HAEMATOLOGICAL CANCER

Early prediction of AML risk

The accumulation of somatic mutations in several genes precedes the onset of acute myeloid leukaemia (AML). Two studies now indicate that such alterations can be detected years before diagnosis — a latency period during which monitoring of patients at risk could be improved.

Blood samples collected at the time of enrolment in large population cohorts with long follow-up durations were used in both studies. In a study published in *Nature*, Abelson and collaborators analysed samples from EPIC trial participants diagnosed with AML at an average of 6.3 years after enrolment ($n=95$) or not diagnosed at an average of 11.6 years after enrolment (control group, $n=414$). In a study published in *Nature Medicine*, Pinkal Desai et al. analysed samples from Women's Health Initiative participants with or without a diagnosis of AML ($n=212$ in each group; median time to diagnosis 9.6 years after enrolment).

In both studies, peripheral blood cells from individuals diagnosed with AML were more likely to harbour mutations than those from individuals in the control group; *DNMT3A*, *TET2*, and *TP53* were the most frequently mutated genes in both cohorts. Alterations in several other genes were found to contribute to the risk of developing AML.

"There is a clear early genetic signal, but further refinement is needed to reliably predict a rare disease such as AML in the general population," explains Moritz Gerstung, involved in the study published in *Nature*. Using a machine-learning approach, these investigators analysed non-genetic information in electronic health records from 4,500 individuals in the Clalit database. They developed a prediction model with which they were able to predict AML 6–12 months before diagnosis with 25.7% sensitivity and 98.2% specificity.

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"We have to improve the accuracy of these prediction markers using additional genomic techniques (such as methylation panels) before testing clinical interventions," clarifies Paul Brennan, involved in the *Nature* study. For both Gerstung and Desai, subsequent studies would involve prospective trials of potential early therapeutic interventions (such as targeted therapies) in large cohorts of individuals with a high risk of AML.

"It's exciting that the mutation patterns leading to AML were largely similar between studies and we both identified a window of opportunity preceding an otherwise acute disease," summarizes Duane Hassane, principal investigator of the *Nature Medicine* study. "This accelerates the momentum for further detection, monitoring, and prevention studies in a way that a single study could not," he concludes.

Diana Romero

ORIGINAL ARTICLES Abelson, S. et al. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature* **559**, 400–404 (2018) | Desai, P. et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat. Med* **24**, 1015–1023 (2018)

GASTROINTESTINAL CANCER

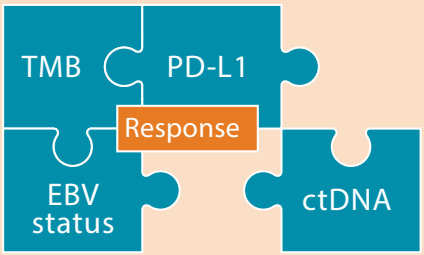
Immunotherapy-responsive gastric cancers identified

The anti-PD-1 antibody pembrolizumab is an FDA-approved treatment of PD-L1-positive metastatic gastric cancer; however, only a subset of patients respond to this agent. Now data from a single-arm phase II trial shed some light on the reasons for these variable responses.

"We designed a phase II trial, with integrated genomic analysis of all baseline tumour tissue samples and genomic profiling of circulating tumour DNA (ctDNA) samples in order to understand the disease characteristics of responders and nonresponders," explains Jyun Lee, a senior investigator on this study. This open-label trial included 61 patients with metastatic and/or recurrent gastric adenocarcinomas. The cohort included six patients with Epstein–Barr virus (EBV)-positive disease and seven with microsatellite-instability high (MSI-H) disease.

Similar to the findings of previous trials, an overall response rate (ORR) of 24.6% was observed. Notably, 85.7% of patients with MSI-H tumours, and all patients with EBV-positive disease, responded to pembrolizumab.

Researchers also investigated the relationship between biopsy-based tumour mutational burden (TMB) and response, observing a positive correlation with response to pembrolizumab (area under the curve 0.74; $P=0.006$). A similar relationship was observed between ctDNA-based TMB, quantified using a 73-gene next-generation sequencing panel, and response to pembrolizumab. In a longitudinal analysis of samples from a subset of patients, changes in ctDNA level at 6 weeks after treatment with pembrolizumab were found to be predictive of a response: all 4 patients with increased ctDNA levels at 6 weeks had disease progression within 100 days of starting treatment.



Credit: S. Bradbrook/Springer Nature Limited

"The most significant finding of this work is that patients with MSI-H and EBV-positive gastric cancer have robust and sustained responses to pembrolizumab monotherapy," summarizes Lee, adding "we also demonstrated that ctDNA mutational burden correlates very well with TMB and that decreasing ctDNA levels are a statistically significant predictor of prolonged PFS." Prospective validation of these findings, which have the potential to substantially improve the treatment of metastatic gastric cancer, is eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLE Kim, S. T. et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat. Med.* https://doi.org/10.1038/s41591-018-0101-z (2018)