SO-19 A multicenter phase II trial of trifluridine/tipiracil in combination with cetuximab in RAS wild-type metastatic colorectal cancer patients refractory to prior anti-EGFR antibody therapy: The WJOG8916G trial

T. Masuishi[1], N. Izawa[2], N. Takahashi[3], H. Shoji[4], Y. Yamamoto[5], T. Matsumoto[6], K. Sugiyama[7], T. Kajiwara[8], K. Kawakami[9], N. Aomatsu[10], C. Kondoh[11], H. Kawakami[12], N. Takegawa[13], T. Esaki[14], Y. Narita[1], H. Hara[3], Y. Sunakawa[2], N. Boku[4], T. Moriwaki[5], M. Shimokawa[15], T. Nakajima[16], K. Muro[1]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [2]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; [3]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan; [4]Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; [6]Department of internal medicine, Himeji Red Cross Hospital, Himeji, Japan; [7]Department of Medical Oncology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [8]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [9]Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan; [10]Department of Surgery, Osaka City General Hospital, Osaka, Japan; [11]Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan; [12]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan; [13]Department of Gastroenterology, Hyogo Cancer Center Hospital, Akashi, Japan; [14]Department of Gastrointestinal and Medical Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [15]Department of Biostatistics, Yamaguchi University Graduate School of Medicine, Ube, Japan; [16]Kyoto Innovation Center for Next Generation Clinical Trials and iPS Cell Therapy (Ki-CONNECT), Kyoto University Hospital, Kyoto, Japan

Background: Trifluridine/tipiracil (FTD/TPI) monotherapy significantly improved survival in metastatic colorectal cancer (mCRC) patients who had previously received standard chemotherapy. However, the median survival time remained as short as 7.1 months. Previous studies showed that the combination of FTD/TPI with anti-epidermal growth factor receptor (EGFR) antibodies was more effective than either monotherapy on human CRC xenografts. Therefore, we conducted a phase II trial (WJOG8916G) to evaluate the efficacy and safety of the combination of FTD/TPI and cetuximab rechallenge in patients with mCRC refractory to prior anti-EGFR antibody therapy.

Methods: The key eligibility criteria were as follows: 1) histologically proven unresectable mCRC, 2) RAS wild-type, 3) refractory or intolerant to fluoropyrimidine, oxaliplatin, irinotecan, and anti-angiogenic agents, 4) refractory to prior anti-EGFR antibody, 5) at least one measurable lesion, 6) ECOG PS 0-1. Eligible patients received FTD/TPI (35 mg/m 2 b.i.d on days 1—5 and 8—12, q4w) plus cetuximab (initial dose 400 mg/m 2 followed by 250 mg/m 2, weekly) until disease progression or unacceptable toxicity. Dose-limiting toxicities (DLTs) were evaluated in the first six patients. Response was assessed every eight weeks and was centrally reviewed. The primary endpoint was disease control rate (DCR). Based on the hypothesis that FTD/TPI plus cetuximab would improve DCR from 45% (null hypothesis) to 65% (alternative hypothesis), 48 patients were required for power of 0.9 with a one-sided alpha of 0.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety. The anti-EGFR antibody-free interval was defined as the period from the last administration date of anti-EGFR antibody in the prior therapy containing anti-EGFR antibody to the enrollment date.

Results: Between June 2017 and June 2019, 56 patients were enrolled. Patient characteristics were: median age 60 years, male 59%, PS 1 45%, left-sided tumor 91%, and multiple sites of metastases 70%. Median anti-EGFR antibody-free interval was 120 days (range: 15—1401). Proportions of patients with partial response (PR), stable disease (SD), or progression disease (PD) to prior therapy containing anti-EGFR antibody were 61%, 21%, or 13%, respectively. Regarding safety, DLT was observed in one of the first six patients that induced a delay of $>$ 15 days to the second cycle due to toxicities. Correspondingly, the planned dose of FTD/TPI and cetuximab was recommended in the next 50 patients. Thirty patients achieved disease control (CR/PR/SD 0/2/28), resulting in 53.6% DCR (80% confidence interval [CI]: 44.2%—62.8%). The ORR was 3.6% (95% CI: 0.4%—12.3%). In subgroup analysis, DCR in patients with PR to prior therapy containing anti-EGFR antibody tended to be higher compared to patients with SD or PD (61.8% vs. 36.8%). The median PFS was 2.4 months (95% CI: 2.1—3.7), and the median OS was 9.8 months (95% CI: 7.4—12.2). The frequent grade 3/4 adverse events were neutropenia (55.4%), anemia (30.4%), hypomagnesaemia (16.1%), platelet count decreased (8.9%), paronychia (7.1%), appetite loss (7.1%), and dermatitis acneiform (7.1%). No treatment-related deaths were observed.

Conclusions: FTD/TPI in combination with cetuximab rechallenge proved to be safe. However, this trial did not show clinically meaningful DCR in RAS wild-type mCRC patients refractory to prior anti-EGFR antibody.

Clinical trial identification: UMIN000027210.

Acknowledgement: This study was supported by the West Japan Oncology Group (WJOG), a non-profit organization. We thank the data managers and other support staff of WJOG, especially Dr. Koji Takeda, Dr. Shinichiro Nakamura and Kaori Mori.

Legal entity responsible for the study: The authors.

Funding: Merck, Taiho Pharma.

Disclosure: T. Masuishi: Honoraria (self): Taiho, Merck Bio Pharma. N. Izawa: Honoraria (self): Taiho Pharmaceutical, Bristol-Myers Squibb, Lillly, Daiichi Sankyo, Ono Pharmaceutical, Takeda, Guardant health Japan. T. Matsumoto: Speaker Bureau / Expert testimony: Sanofi.KK, Eily Lilly, Chugai pharma, Teijin pharma, Taiho pharma, Takeda pharma, Ono pharma, Merck Japan, Bristol-Myers Squibb. T. Kajiwara: Honoraria (self): Chugai. T. Esaki: Honoraria (self): Chugai, Taiho, MSD; Research grant / Funding (institution): Astellas Amgen Biopharma, Ono, MSD. Y. Narita: Honoraria (self): ONO, BMS, Astrazeneca; Speaker Bureau / Expert testimony: ONO, BMS, Astrazeneca. H. Hara: Honoraria (self): Bayer, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Kyowa Hakko Kirin, Lilly, Merck Biopharma, MSD, Ono, Sanofi, Taiho, Takeda and Yakult; Advisory / Consultancy: Boehringer Ingelheim, Daiichi Sankyo, Dainippon Sumitomo, Lilly, MSD and Ono; Research grant / Funding (institution): Astellas, AstraZeneca, Bayel, BeiGene, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Elevar Therapeutics, GSK, Incyte, Merck Biopharma, MSD, Ono, Pfizer, and Taiho. Y. Sunakawa: Honoraria (self): Takeda, Chugai Pharm, Eli Lilly Japan; Advisory / Consul-tancy: MDS, Bristol-Myers Squibb; Research grant / Funding (self): Chugai Pharm, Takeda, Taiho Pharm. N. Boku: Honoraria (self): Taiho, Ono; Research grant / Funding (self): Ono, Takeda. T. Moriwaki: Speaker Bureau / Expert testimony: Taiho Pharmaceutical, Merck; Research grant /Funding (institution): Taiho Pharmaceutical. T. Nakajima: Advisory / Consultancy: Ono Pharm; Research grant / Funding (self): Chugai Pharm, Nippon Kayaku; Research grant / Funding (institu-tion): Chugai Pharm, Nippon Kayaku. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2021.05.043