Randomized Comparison of Tamoxifen and Two Separate Doses of Toremifene in Postmenopausal Patients With Metastatic Breast Cancer

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Purpose: **To perform a randomized three-arm comparison of tamoxifen (TAM; 20 mg/d) and two separate doses of toremifene (TOR; 60 mg/d [TOR60] and 200 mg/d [TOR200]) in postmenopausal patients with hormone receptor-positive or -unknown metastatic breast cancer.**

Materials and Methods: **Six hundred forty-eight patients with hormone receptor-positive or -unknown metastatic breast cancer were randomly assigned to receive TAM (n = 215), TOR60 (n = 221), or TOR200 (n = 212).**

Results: **The combined response rates (by intent to treat) were as follows: TAM, 44%; TOR60, 50%; and TOR200, 48%. Complete and partial response rates were as follows: TAM, 19%; TOR60, 21%, and TOR200, 23% (not statistically different). Median times to progression and overall survival were not significantly different. Adverse events (lethal, serious but nonlethal, and important but non–life-threatening) were similar in all three arms, except that patients in the TOR200 arm had a statistically significantly increased rate of nausea (37% *v* 26% and 26% for TOR200, TAM, and TOR60, respectively; *P* = .027). Quality-of-life assessments were not different among the three arms.**

Conclusion: **The activity, toxicity, and side effects of TOR in postmenopausal women with hormone receptor-positive or -unknown metastatic breast cancer are similar if not equivalent to those of TAM. We detected no clear evidence of a dose-response effect for TOR. TOR60 is an effective and safe agent for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer and can be considered an alternative to TAM as first-line treatment for such patients.**

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TREATMENT OF PATIENTS with metastatic breast cancer is palliative and may consist of either local or systemic therapies.[1,2] Approximately 50% to 60% of all postmenopausal patients will have hormonally responsive disease.[3] Of the available hormone therapies, the antiestrogen tamoxifen (TAM) is generally considered to be the first-line treatment of choice because of its excellent efficacy-to-toxicity ratio.[1]

Toremifene (TOR) is a triphenylethylene derivative that was developed to improve the therapeutic-to-toxic ratio of antiestrogens.[4,5] Like TAM, TOR has both antiestrogenic and estrogenic activities in preclinical in vitro and in vivo studies.[6-10] Also, like TAM, TOR binds with high affinity to cytoplasmic estrogen receptors.[5]

Phase I studies of TOR have demonstrated that it is generally well tolerated, with a clinical toxicity profile similar to that of TAM.[11-13] Phase II trials of TOR in patients with estrogen receptor (ER)-positive or -unknown advanced breast cancer have demonstrated that doses of 60 and 240 mg/d produced response rates up to 68%.[14-17] A randomized phase II trial of three separate doses of TOR (20, 40, and 60 mg/d) suggested less efficacy at 20 mg/d, but similar response rates with 40 and 60 mg/d.[18]

Because of the favorable and promising phase I and II data, a worldwide phase III trial to compare TOR at two doses, 60 mg/d (TOR60) and 200 mg/d (TOR200) with TAM at 20 mg/d was initiated in November 1988. This trial was open to postmenopausal women with ER-positive or progesterone receptor (PgR)-positive or ER/PgR-unknown tumors with measurable or assessable metastatic breast cancer. In this trial, we observed that the efficacy and toxicity of TOR are similar to those of TAM.

MATERIALS AND METHODS

Patient Selection

Eligible patients included postmenopausal or perimenopausal women with a histologically documented prior history of breast cancer that was ER- and/or PgR-positive at either the primary tumor or metastatic site, or for which the ER and PgR status were unknown. Patients must have had either bidimensionally measurable metastatic breast cancer or assessable lytic bone metastases. Patients may have had prior adjuvant chemotherapy, but could not have had prior hormone or cytotoxic chemotherapy for recurrent/metastatic disease, although TAM treatment for ≤ 14 days before entry was allowed. Prior adjuvant TAM was allowed, but the interval between discontinuation of adjuvant TAM treatment and relapse/entry onto trial was

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required to be ≥ 12 months. Patients must have had a performance status of 0 to 2 by the ECOG scale. Patients were not eligible for the trial if they were actively menstruating, had serum bilirubin levels more than 2 mg/dL or AST levels ≥ 100 U/L, or if they had brain metastasis, inflammatory breast carcinoma, or lymphangitic pulmonary metastasis. Patients were also excluded if they had had a second primary malignancy within the 5 years preceding entry onto this trial. Signed, informed consent was obtained before enrollment.

Of note, accrual was originally initiated for two separate but identical multiinstitutional studies. However, since they were performed under the auspices of a single sponsor, and since entry criteria, protocol conduct, data management, and auditing were identical, the results have been combined and analyzed as a single study.

Patients were stratified by whether they had bone-only metastases (with or without other nonmeasurable disease) or nonbony assessable disease and were randomly assigned to treatment with TAM at 20 mg orally per day (TAM), TOR60 orally, TOR200 orally. Following baseline evaluations, patients were reevaluated every 8 weeks, including history, physical examination, ocular examination, performance status, chest radiograph, diagnostic imaging of previously documented sites of disease (bone scintigraphy, bone radiographs, and liver imaging), complete blood cell counts, serum chemistries, antithrombin-III (ATIII) levels, and subjective patient ratings (Visual Analog Scale [VAS] and pain assessment and analgesic requirements). Serial assessments of initially detected tumor sites were continued every 8 weeks for 48 weeks, and then every 12 weeks. Serial assessments of bone disease were performed every 16 weeks in patients with known bony disease if no increase in bone symptoms or serum calcium was noted.

Patients with measurable disease were assessed by their primary care physician at each evaluation to have a complete response or partial response, to be stable, or to have progressive disease according to World Health Organization (WHO) criteria.[19] Quality-of-life assessments were evaluated using several parameters, as follows: serial changes in Eastern Cooperative Oncology Group (ECOG) performance status; mood, pain, and enjoyment of life subjective analysis by VAS; analgesic requirement as assessed by the ECOG Analgesics Requirement Scale; tumor-specific symptoms; solicited clinical toxicities; other treatment-emergent symptoms; and serious adverse events. These data were collected prospectively as part of the required clinical data reporting.

Patients

Six hundred forty-eight patients with metastatic breast cancer were enrolled onto this trial at 129 sites in six countries and randomized to one of three arms (TAM, n = 215; TOR60, n = 221; and TOR200, n = 212). Accrual began November 11, 1988 and was completed August 31, 1991. Of these patients, 546 (84%) were deemed assessable for efficacy analysis, as follows: TAM, 172 patients (80%); TOR60, 187 patients (85%); and TOR200, 187 patients (88%). One hundred two patients were considered nonassessable for response evaluation for the following reasons: (1) Administrative: 34 patients were determined retrospectively to be ineligible according to protocol rules. The most common reasons included negative ER and PgR status, metastatic skin lesions less than 1 cm, patient received prior therapy for metastases, or liver function tests above stated limit (TAM, n = 8; TOR60, n = 10; and TOR200, n = 3). Seven patients were registered, but never received therapy (TAM, n = 5; TOR60, n = 0; and TOR200, n = 2). Six patients did not have assessable or measurable metastatic disease (TAM, n = 4; TOR60, n = 0; and TOR200, n = 2). (2) Received insufficient therapy: 18 patients were taken off study very early. Seven suffered an early adverse event (TAM, n = 1; TOR60, n = 2; TOR200, n = 4); seven refused to continue or were lost to follow-up evaluation (TAM, n = 4; TOR60, n = 3; and TOR200, n = 0); and four did not comply with the treatment regimen (TAM, n = 2; TOR60, n = 1; and TOR200, n = 1). (3) Progressive disease/changing clinical course or insufficient data: 48 patients were treated, but follow-up time or data collection was insufficient to evaluate response. In eight patients, disease progressed within 4 weeks of entry (TAM, n = 4; TOR60, n = 3; and TOR200, n = 1). Nine patients suffered early death on study (TAM, n = 2; TOR60, n = 3; and TOR200, n = 4). Two received radiation therapy to only assessable lesion within the first 8 weeks (TAM, n = 2; TOR60, n = 0; and TOR200, n = 0). Twenty-nine patients were not assessable for response because insufficient data were collected to assess this end point (TAM, n = 9; TOR60, n = 12; and TOR200, n = 8). (4) Physician-related protocol violations: two patients were not assessable due to major protocol violation. One patient on TAM was incorrectly treated, and a second patient on TAM was removed from study at her physician's discretion.

Response rates are provided for all patients by intent to treat and only for assessable patients. All other data are presented for all patients on study by intent to treat.

The three treatment arms were similar regarding race, ER and PgR content, site of dominant disease, disease-free interval between primary diagnosis and first recurrence, and performance status (Table 1).

Statistical Analysis

Data were double-key–entered and subjected to both manual and computerized checks for logic and consistency before being made available for statistical analysis. Since the primary objective of the study was to compare each of the TOR groups with the TAM group, the treatment group comparisons (TOR60 *v* TAM and TOR200 *v*

Table 1. Patient Characteristics by Intent to Treat

Characteristic	Treatment Arm: TAM (n = 215) No.	%	TOR60 (n = 221) No.	%	TOR200 (n = 212) No.	%
Age, years						
Mean	61		63		62	
Range	35-85		37-88		40-85	
Mean no. of metastatic organ sites	1.72		1.85		1.77	
Disease-free interval (mean years)	6.1		5.6		6.4	
Dominant site of disease						
Visceral*	81	38	86	39	82	39
Bone	96	45	100	45	90	42
Soft tissue	35	16	35	16	38	18
ER level (fmol/mg)						
< 10	21	10	14	6	16	8
10-100	79	37	83	38	75	35
> 100	51	24	64	29	48	23
Unknown	64	30	60	27	73	34
PgR level (fmol/mg)						
< 10	35	16	37	17	34	16
10-100	58	27	53	24	58	27
> 100	53	25	62	28	40	19
Unknown	69	32	69	31	80	38

*Data not available for all patients: TAM, n = 212; TOR60, n = 221; TOR200, n = 210.

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TAM) were treated as separate and independent. No adjustments were made for multiple comparisons. As stated in the protocol, efficacy analyses were conducted when (approximately) 70% of enrolled patients had experienced progressive disease. The corresponding data cutoff date was August 31, 1992. Safety analyses were based on all data that were available for analysis as of December 7, 1993.

The pairwise treatment group comparisons with respect to qualitative variables were made using either the χ^2 test or Fisher's exact test. The two-sample t test was used to make comparisons with respect to quantitative variables. Lifetime analyses (ie, time to progression, response duration, and survival) were made using standard Kaplan-Meier methods. All P comparisons were two-sided and were conducted at the .05 level of significance.

RESULTS

Therapeutic Outcome

The response rates for the three treatment arms are listed in Table 2. Response rates were not statistically different between either of the TOR arms and the TAM arm, whether they were evaluated by intent to treat or by assessable patients only. The overall response rate (complete response, partial response, and stable disease) was 50%. The combined response rates when evaluated by intent to treat for the three arms were as follows: TAM, 44%; TOR60, 50%; and TOR200, 48%. If only complete responses and partial responses are considered, the respective response rates were 19%, 21%, and 23%. These differences were not statistically significant.

When only assessable patients were analyzed, combined response rates were 53%, 56%, and 54%, respectively, for TAM, TOR60, and TOR200. Complete and partial response rates were 24%, 24%, and 26%, respectively, for the three arms.

Table 2. Response Rates for TAM, TOR60, and TOR200 by Intent to Treat

	Treatment Arm					
	TAM		TOR60		TOR200	
Variable	No.	%	No.	%	No.	%
All patients						
Total no.	215		222		212	
Complete response	11	5	14	6	11	5
Partial response	30	14	33	15	37	18
Stable disease	53	25	63	29	53	25
Primary progressive disease	89	41	90	41	89	42
Not available	32	15	21	10	22	10
Complete + partial response	41	19	47	21	48	23
Assessable patients						
Total no.	172		187		187	
Complete response	11	6	13	7	11	6
Partial response	30	18	32	17	37	20
Stable disease	50	29	59	32	53	28
Primary progressive disease	81	47	83	44	86	46
Complete + partial response	41	24	45	24	48	26

The median times to progression by intent to treat were 175 days (5.8 months), 168 days (5.6 months), and 167 days (5.6 months) for TAM, TOR60, and TOR200, respectively (Table 3). The differences in the durations of the times to progression were not statistically significant (Fig 1).

Although overall survival was not a primary end point of this study, no statistically significant difference was observed for patients treated on the three arms (Table 3 and Fig 2). Median overall survival times were 950 days (31.7 months), 1,145 days (38.3 months), and 904 days (30.1 months) for patients treated with TAM, TOR60, and TOR200, respectively. Patients on the TOR200 arm fared slightly less well than those on TOR60 or TAM. The hazards ratios for mortality were as follows: TAM/TOR60, 1.04 (95% confidence interval, 0.76 to 1.42); and TAM/TOR200, 0.81 (95% confidence interval, 0.60 to 1.10). However, these small differences were not statistically significant (Wilcoxon P values: TAM/TOR60 = .8 and TAM/TOR200 = .2).

The median response duration between treatment arms for those patients who had a partial or complete response or stable disease (TAM, n = 41; TOR60, n = 47; TOR200, n = 48) was determined by intent to treat (Table 3). At the time of this analysis, 16, 19, and 19 patients were continuing on TAM, TOR60, or TOR200, respectively, without evidence of disease progression. The median response duration from time of randomization was 577 days (19.1 months), 509 days (16.9 months), and 554 days (18.4 months) for the TAM, TOR60, and TOR200 patients, respectively (Fig 3). The transient difference between the response duration curves approached but did not reach statistical significance,

Table 3. Time to Progression and Overall Survival for Patients on TAM, TOR60, and TOR200 by Intent to Treat

	Treatment Arm					
	TAM		TOR60		TOR200	
Variable	No.	%	No.	%	No.	%
All patients						
Total no.	215		221		212	
Median time to progression (days)*	175		168		167	
Progressed†	150	70	160	72	155	73
Median overall survival (days)	950		1,145		904	
Dead	81	38	76	34	95	45
Responders‡						
Total no.	41		47		48	
Median response duration (days)*	577		509		554	
Progressed†	25	61	28	60	29	60

*From randomization.
†At time of analysis.
‡Complete and partial responders.

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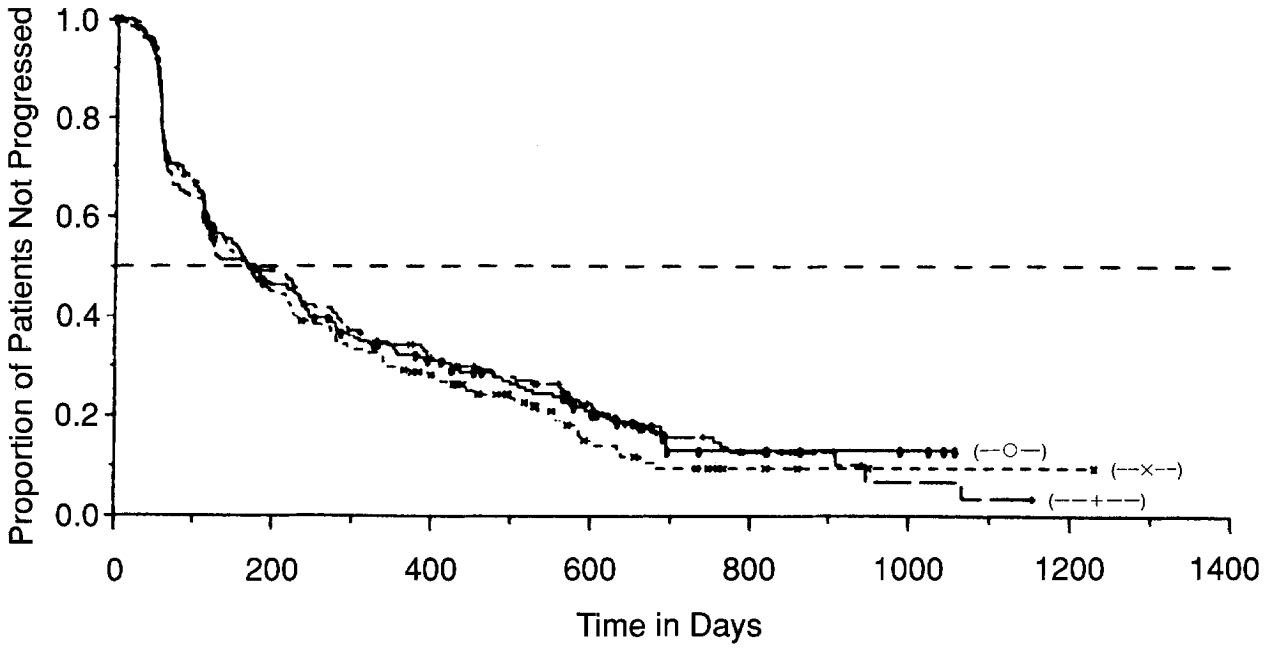

Fig 1. Time to progression for patients treated with TAM (+++, n = 215), TOR60 (○○○, n = 221), and TOR200 (×××, n = 212). Postmenopausal hormone receptor-positive or -unknown patients with metastatic breast cancer were randomly assigned to 1 of 3 arms as designated. Progression determined from time of study entry (*P* values: log-rank = .95; Wilcoxon = .96).

favoring the TAM group over TOR60 (Wilcoxon *P* value for TAM *v* TOR60 = .08, for TAM *v* TOR200 = .2; log-rank *P* values = .3 and .3, respectively).

Outcomes for all patients were analyzed by ER and PgR content. As expected, response rates, times to progression, and overall survival for patients on each arm were superior for ER-positive patients when compared with those whose tumors were ER-negative. However, no statistically significant differences were observed when these outcomes were compared among the three treatment groups (TAM, TOR60, and TOR200) for patients in the following subgroups: ER-, PgR-positive; ER-positive, PgR-negative; ER-, PgR-positive; ER-positive, PgR-unknown; and ER-, PgR-unknown.

Tumor Flare

Clinical tumor flare, defined as a transient increase in bone and/or musculoskeletal pain requiring an elevated analgesic requirement, cutaneous erythema, increased skin lesion site, and/or hypercalcemia within 2 weeks of starting the study drug, has been previously described for TAM.[20] Clinical tumor flare was assessed in 597 of 648 patients (TAM, n = 192; TOR60, n = 206; and TOR200, n = 199). Of these, 105 (17.5%) experienced clinical flare (TAM, 36 of 192 patients [19%]; TOR60, 32 of 206 [16%]; and TOR200 37 of 199 [19%]). None of these differences was statistically significant.

Adverse Events

Thirty-six patients died on study or within 30 days of the last drug dose (TAM, n = 8 [4%]; TOR60, n = 19 [9%]; and TOR200, n = 10 [5%]). Of these deaths, 19 were felt to be secondary to progressive metastatic breast cancer (TAM, n = 6; TOR60, n = 9; and TOR200, n = 4). Other causes of death included hypercalcemia (TAM, n = 1; thromboembolism (TAM, n = 1; TOR60, n = 3; and TOR200, n = 1); sepsis (TOR60, n = 1); gastrointestinal bleeding (TOR60, n = 1; and TOR200, n = 1); cardiovascular events (TOR60, n = 1; and TOR200, n = 1); cerebrovascular events (TOR60, n = 1; and TOR200, n = 1); acute pericarditis (TOR200, n = 1); and causes not determined (TOR60, n = 3; and TOR200, n = 1). In final analysis, deaths not due to breast cancer (treatment-related, possibly treatment-related, or not determined) were similarly distributed, with no significant differences among the three arms (TAM, n = 2 [1%]; TOR60, n = 9 [4%]; and TOR200, n = 6 [3%]).

Serious but nonlethal adverse events are listed in Table 4. The incidence of thromboembolic events was similar. Likewise, cardiac events occurred at a similar rate in the three treatment arms. In this regard, baseline circulating ATIII levels for a selected group of patients (N = 532; TAM, n = 172; TOR60, n = 182; and TOR200, n = 178) were similar (means: 110.2 U/mL, 110.8 U/mL, and

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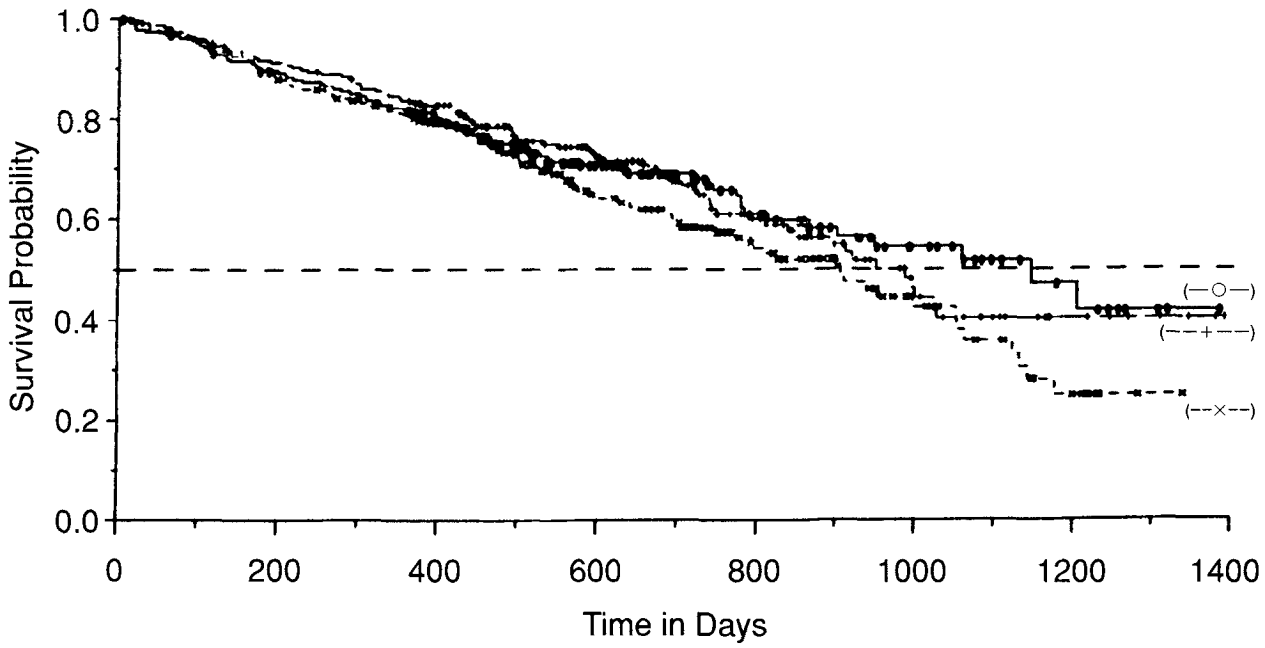

Fig 2. Overall survival for patients treated with TAM (+++, n = 215), TOR60 (○○○, n = 221), and TOR200 (×××, n = 212). Postmenopausal hormone receptor-positive or -unknown patients with metastatic breast cancer were randomly assigned to 1 of 3 arms as designated. Survival determined from time of study entry (*P* values: log-rank = .81; Wilcoxon = .74).

112.2 U/mL, respectively). Serial ATIII data were collected from 347 patients at week 8 and from 240 patients at the time they were taken off treatment. Mean ATIII levels decreased at week 8 to 98.4 U/mL, 99.2 U/mL, and 102.4 U/mL and at time off treatment to 97.5 U/mL, 99.6 U/mL, and 97 U/mL for TAM, TOR60, and TOR200, respectively. The trend of decreasing ATIII levels after treatment was not significant for any of the three groups (analysis of variance test for all three groups), and there were no significant differences between each of the TOR groups and the TAM group (*t* test).

Most hepatic abnormalities observed in the TAM or TOR60 arms could be related to progressive metastatic breast cancer. However, a slightly increased incidence of AST abnormalities (≥ 100 IU/L) not associated with progressive disease was noted in the TOR200 arm (10%) when compared with the TAM arm (2%). Two patients were removed from the TOR200 arm because of marked multiple liver function abnormalities. These abnormalities were temporally related to initiation of TOR and resolved on discontinuation of the drug. Elevations in calcium levels occurred in 3%, 3%, and 5% of the TAM, TOR60, and TOR200 patients, respectively. These differences were not statistically significant.

Important but non–life-threatening side effects that occurred at any time on study were prospectively assessed as part of the protocol (Table 5). Data are available for most, but not all, of the patients on each arm of the study (TAM, 203 of 215 patients; TOR60, 215 of 221; and TOR200, 207 of 212). The incidence of hot flashes, vaginal bleeding, vaginal discharge, peripheral edema, vomiting, and dizziness was similar in all three arms, regardless of whether all reports of these side effects or only those of a moderate to severe nature were considered. Nausea occurred in 20% of women on the TOR200 arm, compared with 14% for patients on the TAM and TOR60 arms (P = .125, Fisher's exact test).

The most common unsolicited and subjectively reported side effects that were assessed by the on-site investigators to be possibly related to the drug or of indeterminate cause were pain and asthenia (TAM, n = 38 [18%]; TOR60, n = 52 [24%]; and TOR200, n = 50 [24%]). Others included anorexia, headache, diarrhea, vaginitis, rash, pruritis, depression, and insomnia. The incidence of all of these was ≤ 5%, and each occurred with similar frequency in all three arms. Because these were collected as spontaneous nonsolicited comments from the patients, and collection depended on the physicians' recording them, no statistical analysis is provided. However, none of these complaints was substantially more common in one arm than in the other two.

Ocular abnormalities have been previously reported to be associated with the use of TAM, and were observed in phase I and phase II trials of TOR.[11,21] Therefore, pro-

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