



Trends in progression-free survival (PFS) and time to progression (TTP) over time within first-line aromatase inhibitors trials in hormone receptor-positive advanced breast cancer

T. Reinert^{1,2,3} · M. Debiasi^{1,4} · J. Bines^{1,5} · C. H. Barrios^{1,2}

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Abstract

Background Over the last 20 years, aromatase inhibitors (AI) have been tested in clinical trials as first-line therapy for hormone receptor-positive (HR-positive) advanced breast cancer (ABC), firstly as experimental arms, when they proved to be effective, and recently as control arms. This analysis aims to evaluate trends in progression-free survival (PFS) and time to progression (TTP) over time.

Patients and methods A literature review was conducted using the MEDLINE database to identify randomized controlled phase II or III trials which reported PFS or TTP of at least one arm using first-line AI HR-positive ABC patients. A linear correlation was used to assess the association between the year of the first patient enrolled and the observed PFS/TTP.

Results The search retrieved 19 trials, accounting for 4552 postmenopausal patients divided into 21 separate AI treatment arms. The PFS/TTP increased from 6 to 9 months in the earlier trials to 13–16 months in the current era, representing an absolute gain of approximately 7 months, without the addition of any other drug. Our analysis showed a positive correlation between the year of the first patient enrolled in these trials and median PFS/TTP reported ($R^2 = 0.34$; $p < 0.01$). No correlation was found between the year of the first patient included in these trials and other potential prognostic factors such as visceral metastasis at baseline ($R^2 = 0.26$; $p = 0.20$) or exposure to adjuvant therapy ($R^2 = 0.05$; $p = 0.18$).

Conclusion Patients treated with first-line AIs in the more recently conducted trials have longer PFS/TTP when compared to their counterparts treated with the same drugs in older studies. These findings have important implications for the estimation of sample size and follow-up periods for the planning of future trials as well as in the translation of the results into clinical practice decisions.

Keywords Aromatase inhibitor · Advanced breast cancer · Endocrine therapy · Hormone receptor-positive · Progression-free survival

Introduction

Breast cancer is the most prevalent type of malignant neoplasm worldwide, and hormone receptor (HR)-positive breast cancer is the most common phenotype. Since their introduction in the 90s, aromatase inhibitors (AIs)—anastrozole, letrozole, and exemestane—became the standard of care for postmenopausal HR-positive breast cancer both in early-stage and advanced disease settings. For patients with HR-positive advanced breast cancer (ABC), clinical guidelines recommend sequential treatment with endocrine therapy, unless they are experiencing visceral crises and/or endocrine resistance is known or suspected [1, 2].

Progression-free survival (PFS) and time to progression (TTP) have been the most frequently used endpoints in ABC.

✉ C. H. Barrios
chbe@via-rs.net

¹ Latin American Cooperative Oncology Group (LACOG),
Porto Alegre, Brazil
² Hospital Do Câncer Mãe de Deus, Rua Costa, 40, 4 Andar,
Porto Alegre, Brazil
³ Post Graduate Program in Medical Sciences, Federal
University of Rio Grande Do Sul (UFRGS), Porto Alegre,
Brazil
⁴ PUCRS School of Medicine, Porto Alegre, Brazil
⁵ Instituto Nacional Do Câncer José de Alencar Gomes Da
Silva (INCA), Rio De Janeiro, Brazil

In recent studies, both PFS and TTP (PFS/TTP) have been considered as surrogate endpoints for overall survival (OS), for the purpose of drug approval regulatory process. PFS/TTP are attractive endpoints because they are available earlier than OS, are less likely than OS to be influenced by competing causes of death, and are not affected by the treatments administered after progression. On the other hand, these endpoints are subject to measurement errors and bias [3].

Recently published randomized clinical trials evaluating new therapeutic approaches used AI monotherapy arms as the control group. Better than expected survival outcomes in patients treated with single-agent AI have been observed. This finding has potential implications for therapeutics decisions regarding the sequencing of endocrine agents as well as for the design and conduct of ongoing and future clinical trials.

This study aims to evaluate the evolution over time of the PFS/TTP obtained in trials testing first-line AI monotherapy in patients with HR-positive ABC.

Methods

A literature review was conducted using the MEDLINE database to identify randomized, controlled phase II or III trials which included at least one arm of first-line AI to treat HR-positive ABC patients using the following strategy: (((((breast cancer[Title]) AND aromatase inhibitor[Title/Abstract])) OR ((breast cancer[Title]) AND anastrozole[Title/Abstract])) OR ((breast cancer[Title]) AND letrozole[Title/Abstract])) OR ((breast cancer[Title]) AND exemestane[Title/Abstract]). For this analysis, first-line treatment was defined as the first endocrine therapy used for ABC irrespective of prior (neo) adjuvant endocrine therapies for early-stage disease. The search strategy included terms applicable to the patient population (postmenopausal women with locally advanced or metastatic breast cancer). Publications reporting PFS or TTP data in patients treated with first-line AI monotherapy (anastrozole, letrozole, or exemestane) were considered eligible for further assessment. However, there are some subtle differences between these outcomes that must be pointed out. While PFS is defined as the time elapsed between treatment initiation and tumor progression or death from any cause; TTP considers only disease progression as event, censoring patients who die from any cause before progression. Language was restricted to English, but there was no date of publication restriction. Data were evaluated from publications reporting either the primary or follow-up analyses. Studies designed for HER2-positive breast cancer were excluded.

The following data were extracted from each relevant publication identified: phase, sample size, year of publication, the period of patients' accrual, estimated median PFS/

TTP used for sample size calculation and median observed PFS/TTP. We also evaluated baseline patients' characteristics such as age, the proportion of patients with visceral disease, previous endocrine therapy exposure, the proportion of patients with confirmed HR positivity and the proportion of patients with confirmed HER2 negativity.

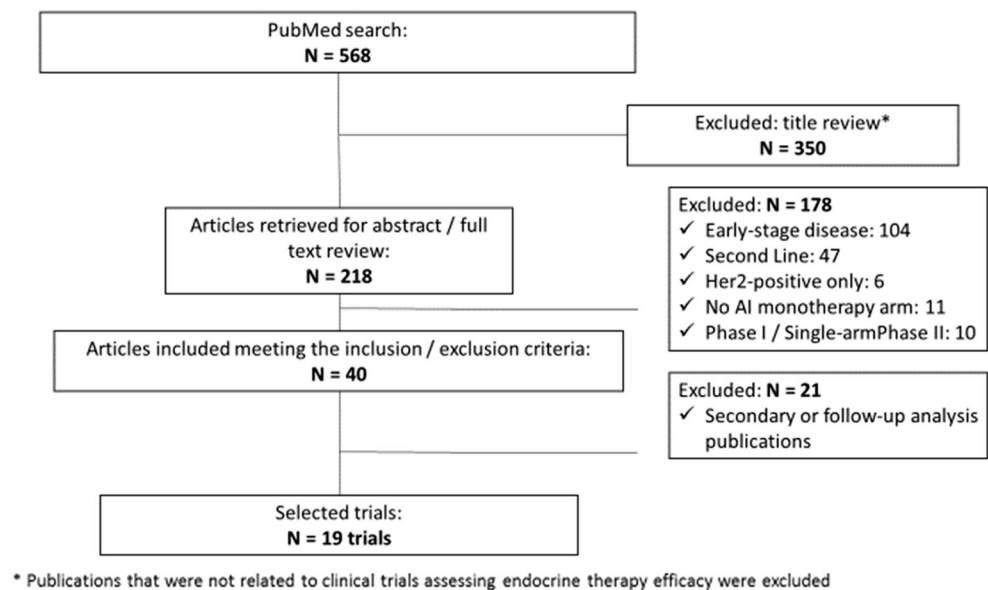
A linear correlation was used to assess the association between the year of the first patient enrolled and the PFS/TTP reported with AI as first-line treatment for HR-positive ABC in each study. We hypothesized that the reported PFS/TTP times would be longer as the year of the first patient enrolled increases. *p* values lower than 5% were deemed to be significant.

Results

The literature search retrieved 568 publications, of which 19 met the inclusion criteria for this review, accounting for 4552 postmenopausal patients divided into 21 separate treatment arms with an AI as first-line monotherapy treatment for HR-positive ABC. Figure 1 summarizes the flowchart for study selection. The studies included in this review are described in Table 1.

The overall median PFS/TTP ranged from 6.1 to 15.6 months among trials. Nine studies reported median PFS/TTP for anastrozole ranging from 8.2 to 15 months [4–14], while seven studies reported PFS/TTP between 9 and 15.6 months with letrozole [15–22] and 6.1 and 13.8 months with exemestane in three studies [7, 14, 23]. Our analysis showed a positive correlation between the year of the first patient enrolled in these trials and median PFS/TTP reported ($R^2 = 0.34$; $p < 0.01$), meaning that patients treated with first-line AIs in the more recently conducted trials have longer PFS/TTP than their counterparts treated with the same drugs but in older studies (see Fig. 2). In univariate analyses, no correlation was found between the year of the first patient included in these trials and other potential prognostic factors such as the proportion of patients with visceral metastasis at baseline ($R^2 = 0.26$; $p = 0.20$), median age ($R^2 = 0.10$; $p = 0.15$), and percentage of patients who had never been exposed to adjuvant therapy ($R^2 = 0.05$; $p = 0.18$). Multivariate analysis was not carried out because of the reduced number of studies available to be included in this exploratory estimation. No other correlations with potential prognostic factors were sought. The number of patients accrued in each individual study is a factor that could influence the precision of the median PFS/TTP times reported by the studies included in this analysis. Univariate linear regression did not show significant variation in the sample size magnitude along time ($R^2 < 0.01$; $p = 0.68$). As described in Table 1, 10 studies reported the estimated 95% confidence interval for their median PFS/TTP, while nine did

Fig. 1 Flowchart for study selection summary. Phase III and randomized phase II clinical trials with at least one AI monotherapy arm for first-line treatment of postmenopausal patients with HR+ HER2 negative advanced breast cancer were included



not. Therefore, this variable was not included in the estimations presented and represents a limitation of this analysis.

Table 2 describes the nine trials in which the estimated PFS/TTP in the AI monotherapy group used for sample size calculations were reported. In all but one trial, the expected PFS/TTP was lower than the observed PFS/TTP.

Discussion

Our analysis suggests that the PFS/TTP achieved with aromatase inhibitors therapy as first-line treatment for advanced breast cancer have shown progressive improvement. The PFS/TTP increased from 6 to 9 months in the earlier trials to 13–16 months in the current era, representing an absolute gain of approximately 7 months, without the addition of any other drug. These advances raise challenges on how to incorporate these findings into the interpretation of available clinical trial data and the design of future research. Immediate implications are related to sample size and follow-up time estimation for ET trials design.

Most likely, a combination of improved medical care and patient selection factors justifies most of this progressive improvement in outcomes obtained with the same therapeutic strategy. While clinical trial entry criteria have not changed significantly over time, more recent studies are probably including a different population of patients. With the widespread use of modern radiology tests, the population included in the latest trials may include a higher proportion of patients with a lower burden of metastatic disease. Exclusion of HER2 patients is routinely done in recently published endocrine therapy trials; however, HER2 status was not available in earlier studies. At the same time, older trials included a minority of patients with unknown HR status.

Therefore, a small fraction of patients with HER2-positive or HR-negative breast cancer was included, and this could lead to inferior PFS/TTP in older studies.

Better outcomes may also be a result of improved loco-regional treatments and increasing experience with managing the expected adverse effects. Additionally, improved general medical care and the use of adjuvant therapies (i.e., radiotherapy, bisphosphonates, and RANKL inhibitors) is another potential explanation for the observed improvement in PFS outcomes using the same therapy on similar population, even though these factors are hard to measure and probably of small importance.

An alternative explanation that may contribute to a trend for better survival outcomes in more recent trials is a change in tumor biologic features, with a hypothetical shift towards a higher proportion of endocrine-sensitive tumors. Some studies have reported a difference in the epidemiology of breast cancer over time, with more ER-positive tumors being observed than in the past [24–26]. Whether these changes occur in the metastatic setting or are simply related to improvements in screening strategies of early-stage indolent tumors has not been adequately studied.

The inclusion of a population with characteristics associated with hormone sensitivity and/or less aggressive disease, such as a higher proportion of endocrine therapy-naïve patients or patients with non-visceral metastases, could lead to longer PFS. However, our analysis shows that there were no significant differences over time in the proportion of endocrine therapy-naïve patients neither on the proportion of patients with non-visceral disease.

Estimating the event rate to proceed with sample size calculation in clinical trials is challenging in this scenario. For instance, PFS/TTP results for the AI monotherapy arms in the trials included in this review have consistently surpassed

Table 1 Randomized controlled trials of endocrine therapies for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in the first-line setting

Study	Treatment	Patient characteristics	PFS/TTP median—months (95% CI); HR (95% CI)	OS median (months); HR (95% CI)
TARGET Bonnetterre et al. [5] Phase III Publication: 2000 Accrual: 1995–1998	Anastrozole (<i>n</i> = 340) versus tamoxifen (<i>n</i> = 328)	Mean age: 6 88% HT naïve 33% visceral disease HER2 NR 44% confirmed HR+	TTP 8.2 (NR) vs. 8.3 (NR); HR 0.99 (0.86–one sided); <i>p</i> = 0.941	38.5 vs. 40.9; HR 0.94 (0.79–NR)
Nabholtz et al. [10] Phase III Publication: 2000 Accrual: 1996–1998	Anastrozole (<i>n</i> = 171) versus tamoxifen (<i>n</i> = 182)	Median age: 68 80% HT naïve 47% visceral metastasis HER2 NR 85% confirmed HR +	TTP 11.1 (NR) vs. 5.6 (NR); HR 1.44 (1.16–one sided); <i>p</i> = 0.005	40.4 vs. 38.5; HR 1.02 (0.81–NR)
International Letrozole Breast Cancer Group [19] Mouridsen et al. Phase III Publication: 2001 Accrual: 1996–1999	Letrozole (<i>n</i> = 453) versus tamoxifen (<i>n</i> = 454)	Median age: 65 years 81% HT naïve 45% visceral metastasis HER2 NR 65% confirmed HR + (34% unknown)	TTP 9.4 (NR) vs. 6.0 (NR); HR 0.70 (0.6–0.82); <i>p</i> < 0.0001	34 vs. 30; <i>p</i> = 0.53
EORTC [23] Phase III Paridaens et al. Publication: 2008 Accrual: 1996–2002	Exemestane (<i>n</i> = 182) versus tamoxifen (<i>n</i> = 189)	Median age: 63 years HT naïve: 89% 47% visceral metastasis HER2 NR 96% confirmed HR+	PFS 9.9 (8.7–11.8) vs. 5.8 (5.3–8.1); HR 0.84 (0.67–1.05); <i>p</i> = 0.121	37.2 vs. 43.3; HR 1.04 (0.76–1.41); <i>p</i> = 0.821
SBCG 2001–03 Lombart-Cussac et al. [34] Phase II Publication: 2011 Accrual: 2001–2003	Exemestane (<i>n</i> = 51) versus anastrozole (<i>n</i> = 52)	Median age 70 years HT naïve 49% 53% visceral metastasis HER2 neg NR 100% confirmed HR+	TTP 6.1 (2.5–9.6) vs. 12.1 (7.3–16.8); HR 1.13 (0.75–1.72); <i>p</i> = 0.558	19.9 vs. 48.3; HR 1.33 (0.78–2.25); <i>p</i> = 0.296
EGF30008 [17] Johnston et al. Phase III Total <i>n</i> : 1286 Publication: 2009 Accrual: 2003–2006	Letrozole plus lapatinib (<i>n</i> = 474) versus letrozole plus placebo (<i>n</i> = 478)	Mean age 59 51% HT naïve Visceral disease NR 95% confirmed HR+ 100% HER2 neg* Only HER2 negative patients (total <i>n</i> = 952) were included in our analysis	PFS 14.7 (NR) vs 15.0 (NR) <i>p</i> = 52	NR
MINT [8] Johnston et al. Phase II Publication: 2016 Accrual: 2003–2006	Anastrozole + AZD8931 20 mg (<i>n</i> = 118) versus anastrozole + AZD8931 40 mg (<i>n</i> = 120) versus anastrozole (<i>n</i> = 121)	Median age: 62 100% ht naïve Visceral NR HER2 NR Confirmed HR + NR	PFS 10.9 vs. 13.8 vs. 14.0 (NR) HR 1.16 (0.77–1.75); <i>p</i> = 0.485	NR

Table 1 (continued)

Study	Treatment	Patient characteristics	PFS/TTP median—months (95% CI); HR (95% CI)	OS median (months); HR (95% CI)
HORIZON [20] Wolff et al. Phase III Publication: 2013 Accrual: 2004–2006	Letrozole + temsirolimus (<i>n</i> = 555) versus letrozole (<i>n</i> = 555)	Median age 63 years 60% HT naïve Visceral metastasis NR 95% confirmed HR+ HER2: positive 18%; negative 47%; unknown 36%	PFS 8.9 (NR) vs. 9.0 (NR) HR 0.90 (0.76–1.07); <i>p</i> = 0.25	NM vs. NM; 0.89 (0.65–1.23); <i>p</i> = 0.50
Cristofanilli et al. [13] Phase II Publication: 2010 Accrual: 2004–2006	Anastrozole + gefitinib versus anastrozole (<i>n</i> = 50)	Mean age 59 44% HT naïve Visceral metastasis NR 81% HER2 negative 85% confirmed HR+	PFS 14.7 (NR) versus 8.4 (NR) HR 0.55 (95% CI 0.32–0.94)	NR
FACT [4] Bergh Phase III Publication: 2012 Accrual: 2004–2008	Fulvestrant 250 mg + Anastrozole (<i>n</i> = 258) vs Anastrozole (<i>n</i> = 256)	Median age 63 HT naïve: 33% Visceral metastasis: 51% Confirmed RH + 98% HER2 neg NR	TTP 10.8 (NR) vs 10.2 (NR) HR 0.99 <i>p</i> = 9	OS 38.8 vs 28.2 HR 1.0
SWOG 0226 [9] Mehta Phase III Publication: 2012 Accrual: 2004–2009	Fulv 250 mg + ANz (<i>n</i> = 350) versus anastrozole (<i>n</i> = 345)	Median age 65 HT naïve 60% Visceral metastasis 59% HER2 neg 91% 100% confirmed HR+	PFS 15 (13.2–18.4) vs 13.5 (12.1–15.1) HR 0.80 <i>p</i> = 0.007	OS 47.7 vs 41.3 HR 0.81 <i>p</i> = 0.05 Obs: OS benefit observed despite 40% cross-over
Iwata [7] Phase III Publication: 2013 Accrual: 2005–2010	Exemestane (<i>n</i> = 149) versus anastrozole (<i>n</i> = 149)	Mean age: 64 years HT naïve: 83% Visceral metastasis: 49% 96% confirmed HR+ HER2 positive: 6%	TTP 13.8 (10.8–16.5) vs. 11.1 (10.8–16.6); HR 1.01 (0.77–1.32); <i>p</i> = 0.558	Not reached vs. 60.1; HR 1.06 (0.73–1.54)
FIRST [12, 35] Robertson et al. Phase II Publication: 2010 Accrual: 2006–2008	Fulvestrant 500 mg (<i>n</i> = 102) versus anastrozole (<i>n</i> = 103)	Median age: 68 years HT naïve: 77% Visceral disease 51% 100% confirmed HR+ HER2: 18% 2 or 3+ 48% negative; 34% unknown	TTP 23.4 (NR) vs. 13.1 (NR); HR 0.66 (0.47–0.92); <i>p</i> = 0.01	54.1 vs. 48.4; HR 0.70 (0.50–0.98); <i>p</i> = 0.04
LEA study [18] Phase III Martin et al. Publication: 2012 Accrual: 2007–2011	Bevacizumab + endocrine therapy (<i>n</i> = 190) versus endocrine therapy (<i>n</i> = 184)	Median age 66 years HT naïve: 48% Visceral metastasis: 47% 100% confirmed HR+ 100% confirmed HER2 neg	PFS 19.3 (16.5–22.1) vs. 14.4 (11.4–17.5) HR 0.83 (0.65–1.06) <i>p</i> = 0.126	52.1 vs. 51.8 HR 0.87 (0.58–1.32) <i>p</i> = 0.518
CALGB 40503 [21] Phase III Dickler et al. Publication: 2015 Accrual: 2008–2011	Letrozole + bevacizumab (<i>n</i> = 174) versus letrozole (<i>n</i> = 174)	Median age: 59 52% HT naïve 74% visceral metastasis 95% her2 negative 100% confirmed HR+	PFS 20.2 (17.0–24.1) vs 15.6 (12.9–19.7); HR 0.75 <i>p</i> = 0.016	OS 47.2 vs 43.9 HR 0.87 <i>p</i> = 0.18

Table 1 (continued)

Study	Treatment	Patient characteristics	PFS/TTP median—months (95% CI); HR (95% CI)	OS median (months); HR (95% CI)
PALOMA-1 Finn et al. Phase II Publication: 2014 Accrual: 2009–2012	Letrozole + palbociclib (<i>n</i> = 84) versus letrozole (<i>n</i> = 81)	Median age 64 years HT naïve: 65% 53% visceral disease 100% confirmed HR+ 100% confirmed HER2-	PFS 20.2 (13.8–27.5) vs. 10.2 (5.7–12.6); HR 0.49 (0.32–0.75); <i>p</i> = 0.0004	37.5 vs. 33.3; HR 0.81 (0.49–1.35); <i>p</i> = 0.42
FALCON [11] Robertson et al. Phase III Publication: 2016 Accrual: 2012–2014	Fulvestrant 500 mg (<i>n</i> = 230) versus anastrozole (<i>n</i> = 232)	Median age: 62 years HT Naïve 100% Visceral metastasis 56% 100% confirmed HR+ 100% confirmed HER2-	PFS 16.6 (13.8–20.9) vs. 13.8 (11.9–16.5) HR 0.797 (0.637– 0.999); <i>p</i> = 0.0486	NM HR 0.88 (0.63–1.22); <i>p</i> = 0.4277
PALOMA-2 [36] Finn et al. Phase III Publication: 2016 Accrual: 2013–2014	Letrozole + palbociclib (<i>n</i> = 444) versus letrozole (<i>n</i> = 222)	Median age : 61 years HT naïve: 43% Visceral metastasis: 48% 100% confirmed HR+ 100% confirmed HER2-	PFS 24.8 (95% CI 22.1-not reached) vs. 14.5 (12.9–17.1); HR 0.58 (0.46–0.72); <i>p</i> < 0.001	NM
MONALEESA-2 [22] Hortobagyi et al. Phase III Publication: 2016 Accrual: 2014–2015	Letrozole + ribociclib (<i>n</i> = 334) versus letrozole (<i>n</i> = 334)	Median age: 66 years HT naïve: 49% Visceral metastasis: 59% 100% confirmed HR+ 100% confirmed HER2-	PFS Not reached (19.3-not reached) vs. 14.7 (13.0–16.5);	NM

The bold values represent the PFS/TTP median within the AI arms

AI aromatase inhibitor, CI confidence interval, HR hazard ratio, MBC metastatic breast cancer, NM not matured, NR not reached, OS overall survival, PFS progression-free survival, TTP time to progression

Fig. 2 Linear correlation between the year of the first patient enrolled within first-line AI trials in HR-positive ABC and median PFS/TTP reported

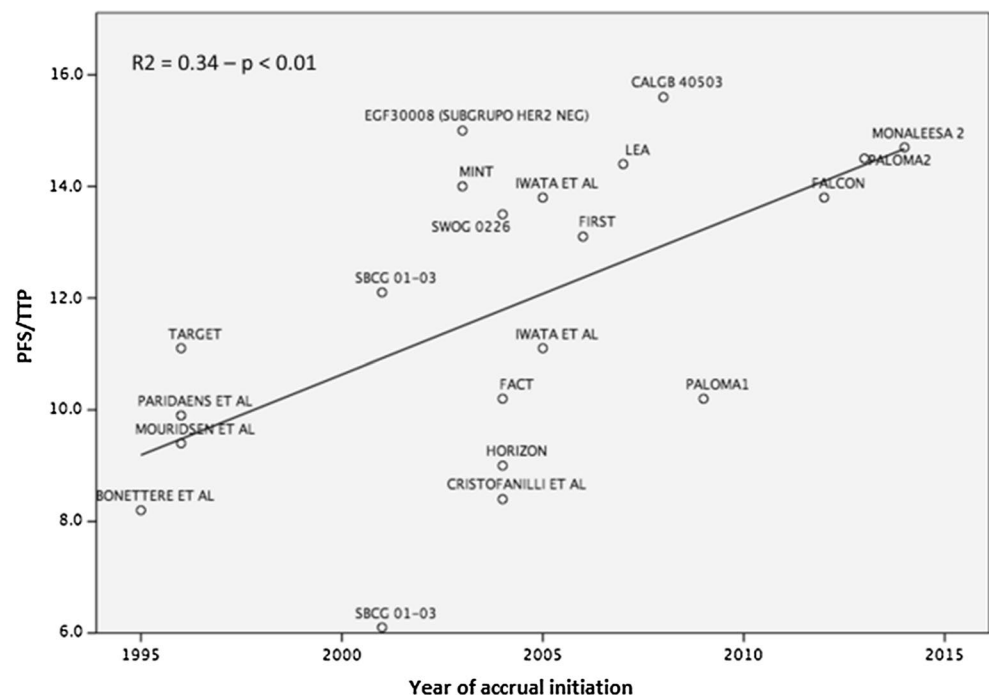


Table 2 Description of the studies reporting the expected and observed PFS/TTP for first-line AI monotherapy

Study	Year first patient included	Reported median PFS/TTP (months)	Estimated (expected) – number used for sample size calculation median PFS/TTP(months)	Difference between estimated and actual median PFS/TTP (months)
MINT [17]	2003	14.0	9.0	– 5.0
HORIZON [20]	2004	9.0	9.4	0.4
FACT [4]	2004	10.2	9.0	– 1.2
SWOG 0226 [9]	2004	13.5	10.0	– 3.5
LEA [18]	2007	14.4	9.0	– 5.4
CALGB 40503 [21]	2008	15.6	6.0	– 9.6
PALOMA1 [16]	2009	10.2	9.0	– 1.2
PALOMA2 [36]	2013	14.5	9.0	– 5.5
MONALEESA 2 [22]	2014	14.7	9.0	– 5.7

the expectations used for calculations of HR and sample size (see Table 2). With the exception of one study, in all studies, the observed rates surpassed the estimated PFS/TTP in trial design. The CALGB 40503 trial provides an extreme example. This phase III study was designed to investigate whether bevacizumab prolongs PFS when added to first-line letrozole as treatment of HR-positive advanced breast cancer [21]. This trial had 90% power to detect a 50% improvement in median PFS from 6 to 9 months based on literature available when the study was designed. Surprisingly, the observed PFS for the letrozole monotherapy arm was 15.6 months.

We expect that ongoing trials will face similar challenges. The VICTORIANE trial is an ongoing randomized phase 3 study assessing the addition of oral vinorelbine

to aromatase inhibitors for the treatment of patients with endocrine therapy-naïve HR-positive ABC. The sample size for this trial was calculated based on an expected PFS for the AI monotherapy arm of only 9 months [27]. The MONARCH 3 is a randomized phase III study of AI plus abemaciclib, a CDK4/6 inhibitor, or placebo in first-line treatment of women with ER+ advanced breast cancer [28]. Similarly, the estimated PFS in the AI monotherapy arm considered for study planning was 10 months. These trials are examples where there is a high probability that the PFS in the AI monotherapy control arm will surpass the estimative. Calculating sample sizes considering a PFS/TTP lower than the actual one and an excessively optimistic hazard ratio may result in underpowered clinical

trials with critical issues impacting sample size and follow-up time.

Interestingly, similar improvements in survival outcomes have also been identified in studies of early-stage breast cancer with AI monotherapy as the control group. Because an annual risk of relapse persists over decades, the development of new adjuvant ET approaches requires protracted follow-up and large sample sizes. In the FACE trial [29], comparing anastrozole versus letrozole in the adjuvant setting, investigators were challenged with a lower-than-expected event rate and decided to report results before reaching the expected number of events. Similarly, in the SOFT [30] and TEXT [31] trials, that evaluated the role of ovarian function suppression and exemestane in premenopausal patients with early-stage HR-positive breast cancer, the expected survival outcomes used for sample size calculation were overly pessimistic. Consequently, the event rate was over-estimated and the duration of follow-up time to reach the targeted number of events for final analysis was under-estimated [32].

Other than the impact on methodological issues for future research, these findings also impact clinical practice. Given continued efforts to develop therapies that delay the emergence of endocrine resistance, the results of this analysis demonstrating the favorable outcome for these endocrine-sensitive subgroups has immediate relevance. With added clinical and financial toxicities, it is important to define HR-positive populations that are more likely to benefit from combination therapy and to identify those patients who may do well with endocrine therapy alone. [33]. Future research on prognostic and predictive biomarkers might assist in estimating the pattern of endocrine sensitivity or resistance and guide therapeutic decisions on ET sequencing strategies.

Conclusion

While acknowledging the inherent cross-trial analyses limitations, our work suggests a progressive improvement in PFS/TTP of first-line endocrine therapy with aromatase inhibitors containing trials over time. Our scrutiny of the data does not reveal any definitive reason that fully explains this phenomenon. Nevertheless, these findings have important implications for the planning and sample calculation of currently ongoing and future randomized clinical trials.

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