CANCER DISCOVERY

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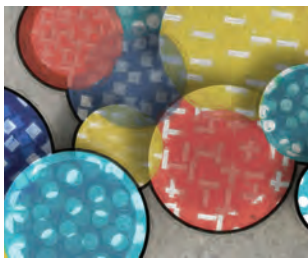
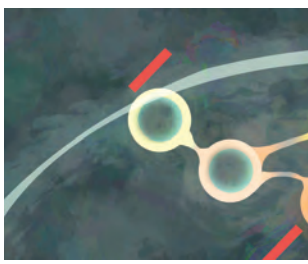
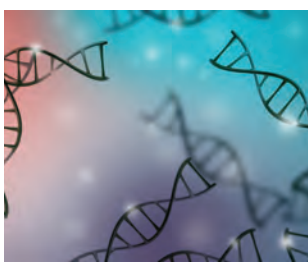
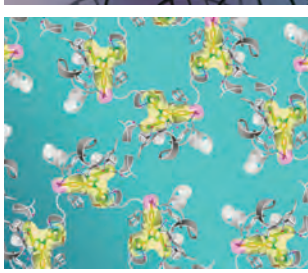
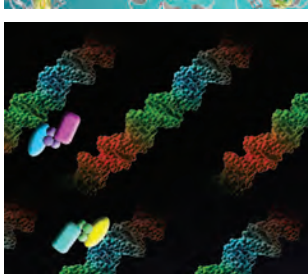
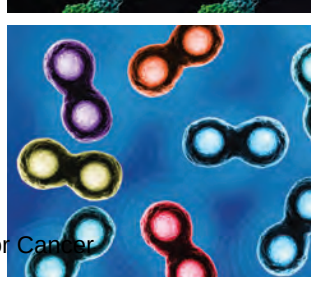






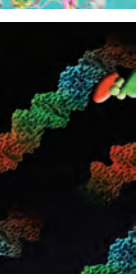
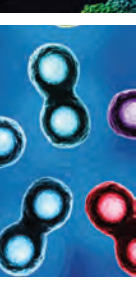

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ON THE COVER In an open-label phase I trial of 142 patients with *BRAF*^{V600}-mutant colorectal cancer, Corcoran and colleagues assess the safety and efficacy of BRAF plus EGFR inhibition (in 20 patients receiving dabrafenib and panitumumab; D+P), MEK plus EGFR inhibition (in 31 patients receiving trametinib and panitumumab; T+P), or "triplet" BRAF, MEK, and EGFR inhibition (in 91 patients receiving dabrafenib, panitumumab, and trametinib; D+T+P) to determine if EGFR inhibition would suppress MAPK reactivation to enhance the efficacy of BRAF inhibition. Overall response rates were 10% for D+P, 0% for T+P, and 21% for D+T+P, with D+T+P achieving the greatest reduction in MAPK pathway activity. Serial cfDNA analysis identified potential resistance mutations linked to disease progression. The results of this trial indicate that combined targeting of BRAF, EGFR, and MEK may suppress adaptive feedback pathways to improve responses in patients with *BRAF*^{V600}-mutant colorectal cancer. For details, please see the article by Corcoran and colleagues on page 428.

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