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Fulvestrant Plus Vistusertib vs Fulvestrant Plus Everolimus vs Fulvestrant Alone for Women With Hormone Receptor–Positive Metastatic Breast Cancer

The MANTA Phase 2 Randomized Clinical Trial

Peter Schmid, FRCP, PhD; Matthias Zaiss, MD; Catherine Harper-Wynne, MD; Marta Ferreira, MD; Sidharth Dubey, FRCR; Stephen Chan, FRCP, DM; Andreas Makris, FRCP; Gia Nemsadze, MD, PhD; Adrian M. Brunt, FRCP; Sherko Kuemmel, MD, PhD; Isabel Ruiz, MD; Antonia Perelló, MD; Anne Kendall, MD; Janet Brown, MD; Hartmut Kristeleit, FRCP; John Conibear, MD; Cristina Saura, MD; Julien Grenier, MD; Károly Máhr, MD; Michael Schenker, MD, PhD; Joohyuk Sohn, MD, PhD; Keun Seok Lee, MD, PhD; Christopher J. Shepherd, PhD; Elisabeth Oelmann, MD, PhD; Shah-Jalal Sarker, PhD; Aaron Prendergast, MSc; Patricia Marosics, BSc; Atiyyah Moosa, BSc; Cheryl Lawrence, BPharm; Carike Coetzee, MSc; Kelly Mousa, MSc; Javier Cortés, MD, PhD

IMPORTANCE Randomized clinical trials have demonstrated a substantial benefit of adding everolimus to endocrine therapy. Everolimus inhibits the mammalian target of rapamycin complex 1 (mTORC1) complex but not mTORC2, which can set off an activating feedback loop via mTORC2. Vistusertib, a dual inhibitor of mTORC1 and mTORC2, has demonstrated broad activity in preclinical breast cancer models, showing superior activity to everolimus.

OBJECTIVE To evaluate the safety and efficacy of vistusertib in combination with fulvestrant compared with fulvestrant alone or fulvestrant plus everolimus in postmenopausal women with estrogen receptor–positive advanced or metastatic breast cancer.

DESIGN, SETTING, AND PARTICIPANTS The MANTA trial is an open-label, phase 2 randomized clinical trial in which 333 patients with estrogen receptor–positive breast cancer progressing after prior aromatase inhibitor treatment underwent randomization (2:3:3:2) between April 1, 2014, and October 24, 2016, at 88 sites in 9 countries: 67 patients were assigned to receive fulvestrant, 103 fulvestrant plus vistusertib daily, 98 fulvestrant plus vistusertib intermittently, and 65 fulvestrant plus everolimus. Treatment was continued until disease progression, development of unacceptable toxic effects, or withdrawal of consent. Analysis was performed on an intention-to-treat basis.

INTERVENTIONS Fulvestrant alone or in combination with vistusertib (continuous or intermittent dosing schedules) or everolimus.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival (PFS).

RESULTS Among the 333 women in the study (median age, 63 years [range, 56-70 years]), median PFS was 5.4 months (95% CI, 3.5-9.2 months) with fulvestrant, 7.6 months (95% CI, 5.9-9.4 months) with fulvestrant plus daily vistusertib, 8.0 months (95% CI, 5.6-9.9 months) with fulvestrant plus intermittent vistusertib, and 12.3 months (95% CI, 7.7-15.7 months) with fulvestrant plus everolimus. There was no significant difference in PFS between those receiving fulvestrant plus daily or intermittent vistusertib and fulvestrant alone (hazard ratio, 0.88 [95% CI, 0.63-1.24]; $P = .46$; and hazard ratio, 0.79 [95% CI, 0.55-1.12]; $P = .16$).

CONCLUSIONS AND RELEVANCE The combination of fulvestrant plus everolimus demonstrated significantly longer PFS compared with fulvestrant plus vistusertib or fulvestrant alone. The trial failed to demonstrate a benefit of adding the dual mTORC1 and mTORC2 inhibitor vistusertib to fulvestrant.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Peter Schmid, FRCP, PhD, Barts Cancer Institute, Centre for Experimental Cancer Medicine, Queen Mary University of London, Old Anatomy Building, Charterhouse Square, London EC1M 6BQ, United Kingdom (p.schmid@qmul.ac.uk).

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Resistance to endocrine therapy remains a major clinical challenge in women with hormone receptor–positive advanced or metastatic breast cancer. There is increasing evidence that aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)–mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in endocrine resistance.[1] Approximately 50% of estrogen receptor (ER)–positive primary breast cancers show abnormal intrinsic activation of the PI3K-mTOR pathway and many patients with advanced or metastatic breast cancer develop acquired upregulation of PI3K-mTOR signaling.[2-4]

Preclinical investigation demonstrates that inhibition of mTOR can overcome endocrine resistance.[5-9] Clinical trials have demonstrated a substantial benefit of adding the mTOR inhibitor everolimus to endocrine agents, especially in endocrine-resistant breast cancer.[10-12] Everolimus is indicated for the treatment of hormone receptor–positive, *ERBB2/HER2*-negative advanced breast cancer in combination with exemestane in postmenopausal women without symptomatic visceral disease after recurrence or progression after treatment with a nonsteroidal aromatase inhibitor (AI).

The mTOR kinase forms 2 distinct multiprotein complexes, mammalian target of rapamycin complex 1 (mTORC1) and mTORC2. Current clinical mTOR inhibitors such as everolimus inhibit the mTORC1 complex only through an indirect mechanism that does not involve the mTOR kinase, and there is increasing evidence that this mechanism sets off a negative feedback loop leading to the activation of mTORC2, AKT phosphorylation, and ultimately treatment resistance.[13] Preclinical studies have demonstrated that rapamycin analogues are unable to completely abrogate mTORC1 signaling and the residual activity of the downstream effector 4E-BP1 can continue to initiate protein translation.[14] Mammalian target of rapamycin kinase inhibitors have been developed to enhance the antitumor activity through more complete TORC1 inhibition and abrogating AKT-mediated TORC2 activation.

Vistusertib (AZD2014) is a dual inhibitor of both mTORC1 and mTORC2 complexes[15]; compared with everolimus, vistusertib has demonstrated more complete growth inhibition and cell death in vitro and in vivo based on a greater inhibitory function against mTORC1 and additional inhibition of mTORC2, especially in ER-positive breast cancer models.[16]

Most preclinical and clinical applications of PI3K inhibitors or mTOR inhibitors use continuous daily dosing schedules. However, high-dose pulsatile administration has been proposed as a way to induce more complete suppression of mTOR signaling to maximize therapeutic benefit while reducing toxic effects by allowing for recovery of nontarget tissues during dosing breaks.[17,18] Using intermittent dosing (2 days on and 5 days off), vistusertib induced rapid tumor regression in preclinical models.[16] The shorter half-life of vistusertib (mean, 3.3 hours) compared with other mTOR inhibitors enables pulsatile administration of the medication. The maximum tolerated doses for both continuous daily and intermittent dosing of vistusertib was established in phase 1 studies with substantial antitumor activity demonstrated for both schedules.[16]

The MANTA trial evaluated whether the addition of vistusertib (AZD2014) increases progression-free survival (PFS) and other measures of antitumor activity of fulvestrant in postmenopausal women with ER-positive advanced or metastatic breast cancer who have failed prior therapy with AIs. The study also evaluated whether dual inhibition of mTORC1 and mTORC2 with vistusertib leads to improved efficacy compared with mTORC1 inhibition with everolimus and explored whether high-dose pulsatile dosing of vistusertib can increase the activity and/or improve tolerability compared with continuous daily treatment.

Key Points

Question Does the addition of vistusertib increase progression-free survival and other measures of antitumor activity of fulvestrant in postmenopausal women with estrogen receptor–positive advanced or metastatic breast cancer that progressed after prior therapy with aromatase inhibitors?

Findings This randomized clinical trial in 333 patients failed to demonstrate a benefit of vistusertib plus fulvestrant vs fulvestrant alone. In addition, the outcomes in both vistusertib groups were inferior to those in the group treated with fulvestrant plus everolimus.

Meaning The results suggest that dual mammalian target of rapamycin inhibition with vistusertib at the maximal tolerated doses is inferior to mammalian target of rapamycin complex 1 inhibition with the rapamycin analogue everolimus.

Methods

Study Design and Participants

In the MANTA trial, an investigator-led, open-label, randomized phase 2 trial, patients were recruited between April 1, 2014, and October 24, 2016, in 88 centers in the United Kingdom, Spain, Germany, South Korea, France, Portugal, Hungary, Romania, and Georgia (trial protocol in Supplement 1). Postmenopausal women with ER-positive, locally advanced or metastatic breast cancer were eligible if they either relapsed while undergoing or within 12 months of the end of adjuvant treatment with an AI or progressed on treatment with an AI. Any number of lines of hormonal therapy were allowed and AI therapy did not have to be the last treatment prior to randomization. Prior chemotherapy in the adjuvant or neoadjuvant setting and 1 line of prior chemotherapy for metastatic disease were allowed. Measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)[19] and adequate hematologic, hepatic, and renal function, and an Eastern Cooperative Oncology Group performance status of 0 to 2 were required. Patients with life-threatening metastatic visceral disease, active or treated brain metastases, significant pulmonary dysfunction, significant cardiac disease, QT prolongation, type 1 diabetes or uncontrolled type 2 diabetes, and previous treatment with fulvestrant, exemestane, mTOR, PI3K, or AKT inhibitors were excluded. All patients provided written informed consent. The relevant institutional review boards and ethics committees for the 88 participating centers approved the study, which was conducted

in accordance with the principles of Good Clinical Practice,[20] the provisions of the Declaration of Helsinki,[21] and other applicable local regulations. The Barts Experimental Cancer Medicine Centre had overall responsibility for trial management; the Trial Management Group was responsible for day-to-day running of the trial, and the trial was overseen by an independent trial steering committee. Safety data were reviewed regularly by the trial steering committee and an independent data monitoring committee.

Randomization

Patients were randomized via Interactive Web Response System (2:3:3:2) to receive fulvestrant, fulvestrant plus vistusertib (daily or intermittent), or fulvestrant plus everolimus, respectively. Computer-generated permuted blocks were used with stratification by disease measurability and previous sensitivity to endocrine therapy, defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting, complete or partial response to prior metastatic endocrine treatment, or stabilization for at least 24 weeks of endocrine therapy for advanced disease.

Procedures

Fulvestrant was given as a 500-mg intramuscular injection loading dose on day 1, followed by 500-mg injections on days 15 and 29. Thereafter, 500-mg intramuscular injections were given every 28 days. Everolimus was given orally once daily at a dose of 10 mg. The continuous daily schedule of vistusertib was given orally twice daily at a dose of 50 mg. Intermittent vistusertib was given orally twice daily on days 1 and 2 of every week at a dose of 125 mg. Treatment was continued until disease progression, unacceptable toxic effects, or withdrawal of consent. The protocol provided detailed guidelines for dose interruptions or reductions for vistusertib and everolimus; dose adjustments for fulvestrant followed local guidelines.

The primary end point was PFS based on results of radiographic studies assessed by the local investigators, with independent central assessment on a subset of patients. Progression-free survival was defined as time from randomization to disease progression or death from any cause, whichever occurred first. Secondary end points included overall survival (OS), objective response rate, clinical benefit rate, duration of response, clinical benefit, and safety.

Tumor assessment with RECIST 1.1 included computed tomography scanning or magnetic resonance imaging of the chest, abdomen, and pelvis at baseline, every 8 weeks during the first 40 weeks, and every 12 weeks thereafter until disease progression. Patients who discontinued 1 or both study treatments for any reason other than progression of disease were required to follow the same schedule of assessments until progression.

Patients were monitored for adverse events (AEs) and changes in laboratory test values, electrocardiogram results, and physical examination findings. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 4.03)[22] and coded with the Medical Dictionary for Regulatory Activities.[23]

Statistical Analysis

Sample size was based on detecting an improvement in median PFS from 3.7 to 11.1 months (hazard ratio [HR], 0.40) in patients allocated to receive fulvestrant plus vistusertib (analyzed separately for each schedule) compared with fulvestrant alone, and detecting an improvement in median PFS from 7.4 to 11.1 months (HR, 0.67) in patients allocated to receive fulvestrant plus vistusertib compared with fulvestrant plus everolimus. With a minimum follow-up of 18 months, a 5% significance level (1-sided), and 99% power, a total of 130 PFS events in the fulvestrant plus vistusertib and fulvestrant comparison were needed for the principal analysis. For the comparison of fulvestrant plus vistusertib vs fulvestrant plus everolimus, 120 PFS events were needed based on a follow-up of 18 months, a 10% significance level (1-sided), and 80% power.

Principal efficacy analyses included all randomized patients on an intention-to-treat basis, with patients analyzed according to the treatment group to which they were randomized. Survival end points were shown graphically with Kaplan-Meier plots, and treatment comparisons were made with the log-rank test. Hazard ratios were obtained from Cox proportional hazards regression models, with HRs of less than 1 favoring fulvestrant plus vistusertib in the comparison with fulvestrant alone, and fulvestrant plus everolimus in the comparison with fulvestrant plus vistusertib.

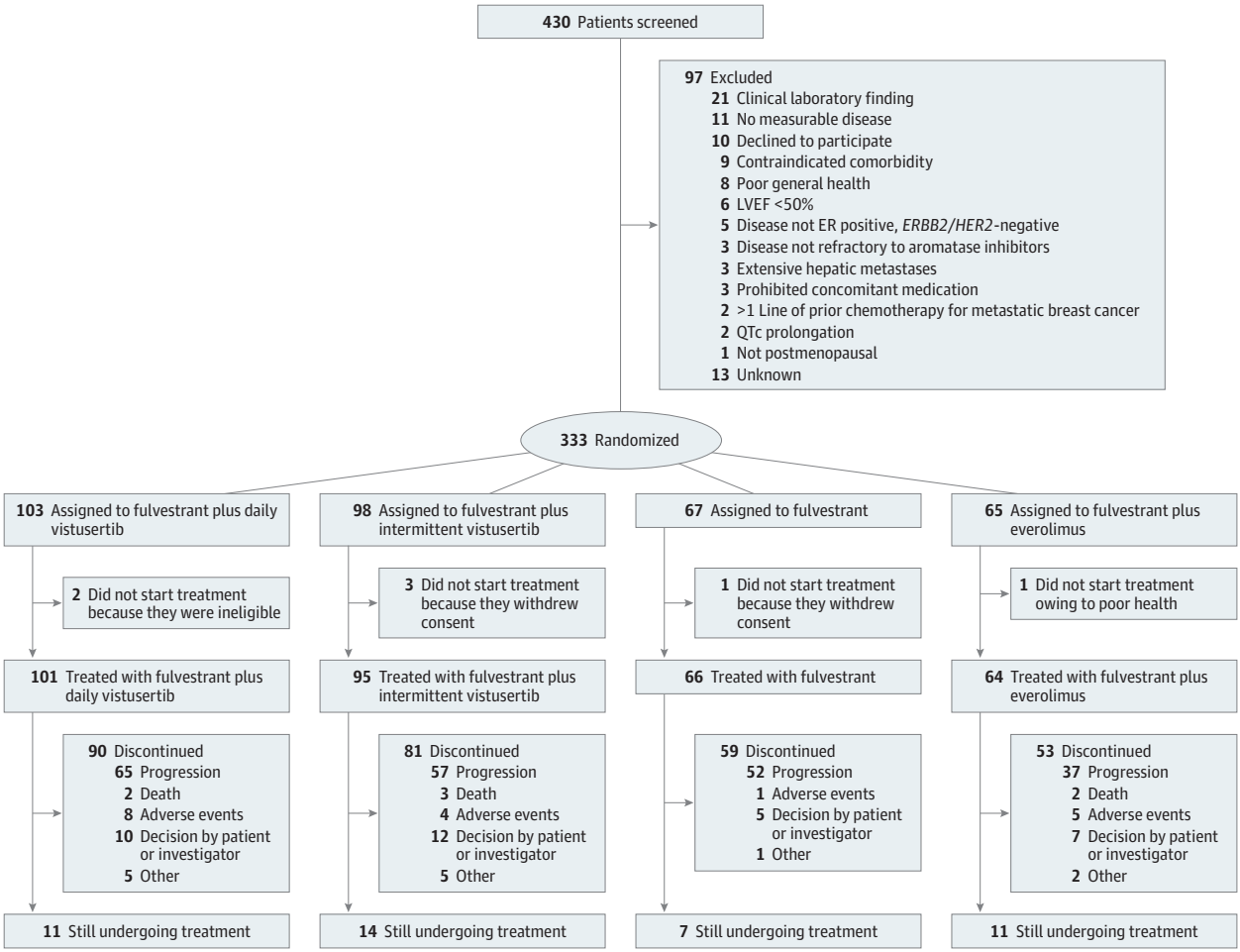
Safety analyses included all patients who received at least 1 dose of trial treatment. The worst grade of AE during trial treatment was reported and compared with Fisher exact tests. All prespecified toxic effects and any Medical Dictionary for Regulatory Activities–coded event satisfying predefined criteria are presented.

Results

Between April 1, 2014, and October 24, 2016, 333 patients underwent randomization (**Figure 1**): 67 patients were assigned to receive fulvestrant, 103 fulvestrant plus vistusertib daily, 98 fulvestrant plus vistusertib intermittently, and 65 fulvestrant plus everolimus. Baseline distributions of patient and tumor characteristics were similar in the treatment groups (eTable 1 in Supplement 2). Median age was 63 years; 202 of 326 patients had visceral involvement (62.0%) and 254 of 326 (77.9%) had measurable disease. A total of 103 of 325 patients (31.7%) had metastases in at least 3 organs and most patients had received systemic therapy for metastatic breast cancer. A total of 282 of 326 patients (86.5%) had previous sensitivity to endocrine therapy.

At the cutoff date (October 13, 2017), 43 patients (12.9%) were still receiving study treatment: 25 of 196 (12.8%) in the fulvestrant plus vistusertib groups, 11 of 64 (17.2%) in the fulvestrant plus everolimus group, and 7 of 66 (10.6%) in the fulvestrant alone group (eTable 1 in Supplement 2). A higher percentage of patients in the 3 combination groups discontinued study treatment because of AEs or withdrawal of consent (fulvestrant plus daily vistusertib, 18 of 101 [17.8%]; fulvestrant plus intermittent vistusertib, 16 of 95 [16.8%]; and fulvestrant plus

Figure 1. CONSORT Diagram



LVEF indicates left ventricular ejection fraction.

everolimus, 12 of 64 [18.8%]) compared with patients treated with fulvestrant alone (6 of 66 [9.1%]), with no significant differences between the combination groups. Treatment adherence was comparable between the 3 combination groups, with 3% to 5% of Investigational Medicinal Product doses being missed and 28.4% to 33.7% of patients (fulvestrant plus daily vistusertib, 34 of 101 [33.7%]; fulvestrant plus intermittent vistusertib, 27 of 95 [28.4%]; and fulvestrant plus everolimus, 21 of 64 [32.8%]) requiring at least 1 dose reduction of vistusertib or everolimus.

Frequency of AEs (any grade) and severe AEs (grade 3 or 4) was higher in patients assigned to the combination groups than in those assigned to receive fulvestrant alone (eTable 2 in Supplement 2). The most common grade 3 or 4 AEs in the combination groups were stomatitis (12 of 92 [13.0%] in vistusertib daily group vs 4 of 92 [4.3%] in vistusertib intermittent group vs 7 of 60 [11.7%] in everolimus group), rash (19 of 92 [20.7%] vs 4 of 92 [4.3%] vs 3 of 60 [5.0%]), asthenia (2 of 92 [2.2%] vs 5 of 92 [5.4%] vs 2 of 60 [3.3%]), diarrhea (2 of 92 [2.2%] vs 5 of 92 [5.4%] vs 1 of 60 [1.7%]), hyperglycemia (4 of 92 [4.3%] vs 3 of 92 [3.3%] vs 2 of 60 [3.3%]), infection (5 of 92 [5.4%] vs 1 of 92 [1.1%] vs 4 of 60 [6.7%]), dyspnea (3 of 92 [3.3%] vs 0% vs 0%), and nausea (0% vs 3 of 92 [3.3%] vs 0%). Intermittent dosing of vistusertib was associated with a lower rate of rash or stomatitis but a higher rate of nausea and vomiting than daily dosing of vistusertib.

After a median follow-up in all patients of 17.1 months (95% CI, 15.9-18.3 months), 255 progression events were reported: 57 in patients assigned to fulvestrant, 81 in those assigned to fulvestrant plus vistusertib daily, 72 in those assigned to fulvestrant plus vistusertib intermittently, and 45 in patients assigned to fulvestrant plus everolimus.

Median PFS in patients assigned to fulvestrant alone was 5.4 months (95% CI, 3.5-9.2 months), 7.6 months (95% CI, 5.9-9.4 months) in those assigned to fulvestrant plus daily vistusertib, 8.0 months (95% CI, 5.6-9.9 months) in those assigned to fulvestrant plus intermittent vistusertib, and 12.3 months (95% CI, 7.7-15.7 months) in those assigned to fulvestrant plus everolimus (**Table**). No significant difference in PFS was seen between the patients assigned to receive fulvestrant plus daily vistusertib and those who received fulvestrant alone (HR, 0.88 [95% CI, 0.63-1.24]; log-rank P = .46),

Table. Primary and Key Secondary Efficacy End Points

End Point	Fulvestrant Plus Daily Vistusertib (n = 101)	Fulvestrant Plus Intermittent Vistusertib (n = 95)	Fulvestrant (n = 66)	Fulvestrant Plus Everolimus (n = 64)
PFS, median (95% CI), mo	7.6 (5.9-9.4)	8.0 (5.6-9.9)	5.4 (3.5-9.2)	12.3 (7.7-15.7)
HR vs fulvestrant (95% CI)	0.88 (0.63-1.24)	0.79 (0.55-1.12)	NA	NA
P value	.46	.16	NA	NA
HR vs fulvestrant plus everolimus (95% CI)	0.63 (0.45-0.90)	0.71 (0.49-1.01)	0.63 (0.42-0.92)	NA
P value	.01	.06	.01	NA
Objective response rate, % (95% CI)	30.4 (20.5-41.8)	28.6 (18.8-40.0)	25.0 (14.0-38.9)	41.2 (27.6-55.8)
Clinical benefit rate, % (95% CI)	43.0 (31.9-54.7)	39.0 (28.0-50.8)	38.5 (25.3-53.0)	56.9 (42.2-70.7)
Duration of response median (95% CI), mo	11.8 (8.4-13.7)	9.4 (5.9-14.5)	16.7 (10.8-19.3)	17.6 (9.1-19.1)
Duration of clinical benefit median (95% CI), mo	12.0 (11.8-16.6)	13.4 (11.2-18.9)	16.7 (12.8-20.2)	14.3 (12.2-18.6)
Overall survival median (95% CI), mo	27.1 (20.0-NR)	24.2 (20.6-NR)	24.4 (17.3-NR)	NR

Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reached; PFS, progression-free survival.

between patients assigned to receive fulvestrant plus intermittent vistusertib and those who received fulvestrant alone (HR, 0.79 [95% CI, 0.55-1.12]; log-rank *P* = .16), and between both fulvestrant plus vistusertib groups (HR, 1.11 [95% CI, 0.81-1.52]; log-rank *P* = .52). Progression-free survival was significantly longer in patients assigned to fulvestrant plus everolimus compared with fulvestrant plus daily vistusertib (HR, 0.63 [95% CI, 0.45-0.90; log-rank *P* = .01) and those assigned to fulvestrant plus everolimus compared with fulvestrant alone (HR, 0.63 [95% CI, 0.42-0.92]; log-rank *P* = .01) (**Figure 2**).

In patients with measurable disease, objective response rate on the basis of local assessment for patients receiving fulvestrant alone was 25.0%; for those receiving fulvestrant plus daily vistusertib, 30.4%; for those receiving fulvestrant plus intermittent vistusertib, 28.6%; and for those receiving fulvestrant plus everolimus, 41.2% (Table). Central assessment showed consistent results. Median duration of response in patients assigned to fulvestrant alone was 16.7 months (95% CI, 10.8-19.3 months); fulvestrant plus daily vistusertib, 11.8 months (95% CI, 8.4-13.7 months); fulvestrant plus intermittent vistusertib, 9.4 months (95% CI, 5.9-14.5 months); and fulvestrant plus everolimus, 17.6 months (95% CI, 9.1-19.1 months).

Overall survival results were relatively immature at the time of the analysis, with a total of 96 deaths: 36 of 101 patients (35.6%) in the daily vistusertib group, 26 of 95 patients (27.4%) in the intermittent vistusertib group, 21 of 66 patients (31.8%) in the fulvestrant alone group, and 13 of 64 patients (20.3%) in the fulvestrant plus everolimus group. Survival was longer in patients assigned to fulvestrant plus everolimus compared with fulvestrant plus daily vistusertib (HR, 0.49 [95% CI, 0.28-0.86]; log-rank *P* = .02). There was also a trend toward improved OS in patients assigned to fulvestrant plus everolimus compared with fulvestrant alone (HR, 0.56 [95% CI, 0.28-1.09]; log-rank *P* = .09).

Discussion

The MANTA trial is the first trial to our knowledge to compare a dual mTOR inhibitor with a rapamycin analogue in postmenopausal women with ER-positive advanced or metastatic breast cancer. The trial did not meet its primary end point and failed to demonstrate a benefit of vistusertib plus fulvestrant compared with fulvestrant alone. Furthermore, both vistusertib groups were inferior to treatment with fulvestrant plus everolimus. As these clinical results are in contrast with the evidence from in vitro and in vivo preclinical models, showing substantial synergistic activity between fulvestrant and vistusertib and also superior activity of vistusertib compared with everolimus in endocrine-sensitive and -resistant breast cancer models,[18] it is important to assess what factors might have contributed to the failure of vistusertib in this trial.

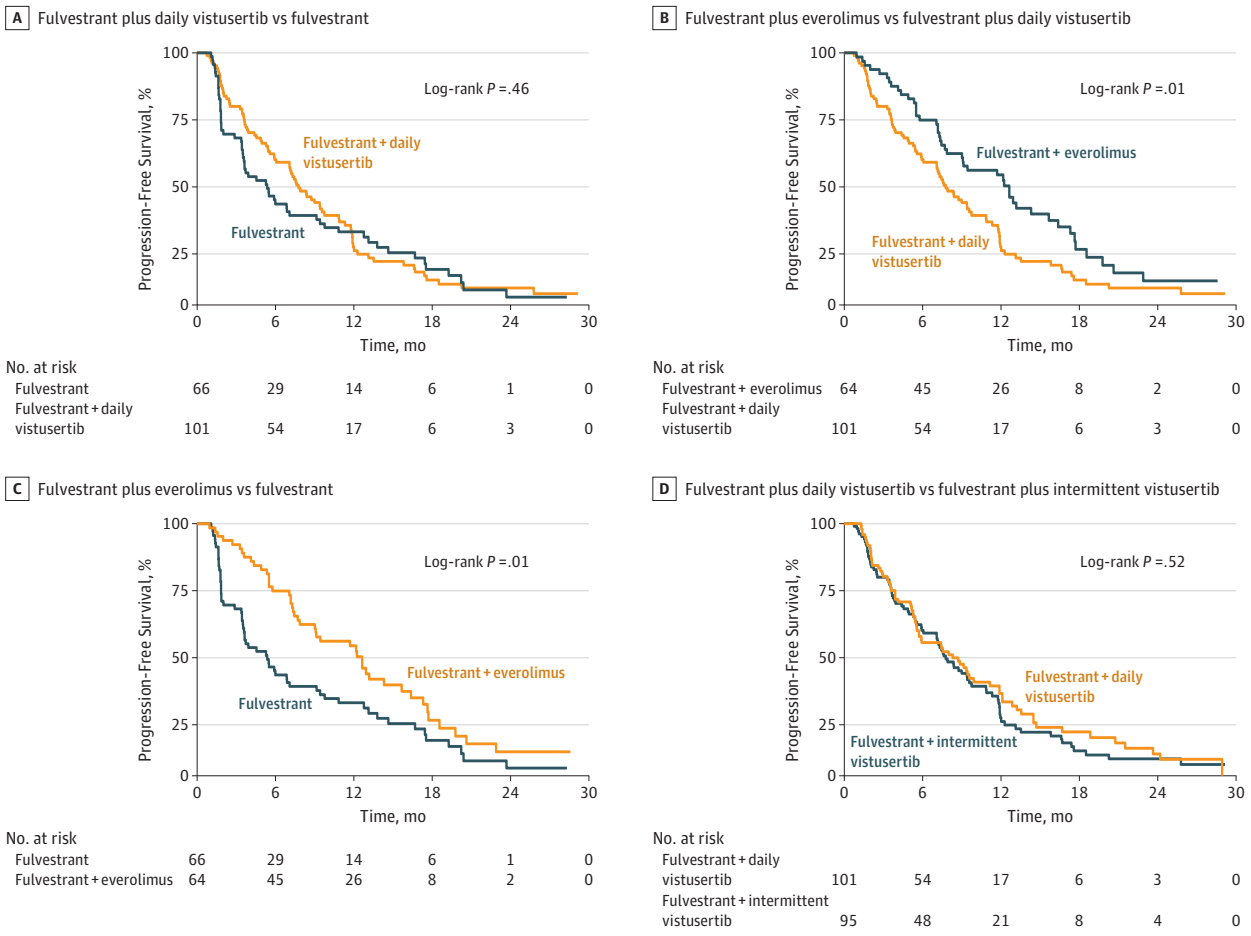
All 4 patient groups were well balanced in terms of baseline patient and disease characteristics (eTable 1 in Supplement 2) and the results of the fulvestrant alone group and the fulvestrant plus everolimus group are consistent with results from other clinical trials, making it unlikely that patient selection or possible imbalances are the key driver for the observed results.

Another question is whether a comparable dose intensity was maintained across the different treatment groups. However, given that there was no difference in the median number and percentage of missed treatment days of vistusertib or everolimus, as well as in the percentage of patients requiring at least 1 dose reduction of everolimus or vistusertib, or in the percentage of patients discontinuing treatment for reasons other than disease progression or death, it seems unlikely that the lack of observed activity of vistusertib can be attributed to differences in treatment adherence and dose intensity.

Instead, the results raise the question whether the selected doses of vistusertib might not have been adequate to fully exert its established preclinical activity. The doses and schedules within the MANTA trial were based on the maximum tolerated doses established in a phase 1 trial of vistusertib and fulvestrant.[16] This study used similar criteria for dose-limiting toxic effects as the dose-finding trials for everolimus.[24-26] Consequently, AE profiles were largely comparable between the daily vistusertib group and the everolimus group.

However, given that vistusertib inhibits both mTORC1 and mTORC2 complexes, a possible explanation could be that the toxic effect-mandated doses of vistusertib achieved only sub-

Figure 2. Kaplan-Meier Plot of Progression-Free Survival (PFS)



A, Fulvestrant plus daily vistusertib vs fulvestrant (median PFS: fulvestrant plus daily vistusertib, 7.6 months; fulvestrant, 5.4 months; hazard ratio, 0.88 [95% CI, 0.63-1.24]; log-rank P = .46). B, Fulvestrant plus everolimus vs fulvestrant plus daily vistusertib (median PFS: fulvestrant plus everolimus, 12.3 months; fulvestrant plus daily vistusertib, 7.6 months; hazard ratio, 0.63 [95% CI, 0.45-0.90]; log-rank P = .01). C, Fulvestrant plus everolimus vs fulvestrant (median PFS: fulvestrant plus everolimus, 12.3 months; fulvestrant, 5.4 months; hazard ratio, 0.63 [95% CI, 0.42-0.92]; log-rank P = .01). D, Fulvestrant plus daily vistusertib vs fulvestrant plus intermittent vistusertib (median PFS: fulvestrant plus daily vistusertib, 7.6 months; fulvestrant plus intermittent vistusertib, 8.0 months; hazard ratio, 1.11 [95% CI, 0.81-1.52]; log-rank P = .52).

optimal inhibition of the mTORC1 complex and that the residual activity of 4E-BP1 is sufficient to negate a substantial treatment effect.[14] Similar observations have been made with pan-PI3K inhibitors and have ultimately resulted in the development of α-specific, β-sparing PI3K inhibitors that are currently in phase 3 trials in a similar indication. Alternative explanations for the observed results could be that inhibition of the mTORC2 complex has limited clinical relevance in breast cancer and/or that everolimus might have additional effects independent of mTORC1 inhibition. As these questions are critical for the future development of agents of the same class, efforts should be made to further evaluate the hypothesis. One way of testing this would be to compare direct target inhibition and downstream effects in tumor samples, but tissue samples while patients were undergoing treatment were not available from the MANTA trial.

As a positive result, the MANTA trial demonstrated that the combination of fulvestrant plus everolimus significantly increases PFS compared with fulvestrant alone, providing further evidence of the benefits of everolimus for the treatment of postmenopausal women with ER-positive breast cancer after loss of response to AIs. The observed benefits in PFS are remarkably similar to the results of the PrE0102 randomized phase 2 trial, which reported that addition of everolimus to fulvestrant improved median PFS from 5.1 to 10.3 months (HR, 0.61; P = .02).[27] A similar benefit was also observed for the combination of everolimus and exemestane in the BOLERO-2 (Breast Cancer Trials of Oral Everolimus-2) phase 3 trial.[10] The preliminary OS data suggest a trend toward improved OS, but results must be interpreted with caution as, at the time of this analysis, only 30% of the overall OS events had occurred.

To our knowledge, the MANTA trial is also the first trial to directly compare a continuous daily treatment schedule with a high-dose pulsatile schedule. Preclinical studies have suggested that intermittent, high-dose treatment might be a means to achieve more complete suppression of mTOR signaling and could

lead to an increase in apoptosis but might also improve the therapeutic index. Although we did not observe relevant differences in any of the efficacy end points (including response rates) between the 2 schedules selected for this trial, intermittent dosing was associated with a lower rate of rash or stomatitis (albeit at the cost of higher rates of short-term nausea and vomiting), suggesting that it might be of interest to further evaluate this hypothesis in future trials. As the same caveat regarding the effective vistusertib dose and the degree of mTORC1 inhibition applies, this trial was ultimately unable to definitively answer the hypotheses around administration of high-dose pulsatile treatment.

Limitations

This trial has some limitations. The main limitations are the small sample size and the open-label design.

Conclusions

Overall, the MANTA trial provides important evidence that dual mTOR inhibition is inferior to mTORC1 inhibition with the rapamycin analogue everolimus, possibly as a result of a toxic effects–mandated compromise in the degree of mTORC1 inhibition owing to the simultaneous inhibition of mTORC2. High-dose intermittent pathway inhibition could not improve the antitumor activity in this randomized trial but was associated with an improved safety profile and might be further evaluated in the future with other agents. The results presented here do not support further evaluation of vistusertib in ER-positive metastatic breast cancer, but also raise important questions around the future of this class of drugs.

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Author Affiliations: Barts Cancer Institute, Centre for Experimental Cancer Medicine, Queen Mary University of London, London, United Kingdom (Schmid, Sarker, Prendergast, Marosics, Moosa, Lawrence, Coetzee, Mousa); Oncology–Clinical, Barts Health National Health Service Trust, London, United Kingdom (Schmid, Conibear); Praxis fuer Interdisziplinaere Onkologie, Freiburg, Germany (Zaiss); Kent Oncology Centre, Maidstone and Tunbridge Wells National Health Service Trust, Tunbridge Wells, United Kingdom (Harper-Wynne); Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal (Ferreira); Oncology, Derriford Hospital, Plymouth Hospitals National Health System Trust, Plymouth, United Kingdom (Dubey); Oncology–Clinical, Nottingham University Hospitals National Health System Trust, Nottingham, United Kingdom (Chan); Mount Vernon Cancer Centre, East & North Herts National Health System Trust, London, United Kingdom (Makris); Institute of Clinical Oncology, Tbilisi, Republic of Georgia (Nemsadze); Cancer Centre, University Hospitals of North Midlands National Health System Trust, Stoke-on-Trent, United Kingdom (Brunt); Kliniken Essen-Mitte, Essen, Germany (Kuemmel); Hospital Universitario Sant Joan De Reus, Tarragona, Spain (Ruiz); Hospital Son Espases, Palma, Spain (Perelló); Cancer Services, Great Western Hospitals National Health System Foundation Trust, Swindon, United Kingdom (Kendall); Academic Unit of Clinical Oncology, University of Sheffield, Sheffield, United Kingdom (Brown); Medical Oncology, Queen Elizabeth Hospital, Woolwich, Lewisham and Greenwich National Health System Trust, London, United Kingdom (Kristeleit); Vall d'Hebron Institute of Oncology, SOLTI Breast Cancer Research Group, Vall d'Hebron University Hospital, Barcelona, Spain (Saura, Cortés); Institut Sainte Catherine, Avignon, France (Grenier); Zala County Hospital, Zalaegerszeg, Hungary (Máhr); Sf Nectarie Oncology Center Societate cu Raspundere Limitata, Craiova, Dolj, Romania (Schenker); Yonsei University Health System, Seoul, Republic of Korea (Sohn); National Cancer Center, Goyang-si Gyeonggi-do, Republic of Korea (Lee); Oncology Translational Medicine Unit, Innovative Medicines and Early Drug Development Biotech Unit, AstraZeneca, Cambridge, United Kingdom (Shepherd, Oelmann); Ramon y Cajal University Hospital, Madrid, Spain (Cortés); Baselga Oncology Institute, Institute of Oncology, QuironGroup, Madrid, Spain (Cortés).

Author Contributions: Dr Schmid had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Schmid was the chief investigator for the trial.
Concept and design: Schmid, Makris, Kuemmel, Brown, Saura, Oelmann, Sarker, Lawrence.
Acquisition, analysis, or interpretation of data: Schmid, Zaiss, Harper-Wynne, Ferreira, Dubey, Chan, Makris, Nemsadze, Brunt, Kuemmel, Ruiz, Perelló, Kendall, Brown, Kristeleit, Conibear, Saura, Grenier, Máhr, Schenker, Sohn, Lee, Shepherd, Oelmann, Sarker, Prendergast, Marosics, Moosa, Coetzee, Mousa, Cortés.
Drafting of the manuscript: Schmid, Chan, Makris, Brown, Conibear, Máhr, Schenker, Sarker, Prendergast, Moosa, Lawrence, Coetzee.
Critical revision of the manuscript for important intellectual content: Schmid, Zaiss, Harper-Wynne, Ferreira, Dubey, Chan, Makris, Nemsadze, Brunt, Kuemmel, Ruiz, Perelló, Kendall, Brown, Kristeleit, Saura, Grenier, Schenker, Sohn, Lee, Shepherd, Oelmann, Prendergast, Marosics, Coetzee, Mousa, Cortés.
Statistical analysis: Nemsadze, Sarker, Prendergast.
Obtained funding: Schmid.
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Supervision: Schmid, Chan, Makris, Kuemmel, Brown, Kristeleit, Saura, Schenker, Oelmann, Sarker, Mousa, Cortés.

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Merck Sharp & Dohme. Dr Saura reported receiving personal financial interests for serving on advisory boards for AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Roche, Genomic, Novartis, Pfizer, Pierre Fabre, Puma, and Synthon; receving institutional financial interests paid directly to her institution from AstraZeneca, Roche, Genentech, Maacrogenics, Novartis, Pfizer, Piour Therapeutics, Puma, and Synthon; and receiving nonfinancial interests from SOLTI breast cancer research group. Dr Grenier reported receiving travel, accommodation, or other expenses from Roche, AstraZeneca, and Amgen. Dr Máhr reported receivng honoraria from Novartis, Roche, and Astellas; serving in a consulting or advisory role for Novartis; serving on the speaker's bureau for Novartis, Roche, and Astellas; and receiving travel, accommodation, or other expenses from Roche. Dr Lee reported receiving research funding from Dong-A Pharm. Dr Shepherd reported being employed by AstraZeneca. Dr Oelmann reported being previously employed by AstraZeneca and owning shares in the company. Dr Cortés reported having stock or ownership in MedSIR; receiving honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, and Samsung; serving in a consulting or advisory role for Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, and Erytech; receiving research funding from Roche; holding patent or intellectual property with MedSIR; and receiving travel, accommodation, or other expenses from Roche, Pfizer, Eisai, and Novartis. No other disclosures were reported.

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