P – 317 Clinical, pathological, and prognostic features of rare BRAF mutations in metastatic colorectal cancer: a bi-institutional retrospective analysis (REBUS study)

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Introduction: Recently, 3 classes of BRAF mutations (MTs) have been described. BRAF V600 MTs, which signify metastatic colorectal cancer (mCRC) with poor prognosis and not benefiting from anti-EGFR drugs, belong to class 1. Class 2 and 3 include BRAF non-V600 MTs, which occur in about 1-2% of mCRC and are associated with a favourable prognosis and specific clinicopathologic features. Class 2 and 3 differ in kinase activity and sensitivity to anti-EGFR: class 2 are activated and RAS-independent MTs; class 3 are kinase-dead and sensitive to inhibition of activated RAS. This study aimed to retrospectively evaluate features and the prognostic role of rare BRAF non-V600 compared to BRAF V600E MTs in mCRC pts treated at 2 Italian Institutions.

Methods: mCRC pts harboring BRAF MTs, assessed by means of NGS, pyrosequencing or RT-PCR, treated between January 2013 and December 2018 at 2 Italian institutions, were retrospectively analyzed. Clinicopathological and treatment characteristics, as well as survival data were collected.

Results: 55 pts bearing BRAF MTs were identified. Of those, 46 (84%) harbored a V600E and 9 (16%) a non-V600 MT. Within the non-V600 group, 3 MTs (K601E, G469A, G469R) belonged to class 2, while 5 MTs (G466E, G466A, 2 D594G, D594N), belonged to class 3. One pt harboured a T599I MT, whose kinase activity is unknown. Compared to BRAF V600E mCRC, BRAF non-V600 mCRC were more frequently left-sided (P = .017) and displayed a lower grade (P = .045). In addition, non-V600 mCRC pts had a lower tumor burden (involving mainly one metastatic site) (P = .026) and underwent more frequent resection of metastases with radical intent (77.7 vs 18%; P = .000175). mOS was significantly longer in the non-V600 compared to the V600E group (61.3 vs 20.4 m; HR 0.41; 95% CI, 0.18-0.93; P = .05). No difference in activity and efficacy of anti-EGFR agents was observed between class 2 and 3.

Conclusion: Despite the small size of our retrospective analysis, the results were consistent with previous evidence. BRAF non-V600 MTs identified a subgroup of mCRC, differing both in terms of clinicopathologic characteristics and prognosis from that of BRAF V600 mCRC. Interestingly, the better prognostic features allowed more frequently radical resection of metastases, positively impacting survival.