GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 30 (Supplement 4): iv122–iv125, 2019
doi:10.1093/annonc/mdz157

SHORT ORALS

SO – 001 Multicenter phase I/II study of nivolumab combined with paclitaxel plus ramucirumab as the second-line treatment in patients with advanced gastric cancer

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Introduction: Nivolumab (Nivo) has a significant survival benefit in the salvage line for advanced gastric cancer (AGC) patients (pts) (Kang YK, Lancet, 2017). Synergistic anti-tumor effect induced by simultaneous blockade of PD-1 and taxanes, and PD-1 and VEGFR-2 has been reported. A phase I/II study was conducted to investigate the safety and efficacy of Nivo combined with paclitaxel (PTX) plus ramucirumab (Ram), which is the standard treatment as the 2nd line for AGC.

Methods: AGC pts with measurable lesions, ECOG PS 0-1, disease progression on the 1st line chemotherapy with fluoropyrimidine and platinum were eligible. Pts received Nivo (3 mg/kg on day 1 and 15) combined with PTX (80 mg/m2 on day 1, 8 and 15) and Ram (8 mg/kg on day 1 and 15) (Level 1), every 4 weeks until unacceptable toxicity or disease progression occurred. After feasibility was evaluated in 6 patients (phase I part), an additional 37 patients were enrolled in a phase II part with the primary endpoint of 6-month progression-free survival (PFS) rate with the threshold of 35%, one-sided alpha of 10% and power of 75%. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival, and safety. PD-L1 tumor expression was assessed by immunohistochemistry (28-8 pharmDx assay) with a cut-off value for PD-L1 positivity set at 1% in tumor cells.

Results: From February 2017 to July 2018, 43 AGC patients were enrolled. Patient characteristics included median age 66 years, ECOG PS 1 48.8%, prior gastrectomy 25.6%, and PD-L1 positive rate 15.4%. Dose-limiting toxicities were observed in 2 pts in the phase I part, febrile neutropenia and neutropenia over a period of 8 days, and the recommended dose was determined as Level 1. Forty (93.0%) patients experienced grade $\geq$ 3 AEs: neutropenia (76.7%), febrile neutropenia (16.3%), anemia (14.0%), diarrhea (7.0%), thrombocytopenia (7.0%). Fourteen (32.6%) pts experienced grade $\geq$ 3 immune-related AEs. There was one treatment-related death related to thrombocytopenia. CR/PR/SD was obtained in 0/16/20 pts respectively with an ORR of 37.2% (95% CI, 23.0-53.5%) and a DCR of 83.7% (95% CI, 69.3-93.2%). With a median follow-up time of 16.8 months, 6-month PFS rate was 46.4% (80% CI, 36.4-55.8%) (P=.067) and median PFS was 5.1 months (95%CI, 4.5-6.5 months).

Conclusion: Nivo combined with PTX plus Ram demonstrated promising antitumor activity as the 2nd-line treatment for AGC pts with manageable toxicities. (UMIN000025947)