Prolonged Response to HER2-Directed Therapy in a Patient With HER2-Amplified, Rapidly Progressive Metastatic Colorectal Cancer

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Abstract

HER2 gene amplifications and activating mutations in the *HER2* receptor tyrosine kinase are present in 4% of metastatic colorectal cancers (mCRCs). *HER2*-targeted therapy is not standard of care, although preclinical and clinical data suggest that patients with *HER2* amplifications and/or *HER2*-activating mutations may benefit from *HER2*-directed therapy. *HER2* amplifications and activating mutations have also been implicated in resistance to anti-epidermal growth factor receptor–based therapy. This report describes a patient with *KRAS*, *NRAS*, and *BRAF* wild-type mCRC who experienced disease progression on first-line treatment with FOLFIRI and cetuximab after only 5 months, and subsequently experienced progression on second-line treatment with capecitabine and oxaliplatin plus bevacizumab after 2 months with significant functional decline. Next-generation sequencing of the primary tumor identified *HER2* amplification, and we were able to obtain trastuzumab-DM1 for off-label use. The patient had symptomatic clinical benefit from trastuzumab-DM1 and had radiographic disease control for 7 months. On progression, therapy was changed to trastuzumab and pertuzumab, but the patient's disease progressed 3 months later. Treatment with the trastuzumab-DM1 resulted in a sustained response that was longer than his prior responses in the first and second lines of treatment, with a dramatic improvement in the patient's functional status. This case represents the first report, to our knowledge, of successful single-agent treatment of *HER2*-amplified CRC with trastuzumab-DM1. Clinical trials targeting patients with *HER2*-mutated and -amplified metastatic colon cancer are currently underway. Molecular insights from investigating *HER2* activation and the impact of *HER2*-directed therapies in a wide variety of solid tumors will create the needed evidence base to more broadly inform patient care.

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progression on first-line treatment with FOLFIRI and cetuximab after only 5 months, and subsequently experienced progression on second-line treatment with capecitabine and oxaliplatin plus bevacizumab after 2 months with significant functional decline. Next-generation sequencing (NGS) of the primary tumor identified *HER2* amplification and we were able to obtain trastuzumab-DM1 for off-label use. The patient had symptomatic clinical benefit from trastuzumab-DM1 and had radiographic disease control for 7 months. On progression, therapy was changed to trastuzumab and pertuzumab, but the patient's disease progressed 3 months later. Treatment with the trastuzumab-DM1 re-

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This case represents the first report, to our knowledge, of successful single-agent treatment of *HER2*-amplified CRC with trastuzumab-DM1. Clinical trials targeting patients with *HER2*-mutated and -amplified metastatic colon cancer are currently underway. Molecular insights from investigating *HER2* activation and the impact of *HER2*-directed therapies in a wide variety of solid tumors will create the needed evidence base to more broadly inform patient care.

Case Report

A 48-year-old Caucasian man presented to his primary care provider with persistent right upper quadrant pain. An ultrasound of the area demonstrated at least 7 heterogeneous lesions throughout the liver. CT and PET imaging confirmed PET-avid liver lesions varying in size from 1 to 6.5 cm. The patient also had many scattered PET-avid pulmonary nodules and a PET-avid rectosigmoid mass with adjacent hypermetabolic lymphadenopathy. A liver biopsy diagnosed metastatic adenocarcinoma (CK20+/CK7+, consistent with a colon primary). Subsequent colonoscopy visualized a nonobstructing, circumferential, ulcerated mass extending 14 to 16 cm from the anal verge. Biopsy confirmed colorectal adenocarcinoma. The serum carcinoembryonic antigen (CEA) level at the time of diagnosis was 39.5 ng/mL. Molecular analysis demonstrated a *KRAS*, *NRAS*, and *BRAF* wild-type tumor with intact mismatch repair proteins. Further NGS of the primary tumor demonstrated *ERBB2* (*HER2*) and *MYC* amplification and a *TP53* R175H mutation and *APC* R1386* mutation. Further testing via immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) for *ERBB2* amplification was not performed because testing was not yet standard in CRC and availability of tissue on the liver biopsy was limited.

First-line treatment with FOLFIRI and cetuximab was initiated, and approximately 2.5 months later interval scans showed a modest response in the liver and lungs and stable focal thickening at the rectosigmoid junction (Figure 1). Treatment was continued, but interval imaging in 2 months showed progressive disease in the liver and lungs, and he

Figure 1 Treatment course.

Abbreviations: CapeOx, capecitabine and oxaliplatin; mCRC, metastatic colorectal cancer; PD, progressive disease; T-DM1, trastuzumab-DM1; XRT, chemoradiation.

was switched to a standard second-line regimen of capecitabine, oxaliplatin, and bevacizumab. Subsequent imaging 2 months later showed continued progression of disease in the liver and lungs, and progressive rectosigmoid luminal narrowing coincident to the patient having worsening right upper quadrant discomfort and more bowel complaints, with increasingly bloody stools and small, frequent bowel movements. His CEA level at the time of progression was 78.9 ng/mL, and he was also complaining of worsening fatigue. Given this rapid progression, off-label treatment with *HER2*-directed therapy was sought. The patient's insurance provided T-DM1 (trastuzumab-DM1) and he was started on this treatment. Within 4 weeks of starting T-DM1, he showed a marked improvement in functional status and tolerated treatment well except for mild diarrhea. His CEA level at this time was 64.3 ng/mL. Interval imaging at 2 months showed a treatment response in the liver, lungs, and primary tumor. He remained on treatment, and imaging 3 months later showed a continued response in the liver and stable disease in the lungs and the primary tumor (Figure 2). His CEA level reached a nadir at 39.1 ng/mL. Treatment was continued and the patient continued to feel well, with an improvement in energy, and reported less blood in his stools. Interval imaging 2 months later, now 7 months after he began treatment with T-DM1, showed progressive disease in the liver, with an increase in size and number of liver lesions and new biliary ductal dilatation. At this time, the patient was also having more bowel complaints, with decreased stool caliber and severe diarrhea, and treatment was paused in order to address the primary tumor. The patient underwent a palliative laparoscopic diverting sigmoid colostomy and a 10-day

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Figure 2 (A) Abdominal CT image before the start of T-DM1 treatment. (B) Abdominal CT image after 5 months of T-DM1 treatment.

course of palliative chemoradiation to the primary because of persistent bleeding. Assessment of circulating cell-free DNA (cfDNA) in the blood at the time of progression showed the *TP53* R175H mutation, APC R1386* mutation, and continued detection of *HER2* amplification.

After recovery from surgery and radiation, given a longer progression-free interval on third-line therapy with T-DM1 than on first- and second-line treatment and persistent *HER2* amplification in cfDNA, authorization was pursued for pertuzumab and trastuzumab. He started treatment with this combination 3 months after T-DM1 was stopped. A new reference laboratory test showed a CEA level of 456 ng/mL at the time of pertuzumab and trastuzumab initiation. Over the next couple of months, his CEA level remained stable and then increased to 851 ng/mL. Imaging performed after 6 cycles of pertuzumab and trastuzumab showed progressive disease, and *HER2*-directed treatment was stopped. Notably, at the time of progression, another liver biopsy was performed

and NGS once again demonstrated a *KRAS*, *NRAS*, and *BRAF* wild-type tumor with *MYC* amplification and the *TP53* mutation but loss of *HER2* amplification. After progression, the patient required decompression for biliary obstruction and then started on TAS-102 while pursuing options for further clinical trials.

Discussion

ERBB2 (*HER2/neu*) encodes the receptor tyrosine kinase of *HER2*. *ERBB2* gene amplification and oncoprotein overexpression lead to tumor proliferation. *HER2* is part of family of 4 related receptor tyrosine kinases—EGFR, *HER2*, *HER3*, and *HER4*—involved in activation of several downstream oncogenic pathways, including signaling through PI3K/AKT and MAPK. The *HER2/HER3* heterodimer is thought to be one of the most significant contributors to tumor proliferation among the family of receptors.¹ *HER2* testing and *HER2*-directed therapy have dramatically improved the treatment of *HER2*-positive breast and gastric cancers.^{2,3}

Patient selection for *HER2*-directed treatment is contingent on pathologic determination of *HER2* status. *HER2* testing in breast and gastric cancers is often a source of confusion, because the staining pattern that defines IHC positivity is different in breast and gastric cancers, and gastric cancers are more heterogeneous in *HER2* expression than breast cancers.⁴ In gastric cancer, the largest survival benefit associated with the *HER2*-targeted monoclonal antibody, trastuzumab, is seen in patients with higher *HER2* expression.⁵ Although *HER2* amplifications have more recently been recognized as an important driver in several other solid tumors, including mCRC, the definition of *HER2* positivity in other solid tumors has not been well-established.⁴ Methodologies for *HER2* testing and defining positivity in mCRC are not yet standardized, and efforts to standardize testing in order to identify patients who may be eligible for *HER2*-directed treatment are underway.^{6–8}

It appears that *HER2* overexpression is more homogenous in mCRC than in gastric cancer, and is associated with left-sided and rectal primaries.⁸ *HER2* overexpression has been noted in 5% of *KRAS* wild-type CRC, and data exist suggesting up to a 7% prevalence of both amplifications and activating mutations.^{9–11} Less is known about *HER2*-activating

mutations in mCRC, but the clinical evidence supporting HER2-directed therapy in mCRC in both amplifications and activating mutations is evolving and suggestive of efficacy.^{12–14} Notably, approximately 15% discordance between HER2 expression in colon primaries and metastases has been reported, and HER2 expression may change over time, highlighting the need to further prospectively study the role of HER2 in mCRC.⁶ The prognostic effect of HER2 overexpression in mCRC remains unclear, with conflicting evidence from retrospective analyses.^{8,14} Another factor yet to be explored in CRC is the interplay of MYC alterations with HER2 overexpression. In early-stage, HER2-positive breast cancer, MYC/chromosome 8 copy number alterations may predict greater benefit from adjuvant treatment with trastuzumab.¹⁵

In colon cancer, as in this case, *HER2* gene amplifications are known to produce resistance to anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab, via activation of the MAPK pathway.^{16–18} There are also several known *HER2*-activating mutations, such as S310F, L755S, V777L, V842L, and L866M, associated with resistance to anti-EGFR monoclonal antibodies in vitro. Regarding *HER2* amplifications, testing in preclinical patient-derived xenograft (PDX) models supports the rationale for dual blockade of *HER2/HER3* and EGFR with trastuzumab and lapatinib.^{9,19} Single-agent trastuzumab did not markedly affect *HER2* and EGFR phosphorylation but produced dose-dependent suppression of *HER3* activation. The addition of lapatinib, a tyrosine kinase inhibitor (TKI) that targets *HER2* and EGFR, caused a strong suppression of *HER2* but an upregulation of *HER3* after a transient blockade, and thus, the 2 together had synergistic inhibitory effects. Single-agent afatinib, an irreversible TKI targeting *HER2*, EGFR, and *HER4*, also seems to be as effective as the combination of reversible small molecule TKIs such as lapatinib and trastuzumab.²⁰ Experiments using CRC PDX models in *HER2*-amplified tumors have also explored mechanisms of resistance to TKIs such as lapatinib, and have found that resistance can also be overcome by the addition of pertuzumab, a monoclonal antibody that inhibits *HER2* heterodimerization with other *HER* family members in addition to homodimerization.¹⁹

In terms of *HER2* mutations, *HER2*-mutant PDX models exhibit tumor regression when treated with dual *HER2*-targeted therapy consisting of trastu-

zumab and a TKI such as lapatinib or neratinib.¹⁰ Afatinib has also been tested in *HER2*-mutant colon cancer cell lines. In these cell lines, the tumors were highly sensitive to afatinib but the addition of the *HER3* ligand, neuregulin, led to afatinib resistance. In these *HER2*-mutant CRC cell lines, resistance to afatinib mediated by neuregulin-1 was overcome by pertuzumab, suggesting that pertuzumab may be able to overcome TKI drug resistance mediated by *HER3* activation.¹³ Although which pathways and mechanisms of resistance to target remain under exploration in *HER2*-amplified and -mutated mCRC, additional clinical data supporting the use of *HER2*-directed therapy are emerging.

Trastuzumab was first evaluated in mCRC in combination with chemotherapy (irinotecan or FLOX) in 2 phase II studies. In these studies there were signals of efficacy, yet low rates of *HER2* overexpression in all-comer populations limited further exploration at that time.^{21,22} HERACLES (*HER2* Amplification for Colo-Rectal Cancer Enhanced Stratification) was the first large phase II clinical trial to evaluate *HER2*-directed therapy—lapatinib in combination with trastuzumab—in patients with *HER2*-amplified mCRC. In HERACLES, *HER2* positivity was defined as 3+ or 2+ by IHC or FISH-positive (defined by a *HER2*:CEP17 ratio >2 in >50% of cells). Lapatinib is approved in combination with chemotherapy in patients with metastatic breast cancer who have progressed on trastuzumab.²³ The HERACLES study found that patients with *HER2*-amplified mCRC refractory to standard therapy, including anti-EGFR therapy, had a 35% response rate to lapatinib plus trastuzumab, with an 8.5-month median duration of response, and a median time to progression of 5.5 months.⁹ In a phase I study of lapatinib and cetuximab in advanced solid tumors, patients with mCRC who responded to this combination included one who had received prior anti-EGFR therapy, suggesting another possible approach to overcoming resistance to anti-EGFR therapy.²⁴

Another phase II clinical trial, HERACLES-RESCUE, evaluating T-DM1 after progression on trastuzumab and lapatinib, is underway in mCRC. T-DM1 is an antibody drug conjugate whereby trastuzumab is connected via a stable thioether linker to emtansine (DM1), a highly potent microtubule chemotherapy agent. Once trastuzumab binds to *HER2*-expressing cells, the linker is broken down, releasing

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DM1 intracellularly.^{25,26} In patients with metastatic breast cancer whose disease had progressed on trastuzumab and taxane, T-DM1 showed improved overall survival compared with capecitabine and lapatinib.²⁷ The rationale for T-DM1 in HERACLES-RESCUE resulted from testing in CRC PDX models among patients with acquired resistance to trastuzumab and lapatinib on the HERACLES study. These PDX models were found to have high levels of *HER2* expression, and treatment with T-DM1 resulted in tumor shrinkage, whereas animals treated with pertuzumab alone had no response. In HERACLES-RESCUE, acknowledging that *HER2* expression may change over time, not only were tumors rebiopsied on progression and tested via IHC/FISH, but also serial liquid biopsies for cfDNA were performed. In the future, as cfDNA is further evaluated for detection of both *HER2* amplifications and mutations in CRC, liquid biopsies may help inform *HER2*-directed therapeutic decision-making over the course of treatment.^{27,28}

Another recently presented study, My Pathway, evaluated trastuzumab plus pertuzumab in *HER2*-amplified and -mutated tumors. Patients were eligible for the study if their tumors were found to have *HER2* amplification or an activating mutation via NGS, and/or *HER2* amplification via IHC/FISH. The 13 patients with *HER2*-positive mCRC all had *HER2* amplifications and had received a median of 5 lines of previous treatment (range, 2–8 lines), and 54% had received prior anti-EGFR antibodies. The overall response rate was 38% and the clinical ben-

efit rate was 54% (defined as complete or partial response or stable disease for at least 6 months if treatment was discontinued, or 5.5 months if treatment was ongoing). The median time to progression was 5.6 months, with ongoing response in 23% of patients at the time of recent data presentation.¹¹

This is the first case, to our knowledge, showing the activity of single-agent T-DM1 in a patient with *HER2*-amplified mCRC before any other *HER2*-directed treatment. T-DM1 treatment after disease progression on lapatinib and trastuzumab is currently being explored in the HERACLES-RESCUE study and data have not yet been reported.

Conclusions

It remains to be seen which agent or combinations of agents targeting *HER2*, *HER3*, and *EGFR*, and in what line of therapy, may be most efficacious for patients with *HER2*-amplified or -mutated mCRC, but targeting this pathway seems to be of increasing clinical importance for these patients. Furthermore, how *HER2* positivity should be defined and tested for in mCRC has yet to be standardized, and this will be an important step toward establishing the evidence base needed to solidify the role of *HER2*-directed therapy in the treatment paradigm for mCRC. This report illustrates a case of T-DM1 therapy demonstrating remarkable clinical benefit in the third line for a patient with *HER2*-amplified, refractory mCRC, and supports the ongoing efforts to understand the role of *HER2* in mCRC.

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