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An Old but Still Unanswered Question in Recurrent or Metastatic Salivary Duct Carcinoma

TO THE EDITOR:

We read with interest the article by Sheth et al recently published in *JCO Precision Oncology*. The authors reported the case of an androgen receptor–positive (AR+) and human epidermal growth factor receptor 2–positive (HER2+) salivary duct carcinoma (SDC) patient responding to alpelisib and bicalutamide[1] after the progression on first-line paclitaxel, carboplatin, and trastuzumab.

A Japanese group posited a new SDC classification according to the combined AR and HER2 expression.[2] In this frame, the case presented by Sheth and colleagues belongs to apocrine HER2 group. In this latter, the risk of death is more than doubled compared with apocrine A (AR+, HER2–, and low proliferation index assessed through MIB1 immunohistochemistry).

There is strong evidence in treating HER2+ salivary gland cancer patients with anti-HER2 targeted agents. For this reason, the authors chose to start targeting the HER2 pathway as a first-line approach, and they observed an initial response up to the development of HER2 resistance, which was deemed to be mediated by *PIK3CA* mutation.

However, we still ignore which are the best options and sequences for recurrent and metastatic HER2+ and AR+ SDC. In the first-line setting, the EORTC1206 randomized controlled trial is a phase II clinical study assessing whether the combined androgen deprivation therapy (bicalutamide + triptorelin) is superior to cytotoxic chemotherapy (cisplatin + doxorubicin or carboplatin + paclitaxel) in AR+ SDC patients regardless of the HER2 status.[3] This study, started in 2014, has been designed to pursue an antiandrogen-centered approach. This choice was because of the fact that AR overexpression and estrogen receptor and progesterone receptor absence are considered histologic hallmarks of SDC while only 25%-30% of them are HER2+,[4] and few pieces of evidence were available at that time supporting the efficacy of anti-HER2 approaches in SDCs. Furthermore, there is evidence that enzalutamide inhibits the growth of HER2 breast cancer cells in vitro.[5] These preclinical findings suggest that the activity of AR inhibition might be anticipated in HER2+ cancers such as SDC, even independently of HER2 inhibitors.

Besides, SDC has a typical male predilection. A differential AR gene activation between sexes has been reported suggesting a ligand-independent AR pathway activation in females.[6] In this regard, women affected by SDC might not benefit from a combined androgen deprivation therapy (ADT). Thus, in this setting, we would support the association of bicalutamide and alpelisib proposed by the authors.

The case published by Sheth et al[1] was *PIK3CA*-mutated. This somatic mutation and several other *PI3K/AKT/mTOR* pathway alterations are often found in salivary gland cancers, especially in SDCs.[7] In our experience of combined ADT for SDC, we observed three cases with *PI3K* pathway aberrations (one case with a *PIK3CA* mutation and two with *PTEN* deletions). Interestingly, all these patients were responsive to combined ADT.[8] Given these observations, one could speculate that bicalutamide plus luteinizing hormone-releasing hormone analog could have been active even without alpelisib. As already suggested before in a similar context,[9] we hypothesize that the clinical response to *PIK3CA* targeting might have been obtained through the AR modulation. This supports the role of ADT as in castration-sensitive prostate cancer, at least in men.

Almost 10 years ago, we wondered how many therapeutic options there were for recurrent or metastatic SDC.[9] Not only this question still remains unanswered but new complexity is also added. This interesting clinical case gave us the opportunity to reflect further on the biologic and clinical intricacies of this malignancy, which also seems to imply a gender-dependent approach.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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