



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

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Comment on: Yarchoan M, Huang CY, Zhu Q, *et al.* A phase 2 study of GVAX colon vaccine with cyclophosphamide and pembrolizumab in patients with mismatch repair proficient advanced colorectal cancer. *Cancer Med* 2020;9:1485-94.

Received: 18 June 2020. Accepted: 29 July 2020; Published: 30 December 2020.

doi: 10.21037/dmr-2020-23

View this article at: <http://dx.doi.org/10.21037/dmr-2020-23>

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<sub>H</sub>1 (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.

## Acknowledgments

*Funding:* MJS is funded by Cancer Research Wales. AG is funded by Cancer Research Wales, Cancer Research UK (C16731/A21200) and the Wellcome Trust Grant 209213/Z/17/Z.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/dmr-2020-23>). The authors have no conflicts of interest to declare.

*Ethical statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## References

1. McCarty M. Principles of prognosis in cancer. *J Am Med Assoc* 1931;96:30-3.
2. Koi M, Carethers JM. The colorectal cancer immune microenvironment and approach to immunotherapies. *Future Oncol* 2017;13:1633-47.
3. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal

- tumors predict clinical outcome. *Science* 2006;313:1960-4.
4. Scurr M, Brown C, Costa Bento D, et al. Assessing the prognostic value of preoperative carcinoembryonic antigen-specific T-cell responses in colorectal cancer. *J Natl Cancer Inst* 2015;107:djv001.
  5. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. *Science* 2013;342:1432-3.
  6. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol* 2018;36:773-9.
  7. Yarchoan M, Huang CY, Zhu Q, et al. A phase 2 study of GVAX colon vaccine with cyclophosphamide and pembrolizumab in patients with mismatch repair proficient advanced colorectal cancer. *Cancer Med* 2020;9:1485-94.
  8. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015;372:2509-20.
  9. Tsujikawa T, Crocenzi T, Durham JN, et al. Evaluation of Cyclophosphamide/GVAX Pancreas Followed by Listeria-mesothelin (CRS-207) With or Without Nivolumab in Patients with Pancreatic Cancer. *Clin Cancer Res* 2020;26:3578-88.
  10. Scurr M, Pembroke T, Bloom A, et al. Effect of Modified Vaccinia Ankara-5T4 and Low-Dose Cyclophosphamide on Antitumor Immunity in Metastatic Colorectal Cancer: A Randomized Clinical Trial. *JAMA Oncol* 2017;3:e172579.
  11. Toulmonde M, Penel N, Adam J, et al. Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas: A Phase 2 Clinical Trial. *JAMA Oncol* 2018;4:93-7.
  12. Lien IC, Pollack SM. Limited activity of metronomic cyclophosphamide and pembrolizumab for soft tissue sarcomas. *Transl Gastroenterol Hepatol* 2018;3:4.
  13. Hughes E, Scurr M, Campbell E, et al. T-cell modulation by cyclophosphamide for tumour therapy. *Immunology* 2018;154:62-8.
  14. Wang W, Kandimalla R, Huang H, et al. Molecular subtyping of colorectal cancer: Recent progress, new challenges and emerging opportunities. *Semin Cancer Biol* 2019;55:37-52.
  15. Long L, Zhang X, Chen F, et al. The promising immune checkpoint LAG-3: from tumor microenvironment to cancer immunotherapy. *Genes Cancer* 2018;9:176-89.
  16. Gabriely G, da Cunha AP, Rezende RM, et al. Targeting latency-associated peptide promotes antitumor immunity. *Sci Immunol* 2017;2:eaaj1738.
  17. Scurr M, Ladell K, Besneux M, et al. Highly prevalent colorectal cancer-infiltrating LAP<sup>+</sup> Foxp3<sup>-</sup> T cells exhibit more potent immunosuppressive activity than Foxp3<sup>+</sup> regulatory T cells. *Mucosal Immunol* 2014;7:428-39.

doi: 10.21037/dmr-2020-23

**Cite this article as:** Scurr MJ, Godkin A. Overcoming resistance to immunotherapy through multimodal approaches: is there hope for colorectal cancer? *Dig Med Res* 2020;3:85.