In Reply Raghav and Strickler raise 3 major questions in their response to our article: (1) was the survival effect in the HERACLES study determined by anti-EGFR or by chemotherapy? (2) was ERBB2 amplification (referred to as “HER2-amplification” in our article, but herein referred to as “ERBB2-amplification”) high enough in those patients deriving a benefit from anti-EGFR therapy? (3) is ctDNA analysis reliable when testing for ERBB2 amplification?

Regarding the first question, we used the PRESSING hyperselection panel criteria to determine anti-EGFR sensitivity, and this approach excluded the effect of chemotherapy. Out of the 14 patients evaluable in the HERACLES cohort (ie, patients in which the effect of chemotherapy could be excluded), 5 (35.7%) were sensitive to anti-EGFR treatment. In addition, the patients in the HERACLES trial were unselected for sidedness and NRAS and BRAF mutations, which are established markers of resistance to anti-EGFR therapy.

As to the degree of ERBB2 amplification, eligibility for the HERACLES trial was determined using the HERACLES diagnostic criteria, meaning intense membrane ERBB2 expression in more than 50% of cells on immunohistochemical analysis or an ERBB2/CEN17 ratio of 2.0 or greater on fluorescence in situ hybridization (FISH). To our knowledge, ongoing anti-ERBB2 therapy trials do not apply stricter criteria. The 14 patients who had disease control for more than 6 months under anti-EGFR treatment had FISH ratios ranging from 2.3 to greater than 10 and qPCR GCNV between 2 and 700, whereas the 5 patients in which the effect of chemotherapy could be excluded had a qPCR GCNV of 3, 50, 125, 500, and 700.

Third, the concordance between tissue testing and ctDNA analysis was recently demonstrated, showing that plasmatic ERBB2 copy number correctly predicted benefit from the trastuzumab-lapatinib combination.

We fully agree with Sartore-Bianchi and colleagues on the unfeasibility of conducting an ad hoc marker-driven trial and on the need for accumulating retrospective evidence on the validity of ERBB2 amplification as a negative predictive marker of response to anti-EGFR therapy. We also agree with international guidelines that do not yet endorse ERBB2 amplification as a negative predictive marker. Negative predictive markers may take years to prove their efficacy. BRAF mutations, for instance, have a prevalence of 5% to 9% in patients with metastatic colorectal cancer, and although the body of evidence to prove they can predict resistance to anti-EGFR had been growing for years, it took retrospective data on more than 400 patients from at least 10 clinical trials to prove the point.

As Sartore-Bianchi et al correctly state, the bulk of the available evidence on the relationship between ERBB2 amplification and resistance to anti-EGFR therapy is preclinical.

We believe that retrospective data and future clinical trials will help shed light on the best therapeutic sequence in patients with metastatic RAS wild-type colorectal cancer with ERBB2 amplification. In the meantime, practice outside of clinical trials should not prevent them from receiving active treatment with anti-EGFR therapy.

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Error in Figure 2B Number at Risk Table: The Research Letter titled, “Evaluation of POLE and POLD1 Mutations as Biomarkers for Immunotherapy Outcomes Across Multiple Cancer Types,”1 published online on August 15, 2019, contained an error in the number at risk table for Figure 2B; the groups were incorrectly matched with their corresponding numbers at risk. The number at risk table has been corrected so that the 3 groups are properly matched to their numbers at risk.


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POETRY AND ONCOLOGY

Old Friend—HCT116

Mihnea P. Dragomir, MD

I don’t know if it’s romantic,
But behold, some worked and are alive.

Cell line:
Man, 48 years old, colorectal carcinoma,
Stage IV, specific mutations, eternal now.

I move you from one flask to another,
One more day.
A soul? A life?
Absurd?

I feed you with calf serum.
Your name is HCT116, and almost famous.

A friend? A good friend?
We talk, and you are the only one in the lab
Who understands my mother tongue
And makes the difference between
Me and the dead,
Between my country and my love.

We laugh,
Sunset,
You go back to the incubator,
Me to the bedroom.

Is this a life?

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