Clinical Medicine Insights: Oncology

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EXPERT REVIEW

Trastuzumab for HER2-Positive Metastatic Breast Cancer: Clinical and Economic Considerations

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Abstract: Trastuzumab is a recombinant humanized monoclonal antibody that selectively targets the extra-cellular domain of the HER2 receptor. It was approved by the FDA in September 1998 as the first targeted therapy for HER2-positive metastatic breast cancer, and has since led to significant improvements in the overall prognosis for patients with HER2-positive metastatic disease. The favourable benefit/risk profile associated with palliative trastuzumab has been demonstrated in a number of clinical trials that examined trastusumab as monotherapy or in combination with chemotherapy, endocrine therapy and other HER2 targeted agents. The clinical benefits of trastuzumab, however should also be examined within the context of its significant drug acquisition costs. This review highlights the significant findings from the landmark clinical trials of trastuzumab for metastatic HER2-positive breast cancer, and the potential "value for money" associated with its use in clinical practice.

Keywords: trastuzumab, HER2-positive, breast cancer, palliative, clinical trials, cost-effectiveness analysis, economics

Clinical Medicine Insights: Oncology 2012:6 179–187

doi: 10.4137/CMO.S6460

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Introduction

Human epidermal growth factor receptor 2 (HER2) protein over-expression and/or gene amplification are observed in approximately 20% of breast cancers, and are associated with more aggressive natural history compared with HER2 negative counterparts.[1] Trastuzumab (Herceptin®) was the first targeted therapy approved by the FDA in September 1998 for HER2-positive breast cancer, and has since led to significant improvements in the overall prognosis for patients with HER2-positive metastatic disease.[2] It is a recombinant humanized monoclonal antibody that selectively targets the extra-cellular domain of the HER2 receptor.[3] Breast cancers with HER2 protein over-expression (3+) and/or gene amplification by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) respectively derive large benefits from trastuzumab therapy, while those with no or weak (0 or 1+) protein expression and non-amplified gene copy do not.[4] Trastuzumab is also associated with significant drug acquisition costs that should be examined within the context of all its associated benefits.[5] We herein review the landmark clinical trials of palliative trastusumab, and the potential "value for money" associated with its use, for metastatic HER2-positive breast cancer.

Mechanism of Action, Pharmacokinetics and Precautions

HER2 is a 185 KD transmembrane glycoprotein receptor with intracellular tyrosine kinase activity.[6] It is one of four well characterized epidermal growth factor receptors (EGFR) that are involved in the activation of subcellular signal transduction pathways controlling epithelial cell growth, differentiation and possibly angiogenesis.[7–10] It is normally expressed at low levels in a variety of epithelial cell types including breast duct epithelium, and is over-expressed in approximately 20% of breast cancers.[11] HER2 receptor over-expression on the surface of tumor cells results in a constitutively activated HER2 signaling pathway, and worse outcomes.[1] Trastuzuamb selectively targets the extra-cellular domain of the HER2 receptor, and has been shown to inhibit the proliferation of HER2-positive tumor cells in both in-vitro and in-vivo studies by down regulating the HER2 receptors.[3] Other possible mechanisms of action include an antibody-dependent cell-mediated cytotoxicity (ADCC) as well as reduction of the S-phase cell cycle progression and decreased vascular epithelium growth factor mediated angiogenesis.[3,12] Other potential therapeutic strategies targeting the HER2 signalling pathway that currently exist and/or in development include tyrosine kinase inhibitors and anti-HER2 vaccines, respectively.[13]

The recommended loading dose for a three-weekly regimen is 8 mg/kg over 90-minute followed by 6 mg/kg maintenance doses, which can be given over 30 minutes if prior treatments were well tolerated. For a weekly schedule, the recommended doses are 4 mg/kg over 90 minute followed by 2 mg/kg over 30 minute, respectively.[14] Trastuzumab has a half life of six days with the weekly schedule doses and sixteen days with the 3-weekly one. An administration of a reloading dose is recommended if the planned maintenance dose is delayed or missed by more than a week. Trastuzumab does not appear to cross the intact blood brain barrier because of its large molecular size, and its disposition is not altered based on serum creatinine level.[14]

A number of trastuzumab-related side effects have been described which may require close monitoring during therapy and/or discontinuation of treatment including infusion reactions, cardiac toxicity and pulmonary toxicity.[3] The development of human antibodies against trastuzumab is rare but trastuzumab should not be administered in patients with prior serious hypersensitivity reactions to trastuzumab or hypersensitivity reaction to Chinese hamster ovary cell proteins.[14] Contraception is also recommended during and for six months after treatment of woman with child bearing potential, as trastuzumab exposure during pregnancy can cause oligohydramnios with resultant pulmonary hypoplasia, skeletal malformations and neonatal death.[14]

Clinical Trials of Palliative Trastuzumab

The favourable benefit/risk profile associated with trastuzumab for the treatment of HER2-positive metastatic breast cancer has been demonstrated in a number of clinical trials that examined trastusumab as monotherapy or in combination with chemotherapy, endocrine therapy and other HER2 targeted agents (Table 1).[15–31] The impact of trastuzumab on

Table 1. Landmark clinical trials of palliative trastuzumab in breast cancer.

Study	Year	Design	N	Arms	Efficacy outcomes
Trastuzumab monotherapy					
Vogel et al[15]	2002	Phase 2	104	TZ (4 mg/kg loading → 2 mg/kg QW or 8 mg/kg loading → 4 mg/kg QW)	RR 26% TTP 18.8 M (in responding patients) OS 24.4 M
Trastuzumab plus chemotherapy					
Slamon et al[16]	2001	Phase 3	469	Chemo Q3 W (A 60 mg/m^2 + C 600 mg/m^2 or E 75 mg/m^2 + C 600 mg/m^2 in anthra-naïve and P 175 mg/m^2 in anthra-pretreated) +/– TZ (4 mg/kg loading → 2 mg/kg QW)	RR 50% vs. 32% ($P < 0.001$) TTP 7.4 vs. 4.6 M ($P < 0.001$) OS 25.1 vs. 20.3 M ($P = 0.001$)
Marty et al[17]	2005	Phase 2	186	Chemo (D 100 mg/m^2 Q3 W) +/– TZ (4 mg/kg loading → 2 mg/kg QW)	RR 61% vs. 34% ($P < 0.001$) TTP 11.7 vs. 6.1 M ($P < 0.001$) OS 31.2 vs. 22.7 M ($P = 0.033$)
Gasparini et al[18]	2007	Phase 2	124	Chemo (P 80 mg/m^2 QW) +/– TZ (4 mg/kg loading → 2 mg/kg QW)	RR 75% vs. 57% ($P = 0.038$) TTP 10.0 vs. 6.8 M ($P = 0.076$) OS not reached
Trastuzumab plus endocrine therapy					
Kaufman et al[25]	2009	Phase 3	207	Anastrozole (1 mg QD) +/– TZ (4 mg/kg loading → 2 mg/kg QW)	RR 20% vs. 7% ($P = 0.018$) PFS 4.8 vs. 2.4 M ($P = 0.002$) OS 28.5 vs. 23.9 M ($P = 0.325$)
Huober et al[26]	2011	Phase 2	57	Letrozole (2.5 mg QD) +/– TZ (4 mg/kg loading → 2 mg/kg QW)	RR 27% vs. 13% ($P = 0.31$) TTP 3.3 vs. 14.1 M ($P = 0.23$) OS not reported
Trastuzumab beyond progression					
Von Minckwitz et al[27,28]	2009	Phase 3	156	Cap (2500 mg/m^2/day Days 1–14 Q3 W) +/– TZ (8 mg/kg loading → 6 mg/kg Q3 W)	RR 48% vs. 27% ($P = 0.012$) TTP 8.2 vs. 5.6 M ($P = 0.034$) OS 25.5 vs. 20.4 M ($P = 0.257$)
Trastuzumab plus other Her-2/neu targeted agents					
Blackwell et al[29]	2010	Phase 3	296	Lapatinib (1000 mg QD) + T (4 mg/kg loading → 2 mg/kg QW) vs. Lapatinib (1500 mg QD)	RR 10% vs. 7% ($P = 0.460$) PFS 12 vs. 8 W ($P = 0.008$) OS 52 vs. 39 W ($P = 0.106$)
Baselga et al[30]	2011	Phase 3	808	TZ (8 mg/kg loading → 6 mg/kg Q3 W) + D (75 mg/m^2 Q3 W) +/– PZ (840 mg loading → 420 mg Q3 W)	RR 80% vs. 69% ($P = 0.001$) PFS 18.5 vs. 12.4 M ($P < 0.001$) OS interim analysis favours PZ arm
Others (trastuzumab-DM1)					
Burris et al[31]	2011	Phase 2	112	Trastuzumab-DM1 3.6 mg/kg Q3W	RR 26% PFS 4.6 M OS not reported

Abbreviations: N, Patient Number; TZ, Trastuzumab; A, Adriamycin; C, Cyclophosphamide; E, Epirubicin; D, Docetaxel; P, Paclitaxel; V, Vinorelbine; Carb, Carboplatin; Cap, Capecitabine; Anthra, Anthracycline; PZ, Pertuzumab; Chemo, chemotherapy; AUC, Area under curve; QW, weekly; QD, Daily; Q3 W, every 3 weeks; IHC, immunohistochemistry; FISH, florescence in situ hybridization; RR, response rate; TTP, time to progression; PFS, progression free survival; OS, overall survival; W, week; M, month.

metastatic breast cancer in these clinical trials has been examined through standard assessments of disease response rate (RR), progression free survival (PFS) and/or time to progression (TTP), and overall survival (OS).

Palliative trastuzumab monotherapy

The activity of first line trastuzumab monotherapy in HER2-positive metastatic breast cancer was demonstrated in a phase II trial, by Vogel et al, which randomized 114 patients to either trastuzumab 4 mg/kg loading followed by 2 mg/kg/week maintenance or 8 mg/kg loading followed by 4 mg/kg/week maintenance.[15] The overall response rate for both cohorts was 26%, and trastuzumab was well tolerated. A sub group analysis showed higher response rates of 35% and 34% in patients with IHC 3+ or FISH positive compared with 0% and 7% in those with IHC 2+ or FISH negative tumors. Three patients (2.6%) experienced cardiac dysfunction, although one was not related to trastuzumab therapy. Based on these results, trastuzumab monotherapy was felt to be an important new first-line

option for patients with HER2-positive metastatic breast cancer.[15]

Palliative trastuzumab plus chemotherapy

The benefits of palliative trastuzumab plus chemotherapy compared with chemotherapy alone for patients with metastatic HER2 positive breast cancer have also been demonstrated in three randomized clinical trials.[16–18] Slamon et al, in a phase III trial, randomized 469 patients with HER2-positive metastatic breast cancer to chemotherapy alone or chemotherapy plus trastuzumab.[16] The chemotherapy regimen consisted of doxorubicin or epirubicin along with cyclophosphamide in anthracycline-naive patients and paclitaxel in anthracycline-pre-treated ones. Trastuzumab plus chemotherapy was associated with more favourable efficacy-outcomes, compared with chemotherapy alone, including higher overall response rate (50% vs. 32%; $P < 0.001$) and longer duration of response (9.1 vs. 6.1 months; $P < 0.001$) as well as longer time to progression (7.4 vs. 4.6 months; $P < 0.001$) and improved overall survival (25.1 vs. 20.3 months; $P = 0.01$). Significant cardiac dysfunction, defined as New York Heart Association class 3 or 4, occurred in 27% of the patients treated with the anthracyclines plus trastuzumab compared with 8% of those treated with the anthracycline chemotherapy alone and in 13% of the patients treated with paclitaxel plus trastuzumab compared with 1% of those treated with paclitaxel alone. Given these results, the combination of anthracyclines and trastuzumab is not currently recommended outside of clinical trials. Marty et al, in a phase II trial, randomized 186 patients to docetaxel alone or docetaxel plus trastuzumab.[17] The chemotherapy plus trastuzumab arm was associated with more favourable efficacy-outcomes compared with the chemotherapy alone one including higher response rate (61% vs. 34%; $P = 0.0002$) and longer duration of response (11.7 v 5.7 months; $P = 0.009$) as well as longer time to progression (11.7 vs. 6.1 months; $P = 0.0001$) and improved overall survival (31.2 vs. 22.7 months; $P = 0.0325$). Higher grade 3–4 neutropenia (32% vs. 22%) and febrile neutropenia (23% v 17%) however were observed in the combination compared with the docetaxel alone arm. Gasparini et al, in a phase II trial, also randomized 124 patients to paclitaxel alone or paclitaxel plus trastuzumab.[18] The chemotherapy plus trastuzaumab arm was associated with higher response rate (75% vs. 57%; $P = 0.038$), longer duration of response (12.1 v 9.3 months; P = not reported) and time to progression (10.0 vs. 6.8 months; $P = 0.076$) as well as improved overall survival (31.2 vs. 22.7 months; $P = 0.0325$) compared with the chemotherapy alone strategy. The median overall survival was not reached at the 16.6-month median follow-up reported. Both treatments were well tolerated and no cardiac toxicities were reported.

A number of clinical trials also examined outcomes associated with trastuzumab in combination with other chemotherapeutic regimens and/or attempted to determine its optimal partner chemotherapy including taxanes, vinca alkaloids, capecitabine, gemcitabine and platinum salts.[19–24] As an example, a phase III trial by Anderson et al randomized 284 patients with HER2-positive metastatic breast cancer to first-line docetaxel plus trastuzumab or vinorelbine plus trastuzumab.[19] No statistically significant differences were observed between the two strategies with regards to time to progression or overall survival, but the former regimen was associated with more toxicity and treatment discontinuations. Another phase III trial by Robert et al randomized 196 patients with HER2-positive metastatic breast cancer to trastuzumab plus paclitaxel or trastuzmab plus paclitaxel and carboplatin.[20] The triplet regimen was associated with higher response rate (52% vs. 36%; $P = 0.04$) and progression-free survival (10.7 vs. 7.1 months; $P = 0.03$) compared with the doublet one but no statistically significant improvement in overall survival (35.7 vs. 32.2 months: $P = 0.76$). Both treatment arms were well tolerated with however more hematological toxicity occurring in the triplet regimen.

Palliative trastuzumab plus endocrine therapy

The combination of palliative trastuzumab and endocrine therapy for patients with endocrine-sensitive HER2-positive metastatic breast cancer was prospectively examined in two randomized clinical trials compared with endocrine therapy alone.[25,26] Kaufman et al, in a phase III trial (TAnDEM study), randomized 207 post-menopausal women with HER2 and hormone-receptor co-positive metastatic breast cancer to anastrozole (1 mg daily) with or without trastuzumab

(4 mg/kg loading then 2 mg/kg weekly maintenance until progression).[25] Compared with the endocrine therapy alone arm, the combination treatment was associated with significant improvement in the primary end point of progression-free-survival (4.8 vs. 2.4 months, $P = 0.0016$) but no statistically significant difference in overall survival (28.5 vs. 23.9 months, $P = 0.325$). The lack of an observed survival benefit could have been due to the 70% cross-over from the anastrozole alone to the combination arm that occurred in the clinical trial after progression on the endocrine therapy alone arm. As expected, the combination arm was also associated with more frequent adverse events compared with the endocrine therapy alone one including higher grade 3–4 toxicities (28% vs. 16%) and one patient experiencing heart failure. Houber et al, in a smaller phase II trial (eLEcTRA trial), also randomized 57 post-menopausal women with HER2 and hormone-receptor co-positive metastatic breast cancer to letrozole (2.5 mg daily) with or without trastuzumab (4 mg/kg loading then 2 mg/kg weekly maintenance until progression).[26] The trial was closed prematurely due to low accrual. A non-statistically significant trend towards higher response rate and time to progression were noted in the combination strategy compared with the endocrine alone arm. No survival outcomes were reported. The small sample size of the study, however, precludes any firm conclusions with regards to the efficacy of the combination arm although the results were concordant with those observed in the larger TAnDEM trial.

Palliative trastuzumab beyond progression

The benefits of continuing trastuzumab beyond progression were prospectively examined in a phase III randomized clinical trial.[27,28] Von Minckwitz et al randomized 156 patients who progressed on first line trastuzumab to second line capecitabine alone or capecitabine plus continuing trastuzumab beyond progression. The latter strategy was associated with higher response rate (48% vs. 21%; $P = 0.0115$) and longer time to progression (8.2 vs. 5.6 months; $P = 0.0338$) compared with the former one but no statistically significant improvement in overall survival (25.5 vs. 20.4 months; $P = 0.257$) even after longer duration of follow-up.[28] The role of palliative trastuzumab in patients with recurrent metastatic disease after adjuvant trastuzumab remains unclear, although it is not uncommonly offered to those with relapses occurring more than 12 months from completion of the adjuvant trastuzumab course.

Palliative trastuzumab plus other targeted agents

Trastuzumab has also been used in combination with other HER2 targeted agents such as lapatinib (a tyrosine kinase inhibitor) and pertuzumab (an anti-HER2 humanized monoclonal antibody that inhibits HER2 receptor dimerization) in second- and first-line settings, respectively.[29,30] Blackwell et al randomized 296 patients with HER2-positive metastatic breast cancer who progressed on prior trastuzumab-continuing regimes, in a phase III trial (EGF104900 trial), to lapatinib in combination with trastuzumab or lapatinib alone.[29] The overall response rate was not significantly different between the two arms (10.3% vs. 6.9%; $P = 0.46$), but the combination strategy was associated with significant improvement in progression free survival (12 vs. 8 weeks; $P = 0.008$) and a trend towards improved overall survival (52 vs. 39 weeks; $P = 0.106$). There were more frequent diarrhea in the combination arm ($P = 0.03$) as well as higher incidence of symptomatic and asymptomatic cardiac events (2% and 3.4% vs. 0.7% and 1.4%, respectively). Baselga et al also randomized 808 patients with HER2-positive metastatic breast cancer in a phase III trial (CLEOPATRA trial) to trastuzumab and docetaxel plus placebo (control group) or trastuzumab and docetaxel plus pertuzumab (pertuzumab group).[30] The pertuzumab arm was associated with higher response rate (80% vs. 69%: $P = 0.001$) and longer progression-free survival (18.5 vs. 12.4 months; $P < 0.001$) compared with the control arm. An interim analysis of overall survival also showed a strong trend in favour of pertuzumab arm that awaits confirmation with longer follow-up. There were more frequent grade 3–4 febrile neutropenia and diarrhea with no increased cardiac toxicity in the pertuzumab arm compared with the control group.

Palliative trastuzumab-DM1 (T-DM1)

The novel antibody-drug conjugate trastuzumab-DM1 (T-DM1) combines the biologic activity of trastuzumab with targeted delivery of a potent anti-

microtubule agent-DM1 to the HER2-positive metastatic breast cancer cells. In a single arm phase II trial by Burris et al, T-DM1 showed robust single-agent activity in 112 heavily pre-treated patients with HER2-positive metastatic breast cancer who had progression after prior HER2 directed therapy and chemotherapy.[31] T-DM1 treated patients experienced a remarkable 25.9% objective response rate and a 4.6 month median progression free survival. The median duration of response has not been reached yet after a follow up of more than 12 months. Overall, T-DM1 was well tolerated with mostly grade 1 or 2 adverse events and no dose-limiting cardiotoxicity. The most frequent grade ≥3 adverse events were hypokalemia (8.9%), thrombocytopenia (8.0%) and fatigue (4.5%). TDM-1 is currently being examined in a number of randomized clinical trials to ascertain its role in the management of HER2-positive metastatic breast cancer.

In summary, anti-HER2 targeted therapy with trastuzumab alone or in combination with other systemic therapeutic agents for HER2-positive metastatic breast cancer has been associated with significant though variable improvements in patient outcomes such as progression free survival and/or overall survival. Overall, trastuzumab appears to be well tolerated although on-therapy monitoring of patients cardiac functions is recommended given its associated cardiac toxicity. Most notably, the novel antibody-drug conjugate trastuzumab-DM1 (T-DM1) and the combination of trastuzumab plus other HER2 targeted agents (eg, lapatinib and pertuzumab) are promising strategies that will likely become new standards of care in the near future.

Economic Evaluations of Palliative Trastuzumab

Trastuzumab is an expensive anti-cancer therapeutic that is associated with significant drug acquisition costs.[32] These incremental costs, however, should be examined within the context of all clinical benefits and toxicities associated with trastuzumab therapy.[33] Indeed, a number of cost-effectiveness analyses (CEA)/cost-utility analyses (CUA) examined the "value for money" associated with palliative trastuzumab therapy in various scenarios (Table 2).[34–41] CEA and CUA incorporate disease outcomes, treatment benefit/toxicity, costs and quality of life to compute the incremental costs per life-year (LY) or quality-adjusted life-year (QALY) gains, respectively associated with an intervention/treatment.[42] CEA/CUE analyses rely on estimates of mean survival gains that incorporate life expectancy as opposed to median survival outcomes from clinical trials that involve relatively shorter follow up.[42] CEA/CUE therefore often require survival modelling beyond the relatively short follow-up in clinical trials and/or extrapolation of survival gains from intermediate patient outcomes such as time to progression or progression free survival.[42] The World Health Organization defines favourable cost-effectiveness based on the Gross Domestic Product (GDP) per

Table 2. Cost-effectiveness of palliative trastuzumab in breast cancer.

Study	Year	Origin	Drug costs (US$)*	Survival benefit	Cost-effectiveness (US$)*
Trastuzumab monotherapy					
NICE Appraisal[34]	2002	UK	£5,300 (US$8,255)	8 months	£19,000 (US$29,293)/QALY
Neyt et al[35]	2005	Belgium	NR	3.1 months	€47,777 (US$61,780)/LY
Trastuzumab plus chemotherapy					
NICE Appraisal[34]	2002	UK	£15,500 (US$24,141)	10 months	£37,500 (US$58,406)/QALY
Norum et al[36]	2005	Norway	€39,454 (US$51,018)	8.4–3.7 months	€63,137–162,417 (US$81,643–210,021)/LY
Poncet et al[37–38]	2008	France	€14,102 (US$18,235)	17 months	€15,370 (US$19,875)/LY
Perez-Ellis et al[39]	2009	France	€17,020 (US$22,009)	18 months	€27,492 (US$35,550)/LY
Trastuzumab plus endocrine therapy					
Fleeman et al[40]	2011	UK	£35,702 (US$55,606)	8.0 months	£69,000 (US$107,468)/QALY
Trastuzumab beyond progression					
Matter-Walstra et al[41]	2010	Swiss	€18,756 (US$24,253)	5.5 months	€98,329 (US$127,149)/QALY

Notes: *Cost-effectiveness estimates in US$ are presented for comparison purposes only and should not be interpreted as the cost-effectiveness of trastuzumab in the USA. Exchange rates on January 20, 2012 (http://money.cnn.com/data/currencies/index.html).
Abbreviations: LY, Life Year; QALY, Quality Adjusted Life Year; NR, Not Reported; NICE, National Institute of Clinical Excellence.

capita in various jurisdictions: highly cost effective (<GDP/capita), cost-effective (1–3 times GDP/capita) and not cost effective (>3 times GDP/capita).[43] In North America and the UK, interventions associated with cost-effectiveness below thresholds of $50,000–100,000 and £20,000–30,000 per QALY gained respectively have been considered economically-favourable.[44,45]

Palliative trastuzumab monotherapy

The cost-effectiveness of palliative trastuzumab monotherapy relative to standard chemotherapy alone was computed based on estimates of net survival benefits from indirect across-studies comparisons, as there were no randomized trials of trastuzumab monotherapy versus chemotherapy. A manufacturer (Roche)[14] economic evaluation, reviewed by the UK' National Institute for Clinical Excellence (NICE), found a cost-utility of £19,000 per QALY gained for trastuzumab monotherapy relative to vinorelbine chemotherapy with an 8 month mean survival benefit (2.6-quality adjusted months).[34] As well, Neyt et al reported a cost-utility of €47,777 per QALY gained in Belgium with a 3.1 month survival benefit for trastuzumab monotherapy relative to docetaxel chemotherapy.[35]

Palliative trastuzumab plus chemotherapy

The cost-effectiveness of palliative trastuzumab plus chemotherapy relative to chemotherapy alone was also computed based on derivation of the net survival benefits achieved with palliative trastuzumab. Analyses based on survival estimates derived from randomized clinical trials [34,36] reported less favourable "value for money" compared with those based on pragmatic / non randomized studies.[37–39] NICE reviewed an economic evaluation by trastuzumab manufacturer (Roche)[14] that found a cost-effectiveness of £37,500 per QALY gained for trastuzumab plus chemotherapy relative to chemotherapy alone,[34] based on a 10-month survival benefit computed from one pivotal clinical trial.[16] NICE appraisal committee however believed that the survival benefit in the model may have been underestimated and that the true cost-effectiveness is likely more favourable. Norum et al[36] also reported an unfavourable cost-effectiveness of €63,137 to €162,417 per QALY gained in Norway, based on 8.4 to 3.7 months survival benefit derived from the two relevant pivotal clinical trials.[16,17] Conversely, Poncet et al reported more favourable cost-effectiveness of €15,370 per QALY gained in France for trastuzumab in combination with chemotherapy relative to chemotherapy alone based on a 17 month survival benefit observed with trastuzumab in a non-randomized study.[37,38] As well, Perez-Ellis also reported cost-effectiveness of €27,492 per QALY gained based on an 18 month survival benefit after compared with before introduction of trastuzumab in France.[39] The 17 to 18 months net survival benefits observed in the latter two non randomized studies however are far superior to the survival benefit observed in the relevant randomized clinical trials.[16,17]

Palliative trastuzumab plus endocrine therapy

A health technology assessment by Fleeman et al reported a CU of £69,000 per QALY for trastuzumab plus anastrozole compared with anastrozole alone based on an 8.0-month mean survival benefit derived from the relevant clinical trial (TAnDEM trial).[40] As well, Fleeman et al also reported a CU of £225,000 per QALY for lapatinib plus letrozole compared with letrozole alone based a 2-month mean survival benefit from a clinical trial (EGF30008 trial). An economic evaluation of trastuzumab plus anastrozole compared with lapatinib plus letrozole, based on indirect across-studies comparison, was not performed by Fleeman et al as it was considered inappropriate given the differences in these two trials cohorts.

Palliative trastuzumab beyond progression

Matter-Walstra et al reported a CE of €98,329 per QALY gained for capecitabine plus trastuzumab beyond progression versus capecitabine alone based on a computed 5.5-month mean survival benefit.[41] As well, Le et al[46] and Delea et al[47] reported CUs for lapatinib plus capecitabine versus capecitabine alone of US$166,113 and £77,993 per QALY gained based on 2.0 and 3.8 month survival benefits, respectively. Economic evaluations of trastuzumab plus capecitabine versus lapatinib plus capecitabine were also conducted, but should be viewed within the methodological limitations of indirect across-studies analyses.[47,48] Younis et al found comparable up-front costs (ie, drug acquisition and administration) for

trastuzumab plus capecitabine relative to lapatinib plus capecitabine in a cost-minimization analysis assuming clinical equivalence between the two strategies,[48] while Delea at al projected 0.4 month QALY gains and £107 fewer costs for the latter strategy (ie, economic dominance) in a cost-utility analysis.[47]

Palliative trastuzumab plus other targeted agents

The cost-effectiveness of combining "trastuzumab-based therapy" with other anti-HER2 targeted agents such as lapatinib or pertuzumab has not been evaluated to date. The incorporation of these novel targeted agents within currently utilized trastuzumab-based strategies however is unlikely to provide good "value for money" at commonly utilized "cost-effectiveness" thresholds given their current and/or anticipated high drug acquisition costs as well as the magnitude of absolute survival gains associated with these strategies in the relevant clinical trials.[43–45]

In summary, the cost-effectiveness of trastuzumab for HER2-positive metastatic breast cancer is primarily driven by its clinical efficacy, in terms of incremental survival benefit, and trastuzumab costs. Indeed, palliative trastuzumab appears to be associated with more favourable "value for money" as first-line treatment with or without chemotherapy relative to continuing trastuzumab treatment beyond progression given the lower magnitude of clinical benefits (survival gains) observed in the latter compared with the former scenarios. It is also unlikely that the incorporation of other expensive albeit effective anti-HER2 targeted therapies (eg, lapatinib or pertuzumab) with trastuzumab would prove to be cost-effective at the currently employed cost-effectiveness thresholds in various jurisdictions.

Author Contributions

Alwin Jeyakumar and Tallal Younis co-designed the review, reviewed the data, and co wrote the manuscript. Both authors reviewed and approved the final manuscript.

Alwin Jeyakumar: Percent contribution to team effort; 50%.

Tallal Younis: Percent contribution to team effort; 50%.

Competing Interests

The authors have no conflicts of interest to declare.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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