initially control the cancer, but most patients eventually experience disease progression due to activation loop mutations, which are resistant to approved drugs. However, results of two trials presented in early December at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany, suggest that GIST is sensitive to two new agents: BLU-285 (Blueprint Medicines) and DCC-2618 (Deciphera Pharmaceuticals).

In an ongoing phase I trial of BLU-285, researchers enrolled 36 patients who had advanced, inoperable GIST, some of whom had worsening disease despite having had at least two prior treatments with TKIs. All of the patients had exon 17 *KIT* or *PDGFRA* D842V activation loop mutations, which are selectively targeted by the drug. CT and MRI scans showed that tumors shrank in 14 of 15 evaluable patients with mutant *PDGFRA* and five of 13 evaluable patients with *KIT*-driven disease, with responses seen in as little as 2 months, reported Michael Heinrich, MD, of Oregon Health and Science University in Portland.

Heinrich noted that the treatment was well tolerated and that 27 patients continue to be treated, including all 18 patients with *PDGFRA*-mutant GIST, with a treatment duration of 0.8 months to 12.3 months. "In addition, there was a more than 10-fold reduction in levels of *PDGFRA*-mutated DNA circulating in the blood, and we saw this even before the imaging scans confirmed that tumors were shrinking," he said.

In a separate trial, researchers enrolled 24 patients with a variety of solid tumors in a phase I dose-escalation trial of DCC-2618, a pan-KIT and PDGFRA inhibitor. All but three of the patients had been diagnosed with GIST; one had wild-type disease and the others had a mutation in either *KIT* or *PDGFRA*. One patient with glioblastoma multiforme (GBM) had amplifications in both. The other two patients were diagnosed with thymic carcinoma with a *KIT* exon 13 mutation and a pelvic desmoid tumor without known mutations, respectively. All of the patients received a baseline PET scan, followed by a second scan after they had taken DCC-2618 for 21 days.

"While it is early, we observed signs of benefit in the GIST patients… whose disease had progressed despite multiple previous treatments," said Filip Janku, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston. "Early partial metabolic responses, a sign of reduced tumor metabolic activity, were observed in 14 of the 15 patients evaluated with *KIT*-mutant GIST." One of two patients with a *PDGFRA* mutation experienced stable disease; the patient with wild-type GIST did not respond.

Janku added that the patient with GBM experienced improvements "relatively early in treatment as the tumor shrank slowly but steadily, and today, more than 12 months later, the patient is continuing to do well. We are very excited to see the response in this patient as it is a very hard cancer to treat."

During the trial, Janku's team captured cell-free DNA from patients' blood and used next-generation sequencing to identify and track molecular alterations to help them understand why patients responded, as well as intrinsic or adaptive resistance to DCC-2618.

"Even though phase I dose escalation is occurring, we see very impressive responses," said Jean-Charles Soria, MD, PhD, of Institut Gustave Roussy in Villejuif, France, who chaired the symposium's scientific committee. Also notable, he said, was that "liquid biopsies revealed in real-time the presence of multiple mutations reflecting tumor heterogeneity that might have been missed even in an invasive tissue biopsy."

Liquid biopsies are expensive, but researchers emphasized that the cost could be offset by savings elsewhere. For example, liquid biopsies could replace more invasive tissue biopsies, said George Demetri, MD, of Dana-Farber Cancer Institute in Boston, MA. More savings could come from not having to do CT scans and from avoiding expensive "wrong" drugs that won't benefit particular patients.

Although conducting serial liquid biopsies won't soon become standard practice, Soria predicted that it will "completely change the rules of engagement for the management of patients." *–Suzanne Rose* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

NOTED

A scant **1.8% of the $26.6 billion collected by state governments from tobacco taxes and settlement funds in this fiscal year will be spent on smoking cessation programs,** according to a report from several organizations (see www.tobaccofreekids.org). The group noted that although it would take less than 13% of total state tobacco revenues to fund such programs at levels recommended by the Centers for Disease Control and Prevention, only North Dakota and Alaska are doing so.

The FDA released a guidance document for industry on clinical pharmacology data to support the demonstration of biosimilarity to a reference product (see www.fda.gov). By law, companies seeking FDA approval of a biologic product that is highly similar to an existing one must show that there are no clinically meaningful differences between the products.

The FDA placed holds on early-stage trials of vadastuximab talirine (Seattle Genetics), an investigational antibody–drug conjugate targeting CD33, in patients with acute myeloid leukemia who had an allogeneic stem cell transplant, to evaluate hepatotoxicity risk. The holds were initiated after six patients were identified with hepatotoxicity and four patients died.

Unlike adults, children with cancer treated with radiotherapy or chemotherapy are at high risk of developing cardiac and neurologic problems later in life. A recent study may explain the disparity: Researchers found that mitochondria of many adult tissues are refractory to pro-apoptotic signaling, leading to cellular resistance to radiation and chemotherapy, whereas **mitochondria from tissues in young mice and children are "primed for apoptosis,"** predisposing them to "cell death in response to genotoxic damage" (Cancer Cell 2017;31:142–56).

Vice President Joe Biden told *The Washington Post* that he will create a nonprofit organization to continue focusing on cancer issues after he leaves office. He indicated his desire to "get Congress and advocacy groups to make sure [cancer] treatments are accessible for everyone… and that we have a more rational way of paying for them while promoting innovation."