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HAEMATOLOGICAL MALIGNANCIES

# Double act in follicular lymphoma

Follicular lymphoma is the most common form of indolent non-Hodgkin lymphoma. It presents as stable disease that can last months, even years, before progression thanks to the activity of the immune system against lymphoma cells. However, this naturally induced immune response against the tumour is eventually rendered ineffective, likely due to immune checkpoints in the microenvironment.

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Programmed cell death 1 (PD-1) is a receptor that inhibits T-cell activation when switched on by its ligand, PD-L1, which is expressed on tumour and stromal cells. Sattva Neelapu and colleagues speculated that blocking of immune checkpoints—by blocking PD-1, for instance—might promote the endogenous antitumour immune response observed in folicullar lymphoma and enhance the efficacy of immunotherapy regimens. “*In vivo* studies in mouse lymphoma xenograft models showed that the combination of an anti-PD-1 monoclonal antibody with rituximab, an anti-CD20 monoclonal antibody that targets B-cell lymphomas, improved the survival of mice compared with either one alone,” explains Neelapu. These observation led Neelapu and his coworkers to initiate a phase II trial reported recently in *The Lancet Oncology*, in which they tested the combination of pidilizumab, a recombinant monoclonal antibody that targets PD-1, and rituximab in patients with relapsed follicular lymphoma.

The results included the analysis of 29 patients who had relapsed after one to four previous therapies and who were followed for a median of 15.4 months. The combination of pidilizumab and rituximab showed both high objective response (66%, 19 patients out of the 29 patients who had been treated) and complete response; “unexpectedly, we observed that the complete response rate (52%) was very high compared with 11% observed historically in patients retreated with rituximab monotherapy,” remarks Neelapu. The median progression-free survival was not reached in the 19 patients with an objective response and only 7 of these responders had progressed at the time the results were published. This also compared favourably with the estimated median time to progression of 17.8 months reported with treatment with rituximab alone. Importantly, this clinical benefit was obtained without any significant toxicity, which makes this combination especially appealing for patients with follicular lymphoma, most of whom are elderly.

But, is pidilizumab really enhancing the antitumour immune response as hypothesized? “Correlative studies on the peripheral blood and tumour samples showed that pidilizumab activated T cells and natural killer cells and enhanced endogenous antitumour immune responses, consistent with its


expected mechanism of action”, clarifies Neelapu. More importantly, the authors identified a 41-gene signature (T-cell activation signature or a signature of genes repressed in follicular helper T cells) in tumour biopsies prior to treatment that was associated with tumour response and improved PFS. Neelapu explains the importance of this finding: “validation of this signature in additional studies may help identify patients that are likely to benefit with this therapy *a priori*”.

Although the benefit of this combination will have to be confirmed in a randomized study, these results indicate that Neelapu and colleagues are on the right track.

***M. Teresa Villanueva***

**Original article** Westin, J. R. *et al.* Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol.* **15**, 69–77 (2014)