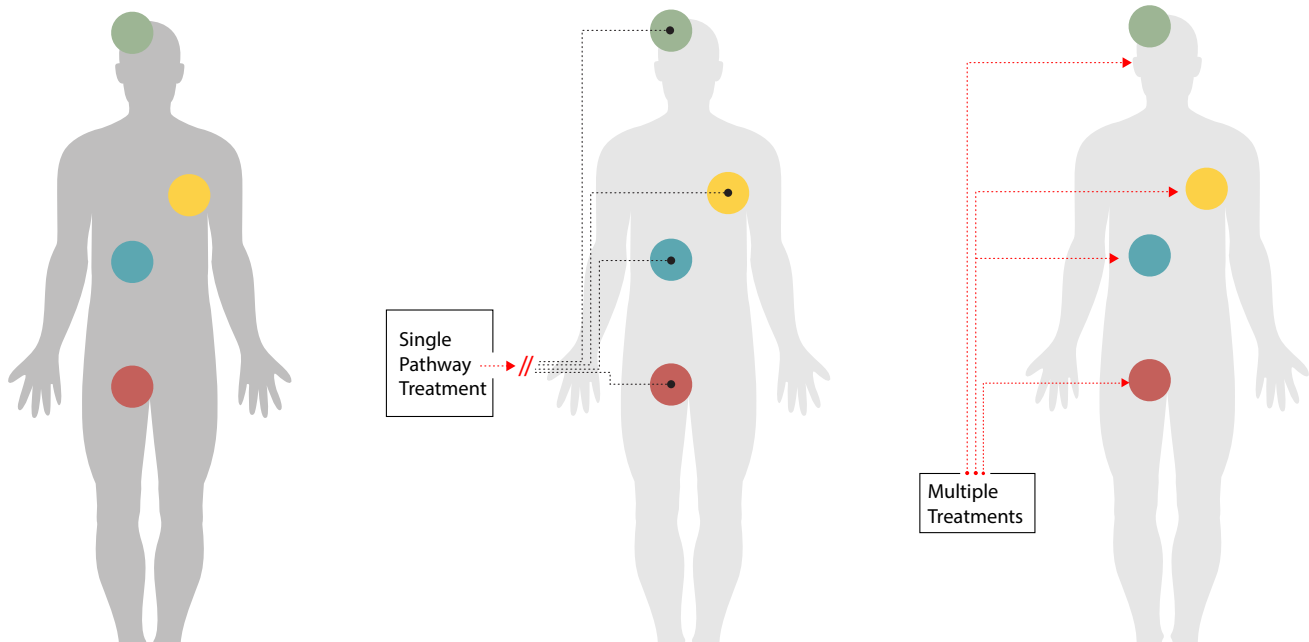


Divergent Resistance Mechanisms in Metastases

Can strategies that target clonal heterogeneity overcome acquired resistance in cancer therapy?



Treating Resistance Strategies Within BRAF Mutations

Figure 1: Illustration showing two ways to treat several metastases (colored circles): The first uses one medication to attack several resistance types (single pathway treatment targeting a convergent signaling node), and the second uses several simultaneous treatments, which overlap and attack the various tumor resistance types at once (multiple treatments).

Acquired resistance in cancer often arises from clonal heterogeneity, as the metastases from an original tumor genetically diverge and come to evolve different resistance mechanisms. This poses a significant therapeutic challenge. “In gastrointestinal (GI) cancers, this clonal variation has become the rule rather than the exception,” says **Ryan Corcoran, MD, PhD**, Principal Investigator in the Center for Cancer Research at the Massachusetts General Hospital Cancer Center and Assistant

Professor of Medicine at Harvard Medical School. “When we’re able to sample multiple metastases from a patient, we typically find that different mechanisms of resistance have emerged in each one.”

Dr. Corcoran and colleagues have explored different avenues for detecting this heterogeneity as it emerges, with the goal of developing effective, durable treatments. This resulted in two important discoveries published in *Cancer Discovery* in April 2018. In the first, the team conducted a clinical trial for BRAF-mutant

colorectal cancer using several combined targeted therapies. In the second, they looked at a way to treat a range of resistance strategies within BRAF-mutant colorectal cancers. Both papers made use of a novel liquid biopsy technique, outlined in a separate paper in *Cancer Discovery*.

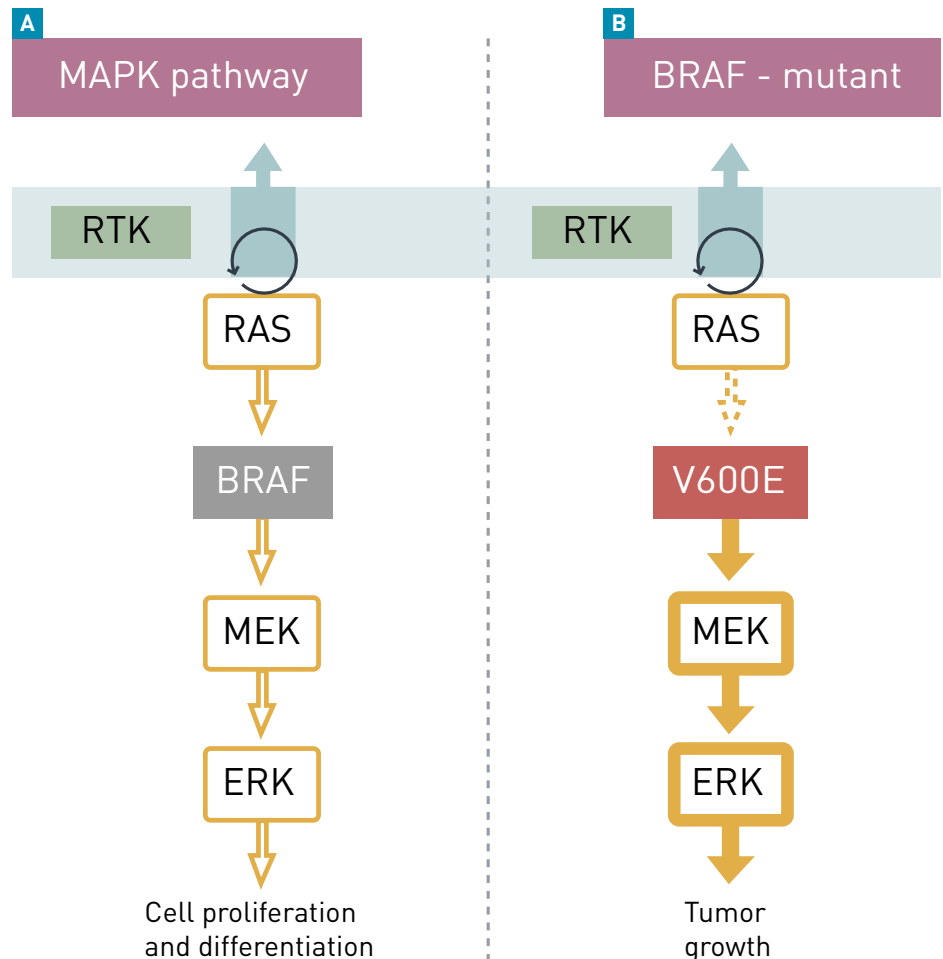
TRIPLE THERAPY EFFECTIVE BUT SHORT-LIVED

In recent years, the team has analyzed colorectal cancer patients with genetic mutations in BRAF. Their most recent clinical trial

among 142 patients with this mutation used a combination of BRAF, MEK and EGFR inhibitors¹—an effort to combat this heterogeneity with a multipronged approach. The results, published in the first *Cancer Discovery* paper, showed that about 32% of patients had an initial response and nearly 90% achieved disease control. “It had the best efficacy we have seen so far for any therapy in this disease,” says Dr. Corcoran, who led the study. “We’ve gone from response rates of 5% just 5-6 years ago.”

In the paper, however, the researchers noted that the duration of therapeutic benefit was very short, with rapid emergence of drug resistance. The overall progression-free survival in patients taking the triple combination was only 4.2 months. “This study clearly highlights the problem of rapid acquired resistance,” says Dr. Corcoran.

Further investigation with liquid biopsy of circulating tumor DNA showed that half of the patients in the trial displayed evidence of specific MAP kinase pathway mutations, mostly *RAS* mutations that were emerging during treatment. “And a number of patients had multiple *RAS* mutations, suggesting there was a clonal heterogeneity inherent in those BRAF-mutant patients,” says Dr. Corcoran. “It was at the root of acquired resistance.”



Normal and Mutant BRAF/MapK Activation Pathways

Figure 2: (A) Normal signaling of the BRAF pathway. The BRAF pathway initiates signaling through activated *RAS* proteins and activation of BRAF, followed by MEK and the final step of phosphorylation of ERK. The result is increased cell survival and decreased apoptosis. (B) BRAF mutant pathway. In the presence of an activating BRAFV600E mutation, BRAF no longer requires activated *RAS* proteins and remains active, leading to tumor growth.

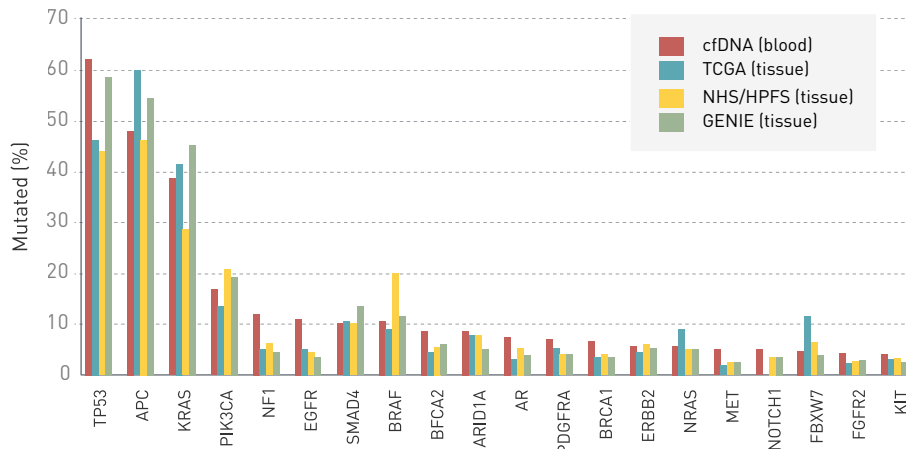
A FOCUS ON CONVERGENT NODES

BRAF relies on the MAP kinase pathway to drive tumor growth (Figure 2), and the team had observed that many resistance

mechanisms in BRAF-mutant colorectal cancer reactivated the MAP kinase pathway despite treatment with several inhibitors.

Based on the trial results and the liquid biopsy revelations, the team

(continued on page 3)



Comparison of ctDNA and Tissue-Based Analysis

Figure 3: The prevalence of mutations in colorectal cancer patients is roughly equivalent when comparing liquid biopsy of ctDNA and three tissue-based tests.

(continued from page 2)

investigated acquired resistance mechanisms in patients with this disease in more detail. In the second *Cancer Discovery* paper, Dr. Corcoran found 14 unique changes in the MAP kinase pathway driving acquired resistance in colorectal cancer patients with the BRAF mutation. One patient displayed as many as 8 different mechanisms. The researchers tracked the outgrowth of resistant clones that developed following therapy with several inhibitor types, including BRAF, EGFR and MEK inhibitor combinations.

“We focused on how we could intercept multiple resistance mechanisms by targeting a convergent point in the pathway,” Dr. Corcoran explains. The team found that by targeting ERK kinase activity, which is the final

step of the MAP kinase pathway, they could intercept the entire spectrum of potential resistant subclones in these patients.² “By taking out this convergent node up-front when resistant clones are rare, we were able to prevent the outgrowth of resistant clones,” he says. “This may suppress development of resistance in these patients and potentially improve their clinical outcomes.”

LIQUID BIOPSY TRACKS RESISTANCE MECHANISMS

To follow the development of resistance in the metastases, Dr. Corcoran and colleagues rely on periodic liquid biopsies to sample cell-free DNA or circulating tumor DNA (ctDNA), genetic matter shed by tumor cells into the bloodstream.

“Liquid biopsy contains the ctDNA from all of the metastases,” says Dr. Corcoran, “and this allows us to dynamically monitor the evolution of the patient’s tumors in real time.” In a third *Cancer Discovery* paper published in February 2018, his team tracked the genomic landscape of 1,397 patients with colorectal cancer using ctDNA analysis.³ After they sequenced the ctDNA, their technique was found to be just as good at identifying resistance mechanisms as three tissue-based sequencing approaches, in terms of the number and type of mechanisms they found (Figure 3).

A systematic liquid biopsy program was initiated throughout the GI cancer program at Mass General Cancer Center about three years ago. The team recently reported results from the first 40 patients who underwent a liquid biopsy process from the start of therapy and continued it throughout their disease progression, with the aim of identifying patterns of resistance and responses to therapy.

The teams were able to identify a mechanism in about 80% of the patients. In more than half of the patients, they identified more than one resistance mechanism—anywhere from two per patient to as many as 12 per patient, with an average of three. “This shows the challenge of eradicating multiple resistant clonal populations,” says Dr. Corcoran.

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TOWARD CONVERGENT TREATMENT OF RESISTANT CLONES

“The major challenge now in BRAF-mutant colorectal cancer and some other cancers is how to make responses more durable,” Dr. Corcoran says. He and his colleagues hope to initiate clinical trials that focus on using convergent targeting approaches (Figure 1). Even if it is not possible to target every resistance mechanism as a single point, it may be effective to target two or three classes of resistance mechanisms, either simultaneously or in staggered fashion to avoid toxicity. “Perhaps we could give targeted therapy for a while, then standard chemotherapy or immunotherapy, applying a different modality to wipe out some of the clones resistant to the initial therapy,” he explains. “Rationally integrating multiple modalities of therapy in this way is important.”

“We’re in a similar place as the researchers who were trying to figure out how to treat HIV,” Dr. Corcoran says. With one or even two treatment types, the virus would rapidly mutate after division and evolve random resistance mechanisms. But perhaps by attacking the cancer with several parallel approaches—similar to the current multidrug cocktail for treating HIV infection—it may knock out resistant clones before

they emerge. “In that way,” says Dr. Corcoran, “maybe cancer will look more like a chronic disease, as HIV is today.”

¹ Corcoran RB, Andre T, Atreya CE, et al. Combined BRAF, EGFR and MEK inhibition in patients with BRAFV600E-mutant colorectal cancer. *Cancer Discov.* 2018; 8(4):428-443.

² Hazar-Rethinam M, Kleyman M, Han GC, et al. Convergent therapeutic strategies to overcome the heterogeneity of acquired resistance in BRAFV600E colorectal cancer. *Cancer Discov.* 2018; 8(4):417-427.

³ Strickler JH, Loree JM, Ahronian LG, et al. Genomic landscape of cell-free DNA in colorectal cancer patients. *Cancer Discov.* 2018; 8(2):164-173.



Contributor

Ryan Corcoran, MD, PhD

Principal Investigator,
Center for Cancer
Research, Massachusetts

General Hospital Cancer Center;
Assistant Professor of Medicine,
Harvard Medical School
rcorcoran@partners.org

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Cancer Center

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

MGHAdvancesinCancer@partners.org

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