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ORIGINAL RESEARCH ARTICLE

Clinical Actionability of Molecular Targets in Multi-Ethnic Breast Cancer Patients: A Retrospective Single-Institutional Study

Irene Kang[1] · Leah Naghi[2] · Susan E. Yost[2] · Joanne Mortimer[2]

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Abstract

Background Precision oncology is making remarkable advancements in optimizing patient care by personalizing treatments. To date, the US Food and Drug Administration (FDA) has approved poly(ADP-ribose) polymerase inhibitors (PARPi) olaparib (Lynparza, AstraZeneca and Merck) and talazoparib (Talzenna, Pfizer Oncology Together™) for germline or somatic *BRCA1/2-mutated* metastatic breast cancer (BC) patients, and PI3K inhibitor alpelisib (Piqray, Novartis) plus fulvestrant for patients with hormone receptor-positive human epidermal growth factor receptor 2-negative (HR+HER2−) *PIK3CA-mutated* advanced BC. In addition, the FDA approved capivasertib (Trucap, AstraZeneca) for HR+HER2− locally advanced or metastatic BC patients with one or more *AKT1, PIK3CA, or PTEN* alterations. Finally, the FDA recently approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal patients with ER+ HER2− *ESR1-mutated* advanced or metastatic BC with disease progression following at least one line of endocrine therapy.

Methods This study presents a single institutional retrospective review of genomic reports of patients with BC. Analysis of genomic reports of 1361 BC sequencing reports was performed for 1010 patients with BC from 2013 to 2023 (23% of patients had multiple reports). Eligible patients had at least one primary or metastatic tumor. Multiple sequencing platforms were used for FFPE specimens including Tempus xT targeted next-generation sequencing (NGS), Foundation One Medicine, HopeSeq, Ashion Analytics GEM ExTra, and Exact Sciences Oncomap. Liquid biopsies were performed by Guardant, Tempus, and Foundation One Medicine. Chart reviews were performed to collect patient characteristics. *BRCA1/2*-mutated, metastatic BC patients who initiated treatment with olaparib or talazoparib, and *PIK3CA*-mutated, HR+ metastatic BC patients who initiated treatment with alpelisib were reported. In addition, patients with *ESR1 or AKT1/PIK3CA/PTEN* mutations were identified. Clinical outcomes, including progression-free survival (PFS) and overall survival (OS) were analyzed for *BRCA1/2* and *PIK3CA*-mutated patients who received PARPi or alpelisib. Survival curves were generated using the Kaplan Meier method.

Results A cohort of 1010 BC patients with 1361 genomic reports was identified. A total of 935/1361 (69%) specimens were formalin-fixed paraffin-embedded (FFPE) tumor biopsies and 426/1361 (31%) were liquid biopsies. Receptor status included 65% HR+HER2−, 8% HR+HER2+, 4% HR-HER2+, and 23% TNBC. Racial and ethnic distribution of these patients included 50% non-Hispanic White, 26% Hispanic, 17% Asian, 6% African American, 1% other (Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, or unknown). Sequencing platforms included 30% Tempus xT, 31% Foundation One, 10% HopeSeq, 20% GEM ExTra, and 9% Exact Sciences. Liquid biopsies included 79% Guardant, 20% Tempus, and 1% Foundation One. Of 1010 patients, the most common mutations were *TP53* (44%), *PIK3CA* (38%), *ESR1* (14%), *PTEN* (12%), *CCND1* (11%), *FGFR1* (10%), *CDH1* (10%), *ERBB2* (9%), *MYC* (9%), *FGF3* (8%), *GATA3* (8%), *FGF19* (8%), *FGF4* (7%), *ARID1A* (6%), *RB1* (5%), *BRCA2* (5%), *MAP3K1* (4%), *AKT1* (4%), *NF1* (4%), *MLL3* (4%), *ZNF703* (4%), *CDKN2A* (4%), *BRCA1* (4%), *MCL1* (3%), *ATM* (3%), *PALB2* (1%), and *CHEK2* (1%). The majority of reports with tumor mutation burden (TMB) results (97%) had low or intermediate TMB. A total of 784 actionable mutations in 1010 patients were reported, including 381/1010 (38%) *PIK3CA*; 144/1010 (14%) *ESR1*; 122/1010 (12%) *PTEN*; 48/1010 (5%) *BRCA2*; 36/1010 (4%) *BRCA1*; 41/1010 (4%) *AKT1*; and 12/1010 (1%) *PALB2.* Of the 96/1010 (10%) patients with *BRCA1, BRCA2, or PALB2* mutations not including variants of uncertain significance (VUS), 33/96 (34.4%) received olaparib and 3/96 (3%) received talazoparib in the metastatic setting, and 28 were eligible for response (one had toxicity, two were lost to follow-up, and two went to hospice). Median PFS was 9.0 months and median OS was 21.8 months for patients receiving PARPi. Of the 381/1010 (38%) patients with *PIK3CA* mutations, 84/381 (22%) received alpelisib and 41 were eligible

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for response (22 had toxicity, 13 were discontinued, six were lost to follow-up, and two went to hospice). Median PFS was 7.9 months and median OS was 31.2 months for patients receiving alpelisib. A total of 544/1010 (54%) patients had *AKT1, PIK3CA, or PTEN* mutations which are now FDA approved for capivasertib in HR+HER2− metastatic BC patients. In addition, 144/1010 (14%) patients had *ESR1* mutations which are FDA approved for elacestrant in HR+HER2− metastatic BC patients.

Conclusions In this study, a total of 784 clinically actionable mutations were reported for 1010 patients with genomic sequencing. Of these, 96/1010 (10%) patients had at least one actionable mutation in homologous recombination repair genes (*BRCA1, BRCA2, PALB2*) and 36/96 (37.5%) patients received PARP inhibitors (33 olaparib and three talazoparib). In addition, 381/1010 (38%) patients had at least one clinically actionable *PIK3CA* mutation, and 84/381 (22%) received alpelisib. Additionally, 544/1010 (54%) of patients had either *AKT1* (41/1010), *PIK3CA* (381/1010), or *PTEN* (122/1010) alterations that were FDA approved in November 2023 for capivasertib in the treatment of HR+HER2− metastatic BC (MBC) patients. Furthermore, 144/1010 (14%) patients in this study had at least one *ESR1* mutation, a clinically actionable mutation that was FDA approved in January 2023 for elacestrant in the treatment of ER+HER2− MBC patients (44% detected by liquid biopsy). Future studies are needed to determine the efficacy of elacestrant and capivasertib for patients with these mutations, and to tailor strategies for optimal patient quality of life and cancer outcome.

Key Points

Clinically actionable mutations in homologous recombination repair genes *BRCA1, BRCA2,* and *PALB2* were identified in 10% of patients, and 37% were treated with poly(ADP-ribose) polymerase inhibitors (PARPi) (median progression-free survival (PFS) of 9.0 months and median overall survival (OS) of 21.8 months).

PIK3CA mutations were identified in 38% of patients, and 22% were treated with alpelisib (median PFS of 7.9 months and median OS of 31.2 months).

Of note, 54% had *AKT1, PIK3CA,* or *PTEN* mutations (FDA approved for capivasertib in ER+HER2− MBC patients), and 14% had *ESR1* mutations (FDA approved for elacestrant in ER+HER2− MBC patients); however, future studies are needed to determine the efficacy of targeted therapy for patients with actionable mutations in a real-world setting.

1 Introduction

Precision oncology has the potential to provide personalized breast cancer (BC) treatment tailored to the patient's specific cancer with the goal of improving outcomes by predicting benefit or lack of benefit to treatment, risk of progression, and possible de-escalation of chemotherapy. To effectively prioritize therapies, genomic alterations are targeted based on proven actionability. However, the complex spatial and temporal heterogeneity of tumors must also be addressed. To date, the US Food and Drug Administration (FDA) has approved selective treatments for metastatic BC patients with germline or somatic *BRCA1/2* or *PALB2* mutations, as well as somatic *PIK3CA, AKT1, PTEN*, and *ESR1* mutations.

Genomic biomarker-driven FDA approvals for BC have guided oncologists in providing personalized treatment in recent years (Fig. 1). Poly(ADP-ribose) polymerase inhibitors (PARPi) are recommended for human epidermal growth factor receptor 2-negative (HER2−) patients with advanced and high-risk early-stage germline *BRCA1* and *BRCA2*-mutated BC [1, 2]. The FDA approved talazoparib (Talzenna, Pfizer Oncology Together™) and olaparib (Lynparza, AstraZeneca and Merck) for germline *BRCA-mutated* HER2− locally advanced or metastatic BC in October 2018 [3, 4]. The first alpha-selective PI3K inhibitor, alpelisib (Piqray, Novartis) combined with fulvestrant was approved for patients with hormone receptor-positive human epidermal growth factor receptor 2-negative (HR+HER2−) *PIK3CA-mutated* advanced BC in May 2019 [5, 6]. A second agent, first-in-class AKT inhibitor, capivasertib (Truqap, AstraZeneca) plus Faslodex, has recently been approved for *PIK3CA, AKT1, or PTEN-mutated* locally advanced or metastatic cancers [7]. In addition, in January 2023, elacestrant (Orserdu, Stemline Therapeutics, Inc.) was approved for treatment of postmenopausal patients with ER+ HER2− *ESR1-mutated* advanced or metastatic BC with disease progression following at least one line of endocrine therapy [8].

Precision oncology provides individually tailored treatments for patients with early-stage localized disease. MyPeBS, a randomized trial comparing risk-stratified to

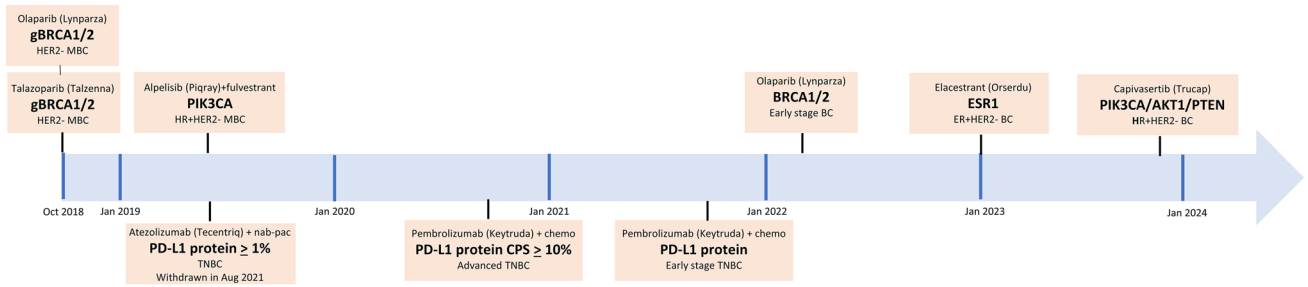

Fig. 1 Genomic biomarker-driven US Food and Drug Administration (FDA) approvals for breast cancer between October 2018 and August 2023. *BC* breast cancer, g*BRCA1/2* germline *BRCA1* or *BRCA2* gene, *HR* hormone receptor, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *PIK3CA* phosphatidylinositol-45-bisphosphate 3-kinase catalytic subunit alpha, *TNBC* triple negative breast cancer, *nab-pac* nab-paclitaxel, *chemo* chemotherapy, *ESR1* estrogen receptor 1, *PD-L1* programmed death-ligand 1, *CPS* combined positive score

standard BC screening showed that BC genomic testing led to 20% reduction in the utilization of chemotherapy [9]. Tumor genomics has the potential to identify patients who may achieve a pathological complete response (pCR) after the first therapeutic treatment without the need for additional therapy. The study by Rassy et al. [10] estimates that around 10% of all cancer patients have genomic alterations that are highly sensitive to treatment, and that focusing on patients at high risk of unfavorable progression reduces the sample size of clinical trials, accelerates the availability of drugs, and reduces development costs.

The ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) classifies alteration-drug pairs based on evidence-based criteria (level I, ready for routine use or level II, investigational). The SAFIR02-BREAST and SAFIR-PI3K trials utilized tumor genomics to individualize treatment of metastatic BC. Targetable genomic alterations were detected in tissue and/or plasma samples from 646/1288 (50%) patients with HER2− metastatic BC, and 238 patients were randomly assigned to receive targeted agents or chemotherapy at a ratio of 2:1. Those receiving genomic-directed treatment had improvement in progression-free survival (PFS) compared to those in the chemotherapy arm [11]. A similar percentage of patients in both treatment arms had ESCAT I/II alterations (48% and 49%). Of the 115 patients with ESCAT I/II genomic alterations, there were 57/115 (50%) *BRCA1/2* alterations, 3/115 (3%) *PALB2* alterations, 31/115 (27%) *PIK3CA* mutations, 16/115 (14%) *AKT1* mutations, 5/115 (4%) *PTEN* mutations and/or deletions, and 3/115 (3%) *HER2* mutations. 8/115 (7%) patients had a somatic-only *BRCA1/2* genomic alteration. PFS was the primary end point. After a median follow-up duration of at least 21.4 months, median PFS was significantly longer in patients receiving targeted therapy in the ESCAT I/II subgroup (9.1 months vs. 2.8 months with chemotherapy; hazard ratio (HR) 0.41; 95% confidence interval (CI) 0.27–0.61; $P = 0.49$). Biomarker analyses revealed PFS benefit from olaparib in patients with germline mutations in *BRCA1* (HR 0.36, 90% CI 0.14–0.89) and *BRCA*2 (HR 0.37, 90% CI 0.17–0.78). This alteration-drug pair was the most common in the ESCAT I/II subgroup (43%).

In this study, we provide evidence to support molecularly guided treatment decisions. Data from studies analyzing similar approaches are in progress. In this retrospective single institution study, we report the clinical actionability of germline and somatic molecular targets *BRCA1, BRCA2, PALB2,* and somatic *PIK3CA, AKT1, PTEN,* and *ESR1* mutations in a cohort of multiethnic BC patients with genomic sequencing results.

2 Materials and Methods

2.1 Patient Selection

This study was approved under City of Hope Institutional Review Board (IRB 15325) for a Waiver of Informed Consent (45CFR46.116(d)) and Waiver of HIPAA Authorization (45CFR164.512(i)(2)(ii)). The study includes a single-institutional retrospective review of patients with BC. Analysis of genomic sequencing reports of tumor specimens ($n = 1361$) was performed for 1010 patients with BC from December 2013 to August 2023. Eligible patients had the following: primary or metastatic BC; at least one tumor formalin-fixed paraffin-embedded (FFPE) specimen (initial surgery or biopsy), and/or at least one FFPE specimen available from relapsed disease biopsy.

2.2 Tempus^{TM} xT Targeted Next-Generation Sequencing

Tempus next-generation sequencing (NGS)-based assay tests for a panel of 648 genes, including single nucleotide variants (SNVs), indels, and translocations. The limit of

detection of the assay is 5% variant allele fraction (VAF). SNVs have 96.4% sensitivity; insertions/deletions (indels) have 92.3% sensitivity; and translocations have 99.9% sensitivity. Tempus defines "potentially actionable alterations" as protein-altering variants with an associated therapy based on clinical evidence. "Biologically relevant alterations" are protein-altering variants that may have functional significance but are not associated with a specific therapy. Variants of unknown significance (VUSs) are protein-altering variants with an unknown effect on function. Tumor mutation burden (TMB) measures the quantity of somatic mutations, including benign mutations (single nucleotide protein-altering mutations per million coding base pairs, Muts/Mb). Microsatellite instability (MSI) measures the hypermutability caused by genetic or acquired defects in the DNA mismatch repair pathway and is reported as MSI-high (MSI-H), microsatellite stable (MSS), and microsatellite equivocal (MSE).

2.3 FoundationOne® Targeted Next-Generation Sequencing

Foundation Medicine is a CLIA-certified CAP-accredited reference laboratory. FoundationOne® identifies base substitutions, insertions, and deletions (indels), amplifications with copy number ≥ 6, and rearrangements, including the coding regions of 395 cancer-related genes and 31 introns of genes that are altered in cancer. The median sequencing depth was greater than 500X [12, 13], and specimens were sequenced on Illumina HiSeq instruments [12]. Base substitutions and indels (short insertions and deletions) were detected based on sequence quality scores and local sequence assembly. Variations were filtered using dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and a custom artifact database generated [14]. COSMIC was used to annotate for known and likely somatic mutations [15]. Copy number alterations were detected by comparing targeted sequence with a normal control sample. Genomic rearrangements were detected by clustering chimeric reads mapped to targeted introns. TMB was defined as the number of somatic, coding, base substitution, and indel mutations per megabase of genome examined and calculated as described previously [16, 17], with ≤ 5 mut/Mb as "TMB-low", ≥ 6–15 as "TMB-intermediate", and 16+ mut/Mb as "TMB- high") [18, 19].

2.4 COH HopeSeq Targeted Next-Generation Sequencing

NGS-based assay includes all genes known to be somatically altered in human solid tumors for which either approved therapy or clinical trials are currently available or have diagnostic and prognostic significance. These include hotspot mutations of 89 genes, entire coding regions of 48 genes, fusion analysis of 51 genes, and copy number analysis of 47 genes. The lower limit of detection for sequence variation is 5% allelic frequency. TMB analysis is scored as "High" for Muts/Mb > 22 and "Low" for Muts/Mb < 4 with minimum criteria (> 75% targeted regions with at least 1000× coverage). MSI analysis is high if instability is observed for two or more markers, low if only one marker, and stable if no instability is observed.

2.5 Ashion's GEM ExTra® Whole-Exome Sequencing

Whole-exome sequencing (WES)-based assay detects SNVs, indels, copy number events, and fusions for 19,396 genes and 169 introns. The key difference between current NGS techniques is the targeted enrichment step where gene panels focus on a limited number of genes; WES is focused on protein coding regions (~ 1−2% of the genome) and whole genome sequencing does not require targeted enrichment. TMB-High is ≥ 20 mut/Mb, TMB-Intermediate is 6–19 mut/Mb inclusive, and TMB-Low is < 5 mut/Mb. MSI is calculated by scanning certain indels indicative of microsatellite instability with > 5 the sample is MSI-High. Otherwise, sample is MSI-Stable. Mean target coverage is 440× unique reads.

2.6 Exact Sciences OncoExTra™ Whole-Exome Sequencing

In February 2021 Exact Sciences Corp. acquired Ashion Analytics, LLC (Ashion) from The Translational Genomics Research Institute (TGen), an affiliate of City of Hope. Ashion is a CLIA-certified and CAP-accredited sequencing lab based in Phoenix, Arizona. OncoExTra WES-based assay detects SNVs, indels, copy number events, and fusions for 19,396 genes and 169 introns.

2.7 Germline Versus Somatic Mutation

Patients with *BRCA1, BRCA2,* or *PALB2* mutations were confirmed as germline by genetic testing, or if germline testing was not available, by genomic sequencing of the tumor. In this retrospective study, there were 15 patients with unknown germline *BRCA1/2* or *PALB2* results. Of those, we reported nine with VAF < 50% as possible somatic, two with VAF > 50% as possible germline, and four with unknown VAF. Although recent studies suggest that somatic testing with VAF 40–60% may indicate germline carrier status, this is not a replacement for germline testing [20].

2.8 Histological Assessments and Clinicopathological Analysis

ER, PR, and HER2 status were determined using standard ASCO/CAP guidelines. Chart review was performed to

collect patient characteristics including age, gender, race/ethnicity, date of birth, and date of death (if applicable). Tumor characteristics such as histology type, grade, lymph node and treatment variables including chemotherapy were also obtained by chart review. Clinical outcomes, including PFS and OS, were also reported. PFS was defined as date of first dose to disease progression or death from any cause, and OS was defined as the date of surgery to date of death or last follow-up.

2.9 Treatment

We identified patients with *BRCA1/2* or *PALB2*-mutated, metastatic BC who initiated treatment with olaparib or talazoparib. We also identified patients with *PIK3CA*-mutated, HR+ metastatic BC who initiated treatment with alpelisib. Patients who dissented to use of their medical data in research were excluded. In addition, *AKT1/PIK3CA/PTEN* and *ESR1* mutations were also identified.

2.10 Survival Analyses

PFS and OS curves were generated using the Kaplan Meier method. For patients with *BRCA1, BRCA2,* or *PALB2* mutations, only patients who received olaparib ($N = 25$) or talazoparib ($N = 3$) in the metastatic setting were included in the survival analysis. Patients with early-stage disease who received PARPi in the adjuvant setting were not included. In addition, five PARPi-treated patients were not included due to toxicity ($n = 1$), lost to follow-up ($n = 2$), or hospice ($n = 2$). For patients with *PIK3CA, AKT1,* and *PTEN* mutations receiving alpelisib ($n = 84$), 41 patients were eligible for response analysis, and 43 were not included due to toxicity ($n = 22$), discontinued treatment ($n = 13$), lost to follow-up ($n = 6$), or hospice ($n = 2$). Chart review was performed to identify date of starting treatment and date of progression. If exact dates were not available in physician's notes, the date prescribed (medStart) or discontinued (medEnd) in Epic was used. For patients who started or stopped treatment early/mid/late-month, dates were adjusted accordingly (1/15/30). One patient switched from olaparib to talazoparib when tumor marker doubled; however, no imaging was done, and patient progressed within one month of talazoparib (date of switch was used as date of progression on olaparib).

3 Results

3.1 Summary of Clinical Characteristics

The cohort in this study consisted of patients with physician-ordered genomic reports. A total of 1010 BC patients and 1361 genomic reports were identified. Receptor status included 659 (65%) HR+HER2−, 76 (8%) HR+HER2+, 36 (4%) HR-HER2+, and 239 (23%) TNBC. The median age (range) of patients was 58 years (22–93 years). Out of 1010 patients, 509 (50%) were non-Hispanic White, 261 (26%) were Hispanic, 169 (17%) were Asian, 64 (6%) were African American, and 7 (1%) identified as "other" including Hawaiian or Pacific Islander ($n = 4$), American Indian or Alaska Native ($n = 2$), and unknown ($n = 1$). The majority, 930 (92%), had invasive ductal cancer (IDC), 76 (7.5%) invasive lobular cancer (ILC), and four (0.5%) other (one metaplastic, two inflammatory, and one pleomorphic lobular inflammatory). Most patients were ≥ stage II at initial diagnosis, including 299 (30%) stage II, 186 (18%) stage III, and 324 (32%) stage IV. The total cohort included 201 (20%) stage 0/1 patients at initial diagnosis (Table 1). Distribution of

Table 1 Baseline characteristics of breast cancer patients with genomic reports between December 2013 and August 2023 ($N = 1010$)

Characteristic	*N* (%)
Median age (range)[1]	58 (22–93)
Gender	
Female	1002 (99%)
Male	8 (1%)
Race/Ethnicity	
Non-Hispanic White	509 (50%)
Hispanic	261 (26%)
Asian	169 (17%)
African American	64 (6%)
Other[2]	7 (1%)
Histology at initial diagnosis	
IDC	930 (92%)
ILC	76 (7.5%)
Other[3]	4 (0.5%)
Tumor stage at initial diagnosis	
Stage 0	8 (1%)
Stage I	193 (19%)
Stage II	299 (30%)
Stage III	186 (18%)
Stage IV	324 (32%)
Receptor status	
HR+HER2−	659 (65%)
HR+HER2+	76 (8%)
HR-HER2+	36 (4%)
TNBC	239 (23%)

n (%) cohort consists of patients with genomic reports, not total number of BC patients seen at City of Hope

[1]Median (range)

[2]Other: Hawaiian or Pacific Islander ($n = 4$), American Indian or Alaska Native ($n = 2$), unknown ($n = 1$)

[3]Other: metaplastic ($n = 1$), inflammatory ($n = 2$), pleomorphic lobular inflammatory ($n = 1$)

Table 2 Total number of genomic reports between December 2013 and August 2023 ($N = 1361$)

Genomic reports ($n = 1361$)	N (%)
Total tumor genomic reports	935/1010 (69%)
Tempus	287 (31%)
FoundationOne	288 (31%)
HopeSeq	94 (10%)
GEM ExTra	184 (20%)
OncoMap	82 (8%)
Total liquid biopsy reports	426/1010 (31%)
Tempus	334 (79%)
FoundationOne tumor	86 (20%)
Guardant	6 (1%)
Number of patient with multiple reports	
1 report	780
2 reports	164
3 reports	32
4 reports	24
≥5 reports	10

disease included 367/604 (61%) visceral metastases (liver, lung, ascites, pleural effusion, and central nervous system) and 237/604 (39%) non-visceral metastases (bone, skin, and lymph node).

3.2 Genomic Landscape of Breast Cancer Subtypes

A total of 230/1010 (23%) patients had multiple reports including 10/1010 (1%) with ≥ five reports per patient. Of $n = 1361$ genomic reports, 935/1361 (69%) were FFPE from tumor biopsies and 426/1361 (31%) were liquid biopsies. Multiple sequencing platforms were used including Tempus xT targeted NGS (287/935, 31%), Foundation One Medicine (288/935, 31%), City of Hope's HopeSeq (94/935, 10%), Ashion Analytics GEM ExTra (184/935, 20%), and Exact Sciences Oncomap (82/935, 8%) (Table 2). Liquid biopsies were performed by Guardant (334/426, 79%), Tempus (86/426, 20%), and Foundation One Medicine (6/426, 1%). The genomic analysis of BC patients included targeted DNA sequencing of $n = 1361$ samples from $N = 1010$ patients (Fig. 2). Among the 1010 patients, the most common mutations were *TP53* (44%), *PIK3CA* (38%), *ESR1* (14%),

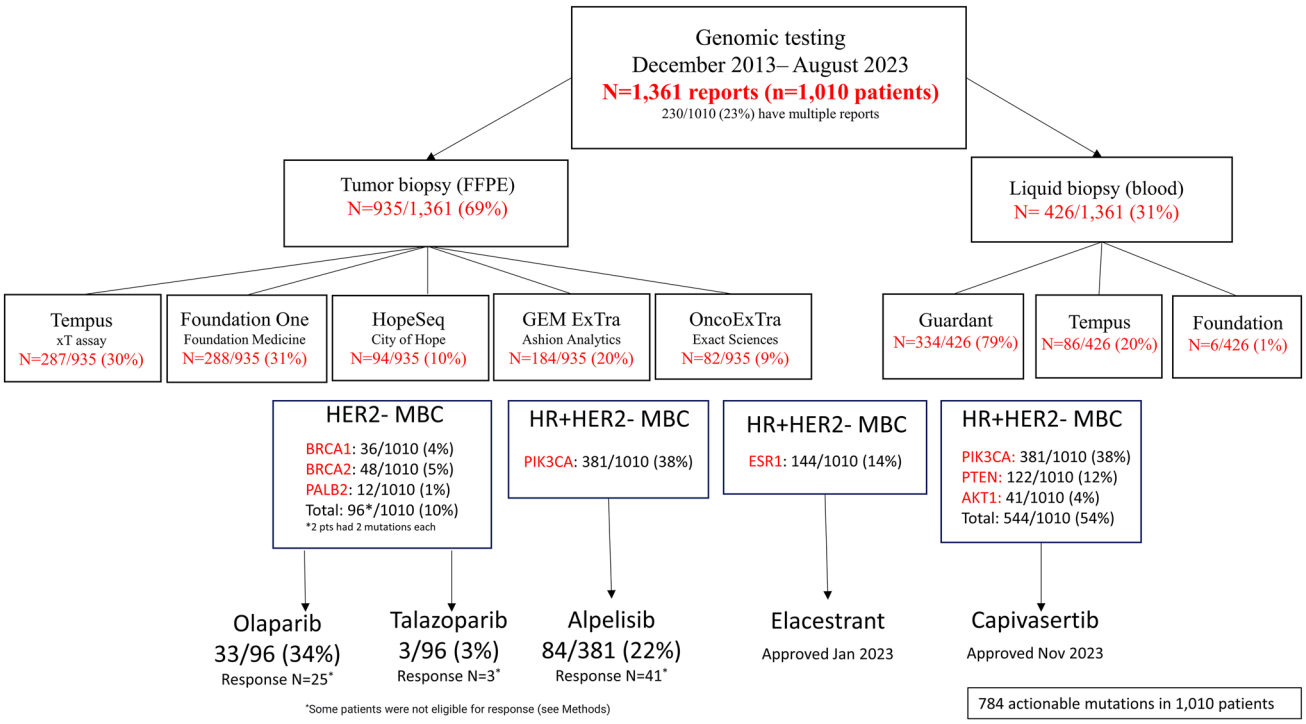

Fig. 2 Breast cancer patients at City of Hope with genomic results between December 2013 and August 2023. A total of 1361 reports from 1010 patients were abstracted into a genomic database. Initial diagnosis included 65% HR+HER2−, 8% HR+HER2+, 4% HR-HER2+, and 23% TNBC. The percentage of TNBC patients with genomic reports was higher than expected because more mTNBC tumors were sent for genomic sequencing than other subtypes during this time period. A total of 935/1361 (69%) were tumor biopsies (FFPE), including 30% Tempus xT assay, 31% FoundationOne Medicine, 10% HopeSeq (City of Hope), 20% GEM ExTra (Ashion Analytics), and 9% OncoExTra (Exact Sciences). 426/1361 (31%) were liquid biopsies, including 79% from Guardant, 20% from Tempus, and 1% from Foundation One. *FFPE* formalin-fixed paraffin-embedded, *HER2−* human epidermal growth factor receptor 2-negative, *HR+* hormone receptor positive

PTEN (12%), *CCND1* (11%), *FGFR1* (10%), *CDH1* (10%), *ERBB2* (9%), *MYC* (9%), *FGF3* (8%), *GATA3* (8%), *FGF19* (8%), *FGF4* (7%), *ARID1A* (6%), *RB1* (5%), *BRCA2* (5%), *MAP3K1* (4%), *AKT1* (4%), *NF1* (4%), *MLL3* (4%), *ZNF703* (4%), *CDKN2A* (4%), *BRCA1* (4%), *MCL1* (3%), *ATM* (3%), *PALB2* (1%), *and CHEK2* (1%) (Fig. 3A).

3.3 Tumor Mutation Burden

A total of 836/1361 (61%) genomic reports included tumor mutation burden (TMB) results with a majority (97%) having low or intermediate TMB. The results included 616/836 (74%) low TMB (< 5 m/MB), 195/836 (23%) intermediate TMB (> 5 and < 20 m/MB), 23/836 (2.8%) high TMB (> 20 and < 50 m/MB), and 2/836 (0.2%) very high TMB (> 50 m/MB) patients resulting in 97% low/intermediate TMB (Fig. 3B).

3.4 Molecular Subtypes

The overall distribution percentage of molecular subtypes was 65% HR+HER2−, 8% HR+HER2+, 4% HR-HER2+, and 23% TNBC (Fig. 3C).

3.5 Patients with Actionable Mutations

A total of 784 actionable mutations in 1010 patients including *PIK3CA*, $n = 381/1{,}010$ (38%); *ESR1*, $n = 144/1{,}010$ (14%), *PTEN*, $n = 122/1{,}010$ (12%); *BRCA2*, $n = 48/1{,}010$ (5%); *BRCA1*, $n = 36/1{,}010$ (4%); *AKT1*, $n = 41/1{,}010$ (4%); and *PALB2*, $n = 12/1{,}010$ (1%). Patients with

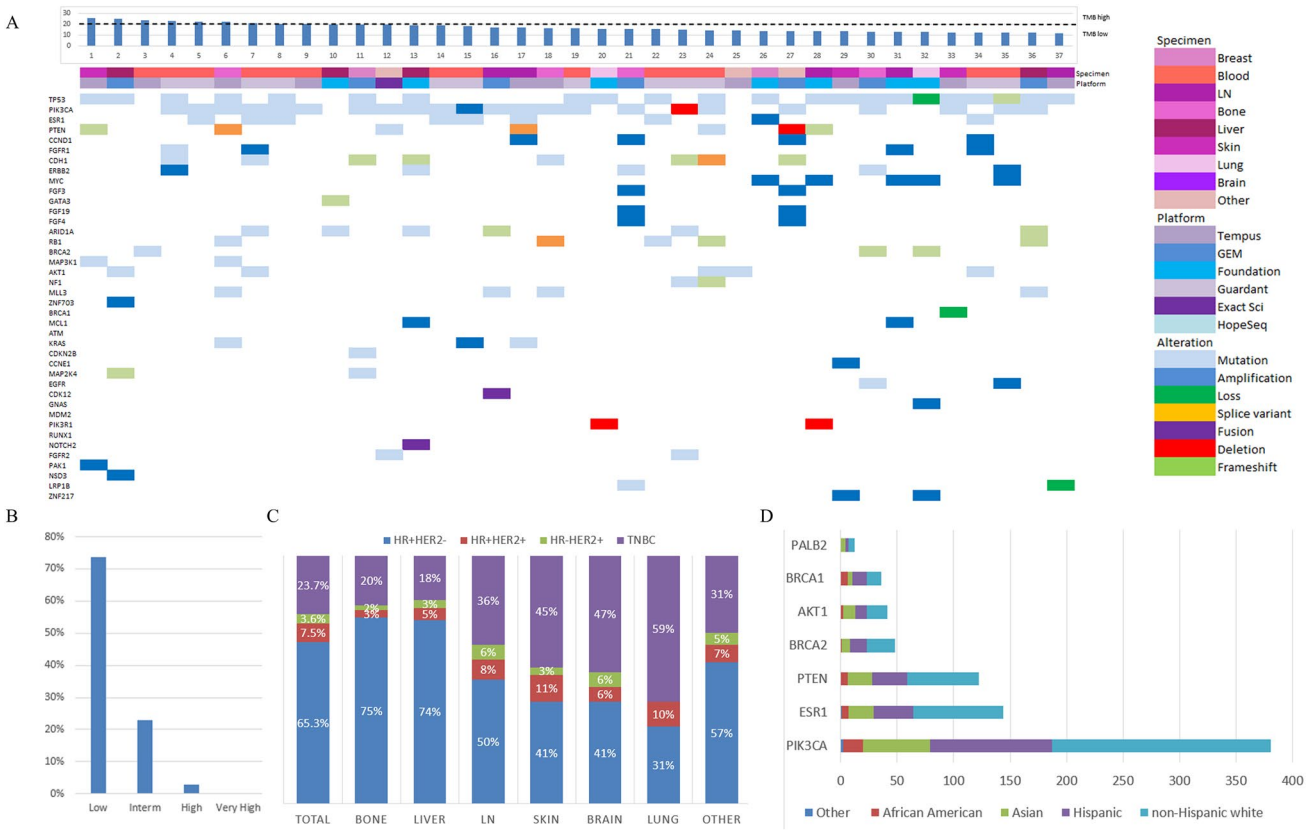

Fig. 3 Genomic landscape of breast cancer (BC) patients at City of Hope from 2013 to 2023. Targeted DNA sequencing was successfully performed for 1361 samples from 1010 patients. **A** The mutational landscape of these tumors was typical of known breast cancer (VUS not included); **B** 836/1361 (61%) had TMB results with a majority (97%) having low or intermediate tumor mutational burden (TMB); these included 616/836 (74%) low (≤ 5 m/MB), 195/836 (23%) intermediate (> 5 and ≤ 20 m/MB), 23/836 (2.8%) high (> 20 and ≤ 50 m/MB), and 2/836 (0.2%) very high (> 50 m/MB) patients. **C** Distribution percentage of molecular subtypes (HR+HER2−, HR+HER2+, HR-HER2+, and TNBC) in patients with genomic reports from bone, lung, liver, and brain metastases; **D** number of BC patients with actionable alterations stratified by ethnicity (Non-Hispanic White, Hispanic, Asian, African American, other). *TMB* tumor mutation burden, *VUS* variants of unknown significance, *m/MB* mutations per megabase, *Other* Hawaiian or Pacific Islander ($n = 4$), American Indian or Alaska Native ($n = 2$), unknown ($n = 1$), *VUS* variants of unknown significance, *TMB* tumor mutation burden, *m/MB* mutations per megabase, *HR+HER2−* hormone receptor positive HER2−, *HR+HER2+* hormone receptor positive HER2+, *HR-HER2+* hormone receptor negative HER2+, *TNBC* triple negative breast cancer, *LN* lymph node

actionable mutations were stratified by ethnicity including non-Hispanic White, Hispanic, Asian, African American, and other (Fig. 3D). A total of 94/1,010 (9%) patients with actionable mutations in homologous recombination repair genes were identified including *BRCA2*, $n = 48$; *BRCA1*, $n = 36$; and *PALB2*, $n = 12$ (two patients each had two mutations, $n = 94$ patients with 96 alterations). Of these patients, four were unknown germline/somatic mutations. Of the 90 patients with confirmed results, 58/90 (64%) were germline mutations (confirmed genetic sequencing or genomic sequencing with VAF high $\geq$ 50%) an 32/90 (36%) were acquired mutations (VAF low < 50%). 43/96 (45%) were Non-Hispanic White, 31/96 (32%) were Hispanic or Latino, 15/96 (16%) were Asian, and 7/96 (7%) were African American. *PIK3CA* mutations were identified in 381/1010 (38%) patients (194 non-Hispanic White, 108 Hispanic or Latino, 59 Asian, 18 African American, and two native Hawaiian or other Pacific Islander). In addition, of 41 patients with *AKT1* mutations, we identified 18/41 (44%) patients were non-Hispanic White, 10/41 (24%) were Hispanic or Latino, 11/41 (27%) were Asian, and 2/41 (5%) were African American. Of 122 patients with *PTEN* loss, we identified 63/122 (52%) patients were non-Hispanic White, 31/122 (25%) were Hispanic or Latino, 22/122 (18%) were Asian, 6/122 (5%) were African American. Finally, we identified 144/1010 (14%) patients with actionable mutations in *ESR1* gene, including 80/144 (56%) non-Hispanic White, 35/144 (24%) Hispanic or Latino, 22/144 (15%) Asian, 6/144 (4%) African American, and 1/144 (1%) American Indian or Alaska Native (Fig. 4).

3.6 Treatment

Out of 96/1010 (10%) *BRCA1, BRCA2,* or *PALB2* mutations, 33/96 (34%) received olaparib and 3/96 (3%) received talazoparib (Table 3). For patients receiving olaparib, 25/33 (76%) were eligible for response (one reported toxicity, two were lost to follow-up, two were early-stage adjuvant treatment, two were discontinued, and one went to hospice). All talazoparib patients were eligible for response. Median PFS was 9.0 months and median OS was 21.8 months for patients receiving PARPi. Of the patients receiving PARPi, 25/36 (69%) had HR+HER2− advanced BC and 11/36 (31%) had triple negative BC (TNBC).

Of the 381/1010 (38%) patients with *PIK3CA* mutation, 84/381 (22%) received alpelisib (Table 4). For patients

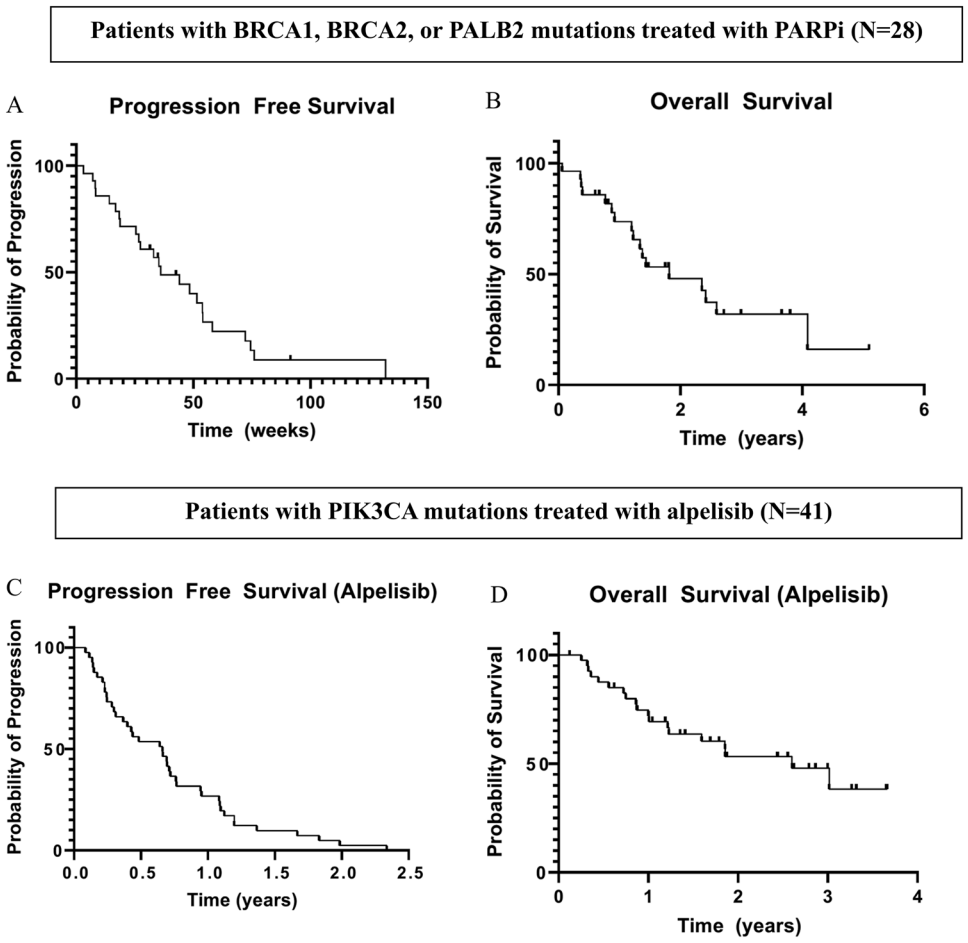

Fig. 4 Kaplan Meier survival curves were generated to investigate the relationship between biomarker-driven treatment and survival (progression-free survival (PFS) and overall survival (OS)). Actionable mutations included ESCAT I/II classified alterations based on evidence-based criteria: **A** PFS for patients with *BRCA1, BRCA2*, or *PALB2* mutations treated with PARPi ($n = 28$); **B** OS for patients with *BRCA1, BRCA2*, or *PALB2* mutations treated with PARPi ($n = 28$); **C** PFS for patients with *PIK3CA* mutations treated with alpelisib ($n = 41$); and **D** OS for patients with *PIK3CA* mutations treated with alpelisib ($n = 41$)

Table 3 Breast cancer patients with *BRCA1* (N = 36), *BRCA2* (*N* = 48), or *PALB2* mutation (*N* = 12) receiving olaparib (*N* = 33) or talazoparib (*N* = 3)

	Total	*BRCA1*	*BRCA2*	*PALB2*	Olaparib	Talazoparib
Total	96/1010 (10%)	36/1010 (4%)	48/1010 (5%)	12/1010 (1%)	33/1010 (3%)	3/1010 (0.3%)
White Non-Hispanic	43/96 (76%)	13/36 (36%)	25/48 (52%)	5/12 (42%)	15/33 (46%)	2/3 (67%)
Hispanic or Latino	31/96 (26%)	13/36 (36%)	15/48 (31%)	3/12 (25%)	10/33 (30%)	0/3 (0%)
Asian	15/96 (13%)	4/36 (11%)	7/48 (15%)	4/12 (33%)	7/33 (21%)	0/3 (0%)
African American	7/96 (7%)	6/36 (17%)	1/48 (2%)	0/12 (0%)	1/33 (3%)	1/3 (33%)
Eligible for response	NA	NA	NA	NA	25/33 (76%)	3/3 (100%)

NA not applicable

Table 4 Breast cancer patients with *PIK3CA* mutations (*N* = 381) receiving alpelisib (*N* = 84)

Mutation status	*PIK3CA*, N (%)	Alpelisib, *N* (%)
Total	381/1010 (38%)	84/381 (22%)
Non-Hispanic White	194/381 (51%)	48/84 (57%)
Hispanic	108/381 (28%)	20/84 (24%)
Asian	59/381 (15%)	10/84 (12%)
African American	18/381 (5%)	5/84 (6%)
Other*	2/381 (1%)	1/84 (1%)
Eligible for response	NA	41/84 (49%)

*American Indian or Alaska Native

Table 5 Breast cancer patients with *ESR1* mutations (*N* = 144)

Mutation status	*ESR1*, N (%)
Total	144/1010 (14%)
Non-Hispanic White	80/144 (56%)
Hispanic	35/144 (24%)
Asian	22/144 (15%)
African American	6/144 (4%)
Other*	1/144 (1%)

*American Indian or Alaska Native

receiving alpelisib, 41/84 (49%) were eligible for response (22 reported toxicity, 13 discontinued treatment, six were lost to follow-up, and two went to hospice). Median PFS was 7.9 months, and OS was 31.2 months. Of the patients receiving alpelisib, 77/84 (91%) had HR+HER2− advanced BC, 1/84 (1%) had HR-HER2+ BC, 3/84 (4%) had HR+HER2+ BC, and 3/84 (4%) had TNBC. Of the 381/1010 (38%) patients with *PIK3CA* mutation, 91% were HR+HER2− advanced BC patients who received endocrine therapy previously.

In addition, 144/1010 (14%) patients had *ESR1* mutation which is now FDA approved in ER+HER2− metastatic BC (MBC) patients for elacestrant (Table 5), and 544/1010 (54%) patients had *AKT1, PIK3CA*, or *PTEN* mutation, FDA approved in ER+HER2− MBC patients for capivasertib (Trucap) (Table 6). At the time of this study, elacestrant and capivasertib were not approved for BC patients.

4 Discussion

4.1 Poly(ADP-Ribose) Polymerase Inhibitors (PARPi) for Patients with Germline or Somatic *BRCA1*, *BRCA2*, or *PALB2* Mutations (*n* = 96)

In the OlympiAD (olaparib) trial for patients with germline *BRCA* mutation, median PFS was 7.0 months versus 4.2 months (HR 0.58; 95% CI 0.43–0.80, $p < 0.001$) for olaparib

Table 6 Breast cancer patients with *AKT1*, *PIK3CA*, or *PTEN* mutations (N = 544)

Mutation status	Total	*AKT1*, N (%)	*PIK3CA*	*PTEN*
Total	544/1010 (54%)	41/1010 (4%)	381/1010 (38%)	122/1010 (12%)
Non-Hispanic White	275/544 (51%)	18/41 (44%)	194/381 (51%)	63/122 (52%)
Hispanic	149/544 (27%)	10/41 (24%)	108/381 (28%)	31/122 (25%)
Asian	92/544 (17%)	11/41 (27%)	59/381 (15%)	22/122 (18%)
African American	26/544 (5%)	2/41 (5%)	18/381 (5%)	6/122 (5%)
Other*	2/544 (0.4%)	0/41 (0%)	2/381 (1%)	0/122 (0%)

*American Indian or Alaska Native

compared to SOC therapy [21]. Median OS was 19.3 months with olaparib versus 17.1 months with treatment of physician's choice [22].

In the EMBRACA (talazoparib) trial, talazoparib showed significant antitumor activity in patients with advanced BC and germline mutations in *BRCA1* and *BRCA2*. Median PFS of talazoparib versus standard treatment of physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine) was 8.6 months versus 5.6 months (HR 0.54; 95% CI 0.41–0.71; $p < 0.001$) [23]. Median OS 19.3 months for the talazoparib arm was not statistically different from treatment of physician's choice [24]. In our study, 36/1010 (4%) *BRCA1*, 48/1010 (5%) *BRCA2*, and 12/1010 (1%) *PALB2* mutations were identified. Of these 96 patients, 33/96 (34%) initiated treatment with olaparib and 3/96 (3%) received talazoparib. 28/36 (78%) were evaluable for response with median PFS of 9.0 months and median OS of 21.8 months. These results are similar to the previously published phase III data of both olaparib and talazoparib use for germline mutation carriers of *BRCA1* or *BRCA2*. In our study, we included patients with germline *PALB2* mutations and somatic *BRCA1* or *BRCA2* mutations based on the TBCRC 048 clinical trial (NCT02032823) with similar results. This phase II study of 54 patients demonstrated that treatment with PARPi prolonged PFS among patients with somatic *BRCA1* and *BRCA2*, or germline *PALB2*-mutated BC, but not *ATM* or *CHEK2* [25]. Including somatic *BRCA1, BRCA2,* and germline *PALB2* further expands the population of patients who are eligible and likely to benefit from PARP inhibition and further supports the use of molecular characterization of solid tumors.

In this retrospective study of 94 patients, there were 15 patients with unknown germline *BRCA1/BRCA2/PALB2* results. Of those, we reported nine with VAF < 50% as possible somatic, two with VAF > 50% as possible germline, and four with unknown VAF. Although recent studies suggest that somatic testing with VAF 40–60% may indicate germline carrier status, this should not be used as a replacement for germline testing [20], and treatment decisions should be made by the patient's healthcare professional.

4.2 Targeted Therapies in HR+HER2− Metastatic Breast Cancer (MBC)

In SOLAR-1, median PFS was 11.0 months in *PIK3CA* mutations carriers compared to 5.7 months in the placebo arm. OS data was not statistically significant. To determine if patients who previously received CDK4/6i would benefit from alpelisib, BYLieve was conducted and concluded that HR+HER2− advanced BC patient with *PIK3CA* mutation following progression on or after previous therapy including prior CDK4/6i (no more than two lines) also derived benefit with a comparable safety profile as SOLAR-1. Roswell Park Comprehensive Cancer Center reported the median duration of response was 5.8 months (range: 5.54–8.98), with 14/27 (51.9%) requiring dose interruption/reduction. Overall, 23/27 (85.19%) patients discontinued alpelisib with 11 (47.8%) due to adverse effects (AEs). Median duration of treatment was 2 months in patients who had grade 3 AEs (range: < 1.00–8.30) and 6.3 (1.15–10.43) in those who did not [26]. This study cautioned only modest benefit of alpelisib in real-world clinical practice when used in later lines of therapy. Capivasertib targets this same pathway, but only became FDA approved after this retrospective review.

4.3 Alpelisib for *PIK3CA*-Mutated MBC Patients

PFS in alpelisib-treated patients in our study was comparable to the SOLAR-1 study. 381/1010 (38%) of patients with genomic results had *PIK3CA* mutation, and 84/381 (22%) initiated treated with alpelisib. Of these, 41/84 (49%) were evaluable for response (22 toxicity, 13 discontinued, six lost to follow-up, and two hospice). Median PFS was 7.9 months and median OS was 31.2 months. Although OS benefit in the SOLAR-1 analysis was not statistically significant, there was a 7.9-month improvement in median OS when alpelisib was added to fulvestrant for patients with PIK3CA-mutated, HR+, HER2− advanced BC [27].

4.4 Elacestrant for Patients with *ESR1* Mutation

With recent FDA approval of elacestrant (Orserdu) for ER+HER2− *ESR1*-mutated BC, there is opportunity for additional focus on genomic results in this population of ER+HER2− MBC patients. The EMERALD trial (NCT03778931) demonstrated a significant improvement in PFS versus SOC therapy in a randomized phase III study in patients with ER-positive/HER2-negative advanced or metastatic BC in the second- or third-line setting with a safety profile consistent with other endocrine therapies. In our study, 144/1010 (14%) of patients with genomic results had *ESR1* mutations which can now potentially offer second- or third-line heavily pretreated ER-positive/HER2− patients a new effective option for precision medicine.

4.5 Capivasertib for Patients with *AKT1*, *PIK3CA*, or *PTEN* Mutation

With recent FDA approval of capivasertib (Trucap) for ER+HER2− MBC patients with *AKT1, PIK3CA*, or *PTEN*-mutated BC, there is increased opportunity for treatment of these patients. In our study, 544/10101 (54%) of patients had a clinically actionable *AKT1* (4%), *PIK3CA* (38%), or *PTEN* (12%) alteration.

4.6 Calling Threshold of Sequencing Platforms

Of note, patients with multiple sequencing platforms do not always report the same genomic mutations. Blood and tumor samples have identified drivers in some specimens that are not captured in subsequent reports, and not all sequencing platforms report the same depth of coverage of unique reads (Tempus 500X, Foundation 500X, HopeSeq 1000X, GEM Extra 440X, Oncomap 440X). In addition, platforms have different limits of detection of variant allele frequency (VAF) (generally 5–10%). Tempus xT uses Illumina MiSeq sequencer and reports 648 genes at 500× depth of coverage with a limit of detection of 5% VAF for single nucleotide variants (SNV) with a sensitivity of 96.6% and specificity of 99.95%; 10% VAF for indels (1–40 bp) with a sensitivity of 93.4% and specificity of 99.90%; and copy number variants (CNVs) and rearrangements with a sensitivity and specificity of 99.9%. In comparison, FoundationOne CDx uses Illumina® HiSeq 2500 or 4000 and reports 315 genes and 28 introns at a 500× depth of coverage with a limit of detection of SNVs between 5% and 10% VAF with a sensitivity of 99.3% (95% CI 98.3–99.8) and positive predictive value (PPV) > 99%; SNVs ≥ 10% VAF are reported with a sensitivity of > 99.9% (95% CI 99.6–100) and PPV > 99%; indels (1–40 bp) between 10% and 20% VAF are reported with a sensitivity of 97.3% (95% CI 90.5–99.7) and PPV > 99%; indels that are ≥ 20% VAF are reported with a sensitivity of 97.9% (95% CI 92.5–99.7) and PPV > 99%; CNVs and rearrangements are reported with different sensitivities depending on % tumor nuclei, and PPV > 99%. Thus, comparing results from different platforms must be interpreted carefully because results may differ depending on calling thresholds.

Other important considerations are inter-patient heterogeneity, patient sensitivity to therapy, in-depth molecular profiling, and implementation of molecular markers into routine clinical oncology practices which may not be sufficient to improve outcome. In the future, improvements in precision oncology will be driven by a better understanding of the dynamic system of biological mechanisms, including not only molecular markers, but also epigenetic alterations, tumor microenvironment, host biology, and earlier identification of high-risk disease. Future improvements in precision oncology to integrate biological mechanisms of cancer progression (primary driver, multiple drivers per tumor, actionability of the target, clonal or subclonal origin, coexisting genomic alterations) in each patient will be critical for improving overall outcome.

4.7 Limitations

This study is limited by small sample size, retrospective analysis, and potentially biased sampling (patients with physician-ordered genomic reports). The sample size also precludes a subset analysis for the association of specific mutations with receptor subtype. The observed longitudinal genomic discrepancies could be a limitation of multiple sequencing platforms with different calling thresholds, and targeted exome sequencing which is unable to capture variants of unknown significance (VUS), genomic changes over time, and epigenomic variations. Finally, the study does not address the complex spatial and temporal heterogeneity of tumors, or real-world clinical practice using later lines of targeted therapy.

5 Conclusion

In this study, 784 actionable mutations were reported for 1010 patients, including 38% *PIK3CA*; 14% *ESR1*; 12% *PTEN*; 5% *BRCA2*; 4% *BRCA1*; 4% *AKT1*; and 1% *PALB2*. A total of 96/1010 (10%) patients had at least one clinically actionable mutation in homologous recombination repair genes (*BRCA1, BRCA2, PALB2*) and 36/96 (37.5%) of these patients were treated with PARPi (olaparib or talazoparib) with a median PFS of 9.0 months and median OS of 21.8 months. A total of 381/1010 (38%) patients had at least one clinically actionable *PIK3CA* mutation, and 84/381 (22%) were treated with alpelisib with a median PFS of 7.9 months, and median OS of 31.2 months. In addition, 144/1010 (14%) had *ESR1* mutation (FDA approved for elacestrant in ER+HER2− MBC patients), and 544/1010 (54%) had *AKT1, PIK3CA*, or *PTEN* mutation (FDA approved for capivasertib in ER+HER2− MBC patients). Future studies are needed to determine the efficacy of targeted therapy for patients with these actionable mutation in a real-world setting.

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Declarations

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Conflicts of Interest Dr. Kang has the following disclosures: consultant for Gilead, Caris Molecular Sciences, Pfizer, and Daiichi Sankyo. Dr. Mortimer has nothing to disclose. Dr. Yost has nothing to disclose. Dr. Naghi has nothing to disclose.

Availability of Data and Material Data are available upon reasonable request.

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of City of Hope's internal review board (IRB) and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Tumor specimens were identified through a City of Hope IRB-approved retrospective protocol for patients consented to City of Hope Biorepository Protocol IRB 07047, and genomic analysis was performed under City of Hope IRB 15325.

Consent to Participate Informed consent was obtained from all participants on this study.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions Conception and design: JM, SEY. Acquisition of data: SEY, LN. Analysis and interpretation of data (e.g., statistical analyses, biostatistics, computational analyses): all authors. Writing, review, and/or revision of the manuscript: all authors. Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): SEY. Study supervision: JM; All authors read and approved the final version of the manuscript.

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Authors and Affiliations

Irene Kang[1] · Leah Naghi[2] · Susan E. Yost[2] · Joanne Mortimer[2]

✉ Irene Kang
ikang@coh.org

[1] Department of Medical Oncology, City of Hope National Medical Center, 1000 Fivepoint, Irvine, CA 92618, USA

[2] Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA, USA