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SHORT COMMUNICATION

Clinicopathological features and genomics of ER-positive/HER2-negative breast cancer relapsing on adjuvant abemaciclib

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Background: Two years of adjuvant abemaciclib with endocrine therapy (ET) is standard for high-risk estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, node-positive early-stage breast cancer. Relapse on adjuvant abemaciclib is poorly characterized.

Patients and methods: Patients with recurrence on adjuvant abemaciclib at Dana-Farber Cancer Institute were identified. ER, progesterone receptor (PgR), and HER2 expression pre- and post-abemaciclib was determined, and the duration of adjuvant abemaciclib, ET, and first-line metastatic treatment recorded. Genomic alterations associated with ET and cyclin-dependent kinase 4 and 6 inhibitor resistance were analyzed if next-generation sequencing (NGS) was carried out at recurrence.

Results: Among 163 patients who received adjuvant abemaciclib (2018-2024), 15 (9.2%) experienced recurrence. Median durations were 8.0 months [interquartile range (IQR) 3.8-21.2 months] for adjuvant abemaciclib, 18.5 months (IQR 7.0-23.0 months) for adjuvant ET, and 3.0 months (IQR 1.6-5.0 months) for first-line metastatic treatment. Among 12 patients with ER, PgR, and HER2 evaluable pre- and post-abemaciclib, 6 (50.0%) with strongly positive ER at diagnosis showed ER $\leq$10% and PgR $<$1% at recurrence. Of 10 patients with NGS at recurrence, 90% had P53 pathway alterations, with one *ESR1* mutation and no *RB1* mutations.

Conclusions: In this series of patients relapsing on adjuvant abemaciclib plus ET, 50% showed ER loss, 90% had P53 pathway alterations, and median first-line metastatic treatment lasted 3 months.

Key words: adjuvant abemaciclib, endocrine therapy, recurrence, breast cancer, precision medicine, translational

INTRODUCTION

Up to 30% of patients with high-risk estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (BC) may experience distant recurrence.[1] Adding 2 years of the cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) abemaciclib to adjuvant endocrine therapy (ET) improves outcomes, as shown in monarchE, with 5-year absolute benefits of 7.6% in invasive disease-free survival and 6.7% in distant recurrence-free survival.[2-4]

The characteristics of patients who relapse on adjuvant abemaciclib are not well defined.[5] This study evaluated clinicopathological and treatment-related features of patients relapsing during or after adjuvant abemaciclib and ET.

PATIENTS AND METHODS

This case series (March 2018-April 2024) identified patients from the Dana-Farber Cancer Institute (DFCI) Clinical Outcomes Quality Database who received adjuvant abemaciclib and experienced recurrence. Clinicopathological data, ER, progesterone receptor (PgR), and HER2 expression pre- and post-abemaciclib, duration of treatment (DoT) for adjuvant ET, abemaciclib, and the first metastatic treatment were collected. Genomic alterations associated with resistance to ET and CDK4/6i were documented if the DFCI next-generation sequencing (NGS) panel (OncoPanel) was carried out at recurrence.

Continuous variables were summarized with medians and quartiles, and categorical variables with frequencies. ER and

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Table 1. Characteristics of the study population

Characteristic	Patients (n = 15)
Age at diagnosis (years), median (IQR)	48 (36.0-60.5)
Female, *n* (%)	15 (100.0)
Race and ethnicity, *n* (%)	
African American	1 (6.7)
Caucasian	14 (93.3)
Non-Hispanic	15 (100.0)
Pathogenic germline mutation, *n* (%)	
BRCA2	2 (13.3)
CHEK2	1 (6.7)
None detected	10 (66.7)
Not carried out/unknown	2 (13.3)
Clinical stage, *n* (%)	
Stage I	2 (13.3)
Stage II	5 (33.3)
Stage III	8 (53.3)
Histology (primary), *n* (%)	
Ductal	9 (60.0)
Lobular	1 (6.7)
Mixed ductal and lobular	5 (33.3)
Grade (primary), *n* (%)	
G1	2 (13.3)
G2	6 (40.0)
G3	7 (46.7)
Pathological T category, *n* (%)	
T1	3 (20.0)
T2	8 (53.3)
T3	4 (26.7)
T4	0 (0.0)
Pathological N category, *n* (%)	
N0	1 (6.7)
N1	3 (20.0)
N2	7 (46.7)
N3	4 (26.7)
Management of primary tumor, *n* (%)	
Upfront surgery	4 (26.7)
Neoadjuvant chemotherapy	8 (53.3)
Neoadjuvant endocrine therapy	3 (20.0)
RCB class (after chemotherapy), *n* (%)	
RCB-0	0 (0.0)
RCB-I	0 (0.0)
RCB-II	1 (6.7)
RCB-III	5 (33.3)
Not applicable/not available	9 (60.0)
Oncotype DX RS, *n* (%)	
1-10	0 (0.0)
11-25	3 (20.0)
26-100	5 (33.3)
Not carried out/not available	7 (46.7)
Adjuvant treatment, *n* (%)	
ET	12 (80.0)
Chemotherapy	0 (0.0)
Both	3 (20.0)
Adjuvant radiation treatment, *n* (%)	
Yes	14 (93.3)
No	1 (6.7)
Adjuvant ET type, *n* (%)	
Aromatase inhibitor	4 (26.7)
Aromatase inhibitor + OFS	7 (46.7)
Aromatase inhibitor + BSO	2 (13.3)
Aromatase inhibitor + OFS + BSO	1 (6.7)
Fulvestrant	1 (6.7)
First recurrence site, *n* (%)	
Bone	4 (26.7)
Liver	6 (40.0)
Lung	2 (13.3)
Lymph node	1 (6.7)
Pleura	1 (6.7)
Soft tissue	1 (6.7)
Estrogen receptor status (primary), *n* (%)	
<1%	0 (0.0)
1%-9%	0 (0.0)
10%	0 (0.0)
>10%	15 (100.0)
Not done	0 (0.0)
Progesterone receptor status (primary), *n* (%)	
<1%	2 (13.3)
1%-9%	5 (33.3)
10%	2 (13.3)
>10%	6 (40.0)
Not done	0 (0.0)
HER2 receptor status (primary), *n* (%)	
0, 1+, NOS	1 (6.7)
0	7 (46.7)
1+	3 (20.0)
2+ ISH negative	4 (26.7)
Not done	0 (0.0)
Estrogen receptor status (recurrence), *n* (%)	
<1%	3 (20.0)
1%-9%	1 (6.7)
10%	2 (13.3)
>10%	6 (40.0)
Not done	3 (20.0)
Progesterone receptor status (recurrence), *n* (%)	
<1%	11 (73.3)
1%-9%	0 (0.0)
10%	1 (6.7)
>10%	0 (0.0)
Not done	3 (20.0)
HER2 receptor status (recurrence), *n* (%)	
0, 1+, NOS	0 (0.0)
0	6 (40.0)
1+	6 (40.0)
2+ ISH negative	0 (0.0)
Not done	3 (20.0)
Duration of treatment (months), median (IQR)	
Adjuvant abemaciclib	8.0 (3.8-21.2)
Adjuvant ET	18.5 (7.0-23.0)
First treatment line (metastatic)	3.0 (1.6-5.0)
Toxicities leading to abemaciclib discontinuation, *n* (%)	6 (40.0)
Gastrointestinal (diarrhea)	4 (26.6)
Decreased kidney function	1 (6.7)
Pneumonitis	1 (6.7)
Recurrence timing, *n* (%)	
While on adjuvant abemaciclib	7 (46.7)
After stopping/completing adjuvant abemaciclib	8 (53.3)
Time from discontinuation (abemaciclib) to recurrence (months), median (IQR)	5.0 (4.0-8.0)
First treatment line (metastatic), *n* (%)	
Clinical trials	4 (26.7)
ADC + immunotherapy	3 (20.0)
PARP inhibitor + immunotherapy	1 (6.7)
Chemotherapy	5 (33.3)
CDK4/6 inhibitor + ET	3 (20.0)
Capivasertib + ET	1 (6.7)
Olaparib	2 (13.3)
Vital status	
Alive	6 (40.0)
Deceased (of breast cancer)	9 (60.0)

ADC, antibody—drug conjugate; *BRCA2*, breast cancer susceptibility gene 2; BSO, bilateral salpingo-oophorectomy; CDK4/6, cyclin-dependent kinases 4 and 6; *CHEK2*, checkpoint kinase 2; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; ISH, *in situ* hybridization; NOS, not otherwise specified; OFS, ovarian function suppression; PARP, poly-ADP ribose polymerase; RCB, residual cancer burden; RS, recurrence score.

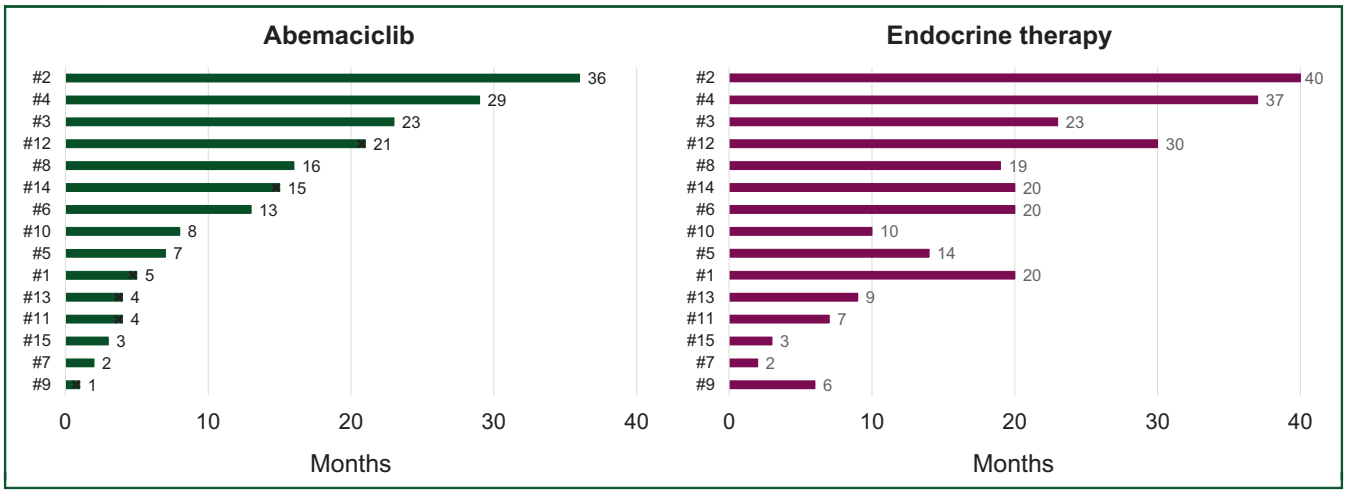

Figure 1. Swimmer plots illustrating the duration of treatment for adjuvant abemaciclib (left) and endocrine therapy (right). The black cross represents toxicity leading to abemaciclib discontinuation (patients #1, #9, #11, #13, #14, #21). Among the eight patients who experienced recurrence after discontinuing/completing adjuvant abemaciclib, six discontinued treatment due to toxicities (diarrhea, $n = 4$; decreased kidney function, $n = 1$; pneumonitis, $n = 1$), while two completed the full course of adjuvant abemaciclib as planned. Specifically, in this subset ($n = 8$), the median duration of treatment for adjuvant abemaciclib was 8.0 months (IQR 3.9-18.6 months) (not shown). None of these eight patients discontinued endocrine therapy before recurrence; rather, endocrine therapy was stopped due to disease recurrence.
IQR, interquartile range.

PgR changes were analyzed using Shapiro—Wilk normality and Wilcoxon signed-rank tests (two-sided $P < 0.05$). Gene enrichment was assessed using Fisher's exact test, with $P < 0.05$ considered statistically significant. When correcting for multiple comparisons, the Benjamini and Hochberg procedure was used and adjusted P values of false discovery rate (FDR) <0.10 are considered statistically significant. Data were analyzed in GraphPad Prism Version 10.4.0 (Boston, MA) and R Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was institutional review board-approved and followed case series reporting guidelines.

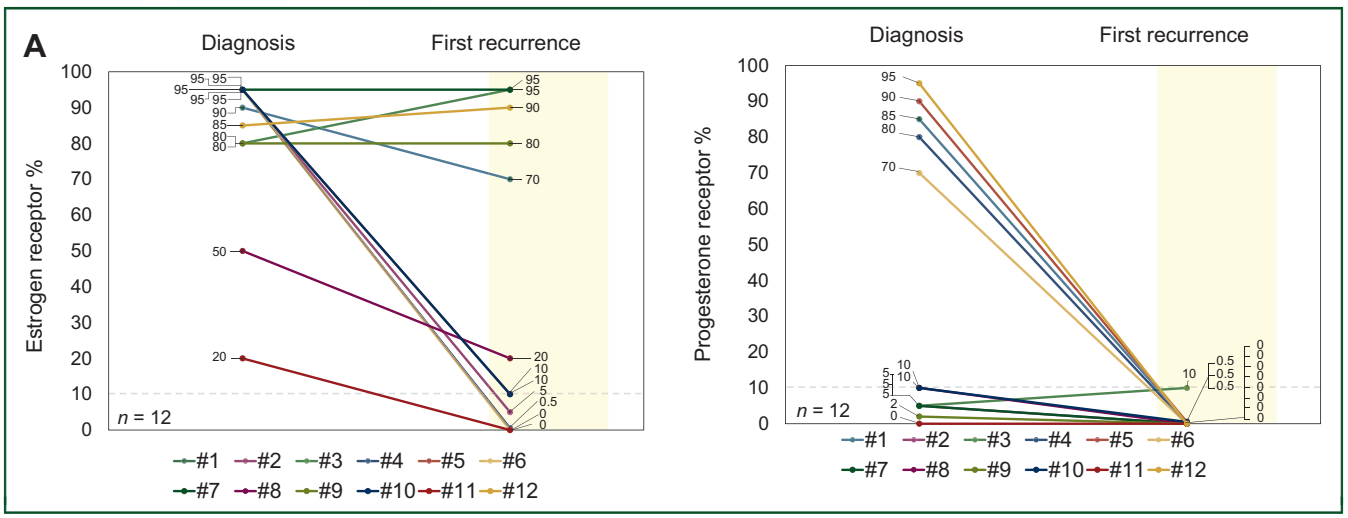

Figure 2. Changes in hormone receptor status between diagnosis and recurrence (Panel A), and genomic alterations identified in recurrence tissue after relapse on adjuvant abemaciclib (Panel B). (A) Individual line plots showing ER (left) and PgR (right) statuses at primary diagnosis compared to recurrence for 12 of 15 patients with hormone receptor data available at both time points. ER and PgR statuses at diagnosis significantly differed from those at recurrence (two-tailed $P = 0.0078$ for ER and $P = 0.0049$ for PgR, Wilcoxon signed-rank test, significance set at $P < 0.05$). (B) Co-mutation plot showing the most frequent genomic alterations in breast cancer genes for 10 of 15 patients who relapsed on or after adjuvant abemaciclib and underwent next-generation sequencing specifically from recurrence tissue. Most patients had genomic alterations in the P53 pathway ($n = 9$, 90%): *TP53* oncogenic mutations ($n = 5$), *TP53* homozygous deletions ($n = 1$), and *MDM2* high amplifications (copy number >20) ($n = 3$). One *ESR1* oncogenic mutation and no *RB1* oncogenic mutations were detected. Additional oncogenic alterations include those in the PI3K pathway [$n = 3$; *PIK3CA* oncogenic mutation ($n = 2$), *PTEN* oncogenic mutation ($n = 1$)], RTK oncogenic alterations [$n = 5$; *FGFR1* high amplification ($n = 2$), *ERBB2* oncogenic mutation ($n = 1$), *FGFR2* high amplification ($n = 2$)], and *CCND1* high amplification ($n = 1$).
BRCA2, breast cancer susceptibility gene 2; *CCND1*, cyclin D1; CNV, copy number variation; Dx, diagnosis; ER, estrogen receptor; *ERBB2*, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; *ESR1*, estrogen receptor 1; *FAT1*, FAT atypical cadherin 1; *FGFR*, fibroblast growth factor receptor; *GATA3*, GATA binding protein 3; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; *MDM2*, murine double minute 2; mut, mutation; PI3K, phosphatidylinositol-3 kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *RB1*, retinoblastoma protein; RTK, receptor tyrosine kinases; *TP53*, tumor protein p53.

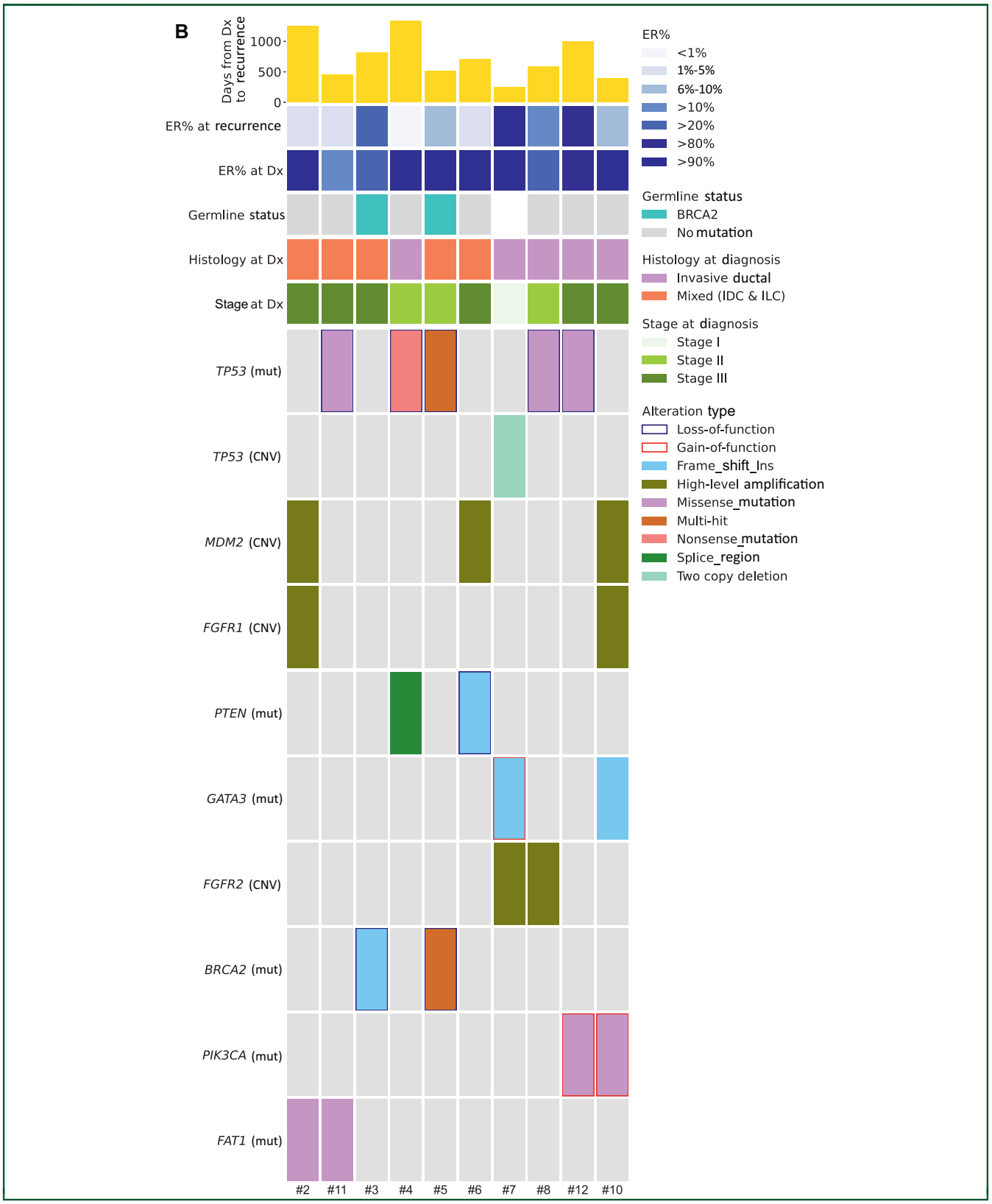

Figure 2. **Continued.**

RESULTS

We identified 163 patients who received adjuvant abemaciclib, of whom 15 (9.2%) experienced recurrence.

The median age at diagnosis was 48.0 years [interquartile range (IQR) 36.0-60.5 years]; two patients (13.3%) had germline (g) *BRCA2* mutations, and one patient (6.7%)

had a g*CHEK2* mutation (Table 1). Most patients presented with stage II (33.3%) or stage III (53.3%) disease, and the majority had ductal histology (60.0%) and poorly differentiated tumors (46.7%). Pathological T and N categories were predominantly T2 (53.3%) and N2 (46.7%), respectively.

Median DoT was 8.0 months (IQR 3.8-21.2 months) for abemaciclib and 18.5 months (IQR 7.0-23.0 months) for ET (Figure 1). The median disease-free interval was 19 months (IQR 10.5-26 months), with all recurrences being distant. The liver (40.0%), bone (26.7%), and lung (13.3%) were the most common recurrence sites.

In the metastatic setting, median DoT for the first treatment line was 3.0 months (IQR 1.6-5.0 months). At data cut-off, two patients remained on first-line treatment. The types of systemic therapy administered as first-line therapy in the metastatic setting are shown in Table 1. BC-specific mortality was 60.0% (9 of 15 patients).

ER, PgR, and HER2 statuses were evaluable both pre- and post-abemaciclib in 12 patients (80.0%). Among them, six patients (50.0%) with strongly positive ER status at diagnosis (ER $\geq$95% in five cases, ER = 20% in one case) showed ER $\leq$10% and PgR $<$1% at first recurrence. Overall, ER and PgR statuses at diagnosis were significantly different from those at recurrence (two-tailed $P = 0.0078$ for ER, $P = 0.0049$ for PgR; Wilcoxon signed-rank test, $P < 0.05$) (Figure 2A).

Among the 10 patients with available NGS data from recurrence tissue, nearly all exhibited genomic alterations in the P53 pathway ($n = 9$, 90%; Figure 2B). We detected five *TP53* oncogenic mutations, one *TP53* homozygous deletion, and three *MDM2* high amplifications (copy number $>$20). One *ESR1* oncogenic mutation and no *RB1* oncogenic mutations were identified. Additional alterations included those in the phosphatidylinositol-3 kinase pathway [$n = 3$; *PIK3CA* oncogenic mutation ($n = 2$), *PTEN* oncogenic mutation ($n = 1$)], RTK oncogenic alterations [$n = 5$; *FGFR1* high amplification ($n = 2$), *ERBB2* oncogenic mutation ($n = 1$), *FGFR2* high amplification ($n = 2$)], *CCND1* high amplification ($n = 1$), and *FAT1* mutations [$n = 2$, variants of unknown significance (VUS)].

We then compared the genomic alterations in this patient cohort to those in The Cancer Genome Atlas PanCancer Breast Cancer hormone receptor-positive HER2-negative cohort (TCGA 'BRCA HR-positive/HER2-negative') (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105126). Only *TP53* and *MDM2* oncogenic alterations were statistically significant (*TP53* $P = 0.010$, *MDM2* $P = 0.0038$; FDR < 0.10 for both) and were enriched in this patient cohort, and combined *TP53* or *MDM2* was also significant ($P = 0.000026$, FDR < 0.10). *FGFR2* ($P = 0.028$, FDR $= 0.19$) and *BRCA2* ($P = 0.028$, FDR $= 0.19$) were statistically significant, but not when correcting for multiple comparisons (FDR > 0.10). When including VUS, *FAT1* enrichment was borderline significant without correcting for multiple comparisons ($P = 0.049$, FDR $= 0.30$), and no additional statistically significant genes were identified.

DISCUSSION

In this first case series of patients relapsing on or after adjuvant abemaciclib, we found no *RB1* gene alterations, which are typically associated with reduced CDK4/6i efficacy in the metastatic setting, and only one *ESR1* alteration, which is linked to acquired resistance to ET in ER-positive/HER2-negative BC.[6,7] We identified alterations in genes with reduced CDK4/6i efficacy (*FAT1*, *FGFR2*), which had higher prevalence when compared with TCGA 'BRCA HR-positive/HER2-negative' but were limited to two cases each and their enrichment was not significant when comparing for multiple comparisons.[6,8]

Importantly, we identified an enrichment and high prevalence of TP53 pathway alterations and ER loss at recurrence, suggesting that a more aggressive, non-luminal/triple-negative BC (TNBC)-like phenotype may be associated with recurrence.

This aligns with TCGA and Memorial Sloan Kettering Cancer Center (MSKCC) data showing that *TP53* alterations are more frequent in TNBC and ER-negative/HER2-positive than ER-positive/HER2-negative cancers.[9,10] TP53 pathway alterations may also directly impair the ER pathway, and mutations are linked to worse survival.[11,12] We found no *MYC* amplifications—prevalent in monarchE baseline samples and linked to reduced abemaciclib benefit[5]—but these too are more common in TNBC and ER-negative/HER2-positive cancers.[9,11]

If this hypothesis is correct, transcriptional subtype (PAM50) changes may be evident in RNA-sequencing data from patients relapsing on or after adjuvant abemaciclib plus ET compared with their primary tumor samples. To confirm this hypothesis, larger studies are needed. These should include comparing the genomic profiles of recurrence biopsies with matched primary samples, evaluating the primary tumor genomic profiles of relapsed patients versus those who did not relapse, and comparing the recurrence biopsy profiles of patients who relapsed after adjuvant abemaciclib plus ET with those of patients who relapsed after ET alone.

As the follow-up of patients treated with adjuvant abemaciclib in clinical practice continues to grow since its regulatory approval, we anticipate that such studies will soon be feasible. Addressing this question is clinically relevant, as TP53 pathway alterations and loss of ER may represent dominant resistance mechanisms in this setting.

If these hypotheses are confirmed by larger validation studies, this would have critical clinical implications. For example, a tumor biopsy at recurrence would become essential, and the prognosis for these patients could be worse than initially expected. This could underscore the urgent need to investigate strategies, assays, and biomarkers to enable the early identification of these patients for treatment optimization-related clinical trials.

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DISCLOSURE

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