Abstract

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Background: HER2 amplified mCRC has emerged as a unique clinical subset, characteriz resistance to anti-EGFR therapy and response to anti-HER2 strategies. Accurate identifica and quantification of HER2amp has predictive value for efficacy of anti-HER2 therapies a appropriate patient selection. Despite availability and use of various tumor tissue-based a blood-based assays for detecting HER2amp, data on cross-performance of these platfor lacking. **Methods:** Leveraging a multicenter international consortium (Italy, Japan and US generated a large cohort (N = 353) of mCRC patients (pts), tested for HER2amp using bo tissue and blood. Tissue testing was done using immunohistochemistry (IHC), in-situ hybridization (ISH) and (NGS). ctDNA NGS was performed using CLIA-certified Guardant3 ctDNA assay, capable of detecting HER2 copy number (CN) variations. The primary endp was to correlate HER2 gene CNs in tissue (tCN) and plasma (pCN). Descriptive statistics, spearman correlation (r) and Fisher's exact test were used. **Results:** Baseline tumors characteristics included right-sided primary in 234 (23%), proficient mismatch repair in 2 (98%) and *RAS/BRAF* wild type (WT) genotype in 194 (67%) pts. Tissue testing was done IHC, ISH and NGS in 76%, 64% and 74% pts, respectively. A total of 177 pts had HER2am detected by at least one test: 116 (66%), 157 (89%) and 96 (54%) of which had tissue +, ctDNA +, and both tissue and ctDNA + disease, respectively. Discordant cases consisted (6%) with positivity in tumor only and 61 (17%) in ctDNA only. Sensitivity, specificity, posi and negative predictive values of ctDNA assay (vis-à-vis tissue) were 83%, 74%, 61% an respectively. Among HER2amp pts, median (range) HER2/CEP17 (ISH) ratio, tCN and pCN 5.2 (2–12), 11.6 (2–700) and 3.5 (2–122), respectively. The pCN showed strong correlatio ISH ratio (r = 0.69) and tCN (r = 0.68) (P < 0.001). Median pCN differed significantly betw pts with HER2 IHC 3+ (12.0), 2+ (2.2) and 0/1+ (2.0) tumors (P < 0.001). High HER2amp (4.0) appeared to be enriched with tissue + cases (69% vs 8% [OR 24.6, P < 0.001]), tumo tissue HER2 + status (IHC3+ [75%] vs IHC2+ISH+ [50%] vs IHC2+/ISH- or IHC0/1+ [12%] 0.001), HER2 tCN > 6 (79% vs 31% [OR 8.7, P < 0.001]) and *RAS/BRAF* WT tumors (41% v 17% [OR 3.5, P = 0.064) but not left sidedness (41% vs 38%; OR 1.1; P = 0.82). **Conclusi** In this large diverse cohort of mCRC, we demonstrated correlation of HER2 tCN and pCN obtained by tissue-based and blood-based ctDNA assay. Further prospective efforts are needed to standardize this cross-platform quantification of HER2amp to facilitate robust clinical application of HER2 therapies. This effort shows the value of strategic internationa partnership in furthering research for rare cancer subsets.

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