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original article

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Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17

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Background: MA.17 evaluated letrozole or placebo after 5 years of tamoxifen and showed significant improvement in disease-free survival (DFS) for letrozole [hazard ratio (HR) 0.57, $P = 0.00008$]. The trial was unblinded and placebo patients were offered letrozole.

Patients and methods: An intent-to-treat analysis of all outcomes, before and after unblinding, on the basis of the original randomization was carried out.

Results: In all, 5187 patients were randomly allocated to the study at baseline and, at unblinding, 1579 (66%) of 2383 placebo patients accepted letrozole. At median follow-up of 64 months (range 16–95), 399 recurrences or contralateral breast cancers (CLBCs) (164 letrozole and 235 placebo) occurred. Four-year DFS was 94.3% (letrozole) and 91.4% (placebo) [HR 0.68, 95% confidence interval (CI) 0.55–0.83, $P = 0.0001$] and showed superiority for letrozole in both node-positive and -negative patients. Corresponding 4-year distant DFS was 96.3% and 94.9% (HR 0.80, 95% CI 0.62–1.03, $P = 0.082$). Four-year overall survival was 95.1% for both groups. The annual rate of CLBC was 0.28% for letrozole and 0.46% for placebo patients (HR 0.61, 95% CI 0.39–0.97, $P = 0.033$).

Conclusions: Patients originally randomly assigned to receive letrozole within 3 months of stopping tamoxifen did better than placebo patients in DFS and CLBC, despite 66% of placebo patients taking letrozole after unblinding.

Key words: extended adjuvant therapy, intent-to-treat, letrozole

original article

introduction

MA.17 was a double-blind, placebo-controlled trial that evaluated the use of letrozole in the extended adjuvant setting following 4.5–6 years of tamoxifen. This study has been extensively reported regarding efficacy and toxicity up to the time of unblinding [1, 2] including according to ethnic status [3], duration of letrozole treatment [4] and outcomes according to estrogen receptor (ER) and progesterone receptor (PgR) status [5]. Substudies examining the impact of letrozole on lipids [6], quality of life [7] and bone density [8] have also been reported. The definitive report of the trial [2], after a median follow-up of 30 months at the time of unblinding, revealed an advantage for letrozole in the primary end point of disease-free survival (DFS) with a hazard ratio (HR) for recurrence or contralateral breast cancer (CLBC) of 0.58 [95% confidence interval (CI) 0.45–0.76, $P < 0.001$]. Distant disease free-survival (DDFS) also favored letrozole with an HR equal to 0.60 (95% CI 0.43–0.84, $P = 0.002$). Overall survival (OS) was not significantly different between letrozole and placebo considering all patients but was significantly better for letrozole in the node-positive cohort with an HR equal to 0.61 (95% CI 0.38–0.98, $P = 0.04$). OS was also significantly improved by letrozole (HR 0.58, 95% CI 0.37–0.90) in the large group of patients ($n = 3809$) whose primary tumor was ER and PgR positive [5]. The value of

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aromatase inhibitors as extended adjuvant therapy after ~5 years of tamoxifen was subsequently corroborated in smaller clinical trials for anastrozole [9] and exemestane [10].

Upon the unblinding of MA.17, patients who had been randomly assigned to receive placebo were offered treatment with letrozole and Goss et al. [11] found that patients who decided to take letrozole after this prolonged delay of a median of 2.8 years from completing tamoxifen experienced a significant improvement in DFS, DDFS, OS and occurrence of CLBC. Given the substantial benefits of this 'delayed' extended adjuvant therapy, we carried out an intent-to-treat (ITT) analysis of outcomes considering all events before and after unblinding on the basis of the original randomization with the goal of determining whether the substantial value seen for letrozole in the final publication of events before unblinding [2] would be maintained.

patients and methods

study design

MA.17 was a randomized, double-blind, placebo-controlled trial of letrozole in postmenopausal women who had received ~5 years of adjuvant tamoxifen therapy for early breast cancer. The eligibility criteria and design of the study have previously been published [1, 2] but, in brief, included women who had received 4.5–6 years of tamoxifen adjuvant therapy for early breast cancer who were then randomly allocated to the study of letrozole (2.5 mg orally daily) or placebo for 5 years. In all, 5187 women were entered in a randomized study with 17 patients excluded because of noncompliance with good clinical practice guidelines resulting in 5170 patients in the analyses of time-to-event end points. Eligibility criteria included a histologically confirmed breast cancer that was ER and/or PgR positive defined as ≥10 fmol/mg protein by a biochemical assay or positive by immunohistochemical stain or hormone receptor unknown provided an effort was made to determine the receptor status of the primary tumor. Hormone receptor status was positive in 97.4%, negative in 0.15% and unknown or missing in 2.4%. Patients were eligible regardless of the status of their axillary lymph nodes at the time of initial diagnosis; 2568 women were known to have nodes that were negative for tumor and 2360 women were known to have nodes that were positive for tumor.

Following the identification of extreme results in favor of letrozole [1] at the first interim analysis, the study was unblinded on the recommendation of the independent Data and Safety Monitoring Committee and women who had been originally randomly assigned to receive placebo and who had not experienced an event were offered 5 years of open-label treatment with letrozole. Active follow-up was continued after the unblinding for all randomized patients. The schema of the study before and after unblinding are shown in Figure 1.

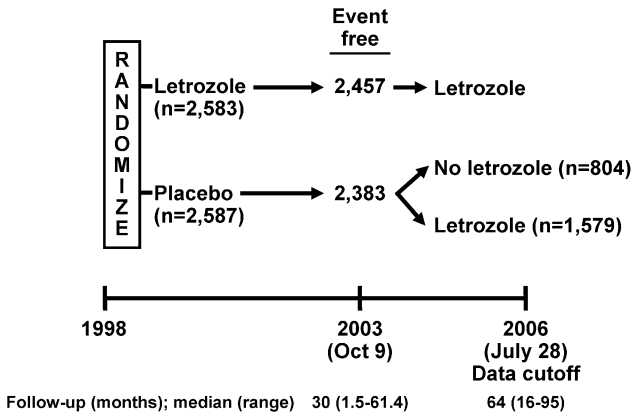

Figure 1. Schema of MA.17 showing initial randomization and post-unblinding use of letrozole on placebo arm.

end points and statistical analyses

DFS was the primary end point of MA.17 and included any breast cancer recurrence and CLBC as events. Secondary end points included DDFS, OS and CLBC. DDFS had distant metastasis as the only event. OS considered death due to any cause as an event. A stratified log-rank test was used to compare DFS, DDFS, OS and incidence of CLBC. The Cox regression model used baseline stratification variables and two prespecified factors, menopausal status at the start of tamoxifen and time on tamoxifen before randomization. Subgroup analyses for DFS and OS were carried out for the two prespecified subsets of node-negative and node-positive patients. All *P* values were two-sided.

results

patient population

The patient characteristics are the same as in the previous report [2]. For this analysis, the database was updated and locked on 28 July 2006. The median follow-up of all patients (calculated as the time from randomization to death for the patients who had died and time from randomization to date of data cut-off for patients still alive) was 64 months with a range

Table 1. Summary of events in the analysis of disease-free survival for all randomized patients on MA.17

	Number of patients (%)	
	Letrozole *n* = 2583	Placebo *n* = 2587
Patients with an event	164 (6.3)	235 (9.1)
Recurrence	136	190
Local breast recurrence only	10	36
Local chest wall recurrence only	3	12
Regional recurrence only	9	5
Distant recurrence only[a]	99	121
Ascites	2	2
Bone marrow	5	6
Lungs	22	30
Bone	81	84
Pleural effusion	8	14
Liver	34	31
CNS	5	4
Other	26	38
Multiple sites	15	16
CLBC only	28	45
Patients who were censored	2419 (93.7)	2352 (90.9)
Death without recurrence or CLBC	88	82
Alive without recurrence or development of CLBC	2331	2270

[a]Patients may have more than one site of recurrence.
CNS, central nervous system; CLBC, contralateral breast cancer.

of 16–95 months at the time of data lock. At the time the study was unblinded, 2383 women who had been originally randomly assigned to receive placebo and who had not experienced an event were offered open-label treatment with letrozole. This offer of letrozole was accepted by 1579 patients and declined by 804 patients.

patient outcomes

A total of 399 events (164 on letrozole and 235 on placebo) were observed at the time of this analysis. Among them, 136 on letrozole and 190 on placebo were recurrent disease only (breast, chest wall, regional or distant) and 28 on letrozole and 45 on placebo were CLBC only. The sites of recurrences are given in Table 1.

The Kaplan–Meier curve for DFS by treatment arm is presented in Figure 2. The 4-year DFS was 94.3% for patients on letrozole and 91.4% on placebo. The HR of letrozole to placebo was 0.68 (95% CI 0.55–0.83). The *P* value of the two-sided log-rank test stratified by the trial stratification factors (receptor status, nodal status and prior adjuvant chemotherapy) at randomization was 0.0001. After adjusting for the other two potential prognostic factors (menopausal status at the start of tamoxifen and time on prior tamoxifen) through a stratified Cox proportional hazards model, the treatment difference was still significant (adjusted HR 0.68, 95% CI 0.56–0.83, $P = 0.0001$) (Table 2).

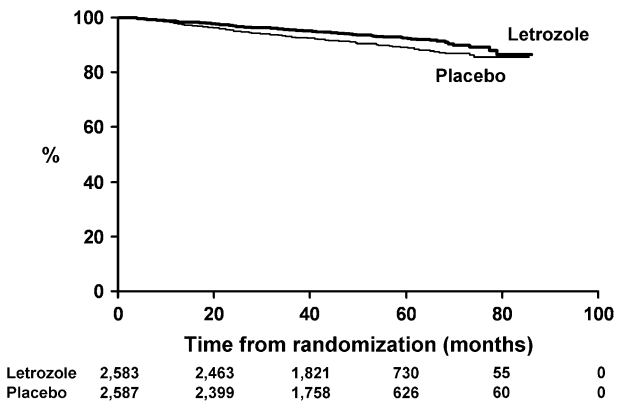

Figure 2. Kaplan–Meier plots for disease-free survival according to initial randomization to letrozole or placebo on MA.17.

The Kaplan–Meier curve for DDFS by treatment arm is presented in Figure 3. The 4-year DDFS was 96.3% for patients on letrozole and 94.9% on placebo. The HR of letrozole to placebo was 0.80 (95% CI 0.62–1.03). The *P* value of the two-sided log-rank test stratified by the stratification factors (receptor status, nodal status and prior adjuvant chemotherapy) at randomization was 0.082. After adjusting for the other two potential prognostic factors (menopausal status at the start of tamoxifen and time on tamoxifen) through a stratified Cox proportional hazards model, there was still only a trend towards a statistical significance (adjusted HR 0.81, 95% CI 0.63–1.03, $P = 0.089$) (Table 2).

A total of 309 patients had died (154 on letrozole and 155 on placebo). The causes of these deaths are summarized in Table 3. More patients on letrozole died of other conditions or circumstances than those on placebo. The Kaplan–Meier curve for OS by treatment arm is presented in Figure 4. The 4-year OS was 95.1% for patients both on letrozole and on placebo. The HR of letrozole to placebo was 0.98 (95% CI 0.78–1.22). The *P* value of the two-sided log-rank test stratified by the stratification factors (receptor status, nodal status and prior adjuvant chemotherapy) at randomization was 0.853. These results are almost identical to that from the stratified Cox proportional hazards model adjusting for the other two potential prognostic factors (menopausal status at the start of tamoxifen and time on tamoxifen) through a stratified Cox proportional hazards model (Table 2).

The analyses of the DFS, DDFS and OS by nodal status, which have their limitations but were prespecified in the final analysis of all events before unblinding, were summarized in Table 4. Letrozole was efficacious in both node-positive and -negative groups in terms of DFS ($P = 0.01$ and 0.0005,

Table 2. Log-rank and Cox regression model for outcomes for all randomized patients on MA.17

End point/treatment arm	Univariate analysis[a]			Multivariate analysis[b]	
	4-year DFS%	HR[c] (95% CI)	Log-rank *P* value[a]	HR[c] (95% CI)	*P* value from Cox regression
DFS					
Treatment arm			0.0001		0.0001
Letrozole	94.3	0.68 (0.55–0.83)		0.68 (0.56–0.83)	
Placebo	91.4				
DDFS			0.082		0.089
Letrozole	96.3	0.80 (0.62–1.03)		0.81 (0.63–1.03)	
Placebo	94.9				
Overall survival			0.853		0.828
Letrozole	95.1	0.98 (0.78–1.22)		0.98 (0.78–1.22)	
Placebo	95.1				

[a]Stratified by receptor status, axillary node status and prior adjuvant chemotherapy at randomization.
[b]Stratified Cox regression with all factors included.
[c]HR of first category over second category.
DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; DDFS, distant disease-free survival.

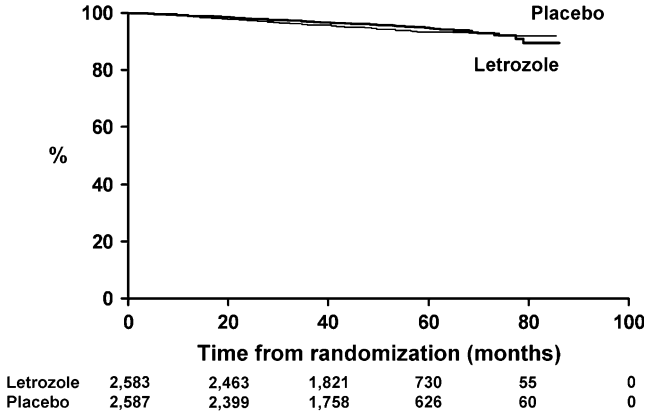

Figure 3. Kaplan–Meier plots for distant disease-free survival according to initial randomization to letrozole or placebo on MA.17.

Table 3. Death summary for all randomized patients on MA, 17

	Number of patients (%)	
	Letrozole $n = 2583$	Placebo $n = 2587$
Patients who died	154 (6.0)	155 (6.0)
Cause of death		
Breast cancer	58	70
Combination of breast cancer and nonprotocol treatment complication	1	1
Nonprotocol treatment complication	2	0
Other primary malignancy	29	31
Other condition or circumstance	60	48
Unknown	4	3
Missing	0	2
Patients who were censored	2429 (94.0)	2432 (94.0)
Known alive	2426 (93.9)	2426 (93.8)
Lost to follow-up	3 (0.1)	6 (0.2)

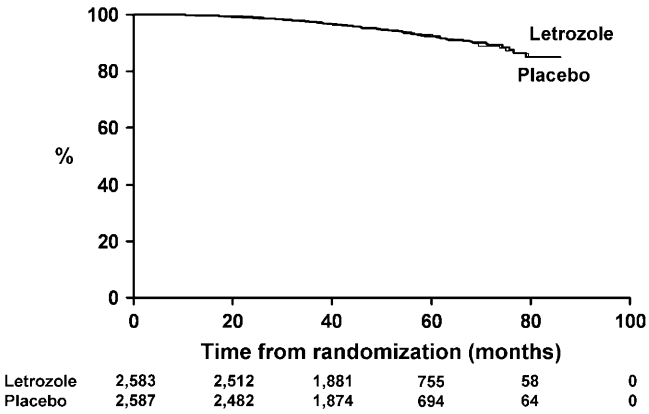

Figure 4. Kaplan–Meier plots for overall survival according to initial randomization to letrozole or placebo on MA.17.

respectively) but was found to be significantly better than placebo only in the node-positive cohort in terms of DDFS ($P = 0.04$). No significant difference between letrozole and placebo was found in any subgroups in terms of OS. The P values of tests for the interaction between nodal status and treatment were not significant for the end points examined being 0.15 for DFS, 0.16 for DDFS and 0.20 for OS.

Analysis of CLBC revealed the annual incidence rate to be 0.28% for patients on letrozole (95% CI 0.18–0.38) and 0.46% for patients on placebo (95% CI 0.33–0.59). The P value of the stratified log-rank test for the difference between the two treatment groups in terms of the time to the development of the CLBC was 0.033 with an HR of 0.61 (95% CI 0.39–0.97) from the stratified Cox model (Table 5). The cumulative incidence plot for the time to the development of CLBC is presented in Figure 5.

discussion

This updated ITT analysis revealed, after a median follow-up of 64 months, that letrozole extended adjuvant therapy following ~5 years of tamoxifen produced a clinically important and statistically significant improvement in the primary end point of DFS. Letrozole therapy was associated with a 2.9% improvement in DFS at 4 years with 94.3% of patients randomly assigned to receive letrozole being free of an event compared with 91.4% randomly assigned to receive placebo. The adjusted HR was 0.68 (95% CI 0.56– 0.83, $P = 0.0001$). This statistically significant DFS advantage for letrozole was also seen in the preplanned analyses according to baseline pathologic lymph node status. Letrozole was superior to placebo whether the lymph nodes had been negative or positive where the HRs for an event were 0.51 (95% CI 0.35–0.75, $P = 0.0005$) and 0.74 (95% CI 0.58–0.94, $P = 0.01$), respectively.

The findings of maintenance of superiority for letrozole in this updated ITT analysis must be considered in the context of the results from the post-unblinding analysis of 2383 patients originally randomly assigned to receive placebo [11] who remained free of an event. This analysis [11] considered only the patients initially randomly assigned to receive placebo who, upon unblinding of the trial, were then offered letrozole and thus considers only this cohort of patients. Two-thirds of the patients accepted the offer of letrozole therapy and one-third declined. At a median follow-up after unblinding of 2.8 years, the HR (patients choosing letrozole/patients declining letrozole) for an event in DFS was 0.37 (95% CI 0.23–0.61, $P < 0.0001$). Despite the fact that the use of letrozole postunblinding was not randomized, the findings are consistent with a substantial benefit of letrozole in this 'late extended adjuvant therapy' setting particularly given the presence of a prognostically worse lymph node profile in the women who chose letrozole. The use of an effective agent in two-thirds of the patients randomly assigned to receive placebo would be expected to substantially dilute the benefit of initial randomization to letrozole. Despite this effect, our ITT analysis revealed a substantial 32% reduction in the hazard for an event in DFS for women originally randomly assigned to receive letrozole.

Our analysis also demonstrated that patients originally randomly assigned to receive letrozole had a superior DDFS (HR 0.81, 95% CI 0.63–1.03) but this did not achieve statistical significance ($P = 0.089$) as it did in the original analysis of

Table 4. Outcomes by nodal status for all randomized patients on MA.17

Outcome/factors	Value	Letrozole		Placebo		HR[a] (95% CI)
		n	% 4-year DFS	*n*	% 4-year DFS	
DFS						
Pathologic node status at baseline	Negative	1295	97.0	1281	94.6	0.51 (0.35–0.75)
	Positive	1174	91.7	1194	87.8	0.74 (0.58–0.94)
	Unknown	108	89.3	106	92.9	1.15 (0.47–2.77)
Distant DFS						
Pathologic node status at baseline	Negative	1295	98.3	1281	98.1	0.90 (0.51–1.56)
	Positive	1174	94.3	1194	90.9	0.74 (0.55–0.98)
	Unknown	108	92.8	106	100	3.19 (0.66–15.37)
Overall survival						
Pathologic node status at baseline	Negative	1295	96.5	1281	97.2	1.24 (0.84–1.82)
	Positive	1174	94.1	1194	92.6	0.84 (0.63–1.12)
	Unknown	108	89.4	106	96.0	1.56 (0.60–4.03)

[a]Letrozole over placebo HR (unstratified).
DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Table 5. Incidence of CLBC for all randomized patients on MA.17

	Number of patients (%) randomized arm		
	Letrozole	Placebo	Total
	n = 2583	*n* = 2587	*n* = 5170
Number of CLBC cases	30 (1.16)	49 (1.89)	79 (1.53)
Person-years of follow-up	10 698.2	10 592.7	
Annual incidence rate, % (95% CI)	0.28 (0.18–0.38)	0.46 (0.33–0.59)	
Hazard ratio[a] (95% CI)			0.61 (0.39–0.97)
Stratified log-rank *P* value[a]			0.033

[a]Stratified by receptor status, nodal status and prior adjuvant chemotherapy at randomization.
CLBC, contralateral breast cancer; CI, confidence interval.

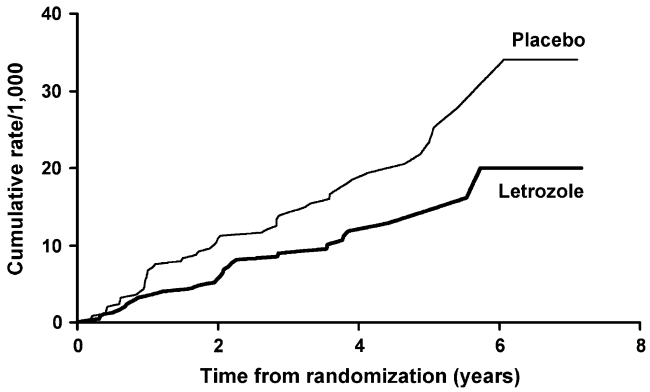

Figure 5. Cumulative incident plots of contralateral breast cancers according to initial randomization to letrozole or placebo on MA.17.

MA.17 that included only events before unblinding [2] where the HR was 0.60 (95% CI 0.43–0.84, $P = 0.002$). Again, these ITT findings should be considered in the context of the post-unblinding analysis where the two-thirds of patients originally randomly assigned to receive placebo who chose to take letrozole had an HR for developing metastatic disease of 0.39 (95% CI 0.20–0.74, $P = 0.004$) compared with those patients who declined letrozole [11]. Thus, it appears that the loss of statistical significance for letrozole in terms of DDFS is explained by the benefit in a large number of patients who were originally randomly assigned to receive placebo and elected to take letrozole.

No significant difference between letrozole and placebo in terms of OS was found in this ITT analysis. In particular, our analysis revealed no survival advantage for letrozole in the node-positive cohort as was demonstrated in the final report of events before unblinding [2] where this advantage just achieved statistical significance (HR 0.61, 95% CI 0.38–0.98, $P = 0.04$). This finding in the node-positive cohort could also be explained by the post-unblinding analysis [11] where there was a highly substantial survival advantage for women who chose to take letrozole (HR 0.30, 95% CI 0.17–0.53, $P < 0.0001$). Thus, it would be expected that a borderline advantage for letrozole would be lost when a substantial number of women originally randomly assigned to receive placebo elected to take an effective drug.

The ITT analysis also revealed a significant advantage for women originally randomly assigned to receive letrozole in terms of development of a CLBC with an HR of 0.61 (95% CI 0.39–0.97, $P = 0.033$). This finding is remarkable given the reduction in CLBC seen in the post-unblinding analysis [11]

where those women who elected to take letrozole experienced an 82% reduction (HR 0.18, 95% CI 0.06–0.58, $P = 0.004$). The report of events up to the point of unblinding [2] had revealed an advantage for women randomly assigned to receive letrozole in terms of CLBC (HR 0.63, 95% CI 0.18–2.21) but this was not statistically significant ($P = 0.12$). It is likely that the CLBC superiority for letrozole seen in the ITT analysis is related to longer follow-up allowing the identification of more CLBC events.

The maintenance of a DFS superiority for letrozole in the ITT analysis indicates that despite the apparent advantage of delayed extended adjuvant therapy in the post-unblinding analysis [11] where the median time from completion of adjuvant tamoxifen to starting letrozole was 2.8 years (range 1.1–7.1 years), starting letrozole sooner, i.e. within 3 months of completing tamoxifen as required for MA.17, is preferable to delaying its initiation beyond that time. This inference is important as it is highly unlikely that the question of optimal time for initiation of letrozole extended adjuvant therapy will be studied prospectively. Survival results from this analysis are confounded by the large number of patients originally randomly assigned to receive placebo who chose to take letrozole after the study was unblinded. The findings from this ITT analysis, with a median follow-up of >5 years, demonstrate the significant efficacy of letrozole when used as extended adjuvant therapy in postmenopausal women with early-stage breast cancer.

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conflict of interest statement

JNI: consulting and lecture honoraria from Novartis; HBM: consulting honoraria from Pfizer and Amgen; NJR: consulting honoraria from Astra Zeneca, Genentech, Pfizer, Genomic Health, Abraxis; lecture honoraria from Novartis and Abraxis; research support from Pfizer and Abraxis; MJP: consulting and lecture honoraria from Novartis, Pfizer and Astra Zeneca; KIP: consulting honoraria from Astra Zeneca, Pfizer, Roche, Novartis and Sanofi-Aventis; EAP: research support from Novartis; DAC: consulting and lecture fees from Novartis, Pfizer and Astra Zeneca; PEG: consulting and lecture honoraria from Pfizer, AstraZeneca and Novartis. The other coauthors report no conflict of interest. Presented in part at the 42nd Annual Meeting of the American Society of Clinical Oncology, June 2006, Atlanta, Georgia.

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