

Exemestane Versus Anastrozole as Front-Line Endocrine Therapy in Postmenopausal Patients With Hormone Receptor-Positive, Advanced Breast Cancer

Final Results from the Spanish Breast Cancer Group 2001-03 Phase 2 Randomized Trial

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BACKGROUND: Several aromatase inhibitor studies have reported variations in the inhibitory potency of these agents that could lead to differences in clinical outcomes. In the current study, the authors formally evaluated the activity of anastrozole and exemestane in postmenopausal women with hormone-responsive, advanced breast cancer. **METHODS:** Postmenopausal women who had measurable disease according to Response Evaluation Criteria in Solid Tumors and had not received previous endocrine therapy for advanced breast cancer were randomized to receive either oral exemestane 25 mg daily or oral anastrozole 1 mg daily until they had disease progression. The primary endpoint was the objective response rate (ORR), and secondary endpoints included the clinical benefit rate (CBR), time to progression (TTP), overall survival, and safety. Crossover to the other aromatase inhibitor was permitted at the time of disease progression; ORR, CBR, and TTP after second-line treatment also were explored. **RESULTS:** In total, 103 patients were enrolled. The median patient age was 71.6 years, 52.4% of patients had visceral disease, and 75.8% of patients had ≥ 2 disease sites. Half of the patients had received previous tamoxifen, and 60% had received previous chemotherapy. The efficacy observed in the exemestane and anastrozole groups was an ORR of 36.2% and 46%, respectively; a CBR of 59.6% and 68%, respectively, and a TTP of 6.1 months and 12.1 months, respectively. At progression, 28 patients crossed over to the other aromatase inhibitor, including 16 patients who switched to exemestane (CBR, 43.7%; TTP, 4.4 months) and 12 patients who switched to anastrozole (CBR, 8.3%; TTP, 2 months). Both drugs were generally well tolerated, and no study drug-related serious adverse events were reported. **CONCLUSIONS:** In this phase 2 randomized trial, no significant differences in clinical activity were observed in favor of exemestane to justify a superiority phase 3 trial design in the first-line setting. *Cancer* 2012;118:241-7. © 2011 American Cancer Society.

KEYWORDS: anastrozole, aromatase inhibitor, exemestane, hormone receptor-positive disease.

Metastatic breast cancer remains incurable, although constant progress in survival has been noted over the last 2 decades.¹ Unlike progress early stage breast cancer, the progress in metastatic disease has been related mostly to the optimization of systemic therapies rather than to more accurate diagnostic procedures.² Improvements in endocrine

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manipulation have contributed definitively to this gain. The third-generation aromatase inhibitors (AIs) after tamoxifen are being discussed as the mainstay of endocrine therapy for postmenopausal patients with advanced breast cancer.³ More recently, the 3 agents anastrozole, letrozole, and exemestane also have improved disease-free survival in patients with early stage disease.⁴

The steroidal AI exemestane differs from the nonsteroidal letrozole and anastrozole by irreversibly inactivating the aromatase. The magnitude of estrogen suppression induced by exemestane is similar to that induced by letrozole and slightly higher than that induced by anastrozole.⁵ It is noteworthy that both exemestane and 17-hydroexemestane, its principal metabolite, exert a positive androgenic effect that is distinct from the effect of the other AIs and has potential significance.⁶ Finally, exemestane has demonstrated consistent activity in patients who were pretreated with the nonsteroidal AIs letrozole and anastrozole.⁷ All together, these data support a possible advantage for exemestane as front-line antiaromatase therapy. To our knowledge, there are no randomized studies confronting 2 different classes of AIs as front-line endocrine therapy or as sequential therapy for patients with advanced breast cancer.

We designed an exploratory open-label randomized phase 2 study (Spanish Breast Cancer Research Group [GEICAM] 2001/2003) to investigate the activity and tolerability of exemestane and anastrozole as first-line hormone therapy and to explore the optimal AI sequence in postmenopausal women with hormone-responsive, advanced breast cancer, and cross-over was permitted.

MATERIALS AND METHODS

Patient Eligibility

Postmenopausal women aged ≥ 18 years who had histologically documented, locally advanced or metastatic breast cancer were eligible if they were positive for estrogen receptor (ER) or progesterone receptor (PgR) (either >10 fmol/mg by biochemical assay or $\geq 10\%$ positive cells by immunohistochemistry) had and adequate bone marrow reserve and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST).⁸ Previous adjuvant tamoxifen was permitted if it was initiated at least 24 months before recurrence. Previous neoadjuvant or adjuvant chemotherapy was permitted if it had been completed 12 months before the diagnosis of recurrent disease. A single line of chemotherapy for metastatic disease with or without trastuzumab was allowed if it had been completed at least 4 weeks

before the beginning of the study drug and if the patient had radiologically documented disease progression. Patients were excluded from the study if they had received previous hormone therapy for metastatic breast cancer or an AI in the adjuvant setting, if they had rapid progressive disease or known central nervous system metastases, if they had inadequate liver or renal function, or if they had received any investigational agent within 4 weeks of study enrollment.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the guidelines for good clinical practice. The protocol was approved by all relevant ethics review boards and by the Spanish Ministry of Health, and all patients provided written informed consent before study enrollment.

Study Design and Treatment

This was a randomized, open-label cross-over, phase 2 study in which patients received exemestane 25 mg or anastrozole 1 mg orally once daily until the developed disease progression. No other targeted therapies were administered. Randomization was performed and stratified using the Pocock and Simon algorithm⁹ for 3 prognostic factors: locally advanced or metastatic disease, previous adjuvant tamoxifen therapy (yes or no), and previous chemotherapy for metastatic disease (yes or no).

The primary endpoint was the objective response rate (ORR). Secondary endpoints included the clinical benefit rate (CBR), time to progression (TTP), overall survival, and toxicity. At the investigators' discretion and upon disease progression, patients were allowed to cross over and receive the other AI until further disease progression; the ORR, CBR, and TTP with second-line treatment were secondary exploratory objectives.

In the event of any study drug-related, grade 3 toxicity according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0),¹⁰ dosing was omitted for a maximum of 2 weeks. Upon resolution of the toxicity, treatment was reinitiated. Patients who had any study drug-related grade 4 toxicity discontinued participation in the study.

Study Assessments

At baseline, all patients had a disease assessment by physical examination and an appropriate radiologic test. In addition, Eastern Cooperative Oncology performance status, hematology, blood chemistry, and coagulation profiles were obtained before randomization. All assessments were repeated every 3 months until patients developed disease progression. The same assessment method that was

used to determine disease status at baseline was used consistently for efficacy evaluation throughout the study.

Patients who were positive for ER and/or PgR, had measurable disease, had baseline tumor measurements, had at least 1 tumor assessment, and had received at least 4 weeks of treatment were eligible for the response analyses. Tumor response (complete response [CR] plus partial response [PR]) was assessed according to RECIST.⁹ Tumor response had to be confirmed at least 4 weeks after a documented response. The CBR was defined as a response plus stable disease that lasted ≥ 6 months. TTP was measured from the time of randomization until the time of documented progressive disease, including death from any cause. Survival was measured from the time from randomization until death from any cause.

Patients who received at least 1 dose of exemestane or anastrozole were evaluable for safety. Adverse events were assessed using the NCI-CTC grading system¹⁰ and was recorded at each patient visit.

Statistical Considerations

A randomized, phase 2 design was chosen not to enable comparison of the efficacy of the 2 drugs but to explore whether the exemestane activity and safety precluded a comparison with anastrozole in a formal, randomized, phase 3 trial to demonstrate the superiority of exemestane over anastrozole.

A Simon 2-stage design method was used to calculate the sample size in the exemestane arm with the null hypothesis of an objective response rate (ORR) equal to 10% against the alternative hypothesis that the ORR is not equal to 25%. Twenty-one patients were accrued in the first stage, and, if 2 or more patients had a response, then 29 additional patients were enrolled in the second stage, resulting in a sample size of 50 patients. No minimum response criteria were proposed for anastrozole, because it was considered the gold standard.

ORR and CBR were calculated with exact 95% confidence intervals (CIs), and the TTP was analyzed using the Kaplan-Meier method with 95% CIs. For hypothesis generation, the Kaplan-Meier method and log-rank tests were used for exploratory analyses comparing the TTP between treatment arms in both the first-line setting and in patients who crossed to the other agent.

RESULTS

Patient Characteristics

Between September 2001 and May 2003, 103 patients with advanced or metastatic, ER/PgR-positive breast cancer were randomized (51 patients to receive exemestane and 52

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients (%)		
	All Patients, n = 103	Exemestane Arm, n = 51	Anastrozole Arm, n = 52
Median age [range], y	71.6 [45-94]	67.9 [45-94]	72.6 [46-85]
ECOG performance status			
0	45 (43.7)	24 (47.1)	21 (40.4)
1	27 (26.2)	15 (29.4)	12 (23.1)
2	20 (19.4)	9 (17.6)	11 (21.2)
Unknown	11 (10.7)	3 (5.9)	8 (15.3)
Tumor stage			
IIIB	15 (14.6)	9 (17.6)	6 (11.5)
IV	88 (85.4)	42 (82.4)	46 (88.5)
No. of disease sites			
1	25 (24.3)	13 (25.5)	12 (23.1)
2	36 (35)	20 (39.2)	16 (30.8)
≥ 3	42 (40.8)	18 (35.3)	24 (46.2)
Visceral disease			
Yes	54 (52.4)	25 (49)	29 (55.8)
No	50 (49)	27 (54)	23 (44.2)
Prior systemic therapy			
Adjuvant tamoxifen	52 (50.5)	26 (51)	26 (50)
Chemotherapy			
(Neo)adjuvant only	34 (33)	17 (33.3)	17 (32.7)
Metastatic only	4 (3.9)	2 (3.9)	2 (3.8)
Both	12 (11.7)	5 (9.8)	7 (13.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

patients to receive anastrozole) in 13 Spanish centers. Six patients (4 in the exemestane arm and 2 in the anastrozole arm) were not evaluable for response, including 1 patient who lacked evidence of metastatic disease, 2 patients who had negative or unknown ER and PgR status, and 3 other patients who lacked evidence of measurable disease.

Table 1 summarizes the baseline characteristics for the 103 patients. All patient characteristics were well balanced between the 2 arms. The median patient age was 71.6 years. Half of the patients had visceral metastasis, and the majority had at least 2 involved sites of disease. Half of the patients had received previous tamoxifen, and almost 66% had been exposed previously to chemotherapy for early or advanced breast cancer.

Efficacy

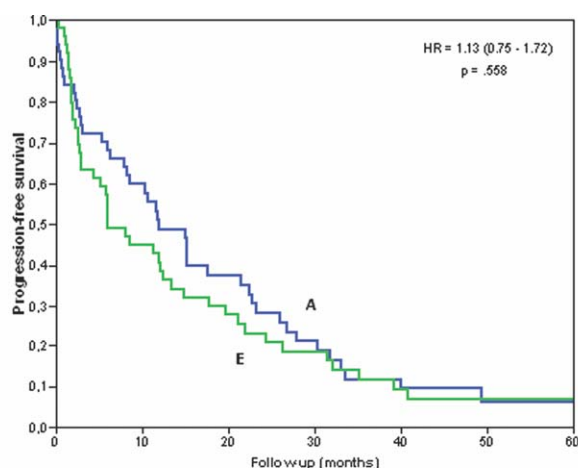
Seventeen patients in the exemestane arm achieved a response (36.2%; 95% CI, 18.5%-45.9%), including 3 CRs (6.4%). In the anastrozole arm, there were 23 responses (46%; 95% CI, 32.2%-59.8%), including 7 CRs (14%). The CBRs were 59.6% and 68% in the exemestane and anastrozole arms, respectively. Table 2

Table 2. Overall Response and Clinical Benefit Rate With First-Line Aromatase Inhibitor Therapy

Response	No. of Patients (%) ^a	
	Exemestane Arm, n = 47	Anastrozole Arm, n = 50
CR	3 (6.4)	7 (14)
PR	14 (29.8)	16 (32)
ORR	17 (36.2)	23 (46)
95% CI	18.5-45.9	32.2-59.8
SD	9 (19.1)	11 (22)
Clinical benefit	28 (59.6)	34 (68)
PD	21 (44.7)	16 (32)

CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

^aNote that there were 6 nonevaluable patients, including 4 patients in the exemestane arm and 2 patients in the anastrozole arm, who were not considered in this table.



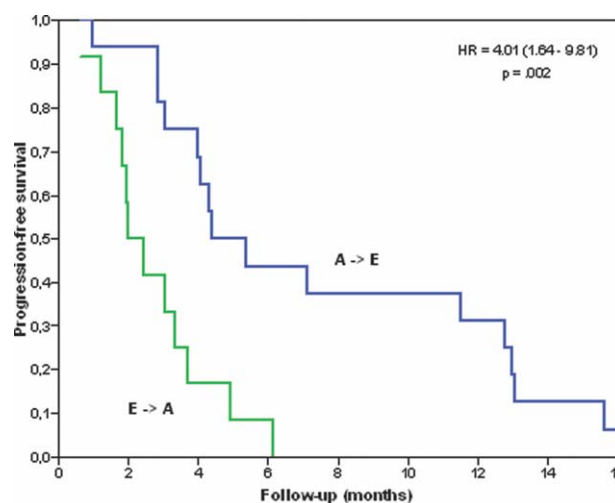
Treatment	II	Events	Censored	Median TTP (95% CI)
Exemestane	49	44	5	6.08 (2.52-9.65)
Anastrozole	51	44	7	12.07 (7.34-16.79)

Figure 1. The time to progression (TTP) after first-line aromatase inhibitor therapy is illustrated in postmenopausal patients with hormone receptor-positive, advanced breast cancer. Note that 3 patients, including 2 in the exemestane arm (E) and 1 in the anastrozole arm (A), were excluded from the analysis. HR indicates hazard ratio; CI, confidence interval.

provides a summary of responses and CBRs as determined by the investigators.

The median follow-up from study enrollment to disease progression or last contact without progression was 9.1 months (range, 0.07-79.96 months). At the time of the current analysis, 3 patients were still on treatment without evidence of progression (2 patients were receiving exemestane, and 1 patient was receiving anastrozole).

The TTP is displayed in Figure 1. The median TTP was 6.1 months (95% CI, 2.5-9.6 months) for patients



	II	Events	Censored	Median TTP (95% CI)
Exemestane	16	15	1	4.41 (2.34-6.47)
Anastrozole	12	12	0	2.01 (1.17-2.84)

Figure 2. The time to progression (TTP) after second-line aromatase inhibitor therapy is illustrated in postmenopausal patients with hormone receptor-positive, advanced breast cancer. HR indicates hazard ratio; E, exemestane; A, anastrozole; CI, confidence interval.

who received exemestane and 12.1 months (95% CI, 7.3-16.8 months) for patients who received anastrozole. In an exploratory analysis, the hazard ratio (HR) was 1.13 (95% CI, 0.75-1.72; log-rank $P = .558$).

At the time of the final analysis, 57 patients had died. The median overall survival was 48.3 months (95% CI, 18.3-78.3 months) for the patients who received anastrozole and 19.9 months (95% CI, 15.32-24.46 months) for patients who received exemestane. In an exploratory analysis, the HR was 1.33 (95% CI, 0.78-2.25; log-rank $P = .296$).

Efficacy at Cross-Over

Of 88 patients who progressed on first-line endocrine therapy, 28 patients (31.8%) switched to the other AI within 1 month. Among the 12 patients who crossed from exemestane to anastrozole, only 1 achieved tumor stabilization (which lasted 6.2 months), and no objective responses were observed. All of the other 11 patients progressed within 5 months. Sixteen patients switched from anastrozole to exemestane. One patient obtained a partial remission in lung and soft tissue. In addition, 7 patients had stable disease that lasted >6 months for a total CBR of 43.7%.

The median TTP for anastrozole and exemestane as second-line therapy (see Fig. 2) was 2.0 months (95% CI, 1.17-2.84 months) and 4.4 months (95% CI, 2.34-6.47 months), respectively. An exploratory analysis indicated an HR of 4.01 (95% CI, 1.64-9.81; log-rank $P = .002$).

Table 3. Grade 3 and 4 Adverse Events: National Cancer Institute Common Toxicity Criteria, Version 2.0

Adverse Event ^a	No. of Patients (%)		
	All Patients, n = 103	Exemestane Arm, n = 51	Anastrozole Arm, n = 52
Hypertension	4 (3.9)	4 (7.8)	-
Asthenia	4 (3.9)	2 (3.9)	2 (3.8)
Constipation	4 (3.9)	3 (5.9)	1 (1.9)
Infection without neutropenia	4 (3.9)	3 (5.9)	1 (1.9)
Neurology	4 (3.9)	2 (3.9)	2 (3.8)
Bone pain	6 (5.8)	2 (3.9)	4 (7.7)
Dyspnea	8 (7.8)	4 (7.8)	4 (7.7)

^a Frequency $\geq 3\%$.

Safety

Both compounds were well tolerated with generally mild adverse events in the 2 arms (see Table 3). None of the reported grade 4 adverse events were considered related to study drug.

Serious adverse events were reported in 35% of patients and were distributed equally between both arms. Two of those events were considered related to study drug (hypertension and arthralgia, both in patients who were receiving exemestane). Dyspnea, which was the most common serious adverse event, occurred in 8 patients, all of whom had lung or pleural involvement from their breast cancer at baseline, and those events were considered disease-related. There were no treatment discontinuations or deaths related to study drug.

DISCUSSION

This randomized, open-label, phase 2 trial was designed to evaluate the efficacy and safety of exemestane in patients with locally advanced or metastatic breast cancer and to make a “go/no-go” decision for a formal phase 3 comparison of this drug versus anastrozole, thus comparing 2 mechanistically different AIs. Both the ORR, which was primary objective of the study (36.2% and 46% for exemestane and anastrozole, respectively), and the CBR (59.6% and 68%, respectively) were lower numerically in the exemestane group. The median time to progression also was worse numerically for the exemestane group (6.1 months and 12.1 months, respectively), although the difference did not reach statistical significance (HR, 1.13; 95% CI, 0.75-1.72; $P = .558$) in an exploratory analysis. The observed results prompted us to discard the planned phase 3 trial.

Other investigators have studied third-generation AIs in patients with advanced breast cancer. The 2 non-

steroidal AIs letrozole and anastrozole were compared in a large phase 3 study by Rose et al.¹¹ In that study, a total of 713 postmenopausal patients with metastatic disease who progressed to tamoxifen were randomized. No significant differences were observed in the primary objective, TTP (24.7 weeks for letrozole vs 24.6 weeks for anastrozole), or in any other efficacy measurement, excluding a modestly increased response rate in favor of letrozole (19.1% vs 12.3%). Campos et al¹² randomized 130 postmenopausal patients with visceral (liver and/or lung), measurable, metastatic breast cancer to a second-line endocrine therapy with exemestane or anastrozole. Again, neither the response rate (11% vs 20%) nor the CBR (38% vs 46%) differed statistically, but both were numerically higher in favor of anastrozole. Ongoing trials in early stage breast cancer are exploring the clinical implications related to the differences in potency with the different AIs.¹³ The first analysis from the MA.27 trial at a median follow-up of 4 years indicates that there are no differences between exemestane and anastrozole as adjuvant therapy in postmenopausal women with hormone receptor-positive early breast cancer.¹⁴ However, the results observed in metastatic disease do not justify further studies in this setting.

In the current study, both exemestane and anastrozole were well tolerated, as expected. There were no study drug-related deaths. Hot flashes, nausea, arthralgia, and weight gain were among the most commonly reported events related to study drug. Serious adverse events, irrespective of causality, were infrequent; and only 2 serious adverse events were related to exemestane or anastrozole.

At the time of this analysis, 88 patients had progressed to first-line endocrine therapy, and 28 patients (31.8%) had switched to the other AI as stipulated in the study protocol. Among the 16 patients who switched to exemestane, 7 patients (43.7%) obtained a clinical benefit as opposed to only 1 of 12 patients who switched to anastrozole after failure on exemestane (8.3%). The median TTP also was significantly better for exemestane as a cross-over option to first-line progression (4.41 months vs 2.0 months; HR, 4.01; 95% CI, 1.64-9.81; $P = .002$). Although, at the time of this analysis, 12 patients had not progressed to first-line therapy, the second-line results must be considered as definitive; because, based on those results, the investigators decided to close the cross-over option, because better endocrine therapy options could be offered to patients who progressed on exemestane.

The activity of exemestane after reversible aromatase inhibition was reported first by Lonning et al,⁷ who demonstrated a 6.6% ORR and a 24.3% CBR in a series that

included 136 patients who progressed to aminoglutethimide and 105 patients who progressed to a third-generation AI (anastrozole, letrozole, or vorozole). In general, exemestane appeared to be more effective after aminoglutethimide than the more effective AI in terms of ORR (8.1% and 4.8%, respectively) and CBR (27.2% and 20.4%, respectively). This partial noncross-resistance between exemestane and the third-generation, nonsteroidal AIs (anastrozole or letrozole) has been detailed by other investigators in small series.^{15,16} Recently, a large phase 3 trial compared exemestane with fulvestrant, an ER down-regulator (Faslodex; AstraZeneca Pharmaceuticals, Wilmington, Del), as second-line endocrine therapy for patients who progressed on anastrozole or letrozole.¹⁷ The median TTP for both agents was equivalent (3.7 months in both arms; $P = .65$) as was the ORR (6.7% vs 7.4% for exemestane and fulvestrant, respectively; $P = .74$) and the CBR (32% for both arms).

Conversely, only 1 previous study analyzed the activity of the nonsteroidal inhibitors after exemestane. Bertelli et al¹⁸ reported a 56% CBR and a median TTP of 9.3 months with the nonsteroidal AIs among 18 patients who previously had progressed to exemestane. Although these results may appear contradictory to ours, it must be noted that 17 patients in that study received letrozole, and only 1 patient received anastrozole as salvage therapy.

It is noteworthy that the current study is the first to report numerical differences in activity between 2 of the third-generation AIs; although, in an exploratory analysis, exemestane appeared to be more effective than anastrozole patients progressed to the other agent. Is this difference in activity supported by their mechanistically different aromatase blockage, or could it be the result of differences in estrogen suppression potency? Enhanced sensitivity to residual estrogen levels has been suggested as a mechanism of breast cancer progression to AIs.¹⁹⁻²¹ Compared with anastrozole, exemestane is a more potent estrogen suppressor agent, and a greater reduction in estrogen levels could reverse this adaptive hypersensitivity mechanism. In addition, the mild androgenic activity of exemestane may induce a second anti-tumor effect. A better understanding of these mechanisms will be of great help in the design of new therapeutic strategies in both the adjuvant and advanced setting. Some of these hypotheses are being explored in several early stage breast cancer studies, because they support the rationale for sequential AI strategies (the MA.27 trial) and intermittent AI strategies (the Study of Letrozole Extension trial).

In conclusion, in this phase 2 randomized trial, we did not observe any difference in clinical activity in

favor of exemestane to justify a superiority phase 3 trial design in the first-line setting. Although it was not the primary objective of the current study, we observed a dissimilar tumor behavior based in the sequential AI approach that we used.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

- Giordano SH, Buzdar AU, Smith TL, et al. Is breast cancer survival improving? *Cancer*. 2004;100:44-52.
- Chia SK, Speers CH, D'yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer*. 2007;110:973-979.
- Abrial C, Leheurteur M, Cabrespine A, et al. Does survival increase in metastatic breast cancer with recently available anticancer drugs? *Oncol Res*. 2006;15:431-439.
- Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst*. 2006;98:1285-1291.
- Brodie A, Lu Q, Long B. Aromatase and its inhibitors. *J Steroid Biochem Mol Biol*. 1999;69:205-210.
- Miki Y, Suzuki T, Hatori M, et al. Effects of aromatase inhibitors on human osteoblast and osteoblast-like cells: a possible androgenic bone protective effects induced by exemestane. *Bone*. 2007;40:876-887.
- Lonning PE, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol*. 2000;18:2234-2244.
- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-216.
- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103-115.
- National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Common Toxicity Criteria Manual, version 2.0. Bethesda, MD: National Cancer Institute; 1999.
- Rose C, Vtoraya O, Pluzanska A, et al. An open randomized trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer*. 2003;39:2318-2327.
- Campos SM, Guastalla JP, Subar M, et al. A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. *Clin Breast Cancer*. 2009;9:39-44.

13. Goss P, von Eichel L. Summary of aromatase inhibitor trials: the past and future. *J Steroid Biochem Mol Biol.* 2007; 106:40-48.
14. Goss PE, Ingle JN, Chapman J-AW, et al. Final analysis of NCIC CTG MA. 27: a randomized phase III trial of exemestane versus anastrozole in postmenopausal women with hormone receptor positive primary breast cancer [abstract]. Paper presented at: 33rd Annual San Antonio Breast Cancer Symposium; December 8-12, 2010; San Antonio, Tex. Abstract S1-1.
15. Iaffaioli RV, Formato R, Tortoriello A, et al. Phase II study of sequential hormonal therapy with anastrozole/exemestane in advanced and metastatic breast cancer. *Br J Cancer.* 2005;92:1621-1625.
16. Gennatas C, Michalaki V, Carvounis E, et al. Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on letrozole or anastrozole. A phase II trial conducted by the Hellenic Group of Oncology (HELGO). *Tumori.* 2006;92:13-17.
17. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFACT. *J Clin Oncol.* 2008;26:1664-1670.
18. Bertelli G, Garrone O, Merlano M, et al. Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology.* 2005;69:471-477.
19. Santen RJ, Song RX, Zhang Z, et al. Adaptive hypersensitivity to estrogen: mechanism for sequential responses to hormonal therapy in breast cancer. *Clin Cancer Res.* 2004;10:337s-345s.
20. Lonning PE. Lack of complete cross-resistance between different aromatase inhibitors; a real finding in search for an explanation? *Eur J Cancer.* 2009;45:527-535.
21. Geisler J, Helle H, Ekse D, et al. Letrozole is superior to anastrozole in suppressing breast cancer tissue and plasma estrogen levels. *Clin Cancer Res.* 2008;14:6330-6335.