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Investigator-Initiated Phase 2 Study of Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy for Microsatellite Instability–High Advanced Gastric or Esophagogastric Junction Cancer (*NO LIMIT*, WJOG13320G/CA209-7W7)

Hisato Kawakami, Shigenori Kadowaki, Kenro Hirata, Masahiro Tsuda, Taito Esaki, Naotoshi Sugimoto, Akitaka Makiyama, Nozomu Machida, Hidekazu Hirano, Hiroki Hara, Takeshi Kawakami, Wataru Okamoto, Hiroshi Yabusaki, Yoshito Komatsu, Shuichi Hironaka, and Kei Muro, for the NO LIMIT Study Group

Department of Medical Oncology, Faculty of Medicine, Kindai University; Department of Clinical Oncology, Aichi Cancer Center Hospital; Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Keio University; Department of Gastroenterological Oncology, Hyogo Cancer Center; Department of Gastrointestinal and Medical Oncology, National Hospital Organization Kyushu Cancer Center; Department of Medical Oncology, Osaka International Cancer Institute; Cancer Center, Gifu University Hospital; Department of Gastroenterology, Kanagawa Cancer Center; Gastrointestinal Medical Oncology Division, National Cancer Center Hospital; Department of Gastroenterology, Saitama Cancer Center; Division of Gastrointestinal Oncology, Shizuoka Cancer Center; Cancer Treatment Center and Department of Gastroenterology and Metabolism, Hiroshima University Hospital; Department of Gastroenterological Surgery, Niigata Cancer Center Hospital; Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center; Department of Gastroenterological Oncology, Saitama Medical University International Medical Center

Background

- Microsatellite instability-high (MSI-H) is an established biomarker for response to immune checkpoint inhibitors (ICIs). ICIs in combination with chemotherapy consisting of fluoropyrimidine and oxaliplatin can be administered in the first-line setting for gastric cancer (GC).
- However, evidence suggests that MSI-H tumors are responsive to nivolumab (NIVO) plus ipilimumab (IPI) but are less responsive to such cytotoxic chemotherapy, and that nivolumab plus low-dose ipilimumab can improve survival with acceptable safety in MSI-H colorectal cancer.

Method

- NO LIMIT (WJOG13320G/CA209-7W7) is an investigator-initiated, single-arm, open-label, 14-center phase 2 trial of NIVO plus low-dose IPI for MSI-H GC in the first-line setting.

Primary Objective

- To assess the overall response rate (ORR) as assessed by blinded independent central review (BICR) which is defined as CR+PR of IPI+NIVO in subject with MSI-H GC.

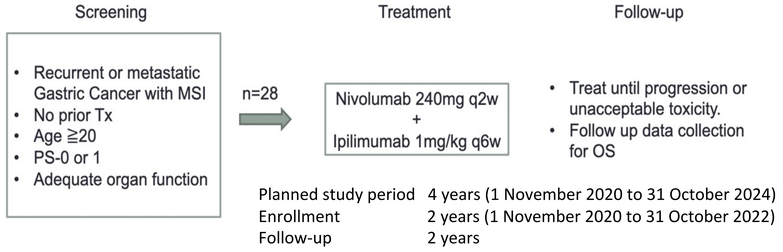
Sample size

- The number of patients was set at **28** based on the threshold and expected ORR values of 35 and 65%, respectively, with a one-sided alpha error of 0.025 and power of 0.80.

Key Inclusion Criteria

- Histologically confirmed adenocarcinoma of gastric or esophago-gastric junction.
- Unresectable advanced, recurrent or metastatic gastric or esophago-gastric junction adenocarcinoma.
- Confirmed MSI-H (by MSI-IVD kit, FALCO). However, subjects who have confirmed MSI-H by other assay, or deficiency of MMR by IHC testing are also eligible. In this case, MSI-H (by MSI-IVD kit, FALCO) must be confirmed after the enrollment.
- No prior systemic anticancer therapy
- ECOG performance status of 0 or 1.
- Subject must have at least one measurable lesion by CT or MRI per RECIST 1.1 criteria

Study Scheme



Primary endpoint

- **ORR as assessed by BICR**

Secondary endpoints

- ORR by investigators, disease control rate, PFS, OS, duration of response, time to response, safety & tolerability, concordance rate of MSI-H between MSI-IVD kit, FALCO and other assays, biomarkers associated with clinical efficacy (ORR, PFS, OS) and/or with incidence of adverse events of IPI+NIVO

Biomarker analysis

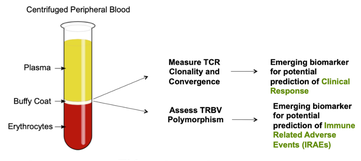
- Tumor tissue and blood will be collected prior to enrollment.
- Samples for serum and buffy coat will also be collected at Cycle 4 Day 1 and follow-up period.

Tumor Samples

- *Oncomine™ Comprehensive Assay Plus*
  - Over 500 unique genes
  - SNVs, indels, CNVs, fusions, and splice variants
  - Microsatellite instability (MSI) and tumor mutational burden (TMB)
- *Oncomine™ Immune Response Research Assay*
  - Expression analysis for 395 genes across 36 functional annotation groups.
  - Lymphocyte regulation, cytokine signaling, lymphocyte markers, checkpoint pathways, and tumor characterization.

Blood Samples

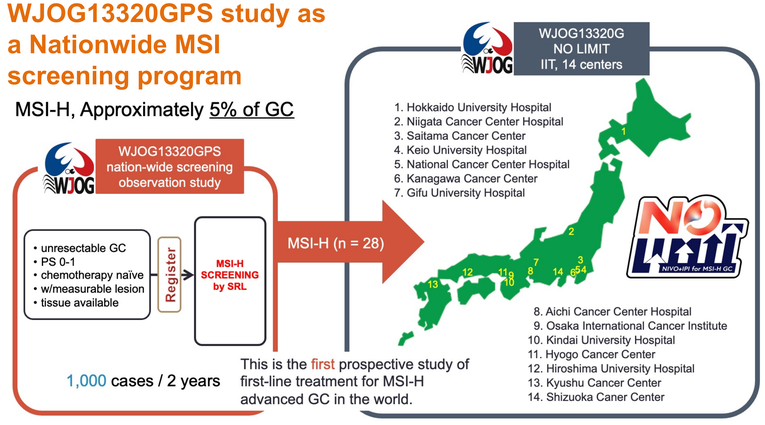
- *Oncomine™ TCR Beta-LR Assay*



- *Oncomine™ BCR IGH-LR Assay*
- *Plasma&Serum*

WJOG13320GPS study as a Nationwide MSI screening program

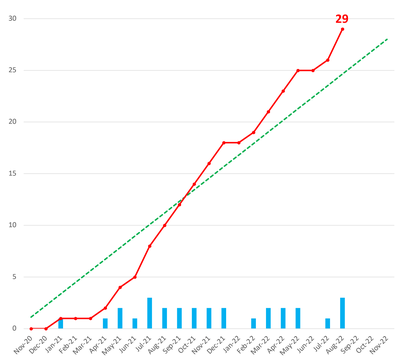
MSI-H, Approximately 5% of GC



Accrual

Study enrollment was successfully completed on Aug 29, 2022, with 29 cases registered.

Study Site	Enrolled
Hokkaido Univ Hosp	1
Niigata Cancer Center	0
Saitama Cancer Center	1
Keio Univ Hosp	4
National Cancer Center	1
Kanagawa Cancer Center	2
Gifu Univ Hosp	3
Aichi Cancer Center Hospital	7
Osaka Intl Cancer Center	3
Kindai Univ Hosp	1
Hyogo Cancer Center	4
Hiroshima Univ Hosp	0
Kyushu Cancer Center	1
Shizuoka Cancer Center	0
Sum	29



For more details, please refer to the protocol paper: Kawakami H, et al. Cancers (Basel). 2021 Feb 15;13(4):805.

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Contact: kawakami_h@med.kindai.ac.jp