health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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n SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NATIONAL ESSENTIAL MEDICINES LIST COMMITTEE
LIMITED REVIEW TEMPLATE FOR UPDATES TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS
TRASTUZUMAB – NEOADJUVANT THERAPY FOR EARLY BREAST CANCER
JUNE 2026

MEDICINE DETAILS

Medicine Class	No	
Medicine/s name **- INN:** **- South African name (if it differs from INN)**	Trastuzumab	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	L01FD01	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	Neoadjuvant therapy for HER2+ early and locally advanced breast cancer (excluding T1N0)	
SAHPRA Approved	Yes	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Injection	
Route of administration/s	Intravenous infusion	
Patient population	Neoadjuvant therapy for HER2+ early and locally advanced breast cancer (excluding T1N0)	
Prevalence and/or incidence of condition	According to the WHO Global Cancer Observatory (Ferlay et al., 2024), breast cancer was the most frequently diagnosed cancer in South Africa, with 14,712 new cases recorded in 2022, representing 13.2% of all cancer diagnoses. Given that approximately 85% of the South African population relies on the public health sector, an estimated 12,505 of these cases would present within public health facilities. Of these, roughly 60% — approximately 7,503 patients — would be expected to present with early-stage or locally advanced (non-metastatic) disease, where curative intent remains possible. Within this cohort, around 20% of breast cancers are HER2-overexpressed, yielding an estimated 1,500 potentially eligible cases. Although these patients could be considered for Trastuzumab-based therapy, not all will be eligible, as further reduced when accounting for mandatory cardiac screening requirements: patients must demonstrate a left ventricular ejection fraction (LVEF) exceeding 55%, and any significant cardiac comorbidities must be identified, optimally managed, and excluded prior to initiation of therapy. This would meaningfully narrow the number of patients who are both clinically eligible and safe candidates for treatment.	
Level of Care	Tertiary	
Prescriber level	Specialist (oncologist)	

CURRENT STANDARD OF CARE

Trastuzumab in the adjuvant setting is currently the standard of care for *early HER-2-positive breast cancer* and was first included in the Essential Medicines List in 2017. Initially, the recommendation was for a 12-month course regimen; however, in 2019, based on updated evidence, the recommendation was amended to a 6-month regimen. See historic review documents below:


UPDATED - Clinical criteria for access to T


Trastuzumab_6 month course - N Dec


Trastuzmab Clinical Review_NHC update_

EXECUTIVE SUMMARY

- We conducted a limited review of the available evidence that assessed the use of neoadjuvant trastuzumab plus chemotherapy in patients with HER2+ non-metastatic breast cancer (including early and locally advanced BC, HR +/-), excluding T1N0; compared to neoadjuvant chemotherapy alone.
- We searched the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) for relevant guidelines (February 2026). We identified four clinical practice guidelines and deemed one appropriate for inclusion: the ASCO guideline, Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer (Korde et al., 2021).
- This guideline outlines the therapy in the neoadjuvant setting and includes recommendations about trastuzumab plus chemotherapy in this setting. A duplicate AGREE II assessment rated the ASCO guideline (Korde et al., 2021) as high quality (77%).
- The ASCO guideline (Korde et al., 2021) recommendations for use of neoadjuvant trastuzumab were: “patients with node-positive or high-risk node-negative, HER2-positive disease should be offered neoadjuvant therapy with an anthracycline and taxane or non–anthracycline-based regimen in combination with trastuzumab. Pertuzumab may be used with trastuzumab in the neoadjuvant setting” *(Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).*
- The most recent network meta-analysis informing the recommendations in the ASCO guideline (Korde et al., 2021) on neoadjuvant trastuzumab was Nakashoji *et al.* (2018). This study included five randomised controlled trials (RCTs) that directly compared chemotherapy (CT) alone with CT combined with trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the neoadjuvant setting: Buzdar *et al*. (2005), NOAH (Gianni et al., 2010), Pierga *et al*. (2010), H2269s (Chang et al., 2010), and ABCSG-24 (Steger et al., 2014). The cytotoxic chemotherapy backbones varied across studies, including paclitaxel followed by fluorouracil-epirubicin-cyclophosphamide (FEC) (Buzdar et al., 2005), doxorubicin-paclitaxel followed by cyclophosphamide-methotrexate-fluorouracil (CMF) (Gianni et al., 2010), epirubicin-cyclophosphamide followed by docetaxel (Pierga et al., 2010), docetaxel plus carboplatin (Chang et al., 2010), and epirubicin plus docetaxel plus capecitabine (Steger et al., 2014). Clinical stages ranged from Stage II to Stage IIIA, and hormone receptor-positive tumours accounted for 35–63% of cases across the included trials.
- Summary of effectiveness results from Nakashoji *et al.* (2018):
  - Pathological complete response (pCR)
    - » Nakashoji et al. (2018) reported this outcome, which was defined as the absence of invasive residual cancer in the breast tissue and nodes. There were a lower number of pCR events in the neoadjuvant chemotherapy (CT) alone (52 out of 258, 20.2%) compared to the neoadjuvant trastuzumab plus chemotherapy (CT + tzmb) (97 out of 261; 37.2%) [Odds ratio (OR) 2.32, 95% CI 1.49 to 3.62, $p < 0.01$, 5 trials, n=519; number needed to treat (NNT) 6].

- Cardiac toxicity
  - » Cardiac events were assessed as a secondary outcome in Nakashoji et al. (2018). These events included both asymptomatic (e.g. less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline) and symptomatic events (e.g. congestive heart failure or cardiac death). There were fewer cardiac events in the neoadjuvant chemotherapy alone group (19 out of 239; 7.9%) compared to the neoadjuvant trastuzumab plus chemotherapy group (26 out of 244; 10.7%) (OR 1.33,95% CI 0.7 to 2.53, p = 0.38, four trials, n=483, number needed to harm (NNH) = 36.
- Other grade 3 or 4 adverse events
  - » *Diarrhoea: Nakashoji et al.* (2018) *reported a higher number of diarrhoea events in the neoadjuvant chemotherapy alone group (4 out of 171, 2.3%) compared to the neoadjuvant trastuzumab plus chemotherapy group (1 out of 177, 0.6%) (OR of 0.24, 95% CI 0.03 to 2.17, 2 studies, n=348, p = 0.44; NNT 57).*
  - » *Neutropenia: Nakashoji et al.* (2018) *reported a slightly lower proportion of neutropenia events in the neoadjuvant chemotherapy alone group (54 out of 190, 28.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (60 out of 200, 30.0%) (OR 1.28, 95% CI 0.33 to 4.29, 3 trials, n=390, p = 0.79; NNH 62).*
  - » *Skin Disorders: Nakashoji et al.* (2018) *reported a higher proportion of skin disorder events in the neoadjuvant chemotherapy alone group (9 events out of 107, 8.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (5 out of 106, 4.7%) (OR 0.55, 95% CI 0.18 to 1.72, 2 trials, n=213, p = 0.31; NNT 27).*
- We were not able to separate the recommendations by early and locally advanced breast cancer, as Nakashoji et.al. (2018) did not perform subgroup analysis by stage of disease for the outcomes reported.
- The review did not analyse the primary outcomes - overall survival and disease-free survival - due to insufficient data. Additionally, outcomes of tumour recurrence and quality of life were not reported.

➡ Overall survival and disease-free survival with the use of adjuvant trastuzumab in HER2-positive early breast cancer have been established in the previous trastuzumab review for inclusion on the EML 2017: *Trastuzumab in the adjuvant setting for early HER-2-positive breast cancer;* and 2019 update.

- The PERSEPHONE trial (Earl et al., 2019) used in the 2019 *Adjuvant trastuzumab (6-month duration)* review showed the following efficacy estimates of 6-month vs 12-month adjuvant trastuzumab:
  - » 4-year disease-free survival (DFS): 6 months = 89.4%; 12 months = 89.8% (hazard ratio [HR] 1.07 [90% CI 0.93-1.24], non-inferiority p=0.011).
  - » 4-year overall survival (OS): 6 months = 93.8%; 12 months = 94.8% (HR for OS = 1.14 [90% CI 0.95–1.37], non-inferiority p=0.0010).
  - » The participant inclusion criteria included invasive early breast cancer with overexpression of the HER2 receptor. Baseline characteristics indicated that participants had nodal status of 1 to 4, ranging tumour size (≤ 2cm, >2 to ≤ 5cm, and >5cm), and tumour grades ranging from I to II.
- From the original review that resulted in the inclusion of trastuzumab on the Essential Medicines List (EML), one of the meta-analyses included was the Cochrane Review examining trastuzumab-containing regimens for early breast cancer (Moja et al., 2012).
  - » OS (36-month median follow-up): HR 0.66; 95% CI 0.57 to 0.77, P < 0.00001 (Quality of Evidence: High).
  - » DFS (36-month median follow-up): HR 0.6; 95% CI 0.5 to 0.71, p < 0.00001 (Quality of Evidence: High).
  - » Participants included were women with HER2-positive breast cancer (early or locally advanced) of any age, menopausal status, nodal or hormone receptor status.

➡ The cost of trastuzumab has come down considerably over the past 8 years (59% - with no inflation adjustments).

KEY RECOMMENDATIONS

<table>
<tr><td rowspan="2">Type of ERC recommendation</td><td>We recommend against the option and for the alternative (strong)</td><td>We suggest not to use the option or to use the alternative (conditional)</td><td>We suggest using the option (conditional)</td><td>We recommend the option (strong)</td></tr>
<tr><td>□</td><td>□</td><td>□</td><td>X</td></tr>
<tr><td>High-level summary of conclusions</td><td colspan="4">• The review showed that compared to neoadjuvant chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy improved pathological complete response in stage 1 to 3 disease (including T1c to T4N3M0) HER2+ breast cancer: odds ratio (OR) 2.32 (95% confidence interval [CI] 1.49 to 3.62), p < 0.01 (5 studies); NNT 6.
• The only change to the current EML trastuzumab recommendations would be to move trastuzumab therapy from the adjuvant to the neoadjuvant setting. The locally advanced HER2+ breast cancer cohort would be an additional cohort for consideration of care. *
• The cost of trastuzumab has come down considerably over the past 8 years (59% - with no inflation adjustments).

(* We were not able to separate the recommendations by early local and locally advanced breast cancer, as subgroup analysis by stage of disease was not reported in the trials.)</td></tr>
<tr><td rowspan="2">NEMLC Ratification</td><td colspan="2">Date</td><td colspan="2">Comments/Recommendation</td></tr>
<tr><td colspan="2">4 June 2026</td><td colspan="2">NEMLC approved the inclusion of neoadjuvant trastuzumab for HER2+ early local and locally advanced breast cancer (excluding T1N0).</td></tr>
<tr><td rowspan="2">EML Status</td><td colspan="2">EML</td><td>Non-EML – contingent on stated reference price threshold in Rand Value</td><td colspan="2">Non-EML</td></tr>
<tr><td colspan="2">X</td><td>□</td><td colspan="2">□</td></tr>
<tr><td rowspan="2">Therapeutic Interchange Considerations (if applicable) *</td><td rowspan="2">If YES:</td><td>Alternative medicine/s name (INN)</td><td>Alternative/s SAHPRA registered?</td><td>Formulation/s</td><td>Equipotent dose/Dose range and dosing interval</td><td>If NO, tick the box</td></tr>
<tr><td>n/a</td><td>n/a</td><td>n/a</td><td>n/a</td><td>X</td></tr>
<tr><td>Trigger for review</td><td colspan="5">An alternative therapeutic agent at a lower price. Update based on new trial results.</td></tr>
</table>

BACKGROUND AND RATIONALE

Description of the condition

Breast cancer is the most frequently diagnosed cancer globally, accounting for a disproportionate burden of cancer-related morbidity and mortality (Ferlay et al., 2024). Human epidermal growth factor receptor 2 (HER2)-positive breast cancer, defined by overexpression or amplification of the HER2 proto-oncogene, represents approximately 20% of all breast cancer cases and is associated with a historically poor

prognosis characterised by aggressive tumour behaviour, higher rates of recurrence, and reduced survival compared to HER2-negative subtypes (Slamon et al., 2001).

Breast cancer management has traditionally involved initial surgical resection of the primary tumour, followed by adjuvant systemic therapy to eradicate micrometastatic disease and reduce the risk of recurrence (Gradishar et al., 2022). Neoadjuvant therapy — the administration of systemic treatment prior to surgery or radiotherapy — has increasingly been adopted in clinical practice, aiming to transform inoperable tumours into operable ones, enhance breast-conservation rates, and allow direct in vivo assessment of tumour sensitivity to treatment (Kaufmann et al., 2012). In patients who do not achieve a pathological complete response (pCR) at surgery, histological findings guide subsequent treatment decisions (Chen et al., 2023). A pCR, defined as the absence of invasive residual cancer in the breast tissue and axillary nodes (Buzdar et al., 2005), is consistently associated with improved disease-free survival (DFS) and overall survival (OS), making it a critical surrogate endpoint in neoadjuvant trials (Cortazar et al., 2014; Petrelli et al., 2011).

Description of the intervention and how it might work

Trastuzumab is a humanised monoclonal antibody that binds selectively to the extracellular domain of the HER2 receptor, inhibiting downstream signalling pathways involved in tumour cell proliferation and survival (Vu & Claret, 2012). It is the foundational anti-HER2 agent in both the adjuvant and neoadjuvant settings (Nakashoji et al., 2018) and was first approved for inclusion on the Essential Medicines List (EML) in June 2017 for adjuvant treatment of early-stage HER2-positive breast cancer, with the duration subsequently revised from 12 to 6 months in December 2019.

Randomised controlled trials (Buzdar et al., 2005; Buzdar et al., 2005). The NOAH trial (Gianni et al., 2010), conducted in locally advanced or inflammatory HER2-positive breast cancer, demonstrated significantly improved event-free survival (EFS) with the addition of trastuzumab to neoadjuvant chemotherapy (hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.38–0.90; p = 0.013) and a higher pCR rate (38% *vs*. 19%). Petrelli et al. (2011) subsequently pooled these two trials, confirming that trastuzumab more than doubles the likelihood of achieving pCR (relative risk [RR] 2.07; 95% CI 1.41–3.03; p = 0.0002), reduces relapse risk (RR 0.67; 95% CI 0.48–0.94; p = 0.02), and does not significantly increase cardiac toxicity (RR 1.09; 95% CI 0.60–1.98; p = 0.77).

It is important to note that dual HER2 blockade with pertuzumab will not be assessed in the present review, which focuses exclusively on trastuzumab in the neoadjuvant setting. Neoadjuvant regimens are generally considered equivalent to adjuvant regimens with identical dosing schemes; however, neoadjuvant therapy provides the additional advantage of immediate histological assessment of treatment response, which informs subsequent management (Von Minckwitz et al., 2010).

Why it is important to do this review

Despite the established efficacy of trastuzumab in the adjuvant setting, its role in the neoadjuvant setting remains clinically important, particularly in resource-limited settings where access to dual HER2 blockade may be constrained. The potential for improved surgical outcomes — including conversion of inoperable to operable disease and enhanced breast-conservation rates — makes this intervention particularly relevant in the locally advanced, non-metastatic setting, which has been prioritised in the PICO framework of this review. Accumulating evidence suggests that the risk of cardiotoxicity is manageable when cumulative anthracycline doses are kept below established safety thresholds (Petrelli et al., 2011). This review aimed to summarise the evidence on the efficacy and safety of trastuzumab-based neoadjuvant therapy in patients with HER2+ non-metastatic breast cancer (including early local and locally advanced BC, hormone receptor positive or negative) compared to neoadjuvant chemotherapy alone.

PURPOSE/OBJECTIVE I.E., PICO QUESTION

Population Subgroups	Patients with HER2+ non-metastatic breast cancer (including early and locally advanced BC, HR +/-), excluding T1N0
Intervention(s)	Neoadjuvant trastuzumab plus chemotherapy
Comparator(s)	Neoadjuvant chemotherapy alone
Outcome(s)	Primary outcomes: 1. Overall survival (OS): time from randomisation to death (from any cause). 2. Disease-free survival (DFS): *time from randomisation to date of recurrence of tumour or death from any cause.* 3. Pathologic complete response (pCR): *the proportion of patients with a complete or partial response. Partial response is defined as a decrease in tumour size or the extent of cancer in the body in response to treatment. pCR is defined as the absence of invasive residual cancer in the breast tissue and nodes* Secondary outcomes: 4. Tumour recurrences: *local breast cancer recurrence or development of metastatic disease. We defined 'recurrence rate' as the proportion of patients with local breast cancer recurrence or metastatic disease; 'time to recurrence' (also referred to as 'disease-free interval') was the time from randomisation to the first recurrence. Within distant recurrences, we considered the risk of disease progression due to metastasis of the central nervous system (CNS).* 5. Cardiac toxicity: *congestive heart failure (CHF) and decline of left ventricular ejection fraction (LVEF). We considered the following definitions of CHF: New York Heart Association class III-IV; severe CHF; symptomatic CHF; or confirmed CHF. The decline in LVEF was defined as reported by the authors, who used different thresholds.* 6. Quality of life (QoL): *Expression of well-being, measured through a validated scale (i.e. SF-36, European Organisation for Research and Treatment of Cancer (EORTC), Functional Assessment of Cancer Therapy (FACT).*
Study types	CPGs Systematic reviews/RCTs (if needed)

METHODS

1. Data Sources

A tiered approach was implemented: first, we considered high-quality, relevant, and up-to-date clinical practice guidelines; then, systematic reviews (SRs); and, finally, randomised controlled trials (RCTs) and other observational study designs as needed (Cochrane Collaboration, 2020). We searched for relevant guidelines in the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO). Due to the guideline search result, progression to SR, RCT, and observational trial stages *was not required.*

2. Search Strategy

We searched the relevant guideline repositories using the keywords “breast cancer”, “neoadjuvant therapy”, and “trastuzumab”.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

Relevant clinical practice guidelines were identified by one reviewer (AS) and checked by a second reviewer (JR/SD). Potentially eligible guidelines were screened to determine how well the recommendations in the guideline matched the PICO of interest and whether there was a clear link to the evidence used to inform the recommendation *(see Appendix 1)*. Relevant recommendations were extracted from the included guideline by one reviewer (JR) and checked by a second reviewer (SE). The underlying evidence synthesis for the relevant guidelines/recommendations was assessed. When multiple eligible SRs were included, we reported evidence from the most relevant, recent, and highest-quality-assessed review. Although results from eligible reviews that were not up to date, credible, or failed to report on critical outcomes were not prioritised, the results and direction of effects were cross-checked.

4. Assessment of methodological quality

We used the AGREE II tool (Brouwers et al., 2010) to assess the selected clinical practice guideline, and the AMSTAR II (Shea et al., 2017) tool to assess the systematic review included in the selected guideline (Korde et al., 2021). Guideline and SR appraisals were conducted in duplicate, and discrepancies were resolved through consensus.

Data synthesis

Results from the included review were presented. For outcomes not reported in the Nakashoji et al. (2018) review, we extracted information from the included trials. Nakashoji et al. (2018) did not assess the certainty of the evidence; however, given the limited nature of this review, we did not conduct these assessments.

RESULTS

1. Result of the search

We identified four clinical practice guidelines *(see Appendix 1)* and deemed one appropriate for inclusion: the ASCO guideline, Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer (Korde et al., 2021). Of the other three, two were excluded because there was no clear link to the evidence that informed the recommendation, and one did not match the PICO of interest (Appendix 1).

2. Description of included studies

a. Clinical Practice Guideline:

The ASCO guideline (Korde et al., 2021) outlines adjuvant therapy and includes recommendations for trastuzumab plus chemotherapy in this setting. The relevant recommendations from this guideline (Korde et al, 2021) were the following:

- Patients with node-positive or high-risk node-negative, HER2-positive disease should be offered neoadjuvant therapy with an anthracycline and taxane or non–anthracycline-based regimen in combination with trastuzumab. Pertuzumab may be used with trastuzumab in the neoadjuvant setting. (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

- Patients with T1a N0 and T1b N0, HER2-positive disease should not be routinely offered neoadjuvant chemotherapy or anti-HER2 agents outside of a clinical trial. (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate)

Authors mention that "ASCO adopted the GRADE Methodology as a recognised standard in guideline development methodology"; however, when contacted, authors did not share the GRADE summary of findings (SoF) tables with us.

The evidence linked to the recommendation around trastuzumab plus chemotherapy in the neoadjuvant setting involved several reviews (Bria et al., 2014; Clavarezza et al., 2016; Hicks et al., 2015; Nagayama et al., 2014; Nakashoji et al., 2018; Petrelli et al., 2011; Valachis et al., 2012; Von Minckwitz et al., 2011), see *Appendix 2*. The SR by Nakashoji *et. al*. (2018) was found to be the most relevant and up-to-date SR and was included in this review.

b. Systematic reviews:

Nakashoji *et al*. (2018) is an updated network meta-analysis of randomised trials comparing anti-HER-2 regimens in the neoadjuvant setting (Nagayama et al., 2014). Direct and indirect comparisons were performed, and the direct comparisons of neoadjuvant trastuzumab plus chemotherapy and neoadjuvant chemotherapy were included in this review. Table 1 provides details of the five trials included in Nakashoji 2018 that were relevant to this review.

Table 1: Characteristics of included RCTs (Nakashoji et al., 2018)

	No. of patients	Clinical stage	Neoadjuvant chemother-apy	Neoadjuvant anti-HER2 agent	Arms	HR positive patients (%)	Duration (week)	Adjuvant therapy
Buzdar et al. (2005)	42	II-IIIA	Paclitaxel/FEC	Trastuzumab -	23 19	13 (56) 11 (58)	24	None
Gianni et al. (2010)/ NOAH	235	T3N1, T4, any TN2-3: IIIA, IIIB, and IIIC	AP/Paclitaxel/ CMF	Trastuzumab -	117 118	40 (35) 40 (35)	33	Trastuzumab None
Pierga et al. (2010)	120	II-III	EC/docetaxel	Trastuzumab -	62 58	34 (55) 37 (63)	24 12	Trastuzumab ± 5-FU ± vi-norelbine
Chang et al. (2010)/H2269s	29	T2-4: II-III	Docetaxel + carboplatin	Trastuzumab -	15 14	NR NR	12	Docetaxel + carboplatin + Trastuzumab
Steger et al. 2014)/ ABCSG-24	89	T1-4: I-IIIB	Epirubicin + docetaxel + capecitabine	Trastuzumab -	44 49	26 (59) 30 (61)	18	NR

HR = hormone receptor; tzmb = trastuzumab; lpnb = lapatinib; pzmb = pertuzumab; NR = not reported; FEC = fluorouracil-epirubicin-cyclophosphamide; AP = doxorubicin-paclitaxel; CMF = cyclophosphamide-methotrexate-fluorouracil; EC = epirubicin-cyclophosphamide.

3. Methodological quality of included studies

a. A duplicate AGREE II assessment rated the ASCO guideline (Korde et al., 2021) as high quality (77% overall) (*Appendix 3*). It scored high across most domains: 92% for scope and purpose, clarity of presentation, and rigour of development; 72% for stakeholder involvement; 79% for editorial independence; and 50% for applicability.

b. Appraisal of Nakashoji *et al*. (2018): AMSTAR II assessed in duplicate found this review to be of low quality *(Appendix 4)*. It had one critical flaw – it did not investigate publication bias- and one non-critical flaw – it did not report the funding sources of the included studies.

c. Risk of Bias (RoB) of included trials in the Nakashoji *et al*. (2018) SR, using the Cochrane RoB 1.0 tool (Higgins & Altman, 2008), reported an unclear risk of bias in most domains across the 5 included RCTs (Table 2).

Table 2: Risk of bias summary (Nakashoji et al., 2018)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Steger et al., 2014)/ABCSG-24	?	?	-	?	?	+	?
Buzdar et al. (2005)	+	+	?	?	?	+	-
Chang et al. (2010)/H2269s	?	?	-	?	-	-	?
Gianni et al. (2010)/NOAH	+	+	-	?	+	+	+
Pierga et al. (2010)	?	?	?	+	+	+	+
** +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.*							
† Other bias is defined as the manner of diagnosis of HER2 positivity (i.e., whether it is confirmed centrally).							
‡ Risk of bias tool, developed by the Cochrane Collaboration, to assess the potential limitations in randomised trials separates a judgment about risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias.							

4. Effectiveness and/or safety

Comparison: Neoadjuvant trastuzumab plus chemotherapy vs neoadjuvant chemotherapy alone

Outcome 1: overall survival (OS)

Overall survival (OS) was not assessed by Nakashoji et.al. (2018) due to insufficient data. Of the five trials included in Nakashoji et al. (2018), only the NOAH trial (Gianni et al., 2010) reported OS, showing a reduced risk of death in the Trastuzumab group (Table 4).

Table 4: Overall survival (OS) reported in five neoadjuvant chemotherapy trials included in Nakashoji et al. (2018)

Trial	Follow-up	Overall Survival (OS)
Buzdar et al. (2005)	Median 20 months	Not formally reported; no treatment-related deaths
Gianni et al. (2010)/ NOAH	Median 3.2 years	3-year OS: 87% (trastuzumab) vs 79% (no trastuzumab); HR 0.62 (p=0.114)
Pierga et al. (2010)	Not stated	Not reported — authors explicitly state survival data not yet available; no treatment-related deaths
Chang et al. (2010)/ H2269s	Median 1.9 years	Not formally reported as rates; no treatment-related deaths
Steger et al., 2014)/ ABCSG-24	Not reported	Not reported; DFS/OS listed as secondary endpoints, but no data presented

Abbreviations: pCR, pathologic complete response; cCR, clinical complete response; EFS, event-free survival; RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; TC, docetaxel + carboplatin; P, paclitaxel; FEC, fluorouracil + epirubicin + cyclophosphamide; ED, epirubicin + docetaxel; EC-D, epirubicin + cyclophosphamide followed by docetaxel; HR, hazard ratio.

Outcome 2: Disease-free survival (DFS)

Nakashoji 2018 did not assess disease-free survival (DFS) due to insufficient data. Of the five trials included in Nakashoji et al. (2018), only the NOAH trial (Gianni et al., 2010) reported mature survival data, demonstrating an improvement in event-free survival (EFS) with trastuzumab (3-year EFS 71% vs 56%; HR 0.59, p=0.013). The Chang *et al.* (2010) trial reported a trend toward improved recurrence-free survival (RFS) in patients achieving pCR compared with those who did not (p=0.12). However, the study was underpowered to achieve statistical significance. The other trials did not report on survival. The Buzdar *et al.* (2005) and Steger *et al.* (2014) trials were primarily designed around pathologic complete response (pCR) as the primary endpoint, with insufficient follow-up or subgroup size to draw survival conclusions. The Pierga *et al*. (2010) trial explicitly deferred survival reporting at the time of publication.

Table 4: Disease-free/ event-free/ recurrence-free survival (DFS/EFS/RFS) outcomes reported in five neoadjuvant chemotherapy trials included in Nakashoji et al. (2018)

Trial	Follow-up	Disease-Free/Event-Free/Recurrence-Free Survival
Buzdar et al. (2005)	Median 20 months	Not formally reported; only one recurrence observed (in the chemotherapy-alone arm)
Gianni et al. (2010)/NOAH	Median 3.2 years	3-year EFS: 71% (trastuzumab) vs 56% (no trastuzumab); HR 0.59 (p=0.013)
Pierga et al. (2010)	Not stated	Not reported — authors explicitly state survival data not yet available
Chang et al. (2010)/H2269s	Median 1.9 years	RFS at 2 years: 93.8% (pCR) vs 78.4% (no pCR); at 3 years: 83.3% vs 58% (p=0.12). RFS by cCR status was not predictive (p=0.999)
Steger et al. (2014)/ ABCSG-24	Not stated	Not reported; trial focused on pCR as primary endpoint

Abbreviations: pCR, pathologic complete response; cCR, clinical complete response; EFS, event-free survival; RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; TC, docetaxel + carboplatin; P, paclitaxel; FEC, fluorouracil + epirubicin + cyclophosphamide; ED, epirubicin + docetaxel; EC-D, epirubicin + cyclophosphamide followed by docetaxel; HR, hazard ratio.

Outcome 3: Pathological complete response (pCR)

Nakashoji 2018 reported this outcome, which was defined as the absence of invasive residual cancer in the breast tissue and nodes. There were a lower number of pCR events in the neoadjuvant chemotherapy (CT) alone (52 out of 258, 20.2%) compared to the neoadjuvant trastuzumab plus chemotherapy (CT + tzmb) (97 out of 261; 37.2%) [Odds ratio (OR) 2.32, 95% CI 1.49 to 3.62, p < 0.01, 5 trials, n=519; number needed to treat (NNT) 6] (Figure 1)

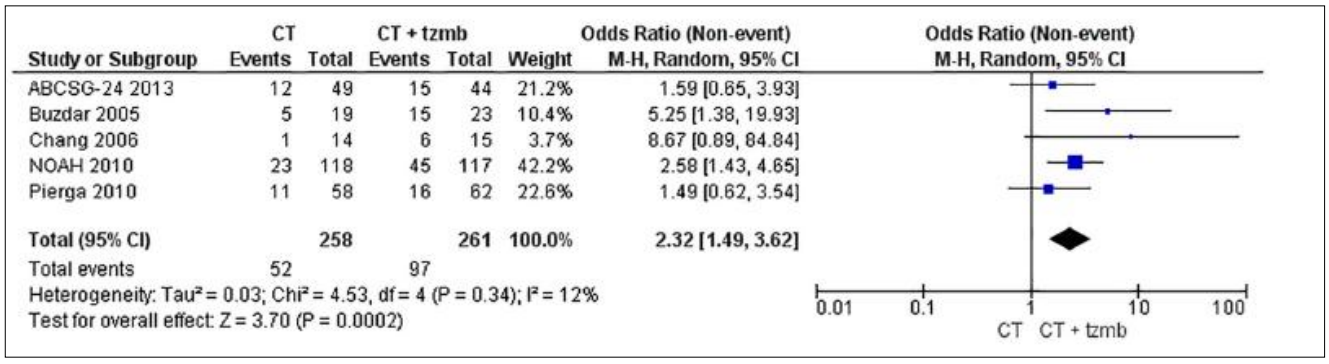

Figure 1: Forest plot of OR for pCR in CT and CT + trastuzumab arms

Outcome 4: Tumour recurrences

Not reported in the included review or the trials included in the review. Buzdar et al. (2005), Gianni et al. (2010), and Chang et al. (2010) reviewed recurrence in relation to event- or disease-free survival, see Table 4.

Outcome 5: Cardiac toxicity

Cardiac events were assessed as a secondary outcome in Nakashoji et al. (2018). These events included both asymptomatic (e.g. less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline) and symptomatic events (e.g. congestive heart failure or cardiac death). There were fewer cardiac events in the neoadjuvant chemotherapy alone group (19 out of 239; 7.9%) compared to the neoadjuvant trastuzumab plus chemotherapy group (26 out of 244; 10.7%) (OR 1.33,95% CI 0.7 to 2.53, p = 0.38, four trials, n=483; number needed to harm (NNH) = 36.

Other grade 3 or 4 adverse events *(National Cancer Institute Common Terminology Criteria [NCI-CTC], 2009)*

Diarrhoea

Nakashoji et al. (2018) reported a higher number of diarrhoea events in the neoadjuvant chemotherapy alone group (4 out of 171, 2.3%) compared to the neoadjuvant trastuzumab plus chemotherapy group (1 out of 177, 0.6%)
(OR of 0.24, 95% CI 0.03 to 2.17, 2 studies, n=348, p = 0.44; NNT 57).

Neutropenia

Nakashoji et al. (2018) reported a slightly lower proportion of neutropenia events in the neoadjuvant chemotherapy alone group (54 out of 190, 28.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (60 out of 200, 30.0%) (OR 1.28, 95% CI 0.33 to 4.29, 3 trials, n=390, p = 0.79; NNH 62).

Skin Disorders

Nakashoji et al. (2018) reported a higher proportion of skin disorder events in the neoadjuvant chemotherapy alone group (9 events out of 107, 8.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (5 out of 106, 4.7%) (OR 0.55, 95% CI 0.18 to 1.72, 2 trials, n=213, p = 0.31; NNT 27).

Outcome 6: Quality of life (QoL)

Not reported in the included review or the trials included in the review.

5. Survival Outcomes in Adjuvant Breast Cancer Evidence

- The PERSEPHONE trial (Earl et al., 2019) used in a previous review showed the following efficacy estimates of 6-month vs 12-month adjuvant trastuzumab:
  - 4-year DFS: 6 months = 89.4%; 12 months = 89.8% (HR 1.07 [90% CI 0.93-1.24], non-inferiority p=0.011).
  - 4-year OS: 6 months = 93.8%; 12 months = 94.8% (HR for OS = 1.14 [90% CI 0.95–1.37], non-inferiority p=0.0010).
  - The participant inclusion criteria included invasive early breast cancer with overexpression of the HER2 receptor. Baseline characteristics indicated that participants had nodal status of 1 to 4, ranging tumour size (≤ 2cm, >2 to ≤ 5cm, and >5cm), and tumour grades ranging from I to III.
- From the original review that resulted in the inclusion of trastuzumab on the Essential Medicines List (EML), one of the meta-analyses included was the Cochrane Review examining trastuzumab-containing regimens for early breast cancer (Moja et al.,2012).

- OS (36-month median follow-up): HR 0.66; 95% CI 0.57 to 0.77, p < 0.00001 (Quality of Evidence: High).
- DFS (36-month median follow-up): HR 0.6; 95% CI 0.5 to 0.71, p < 0.00001 (Quality of Evidence: High).
- Participants included were women with HER2-positive breast cancer (early local or locally advanced) of any age, menopausal status, nodal or hormone receptor status.

COSTS

National tender prices

Trastuzumab has been included in all National tenders (*Supply and Delivery of Oncology and Immunological Agents to the National Department of Health*) since July 2018. Over these 8 years, the price of trastuzumab has significantly reduced. *See Table 4 and Figure 2.*

Table 4: Oncology and Immunological Tenders since 2018

Tender	Date tender start	Date tender ending	Company	Volume	Price
RT290-2018	1-Jul-18	30-Jun-20	Roche	990	**R6,531.61**
HP04-2020ONC	1-Jul-20	30-Jun-22	Mylan	1952	**R5,000.00**
HP04-2022ONC	1-Jul-22	30-Jun-24	Cipla	4300	**R3,450.00**
HP04-2024ONC	1-Jul-24	30-Jun-24	Viatris	6515	**R3,149.00**
HP06-2026ONC	1-Jul-26	30-Jun-28	Equity	9660	**R2,676.65**

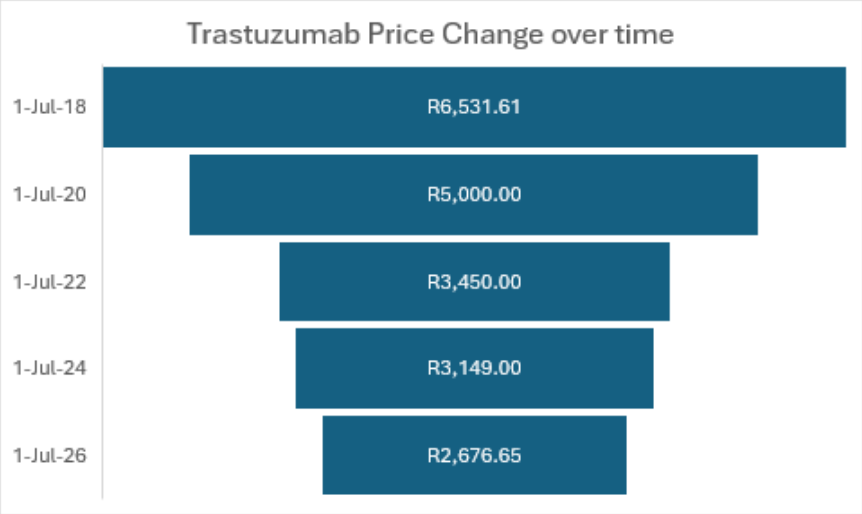

Figure 2: Trastuzumab price change from 2018 to date

There has been a consistent reduction in the price of trastuzumab with each subsequent tender, with an overall decrease of 59% over the last 8 years (see Table 5: Percentage decrease in price). If inflation is taken into account, the overall price decrease amounts to 71%; see Table 6.

Table 5: Percentage decrease in price

Date tender start	Price	% decrease from last tender	% decrease from first introduction
1-Jul-18	R6,531.61		
1-Jul-20	R5,000.00	23%	23%
1-Jul-22	R3,450.00	31%	47%
1-Jul-24	R3,149.00	9%	52%
1-Jul-26	R2,676.65	15%	59%

Table 6: Percentage decrease from 2018 with inflation-adjusted price

Date tender start	Inflation amended price	% decrease from 2018, taking inflation into account*	SEPA**
1-Jul-18	R9,090.47*		
1-Jul-26	R2,676.65	71%	69%

**https://inflationcalc.co.za/ (Note inflation measured to March 2026 (financial year end) - total 7-year increase: 39.2%, Annual increase 4.84%; Starting value: R6531.61 – price in 2018)*
*** Annual Single Exit Price Adjustment (SEPA) https://www.health.gov.za/nhi-pee/*

National Tender Volumes

Over the past 8 years, the volume estimates for tenders have also increased (Figure 3).

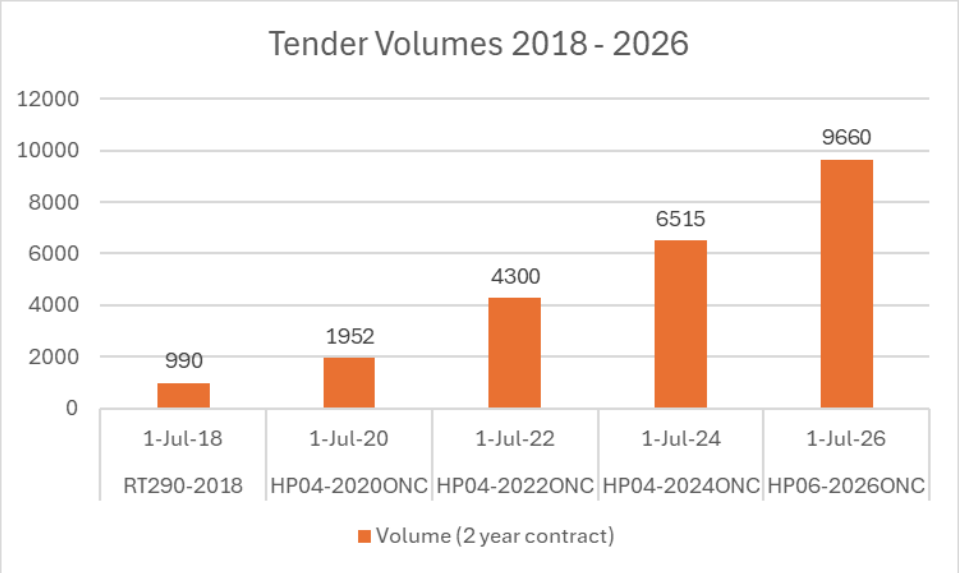

Figure 3: Tender volumes awarded 2018 to 2026

Based on the volumes awarded and the approved regimens, assuming an average weight of 70kg, the estimated number of patients that could be treated per year was calculated, ranging from 26 in 2018 to 483 in 2026. (Figure 4).

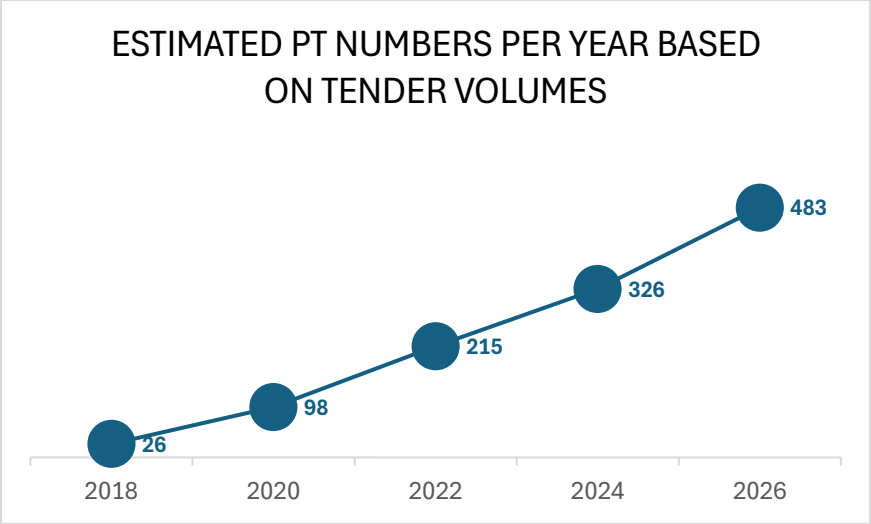

Figure 4: Estimated patient numbers per year (based on volumes tendered)

National Surveillance Centre Procurement Data

Data from the National Surveillance Centre on Trastuzumab utilisation was requested. Note: This data showed minimal utilisation until 2022, and only Western Cape procurement data was included. The figure below shows procurement of trastuzumab vials on a National level, with the estimated patient numbers calculated (with the same assumptions as above (See Figure 4).

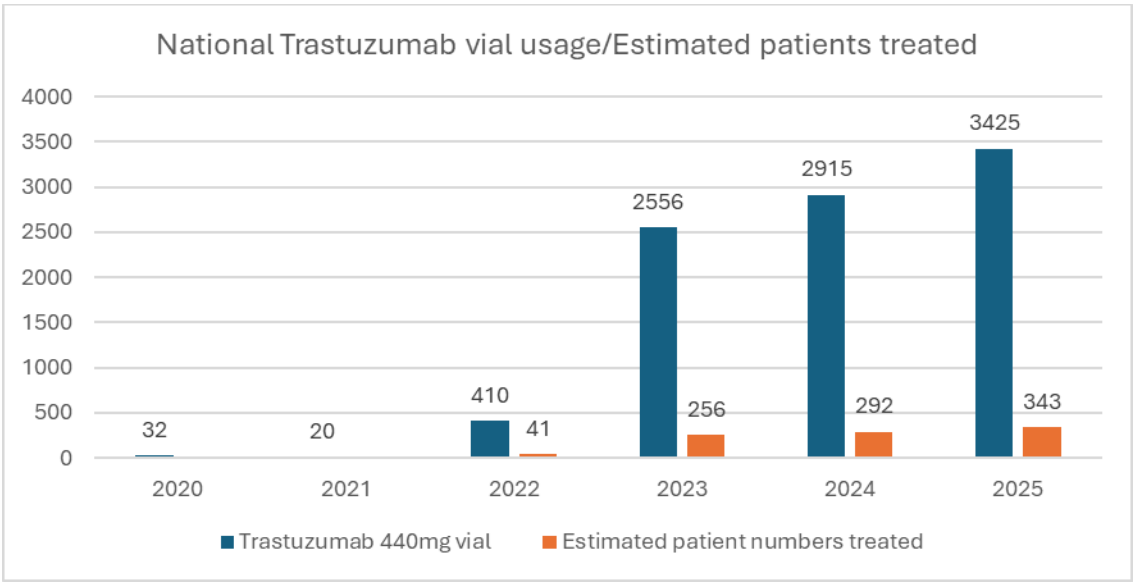

Figure 5: National trastuzumab vial usage and estimated patient numbers based on this usage

The hospital-level procurement data is displayed in Figure 6 below, showing procurement across hospitals from 2022 to 2025.

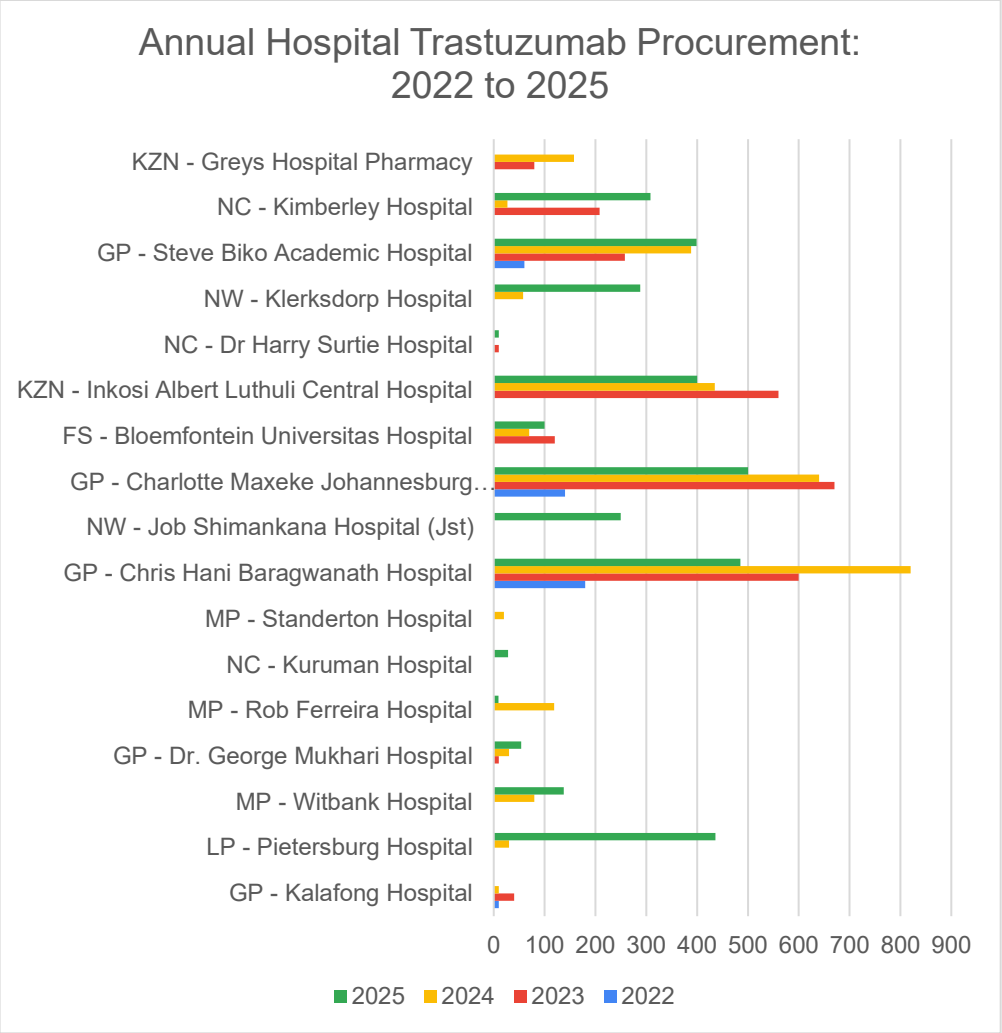

Figure 6: Annual hospital trastuzumab procurement: 2022 to 2025

Trastuzumab regimen costs

The currently approved trastuzumab regimen in the adjuvant setting is as follows: *Initially, 8 mg/kg IV infusion (week 1), then 6 mg/kg IV infusion (from week 4) every 3 weeks for 6 months (initially 12 months, updated in 2019). Based on this regimen, the estimated regimen costs of trastuzumab since its first introduction are displayed in Table 7.*

Table 7: Trastuzumab regimen – cost per patient per course

Tender period	Cost per patient per course #
2018	R65,316.10
2020	R50,000.00
2022	R34,500.00
2024	R31,490.00
2026	R26,766.50

 # Based on dosing for a 70kg individual with no vial sharing – 10 vials per patient

Budget Impact Analysis

Patient number estimates:

Table 8: Patient number estimates and assumptions

		Patient Numbers	Source
Annual new cases of breast cancer		14712	WHO 2022 - SA - Global Cancer Observatory
HER2+ pts	25%	3678	https://doi.org/10.4102/safp.v68i1.6200
Public sector	80%	2942	
Early local	35%	1030	Expert opinion – half/half split*
Locally advanced	35%	1030	
Metastatic (stage 4)	30%	883	Expert opinion for the public sector*
T1a N0 and T1b N0	1%	29	Expert opinion - Less than 1 % in the public sector*
Early local (excluding T1aN0 and T1bN0) plus locally advanced	69%	**2030**	

**No data on a National Level for public sector patient volumes*

Annual Budget Impact

Annual budget impact based on pricing for the new HP04-2026ONC contract taking effect in July 2026.

Table 9: Annual budget impact

	Patient numbers	Annual budget Impact*
Early Local Breast Cancer (excluding T1aN0, T1bN0)	1000	R26,777,634.86
Locally Advanced	1030	R27,565,212.36
Early local plus locally advanced	2030	R54,342,847.22

**HP04-2026ONC National Contract Pricing*

**For reference, when trastuzumab was first approved in 2017, the budget impact for treating less than 500 patients per annum was in the region of R40 million in the first year (12-month regimen).*

DISCUSSION

Summary of main findings (Nakashoji et al., 2018)

- Pathological complete response (pCR)
  - » Nakashoji et al. (2018) reported this outcome, which was defined as the absence of invasive residual cancer in the breast tissue and nodes. There were a lower number of pCR events in the neoadjuvant chemotherapy (CT) alone (52 out of 258, 20.2%) compared to the neoadjuvant trastuzumab plus chemotherapy (CT + tzmb) (97 out of 261; 37.2%) [Odds ratio (OR) 2.32, 95% CI 1.49 to 3.62, p < 0.01, 5 trials, n=519; number needed to treat (NNT) 6].

    Cardiac toxicity
  - » Cardiac events were assessed as a secondary outcome in Nakashoji et al. (2018). These events included both asymptomatic (e.g. less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline) and symptomatic events (e.g. congestive heart failure or cardiac death). There were fewer cardiac events in the neoadjuvant chemotherapy alone group (19 out of 239; 7.9%) compared to the neoadjuvant trastuzumab plus chemotherapy group (26 out of 244; 10.7%) (OR 1.33,95% CI 0.7 to 2.53, p = 0.38, four trials, n=483; number needed to harm (NNH) = 36.
- Other grade 3 or 4 adverse events

  - » *Diarrhoea:* Nakashoji et al. (2018) *reported a higher number of diarrhoea events in the neoadjuvant chemotherapy alone group (4 out of 171, 2.3%) compared to the neoadjuvant trastuzumab plus chemotherapy group (1 out of 177, 0.6%) (OR of 0.24, 95% CI 0.03 to 2.17, 2 studies, n=348, p = 0.44; NNT 57).*
  - » *Neutropenia:* Nakashoji et al. (2018) *reported a slightly lower proportion of neutropenia events in the neoadjuvant chemotherapy alone group (54 out of 190, 28.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (60 out of 200, 30.0%) (OR 1.28, 95% CI 0.33 to 4.29, 3 trials, n=390, p = 0.79; NNH 62).*
  - » *Skin Disorders:* Nakashoji et al. (2018) *reported a higher proportion of skin disorder events in the neoadjuvant chemotherapy alone group (9 events out of 107, 8.4%) compared to the neoadjuvant trastuzumab plus chemotherapy group (5 out of 106, 4.7%) (OR 0.55, 95% CI 0.18 to 1.72, 2 trials, n=213, p = 0.31; NNT 27).*
- We were not able to separate the recommendations by early and locally advanced breast cancer, as Nakashoji et al. (2018) did not perform subgroup analysis by stage of disease for the outcomes reported.
- The review did not analyse the primary outcomes - overall survival and disease-free survival - due to insufficient data. Additionally, outcomes of tumour recurrence and quality of life were not reported.

Costs

The price of trastuzumab has decreased considerably since it was first introduced on the essential medicines list 8 years ago (2017), with an absolute decrease in vial price of 59% and, if Single Exit Price Adjustment (SEPA) is considered, a 69% decrease. Estimations of potential budget impact were undertaken for the hypothesised patient population, showing an estimated R54 million annual budget impact for both the early and locally advanced breast cancer cohorts (Early breast cancer: estimated 1,000 patients; locally advanced breast cancer: 1,030 patients). Although current procurement data for trastuzumab indicate an estimated patient volume of approximately 348 per year (only the early setting is currently approved), uptake may not reach these levels.

Other reviews on this topic

The benefits of trastuzumab in the adjuvant treatment of HER2-positive breast cancer are well established, with adjuvant systemic treatment incorporating trastuzumab demonstrably reducing the risk of recurrence and death in this patient population (Clavarezza et al., 2016). The subsequent translation of trastuzumab into the neoadjuvant setting offers several important advantages over its use alone in the adjuvant setting. Neoadjuvant regimens incorporating trastuzumab are considered therapeutically equivalent to adjuvant regimens with identical dosing schemes. However, the neoadjuvant approach provides the additional benefit of allowing immediate histopathological assessment of treatment response following surgical resection of the primary tumour (von Minckwitz et al., 2011). This is clinically significant given that pathological complete response (pCR), defined as the absence of invasive residual tumour in the breast and axillary lymph nodes, is consistently associated with favourable long-term outcomes and has been proposed as a surrogate marker for survival (von Minckwitz et al., 2011).

The addition of trastuzumab to neoadjuvant anthracycline and taxane-based chemotherapy has been shown to more than double the likelihood of achieving pCR in the breast and axillary nodes (RR 2.07; 95% CI 1.41–3.03; p = 0.0002), while simultaneously reducing the risk of disease relapse by 33% (RR 0.67; 95% CI 0.48–0.94; p = 0.02), without a statistically significant increase in cardiac toxicity (RR 1.09; 95% CI 0.60–1.98; p = 0.77) (Petrelli et al., 2011). Furthermore, in patients with HER2-positive tumours, concurrent trastuzumab during neoadjuvant chemotherapy increases the odds of achieving pCR approximately 3.2-fold (OR 3.20; 95% CI 2.19–4.67; p < 0.001) (von Minckwitz et al., 2011). The clinical significance of

improvements in pCR in the neoadjuvant setting is underscored by evidence from the NOAH trial, in which an absolute 20% increase in pCR achieved by adding trastuzumab to neoadjuvant chemotherapy translated into an absolute 8% increase in three-year overall survival (Gianni et al., 2010).

Limitations in the review

Evidence on long-term overall and disease-free survival is limited, as most neoadjuvant trastuzumab studies were designed around pathological complete response. However, long-term overall and disease-free survival have been established in the adjuvant setting, which is considered concordant with use in the neoadjuvant setting.

GRADE Summary of Findings tables were not provided by the ASCO guideline (Korde et al., 2021) authors and were not available in the Nakashoji *et al*. (2018) review. Furthermore, we did not perform a GRADE certainty of evidence assessment for the outcomes reported in the Nakashoji *et al*. (2018) SR. Review authors did not perform subgroup analyses by stage of disease for the reported outcomes (Nakashoji et al., 2018), and these were also not reported in the individual trials.

CONCLUSION AND RECOMMENDATION

This review shows that neoadjuvant trastuzumab plus chemotherapy improves pathological complete response compared to neoadjuvant chemotherapy alone for both early local and locally advanced HER2+ breast cancer. The use of trastuzumab increased cardiac toxicity and neutropenia rates; this is consistent with what was seen in the adjuvant trastuzumab setting. Neoadjuvant trastuzumab plus chemotherapy was associated with less diarrhoea and skin disorders than neoadjuvant chemotherapy alone. Taken together, these findings support the neoadjuvant use of trastuzumab not only as a means of improving surgical outcomes and breast-conservation rates but also as a strategy to identify early treatment response, guide subsequent management, and potentially improve long-term survival in patients with early local and locally advanced HER2+ breast cancer. In terms of early local breast cancer, the only change to the current recommendations would be to move trastuzumab therapy from the adjuvant to the neoadjuvant setting. The locally advanced HER2+ breast cancer cohort would be an additional cohort for consideration of care.

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of included studies	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Jane Riddin[1]	None to declare	X	X	X	X	X	X	X	N/A	X	-	X
Sumayyah Ebrahim[2, 3]	None to declare	X	X	X	X	X	X	X	N/A	X	-	X
Alicia Sherriff[4]	None to declare	X	X	X	X	-	-	-	N/A	X	X	X
Solange Durao[2]	None to declare	X	X	X	X	-	X	-	N/A	X	-	X
Derusha Frank[5]	None to declare	-	-	-	-	-	X	-	N/A	-	-	X

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5. Clinton Health Access Initiative, supporting the Essential Drug Programme

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APPENDIX 1: GUIDELINE REVIEW AND SELECTION

Guideline	Guideline includes recommendation(s) that match the priority PICO question					There is a clear link to evidence used to inform the recommendation (yes/no) [if no, exclude]	Final judgement re inclusion
	Patients	Intervention	Control	Outcomes	Overall judgement re alignment of recommendations with PICO question		
ESMO[i]	• HER2-positive EBC • HR+ and –	Matching recommendation: "HER2-directed therapy (with initial concurrent ChT) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment [I, A; ESCAT score: I-A]."	Unclear. From table S8 seems like the comparison is ChT (HERA trial)	Unclear. Seems like evidence on trastuzumab vs chT specifically focuses on DFS outcome (Supplementary Table S8)	Seems aligned, but not too clear from the CPG document	No. The potential matching recommendation for neoadjuvant treatment lacks specific evidence.	No
NCCN[ii]	HR + and - HER2+ breast cancer	Unclear re: neoadjuvant therapy. Main treatment algorithms only refer to 'systemic adjuvant treatment'. Section BINV-M refers to 'preoperative/adjuvant therapy" with some regimens recommended that include Trastuzumab	Unclear	Recurrence, breast cancer-specific survival, recurrence-free survival	Seems aligned but unclear. Page MS 47 refers to adjuvant therapy for HER2-positive tumours where trastuzumab is mentioned:	No. Some refs mentioned in the written section (MS 47 onwards), but related to adjuvant therapy No evidence synthesis mentioned	No
NICE EBC[iii]	HER2-positive breast cancer	No. Trastuzumab + ChT seems linked to a recommendation for adjuvant therapy only, not neoadjuvant	Yes		Intervention not aligned. Trastuzumab +pertuzumab recommended for neoadjuvant therapy, and other types of neoadjuvant ChT (platinum and taxane)	Yes, but does not match PICO	No
ASCO[vi]	Non-metastatic breast cancer, including HER2+	Trastuzumab plus chemotherapy included	Yes	Pathological complete response Adverse events	Intervention aligned. Key outcome of PCR included ADRs.	Yes	Yes

i. https://www.annalsofoncology.org/article/S0923-7534(23)05104-9/fulltext
ii. https://www.nccn.org/guidelines/guidelines-detail?id=1419
iii. https://www.nice.org.uk/guidance/ng101
iv. http://ascopubs.org/doi/full/10.1200/JCO.20.03399

APPENDIX 2: SUMMARY RESULTS OF SYSTEMATIC REVIEWS AND META-ANALYSES (KORDE ET AL., 2021/ASCO GUIDELINE)

Authors/Year/ Clinical Question (CQ)	Number of studies/patients	Intervention	Key Findings of Meta-Analysis	Journal/ Source
Neoadjuvant treatment for patients with HER2-positive disease				
Nakashoji et al. (2018). (Update of analyses reported in Nagayama et al., 2014)	3,160 patients from 13 trials. Five trials with 519 patients compared neoadjuvant trastuzumab plus chemotherapy to neoadjuvant chemotherapy alone	Anti-HER2 regimens in the neoadjuvant setting	• Pooled analyses demonstrate that combining two anti-HER2 agents with chemotherapy is most effective against HER2-positive breast cancer in the neoadjuvant setting. • Dual anti-HER2 agents with chemotherapy achieved a better pCR rate vs. the other arm. • Chemotherapy plus trastuzumab plus pertuzumab had the highest probability of being the best treatment arm for pCR based on the values of the surface under the cumulative ranking.	Cancer Treatment Reviews
Clavarezza et al. (2016).	1,155 patients from six RCTs	Neoadjuvant dual block with lapatinib and trastuzumab versus trastuzumab alone in HER2(+) breast cancer	• Lapatinib-trastuzumab dual block associated with a 13% absolute improvement in pCR rate vs. single-agent trastuzumab (summary risk difference [SRD], 0.13; 95% CI, 0.08-0.19). • Activity greater in HR- patients who received chemotherapy with taxanes alone (SRD 0.25; 95% CI, 0.13-0.37) vs. HR+ or HR- disease treated with anthracyclines plus taxanes or the docetaxel-carboplatin regimen • (SRD 0.09; 95% CI, 0.02-0.15; P interaction = 0.05).	Clinical Cancer Research
Hicks et al. (2015).	1,017 patients from five trials	Neoadjuvant chemotherapy plus dual HER2-targeted therapy with lapatinib and trastuzumab	• There was a statistically significant improvement in pCR (defined as no residual carcinoma in breast and lymph nodes) based on the combined analysis of four trials of the addition of lapatinib to trastuzumab plus NACT: pCR rate of 55.76% (lapatinib plus trastuzumab arm) vs. 38.36% (trastuzumab plus NACT arm), OR, 1.94; 95% CI 1.44–2.60. • There was also a statistically significant improvement in pCR (defined as no residual invasive carcinoma in breast only) based on combined analysis of three trials: pCR rate of 55.01% (lapatinib plus trastuzumab) vs. 40.70% (trastuzumab alone), OR, 1.78; 95% CI: 1.27–2.50.	The Oncologist
Nagayama et al. (2014).	2,247 patients in seven different treatment arms	Anti-HER2 agents, including trastuzumab, lapatinib, and pertuzumab	• No statistically significant difference in pCR between dual targeting treatment arms. • Patients in the dual targeting arms had statistically significantly more pCR than patients in other treatment arms (chemotherapy • + trastuzumab, trastuzumab + pertuzumab vs chemotherapy + trastuzumab; OR, 2.29, 95% credibility interval = 1.02 to 5.02, P = 0.02). • In terms of pCR, chemotherapy + trastuzumab + pertuzumab had the highest probability of being the best treatment based on the surface under the cumulative ranking probability curve.	Journal of the National Cancer Institute

Authors/Year/ Clinical Question (CQ)	Number of studies/patients	Intervention	Key Findings of Meta-Analysis	Journal/ Source
Bria et al. (2014).	1,820 patients from six trials and 3,580 patients from 31 arms (14 trials) in the event-based pooled analysis	Neoadjuvant single or dual HER2 inhibition and chemotherapy	• A combination of taxanes, anthracyclines, and anti-HER2 agents should currently be considered the standard of care. • Regardless of the chemotherapy backbone, dual HER2 inhibition significantly improves pCR rate (range=16-19%; RR, 1.37, 95% CI 1.23-1.53, p < 0.0001). • pCR significantly higher in HR- population, regardless of the HER2 inhibition and type of chemotherapy. • Regardless of the HER2 inhibition, the pCR rate is higher when anthracyclines are added to taxanes. • Severe neutropenia was higher with the addition of anthracyclines to taxanes (absolute difference of 19.7%), although there were no differences in febrile neutropenia.	Cancer Treatment Reviews
Valachis et al. (2012).	1,494 patients from six trials	Addition of lapatinib versus trastuzumab or their combination to neoadjuvant chemotherapy in HER2+ breast cancer	• Lapatinib is inferior in terms of pCR rate and is associated with a higher toxicity risk. Dual-HER2 inhibition superior for the treatment of HER2-positive breast cancer. • Probability to achieve pCR higher for the trastuzumab plus chemotherapy arm compared to lapatinib plus chemotherapy (RR, 1.25, 95% CI 1.08-1.43; p = 0.003; six trials; 1,494 patients). • Probability to achieve pCR was significantly higher in the group receiving lapatinib and trastuzumab vs in the group with trastuzumab alone (RR, 1.39, 95% CI 1.20-1.63; p < 0.001; four trials; 779 patients). • Grade III-IV diarrhoea and dermatologic toxicities were statistically more frequent in patients receiving lapatinib.	Breast Cancer Research and Treatment
Petrelli et al. (2011).	277 patients from two trials	Addition of concomitant trastuzumab to neoadjuvant (anthracycline and taxane-based) chemotherapy	• Adding concomitant trastuzumab to neoadjuvant chemotherapy doubles the risk of achieving pCR in both breast and nodes vs controls: RR, 2.07 (1.41–3.03; P = 0.0002; P for heterogeneity, 0.63). • Adding concomitant trastuzumab significantly reduces the risk of relapse (RR, 0.67; 0.48–0.94; P = 0.02) and does not increase the risk of cardiotoxicity (RR, 1.09; 0.6–1.98; P =0.77).	Anticancer Drugs
von Minckwitz et al. (2011).	3,332 patients from seven Neoadjuvant trials (IPD meta-analysis)	Characteristics of neoadjuvant therapy associated with pCR	• pCR associated with an increase in the number of chemotherapy cycles (odds ratio [OR] 1.2 for every two additional cycles; P = 0.009); with higher cumulative anthracycline doses (OR 1.6; P = 0.002); with higher cumulative taxane doses (OR 1.6; P = 0.009); and with capecitabine-containing regimens (OR 1.62; P = 0.022). • Association between a higher number of cycles and pCR is more pronounced in HR+ tumours (OR 1.35) vs HR- tumours (OR 1.04; P for interaction = 0.046). • In HER2+ tumours, simultaneous treatment with trastuzumab increased odds of pCR 3.2-fold (P < 0.001).	Breast Cancer Research and Treatment

APPENDIX 3: AGREE II – ASCO GUIDELINE

	ASCO Guideline - Neoadjuvant Chemo for breast cancer																						
	Scope & Purpose			Stakeholder Involvement			Rigour of Development								Clarity of Presentation			Applicability				Editorial Independence		Overall Assessment
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	
Appraiser 1	7	7	7	6	2	7	5	7	5	5	7	5	5	4	7	7	7	5	5	4	3	6	6	
Appraiser 2	5	7	6	6	5	6	5	5	5	5	6	5	5	5	6	6	6	4	5	4	2	5	6	
Item total	12	14	13	12	7	13	10	12	10	10	13	10	10	9	13	13	13	9	10	8	5	11	12	0
Domain total	39			32			84								39			32				23		249
Min possible score	6			6			16								6			8				4		46
Max possible score	42			42			112								42			56				28		322
score	**92%**			**72%**			**71%**								**92%**			**50%**				**79%**		**77%**

APPENDIX 4: AMSTAR II – Nakashoji *et al*. (2018)

No.	Criteria	Judgement
1	Research questions and inclusion criteria for the review included the components of PICO	Yes
2*	*Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol*	Yes
3	Review authors explained the selection of the study designs for inclusion in the review	Yes
4*	*Review authors used a comprehensive literature search strategy*	Yes
5	Review authors perform study selection in duplicate	Yes
6	Review authors perform data extraction in duplicate	Yes
7*	*Review authors provided a list of excluded studies and justified the exclusions*	Partial yes
8	Review authors described the included studies in adequate detail	Partial yes
9*	*Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review*	Partial yes
10	Review authors reported on the sources of funding for the studies included in the review.	No
11*	*For meta-analyses, review authors used appropriate methods for the statistical combination of results*	Yes
12	For meta-analyses, review authors assessed the potential impact of RoB in RCTs on the results of the meta-analysis/other evidence synthesis	Yes
13*	*Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review*	Yes
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes
15*	*For quantitative synthesis, the review authors carried out an adequate investigation of publication bias (small study bias) and discussed the likely impact*	No
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes
OVERALL QUALITY ASSESSMENT:		**LOW quality**
Rationale and conclusion:		See below for the respective rating

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence.