inhibitor, BI 1701963, alone and in combination with the MEK inhibitor Mekinist (trametinib).

Concerns about their likely toxicity persist, however. “At the moment, I remain unconvinced about where the therapeutic index comes from. You’re targeting all cells that use those pathways,” says Downward. Revolution Medicines CEO Mark Goldsmith says his company has already established that MEK inhibition and SHP-2 inhibition are highly synergistic in preclinical models. “The onus is on us to demonstrate that kind of activity in patients,” says Goldsmith. Other potential combination candidates include mammalian target of rapamycin (mTOR) inhibitors and insulin-like growth factor receptor inhibitors. “RAS inhibitors can combine quite well with mTOR inhibitors in terms of growth inhibition,” says Downward. “It’s very clear that IGF-1 [insulin-like growth factor 1] signaling is important in cancer generally.”

Important as KRAS^{G12C} is — particularly in lung adenocarcinomas, where it occurs in about 13% of cases — it is not the most prevalent oncogenic KRAS mutation. “G12D and G12V are number one and number two in terms of frequency,” Der says. Revolution Medicines is also taking a lead in getting beyond the KRAS^{G12C} mutation. Revolution Medicines is employing a novel KRAS-targeting technology that allows it to address the three key mutational hotspots on KRAS, at positions 12, 13 and 61. Each can be substituted by half a dozen different amino acids. “The vast majority of oncogenic KRAS mutations that cause human cancer are at one of those hotspots,” Goldsmith says. “They all happen to be very close to each other.” The approach was originally developed at Warp Drive Bio, which Revolution Medicines acquired in October 2018. It exploits a binding interaction between an immunosuppressive natural product, sanglifehrin A, and cyclophilin A, an abundant chaperone protein involved in protein folding. By attaching

different chemical groups to the cyclophilin-A binding moiety of sanglifehrin A, Revolution Medicines can generate composite surfaces that can engage different RAS mutations and block their interaction with RAF. The company’s inhibitors bind the GTP-bound active form of RAS, which, it claims, makes them less susceptible to resistance driven by upstream pathway activation. Revolution has yet to disclose when it will move any of its ‘KRAS(ON)’ inhibitors into the clinic, but Moderna and its partner Merck are already in the clinic with a therapeutic vaccine that targets several KRAS mutations, and Mirati is about to enter Investigational New Drug-enabling studies with a KRAS^{G12D} inhibitor. The race to drug KRAS — in all its forms — is now on. □

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Published online: 9 January 2020
<https://doi.org/10.1038/s41587-019-0382-x>

Around the world in a month

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Published online: 9 January 2020
<https://doi.org/10.1038/s41587-019-0378-6>