Evaluation of *Kras* and *Nras* mutations in a three-year study of 3975 samples for guiding the treatment of patients with metastatic colorectal cancer in Turkey

ABSTRACT

BACKGROUND: Mutations in *Kras* and *Nras* genes in primary colorectal tumors are the reasons for non response to anti-epidermal growth factor receptor (EGFR) antibodies in patients with metastatic colorectal cancer (mCRC). Mainly *Kras* and *Nras* mutations are seen at codons 12, 13 and 61. Mutations can also be detected at codons 59, 117 and 146, although rarely. This study is performed in order to evaluate the *Kras* and *Nras* mutation data using 3975 samples from mCRC patients which were collected between January 2015 - September 2018 and also to understand the efficacy of the Minisequencing method used in the study.

METHODS: Two round nested PCR was performed for the amplification of Exons 1, 2, 3 of *Kras* and *Nras* genes harboring codons 12, 13, 59, 61, 117 and 146, followed by a multiplex Minisequencing reaction for the detection of potential mutations.

RESULTS: A total of 3975 patients were analyzed for the mutations in codons 12, 13, 59, 61, 117 and 146 of *Kras* and *Nras* genes. 13 patients were directly studied for *Nras* mutations. Results were obtained from 3932 out of 3958 (99%) patients for *Kras* mutations and no results were obtained from 26 (1%) of the cases. 2269/3958 (57.3%) patients were wild-type for *Kras* mutations while 1725 of them carried a *Kras* mutation (42.7%). 36 of 1725 (2.08%) patients carried two mutations. *Kras* mutation rates were 1136/1725 (65.8%), 387/1725 (22.4%), 20/1725 (1.15%), 69/1725 (4%), 17/1725 (0.98%), 96/1725 (5.56%) in codons 12, 13, 59, 61, 117, 146 respectively. Additional *Nras* mutation analysis was performed for 2250 patients which were found to be wild-type for *Kras* mutations. 151/2250 (6.7%) patients were found to carry *Nras* mutations while 2099 (93.2%) of them were wild-type for *Nras* mutations. 2 of 151 (1.3%) patients carried two mutations which made a total of 153 *Nras* mutations.

CONCLUSIONS: After the analysis of 3975 samples from mCRC patients, it was shown that there is a high rate (42.7%) of mutation finding in *Kras* and *Nras* genes. These findings show that *Kras/Nras* molecular testing is a highly effective approach to select patients who are more likely to respond to anti-EGFR immunotherapy or rule out this treatment for those who are not likely to respond. Furthermore, Minisequencing technique used during the study is shown to be an ideal method for studying *Kras/Nras* mutations due to its high sensitivity and cost-effectiveness.

Keywords: Kras, Nras, Braf, Minisequencing, Metastatic colorectal cancer (mCRC)