MET-amplification into a Phase II clinical trial using AMG 337 at the 300 mg once-daily dose.

iPad Extra!

VIDEO: Watch a video of Dr. Kwak further discussing her findings on the iPad edition of this issue with *OT* reporter Sarah Maxwell in an interview conducted at the symposium.

OT Video News

If you are not yet receiving our iPad issues, download the free Oncology Times app from the App Store today! Visit ***http://bit.ly/OT-iPadApp****, search in the App Store, or follow the link on* ***oncology-times.com****.*