Phase I trial of FOLFOXIRI in combination with Panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer (JACCRO CC-14)

A. Tsuji1, M. Nakamura2, M. Ogawa3, H. Satake4, T. Kotake4, Y. Hatachi5, A. Takagane3, Y. Okita5, K. Nakamura6, T. Onikubo6, M. Takeuchi7, M. Fujii8, T. Nakajima9

1Department of Medical Oncology, Kagawa University Hospital, Kida-gun, Japan
2Aizawa Hospital, Matsumoto, Japan
3Hakodate Goryoukaku Hospital, Hakodate, Japan
4Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan
5Kagawa University Hospital, Kita-gun, Japan
6Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan
7Kitasato University, Minato-ku, Japan
8Nihon University School of Medicine, Itabashi-ku, Japan
9Japan Clinical Cancer Research Organization, Chuo-ku, Japan

Introduction: TRIBE trial demonstrated that FOLFOXIRI plus bevacizumab (BV) has higher activity and efficacy compared with FOLFIRI plus BV. Therefore, FOLFOXIRI is regarded as one of the platform regimen of colorectal cancer chemotherapy. However, safety and efficacy of FOLFOXIRI plus panitumumab has not been demonstrated for Japanese patients. We conducted this phase I study to determine the recommended dose of FOLFOXIRI plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer (mCRC).

Methods: Patients received the combination of panitumumab (6 mg/kg on day 1) with FOLFOXIRI (irinotecan (CPT-11), oxaliplatin (L-OHP) 85 mg/m², and folinate (LV) 200 mg/m² on day 1, followed by fluorouracil (5-FU) 3200 mg/m² infused as a 46-hour Continuous infusion starting on day 1) repeated every 2 weeks as first-line treatment of RAS wild-type mCRC patients. Starting from the standard dose of FOLFOXIRI, to determine the recommended dose was reduced in accordance with the toxicity. (A decrease of the CPT-11 dose was planned from level 1: CPT-11 165 mg/m²). Induction treatment was scheduled for a maximum of 12 cycles, followed by panitumumab ± 5-FU/LV maintenance until progression. DLT was defined as any of the following adverse events occurring in the first cycle: (i) grade 4 neutropenia lasting 4 days; (ii) grade 4 thrombocytopenia (<2.5 × 10⁴/mm³); (iii) febrile neutropenia; (iv) grade 3 or 4 non-hematological toxic effects; (v) discontinuation of treatment due to an adverse event; or (vi) treatment-related death.

Results: Seven patients were enrolled, and six patients were assessed for safety and efficacy. Maximum tolerated dose was not reached at level 1. CPT-11 165 mg/m² and L-OHP 85 mg/m² in combination with LV 200 mg/m² and 5-FU 3,200 mg/m² could be administered with acceptable toxicities; all patients were treated at these levels. The common grade 3 or 4 relevant toxicities were diarrhea (50 %), hypokalemia (33 %) and stomatitis (33 %), and no toxic deaths occurred. In four (66.7 %) a partial response was demonstrated, namely, an objective response rate was 66.7 %. Time to protocol treatment failure was 7.2 months (1.4 - 7.3 months). Four of the six patients had partial response (PR) and the other two patients had stable disease (SD), yielding a response rate of 66.7% (95% confidential interval: 30.0–90.3 %) and disease control rate of 100%. With a median follow-up period of 11.6 months, all patients remain alive.

Conclusion: This biweekly triplet plus panitumumab regimen is well tolerated and has very promising anti-tumor activity for Japanese patients with mCRC. The recommended phase II dose was determined to be the same as the standard doses for this regimen used worldwide.