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Letter to the editor

Successful treatment with trastuzumab in HER2-positive squamous cell carcinoma of the head and neck

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Squamous cell carcinoma of the head and neck (SCCHN) is the seventh most common cancer worldwide [1]. Patients with unresectable recurrent or metastatic disease have poor prognosis with a median overall survival (OS) of less than one year [2]. Epidermal growth factor receptor (EGFR) is overexpressed in 80–90% of patients with SCCHN [3]. To date, Cetuximab which is an IgG1 chimeric monoclonal antibody targeting EGFR is the only targeted therapy approved by the Food and Drug Administration in the treatment of SCCHN [4]. Human epidermal growth factor 2 (HER2) amplification was only observed in 1.8% of patients with SCCHN according to the Cancer Genome Atlas Network [5]. In the MOSCATO-01 trial, 3 out of the 105 (2.9%) enrolled patients with SCCHN presented *HER2* amplification [6]. This amplification was detected using the Comparative Genomic Hybridization (CGH) -performed using SurePrint G3 Human aCGH Microarray 4 × 180 K, Agilent technologies, Palo alto, CA- and confirmed with fluorescent is situ hybridization (FISH). After discussion in our molecular tumor board, all these patients were treated with trastuzumab which is an anti-HER2 humanized monoclonal antibody approved in the treatment of breast and gastric cancers. We detail herein the case of one patient who presented a prolonged response to trastuzumab in combination with paclitaxel after progression on immunotherapy.

A 56-year-old male patient with history of 72 pack-year smoking history and controlled type 2 diabetes mellitus was diagnosed with laryngeal squamous cell carcinoma, T2N2bM0 according to TNM7 classification in December 2013. The patient was treated with concomitant cisplatin and radiation therapy as standard of care. Then, he was included on September 2014 in a double-blind, placebo-controlled phase III clinical trial evaluating afatinib –a protein kinase inhibitor which irreversibly inhibits HER2 and EGFR kinases- as adjuvant therapy. After 4 months of treatment with afatinib or placebo, the patient experienced disease recurrence with lung metastasis. He received metastatic first-line treatment in February 2015 with 6 cycles of docetaxel, carboplatin and cetuximab followed by cetuximab maintenance with initial partial response. After seven months of treatment, he developed neck recurrence in the left level II, mediastinal recurrence and lung progression. The patient was included in an immune checkpoint inhibitor clinical trial. He received programmed death ligand-1 (PD-L1) inhibitor treatment for 11 months with a partial response (−62% according to RECIST 1.1 criteria) as best response to PD-L1 inhibitor. The patient presented dissociated response with progression of preexistent cervical lymph nodes and emergence of new axillary lymph node. Molecular analysis was done in the MOSCATO-01 trial. The CGH showed an *HER2* gain of function with a log ratio of 0.42 (Fig. 1) and next generation sequencing (NGS) performed using Ion torrent (Ion Torrent PGM, Life Technologies®) showed *TP53* mutation. *HER2* amplification was confirmed by FISH with copy number of 10.33 and *HER2/CEN17* ratio of 5.08 (Fig. 2). The tumor was HPV16 negative on immunohistochemistry and FISH. A third line treatment with paclitaxel and trastuzumab was initiated in October 2016. Paclitaxel was given at a dosage of 175 mg/m^2 and trastuzumab 8 mg/kg on the first cycle and 6 mg/kg on the following cycles every three weeks. Partial response according to RECIST criteria was the best response to paclitaxel/trastuzumab with complete response of left axillary lymph node. The patient presented prolonged response of 14 months from the beginning of this third line treatment. Afatinib was rechallenged as a fourth line treatment on January 2018 after enrollment in a phase 2 clinical trial. He showed disease progression on March 2018 and progressive disease was the best response to afatinib.

We report here, for the best of our knowledge, the first case of *HER2* amplified advanced SCCHN with a long lasting response (14 months) with a combination of taxane and trastuzumab. In metastatic *HER2* amplified breast cancer, the addition of trastuzumab to docetaxel in first-line treatment was associated with significant higher overall response rate, overall survival and time to progression leading to trastuzumab approval by the FDA in the treatment of metastatic *HER2* amplified breast cancer [7]. Similarly, trastuzumab was approved in the treatment of HER2 + metastatic gastric cancer in combination with cisplatin and either capecitabine or 5-FU based on the ToGA trial [8]. In SCCHN, available data suggest that *HER2* alterations are associated with worse prognosis with shorter OS and increased likelihood of recurrence [9]. Trastuzumab was evaluated in combination with paclitaxel and cisplatin in a phase II trial regardless of *HER2* status but failed to improve the response rate. The authors concluded that can be explained by the rarity of *HER2* mutation or amplification in SCCHN [10]. In fact, our patient presented a prolonged partial response of 14 months

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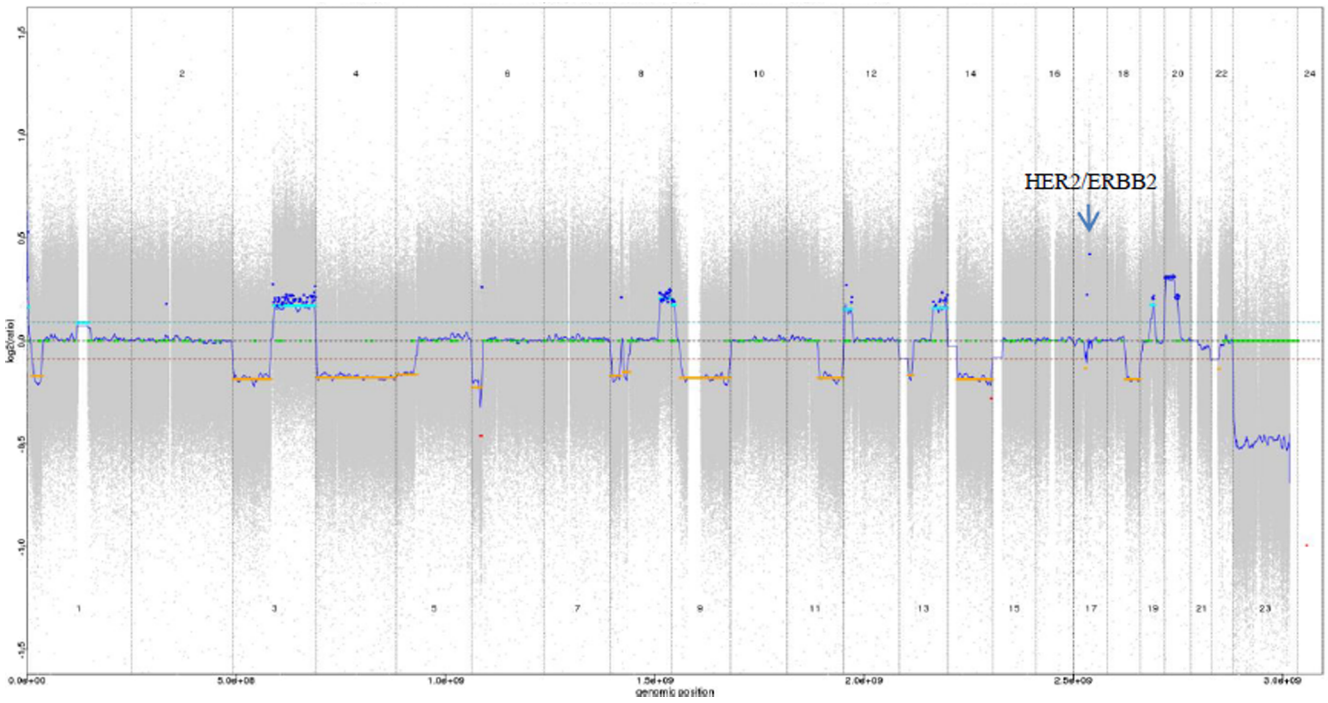

Fig. 1. CGH showed a gain of function of HER2 with a log ratio of 0.42.

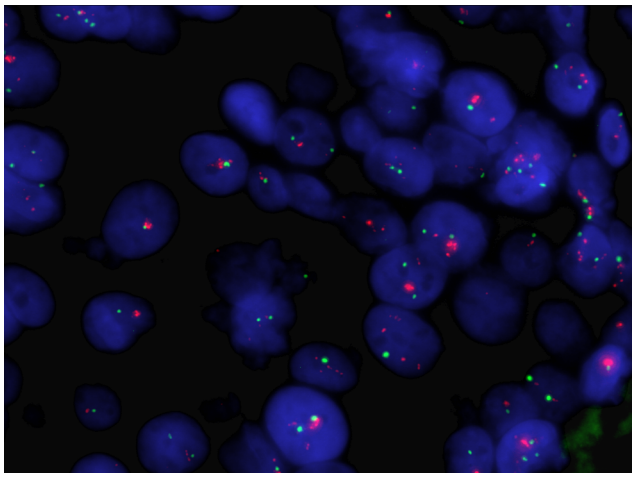

Fig. 2. FISH confirm *HER2* amplification.

to trastuzumab combined with paclitaxel suggesting that targeted therapy with trastuzumab might improve outcome in patients with *HER2* amplification. Two other patients of MOSCATO-01 trial with *HER2*-amplified SCCHN were treated with paclitaxel and trastuzumab. The first patient received the combination as first-line treatment with a partial response and progression-free survival (PFS) of 5 months. The second patient was treated in second-line setting without response. We don't know if previous treatment with immunotherapy has increased sensitivity to paclitaxel in the presented patient or if immunotherapy can modify response to targeted therapy like trastuzumab in *HER2* amplified tumors. At last ASCO, it has been presented that immunotherapy can increase sensitivity to salvage chemotherapy after progression on immune checkpoint inhibitor in patients with SCCHN [11]. In addition, our patient experienced prolonged partial response (11 months) to PD-L1 inhibitor. To date, we don't know the relationship between *HER2* amplification and response to immune checkpoint inhibitor in solid tumors. Several ongoing trials are evaluating response to anti-PD-1 or anti-PD-L1 alone or in combination with other agents in patients with *HER2* tumors. One completed phase I/II study is evaluating response to durvalumab, a PD-L1 inhibitor, in patients with HER2-expressing advanced solid tumors (NCT02576548).

In conclusion, we reported a documented response of 14 months in third line treatment with trastuzumab combined with paclitaxel in patient with *HER2*-amplified SCCHN. Further studies are needed to evaluate the role of trastuzumab and immunotherapy in SCCHN with *HER2* amplification.

Conflict of interest

The authors declared that there is no conflict of interest.

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