The role of concomitant RAS and BRAF mutations in influencing clinical outcome during BRAF-targeted treatment for metastatic colorectal cancer

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RAS and BRAF alterations are both prognostic and predictive factors in metastatic colorectal cancer. Recent literature has described cases of RAS and BRAF mutations (mut) coexistence in colorectal cancer. This association appears to be related to poor median overall survival (mOS), median progression free survival (mpFS) and treatments responses. The aim of this study was to evaluate outcomes in patients (pts) harboring BRAF plus RAS mut.

We retrospectively collected data from 152 pts affected by BRAF mut metastatic colorectal cancer referring from 2007 to 2021 to the Medical Oncology Units of: University Hospital and University of Cagliari, Businco Hospital of Cagliari, Istituto Oncologico Veneto (Padua) and Istituto Nazionale Tumori (Milan). All pts received first line (1st L) treatment and second line (2nd L) treatment. All pts had more than one metastatic site. Statistical analysis were performed with MedCalc package. Survival distributions were assessed by Kaplan-Meier curves.

**RESULTS**

Median age was 64 y.o., 74 were male and 78 female. 152 pts were included in the outcomes analysis. 40 (26%) had BRAF+RAS mut, 84 (55%) had BRAF V600E single mut, and 28 (19%) had BRAF non-V600E single mut. Among the 40 BRAF+RAS mut, 26 (17%) had BRAF+KRAS mut and 14 (9%) had BRAF+NRAS mut. BRAF+KRAS showed worse median overall than BRAF+NRAS (11 versus 26 months [mo], p = 0.02). Subsequently, we compared mOS and mpFS in both BRAF+RAS mut and BRAF V600E single mut treated with encorafenib-cetuximab. No differences were showed between mutated BRAF+RAS and single BRAF V600E in terms of OS (16 vs 13 mo, respectively) and PF (4,8 vs 4,2 mo, respectively).

**CONCLUSIONS**

The results of this study, although retrospective, show that concomitant BRAF and RAS mutations are not common but they could relate to different prognosis than patients with single mutation. The study also showed that double mutations are responsive to encorafenib plus cetuximab therapy. Further studies are needed to better understand and characterize this setting.

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**METHODS**

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