# Treatment of Metastatic Extramammary Paget's Disease Associated With Adnexal Adenocarcinoma, With Anti-HER2 Drugs Based on Genomic Alteration ERBB2 S310F

Extramammary Paget's disease (EMPD) is a rare intraepithelial malignant condition affecting the apocrine gland-bearing skin, composed of characteristic large glycogen-rich (Paget) cells scattered in the epidermis [1]. Metastases are uncommon and associated with adenocarcinoma.

The current case presents a 76-year-old man, first diagnosed with adnexal adenocarcinoma with Paget's disease in 2009 after resection of a skin lesion in the left perineal region. In January 2012, due to severe lower back pain, positron emission tomography-computed tomography (PET-CT) scan was done and demonstrated multiple bone metastases. CT-guided biopsy from a lumbar vertebra was positive for metastatic carcinoma, similar to the earlier resected perineal skin lesion. Hormone receptor stains were positive for estrogen in 10%–20% of tumor cells and HER-2/neu staining, including fluorescence in situ hybridization, was negative. Systemic therapy with adriamycin and cyclophosphamide was given, with partial response after six cycles. Maintenance treatment with letrosole was started, but the tumor progressed after 4 months of treatment (Fig. 1A).

The FoundationOne genomic test (Foundation Medicine Inc., Cambridge, MA, http://www.foundationmedicine.com) was performed, and a genomic alteration, ERBB2 S310F mutation, was discovered. Accordingly, treatment with lapatinib and capecitabine was started. Continuing partial response was shown in repeated PET-CT scans (Fig. 1B). During the treatment period, the patient underwent hip replacement due to a pathological fracture. Treatment with capecitabine was discontinued for 6 weeks and only lapatinib was given, with continued reduction in tumor markers. Nevertheless, the role of each medication in this prolonged response is not known. The patient has continued with the same treatment for more than 1 year.

Several case reports have been published describing the use of chemotherapy combinations including 5-fluorouracil (5-FU) with mitomycin C [2] or carboplatin and leucovorin [3] for metastatic EMPD. 5-FU is the basic drug for this diagnosis, and the combination with lapatinib, as in the current case, was a logical option.

Amplification of HER2 in breast Paget's disease and in EMPD has been reported [4]. The role of the *ERBB2* signal pathway in EMPD has also been assessed [5]. HER2 overexpression reflecting gene amplification was found in 33%–52% of EMPD invasive lesions in previously published studies [4, 5]. Treatment with trastuzumab and chemotherapy in amplified HER2 metastatic EMPD has been reported with prolonged response longer than 6 months [6, 7].

As opposed to *ERBB2* amplification, point mutations in *ERBB2* are quite rare, with only 318 mutations reported thus far in the Catalog of Somatic Mutation in Cancer (COSMIC) database [8]. Interestingly, mutation p.S310F, identified in the current patient, is the second most common mutation in *ERBB2*. The occurrence of this mutation in different types of tumors suggests that it is actually a cancer-driven mutation. The mutation is present in the extracellular domain of *ERBB2* and, therefore, is predicted to be responsive to *ERBB2* inhibitors.

Greulich et al. discussed mutations in the extracellular domain of *ERBB2*, including S310F, in lung adenocarcinoma. This type of mutation was examined on NIH 3T3 cells. A number of proteins regulating cytoskeletal dynamics and cell motility were found to be prominently hyperphosphorylated in the ERBB2 S310F cells. For example, PTPN11, a phosphatase involved in activation of Erk proteins that, intriguingly, is required for growth and metastasis of HER2-positive breast cancer cells, was also prominently phosphorylated in the ERBB2 S310F cells, correlating with oncogenic activity of this mutation (Fig. 2) [9].

These *ERBB2* extracellular domain mutants were activated by two distinct mechanisms, characterized by elevated C-terminal tail phosphorylation or by covalent dimerization mediated by intermolecular disulfide bond formation [9]. Bose and colleagues reviewed data from eight genome-sequencing studies that included nearly 1,500 patients. Twenty-five patients had 13 different *ERBB2* mutations. In a xenograft model, all of these mutations were sensitive to the irreversible kinase inhibitor neratinib [10]. According to this case, ERBB2 S310F mutation seems to be a transforming mutation that should be targeted with anti-HER2 drugs. Genomic tests are justified in rare tumors.

**Olga Vornicova**
Division of Oncology, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel

**Dov Hershkovitz**
Institute of Pathology, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel

**Tamar Yablonski-Peretz**
Sharett Institute of Oncology, Hadassah Medical Center, Hebrew University, Jerusalem, Israel

**Ofer Ben-Itzhak**
Institute of Pathology, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel

**Zohar Keidar**
Department of Nuclear Medicine, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel

**Gil Bar-Sela**
Division of Oncology, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel

## Disclosures

The authors indicated no financial relationships.

## References

1. Dubreuilh W. Paget's disease of the vulva. Br J Dermatol 1901;13: 407–413.

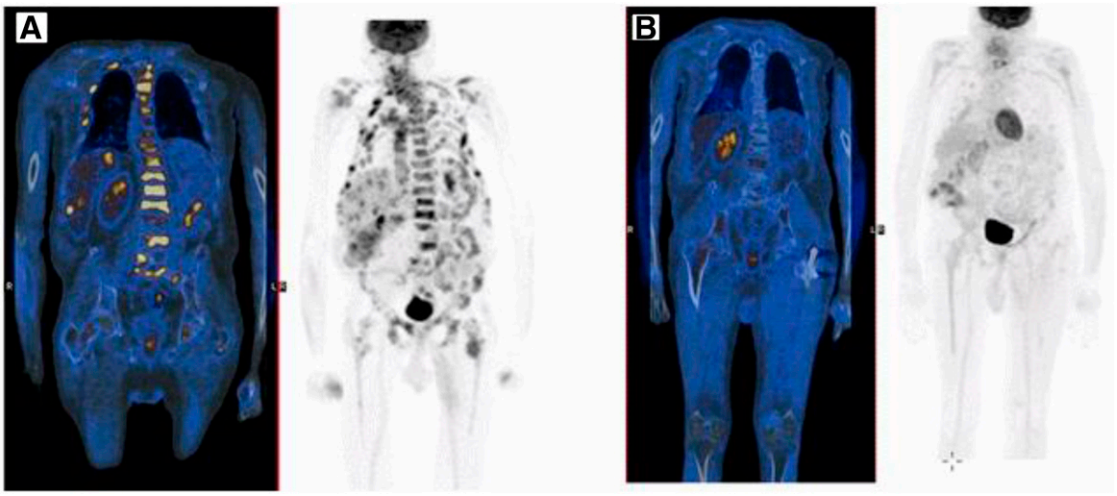


**Figure 1.** Positron emission tomography-computed tomography-selected coronal slices demonstrate multiple foci of pathological increased fludeoxyglucose (FDG) uptake in lytic and sclerotic bone lesions and in hypodense liver lesions **(A)** and significant improvement with few low-intensity foci of FDG uptake in the skeleton and no evidence of liver metastases **(B)** after 6 months of treatment.

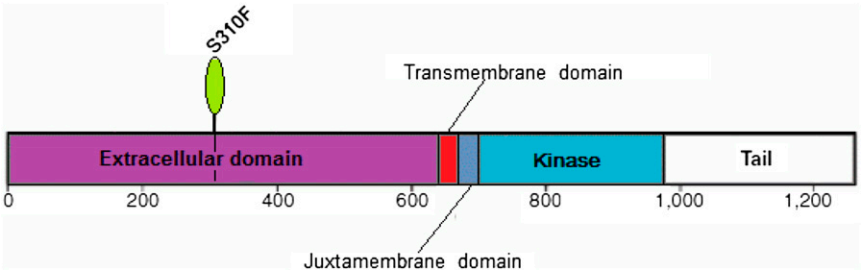


**Figure 2.** The position of the S310F mutation in the external domain of the *ERBB2* gene.

**2.** Balducci L, Athar M, Smith GF et al. Metastatic extramammary Paget's disease: Dramatic response to combined modality treatment. J Surg Oncol 1988;38:38–44.

**3.** Voigt H, Bassermann R, Nathrath W. Cytoreductive combination chemotherapy for regionally advanced unresectable extramammary Paget carcinoma. Cancer 1992;70:704–708.

**4.** Takata M, Fujimoto A, Aoki H et al. erbB-2 Overexpression but no activation of beta-catenin gene in extramammary Paget's disease. J Invest Dermatol 1999;113:258–262.

**5.** Ogawa T, Nagashima Y, Wada H et al. Extramammary Paget's disease: Analysis of growth signal pathway from the human epidermal growth factor receptor 2 protein. Hum Pathol 2005;36:1273–1280.

**6.** Hanawa F, Inozume T, Harada K et al. A case of metastatic extramammary Paget's disease responding to trastuzumab plus paclitaxel combination therapy. Case Rep Dermatol 2011;3:223–227.

**7.** Takahagi S, Noda H, Kamegashira A et al. Metastatic extramammary Paget's disease treated with paclitaxel and trastuzumab combination chemotherapy. J Dermatol 2009;36:457–461.

**8.** Forbes SA, Bindal N, Bamford S et al. COSMIC: Mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. Nucleic Acids Res 2011;39:D945–D950.

**9.** Greulich H, Kaplan B, Mertins P et al. Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. Proc Natl Acad Sci USA 2012;109:14476–14481.

**10.** Bose R, Kavuri SM, Searleman AC et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. Cancer Discov 2013;3:224–237.

http://dx.doi.org/10.1634/theoncologist.2014-0054