Metastatic Parotid Gland Carcinoma With ERBB2 Amplification With Complete Response to Fam-Trastuzumab Deruxtecan

Navika D. Shukla, BA¹; Ryan S. Chiang, MD²; and Alexander D. Colevas, MD³

ABSTRACT

HER2 mutations have been shown to be targetable in select cases of salivary gland cancers with overexpression or amplification of the *HER2* oncogene. Fam-trastuzumab deruxtecan, a novel antibody–drug conjugate that combines trastuzumab with a topoisomerase I inhibitor, has recently demonstrated efficacy as a third-line agent in *HER2*-overexpressing breast cancer after trastuzumab failure. These promising results in breast cancer suggest a potential paradigm for use in other tumors with known *HER2* alterations, including salivary gland cancer. This report describes a 67-year-old man with *HER2*-positive metastatic parotid gland carcinoma who experienced disease progression after parotidectomy with adjuvant cisplatin-based chemoradiation, neratinib, and ado-trastuzumab emtansine. After disease progression on the latter *HER2*-directed therapy, his malignancy demonstrated complete response to fam-trastuzumab deruxtecan, which has been sustained for the past 7 months. Fam-trastuzumab deruxtecan appears to be a well-tolerated therapeutic option in patients with *HER2*-positive salivary gland carcinoma, with activity demonstrated after progression on ado-trastuzumab emtansine and *HER2*-directed kinase inhibition. Further studies should be conducted to explore the use of this agent in *HER2*-positive salivary gland cancers.

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HER2 is a member of the epidermal growth factor receptor (EGFR) family overexpressed in several malignancies. Although typically used in *HER2*-positive gastric and breast cancers, several studies have shown a role for *HER2*-targeted therapies in other cancer settings. This includes salivary duct carcinomas (SDCs), which have been commonly linked to the overexpression or amplification of *HER2* in gene profiling studies.^{1–7} More recently, newer second- and third-generation anti-*HER2* agents have emerged, including ado-trastuzumab emtansine (T-DM1) and fam-trastuzumab deruxtecan. In breast and gastric cancer, repeated targeting of the *HER2* receptor with these newer agents has demonstrated promise as an effective treatment strategy, suggesting a potential role for these agents in the resistant setting in salivary gland cancer as well.^{8,9} Although the literature thus far demonstrates that both trastuzumab emtansine and trastuzumab deruxtecan alone hold promise in salivary gland cancers, there have been no studies to date evaluating trastuzumab deruxtecan after trastuzumab emtansine failure in this population.^{10–12}

This report describes a patient who presented with high-grade stage IV SDC arising from a pleomorphic adenoma of the left parotid gland with *HER2* amplification. Our patient experienced disease progression despite initial response to multiple lines of therapy, including adjuvant chemoradiation with cisplatin; neratinib, a dual inhibitor of the *HER2* and EGFR kinases; and T-DM1, an antibody–drug conjugate of an *HER2*-directed monoclonal antibody and microtubule poison, before achieving a sustained complete response on fam-trastuzumab deruxtecan.

Case Presentation

A 67-year-old White man presented with left-sided ear discomfort and facial paresis. MRI revealed the presence of a 3-cm left parotid mass without lymphadenopathy. A core needle biopsy was performed, and pathology revealed adenocarcinoma with perineural invasion. He underwent parotidectomy with findings consistent with T4aN0 SDC ex pleomorphic adenoma, and he completed adjuvant chemoradiation with cisplatin for 6 weeks. Nine months later, he presented with worsening back pain.

¹Stanford University School of Medicine; and ²Department of Medicine, and ³Division of Medical Oncology, Department of Medicine, Stanford University Medical Center, Stanford, California.

Imaging showed a new T8 compression fracture concerning for metastatic disease and impending cord compression. He underwent T5 to T10 posterior spinal fusion with T8 costotransversectomy. Consistent with the original primary parotid neoplasm, surgical pathology confirmed metastatic adenocarcinoma that was androgen receptor (AR)-positive by immunohistochemistry and *ERBB2* (*HER2*)-amplified, *DNMT3A*-mutated, and microsatellite stable by FoundationOne genetic testing. Additional *HER2* staining by immunohistochemistry showed strong circumferential membrane staining in >10% of the SDC cells and was scored as 3+. PET imaging revealed diffuse osseous metastatic disease throughout the cervical and thoracic spine, left scapula, ribs, and femoral head. The patient underwent additional stereotactic body radiotherapy to the thoracic spine and was started on bone-directed therapy with denosumab. He received no AR-directed therapy. Given his known *HER2* amplification, he was eligible for neratinib under the SUMMIT clinical trial (ClinicalTrials.gov identifier: NCT01953926). Despite initial complete response, treatment was subsequently discontinued 7 months after initiation when interval PET imaging demonstrated an increased size and number of bilateral pulmonary nodules. Given disease progression, he was transitioned to T-DM1. Follow-up PET imaging 5 months after starting T-DM1 showed a radiologic complete response. After 10 months of T-DM1, repeat PET revealed increased disease burden of pulmonary nodules and bony disease. He was initiated on fam-trastuzumab deruxtecan, with radiologic complete response seen after 2 months (Figure 1). At the time of writing, serial imaging for the past 7 months has

not shown any evidence of recurrence or metastatic disease, and he continues on surveillance imaging every 4 months. He has tolerated the drug well; adverse effects from infusion included transient fatigue and grade 1 nausea, vomiting, and gastroparesis.

Discussion

This report describes a patient with metastatic carcinoma ex pleomorphic adenoma with *HER2* amplification who demonstrated a complete response after receiving fam-trastuzumab deruxtecan despite disease progression on neratinib and T-DM1. To our knowledge, there has not been a similar case reported.

Pharmacologically, trastuzumab deruxtecan is an antibody–drug conjugate composed of an anti-*HER2* antibody, a peptide linker, and a topoisomerase I inhibitor. Structurally, the drug is optimized for improved efficacy even in the setting of low *HER2* expression when compared with previous anti-*HER2* agents.¹³ It is generally well tolerated, although notable toxic effects include myelosuppression and interstitial lung disease.^{8,9}

The reported prevalence of *HER2* overexpression in salivary gland cancers is 7% to 56% and has been shown to vary by histologic subtype, with a higher prevalence in salivary duct subtypes, highlighting the utility of molecular profiling in treatment determination.¹ The NCI-MATCH trial assessed the efficacy of T-DM1 in *HER2*-amplified nonbreast and nongastroesophageal malignancies and found evidence of durable partial response in salivary gland tumors.¹² In a larger phase II basket trial, a cohort of 10 patients with *HER2*-amplified salivary gland tumors were treated with T-DM1.¹¹ The overall response rate was 90%, with 50% of patients demonstrating a complete response. Few studies to date, however, have evaluated trastuzumab deruxtecan in salivary gland cancer. Preliminary results of evaluating the agent in a heterogeneous cohort of solid tumors that included 8 salivary gland cancers have shown *HER*-amplified salivary gland tumors to be responsive to trastuzumab deruxtecan, but further studies are needed to better understand this effect. The complete response demonstrated by our patient on fam-trastuzumab deruxtecan despite disease progression while receiving neratinib and T-DM1 indicates a potential role for this drug in recurrent *HER2*-amplified salivary gland carcinoma cases that have progressed on prior lines of *HER2*-directed therapy.

In breast and gastric cancer settings, fam-trastuzumab deruxtecan has shown promise in patients who have experienced disease progression on prior therapy. Per the DESTINY-Breast01 trial, trastuzumab deruxtecan demonstrated durable antitumor activity in patients with *HER2*-positive metastatic breast cancer who had already received trastuzumab emtansine.⁹ Likewise, the

Figure 1. Progression of metastatic disease on ado-trastuzumab emtansine (right) followed by complete resolution of FDG-avid pulmonary nodules after 3 months of treatment with fam-trastuzumab deruxtecan (left).

DESTINY-Gastric01 trial selected patients with advanced gastric or gastroesophageal junction adenocarcinoma who had experienced progression on ≥ 2 prior lines of therapy, at least 1 of which included an anti-HER2 agent, and randomized them to receive either trastuzumab deruxtecan or their physician's choice of chemotherapy.⁸ Fam-trastuzumab deruxtecan was associated with an increased objective response rate and improved overall survival.⁸ Response to this agent also suggests that resistance to prior therapy likely occurred through mechanisms other than HER2 alteration or downregulation. Perhaps resistance to these other agents occurred through increased expression of substrate-specific drug efflux transporters or, in the case of resistance to T-DM1, through mitotic catastrophe escape.¹⁴ Further studies are needed to elucidate mechanisms of resistance.

Other than HER2-directed therapy, another potential therapeutic option for many cases of recurrent or metastatic SDC includes androgen deprivation therapy (ADT).^{15–17} Although standardized guidelines for ADT in this setting have not yet been established, several studies have demonstrated excellent response with abiraterone, single-agent bicalutamide, or a combination of triptore-

lin and bicalutamide. However, with no data yet available to support ADT versus HER2-directed therapy as an initial treatment strategy, this remains an area for further exploration.

Conclusions

This case report shows a complete response to trastuzumab deruxtecan with limited toxicity in the setting of recurrent, metastatic salivary gland cancer. This study provides anecdotal evidence that recurrent engagement of HER2-targeted therapies may have utility as a treatment pathway in salivary gland cancer similar to the model currently used in *HER2*-amplified breast and gastric cancer.

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Correspondence: Ryan S. Chiang, MD, Department of Medicine, Stanford University Medical Center, Stanford Hospital and Clinics, 300 Pasteur Drive, Stanford, CA 94305. Email: rschiang@stanford.edu

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