Clinical Response to T-DM1 in *HER2*-Amplified, *KRAS*-Mutated Metastatic Colorectal Cancer

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ABSTRACT

HER2 amplification has been identified in 2% to 3% of all colorectal cancers (CRCs). Although the prognostic role of *HER2* amplification in metastatic CRC (mCRC) is unclear, studies have highlighted it as a therapeutic target. In addition, several studies have shown that *HER2* amplification is implicated in the resistance to EGFR-targeted therapies. Other studies have provided scientific evidence to support the use of HER2-directed therapies in *HER2*-amplified CRC; however, thus far this benefit has been limited to the *RAS* wild-type population. There is an ongoing clinical need to identify novel means of targeting *HER2* amplifications in the rare settings of *HER2*-amplified, *RAS*-mutated CRC. This case report presents a 58-year-old man with *HER2*-amplified mCRC and a *KRAS* G12D mutation whose disease progressed on all standard cytotoxic therapies as well as dual HER2 targeting using trastuzumab and pertuzumab. He subsequently derived a clinical benefit with metastatic lung disease regression on trastuzumab emtansine (T-DM1). He eventually experienced disease progression in the liver after 6 every-3-week cycles. The patient's response and disease progression were associated with ongoing decline in the *HER2* copy number on the circulating tumor DNA assay, suggesting that the mechanism of resistance was related to the loss of *HER2* amplification or the emergence of non–*HER2*-amplified CRC clones. This represents the first report of clinical benefit with T-DM1 in *KRAS*-mutated *HER2*-amplified CRC.

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***HER2* amplification has been** detected in 2% to 3% of all colorectal cancers (CRCs).[1,2] The frequency increases up to 5% in *KRAS/BRAF* wild-type (WT) patients.[2–4] *HER2*-amplified tumors are more frequently found in association with left-sided CRC and are uncommon in the setting of *KRAS*, *NRAS*, and *BRAF* mutations.[5–7] Although the prognostic role of *HER2* amplification in metastatic CRC (mCRC) is unclear, studies have highlighted it as a therapeutic target.[1,3,8] In addition, several studies have shown that *HER2* amplification is implicated in the resistance to EGFR-targeted therapies.[1,4,9,10]

Multiple studies have provided scientific evidence to support HER2-directed therapies in CRC.[3,8] These studies interrogated dual HER2 targeting based on preclinical models showing minimal efficacy using trastuzumab or HER2 tyrosine kinase monotherapy.[1,11] Although the HERACLES-A trial investigated trastuzumab + lapatinib in patients with *KRAS*-WT only,[3] the MyPathway trial included patients with both *RAS*-WT and *RAS*-mutated.[8] HERACLES-A and MyPathway showed significant clinical activity in patients with *KRAS*-WT tumors with response rates of 30% and 40%, progression-free survival (PFS) of 4.8 and 5.3 months, and overall survival of 10.6 and 14 months, respectively.[3,8] Consistent with the preclinical data demonstrating resistance to dual HER2 targeting in the *KRAS*-mutated setting,[12] MyPathway demonstrated a lack of clinical activity of trastuzumab + pertuzumab in *KRAS*-mutated, *HER2*-amplified CRC.[8] There is an ongoing clinical need to identify novel means of targeting *HER2* amplifications in the rare settings of *HER2*-amplified, *RAS*-mutated CRC. HER2-targeting immunoconjugates such as trastuzumab emtansine (T-DM1) or DS-8201 could hypothetically have clinical activity in *HER2*-amplified, *RAS*-mutated cancers given their unique mechanism that uses HER2-targeting antibodies as chemotherapy delivery vehicles to HER2-overexpressing cancers.

This report presents a 58-year-old man with *HER2*-amplified, *KRAS* G12D–mutated mCRC treated with T-DM1 who experienced disease progression on standard chemotherapy with 5-FU, oxaliplatin, irinotecan, and TAS-102, as well as dual HER2 targeting with trastuzumab and pertuzumab as part of a clinical trial.

Case Presentation

A man aged 58 years presented in February 2015 with the chief complaint of bloating, change in bowel movements, thinning of stools, and intermittent bleeding. Initial radiologic screening displayed a heterogeneous mass in the right lobe of the liver consistent with metastatic disease, along with irregular thickening of the rectosigmoid colon, implicating it as the primary tumor site. Colonoscopy revealed a mass at 12 cm from the anal verge. Histology showed a moderately differentiated invasive adenocarcinoma with mismatch repair proficiency. Next-generation sequencing was performed by FoundationOne and revealed *HER2* (*ERBB2*) amplification (77 copies) in addition to *KRAS* G12D and *TP53* E51fs*72 mutations.

Given the patient's right liver–limited disease, he underwent 3 months of FOLFOX chemotherapy, which was complicated by grade 3 neuropathy, followed by right hepatectomy. This was followed by protracted chemoradiation to the pelvis and low anterior resection. No further adjuvant therapy was warranted. The patient remained in clinical remission for 5 months, when a PET/CT in comparison with the postsurgical CT scan revealed an FDG-avid enlarged right midabdominal mesenteric lymph node along with intense FDG uptake at the rectosigmoid anastomosis, supporting recurrent disease. Anastomotic reccurrence was proven via endoscopic biopsies. Given his *HER2* amplification, prior disease progression after FOLFOX treatment, and refusal of further chemotherapy, the patient was enrolled on the pertuzumab + trastuzumab arm of the MyPathway clinical trial.[8] His best response was stable disease, followed by clear progression after 5 months of treatment. The patient subsequently received a total 22 cycles of FOLFIRI with stable disease as the best response. He eventually experienced disease progression in the lungs and liver after 14 months of treatment, and was subsequently treated with trifluridine/tipiracil for 2 months, with radiographic progression.

Given the patient's *HER2*-amplified, *KRAS*-mutated tumor and his progression on all standard therapies and on prior trastuzumab + pertuzumab, he was offered T-DM1 on compassionate grounds. Circulating tumor DNA (ctDNA) using Guardant360 and tumor HER2 immunohistochemistry (IHC) confirmed a high-plasma *HER2* copy number (56.1) and an HER2 IHC of 3+. He was started on T-DM1 in January 2019. Clinical benefits were noted after the first cycle of T-DM1, with a decrease

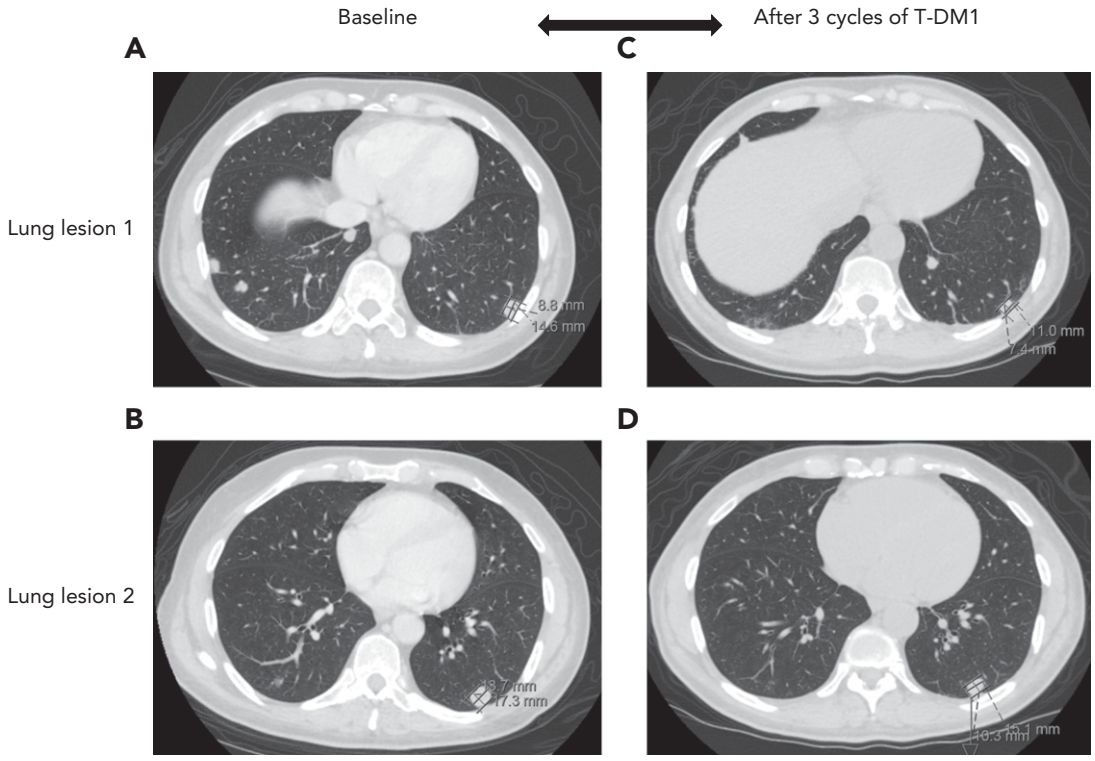

Figure 1. Radiographic response to T-DM1 in *HER2*-amplified, *KRAS*-mutated metastatic colorectal cancer. Baseline of (A) lung lesion 1 (14.6 × 8.8 mm) and (B) lung lesion 2 (17.3 × 13.7 mm). Status of (C) lung lesion 1 (11 × 7.4 mm) and (D) lung lesion 2 (15.1 × 10.3 mm) after 3 cycles of T-DM1.

Abbreviation: T-DM1, trastuzumab emtansine.

in pelvic pain and narcotic requirements. Treatment was well tolerated without any significant adverse effects. After 3 cycles of every-3-week T-DM1, imaging studies showed stable disease, with several tumors in the lungs exhibiting disease regression (Figure 1). In addition, ctDNA assay confirmed a decrease in mutation allele frequency (MAF) of all somatic mutations and in the *HER2* copy number, consistent with disease regression. Unfortunately, disease progression occurred after cycle 6 of treatment, with an increase in hepatic metastases and pelvic disease while the patient's lungs continued to show a mixed response. Despite disease progression, ctDNA assay indicated a significant ongoing decline in the *HER2* copy number from 13.1 to 8.6 (Figure 2), with an increase in the MAF of multiple somatic tumor mutations (Figure 3). After disease progression, the patient was treated with FOLFOX rechallenge, which was poorly tolerated, and he enrolled in hospice care and died shortly afterward.

Discussion

HER2 amplification is a key genetic driver occurring in approximately 2% to 3% of all CRCs.[1,2] Although *HER2*-amplified, *RAS*-WT CRCs demonstrate relative resistance to anti-*EGFR* therapies, dual HER2 targeting has been met with clinical success whether using trastuzumab + lapatinib or trastuzumab + pertuzumab, which has resulted in endorsement of these 2 treatment strategies by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer.[3,8,13] However, *RAS*-mutated, *HER2*-amplified CRCs do not seem to derive any clinical benefit from combinations of HER2-targeted therapies.[8] We hypothesized that a HER2 immunoconjugate may result in antitumor activity through targeted cytotoxic drug administration that is independent of *RAS* status. This case report showed for the first time that the immunoconjugate T-DM1 can be associated with clinical benefits in *KRAS*-mutated, *HER2*-amplified CRC. The regression in multiple pulmonary metastases confirmed on-target activity of T-DM1. In addition, the major reduction in *HER2* copy number on ctDNA even in the setting of disease resistance indicated debulking of the HER2-positive tumor with T-DM1. Concurrent increase in MAF was seen across all the somatic mutations at the time of resistance, which included *KRAS*, *SMAD4*, and *TP53* (Figure 3). This was noted without the emergence of any new driver mutations. As such, we cannot attribute resistance to any of these individual mutations. Notably, *KRAS* and *BRAF* amplifications were also seen at the time of resistance (Figure 2). Whether these alterations conferred resistance to T-DM1 or reflected a higher burden of disease cannot be confirmed. Our findings are consistent with multiple other reports, across different tumor types, that link resistance to HER2 targeting to loss of HER2 expression.[14–17] T-DM1 treatment is known to decrease *HER2* expression and amplification.[17] HER2 overexpression is vital for the efficacy of T-DM1. Retrospective analysis of 2 phase II trials suggests that clinical response to T-DM1 is linked with HER2 levels.[18–20]

HERACLES-RESCUE, a phase II clinical trial, is examining the response of patients with *HER2*-amplified mCRC treated with T-DM1 who had shown progression on anti-HER2 therapy (trastuzumab + lapatinib).

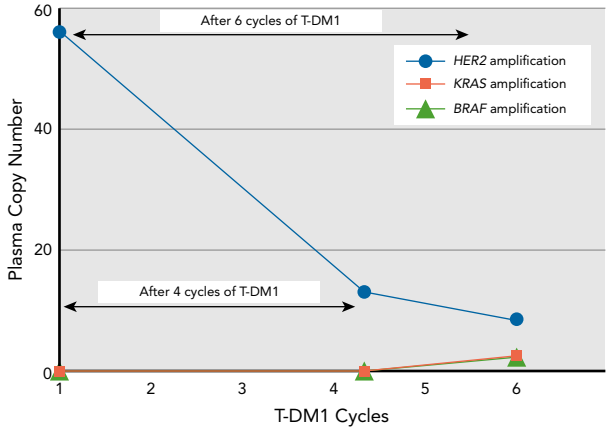

Figure 2. Biochemical response showing decreasing *HER2* plasma copy number with T-DM1 treatment (baseline, 56.1; after 4 treatment cycles, 13.1; at time of progression after 6 cycles, 8.6) and abrupt increase in plasma copy number of *KRAS* (baseline, 0; after 4 treatment cycles, 0; at time of progression after 6 cycles, 2.6) and *BRAF* (baseline, 0; after 4 treatment cycles, 0; at time of progression after 6 cycles, 2.3) at time of progression on T-DM1.
Abbreviation: T-DM1, trastuzumab emtansine.

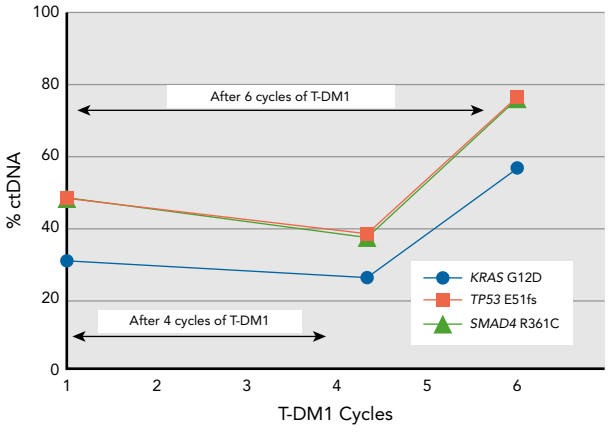

Figure 3. Increase in MAF of multiple somatic tumor mutations at time of disease progression on T-DM1 (*KRAS* G12D: baseline, 30.6%; after 4 treatment cycles, 25.9%; at time of progression after 6 cycles, 56.6%; *TP53* E51fs: baseline, 48.3%; after 4 treatment cycles, 38.2%; at time of progression after 6 cycles, 76.5%; *SMAD4* R361C: baseline, 48%; after 4 treatment cycles, 37.1%; at time of progression after 6 cycles, 76%).
Abbreviations: ctDNA, circulating tumor DNA; MAF, mutation allele frequency; T-DM1, trastuzumab emtansine.

The rationale of evaluating T-DM1 in *HER2*-amplified mCRC originates from testing CRC in patient-derived xenograft (PDX) models after patients experienced progression on trastuzumab + lapatinib in the HERACLES-A trial. These PDX models demonstrated tumor responses with T-DM1.[21] The results from this clinical trial are currently awaited and may support our findings.

Another trial, the NCI-MATCH, investigated T-DM1 in a range of *HER2*-amplified cancers that were not exposed to prior HER2-targeted therapies. In a subgroup of CRCs, T-DM1 showed stable disease as the best response in 27% (3 of 11) of patients. However, the population was heterogeneous in the trial, making it difficult to infer a T-DM1 response against *HER2*-amplified, *KRAS*-mutated CRC.[22]

Conclusions

This report presents a patient with *HER2*-amplified, *KRAS*-mutated mCRC who achieved tumor shrinkage and clinical benefits after treatment with T-DM1. He received a total of 6 cycles of T-DM1. Although radiologic images showed modest tumor shrinkage, the patient achieved stable disease as the best response with 4 months of PFS. In comparison, the MyPathway trial reported a median PFS of 1.4 months in patients with *KRAS*-mutated treated using trastuzumab + pertuzumab.[8] This case report provides further support for investigating HER2-targeting immunoconjugates in *HER2*-amplified, *KRAS*-mutated mCRC.

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