case reports

Excellent Response With Alpelisib and Bicalutamide for Advanced Salivary Duct Carcinoma With PIK3CA Mutation and High Androgen Receptor Expression—A Case Report

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INTRODUCTION

Salivary duct carcinoma (SDC) is an aggressive adenocarcinoma of the salivary gland with high rates of metastasis and mortality with 5-year survival rates between 23%-42% versus other more common, salivary gland carcinomas such as adenoid cystic carcinoma (89%) and mucoepidermoid carcinoma (79.3%).[1] Even for SDCs managed with curative intent with surgery with or without adjuvant radiation, there is a high rate of locoregional recurrence (48%) or distant metastasis (48%).[2] The sensitivity of advanced SDC (aSDC) to chemotherapy has been reported in the past with variable responses.[3,4] However, in recent years, large numbers of somatic mutations have been identified where targeted therapies have shown great success. We explore a *PIK3CA* and androgen receptor (AR)-positive aSDC case that responded favorably to phosphoinositide 3-kinase (PI3K)α isoform inhibitor alpelisib and AR inhibitor bicalutamide. To the best of our knowledge, this is the first such case of aSDC treated with alpelisib and bicalutamide.

CASE HISTORY

A 64-year-old gentleman, with history of hypothyroidism, presented with severe back pain and stiffness. Total spine magnetic resonance imaging with contrast showed marrow infiltration at C6, C7, D12, L1, L3, and S2 vertebrae without cord edema and a paravertebral soft tissue component. Multiple myeloma was ruled out by investigations. Whole-body positron emission tomography-computed tomography (PET-CT) scan showed a soft tissue mass involving superficial lobe of right parotid gland invading the temporalis and masseter muscles and multiple lymph nodes. Distant metastasis was reported as right upper-lobe lung nodules and multiple skeletal lesions. Biopsy of the right parotid mass showed human epidermal growth factor receptor 2 (HER2)-positive, AR-positive SDC by immunohistochemistry (Figs 1A-1F). *HER2* amplification was confirmed by fluorescent in-situ hybridization. However, the tissue was insufficient for next-generation sequencing (NGS) testing. Biopsy of the sacral mass confirmed metastasis from a parotid SDC.

In view of distant metastasis, the patient was not deemed fit for surgical intervention or definitive radiotherapy. Based on prior experience and published data by Limaye et al,[5] the patient was started on systemic chemotherapy and targeted therapy with intravenous paclitaxel 175 mg/m^2, carboplatin AUC5, and trastuzumab 8 mg/kg loading followed by 6 mg/kg q3weeks and zoledronic acid and calcium-vitamin D for bony involvement. The patient responded well to medical management of pain, and palliative radiation was not required. A reassessment scan after three cycles showed significant partial response and the same therapy was continued for six cycles followed by maintenance trastuzumab. However, after his fourth cycle of maintenance trastuzumab, a reassessment scan showed disease progression consistent with resistance to HER2-directed therapy.

To understand the cause of the newly developed HER2-targeted therapy resistance, a fresh biopsy and broad-panel NGS was performed to test for molecular alterations. The data analysis revealed genomic alterations (Table 1) including *PIK3CA* mutation (Fig 3A), which was considered targetable.

Since immunohistochemistry showed high expression of AR (Fig 1C), the patient was started on tab alpelisib 300 mg and tab bicalutamide 50 mg orally daily to target the *PIK3CA* and AR pathways, respectively. While on alpelisib, he developed hyperglycemia at 2 weeks of therapy requiring treatment with oral metformin and dose reduction of alpelisib from 300 mg to 250 mg and eventually to 200 mg orally daily, which was well tolerated. He has been continued on this regimen for the past 12 months, and subsequent scans have shown near-complete metabolic response to treatment with alpelisib and bicalutamide combination. Figures 2A-2C compare recent PET-CT reports with the ones done 8 months before. A timeline overview of the patient's management is summarized in Figure 3.

Author affiliations and support information (if applicable) appear at the end of this article.

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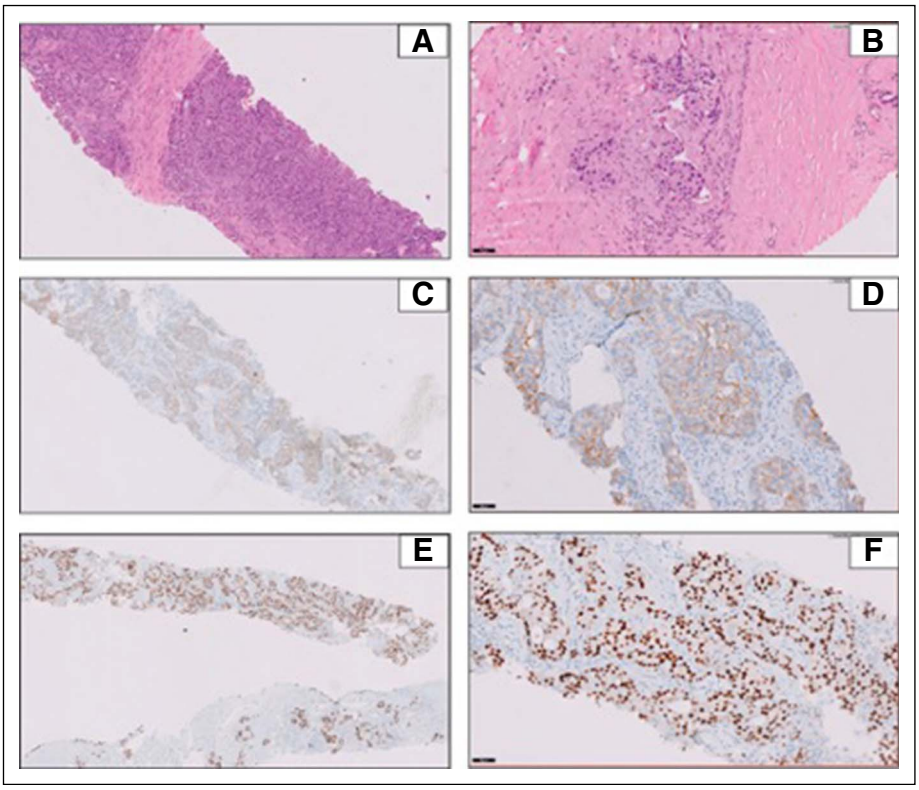

FIG 1. (A) Histopathologic findings on hematoxylin and eosin (H&E) staining of the salivary ductal carcinoma case at diagnosis (5×). (B) H&E staining of the salivary ductal carcinoma case at diagnosis (20×). (C) Immunohistochemistry (IHC) analysis for human epidermal growth factor receptor 2 (HER2)-overexpression showing HER2-positive score 3+ complete membranous in more than 10% tumor at diagnosis (5×). (D) IHC analysis for HER2-overexpression showing HER2-positive tumor cells (20×). (E) Nuclear staining of androgen receptor (AR) showing strong positive AR expression in all tumor cells at diagnosis (5×). (F) Nuclear staining of AR showing strong positive AR expression in all tumor cells at diagnosis (20×).

To interrogate the *PIK3CA* mutation status at presentation, we located the original tissue block and performed NGS testing. The patient was found to be *PIK3CA*-mutated on droplet digital polymerase chain reaction (ddPCR) testing, which is plausibly one of the causative links to the HER2-directed therapy resistance.

This case report was approved by the institutional review board.

The patient has provided his consent for publishing his case in a journal, web site, or other forms of publication including images or other clinical information relating to his case. He understands that his name and initials will not be published and that his identity will not be disclosed.

DISCUSSION

SDC is an aggressive adenocarcinoma similar to high-grade ductal breast cancer.[1] Local invasion may involve the extracranial portion of the facial nerve and the temporal bone via perineural spread. Distant metastases are seen in more than 50% cases with the most common being pulmonary, intracranial, bone and cutaneous sites.[6] There are no established guidelines for the management of aSDC. Platinum-based anthracyclines and taxane-based chemotherapy regimens have been studied in aSDC with variable responses.[3]

Majority of SDC cases express AR (66.7%-96.4%) and/or HER2 (15%-44%), thus making HER2-directed therapy a viable treatment option. Studies have shown that trastuzumab with chemotherapy is superior to chemotherapy alone in the treatment of HER2-positive aSDC.[5] In a single-arm phase II study, 57 patients with HER2-positive aSDC received trastuzumab and docetaxel[7] with an overall response rate (ORR) of 70.2%, and median progression-free survival and overall survival of 8.9 and 39.7 months, respectively. These findings were further supported in a study by Hanna et al[8] who compared the clinical outcomes of patients with aSDC receiving chemotherapy-trastuzumab combination to chemotherapy alone in an adjuvant setting along with concurrent radiation therapy with significant benefit in survival in the chemotherapy-trastuzumab arm. Li et al reported an ORR of 90% and minimal adverse events with ado-trastuzumab emtansine in 10 patients with *HER2*-amplified salivary gland carcinomas who had received a median of two lines of prior therapy (0-3).[9]

In AR-positive aSDC, androgen deprivation therapy has shown to have a better ORR and lower adverse events when compared with standard chemotherapy.[11] A nationwide case

TABLE 1. Summary of Molecular Analysis—Variants Identified Through NGS Analysis

Molecular Analysis	Post HER2-Directed Therapy Resistance		
Tumor DNA NGS	**Gene**	**Amino Acid Variant**	**Variant Frequency (%)**
	PIK3CA	p.E545K	15.0
	TP53	p.R196*	17.5
	HRAS	p.Q61R	40.0
	ACVR2A	p.D177E	7.0

Abbreviations: ACVR2A, activin receptor type-2A; HER2, human epidermal growth factor receptor 2; NGS, next-generation sequencing.

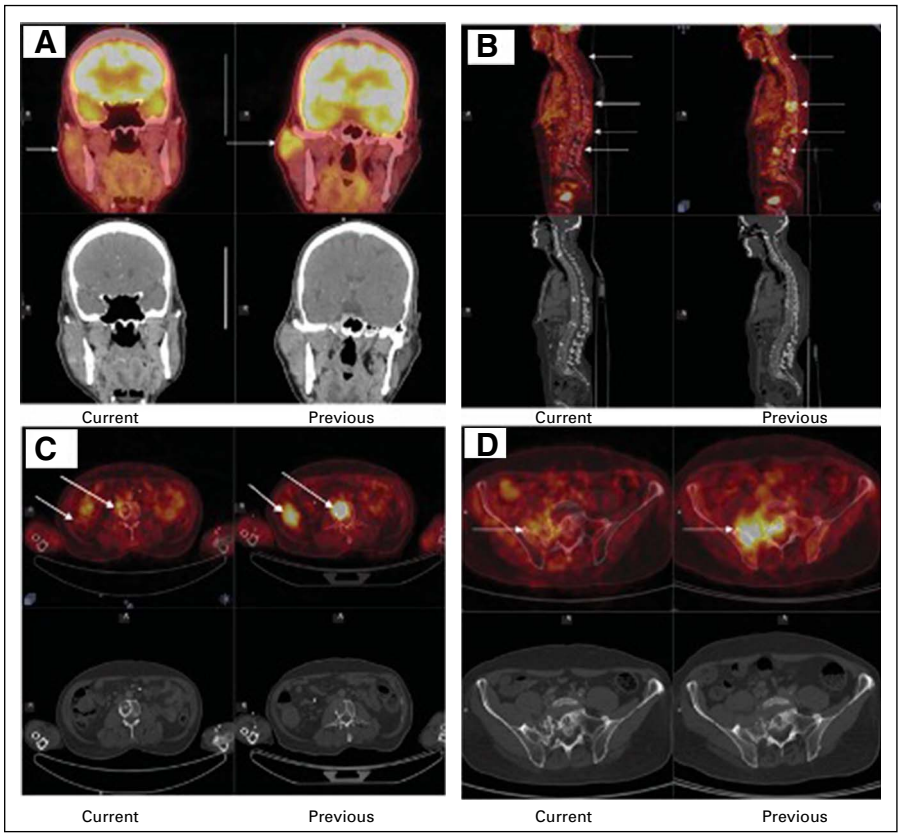

FIG 2. Current and previous positron emission tomography-computed tomography scans demonstrating response to treatment from *PIK3CA* and androgen receptor inhibitors. (A) Arrows show near-complete metabolic resolution of the primary lesion when compared with prior scans. (B) Arrows show complete metabolic resolution of the vertebral metastasis when compared with prior scans. (C) Arrows show complete metabolic resolution of the lung and vertebral metastasis when compared with prior scans. (D) Arrows show near-complete metabolic resolution of the primary lesion when compared with prior scans.

series involving 35 patients with AR-positive aSDC treated with either monotherapy (luteinizing hormone-releasing hormone analogues or the AR antagonists: enzalutamide or bicalutamide) or combined androgen blockade (luteinizing hormone-releasing hormone analogue and bicalutamide) had a clinical benefit rate of 50%.[10,12]

Several genomic studies have reported somatic mutations associated with SDC in genes such as *EGFR* (20%), *PDGFRA* (27%), *HRAS* (27%), *KIT* (33%), *PIK3CA* (53%), and *PTEN* (53%),[13] which has maximized the opportunities for potential targeted therapies. *PIK3CA* mutation is commonly described in several malignancies and activates PI3K-PTEN-AKT pathway causing oncogenic transformation independent of RAS or RAF mutation.[14-18] Hyperactivity of PI3K signaling is associated with AKT activation leading to cell proliferation, resistance to apoptosis, and increased

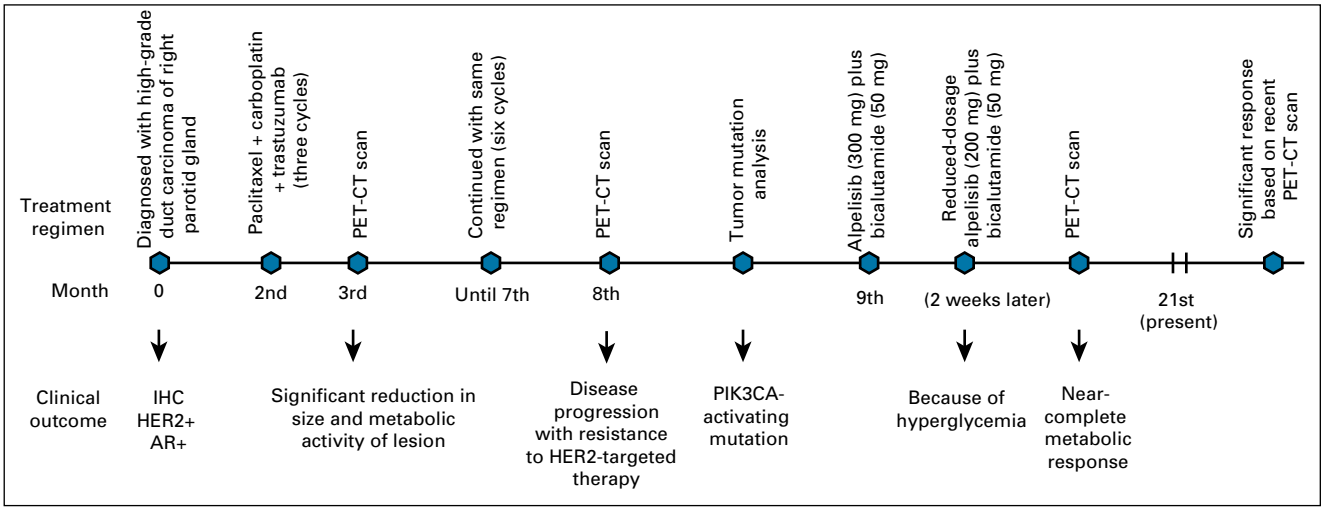

FIG 3. Depiction of treatment regimen and timeline of the patient with salivary duct carcinoma. AR, androgen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PET-CT, positron emission tomography-computed tomography.

invasion.[19] Mutations in E545 and H1047 have been linked to resistance to HER2-directed therapies in breast cancer.[20]

PI3K inhibitors can be broadly classified as dual PI3K and mammalian target of rapamycin (mTOR) inhibitors, pan-PI3K inhibitors, and isoform-specific inhibitors. Based on the positive results of SOLAR-1 trial, and improvement in median progression-free survival with alpelisib plus fulvestrant versus fulvestrant alone (11 *v* 5.7 months), alpelisib was US Food and Drug Administration–approved for hormone receptor-positive, HER2-negative, *PIK3CA*-mutated metastatic breast cancer (MBC) with progression on or after endocrine therapy.[21] In a systemic review of targetable mutations in aSDC, two patients with *PIK3CA* mutation were treated with PI3K and mTOR inhibitor with limited benefit.[22] Our decision to treat this case with alpelisib and endocrine therapy was based on the SOLAR-1 trial results. A summary of the clinical trials is included in Table 2.

Studies conducted by Lehmann et al and Yadav et al demonstrated the additive effect of bicalutamide with either a pan-PI3K inhibitor or a dual PI3K and mTOR inhibitor on AR-positive triple-negative breast cancer and prostate cancer, respectively.[23,24] Interestingly, a study involving AR-positive prostate cancer that focused on the role of glucocorticoid receptor expression in development of resistance to AR-inhibitor therapy demonstrated that by targeting PI3K and AKT pathway, there was increased canonical AR activity, decreased glucocorticoid receptor expression, and marked antitumor activity.[25] Figure 4B depicts the rationale behind the synergy of PI3K and mTOR pathway inhibition and AR deregulation. Here, we present a case where a combination therapy with PIK3CA inhibitor alpelisib and AR inhibitor bicalutamide was considered as the most appropriate second-line therapy.

Initially, the patient responded well to chemotherapy and trastuzumab; however, he subsequently developed

TABLE 2. Summary of Clinical Trials With HER2-Directed Therapy, *PIK3CA*, and AR Inhibitors

Targetable Mutations	Study Name	Primary Disease	Therapy	Response (Median)	Toxicity
HER2	Single-institute retrospective study[5]	HER2-positive SDC	Adjuvant therapy with concurrent radiation and chemotherapy with weekly TCH for 6 weeks followed by TCH for 12 weeks and trastuzumab alone for 1 year Palliative treatment with TCH every 3 weeks for six cycles followed by trastuzumab for variable periods with or without second-line chemotherapy for progression	ORR: 18 months	Grade 3 or higher with TCH: 1/13 (7.6%)
HER2	Single-arm phase II study[7]	HER2-positive SDC	Trastuzumab at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks while docetaxel was given at 70 mg/m^2 every 3 weeks	ORR: 70.2% PFS: 8.9 months OS: 39.7 months	Grade 3 or 4 febrile neutropenia: 74% (no significant cardiac toxicity was reported)
HER2	Single-institute retrospective study[8]	HER2-positive SDC	Weekly carboplatin (area under the curve, 1.5) with paclitaxel (45 mg/m^2) and trastuzumab (TCH; 2 mg/kg after a 6 mg/kg week 1 loading dose) intravenously concurrently with adjuvant RT *v* TC	DFS: 117 months *v* 9 months OS: 74 months *v* 47 months	—
HER2	Phase II basket trial[9]	HER2-amplified SGC	Ado-trastuzumab emtansine 3.6 mg/kg IV every 3 weeks	ORR: 90%	Grade 1 or 2 infusion reaction, thrombocytopenia, and transaminitis
AR	Netherlands nationwide case series[12]	AR SDC	150 mg bicalutamide once daily or a combination of an LHRH analogue (ie, goserelin 3.6 mg subcutaneously every 4 weeks, with 50 mg bicalutamide once daily)	PFS: 4 months CBR: 50% OS: 17 months	—
PIK3CA E545K	Phase I clinical trial[23]	PIK3CA-positive SDC	Combination of PI3K inhibitor plus MEK inhibitor	PFS: 8.7 months	—
PIK3CA H1047R	Phase I clinical trial[23]	PIK3CA-positive SDC	Dual PI3K/mTOR inhibitor	PFS: 8 weeks	—

Abbreviations: AR, androgen receptor; CBR, clinical benefit ratio; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; IV, intravenous; LHRH, luteinizing hormone-releasing hormone; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RT, radiotherapy; SDC, salivary duct cancer; SGC, salivary gland cancer; TC, paclitaxel, carboplatin; TCH, paclitaxel, carboplatin, trastuzumab.

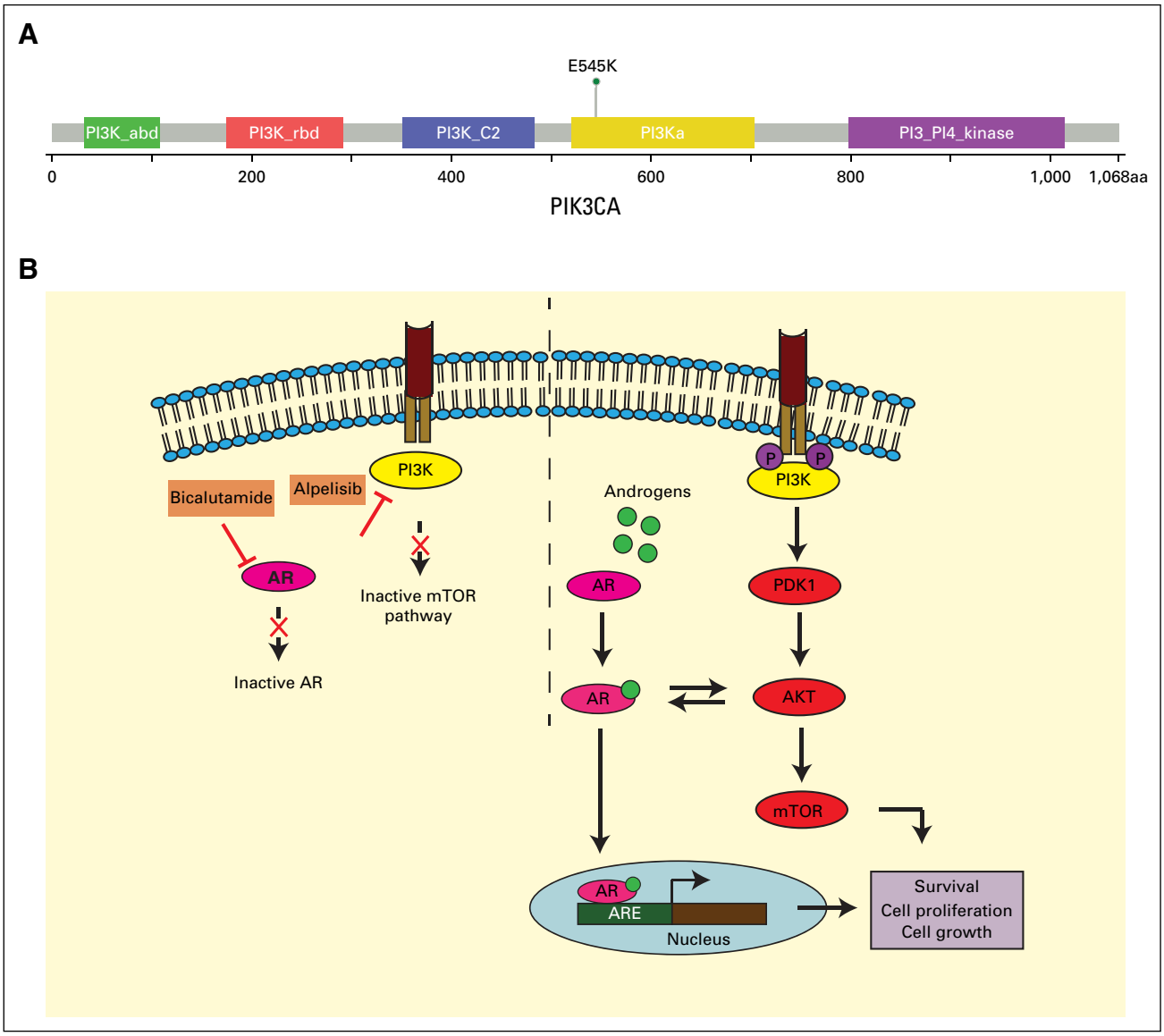

FIG 4. (A) Overview of *PIK3CA* gene with p.E545K domain-specific mutation. (B) A model of PI3K/mTOR pathway inhibition and AR deregulation in HER2-positive salivary duct carcinoma. AKT, XXX; AR, androgen receptor; ARE, androgen receptor element; CT, computed tomography; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PDK1, 3 phosphoinositidine-dependent kinase 1; PET, positron emission tomography.

progression on maintenance trastuzumab indicating resistance to HER2-directed therapy. *PIK3CA* mutation has been linked to development of resistance in HER2-positive breast cancer and we believe the presence of *PIK3CA* mutation in this case led to the resistance to trastuzumab. Based on the available data with alpelisib and fulvestrant in MBC, we decided to treat with alpelisib and bicalutamide.[19] However, one of the limitations of this study is that *PIK3CA* mutation analysis was unable to be performed at presentation. The other limitation is that the exact role of combination therapy versus a pure AR-based approach remains unclear. In their work on breast cancer cell lines, He et al[26] have demonstrated the critical role of AR crosstalk with HER2 leading to HER2-directed therapy resistance. It was only upon progression on initial regimen that we evaluated the patient further for pathways of resistance.

To the best of our knowledge, this is the first *PIK3CA*-mutated, AR-overexpressed aSDC case to have excellent response to a combination therapy with alpelisib and bicalutamide in the setting of HER2-directed therapy resistance. The patient had near-complete metabolic response on follow-up PET-CT scan, which is sustained through the past several months. Further research along the lines of targeted therapies seems to be the way forward in terms of treatment options for aSDC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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