Patient with Lobular Carcinoma of the Breast and Activating **AKT1 E17K** Variant

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**Abstract**

**Objective.** To present the characteristics of the AKT1E17K gene variant and a description of the clinical application in a patient with metastatic breast cancer. **Results.** 63 y/o woman with Stage IV Invasive lobular carcinoma at diagnosis was treated with Palbociclib and aromatase inhibitors (AI). At progression, tissue was sent for comprehensive genomic profiling to Foundation Medicine (FM) which revealed AKT1E17K mutation. In lieu of available clinical data within the patient's tumor type (HR+ HER2- breast cancer), extrapolated data from the Flatiron Health-FM (FH-FMI) Clinico-genomic Database (CGDB) was discussed at our Molecular Tumor Board (MTB). After multidisciplinary discussion, the consensus recommendation was to start treatment with the combination of mTOR inhibitor everolimus, and AI, exemestane. Patient tolerated treatment without major side effects. By the second clinical visit the patient's breast showed signs of improvement. PET/CT showed diminished left axillary uptake, decreased right paratracheal lymph node PET avidity, and stable bone disease consistent with a partial response. The most recent office visit in January 2021, breast exam revealed a normal-appearing skin with only faint erythema. All other skin lesions have resolved. Although, the role of AKT1 variant described here is not well defined and therapeutic significance of M-Tor inhibitors not established in metastatic breast cancers, comprehensive approach to this case unraveled new and successful therapeutic option in this patient. **Conclusion.** This demonstrates that applying available Precision Medicine tools like MTB and real world data sets from patient populations with similar clinical and genomic profiles may provide more options for treatment.

**Key Words:** AKT1 • Breast Cancer • Molecular Tumor Board (MTB) • CGDB – Comprehensive Genomic Data Base.

**Introduction**

Invasive lobular carcinoma (ILC) is the most common of the breast cancer special types, accounting for up to 15% of all breast cancer cases. ILCs are noted for their lack of E-cadherin function, which results in non-cohesive growth pattern, with the knowledge from genomic profiling now there is huge amount of new data, from the genomic landscape of ILC and in particular somatic alterations associated with therapy resistance, and the evolution of several potential therapeutic avenues. Many targeted and chemotherapy options are being evaluated.

Here we present a case of ILC treated at our cancer center based on the precision medicine tools. The information provided by genomic profile is used clinically to guide treatments decisions for approved targeted therapies and in clinical trials. In this case none of that could be used. We found an effective treatment for this patient based on the MTB discussion and the real world data of the AKT1E17K variant and AKT1 WT breast cancer patients.

**Results**

**Clinical Presentation**

A 63-year-old pleasant woman with no major past medical history presented in January 2019 with a palpable left breast mass. On physical exam, besides the breast mass, the patient had palpable lymph nodes in the left axilla. She was referred for
diagnostic mammography and ultrasound, which revealed a diffuse nonhomogeneous density at the site of palpable finding. A core needle biopsy was performed, and pathology revealed classic invasive lobular carcinoma infiltrating the fibrous tissue of the breast as single cells and in cords or linear strands of cells, most often found in the breast fibrous stroma (Figure 1A).

The infiltrating cells are monotonous, small in size, and possess round nuclear contours. This pattern of invasion can at times encircle benign ducts in a concentric or “targetoid” fashion. These cells can be seen infiltrating together, as in the image (Figure 1B) or in a rather insidious fashion separated by the fibrous stroma of the breast, presenting a challenge to find for even an experienced pathologist. This is especially challenging when the amount of tumor present is limited, as in needle biopsy material. The classic invasive lobular carcinoma typically expresses estrogen (ER) and progesterone receptors (PR) and is negative for HER2 expression. In this case, the cancer cells were ER-positive while PR and HER2 receptors were negative. The proliferation rate was ~50% (measured by Ki-67).

On February 5, 2019, the patient underwent a PET/CT scan, which revealed diffuse skeletal metastases and extensive left axillary lymphadenopathy (LADP) extending into the pectoralis minor muscle and the thoracic outlet. After this workup, the patient was staged as Stage IV Invasive Lobular Carcinoma of the left breast cT3N3M1, grade 2. The patient has an indeterminate right middle lobe pulmonary nodule, which was slightly fluorodeoxyglucose (FDG) avid. Genetic testing by the Invitae Panel was done on 5/7/19 and was negative for any deleterious mutations. At that time patient was treated with a combination of CDK4/6 inhibitor palbociclib and aromatase inhibitor (AI) letrozole. Zoledronic acid was also initiated as bone targeting treatment. The patient tolerated treatment with the support of growth factors for low counts and palbociclib dose reduction to 100 mg from May 2019. She tolerated further treatments without any major side effects. PET/CT scan in August 2019 showed significant positive interval response with resolution of hypermetabolic thoracic outlet and left axillary LADP, as well as decreasing left breast activity and decreasing FDG avidity of several osseous lesions. Scan in January 1/31/20 was reported as no evidence of disease (NED).

However, on a follow-up visit in February 2020, the patient complained that her left breast was feeling “heavier”. She denied pain and struggled to describe the change. On physical exam, the patient had an erythematous rash involving
the medial half of the breast. The breast was not tender, and there were no palpable masses. Biopsy of the involved skin was done, and pathology confirmed lobular carcinoma with no changes in receptor status. A repeated PET/CT scan in March 2020 showed increased left anterior breast skin thickening, a mildly increased uptake within the left axillary lymph nodes, and an increased overall number and extent of osseous metastases. The patient also had several small skin lesions on the neck and chest. Biopsy of the left neck lesion confirmed metastatic lobular carcinoma with the same characteristics as previously reported. The patient continued on palbociclib, while the treatment with letrozole was changed to the ER antagonist, fulvestrant. She enjoyed a clinical response from April to August 2020. However, on her office follow-up in August, the left breast was again increasingly erythematous and swollen. The erythema involved about three-quarters of the breast, and PET/CT scan confirmed increasing osseous metastatic burden.

Genomic Analysis
To determine whether the patient was a candidate for the use of targeted therapy based on her tumor genomics, tissue from her neck skin biopsy was sent for Foundation One CDx (F1CDx) solid biopsy CGP and evaluation of PD-L1 receptor. F1CDx is a hybrid-capture-based CGP assay that baits exonic regions of 324 genes and selects intronic regions for rearrangements (FMI 2021). The test can detect gene alterations (GA) in the form of short variants (SV), rearrangements (RE), and copy number alterations (CNA), including amplifications / homozygous deletions. The patient's CGP results showed detection of a previously characterized and predicted activating AKT1 E17K mutation. We characterize this gene variant and attempt to assign its clinical significance below.

AKT1 is an intracellular serine/threonine kinase that can phosphorylate and activate the serine/threonine kinase mTORi (1). Upon activation, the mTORi complex can stimulate cell proliferation and growth through a variety of oncogenic mechanisms. AKT1 is situated downstream of PI3K and upstream of mTORi in the PI3K-mTOR signaling pathway, which suggests inhibition of AKT1 or downstream signaling components could be an effective treatment in AKT1 altered cancers. It is important to note that the AKT1 kinase phosphorylates other proteins, which may have inhibitory effects on cell growth. This diverse biology suggests that AKT1 influences several mechanisms spanning both oncogenic and anti-oncogenic effects (2-5).

AKT1 E17K variant has been extensively characterized preclinically in a variety of cancer cell types and model systems (6-11). AKT1 E17K is a hotspot mutation occurring at the N-terminal of the AKT1 protein (1, 12). In breast cancer cell line models, ectopic expression of AKT1 E17K leads to increased phosphorylation of AKT1 target genes, inhibition of apoptosis, increased colony formation, and increased tumor growth in mouse xenograft models (6, 7). Furthermore, AKT1 E17K mutant breast cancer preclinical models demonstrate sensitivity to inhibition of the mTORi pathway using several targeted therapy agents.

AKT1 mutations occur in 4% of breast cancer patients, and AKT1 E17K mutations account for ~80% of those AKT1 mutations (COSMIC database 2021). AKT1 is still in an early stage clinical development as a biomarker for mTOR pathway targeted therapy, but clinical trials are underway (13-17). Interestingly, oncogenic properties that AKT1 E17K cancer cells displayed in a preclinical setting have been recapitulated in a clinical setting. The mTOR pathway activity that has been demonstrated in preclinical AKT1 E17K mutant breast cancer models has also been shown in breast cancer patient samples through pharmacodynamic analysis (i.e., mTORC1 activation and target gene activation). Clinical study also suggests that AKT1 E17K breast cancer patients may spend longer time on mTORi therapy (i.e., everolimus) than AKT1 wild- type (WT) patients (16), and early phase clinical data suggests that AKT1 E17K mutant ER+ breast cancer patients may benefit from AKT inhibitors such as capivasertib (15, 17).
Collectively, these data indicate that inhibition of mTOR pathway components may be a treatment option for AKTI E17K mutant breast cancer patients.

**Application of Precision Medicine Tools**

This report was discussed at our Molecular Tumor Board (MTB) joint activity between Sparrow Herbert-Herman Cancer Center and Foundation Medicine Inc. (FMI) (18). As an educational program, the goal of an FMI MTB program is to discuss the targetability of genomic alterations that are identified by FMI CGP. The focus of discussion during the MTB was whether mTORi pathway inhibition is a viable treatment option for AKTI E17K altered breast cancer patients. As noted earlier, the available clinical data for AKTI targetability is still accumulating. In lieu of clinical data within the patient’s tumor type (HR+ HER2- breast cancer), extrapolated data was discussed. However, this is not always appropriate or useful to ascertain treatment options for the MTB patient. One tool available to FMI cancer researchers is the Flatiron Health-Foundation Medicine (FH-FMI) Clinicogenic Database (CGDB). Retrospective longitudinal clinical data were derived from electronic health record (EHR) data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI comprehensive genomic profiling (CGP) tests in the FH-FMI CGDB by de-identified, deterministic matching (19-22).

To better understand how the present patient may respond to mTORi treatment, a real-world data cohort consisting of HR+/HER2- breast cancer patients with AKTI E17K alteration were analyzed for treatment use by a line of therapy from the CGDB. Clinical characteristics and treatment history were obtained via technology-enabled abstraction of clinician notes and radiology/pathology reports for 3155 HR+/HER2- BC patients. AKTI E17K mutations were found in 143 patients while 2964 patients had AKTI WT. Thirty-one AKTI E17K and 627 of AKTI WT patients received mTORi (Figure 2).

![Figure 2. CGDB Cohort of HR+/HER2- Breast Cancer Patients with AKTI E17K Mutation that Received mTORi.](image)

Time to next treatment (TTNT) was also estimated with Kaplan-Meier analysis and hazard ratios from Cox proportional hazards models. Propensity-score matching (PSM) was used to account for the characteristics that predict receiving of the treatment. The cohort of patients with AKTI E17K mutant BC receiving mTORi did not significantly differ on major demographic, clinical, and genetic characteristics from the AKTI WT cohort receiving the same treatment (Table 1). To compare TTNT on mTORi in the two cohorts, we matched the AKTI E17K patients to AKTI WT patients on age, tumor type, ECOG, TMB, and mTORi line using PSM. The TTNT on mTORi of AKTI E17K vs. AKTI WT patients was 6.5 months (95% CI 4.6 – n/a) and 8.7 months (95%CI 6.4 – na), respectively. The relative efficacy of receiving mTORi was not significantly higher in AKTI E17K group (HR=1.2 [95%CI: 0.6 – 2.3], P=0.6). The only characteristic by which the AKTI E17K cohorts receiving chemo vs. mTORi were different was the line of treatment (Table 2). A noticeably higher percentage of patients received chemotherapy in earlier lines (79.7% in lines 1-2), while mTORi was chosen in later lines of treatment (77.4% in lines 3+). To compare TTNT on mTORi vs. on chemotherapy in these cohorts, we matched the patients who received chemotherapy to the patients who received mTORi on age, tumor
Table 1. Demographic Information for HR+ HER2- Breast Cancer Patients with or without AKT1 E17K Mutation that Received mTORi from the CGDB

| Demographics          | AKT1 E17K (N=31) | AKT1 WT (N=767) | P-value | P adjusted (FDR) |
|-----------------------|------------------|-----------------|---------|-----------------|
| Age at Dx, yrs, Median (IQR) | 52.0 (46.0, 58.0) | 54.0 (46.0, 62.0) | 0.315 | 0.999          |
| Female                | 31 (100.0%)      | 760 (99.1%)     | 0.593 | 0.999          |
| Race                  |                  |                 | 0.808 | 0.999          |
| Asian                 | 1 (3.2%)         | 14 (1.8%)       | -     | -              |
| Black or African-American | 1 (3.2%)       | 45 (5.9%)       | -     | -              |
| Hispanic or Latino    | 0 (0.0%)         | 2 (0.3%)        | -     | -              |
| White                 | 25 (80.6%)       | 541 (70.5%)     | -     | -              |
| Other Race            | 3 (9.7%)         | 134 (17.5%)     | -     | -              |
| Not documented        | 1 (3.2%)         | 31 (4.0%)       | -     | -              |
| Stage at Dx           |                  |                 | 0.11   | 0.999          |
| I-II                  | 18 (58.1%)       | 305 (39.8%)     | -     | -              |
| III-IV                | 12 (38.7%)       | 399 (52.0%)     | -     | -              |
| Not documented        | 1 (3.2%)         | 63 (8.2%)       | -     | -              |
| Tumor Grade           |                  |                 | 0.874 | 0.999          |
| Grade 1               | 1 (3.2%)         | 40 (5.2%)       | -     | -              |
| Grade 2               | 10 (32.3%)       | 205 (26.7%)     | -     | -              |
| Grade 3               | 8 (25.8%)        | 193 (25.2%)     | -     | -              |
| Not documented        | 12 (38.7%)       | 329 (42.9%)     | -     | -              |
| Tumor Type            |                  |                 | 0.954 | 0.999          |
| IDC                   | 10 (32.3%)       | 255 (33.2%)     | -     | -              |
| ILC                   | 2 (6.5%)         | 59 (7.7%)       | -     | -              |
| Other                 | 19 (61.3%)       | 453 (59.1%)     | -     | -              |
| Community practice    | 28 (90.3%)       | 708 (92.3%)     | 0.686 | 0.999          |
| MFI, yrs, Median (IQR) | 3.7 (0.2, 7.4)   | 3.0 (0.0, 7.25) | 0.656 | 0.999          |
| Solid biopsy          | 27 (87.1%)       | 668 (87.1%)     | 0.999 | 0.999          |
| Metastases sites      |                  |                 | 0.876 | 0.999          |
| Bone-only             | 3 (9.7%)         | 62 (8.1%)       | -     | -              |
| CNS                   | 8 (25.8%)        | 177 (23.1%)     | -     | -              |
| Visceral              | 20 (64.5%)       | 527 (68.8%)     | -     | -              |
| ECOG                  |                  |                 | 0.0353 | 0.635            |
| 1                     | 7 (31.8%)        | 230 (47.3%)     | -     | -              |
| 2                     | 2 (9.1%)         | 53 (10.9%)      | -     | -              |
| 3                     | 2 (9.1%)         | 7 (1.4%)        | -     | -              |
| PD-L1 status          |                  |                 | 0.388 | 0.999          |
| Negative              | 2 (6.5%)         | 86 (11.2%)      | -     | -              |
| Positive              | 0 (0.0%)         | 26 (3.4%)       | -     | -              |
| Not documented        | 29 (93.5%)       | 655 (85.4%)     | -     | -              |
| TMB (RUCI), muts/mB, Median (IQR) | 2.6 (1.3, 4.5) | 2.6 (1.3, 5.2) | 0.541 | 0.999          |
| MSI (RAW)             |                  |                 | 0.933 | 0.999          |
| MSI-H                 | 0 (0.0%)         | 2 (0.3%)        | -     | -              |
| MSI-I                 | 0 (0.0%)         | 4 (0.5%)        | -     | -              |
| MSS                   | 21 (67.7%)       | 543 (70.8%)     | -     | -              |
| Not documented        | 10 (32.3%)       | 218 (28.4%)     | -     | -              |
| mTORi                 |                  |                 | 0.727 | 0.999          |
| Everolimus            | 31 (100.0%)      | 764 (99.6%)     | -     | -              |
| Temsirolimus          | 0 (0.0%)         | 3 (0.4%)        | -     | -              |
| Start Date, Median (Range) | 2017-09-18 (2013-03-01 - 2020-06-09) | 2017-08-22 (2011-12-29 - 2020-09-23) | 0.84 | 0.999          |
| mTORi line            |                  |                 | 0.31  | 0.999          |
| 1-2                   | 7 (22.6%)        | 239 (31.2%)     | -     | -              |
| 3+                    | 24 (77.4%)       | 528 (68.8%)     | -     | -              |
| Deceased              | 22 (71.0%)       | 492 (64.1%)     | 0.437 | 0.999          |

MFI=Metastasis-free interval.
Table 2. Demographic Information for HR+ HER2- Breast Cancer Patients with AKT1 E17K Mutation that Received mTORi vs. Chemotherapy from the CGDB

| Demographics                      | Chemotherapy (N=74) | mTORi (N=31) | P-value | P adjusted (FDR) |
|-----------------------------------|---------------------|--------------|---------|------------------|
| Age at Dx, yrs, Median (IQR)      | 55.0 (46.0; 62.0)   | 52.0 (46.0; 58.0) | 0.366   | 0.93             |
| Female                            | 74 (100.0%)         | 31 (100.0%)  | 0.932   | 0.932            |
| Race                              |                     |              | 0.932   | 0.932            |
| Asian                             | 2 (2.7%)            | 1 (3.2%)     | -       | -                |
| Black or African American         | 2 (2.7%)            | 1 (3.2%)     | -       | -                |
| White                             | 55 (74.3%)          | 25 (80.6%)   | -       | -                |
| Other race                        | 12 (16.2%)          | 3 (9.7%)     | -       | -                |
| Not documented                    | 3 (4.1%)            | 1 (3.2%)     | -       | -                |
| Stage at Dx                       |                     |              | 0.678   | 0.93             |
| I-II                              | 36 (48.6%)          | 18 (58.1%)   | -       | -                |
| III-IV                            | 35 (47.3%)          | 12 (38.7%)   | -       | -                |
| Not documented                    | 3 (4.1%)            | 1 (3.2%)     | -       | -                |
| Tumor Grade                       |                     |              | 0.652   | 0.93             |
| Grade 1                           | 5 (6.8%)            | 1 (3.2%)     | -       | -                |
| Grade 2                           | 30 (40.5%)          | 10 (32.3%)   | -       | -                |
| Grade 3                           | 18 (24.3%)          | 8 (25.8%)    | -       | -                |
| Not documented                    | 21 (28.4%)          | 12 (38.7%)   | -       | -                |
| Tumor Type                        |                     |              | 0.672   | 0.93             |
| IDC                               | 19 (25.7%)          | 10 (32.3%)   | -       | -                |
| ILC                               | 8 (10.8%)           | 2 (6.5%)     | -       | -                |
| Other                             | 47 (63.5%)          | 19 (61.3%)   | -       | -                |
| Community practice                | 68 (91.9%)          | 28 (90.3%)   | 0.793   | 0.932            |
| MFI, yrs, Median (IQR)            | 2.9 (1.3, 7.1)      | 3.7 (0.2, 7.4) | 0.534   | 0.93             |
| Solid biopsy                      | 65 (87.8%)          | 27 (87.1%)   | 0.916   | 0.932            |
| Metastases sites                  |                     |              | 0.343   | 0.93             |
| Bone-only                         | 5 (6.8%)            | 3 (9.7%)     | -       | -                |
| CNS                               | 11 (15.1%)          | 8 (25.8%)    | -       | -                |
| Visceral                          | 57 (78.1%)          | 20 (64.5%)   | -       | -                |
| ECOG                              |                     |              | 0.711   | 0.93             |
| 0                                 | 21 (40.4%)          | 11 (50.0%)   | -       | -                |
| 1                                 | 24 (46.2%)          | 7 (31.8%)    | -       | -                |
| 2                                 | 3 (5.8%)            | 2 (9.1%)     | -       | -                |
| 3                                 | 4 (7.7%)            | 2 (9.1%)     | -       | -                |
| PD-L1 status                      |                     |              | 0.277   | 0.93             |
| Negative                          | 7 (9.5%)            | 2 (6.5%)     | -       | -                |
| Positive                          | 5 (6.8%)            | 0 (0.0%)     | -       | -                |
| Not documented                    | 62 (83.8%)          | 29 (93.5%)   | -       | -                |
| TMB (RU), muts/mB, Median (IQR)   | 2.5 (1.3, 6.1)      | 2.6 (1.3, 4.5) | 0.86    | 0.932            |
| MSI (RAW)                         |                     |              | 0.491   | 0.93             |
| MS5                               | 55 (74.3%)          | 21 (67.7%)   | -       | -                |
| Not documented                    | 19 (25.7%)          | 10 (32.3%)   | -       | -                |
| Start Date, Median (Range)        | 2018-01-21 (2012-02-14 - 2020-09-24) | 2017-09-18 (2013-03-01 - 2020-6-09) | 0.429 | 0.93             |
| Treatment Line                    |                     |              | 3.23e-08 | 0               |
| 1-2                               | 59 (79.7%)          | 7 (22.6%)    | -       | -                |
| 3+                                | 15 (20.3%)          | 24 (77.4%)   | -       | -                |
| Deceased                          | 47 (63.5%)          | 22 (71.0%)   | 0.463   | 0.93             |

*Denotes a statistically significant difference.
type, ECOG, TMB, and treatment line using PSM. The TTNT on mTORi vs. chemotherapy was 6.5 months (95% CI 4.6 – n/a) and 5.8 months (95% CI 4.6 – na), respectively. The relative efficacy of receiving mTORi was not significantly higher than receiving chemo (HR=0.8 [95% CI: 0.4 – 1.5], P=0.5).

After multidisciplinary discussion, the consensus recommendation was to start treatment with the combination of mTORi, everolimus, and AI, exemestane. Treatment was initiated on 8/28/20, and the everolimus dose was decreased from 10 mg to 7.5 mg daily due to the episode of neutropenia after the first cycle. Otherwise, the patient tolerated treatment without major side effects. By the second clinical visit in October 2020, the patient's breast was less erythematous, and the density of the tissue was lessening. There was no tenderness on palpation. PET/CT showed diminished left axillary uptake, decreased right paratracheal lymph node PET avidity, and stable bone disease consistent with a partial response. The most recent office visit in January 2021, breast exam revealed a normal-appearing skin with only faint erythema. All other skin lesions have resolved. The patient feels well and reports no pain.

Discussion

Roughly 10% of all breast cancers are invasive lobular carcinomas (23, 24). Invasive lobular carcinoma is strongly associated with exposure to female hormones, and its incidence is more subject to variation. It is more strongly associated with early menarche, late menopause, and late age of first birth. Of high-penetrance genes, BRCA1 and TP53 are predominantly associated with invasive ductal carcinoma (IDC), BRCA2 mutations are associated with both IDC and invasive lobular cancer (ILC), while mutations in CDH1 (encoding E-cadherin protein) are exclusively associated with ILC (25). It is characterized by functional loss of E-cadherin, resulting in cellular adhesion defect. Besides E-cadherin loss, Ciriello et al. identified mutations targeting PTEN, TBX3, and FOXA1 as ILC enriching features (26). PTEN loss is associated with increased AKT phosphorylation, which was highest in ILC among all breast cancer subtypes. Spatially clustered FOXA1 mutations correlated with increased FOXA1 expression and activity. Conversely, GATA3 mutations and high expression characterized Luminal A IDC, suggesting differential modulation of the ER activity in ILC and IDC. The proliferation and immune-related signatures determined three ILC transcriptional subtypes associated with survival differences. Mixed IDC/ILC cases were molecularly classified as ILC-like and IDC-like revealing no true hybrid features. This points to the heterogeneity of ILC and particularly to a distinct molecular profile of ILC vs. IDC. The case presented herein, however, seems to rather represent the Luminal B category, based on PR negative status and high Ki-67 (50%) for ILC. Generally, ILC is considered as cancer with a good short-term prognosis. Metastatic ILC spreads more commonly to the ovaries, colon, omentum, and stomach. Interestingly, a high tumor mutational burden (TMB) is associated with metastatic ILC, with 8.9% of metastatic ILC classified as TMB-high (27).

The patient presented herein was treated with standard of care targeted therapy and aromatase inhibitors with some short-term success and ultimate progression. However, CGP opened another avenue of treatment that otherwise would not be one on the mind of treating physician. In addition, basic analysis of the CGP results did not directly point to the use of mTORi. The deeper up-and-downstream analysis and discussion at our Molecular Tumor Board (MTB) uncovered those therapeutic options. An MTB also provides a unique setting for the application of RWD. During this MTB, RWD provided treatment information from patients in the CGDB that were genomically similar to the MTB patient. This, at least, at present, shows to be highly effective for this patient. When clinical literature for a biomarker is limited (such as AKT1), the CGDB can provide clinical utility through decision support. Future studies should seek to understand which controls and confounders can improve clinical decision support using RWD. Our experience with MTB showed that al-
most half of the patients (46%) presented at MTB were offered genomically matched therapy or clinical trials (18). The patient presented here is one of 22% of patients who received recommended treatment. Others did not for different reasons, including physicians and patients’ preferences, poor performance status, lack of coverage, etc. In the future, more extensive use of CGP, more wide availability of MTB’s to treating physicians, wider accessibility to clinical trials, better education of physicians and community, and collaboration with third-party payers will open more possibilities for effective treatment of patients with advanced malignant diseases.

Conclusion

AKT1 mutations occur in 4% of breast cancer patients, and AKT1 E17K mutations account for ~80% of those mutations (28). AKT1 E17K variants have been previously characterized as activating and oncogenic. The AKT1 E17K mutation is proposed to induce hyper activation of the mTOR pathway through constitutive AKT1 signaling and activation of the downstream components of the mTOR pathway (29, 30). Clinical study of mTOR pathway targeted therapy in AKT1 mutant breast cancer is still early in development. However, targeting AKT1 and downstream mTOR pathway components has shown efficacy in a limited number of AKT1 E17K mutant breast cancer patients (28, 31, 32).

There is no consensus model for the application of comprehensive genomic profiling (CGP) and real-world data (RWD) in the treatment of cancer patients. This case study provides an example for the use of RWD and CGP in the context of a multidisciplinary Molecular Tumor Board (MTB). Furthermore, the study adds to the growing body of clinical literature that suggests that AKT1 mutant breast cancer patients may be sensitive to mTOR pathway targeted therapy in the advanced setting.

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Ethical (IRB) Approval: The case report was submitted to Sparrow IRB, and they have determined that this project does not meet the definition of human subject research under the purview of IRB according to federal regulations. Verbal approval of the patient was obtained by the treating physician to publish the case report.

Conflict of Interest: All authors have signed the journal’s COI form. HT, BT, and JR have no conflict of interest in relation to this article. GS is on the Speaker’s Bureau of Foundation Medicine, SW and MJF are consultants to Foundation Medicine; OH, KS, BA, AM, LZ, MF, and KR are employees of Foundation Medicine- Roche group.

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