A PHASE II STUDY OF NIVOLUMAB IN PATIENTS WITH GENETIC ALTERATIONS IN DNA DAMAGE REPAIR AND RESPONSE WHO PROGRESSSED AFTER STANDARD TREATMENT FOR METASTATIC SOLID CANCERS (KM-06)

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Background: Immune-modulating antibodies targeting PD-1/PD-L1 have demonstrated promising anti-tumor efficacy in various types of cancers, especially in highly mutated ones. Genetic alterations in DNA damage response and repair (DDR) genes can lead to genetic instability, often accompanied by a high tumor mutation burden (TMB). However, a limited number of studies have validated the aberration of DDR genes as a predictive biomarker for response to immune-modulating antibodies.

Methods: KM-06 was an open-label, multicenter, single-arm, phase II trial to evaluate the safety and efficacy of nivolumab in refractory solid cancers with DDR gene mutations. DDR gene mutations were assessed by clinical targeted sequencing. Patients with a history of any prior treatment with PD-1 or PD-L1 inhibitors were excluded. Nivolumab was administered every 2 weeks at a dose of 3mg/kg until disease progression, unacceptable toxicity, or 24 months of treatment. The primary endpoint was the objective response rate (ORR) as per RECIST v1.1 criteria.

Results: A total of 48 patients were enrolled in the study, with a median age of 61 years and 58.3% being male. The most common cancer type was colorectal cancer (41.7%), followed by prostate and biliary tract cancer (8.3%, each). Among the participants, 45 patients were eligible for assessing tumor response. 8 patients achieved partial response as their best response. 8 patients achieved partial response as their best response. 3 occurred in 44 (91.7%) and 3 (6.3%) patients. Both TMB and microsatellite instability (MSI) were inferred by clinical targeted sequencing data. Using a TMB cutoff of 12mut/Mb, there were significant differences in PFS (p=0.0061) and ORR (p=0.05). Also, patients with high MSI scores (>2.5) demonstrated an increased response to nivolumab. In the RNA sequencing analysis, nivolumab responders showed activation of the interleukin signaling pathway. Patients who experienced early progression presented high activation of the epithelial-mesenchymal transition signaling pathway. No significant difference was found in PD-1+ CD8 T cells between nivolumab responders and non-responders. However, responders exhibited a marked increase in PD-1+/Ki67+ CD8 T cells at the early stage of treatment (C3D1) compared to non-responders (p=0.03).

Conclusions: In this phase II trial, nivolumab demonstrated moderate efficacy and manageable toxicity in patients with solid cancer harboring DDR gene mutations. A high TMB (>12mut/Mb) and MSI score (>2.5) determined through clinical target sequencing presented significant discriminatory power for nivolumab response.

Trial Registration: ClinicalTrials.gov Identifier: NCT04761744

Consent: Written informed consent was obtained from the patient for publication of this abstract.

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