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PANCREATIC CANCER

Disrupting the chemokine axis in PDAC

The pancreatic tumour microenvironment is unique in that at least 80% of the cells within the tumour are stromal cells rather than cancer cells. David Linehan and colleagues wondered whether "these noncancer cells that infiltrate the tumour could explain why pancreatic cancer is so refractory to treatment". In preclinical studies, Linehan's team had shown that a chemotactic process exists by which tumours mobilize inflammatory monocytes from the bone marrow to the peripheral blood and, ultimately, to the tumour, where they then become immunosuppressive tumour-associated macrophages (TAMs). They also showed that this process was controlled by the CCR2–CCL2 chemokine axis, and that inhibiting CCR2 enhanced the effects of chemotherapy.

This preclinical work prompted Linehan and co-authors to assess whether the CCR2 inhibitor PF-04136309 was safe and tolerable when combined with FOLFIRINOX chemotherapy in patients with untreated, borderline resectable or locally advanced pancreatic cancer. Of 33 patients included in a phase I dose-expansion cohort, 16 (49%) achieved an objective tumour response, with local control achieved in 32 patients (97%). No patients in the FOLFIRINOX group had an objective response, although 80% had stable disease.

The researchers showed that "CCR2 inhibition in combination with standard chemotherapy had better than expected response rates and several patients with locally advanced disease were downstaged to resectability". Moreover, assessement of serially collected tumour, bone marrow and peripheral blood samples showed that TAMs were depleted from the tumour microenvironment, and were reprogrammed from an immunosuppressive to an immune-activated type. "Based on the promising results of this trial, we are initiating a phase II randomized trial in patients with metastatic disease", says Linehan.

Lisa Hutchinson

ORIGINAL ARTICLE Nywening, T. M. *et al.* Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase Ib trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(16)00078-4 (2016)

FURTHER READING Garrido-Laguna, I. & Hidalgo, M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat. Rev. Clin. Oncol.* **12**, 319–334 (2015)