A case of sequential alpelisib and capivasertib in a patient with metastatic breast cancer harboring both PIK3CA and AKT mutations

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INTRODUCTION

- Somatic mutations in the *PIK3CA/AKT/mTOR* pathway are associated with resistance to endocrine therapy in hormone-receptor positive (HR+) breast cancer (BC)
- *PIK3CA* and *AKT1* mutations are reported in 35-40% and 4-7% of HR+ BC respectively, little is published about the rates of co-occurrence
- Therapies targeting mutations in this pathway approved in conjunction with endocrine therapy include alpelisib, everolimus and capivasertib.
- As Capitello-291, BYLieve, and SOLAR-1 excluded patients with prior *PIK3CA/AKT/mTOR* inhibitors, minimal data exists on how to optimally select and sequence these therapies

BACKGROUND

- **Patient:** 64-year-old female
- **History:** Prior estrogen receptor positive (ER+), human epidermal growth factor negative (HER2-) left mixed ductal and lobular carcinoma (pT2pN1a) 17 years ago, treated with lumpectomy, chemotherapy, radiation and 10 years of adjuvant endocrine therapy.
- **Current presentation:** Presented with a left-sided parasternal mass 7 years after previous cancer.
- **Workup:** PET-CT showed metastatic disease in the sternum and supraclavicular lymph nodes. Biopsy of the parasternal mass noted invasive ductal carcinoma, grade II, ER low+ (11-20%), progesterone receptor negative (PR-), HER2-. A second site biopsy was ER-, PR-, and HER2-
- Tempus tumor sequencing of this tissue sample noted both *AKT1 E17K* [variant allele fraction (VAF) 21.4%] as well as *PIK3CA E545K* mutation (VAF 8.1%)

CLINICAL COURSE

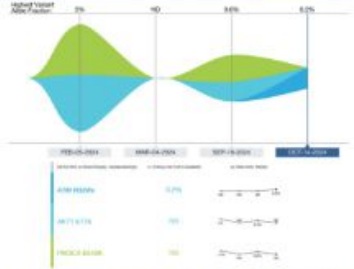

FIGURE 1: GUARDANT TESTING BEFORE AND DURING CAPIVASERTIB

- The patient progressed on several lines of therapy as above due to adverse effects and disease progression
- Guardant 360 liquid biopsy testing revealed the same prior *AKT1 E17K* and *PIK3CA E454K* alteration (Figure 1)
- Response assessment after 4 weeks noted clearing of the *AKT1* and *PIK3CA* mutations with no cfDNA detectable
- Reemergence of the *AKT* and *PIK3CA* variants occurred at 6.5 months, with subsequent clearance while on same therapy with new *ATM* mutation

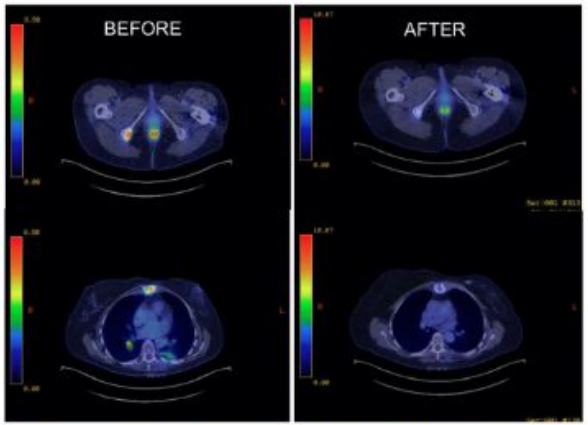

FIGURE 2: RIGHT ISCHIAL AND RIGHT HILAR METASTASIS BEFORE AND AFTER 5 MONTHS ON CAPIVASERTIB

- Follow-up PET-CTs revealed significant favorable response to treatment (Figure 2)
- At 8-month follow-up, the patient continues on this treatment

DISCUSSION

- This case highlights a response of *AKT1* targeted therapy with capivasertib in a patient who previously progressed on *PIK3CA* targeted therapy with alpelisib
- Publicly available datasets in TCGA, MSK-IMPACT, METABRIC, and AURORA note that across 7204 samples, mutation prevalence for *PIK3CA* and *AKT1* was 39% and 5%, with significant mutual exclusivity and co-occurrence observed in only 41/7204 samples (0.6%)
- Recent data notes that *AKT* emergent mutations may be a resistance mechanism to *PIK3CA* inhibition
- Comprehensive biomarker assessment may help identify patients who may benefit from sequential therapies.
- There is a need for trials comparing therapies that target the PI3K pathway at distinct points, potential sequencing of these therapies, and the optimal sequence strategy.

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