P — 207 **Clinico-pathological and molecular characterization of BRAF mutant metastatic colorectal cancer (mCRC): Are all mutations created equal?**

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Introduction: Functional studies on preclinical models (Yao et al. Nature 2017) identified 3 classes of BRAF mutations: activating RAS -independent BRAF mutations signaling as monomers (class 1- BRAF V600E) or as dimers (class 2-codons 601/597) and RAS -dependent BRAF mutations with impaired kinase activity (class 3-codons 594/596). While clinico-pathological and molecular features of class 1 mutation are well known, limited data are available with regard to class 2 and 3 mutations, due to their rarity in CRC.

Methods: Clinico-pathological, molecular and outcome data from BRAF mutated (codons 594, 596, 597, 600, 601) mCRC patients were collected. A group of BRAF wild-type patients was included as control. IHC analyses were performed to determine the consensus molecular subtypes (CMS). Clinical features were compared by chi-square or fisher's exact test. PFS and OS were evaluated by Kaplan-Meier and log-rank test.

Results: Class 1, 2 and 3 included 92, 12 and 13 patients respectively. BRAF wild-type patients were 540. No clinico-pathological differences were observed comparing class 1 to class 2 BRAF mutated. Conversely, BRAF class 3 mutated were more frequently left sided (p = 0.0028), well differentiated (p = 0.0120), pN0 (p = 0.0159), and with no peritoneal metastases (p = 0.0176) compared to class 1. With regard to CMS, class 2 and 3 tumors were all assigned to CMS2-3. Class 1 tumors were assigned to CMS1, 2-3 and 4 in 39%, 44% and 17% of cases. Median OS for BRAF wt, BRAF mutant class1, 2 and 3 were 42.2, 21, 23.4 and 44.5 months respectively. HR for OS was 2.38 (95% CI 1.61-3.54) for class 1, 1.90 (95% CI 0.85-4.26) for class 2 and 0.93 (95% CI 0.51-1.69) for class 3, compared to BRAF wt (p < 0.0001). Median PFS for BRAF wt, BRAF mutant class1, 2 and 3 were 10.1, 7.3, 7.0 and 13.8 months respectively. HR for PFS was 2.02 (95% CI 1.39-2.94) for class 1, 2.49 (95% CI 0.92-6.74) for class 2 and 0.85 (95% CI 0.47-1.54) for class 3, compared to BRAF wt (p < 0.0001).

Conclusion: Our data confirm previous findings describing specific features associated with BRAF rare mutations. For the first time clinico-pathological characteristics and outcome data are reported according to the 3 classes categorization of BRAF mutations. In particular, class 1 and 2 share similar features and worse outcome compared to class 3 and wild type patients