

Clinical and Economic Burden of HER2-Positive Breast Cancer Recurrence in the US: A Literature Review

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Background

- Among women worldwide, breast cancer (BC) is the most commonly occurring malignancy (estimated 1,676,600 new cases in 2012) and the leading cause of cancer mortality (estimated 521,900 deaths in 2012).¹
- Although there is wide international variability in stage distribution at diagnosis, > 75% of incident BCs in developed countries are early stage (I or II).¹
- Approximately 15% of all invasive breast cancers with known subtype are HER2+.²
- Despite available treatment, 15%-25% of patients with early stage Human epidermal growth factor receptor 2-positive (HER2+) BC eventually experience recurrence after initial treatment.³⁻⁴
- Most recurrences involve incurable metastatic disease.^{2,4,5}
- The prognosis for women with BC recurrence is poor and associated with significant morbidity, mortality, and cost.⁶
- In the United States (US), the total cost to society attributable to metastatic BC was \$12.2 billion accrued over 5 years, or \$2.4 billion per year (\$98,571 per patient-year).⁷
- Treatment-related cost, 57% of total costs, was the largest contribution, with more than \$1.0 billion per year.⁷
- A recently published cost study estimated the mean total health care cost per patient to be \$168,248 in the first 12 months and cumulative mean costs to be \$262,538 over 24 months and \$310,589 over 36 months.⁸
- HER2+ BCs represent a distinct subgroup that are amenable to treatment with HER2-directed therapies.
- Limited published data are available on the clinical and economic burden of HER2+ BC recurrence.

Objective

- The purpose of this study was to assess the clinical and economic burden of recurrence in patients with early stage HER2+ BC.

Methods

- A clinical and economic systematic literature review (SLR) and a burden-of-illness (BOI) targeted literature review (TLR) were conducted in PubMed, Embase, and Cochrane databases.

The clinical SLR did not have a publication date limit and was conducted on November 8, 2016. It searched randomized clinical trials of neratinib and other treatments.

The economic SLR did not have a publication date limit and was conducted on October 25, 2016. It searched for economic data such as models, utility weights, resource use, and cost.

The BOI TLR searched for publications published from January 2006 to September 2016 to identify additional studies in early stage HER2+ BC.

- Conference abstracts for 2015 and 2016 from six scientific meetings also were searched:

- American Society of Clinical Oncology (ASCO)
- San Antonio Breast Cancer Symposium (SABCS)
- European Society for Medical Oncology (ESMO)
- European Breast Cancer Conference (EBCC)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- St. Gallen International Breast Cancer Conference (SG-BCC)

- Examples of search terms used for all three literature reviews included:

- Disease-specific terms, such as "breast neoplasms"[Mesh] OR breast neoplasm*[Text Word] OR breast cancer*[Text Word] OR breast carcinoma*[Text Word] OR breast tumor*[Text Word] OR mammary cancer*[Text Word] OR mammary carcinoma*[Text Word] OR mammary neoplasm*[Text Word]

- Various terms to identify the specific HER2+ patient population, such as ("Receptor, ErbB-2"[Mesh] OR erbB-2[Text Word] OR erbB2[Text Word] OR erbB 2[Text Word] OR "human epidermal growth factor receptor 2"[Text Word] OR (oncogene[Text Word] AND neu[Text Word]) OR HER2[Text Word] OR HER-2[Text Word] OR HER 2[Text Word] AND adjuvant[Text Word])
- ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] AND recur[Title] OR "Quality of Life"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Patient Measurement"[Mesh] OR "Caregivers"[Mesh] OR "Patient Outcome Assessment"[Mesh] OR "Health Status Indicators"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Personal Autonomy"[Mesh] OR "Self Care"[Mesh] OR "quality of life"[Title] OR "QoL"[Text Word] OR "hrqol"[Text Word] OR "hrql"[Text Word])
- "Breast Neoplasms/ economics"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Economics"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Health Resources/Utilization"[Mesh] OR "Fees and Charges"[Mesh] OR "Employment"[Mesh] OR "Work"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Care Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Absenteeism"[Mesh] OR "Presenteeism"[Mesh] OR "Sick Leave"[Mesh] OR "Return to Work"[Mesh] OR "Hospitalization"[Mesh] OR "Budgets"[Mesh] OR "Recurrence/ economics"[Mesh] OR "Neoplasm Recurrence, Local/economics"[Mesh]

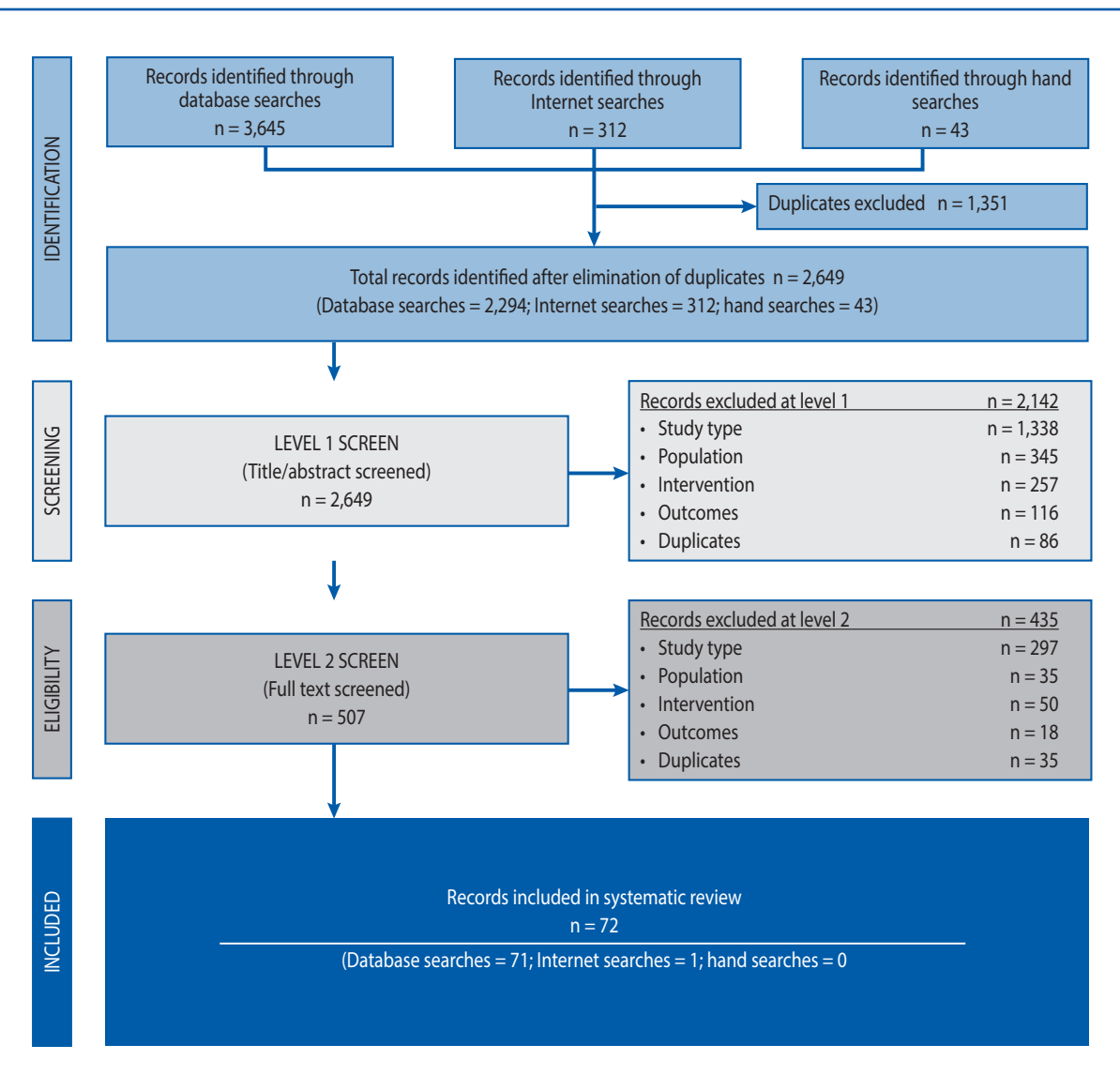
- Based on the literature review, different methods were implemented when screening titles and abstracts according to predefined inclusion and exclusion criteria. The inclusion and exclusion criteria are available upon request.

- The clinical SLR was screened by two reviewers for both level 1 and level 2, and a consensus meeting occurred upon disagreement of the inclusion/exclusion decision.
- The economic SLR was screened by an independent reviewer, and 10% was checked by a second reviewer.
- The BOI TLR was screened by an independent reviewer.

Results

- A total of 4,708 abstracts (2,649 clinical SLR, 969 economic SLR, 1,090 TLR) were identified from all searches, and full-text review was conducted for 796 articles (507 clinical SLR, 151 economic SLR, 138 TLR). Of these, 159 (72 clinical SLR, 33 economic SLR, 54 TLR) followed protocol-specified criteria for inclusion.

Figure 1. Clinical SLR PRISMA Flowchart

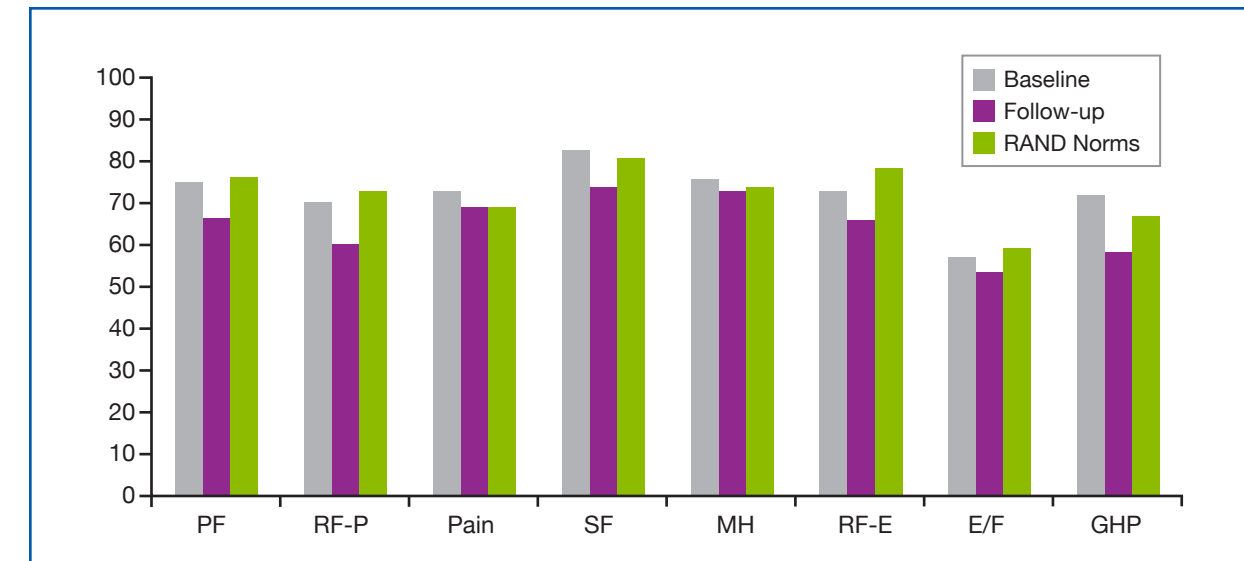


- The clinical and economic SLR Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts are presented in Figure 1 and Figure 2. A PRISMA flowchart was not developed for the BOI TLR.

Clinical Burden

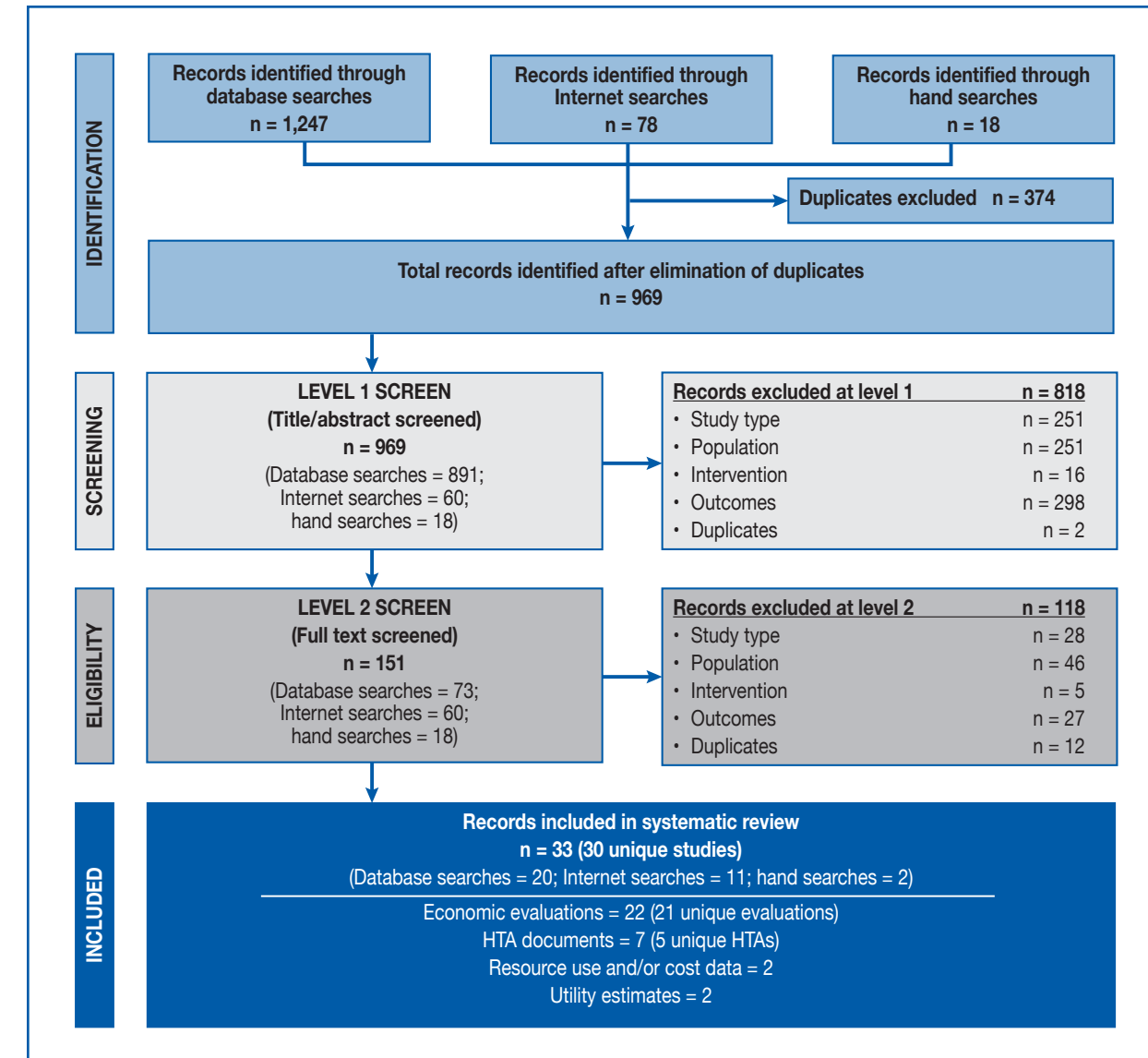
- The clinical studies related to the clinical burden, invasive disease-free survival (iDFS), or disease-free survival (DFS) of BC recurrence included patients with early stage HER2+BC. However, clinical studies related to the quality of life (QOL) of BC recurrence included patients with early stage BC, regardless of HER2 status.
- Four clinical trials related to the clinical burden of HER2+ BC recurrence were identified from the literature reviews.^{3,9-11}
 - Based on clinical trials in the adjuvant setting, DFS rates at 4 years ranged from 78% to 90% (Table 1).^{3,10-12}
- HER2-targeting adjuvant regimens such as adding lapatinib to trastuzumab and extending trastuzumab to 2 years have been unsuccessful in reducing the risk of recurrence.^{9,11}
- Two clinical studies related to the QOL of BC recurrence, regardless of HER2 status, were identified from the literature reviews.^{13,14}
- Women who had a recurrence, regardless of HER2 status, reported significantly poorer functioning on various QOL domains compared with women who remained disease-free (Figure 3).¹⁵

Figure 3. RAND SF-36 Baseline and Follow-up Scores for Survivors of Recurrent BC Compared to Norms¹⁵



Note: RAND SF-36 is also known as the Medical Outcomes Study SF-36. Physical functioning = PF; Role functioning-Physical = RF-P; Social functioning = SF; Mental health = MH; Role functioning-Emotional = RF-E; Energy/fatigue = E/F; General health perceptions = GHP.

Figure 2. Economic SLR PRISMA Flowchart



HTA = health technology assessment.

- Reported differences between women who had a recurrence compared to women who remained disease-free were largely due to the poorer QOL of women with metastatic disease.¹⁴

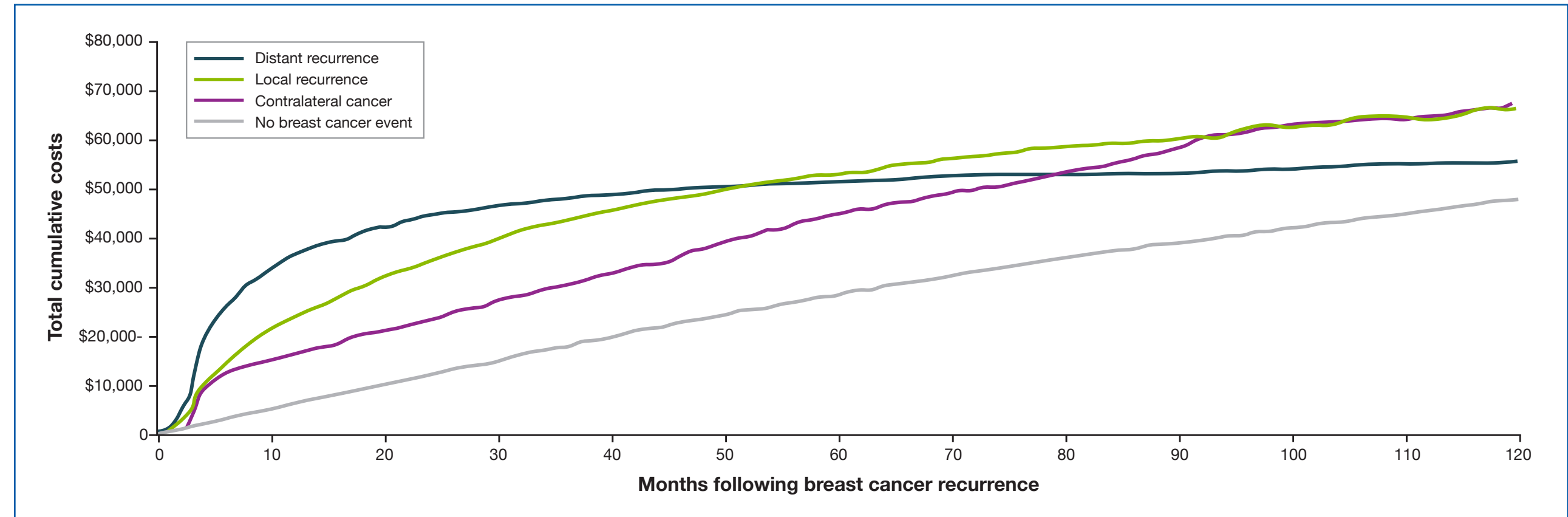
- All patients with early stage BC, regardless of HER2 status, diagnosed with their first recurrence experienced cancer-related distress and no improvement in QOL (physical health and functioning) after 1 year.¹⁶

Table 1. Key Efficacy Endpoints in iDFS or DFS

Trial Number (Acronym)	Subgroup	Treatment	iDFS or DFS Rate, Median (95% CI)	Effect Size (95% CI)
ALTO Piccart-Gebhart, Holmes ¹¹	Overall ITT population	Lapatinib + trastuzumab (concurrent) (n = 2,093)	DFS rate: 88% (NR)	Hazard ratio: 0.84 (0.70-1.02)
		Trastuzumab → lapatinib (sequential) (n = 2,091)	DFS rate: 88% (NR)	Hazard ratio: 0.96 (0.80-1.15)
	HR+	Trastuzumab (n = 2,097)	DFS rate: 87% (NR)	Ref
		Lapatinib (n = 2,100)	DFS rate: 82% (NR)	Hazard ratio: 1.34 (1.13-1.60)
BCIRG 006 Slamon, Eiermann ¹² Au, Eiermann ¹⁵	Overall	Lapatinib + trastuzumab (concurrent) (n = 1,203)	DFS rate: 90% (NR)	Hazard ratio: 0.87 (0.62-1.13) (97.5% CI)
		Trastuzumab (n = 1,200)	DFS rate: 88% (NR)	Ref
	HR-	Lapatinib + trastuzumab (concurrent) (n = 890)	DFS rate: 86% (NR)	Hazard ratio: 0.82 (0.62-1.08) (97.5% CI)
		Trastuzumab (n = 897)	DFS rate: 83% (NR)	Ref
HERA ⁹	Overall, ITT	AC-T (n = 1,073)	DFS rate: 78% (NR)	NR
		AC-TH + trastuzumab (n = 1,074)	DFS rate: 86% (NR)	NR
	TCH (n = 1,075)	DFS rate: 84% (NR)	NR	
TEACH Goss, Smith ¹⁰ Boyle, Smith ¹³	Overall	Lapatinib	210 events (13%)	Hazard ratio: 0.83 (0.70-1.00) P = 0.053
	Observation (n = 1,697)	DFS rate: 72.2% (NR)	Ref	
HERA ⁹	Overall, ITT	1 year of trastuzumab (n = 1,702)	369 events DFS rate: 78.6% (NR)	Hazard ratio: 0.76 (0.66-0.87)
		Observation (n = 1,697)	DFS rate: 72.2% (NR)	Ref
	HR+	Lapatinib	DFS rate: 83.1% (NR)	Hazard ratio: 0.98 (0.77-1.25) P = 0.89
		Placebo	264 events (17%)	Ref
HR-	Lapatinib	DFS rate: 84.0% (NR)	Hazard ratio: 0.68 (0.52-0.89) P = 0.006	
	Placebo	DFS rate: 77.7% (NR)	Ref	

ACT-T = doxorubicin plus cyclophosphamide for four cycles followed by docetaxel for four cycles; AC-TH = doxorubicin plus cyclophosphamide for four cycles followed by docetaxel with trastuzumab for 1 year; CI = confidence interval; ITT = intent to treat; NR = not reported; TCH = docetaxel plus carboplatin for six cycles with trastuzumab for 1 year.

Figure 4. Cumulative Medical-Care Costs Attributable to BC Recurrent Over 10 Years⁸



Economic Burden

- Two studies related to the economic burden of BC recurrence were identified from the literature reviews.^{6,17}
- In the US, the total expected per-patient costs for all BC, regardless of HER2 status, over 10 years was \$53,454 with metastatic recurrence, \$61,601 with locoregional recurrence, and \$61,188 with contralateral recurrence compared with \$42,005 (background costs) with no recurrence (2004 US \$) (Figure 4).⁸
- The overall cost of recurrence in women with HER2+ BC in the US was estimated to be \$240 million to \$1.7 billion over the lifetimes of each 1-year cohort of 7,298 patients (2008 US \$).¹⁷
 - Table 2 presents the annual cost of HER2+ BC recurrence by age group. Including the cost of death, the total recurrence cost was largest in the 30- to 49-year-old age group.¹⁶

Table 2. Annual Cost of HER2-Positive BC Recurrence (2008 US Dollars)

Recurrence Cost	Age 30-49 Years, No. (95% CI)	Age 50-69 Years, No. (95% CI)	Age ≥ 70 Years, No. (95% CI)
Excluding lost productivity (death)			
Per patient (thousands)	\$77 (\$47-\$152)	\$107 (\$59-\$227)	\$35 (\$30-\$46)
Total cost (millions)	\$53 (\$24-\$114)	\$144 (\$61-\$330)	\$27 (\$14-\$40)
Including lost productivity (death)			
Per patient (thousands)	\$1,458 (\$706-\$2,694)	\$427 (\$194-\$844)	\$119 (\$102-\$139)
Total cost (millions)	\$1,009 (\$399-\$2,008)	\$575 (\$217-\$1,233)	\$89 (\$50-\$132)

Values in parentheses reflect the middle 95% of the empirical distribution (95% CI). Source: Danese, Lalla¹⁶

Conclusions

- This search identified few studies on patients with early stage HER2+ BC and suggest that future studies are warranted.
- After adjuvant therapy, the 10-year risk of recurrence can be up to 22%. The clinical and economic burden of early stage HER2+ BC remains substantial.
- Recurrence in women with BC, regardless of HER2 status, is associated with high costs and a likelihood of decreased QOL.
- Therefore, there is an unmet medical need in early stage HER2+ BC for new therapies that can reduce the risk of recurrence and the consequent clinical and economic burden of advanced disease.
- Economic studies on the cost of recurrence should be conducted given the higher cost of recently approved HER2+ targeted therapies in the metastatic setting.

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