Received: 18 September 2023 | Accepted: 27 May 2024 | Published on: 16 June 2024

DOI: 10.1111/ajco.14096

ORIGINAL ARTICLE

WILEY

# Beyond the median: Estimating survival times for patients starting endocrine therapy for estrogen receptor-positive, metastatic breast cancer from recent randomized trials

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## Abstract

**Aim:** To estimate scenarios for survival for patients with estrogen receptor (ER) positive, metastatic breast cancer (MBC) and to help communicate prognosis to patients starting endocrine therapy (ET)

**Methods:** We searched for randomized trials of ET for ER-positive MBC and extracted the following percentiles (representative survival scenarios) from each overall survival (OS) curve: 90th (worst-case), 75th (lower-typical), 50th (median), 25th (upper-typical), and 10th (best-case). We then assessed the accuracy of estimating these percentiles for each OS curve by multiplying the median OS by four simple multiples: 0.25 (to estimate the 90th percentile), 0.5 (75th), 2 (25th), and 3 (10th). Estimates were deemed accurate if it fell within 0.75–1.33 times the actual value.

**Results:** We identified 25 trials with 10,566 patients. The median OS (interquartile range) was: 61.3 months (53.4–64.8) for first-line ET with cyclin-dependant kinase 4/6 inhibitors (four treatment groups); 42.6 months (40.9–50.4) for first-line ET alone (21 treatment groups) and 29.2 months (24.8–33.4) for subsequent line ET (19 treatment groups). Simple multiples of the median OS accurately estimated the 90th percentile in 80%; 75th percentile in 93%; and 25th percentile in 76% of curves. The 10th percentile was only available for four OS curves and could not be evaluated.

**Conclusion:** Simple multiples of the median OS are a helpful and accurate method to assist in estimating and discussing scenarios for survival for MBC patients starting ET. Longer follow-up of trials is required to help clinicians estimate the best-case scenario.

KEYWORDS
endocrine therapy, estimating survival times, estrogen-receptor-positive, metastatic breast cancer, prognosis

## 1 | INTRODUCTION

Metastatic breast cancer (MBC) has a broad spectrum of survival outcomes dependent on a multitude of factors, including receptor subtype and administered treatment. Note that, 70%–80% of all breast cancers are estrogen receptor (ER) positive.[1] ER-positive breast cancers typically respond to estrogen suppression and traditionally, patients with ER-positive breast cancer have been treated with endocrine therapies (ET) as well as chemotherapy. In recent years, both progression-free survival (PFS) and overall survival (OS) of patients with ER-positive MBC have been significantly prolonged by the addition of cyclin-dependant kinase 4/6 inhibitors (CDK4/6i) to ET. As such combination ET with CDK4/6i is now standard of care for patients with ER-positive MBC as first-line treatment.

Oncologists are often asked to provide information about expected survival times for patients with metastatic cancer. We have previously shown that using estimates of best-case, typical, and worst-case scenarios for survival to explain life expectancy as a communication aid is more helpful to patients than providing single-point estimates of the median OS.[2] In prior work, we also demonstrated that certain percentiles of an OS curve can be used to approximate these worst-case, typical, and best-case scenarios for survival, and these percentiles can be estimated from the median OS using simple multiples.[3–6] For example, the 90th percentile, representing the upper bound of the worst-case scenario, is approximately one-quarter of the median OS, the 75th percentile, representing the lower bound of the typical scenario is approximately half the median OS, the 25th percentile, representing the upper bound of the typical scenario is approximately double the median OS and the 10th percentile, representing the lower bound of the best-case scenario is approximately three times the median OS.[7,8]

Oncologists frequently use data from clinical trials as a basis for estimating survival times for their patients with advanced cancer. In this study, we sought to summarise scenarios for survival times for patients with ER-positive MBC starting ET alone or with CDK4/6 inhibitors. We also aimed to determine whether the same simple multiples of the median OS from our prior work predominantly in chemotherapy trials can be used to accurately estimate worst-case, typical, and best-case scenarios for survival in patients starting ET.

## 2 | MATERIALS AND METHODS

We searched the Cochrane Database of Systematic Reviews and MEDLINE for trials published in or after 1995. We used the keywords: "metastatic breast cancer" and "overall survival", and the individual therapeutic agents included CDK4/6 inhibitors, tamoxifen, aromatase inhibitors, and fulvestrant. The search results were verified by cross-referencing the references of several recently published systematic reviews.[9–11]

Trials were deemed eligible if they met the following eligibility criteria: a randomized trial of endocrine-based therapy in MBC; at least 80 participants per treatment group; < 10% of participants with hormone receptor unknown or negative tumors; at least one treatment group of non-cytotoxic, non-human epidermal growth factor receptor 2 (non-HER2) targeted therapies; and included a Kaplan-Meier curve for OS. We excluded trials of endocrine agents not used in contemporary practice. For each trial, we recorded the year of publication, number of treatment groups, treatment regimen, number of participants, median follow-up, patient demographics, and tumor characteristics. We recorded the median OS in each treatment group as well as PFS, time-to-progression, or time-to-failure. If a trial had updated OS results published, the updated results were used for the final analyses. We categorized the trials according to first or subsequent line of treatment; type of ET; single agent or combination ET and; inclusion of CDK4/6i.

Two authors independently traced each OS curve using the UN-SCAN-IT graph digitizing software.[12] The median and following percentiles (represented scenarios) were extracted from each OS curve: 90th (worst-case), 75th (lower-typical), 25th (upper-typical), and 10th (best-case) (Figure 1). Inconsistencies between the two measurements were resolved by repeated measurement and discussion.

On the basis of our previous work in chemotherapy and HER2-targeted therapy trials, we hypothesized that multiplying the median of each OS curve by four simple multiples would allow us to estimate its percentiles (representative scenarios), as follows; 0.25 for the 90th (worst-case), 0.5 for the 75th (lower-typical), 2 for the 25th (upper-typical) and 3 for the 10th (best-case).[4,5] As in our previous work we deemed each estimate to be accurate if it was within 0.75–1.33 times the actual value extracted from the OS curve. This range was decided a priori in previous work as an arbitrary range for reasonable accuracy, as there is currently no standard for accuracy for clinicians' prediction of survival. Based on our findings in a review of first-line chemotherapy in MBC, we hypothesized that for each treatment group in the first-line trials, the median OS would be approximately three times the median PFS (ratio 3:1).[4]

Multiple linear regression was used to assess associations between the following characteristics of each trial and median OS: year of publication, the median age of participants, the proportion of participants with de novo metastatic disease, the proportion of participants who received adjuvant chemotherapy, the proportion of participants that received adjuvant endocrine therapy, and proportion of participants with visceral metastases.

## 3 | RESULTS

The combined search strategies identified 603 references, of which 25 trials met our eligibility criteria for inclusion. The reasons for exclusion are summarized in Figure 2.

There were a total of 10,566 participants in 44 treatment groups. There were 15 first-line trials including 5535 participants in 25 treatment groups.[13–27] There were 10 subsequent or mixed line trials including 5026 patients in 19 treatment groups.[14,28–38] The characteristics of the trials, including the endocrine and other agents used, are

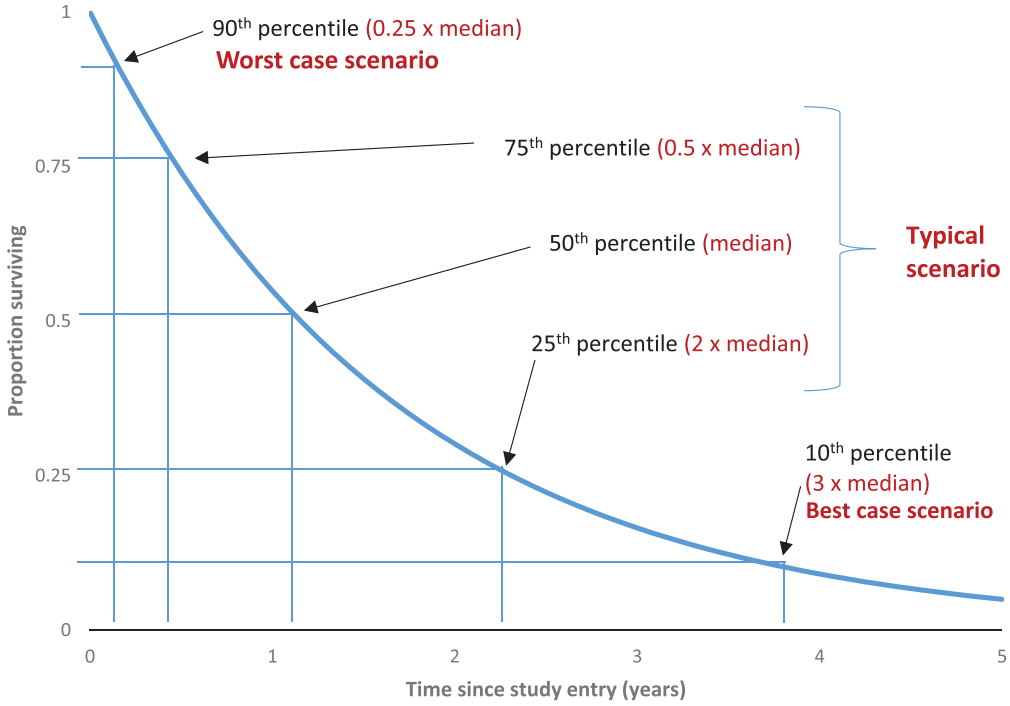


**FIGURE 1** Kaplan-Meier overall survival (OS) curve percentiles and their corresponding scenarios.

summarized in Table 1. The median follow-up for the 25 trials ranged from 9 to 84 months with a median of 29 months for first-line trials and 39.3 months for subsequent-line trials. The majority of trials had two treatment groups and most participants were post-menopausal women with an ECOG performance status of 0 or 1. Two trials had not reached a median OS in one of their treatment groups at the time of reporting, including one treatment group with CDK4/6i. Similarly, the follow-up was insufficient for the 25th and 10th percentile to be obtained from the OS curve in 19 and 40 treatment groups, respectively.

Note that, 44% of participants received adjuvant chemotherapy and 52% had received adjuvant endocrine therapy. Seventeen (72%) trials excluded participants with central nervous system (CNS) metastases and six (26%) trials did not report on the presence of CNS metastases.

The median OS and scenarios for survival are summarised in Tables 2 and 3. There were four first-line trials of ET plus CDK4/6i that had reported median OS. The median of the median OS times from the four treatment groups of first-line ET with CDK4/6i was 61.3 months (interquartile range [IQR], 53.4–64.8 months). The median OS times of nine treatment groups of first-line single-agent aromatase inhibitors was 37.4 months (IQR, 33.5–43.4) and the median of the median OS times of three treatment groups of first-line Tamoxifen was 16.0 months (IQR, 14.2–29.7 months). The median of the median OS times of the four treatment groups of first-line fulvestrant was 37.5 months (IQR, 22.9–52.4 months).

Of the 19 treatment groups examining subsequent line ET, there were three combination fulvestrant and CDK4/6i that had reported the median OS, and the median value of median OS was 39.7 months (IQR, 37.3–43.2 months). In four trials of subsequent line single-agent aromatase inhibitor the median of the median OS times was 28.8 months (IQR, 26.6–32.2), and in eight treatment groups of single-agent fulvestrant the median of the median OS times was 28.6 months (IQR, 25.5–31.2months).

The median value of median PFS from all first-line trials was 14.7 months (IQR 10.1 – 19.5) and from all subsequent line trials 6.8 months (IQR 4.6–9.1). In the first-line trials, the median ratio of median OS to median PFS was 2.9:1 (IQR 3.5:1–2.7:1).

Simple multiples of the median OS were accurate for estimating the percentiles (scenarios) in the majority of OS curves (in both first and subsequent-line settings): 0.25 x median OS accurately estimated the 90th percentile (worst-case) in 80% of all curves (71% for first line, 86% for subsequent line); 0.5 x median OS accurately estimated the 75th percentile (lower typical) in 93% of all curves (86% for first line, 100% for subsequent line); and 2 x median OS accurately estimated the 25th percentile (upper-typical) in 76% of all curves (67% for first line, 85% for subsequent line). The accuracy of using 3 x median OS to estimate the 10th percentile (best-case scenario) could not be determined because only four OS curves reached this time point in their follow-up (all first-line studies).

Multiple linear regression was used to test if patient characteristics significantly predicted OS. Several patient characteristics in trials predicted a longer median OS [95% confidence interval]. This included the proportion of patients who had exposure to adjuvant endocrine therapy ($\beta = 0.014$, [0.0042, 0.024], $p < 0.009$) and the proportion of patients with de novo metastatic disease ($\beta = 0.39$, [0.083, 0.70], $p = 0.01$). Patient characteristics that predicted for shorter median OS included the proportion of patients exposed to adjuvant chemotherapy ($\beta = -0.01$, [−0.027, −0.0087, $p < 0.000$), older patient age

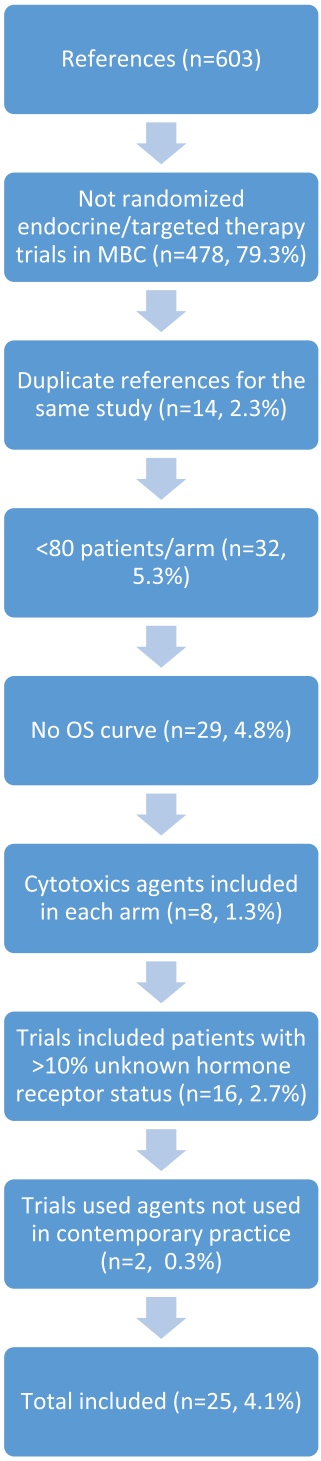


**FIGURE 2** Reasons for exclusion of trials. MBC, metastatic breast cancer; OS, overall survival.

($\beta$ = −0.072, [−0.12, −0.02], $p$ = 0.005) the older trial publication date ($\beta$ = −3.83, [−4.79, −2.86], $p$ < 0.000). However given the heterogeneity of the reported patient characteristics across trials, definitive conclusions cannot be made regarding the impact of certain characteristics on median OS in this analysis.

## 4 | DISCUSSION

This summary of survival times for patients starting ET for ER-positive MBC shows that survival is longest for patients starting first-line combination ET with CDK4/6i where the median PFS was 25.3 months and median OS 61.3 months. For the majority of OS curves, simple multiples of each curve's median accurately estimated the worst-case and typical scenarios for survival. The survival time for the 10% of participants with the shortest survival (worst-case scenario) could be accurately estimated as one-quarter of the median OS or less, and the survival time of the middle 50% of participants (typical scenario) was accurately estimated as half to double the median. The accuracy of estimating the survival of the 10% of participants living the longest (best-case scenario) was not reliable given the small number of trials with sufficient follow-up.

The trials examined in this review span a period of 25 years. Over this time, the treatments have changed dramatically, from the earliest trials that included the introduction and establishment of aromatase inhibitors over the previous mainstay of tamoxifen to the use of fulvestrant and more recently the addition of new targeted therapies such as CDK4/6i. Given the data are not a result of randomization, direct comparisons of OS times between the different agents should not be made.

Despite this review examining a range of therapies, the OS curves follow a similar exponential shape allowing for simple multiples of the median to accurately estimate the 90th, 75th, and 25th percentiles. An important factor in the accuracy of estimating the worst-case scenario is the caveat that those patients with the worst prognoses were likely excluded from trial participation but despite this, the simple multiple of 0.25 still accurately estimated survival in the majority of OS curves. This extends our hypothesis that the simple rules of thumb are not limited to chemotherapy trials and are accurate for estimating and explaining expected survival in a range of advanced cancers and treatment types.

We found that the median OS in the first-line trials was approximately three times the median PFS, similar to our previous work in first-line chemotherapy trials and the work of Saad et al.[2,4,5,39,40] This observation leads to the hypothesis that tripling the time to progression is a useful estimate of post-progression survival and could be useful in planning future trials.

It is well known that clinical trial participants are highly selected, without the comorbidities of those patients outside of clinical trials. Real-world survival data of patients treated with CDK4/6i and endocrine therapy has been similar to those demonstrated in clinical trials. In one study using the Flatiron health database, patients treated first-line with a combination of CDK4/6i with endocrine therapy versus endocrine therapy alone showed a median OS of 44.9 versus 35.8 months.[41] In other real-world studies across all lines of therapy, the estimated median OS was 24.5 months for Palbociclib plus fulvestrant and 21.1 months for Palbociclib and aromatase inhibitor, similar to the median of subsequent therapies extracted from subsequent-line clinical trials.[42,43] Real-world data of CDK4/6i complements the findings

**TABLE 1** Trial characteristics.

| Trial characteristic | Number | |
|---|---|---|
| **Year of publication** | **No of trials** | **%** |
| 2000–04 | 3 | 124 |
| 2005–09 | 1 | 4 |
| 2010–14 | 6 | 24 |
| 2015–20 | 15 | 60 |
| **Endocrine therapy** | **No. of treatment groups** | **%** |
| ***First-line endocrine regimen*** | | |
| Abemaciclib + Endocrine therapy | 1 | 4 |
| Ribociclib + Letrozole | 2 | 8 |
| Ribociclib + Fulvestrant | 1 | 4 |
| Ribociclib + Endocrine therapy | 1 | 4 |
| Palbociclib + Letrozole | 1 | 4 |
| Anastrazole + Fulvestrant | 2 | 8 |
| Letrozole + Fulvestrant | 1 | 4 |
| Letrozole alone | 3 | 12 |
| Anastrazole alone | 5 | 20 |
| Exemestane alone | 1 | 4 |
| Fulvestrant alone | 4 | 16 |
| Tamoxifen alone | 2 | 8 |
| Endocrine therapy unspecified | 1 | 4 |
| ***Subsequent-line endocrine regimen*** | | |
| Ribocliclib + Fulvestrant | 1 | 5 |
| Palbociclib + Fulvestrant | 1 | 5 |
| Abemaciclib + Fulvestrant | 1 | 5 |
| Anastrazole + Fulvestrant | 1 | 5 |
| Letrozole alone | 2 | 11 |
| Exemestane alone | 2 | 11 |
| Fulvestrant alone | 8 | 42 |
| Everolimus + Exemestane | 2 | 11 |
| Everolimus alone | 1 | 5 |
| **Patient characteristics in trials** | **Median** | **Range** |
| No. of patients per group | 193.5 | 81–571 |
| Median age, years | 63 | 43–68 |
| Median follow-up, months | 38 | 9–84 |
| Adjuvant chemotherapy, % | 44 | 24–61 |
| Adjuvant endocrine therapy, % | 51 | 0–100 |
| ECOG performance status 0–1, % | 99 | 87–100 |
| De novo metastatic disease, % | 35 | 0–78 |
| Visceral metastases, % | 56 | 28–73 |
| Bone-only disease, % | 23 | 8–49 |
| Liver metastases, % | 28 | 14–47 |
| Lung metastases, % | 30 | 26–47 |
| Brain metastases, % | 0 | 0–1 |

**TABLE 2** Summary of scenarios for overall survival.

| Trials | Treatment Groups (*n*) | Participants (*n*) | Median (IQR) OS in months for each scenario | | | | |
|---|---|---|---|---|---|---|---|
| | | | Worst-case | Lower typical | Median | Upper typical | Best-case |
| First-line | 25 | 5042 | 12.6 (9.2–15.6) | 26.1 (19.3–30.4) | 43.3 (35.3–51.6) | 58.4 (35.2–51.6) | 103.2 (76.3–114.3) |
| Subsequent-line | 19 | 5026 | 7.1 (5.9–8.7) | 15.3 (12.1–17.4) | 29.2 (26.4– 34.8) | 48.5 (42.6-53.3) | NE |

**TABLE 3** Scenarios for overall survival by treatment.

| Trials | Treatment groups (*n*) | Participants (*n*) | Median (IQR) in months for each scenario | | | | |
|---|---|---|---|---|---|---|---|
| | | | Worst-case | Lower typical | Median | Upper-typical | Best-case |
| **First-line CDK 4/6 inhibitors + ET** | 4 | 990 | 16.9 (14.60–20.2) | 34.5 (30.4–35.5) | **61.3 (53.4–64.8)** | NE | NE |
| **First-line Fulvestrant + AI** | 3 | 791 | 12.8 (10.5– 16.1) | 28.2 (24.5–31.4) | **49.8 (43.8–50.8)** | 54.3 (53.7–71.1) | 118.4 |
| **First-line Fulvestrant** | 4 | 617 | 9.6 (4.6–15.0) | 11.2 (10.8–29.7) | **37.5 (22.9–52.4)** | 44.3 (42.5–46.0) | NE |
| **First-line AI** | 11 | 1890 | 12.0 (9.6–15.3) | 25.06 (20.5 – 29.7) | **37.4 (33.5–43.4)** | 63.6 (63.2–73.5) | 93.34 (98.3–108.1) |
| **First-line Tamoxifen** | 3 | 417 | 6.0 (4.5–6.5) | 10.2 (8.3–13.8) | **16.0 (14.2–29.7)** | 20.20 (20.1–41.6) | NE |
| **Second-line CDK 4/6 inhibitors + FLV** | 3 | 1277 | 11.2 (10.1–12.2) | 22.5 (20.2–23.1) | **39.7 (37.3–43.2)** | 56.9 | NE |
| **Second-line AI + FLV** | 1 | 243 | 4.9 | 10.8 | **20.2** | NE | NE |
| **Second-line FLV** | 8 | 1929 | 7.4 (6.3–9.7) | 15.7 (14.4-18.2) | **28.6 (25.5–31.2)** | 47.9 (42.8–53.6) | NE |
| **Second-line AI** | 4 | 1070 | 6.7 (6.1–7.6) | 14.8 (13.6–15.5) | **28.9 (26.6–33.3)** | 50.5 (44.9–55.3) | NE |
| **Second-line Everolimus + AI** | 2 | 586 | 7.30 (6.7–7.2) | 13.2 (12.0–14.5) | **27.1 (25.1–29.0)** | 47.65 | NE |
| **Second-line Everolimus alone** | 1 | 103 | 5.70 | 12.03 | **29.1** | 42.31 | NE |

from this study, with the caveat that longer-term follow-up is required in order to accurately capture the survival times of the longest-living patients.

Many patients with advanced cancer have a poor understanding of their life expectancy and often overestimate their prognosis.[44] While there is a considerable amount of literature on how to discuss prognosis with patients with advanced cancer, there is less information available on how to estimate survival times, especially in the current era, where targeted and immunotherapies can be the mainstay of treatment for many patients. This study has important clinical applications. For a patient with ER-positive, HER2-negative MBC who is starting first-line treatment with ET plus a CDK4/6i, ranges for the three scenarios for survival can be estimated as follows. Using the median OS of 61 months, the worst-case scenario is 15 months or less (0.25 × 61), the typical scenario is between 2.5 and 10 years (0.5 × 61 to 2 × 61) and assuming the simple multiple remains accurate for estimating the best-case scenario it is likely to be 15 years or longer (3 × 61). These scenarios for survival can be explained to a patient as follows: "If we imagine a group of 100 people exactly like you receiving this treatment, then based on the survival of people in the trial, we would expect approximately 5–10 people to die within 15 months, the middle 50 people to live 2.5–10 years and 5–10 people to live longer than 15 years".

Similarly, using the median OS of 37 months from the first-line aromatase inhibitor trials, the worst-case scenario is 9 months or less (0.25 × 37), the typical scenario is 1.5–6 years (0.5 × 37–2 × 37), and the best case scenario is 9 years or longer (3 × 37), although again the best-case scenario information is not available due to insufficient follow-up.

It should be noted that not all patients want quantitative survival information so our method of estimating and explaining survival time is not appropriate for these patients.

Our study examined several characteristics associated with survival however reporting of participant characteristics was inconsistent and heterogeneous across the examined trials. Standardization of patient characteristics reporting will aid in trial reporting and prognostic estimation for clinicians.

This review has examined survival data from endocrine therapy trials spanning the last 25 years. The strengths of this study are that it is a contemporary systematic overview of survival estimates for ER-positive MBC patients commencing treatment, and it provides oncologists with simple rules of thumb to help them estimate and explain survival times to these patients. Our previous work has demonstrated that patients prefer to receive information on survival time in the format of multiple survival scenarios in this way, rather than receiving a single number estimate of median survival.[2]

One of the limitations of this study is that it includes a population of clinical trial participants who are likely to have a better prognosis than patients treated in routine clinical practice who are often older, frailer, or have more comorbidities than the patients in the trial. Given there is limited data for patients treated outside of clinical trials it would be appropriate for clinicians to use the median OS from an appropriate clinical trial as the starting point and adjust the estimate down according to the characteristics of the individual patient in question. Data on the best-case and upper-typical scenarios are limited due to a lack of long-term follow-up. Publication of updated survival outcomes after longer follow-up is needed to provide better estimates of long-term survival. The survival data from the older trials may not be as relevant to current practice, as post-progression survival has also significantly improved as more lines of therapy and newer agents become available for use in similar cohorts of patients. Thus patients starting treatment today may live longer due to the presumption of more effective subsequent line therapies. The estimates of survival for subsequent therapy do not include trials where patients have received prior CDK4/6i. Survival data were also less reliable when there were a limited number of patients in follow-up at the longer survival times. Another limitation is the small proportion of trial participants with brain metastases, a subgroup likely to have a worse prognosis. This highlights the importance of real-world databases that include patients who do not fit clinical trial criteria.

In summary, patients with ER-positive MBC commencing first-line ET with CDK4/6i have a median OS of over 5 years. In this setting, simple multiples of an OS curve's median can be used to accurately estimate worst-case (0.25 times median OS) and typical (0.5–2 times median OS) scenarios for survival. Data are limited to estimate the best-case scenario, but it is likely that 5–10% of patients will live beyond 15 years. Extended follow-up of trials and publication of this data will ensure clinicians and patients are better informed on possible long-term outcomes.

## ACKNOWLEDGMENTS

Open access publishing facilitated by Macquarie University, as part of the Wiley - Macquarie University agreement via the Council of Australian University Librarians.

## CONFLICT OF INTEREST STATEMENT

Belinda E. Kiely has received honoraria for advisory board participation from Roche and Gilead, speaker fees from MSD Oncology, Novartis, and Eisai, and registration expenses for virtual meetings from Pfizer, MSD Oncology, and Novartis. The other authors declare no conflict of interest.

## FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the references and further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

As only previously published clinical trial data was used, human research ethics committee approval was not required for this manuscript.

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**How to cite this article:** Parsonson AO, Sarkar S, Brown L, Low GKK, Kiely BE, Vasista A. Beyond the median: Estimating survival times for patients starting endocrine therapy for estrogen receptor-positive, metastatic breast cancer from recent randomized trials. *Asia-Pac J Clin Oncol*. 2024;20:714–722. https://doi.org/10.1111/ajco.14096