# Letters

COMMENT & RESPONSE

## The Amount of Evidence Needed to Support ERBB2 as a Biomarker for Resistance to EGFR Inhibitors in Metastatic Colorectal Cancer

**To the Editor** Bregni et al[1] reinterpreted the therapeutic history of 27 patients with ERBB2-amplified (referred to as "*HER2*-amplified" by the authors, but herein referred to as "ERBB2-amplified") metastatic colorectal cancer (mCRC) in our HERACLES trial,[2] concluding that ERBB2-amplification is not a biomarker of resistance to epidermal growth factor receptor (EGFR) inhibitors, thus suggesting that ERBB2 positivity screening (and anti-HER2 treatment) should be withheld until resistance to these agents has been proven. We are obliged to *JAMA Oncology* for this opportunity to argue otherwise and corroborate the value of ERBB2 screening in the treatment algorithm of mCRC.

In addition to its role as a therapeutic target,[2] robust preclinical studies have established by genotype-response correlations in patient-derived mCRC xenografts[3] that ERBB2 amplification plays a pivotal role as a molecular biomarker of resistance to EGFR-targeted therapy. The counter argument provided by Bregni et al[1] to this hypothesis is that 14 of 26 patients experienced disease stabilization for 6 months or longer under prior anti-EGFR treatment.[2] However, none of those patients achieved an objective response. Moreover, in 10 of 14 patients, the anti-EGFR treatment was delivered with chemotherapy, making it impossible to dissect the real contribution of the anti-EGFR component, as already reported in our study, by adopting stringent criteria for the attribution of response.[2] To shed more light on this topic, we recently analyzed the clinical outcomes of anti-EGFR therapy in 100 patients with ERBB2-positive *KRAS* wild-type mCRC who were phenotype-matched with 116 patients with ERBB2-negative mCRC.[4] The patients with ERBB2-positive disease were 50% less likely to achieve an objective response (OR, 0.51; 95% CI, 0.28-0.94) and displayed a trend toward worse progression-free survival (PFS) (ERBB2-positive, 5.7 months; 95% CI, 4.9-6.0 vs ERBB2-negative, 7.0 months; 95% CI, 6.0-8.0). Although more an expansion rather than a confirmation of our previous observation, these results strongly support the notion of resistance to anti-EGFR therapy in patients with ERBB2-positive mCRC.

Further proof of the theory proposed by Bregni et al[1] comes from a retrospective study of 170 with mCRC.[5] However, Bregni et al[1] failed to report that while the patients with partial amplification displayed long PFS, those with complete amplification experienced the shortest PFS. Cumulative response-genotype results from HERACLES[2] strongly suggest that only these patients (about 5% of those with *KRAS* wild-type mCRC) harbor ERBB2-driven tumors that might benefit from anti-ERBB2 therapy.

Pristine proof of ERBB2 as a negative predictor for anti-EGFR therapy could only be achieved with a marker-validation designed trial; however, independent clinical research cannot support such trials when the biomarker has a low prevalence, such as ERBB2. Perhaps, and more realistically, the understandable concerns raised by the Bregni et al[1] could be addressed by approximation and limited risk to patients by accumulating retrospective evidence from multiple independent groups as was already fruitfully done for other biomarkers with a much higher prevalence, such as *RAS*.

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