

CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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HER2 Testing in Metastatic Colorectal Cancer: Ready for Prime Time?



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H&O What are the limitations of the current treatments for colorectal cancer?

HH Our current therapies for colorectal cancer are effective for many patients, and much better than they were a decade ago. However, we still need better therapies, and we need to be able to identify subsets of patients who will respond particularly well to specific targeted therapies.

H&O How common are human epidermal growth factor 2 (*HER2*) amplifications in patients with colorectal cancer, and how does this compare with the prevalence of these amplifications in other types of cancer?

HH *HER2* amplification occurs in approximately 3.5% of all patients with colorectal cancer, and in approximately 5% to 6% of patients with colorectal cancer who have wild-type *RAS* and *BRAF*. *HER2* amplification also occurs in approximately 15% to 20% of patients with breast cancers, 10% to 15% of those with gastroesophageal junction cancers, and 9% to 10% of those with biliary cancers.

H&O How often are patients with colorectal cancer evaluated for *HER2* status?

HH It is unclear how many patients are routinely tested for *HER2* alterations. Now that we have data suggesting that anti-*HER2* therapies may be active in relevant patients with colorectal cancer, testing probably should be done in the majority of patients with metastatic colon cancer, particularly those whose disease has progressed on

prior therapy and those who have tumors with wild-type *RAS* and *BRAF*.

H&O Does the presence of *HER2* amplification have any prognostic significance in colorectal cancer?

HH It is unclear whether *HER2* amplification has any meaningful prognostic importance. The main value of testing is to identify patients in whom anti-*HER2* therapy may provide some benefit.

In practical terms, a score of 1+ on immunohistochemistry (IHC) testing means that the patient is negative for *HER2*, and a score of 3+ means that the patient is positive for *HER2*. Patients with a score of 2+ should have the IHC result checked by what is often called “reflex” fluorescence in situ (FISH) testing, which is the approach used in breast cancer and gastroesophageal cancer.

H&O Should anti-*HER2* therapy be used in all patients with colorectal cancer that is positive for *HER2* amplification?

HH I would not say that anti-*HER2* therapy should be automatic for all patients who have colorectal cancer with *HER2* amplification, but referral to a trial or the off-label use of anti-*HER2* therapy should at least be considered for most of these patients. Currently, the data from HERACLES (*HER2* Amplification for Colorectal Cancer Enhanced Stratification) and MyPathway (A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf, and Erivedge Treatment Targeted Against Certain Mutations

Table. Therapies Used in the MyPathway Study to Target Specific Mutations

Pathway	Molecular Alteration	Treatment(s)
HER2	Overexpression of HER2 or activating mutation of <i>HER2</i>	Trastuzumab and pertuzumab
EGFR	Activating mutation of <i>EGFR</i>	Erlotinib
BRAF	Activating mutation of <i>BRAF</i> (V600E and others)	Vemurafenib
Hedgehog	Activating mutation of <i>SMO</i> or loss-of-function mutation of PTCH1	Vismodegib

BRAF, serine/threonine-protein kinase B; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor 2; SMO, smoothed (gene); PTCH1; protein patch homologue 1 (gene).

Source: Burris HA et al. ASCO abstract TPS11111. *J Clin Oncol.* 2015;33(15)(suppl).

in Cancer Patients) are promising, but the numbers of patients in these reports remain modest, and follow-up is limited. More studies to validate these promising, albeit preliminary, data are urgently needed.

H&O How common are activating *HER2* mutations in patients with colorectal cancer?

HH The exact number is still a bit controversial, but probably 3% to 4% of patients with colorectal cancer have a potentially activating mutation in *HER2*. The relevance of these mutations to sensitivity to anti-*HER2* therapy, especially antibody treatment vs small-molecule tyrosine kinase inhibitors, is not yet known.

H&O How should patients with these mutations be treated?

HH Patients with *HER2* amplifications have been examined in 2 modestly sized studies, which are the largest ones to date in this area: HERACLES and the MyPathway colorectal cancer cohort. Patients with *HER2* mutations—as opposed to amplifications—have not been well studied, so we do not know how well they might respond to anti-*HER2* therapy, antibody therapy, combination antibody therapy, or a tyrosine kinase inhibitor.

H&O Could you talk more about what HERACLES found?

HH HERACLES was presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting by Dr Salvatore Siena. This study screened 683 patients who had wild-type *KRAS* exon 2 for *HER2* positivity by the definitions I mentioned earlier. The rate of *HER2* positivity in this group was approximately 5.3% and resulted in a group of 23 patients, of whom data were available for 22. The objective response rate to anti-*HER2* therapy with trastuzumab (Herceptin, Genentech) plus lapatinib (Tykerb, Novartis) in these patients was 32%, with many of them having minor responses or stable disease. When

responses occurred, they were often fairly durable, lasting for 6 months or more. The median time to progression for all patients was 5.5 months. This was a nonrandomized study, so time to progression may have been affected by tumor biology, patient health, and any treatment. However, time to progression of 5.5 to 6 months is a very promising sign of activity, and certainly the 32% response rate suggests that the treatment was active.

Also of note in HERACLES was seeing drug activity in patients who were fairly heavily pretreated; all of the patients had disease resistant to cetuximab (Erbix, Lilly) or panitumumab (Vectibix, Amgen), and their disease had failed to respond to multiple chemotherapeutic agents, including fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab (Avastin, Genentech), and aflibercept (Eylea, Regeneron).

H&O Could you talk more about what MyPathway found?

HH MyPathway is a large umbrella study; the results that were presented at the 2015 ASCO Annual Meeting were from just one cohort. The study is looking at patients with molecular alterations that are linked to several drugs already approved by the US Food and Drug Administration (FDA) for a different indication (Table). The treatments used in this study are trastuzumab and pertuzumab (Perjeta, Genentech) for *HER2* mutations, erlotinib (Tarceva, Genentech/Astellas) for epidermal growth factor (*EGFR*) mutations, vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) for *BRAF* alterations, and vismodegib (Erivedge, Genentech) for alterations in the Hedgehog pathway.

A total of 16 patients in the gastrointestinal cancer cohort had colorectal cancer. The majority of alterations in the patients with colorectal cancer were *HER2* amplifications; none of the patients with colorectal cancer had *HER2* mutations.

The treatment response rate among the patients with colorectal cancer was 38%, and the clinical benefit rate—clinical response or stable disease for at least 4

months—was 54%. The responses were fairly durable. As in HERACLES, the median time to progression across all patients was 5.6 months.

Of course, these data are still immature. Many patients are still enrolled in the study, however, so the time on treatment is likely to increase. Because of the activity seen with treatment, the study has been increased from the initial basket of a dozen patients to 30 or 40 patients.

H&O Are there any questions that future studies in this area should attempt to answer?

HH The data from both HERACLES and MyPathway are based on a very limited number of patients. So the first thing we need to do is study a larger number of patients. The second step we should take is to better define the potential importance of molecular subgroups. The third step is to determine what is driving acquired resistance after initial response. The fourth step is to define the level of amplification that predicts response.

Another study of interest, presented by Dr Ron Bose at the most recent ASCO Gastrointestinal Cancers Symposium, looked at rates of HER2 positivity in the database

of Foundation Medicine, in Cambridge, Massachusetts. The key findings of that report are that *HER2* amplifications and mutations can be seen in several gastrointestinal cancers, including colorectal cancer. In addition, the rates of these genetic alterations in the large number of clinical samples processed by Foundation Medicine were consistent with the rates seen in the Cancer Genome Atlas of the National Cancer Institute and National Human Genome Research Institute.

Suggested Readings

Bose R, Ali S, Jain N, et al. Frequency of HER2 mutations and amplification in GI malignancies and ability of pertuzumab to overcome neuregulin1 mediated drug resistance to a HER2 tyrosine kinase inhibitor in colon cancer. [ASCO GI abstract 630]. *J Clin Oncol*. 2016;34(suppl 4S).

Burris HA, Hurwitz H, Perez EA, et al. MyPathway: an open-label phase IIa study of trastuzumab/pertuzumab, erlotinib, vemurafenib, and vismodegib in patients who have advanced solid tumors with mutations or gene expression abnormalities targeted by these agents [ASCO abstract TPS11111]. *J Clin Oncol*. 2015;33(15)(suppl).

Seo AN, Kwak Y, Kim DW, Kang SB, Choe G, Kim WH, Lee HS. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. *PLoS One*. 2014;9(5):e98528.

Siena S, Sartore-Bianchi A, Trusolino L, et al. Therapeutic dual inhibition of HER2 pathway for metastatic colorectal cancer (mCRC): The HERACLES trial [ASCO abstract 565]. *J Clin Oncol*. 2015;33(suppl 3).