

Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor–Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial

Thomas Ruhstaller, MD¹; Anita Giobbie-Hurder, MS²; Marco Colleoni, MD³; Maj-Britt Jensen⁴; Bent Ejler Jensen, MD⁴; Evandro de Azambuja, MD, PhD⁵; Patrick Neven, MD, PhD⁶; István Láng, MD, PhD⁷; Erik Hugger Jakobsen, MD⁸; Laurence Gladiéff, MD⁹; Hervé Bonnefoi, MD¹⁰; Vernon J. Harvey, MD¹¹; Simon Spazzapan, MD¹²; Carlo Tondini, MD¹³; Lucia Del Mastro, MD¹⁴; Corinne Veyret, MD¹⁵; Edda Simoncini, MD¹⁶; Lorenzo Gianni, MD¹⁷; Christoph Rochlitz, MD¹⁸; Elena Kralidis, MD¹⁹; Khalil Zaman, MD²⁰; Jacek Jassem, MD, PhD²¹; Martine Piccart-Gebhart, PhD⁵; Angelo Di Leo, MD, PhD²²; Richard D. Gelber, PhD^{2,23,24}; Alan S. Coates, MD^{25,26}; Aron Goldhirsch, MD^{3,26}; Beat Thürlimann, MD^{1,26}; and Meredith M. Regan, ScD^{2,23} for the members of the BIG 1-98 Collaborative Group and the International Breast Cancer Study Group

abstract

PURPOSE Luminal breast cancer has a long natural history, with recurrences continuing beyond 10 years after diagnosis. We analyzed long-term follow-up (LTFU) of efficacy outcomes and adverse events in the Breast International Group (BIG) 1-98 study reported after a median follow-up of 12.6 years.

PATIENTS AND METHODS BIG 1-98 is a four-arm, phase III, double-blind, randomized trial comparing adjuvant letrozole versus tamoxifen (either treatment received for 5 years) and their sequences (2 years of one treatment plus 3 years of the other) for postmenopausal women with endocrine-responsive early breast cancer. When pharmaceutical company sponsorship ended at 8.4 years of median follow-up, academic partners initiated an observational, LTFU extension collecting annual data on survival, disease status, and adverse events. Information from Denmark was from the Danish Breast Cancer Cooperative Group Registry. Intention-to-treat analyses are reported.

RESULTS Of 8,010 enrolled patients, 4,433 were alive and not withdrawn at an LTFU participating center, and 3,833 (86%) had at least one LTFU report. For the monotherapy comparison of letrozole versus tamoxifen, we found a 9% relative reduction in the hazard of a disease-free survival event with letrozole (hazard ratio [HR], 0.91; 95% CI, 0.81 to 1.01). HRs for other efficacy end points were similar to those for disease-free survival. Efficacy of letrozole versus tamoxifen for contralateral breast cancer varied significantly over time (0- to 5-, 5- to 10-, and > 10-year HRs, 0.62, 0.47, and 1.35, respectively; treatment-by-time interaction $P = .005$), perhaps reflecting a longer carryover effect of tamoxifen. Reporting of specific long-term adverse events seemed more effective with national registry than with case-record reporting of clinical follow-up.

CONCLUSION Efficacy end points continued to show trends favoring letrozole. Letrozole reduced contralateral breast cancer frequency in the first 10 years, but this reversed beyond 10 years. This study illustrates the value of extended follow-up in trials of luminal breast cancer.

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INTRODUCTION

Hormone receptor–positive early breast cancer has a long natural history, with disease and potentially adverse events (AEs) occurring beyond 10 years since initiation of treatment.^{1,2} Because regulatory bodies often require, at most, 10 years of follow-up in clinical trials, pharmaceutical partners rarely fund data collection beyond this point. The current study describes extended follow-up of the Breast International Group (BIG) 1-98 trial, one of the pivotal studies establishing the role of aromatase inhibitors (AIs) in the

adjuvant treatment of postmenopausal women with steroid hormone-receptor–positive early breast cancer.

The BIG 1-98 trial has been described elsewhere.³⁻⁸ Briefly, it compared 5 years of tamoxifen versus letrozole as monotherapy, and sequential treatment with 2 years of one of these drugs followed by 3 years of the other in postmenopausal women with hormone receptor–positive early breast cancer. In our most recent report,⁸ we found letrozole monotherapy provided a significant improvement in disease-free

ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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Written on behalf of the BIG 1-98 Collaborative Group and the International Breast Cancer Study Group (IBCSG). The investigators in the BIG 1-98 Collaborative Group and the IBCSG are listed in the Data Supplement pages 2-7.

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survival (DFS), overall survival, distant recurrence-free interval, and breast cancer–free interval (BCFI) compared with tamoxifen monotherapy at median follow-up of 8.1 years since randomization.

When the BIG 1-98 trial started as a Novartis-sponsored trial, it was intended to conduct long-term follow-up.³ In 2010, however, Novartis discontinued sponsorship and financing of follow-up. The International Breast Cancer Study Group (IBCSG), in collaboration with Breast International Group (BIG) partners, decided to continue follow-up and reporting from centers and groups that had conducted BIG 1-98 under contracts with academic organizations. This report presents results from the BIG 1-98 trial at a median follow-up of 12.6 years.

PATIENTS AND METHODS

Patients

BIG 1-98 was a randomized, phase III, double-blind trial that recruited postmenopausal women with early breast cancer positive for estrogen receptor, progesterone receptor, or both. The details of trial design, eligibility criteria, and study procedures for BIG 1-98 have been presented previously.³⁻⁸ Initially, from 1998 to 2000, in centers under contract with Novartis, women were randomly assigned to receive monotherapy with letrozole (Femara; Novartis, Basel, Switzerland) 2.5 mg orally daily or tamoxifen 20 mg orally daily for 5 years. In 1998, Novartis and IBCSG agreed to activate the four-arm BIG 1-98 trial in the BIG network, incorporate the prior two-arm randomizations and follow-up into BIG 1-98, and end random assignment to the two-arm option in 2000. Thus, from 1999 to 2003, patients were randomly assigned to one of four groups: monotherapy with tamoxifen or letrozole for 5 years or sequential therapy consisting of letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years (four-arm option). The intention-to-treat (ITT) population included 8,010 patients from 247 participating centers in 27 countries. The schema for BIG 1-98 is shown in the Data Supplement.

The BIG 1-98 long-term follow-up study (BIG 1-98 LTFU) was an observational extension of the BIG 1-98 trial, activated in 2011 to continue collection of a yearly update of survival, disease status, and long-term AEs beyond Novartis sponsorship. Patients who were alive and not withdrawn at the end of the original study could participate if they were enrolled from centers that had conducted the four-arm portion and had activated BIG 1-98 LTFU. A single-page data collection form was required annually for all patients, with additional pages as needed to document death, recurrence, second malignancy, specified AEs, or use of certain medications. Information was obtained by clinic visit, telephone contact with patient, general physician, or family member, or from the Danish Breast Cancer Cooperative Group (DBCG) Registry for Danish

participants (Data Supplement). A summary of the number of patients participating in the LTFU study is shown in Figure 1. A detailed figure of patient disposition according to treatment group is available in the Data Supplement.

Statistical Analysis

The primary efficacy end point was DFS, defined as the time since random assignment to the first of the following events: invasive recurrence in local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second (nonbreast) primary cancer; or death without a previous cancer event. Other end points previously reported were defined using standardized definitions for efficacy end points in adjuvant breast cancer trials criteria⁹ and include overall survival, distant recurrence-free interval, and invasive BCFI. We also analyzed breast cancer mortality, censoring deaths reported without a breast cancer event (ie, BCFI event), because median age at BIG 1-98 study entry was 61 years and deaths unrelated to breast cancer were expected during prolonged follow-up. Time to contralateral breast cancer was also analyzed, ignoring other events and censoring at last follow-up or death.

For each time-to-event end point, separate analyses were performed for the monotherapy comparison (letrozole *v* tamoxifen using patients randomly assigned during either two-arm or four-arm options) and for sequential therapy comparisons versus tamoxifen monotherapy. Analyses were by ITT principle according to random assignment, ignoring the fact that 619 (25.2%) of 2,459 patients assigned to tamoxifen for the monotherapy comparison and 612 (39.5%) of 1,548 assigned to tamoxifen for the four-arm comparisons (Data Supplement) selectively crossed over to receive letrozole after release of first results in 2005.^{3,5,8}

Time-to-event end point analyses used data from all 8,010 patients in the BIG 1-98 ITT population. Because not all patients initially enrolled in BIG 1-98 were eligible for the BIG 1-98 LTFU study (Fig 1), weighted analyses as routinely applied in observational studies¹⁰⁻¹² were used for Kaplan-Meier and Cox model estimates. The details of the weighting methods and other statistical analyses are presented in the Data Supplement. Briefly, intervals of risk and events recorded during the original trial follow-up received a weight of 1, whereas those recorded during LTFU received a weight > 1 such that the information provided by each patient observed in the LTFU study counted not only for herself but also for other women with similar disease, treatment, demographics, and original trial experiences who did not have LTFU data collection.

Cumulative incidence percentages for events defining efficacy end points were estimated as 100 minus the weighted Kaplan-Meier estimates. Weighted Cox models, stratified according to chemotherapy randomization

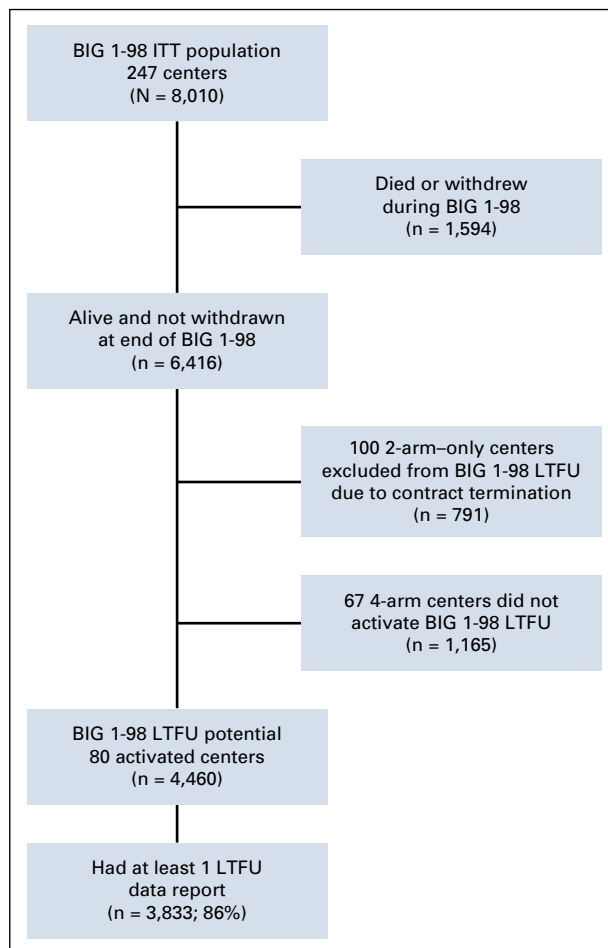


FIG 1. Flow diagram of patients and centers providing data for efficacy analyses. Per contract, centers participating in the four-arm option (with or without prior participation in the two-arm option) could activate BIG 1-98 LTFU, whereas those participating only in the two-arm option could not activate BIG 1-98 LTFU. ITT, intention to treat; LTFU, long-term follow-up.

stratum, estimated hazard ratios (HRs) and 95% CIs were determined on the basis of robust variance estimation. *P* values for tests of whether the HR differed from 1.0 were reported, not to make inference of whether the treatments were more efficacious than tamoxifen, but as a complement to the CI for judging the play of chance in these analyses. All Cox models were assessed for nonproportional hazards by including an interaction term between treatment and time (continuous) as a time-dependent covariate. In instances where the *P* value for interaction was $< .15$, a piecewise Cox model was used to estimate HRs over three predefined time intervals (0 to 5, 5 to 10, and > 10 years) to characterize the relationship between treatment effect and time (Data Supplement).

Prespecified AEs recorded during LTFU were summarized using number and incidence per 1,000 patient-years of follow-up. Because Danish centers reported a subset of the

AE categories on the basis of the National Patient Registry, the incidences are presented overall and separately for Danish and non-Danish centers.

RESULTS

Population

Median follow-up for this extended analysis was 12.6 (interquartile range: 9.1 to 13.9) years, with a maximum follow-up of 17.7 years. This compares with a median follow-up of 8.1 (interquartile range: 7.3 to 9.5) years, with a maximum of 12.4 years at the most recent previous analysis of the original BIG 1-98 study.⁸ This LTFU report is based on a total of 83,271 patient-years of follow-up, a 32% increase in years of follow-up compared with the previous analysis.

The characteristics of the patients with at least one LTFU contact were compared with those of the patients who were alive and not withdrawn at the end of the original BIG 1-98 but who did not have data provided for LTFU (Table 1). The patients with LTFU data were slightly younger at the time of enrolment in BIG 1-98 and had more advanced disease with slightly less node-negative disease and T1 stage compared with the cohort without any LTFU information. Fewer patients with BIG 1-98 LTFU data received adjuvant chemotherapy, and more received breast-conserving surgery than those not submitting LTFU data. There were no imbalances according to randomized treatment assignment.

Efficacy Results

The cumulative incidence of efficacy end point events for the monotherapy comparison of letrozole for 5 years versus tamoxifen for 5 years are shown in Figure 2. There was a nonsignificant, 9% reduction in the hazard of a DFS event with letrozole compared with tamoxifen over the entire time of observation (HR, 0.91; 95% CI, 0.81 to 1.01; $P = .08$; Fig 2A). The early effect of letrozole was maintained over time; however, the magnitude in favor of letrozole seemed to be slightly diminished compared with the results at 8.1 years of median follow-up. For the monotherapy population, there was no evidence of variation of the treatment effect over time (treatment-by-time interaction $P = .22$).

Other end points including overall survival, time to distant recurrence-free interval, and BCFI maintained similar HRs as in earlier reports, though the magnitude of the advantage for letrozole was numerically reduced (Fig 2B-2D; see Data Supplement for results of ITT analyses at 8.1 years and 12.6 years of follow-up).

Breast cancer mortality showed no evidence of variation of the treatment effect over time (treatment-by-time interaction $P = .80$) in the monotherapy comparison. The results showed a nonsignificant 11% reduction in breast cancer mortality with letrozole (HR, 0.89; 95% CI, 0.74 to 1.07; $P = .20$; Fig 2E).

TABLE 1. Patient, Disease, and Treatment Characteristics at Enrollment in the BIG 1-98 Trial for Those Alive and Not Withdrawn at the 2010 Trial Closure According to Whether LTFU Data Were Provided (N = 6,416)

| Characteristic | No. of Patients | No LTFU Data (n = 2,583) | | LTFU Data (n = 3,833) | |
|---|-----------------|--------------------------|------|-----------------------|------|
| | | No. | % | No. | % |
| Age, years | | | | | |
| < 65 | 4,344 | 1,690 | 65.4 | 2,654 | 69.2 |
| ≥ 65 | 2,072 | 893 | 34.6 | 1,179 | 30.8 |
| Tumor size, cm | | | | | |
| ≤ 2 | 4,227 | 1,751 | 67.8 | 2,476 | 64.6 |
| > 2 | 2,123 | 798 | 30.9 | 1,325 | 34.6 |
| Missing | 66 | 34 | 1.3 | 32 | 0.8 |
| Nodal status | | | | | |
| N0/Nx | 3,993 | 1,703 | 65.9 | 2,290 | 59.7 |
| 1-3 positive | 1,818 | 657 | 25.4 | 1,161 | 30.3 |
| ≥ 4 positive | 600 | 219 | 8.5 | 381 | 9.9 |
| Missing | 5 | 4 | 0.2 | 1 | 0.0 |
| Tumor grade (BRE) | | | | | |
| 1 | 1,451 | 585 | 22.6 | 866 | 22.6 |
| 2 | 3,588 | 1,389 | 53.8 | 2,199 | 57.4 |
| 3 | 1,239 | 502 | 19.4 | 737 | 19.2 |
| Missing | 138 | 107 | 4.1 | 31 | 0.8 |
| Peritumoral vascular invasion | | | | | |
| No | 5,592 | 2,175 | 84.2 | 3,417 | 89.1 |
| Yes | 671 | 297 | 11.5 | 374 | 9.8 |
| Unable to assess | 153 | 111 | 4.3 | 42 | 1.1 |
| ER status | | | | | |
| Absent | 135 | 77 | 3.0 | 58 | 1.5 |
| Present (≥ 1%) | 6,277 | 2,502 | 96.9 | 3,775 | 98.5 |
| Unknown | 4 | 4 | 0.2 | — | — |
| PgR status | | | | | |
| Absent | 1,331 | 562 | 21.8 | 769 | 20.1 |
| Present (≥ 1%) | 4,941 | 1,916 | 74.2 | 3,025 | 78.9 |
| Unknown | 144 | 105 | 4.1 | 39 | 1.0 |
| Local treatment | | | | | |
| Less than Mx/radiotherapy | 3,720 | 1,422 | 55.1 | 2,298 | 60.0 |
| Less than Mx/no radiotherapy | 172 | 96 | 3.7 | 76 | 2.0 |
| Mx/radiotherapy | 991 | 365 | 14.1 | 626 | 16.3 |
| Mx/no radiotherapy | 1,517 | 691 | 26.8 | 826 | 21.5 |
| Other | 16 | 9 | 0.3 | 7 | 0.2 |
| Chemotherapy strata | | | | | |
| No chemotherapy | 4,811 | 1,801 | 69.7 | 3,010 | 78.5 |
| Chemotherapy | 1,605 | 782 | 30.3 | 823 | 21.5 |
| Endocrine therapy randomly assigned arm | | | | | |
| (continued on following page) | | | | | |

TABLE 1. Patient, Disease, and Treatment Characteristics at Enrollment in the BIG 1-98 Trial for Those Alive and Not Withdrawn at the 2010 Trial Closure According to Whether LTFU Data Were Provided (N = 6,416) (continued)

| | | No LTFU Data (n = 2,583) | | LTFU Data (n = 3,833) | |
|-------------------------------|-----------------|--------------------------|------|-----------------------|------|
| Characteristic | No. of Patients | No. | % | No. | % |
| Monotherapy comparison | | | | | |
| Letrozole (two- and four-arm) | 1,932 | 901 | 50.5 | 1,031 | 50.5 |
| Tamoxifen (two- and four-arm) | 1,895 | 883 | 49.5 | 1,012 | 49.5 |
| Four-arm option only | | | | | |
| Letrozole | 1,297 | 407 | 25.4 | 890 | 24.9 |
| Tamoxifen | 1,286 | 394 | 24.6 | 892 | 25.0 |
| Letrozole → tamoxifen | 1,300 | 404 | 25.3 | 896 | 25.1 |
| Tamoxifen → letrozole | 1,289 | 395 | 24.7 | 894 | 25.0 |

Abbreviations: BRE, Bloom–Richardson–Elston; ER, estrogen receptor; LTFU, long-term follow-up; Mx, mastectomy; PgR, progesterone receptor.

Efficacy end point results according to nodal status are shown in the Data Supplement. The HRs comparing letrozole versus tamoxifen were similar across nodal groups, but, as expected, the absolute differences favoring letrozole were greater for the node-positive cohort.

Contralateral and Nonbreast Primaries

We detected a clear benefit of letrozole over tamoxifen in preventing contralateral breast cancer over the first 10 years, which was numerically reversed over the period beyond 10 years. During the original study, 48 contralateral breast cancer events were reported in the letrozole arm versus 75 in the tamoxifen arm, whereas during the LTFU study, there were 29 in the letrozole arm and 15 in the tamoxifen arm (Table 2). HRs for time to contralateral breast cancer for letrozole versus tamoxifen were 0.62 (95% CI, 0.36 to 1.09) for years 0 to 5, 0.47 (95% CI, 0.23 to 0.97) for years 5 to 10, and 1.35 (0.53 to 3.41) for years 10 or longer (treatment-by-time interaction $P = .005$).

Throughout follow-up, there was an 18% increase in the occurrence of second nonbreast primaries in patients receiving tamoxifen monotherapy, largely owing to an excess of endometrial cancer during the original study period (Table 2).

AEs Reported Clinically and by a Registry

Most of the predefined AEs were reported at similar rates in the two arms during LTFU (Table 3). Of particular note is the lack of difference in osteoporosis/osteopenia and fracture rate between tamoxifen and letrozole. Myocardial infarction and cerebrovascular events showed no significant differences between the arms, but a higher rate of other cardiac events (hypertension, cardiac insufficiency, supraventricular arrhythmia and valve disorders) was reported in the letrozole arm. Thromboembolic events were more commonly reported in the letrozole arm during LTFU.

In this trial two different kinds of reporting of long-term AEs were used. The data of Danish patients were uploaded annually from DBCG (capturing data from nationwide

Danish health registries). As seen in Table 3, the Danish DBCG registry reported more specific events like myocardial infarction, transient ischemic attack or cerebrovascular accident, and thromboembolism, whereas additional “other cardiac events” were recorded from centers using nonregistry reporting.

Comparisons of Sequential Arms Versus Monotherapy

The cumulative incidence of efficacy end points for the four-arm comparisons of letrozole, tamoxifen, and their sequences are shown in the Data Supplement. Outcomes achieved with the sequence of letrozole taken for 2 years followed by tamoxifen for 3 years were close to those obtained by assignment to 5 years of letrozole monotherapy. For example, cumulative incidence for a DFS event, comparing letrozole monotherapy versus the letrozole to tamoxifen sequence, were within one percentage point of each other during follow-up: 12.3% versus 12.6% at 5 years, 26.0% versus 26.8% at 10 years, and 35.5% versus 36.2% at 14 years, respectively.

DISCUSSION

Over the past 20 years, there has been a trend to cease follow-up of adjuvant therapy clinical trials after approximately 10 years, which has limited the available data about AIs for postmenopausal women. Other adjuvant endocrine therapy trials like the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, and the Intergroup Exemestane Study (IES) reported their long-term outcome at 10 years,¹³⁻¹⁵ whereas the Austrian Breast and Colorectal Cancer Study Group (ABCSCG) reported a cohort of their Trial 8 at 11 years correlating the risk of late recurrence with PAM50 risk of recurrence.^{16,17} The present report of LTFU at a median of 12.6 years in the BIG 1-98 study thus represents the longest currently available follow-up of trials investigating adjuvant AI therapy. Methodologically, the additional long-term follow-up constitutes a long-term observational study within a clearly defined study

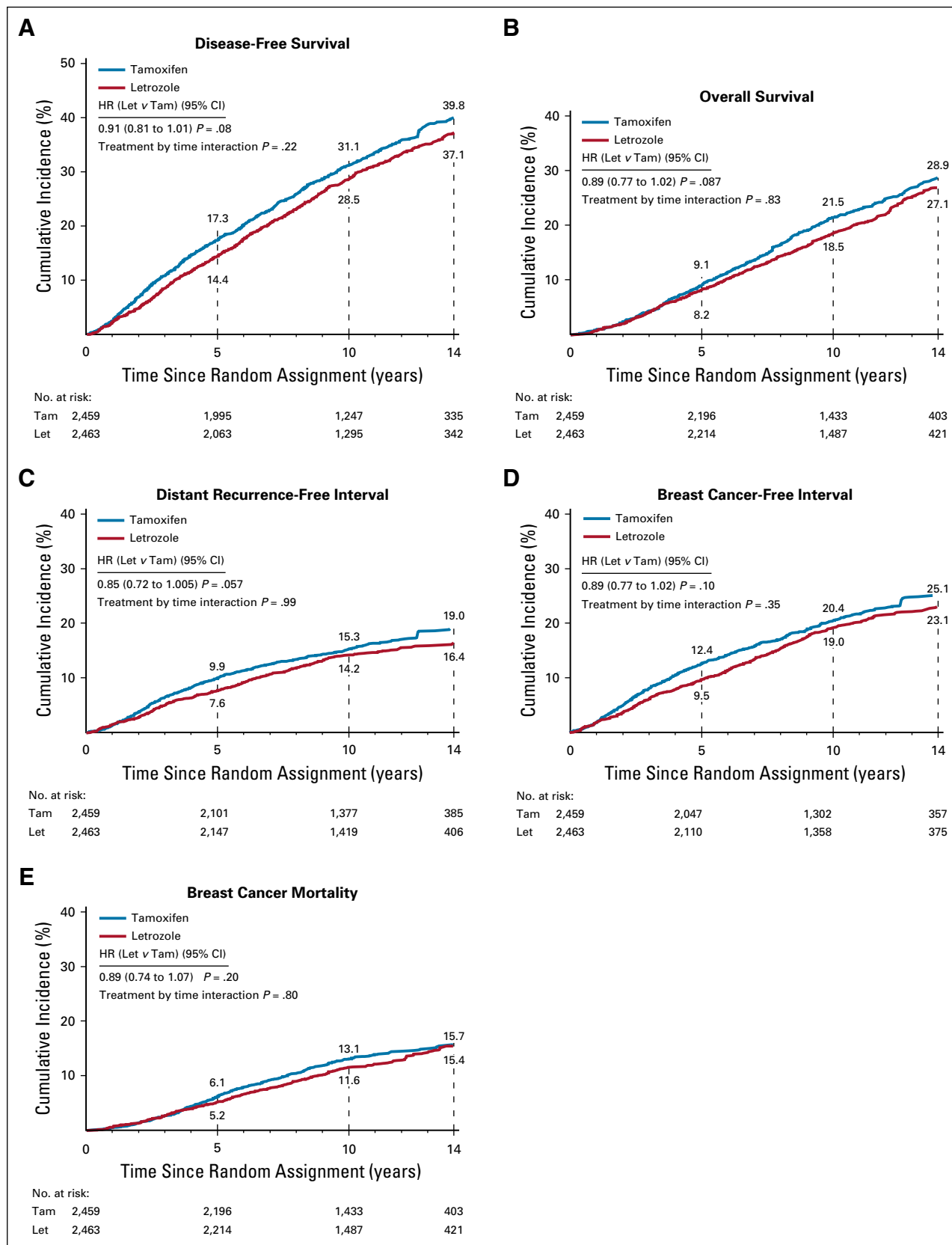


FIG 2. Cumulative incidence of events defining five efficacy end points for the monotherapy comparison of letrozole (Let; $n = 2,463$) versus tamoxifen (Tam; $n = 2,459$) based on weighted analyses incorporating data from the BIG 1-98 original study and the data collected during the BIG 1-98 LTFU observational component. HR, hazard ratio.

TABLE 2. Number and Incidence (per 1,000 Patient-years of Follow-up) of Contralateral Breast Cancers and Second Nonbreast Primaries Diagnosed at Any Time During the Original BIG 1-98 Study and During the BIG 1-98 LTFU According to Letrozole Versus Tamoxifen Treatment Assignment (Monotherapy Comparison)

| Second Cancers | Reported During Original BIG 1-98 Study | | | | Reported During BIG 1-98 LTFU Study | | | |
|---------------------------------------|---|-----------------------------------|-----------------|-----------------------------------|-------------------------------------|-----------------------------------|-----------------|-----------------------------------|
| | Letrozole | | Tamoxifen | | Letrozole | | Tamoxifen | |
| | No. of Patients | Incidence per 1,000 Patient-Years | No. of Patients | Incidence per 1,000 Patient-Years | No. of Patients | Incidence per 1,000 Patient-Years | No. of Patients | Incidence per 1,000 Patient-Years |
| Patient-years of follow-up | | 20,445 | | 20,250 | | 5,094 | | 4,946 |
| Contralateral breast cancer | 48 | 2.3 | 75 | 3.7 | 29 | 5.7 | 15 | 3.0 |
| Second nonbreast primary | 138 | 6.7 | 163 | 8.0 | 38 | 7.5 | 37 | 7.5 |
| Lung/pleura | 17 | 0.8 | 21 | 1.0 | 11 | 2.2 | 6 | 1.2 |
| Colorectal | 27 | 1.3 | 33 | 1.6 | 7 | 1.4 | 9 | 1.8 |
| Kidney | 3 | 0.1 | 11 | 0.5 | 1 | 0.2 | 2 | 0.4 |
| Skin (nonmelanoma) | 0 | 0.0 | 0 | 0.0 | 1 | 0.2 | 0 | 0.0 |
| Melanoma | 15 | 0.7 | 7 | 0.3 | 1 | 0.2 | 3 | 0.6 |
| Ovary | 10 | 0.5 | 10 | 0.5 | 2 | 0.4 | 1 | 0.2 |
| Uterine/endometrium | 7 | 0.3 | 33 | 1.6 | 2 | 0.4 | 4 | 0.8 |
| Lymphoma, myeloma, blood, bone marrow | 18 | 0.9 | 12 | 0.6 | 4 | 0.8 | 4 | 0.8 |
| Other sites | 41 | 2.0 | 36 | 1.8 | 9 | 1.8 | 8 | 1.6 |

Abbreviation: LTFU, long-term follow-up.

subpopulation from a prospective randomized trial. We used a weighted analysis methodology to include efficacy data for patients unavailable for LTFU. Another special feature of this investigation was the availability of efficacy end point data and AEs captured annually from a central registry for all Danish participants.

The protocol-defined primary DFS end point still showed a relative risk reduction of 9% in favor of the letrozole arm after a median follow-up of 12.6 years, the same as the 9% risk reduction seen with anastrozole in the 10-year analysis of the ATAC trial.¹³ In BIG 1-98, the letrozole advantage in terms of DFS in this ITT analysis was marginally less than in previous reports. The other efficacy end points also showed slightly attenuated HRs in favor of the letrozole arm compared with the previous ITT analysis after 8.1 years of follow-up (see Data Supplement for discussion).⁸

A reason for some attenuation of letrozole benefit in DFS over time may be the accumulation of nonbreast events as a result of the age of the observed population. The median age at inclusion was 61 years; after 12.6 years of follow-up, on average, many of these women are approaching their eighties and are at risk for death without a previous cancer event. The end point breast cancer mortality, perhaps the least likely to be diluted by intercurrent deaths, showed a relative hazard reduction of 11% in favor of letrozole therapy. Another reason for reduced DFS difference could be a more effective carryover of prevention of contralateral breast cancer seen with tamoxifen during LTFU. The long carryover effect of tamoxifen was also seen in the 16-year

follow-up of the IBIS-I study, in which 5 years of preventive tamoxifen was compared with placebo and the preventive effect of tamoxifen remained similar throughout 20 years.¹⁸ In the long-term follow-up of ATAC and the IES, more contralateral breast cancer events were reported in the tamoxifen arm, but without analysis of the incidence during different time periods.^{13,14} New primary cancers at non-breast sites were numerically similar in the various treatment arms during BIG 1-98 LTFU. Finally, the selective crossover to letrozole of 25.2% of patients assigned to tamoxifen for the monotherapy comparison and 39.5% of the patients assigned to tamoxifen for the four-arm comparison could also have contributed to improved outcome for those assigned to tamoxifen and the attenuation of letrozole benefit observed in these ITT analyses.

We found no relevant differences between the arms regarding occurrence of myocardial infarction, cerebrovascular events, osteoporosis, or fracture rates during LTFU. These reassuring observations are consistent with the result of the long-term follow-up of the ATAC trial.¹³ Previously expressed concerns about the potential long-term increased risk for ischemic cardiovascular events associated with AI therapy¹⁹ seem to be unfounded. The thromboembolic event rate was lower in the tamoxifen arm during LTFU. This may reflect more effective prophylaxis administered for patients deemed to be at higher risk as a result of earlier tamoxifen exposure. The higher incidence of other cardiac events in the letrozole arm included many different disorders and is difficult to interpret in an ageing population.

TABLE 3. Targeted Adverse Events Reported During the BIG 1-98 LTFU Period

| Analysis Cohort and Adverse Events | Treatment (Monotherapy Comparison) | | | |
|------------------------------------|------------------------------------|-----------------------------------|------------------------|-----------------------------------|
| | Letrozole | | Tamoxifen | |
| | No. of Patients | Patient-Years of Follow-Up | No. of Patients | Patient-Years of Follow-Up |
| BIG 1-98 LTFU | 1,031 | 5,094 | 1,012 | 4,946 |
| BIG 1-98 LTFU (non-Danish) | 741 | 3,608 | 724 | 3,422 |
| BIG 1-98 LTFU (Danish) | 290 | 1,488 | 288 | 1,524 |
| Adverse event | No. with Adverse Event | Incidence per 1,000 patient-years | No. with Adverse Event | Incidence per 1,000 patient-years |
| MI | | | | |
| BIG 1-98 LTFU | 20 | 3.9 | 17 | 3.4 |
| BIG 1-98 LTFU (non-Danish) | 7 | 1.9 | 1 | 0.3 |
| BIG 1-98 LTFU (Danish) | 13 | 8.7 | 16 | 10.5 |
| Thromboembolic | | | | |
| BIG 1-98 LTFU | 21 | 4.1 | 10 | 2.0 |
| BIG 1-98 LTFU (non-Danish) | 9 | 2.5 | 4 | 1.2 |
| BIG 1-98 LTFU (Danish) | 12 | 8.1 | 6 | 3.9 |
| CVA/TIA | | | | |
| BIG 1-98 LTFU | 23 | 4.5 | 26 | 5.3 |
| BIG 1-98 LTFU (non-Danish) | 8 | 2.2 | 9 | 2.6 |
| BIG 1-98 LTFU (Danish) | 15 | 10.1 | 17 | 11.2 |
| Other cardiac conditions* | | | | |
| BIG 1-98 LTFU | 43 | 8.4 | 15 | 3.0 |
| BIG 1-98 LTFU (non-Danish) | 40 | 11.1 | 15 | 4.4 |
| BIG 1-98 LTFU (Danish) | 3 | 2.0 | 0 | 0 |
| Arthralgia GE grade 2† | | | | |
| BIG 1-98 LTFU (non-Danish) | 76 | 21.1 | 63 | 18.4 |
| Myalgia GE grade 2† | | | | |
| BIG 1-98 LTFU (non-Danish) | 17 | 4.7 | 17 | 5.0 |
| Osteoporosis/osteopenia† | | | | |
| BIG 1-98 LTFU (non-Danish) | 91 | 25.2 | 89 | 26.0 |
| Bone fracture‡ | | | | |
| BIG 1-98 LTFU | 76 | 14.9 | 77 | 15.6 |
| BIG 1-98 LTFU (non-Danish) | 38 | 10.5 | 38 | 11.1 |
| BIG 1-98 LTFU (Danish)‡ | 38 | 25.5 | 39 | 25.6 |

NOTE. The number of patients with the adverse event and the incidence rate per 1,000 patient-years of follow-up are reported both for all patients with data submitted for BIG 1-98 LTFU and separately for the non-Danish and Danish participants, owing to differences in the data sources.

Abbreviations: CVA, cerebrovascular accident; GE, greater than or equal to; LTFU, long-term follow-up; MI, myocardial infarction; TIA, transient ischemic attack.

*Other cardiac conditions comprised primarily hypertension, cardiac insufficiency, supraventricular arrhythmia, and several valve disorders, with some deaths finally recorded as heart failure.

†Arthralgia GE grade 2, myalgia GE grade 2, and osteoporosis/osteopenia data were not available from Denmark, so denominators and results are exclusively from the non-Danish patient cohorts.

‡Danish data report bone fractures only if the event required hospitalization.

This study affords the opportunity to compare AE reports from clinical and registry sources. For the monotherapy comparison (Table 3), 29 (78%) of the 37 myocardial infarctions were reported from Danish centers, which had 28%

of LTFU patients. The results illustrate the value of national health registries in those countries such as Denmark, which include detailed clinical information on registered patients with cancer.

An important feature of the BIG 1-98 study is the ability to compare letrozole monotherapy for 5 years versus the sequence of letrozole for 2 years followed by tamoxifen for 3 years. AIs and tamoxifen have toxicity profiles leading to nonadherence in a meaningful proportion of patients. The similar outcomes in the four-arm comparison for letrozole monotherapy or the sequence of letrozole followed by tamoxifen suggest switching to tamoxifen instead of stopping all therapy is a viable option for patients who are intolerant to initial AI therapy, especially because the toxicity profiles of an AI and tamoxifen are often individually different.

Although there are challenges to the successful conduct of LTFU,²⁰ it is important to prospectively plan for the long-term follow-up of clinical trials that support regulatory approval of a new widely used treatment regimen, especially for a disease such as early, endocrine-responsive breast cancer. A limitation of our study is the closure of 167 of the 247 participating centers upon withdrawal of

pharmaceutical company support, resulting in attenuated follow-up for approximately 30% of eligible patients (Fig 1). This limitation was mitigated by use of weighted analyses adjusting for differences in characteristics between patients with and without LTFU data, and the fact that closure of entire centers rather than exclusion of individual patients accounted for 75% of patients without LTFU data.

The BIG 1-98 LTFU study shows continued, albeit modest and slightly attenuated, benefit of initial letrozole rather than tamoxifen for postmenopausal women with endocrine-responsive early breast cancer. Contralateral breast cancer incidence was lower in the first 10 years with letrozole, whereas after year 10 it was less frequent following tamoxifen with a statistically significant interaction between treatment and time. Second nonbreast primary cancer was not different during LTFU. The reporting of some long-term AEs was apparently more complete from a nationwide clinical registry than with routine clinical follow-up.

AFFILIATIONS

¹Kantonsspital St Gallen, St Gallen, Switzerland

²Dana-Farber Cancer Institute, Boston, MA

³European Institute of Oncology Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy

⁴Rigshospitalet, Copenhagen, Denmark

⁵Institut Jules Bordet and L'Université Libre de Bruxelles, Brussels, Belgium

⁶KU Leuven, Leuven, Belgium

⁷National Institute of Oncology, Budapest, Hungary

⁸Lillebaelt Hospital, Vejle, Denmark

⁹Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France

¹⁰Université de Bordeaux, Bordeaux, France

¹¹Auckland City Hospital, Auckland, New Zealand

¹²CRO National Cancer Institute, Aviano, Italy

¹³Ospedale Papa Giovanni XXIII, Bergamo, Italy

¹⁴Ospedale Policlinico San Martino, Genoa, Italy

¹⁵Centre de Cancérogie Henri Becquerel, Rouen, France

¹⁶ASST Spedali Civili di Brescia, Brescia, Italy

¹⁷Ospedale Infermi di Rimini, AUSL della Romagna, Ravenna, Italy

¹⁸Universitätsspital, Basel, Switzerland

¹⁹Kantonsspital, Aarau, Switzerland

²⁰University Hospital Vaud University Hospital Center, Lausanne, Switzerland

²¹Medical University of Gdansk, Gdansk, Poland

²²Hospital of Prato-AUSL Toscana Centro, Prato, Italy

²³Harvard Medical School, Boston, MA

²⁴Harvard TH Chan School of Public Health and Frontier Science and Technology Research Foundation, Boston, MA

²⁵University of Sydney, Sydney, NSW, Australia

²⁶International Breast Cancer Study Group, Bern, Switzerland

CORRESPONDING AUTHOR

Thomas Ruhstaller, MD, Breast Center St Gallen, Kantonsspital St Gallen, Rorschacher Strasse 95, CH-9007 St Gallen, Switzerland; e-mail: thomas.ruhstaller@kssg.ch.

PRIOR PRESENTATION

Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, December 6-10, 2016.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: Anita Giobbie-Hurder, Maj-Britt Jensen, Bent Ejlersen, Edda Simoncini, Richard D. Gelber, Alan S. Coates, Aron Goldhirsch, Beat Thürlimann, Meredith M. Regan

Provision of study material or patients: Thomas Ruhstaller, Marco Colleoni, Bent Ejlersen, Evandro de Azambuja, Vernon J. Harvey, Carlo Tondini, Lucia Del Mastro, Corinne Veyret, Lorenzo Gianni, Christoph Rochlitz, Khalil Zaman, Jacek Jassem, Aron Goldhirsch, Beat Thürlimann

Collection and assembly of data: Thomas Ruhstaller, Anita Giobbie-Hurder, Marco Colleoni, Maj-Britt Jensen, Bent Ejlersen, Evandro de Azambuja, Patrick Neven, István Láng, Erik Hugger Jakobsen, Laurence Gladiéff, Hervé Bonnefoi, Vernon J. Harvey, Simon Spazzapan, Lucia Del Mastro, Corinne Veyret, Edda Simoncini, Lorenzo Gianni, Christoph Rochlitz, Elena Kralidis, Khalil Zaman, Richard D. Gelber, Aron Goldhirsch, Beat Thürlimann, and Meredith M. Regan

Data analysis and interpretation: Thomas Ruhstaller, Anita Giobbie-Hurder, Maj-Britt Jensen, Evandro de Azambuja, Patrick Neven, István Láng, Carlo Tondini, Corinne Veyret, Khalil Zaman, Jacek Jassem, Martine Piccart-Gebhart, Angelo Di Leo, Richard D. Gelber, Alan S. Coates, Aron Goldhirsch, Beat Thürlimann, Meredith M. Regan

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor–Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial**

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Thomas Ruhstaller

Honoraria: Pfizer

Consulting or Advisory Role: Novartis, Roche, AstraZeneca, Eli Lilly
Travel, Accommodations, Expenses: Roche, Amgen, Pierre Fabre

Marco Colleoni

Honoraria: Novartis

Consulting or Advisory Role: Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, Celldex, AstraZeneca

Maj-Britt Jensen

Honoraria: AstraZeneca

Travel, Accommodations, Expenses: Celgene, Novartis, AstraZeneca

Bent Ejlersen

Research Funding: NanoString Technologies (Inst), Roche (Inst), Novartis (Inst)

Travel, Accommodations, Expenses: Roche, AstraZeneca

Evandro De Azambuja

Honoraria: Roche

Consulting or Advisory Role: Roche

Research Funding: Roche (Inst)

Travel, Accommodations, Expenses: Roche, GlaxoSmithKline, Novartis

Patrick Neven

Consulting or Advisory Role: Novartis (Inst), Eli Lilly (Inst), Ipsen (Inst)

Travel, Accommodations, Expenses: Pfizer, Roche

Erik Hugger Jakobsen

Consulting or Advisory Role: Novartis, Pfizer, Roche, Eli Lilly

Travel, Accommodations, Expenses: Roche, Pfizer

Laurence Gladieff

Honoraria: AstraZeneca, Tesaro, Clovis Oncology, Roche

Travel, Accommodations, Expenses: Roche, PharmaMar, Tesaro

Hervé Bonnefoi

Consulting or Advisory Role: AbbVie, Astellas Pharma, Bayer, Innocrin Pharma, Puma Biotechnology, Pfizer

Research Funding: Bayer (Inst), Roche

Travel, Accommodations, Expenses: Pfizer

Simon Spazzapan

Honoraria: Takeda, Novartis, Roche, Eisai, Celgene, Pierre Fabre

Consulting or Advisory Role: Novartis

Travel, Accommodations, Expenses: Roche Italia, Celgene, Teva

Carlo Tondini

Consulting or Advisory Role: Myriad Genetics

Speakers' Bureau: Amgen

Travel, Accommodations, Expenses: Roche, Novartis, Celgene

Lucia Del Mastro

Honoraria: Roche, Pfizer, Ipsen, Eli Lilly, Eisai, Novartis, Takeda

Consulting or Advisory Role: Eli Lilly, Roche, MSD

Travel, Accommodations, Expenses: Roche, Pfizer, Celgene

Edda Simoncini

Consulting or Advisory Role: Genomic Health, Amgen, Pfizer, Novartis, AstraZeneca

Travel, Accommodations, Expenses: Pfizer, AstraZeneca, Eli Lilly, Roche, Ipsen, Celgene

Lorenzo Gianni

Consulting or Advisory Role: Celgene, AstraZeneca, Amgen, Pfizer, Roche
Travel, Accommodations, Expenses: Roche, Novartis, Pfizer

Christoph Rochlitz

Consulting or Advisory Role: Amgen

Travel, Accommodations, Expenses: Roche, Novartis, Amgen

Elena Kralidis

Honoraria: Novartis

Travel, Accommodations, Expenses: Eli Lilly, Astellas Pharma, Vifor Pharma, Amgen

Khalil Zaman

Consulting or Advisory Role: Amgen (Inst), AstraZeneca (Inst), Celgene (Inst), Genomic Health, Eli Lilly (Inst), Novartis (Inst), Pfizer (Inst), Eisai (Inst), Roche (Inst)

Travel, Accommodations, Expenses: Roche, Pfizer, Celgene, AstraZeneca

Jacek Jassem

Consulting or Advisory Role: AstraZeneca, AbbVie, G1 Therapeutics, Merck Boehringer, Bristol-Myers Squibb, Celgene, Eisai, Pfizer, Pierre Fabre, Roche

Travel, Accommodations, Expenses: Roche

Martine Piccart-Gebhart

Consulting or Advisory Role: AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer, Roche, Crescendo Biologics, Periphagen, HUYA Bioscience International, Debiopharm Group, PharmaMar, Odonate Therapeutics, G1 Therapeutics, Menarini, Seattle Genetics

Research Funding: AstraZeneca (Inst), Eli Lilly (Inst), MSD (Inst), Novartis (Inst), Pfizer (Inst), Roche (Inst), Radius Health (Inst), Synthon (Inst), Servier (Inst)

Other Relationship: Radius Health

Angelo Di Leo

Honoraria: Roche, Novartis, Pfizer, AstraZeneca, Genomic Health, Eisai, Eli Lilly, Pierre Fabre, Bayer, Celgene, Amgen, Daiichi Sankyo, Ipsen, Roche

Consulting or Advisory Role: Roche, Novartis, Pfizer, AstraZeneca, Pierre Fabre, Eli Lilly, Bayer, Celgene, Puma Biotechnology, Daiichi Sankyo, Ipsen, Genomic Health, Genentech, Amgen, Eisai

Research Funding: Novartis, Pfizer, AstraZeneca

Travel, Accommodations, Expenses: Roche, Novartis, Pfizer, AstraZeneca, Eisai, Bayer, Celgene, Eli Lilly, Pierre Fabre, Puma Biotechnology, Daiichi Sankyo

Richard D. Gelber

Research Funding: AstraZeneca (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Merck (Inst), Pfizer (Inst), Ipsen (Inst), Ferring (Inst)

Beat Thürlimann

Stock and Other Ownership Interests: Roche (I), Novartis (I)

Consulting or Advisory Role: Roche, AstraZeneca, Pfizer, Amgen, Eli Lilly

Travel, Accommodations, Expenses: Roche

Meredith M. Regan

Consulting or Advisory Role: Merck, Ipsen (Inst)

Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Ipsen (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Roche (Inst)

Travel, Accommodations, Expenses: Bristol-Myers Squibb

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