

# Overcoming resistance to immunotherapy through multimodal approaches: is there hope for colorectal cancer?

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The immune response to cancers may shape the course of the disease: patients whose tumours are rich in tumour infiltrating lymphocytes have a better prognosis, an observation first made nearly a hundred years ago for several epithelial solid tumours (1). Recent investigations have revealed different immune cells types with particular immunological functions may contribute to colorectal cancer (CRC) cell growth or death (2), building upon much cited work demonstrating that the function, location and number of colorectal tumour-infiltrating T cells impacts on cancer progression (3). Indeed, even the specificity of antigenic targets in CRC may affect outcome: it has been shown that the presence of *ex vivo* CEA-specific T cell responses measured pre-operatively is associated with worse prognosis (4). The increasing recognition in recent years of the role of the immune system in tumour control, and the consequent remarkable success in treating certain tumours like melanoma with checkpoint inhibitors, has led to a paradigm shift in thinking about immune-based interventions in cancer (5). Moderate success has been achieved in a subgroup of CRC patients given anti-PD1 blocking antibodies, almost exclusively with tumours exhibiting microsatellite instability (MSI) (6). It is reasoned these tumours expressing a relatively high neoantigen load have an enhanced capability of stimulating immunological responses.

However, less than 20% of CRCs contain a high

neoantigen load/MSI. Indeed, microsatellite stable (MSS) tumours, account for nearly all advanced CRC cases, and these have remained stubbornly resistant to most immunotherapies, most notably immune checkpoint inhibitors. In addition, anti-cancer vaccines are rarely efficacious in this situation, frequently coming up against immunosuppressive responses that counteract the induction of beneficial anti-tumour immunity. Going forward, it has become clear that for MSS CRC, we must target distinct immunological functions that both augment anti-tumour immunity and inhibit the tumour-induced immunosuppression, warranting a multimodal approach. Yarchoan and colleagues attempted to overcome the inherent resistance of MSS CRC to immune checkpoint inhibitor therapy by combining pembrolizumab (anti-PD-1) with GVAX, an allogenic whole-cell vaccine that induces colorectal tumour antigen-specific T cell responses (7). This open-label, single arm study determined the objective response rate of 17 MSS+ CRC patients as the primary outcome measure, alongside secondary measures of 1-year progression free/overall survival, duration of response and safety. This trial is essentially a Phase I study, and with no control arm, it is difficult to interpret end-points other than safety and tolerability (listed as secondary endpoints). Whilst no objective responses to study therapy were observed, three patients had stable disease (SD) by RECIST 1.1 criteria, although two additional patients demonstrated SD using

immune related response criteria (irRC). In addition, there were hints that anti-tumour immunity had been successfully induced amongst a further six patients who did not exhibit radiological-assessed tumour control. The tumour marker carcinoembryonic antigen (CEA) was measured as a biochemical readout of possible tumour control via the induction of anti-tumour immunity; a 30% decrease over baseline in CEA was observed in 7/17 patients. Crucially, pembrolizumab monotherapy in a prior cohort of advanced MSS+ CRC patients failed to reduce CEA level in any patient (8), indicating that combination with vaccine and/or cyclophosphamide is responsible for the additional anti-tumour immunity being induced in certain trial participants. Further indications that this treatment regimen could induce beneficial immunologic changes were highlighted in a corresponding trial evaluating a very similar treatment course in pancreatic cancer (9). Increased T and NK cell densities and reduced tumour-associated macrophages were only observed in long-term survivors receiving nivolumab alongside GVAX and cyclophosphamide. Thus, checkpoint inhibition used in combination with immune potentiating therapies can yield additional, beneficial immunologic changes not seen with monotherapy.

Whilst multi-faceted immunotherapeutic treatment strategies are necessary, this brings new challenges with anticipating those treatments that provide maximal synergistic benefit. Of note, the aforementioned studies employed low-dose cyclophosphamide, having prior confirmed efficacy in reducing tumour-induced immunosuppression and enhanced immunological responses to GVAX. However, combination with other vaccines for CRC have not revealed significant additive effects; depletion of regulatory T cells and induction of anti-tumour  $T_H1$  (IFN- $\gamma$ +) responses were distinct events that independently prolonged patient survival, but no significant benefit was found when used in combination (10). Concerningly, there are recent reports that low-dose cyclophosphamide, an increasingly employed adjunct used to bolster anti-tumour immunity, may dampen or reverse the effectiveness of immune checkpoint inhibitors (11,12), by lymphodepleting effector T cells alongside regulatory T cells. Hence its continued use, timing and route of administration (i.e., oral or i.v.) in treatment schedules should be carefully evaluated before proceeding (13).

Future immunotherapeutic trials in CRC may benefit from dividing patients up into well-defined groups [e.g., consensus molecular subtypes (CMS) which looks at features such as immune cell infiltrate and microsatellite

stability, levels of TGF- $\beta$  pathway activation etc.], and directing groups of CRC patients towards more rational immunotherapy (14); for example, co-administration of TGF- $\beta$  inhibitors for CMS-4 tumours. In addition, the next generation of treatments targeting molecules known to be enacting significant immunosuppression within colorectal tumours, e.g., LAG-3 (NCT03642067) (15), LAP (16,17) and IDO (NCT02959437), may yet enable the potential for immunotherapy in CRC to be realised.

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## Footnote

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