Ten-Patient Trial: Remarkable Responses in Pediatric Cancers

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SUMMARY

A clinical trial of nivolumab in 10 patients with pediatric cancer with high tumor mutational burden demonstrated complete responses in 50% of patients. This result recapitulates multiple clinical trial results in high mutation–burden adult cancers and may redefine best practice in the setting of germline DNA mismatch repair–based susceptibility.

See related article by Das et al., p. 4770

In this issue of *Clinical Cancer Research*, Das and colleagues describe a single-arm clinical trial (NCT02992964) evaluating responses of pediatric solid tumors with high mutational burden (defined as ≥5 mutations per megabase), diagnosed with mismatch repair deficiency (MMRD), or prior treatment with temozolomide, to nivolumab, an anti-PD-1 inhibitor (1). After screening 20 patients by multiple assays, 11 were qualified to the trial, with 1 patient withdrawing following the initial therapy dose. Most patients had a malignant glioma diagnosis (7), with one each having neuroblastoma, colorectal carcinoma, and adrenal cortical carcinoma. All had failed first-line therapy and if radiotherapy had been received, over 6 months had passed prior to trial enrollment. Nine of 10 patients had germline susceptibility including constitutional MMRD or Lynch syndrome diagnoses. The only patient without germline susceptibility had alkylator chemotherapy-related high tumor burden after temozolomide therapy and focal loss of MSH6 staining. Every patient had measurable disease burden, except the patient with neuroblastoma with evaluable-only disease.

The primary objective of the trial was to evaluate objective response rate (ORR) to nivolumab treatment, defined as a combination of complete response (CR) and partial response (PR) as judged by imaging at 2-month intervals coupled with medically accepted criteria for response evaluation. Beyond these metrics, the patients were evaluated for immune best overall response which was indicated by the best response since treatment initiation and prior to progression, even after stopping treatment. Remarkably, although the initial evaluation of patients on trial yielded only a 20% ORR (one CR and one PR), there were delayed responses observed in multiple patients, yielding CR in 3 patients and PR in 2 patients. Thus, the best overall response was 50% and all patients continuing treatment were alive at time of reporting with a median follow-up of 37 months. Beyond this remarkable set of responses, the authors provide in-depth clinical profiles of 4 trial participants who achieved CR, highlighting the unique, case-specific aspects of multi-disciplinary care that may be required in this setting.

Importantly, the trial pursued several correlative assays to evaluate genomic and immune correlates of disease response and patient outcomes. These included an evaluation of tumor mutational and microsatellite instability burden, IHC for CD8 and PD-L1 expression, and both flow cytometry of multiple surface markers and intracellular FOXp3 expression, as well as T-cell receptor (TCR) rearrangement assays from peripheral blood. Here, one critical observation was that children with elevated tumor mutational burden (TMB) and higher than median total indel and microsatellite indel burden due to MMRD, had improved survival, whereas CD8 and PD-L1 IHC expression had a variable association with response and survival. This reflects an ongoing controversy regarding the best metric for predicting response to checkpoint blockade inhibitor therapy (2–4). In contrast, the patient with temozolomide-related high TMB did not have a response to nivolumab. In the immune profiling of peripheral blood, it was further observed that responders including those with delayed responses after sustained initial progression, had higher 4-1BB+ CD8 T cells in the peripheral blood at baseline and achieved a higher peak of these activated T-cell populations on therapy. Conversely, non-responders had higher $CD4^+$ regulatory T cells at baseline, these remained high throughout treatment across serial sampling and imparted association with a higher risk of death if persistently elevated after the first 3 months on trial. In addition, serial peripheral blood TCRβ rearrangements showed a higher total clone count and richness of diversity, as well as a more even clonal distribution in 3 responders evaluated in comparison with 3 non-responders.

Takeaways from this small trial, as outlined in **Fig. 1**, include the essentiality of MMRD to immune checkpoint blockade therapy response in this patient cohort, likely due to mutational processes that are continuously generating new neoantigenic peptides and in turn, new $CD8^+$ T-cell responses. Although the authors did not raise this notion, the fact that these patients sustained durable responses without the emergence of new malignancies, may indicate the use of immune checkpoint blockade therapy as a preventive therapeutic in children (and adults) with known MMRD-based cancer predisposition. Their results further emphasize the importance of evaluating immune correlates from peripheral blood for the prediction and monitoring of immunotherapy

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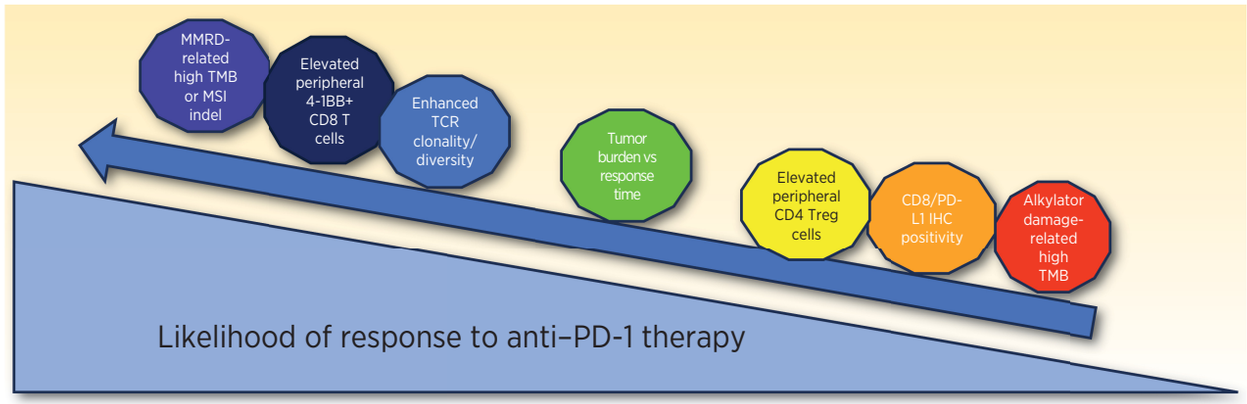

Figure 1.
This figure illustrates the relative importance of various measurements and metrics related to nivolumab response in the pediatric patient cohort reported upon by Das and colleagues (1).

responses, especially given the "unique trajectories" outlined in the article, for 4 of the trial participants on their paths to CRs. Finally, another ongoing uncertainty in predicting checkpoint blockade response is tumor burden (5, 6), wherein this trial demonstrated relatively earlier responses in 2 patients with central nervous system (CNS) tumor with lower tumor burden, in comparison with 2 patients with CNS tumor with higher tumor burden. The latter ultimately had favorable genomic features and durable responses yet had delayed responses beyond 6 months from start of therapy. Obviously, these results come from a small number of patients in an admittedly rare genetic cancer susceptibility circumstance yet are important results that inform treatment of similar patients who have no effective therapeutic options. Until now, perhaps!

Author's Disclosures

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