

Jan/Feb 2023 Winning E-Journal Club Submission by Dr Ciara McNevin

Title of review A Tale of Tumours

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Introduction/Aim:

Curative treatment of locally advanced rectal cancer (LARC) is arduous, typically including chemotherapy followed by radiation with chemotherapy followed by surgery. It is associated with a lifetime of urinary, bowel and sexual dysfunction in a young population. Some LARC will have missing proteins that can be targeted by immunotherapy. The aim of this study was to examine if patients could be saved the morbidity associated with standard of care treatment by selected them for immunotherapy treatment.

Design and Methods:

Patients with LARC identified as having mismatch repair-deficient (dMMR) tumour were treated with Dostarlimab an immunotherapy that targets the PD-1 ligand. The primary end points are (i) clinical complete response or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and (ii) overall response to dostarlimab with or without chemoradiotherapy.

Results and Conclusion:

12 patients were treated with dostarlimab. 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumour on examination, imaging and biopsy. Patients were followed for 6 months. At time of paper publication, no patients had received chemotherapy or radiotherapy or had undergone surgery. No cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

Strengths and Limitations:

The study only included 12 patients, which is very rare to see in a NEJM paper. However, the remarkable response to treatment by these patients warranted publication.

Applicability and Future Direction:

A Tale of Two Cities opens with “It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity”.

One could attest to the quotes applicability in the health services we live and work in today. Amidst the greatest of scientific achievements and mind boggling of human triumphs, lies profound failures. Vaccines are developed quickly, but are available to all too slowly. Health awareness rises, yet misinformation spreads. Patients are living longer, and yet on the crudest of metrics such as waiting lists and electronic records, progress is stagnate.

This trial encompasses the achievement arising from reverse engineering target therapies and stacking towers of science, from bench to bedside. That patients may avoid triplet therapy of chemotherapy, radiation therapy and surgery, and be cured from an invasive cancer from one course of a highly selected drug, is nothing short of outstanding and the epitome scientific advancement. It encourages us to continue our quest for better treatments for those who need it.

Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, Stadler Z, Yaeger R, Smith JJ, Rousseau B, Argiles G, Patel M, Desai A, Saltz LB, Widmar M, Iyer K, Zhang J, Gianino N, Crane C, Rommesser PB, Pappou EP, Paty P, Garcia-Aguilar J, Gonen M, Gollub M, Weiser MR, Schalper KA, Diaz LA Jr. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med*. 2022 Jun 23;386(25):2363-2376. doi: 10.1056/NEJMoa2201445. Epub 2022 Jun 5. PMID: 35660797; PMCID: PMC9492301.