Phase II study of biweekly cetuximab and irinotecan as third-line therapy in patients with pre-treated KRAS exon2 wild-type metastatic colorectal cancer

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Introduction: Although there are several supported data that evaluated efficacy and safety about administering bi-weekly C-mab plus CPT-11 in European trials, there is a little data in Japan. The aim of this phase II study was to evaluate the efficacy, safety and to perform molecular analysis of C-mab and CPT-11 as third-line treatment in patients with pre-treated KRAS exon2 wild-type mCRC in Japan.

Methods: From October 2011 to November 2014, a total of 40 patients with failure to CPT-11, oxaliplatin, and fluoropyrimidines received C-mab 500 mg/m2 and CPT-11 150 mg/m2 every 2 weeks until disease progression. The primary endpoint was response rate (RR). The secondary endpoints included adverse events, progression-free survival (PFS), overall survival (OS), molecular analysis, and deepness of Response (DpR). Gene mutations of EGFR pathway were analyzed using Luminex technology (GENOSEARCH Mu-PACK). DpR was defined as the maximum reduction ratio compared with baseline tumor regardless of the period.

Results: The RR and the disease control rate were 25% and 72.5%, respectively (CR0, PR10, SD19, PD10, NE1). The median PFS was 6 months (4-8) and the median OS was 15.1 months (11.8-19.0). Grade 3/4 adverse events were observed in 12 patients (29.2%), however there was no grade 4 adverse event. Grade 3 events included: diarrhea (9.7%), fatigue, skin toxicity (7.3%), nausea, stomatitis (4.8%) and neutropenia (2.4%). The median number of courses was 10.5 (range 3-31). Dose intensity of C-mab and CPT-11 was 97.8% and 91.9%, respectively. Molecular analysis of EGFR pathway (n = 36) showed that the frequencies of KRAS exon 3 and 4, NRAS, BRAF, and PIK3CA mutations were 5.5%, 2.7%, 8.3%, 5.5%, respectively. All wild type of these genes was associated with prolongation of OS and PFS compared to any gene mutations; especially BRAF mutation was a significant poor prognostic factor (OS, PFS p < 0.01). Mean DpR was 13% (interquartile range: -5%, 29%) and a minimum DpR of -77%. DpR ≥ 13% was associated with significantly longer OS and PFS when compared with DpR < 13%. There was a moderate positive correlation between DpR and clinical outcomes (OS: r = 0.52, PFS: r = 0.49, P < 0.05).

Conclusion: Both efficacy and feasibility of using combination chemotherapy with biweekly C-mab and CPT-11 in Japanese patients were comparable with those in western country. BRAF mutation was significant negative prognostic marker and DpR indicated a potential measure of efficacy in mCRC patients performed as third-line treatment.