Activity and safety of enobosarm, a novel, oral, selective androgen receptor modulator, in androgen receptor-positive, oestrogen receptor-positive, and HER2-negative advanced breast cancer (Study G200802): a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial

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Summary

Background The androgen receptor is a tumour suppressor in oestrogen receptor-positive breast cancer. The activity and safety of enobosarm, an oral selective androgen receptor modulator, was evaluated in women with oestrogen receptor (ER)-positive, HER2-negative, and androgen receptor (AR)-positive disease.

Methods Women who were postmenopausal (aged ≥18 years) with previously treated ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled in a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial done at 35 cancer treatment centres in nine countries. Participants were stratified on the setting of immediately preceding endocrine therapy and the presence of bone-only metastasis and randomly assigned (1:1) to 9 mg or 18 mg oral enobosarm daily using an interactive web response system. The primary endpoint was clinical benefit rate at 24 weeks in those with centrally confirmed AR-positive disease (ie, the evaluable population). This trial is registered with ClinicalTrials.gov (NCT02463032).

Findings Between Sept 10, 2015, and Nov 28, 2017, 136 (79%) of 172 patients deemed eligible were randomly assigned to 9 mg (n=72) or 18 mg (n=64) oral enobosarm daily. Of these 136 patients, 102 (75%) patients formed the evaluable population (9 mg, n=50; 18 mg, n=52). The median age was 60·5 years (IQR 52·3–69·3) in the 9 mg group and 62·5 years (54·0–69·3) in the 18 mg group. The median follow-up was 7·5 months (IQR 2·9–14·1). At 24 weeks, 16 (32%, 95% CI 20–47) of 50 in the 9 mg group and 15 (29%, 17–43) of 52 in the 18 mg group had clinical benefit. Six (8%) of 75 patients who received 9 mg and ten (16%) of 61 patients who received 18 mg had grade 3 or grade 4 drug-related adverse events, most frequently increased hepatic transaminases (three [4%] of 75 in the 9 mg group and two [3%] of 61 in the 18 mg group), hypercalcaemia (two [3%] and two [3%]), and fatigue (one [1%] and two [3%]). Four deaths (one in the 9 mg group and three in the 18 mg group) were deemed unrelated to the study drug.

Interpretation Enobosarm has anti-tumour activity in patients with ER-positive, HER2-negative advanced breast cancer, showing that AR activation can result in clinical benefit, supporting further clinical investigation of selective AR activation strategies for the treatment of AR-positive, ER-positive, HER2-negative advanced breast cancer.

Funding GTx.

Introduction

Pre-clinical models of oestrogen receptor (ER)-positive, HER2-negative breast cancer have established that the androgen receptor (AR) functions as a tumour suppressor[1] and activation of this receptor strongly suppresses the growth of AR-positive, ER-negative breast cancer, both in the context of disease sensitive to endocrine therapy as well as disease resistant to endocrine therapy, with or without inhibition of cyclin-dependent kinase (CDK) 4 and 6.[1,2] Historically, androgen therapies, such as testosterone propionate or fluoxymesterone, produced disease regression in up to 30% of patients with advanced breast cancer.[3–6] Despite the therapeutic benefits of androgen therapy for breast cancer, this strategy was supplanted due to the virilising side-effects of such androgen formulations and the advent of ER-directed strategies.[7]

Preclinical and mechanistic insights from the last 3 years[1] and the availability of selective AR modulators (SARMs)

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Research in context

Evidence before this study

We searched PubMed for reports of clinical trials published in English between Nov 1, 2000, and July 1, 2023, using the terms "breast cancer" and "oestrogen receptor" and "metastatic" and "Selective Androgen Receptor Modulator". We also searched PubMed for publications in the same date range using the terms "GTX024" or "MK-2866" or "Ostarine" or "enobosarm". We found no reports of randomised controlled trials investigating the use of a selective androgen receptor modulator (SARM) in oestrogen receptor (ER)-positive, HER2-negative breast cancer. Preclinical data support a role for agonism of the androgen receptor in the treatment of ER-positive breast cancer.

Added value of this study

To our knowledge, Study G200802 is the first phase 2 study to test the anti-tumour activity of androgen receptor activation with a SARM for the treatment of postmenopausal advanced ER-positive, androgen receptor (AR)-positive, HER2-negative breast cancer that has progressed after previous endocrine therapy. Our results show that enobosarm, an oral SARM, results in clinical benefit and a progression-free survival that is acceptable for the line of therapy in which it was used. These results provide the first clinical data showing a role for SARMs in breast cancer treatment. Adverse events were low grade and manageable. Two doses were tested in parallel, 9 mg and 18 mg, with no additional benefit at the 18 mg dose.

Implications of all the available evidence

This study provides proof of concept that activating the AR in ER-positive, AR-positive, HER2-negative breast cancer with a SARM can result in clinical activity. These data are consistent with historical data that showed the clinical efficacy of non-selective androgenic drugs. These previous studies were done in an era before the ability to assess ER or AR expression in breast tumours. Crucially, SARMs are not limited by the toxicities seen with pharmacological doses of steroidal androgens. This study supports further investigation of SARMs and other selective AR activation strategies for the treatment of ER-positive, AR-positive, HER2-negative breast cancer.

have provided both the rationale for and ability to revisit AR agonism in ER-positive breast cancer. SARMs have a high specificity for binding to ARs, act in a tissue-selective manner, and do not cause virilising effects in women.[8] Enobosarm (GTx-024) is an oral aryl-propinamide non-steroidal SARM[9] that durably inhibits in-vivo growth of ER-positive breast cancer and inhibits tumour growth in models of endocrine resistance.[1] In women who are postmenopausal, enobosarm at a dose of 3 mg had no significant virilising side-effects[10–12] and anti-tumour activity was seen in a pilot phase 2 study in 22 women with heavily pretreated ER-positive metastatic breast cancer (NCT01616758).[13] The study met its primary endpoint; six (35%) of 17 women with ER-positive, AR-positive breast cancer had clinical benefit, with a median progression-free survival of 3·2 months (IQR 0·2–10·1). We aimed to assess the activity and safety of enobosarm given at two doses in a larger cohort of women with AR-positive, ER-positive, and HER2-negative advanced breast cancer.

For the **trial protocol** see https://health.adelaide.edu.au/dame-roma-mitchell-cancer-research-laboratories/transforming-endocrine-therapy-for-breast-and-prostate-cancer/translational-research-outcomes/human

See Online for appendix

Methods

Study design and participants

We undertook a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial (Study G200802) in women who were postmenopausal (aged ≥18 years) with ER-positive, AR-positive, and HER2-negative locally advanced or metastatic breast cancer. Patients were recruited from 35 cancer treatment centres in nine countries (USA, UK, Hungary, Bulgaria, Australia, Lithuania, Romania, Czech Republic, and Ukraine; appendix pp 6–7).

Eligible patients had an Eastern Cooperative Oncology Group performance status of 0–2 and measurable or bone-only non-measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1,[14] with evidence of disease progression within 30 days of registration. Patients must have received at least one previous endocrine therapy and have shown initial endocrine sensitivity defined by either a 3-year disease-free interval in the adjuvant setting or 6 months of progression-free survival on endocrine treatment for metastatic disease. One previous course of chemotherapy for the treatment of metastatic breast cancer was allowed. Adequate haematological, hepatic, and renal function was required.

The study was approved by an institutional review board or equivalent ethics committee at each participating site and country, and all patients provided written informed consent before enrolment. The study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. The trial protocol is available online.

Randomisation and masking

Patients enrolled by trial investigators were randomised centrally (1:1) using Cenduit Interactive Response Technology, an interactive web response system (Cenduit, Research Triangle Park, NC, USA) to receive either 9 mg or 18 mg of oral daily enobosarm. Randomisation was stratified by two variables: (1) the presence of bone-only metastases (yes or no) versus other sites of disease with or without bone involvement and (2) the setting of immediately preceding endocrine therapy (adjuvant, neoadjuvant, or metastatic). The study was open-label and only the central imaging facility was masked to the dose of enobosarm received. Due to financial issues, GTx

(the funder) discontinued supply of enobosarm in December, 2018. Hence, the trial, including follow-up and all ongoing therapy, was discontinued in January, 2019. Further detail is available in the statistical analysis plan.

Procedures

Patients were administered either 9 mg or 18 mg oral enobosarm daily. Treatment with enobosarm continued for up to 24 months, or until evidence of disease progression, occurrence of unacceptable toxicity, death, or discontinuation of study by the funder. Subsequent anti-cancer treatment data following enobosarm therapy were not collected. Ethnicity data were self-reported.

Assessment of AR positivity is described in the appendix (p 2). Dose reductions were not permitted except for patients in the 18 mg treatment group who had an adverse event that was grade 3 or higher or an intolerance, or both. These patients were permitted one dose reduction from 18 mg to 9 mg or a drug interruption on the basis of medical judgement. Once the adverse event had resolved or reduced to grade 1, the patient could be re-challenged with an 18 mg dose. Drug interruptions were allowed for up to 7 days for patients in both treatment groups who had an adverse event that was grade 3 or higher or a drug intolerance, after which the patient was either rechallenged with the study drug or removed from the study.

Tumour assessments were performed locally and consisted of bone scans and imaging of chest, abdomen, and pelvis by either CT or MRI, or both. All imaging was done within 4 weeks of randomisation and repeated every 12 weeks until disease progression or withdrawal from the study. See the trial protocol online for a detailed schedule of assessments. Confirmatory imaging was done 3 days after the final dose of enobosarm. A masked independent central review of imaging was done to assess disease response. Clinical assessment for disease response and adverse event monitoring (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), along with patient-reported outcomes, occurred every 6 weeks up to week 24, then every 12 weeks while receiving enobosarm. Serological evaluation, including haematology profile, lipid panel, coagulation profile, and complete metabolic panel, coincided with clinical assessments, and were repeated 3 days and 28 days after the final dose of enobosarm. A complete metabolic panel was also assessed on week 1, week 3, and week 5 of treatment. A comprehensive eye examination was performed at screening and 3 days after the final dose of enobosarm. Long term follow-up began 28 days after the final dose of enobosarm and continued every 2 months up to 12 months after treatment.

The effect of treatment with enobosarm on health status as reported by the patient was assessed at baseline, week 6, week 12, week 24, and end of treatment using the EuroQol-5 dimensions visual analogue scale (EQ-5D VAS; appendix pp 2–3).[16]

Outcomes

The primary endpoint was the clinical benefit rate at 24 weeks in patients with centrally confirmed AR positivity ≥10% (ie, the evaluable population), defined by RECIST (version 1.1) as complete response, partial response, and stable disease and assessed by independent, masked, central radiology review.

Secondary endpoints were the clinical benefit rate at 24 weeks in all patients who received at least one dose of enobosarm regardless of AR status (ie, the intention-to-treat [ITT] population) and clinical outcomes assessed in both the evaluable population and the ITT population: objective response rate (defined as attainment of a complete response or partial response at week 24), best overall response (defined as best disease response from the start of study treatment until end of therapy), progression-free survival (defined as time between randomisation and tumour progression or death due to any cause), time-to-tumour progression (defined as time elapsed between randomisation and tumour progression or death due to disease progression), and duration of response (defined as time from documentation of tumour response to disease progression or death);

For the **statistical analysis plan** see https://health.adelaide.edu.au/dame-roma-mitchell-cancer-research-laboratories/transforming-endocrine-therapy-for-breast-and-prostate-cancer/translational-research-outcomes/human

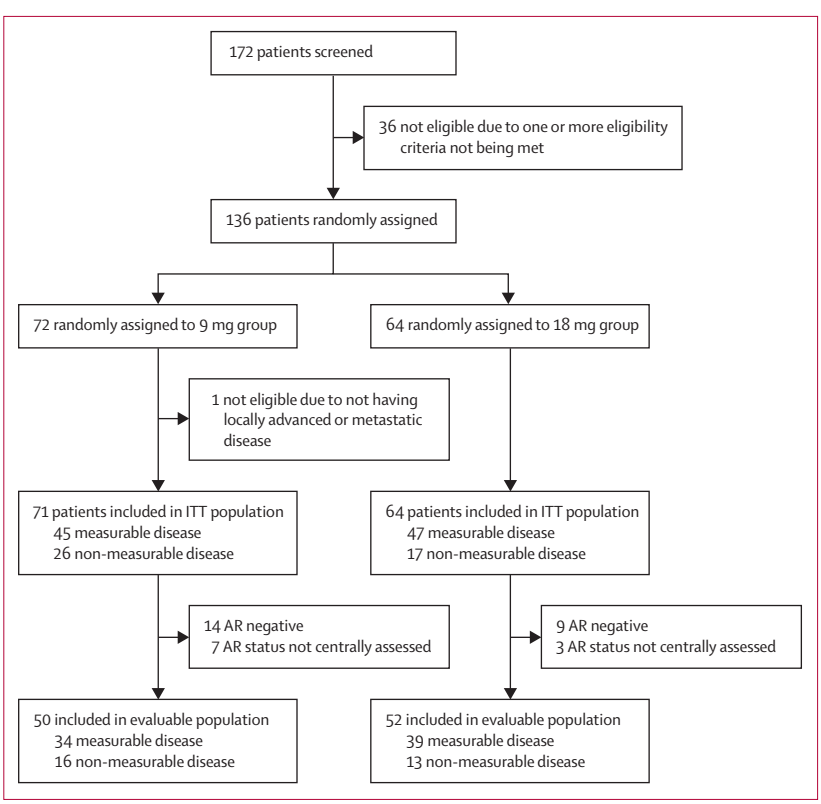

Figure 1: **Trial profile**
The ITT population included all patients who received at least one dose of enobosarm regardless of AR status. The evaluable population included patients with centrally confirmed AR positivity ≥10%. AR=androgen receptor. ITT=intention-to-treat.

duration of response could not be calculated and is not reported. All patients who received at least one dose of enobosarm were assessed for safety.

The tertiary endpoint was patient-reported health status as measured by the EQ-5D VAS.[15]

Statistical analysis

The study was not powered to directly compare the activity between the two enobosarm dose groups (9 mg and 18 mg), but rather to assess if either or both doses resulted in a clinical benefit rate of 30% at 24 weeks within the evaluable population, while maintaining an acceptable safety profile. Censoring details are available in the statistical analysis plan online. Each treatment group was analysed independently using Simon's two-stage (optimal) design. All patients with centrally confirmed AR (positive or negative) were assessable. Within the evaluable population, the first stage required three of 18 patients in each group to have clinical benefit at 24 weeks before proceeding to the second stage, which included up to 44 patients within the evaluable population in each group. Enobosarm, in either the 9 mg or 18 mg groups, would be considered worthy of further evaluation if at least nine (20%) of 44 evaluable patients had clinical benefit by masked central review at 24 weeks using a Simon's two-stage design independently for each group (assumptions ≤10% *vs* ≥30%; target one-sided α=0·025, power=90%). Over-enrolment was permitted to allow for replacement of patients without centrally confirmed AR-positive disease in order to accrue 44 patients in each dose group for primary endpoint analysis. The exact 95% CIs of the primary endpoint were constructed. These 95% CIs were two-sided with the lower bound observed applying the Clopper-Pearson CI method. For the secondary endpoints (ie, progression-free survival, time-to-tumour progression, duration of response, and overall response) within the evaluable population and the ITT population, the median time-to-event and two-sided 95% CIs were constructed using log-log transformation and change from baseline analysed using the Wilcoxon Signed Rank Test, with associated 95% CIs for the median change based on the Hodges-Lehmann estimator. Statistical analyses were conducted by Cmed Clinical Research Services (Horsham, UK) using SAS version 9.4. An independent data and safety monitoring committee was utilized to review safety data.

An exploratory post-hoc analysis of progression-free survival was done in the evaluable population with measurable disease who had received treatment with CDK4/6 inhibitors in combination with endocrine therapy before study enrolment. This trial is registered with ClinicalTrials.gov, NCT01616758.

	Enobosarm 9 mg group (n=50)	Enobosarm 18 mg group (n=52)
Age (years)	60·5 (52·3–69·3)	62·5 (54·0–69·3)
BMI (kg/m²)	26·9 (22·6–30·4)	26·3 (23·9–29·3)
Race or ethnicity		
White, non-Hispanic or Latino	47 (94%)	49 (94%)
Black, non-Hispanic or Latino	0	2 (4%)
Hispanic or Latino	2 (4%)	0
Other	1 (2%)	1 (2%)
Tumour hormonal status		
Progesterone receptor-positive	40 (80%)	39 (75%)
Percentage androgen receptor nuclear positivity staining	53% (33–74)	51% (28–76)
Estimated time from initial breast cancer diagnosis to study enrolment (months)	110·0 (64·8–178·3)	86·0 (59·0–143·3)
Estimated time from metastatic breast cancer diagnosis to study enrolment (months)	34·3 (18·3–62·8)	27·4 (15·0–49·0)
Most common sites of metastatic disease at time of study enrolment		
De-novo metastatic breast cancer	6 (12%)	14 (27%)
Bone-only disease	19 (38%)	17 (33%)
Liver	18 (36%)	24 (46%)
Lung	10 (20%)	11 (21%)
Lymph nodes	11 (22%)	7 (13%)
Previous treatment		
Chemotherapy (any setting)	45 (90%)	49 (94%)
Endocrine therapy: adjuvant or neoadjuvant	35 (70%)	36 (72%)
Adjuvant or neoadjuvant tamoxifen	26 (52%)	25 (48%)
Adjuvant or neoadjuvant aromatase inhibitor	21 (44%)	22 (42%)
Advanced disease: endocrine therapy	42 (84%)	42 (81%)
Advanced disease: aromatase inhibitor	31 (62%)	29 (56%)
Advanced disease: aromatase inhibitor therapy and targeted therapy*	3 (6%)	15 (29%)
Advanced disease: selective oestrogen receptor degrader	18 (36%)	28 (35%)
Advanced disease: selective oestrogen receptor degrader and targeted therapy*	1 (2%)	1 (2%)
Advanced disease: tamoxifen	5 (10%)	14 (27%)
Number of previous endocrine therapy regimens (adjuvant, neoadjuvant, and advanced disease)†	2 (2–3)	3 (2–3)

Data are median (IQR) or n (%). Some percentages do not add up to 100% because of rounding. *Endocrine therapy combined with targeted therapy: either a CDK4/6 inhibitor or mTOR inhibitor. †Administered in the adjuvant, neoadjuvant, and metastatic treatment setting combined.

Table 1: **Baseline characteristics of evaluable population**

Role of the funding source

The funder (GTx) provided financial support to the investigators for study design, conduct, treatment administration, data collection, and data analysis. The trial was designed and conducted by representatives of GTx in collaboration with the trial scientific steering committee. Vector Oncology Solutions (Memphis, TN, USA) and Cmed Clinical Research Services were responsible for overseeing the collection and analysis of the data. The study database was held by Cmed Clinical Research Services. GTx and Veru, the current owner of license to enobosarm, obtained tables, listing, and figures from Cmed Clinical Research Services. The funder had no role in data interpretation or writing of the report.

Results

Between Sept 10, 2015, and Nov 28, 2017, 172 women who were postmenopausal with locally advanced or metastatic

ER-positive, HER2-negative breast cancer were recruited, consented, and were screened for eligibility (figure 1). 136 patients were subsequently randomly assigned to two orally administered daily enobosarm dose groups: 72 (52%) patients to the 9 mg group and 64 (48%) patients to the 18 mg group.

Among the 136 patients who were randomly assigned, 21 (29%) of 72 patients in the 9 mg group and 12 (19%) of 64 patients in the 18 mg group were excluded from the evaluable population because of the inability to centrally confirm a positive AR status. Therefore, 50 (69%) of 72 patients in the 9 mg group and 52 (81%) of 64 patients in the 18 mg group were included in the evaluable population.

Baseline demographics for the evaluable population are presented in table 1. The median age was 60·5 years (IQR 52·3–69·3) in the 9 mg group and 62·5 years (54·0–69·3) in the 18 mg group. 47 (94%) of 50 patients in the 9 mg group and 49 (94%) of 52 patients in the 18 mg group were White (not Hispanic or Latino). The distribution of measurable and bone-only non-measurable disease was similar for both groups, with bone being the most common site of metastatic disease (19 [38%] of 50 patients in the 9 mg group and 17 [33%] of 52 patients in the 18 mg group), followed by liver (18 [36%] and 24 [46%]), lung (ten [20%] and 11 [21%]), and lymph nodes (11 [22%] and seven [13%]). More patients in the 18 mg group had de novo metastatic disease than in the the 9 mg group (14 [27%] of 52 *vs* six [12%] of 50; table 1).

Patients in the evaluable population received a median of two lines (IQR 2–3) of previous endocrine therapy, in either the adjuvant, neoadjuvant, or advanced disease setting before study enrolment. The median duration of disease response to endocrine therapy administered immediately prior to study enrolment within the evaluable population was 17·5 months (IQR 8·8–36·0) in the 9 mg group and 15·0 months (9·9–38·0) in the 18 mg group. The median duration of treatment and compliance for all treated patients are outlined in the appendix (p 4).

In the evaluable population at 24 weeks, 16 (32%, 95% CI 20–47) of 50 patients in the 9 mg group and 15 (29%, 17–43) of 52 in the 18 mg group had clinical benefit (appendix p 5). The median follow-up was 7·5 months (IQR 2·9–14·1). The median progression-free survival was 5·6 months (IQR 2·8 to not reached) in the 9 mg group and 4·2 months (2·7–11·8) in the 18 mg group (appendix p 5). The median time to tumour progression in the evaluable population was similiar to the progression-free survival: 5·6 months (IQR 2·8 to not reached) in the 9 mg group and 4·2 monts (2·7–14·1) in the 18 mg group.

Within the evaluable population, 34 (68%) of 50 patients in the 9 mg group and 39 (75%) of 52 patients within the 18 mg group were found to have measurable disease by RECIST version 1.1 criteria. After independent central radiology review of the measurable disease response, the objective response rate at 24 weeks was zero (0%, 95% CI 0–10) of 34 patients in the 9 mg group and one partial response (2%, 0–14) of 52 patients in the 18 mg group.

	Enobosarm 9 mg group	Enobosarm 18 mg group
Baseline	76·8 (15·1); 49	77·9 (15·4); 49
Week 6	77·6 (15·6); 44	77·5 (16·0); 45
Week 12	74·3 (15·1); 38	75·9 (14·9); 37
Week 18	71·8 (18·3); 25	75·6 (14·2); 24
Week 24	76·8 (14·7); 19	76·9 (15·4); 17

Patient-reported outcomes data are mean (SD); n. EQ-5D VAS=EuroQol-5 dimensions visual analog scale.

Table 2: **EQ-5D VAS scores for the evaluable population at each timepoint**

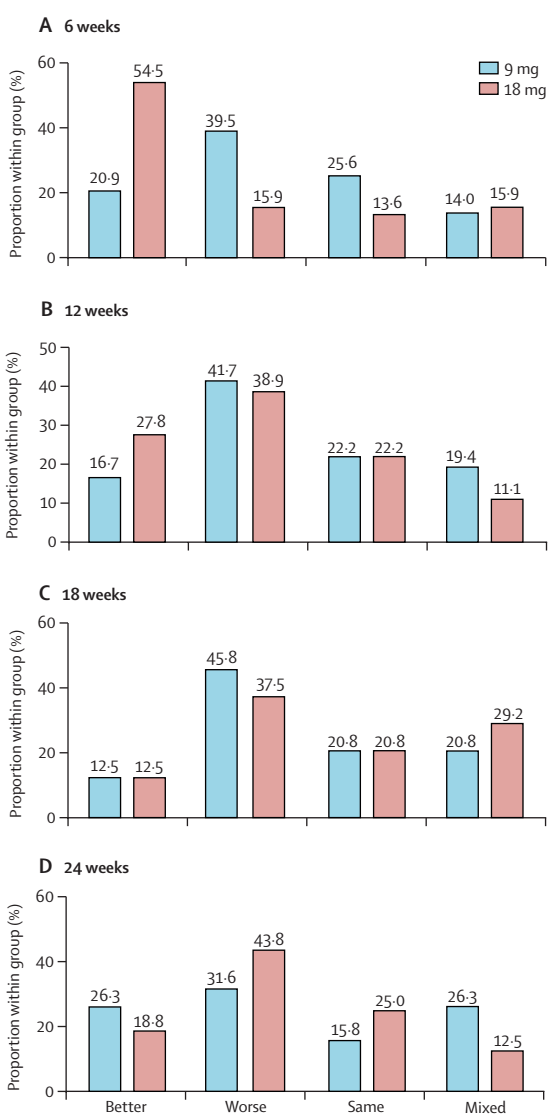

Figure 2: **EQ-5D health profiles compared with baseline**
(A) 6 weeks. (B) 12 weeks. (C) 18 weeks. (D) 24 weeks. Q-5D=EuroQol-5 dimensions scale.

The best overall response was four (12%, 95% CI 3–28) of 34 patients in the 9 mg group and two (5%, 1–17) of 39 in the 18 mg group: including two (6%) of 34 patients with complete responses and two (6%) of 34 patients with partial responses in the 9 mg group, and two (5%) of 39 patients with partial responses in the 18 mg group.

Within the ITT population, 45 (63%) of the 71 patients in the 9 mg group and 47 (73%) of the 64 patients in the 18 mg group had measurable disease. By central independent review, the objective response rate at 24 weeks was zero (0%, 95% CI 0–8) of 45 patients in the 9 mg group and 1 (2%, 0–11) partial response of 47 patients in the 18 mg group. The best overall response was four (9%, 95% CI 3–21) of 45 patients in the 9 mg group and three (6%, 1–18) of 47 patients in the 18 mg group, including two (4%) complete responses and two (4%) partial responses in the 9 mg group and three (6%) partial responses in the 18 mg group. 18 (25%, 95% CI 16–37) of 71 patients in the 9 mg group and 17 (27%, 16–39) of 64 in the 18 mg group had clinical benefit at 24 weeks. The median progression-free survival was 5·3 months (IQR 2·7–13·8) in the 9 mg group and 2·9 months (2·6–13·3) in the 18 mg group. The median time to tumour progression was similiar to the progression-free survival: 5·3 months (2·7–13·8) in the 9 mg group and 2·9 months (2·6–14·1) in the 18 mg group.

13 (13%) of 102 patients within the evaluable population received previous treatment with endocrine therapy in combination with a CDK4/6 inhibitor before study enrolment. These patients received a median of three previous endocrine therapies (IQR 2–4) and all patients received chemotherapy before enrolment. Of these 13 patients, ten (77%) had measurable disease (appendix p 8). A post-hoc analysis of these patients showed a median progression-free survival of 2·9 months (IQR 2·4–9·5; appendix p 8).

Descriptive statistics for EQ-5D VAS scores in the evaluable population are shown for each enobosarm dose group in table 2. There were no significant changes to the EQ-5D VAS score over time in either dose group (9 mg group p=0·93; 18mg group p=0·54). The percentage of patients whose health profile score improved, worsened, stayed the same, or had mixed results compared with baseline are summarised for each timepoint in figure 2. In both dose groups, less than half of the patients had a worse health profile compared with baseline at each timepoint, including at the time of documented disease progression.

All 136 randomly assigned patients were evaluated for safety. Three patients in the 18 mg group never received their allocated dose due to erroneous administration of the study pack, meaning they were dispensed and treated with the 9 mg daily dose of enobosarm. Therefore, the safety analysis population consisted of 75 patients in the 9 mg group and 61 patients in the 18 mg group. 49 (65%) of 75 patients receiving 9 mg daily dosing and 42 (69%) of 61 patients receiving 18 mg daily dosing had at least one treatment-related adverse event of any grade (table 3). There were no deaths due to study treatment. The majority of treatment-related adverse events occurring at either dose of enobosarm were grade 1 or 2 (table 4). Grade 3 or 4 treatment-related adverse events occurred in six (8%) of 75 patients receiving 9 mg and and in ten (16%) of 61 receiving 18 mg, most frequently increased hepatic transaminases (three [4%] in the 9 mg group and two [3%] in the 18 mg group), hypercalcaemia (two [3%] and two [3%]), and fatigue (one [1%] and two [3%]). Five (8%) of 61 patients in the 18 mg group required a dose adjustment to 9 mg due to grade 3 or 4 treatment-related adverse event. Grade 1 or 2 musculoskeletal toxicity was seen 11 (15%) of 75 patients in the 9 mg group and 12 (20%) of 61 patients in the 18 mg group.

	Enobosarm 9 mg (N=75)*	Enobosarm 18 mg (N=61)
Treatment-emergent adverse events	71 (95%)	56 (92%)
Treatment-related adverse events	49 (65%)	42 (69%)
Grade 3 or higher treatment-emergent adverse events	19 (25%)	21 (34%)
Grade 3 or higher treatment-related adverse events	6 (8%)	10 (16%)
Fatal treatment-emergent adverse events†	1 (1%)	3 (5%)

*Three patients who were randomly assigned to the 18 mg dose group were treated with 9 mg daily dosing, never receiving a dose of 18 mg, therefore they were analysed for safety in the 9 mg dose group. †No deaths were drug related.

Table 3: **Summary of adverse events in the safety population**

	Enobosarm 9 mg (N=75*)			Enobosarm 18 mg (N=61)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Increased alanine aminotransferase	8 (11%)	1 (1%)	0	7 (11%)	2 (3%)	0
Increased aspartate aminotransferase	7 (9%)	2 (3%)	0	6 (10%)	0	0
Nausea	16 (21%)	0	0	8 (13%)	0	0
Hypercalcaemia	0	1 (1%)	1 (1%)	4 (7%)	1 (2%)	1 (2%)
Headache	7 (9%)	1 (1%)	0	4 (7%)	1 (2%)	0
Anaemia	3 (3%)	1 (1%)	0	0	0	0
Dry mouth	1 (1%)	0	0	0	1 (2%)	0
Decreased white blood cell count	0	0	0	0	1 (2%)	0
Decreased appetite	3 (4%)	0	0	4 (7%)	1 (2%)	0
Fatigue	30 (27%)	1 (1%)	0	7 (12%)	2 (3%)	0
Constipation	8 (11%)	0	0	6 (10%)	0	0
Tumour flare	0	0	0	0	2 (3%)	0
Agitation	0	0	0	0	1 (2%)	0
Lymphadenopathy	0	0	0	0	1 (2%)	0
Acute kidney injury	0	0	0	0	1 (2%)	0
Musculoskeletal and connective tissue disorders (general category)	11 (15%)	0	0	12 (20%)	0	0

Grade 1–2 TEAEs occurring in ≥10% of the safety population and are shown; all grade ≥3 adverse events are shown. *Three patients who were randomly assigned to the 18 mg dose group were treated with 9 mg daily dosing, never receiving a dose of 18 mg, therefore their toxicity was allocated to the 9 mg dose group.

Table 4: **Summary of treatment-related adverse events in the safety population**

Most of the 136 randomly assigned patients discontinued enobosarm treatment because of disease progression—61 (85%) of 72 in the 9 mg group and 50 (78%) of 64 in the 18 mg group. Nine patients (13%) in the 9 mg group had dose interruptions, none resulting in the discontinuation of enobosarm. Four deaths occurred. One (1%) patient in the 9 mg group died due to acute kidney failure, and three (5%) patients in the 18 mg group died due to hypertension and cardiac failure, anaemia and bone marrow failure, and sepsis (table 3). None of these deaths were deemed to be related to the study drug.

Discussion

To our knowledge, this is the first published study to explore the activity of activating the AR with a SARM in advanced breast cancer. The results of this open-label phase 2 study show that patients with ER-positive, AR-positive, and HER2-negative advanced breast cancer derived clinical benefit when treated with enobosarm following previous treatment with conventional endocrine therapy. Additionally, the proportion of patients who had clinical benefit were similar for both 9 mg and 18 mg daily.

For the past 50 years, endocrine treatment for advanced ER-positive, HER2-negative breast cancer has focused on modulating the activity of ER either by reducing the production of oestradiol (oophorectomy, ovarian suppression with luteinising hormone releasing hormone, and aromatase inhibitors), blocking the binding of oestradiol to the ER (tamoxifen), or modulating degradation of the receptor (fulvestrant or elacestrant).[17] In the past decade, ER-directed therapy in combination with targeted therapy, aimed at modulating the activity of either CDK4/6 or the PI3K/mTOR pathway, have been shown to be more efficacious than endocrine therapy alone in advanced breast cancer.[18–20] Endocrine therapies, both alone and in combination with targeted therapy, are associated with drug resistance[17] and adverse effects that can affect quality of life[21] and adherence to treatment, which can lead to poorer outcomes.[22,23] Given these issues, novel endocrine therapies are needed.

Preclinical data from clinically relevant cell lines and patient-derived tumour models have shown that AR activation exerts potent anti-tumour activity in ER-positive breast cancer.[1] Mechanistically, agonist activation of ARs altered the genomic distribution of ER resulting in repression of ER-regulated cell cycle genes and upregulation of AR target genes, including known tumour suppressors.[1] Our study results provide the first clinical validation of these preclinical data and further support the development of SARMs for the treatment of ER-positive, AR-positive, and HER2-negative breast cancer.

It has been proposed that AR activity could serve as a mechanism for endocrine resistance and that an antagonistic approach should be taken to modulating AR activity in ER-positive breast cancer.[24] However, clinical studies of this approach have shown little clinical benefit. A randomised phase 2 study of the AR antagonist enzalutamide, combined with exemestane, did not improve progression-free survival compared with exemestane alone in patients with ER-positive, AR-positive breast cancer.[25] A single group study of fulvestrant in combination with enzalutamide in advanced ER-positive, HER2-negative breast cancer also did not meet its prespecified primary endpoint as defined by clinical benefit rate.[26] Hence, there are no clinical data to support the use of AR antagonists in the treatment of ER-positive breast cancer.

During the course of this study, CDK4/6 inhibitors entered clinical practice for advanced breast cancer.[17] As a result, a small number of patients had exposure to these agents before study entry. The median progression-free survival of 2·9 months within this small group is noteworthy given the extent of previous therapies this patient cohort had been exposed to. The reported progression-free survival for single agent endocrine therapy in patients with disease progression on CDK4/6 inhibitors is short, with reported progression-free survival of 2–3 months.[27,28] Therefore, although the subset analysis in this study is limited, they are within the range of activity for single agent endocrine therapy after CDK4/6 inhibitor treatment. Given the fact that some of these patients who were highly pretreated had a disease response to enobosarm, SARMs could be a potential alternative endocrine therapy approach in patients progressing on CDK4/6 inhibition and should be further explored.

In this study, screening for *ESR1* mutations was not performed but it is highly probable that a substantial number of tumours harboured such mutations. Further work is required to understand the efficacy of enobosarm in patients with *ESR1*-mutated, ER-positive, AR-positive breast cancer. However, preclinical studies have shown efficacy of enobosarm in contemporary patient-derived models, including advanced, therapy-resistant disease states harbouring *ESR1* mutations.[1]

Our results show that enobosarm is safe and well tolerated with no concerning adverse effects or serious clinical outcomes. The majority of treatment-related adverse events seen in both the 9 mg and 18 mg enobosarm dose groups were grade 1 or 2. The most serious toxicities seen were transient elevations of transaminases, which have been reported in previous studies with enobosarm,[11,29] and in the phase 1 study of the SARM RAD-140.[30] The increased amounts of transaminases might not be hepatic in origin given the known regulation of alanine aminotransferase by ARs in muscle and the increase in its transcription with androgen administration.[31] However, this hypothesis requires further investigation.

Our study showed no significant changes in health status over time in both dose groups and less than half of

the patients had a worse health profile at each timepoint compared with baseline, including at the time of documented disease progression. A key challenge of ER-directed endocrine therapy are adverse effects such as early or worsened menopausal symptoms, sexual dysfunction, and arthralgia, which can adversely affect quality of life and therapy adherence.[32] In this study, enobosarm administration was associated with low rates of arthralgias, with grade 1 or 2 occurring in less than 20% of 136 enrolled patients. The frequency of vasomotor and urogenital symptoms with SARMs needs to be investigated further in larger studies.

Our findings need to be interpreted in the context of several limitations. Specifically, the open-labelled nature of the study, the relatively small number of patients enrolled in each group, the absence of a placebo control group, and the heterogeneity of patients in this heavily pretreated population.

In conclusion, the data from this study provide proof-of-concept for the activity and safety of a novel SARM, enobosarm, in AR-positive, ER-positive, and HER2-negative metastatic breast cancer, thus supporting the premise that activating AR can exert anti-tumour effects. Enobosarm was found to be well tolerated with no negative effects on quality of life. These data support further development and assessment of the efficacy of enobosarm and other selective AR activation strategies for the treatment of AR-positive, ER-positive, HER2-negative advanced breast cancer.

Contributors

BO, CP, TEH, and WDT contributed to study conception and design. CP, HL, SNB, SW, EL, LSS, HSR, PC, JAO, SJ, AB, and BO were principal investigators and contributed to study initiation. All authors had unrestricted access to final study data, and were responsible for data interpretation, preparation of the manuscript, and the decision to submit for publication. The manuscript was written and compiled by CP, BO, WDT, TEH, and ARD. BO, CP, WDT, and ARD have accessed and verified the data. All authors attest to study completeness and the accuracy of the data and data analysis and approved the final version of the manuscript.

Declaration of interests

CP reports grants or contracts from Seagen, Daiichi-Sankyo, Pfizer, and Exact Science (outside of this work); consulting for Seagen, Daiichi-Sankyo, Exact Science, MEDAC, Gilead, and Pfizer; honoraria from Pfizer, Seagen, AstraZeneca, Roche, Eisai, and Novartis; travel support from Roche and Novartis; leadership role in Advise Make 2nd Count (unpaid); and stock in Digistain. HL reports grants or contracts from Sanofi, Zionexa, Tolmar, Pfizer, Zeno Pharmaceutical, Zymeworks, and Veru (outside of this work); consulting for Sanofi, GE Healthcare, Lilly, Novartis, and Gilead; and honoraria from Sanofi, GE Healthcare, Lilly, Novartis, and Gilead. EL reports research funding from Pfizer and Ellipses Pharma (outside of this work); honoraria for Ellipses Pharma, Pfizer, AstraZeneca, Gilead, MSD, and Lilly; patents planned, issued, or pending with Walter & Eliza Hall Institute; advisory board with Ellipses Pharma, Novartis, Pfizer, AstraZeneca, Gilead, MSD, Lilly (all paid to institution); and leadership in Breast Cancer Trials Australia, American Society of Clinical Oncology Research Committee. TEH reports grant funding from Australian National Health and Medical Research Council and National Breast Cancer Foundation (Australia). ARD reports grant funding from Australian National Health and Medical Research Council and National Breast Cancer Foundation (Australia); research support from Ellipses Pharma (outside of this work); and travel support from Fusion Conferences. HSR reports grants from Astellas Pharma, AstraZeneca, Daiichi Sankyo, F. Hoffmann-La Roche AG/Genentech, Gilead Sciences, GlaxoSmithKline, Lilly, Merck, Novartis Pharmaceutical Corporation, Pfizer, Fionyr Immunotherapeutics, Sermonix Pharmaceuticals, Taiho Oncology, and Veru; and honoraria from Daiichi Sankyo, Mylan, NAPO, and Puma Biotechnology. PC reports research support from GTx. JAO reports consulting for AbbVie, Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Carrick Therapeutics, GlaxoSmithKline, Genentech, Genzyme, Gilead Sciences, Immunomedics, Incyte Corporation, Lilly, Merck, Novartis, Ontada, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Prime Oncology, Roche, Samsung Bioepis, Sanofi, Seagen, Stemline Therapeutics, Theralink, Synthon and Veru; and honoraria from AbbVie, Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Carrick Therapeutics, GlaxoSmithKline, Genentech, Genzyme, Gilead Sciences, Immunomedics, Incyte Corporation, Lilly, Merck, Novartis, Ontada, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Prime Oncology, Roche, Samsung Bioepis, Sanofi, Seagen, Stemline Therapeutics, Theralink, Synthon and Veru. SJ reports research funding from Pfizer, Puma Biotechnology, Lilly, AstraZeneca, Novartis, Roche/Genentech (outside of this work); consulting or advisory role for Lilly, AstraZeneca, Puma Biotechnology, Pfizer, Novartis, and Sanofi Genzyme; and honoraria from Pfizer, Eisai, AstraZeneca, and Roche/Genentech. WDT reports grant funding from Australian National Health and Medical Research Council; research support from Ellipses Pharma (outside of this work); and consulting for HavaH. AB reports consulting for AstraZeneca, Pfizer, Novartis, Lilly, Genentech/Roche, SeaGen, Daiichi Sankyo, Merck, Agendia, Sanofi, Puma Biotechnology, Myriad, and Gilead. BO reports funding from GTx; research support from Eisai and Incyte (outside of this work); and Chief Medical Advisory role for the Milburn Foundation (unpaid).

Data sharing

Patient data will be provided by Veru on request. Any request should be sent to Veru, with a detailed description of the research protocol. Veru reserves the right to decide whether to share the data or not. Access will be provided after a proposal has been approved by an independent review committee established for this purpose and after receipt of a signed data sharing agreement.

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References

1 Hickey TE, Selth LA, Chia KM, et al. The androgen receptor is a tumor suppressor in estrogen receptor-positive breast cancer. *Nat Med* 2021; **27:** 310–20.
2 Freelander A, Laven-Law G, Eshraghi L, et al. Combination CDK4/6 inhibition and AR agonism suppresses the growth of CDK4/6 inhibitor resistant breast cancers. *Cancer Res* 2022; **82** (suppl)**:** PD2-02-PD2- (abstr).
3 Adair FE, Herrmann JB. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. *Ann Surg* 1946; **123:** 1023–35.
4 Kennedy BJ. Fluoxymesterone therapy in advanced breast cancer. *N Engl J Med* 1958; **259:** 673–75.
5 Goldenberg IS. Testosterone propionate therapy in breast cancer. *JAMA* 1964; **188:** 1069–72.
6 Goldenberg IS, Hayes MA. Hormonal therapy of metastatic female breast carcinoma. II. 2alpha-Methyl dihydrotestosterone propionate. *Cancer* 1961; **14:** 705–06.
7 Westerberg H. Tamoxifen and fluoxymesterone in advanced breast cancer: a controlled clinical trial. *Cancer Treat Rep* 1980; **64:** 117–21.

8 Mohler ML, Bohl CE, Jones A, et al. Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. *J Med Chem* 2009; **52:** 3597–617.

9 Jones A, Coss C, Steiner M, Dalton J. An overview on selective androgen receptor modulators: focus on enobosarm. *Drugs Future* 2013; **38:** 309–16.

10 Coss CC, Jones A, Dalton JT. Selective androgen receptor modulators as improved androgen therapy for advanced breast cancer. *Steroids* 2014; **90:** 94–100.

11 Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. *J Cachexia Sarcopenia Muscle* 2011; **2:** 153–61.

12 Marcantonio EE, Witter RE, Ding Y, et al. A 12-week pharmacokinetic and pharmacodynamic study of two selective androgen receptor modulators (SARMs) in postmenopausal subjects. *Endocr Rev* 2010; **31.**

13 Overmoyer B, Sanz-Altimira P, Partridge AH, Extermann M, Liu J, Winer E, et al. Enobosarm for the treatment of metastatic, estrogen and androgen receptor positive, breast cancer. Final results of the primary endpoint and current progression free survival. *Cancer Res* 2015; **75** (suppl): P1-13-04-P1-13-04 (abstr).

14 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

15 Feng Y, Parkin D, Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. *Qual Life Res* 2014; **23:** 977–89.

16 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–36.

17 Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. *N Engl J Med* 2020; **383:** 2557–70.

18 Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; **366:** 520–29.

19 Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med* 2022; **386:** 942–50.

20 André F, Ciruelos E, Rubovszky G, et al. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* 2019; **380:** 1929–40.

21 Ciruelos EM, Rugo HS, Mayer IA, et al. Patient-reported outcomes in patients with *PIK3CA*-mutated hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer from SOLAR-1. *J Clin Oncol* 2021; **39:** 2005–15.

22 Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. *Cancer Prev Res (Phila)* 2014; **7:** 378–87.

23 Makubate B, Donnan PT, Dewar JA, Thompson AM, McCowan C. Cohort study of adherence to adjuvant endocrine therapy, breast cancer recurrence and mortality. *Br J Cancer* 2013; **108:** 1515–24.

24 Cochrane DR, Bernales S, Jacobsen BM, et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res* 2014; **16:** R7.

25 Krop I, Abramson V, Colleoni M, et al. A randomized placebo controlled phase II trial evaluating exemestane with or without enzalutamide in patients with hormone receptor-positive breast cancer. *Clin Cancer Res* 2020; **26:** 6149–57.

26 Elias AD, Spoelstra NS, Staley AW, et al. Phase II trial of fulvestrant plus enzalutamide in ER+/HER2- advanced breast cancer. *NPJ Breast Cancer* 2023; **9:** 41.

27 Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol* 2022; **40:** 3246–56.

28 Lindeman GJ, Fernando TM, Bowen R, et al. VERONICA: Randomized phase II study of fulvestrant and venetoclax in ER-positive metastatic breast cancer post-CDK4/6 inhibitors—efficacy, safety, and biomarker results. *Clin Cancer Res* 2022; **28:** 3256–67.

29 Dobs AS, Boccia RV, Croot CC, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol* 2013; **14:** 335–45.

30 LoRusso P, Hamilton E, Ma C, et al. A first-in-human phase 1 study of a novel selective androgen receptor modulator (SARM), RAD140, in ER+/HER2- metastatic breast cancer. *Clin Breast Cancer* 2022; **22:** 67–77.

31 Coss CC, Bauler M, Narayanan R, Miller DD, Dalton JT. Alanine aminotransferase regulation by androgens in non-hepatic tissues. *Pharm Res* 2012; **29:** 1046–56.

32 Bernhard J, Luo W, Ribi K, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. *Lancet Oncol* 2015; **16:** 848–58.