A phase 2 trial of nivolumab monotherapy in rare cancer patients with mismatch repair deficiency or MSI-high: ROCK Trial (NCCH1709) from MASTER KEY Project

Kenji Tsuchihashi1, Hitomi Okuma2,3, Ryunosuke Machida2, Ryo Sadachi2, Akihiro Hirakawa1, Hiroshi Ariyama1, Masafumi Kanai5, Natsuko Okita2, Kenichi Nakamura2, Kan Yonemori3

1Department of Hematology, Oncology and Cardiovascular Medicine, 2Clinical Research Support Office, National Cancer Center Hospital, 3Department of Medical Oncology, National Cancer Center Hospital, 4Department of Clinical Biostatistics, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 5Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University

BACKGROUND
Mismatch repair deficiency (dMMR) / microsatellite instability-high (MSI-H) lead to neoplastic development and progression. Nivolumab, a PD-1 inhibitor, is approved for patients with dMMR/MSI-H colorectal cancers. We hypothesized that nivolumab would have activity in a subset of rare cancers that share this characteristic.

METHODS
The trial was a phase 2, open-label, single arm study designed to investigate the efficacy and safety of nivolumab in patients with advanced rare tumors with dMMR/MSI-H. This study was conducted as a sub-study of the MASTER KEY Project (UMIN000027552). Main inclusion criteria were: age ≥ 16, ECOG-PS of 0-1, unresectable lesion and have completed standard treatment. Patients received intravenous nivolumab monotherapy of 240 mg every 2 weeks. Primary endpoint was response rate (central assessment), and secondary endpoints included progression free survival (PFS), overall survival (OS), disease control rate (DCR), and toxicity. Translational research was conducted in parallel using blood samples and tissue samples collected from the patients.

RESULTS
Between May 2018 and March 2021, 11 patients were enrolled and 10 patients were included in the full analysis. Median follow-up was 24.7 months (IQR 12.4-31.5). The objective response rate was 60% (95% CI 26.2-87.8) by central assessment and 70% (95% CI 34.8-93.3) by local investigators. DCR was 70.0% (95% CI 34.8-93.3). Median PFS was 9.0 months (95% CI 0.9-11.1), and median OS was not yet reached. No treatment-related grade 3 or above adverse events were observed. Patients with tumor mutation burden ≥ 10/Mb showed a 100% response rate (95% CI 47.8-100). Responders had increased T-bet+PD-1+ T cells in the peripheral blood compared to non-responders (p<0.01).

CONCLUSION
Nivolumab demonstrated robust and durable clinical benefit in advanced MSI-H/dMMR rare solid cancer. The proportion of T-bet+PD-1+T cells may serve as a novel predictive biomarker.

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