Background: Programmed death 1 (PD-1) and CTLA-4 blockade demonstrated durable clinical benefit in patients with advanced mismatch repair deficient (dMMR) colorectal cancer. This is the first neoadjuvant study to test ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD1) in early stage dMMR and MMR proficient (pMMR) colorectal cancer. This is the first neoadjuvant study to test ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD1) in early stage dMMR and MMR proficient (pMMR) colorectal cancer. This is the first neoadjuvant study to test ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD1) in early stage dMMR and MMR proficient (pMMR) colorectal cancer. This is the first neoadjuvant study to test ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD1) in early stage dMMR and MMR proficient (pMMR) colorectal cancer. This is the first neoadjuvant study to test ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD1) in early stage dMMR and MMR proficient (pMMR) colorectal cancer.

Methods: Patients with resectable, early stage CC received ipilimumab 1mg/kg on day (D) 1 and nivolumab 3mg/kg on D1 + 15. Surgery was planned a maximum of 6 weeks after informed consent. Primary endpoints were safety and feasibility. Secondary endpoints included: efficacy assessed by pathological response criteria, and associations between response and tumor mutational burden (TMB), interferon (IFN), gene signatures, T-cell infiltration and T-cell receptor (TCR) clonality.

Results: So far, 14 patients with either pMMR (n = 8) or dMMR (n = 7) tumors were treated. Treatment was well-tolerated and all patients underwent radical resection of 15 tumors without delays in surgery. Major pathological responses (≥5% viable tumor cells) were observed in 7/7 (100%) dMMR CC, with 4/7 (57%) complete responses. Four of these dMMR tumors were clinically stage IIIIB/C before start of treatment. Even though no major pathological responses were seen in pMMR tumors, significant increases in T-cell infiltration, particularly CD8+ T-cells, were seen post-treatment in both pMMR and dMMR tumors, with a median fold change of 2.4 (p = 0.018) and 4.8 (p = 0.0009), respectively. Strikingly, in spite of the major difference in TMB between dMMR and pMMR tumors (p = 0.008), pre-treatment TCR clonality and IFN, gene signatures did not differ substantially between these tumors. In contrast, post-treatment IFN, signatures increased the ability to distinguish responders (dMMR) from non-responders (pMMR).

Conclusions: Short-term, neoadjuvant ipilimumab plus nivolumab resulted in major pathological responses in 100% of dMMR tumors and did not compromise surgery. While dMMR status and TMB were associated with response, pre-treatment measures of tumor inflammation may have limited predictive value. Our data suggest that neoadjuvant immunotherapy in dMMR CC warrants further research and has the potential to change the current standard of care.

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