**Trastuzumab uptake in HER2-positive breast cancer patients: a systematic review and meta-analysis of observational studies**

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## Abstract

Overexpression of the HER2 gene is predictive of treatment benefit with trastuzumab therapy for breast cancer (BC) patients. The study objective was to investigate whether all eligible patients with HER2-positive BC initiated trastuzumab therapy.A systematic search was conducted through PubMed, Web of Science PsycINFO**,** Cumulative Index to Nursing and Allied Health Literature(CINAHL) and Cochrane Library. From 2651 studies identified, 107 observational studies were included for full text review, of which 26 met the inclusion criteria and an additional 7 studies were identified through citation searching. Two independent reviewers extracted data for accuracy and completeness.

From33 observational studies, 14,644 patients were exposed to trastuzumab therapy.Age range varied across studies; the youngest cohort had a median age of 50 and the oldest had a median age of 84. Sample sizes ranged from 11 to 1928 and included patients from 10 countries. Studies were heterogenous and few studies accounted for confounders. We identified large variability in uptake of trastuzumab in HER2-positive early BC patients (9.1-100%) and metastatic BC patients (50.8-84.0%). The pooled uptake was 71.3% (95% CI 64.6-77.9%), with high heterogeneity (I2=99.05%). The most conservative predictors of higher uptake included younger age (OR 2.09; 95% CI 1.36-3.20) and lower Charlson Comorbidity Index of patients (OR 1.62; 95% CI 1.32-1.99). In addition, tumour characteristics including higher tumor grade (OR 1.73; 95% CI 1.23-2.45), larger tumor size (OR 1.80; 95% CI 1.54-2.10), advanced tumor stage (OR 2.07; 95% CI 1.44-2.96) and hormone receptor negative tumor (OR 1.54; 95% CI 1.35-1.77) were associated with higher uptake.

The uptake of trastuzumab therapy varied widely between studies and across subgroups suggesting that there may be some inequalities in the use of this agent. However, our findings should be interpreted with caution due to study heterogeneity and potential confounding, and thus additional studies of individual level data which control for confounders are needed to understand more about inequalities in uptake.

**Registration:** Systematic review protocol was registered with PROSPERO, identification number: CRD42017073218

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## Introduction

Trastuzumab (Herceptin) is a monoclonal antibody which targets the extracellular domain of the HER2 receptor and acts by different mechanisms to inhibit cell growth by prevention of HER2 dimerization, downregulation of the HER2 receptor by endocytic destruction of the receptor, accumulation of the cyclin-dependent kinase (CDK) inhibitor p27 and cell cycle arrest, induction of antibody-dependent cellular cytotoxicity, and inhibition of constitutive HER2 cleavage/shedding mediated by metalloproteases.1 Over-expression of the human epidermal growth factor receptor 2 (HER2) is seen in approximately 15-30% of breast cancers in women and is of both prognostic value and predictive of treatment benefit.2,3 Indeed, trastuzumab therapy has revolutionized the treatment of HER2-positive disease in both adjuvant2,4–7 and metastatic settings.3

Since approval for use by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), trastuzumab targeted therapy has been rapidly adopted for use.8 The American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommend testing every primary invasive breast cancer to guide HER2-targeted therapy.9,10 Trastuzumab therapy is widely considered a highly effective treatment with a favorable benefit/risk profile with gains in overall survival.11,12 Despite concern of a relatively high acquisition cost, trastuzumab therapy in HER2 positive breast cancer patients was widely found to be a cost-effective oncology therapy across payers within developed countries.11–13 However, little is known about inequalities in the implementation of targeted trastuzumab therapy in clinical practice.8

By 2030, the global rate of women diagnosed with breast cancer is predicted to increase to 3.2 million per year. The economic cost of cancer is estimated to be up to 4% of global GDP and improvements in both treatments and reductions in health disparities provide an opportunity to deliver significant economic benefits.14 Since 2012, the recorded incidence of breast cancer in the USA has converged between black and white women,15 but substantial racial disparities have previously been identified in the stage of diagnosis, treatment patterns and mortality rate.16,17 The objective of this systematic review was to investigate whether all eligible patients with HER2-positive breast cancer initiated trastuzumab therapy.

## Methods

The systematic review protocol was registered with PROSPERO, the international database of prospectively registered systematic reviews (identification number CRD42017073218), conducted according to the Centre for Reviews and Dissemination’s guidance for undertaking reviews in healthcare 18 and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis with a focus on health equity (PRISMA-E) guidelines.19

### Data Sources and Searches

A systematic search of PubMed, Web of Science, PsychINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methods search was conducted to July 2017. The search terms consisted of two clauses combined with the Boolean ‘AND’ operator. Filters were applied to restrict studies to human subjects and English-language. Further articles were identified from searching reference lists of included studies and forward citation searching using Google Scholar. In addition, grey literature was searched by applying a combination of the search terms from the original search using Google Scholar. The full search strategy is detailed in Supplementary Table 4 in Appendix 1.

### Study Selection

Prospective and retrospective observational studies, case-control and cross-sectional studies were included if they assessed the uptake of trastuzumab therapy in eligible HER2-positive early breast cancer or metastatic breast cancer adult patients (>16 years). The review included studies which measured outcomes directly and indirectly (e.g. self-reported).

Studies were excluded if patients were HER2-negative or where information on uptake of trastuzumab therapy was absent. Studies which examined time to initiation, duration and completion of trastuzumab therapy were beyond the scope of this review. We excluded editorials, letters, historical articles, reviews and abstracts published before 2010. As no evidence of a systematic bias exists from the use of English-language restrictions in systematic review-based meta-analyses in conventional medicine, this review included only peer-reviewed, English-language publications.20 The evidence appraisal was conducted in the context of clinical guidelines from developed countries; however evidence from developing countries was also included. Further information about our inclusion criteria is provided in Supplementary Table 5 in Appendix 2.

### Data Extraction and Quality Assessment

Search results from databases were combined and duplicates removed. Titles and abstracts were screened to determine whether they met the pre-specified inclusion criteria by one reviewer (AM) and 10% were double screened by a second independent reviewer (MC). Full texts were retrieved where reviewers agreed that the article met the inclusion criteria (95.6% agreement) and consensus was reached. After determining article inclusion, one reviewer entered study data into evidence tables (AM); a second reviewer (JD) checked 30% of data extracted for accuracy and completeness.

Data were extracted on the following study characteristics: year of publication, study type, setting, sample population, source of information, study period, cancer status, rate of trastuzumab initiation, and reported clinical, psychosocial and sociodemographic factors. The quality of evidence was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies.21 The pre-defined quality assessment criteria include six components: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, and global rating. With any study where the inclusion or data quality was unclear, the study was discussed with up to two additional reviewers (MC and JD).

### Data Synthesis and Analysis

Results are presented as summaries of individual studies. Data presented includes study type, country, age of participants, study duration, source of information, cancer status of participants and the proportion of trastuzumab uptake. In addition, a summary of associations between reported clinical, psychosocial and sociodemographic factors and uptake of trastuzumab is presented. Each association was classified as tested and statistically significant in multivariable analyses, or tested and significant in univariable analyses, or tested and not significant.

For each study, the reported proportions of patients who received or did not receive trastuzumab were included in a meta-analysis of pooled uptake. The initiation of trastuzumab therapy was largely defined as the receipt of trastuzumab therapy within one year of diagnosis. Forest plots of pooled data were prepared with RevMan V5.3 (RevMan, 2014) using the Mantel-Haenszel method and assuming a random effects model to account for heterogeneity between studies. The extent of heterogeneity was examined using visual inspection of data, clinical aspects, methodological aspects and the Higgin’s I2 statistic.22 Approximately, heterogeneity was classified as low, moderate and high with an I2 of 25%, 50% and 75%.23 In addition, the non-parametric Cochran’s Q test assessed statistical differences in proportions of uptake by matched sets. The weighted mean estimate from each study was used and 95% confidence intervals (95% CI) were calculated using normal approximation.

The uptake of trastuzumab therapy were pooled by the geographical location of each individual study and due to large variability in uptake by country, studies were grouped by continent. Meta-analyses were also conducted where the proportion of uptake were classified by subgroup of clinical, psychosocial or sociodemographic factor. Clinical factors included tumour stage, tumour grade, tumour size, lymph node spread, hormone receptor status, number of comorbidities, cardiovascular events, surgery type and year of diagnosis. Psychosocial factors included the interrelation of social factors and patient behavior. Sociodemographic factors included education level, socioeconomic status, employment, insurance coverage, marital status, age, race/ethnicity and geography.

## Results

### Study Selection and Characteristics

Following removal of duplicates, a total of 2651 papers were identified by the search of electronic databases. A total of 107 observational studies, of which 26 met the inclusion criteria for the review and 7 additional articles were identified from a search of reference lists and citations searching which resulted in 33 studies which met the inclusion criteria. The review flow diagram and reasons for exclusion are presented in Figure 1 and the details of included studies are summarized in Table 1.

Studies comprised a variety of observational research designs including retrospective cohort studies (n = 26),24–49 prospective cohort studies (n = 3),50–52 audits (n = 2),53,54 and cross-sectional surveys (n = 2).55,56 The results of each study quality assessment is outlined in Appendix 3 in Supplementary Table 6. Few studies failed to meet a moderate score on one or more items of the EPHPP quality assessment checklist for quantitative studies and none of the studies which met the inclusion criteria were deemed ineligible for inclusion following quality assessment. Seven studies received strong global ratings.33,40,42,46,47,51 Over half of the studies received moderate global ratings based on confounders (e.g. control of confounders not well described),27,28,30–32,34,35,37,39,41,43–45,48–50,53,54 withdrawals and dropouts (e.g. did not report the number of participants who withdrew, dropped out, or completed the study),26,38 and selection bias.25 The remaining studies received weak global ratings due to low scores on study design due to the use of cross-sectional surveys,55,56 and limited sample size may have precluded controlling for confounders.24,29,36 Overall, the quality rating for the 33 reviewed studies was moderate largely due to the features of observational study design and limited control of confounders in the analyses. Two of the included studies were part of the registHER study,51,52 a large prospective, multicenter, US based cohort study which described the natural history of disease and treatment patterns for patients with HER2-positive metastatic breast cancer. Data from both studies were included in the results, and there is likely to be some data duplication.31,32 Similarly, data were included in our analysis from three studies that used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database but covered different time periods, with some overlap, and assessed different outcomes.42,45,47

Sample size of studies ranged from 1129 to 1928.37 Studies were from identified from 10 different countries, including 14 from the USA,25,27,29–33,38,42,45–47,51,52 five from the Netherlands,26,35,37,43,44 four from the UK,28,40,48,53 three from Australia34,50 and one also from New Zealand,54 two from Canada,39,49 two from Germany,41,56 one from China,36one from India24 and one from Mexico.55 Age was variably reported, but the lowest recorded was a median of 50 years24 and the highest was a median of 84 years.29

### Uptake of trastuzumab therapy for breast cancer

From33 observational studies, 14,644 patients were exposed to trastuzumab therapy. Uptake of trastuzumab therapy was defined as the initiation of trastuzumab therapy following diagnosis within the study period. A large variability in uptake of trastuzumab in HER2-positive early breast cancer patients (9.1-100%) and metastatic breast cancer patients (50.8-84.0%) was identified. The pooled uptake estimate was 71.3% (95% CI 64.6-77.9), with high heterogeneity between studies (I2=99.05%, P<0.001) (Figure 2). Due to large variability in study location, studies were grouped by continent and the pooled uptake of trastuzumab was found to be higher in Australia/Oceana with 93.7% (95% CI 89.5-97.9%), followed by Europe (75.4%; 95% CI 70.0-80.8%) and North America (69.6%; 95% CI 59.7-79.5%), with the lowest uptake in Asia based on two studies (39.1%; 95% CI 34.9-43.3%) (P<0.001).

### Subgroup analyses

As presented in Table 2, 21 studies tested in univariate or multivariate analyses at least one factor associated with initiation of trastuzumab and these were categorized as clinical, psychosocial or sociodemographic. Subgroup analyses of clinical factors included advanced tumour stage, tumour grade, tumour size, lymph node involvement, Charlson Comorbidity Index (CCI) score and hormone receptor status. Given an absence of evidence, subgroup analyses of psychosocial factors was precluded. Subgroup analyses of socioeconomic factors included: age, ethnicity, education, socioeconomic status, marital status and geography. Associations between trastuzumab initiation and predictors identified are summarized in Table 3.

**Tumour stage**

Overall, 9 studies24,25,30,33,34,38,46–48 reported data facilitating comparison of trastuzumab initiation by tumour stage. The pooled estimate of patients with stage ≥II in comparison to stage I, indicated on average higher initiation of trastuzumab with more advanced tumour stage, although there was high evidence of heterogeneity between studies (combined OR 3.55, 95% CI: 2.41-5.23, P<0.00001, I2=76%). However all eight studies which compared trastuzumab initiation between stage ≥II and stage I indicated that patients with more advanced tumour stage had a higher odds of trastuzumab initiation.24,25,30,33,38,46–48 The pooled estimate of patients with stage ≥III in comparison to stage I-II also indicated higher initiation by more advanced tumour stage with moderate heterogeneity between studies (combined OR 2.07, 95% CI: 1.44-2.96, P<0.0001), I2=54%) (SupplementalFigure 3). Of eight studies, four indicated that more advanced tumour stage had a higher odds of initiation30,46–48 and four were equivocal.24,25,33,38

**Tumour grade**

There were 10 studies30,34,38–40,42,43,46,48,57 that reported trastuzumab initiation by tumour grade. The pooled estimate of patients with grade ≥2 in comparison to grade 1, indicated higher trastuzumab initiation by higher tumour grade. However, there was moderate evidence of heterogeneity between studies (combined OR 2.55, 95% CI:1.53-4.25, P=0.0003, I2=63%). Of eight studies, four studies38,42,46,47 indicated that patients with grade ≥1 in comparison to grade 1 had a higher odds of initiation by higher grade and four were equivocal.39,40,43,48 The pooled estimate of patients with grade ≥3 and grade ≤2, also indicated higher uptake by higher tumour grade with high heterogeneity between studies (combined OR 1.73, 95% CI: 1.23-2.47, P<0.00001, I2=81%) (Supplemental Figure 4). Of eight studies comparing trastuzumab initiation between grade ≥3 and grade ≤2, four indicated higher odds of initiation by higher grade30,46–48 and four were equivocal.38,40,43,58

**Tumour size**

There were 9 studies39,40,42–44,46–48,54 that reported trastuzumab initiation by tumour size. The pooled estimate of patients with tumour size ≥1cm in comparison to <1cm, indicated higher trastuzumab initiation by larger tumour size. There was no evidence of heterogeneity between studies (combined OR 3.16, 95% CI:2.43-4.11, P<0.00001, I2=0%). Of two studies comparing trastuzumab initiation between tumour size ≥1cm and to <1cm, one indicated a higher odds of initiation by larger tumour54 and one was equivocal.48 The pooled estimate of patients with tumour size ≥2cm in comparison to <2cm indicated higher trastuzumab initiation by larger tumour size. There was no evidence of heterogeneity between studies (combined OR 2.02, 95% CI:1.76-2.32, P<0.00001, I2=0%). Of seven studies comparing trastuzumab initiation between tumour size ≥2cm and to <2cm, four indicated a higher odds of initiation by larger tumour40,42,46,47 and three were equivocal.39,43,44 The pooled estimate of patients with tumour size ≥3cm in comparison to <3cm also indicated higher initiation by larger tumour size (combined OR 1.80, 95% CI: 1.54-2.10, P<0.00001, I2=0%)) with no evidence of heterogeneity between studies (Supplemental Figure 5). Of six studies comparing trastuzumab initiation between tumour size ≥3cm and to <3cm, four indicated a higher odds of initiation by larger tumour40,42,46,47 and two were equivocal.43,44

**Lymph node**

There were 7 studies38–40,42,43,46,47 that reported trastuzumab initiation by tumour lymph node status. The pooled estimate of patients with node positive in comparison to node negative was not significant (combined OR 1.63, 95% CI: 0.95-2.80, P=0.08, I2=90%) with high evidence of heterogeneity between studies (Supplemental Figure 6). Of seven studies comparing trastuzumab initiation between node positive and negative, four indicated a higher odds of initiation in lymph node positive patients40,42,43,46 and three were equivocal.38,39,47

**Hormone receptor status**

There were 12 studies24,25,30,33,38–40,42,43,46–48 that reported trastuzumab initiation by hormone receptor (HR) status (including estrogen receptor (ER) and progesterone receptor (PR). The pooled estimate of patients with HR negative status in comparison to positive, indicated higher trastuzumab initiation in patients with HR negative status (combined OR 1.55, 95% CI:1.35-1.78, P<0.00001, I2=65%) with moderate heterogeneity between studies. Of nine studies comparing trastuzumab initiation between HR status, four indicated a higher odds of initiation in HR negative,30,42,46,47 and five were equivocal.25,38,40,43,48 The pooled estimate of patients with ER negative status in comparison to positive was not significant (combined OR 1.05, 95% CI:0.74-1.50, P=0.78, I2=14%) with minimal evidence of heterogeneity between studies. Of five studies comparing trastuzumab initiation between ER status, all five were equivoval.24,25,33,39,40 The pooled estimate of patients with PR negative status in comparison to positive was not significant (combined OR 0.79, 95% CI:0.44-1.42, P=0.44, I2=0%) with no evidence of heterogeneity between studies (Supplemental Figure 7). Of two studies comparing trastuzumab initiation between PR status, both were equivocal.25,40

**Comorbidities**

There were 6 studies30,33,38,42,43,47 that reported trastuzumab initiation by CCI score. The pooled estimate of patients with CCI =0 in comparison to >0, indicated higher trastuzumab initiation by patients with a lower CCI score with moderate evidence of heterogeneity between studies (combined OR 1.62, 95% CI:1.32-1.99, P<0.00001, I2=29%). Of six studies comparing trastuzumab initiation between CCI =0 and >0, three indicated higher odds of initiation in patients with a CCI score equal to zero30,42,43 and three were equivocal.33,38,47 The pooled estimate of patients with CCI 0-1 in comparison to >1, indicated higher uptake of trastuzumab by patients with a lower CCI score (combined OR 1.52, 95% CI:1.22-1.88, P=0.0001, I2=0%) with no evidence of heterogeneity between studies (Supplemental Figure 8). Of five studies comparing trastuzumab initiation between CCI 0-1 and >1, two indicated higher odds of initiation in patients with a lower CCI score30,42 and three were equivocal.33,43,47

**Treatment characteristics**

Although not included in meta-analyses, three studies found that more recent year of diagnosis was a predictor of higher initiation of trastuzumab therapy30,42,46 and one study found year of diagnosis was equivocal.37 Whitfield et al (2012)54 found a positive association between surgeon caseload and trastuzumab initiation. Reeder-Hayes et al (2016)42 found that patients were more likely to initiate trastuzumab therapy if patients received breast conserving surgery compared to mastectomy but found an inverse relationship if breast conserving surgery was delivered in combination with radiotherapy. Further, the study did not identify a significant association between trastuzumab initiation in patients who had a mastectomy and patients who had a mastectomy in combination with radiotherapy. In a study by Seferina et al. (2015), mastectomy versus breast conserving strategy, breast conserving versus no surgery, receipt of adjuvant endocrine therapy, and receipt of radiotherapy were not predictors of trastuzumab initiation.43 Noonan et al. (2012)39 also failed to identify a significant relationship between trastuzumab initiation and receipt of radiotherapy. Seferina et al. (2015)43 found that there was a significant positive association between receipt of neoadjuvant chemotherapy and trastuzumab initiation. Neugut et al. (2014)38 found that recommendation for chemotherapy and use of adjuvant chemotherapy were predictors of trastuzumab initiation. Noonan et al. (2012)39 did not identify a significant relationship between trastuzumab initiation in patients receiving anthracycline-based versus non-anthracycline-based chemotherapy.

**Age**

There were 10 studies30,33,38,40,41,43,46,47,51,54 that reported trastuzumab initiation by age of patient. The pooled estimate of younger patients less than 50 years in comparison to patients older than 50 years, indicated that as age increased, initiation reduced but there was high heterogeneity between studies (combined OR 2.15, 95% CI:1.58-2.92, P<0.00001, I2=68%). Of eight studies comparing trastuzumab initiation between <50 years and ≥50 years, six indicated a higher odds of initiation in younger patients30,40,41,43,46,54 and two were equivocal.33,38 The pooled estimate of younger patients less than 60 years in comparison to patients older than 60 years, found that as age increased, initiation reduced (combined OR 2.59, 95% CI:1.88-3.56, P<0.00001, I2=71%) with high heterogeneity between studies. Of seven studies comparing trastuzumab initiation between <60 years and ≥60 years, six indicated a higher odds of initiation in younger patients30,38,40,41,43,54 and one was equivocal.46 The pooled estimate of patients less than 70 years in comparison to patients older than 70 years, found that as age increased, initiation reduced (combined OR 3.90, 95% CI:2.53-6.03, P<0.00001, I2=81%) with high heterogeneity between studies (Supplemental Figure 9). Of six studies comparing trastuzumab initiation between <70 years and ≥70 years, four indicated a higher odds of initiation in younger patients30,41,47,54 and two were equivocal.38,51

**Ethnicity**

There were 6 studies30,38,42,46,47,52 that reported trastuzumab initiation by ethnicity of patient. The pooled estimate of white patients in comparison to black patients was not significant (combined OR 1.26, 95% CI:0.92-1.72, P=0.16, I2=38%) with low heterogeneity between studies. Of six studies comparing trastuzumab initiation between white and black patients, one study indicated a higher odds of initiation in white patients47 and five were equivocal.30,38,42,46,52 The pooled estimate of white patients in comparison to other patients was not significant (combined OR 0.82, 95% CI:0.66-1.10, P=0.06, I2=0%,) with no evidence of heterogeneity between studies. Of five studies comparing trastuzumab initiation between white and other patients, all five were equivocal.30,38,42,46,47 The pooled estimate of white patients in comparison to non-white (including ‘black’, ‘Latina’ and ‘Asian’) patients was not significant (combined OR 0.99, 95% CI:0.79-1.24, P=0.90, I2=44%) with low heterogeneity between studies (Supplemental Figure 10). Of six studies comparing trastuzumab initiation between white and non-white patients, one study indicated a higher odds of initiation in non-white patients and five studies were equivocal.38,42,46,47,52

**Education**

There were 3 studies30,46,47 that reported trastuzumab initiation by education status of patient. The pooled estimate of patients with more education in comparison to less education was not significant (combined OR 1.13, 95% CI:0.94-1.36, P=0.19, I2=0%) with no evidence of heterogeneity between studies (Supplemental Figure 11). Of three studies comparing trastuzumab initiation between higher educated and less, all were equivocal. 30,46,47

**Socioeconomic status**

There were 5 studies30,33,42,46,47 that reported trastuzumab initiation by socioeconomic status of patient. The pooled estimate of economically advantaged patients in comparison to deprived patients was not significant (combined OR 1.03, 95% CI:0.86-1.25, P=0.74, I2=43%) with low heterogeneity between studies (Supplemental Figure 12). Of five studies comparing trastuzumab initiation between economically advantaged and disadvantaged, all were equivocal.30,33,42,46,47

**Marital status**

There were 3 studies42,46,47 that reported trastuzumab initiation by marital status of patient. The pooled estimate of married patients in comparison to single patients was not significant (combined OR 0.84, 95% CI:0.68-1.04, P=0.11, I2=44%) with low heterogeneity between studies (Supplemental Figure 13). Of three studies comparing trastuzumab initiation between married and single, one study indicated a higher odds of initiation in married patients47 and two studies were equivocal.42,46

**Geography**

There were 3 studies46,47,54 that reported trastuzumab initiation by geography in terms of urban or rural location. The pooled estimate of rural initiation in comparison to urban initiation was not significant (combined OR 0.83, 95% CI:0.61-1.12, P=0.23, I2=0%) with low heterogeneity between studies (Supplemental Figure 14). Of three studies comparing trastuzumab initiation between urban and rural location, all were equivocal.46,47,54 Although not included in meta-analysis across five other studies, geographical location of care facility was a significant predictor of trastuzumab initiation in three studies30,36,37 and equivocal in two other studies.33,42

## Discussion

This study identified variability in trastuzumab initiation in HER2 positive breast cancer patients, both between study settings and within studies. The presence of comorbidities and lower disease burden in terms of lower stage, lower grade and smaller tumour size were found to be associated with significantly lower trastuzumab initiation. Further, therapy initiation was also found to be significantly lower in hormone receptor positive patients. In terms of patient sociodemographics, this review did not identify any significant association in trastuzumab initiation by ethnicity, education status, socioeconomic status, marital status and geographical region. However, older age was found to be significantly associated with lower initiation.

According to ASCO and ESMO guidance, in special circumstances, such as low disease burden (dependent on tumour stage, grade and size), presence of comorbidities, and/or presence of a long disease-free interval, clinicians may offer first-line endocrine therapy only.10,59 There has been debate on the necessity for trastuzumab-based chemotherapy in patients with low disease burden (T1N0),60 but a meta-analysis of trastuzumab trials has shown that this patient groups derives clinically relevant treatment benefit.61 Therefore in accordance with guidance, clinicians are recommended to provide HER2-targeted therapy based combinations for first-line treatment.

Pivotal trials (HERA trial,62 the BCIRG 006 trial,63 and N9831/B-315,64) found that patients, regardless of age, lymph node status, menopausal status or hormone status saw an increase in disease-free survival.65 It has also been recommended that large post-registration studies are conducted as subgroups, such as node negative patients were underrepresented in trials (HERA and (BCIRG)-006) and in randomized trials, a high proportion of tumors tended to be more aggressive than those seen in clinical practice.30,60,66,67 <sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>30,66,67</sup><sup>29,65,66</sup><sup>29,65,66</sup><sup>29,65,66</sup><sup>29,65,66</sup>

Underrepresentation of elderly populations in clinical trials is widely reported and our study also found that age was associated with lower initiation of therapy, with patients under 50 years old being 2.15 times more likely than those over 50 years to start trastuzumab therapy. The odds were even higher with patients older than 60 and 70 years. This is consistent with the fact that older breast cancer patients are less likely to receive adjuvant chemotherapy despite the fact that older patients benefit to an equivalent extent from adjuvant chemotherapy as younger patients.68 Given the sizeable treatment benefit from trastuzumab therapy and the aggressive biology of HER2-expressing tumours, ESMO have recommended that despite absence of evidence from randomized studies, treatment decisions should be based on biological factors.10

According to SEER data, in the USA, approximately 50% of diagnosed breast cancer patients are 65 years or older and 35% are 75 years or older.69 Yet in clinical trials and in published studies, the overall proportion of patients older than 60 years was approximately 10% and subgroup analyses by age has largely been poorly reported.70 While the HERA study had comparatively unrestricted inclusion criteria, the proportion of patients older than 60 years was only 16.2%, diverging from the typical population served in routine clinical practice.60 Larger studies which reflect the entire age spectrum of patients are needed to determine safety and efficacy within older and also comorbid patients.54

Before initiation of therapy, many patients need to undergo primary breast surgery and therefore need to be sufficiently fit for surgery. As elderly patients are likely to have co-morbidities, and therefore may not be fit for surgery, this may be one reason for the lower usage of trastuzumab in the elderly. Another reason for the lower use of trastuzumab in older patients may be its potential to cause cardiotoxicity; in the Slamon et al. phase III trial,3 cardiac events were reported in 27% and congestive heart failure (CHF) was reported in 16% of metastatic breast cancer patients treated concurrently with anthracyclines. A recent meta-analysis found that trastuzumab induced cardiotoxicity (TIC) occurred in 12% (CI: 11.3-12.9%) of patients and age, hypertension, diabetes and previous anthracycline use were identified as risk factors for TIC.71 Therefore, older patients may be less likely to receive therapy to avoid exposure to a potentially cardiotoxic treatment, especially if there is underlying cardiovascular comorbidity. Thus, while our findings may suggest that there is inequity of access with older age, this may not be the case as there may have been good clinical reasons to avoid the use of trastuzumab in older patients. An individual patient data meta-analysis would be required to determine the likely reasons for lower use of trastuzumab in the elderly.

While findings from this review did not reveal consistent disparities in uptake of targeted-therapy by ethnicity, there remains a general underrepresentation of research in diverse ethnic groups.72 Indeed, evidence from one study identified disparities by ethnicity, despite the presence of a clear biologic predictor of treatment benefit.47 In the USA between 2000 and 2010, breast cancer mortality decreased annually by 2%, primarily due to earlier diagnosis and improved treatment strategies,52,73,74 although this decline was slower in black patients and a widening disparity ratio in breast cancer mortality was observed between white and black patients increasing from 30.1% to 41.8%.73,75 Furthermore, to successfully address the persistent mortality gap in minority patients, and given their underrepresentation in clinical trials, additional research into underlying tumor and host biology is needed to improve treatment response.

Treatment disparities remain despite widespread efforts to improve access to care among minority groups. One study found that 8% of breast cancers were reported at an advanced stage in black patients compared to 5% in white patients and delayed diagnosis resulted from lower frequency of mammograms, longer waiting times between mammograms and less consistent follow-up of suspicious mammogram results among black patients in the USA.76 Within Europe, concerns have been raised regarding challenges in funding the HER2 test which also may have impacted trastuzumab utilization.77 Studies have also found that following diagnosis, black patients with HER2 positive metastatic breast cancer have poorer prognostic factors and independently worse clinical outcomes than white patients.52,76 Another study found that of patients diagnosed with small breast tumors (≤2cm) during 2004 and 2011, 24% of black patients and 18% of white patients were likely to present with lymph node metastases.15 Therefore, disparities in mortality may exist in part due to later stage diagnosis, but also poorer stage specific survival due to greater prevalence of aggressive subtypes of cancer in black patients.78,79

Trastuzumab is an expensive therapy and aspects of health care delivery may contribute to underuse in deprived populations.80 Even for insured patients, the burden of care may be significant due to outpatient expenses and thus, lack of affordability may be associated with factors such as age, education and race.42 Moreover, in some lower-middle income countries where trastuzumab has been provided for a relatively small numbers of patients, trastuzumab has contributed appreciably to the financial burden of health care.81,82 Within the USA, the burden of cancer care is evident as some patients have had to sell their homes to provide funding.83 Pricing of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs which has been challenged by leading CML experts and oncologists.84 Consequently, issues of affordability affect not only lower-middle income countries but also higher income countries. However, following patent expiry, biosimilars may provide more financially accessible alternatives; however, greater efforts are needed to address barriers faced by patients.

Further, trastuzumab therapy is typically recommended for a duration of 12 months.9,10 As such, the pairing of trastuzumab with intensive chemotherapy regimens and long duration of treatment may be a significant barrier to patients with limited transport options, employment uncertainty, poor support network and this may be combined with a preconception from providers that patients identified as vulnerable, may be less able to tolerate and complete therapy.30,42

Further research is needed into other aspects of the care pathway of trastuzumab therapy as disparities have been identified in time to initiation,85 duration86–89 and completion26,30,38,44,50,69,90–92 of therapy. Disparities in long term adherence have been found to be associated with ethnicity,85,92 socioeconomic status,36 education attainment,30,92 employment and insurance status.30 These differences in treatment duration and completion may have been amplified by the need for frequent infusions over a prolonged period. While it is possible that patients may benefit from shorter durations of therapy,93 this has not been well studied, and guidelines recommend one year of therapy for all patients, until disease progression and/or unacceptable toxicity.59,94

This review has identified a pattern of care delivery which requires further exploration to ensure equitable access in clinical practice. However, relevant comorbidities, and cardiac risk factors vary by subgroup, and therefore initiation of trastuzumab therapy may be influenced by a number of confounders which is a limitation in the assessment of uptake in observational studies. In addition, while the treatment regimens may reflect local clinical practice, these studies may not be representative of general clinical practice due to sample selection bias.

The meta-analyses presented in this paper identified substantial heterogeneity that could be attributed to methodological and/or clinical variations in the characteristics of the included studies. Moreover, changing patterns of therapy delivery, scheduling, and settings could have resulted in differences in uptake at different time periods. Furthermore, it is also possible that some of the findings may be due to factors unique to each study and which could not be identified by means of a systematic review or meta-analysis.

A limitation specific to this review is that screening may have failed to identify relevant studies which did not comment on initiation of trastuzumab therapy in the title or abstract. In addition, studies did not address the full range of factors which may explain underuse of therapy in certain groups of patients and psychosocial factors remain understudied. Further, included studies focused on HER2 positive patients but the proportion of HER2 borderline patients and how therapy varied was not extracted. In addition, information on why patients were not selected for trastuzumab therapy was not consistently described and thus precluded from this review. Additional research should examine prescribing behavior at the provider level to explore other stakeholder factors, as well as explore other inequalities in the HER2 positive breast cancer care pathway, such as receipt of chemotherapy and hormone therapy.58,95

## Conclusion

Trastuzumab is a pioneering therapy with important treatment benefits for HER2 positive breast cancer patients. This review has demonstrated that disparities in initiation of trastuzumab therapy exist dependent on disease burden, comorbidities and age of patients. These findings may have wider implications for other targeted therapies. Further research is needed to address unequal access to high quality treatments, delay from diagnosis to treatment and disparities in therapy completion.

System-level interventions that identify eligible patients objectively and consistently, as well as interventions that focus on removing barriers to therapy at the patient and provider level are needed to ensure treatment reaches deprived populations. Studies assessing individual level data are needed to better characterize factors underlying disparities in breast cancer treatment. Fortunately, the increasing use of electronic data records provides an opportunity to better identify eligible patients and more effectively assess accessibility.

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## Figures

Figure 1 PRISMA flow diagram displaying articles included and excluded in this review

Full-text articles assessed for eligibility
(n = 107)

Records screened
(n = 2651)

Records after duplicates removed
(n = 2651)

Additional records identified through other sources
(n = 14)

Records identified through database searching
(n = 3968)

*Identification*

*Screening*

Records excluded
(n = 2544)

*Eligibility*

Full-text articles excluded
(n = 74)

* Not HER2 positive (n = 6)
* Uptake, utilisation, access, inequalities or barriers not discussed (n = 19)
* Differences in treatment duration or completion (n = 20)
* Not relevant publication type (excluding letters, case reports, editorials and conference abstracts before 2010 (n = 10)
* Duplicate (n = 9)
* Other reason (n = 10)

*Included*

Studies included for review
(n = 33)

## Tables

Table 1 Summary of studies included in review

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Study type | Country | Mean age (range) | Study period time | Source of information | Cancer status | TTT initiation |
| Adusumilli et al. (2017) | Retrospective cohort study | India | 50 (27-76) | January 2007 to December 2013 | Private payment for therapy, Department of Medical Oncology, Nizam’s Institute of Medical Sciences, Hyderabad, Telangana | EBC | 76/212 (35.8%)c |
| Barron et al. (2009) | Retrospective cohort study | USA | 53.8 (SD 10.9) | 1 June 2005 to 30 June 2006 | Administrative health claims from three commercial health plans located in westem and southeastern U.S | MBC | 51/72 (70.8%)d |
| Boons et al. (2016) | Retrospective cohort study | Netherlands | - | June 2008 to December 2009 | 7 randomly selected Dutch hospitals (3 general hospitals, 2 top clinical hospitals, 1 academic hospital, and 1 specialized oncology hospital) | EBC MBC | EBC: 147/160 (91.9%)cMBC: 75/91 (82.4%)c  |
| Byfield et al. (2016)  | Retrospective cohort analysis | USA | 52 (SD 9) | 1 January 2008 to 31 August 2013 | Physician-reported data for insured patients, Oncology Management Registry linked with Optum Research Database | EBC | 662/915 (72.3%)d |
| Chan and McGregor (2012) | Prospective cohort study | Australia  | 56 (29-90) | 1 October 2006 to 31 March 2009 | Private hospital, Mount Hospital | EBC | Private hospital: 110/110 (100.0%)c Other setting: 13/25 (52.0%)c |
| Chavarri-Guerra et al. (2014) | Cross-sectional survey | Mexico | - | - | Web-based survey of Mexican Oncologists (18.6% response) | BC | <1 cm tumors: 54.3%c>1 cm tumors: 77.5%c  |
| Coulson et al. (2010) | Retrospective cohort study | UK | 68 (34-91) | September 2007 to August 2008 | North Trent Cancer Network  | EBC | 129/185 (69.7%)d4/14 (28.6%) borderline HER2+d |
| Cyr et al. (2011) | Retrospective cohort study | USA | 84 (80-96) | 1 January 1998 to 30 June 2009 | John Cochran Veterans Hospital, St. Louis, Missouri | EBC | 1/11 (9.1%)c  |
| Freedman et al. (2013) | Retrospective cohort study | USA | - | September 2005 to December 2009 | NCCN Breast Cancer Outcomes Database Project  | EBC | 920/1109 (83.0%)f |
| Goddard et al. (2012)a | Retrospective cohort study | USA | - | 1 January 1998 to 31 December 2007 | Kaiser Permanente Northwest (KPNW), Oregon and Southwest Washington | EBC MBC | 1998-2004: 35/366 (9.6%)c2005-2007: 71/130 (54.6%)c |
| Goddard et al. (2012)a | Retrospective cohort study | USA | - | 1 January 1999 to 31 December 2007 | KPNW Oregon and Southwest Washington | EBC MBC | 1999-2005: 33/63 (52.4%)c2006-2007: 28/33 (84.8%)c |
| Haas et al. (2011) | Retrospective cohort study | USA | 54 (35-65) | 1 July 2006 to 30 June 2008 | Claims from large national health plan, Aetna, Hartford, CT | EBC | 79/137 (57.7%)c |
| Harris et al. (2013) | Retrospective cohort study | Australia | 55 (21-91) | 2008 to 2011 | Four Sydney-based cancer centers | EBC | 168/176 (86.7%)c |
| Herk-sukel et al. (2013) | Retrospective cohort study | Netherlands | 48.8 (-)b | 1 January 2000 to 31 December 2008 | Eindhoven Cancer Registry linked to the PHARMO Record  | BC | Adjuvant chemo 43/58 (74.1%)cPalliative chemo 22/24 (91.7%)c |
| Kaufman et al. (2012)a | Prospective cohort study | USA | 54.6 (20-92)b | December 2003 to February 2006 | registHER study  | MBC | 841/1001 (84.0%)c |
| Li et al. (2017) | Retrospective cohort study | China | - | 2010 to 2015 | 13 hospitals in Eastern China | EBC MBC | EBC: 412/1017 (40.5%)cMBC: 366/720 (50.8%)c |
| Liebrich et al. (2007) | Cross-sectional survey | Germany | 57.4 (20-89) | 2007 | ONkeyLINE (voluntary tumour registry), Lower Saxony | EBC  | 334/433 (77.1%)f |
| Marla et al. (2010) | Audit | UK | - | 2007 to 2008 | Six UK hospitals | EBC | 238/386 (61.7%)c |
| Munck et al. (2011) | Retrospective cohort study | Netherlands | 60 (21-101) | September 2005 to January 2007 | Netherlands Cancer Registry | EBC | 1057/1928 (54.8%)c1057/1114 (94.9%) (with adjuvant chemotherapy)c |
| Neugut et al. (2014) | Retrospective cohort study | USA | 56.0 (40-79)b | May 2006 and June 2010 | BQUAL study: New York City  | EBC  | 119/152 (78.3%)c |
| Noonan et al. (2012) | Retrospective cohort study | Canada | 56 (-) | January 2005 to January 2010 | Newfoundland and Labrador Provincial Tumour Registry | EBC | 113/148 (76.4%)c |
| Palmieri et al. (2011) | Retrospective cohort study | UK | 52.3 (31.1-80.7) | January 2006 and December 2008 | Imperial College Healthcare NHS Trust | EBC | 128/177 (72.3%)c |
| Peters et al. (2015) | Retrospective cohort study | Germany | 64 (-)b | 2006 to 2013 | Patients’ Tumor Bank of Hope database | EBC | 255/331 (77.0%)c |
| Reeder-Hayes et al. (2016) | Retrospective cohort study | USA | 75.4 (-)b | 2009 to 2013 | Surveillance, Epidemiology, and End Results SEER-Medicare–linked data set | EBC | 672/690 (97.4%)f |
| Rugo et al. (2013)a | Prospective cohort study | USA | 53.5 (20-93) | December 2003 to February 2006 | registHER study  | MBC | 772/919 (84.0%)g |
| Seferina et al. (2015)a | Retrospective cohort study | Netherlands | 51 ( 27–72) | January 2005 to December 2007 | Five Dutch hospitals in southeast Netherlands | EBC | 196/251 (78.1%)c |
| Seferina et al. (2016)a | Retrospective cohort study | Netherlands | - | January 2005 to December 2007 | Five Dutch hospitals in southeast Netherlands | EBC | 230/269 (85.5%) (with adjuvant chemotherapy)c |
| Stenehjem et al. (2014)a | Retrospective cohort study | USA | 57 (SD 13)c | 1 January 2005 to 31 December 2012 | Huntsman Cancer Institute Tumor Registry, SEER reporting registry, Utah | EBC | 186/245 (75.9%)c |
| Tsai et al. (2017) | Retrospective cohort study | USA | 49.9 (24-63)b | 2006 to 2011 | Cancer registry and claims-linked data set | EBC | 680/934 (72.8%)e |
| Vaz-Luis et al. (2016)a | Retrospective cohort study | USA | 75.4 (-)b | 2011 to 2013 | SEER Medicare database | EBC | 428/770 (55.6%)e |
| Webster et al. (2012) | Retrospective cohort study | Wales - UK | - | 1 January 2005 to 31 December 2008 | South East Wales Cancer Network | EBC | 237/336 (70.5%)c |
| Whitfield et al. (2012) | Audit | Australia and New Zealand | - | January 2006 to December 2008 | Royal Australasian College of Surgeons – National Breast Cancer Audit  | EBC | 2006 - 356/707 (50.4%) 2007 - 474/714 (66.4%) 2008 - 668/908 (73.6%)f |
| Zurawska et al. (2013) | Retrospective cohort study | Canada | 53 (40.9-65.1) | 1 January 2005 to 31 December 2006 | Odette Cancer Centre, Toronto, Ontario | EBC | 76/94 (80.9%)c |

BC, breast cancer; EBC, early breast cancer; MBC, metastatic breast cancer.

aResearch conducted in same cohort.

bWeighted mean calculated from group averages.

c Receipt of trastuzumab within study period

d Receipt of trastuzumab within 6 months of diagnosis

e Receipt of trastuzumab within first 9 months of diagnosis

f Receipt of trastuzumab within 1 year of diagnosis

g Receipt of trastuzumab-based first-line regimens (>=21 days of trastuzumab in first-line therapy) prior to first disease progression

f Receipt of trastuzumab (defined as having start date for trastuzumab at any time after diagnosis but before any recurrence)

Table 2 Summary of factors associated with uptake of targeted trastuzumab therapy

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Adusumilli et al. (2017) | Barron et al. (2009) | Boons et al. (2016) | Byfield et al. (2016)  | Chan and McGregor (2012) | Chavarri-Guerra et al. (2014) | Coulson et al. (2010) | Cyr et al. (2011) | Freedman et al. (2013) | Goddard et al. (2012) | Goddard et al. (2012) | Haas et al. (2011) | Harris et al. (2013) | Herk-sukel et al. (2013) | Kaufman et al. (2012) | Li et al. (2017) | Liebrich et al. (2007) | Marla et al. (2010) | Munck et al. (2011) | Neugut et al. (2014) | Noonan et al. (2012) | Palmieri et al. (2011) | Peters et al. (2015) | Reeder-Hayes et al. (2016) | Rugo et al. (2013) | Seferina et al. (2015) | Seferina et al. (2016) | Stenehjem et al. (2014) | Tsai et al. (2017) | Vaz-Luis et al. (2016) | Webster et al. (2012) | Whitfield et al. (2012) | Zurawska et al. (2013) |
| **Clinical factors** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tumour stage  | ✓ | ~ |  |  |  |  |  |  | ✓✓ |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  |  | ~ | ~ |  |  |
| Tumour grade  |  |  |  |  |  |  |  |  | ✓✓ |  |  | ~ | ✓ |  |  |  |  |  |  | ✓ | ~ | ~ |  | ✓✓ |  | ~ |  |  | ✓ | ✓✓ | ~ |  |  |
| Tumour size |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  | ~ | ✓ |  | ✓✓ |  | ✓ |  |  | ✓ | ~ | ~ |  |  |
| Lymph nodes (positive/number) |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ | ✓ | ✓ |  | ✓✓ |  | ✓ |  |  | ✓ | ~ |  |  |  |
| Hormone receptor status (ER/PR) | ✓ | ~ |  |  |  |  |  |  | ~ |  |  | ~ |  |  |  |  |  |  |  | ~ | ~ | ~ |  | ~ |  | ~ |  |  | ✓ | ✓✓ | ~ | ✓ |  |
| Comorbidity (CCI) |  | ~ |  |  |  |  |  |  | ✓✓ |  |  | ~ |  |  |  |  |  | ~ | ~ | ~ |  |  |  | ✓✓ |  | ✓ |  |  | ~ | ~ |  |  |  |
| Menopause |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Year of diagnosis |  |  |  |  |  |  |  |  | ✓✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓✓ |  |  |  |  | ✓ |  |  | ✓ |  |
| Caseload of surgeon |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |
| Mastectomy vs. breast conserving |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓✓ |  | ~ |  |  |  |  |  |  |  |
| Mastectomy vs. mastectomy and radiation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |
| Mastectomy vs. mastectomy and radiation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓✓ |  |  |  |  |  |  |  |  |  |
| Mastectomy vs. lumptectomy |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |
| Adjuvant endocrine/hormonal therapy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  | ~ |  |  |  |  |  |  |  |
| Chemotherapy anthracycline- vs. non-anthracycline-based |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |
| Adjuvant radiotherapy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |
| Adjuvant chemotherapy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ~ |  |  |  |  |  |  |  |  |  |  |  |  |
| Neoadjuvant chemotherapy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  |
| **Psychosocial factors** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Patient refused therapy |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  | ~ | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinician withheld therapy and no reason given/not indicated |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Sociodemographic factors** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Education |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ | ✓✓ |  |  |  |
| Socioeconomic status | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓✓ |  |  |  |  |  | ~ |  |  |  |
| Income |  |  |  |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Employment |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Insurance status |  |  |  |  |  |  |  |  | ~ |  |  | ~ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Marital status |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  |  | ~ | ~ |  |  |  |
| Age |  | ~ |  |  |  |  | ~ | ~ | ✓✓ |  |  | ~ | ✓ |  | ~ |  |  | ~ |  | ✓ | ✓ | ✓ | ✓ | ✓✓ |  | ✓ |  |  | ~ | ✓✓ |  | ✓ |  |
| Ethnicity |  |  |  |  |  |  |  |  | ~ |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  | ✓✓ | ~ |  |  |  | ~ | ~ |  |  |  |
| Geographical region (urban/rural, SEER region) |  |  |  |  |  |  |  |  |  |  |  | ~ |  |  |  | ✓ |  |  | ✓ |  |  |  |  | ~ |  |  |  |  | ~ | ~ |  | ~ |  |
| Institution |  |  |  |  |  |  |  |  | ✓✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Notes: ~, tested, but not statistically significant; ✓, tested in univariable analyses, and significant; ✓✓, tested multivariable, and significant. |

Figure 2 Meta-analysis of individual-level data for trastuzumab therapy uptake by continent



Table 3 Summary of meta-analysis of factors associated with initiation of trastuzumab therapy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Studies included | Total events | Total events (ref) | Heterogeneity  | Summary unadjusted odds ratio M-H, Random, 95% CI |
| Tumour stage:≥Stage II vs. stage I (ref)≥Stage III vs. stage I-II (ref) | 24,25,30,33,38,46–4824,25,30,33,38,46–48 | 1834/2328652/796 | 747/12831929/2815 | P=0.0002, I2=76%P=0.03, I2=54% | 3.55 (2.41-5.23)\*\*\*\*2.07 (1.44-2.96)\*\*\* |
| Tumour grade:≥Grade 2 vs. grade 1 (ref)≥Grade 3 vs. ≤grade 2 (ref) | 38–40,42,43,46–4830,38,40,43,46–48,58 | 1920/32741874/2754 | 184/4251018/1873 | P=0.008, I2=63% P=<0.00001, I2=81% | 2.55 (1.53-4.25)\*\*1.74 (1.23-2.47)\* |
| Tumour size:≥1cm vs. <1cm (ref)≥2cm vs. <2cm (ref)≥3cm vs. <3cm (ref) | 48,5439,40,42–44,46,47 40,42–44,46,47 | 559/9401297/1844794/1133 | 108/3411096/20182500/2601 | P=0.41, I2=0%P=0.79, I2=0%P=0.88, I2=0% | 3.16 (2.43-4.11)\*\*\*\*2.02 (1.76-2.32)\*\*\*\*1.80 (1.54-2.10)\*\*\*\* |
| Lymph node status:Positive vs. negative | 38–40,42,43,46,47 | 1072/1514 | 1218/2221 | P<0.00001, I2=90% | 1.63 (0.95-2.80) |
| Hormone receptor status:HR positive vs. negative (ref)ER positive vs. negative (ref)PR positive vs. negative (ref) | 25,30,38,40,42,43,46–4824,25,33,39,4025,40 | 1227/1733213/374103/147 | 2068/3345231/33771/95 | P=0.74, I2=0%P=0.32, I2=14%P=0.99, I2=0% | 1.54 (1.35-1.77)\*\*\*\*1.05 (0.74-1.50)0.79 (0.44-1.42) |
| Comorbidity (CCI):CCI 0 vs. >0 (ref)CCI ≤1 vs. >1 (ref) | 30,33,38,42,43,4730,33,42,43,47 | 1802/26112094/3205 | 595/1127193/407 | P=0.22, I2=29%P=0.55, I2=0% | 1.62 (1.32-1.99)\*\*\*\*1.52 (1.22-1.88)\*\*\* |
| Age: <50 vs. ≥50 (ref)<60 vs. ≥60 (ref)<70 vs. ≥70 (ref) | 30,33,38,40,41,43,46,5430,38,40,41,43,46,5430,38,41,47,51,54 | 1558/19262710/33983409/4235 | 2413/3525978/1534485/1034 | P=0.002, I2=68%P=0.002, I2=72% P<0.00001, I2=81% | 2.15 (1.58-2.92)\*\*\*\*2.59 (1.88-3.56)\*\*\*\*3.90 (2.53-6.03)\*\*\*\* |
| Ethnicity:White vs. black (ref)White vs. other (ref)White vs. non-white (ref) | 30,38,42,46,47,5230,38,42,46,4738,42,46,47,52 | 2870/42052200/34122870/4205 | 296/440421/575717/1015 | P=0.15, I2=38%P=0.57, I2=0%P=0.11, I2=44% | 1.26 (0.92-1.72)0.82 (0.66-1.01)0.99 (0.79-1.24) |
| Education:High vs. low (ref) | 30,46,47 | 996/1349 | 802/1183 | P=0.82, I2=0% | 1.13 (0.94-1.36) |
| Socioeconomic status:High vs. low (ref)  | 30,33,42,46,47 | 1121/1795 | 1650/2499 | P=0.14, I2=43% | 1.03 (0.86-1.25) |
| Marital status:Married vs. single (ref) | 42,46,47 | 694/1276 | 1078/1766 | P=0.17, I2=44% | 0.84 (0.68-1.04) |
| Geographical region:Rural vs. urban (ref) | 46,47,54 | 461/798 | 1798/2433 | P=0.90, I2=0% | 0.83 (0.61-1.12) |

Test for overall effect: \*\*\*\* = P<0.00001, \*\*\*=P<0.0001, \*\*=P<0.001, \*=P<0.01; Ref = Reference.