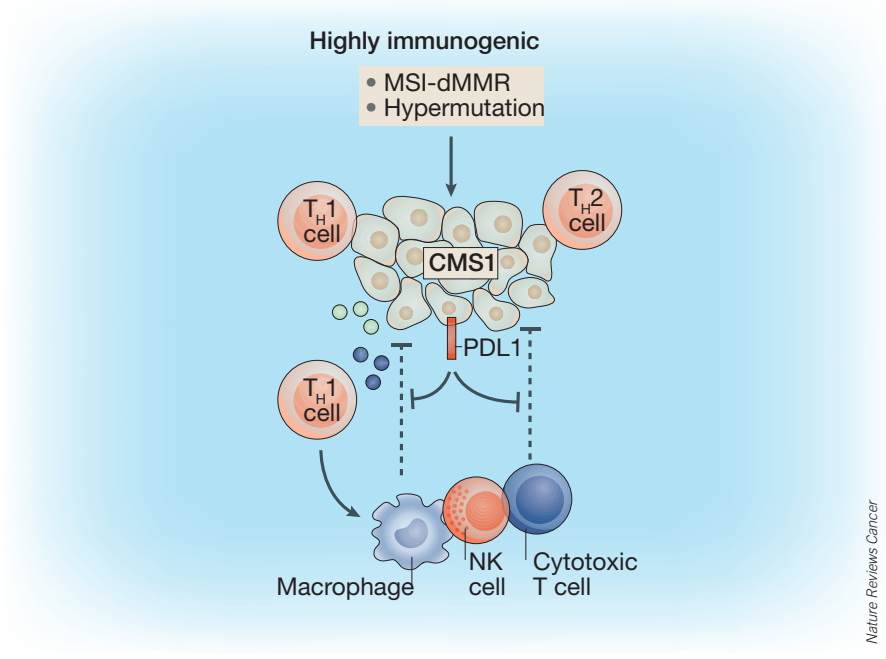
Oncologists await historic first: a pan-tumor predictive marker, for immunotherapy

The first cancer drug approval based on a marker, not a tumor type, appears imminent. The FDA has set a June 9 action date to decide whether Merck's checkpoint inhibitor Keytruda (pembrolizumab) can be used with a test for microsatellite instability in previously treated cancer patients. "It will be the first pan-tumor marker in the history of oncology or FDA approval," says Luis Diaz, head of solid tumor oncology at Memorial Sloan-Kettering Cancer Center in New York and a Keytruda trial lead investigator. Keytruda, an anti-programmed death-1 (PD-1) antibody made by the Kenilworth, New Jersey–based pharma, is already approved for metastatic melanoma, Hodgkin lymphoma and certain lung and head and neck cancers (*Nat. Biotechnol.* **33**, 1217–1218, 2015). But should the US Food and Drug Administration (FDA) give the go-ahead to the drug/test combination, its blanket approval across all tumor types would mean that all advanced cancers will probably be tested for high-level microsatellite instability (MSI-H) or its underlying cause, a DNA repair pathway defect. This would be the first purely molecular indication for a cancer drug—a major advance in clinical oncology.

An estimated 1 in 25 tumors (all types combined) displays a high degree of microsatellite instability. This hypermutation phenotype usually results from replication errors due to a failure in the DNA mismatch repair system (MMR).

A deficient MMR generates a mutation burden typically one to two orders of magnitude higher than in MMR-proficient cells. Tumor cells are unable to correct erroneous base insertions or deletions, leading to many subsequent missense mutations across the genome. Because short tandem repeats, called microsatellites, are especially vulnerable to mutations, they have proved useful as hypermutation markers.

This dramatically increased mutation burden in turn makes MMR-deficient tumors very sensitive to checkpoint blockade, because many of the randomly mutated genes generate mutant proteins seen as foreign by T cells. Early clinical data seemed to back this hypothesis. An investigator-sponsored phase 2 trial at Johns Hopkins University in Baltimore showed four of ten MMR-deficient advanced colorectal cancer patients had an objective response to Keytruda by standard criteria, whereas no patients with MMR-proficient tumors responded. In patients with cancers other than colorectal, who were also MMR-deficient, five of seven responded (*N. Engl. J. Med.* **372**, 2509–2520, 2015).



Tumor cells deficient in the mismatch repair system are highly immunogenic, presenting many neoantigens to the immune system, but checkpoint activation stops immune cells from attacking the tumor.

Top heart-failure contender serelaxin flops

Novartis has announced that acute heart failure drug serelaxin (RLX030) has failed to meet its primary endpoints in a phase 3 trial, casting doubts over the future of a drug once thought to be a strong candidate for blockbuster status. The Basel, Switzerland–based pharma harbored high hopes for the recombinant full-length human relaxin-2 hormone, following early results where serelaxin reduced deaths in people with acute heart failure by 37%, compared with conventional treatment. The outcomes of later trials were mixed, in part, it was thought, because of the difficulties in defining worsening heart failure. Then in 2014, both the US Food and Drug Administration and the European regulator rejected serelaxin. (*Nat. Biotechnol.* **32**, 602–603, 2014), stating that the drug failed statistically to meet its primary endpoint of relief of dyspnea or shortness of breath in a single-arm trial. Novartis revised the trial design addressing the points that led to the rejection. Even so, in the latest study, a 6,600-patient phase 3 trial dubbed RELAX AHF-2, which evaluated serelaxin in addition to standard of care, the drug fell short of its primary endpoints of reducing cardiovascular death or ameliorating worsening heart failure. The rationale for looking at relaxin in heart failure was compelling: the hormone is produced by the ovaries and placenta during the normal course of pregnancy, to help remodel connective tissue for cervical ripening, as well as support physiological changes to accommodate the increased demands on the cardiovascular system. Following the most recent setback, Novartis has announced it will continue to analyze the data for serelaxin to learn from the results and determine its next steps.

Real world points to SGLT-2 blockers advantage

A post-marketing study showing that sodium glucose cotransporter-2 (SGLT-2) inhibitors trump other glucose-lowering medications in cutting cardiovascular risk could shake up how diabetologists and cardiologists treat type-2 diabetes. Researchers from Cambridge, UK-based AstraZeneca sifted through records of more than 300,000 patients across six countries in the CVD-REAL study presented at the American College of Cardiology's Annual meeting in Washington, DC, on March 19. The investigators found that the SGLT-2 inhibitors slashed heart failure hospitalization rates by 39% compared with other diabetes treatments and cut deaths from any cause by 51%. The SGLT2s targeted by these drugs are located in the proximal tubule of the nephron. SGLT-2 inhibitors thus lower blood glucose by a novel mechanism: they block glucose reabsorption in the kidney. The first SGLT-2 inhibitor to market was AstraZeneca and Bristol-Myers Squibb's Forxiga (dapagliflozin), approved in November 2012 in Europe. (*Nat. Biotechnol.* **31**, 469–470, 2013). Other approved SGLT-2 inhibitors include Johnson & Johnson's Invokana (canafliflozin) and Eli Lilly/Boehringer Ingelheim's Jardiance (empagliflozin). In this study, more than 90% of patients were on Forxiga or Invokana. Merck and Pfizer are also collaborating to bring an SGLT2 rival drug, ertugliflozin, to market as well as on two combinations containing the drug to treat type 2 diabetes.