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)

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**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, 1:1-center phase 2 trial of MSI-H plus IPI-NIVO 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.

**Secondary objective**
- 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, FACOLO and other assays, biomarkers associated with clinical efficacy (ORR, PFS, OS) and/or with incidence of adverse events of IPI-NIVO.

**Biomarker analysis**
- **Tumor Samples**
  - Oncomine™ Comprehensive Assay Plus
  - Over 500 unique genes
  - SNV, indels, CNVs, fusions, and splice variants
  - Microsatellite instability (MSI) and tumor mutational burden (TMB)
- **Oncomine™ Immune Response Research Assay**
  - Expression analysis for 505 genes across 36 functional annotation groups.
  - Lynphocyte regulation, cytokine signaling, cytotoxic markers, checkpoint pathways, and tumor characterization.

**WJOG13320G study as a Nationwide MSI screening program**

- **MSI-H, Approximately 5% of GC**
  - 1,000 cases / 2 years

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