O-6 Gene alterations in ctDNA related to the resistance mechanism of anti-EGFR antibodies and clinical efficacy outcomes of anti-EGFR antibody rechallenge plus trifluridine/tipiracil in metastatic colorectal cancer patients in WJOG8916G trial

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Background: We conducted a phase II trial (WJOG8916G) to evaluate the efficacy and safety of the combination of trifluridine/tipiracil and cetuximab rechallenge in patients (pts) with metastatic colorectal cancer (mCRC) refractory to anti-epidermal growth factor receptor (EGFR) antibodies. This biomarker study investigated the association between gene alterations related to the resistance mechanism of anti-EGFR antibodies in circulating tumor DNA (ctDNA) before protocol treatment and clinical efficacy outcomes.

Methods: Major eligibility criteria were the following: histologically proven unresectable mCRC; RAS (KRAS and NRAS) exon 2,3,4 wild-type in archived tumor tissues; refractory or intolerance to fluoropyrimidines, oxaliplatin, irinotecan, and anti-angiogenic agents; refractory to anti-EGFR antibodies; and ECOG PS 0—1. The primary endpoint was the disease control rate (DCR). Potential anti-EGFR antibody-resistant alterations, defined as RAS exon 2,3,4 (at codon 12, 13, 59, 61, 117, and 146), BRAF exon 15 (at codon 600), PIK3CA exon 2,5,9,10,12,21 (at codon 38, 345, 511, 545, 593, 1047), or copy number variant (CNV) in ERBB2 and MET, in ctDNA contained in the plasma immediately before protocol treatment were analyzed using the Guardant360 assay.

Results: Of the enrolled 56 pts, characteristics of 53 pts evaluable for ctDNA were median age of 60-y, male 60%, left-sided tumors 91%. The number of pts with partial response, stable disease, or progressive disease to prior therapy containing anti-EGFR antibody were 31 (58%), 12 (23%), and 7 (13%), respectively. Among 53 pts with available results of ctDNA analysis, 32 (60%) had at least one anti-EGFR-resistant alteration, RAS mutation (mut) in 24 pts (45%), BRAF mut in 10 pts (19%), PIK3CA mut in 7 pts (13%), ERBB2 CNV in 6 pts (11%), and MET CNV in 4 pts (8%), whereas the other 21 pts (40%) had none of the abovementioned gene alterations. DCR in pts without RAS, BRAF, or PIK3CA mut was numerically higher than those with each mut (66% vs. 38%, 61% vs. 20%, 57% vs. 29%, respectively). Pts without RAS mut achieved significantly longer progression-free survival (PFS) [median: 3.8 vs. 2.1 m, hazard ratio (HR): 2.60, P = 0.0015] and overall survival (OS) [median: 11.6 vs. 8.9 m, HR: 2.07, P = 0.022] than those with it. Similarly, pts without BRAF or PIK3CA mut had longer PFS [median: 3.7 vs. 1.9 m, HR: 3.71, P = 0.0002; 3.7 vs. 1.9 m, HR: 2.27, P = 0.045] and OS [median: 10.3 vs. 5.4 m, HR: 2.94, P = 0.0064; 10.6 vs. 5.4 m, HR: 4.14, P = 0.0014] than those with each mut. Neither MET nor ERBB2 CNV had a significant impact on PFS or OS. Pts with no gene alterations demonstrated higher DCR (76% vs. 38%), significant prolonged PFS [median: 5.5 vs. 2.1 m, HR: 2.44, P = 0.0023], and OS [median: 14.2 vs. 8.3 m, HR: 2.84, P = 0.0022] than those with gene alterations.

Conclusions: RAS, BRAF, and PIK3CA muts in ctDNA were associated with worse clinical efficacy outcomes in mCRC patients receiving anti-EGFR antibody rechallenge plus trifluridine/tipiracil. A comprehensive genomic test using ctDNA immediately before anti-EGFR antibodies rechallenge might help determine its indication.

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