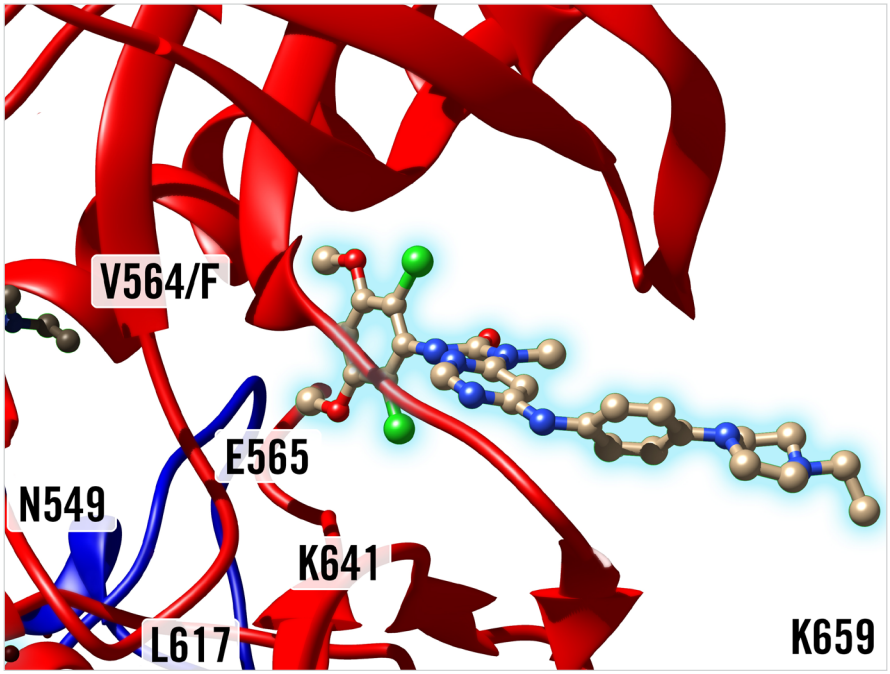
Secondary FGFR2 Mutations Drive Drug Resistance to FGFR Inhibitors in Bile Duct Cancer

Can understanding the genetic mechanisms driving resistance to the FGFR inhibitor BGJ398 lead to better therapies for bile duct and other cancers?



Binding site targeted by FGFR inhibitors

FGFR point mutations confer resistance to BGJ398 and other FGFR inhibitors. Pictured here, an in silica model of how BGJ398 blocks the "binding pocket"—or binding site on a region of DNA—of FGFR2 when a V564F mutation is present. This model is meant to demonstrate "steric clash," or the unnatural overlap of nonbinding atoms in a protein structure.

Intrahepatic cholangiocarcinoma (ICC) is a rare cancer of the bile ducts in the liver, with limited treatment options and a poor prognosis. In its advanced stages, only one chemotherapy regimen has been shown to improve survival, but those treated usually don't live more than a year. In 2013, however, researchers at the University of Michigan discovered that a specific kind of genetic alteration in the fibroblast growth factor receptor (FGFR) pathway recurs in patients with bile duct cancer. These so-called FGFR2 "fusions" were subsequently found to have an incidence of about 10% to 20% in ICC—and are now promising therapeutic targets in this disease.

Massachusetts General Hospital Cancer Center was one of the lead sites in a phase II multicenter clinical trial of the selective FGFR inhibitor BGJ-398 in patients with advanced bile duct cancer harboring FGFR alterations. Researchers found that BGJ398 led to significant tumor shrinkage in 22% of the study population, but in many cases, the tumor started to regrow within a few months. To understand these responses, Lipika Goyal, MD, MPhil, an oncologist at the Mass General Cancer Center, and colleagues set out to explore the molecular foundations of acquired resistance.

MUTATION AND INHIBITOR RESISTANCE

Preliminary findings from research on three patients treated at Mass General were published in December 2016 in the *American Association for Cancer Research* journal *Cancer Discovery* and suggest that treatment with BGJ398 led to the acquisition of a stunning variety of secondary mutations in the same FGFR2 gene targeted by the drug. The researchers believe these secondary FGFR2 mutations are among the mechanisms

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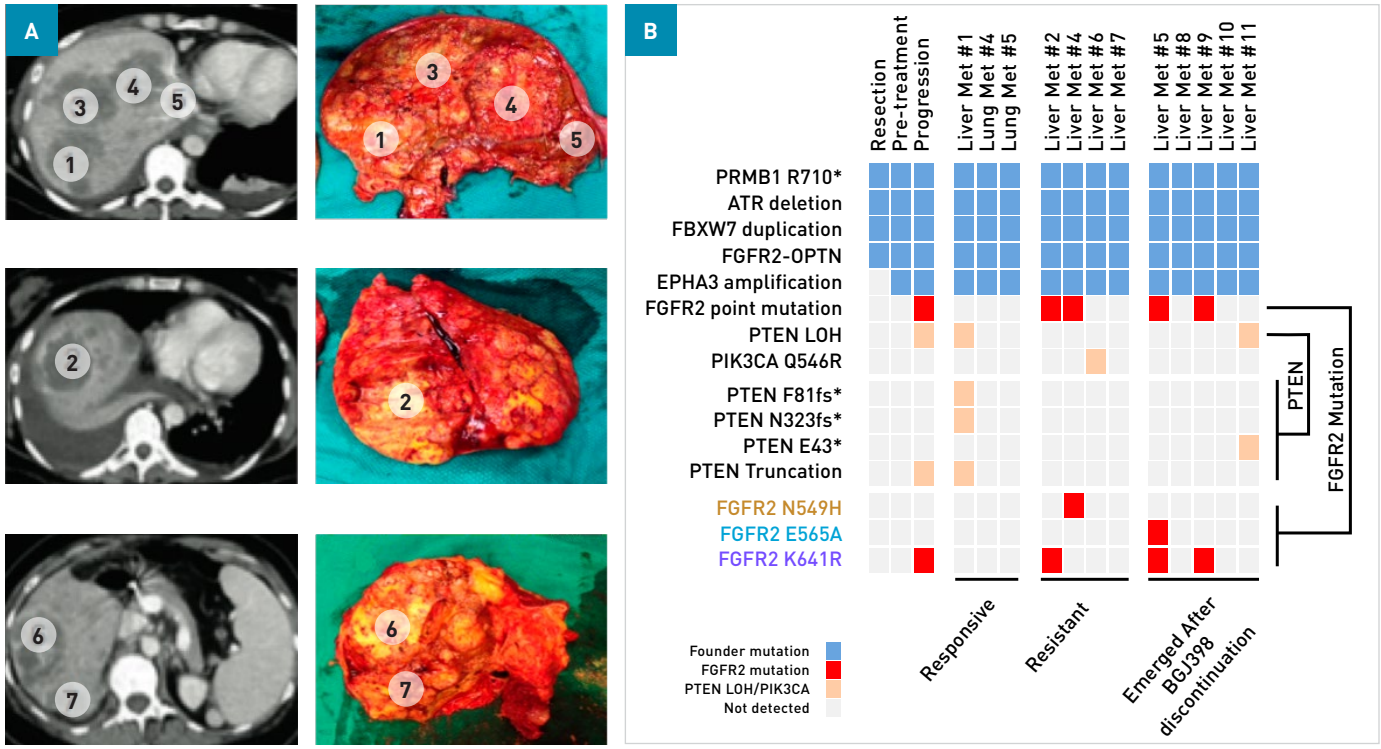

Heterogeneity and acquired resistance mutations

A. Axial contrast-enhanced CT images and autopsy photographs of seven liver metastases from a single patient. **B.** Heatmap illustrating mutations detected in the indicated autopsy lesions. Three distinct *FGFR2* point mutations and four distinct *PTEN* mutations were identified.

that drive resistance. Molecular modeling and cell line studies built on previously published work confirmed that the secondary mutations in FGFR2 led to BGJ398 resistance—and that this resistance could be overcome with additional FGFR inhibitors that are structurally distinct from BGJ398.

The findings represent the first time the genetic mechanisms of clinical acquired resistance to FGFR inhibition have been identified in patients. If the findings can be repeated in a larger population, they could guide the development of more durable therapeutic strategies for bile duct cancer, as well as for the wide variety of other cancers that are driven by alterations in the FGFR pathway in a subset of patients. These include breast cancers, urothelial carcinomas, stomach cancers and glioblastoma multiforme, among others.

SAMPLING OF SECONDARY MUTATIONS

To identify mechanisms of acquired resistance, Dr. Goyal and colleagues collected serial tumor biopsies and serial blood plasma samples; the latter were used to genomically characterize circulating tumor DNA, which can often offer a broader snapshot of the cancer's genome than an individual tumor biopsy. Interestingly, all of the patients acquired the same

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mutation in FGFR2: the gatekeeper V564F, which interferes with BGJ398 binding to its target. Two patients developed four additional FGFR2 mutations on post-progression ctDNA analysis, suggesting a polyclonal resistance mechanism to FGFR inhibition. In one patient, a discordant finding of five FGFR2 mutations in the blood and one in the liver biopsy tissue led researchers to perform an autopsy on the patient through the Mass General Rapid Autopsy Program. Across the twelve sites in the liver and lungs analyzed, spatially distinct metastases were found to harbor different FGFR2 mutations; and one individual tumor had more than one FGFR2 mutation, demonstrating both interlesional and intralesional heterogeneity.

"If the cancer is able to evolve multiple mechanisms of resistance within the same patient, it makes the disease a bigger challenge because you have to find a drug or drug combination that can overcome multiple potential resistance mechanisms," says Dr. Goyal.

Aside from repeating the study with a larger clinical population, critical next avenues for FGFR resistance research include studying downstream signaling pathways in FGFR-sensitive and -resistant patient derived models, understanding primary resistance and non-genetic mechanisms of secondary resistance, and testing therapeutic strategies in the lab that can be translated into the clinic to improve patient outcomes.

Contributor

Lipika Goyal, MD, MPhil

Medical Oncologist, Tucker Gosnell Center for Gastrointestinal Cancers, Massachusetts General Hospital Cancer Center; Instructor in Medicine, Harvard Medical School
lgoyal@partners.org

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Cancer Center
55 Fruit Street | LRH 200
Boston, MA 02114

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