

2 Incidence, Clinical and Laboratory Predictors of Adverse Events (AEs) and Outcomes in Patients (Pts) With Breast Cancer Receiving Alpelisib in the Real World: A Single Institution Experience

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Background/Aim

The aim was to identify the incidence and predictors of alpelisib (Piqray)-related AEs in clinical practice. Although clinical trials provided data on AEs of alpelisib, there is a need to study AEs in the real world due to differences in patient characteristics and alpelisib use following multiple lines of therapy.

Methods

We reviewed charts of pts with metastatic, hormone receptor (HR)-positive, HER2-negative, *PIK3CA*-mutated breast cancer who were treated with alpelisib from 2019 to 2021. Laboratory and clinical variables including comorbidities, metastasis site, prior therapy, clinical responses, time from alpelisib initiation to progression, and last follow-up were collected. Association of these factors with AEs and clinical response were evaluated using a logistic regression model. SAS statistical software,

version 9.4 (SAS Institute Inc) was used to perform statistical analysis at a significance level of 0.05.

Results

Twenty pts were included. Median age was 67 years (48-77 years); 80% of pts (16/20) had received 2 or more lines of prior treatment, 36.8% (7/19) had no comorbidities, and 95% (19/20) had more than 1 site of visceral metastases. Eighty-five percent of pts (17/20) experienced AEs; the most common were hyperglycemia (76.5%), nausea (41.2%), diarrhea (35.3%), and fatigue (29.4%). The most common grade 3 (G3) AEs leading to alpelisib interruption/dose reduction/discontinuation were hyperglycemia (60%) and skin rash (30%). No significant difference in clinical characteristics between pts who did or did not experience an AE was observed. Median duration of alpelisib treatment was 2 months (IQR, 0.6-8.5) for pts who developed AEs and 5.5 months (IQR, 1.2-10.4) for pts without AEs ($P = .5$). As expected, 88.9% of pts (8/9) who experienced grade 3 or greater AEs had a dose reduction and 80% (8/10) interrupted/discontinued the treatment, while only 22.2% (2/9) who did not have grade 3 or greater AEs had a dose reduction and only 12.5% (1/8) discontinued/interrupted the treatment ($P = .015$ for both); 44.4% of pts (8/18) achieved a partial response (PR). Pts with a PR had a lower likelihood of visceral metastases (38%) compared with those having stable/progressive disease (90%; $P = .043$). Lower median absolute lymphocyte count ($1.23 \times 10^9/L$) was associated with a higher likelihood of PR ($P = .046$).

Conclusion

In this single-institution study, we found a higher incidence of AEs than reported in prior trials with promising responses in a heavily pretreated population. This emphasizes the need for strategies to mitigate toxicities that would allow continuation of alpelisib, given the observed clinical benefit.

6 Real-world Adherence and Persistence With Palbociclib Treatment Among Insured Patients With HR+/HER2- Metastatic Breast Cancer in the United States

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Background/Significance

Palbociclib (Ibrance), the first oral cyclin-dependent kinase inhibitor, is standard care for hormone receptor-positive (HR+), HER2- advanced or metastatic breast cancer (mBC). Palbociclib adherence and persistence are necessary to achieve optimal clinical outcomes in patients treated in real-world settings.

Materials and Methods

This was a retrospective cohort study of insured adults in the Optum Research Database, an administrative health care claims database capturing about 20% of commercial

and Medicare Advantage Part D enrollees in the United States. Adults diagnosed with mBC between February 2015 and December 2019 who initiated palbociclib in the first-line (1L) setting were selected for analysis. The index date was the first fill date of palbociclib before or anytime after the mBC diagnosis. Continuous enrollment 12 or more months pre- and 1 or more months post index was required. Palbociclib treatment was evaluated over the variable follow-up period. Medication possession ratio (MPR) was calculated as palbociclib days' supply between the first and last fill divided by the total time treated. MPR of 80% or more was considered adherent. Palbociclib discontinuation was defined by the occurrence of a 60- or 90-day gap in days' supply, adjusted for inpatient stays during which time medication was assumed to be supplied by the facility. Persistence was calculated as the time to palbociclib discontinuation using Kaplan-Meier methods over variable follow-up.

Results

One thousand sixty-six patients initiated 1L palbociclib, with 811 patients receiving palbociclib with aromatase inhibitors (P+AI) and 255 patients receiving palbociclib with fulvestrant (P+F). Mean follow-up time was 17 (P+AI) and 16 months (P+F). Mean age was 67 years for P+F and 66 years for P+AI. Overall, 79.9% of patients were adherent; mean MPR was 0.88 (median, 0.94) within each group. During the variable follow-up period, 41.3% of patients receiving P+AI and 45.9% receiving P+F discontinued palbociclib. Among those who discontinued, 23.9% and 21.4% discontinued within the first 3 months, respectively. Median time to discontinuation was 19.9 months (P+AI) and 15.2 months (P+F); 59.1% receiving P+F and 68.7% receiving P+AI remained on palbociclib at 12 months post index (90-day gap).

Conclusions

This analysis suggests most patients are well adherent with 1L palbociclib and persist on therapy. Further research is needed to understand reasons for early discontinuation in real-world practice.

7TiP Randomized, Multicenter, International Phase 3 ARTEST Study to Evaluate the Efficacy and Safety of Enobosarm Versus Active Control for the Treatment of AR+, ER+, HER2- Metastatic Breast Cancer in Patients Who Previously Received an Estrogen-Blocking Agent and CDK4/6 Inhibitor

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Background/Significance

Targeting the androgen receptor (AR) may be the next important endocrine therapy for women with advanced breast cancer. AR, the most abundantly expressed steroid receptor in breast cancer, has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral, selective AR-targeting agonist that activates the AR in breast cancer. Enobosarm has an extensive clinical experience in 25 clinical trials and 1450 dosed subjects, including in 2 phase 2 studies conducted in women (158 subjects) who had AR-positive (AR+), estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer (mBC). An open-label, parallel-design, phase 2 study was conducted in women with heavily pretreated ER+, HER2- mBC who were randomized to daily oral enobosarm at a dose of 9 mg or 18 mg. The evaluable group were patients who were AR+ (> 10% AR nuclear staining). The primary end point was clinical benefit rate (CBR) at 24 weeks. The CBRs at 24 weeks were 32% with the 9-mg dose and 29% with 18 mg. Median duration of clinical benefit was not reached in the 9-mg group (range, 8.2 months to not reached) and 14.1 months for the 18-mg group (range, 11-16.5 months). A post hoc AR expression subset analysis conducted in the intent-to-treat population who had measurable disease at baseline revealed that the best overall response rate (ORR) was significantly higher in patients with 40% or greater AR nuclear staining versus

those less than 40%, at 34% and 2.7%, respectively ($P = .0003$). CBR at 24 weeks was significantly higher for those with 40% or greater AR nuclear staining versus less than 40%, at 52% and 14%, respectively ($P < .0004$). Median radiographic progression-free survival (PFS) for 40% or greater AR was 5.47 months (95% CI, 2.83-11.13) versus 2.73 months for less than 40% AR (95% CI, 2.63-2.80; $P < .001$). Overall, treatment with enobosarm was well tolerated with significantly positive effects on quality-of-life measurements.

Design and Methods

The ARTEST trial (NCT04869943) is a phase 3, multicenter, international, randomized, open-label, 2 treatment-arm efficacy and safety study. Approximately 210 subjects with AR+, ER+, HER2- mBC and with AR nuclei staining of 40% or greater are being randomized 1:1 to either enobosarm 9-mg

oral daily dose or an active comparator (either exemestane, everolimus [Afinitor], or a selective estrogen receptor modulator; physician's choice). Subjects are being treated until disease progression or an unacceptable adverse event is observed. The primary end point of the study is imaging-based progression-free survival as measured by RECIST 1.1. The secondary objectives/end points of this study include the objective response rate, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), and change in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ).

Status

The study is currently ongoing, and it is anticipated that enrollment will be completed this year.

8TiP Randomized, Multicenter, Phase 3 Study to Evaluate the Combination of Enobosarm and Abemaciclib Compared With Estrogen-Blocking Agent for the Second-Line Treatment of AR+, ER+, HER2- Metastatic Breast Cancer in Patients Who Have Previously Received Palbociclib and an Estrogen-Blocking Agent Combination Therapy

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Background/Significance

Targeting the androgen receptor (AR) may be the next important endocrine therapy for women with advanced breast cancer. AR, the most abundantly expressed steroid receptor in breast cancer, has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral selective AR-targeting agonist that activates the AR in breast cancer. Enobosarm has an extensive clinical experience in 25 clinical trials and 1450 dosed subjects including in 2 phase 2 studies conducted in women (158 subjects) who had AR+, estrogen receptor-positive (ER+), HER2-negative metastatic breast cancer (mBC). An open-label, parallel-design phase 2 study was conducted in women with heavily pretreated ER+, HER2- metastatic breast cancer who were randomized to oral daily enobosarm at a dose of 9 mg or 18 mg. The evaluable group (EE) were patients who were AR-positive (> 10% AR nuclear staining). In the EE population with measurable disease at baseline, 10 patients had received prior endocrine therapy plus a CDK4/6 inhibitor. Subsequent treatment with enobosarm in this cohort resulted in a clinical benefit rate of 50%, and the best objective response rate (ORR) was 30% (2 complete responses and 1 partial response). Of the 10 patients, 7 had AR nuclei staining of 40% or greater, which included the 3 patients who achieved partial and complete disease responses to enobosarm. None of the 3 patients in this cohort with AR nuclear staining less than 40% responded to enobosarm. Although in a small subset of the entire study, it appears that enobosarm monotherapy had activity in patients who had 40% or greater AR staining and who had progressed on standard endocrine therapy with

a CDK4/6 inhibitor. Overall, treatment with enobosarm was well tolerated with significant positive effects on quality-of-life measurements.

Design and Methods

The phase 3 ENABLAR-2 trial is a multicenter, randomized, open-label, 2 treatment-arm efficacy and safety study. Patients are being randomized to 2 treatment arms in a 1:1 fashion. If first-line therapy for mBC was a nonsteroidal aromatase inhibitor (AI) plus palbociclib (Ibrance), then the patient is randomized to either enobosarm plus abemaciclib (Verzenio) or fulvestrant. If first-line therapy for metastatic breast cancer was fulvestrant plus palbociclib, then the patient is randomized to either enobosarm plus abemaciclib or an AI (steroidal or nonsteroidal). The key objectives are

to determine the safety and efficacy of the enobosarm and abemaciclib combination versus an alternative estrogen blocking agent in the treatment of AR+, ER+, HER2-negative (AR% nuclei staining $\geq 40\%$) mBC with a primary end point of imaging progression-free survival. Secondary end points include objective response rate, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), change in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ), and change in body composition as measured by dual-energy x-ray absorptiometry (DEXA).

Status

The study is currently ongoing, and it is anticipated that enrollment will be completed this year.

9 Real-world Treatment Patterns and Clinical Outcomes in Patients Treated With Eribulin After Prior Immunotherapy (IO) or Antibody-Drug Conjugate (ADC) for Metastatic Breast Cancer

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Background

Eribulin was FDA approved in 2010 for the treatment of metastatic breast cancer (mBC) in the United States. Recently, several immunotherapy (IO) regimens and an antibody-drug conjugate (ADC) have been FDA approved for patients with triple-negative breast cancer (TNBC). This study aimed to assess the treatment patterns and clinical outcomes in patients with mBC treated with eribulin following either IO or ADC therapy in US clinical practice.

Methods

A retrospective, noninterventional patient medical chart review study was conducted. Consenting oncologists provided deidentified patient data via an electronic case report form. Adult female patients diagnosed with mBC and

who began treatment with eribulin between March 1, 2019, and September 30, 2020, following prior therapy with an IO (atezolizumab [Tecentriq]) or ADC (sacituzumab govitecan [Trodelvy]) were included. Eribulin treatment characteristics were recorded. Overall survival (OS) since eribulin initiation was assessed using Kaplan-Meier methods.

Results

This analysis included 91 eligible patients, of whom 53 received prior atezolizumab, and 38 had prior sacituzumab govitecan. Patients' median age was 63 years at eribulin treatment initiation, and 57% were Caucasian. The majority of eribulin-treated patients had TNBC (74.7%); 13.2% had hormone receptor-positive/HER2-negative disease. In the study cohort, eribulin was classified as second-line, third-line, and fourth- or later-line in 76%, 13%, and 11% of patients, respectively, in regard to line of therapy in the metastatic setting. At last follow-up, eribulin treatment was ongoing for 36.3% of patients. The median treatment duration was 5.1 months (q1, q3: 3.5-7.3) among those who had discontinued eribulin, and 12.2 months (q1, q3, 11-14) among those who were still on treatment. At last follow-up, 63.7% of patients were alive. Median was not reached for OS subsequent to initiation of eribulin. The estimated OS rates at 12 and 24 months were 77.8% (95% CI, 67.3%-85.3%) and 53.6% (95% CI, 35.1%-68.9%), respectively.

Conclusion

Among patients with mBC who initiated eribulin following an IO or ADC, more than 50% were estimated to be alive after 2 years. Eribulin may be a promising treatment option for patients for whom IO or ADC failed.

13 Assessing Intratumor Heterogeneity in Programmed Death-Ligand 1 (PD-L1) Protein Expression in Early-Stage Breast Cancer

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Background

Programmed death-ligand 1 (PD-L1) expression is required for benefit from immune checkpoint inhibitors in metastatic triple-negative breast cancer (TNBC), although in the neoadjuvant setting, patients benefited regardless of PD-L1 expression. We aimed to examine intratumor spatial heterogeneity of PD-L1 protein expression in multiple regions of primary breast cancers.

Materials and Methods

Biopsies were collected from 3 separate tumor regions of surgically resected primary tumors without prior neoadjuvant systemic therapy. E1L3N antibody was used to assess PD-L1 status. The combined positivity score (CPS) method was used for scoring (PD-L1 positive defined as CPS >10). Fleiss Multirater Kappa assessed heterogeneity of PD-L1 expression among the different samples of the

same tumor. Optimal agreement is suggested by a kappa agreement coefficient of 0.6 or more. Association between PD-L1 status and tumor-infiltrating lymphocyte (TIL) counts was assessed using Mann-Whitney test.

Results

Of the 33 included patients, 9 (27%) had TNBC, 5 (15%) had HER2-positive disease, and 19 (58%) had hormone receptor-positive, HER2-negative disease. Four of 33 patients (12%) had 1 biopsy sample showing PD-L1 positive status with additional biopsies of different regions of the tumor showing negative results. Fleiss' kappa analysis on patients with all 3 biopsies per tumor available and able to be stained for PD-L1 (29 of 33 [88%]) showed an overall agreement of -0.36 (95% CI, -0.246 to 0.174; $P = .739$) when using CPS as categorical variable (positive vs negative) and 0.410 (95% CI, 0.286-0.535; $P < .01$) when using CPS as continuous variable. PD-L1 status was associated with TIL counts, with a median TIL count of 5% for PD-L1 positive and 0% for PD-L1 negative ($P = .2949$).

Conclusions

Our study showed that in 12% of the cases, PD-L1 was found to be positive in one of the tumor areas and all remaining biopsy samples of the same tumor were found to be negative, suggesting intratumor spatial heterogeneity regarding PD-L1 expression in early-stage breast cancer. However, due to the overall low incidence of PD-L1 positivity, it seems unlikely that the benefit of immunotherapy in early-stage breast cancer would be simply explained by sampling error. Further studies are required to investigate effective predictive biomarkers of response to immunotherapy, as well as to standardize PD-L1 assessment in breast cancer.

19 Real-world Patient Characteristics, Treatment Patterns, and Clinical Outcomes Among Talazoparib-Treated Patients With HER2-Negative, Locally Advanced or Metastatic Breast Cancer and Germline BRCA Mutations

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Background

Germline *BRCA* (*gBRCA*) mutations are detected in less than 5% of unselected patients with metastatic breast cancer (mBC). Talazoparib (Talzenna) is a PARP inhibitor approved by the FDA on October 16, 2018, for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (*gBRCAm*), HER2-negative locally advanced or metastatic breast cancer (LA/mBC). The objective of this retrospective chart review study is to describe the demographic and clinical characteristics, treatment patterns, and clinical outcomes among adult patients with

gBRCAm, HER2-negative LA/mBC treated with talazoparib in the real-world setting in the United States.

Methods

A subset of physicians from the Cardinal Health Oncology Provider Extended Network abstracted data from the medical records of US adult patients with gBRCAm, HER2-negative LA/mBC who initiated talazoparib monotherapy on or after October 16, 2018. Demographic and clinical characteristics, treatment patterns, and clinical outcomes were reported using descriptive statistics. The Kaplan-Meier method was used to describe time-to-event outcomes.

Results

Eighty-four patients treated by 9 community practice physicians met eligibility criteria and were included in this study. Among eligible patients, 98% were female, median age at initiation of talazoparib was 62 years, and 71% were White. Hormone receptor-positive status was reported for 36% of patients, while triple-negative breast cancer classification was reported for 64% of patients. At the time of talazoparib initiation, all patients had stage IV disease, 30% had an ECOG performance status ≥ 2 , 19% had brain

metastases, and 96% had visceral metastases. A gBRCA1 mutation was detected among 64% of patients, while a mutation in gBRCA2 was detected among 36%. Talazoparib was given as first-line therapy for LA/mBC in 14% of patients, as second-line in 41%, and as third- or fourth-line in 45%. Patients had a median of 8.2 months duration of follow-up from initiation of talazoparib. Median time to talazoparib treatment discontinuation for any reason was 8.6 months (95% CI, 8.0-9.7). Median progression-free survival for talazoparib was 8.7 months (95% CI, 8.0-9.9). The overall tumor response rate during talazoparib treatment was 63%.

Conclusion

Findings from this study show the clinical benefits of talazoparib treatment in gBRCAm, HER2-negative LA/mBC in real-world practice in the United States. Clinical outcomes in this real-world population were consistent with those reported in the phase 3 EMBRACA randomized clinical trial (NCT01945775).

Funding: Pfizer, Inc

24 Real-world Use of Neratinib Post-Pertuzumab (P) and -Ado-Trastuzumab Emtansine (T-DM1)

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Background

Neratinib's (Nerlynx) pivotal study was performed before pertuzumab (Perjeta) and trastuzumab emtansine (Kadcyla; T-DM1) adjuvant approvals. There is interest in neratinib's treatment patterns after pertuzumab and T-DM1 use. Neat-HER was a United States virtual registry pilot of patients with early HER2-positive breast cancer (EBC) receiving neratinib as extended adjuvant therapy in clinical practice.

Methods

Eligibility included age 18 years and older and no clinical trial participation. Patients were recruited mainly through social media, patient advocacy group and the Puma patient texting program. Electronic health records (EHRs) for EBC treatment were collected 7 years pre- to 1 year post enrollment. We evaluated personal/tumor characteristics for those who did and did not receive neoadjuvant therapy and treatment received. Treatment information came from EHR via machine learning with physician review. Neratinib status and start/stop dates were abstracted from the physician narrative, and duration of neratinib treatment was the difference between the start and stop dates, inclusive of dose holds.

Results

Forty-six patients with EBC who received neratinib as extended adjuvant treatment enrolled in the registry in December 2018. The majority, 76% (n = 35), had neoadjuvant therapy with adjuvant treatment and 24% (n = 11) had only adjuvant treatment. Median age (50 vs 48 years) and race (91% White) were similar for neoadjuvant and adjuvant-only patients. Treatment settings were mostly in the South (52% overall), followed by the Midwest (22% overall). Among neoadjuvant therapy patients, 80% had hormone receptor

(ER/PR)-positive and 74% had lymph node-positive EBC. In adjuvant-only patients, 91% had hormone receptor-positive and 46% had lymph node-positive EBC. Fifty-four percent of neoadjuvant therapy (vs 82% adjuvant only patients) had high-grade EBC. The most common neoadjuvant therapy agents used were in order: taxanes, trastuzumab, pertuzumab, and platinum. For adjuvant treatment, pertuzumab use was less frequent (34% vs 64% of patients) and T-DM1 use more frequent (14% vs 0%) among neoadjuvant therapy patients vs those with only adjuvant treatment. Median duration of neratinib treatment in patients who had received neoadjuvant therapy was 12 months (mean, 11 months) with 94% of these patients completing or having ongoing treatment. In patients

who received adjuvant treatment, only 55% of patients either completed or had ongoing neratinib treatment at the time of this analysis.

Conclusions

Neat-HER provided useful information on neoadjuvant therapy/adjuvant treatment patterns in patients receiving extended adjuvant neratinib. It was the first known examination of real-world treatment patterns of neratinib post pertuzumab and T-DM1. The high proportion of neoadjuvant therapy use and long duration of neratinib suggest the select nature of these patients. Results need to be reproduced in larger patient cohorts.

32 Impact of Comorbid HIV Infection on Breast Cancer Time to Treatment and Chemotherapy Relative Dose Intensity

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Background/Significance

Patients with breast cancer (BC) living with comorbid HIV (BCLWH) have poorer survival than patients with BC without HIV. Delayed time of treatment initiation (TTI) after BC diagnosis and reduced adjuvant chemotherapy relative dose intensity (RDI) both increase BC mortality. We aim to understand whether patients with BC with and without comorbid HIV experience differences in receipt of timely and complete BC treatment, which could contribute to survival disparities.

Materials and Methods

We used diagnostic codes from 2 centers to identify a cohort of women with stage I to III BC diagnosed between January 1, 2000, and December 31, 2018, and concurrent HIV infection. Tumor registry data were then used to identify a control cohort of patients with BC without HIV, with 2 controls matched by institution, BC stage, and year of diagnosis for each patient with BC living with HIV. Our primary end point was TTI after BC diagnosis. For patients who received

neoadjuvant or adjuvant chemotherapy, we also measured RDI. We used a Cox proportional hazards model to compare TTI and a linear regression model to compare RDI.

Results

We identified 38 patients with BCLWH and matched 76 women with BC alone. They differed by race/ethnicity, relationship status, and estrogen receptor (ER) status, but had similar stage, HER2 status, and BC grade. Median TTI was 50 days (interquartile range IQR, 35-68) for patients with BCLWH and 44.5 days (IQR, 36-59.5) for control patients (HR adjusted for ER, race, and relationship status, 0.85; 95% CI, 0.58-1.56). Median chemotherapy RDI was 0.92 (IQR, 0.86-0.96) in 22 patients with BCLWH and 0.98 (IQR, 0.92-1.00) in 43 control patients (adjusted $P = .008$).

Conclusions

RDI was lower in patients with BCLWH; TTI was not significantly different. RDI differences do not entirely explain survival disparities in patient with BC living with HIV but may point to further differences in treatment quality. Future work will explore whether patients with BCLWH experience increased chemotherapy toxicity or if social determinants limit chemotherapy access.

42 Tissue and Liquid Biopsy-Based Comprehensive Genomic Profiling Reveal Mechanisms of Therapy Resistance and Rare Targetable Alterations in Breast Cancer

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Background

Pathological and genomic profiling aid in the selection of targeted treatments for patients with breast cancer. However, tumors often evolve and evade therapeutic interventions. Here we examine patients profiled with tissue and liquid biopsy, to characterize the genomic landscape and identify potential vulnerabilities in the relapsed setting.

Patients and Methods

Comprehensive genomic profiling (CGP) was carried out on 29,704 patients with breast cancer profiled with tissue biopsy, 3339 with liquid biopsy (targeting up to 70 genes), and 712 patients profiled on both platforms during routine clinical care. Additionally, CGP profiles from 1430 patients tested on the most recent liquid biopsy assay (FoundationOne Liquid CDx) targeting 324 genes were also examined.

Results

Potentially actionable driver alterations were observed in both cohorts, including *PIK3CA* (34.0% tissue biopsy vs 33.3% liquid biopsy) and *BRCA1/2* (7.1% vs 7.4%). In an analysis limited to the recent liquid biopsy assay, similar results were seen (*PIK3CA* 30.2% vs *BRCA1/2* 7.9%). Among 712 patients with paired tissue/liquid biopsies, presumably tumor-initiating truncal alterations were frequently shared. When sufficient circulating tumor DNA was present ($\geq 10\%$ tumor fraction), positive percent agreement was high, especially for *PIK3CA* (93.4%), *BRCA* (95.0%), and *TP53* (92.8%). Acquired liquid biopsy alterations were detected in a majority of patients, with the highest frequency in estrogen receptor-positive disease (60%) and in patients with longer biopsy intervals (71% for biopsies taken >3 years apart). In addition to well-characterized resistance mutations (*ESR1*, *NF1*, *RB1*, and *ERBB2*), a diversity of potentially actionable

alterations were identified in follow-up liquid biopsies, including activating mutations in *PIK3CA*, *HRAS*, *NRAS*, *KRAS*, *FGFR1/2/3*, and *BRAF*. Rare, acquired fusions included *FGFR1/2* fusions in multiple patients with estrogen receptor-positive/HER2-negative disease, an *ERBB2* fusion in a patient with HER2-positive disease, and an acquired *RET* fusion. Acquired mutations were primarily identified at a low clonal fraction and were often polyclonal, suggesting convergent evolutionary mechanisms to evade therapeutic pressure.

Conclusions

Liquid biopsy profiling provides evidence for therapeutic and selection-driven evolution, with a high frequency of shared driver alterations and a diverse set of in-pathway subclonal acquired alterations. Potentially actionable baseline and acquired alterations identified in liquid biopsies may provide insights into additional treatment options, potentially through combinatorial strategies.