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Mismatch-repair deficiency (dMMR) is a feature of a considerable proportion of tumours, across a range of cancer types. These tumours typically harbour thousands of mutations and are postulated to present neoantigens that might be exploited for effective immunotherapy. New data reported by Dung Le *et al.* support this hypothesis, underscoring MMR as a predictive biomarker and expanding the indications for PD-1 blockade.

In a previous trial, Le *et al.* showed that dMMR can be used to select a subset of patients with colorectal cancer (CRC) who are likely to respond to anti-PD-1 antibodies, such as pembrolizumab. "To test the hypothesis that diverse dMMR tumours would respond to pembrolizumab, in the current trial, we studied two cohorts of patients with either dMMR CRC or dMMR cancers of any other type," Le explains. The trial population encompassed 12 cancer types (including CRC, cholangiocarcinoma, osteosarcoma, pancreatic, prostate, and endometrial tumours), and comprised 86 patients with progressive advanced-stage disease after at least one prior therapy. The patients were selected using widely available PCR or immunohistochemical assays for dMMR. "The basket design of the trial made it feasible to study a genomic mutation phenotype that is rare in some cancers," adds co-author Hao Wang.

Among 78 evaluable patients, the rates of objective, complete, and stable-disease responses were 53%, 21%, and 77%, respectively. "The objective response rate was virtually identical in both cohorts, supporting the notion that dMMR is predictive of a response regardless of histology; the responses have been so durable that the median duration of response has not been reached," Le states. Indeed, the 2-year progression-free and overall survival estimates were better than expected based on the characteristics of the trial population: 53% and 64%, respectively, with a plateau beyond this timepoint. Of note, 18 patients discontinued treatment, none of whom had evidence of progression after ~8 months off therapy.

Kellie N. Smith, another of the investigators involved, describes how they plan to take this work forward: "from an immunology standpoint, we want to perform in-depth studies on samples from these patients to determine why, despite having dMMR tumours, not all of them responded. Clearly, this genetic marker helps to select patients who are most likely to benefit, but it isn't the entire puzzle." Interestingly, the researchers found no evidence that a low mutational burden or mutations in the *B2M* gene, encoding the MHC class I subunit β_2-microglobulin, have a role in intrinsic (primary) resistance; however, *B2M* mutation was implicated in acquired resistance.

Le concludes: "the FDA has now approved the use of pembrolizumab for 'microsatellite-instability-high' or dMMR cancers, regardless of tissue of origin — the first tissue-agnostic indication of a therapeutic. This approval brings an effective new option that could apply to almost any patient with an advanced-stage solid tumour, and opens the door for the possibility of other approvals that are tissue-agnostic."

David Killock

ORIGINAL ARTICLE Le, D. T. *et al.* Mismatch-repair deficiency predicts response of solid tumours to PD-1 blockade. *Science* http://dx.doi.org/10/1126/science.aan6733 (2017)