Potential Long-Term Benefits of Extended Adjuvant Neratinib in Patients with High-Risk Hormone Receptor Positive (HR+) HER2+ Early-Stage Breast Cancer (ESBC) Following Use of T-DM1 or Pertuzumab: A Population Effectiveness Model

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Background

- The incidence of breast cancer among the US population in 2022 was approximately 300,000, with HR+ HER2+ comprising 9.5% of those cases.[1,2]
- In HER2+ ESBC, adjuvant treatment options include trastuzumab or dual HER2-blockade with pertuzumab plus trastuzumab, with or without chemotherapy depending on prior neoadjuvant therapy, and T-DM1, an antibody drug conjugate.[3]
- Neratinib (NERLYNX®) is an irreversible pan-HER tyrosine kinase inhibitor approved for the extended adjuvant treatment of patients with HER2+ ESBC following trastuzumab-based therapy, with greater benefit consistently shown in patients with HR+ disease.[4,5]
- The potential clinical benefits of extended adjuvant neratinib following adjuvant T-DM1 or dual blockade with pertuzumab + trastuzumab among the incident U.S. HR+ HER2+ high-risk ESBC patient population have not been quantified.

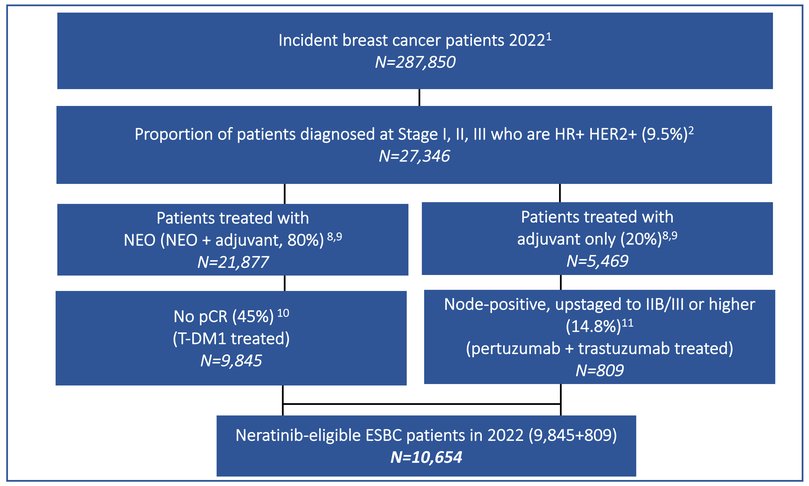
Objective

- To estimate the long-term potential treatment benefits of extended adjuvant neratinib following use of T-DM1 or pertuzumab in the U.S. high-risk HR+ HER2+ ESBC patient population.

Methods

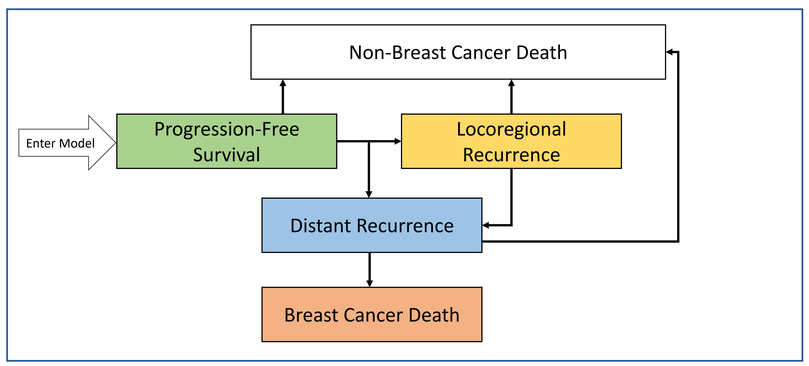
- We estimated the annual number of patients in the US with incident high-risk HR+ HER2+ ESBC in 2022 (total n = 10,654, [no pathologic complete response (no pCR) n = 9,845, upstaged adjuvant n = 809]) using data from SEER and National Cancer Database electronic registries, clinical trials, and expert clinical opinion (Figure 1).
- High risk was defined as patients with 1) HR+ disease who did not achieve pCR following neoadjuvant therapy or who were 2) HR+/node-positive, upstaged to stage IIB/III or higher following surgery and only treated adjuvantly.
- A Markov model (Figure 2) was developed to simulate the mean number of recurrences and deaths following neratinib (compared to no neratinib) over a lifetime time horizon for the estimated population of 10,654 high-risk patients.
- Invasive and distant disease-free survival (iDFS and DDFS) were extrapolated to a 10-year time horizon using parametric survival models applied to clinical trials of adjuvant T-DM1 (KATHERINE) and adjuvant pertuzumab plus trastuzumab (APHINITY).[5-7]
  - To estimate the iDFS and DDFS for T-DM1 in the HR+ population, a hazard ratio was calculated such that the KATHERINE ITT iDFS curve at 3 years matched the HR+ population 3-year iDFS.[6]
  - To estimate the iDFS and DDFS for pertuzumab in the node-positive/HR+ population, a hazard ratio was calculated such that the APHINITY node-positive iDFS curve at 6 years matched the 6-year iDFS of the node-positive/HR+ population.[7]
  - The neratinib hazard ratios from ExteNET[5] were applied to these adjusted curves.
  - The treatment effect was assumed to fade beyond the trial duration and be null after 10 years. For recurrences observed beyond 10 years, women with distant recurrences only would be at a risk of death from breast cancer using age-specific breast cancer mortality. All women were at risk of non-breast cancer mortality.
  - Model outputs were recurrences (locoregional and distant) prevented, deaths (breast cancer and non-breast cancer) avoided, and life-years gained following neratinib treatment.
- A probabilistic sensitivity analysis was performed to account for uncertainty in the model and to provide a range of results.

Figure 1: Estimated Annual Number of U.S. Neratinib-Eligible ESBC Patients in 2022



ESBC, early-stage breast cancer; HR+, hormone receptor positive; NEO, neoadjuvant; pCR, pathological complete response; T-DM1, ado-trastuzumab emtansine

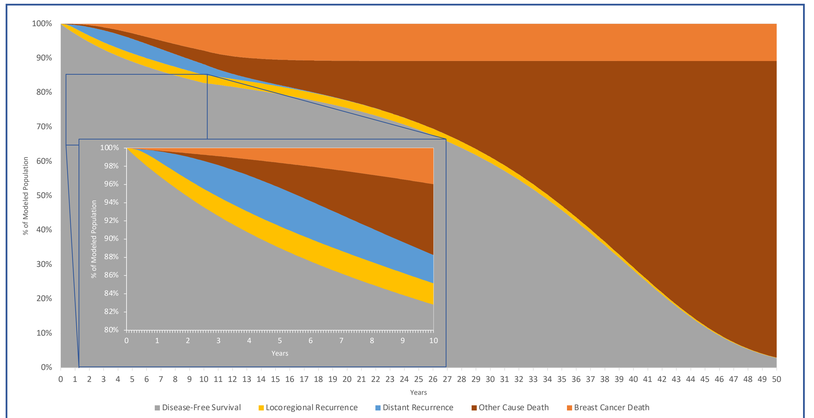
Figure 2: Population Effectiveness Model Design



Results

- Among the estimated 2022 U.S. high-risk ESBC patient cohort (n=10,654), model results estimated that over a lifetime time horizon, the use of neratinib could potentially (Table 1 and Figure 3):
  - Prevent a total of 864 recurrences, including 87 locoregional recurrences and 777 distant recurrences.
    - No pCR: prevent 79 locoregional and 742 distant recurrences
    - Node-positive, upstaged: prevent 8 locoregional and 35 distant recurrences
  - Avoid 782 (no pCR: 747; upstaged: 35) breast cancer-related deaths.
  - Result in 21,854 (no pCR: 20,885; node-positive, upstaged: 969) life-years gained.
- In the sensitivity analyses, results ranged from 590 to 959 locoregional/distant recurrences prevented, 530 to 859 breast cancer deaths avoided, and 15,597 to 23,537 life-years gained.

Figure 3: Modeled High-Risk HR+ HER2+ ESBC Population in the U.S., Neratinib Arm Only



The color-coded areas under the curve represent the percentage of patients in each model health state over time.
The inset displays details over the first 10 years of the simulation.

Table 1: Incremental Outcomes in Neratinib vs. No Neratinib Group for High-Risk HR+ HER2+ ESBC Population in the U.S. Over a Lifetime Time Horizon

Population (n=10,654)	Locoregional Recurrences Prevented (n)	Distant Recurrences Prevented (n)	Breast Cancer Deaths Avoided (n)	Life-Years Gained
No pCR (n= 9,845)	79	742	747	20,885
Node-positive, upstaged to IIB/III or higher (n= 809)	8	35	35	969
Combined (high-risk ESBC)	**87**	**777**	**782**	**21,854**

ESBC, early-stage breast cancer; pCR, pathological complete response

Conclusions

- Our model suggests that treatment with extended adjuvant neratinib may substantially reduce locoregional/distant recurrences and deaths in the high-risk HR+ HER2+ ESBC population in the U.S.

References

1. SEER Cancer Stat Facts: Female Breast Cancer. Available from: https://seer.cancer.gov/statfacts/html/breast.html [Also available from: Siegel RL et al. Cancer Statistics, CA CANCER J CLIN 2022].
2. Howlader N, Altekruse SF, Li CI, et al. *J Natl Cancer Inst*. 2014;106(5):dju055.
3. National Comprehensive Cancer Network. (2021). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 4.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
4. Neratinib. Prescribing information. Puma Biotechnology. Accessed October 28, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf.
5. Chan A, Moy B, Mansi J, et al. *Clin Breast Cancer*. 2021;21(1):80-91.e7.
6. von Minckwitz G, Procter M, de Azambuja E, et al. *N Engl J Med* 2017;377:122–31. Erratum in: N Engl J Med 2018;379:1585.
7. von Minckwitz G, Huang CS, Mano MS, et al. *N Engl J Med* 2019;380:617–28.
8. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. *Ann Surg Oncol*. 2018;25(8):2241-2248.
9. Personal correspondence A. Brufsky, MD September 9, 2022.
10. Hurvitz SA, Martin M, Symmans WF, et al. *Lancet Oncol*. 2018;19(1):115–126.
11. Hills, N., Leslie, M., Davis, R., et al. *Ann Surg Oncol.* 2021;28(11): 5895–5905.

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