When a patient of Adil Daud started to take an experimental combination of immunotherapy drugs for melanoma in 2015, he had a grapefruit-sized growth bulging under his armpit. The tumour was inoperable, and Daud suspected that the cancer had spread to the 69-year-old man's lungs. But the two immunotherapeutic agents — the antibodies nivolumab and ipilimumab — had a remarkable effect. "The tumour just melted away," says Daud, an oncologist at the University of California, San Francisco Medical Center. "Within a few weeks, it had vanished."

By giving immunotherapies to people with cancer, doctors hope to spark a self-sustaining attack against cancer cells by immune cells known as T cells that produces long-term clinical benefits, or even a cure. More than 2,400 immunotherapeutic agents are in clinical development, reports the Cancer Research Institute in New York City. But some people will respond better to the drugs than do others, and many don't respond to them at all. Moreover, tumours can become resistant to such agents over time.

These limitations have pushed immunotherapy researchers towards the use of several drugs in combination. "There's lots of interest in these trials, and people are tripping over each other trying to test as many combinations as possible," says Leena Ghandi, a thoracic medical oncologist at the Laura and Isaac Perlmutter Cancer Center of the New York University Langone Medical Center. Other data gathered by the Cancer Research Institute show that 403 such trials opened worldwide in the first six months of 2017 (see 'More trials, better targeted'). More than 1,100 are in progress.

By combining immunotherapies, or pairing them with other types of cancer treatment such as chemotherapy or radiation, researchers hope to enhance and broaden their benefit. But combination treatments for cancer that include immunotherapies face specific challenges, both clinical and economic. Immunotherapies send cancer-cell-killing T cells into overdrive, and some trigger dangerous autoimmune reactions that combination treatments can exacerbate. And the cost of the drugs is much greater than that of conventional treatments for cancer — a prescription for a single immunotherapy drug can easily exceed US$100,000 per year, so combining them only drives up the expense.

"It's imperative that two- and three-drug regimens lead to clinical benefits that justify
Inhibitors show greater toxicity. That's because the activity of CTLA-4 is distributed more widely throughout the body, meaning that inhibiting it may harm the body's natural ability to fight off autoimmune side effects.

Researchers are testing recipients of checkpoint inhibitors also varies by tumour type. According to Ott, 60% of people with melanoma, 20% of those with breast, and 10% of those with Merkel cell carcinoma (an aggressive form of skin cancer) never respond to treatment that consists of checkpoint inhibitors alone.

Duda says that researchers were drawn initially to the combination of PD-1 and CTLA-4 inhibition because drugs with these two targets are well established. Ipilimumab was the first checkpoint immunotherapy to reach the market in 2011, and the first two PD-1 inhibitors, pembrolizumab and nivolumab, won regulatory approval in 2014. Nevertheless, the combination seems to make sense, says Duda.

The combination of PD-1 and CTLA-4 inhibitors has since moved into clinical trials for other malignancies, including stomach, breast, bladder, pancreatic, renal, lung and head and neck cancer. The pairing still makes up the lion's share of immunotherapy combination trials. As of September 2017, for example, 69% of those with advanced melanoma had received checkpoint treatment. But the approach also exposes the cancer cell to PD-1, nivolumab prevents it binding to PD-L1, which is expressed in many cancer cells,