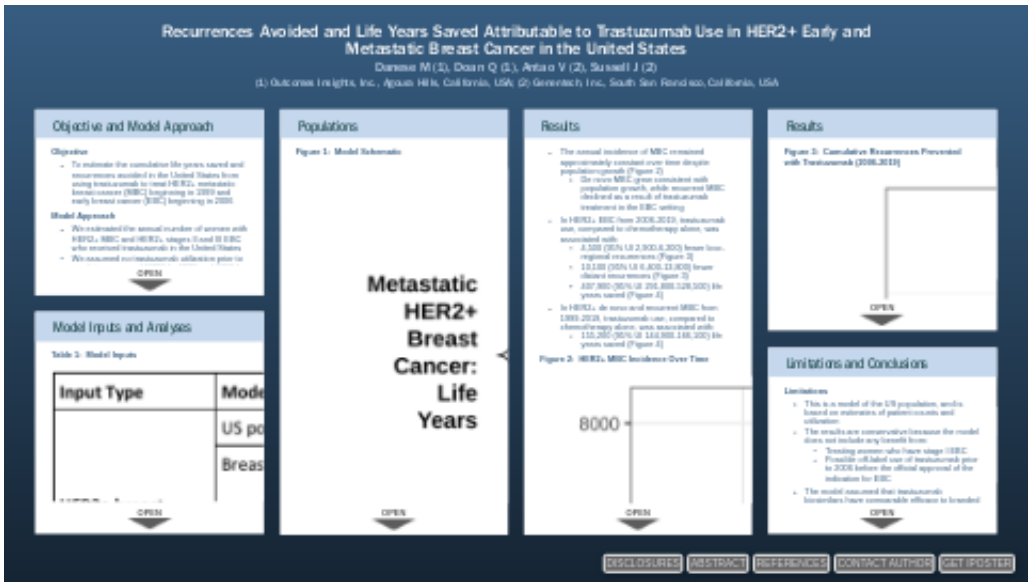
# Recurrences Avoided and Life Years Saved Attributable to Trastuzumab Use in HER2+ Early and Metastatic Breast Cancer in the United States




**Danese M (1), Doan Q (1), Antao V (2), Sussell J (2)**

**(1) Outcomes Insights, Inc., Agoura Hills, California, USA; (2) Genentech, Inc., South San Francisco, California, USA**

**PRESENTED AT:**

# OBJECTIVE AND MODEL APPROACH

**Objective**

- To estimate the cumulative life years saved and recurrences avoided in the United States from using trastuzumab to treat HER2+ metastatic breast cancer (MBC) beginning in 1999 and early breast cancer (EBC) beginning in 2006

**Model Approach**

- We estimated the annual number of women with HER2+ MBC and HER2+ stages II and III EBC who received trastuzumab in the United States
- We assumed no trastuzumab utilization prior to regulatory approval (1999 for MBC and 2006 for EBC)
  - Clinical trial use was not included in the model
- In the EBC population, patients were modeled to be at risk for recurrence for 15 years following initial diagnosis
  - Model includes recurrences from patients with EBC initially diagnosed as early as 1985
- Recurrences were counted in the model through 2019
- We estimated total life years and cumulative population-level recurrences for two scenarios:
  - Actual: Trastuzumab plus chemotherapy was used
  - Counterfactual: Trastuzumab did not exist and chemotherapy alone was used
- We compared the actual and counterfactual scenarios to estimate the life years saved and recurrences prevented attributable to the use of trastuzumab
- The model was built in R (version 3.6.3)

# MODEL INPUTS AND ANALYSES

**Table 1: Model Inputs**

| Input Type | Model Input | Description or Value | Reference |
|---|---|---|---|
| **HER2+ breast cancer population counts by calendar year** | US population counts | Ages 0-100 for 1985-2019 | US Census |
| | Breast cancer incidence rates | Ages 0-100 for 1985-2019 | SEER 18 data, released 2020 |
| | EBC HER2+ proportion | Estimated within subgroups for estrogen receptor (ER), progesterone receptor (PR), and nodal status | SEER 18 data, released 2020 |
| | MBC HER2+ proportion | Estimated within subgroups for ER and PR | SEER 18 data, released 2020 |
| **Recurrence in EBC population** | Annual rate per person-year with chemotherapy alone, node positive | Varies by year since treatment initiation from 0.098 to 0.022 | Perez, 2014 |
| | Relative rate with chemotherapy, node negative vs. node positive | 0.541 | BCIRG 006 Clinical Study Report |
| | Hazard ratios for trastuzumab vs. chemotherapy alone | 0.68 (node positive)<br>0.47 (node negative) | BCIRG 006, Slamon, 2011 |
| **Recurrence type** | Distant | 58.8% | Perez, 2014<br>Cameron, 2017 (pooled across studies) |
| | Regional | 4.2% | |
| | Local | 22.4% | |
| | All other (death or other secondary cancer) | 14.7% (not considered to be a recurrence in the model) | |
| **Survival in MBC** | Pooled across 7 trials of first-line trastuzumab vs. chemotherapy alone | Kaplan-Meier curve, varies by time since treatment initiation | Danese, 2015 |
| **Survival in locally and regionally recurrent EBC** | 5-year relative survival in local or regional EBC | Proportions by age group and stage | SEER 18 data, released 2020 |
| | US life table for females, 2009 | Probabilities by single year of age from 0-100 | National Vital Statistics Report, Volume 62, 2013 |
| **Trastuzumab utilization** | EBC trastuzumab utilization percentages | Varies by year from 57% to 87% for women under 65, modified by relative rate in older patients | Tsai, 2011<br>Reeder-Hayes, 2016 |
| | MBC utilization | Varies by year and age | Danese, 2015 |

**Probabilistic Sensitivity Analysis**

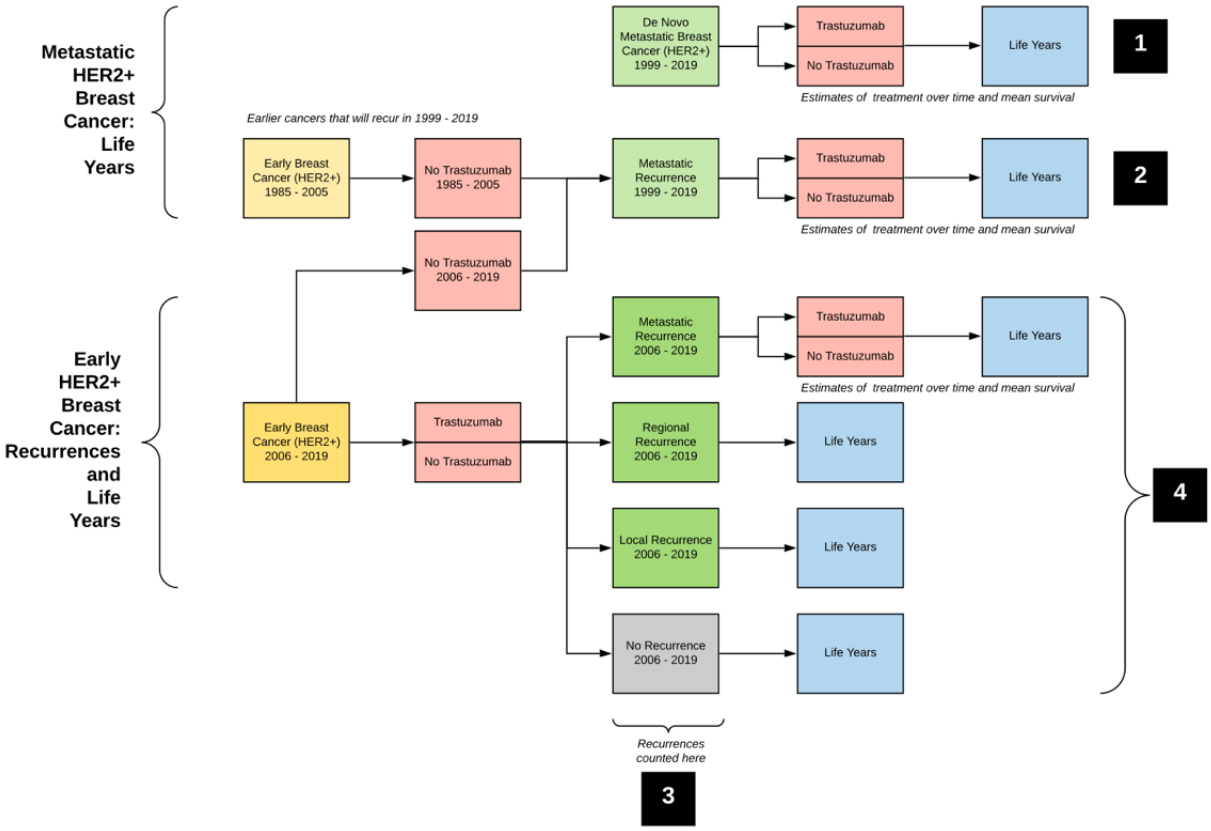
- We used a Monte Carlo process to repeatedly re-sample all inputs that had associated measures of uncertainty

and recalculated all model results using these resampled inputs. We repeated this process 500 times and used the 2.5 and 97.5 percentiles of the resulting distribution to estimate 95 percent uncertainty intervals (UIs)

- Distributions were sampled from the lognormal distribution for hazard ratios, from the Poisson distribution for rates, from the Dirichlet for contingency tables, and from the beta distribution for proportions

# POPULATIONS

**Figure 1: Model Schematic**




**MBC** (elements 1 and 2 in Figure 1)

- Women diagnosed from 1999 through 2019 with de novo MBC who received trastuzumab plus chemotherapy following their MBC diagnosis
- Women diagnosed with EBC from 1985 to 2005 who experienced distant (metastatic) recurrences between 1999 and 2019 and received trastuzumab plus chemotherapy following distant recurrence
- Women diagnosed with EBC from 2006 to 2019 who were not treated with trastuzumab for EBC, who experienced distant (metastatic) recurrences between 2006 and 2019 (i.e., after approval for EBC), and who received trastuzumab plus chemotherapy following distant recurrence

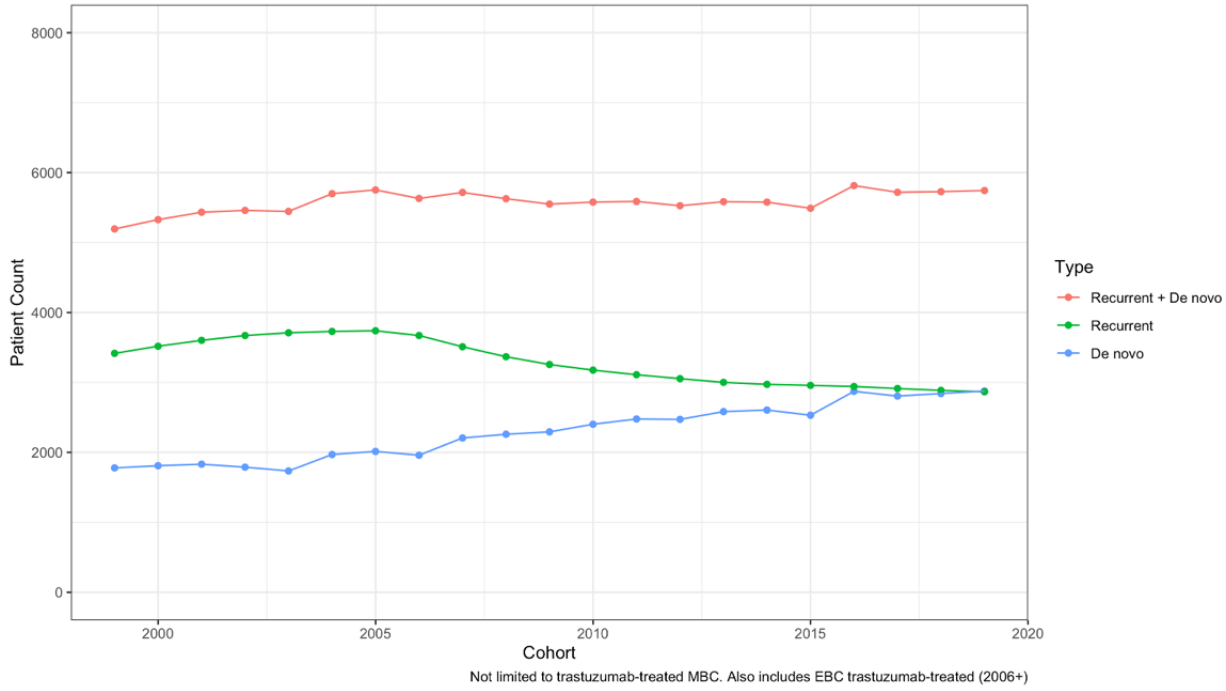
**EBC** (elements 3 and 4 in Figure 1)

- Women diagnosed with node-positive or high-risk node-negative EBC from 2006 to 2019 and received trastuzumab at the time of diagnosis
- Women with low-risk (tumor size < 2 cm) node-negative (i.e., Stage 1) cancer were excluded to align with the US prescribing information

# RESULTS

- The annual incidence of MBC remained approximately constant over time despite population growth (Figure 2)
  - De novo MBC grew consistent with population growth, while recurrent MBC declined as a result of trastuzumab treatment in the EBC setting
- In HER2+ EBC from 2006-2019, trastuzumab use, compared to chemotherapy alone, was associated with:
  - 4,500 (95% UI 2,900-6,200) fewer loco-regional recurrences (Figure 3)
  - 10,100 (95% UI 6,400-13,800) fewer distant recurrences (Figure 3)
  - 407,900 (95% UI 291,800-528,500) life years saved (Figure 4)
- In HER2+ de novo and recurrent MBC from 1999-2019, trastuzumab use, compared to chemotherapy alone, was associated with:
  - 155,200 (95% UI 144,900-166,100) life years saved (Figure 4)

**Figure 2: HER2+ MBC Incidence Over Time**



# RESULTS

**Figure 3: Cumulative Recurrences Prevented with Trastuzumab (2006-2019)**

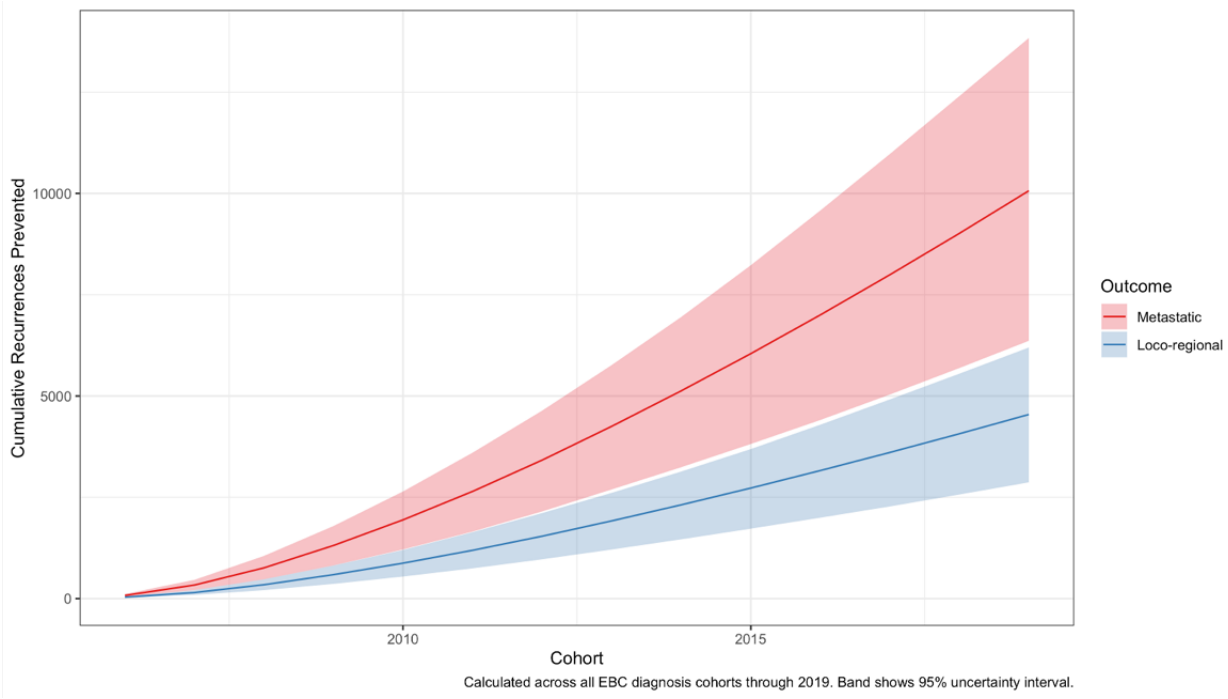
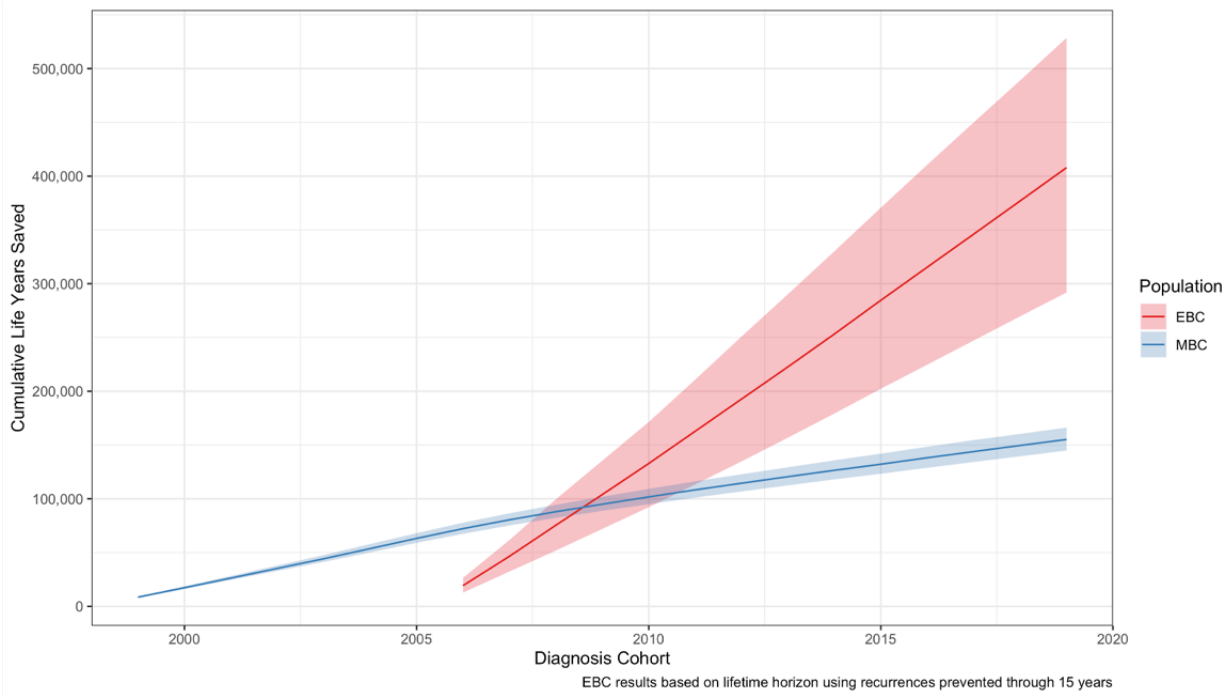



**Figure 4: Cumulative Life Years Saved with Trastuzumab in EBC and MBC**



# LIMITATIONS AND CONCLUSIONS

**Limitations**

- This is a model of the US population, and is based on estimates of patient counts and utilization
- The results are conservative because the model does not include any benefit from:
  - Treating women who have stage I EBC
  - Possible off-label use of trastuzumab prior to 2006 before the official approval of the indication for EBC
- The model assumed that trastuzumab biosimilars have comparable efficacy to branded trastuzumab (Herceptin)
- The model does not account for the incremental benefit of combination dual targeted therapy with pertuzumab, which in recent years has become standard of care in both the MBC and EBC settings

**Conclusions**

- The use of trastuzumab to treat HER2+ breast cancer has:
  - Saved a substantial number of women with EBC from recurrence
  - Extended life in women with both EBC and MBC
- Future research should consider the incremental population-level health impact of dual targeted therapy with pertuzumab in addition to trastuzumab in EBC and MBC

# DISCLOSURES

Mark Danese is an employee and owner of Outcomes Insights, Inc. Quan Doan was an employee of Outcomes Insights at the time this work was completed. Vince Antao and Jesse Sussell are employees of Genentech and own stock in F. Hoffmann-La Roche, which together are the commercial manufacturers of Herceptin. Outcomes Insights received funding from Genentech for this research.

# ABSTRACT

OBJECTIVES: We estimated the cumulative life years saved and recurrences avoided after incorporating trastuzumab as therapy for metastatic breast cancer (MBC) in 1999 and early breast cancer (EBC) in 2006 in the United States.

METHODS: We constructed a model to estimate population survival and recurrence among patients who received trastuzumab each year, and compared it to a counterfactual model in which trastuzumab treatment was not available. We incorporated US population counts, the age-, year-, and nodal status-specific incidence rates of HER2+ EBC, the age- and year-specific rates of de novo MBC, recurrence rates in HER2+ EBC, and year-specific trastuzumab utilization rates in EBC and MBC. Women with low-risk, node-negative EBC were excluded. The risk of recurrence with and without trastuzumab were based on 10-year trial data. Recurrences were estimated for 15 years after diagnosis by carrying the year 10 rate forward. Survival after local and regional recurrences was estimated using the 5-year relative survival for HER2+ EBC. In MBC, the survival estimates with and without trastuzumab were pooled across seven studies. Uncertainty intervals (UI) were estimated using Monte Carlo simulation with 500 replicates.

RESULTS: We estimate that between 2006-2019, trastuzumab use in HER2+ EBC led to the avoidance of 4,500 (95% UI 2,900-6,200) loco-regional and 10,100 (95% UI 6,400-13,800) distant recurrences. This in turn resulted in an incremental 407,900 (95% UI 291,800-528,500) life years saved compared to projected survival with chemotherapy alone. In HER2+ MBC from 1999-2019, there were 72,300 (95% UI 68,300-76,900) women with de novo or recurrent metastatic cancer treated with trastuzumab, leading to an additional 155,200 (95% UI 144,900-166,100) life years relative to projected survival with chemotherapy alone.

CONCLUSION: Trastuzumab has substantially increased the years lived, and reduced recurrences for women with HER2+ MBC and EBC in the United States.

# REFERENCES

Cameron D, et al. 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

Danese MD, et al. Estimated Life-Years Saved in Women with HER2-Positive Metastatic Breast Cancer Receiving First-Line Trastuzumab and Pertuzumab in the United States. Value Health 2015

Perez EA, et al. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014

Reeder-Hayes K, et al. Disparities in Use of Human Epidermal Growth Hormone Receptor 2-Targeted Therapy for Early-Stage Breast Cancer. J Clin Oncol 2016

Slamon D, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011

Tsai H-T, et al. Initiation of Trastuzumab by Women Younger Than 64 Years for Adjuvant Treatment of Stage I–III Breast Cancer. J Natl Compr Cancer Netw. 2017