here at the ASCO Annual Meeting, investigators identified those markers and showed the agent's potential in gastrointestinal stromal tumors (GIST) and neuroendocrine tumors.

"The key issue here for the practicing oncologist is the excitement of probing the activity of new and highly potent antiangiogenic agents with new biomarkers," said George D. Demetri, MD, who served as the senior investigator for two studies involving the role of SU11248 in GIST.

"We have chosen to explore rather novel biomarkers of activity in our GIST trials."

Dr. Demetri, Director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute and partments in GIST lesions.

The team focused on this particular potential treatment response because GIST lesions contain activating mutations of both KIT and platelet-derived growth factor receptor (PDGFR), which are both tyrosine kinase receptors.

Because SU11248 had been shown to inhibit these mutations in patients who had developed resistance to imatinib, the investigators wanted to know if this pattern could also indicate a response to SU11248.

Therefore, they obtained paired tumor biopsies from 19 GIST patients who were being treated with SU11248. Biopsies were performed at baseline and after at least 14 days of treatment

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Ovarian Cancer

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lated that it might be best used in combination with conventional chemotherapy. After being immobilized by RAD001, ovarian cancer cells would be more vulnerable to the cytotoxic drugs, Dr. Testa explained.

Robert J. Morgan, MD: "The rapamycin analogues are early promising agents targeting a promising pathway."

This strategy, it was hoped, would increase five-year survival substantially, Dr. Mabuchi said.

Dr. Testa pointed out that since RAD001 targets a specific pathway, there should be fewer side effects than with conventional chemotherapy. "In the mice, it appears to do nothing to other tissue," he said.

The strategy is to block mTOR downstream of AKT, therefore avoiding the side effects of a direct attack.

Important Signal Transduction Pathway in Variety of Cancers

Robert J. Morgan, MD, a staff physician in the Department of Medical Oncology and Therapeutics Research at City of Hope National Medical Center, said that AKT has been shown to be an important signal transduction pathway in a variety of cancers. Among them: Leukemia, lymphoma, and numerous solid tumors.

"This is allowing researchers to design targeted therapies that interfere with this pathway and therefore with tumor development," he said.

At least two dozen pharmaceutical companies are trying to target the AKT pathway, according to Dr. Testa. Some have already reached Phase I/II trials.

The rapamycin analogues "are early promising agents targeting a promising pathway," said Dr. Morgan, who was not involved with the research.

RAD001 is made by Novartis Pharmaceuticals, which did not fund this research.

Refining Strategies That Target EGFR

Yet another targeted therapy being tested in ovarian cancer is gefitinib, an inhibitor of epidermal growth factor receptor (EGFR). In other new research presented at the meeting, other Fox Chase researchers reported that gefitinib appears to be effective only in women with mutations in the tyrosine kinase portion of EGFR.

For the study, led by Russell Schilder, MD, of the Clinical Molecular Genetics Laboratory, archived tissue was examined from Phase II trials designed to assess the efficacy and tolerability of gefitinib in patients with recurrent or persistent ovarian carcinoma or primary peritoneal cancer.

"We did a blinded mutational analysis, and the one patient who had the only objective response to gefitinib during the 23-month trial had a mutation in the tyrosine kinase portion of EGFR," he said. In contrast, no mutations were observed in 23 of the cases with no measurable response to the drug.

Overall, the researchers detected mutations in the tyrosine-kinase domain region in two of 56 (3.6%) of ovarian carcinomas.

"This is proof of principle, a window into the future suggesting that by screening for such mutations, we can improve the response rate," Dr. Schindler said. "The practical issue right now is that if only 4% of women have the mutation, screening

Russell Schild of principle, future sugges screening for can improve The practical only 4% of w mutation, scr particular mu Ultimately w for a variety and different choosing the therapy."

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responders from non-responders. They're not rare cells, and it shouldn't be difficult to find them."

The tumors in patients with clinical benefit showed a 3.6-fold increase in endothelial cell apoptosis and a sixfold increase in tumor cell apoptosis. Among patients with progressive disease, there was little or no change in endothelial and tumor cell apoptosis compared with baseline.

Circulating Endothelial Cells & Monocytes

In another study of SU11248 in GIST, investigators found that both endothelial cells and monocytes may be valuable biomarkers to tell if a patient has responded to treatment.

"We have to look for different biomarkers other than tumor shrinkage when we use antiangiogenic agents," said principal investigator Anat Norden-Zfoni, MD, a fellow in the Vascular Biology Program at Children's Hospital Boston.

"Antiangiogenesis causes less tumor shrinkage than we typically look for in chemotherapy. So we need to show benefit from treatment in a different way. We looked at both circulating endothelial cells and monocytes and found that responders had higher levels of both after treatment compared with non-responders."

A rise in circulating endothelial cells, which express vascular endothelial growth factor (VEGF), is a sign that the tumor's vasculature is being destroyed, she explained.

The manufacturer of SU11248, Pfizer, which makes the drug under the trade name Sutent, supplied the drug and placebo tablets, but provided no other funding, Dr. Norden-Zfoni said.

She and her colleagues theorized that monocytes would decrease but that circulating endothelial cells would increase in responders, because monocytes express VEGF receptor-1 (VEGF-R1) and circulating endothelial cells express VEGF-R2.

By targeting tumor vasculature, treatment with GIST could cause more circulating endothelial cells to be released as the result of blood vessel

cells/μl at baseline to 350 cells/μl on Day 14. Not surprisingly, monocytes then increased during the hiatus in 64 patients. Surprisingly, though, the decrease in monocytes was greater in patients with progressive disease, averaging 58%, then in patients with clinical benefit, who had an average decrease of 48%.

Among the subset of 16 patients in whom the circulating endothelial cells were assessed, the levels were similar at baseline. In the seven patients with clinical benefit, there was a rise in mature circulating endothelial cells after six to 20 days of therapy, rising from a baseline average of 1.6 cells/μl to an average of 24.4 cells/μl).

Among the nine patients with progressive disease, four had a rise in circulating endothelial cells, from a baseline average of 3.9 cells/μl to a post-treatment average of 6.8 cells/μl. There was also a statistically significant difference in the rate of change per day in circulating endothelial cells, so that those with clinical benefit had an average daily increase of 3.8 cells/μl compared with an average daily decrease of 0.01 cells/μl in those with progressive disease.

"The findings support the hypothesis that SU11248-mediated inhibition of angiogenesis contributes to clinical responses in GIST patients."

Dr. Norden-Zfoni added that monocytes may be a more feasible biomarker, because there are more of them than there are circulating endothelial cells, which are rare and require color cytometry to detect.

Neuroendocrine Tumors

In other research, investigators are exploring the potential for SU11248 in metastatic, unresectable neuroendocrine tumors (NETs). Matthew Kulke, MD, the principal investigator, noted that conventional chemotherapy has limited efficacy in such patients.

Matthew Kulke, MD: "The most exciting aspect of our results is that treatment with SU11248 represents a completely different way of thinking about treating neuroendocrine tumors, with a VEGF inhibitor. This may be the beginning of a new paradigm for thinking about how to treat these tumors."

Dr. Kulke, a medical oncologist at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School, explained that because neuroendocrine tumors are known to be highly vascular and to express high levels of both VEGF and VEGFR, the hope was that SU11248 would be a feasible treatment method.

In an ongoing Phase II study, 106 patients with advanced, unresectable NETs were treated with repeated six-week cycles of SU11248 at a dose of 50 mg daily for four weeks, followed by a two-week hiatus. Conventional chemotherapy was allowed, as was treatment with octreotide in patients who had begun treatment with it before the study.

Among the 93 evaluable patients, the responses were as follows: Among the 52 patients with islet cell NETs, seven (13.5%) were partial responders, and 40 (77%) had stable disease, with three patients (5.5%) having progressive disease. The status of the remaining two was not yet confirmed.

Among the 39 patients with carcinoid NETs, two (5.1%) were partial responders, and 36 (92.3%) had stable disease, with one patient (2.6%) experiencing progressive disease.

Among the evaluable patients, 86 had treatment-related toxicities. Grade 3/4 toxicities included diarrhea in three