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PII: S1526-8209(22)00189-6
DOI: https://doi.org/10.1016/j.clbc.2022.08.012
Reference: CLBC 1507

To appear in: *Clinical Breast Cancer*

Received date: Apr 27, 2022
Revised date: Jul 30, 2022
Accepted date: Aug 26, 2022

Please cite this article as: Nathaniel Hendrix , Nina Oestreicher , Deepa Lalla , Chantal M. Dolan , Kathryn A. Fisher , David L. Veenstra , Beverly Moy , Residual Disease Burden After Neoadjuvant Therapy Among US Patients With High-Risk HER2-positive Early-Stage Breast Cancer: A Population Effectiveness Model, *Clinical Breast Cancer* (2022), doi: https://doi.org/10.1016/j.clbc.2022.08.012

Highlights

- HER2-positive ESBC often recurs in patients not achieving neoadjuvant therapy pCR
- The burden of recurrence has not previously been quantified in this population
- Each year, approximately 9,300 new patients fit into this high risk category
- We used a decision model to extrapolate 10-year outcomes for a 1-year cohort
- Recurrence causes 1,390 cancer deaths and $644 million in costs

Residual Disease Burden After Neoadjuvant Therapy Among US Patients With High-Risk HER2-positive Early-Stage Breast Cancer: A Population Effectiveness Model

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Abbreviations: CR, credible range; ESBC, early-stage breast cancer; pCR, pathological complete response; T-DM1, ado-trastuzumab emtansine.

Disclosures

Nathaniel Hendrix has received consulting fees from Puma Biotechnologies, Incyte Corporation, Pfizer, Insightec, and Teleflex Interventional Radiology. Nina Oestreicher was employed by and owned stocks or stock options in Puma Biotechnology at the time the work was done. Deepa Lalla was employed by and owned stocks or stock options in Puma Biotechnology at the time the work was done. Chantal M. Dolan has received consulting fees through CMD Consulting, Inc. from Puma Biotechnologies, Genentech, Gilead Sciences, Coagulant Therapeutics, Bristol Myers Squibb, Global Blood Therapeutics, Regenxbio, Elekta, Lyell Immunopharma, Portola Pharmaceuticals, and Halozyme. Kathryn A. Fisher has received consulting fees through CMD Consulting, Inc. from Puma Biotechnologies, Genentech, Gilead Sciences, Coagulant Therapeutics, Bristol Myers Squibb, Global Blood Therapeutics, Regenxbio, Elekta, Lyell Immunopharma, Portola Pharmaceuticals, and Halozyme. David L. Veenstra has received consulting fees from Genentech, Mirati Therapeutics, Halozyme Therapeutics, and Puma Biotechnologies Inc., and has received research funding from Foundation Medicine and Genentech. Beverly Moy has received consulting fees from Motus and research funding from Puma Biotechnology.

Micro Abstract (Original Studies)

Approximately half of patients with high-risk HER2-positive early-stage breast cancer do not have pathologic complete response after neoadjuvant therapy. We used decision-modeling techniques to estimate the residual burden of recurrence among a 1-year cohort of US patients. We estimated that recurrence caused approximately 1,320 additional deaths, 6,440 years of life lost, and $644 million in healthcare-related costs over 10 years.

Clinical Practice Points

- Approximately half of patients with HER2-positive early-stage breast cancer do not have pathologic complete response after neoadjuvant therapy. These patients are at high risk of recurrence. The burden of residual recurrence, though, has not previously been quantified.
- We used decision analytic modeling to extrapolate survival curves from the KATHERINE trial of ado-trastuzumab emtansine (T-DM1) to 10 years. This allowed us to estimate the residual burden of recurrence for a typical 1-year cohort of newly diagnosed patients. We estimated that recurrence among this cohort causes 1,390 breast cancer deaths; 6,440 lost years of life; and $644 million in healthcare-related costs, primarily associated with the treatment of distant recurrences.
- After HER2-positive early-stage breast cancer patients receive adjuvant therapy, there is still a substantial residual burden of disease. As such, there is a need for innovative treatments and strategies to reduce that burden.

Abstract

Background: Approximately half of patients with high-risk HER2-positive early-stage breast cancer (ESBC) do not have pathologic complete response (pCR) after neoadjuvant therapy. The residual burden of disease among this population has not been previously quantified.

Methods: We used decision-modeling techniques to simulate recurrence, progression from locoregional to distant cancer, breast cancer-related mortality, and mortality from other causes over a 10-year period in a hypothetical cohort. We derived progression probabilities primarily from the KATHERINE trial of T-DM1 (ado-trastuzumab emtansine) and mortality outcomes from the published literature. Modeled outcomes included recurrences, breast cancer deaths, deaths from other causes, direct medical costs, and costs due to lost productivity. To estimate the residual disease burden, we compared outcomes from a cohort of patients treated with T-DM1 versus a hypothetical cohort with no disease recurrence.

Results: We estimated that 9,300 people would experience incident high-risk HER2-positive ESBC in the US in 2021 based on cancer surveillance databases, clinical trial data, and expert opinion. We estimated that in this group, 2,118 would experience disease recurrence, including 1,576 distant recurrences. They would also experience 1,385 breast cancer deaths. This residual disease burden resulted in 6,435 life-years lost versus the recurrence-free cohort and healthcare-related costs totaling $644 million, primarily associated with treating distant cancers.

Conclusion: Patients with HER2-positive ESBC who do not achieve pCR after neoadjuvant therapy are at ongoing risk of recurrence despite the effectiveness of neoadjuvant treatment. There is substantial clinical and economic value in further reducing the residual disease burden in this population.

Keywords: Disease burden, Cost, HER2-positive early-stage breast cancer, Neoadjuvant therapy, Decision modeling

Introduction

HER2 protein overexpression and/or *HER2* gene amplification is found in approximately 15–20% of all early-stage breast cancer (ESBC) cases and is associated with increased recurrence and poorer survival.[1-3] Blocking the HER2 protein with targeted agents has been shown to substantially improve the prognosis for patients with HER2-positive cancers.[4,5]

Additionally, neoadjuvant therapy is increasingly used as initial therapy for select patients with high-risk locally advanced breast cancer.[6,7] General criteria for consideration of neoadjuvant therapy include the patient having a preference for breast-conserving surgery but not being a candidate due to tumor size or location and axillary nodal involvement.[8] Patients treated systemically before surgery and who have residual disease face a significantly worse prognosis compared with those who achieve a pathological complete response (pCR).[9,10] This is particularly the case in aggressive breast cancer subtypes including HER2-positive tumors.[11] However, only 45–56% of patients with HER2-positive breast cancer achieve pCR with neoadjuvant treatment.[12,13] Initially used to decrease tumor burden and increase breast-conservation rates, recent trials of neoadjuvant therapy have demonstrated survival benefits with specific treatments for patients with residual disease.[14]

The phase 3 KATHERINE trial randomized patients with HER2-positive residual invasive breast cancer after undergoing neoadjuvant therapy plus trastuzumab to either ado-trastuzumab emtansine (T-DM1) or to continue with adjuvant trastuzumab in the adjuvant setting.[15] Patients in the T-DM1 arm had significantly greater invasive disease-free survival after a median follow-up of 41.4 months (hazard ratio 0.50, 95% confidence interval: 0.39–0.64, $P<.001$). The rate of distant recurrence was 10.5% for the TDM-1 arm versus 15.9% in the trastuzumab arm. As a result, T-DM1 is now considered the standard of care for patients with residual disease after neoadjuvant taxane- and trastuzumab-based treatment. After 3 years, however, 12.2% of patients who received T-DM1 in the KATHERINE study had an invasive disease event.[15] The long-term clinical and economic impacts of these recurrences are not well understood.

The objective of our study was to estimate the residual burden of recurrence following treatment with T-DM1 among US patients with high-risk HER2-positive ESBC who did not achieve pCR after neoadjuvant therapy.

Methods

Model Description

We developed a decision-analytic model to simulate long-term breast cancer outcomes in a hypothetical cohort of patients similar to participants in the KATHERINE trial.[15] We selected a 10-year time horizon for this model as breast cancer recurrence and mortality occur primarily during this period. To estimate the residual disease burden, we compared the at-risk cohort against a hypothetical cohort who did not experience recurrence.

We created a Markov model using a monthly cycle length with the following five health states (Figure 1): "progression-free survival," "locoregional recurrence," "distant recurrence," "breast cancer death," and "deaths from other causes." Patients entered the model in the "progression-free survival" state and were assumed to be 50 years of age.

Model Population

For the model population, we defined patients with incident high-risk HER2-positive ESBC as those treated with neoadjuvant therapy who do not achieve pCR (Table 1). To estimate the annual number of these patients in the US, we used the reported number of incident breast cancer cases in 2021 of 281,550 and the proportion diagnosed at either the local or regional stage as 92% (*see Supplementary Appendix A*, Table A.1).[16] The proportion of incident early-stage cases that are HER2-positive was estimated as 16% from a population-based National Cancer Institute Patterns of Care study of women.[1] Data from 2015 for the National Cancer Database were used to estimated that 50% of HER2-positive early-stage cases are treated with neoadjuvant therapy (personal correspondence B. Moy, MD, January 21, 2022 [expert opinion]),[6] estimating approximately 20,700 persons per year with newly diagnosed HER2-positive ESBC. Of early-stage cases treated in the neoadjuvant setting, approximately 45% do not achieve pCR (high risk) (personal correspondence B. Moy, MD, January 22, 2022 [expert opinion]).[13,16]

We made the following key assumptions. First, patients with locoregional recurrence could progress to distant recurrence at any time after their initial recurrence. We made this assumption as a way of avoiding the imposition of a period for which the patient was risk-free. Second, all patients in the "locoregional recurrence" state had the same probability of distant recurrence. Since our model concerns population benefits, we assumed that all patients had the population average risk of distant recurrence. Third, all patients were eligible for treatment with T-DM1. We chose to assume this to provide all patients in the population with the highest chance of survival and, thus, to conservatively estimate the burden of disease. Lastly, patients in the "distant recurrence" state were ineligible for remission. While survival varies for patients with distant recurrence due to type and extent of metastases, we captured average patient survival by applying the mean hazard of mortality for these patients.

Clinical Probabilities

Recurrence risk for recurrence-susceptible persons varied by month and was estimated from digitized survival curves taken directly from the KATHERINE trial (see description in *Supplementary Appendix B*).[15] The KATHERINE trial reported invasive disease-free survival and distant recurrence-free survival. In the trial analysis, patients were censored from the invasive disease-free survival curve when they first experienced locoregional recurrence, distant recurrence, or death from any cause; patients were censored from the distant recurrence-free survival curve only at the first of either distant recurrence or death from any cause.

We used the first 4 years of trial results given the small proportion of patients followed for the trial's full 5 years. We projected beyond the trial data based on the shape of the survival curves from the combined trastuzumab arms (1 versus 2 years of treatment) in the long-term HERA trial.[4] Specifically, to estimate the extrapolated control arm in the KATHERINE trial, we applied a hazard ratio for the first 4 years of the HERA trastuzumab arms compared with the trastuzumab arm of the KATHERINE trial.[4,15]

To estimate survival for the T-DM1 arm, we assumed that the protective effect of T-DM1 observed in year 4 of the KATHERINE trial gradually decreased over the remainder of the 10-year period, similar to previous models in ESBC.[17,18]

The monthly risk of age-specific background mortality was based on the 2019 US Social Security Administration life tables for women.[19] We subtracted age-specific breast cancer mortality from the actuarial life tables to isolate background mortality not due to breast cancer.[20] Only patients with distant recurrences could die from breast cancer. All patients in the "distant recurrence" state were subject to a monthly probability of 0.0317% risk of breast cancer death.[17,21]

Costs

All direct costs were derived from published literature and were inflated to 2020 US dollars using the medical consumer price index inflator (Table 1).[17,22-24]. Patients incurred one-time costs when transitioning into the "locoregional recurrence" and "breast cancer death" states [22,23] In addition to direct medical costs, we estimated the costs of lost productivity associated with treatment of distant recurrences, which we inflated to 2020 US dollars using the consumer price index.[24,25] We did not include lost productivity due to death.

Analyses

Our estimates of the residual burden of disease following the use of T-DM1 in patients with high-risk HER2-positive ESBC were based on calculations of locoregional recurrences, distant recurrences, mortality, and costs for the 2021 cohort of 9,300 patients over a 10-year timeframe. We calculated the burden of disease attributable to recurrence as the difference of the counts of outcomes in the recurrence-free and at-risk cohorts.

Evaluation of Uncertainty

Because of uncertainty in our methods for extrapolating the protective effect of T-DM1 over the entire modeled time period, we also conducted a scenario analysis in which the protective effect of treatment finished at the end of year 4 of the KATHERINE trial. We conducted a scenario analysis in which we estimated outcomes for 10 annual cohorts of patients, each of whom we followed for 10 years. This allowed us to estimate the residual burden of recurrence over a longer time horizon, including overlapping cohorts.

We conducted two sensitivity analyses to estimate the influence of input uncertainty in our model. First, we conducted one-way sensitivity analyses, which showed the influence of the

uncertainty around each input individually on the results within the pre-defined ranges (Table 1). We also conducted a probabilistic sensitivity analysis in which we performed 10,000 simulations as the basis for reporting 95% credible ranges (CRs; the central range of results from the 2.5th percentile to the 97.5th percentile). In each of the 10,000 simulations, random values for each input were drawn from the pre-defined ranges for each model input range according to an assigned statistical distribution. As such, the probabilistic sensitivity analysis showed the simultaneous impact of multiple sources of uncertainty on the modeled outcomes.

We used confidence intervals from published sources when available to estimate the plausible ranges of inputs for the probabilistic sensitivity analysis. We calculated the confidence intervals of the survival curves using two different methods for the observed period of the KATHERINE trial and the extrapolated period that lasted between years 5 and 10 (Figure 2). For the observed period, we used the reported confidence interval for the hazard ratio of recurrence for the T-DM1 arm versus the trastuzumab arm. For the extrapolated period, we used the calculated confidence interval from the Cox proportional hazards regression that we conducted on the KATHERINE versus HERA trastuzumab arms. We used a fixed range of ±10% for costs when the sources did not contain information about uncertainty around their estimates.

Results

We estimated that 9,300 people would experience incident high-risk HER2-positive ESBC in the US in 2021.

Clinical Events

Over 10 years, we estimated the at-risk cohort would experience 542 locoregional recurrences (95% CR: 519–555) and 1,576 distant recurrences (95% CR: 1,283–1,860; Table 2, Figure 3). Most distant recurrences occurred within the first 5 years after initial treatment. Approximately 14.9% of the at-risk cohort died of breast cancer, and 3.9% died of other causes. In the recurrence-free cohort, 4.3% died of other causes. Deaths primarily occurred in years 2 through 5 as a consequence of when distant recurrences occurred and the duration of expected survival among persons with distant recurrence.

Life Expectancy

The at-risk cohort experienced a total of 1,791 (95% CR: 1,705–1,797) person-years spent with locoregional recurrence and 3,621 (95% CR: 2,863–4,432) person-years spent with distant recurrence (Figure 4). At the end of the modeled period, 76.1% of the at-risk cohort remained in the recurrence-free state and had accumulated a total of 79,422 (95% CR: 76,643–81,085) person-years in the recurrence-free state.

We calculated the at-risk cohort of 9,300 patients would accumulate 84,834 (95% CR: 83,301–86,374) life-years, or an average life expectancy over the 10-year time period of 9.12 years (Table 2). In contrast, the recurrence-free cohort accumulated 91,268 life-years (95% CR not calculated), or a life expectancy of 9.81 years. We therefore estimated the residual burden of breast cancer recurrence after T-DM1 treatment was 6,435 (95% CR: 4,894–7,966), or 0.69 years of life lost per person, on average, over 10 years.

Costs

Approximately 61.1% of costs in the at-risk cohort were associated with distant recurrence (Table 2). Locoregional recurrence was associated with 15.3% of costs, and end of life costs represented 18.8% of overall costs. Indirect costs accounted for 1.7% of total costs. ESBC-

related healthcare costs for the at-risk cohort totaled $669 million (95% CR: $548 million–$800 million). Costs accumulated at the quickest rate during the first 4 years of the modeled period. All costs in the recurrence-free cohort were associated with the recurrence-free health state. Costs for the recurrence-free cohort totaled $24 million (95% CR: $22 million–$27 million), all of which is attributable to the cost of monitoring for disease recurrence. The residual economic burden of disease was $645 million (95% CR: $524 million–$776 million).

Sensitivity and Scenario Analyses

We conducted a scenario analysis to estimate the impact of our assumptions about the remaining protective effect of T-DM1 after the end of the KATHERINE trial. This analysis estimated that the most influential input on both costs and life-years was distant recurrence-free survival (Figure 5). The cost of treating distant disease was also highly influential on costs. The probability of death for patients with distant recurrence was more influential on the costs than on the burden of illness. Inputs associated with the risk and cost of locoregional disease were notably less important than the inputs associated with distant recurrence.

The probabilistic sensitivity analyses (Figure 3) showed the credible range of the residual clinical and economic burden associated with recurrence. Each point on the figure shows the result of one simulated run of the model and the burden that resulted from the distribution of model inputs. Because these were incremental estimates, the origin corresponded to the estimated costs and life-years in the recurrence-free cohort. There was a dense central region indicating the most credible estimates, while outliers showed fewer probable estimates of the residual burden of recurrence.

Discussion

We developed a decision-analysis model to simulate long-term breast cancer outcomes in a hypothetical cohort of patients with high-risk HER2-positive ESBC similar to the KATHERINE trial participants.[15] We evaluated the residual burden of breast cancer by estimating the total number of breast cancer recurrences, deaths, life-years, and costs attributable to breast cancer over a 10-year time horizon. We found the residual burden of disease for a cohort of 9,300 patients in the US was 1,576 cases of distant recurrence, 1,346 deaths, 6,435 life-years, and $644,562,000 in total costs.

Our findings suggest that despite the significant benefits of treatment with TDM-1 in patients with HER2-positive ESBC, those who do not achieve pCR face meaningful clinical risk over the next decade, particularly in the first 5 years after treatment. Healthcare costs are also impactful, with an estimated $71,900 per person in economic burden attributable to recurrence initially treated.

These results have important implications. First, despite the great success in treating people with HER2-positive ESBC, it is crucial to recognize that further strategies are needed to improve clinical outcomes in patients with high-risk HER2-positive disease, particularly those with residual disease after neoadjuvant therapy. Second, given the residual burden of ESBC in this patient population, our results suggest that treatments should be optimized to help address the remaining disease risk.

Previous analyses have projected the potential long-term clinical and economic outcomes of treatment with HER2-targeted therapies in patients with HER2-positive ESBC. These studies used similar approaches to ours, although comparisons are challenging as these studies focused on cost-effectiveness rather than residual disease burden, and thus measured discounted quality-adjusted life-years and discounted costs rather than focusing on non-discounted clinical events, life expectancy, and economic burden.

Kunst and colleagues modeled clinical and economic outcomes based on the KATHERINE trial within a cost-effectiveness analysis.[26] Their analysis was conducted over a lifetime horizon and when their results were discounted, they found that treatment with T-DM1 was cost-effective for patients with residual disease following neoadjuvant therapy. Similarly, Sussell et al. found that

treatment with T-DM1 was cost-saving and improved outcomes compared with trastuzumab.[27] In summary, to our knowledge, no previous studies have evaluated the residual burden of disease in a patient population similar to that of the KATHERINE trial, multiple studies have suggested that novel treatments to reduce the residual burden of recurrence in persons with HER2-positive ESBC could be cost-effective.

Our study has several important limitations. First, as with most decision-analysis models in oncology, we projected outcomes beyond the observed trial period. We used standard analytic approaches in decision analysis to estimate future recurrences and relied on the long-term follow-up results of the HERA trial to guide our analysis.[4,28] Second, there is uncertainty in the model inputs. We assessed the impact of this uncertainty using one-way and probabilistic sensitivity analysis; the results varied by approximately ±20% in our simulations. Third, we made several clinical assumptions, most notably regarding the duration of treatment effect. We assessed the impact of this assumption by varying the duration in a scenario analysis. Fourth, we assumed that all persons in the cohort were eligible for treatment with T-DM1, although the drug has three "black box" warnings that may cause prescribers to avoid its use in some persons.[29] Because T-DM1 is among the most effective treatments for patients who can use it, our estimate of the residual burden of disease was conservative compared with an analysis that included less-effective drugs. Lastly, we did not include productivity costs due to mortality, as years of life lost was the primary measure of the impact of mortality, and inclusion of these costs would have implied the need to also include cost savings from avoided future unrelated healthcare costs, which we felt would unnecessarily complicate the results.[30]

Conclusions

In conclusion, we modeled the 10-year burden of disease for patients with HER2-positive ESBC and residual disease after neoadjuvant therapy and estimated that with no further treatment beyond TDM-1, a cohort diagnosed in 2021 could be expected to experience 2,118 recurrences and 6,435 years of life lost, and the health-related cost impact would be over $644 million. These findings suggest the need for additional innovative treatments to be considered in this patient population.

Acknowledgments

Editorial support was provided by CMD Consulting and Miller Medical Communications.

Funding

This work was supported by Puma Biotechnology Inc., Los Angeles, CA, USA (no grant number is applicable). Puma Biotechnology Inc. also funded the provision of editorial support provided by CMD Consulting and Miller Medical Communications.

Data Availability Statement

The data used to support the findings of this study are included within the article. All data were derived from published sources.

Author Contributions

Nathaniel Hendrix: Conceptualization, Methodology, Data collection and analysis, Writing - Original Draft, Writing - Review & Editing. **Nina Oestreicher:** Conceptualization, Writing - Review & Editing. **Deepa Lalla:** Conceptualization. **Chantal M. Dolan:** Conceptualization, Writing - Review & editing. **Kathryn A. Fisher:** Data Curation, Formal Analysis, Writing - Original Draft, Writing - Review & Editing. **David L. Veenstra:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing. **Beverly Moy:** Conceptualization, Writing - Review & Editing.

References

1. Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive breast cancer tumors for early stage patients in the US. *Cancer Invest.* 2010;28(9):963–968.

2. O'Brien KM, Cole SR, Tse CK, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. *Clin Cancer Res.* 2010;16(24):6100–6110.

3. Haque R, Ahmed SA, Inzhakova G, et al. Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1848-1855.

4. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet.* 2017;389(10075):1195-1205.

5. Early Breast Cancer Trialists' Collaborative group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. *Lancet Oncol.* 2021;22(8):1139-1150.

6. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Neoadjuvant chemotherapy use in breast cancer is greatest in excellent responders: Triple-negative and HER2+ subtypes. *Ann Surg Oncol.* 2018;25(8):2241–2248.

7. Asaoka M, Gandhi S, Ishikawa T, Takabe K. Neoadjuvant chemotherapy for breast cancer: Past, present, and future. *Breast Cancer.* 2020;14:1178223420980377.

8. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. *Lancet.* 2021;397(10286):1750–1769.

9. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: A comprehensive meta-analysis. *Clin Cancer Res.* 2020;26(12):2838–2848.

10. Nekljudova V, Loibl S, von Minckwitz G, et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). *Contemp Clin Trials.* 2018;71:194–198.

11. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet (London, England).* 2014;384(9938):164–172.

12. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol.* 2016;34(6):542–549.

13. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2018;19(1):115–126.

14. Leon-Ferre RA, Hieken TJ, Boughey JC. The landmark series: Neoadjuvant chemotherapy for triple-negative and HER2-positive breast cancer. *Ann Surg Oncol.* 2021;28(4):2111–2119.

15. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *New Engl J Med.* 2019;380(7):617–628.

16. SEER. Cancer Stat Facts: Female Breast Cancer. National Cancer Institute. https://seer.cancer.gov/statfacts/html/breast.html. Published 2021. Accessed March 15, 2022.

17. Garrison LP J, Babigumira J, Tournier C, Goertz HP, Lubinga SJ, Perez EA. Cost-effectiveness analysis of pertuzumab with trastuzumab and chemotherapy compared to trastuzumab and chemotherapy in the adjuvant treatment of HER2-positive breast cancer in the United States. *Value Health.* 2019;22(4):408–415.

18. NICE. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. Technology Appraisal

Guidance Web site. https://www.nice.org.uk/guidance/ta612. Published 2019. Accessed March 15, 2022.

19. Social Security Administration. Actuarial Life Table. https://www.ssa.gov/oact/STATS/table4c6.html. Published 2019. Accessed March 15, 2022.

20. Centers for Disease Control and Prevention. United States and Puerto Rico Cancer Statistics, 1999-2016 Mortality Archive Request, WONDER Online Database. United States Department of Health and Human Services. https://wonder.cdc.gov/CancerMort-v2016.html. Published 2019. Accessed March 15, 2022.

21. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519–530.

22. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. *Am Health Drug Benefits.* 2016;9(1):23-32.

23. Chastek B, Harley C, Kallich J, Newcomer L, Paoli CJ, Teitelbaum AH. Health care costs for patients with cancer at the end of life. *J Oncol Pract.* 2012;8(6):75s-80s.

24. US Bureau of Labor Statistics. CPI Inflation Calculator. https://www.bls.gov/data/inflation_calculator.htm Published 2020. Accessed March 15, 2022.

25. Wan Y, Gao X, Mehta S, Wang Z, Faria C, Schwartzberg L. Indirect costs associated with metastatic breast cancer. *J Med Econ.* 2013;16(10):1169–1178.

26. Kunst N, Wang SY, Hood A, et al. Cost-effectiveness of neoadjuvant-adjuvant treatment strategies for women with ERBB2 (HER2)-positive breast cancer. *JAMA Netw Open.* 2020;3(11):e2027074.

27. Sussell J, Singh Jhuti G, Antao V, Herrera-Restrepo O, Wehler E, Bilir SP. Cost-effectiveness analysis of ado-trastuzumab emtansine (T-DM1) for the adjuvant treatment of patients with residual invasive HER2+ early breast cancer in the United States. *Am J Clin Oncol.* 2021;44(7):340–349.

28. Rutherford MJ, Lambert PC, Sweeting MJ, et al. *Flexible methods for survival analysis.* 2020.

29. Food and Drug Administration. Ado-trastuzumab emtansine [package insert]. Genentech, Inc. A Member of the Roche Group https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf. Published 2013. Accessed March 15, 2022.

30. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093–1103.

Table 1 Model Inputs

Input	Value	Modeled range	Reference
Cohort			
Annual number of US patients with incident high-risk HER2-positive ESBC (2021)	9,300	Not varied	SEER 2021, Cronin 2010, Hurvitz 2018, Murphy 2018[1,6,13,16]
Recurrence			
Probability of recurrence – T-DM1 and trastuzumab: first 5 years	See Figure 2		von Minckwitz 2019[15]
Probability of recurrence after year 5	See Figure 2		von Minckwitz 2019, Cameron 2017, see text[4,15]
Mortality			
Mortality from other causes	Age-based	Not varied	CDC 2019[20]
Probability of death from distant recurrence (per month)	0.0317	0.0284–0.0347	Swain 2015, Garrison 2019[17,21]
Costs, $[a]			
Progression-free survival (per month)	22	20–24	Garrison 2019[17]
Locoregional recurrence (one-time cost)	183,100	164,800–201,400	Blumen 2016[22]
Locoregional recurrence (maintenance; per month cost)	33	30–36	Garrison 2019[17]
Distant recurrence, direct medical costs (per month)	9,400	8,500–10,300	Blumen 2016[22]
Distant recurrence, indirect costs (one-time cost)	7,100	5,300–8,900	Wan 2014[25]
End of life costs due to breast cancer (one-time cost)	91,000	89,400–92,600	Chastek 2012[23]

[a]All costs in 2020 US dollars. Direct medical costs were inflated using the medical consumer price index; indirect costs were inflated using the consumer price index.

Abbreviations: ESBC = early-stage breast cancer; T-DM1 = ado-trastuzumab emtansine.

Table 2 Clinical Outcomes and Costs Associated With Breast Cancer Recurrence After Treatment With Ado-Trastuzumab Emtansine Versus a Scenario Without Recurrence

Outcome	With recurrence (95% credible range)	Without recurrence (95% credible range)	Difference (95% credible range)
Clinical outcomes			
Locoregional recurrences	542 (519–555)	0	542 (519–555)
Distant recurrences	1,576 (1,283–1,860)	0	1,576 (1,283–1,860)
Breast cancer deaths	1,385 (1,117–1,647)	0	1,385 (1,117–1,647)
Deaths from other causes	365 (358–373)	404 (not varied)	-39 (-46 to -31)
Life-years	84,834 (83,301–86,374)	91,268 (not varied)	6,435 (4,894–7,966)
Costs, millions of US$			
Disease-free survival	20.8 (18.7–23.0)	24.1 (21.8–26.5)	-3.3 (-4.0 to -2.6)
Locoregional recurrence:			
Acute	99.3 (88.3–110.0)	0	99.3 (88.3–109.5)
Locoregional recurrence:	2.8 (2.2–3.6)	0	2.8 (2.2–3.6)
Maintenance			
Distant recurrence	408.5 (314.6–517.2)	0	408.5 (314.6–517.2)
End of life	126.0 (99.4–154.1)	0	126.0 (99.4–154.1)
Indirect costs	11.2 (8.9–13.8)	0	11.2 (8.9–13.8)
Total costs	668.7 (547.8–799.8)	24.1 (21.8–26.5)	644.6 (523.6–776.3)

[a]All costs in 2020 US dollars.

Figure Legends

Figure 1 Schematic of the Markov Model. Patients begin in the "progression-free survival" state, then experience recurrence or death from other causes

Figure 2 Plot of Invasive Disease-Free Survival and Distant Recurrence-Free Survival Showing Ranges Used in Sensitivity Analysis and Values Extrapolated After the KATHERINE Trial's End

Figure 3 Results of the Probabilistic Sensitivity Analysis, Which Used 10,000 Independent, Random Draws From the Uncertainty Distributions Around the Inputs to Calculate Credible Ranges for Results. Results are expressed as incremental costs and life-years relative to the "no recurrence" cohort

Figure 4 (A) Percent of Cohort in Each State By Month. (B) Costs Attributable to Different Health-Related Causes. Costs are stacked and cumulative over time

Figure 5 One-Way Sensitivity Analyses of (A) Costs and (B) Life-years Lost Due to Recurrence. Bars show the cost due to recurrence as a function of the uncertainty interval around the different inputs. Input values are displayed at the ends of bars. Disease-free survival intervals are displayed as hazard ratios relative to the control arm of the KATHERINE trial. Abbreviation: Pr = probability.

Figure 1:

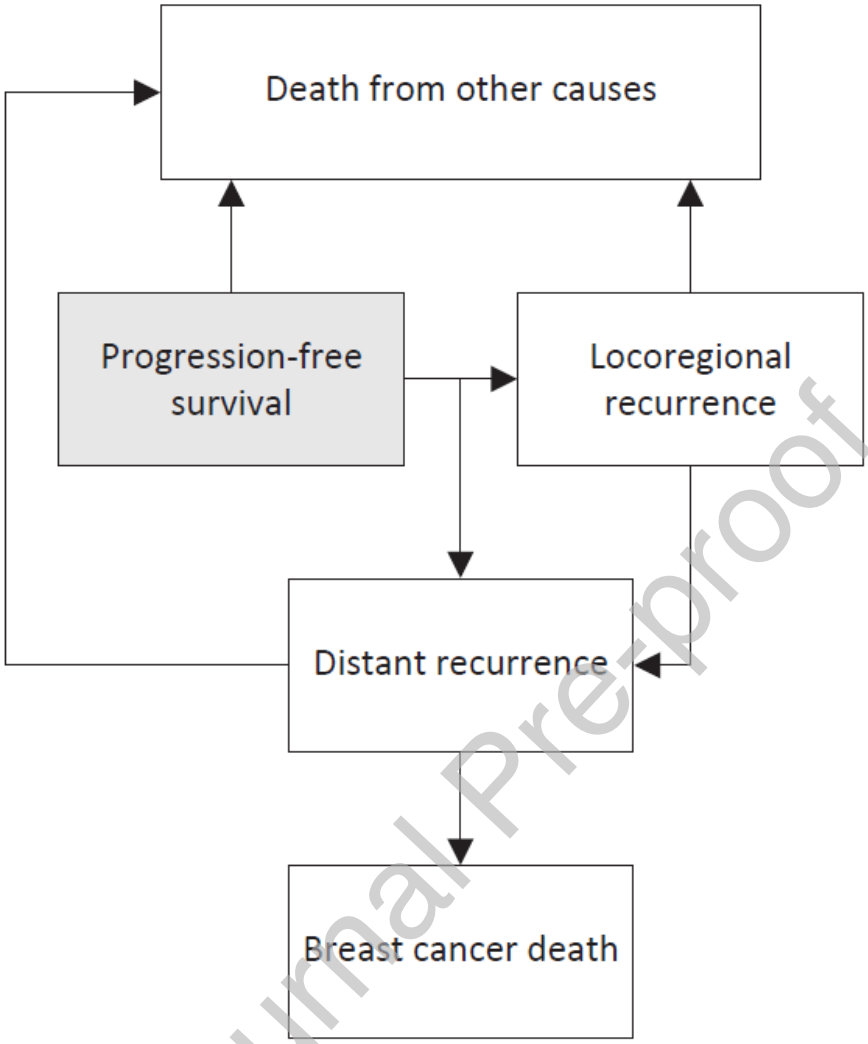


Figure 2:

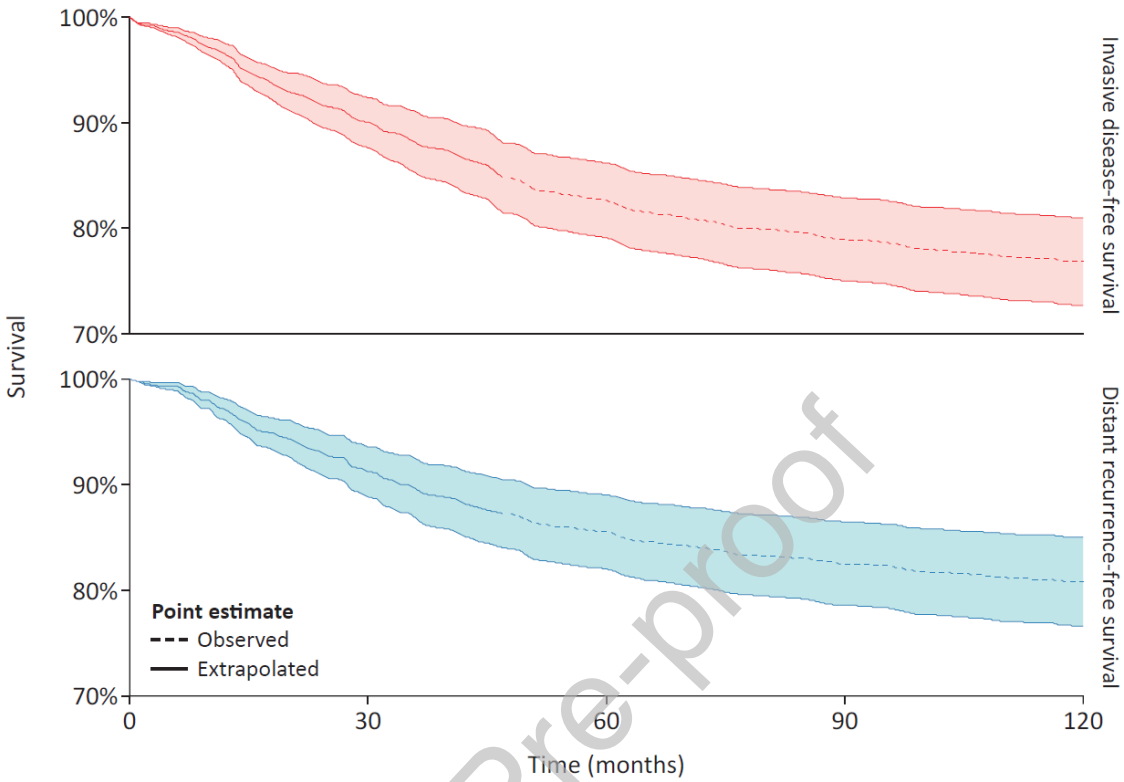


Figure 3:

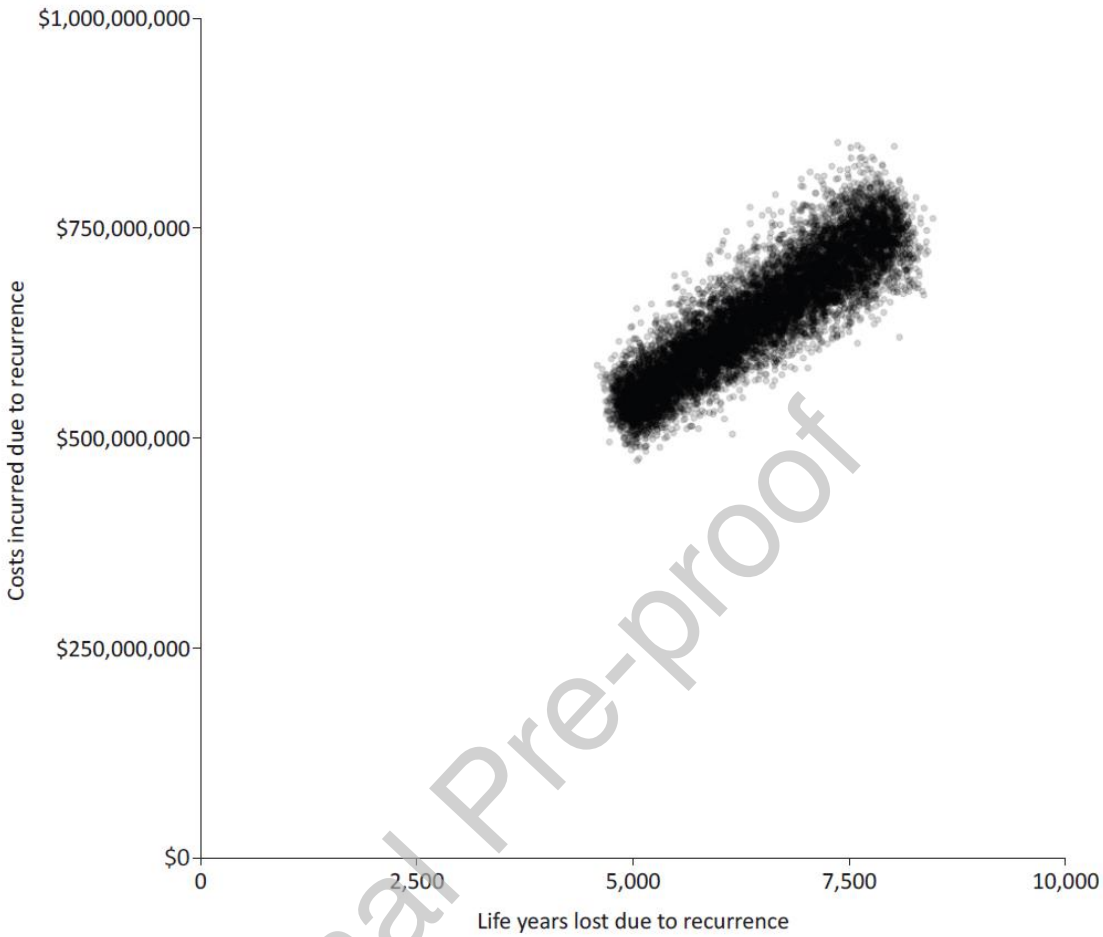
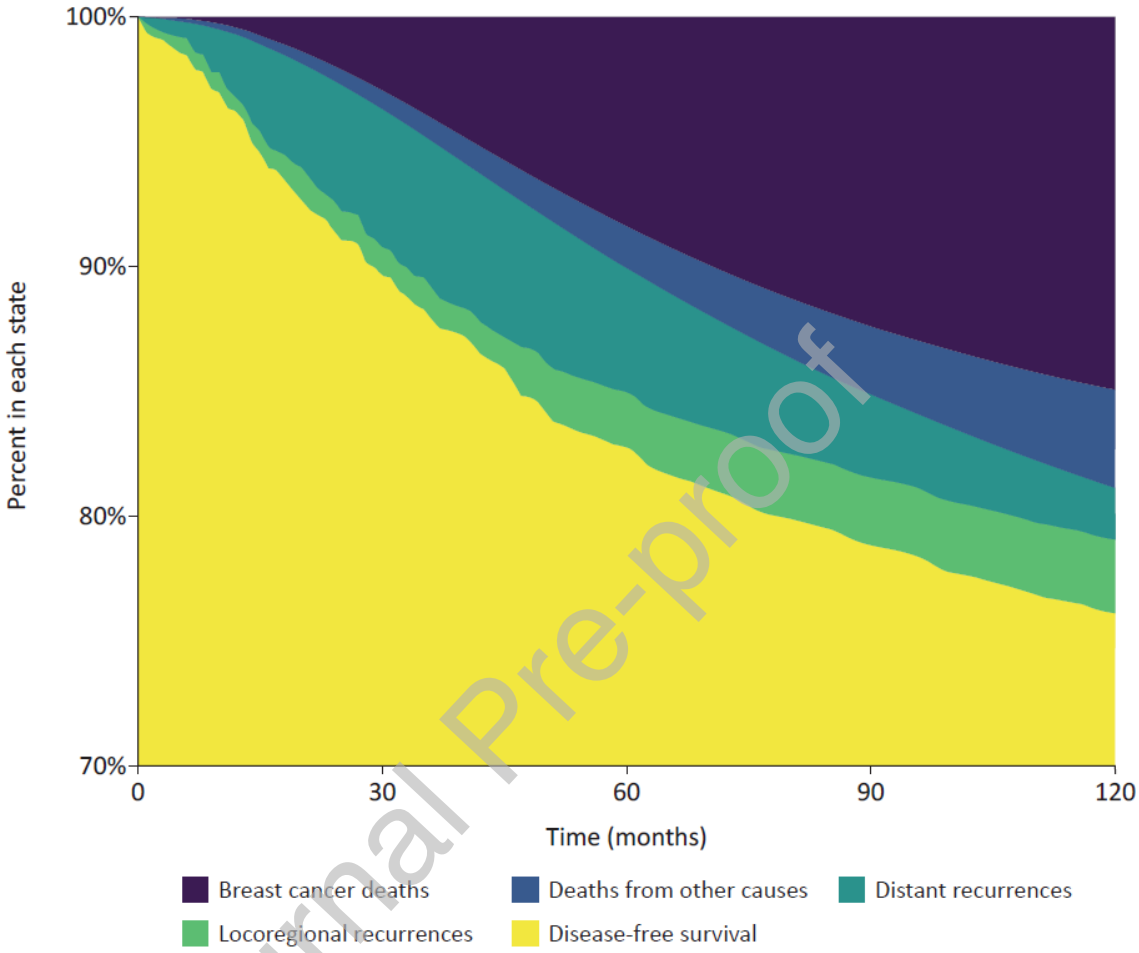


Figure 4:

A



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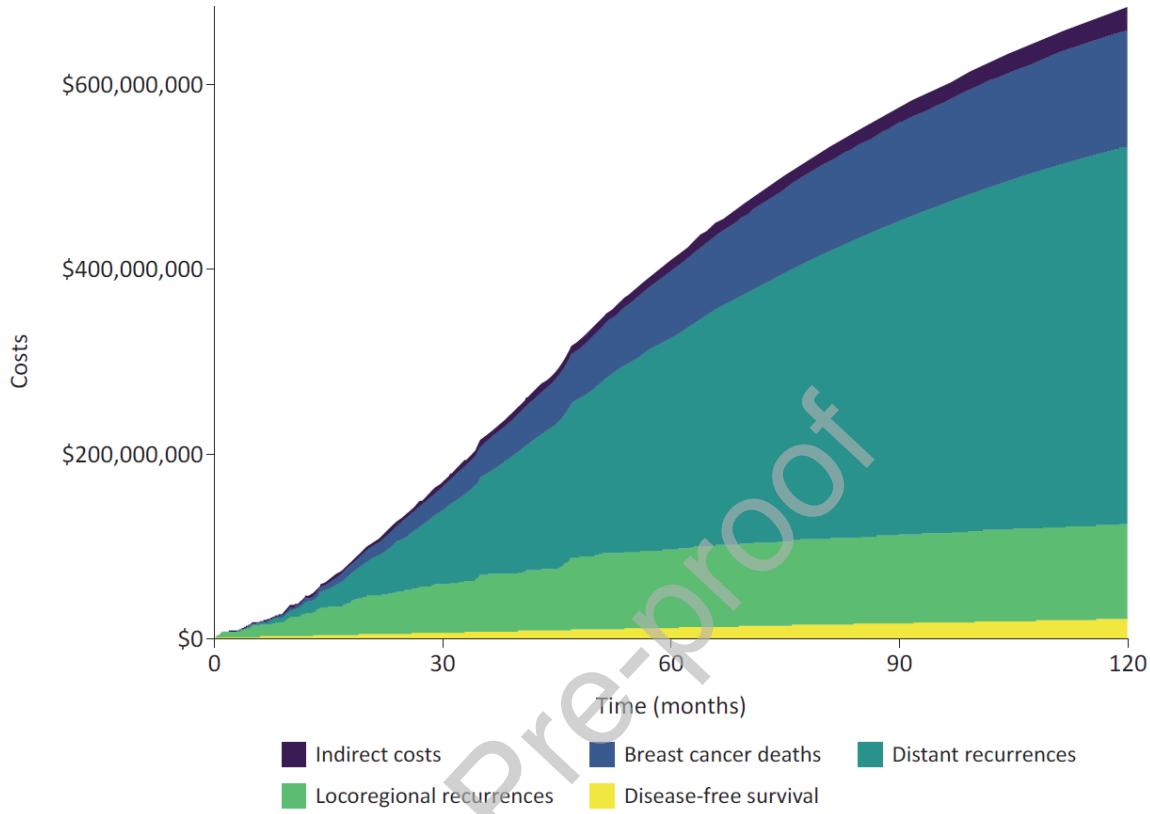
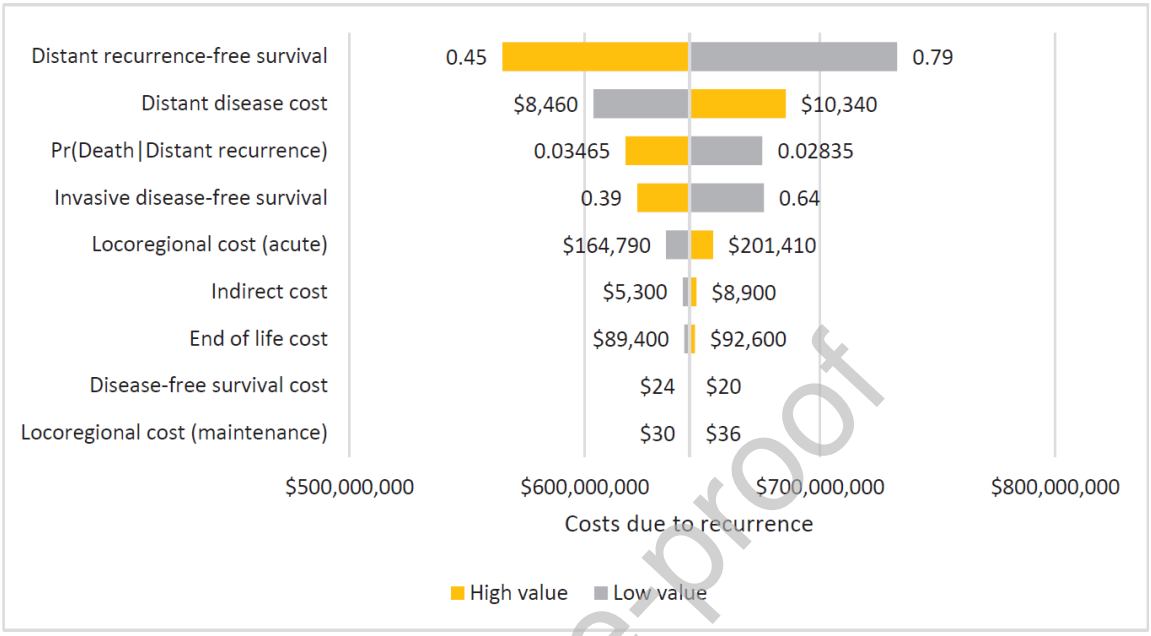


Figure 5:

A



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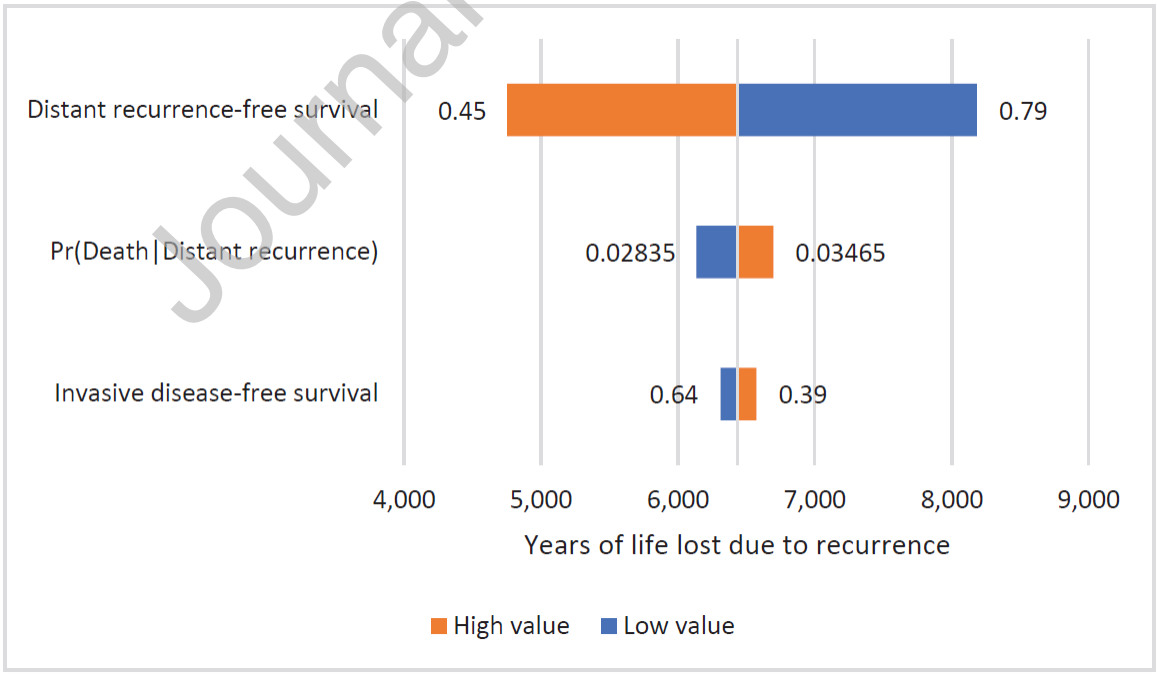

Appendices

Appendix A: Population Model

Table A.1 Population model – Estimated Number of US Persons With Incident HER2-Positive High-Risk Early-Stage Breast Cancer in 2021

Input	2021 estimate	Source
Incident number of breast cancer cases	281,550	SEER 2021[16]
Proportion of incident cases that are early stage (localized or regional)	92%	SEER 2021[16]
Estimated number of incident early-stage cases	259,026	
Proportion of early-stage cases that are HER2-positive	16%	Cronin 2010[1]
Estimated number of persons with incident HER2-positive early-stage cases	41,444	
Proportion of HER2-positive cases treated with neoadjuvant therapy	50%	Murphy 2018[6], personal correspondence B. Moy, MD, January 21, 2022
Estimated number of incident HER2-positive early-stage cases treated with neoadjuvant therapy	20,722	
Proportion of HER2-positive cases treated with neoadjuvant therapy that do not achieve a pathological complete response	45%	Hurvitz 2018[13], personal correspondence B. Moy, MD, January 22, 2022
Estimated number of incident HER2-positive early-stage cases	9,325	

treated with neoadjuvant therapy who do not achieve a pathological complete response

References

1. SEER. Cancer Stat Facts: Female Breast Cancer. Available from: https://seer.cancer.gov/statfacts/html/breast.html. [Last accessed on March 15].
2. Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive breast cancer tumors for early stage patients in the US. *Cancer Invest.* 2010;28:963–968.
3. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Neoadjuvant chemotherapy use in breast cancer is greatest in excellent responders: Triple-negative and HER2+ subtypes. *Ann Surg Oncol.* 2018;25:2241–2248.
4. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2018;19:115–126.

Appendix B: Interpretation of Digitized Recurrence-Free Survival Curves

The KATHERINE trial's use of composite endpoints meant that we could not distinguish between certain clinical scenarios. For example, when the invasive disease-free survival (IDFS) and distant recurrence-free survival (DRFS) curves changed identically over a given time period, two explanations were equally plausible: first, that a number of persons had a DRFS-eligible event as their first recurrence event, which would cause them to be censored in both the IDFS and DRFS curves; alternatively, some previously recurrence-free persons may have had a locoregional recurrence and, simultaneously, an equal number of persons with locoregional recurrence had a DRFS-eligible event.

We developed a set of assumptions to guide our conversion of the survival curves into monthly probabilities of progression by type of recurrence. We opted to model the scenario in which the fewest number of events needed to happen simultaneously to reproduce the observed change in both survival curves. We calculated the hazard of first clinical event in the IDFS and DRFS curves. We first adjusted these hazards for background mortality. If the hazard of first clinical event in the DRFS curve exceeded the hazard of first clinical event in the IDFS curve, we assumed that no persons had a locoregional recurrence – the hazard of first clinical event in the IDFS curve was accounted for by persons whose first recurrence was distant, and the difference in hazards was accounted for by persons with progression from locoregional to distant recurrence. When the hazard of first clinical event in the IDFS curve exceeded the hazard of censoring in the DRFS curve, the latter was entirely accounted for by progression-free persons whose first recurrence was distant, and the difference between the two hazards reflected the probability of a progression-free patient developing a locoregional recurrence.