

INTERIM RESULTS OF A PHASE 2 STUDY OF NIVOLUMAB AND RELATLIMAB IN ADVANCED MISMATCH REPAIR DEFICIENT (dMMR) CANCERS RESISTANT TO PRIOR PD-(L)1 INHIBITION

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Background Cancers deficient in DNA mismatch repair (dMMR) are highly immunogenic but exhibit variable benefit from immune checkpoint inhibitors targeting programmed cell death-1 (PD-1)/PD-1 ligand (PD-L1). Other immune checkpoints are upregulated in these tumors and may be acting in parallel, in particular, lymphocyte activation gene 3 (LAG-3) which mediates exhaustion of activated T cells. The clinical relevance of the LAG-3 pathway has recently been demonstrated in 1L advanced melanoma (Tawbi NEJM 2022). We hypothesized that the addition of a LAG-3 blocking antibody (relatlimab) to a PD-1i (nivolumab) may overcome resistance to PD-(L)1 blockade in advanced dMMR tumors.

Methods Patients with advanced dMMR cancers that progressed during or within 6 months of PD-(L)1 inhibitor-containing therapy and after at least 12 weeks of therapy, and met other eligibility criteria were enrolled. Patients were treated with relatlimab 160 mg + nivolumab 480 mg (Cohort 1) every 4 weeks until intolerance or progression. Biopsies were obtained at baseline and on-treatment. The primary endpoint of the study is objective response rate according to RECIST 1.1. The outcomes of patients enrolled on Cohort 1 as of April 2022 are reported herein.

Results 15 patients were enrolled on Cohort 1 between November 2018 and April 2022. Of 13 patients evaluable for response (median follow up=12.4 months), partial response by RECIST 1.1 was observed in 1 patient with small bowel adenocarcinoma at 17 months (response duration of 11+ months), and 1 patient with colorectal cancer achieved a complete response at 18 months. An additional 5 patients achieved a best response of stable disease (SD), including one patient with 24% reduction in SLD ongoing at 41+ months. Treatment related adverse events (trAEs) occurred in 6 patients (40%) and were all G1-2 in severity. One patient discontinued treatment due to trAE (G2 oral pain/mucositis). Updated results will be presented at the time of the conference.

Conclusions Relatlimab + nivolumab is well tolerated and results in response or prolonged disease stability in some patients with advanced dMMR cancers that progressed on anti-PD-(L)1 therapy. Correlative analysis is ongoing to evaluate markers predictive of clinical benefit.

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Trial Registration Clinical trial information: NCT03607890.

Ethics Approval This study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00173534). Written informed consent was obtained from participants prior to their participation.

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