Metastatic Breast Cancer Patient With Activating *HER2* Exon 20 Insertion Mutation With Response to Poziotinib: Case Report of Compassionate Drug Use

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Clinical Practice Points

- Mutation of the *HER2* transmembrane receptor provides another possible mechanism of resistance of breast cancer to hormone therapy and endocrine therapy, especially in tumors without amplification of the *HER2* locus on chromosome 17.
- *HER2* TKIs may provide a therapeutic option for patients with tumors that have HER2 tyrosine kinase mutations.
- We report a case of a woman with estrogen receptor −positive metastatic breast cancer with an insertion in the HER2 tyrosine kinase domain of her breast cancer.
- Consistent with results seen in a case of lung cancer, this tumor was sensitive to the *HER2* TKI poziotinib while resistant to other *HER2* TKIs.
- In the future, selection of a *HER2* TKI may possibly depend on the mutation in the HER tyrosine kinase domain.

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Introduction

In 2018, an estimated 266,120 new cases of invasive breast cancer will be diagnosed in the United States.[1] Approximately 20% of breast cancers have human epidermal growth factor receptor 2 (*HER2*) overexpression and are characterized as belonging to a clinically aggressive phenotype.[2] *HER/neu*-positive breast cancers have decreased apoptosis and increased angiogenesis, proliferation, and motility.[2-4] An improved understanding of the Her2 pathway in breast cancer and other cancers led to the development of anti-*HER2/neu* receptor inhibitors and tyrosine kinase inhibitors (TKIs).

Resistance to *HER2* continues to be a challenge. The human epidermal growth factor receptor (EGFR) belongs to ErbB family of cell-surface receptor tryrosine kinases that includes 4 members: *EGFR/HER1* (ErbB-1), *HER2* (ErbB-2), *HER3* (ErbB-3), and *HER4* (ErbB-4).[5] Most common *EGFR* activating and resistance mutations include exon 19 deletions, L858R (exon 21), exon 20 insertions, G719X, L861X, exon 19 insertions, and T790M.[5]

Poziotinib (HM781-36B) is an oral quinazoline-based, irreversible pan-*HER* inhibitor. It has shown to be effective in *EGFR*-resistant mutations, including exon 20 insertions.[6,7]

We report a unique case where poziotinib was effective in a patient who had *HER2*-positive metastatic breast cancer with exon 20 insertion mutation resistant to other *HER2* TKIs.

Case Report

A 51-year-old postmenopausal woman sought care for a 5 cm right breast mass in October 2010. Biopsy was performed, and results were positive for an adenocarcinoma, estrogen receptor positive at 95%, progesterone receptor positive at 80%, Ki-67 < 10%, and *HER2* equivocal with immunohistochemical 2+ staining, fluorescence in-situ hybridization (FISH) ratio of 1.93, and *HER2* copy number of 5.45.

She was treated with neoadjuvant paclitaxel for 3 weeks, which was discontinued because of poor tolerability. This was to neoadjuvant nab-paclitaxel for 6 weeks, which was discontinued because of poor tolerability. Finally she received neoadjuvant

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doxorubicin–cyclophosphamide for 2 cycles, which was again discontinued because of poor tolerability.

She underwent right modified radical mastectomy in August 2011, which found a 4.0 cm residual tumor with 7 of 25 axillary lymph nodes positive for tumor. She declined adjuvant chest wall radiation and was placed on 1 year of adjuvant trastuzumab treatment as well as a planned 5 years of letrozole.

In September 2013, her cancer progressed with new positron emission tomography (PET)-avid enlarged mediastinal, hilar, and bilateral axillary lymph nodes, a small (< 1 cm) PET-avid liver lesion, and PET-avid right-sided pleural thickening. Biopsy of a right-sided lymph node was performed and revealed metastatic adenocarcinoma, estrogen receptor positive, progesterone receptor negative, Ki-67 30% to 40%, and *HER2* negative (FISH ratio 1.25, copy number 3.70).

She was treated with a variety of sequential single-agent therapies over the next 18 to 24 months, including fulvestrant, tamoxifen, and exemestane; trastuzumab/pertuzumab and trastuzumab–emtansine (using her primary tumor as a rationale for *HER2*-based therapy); and capecitabine. All of these therapies resulted in brief periods of stability (3-6 months), followed by slow progression of computed tomography imaging (with bilateral interstitial lung disease consistent with lymphangitic spread) and gradual increase in dyspnea, increasing fatigue, and decreasing exercise tolerance.

In April 2015, Foundation One next-generation sequencing was performed on the mastectomy specimen from August 2011. The following alterations were found: ErbB2 P780-Y781 ins GSP; AURKA amplification; GNAS amplification; TP53 Y220C; MAP3K1 R248* and R273fs*40; MLL2 Q928*; and ZNF217 amplification.

In May 2015, lapatinib was provided for 2 months with stable disease on imaging but was discontinued as a result of severe diarrhea despite antidiarrheals and dose reduction. This was followed by nab-paclitaxel for 6 months, then eribulin for 6 months, with stability followed by slow progression of lymphangitic spread and continued dyspnea.

In August 2016, neratinib was obtained for compassionate use after US Food and Drug Administration approval, and with aggressive diarrhea prophylaxis, this agent was tolerated with a 25% dose reduction. This resulted in stabilization of her disease and improved dyspnea, with decreasing requirements for supplemental oxygen and increased exercise tolerance.

In February 2017, the patient's disease had progressed with worsening lymphangitic spread, increasing dyspnea, and increasing size of liver metastases. Gemcitabine therapy was initiated in February 2017, but by May 2017 the patient developed severe dyspnea and high tumor burden in her liver and lungs on imaging (Figure 1).

In June 2017, the US Food and Drug Administration granted approval for compassionate use of poziotinib. The typical starting dosage of poziotinib is 16 mg orally daily; however, because of grade 3 diarrhea and skin rash, as well as dose-limiting toxicities, the dose was lowered to 8 to 12 mg daily from June 2017 to October 2017. Her liver lesions resolved on computed tomography as of August 2017 (Figure 2), and CA27.29 dropped from over 400 U/mL in May 2017 to 27 in September 2017 (Figure 3). By September 2017 the patient had discontinued supplemental oxygen, and her exercise tolerance had markedly improved.

In October 2017, despite aggressive supportive management, the patient was unable to tolerate a dose of > 6 mg of poziotinib without grade 3 diarrhea. With substantial dose delays and an inability to administer higher doses of the drug, her symptoms of dyspnea gradually worsened. Consistent with the symptoms, CA27.29 increased and lymphangitic spread worsened. The patient entered hospice care in late November 2017 and died in December 2017.

Figure 1 Positron Emission Tomography/Computed Tomography of Abdomen

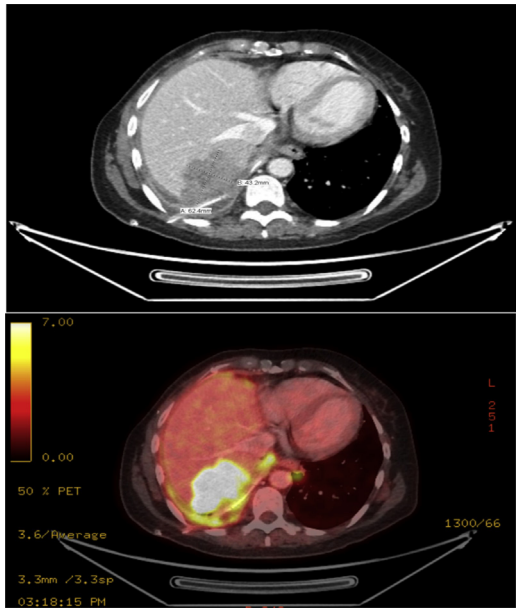


Figure 2 Computed Tomography of Abdomen

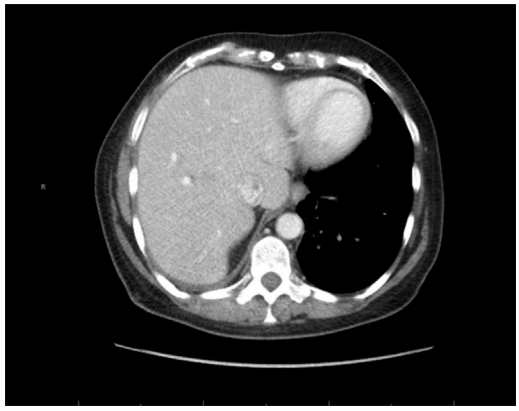
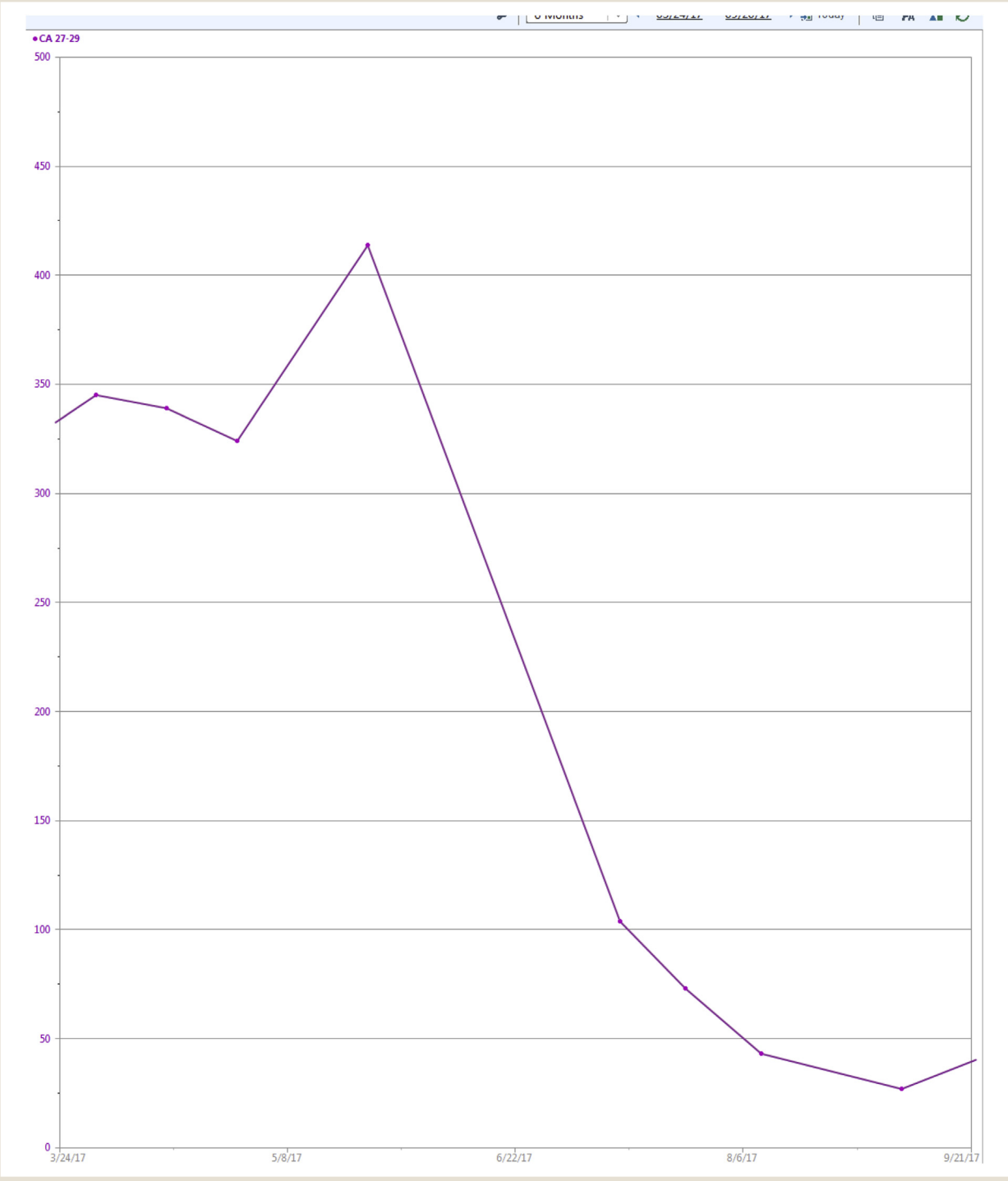


Figure 3 Cancer-Associated Antigen Reduction



Discussion

HER2 mutations are found in 5% of gastric carcinomas, 2.9% of colorectal cancers, and 4.3% of breast carcinomas.[8] These somatic mutations typically occur in the absence of gene amplification.[9] While mutations in *HER2* can occur in the extracellular, transmembrane, and kinase domains, mutations in *HER3* commonly occur in the extracellular domain or in the kinase domain. These somatic mutations result in ligand-independent *HER2* receptor signaling and tumor proliferation by increasing *HER2* kinase activity or receptor dimerization.

Neratinib is an irreversible *HER2* TKI. In a global multihistology basket trial (SUMMIT), patients with *HER2* and *HER3* mutations

were treated with neratinib.[10] The study enrolled 141 patients, 125 patients with *HER2*-mutant tumors and 16 with *HER3*-mutant tumors. All of these patients were classified as having *HER2*-negative (non-FISH amplified) disease per established American Society of Clinical Oncology−College of American Pathologists guidelines. The trial subjects had 31 *HER2* and 11 *HER3* mutations. The most common mutated alleles were S310, L755, Y772_A775dup, and V777. The frequent mutated protein domains were the *HER2* kinase region (66%), the extracellular domain (26%), and the transmembrane domain (8%). In the metastatic breast cancer population (n = 25), the objective response at 8 weeks was 32% in patients with *HER2* missense mutations and the *HER2* kinase domain. There was no response to neratinib in patients with breast cancer and *HER3* mutations.

Poziotinib blocks signaling of multiple members of the *EGFR* family.[6,7] Preclinical and early clinical studies indicate that it is a drug of interest to treat both *EGFR*- and *HER2*-driven cancers.[6,7,11,12] Both in vitro and in vivo studies have demonstrated that poziotinib is a potent *EGFR* and *HER2* inhibitor.[7] In vitro assays conducted with poziotinib inhibited wild-type *EGFR* family kinases, including *EGFR*, *HER2*, and *HER4* with nanomolar 50% inhibitory dose (IC_{50}) values of 3.2, 5.3, and 23.5 nM, respectively. Poziotinib also inhibited mutated $EGFR_{T790M}$ and $EGFR_{L858R/T790M}$ with nanomolar IC_{50} values of 4.2 and 2.2 nM, respectively.[6] In vivo poziotinib treatment of *EGFR* delE746_A750-harboring erlotinib-sensitive HCC827 and *EGFR* L858R/T790M-harboring erlotinib-resistant NCI-H1975 non−small-cell lung cancer (NSCLC) cells resulted halting *EGFR* phosphorylation and deactivation of downstream signaling proteins. Furthermore, xenograft animal models with human breast cancer overexpressing *HER2* (SK-BR-3) were studied with poziotinib. Poziotinib prevents tumor growth at a faster rate compared to other TKIs including erlotinib, lapatinib, and afatinib (BIBW 2992).[6] Additionally, poziotinib exhibited potent activity against the gefitinib- and erlotinib-resistant *EGFR* T790M mutant model and the *HER2*-expressing breast cancer model.

A small phase 2 trial was conducted on 11 patients with NSCLC with *EGFR* exon 20 mutations who received poziotinib, with a confirmed objective response rate of 64%. Robichaux et al conducted in vitro and in vivo testing to model structural alterations induced by *EGFR* and *HER2* exon 20 mutations.[13] This work tested the sensitivity of exon 20 insertions to first-generation (gefitinib and erlotinib), second-generation (afatinib, comitinib, and neratinib) and third-generation TKIs (ie, osimertinib, rociletinib, nazatinib, olmutinib, ibrutinib). *HER2* exon 20 mutants were resistant to both first- and second-generations TKIs. In contrast, second-generation TKIs had some activity in Ba/F3 *HER2* exon 20 mutated cell lines. In vitro, poziotinib had average IC_{50} value of 1.9 nM in Ba/F3 cell lines with *HER2* exon 20 mutations, resulting in 200 times more potency than osimertinib and 6 more times more potency than afatinib.

Three-dimensional modeling of solved crystal structures comparing *EGFR* D770insNPG with *EGFR* T790M and wild-type *EGFR* to visualize changes within the drug binding pocket was performed in this study. This modeling demonstrated that *EGFR* exon 20 insertion mutants are similar to *EGFR* T790M in the alignment of the gatekeeper residue Thr790. This proposed alignment not only should result in greater affinity for ATP but also decreased binding of first-generation *HER2* TKI inhibitors. Lapatinib, a noncovalent *HER2* inhibitor, binds to *HER2* in this inactive conformation but is unable to bind as a result of active conformations induced by *HER2* exon 20 insertions. Poziotinib has several characteristics, including smaller and greater flexibility, that allow it overcome steric hindrance created by exon 20 insertion mutants, which may explain its activity in tumors that have progressed while being treated with earlier-generation TKIs.[11]

Poziotinib has been studied as a monotherapy in open-label clinical trials in more than 200 patients, with doses ranging from 0.5 mg per day to 32 mg per day on an intermittent dosing schedule, and from 12 mg per day to 24 mg per day on a continuous dosing schedule. There is synergism when poziotinib is combined with trastuzumab chemotherapy in *HER2*-driven cancer models such as breast cancer and gastric cancer.[12,14] In South Korea, 109 patients across 3 clinical studies experienced partial response in 15 patients, including breast cancer (n = 6; 5.5%), NSCLC (n = 6, 5.5%), and gastric, colorectal, and other types of cancers (n = 1 each; 0.9%). A further analysis of the two phase 1 studies showed that patients who had advanced breast cancer despite multiple *HER2*-directed therapies demonstrated promising preliminary antitumor activity, with an overall response rate of 60%. All of them experienced relapse after multiple *HER2*-directed therapies[12,14] The safety profile included adverse effects including diarrhea, rash, and stomatitis, and dose-limiting toxicity was grade 3 anorexia (only in continuous dosing) and grade 3 diarrhea (with both intermittent and continuous dosing).

Exon 20 insertion mutation accounts for 5% to 10% of all *EGFR* mutations in lung adenocarcinoma and is associated with primary resistance to *EGFR* TKI.[6] Poziotinib decreased tumor size by at least 30% in 8 (73%) of 11 patients with NSCLC whose cancer included a *EGFR* exon 20 insertion mutation. Currently phase 2 clinical trials of poziotinib are under way in patients with breast cancer and NSCLC (NCT02659514, NCT03066206, and NCT03318939).

Conclusion

To our knowledge, this is the first case report to demonstrate poziotinib activity in metastatic breast cancer with an activating *HER2* exon 20 insertion mutation. This patient had a partial response per Response Evaluation Criteria in Solid Tumors to poziotinib despite disease progression while receiving therapy with *HER2* TKIs.

Disclosure

Dr Brufsky is a consultant for Roche, Puma, and Spectrum Pharmaceuticals.

References

1. American Cancer Society. Cancer facts and figures, 2018, Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed October 11, 2018.
2. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the *HER-2*/neu oncogene. *Science* 1987; 235:177-82.
3. Izumi Y, Xu L, Di Tomaso E, Fukumura D, Jain RK. Herceptin acts as an anti-angiogenic cocktail. *Nature* 2002; 416:279.
4. Pietras RJ, Arboleda J, Reese DM, et al. *HER*-3 tyrosine kinase pathway targets estrogen-receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene* 1995; 10:2435-46.

5. Chong CR, Jänne PA. The quest to overcome resistance to *EGFR*-targeted therapies in cancer. *Nat Med* 2013; 19:1389-400.
6. Cha MY, Lee KO, Kim M, et al. Antitumor activity of HM781-36B, a highly effective pan-*HER* inhibitor in erlotinib-resistant NSCLC and other *EGFR*-dependent cancer models. *Int J Cancer* 2012; 130:2445-54.
7. Elamin Y, Robichaux J, Heymach J. Preliminary results of a phase II study of poziotinib in *EGFR* exon 20 mutant advanced NSCLC. *J Thorac Oncol* 12, 2017, S1536.
8. Lee JW. Somatic mutations of *ERBB2* kinase domain in gastric, colorectal, and breast carcinomas. *Clin Cancer Res* 2006; 12:57-61.
9. Bose R, Kavuri SM, Searleman AC, et al. Activating *HER2* mutations in *HER2* gene amplification negative breast cancer. *Cancer Discov* 2013; 3:224-37.
10. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with *HER2*-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2016; 17:367-77.
11. Zacharakis N, Chinnasamy H, Black M, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. *Nat Med* 2018; 24:724-30.
12. Nam HJ, Kim HP, Yoon YK, et al. Antitumor activity of HM781-36B, an irreversible pan-*HER* inhibitor, alone or in combination with cytotoxic chemotherapeutic agents in gastric cancer. *Cancer Lett* 2011; 302:155-65.
13. Robichaux JP, Elamin YY, Tan Z. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med* 2018; 24:638-46.
14. Kim TM, Lee KW, Oh DY, et al. Phase 1 studies of poziotinib, an irreversible pan-*HER* tyrosine kinase inhibitor in patients with advanced solid tumors. *Cancer Res Treat* 2018; 50:835-42.