Case Report

Case Report: Sustained Complete Response to PI3K Inhibition in a Patient with Metastatic Breast Cancer Harboring *PIK3CA*, *NF1*, and *CDH1* Mutations

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ABSTRACT

PIK3CA mutations resulting in disinhibition of the phosphoinositide 3-kinase (PI3K) pathway are present in approximately a third of estrogen receptor (ER)-positive breast cancer. Recent clinical trials of PI3K inhibition in *PIK3CA*-mutated metastatic breast cancer have shown improvement in progression-free survival of up to 11 months. We report a 68-year-old woman with metastatic ER-positive breast cancer with *PIK3CA* mutation who despite having disease progression after four lines of endocrine therapy (ET) attained a complete response (CR) after subsequent addition of a PI3K inhibitor. Remarkably, her CR is still maintained at 5 years. We believe this may be due to the co-occurrence of an *NF1* mutation, which increases sensitivity to PI3K inhibition. Our case demonstrates restoration of sensitivity to ET by additional inhibition of PI3K, which resulted in exceptional disease response, far exceeding the expected duration. Hence, we believe that PI3K inhibition in addition to ET should be considered in patients with simultaneous *PIK3CA* and *NF1* mutations.

Keywords: breast cancer, *PIK3CA* mutation, *NF1* mutation, endocrine resistance, PI3K inhibitors

INTRODUCTION

Phosphoinositide 3-kinases (PI3Ks) mediate important biological functions, such as cell survival, differentiation, and proliferation.[1] In breast cancer, mutations of *PIK3CA*, which encodes the p110α catalytic subunit of class IA PI3K, are present in 36% of patients.[2] *PIK3CA* mutations are oncogenic and are thought to represent important events in the initiation and progression of cancer. Research is attempting to exploit mutated *PIK3CA* as a therapeutic target. We present a case of metastatic estrogen receptor (ER)-positive breast cancer that had progressive disease (PD) on second-line fulvestrant that subsequently attained a complete response (CR) with the addition of PI3K inhibition, which is still ongoing at 5 years.

CASE DISCUSSION

In 2004, the patient, aged 53 and premenopausal, underwent right mastectomy for a 30-mm (pT2) infiltrating lobular carcinoma grade 2, involving 3 of 11 nodes (pN1a), ER positive, HER2 negative. She received doxorubicin-cyclophosphamide for four cycles, followed by local radiation therapy, then tamoxifen for 3 months, followed by anastrozole for 1 year, subsequently discontinued secondary to arthralgia.

In 2011, the patient developed a 12-cm ovarian mass and ascites. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. CA125 was minimally raised presurgery and normalized postoperatively. All other and subsequent markers (CEA, CA153) were and remain normal. Histology confirmed metastatic lobular breast cancer, ER positive (+ in 65% nuclei), PR positive (+++ in 70% nuclei). The patient was radiologically disease-free postoperatively. Letrozole was commenced.

Twelve months later, imaging revealed new para-aortic lymphadenopathy (Figure 1A). The patient was enrolled on the phase 2 FERGI trial comparing fulvestrant plus pictilisib to fulvestrant plus placebo in aromatase inhibitor-resistant breast cancer. She commenced fulvestrant and blinded oral agent. She achieved stable disease as best response, but with eventual PD at month 12 (Figure 1B). Blinded randomization was broken as per

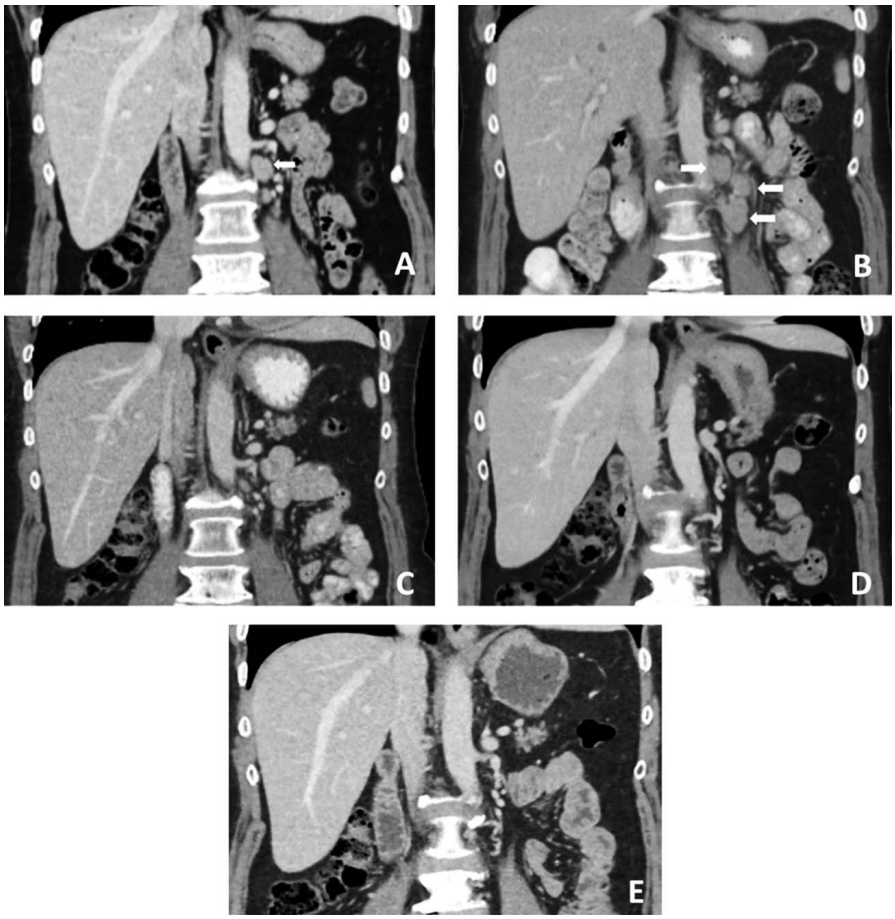

Figure 1.—(A) May 2012: new para-aortic lymphadenopathy (arrow) after 12 months of letrozole. (B) August 2013: progression of lymphadenopathy (arrows) after 12 months of fulvestrant and blinded oral agent. (C) July 2014: radiological complete response (CR) after 24 months of pictilisib. (D) August 2017: maintained radiological CR when transitioning to taselisib. (E) September 2019: maintained radiological CR on taselisib.

protocol, revealing the patient had been receiving placebo. An extension to the trial allowed continuation of fulvestrant and commencement of open-label pictilisib 330 mg daily from August 2012. The para-aortic nodes slowly regressed, achieving radiologic CR by July 2014 (Figure 1C). Toxicity included nausea, fatigue, and mood disorder, all grade 1. Hypertension developed at 6 months, requiring pharmacological intervention.

Unfortunately, FERGI failed to achieve its primary endpoint, and pictilisib development ceased. After global stocks of pictilisib were exhausted in 2017, we sought to maintain PI3K inhibition by transitioning the patient onto taselisib 4 mg daily via an access program. Fulvestrant was continued. She developed grade 2 toxicities (rash, stomatitis, and proctitis) necessitating a 2-month treatment interruption. Taselisib resumed at 2 mg daily and has since been well tolerated. The patient is now in her sixth year on a PI3K inhibitor and fulvestrant, with continued CR demonstrated on latest imaging (Figure 1E). Next-generation sequencing (NGS) retrospectively performed in 2017 on the ovarian mass identified alterations in *PIK3CA* (glu545lys), *NF1* (loss of exons 1–35), and *CDH1* (C28fs*6). The timeline of events is summarized in Table 1.

Table 1.—Timeline of events

03/2004	Mastectomy and axillary lymph node dissection
09/2004	Completes adjuvant ACx4. Starts adjuvant ET
01/2007	Stops adjuvant ET due to AE
03/2011	Relapse with ovarian mass (resected). Starts letrozole
05/2012	Relapse with para-aortic nodes
07/2012	Fulvestrant + placebo (FERGI trial)
08/2013	PD. Crossover to fulvestrant + pictilisib (FERGI trial)
07/2014	Achieves CR
09/2019	Fulvestrant + taselisib. CR maintained at time of writing

AC: doxorubicin and cyclophosphamide; AE: adverse effects; CR: complete response; ET: endocrine therapy; PD: progressive disease.

The FERGI trial in which the patient participated was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The trial obtained written informed consent from the patient before enrollment, in agreement with approved protocols from respective ethics committees at each site. We confirm that written informed consent was obtained from the patient to publish her information and images. Further clinical data on the patient is available on request.

DISCUSSION

PI3Ks are heterodimers consisting of a catalytic (p110) and a regulatory (p85) subunit. The p85 subunit stabilizes the p110 subunit in quiescent cells, suppressing PI3K activity.[3] On growth factor stimulation, the p110 subunit is relieved from inhibition by the p85 subunit, mediating PI3K recruitment to the plasma membrane. The activated p110 subunit catalyzes phosphorylation of phosphatidylinositol-4,5-bisphosphate, ultimately leading to induction of the multiple biologic effects of the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway.[4]

PIK3CA gene mutations are the commonest molecular alterations of the PI3K pathway in breast cancer, reported in up to 53% of metastatic lobular breast cancer.[5] These mutations display a nonrandom distribution, clustering within the helical domain (exon 9, commonly glu542lys and glu545lys, as in our patient) and the kinase domain (exon 20, commonly his1047arg).[6]

Preclinical models have shown that estrogen-independent breast cancer cell growth can be associated with hyperactivation of the PI3K/mTOR pathway. Direct PI3K inhibition can effectively suppress hormone-independent growth of both estrogen-independent and estrogen-dependent cells.[7] Recent efforts have sought to capitalize on the synergy between hormonal therapy and PI3K inhibition. Disappointingly, several early-phase and randomized phase 2 studies have shown at most modest benefit of PI3K inhibitors in *PIK3CA*-mutant breast cancer. BELLE-2 (BKM120/Placebo With Fulvestrant in Postmenopausal Patients With Hormone Receptor Positive HER2-negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor) and BELLE-3 studied the addition of the pan-PI3K inhibitor buparlisib or placebo to fulvestrant in patients who had been pretreated with endocrine therapy (ET) and up to one line of chemotherapy; and ET and mTOR inhibitor, respectively.[8,9] In BELLE-2, median progression-free survival (PFS) in the intention-to-treat (ITT) population ($n = 1147$) was 6.9 versus 5 months (one-sided $p = 0.00021$), and 6.8 versus 4.0 months (one-sided $p = 0.014$) in the subgroup with activated PI3K ($n = 372$).[8] BELLE-3 demonstrated PFS of 3.9 versus 1.8 months ($p = 0.0003$) in the ITT population ($n = 432$).[9] The subgroup with *PIK3CA* mutation had a nonsignificant median PFS difference of 3.9 versus 2.7 months ($p = 0.113$). Short exposure to buparlisib (median 1.9 months) owing to significant toxicity may explain the limited benefit in both trials.

Pictilisib, also a nonspecific inhibitor of all four class I PI3K isoforms, showed significant activity in preclinical breast cancer models.[10] The FERGI trial of 168 patients, including our patient, failed to demonstrate a significant PFS benefit of the addition of pictilisib to fulvestrant (median PFS 6.6 versus 5.1 months, $p = 0.096$) and in the 84 patients with *PIK3CA* mutations (median PFS 6.5 versus 5.1 months, $p = 0.268$). Again, significant toxicity may explain the negative result with median exposure to pictilisib only 2.9 months in part 1 of the trial, improving to 4.2 months in part 2 with dose reduction.[11]

Subsequent studies have used PI3K inhibitors with more p110α selectivity.[12,13] SANDPIPER, a Phase III study of 516 patients with *PIK3CA*-mutant breast cancer comparing the addition of the p110β-sparing PI3K inhibitor taselisib or placebo to fulvestrant showed a modest PFS improvement of 7.4 versus 5.4 months ($p = 0.0037$).[12]

More encouraging results were reported from the SOLAR-1 trial with alpelisib, which has approximately 50 times more selectivity for p110α than the other isoforms. The trial recruited 572 patients who had previously received ET and compared alpelisib plus fulvestrant with placebo plus fulvestrant. In the *PIK3CA*-mutated cohort ($n = 341$), PFS was 11 months in the experimental arm versus 5.7 months in the control arm ($p < 0.001$). The overall response rate was 26.6% in the experimental arm. In the *PIK3CA* wild-type group, there was a nonsignificant difference in PFS (7.4 versus 5.6 months).[13] Based on these results, alpelisib gained Food and Drug Administration approval in May 2019 and became the new standard of care, in combination with fulvestrant, for ER-positive, HER2-negative, *PIK3CA*-mutated metastatic breast cancer.[14]

We note another case of unexpected benefit from fulvestrant combined with a PI3K inhibitor (alpelisib).[15] The patient in that report experienced an extensive intra-abdominal relapse of infiltrating lobular breast cancer 8 years after first presentation. Fulvestrant used as first-line metastatic treatment resulted in stable disease at 3 months and PD by month 5. Subsequent lines of therapy were exemestane plus everolimus (13 months), tamoxifen (3 months), capecitabine (8 months), palbociclib plus letrozole (no response), and paclitaxel (no response). NGS identified a *PIK3CA* mutation in the helical domain in exon 9 (gln546lys; a known oncogenic driver mutation with previously documented response to alpelisib). The patient was commenced on alpelisib plus fulvestrant. CA 15-3 declined substantially after 1 week, with marked symptomatic improvement by week 4. Week 12 imaging demonstrated significant response in her diffuse peritoneal carcinomatosis, retroperitoneal adenopathy, and ascites. Unfortunately, PD was noted at 24 weeks of treatment.

Duration of expected benefit from PI3K inhibition can be estimated from the original phase 1B study of alpelisib plus fulvestrant. Eighty-seven patients were studied. There was a single CR (in a fulvestrant-naive patient). Eight of 87 patients continued treatment for more than 2 years. The longest duration of response was 208 weeks in a patient who had prior combination of ET and an mTOR inhibitor.[16]

Thus, although extended control has been reported, our patient's experience is of greater duration (6 years), more substantial (CR), and even more remarkable in that it represents synergy restoring responsiveness to an agent (fulvestrant) on which she had experienced PD.

Given the limited benefit demonstrated in FERGI and BELLE our patient's response to pictilisib, subsequently maintained on taselisib, is noteworthy and difficult to explain. Our patient's NGS demonstrated mutation in *PIK3CA* (glu545lys), loss of exons 1 to 35 of *NF1*, and the *CDH1* mutation C28fs*6. *NF1*, the key negative regulatory gene of the RAS pathway, is situated upstream of PI3K and is mutated in 2% to 4% of sporadic breast cancer[17] and up to 12.2% in metastatic lobular cancer.[5] *NF1* deletion in Chaos3 mammary tumors leads to increased activated RAS and sensitivity to PI3K and MAPK inhibitors.[18] A study examining *NF1* in glioma found PI3K/AKT signaling essential for *NF1*-mediated proliferation.[19] Other studies have shown *NF1* cross talk with mTOR signaling.[20] Although it is unclear whether biallelic loss of *NF1* is common or if only heterozygous mutations of *NF1* contribute to progression in sporadic tumors, mouse cells heterozygous for *NF1* mutations show abnormal growth and invasion.[21,22] *NF1* loss is significantly co-occurrent with *CDH1* and *AKT* pathway alterations; either or both of which may potentiate ET resistance.[5] We note as limitations the absence of germline genetic testing and serial circulating tumor DNA analysis, both of which may have provided additional information of interest.

We speculate the exceptional response in our case may relate to the co-occurrence of *PIK3CA* and *NF1* mutations. We suggest that in individuals demonstrating these simultaneous mutations, PI3K inhibition plus fulvestrant is a valid therapeutic consideration.

In April 2020 the patient continued to receive Taselisib and Fulvestrant when an omental nodule enlarged rapidly to 18mm. This was first noted June 2016 (5mm) and presumed to represent benign fat necrosis. Unfortunately biopsy confirmed this as a site of recurrence. The patients imaging otherwise indicates ongoing exceptional control of disease, including the retroperitoneum, which remains radiologically normal.

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