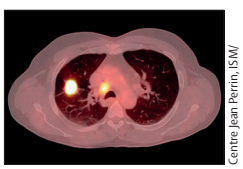
Can pegylated IL-10 add to a backbone of PD-1 inhibition for solid tumours?



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With the activity of checkpoint inhibitor monotherapy well documented in several diseases, attention has turned to developing effective combinations. Adding to the backbone of PD-1 inhibition, perhaps the most successful combination strategy to date has been with CTLA-4 inhibition. The combination of nivolumab (a PD-1 inhibitor) with ipilimumab (a CTLA-4 inhibitor) has been approved by the US Food and Drug Administration for the treatment of melanoma, renal cell carcinoma, and mismatch repair deficient or microsatellite unstable colorectal cancer. However, not all pairings of immunotherapy have been successful. A phase 3 study[1] that assessed the combination of the IDO1 inhibitor epacadostat with pembrolizumab (a PD-1 inhibitor) in patients with advanced melanoma showed no benefit versus pembrolizumab with placebo. The findings from this study suggested that not all immunotherapy combinations will have clinical synergy in an unselected population.

Success with immunotherapy combinations starts with a strong biological rationale. In *The Lancet Oncology*, Aung Naing and colleagues[2] present data from their phase 1b study of pegilodecakin (pegylated IL-10) combined with either pembrolizumab or nivolumab for patients with advanced solid tumours. The anticancer effect of IL-10 is complex albeit well studied, and probably occurs through two mechanisms: (1) reduction of tumour-promoting inflammation and (2) stimulation of CD8+ T cells in the tumour milieu.[3] In support of the first mechanism, one study[4] examining IL-10-deficient mice showed that they had a marked increase in entercolitis and subsequent development of colorectal adenocarcinomas compared with wild-type mice. These differences were driven by uninhibited cytokine production by activated macrophages and CD4+ T-helper-1-like T cells. Treatment of these mice with IL-10 delayed cancer progression. In another study investigating the second mechanism of IL-10-mediated CD8+ T cell stimulation, researchers[5] examined *HER2* transgenic mice with mammary carcinomas. Treatment with pegylated IL-10 induced a significant increase in CD8+ T-cell infiltration in the tumours. By contrast, depletion of CD8+ T cells through antibody treatment diminished the antitumour effect of IL-10. Beyond these preclinical studies, clinical rationale for combining PD-1 inhibition with pegylated IL-10 was shown in a phase 2 study[6] in patients with advanced melanoma, linking increased baseline IL-10 concentrations to a greater number of patients achieving a tumour response.

In their study, Naing and colleagues[2] recruited 111 patients, 53 of whom received pegilodecakin plus pembrolizumab and 58 of whom received pegilodecakin plus nivolumab. 34 (31%) of 111 patients had non-small-cell lung cancer, 37 (33%) had melanoma, and 38 (34%) had renal cell carcinoma. One patient each had triple-negative breast cancer and bladder cancer, and recruitment to these two groups was stopped. 12 (43%) of 28 evaluable patients with non-small-cell lung cancer and 14 (40%) of 35 evaluable patients with renal cell carcinoma achieved a response, which is higher than historical efficacy data with single agent PD-1 inhibitors in unselected patients with these tumour types. However, only three (10%) of 31 evaluable patients with melanoma achieved a response.[7,8] Differences in previous therapy could account for this difference—all patients with non-small-cell lung cancer and all but one patient with renal cell carcinoma were checkpoint inhibitor-naive. By contrast, 68% of patients with melanoma had received previous checkpoint inhibitor therapy. The investigators concluded that these results did not support further exploration in patients with melanoma; however, these data could simply imply that the addition of pegylated IL-10 might not overcome checkpoint inhibitor resistance in this setting.

The outlook for pegylated IL-10 with checkpoint inhibitor therapy in patients with non-small-cell lung cancer and renal cell carcinoma is encouraging, but further clinical development can be challenging without fully understanding how to select the patient population. The phase 3 CheckMate-214 study[9] compared nivolumab plus ipilimumab versus the VEGF inhibitor sunitinib in patients with treatment-naive advanced renal cell carcinoma. Nivolumab plus ipilimumab significantly improved survival in intermediate-risk and poor-risk patients, with 46% achieving a response and 9% achieved a complete

response. In a phase 3 study,[9] nearly 60% of patients with advanced renal cell carcinoma achieved a response with combinations such as axitinib (a VEGF inhibitor) with pembrolizumab. Similarly, for patients with non-small-cell lung cancer and high tumour mutational burden (≥ten mutations per megabase), in the phase 3 CheckMate 227 trial[10] 45% achieved a response rate with nivolumab plus ipilimumab compared with 27% achieving a response with chemotherapy.

Considering the caveats of cross-trial comparisons, pegylated IL-10 with checkpoint inhibition seems to produce similar results at best, suggesting that it would not displace these combinations in a randomised study designed to assess its superiority as initial therapy in patients with renal cell carcinoma and without any patient selection. One advantage offered by the combination of pegilodecakin with pembrolizumab or nivolumab[2] was the favourable adverse event profile with an easily managed spectrum of toxicities (most notably anaemia, thrombocytopenia, and fatigue). The presented data did not address the possibility of pegylated IL-10 in the salvage setting for renal cell carcinoma and non-small-cell lung cancer; however, the data for melanoma (in a largely checkpoint-inhibitor pre-treated cohort) did not provide much support for this approach. The key next step for further development of this combination, and all combination strategies designed to improve the efficacy of checkpoint inhibitors, is to fully understand the mechanisms of response of each combination and develop biomarkers to select patients who would most likely respond.

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Complete mesocolic excision for colon cancer: is now the time for a change in practice?

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Complete mesocolic excision for colon cancer has gained increasing popularity over recent years following publication of the Erlangen experience in 2009.[1] The investigators of this study[1] standardised their surgical approach for potentially curative disease, leading to a reduction in local recurrence (from 6·5% to 3·6%) and improvement in cancer-related 5-year survival (from 82·1% to 89·1%) over a 24-year period. Complete mesocolic excision is based on similar principles to total mesorectal excision for rectal cancer, a technique now considered the international gold standard. Total mesorectal excision has led to substantial improvements in outcomes through removal of the tumour in an intact package containing all major routes of dissemination.[2]

Optimal complete mesocolic excision surgery comprises three important components: the specimen should be removed in the mesocolic plane ensuring