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Alternating 17β-Estradiol and Aromatase Inhibitor Therapies Is Efficacious in Postmenopausal Women with Advanced Endocrine-Resistant ER+ Breast Cancer

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Abstract

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Purpose: Strategies to implement estrogen therapy for advanced estrogen receptor–positive (ER^+) breast cancer are underdeveloped. Preclinical data suggest that cycling treatment with 17β-estradiol followed by estrogen deprivation can control tumor growth long-term.

Patients and Methods: Postmenopausal women with advanced $ER^+/HER2^-$ breast cancer with recurrence or progression on ≥ 1 antiestrogen or aromatase inhibitor (AI)-based therapy were eligible. Patients received 17β-estradiol (2 mg orally, three times a day) for 8 weeks followed by AI (physician's choice) for 16 weeks, alternating treatments on an 8-week/16-week schedule until disease progression. Patients then optionally received continuous single-agent treatment until a second instance of disease progression. Endpoints included 24-week clinical benefit and objective response per RECIST, and tumor genetic alterations.

Results: Of 19 evaluable patients, clinical benefit rate was 42.1% [95% confidence interval (CI), 23.1%–63.9%] and objective response rate (ORR) was 15.8% (95% CI, 5.7%–37.9%). One patient experienced a grade 3 adverse event related to 17β-estradiol. Among patients who received continuous single-agent treatment until a second instance of disease progression, clinical benefit was observed in 5 of 12 (41.7%) cases. Tumor ER (*ESR1*) mutations were found by whole-exome profiling in 4 of 7 (57.1%) versus 2 of 9 (22.2%) patients who did versus did not experience clinical benefit from alternating 17β-estradiol/AI therapy. The only two patients to experience objective responses to initial 17β-estradiol had tumor *ESR1* mutations.

Conclusions: Alternating 17β-estradiol/AI therapy may be a promising treatment for endocrine-refractory ER^+ breast cancer, including following progression on CDK4/6 inhibitors or everolimus. Further study is warranted to determine whether the antitumor activity of 17β-estradiol differs according to *ESR1* mutation status.

Introduction

Patients with estrogen receptor α–positive (ER^+) breast cancer are typically treated with endocrine therapies that inhibit ER signaling. These include the selective ER modulator (SERM) tamoxifen, aromatase inhibitors (AI) that suppress estrogen biosynthesis (e.g., exemestane, letrozole, and anastrozole), and selective ER downregulators (SERD) such as fulvestrant. Within the past decade, drugs that target mTORC1 inhibitors (mTORC1i; everolimus), PI3K inhibitors (PI3Ki; alpelisib), AKT inhibitors (capivasertib), or cyclin-dependent kinases 4 and 6 (CDK4/6i; palbociclib, ribociclib, and abemaciclib) have been combined with endocrine therapies to address common pathways of resistance. In the case of CDK4/6i, these drugs are now routinely used in the metastatic (palbociclib, ribociclib, and abemaciclib) and adjuvant (abemaciclib) settings. Although these therapies have changed the natural history of ER^+ breast cancer, nearly all patients in the advanced disease setting develop drug resistance.

Prior to the advent of tamoxifen, synthetic estrogens such as diethylstilbestrol (DES) were used for the treatment of breast cancer (1, 2). Ethinylestradiol and 17β-estradiol also became moderately utilized therapies after disease progression on antiestrogens. Response rates to estrogens are similar to those of antiestrogens in the advanced disease setting (1–5). Historically, responses to estrogens were three times more frequent in women >60 years of age than those younger (6). This phenomenon may occur because the postmenopausal period

creates a low-estrogen environment, and tumors growing under low-estrogen conditions may be hypersensitized to estrogen (7–10). Pharmacologic suppression of ER signaling (via modern antiestrogens and AIs) may similarly sensitize cancers to estrogen therapy. Indeed, a prospective study found that 12 of 32 (38%) postmenopausal patients with AI-resistant advanced breast cancer experienced clinical benefit (CB) from DES (11), and a retrospective study showed CB from DES or 17β-estradiol in 12 of 26 (46%) of patients with endocrine-resistant disease (12). In addition, some ER^+ breast cancers respond to withdrawal of antiestrogen therapy (3, 13–18), which may be caused by (i) return of ER signaling to physiologic levels induced by endogenous estrogens, and/or (ii) cessation of agonistic effects on ER in the case of tamoxifen.

Although ER^+ breast cancers are often responsive to antiestrogens and estrogens, the concept of alternating antiestrogen/estrogen therapies has not yet been formally tested. Anecdotal observations indicate that such a strategy of alternating therapies is effective in some patients (5). Preclinical evidence suggests that antiestrogen-resistant ER^+ breast cancers are sometimes sensitized to the antitumor effects of estrogens (7, 8, 19–25). Such preclinical models harbor subpopulations that can ultimately regain the ability to grow in the presence of estrogens and revert to their antiestrogen-sensitive state. Although estrogen therapy has been used for decades to treat advanced ER^+ breast cancer, prior reports did not address estrogen efficacy following exposure to tumor-targeted therapeutics such as CDK4/6i. We thus conducted a clinical study to formally test whether alternation of 17β-estradiol and AI therapies is effective for the management of advanced ER^+ disease, and to identify molecular biomarkers that may predict tumor response.

Patients and Methods

Study oversight—This clinical study was first approved by the Dartmouth Health Human Research Protection Program, registered on clinicaltrials.gov (NCT02188745), and conducted in accordance with ICH Good Clinical Practice. The study was monitored by the Dartmouth Cancer Center Data, Safety Monitoring, and Accrual Committee. Written informed consent was obtained from all participants prior to performing study-related procedures. All procedures performed involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study design and participants—We conducted a single-arm trial alternating 17β-estradiol/AI therapy in patients with advanced (locally recurrent or metastatic) $ER^+/HER2^-$ breast cancer. Our primary objective was to determine the CB rate (CBR). Patients were recruited at Dartmouth-Hitchcock Medical Center, Mayo Clinic, and Baystate Medical Center. Postmenopausal patients with advanced disease were eligible if they previously received ≥ 1 endocrine agent and experienced disease progression. The most recent line of therapy must not have included fulvestrant within the prior 4 months due to its long half-life (26). Patients with disease treated in the advanced setting must have been progression-free for ≥ 3 months during the most recent line of therapy (except in the case of investigational therapies). Up to one line of prior chemotherapy was allowed.

Histologic documentation of advanced breast cancer using a tissue specimen acquired within the past 4 months was required except in cases of bone-dominant metastatic disease or disease not amenable to safe/accurate biopsy, where patients must have had a history of $ER^+/HER2^-$ disease. The most recently acquired tumor specimen must have been strongly ER^+ as determined by IHC (≥ 50% of malignant cell nuclei with intensity ≥ 2+ on a scale of 0–3+) and $HER2^-$ (IHC score of 0–1+, or FISH ratio of < 2 if IHC was 2+ or not performed).

This study was designed using Simon two-stage design. The null hypothesis that the true CBR is 10% was tested against a one-sided alternative. In the first stage, 10 patients would be accrued. If ≤ 1 patient experienced CB among these first 10 patients, the study would be stopped for futility. Otherwise, 19 additional patients were planned to be accrued for a total of 29 patients. The null hypothesis would be rejected if ≥ 6 patients experience CB among 29 total patients. This design yields a type I error rate of 5% and power of 80% when the true CBR is 30%.

Treatment—Written informed consent for study participation was obtained from eligible patients. Patients were treated with 17β-estradiol (tablets administered orally as 2 mg TID) for 8 weeks followed by an AI for 16 weeks, alternating 17β-estradiol and AI treatments on this schedule until disease progression. The choice of an oral AI drug (letrozole 2.5 mg/day, anastrozole 1 mg/day, or exemestane 25 mg/day) was the decision of the treating physician.

At the time of disease progression on alternating therapy, patients were given the option of being treated continuously with either 17β-estradiol if the subject progressed on the AI, or the AI as a single-agent if the subject progressed on 17β-estradiol, at the physician's discretion until a second instance of disease progression.

Outcomes—Patients were monitored for tumor response by imaging [either PET/CT, or bone scan and conventional contrast CT (chest, abdomen, and pelvis)] performed for disease staging as clinically indicated approximately every 8 weeks. Disease progression, objective response (OR), and CB were determined using RECIST 1.1 (27). CB is stable disease (SD) at 24 weeks, complete response (CR), or partial response (PR). Progression-free survival (PFS) during alternating 17β-estradiol/AI therapy (PFS_1) and during continuous monotherapy (PFS_2) were measured.

Safety (adverse events and hematologic/chemistry laboratory parameters) and physical status (including ECOG performance status) were assessed at baseline and at the end of each 28-day cycle. Adverse event severity was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Molecular analysis—DNA extracted from tumor tissue specimens was used for whole-exome sequencing (WES; for details, see Supplementary Data). Variants detected at ≥ 5% allelic frequency with ≥ 20× locus coverage were considered mutations. When available, tumor mutational profiles obtained through clinically indicated tumor DNA and RNA sequencing (RNA-seq) were also examined.

Statistical analysis—Exact methods were used for confidence interval (CI) estimation to account for small sample sizes. The 95% CI was computed on the basis of beta distribution approximation for the binomial proportion (28, 29). The nonparametric beta distribution CI for median PFS was calculated (30, 31). PFS was used to generate Kaplan–Meier curves.

Data availability—Tumor DNA-sequencing results are publicly available on NCBI SRA (PRJNA879415). Deidentified data are available from the corresponding authors upon request.

Results

Patient population

Among 23 patients screened for eligibility, 20 initiated study treatment (Supplementary Fig. S1; Supplementary Tables S1 and S2). One patient was not evaluable because of their decision to withdraw < 4 weeks after initiating study treatment. Accrual was stopped due to lack of additional funding. The remaining 19 eligible patients were treated with 17β-estradiol for ≥ 4 weeks and evaluable for the endpoints of CB, OR, and toxicity. The median age was 61 and the median number of prior regimens containing an endocrine agent in the advanced disease setting was three. All patients experienced disease progression during prior endocrine treatment (Table 1). Most (84.2%) received prior CDK4/6i (73.7%) or everolimus (63.2%) in combination with an endocrine agent in the advanced setting.

Safety

Patients received alternating treatment with 17β-estradiol followed by either letrozole (n = 11) or exemestane (n = 4). Four patients who experienced disease progression during cycles 1–2 of 17β-estradiol were subsequently treated continuously with anastrozole (n = 2) or exemestane (n = 1), or discontinued study participation (n = 1). Study treatments were generally well-tolerated. One subject experienced a grade ≥ 3 adverse event attributed to study treatment (grade 3 thromboembolism) during cycle 9 of 17β-estradiol (Supplementary Table S3). The subject was treated with anticoagulation and remained on study, receiving two cycles of letrozole and ≥ 10 cycles of 17β-estradiol (the subject remains on study). No subject withdrew from the study due to toxicity.

Efficacy

Among 19 evaluable patients, PR occurred in three cases (two confirmed and one nonconfirmed) and five patients experienced SD lasting ≥ 24 weeks during alternating 17β-estradiol/AI therapy, yielding a CBR of 42.1% (95% CI, 23.1%–63.9%) and an ORR of 15.8% (95% CI, 5.7%–37.9%; Table 2). Median PFS during alternating treatment (PFS_1) for the subject population was 16.9 weeks (95% CI, 8.9–23.0; Fig. 1). CB was observed in 4/14 (28.6%) patients previously treated with a CDK4/6i-containing regimen, and in 5/12 (41.7%) patients previously treated with an everolimus-containing regimen (Fig. 2).

Following disease progression on alternating 17β-estradiol/AI therapy, 12 patients chose to receive continuous (nonalternating) treatment with a single-agent (Supplementary Table S1). This included eight patients treated with 17β-estradiol and four with an AI. Among these

12 patients, five (41.7%) experienced CB from continuous single-agent treatment (all SD for ≥ 24 weeks; range of 24.0 to ≥ 65.2 weeks); this included four treated with 17β-estradiol and one with an AI. Median PFS during continuous treatment (PFS_2) was 20.0 weeks [95% CI, 15.0–56.0 weeks (censored)]. At the time of manuscript writing, two patients remain on study treatment. Notably, all five who benefitted from continuous single-agent treatment had experienced prior CB from alternating 17β-estradiol/AI therapy.

Molecular analysis

We performed WES on 19 tumor specimens acquired from 16 patients (Supplementary Tables S4 and S5). Analysis revealed enrichment for mutations in genes among patients who did versus did not experience CB from alternating 17β-estradiol/AI therapy (Fig. 3A; Supplementary Table S6). Examples of genes associated with endocrine resistance were detected in this analysis, such as mutations in the tumor suppressor *NF1* (32) occurring in 6/9 (66.7%) patients who did not experience CB. In contrast, only 1/7 patients with CB harbored an NF1 mutation.

Mutation enrichment analysis revealed an increased proportion of *ESR1* mutations in tumors from patients who did versus did not have CB from alternating 17β-estradiol/AI (Fig. 3A; 57.1% vs. 22.2%). Clinical-grade targeted DNA sequencing showed concordance with WES for *ESR1*-mutant or wild-type (WT) status in 8/9 patients (Supplementary Tables S7 and S8). Among the 7/16 patients with *ESR1* mutations as detected by WES or targeted DNA sequencing, Y537S and/or D538G mutations in a hotspot region of *ESR1* were identified in six patients. Among the 13 patients with measurable disease and known *ESR1* status, 4/5 patients with *ESR1*-hostpot mutations experienced tumor regression during the first 8 weeks of 17β-estradiol treatment, including two who met the criteria for PR (one confirmed; one nonconfirmed; Fig. 3B and C). In contrast, none of the eight patients with *ESR1*-WT tumors met the criteria for PR (Fig. 3B).

One patient with prominent pleural metastasis experienced a PR during the first 8 weeks of 17β-estradiol therapy as her 5th line of therapy (Fig. 3C). She experienced pleural disease progression during subsequent alternation to AI therapy. Thereafter, continuous treatment with 17β-estradiol provided SD for 56.1 weeks before disease progression due to the appearance of a new scalp metastasis, which was surgically resected. Of note, following progression on study treatment, the patient received 104.4 weeks of fulvestrant and intermittent CDK4/6 inhibitors (which were not tolerated due to adverse events). Following disease progression, she was retreated with 17β-estradiol off study and experienced SD for 36.5 weeks (without disease progression) before transitioning onto another clinical trial.

Discussion

In this single-arm study evaluating the role of alternating 17β-estradiol/AI therapy in patients with advanced ER^+ breast cancer, 8/19 (42.1%) experienced CB from an 8-week/16-week schedule, and three patients experienced a PR. This degree of efficacy compares favorably with prior reports that used RECIST to evaluate continuous estrogen therapy in analogous cohorts of postmenopausal patients with advanced endocrine-resistant ER^+ breast cancer. Ellis and colleagues observed CB in 10/34 (29.4%) patients treated with the same

dose and schedule of 17β-estradiol used herein, with three (8.8%) patients experiencing a PR (5). In a study evaluating estradiol valerate in 19 patients, Zucchini and colleagues reported a 26.3% CB rate, where the five benefiting patients experienced SD (33). In a study of 18 patients treated with ethinylestradiol, Iwase and colleagues reported a 55.6% CB rate, where nine patients experienced a PR (34). Results of the current study suggest that treatment with 17β-estradiol/AI therapy on an alternating schedule is an effective treatment option for patients with advanced ER^+ breast cancer.

We observed that 2/3 PRs to alternating 17β-estradiol/AI therapy occurred during cycles 1–2 (with 17β-estradiol). Our finding that 4/8 subjects experienced CB from continuous 17β-estradiol (following disease progression on alternating therapy) suggests that tumor responses to 17β-estradiol may be most evident early, while longer-term treatment may provide SD. It remains to be determined whether there is an optimal duration of estrogen therapy for all, or whether this duration would best be personalized for a given patient. The current study used 16 weeks of AI therapy alternating with 8-week 17β-estradiol regimens. Although it is generally accepted that long-term exposure to endocrine therapy is needed to yield cancer cells sensitized to the therapeutic effects of estrogen (7–12), it is unknown whether 16 weeks is sufficiently long to restore estrogen sensitivity.

Importantly, all reports on the efficacy of estrogen therapy were made prior to the widespread use of CDK4/6i, mTORC1i, and PI3Ki. We found that alternating 17β-estradiol/AI therapy remains effective following exposure to such targeted agents, with CB rates of 28.6% or 41.7% among patients previously treated with a CDK4/6i or mTORC1i, respectively. After disease progression on alternating therapy, 4/8 patients experienced CB from continuous single-agent 17β-estradiol; all four were previously treated with a CDK4/6i ($n = 3$) and/or everolimus ($n = 3$).

Preclinical *in vitro* and *in vivo* data (7, 8, 19–25) and clinical observations (5, 6) indicate that a common prerequisite for ER^+ breast cancer cell sensitivity to estrogen therapy is adaptation to growth in low-estrogen conditions. Conversely, cancer cells that survive and grow during estrogen therapy may be resensitized to estrogen deprivation (7). In the study by Ellis and colleagues, seven patients with CB during 17β-estradiol therapy ultimately showed disease progression and were retreated with an AI; three (42.9%) of them experienced CB (2 SD, 1 PR; ref. 5). Chalasani and colleagues treated 13 patients bearing endocrine-resistant disease with 17β-estradiol for 3 months followed by exemestane; seven patients had progressive disease (PD) during 17β-estradiol treatment, and 1/6 patients experienced SD during exemestane. Upon disease progression on exemestane, 2/4 patients retreated with 17β-estradiol experienced CB (35). Among the patients who experienced disease progression on alternating therapy in the current study, 5/12 (41.7%) experienced CB (all 5 had SD) from secondary continuous single-agent treatment: four from 17β-estradiol; one from letrozole. These results suggest that tumor cells adapted to growth in ER-inhibiting conditions are sensitized to ER-activating (estrogen) therapy, while cells adapted to growth in ER-activating (estrogen-replete) conditions are sensitized to ER-inhibiting therapy. Results from the SOLE trial appear to support these conclusions. SOLE evaluated 4,851 disease-free postmenopausal patients after 4–6 years of adjuvant ER-inhibiting therapy who were then randomized to continuous versus intermittent (9 months on, 3 months off)

letrozole therapy for 4 years followed by continuous therapy in the 5th year. It was proposed that letrozole holidays would periodically increase systemic estrogen levels to target occult micrometastatic disease. Although recurrence-free survival was nearly identical between those treatment arms (HR = 1.03), a subgroup analysis of the 2,022 patients receiving prior treatment with only AIs revealed that intermittent letrozole provided fewer breast cancer events and death compared with continuous letrozole (36, 37). By contrast, no such effects were observed for intermittent letrozole in the cohorts that had previously received only SERMs or both SERMs and AIs. Although the number of subjects evaluated in the current study was smaller, we did not discern a pattern of CB from alternating 17β-estradiol/AI therapy based on most recent prior drug received: 6/14 and 1/4 patients who received an AI or a cytotoxic chemotherapeutic in the most recent line of prestudy therapy experienced CB from alternating 17β-estradiol/AI therapy.

Identification of a biomarker that predicts response to 17β-estradiol would allow selection of patients likely to benefit. Two case reports have described *ESR1* gene amplification in ER^+ tumors that responded to 17β-estradiol. The 17β-estradiol-sensitive WHIM16 patient-derived xenograft model, which grows in ovariectomized mice, was established from an *ESR1*-amplified tumor from a patient who also benefitted from 17β-estradiol (8). A second report described a patient with endocrine-resistant metastatic breast cancer who experienced a PR from 17β-estradiol/abraxane therapy; genetic analysis of her primary tumor revealed *ESR1* amplification (38). However, *ESR1* amplification occurs in only approximately 3% of metastatic ER^+ breast cancers, while ligand-binding domain mutations occur in approximately 20% of cases (39–42). Such mutations confer ligand-independent ER activation and are detected following the acquisition of endocrine resistance, but not in primary tumors (39–42). Although tumor-targeted agents such as CDK4/6i, PI3Ki, and mTORC1i are effective in patients with *ESR1*-mutant tumors, outcomes are still worse than those of patients with *ESR1*-nonmutant tumors (43–45). Findings described herein provide the first demonstration of an agent (17β-estradiol) that may be more effective against *ESR1*-mutant than nonmutant tumors. However, the use of intermittent AI therapy in alternation with 17β-estradiol may enable *ESR1*-mutant tumor cells to grow. Indeed, 6 of 12 versus 7 of 7 patients with *ESR1*-nonmutant versus *ESR1*-mutant tumors experienced disease progression during a cycle of AI therapy (in alternation with 17β-estradiol), suggesting that inclusion of single-agent AI may not be the best approach in patients with *ESR1*-mutant disease. The contributions of different *ESR1* mutations to ER transcriptional and cellular responses to 17β-estradiol requires in-depth preclinical study. These observations warrant further study in a larger cohort to enable evaluation of *ESR1* status as a potential biomarker to predict response to estrogen therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

Estrogens, including 17β-estradiol, have been used to treat patients with advanced estrogen receptor–positive (ER^+) breast cancer for decades. However, strategies to implement estrogen therapy remain underdeveloped. Preclinical findings suggest that alternating 17β-estradiol and estrogen deprivation therapies is effective for the control of endocrine-resistant disease. We conducted a clinical trial that evaluated 19 patients treated with alternating 17β-estradiol and aromatase inhibitor (AI) therapy. Clinical benefit was observed in 42.1% of patients, including in patients previously treated with CDK4/6 inhibitors and/or everolimus. Objective responses were observed in tumors with ER (*ESR1*) hotspot mutations known to confer endocrine resistance. Alternating 17β-estradiol and AI therapies should be further evaluated in endocrine-resistant advanced breast cancer following progression on a CDK4/6 inhibitor or everolimus. Further study is warranted to determine the contribution of *ESR1* mutations to 17β-estradiol sensitivity.

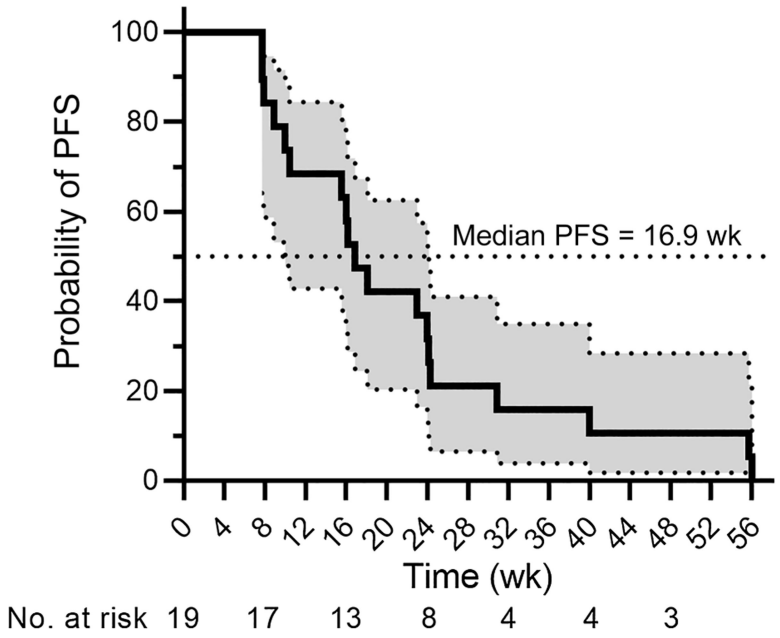

Figure 1.

PFS during alternating 17β-estradiol/AI therapy. Probability of PFS is indicated by thick line. Gray shading indicates 95% CI.

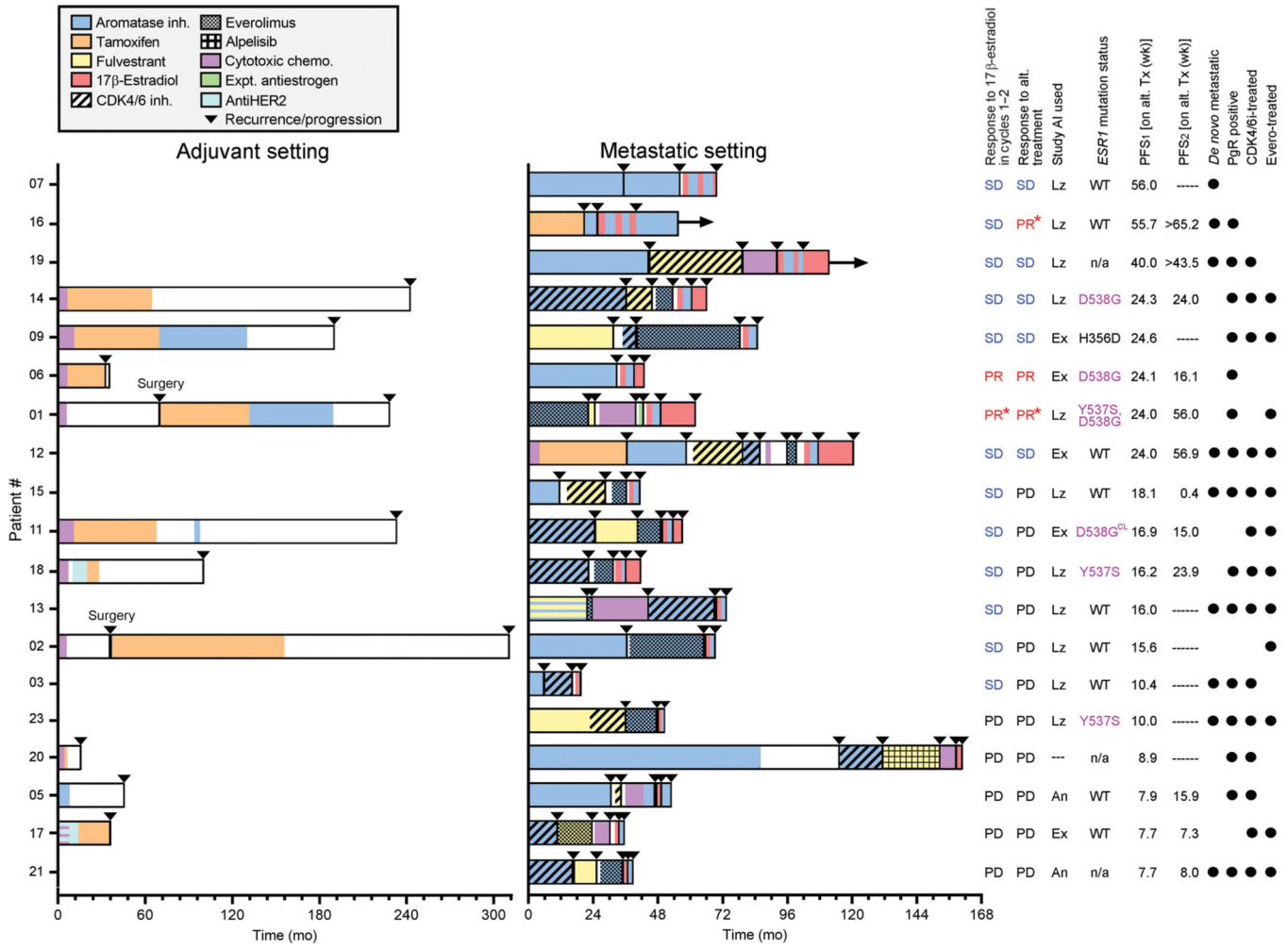

Figure 2.

Treatment histories. Drug treatment timelines are indicated for each subject. Instances of cancer recurrence and progression are indicated by black triangles. Patients 16 and 19 remain on study treatment at the time of this reporting. *Confirmed PR. ^{CL}Mutation was detected by clinical-grade DNA sequencing, but not by exome sequencing.

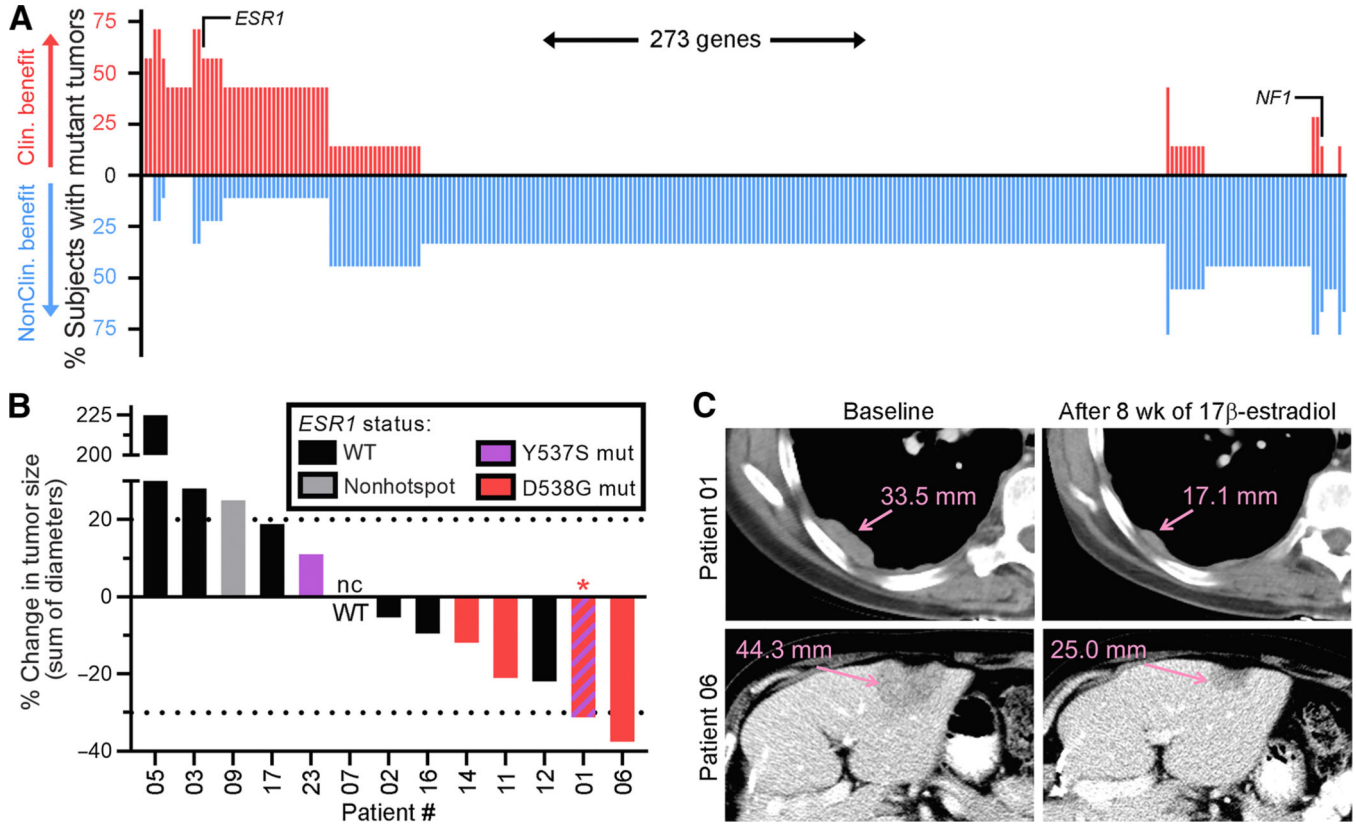

Figure 3.

Tumors harboring *ESR1* mutations exhibit response to 17β-estradiol therapy. **A,** Coding mutations detected by exome sequencing of tumors from 16 patients who did (n = 7) versus did not (n = 9) experience CB from alternating 17β-estradiol/AI therapy were compared. Proportions of patients with a mutation in a given gene are shown. Each column reflects one gene. Genes more frequently mutated in a subgroup by ≥ 30% are shown. **B,** Patients with measurable disease were evaluated for change in tumor size (sum of longest diameters) from baseline to the end of cycle 2 after completion of 8 weeks of 17β-estradiol therapy. *ESR1* mutation status is indicated by colors as in key. Y537S and D538G mutations detected in patient 01 occurred on separate alleles. Patient 09 harbored a nonhotspot H356D mutation. nc/WT, no change in an *ESR1*WT subject. *PR confirmed by imaging after 8 weeks of AI therapy. **C,** Representative CT images of patients experiencing PRs during 17β-estradiol.

Table 1.

Baseline clinical and pathologic characteristics of cohort.

Number of patients evaluated	19
Age, median (range) in years	61 (45–80)
Duration of advanced disease, median (range) in years	4.2 (1.4–28.3)
Location of metastasis	
Bone	14 (73.7)
Visceral	15 (78.9)
Race	
White	19 (100.0)
Prior therapy in adjuvant setting	
Adjuvant endocrine	10 (52.6)
Adjuvant chemotherapy	9 (47.4)
Neither	8 (42.1)
Prior therapy in advanced setting	
n lines of endocrine-based therapy, median (range)	3 (1–5)
n lines of any therapy, median (range)	3 (1–6)
Tamoxifen	2 (10.5)
Letrozole	13 (68.4)
Anastrozole	4 (21.1)
Exemestane	13 (68.4)
Fulvestrant	13 (68.4)
CDK4/6i-containing	14 (73.7)
Everolimus-containing	12 (63.2)
Alpelisib-containing	1 (5.3)
Chemotherapy	7 (36.8)
Experimental agent	2 (10.5)

Table 2.

Treatment response.

	During cycles 1–2 of 17β-estradiol[a] *n* (%)	During alternating Tx[a] *n* (%)
Best response by RECIST PR	2 (10.5)[b]	3 (15.8)[b]
SD	12 (63.2)	5 (26.3)
Disease progression	5 (26.3)	11 (57.9)
Total evaluable	19 (100.0)	19 (100.0)
Clinical benefit[c]	—	8 (42.1)

[a]Response as measured compared with baseline.

[b]One PR was nonconfirmed.

[c]Defined as SD ≥ 24 weeks or PR.