A PHASE II STUDY OF CETUXIMAB AND MFOLFOX6 IN MCRC INCLUDING PROSPECTIVE EARLY TUMOR SHRINKAGE ANALYSIS (JACCRO-CC05)

Akihito Tsuji1, Masato Nakamura2, Yu Sunakawa3, Mitsugu Kochi4, Tadamichi Denda5, Tatsuro Yamaguchi6, Ken Shimada7, Satoshi Tani8, Akinori Takagane9, Masahito Kotaka10, Izuma Nakayama11, Yutaka Yonemura12, Hidekazu Kuramochi13, Junichi Koike14, Masahiro Takeuchi15, Wataru Ichikawa16, Masashi Fujii17, Toshifusa Nakajima18

1Kobe City Medical Center General Hospital, Kobe, Japan, 2Aizawa Hospital, Matsumoto, Japan, 3Showa University Northern Yokohama Hospital, Yokohama, Japan, 4Nihon University School of Medicine, Tokyo, Japan, 5Chiba Cancer Center, Chiba, Japan, 6Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyō-ku, Tokyo, Japan, 7Saitama Medical University International Medical Center, Hidaka, Japan, 8Konan Hospital, Kobe, Japan, 9Hakodate Goryukaku Hospital, Hakodate, Japan, 10Sano Hospital, Kobe-shi, Japan, 11JNT Medical Center Tokyo, Shinagawa-ku, Tokyo, Japan, 12Kishiwada Tokushukai Hospital, Kishiwada, Japan, 13Tokyo Women’s Medical University Hospital, Shinjuku-ku, Tokyo, Japan, 14Teho University School of Medicine, Ota-ku, Tokyo, Japan, 15Kokusai University, Minato-ku, Tokyo, Japan, 16National Defense Medical College Hospital, Tokorozawa, Japan, 17Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan, 18Japan Clinical Cancer Research Organization, Chuo-ku, Tokyo, Japan

Background: FOLFOX4 combined with cetuximab (cet) for metastatic colorectal cancer (mCRC) patients with KRAS wild tumor demonstrated the prolonged progression-free survival (PFS) with higher response rate in the OPUS study. Recently, it has been shown early tumor shrinkage (ETS; over 20% regression at 8 weeks) was correlated with the prolongation of progression-free survival (PFS) and overall survival (OS) in the cet regimen by retrospective subgroup analyses. To evaluate the clinical efficacy and safety of the cet + MFOLFOX6, we conducted a multi-center phase II study including prospective ETS analysis as an endpoint.

Methods: In this trial, patients with KRAS wild type tumor and not receiving prior chemotherapy for mCRC were treated with cetuximab (initial dose 400, and 250 mg/m² weekly) followed by MFOLFOX6 (oxaliplatin 85mg/m², l-leucovorin 200 mg/m², fluorouracil, as 400mg/m² intravenous bolus then 2,400mg/m² 46-hour continuous infusion). Two-week treatment was defined as one course. The primary endpoint was response rate (RR) evaluated by the external review board. Secondary endpoints included PFS, OS, the best response (% change at the base line) and safety. In addition, we prospectively evaluated the correlation between ETS and PFS. This trial was designed to have a target activity level of 57% and a minimum activity level of 34%, with an α error of 0.05 and a β error of 0.10, showing that a minimum of 51 patients were required. Thus, the nominal sample size was determined to be 54 patients considering dropping-out.

Results: A total of 57 patients were enrolled from August 2010 to September 2011. The median ECOG performance status was 0 (0-1), the median age was 60 yrs (range 34-78). All patients had EGFR-expressing disease. The median treatment courses were 21 (cet) and 10 (FOLFOX). The RR was 66.7% (95%CI, 53.4 to 77.7). Complete remission was observed in 5 cases (9.3%). The best response was 68.5% (95%CI, 55.3 to 79.3) and the disease control rate (CR/PR/SD over 6months) was 85.2% (95%CI, 73.4 to 92.3). The median PFS was 11.1 months (95%CI, 8.0 to 14.7). ETS was observed in 80% of patients, and the PFS for patients with ETS was statistically significantly prolonged as compared with patients without ETS (median PFS, 11.5 v.s. 3.7 months; hazard ratio 0.25; 95% CI, 0.12 to 0.58; p = 0.0002). The OS was not reached at the time of median follow-up (19.2 months). Grade 3 or worse adverse events were neutropenia (48.2%), leukocytopenia (22.2%), rash acneform (20.4%) and peripheral neuropathy (18.5%).

Conclusion: The first line cet + MFOLFOX6 has an acceptable safety profile and demonstrates advantages in response rate for patients with KRAS wild tumor. And to our knowledge, this study is the first prospective study focusing on the correlation between ETS and PFS. The first line cet + MFOLFOX6 should be considered as one of the recommended treatment regimens for patients with KRAS wild tumor.

© The Author 2013. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.