National Essential Medicine List
Tertiary Medication Review Process:

MEDICINE REVIEW:

1. Executive Summary

Date: 15 October 2019
Medicine (INN): Trastuzumab (6 months vs 12 months of adjuvant therapy)
Medicine (ATC): L01XC03
Indication (ICD10 code): C50 - Malignant neoplasm of the breast
Patient population: Adjuvant treatment for female patients with early stage HER-2 positive breast cancer
Prevalence of condition: 21.8% of all cancers and an age standardized incidence rate (ASR) of 0.33/1000 people[1]. Approximately 20% of breast cancer patients are HER-2 positive[4]. This equates to approximately 1650 patients of the 8230 new cases reported in South Africa during 2014[1]. 62% of breast cancers detected are localized to the breast[2]. Thus, approximately ~1025 patients would be eligible for trastuzumab.
Level of Care: Tertiary
Prescriber Level: Specialist - Oncologist
Current standard of Care: Trastuzumab 12-months (8mg/kg loading dose, followed by 6mg/kg administered 3-weekly thereafter)
Efficacy estimates: PERSEPHONE[3]:
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).

Safety estimates:
Severe adverse events:
6 months = 19%; 12 months = 24% (p=0.0002). NNH = 20

Study discontinuation due to cardiotoxicity:
6 months = 3%; 12 months = 8% (p<0.0001). NNH = 20

2. Lead reviewer: Mr R Wiseman
Recommendation peer-reviewed and endorsed by the Tertiary/Quaternary Expert Review Committee
Technical assistance: Dr Tamara Kredo (critical appraisal of systematic reviews)

3. Author affiliation and conflict of interest details:
Vice-chair: Tertiary/Quaternary Expert Review Committee
Liberty Health (Pty) Ltd
No financial conflicts declared. However, Liberty Health is a private health insurer operating in South Africa and across the broader African continent. In South Africa, Liberty Health offers managed health care services to a contracted closed medical scheme consisting of ~13 000 beneficiaries and derives revenue for these services on a fee per member per month basis. The South African Essential Medicines List has been used by the Council for Medical Schemes, the associated medical schemes regulator, as a determinant of the prevailing standard of care in the private sector.

Other conflicts: Prof Ruff – Mylan (manufacturer of trastuzumab biosimilar) – honorarium to the University of Witwatersrand for presentation at launch of biosimilar.

Management of conflict:
Dr Grobler assumed the chairperson role for the duration of the associated discussion. Prof Ruff and Mr Wiseman recused themselves from the final decision-making process.

4. Background

Trastuzumab as adjuvant therapy for the management of early stage breast cancer was first reviewed by the National Essential Medicines List Committee in March 2015 and then added to the Tertiary/Quaternary EML in June 2017. According to the associated clinical criteria document (see Appendix A), therapy is indicated in eligible patients at a dose of 8mg/kg as a loading dose followed by 6mg/kg thereafter administered 3-weekly for a period of 12 months (17 to 18 cycles). Notwithstanding its inclusion on the EML, access to trastuzumab remains inconsistent as several provinces continue to regard trastuzumab as unaffordable within the contexts of their respective oncology budgets. Thus, the intention of expanding access through its inclusion on the EML has not been met.

5. Rationale for review

As new and relevant literature is published, the Expert Review Committee is obliged to review the information in the context of any predefined review indicators. As part of the initial Tertiary/Quaternary review, the following review indicators were outlined for trastuzumab:

- Randomised controlled trials (RCTs) investigating the impact of shorter trastuzumab treatment periods on clinical effectiveness and safety.
- Randomised controlled trials investigating the optimal dosing schedule of trastuzumab treatment with different chemotherapy regimens.
- Long-term follow-up data of women who have been treated with trastuzumab.
- Studies that examine the risk of disease recurrence in specific subgroups (for example, those with nodal involvement, those with tumours with and without hormone receptors).
- Pricing changes, including introduction of generic products and biosimilars.
- Randomised controlled trials investigating the impact of trastuzumab versus novel agents on clinical effectiveness and safety.

Several papers[3, 13-18] have been published subsequent to this initial review. It is well established that the 12-month treatment duration was selected arbitrarily[3, 4]. Given that this treatment duration was used in the pivotal licensing trials, 12-months' therapy has become the de facto standard of care.[3] However, longer durations of trastuzumab therapy have been associated with an increased risk of harm[3], and the EML inclusion of trastuzumab is associated with substantial budget impact. This latter aspect has resulted in the unintended consequence of increasing inequity of access.

This review therefore serves to assess whether a shorter duration of therapy can decrease risk and promote equity of access while continuing to demonstrate clinical non-inferiority when compared with the 12-month regimen. This new information thus needs to be analysed to assess what impact a shorter trastuzumab treatment period has on its clinical efficacy and safety and whether any of the concerns raised above can be mitigated.

6. PICO question:

- **P**atient/population: Female patients with early stage HER2 positive breast cancer
- **I**ntervention: Trastuzumab 8mg/kg loading dose followed by 6mg/kg 3-weekly for 6 months
- **C**omparator: Trastuzumab 8mg/kg loading dose followed by 6mg/kg 3-weekly for 12 months
- **O**utcome: Disease Free Survival (DFS, primary), Overall Survival (OS, secondary)

7. Summary of safety and efficacy

NEMLC's 2017 assessment included 7 randomised controlled trials, investigating the use of trastuzumab as adjuvant therapy in patients with HER2 positive breast cancer. The studies demonstrated that trastuzumab led to a statistically significant reduction in disease progression (absolute difference 12% to 18% across 5 RCTs). Furthermore, the pooled odds ratio for disease free progression was 0.53 (95%CI 0.46 to 0.60). Overall survival was also improved (pooled OR 0.52 (95% CI 0.44-0.62), resulting in an absolute mortality reduction of 2.5%.

It was noted that the clinical evidence presented demonstrated that adjuvant trastuzumab improved DFS and OS outcomes compared with no trastuzumab but that DFS did not differ significantly when trastuzumab was given for less than or more than 6 months[3,4]. However, a longer treatment period (i.e. more than 6 months) was superior for OS compared with a shorter treatment period (i.e. less than 6 months). Treatment with trastuzumab for longer than 1 year (e.g. 2 years) did not offer additional DFS benefit to 1-year treatment[6-9]. Overall DFS was improved when trastuzumab was administered either concurrently or sequentially[6,10]. Overall improvement in OS was found with concurrent administration of trastuzumab, but not with sequential therapy[6, 10, 11].

Exposure to trastuzumab is associated with an increased risk of cardiotoxicity. Moreover, the longer the duration of exposure, the increased risk of harm. When compared with observation, the HERA study[12] reflected that for the parameter of "patients experiencing significant worsening of LVEF", the addition of trastuzumab for 1-year was associated with an absolute increase of 3.2% (95% CI 2.2% - 4.3%; Number Needed to Harm = 32). When administered for 2 years, trastuzumab increased the absolute risk to 6.3% vs observation (95% CI 5.0% - 7.6%) (NNH = 16). In the safety analysis of an associated Cochrane review[6], an overall higher risk of CHF was found with trastuzumab (RR 5.11; 90% CI 3.00-8.72). This risk increased significantly when trastuzumab was given for more than 6 months (RR 5.39; 90% CI 3.56-8.17), whereas a shorter treatment duration did not appear to increase the risk of CHF (RR 0.50; 90% CI 0.07-3.74). The risk of CHF was high whether trastuzumab was given sequentially (RR 11.05; 90% CI 3.46-35.29) or concurrently (RR 3.90; 90% CI 2.42-6.28).

8. Search Strategy

The following search strategy was used to source updated and relevant information:

Data sources: Pubmed, Cochrane Library, Google scholar

Search terms

("Trastuzumab"[Mesh] AND "Breast Neoplasms"[Mesh]) AND "Chemotherapy, Adjuvant"[Mesh] AND (Randomized Controlled Trial[ptyp] AND "2014/10/12"[PDat]: "2019/10/10"[PDat] AND "humans"[MeSH Terms])

48 results – only 2 (PHARE and PERSEPHONE) relevant for PICO evaluating 6 vs 12 months

- HORG identified through reference searches

("Trastuzumab"[Mesh] AND "Breast Neoplasms"[Mesh]) AND "Chemotherapy, Adjuvant"[Mesh] AND ((systematic[sb] OR Meta-Analysis[ptyp]) AND "2014/10/12"[PDat]: "2019/10/10"[PDat] AND "humans"[MeSH Terms])

10 results – 5 relevant to question

- Chen et. al. 2019[14] – included 9 weeks and 6-months in the short duration
- Inno et. al. 2019[15] – included 9 weeks and 6-months in the short duration
- Niraula et. al. 2019[16] – included 9 weeks in the short duration
- Gyawali et. al. 2017[17] – included 9 weeks and 6-months in short duration but excluded PERSEPHONE

- Genuino et. al. 2019[18] – PERSEPHONE, PHARE and HORG data not included

- Goldvaser et. al. 2019[13] identified through reference searches

See **Appendix B** for a tabular summary of the relevant trials, assessment of RCT quality and reasons for study exclusions.

Appendix C provides a critical appraisal of the Goldvaser et. al. 201913, Chen et. al. 2019[14] and Inno et. al. 2019[15] meta-analyses.

9. New data

PERSEPHONE - (Earl et. al, 2019)[3]

The PERSEPHONE study[3] was an open-label randomised phase 3 non-inferiority trial that aimed to investigate whether 6-month adjuvant trastuzumab treatment is noninferior to the standard 12-month treatment regarding disease-free survival. A total of 4089 female patients, aged 18 years of older, with a diagnosis of invasive early HER2 positive breast cancer were randomised to receive either 12-month trastuzumab treatment (n = 2045 patients) or 6-months treatment (n = 2044 patients). The patient population was considered to be heterogeneous: <5% had a primary tumour >5cm in size; >60% of patients had a tumour grading of Grade 3 (poorly differentiated); <15% of patients demonstrated N2 nodes and above (i.e. >4 nodes positive); and ~40% of patients received anthracyclines alone.

Both treatment regimens were delivered every 3 weeks intravenously (loading dose of 8 mg/kg followed by maintenance doses of 6 mg/kg) or subcutaneously (600 mg), given in combination with chemotherapy (concurrently or sequentially). The primary endpoint was disease-free survival, analysed by intention to treat, with a non-inferiority margin of 3% for 4-year disease-free survival. Secondary endpoints included overall survival and cardiac function as assessed by LVEF during treatment. Patients were followed-up for a median of 5.4 years.

A disease-free survival event was reported in 13% of patients in the 6-month group and 12% of patients in the 12-month group. 4-year disease-free survival was 89.4% (95% CI 87.9-90.7) in the 6-month group and 89.8% (88.3-91.1) in the 12-month group (hazard ratio 1.07 [90% CI 0.93-1.24], non-inferiority p=0.011). The absolute difference in overall survival between treatment groups at 4 years was 1% and was found to be non-inferior (4-year overall survival of 94.8% [95% CI 93.7–95.8] in the 12-month group and 93.8% [92.6–94.9] in the 6-month group). The noninferiority limit for the HR was set at 1.60. The HR for overall survival was 1.14 (90% CI 0.95–1.37, non-inferiority p=0.0010).

From a safety perspective, there were significantly fewer severe adverse events associated with the 6-month regimen (373 [19%] of 1939 patients vs 459 [24%] of 1894 patients, p=0.0002). Additionally, the 6-month regimen was associated with fewer patients terminating the study due to cardiotoxicity (61 [3%] of 1939 patients vs 146 [8%] of 1894 patients, p<0.0001).

PHARE and HORG Studies[4, 5]

For further contextulisation, the results of the PHARE and HORG studies[4, 5] are also included as two other studies comparing 6-month trastuzumab to 12-month trastuzumab.

The **PHARE study**[5] was an open-label, randomised, phase 3 trial involving 3384 female patients with HER2-positive early breast cancer who had received at least four cycles of chemotherapy, had breast-axillary surgery, and had received up to 6 months of trastuzumab (administered by intravenous infusions over 30–

90 min every 3 weeks; initial loading dose 8 mg/kg; 6 mg/kg thereafter) before randomisation. Patients were randomised to either discontinue trastuzumab at 6 months (6 months total duration; n = 1693 patients) or continue trastuzumab for a further 6 months (12 months total duration; n = 1691 patients). The primary endpoint was disease-free survival, with a prespecified non-inferiority margin of 1·15, as derived from an estimated absolute difference in 2-year disease-free survival of 2%. Patients were followed for a median duration of 42·5 months (3.5 years). 2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; p=0.29). In terms of safety, 119 (93%) of the 128 cardiac events (clinical or based on assessment of left ventricular ejection fraction) occurred while patients were receiving trastuzumab. More patients in the 12-month group experienced a cardiac event than did those in the 6-month group (96 [5·7%] of 1690 patients vs 32 [1·9%] of 1690 patients, p<0·0001).

The **HORG** study[4] was a randomized study to compare the efficacy of 12 versus 6 months of adjuvant trastuzumab administered concurrently with dose-dense chemotherapy in women with node-positive or high-risk node-negative HER2-positive early breast cancer. 481 female patients were randomised to receive either 12 months (n = 241 patients) or 6 months (n = 240 patients) of adjuvant trastuzumab. I.V trastuzumab was administered every 2 weeks (loading dose 6 mg/kg; 4 mg/kg thereafter) in both groups, starting concurrently with docetaxel. Thereafter, trastuzumab 6 mg/kg was administered every 3 weeks until the completion of 12 or 6 months of therapy according to randomization. The primary end point was 3-year DFS. Secondary end points included OS and toxicity. Median follow up was 47 months for the 12-month group and 51 months for the 6-month group. 3-year DFS was 95.7% for the 12-month group versus 93.3% for the 6-month group (hazard ratio = 1.57; 95% confidence interval 0.86–2.10; P = 0.137). There was no difference in terms of overall survival and cardiac toxicity between the two groups. There was also a non-significant difference in disease relapses between the two groups (7.1% vs. 11.7%; p = 0.08).

Comment

For eligibility in the HORG study, patients were required to have undergone either lumpectomy or modified radical mastectomy with tumor-free surgical margins plus axillary node dissection, and the tumor had to be invasive carcinoma with at least one positive axillary node. In May 2008, the HORG scientific committee amended the protocol and women with high risk node-negative disease were allowed to participate in the study.

Goldvaser et. al (2019)[13]: Systemic Review and Meta-Analysis

Goldvaser and colleagues[13] report on a meta-analysis evaluating the efficacy and toxicity of shorter duration of adjuvant trastuzumab compared with 1 year of treatment in women with HER2- positive early-stage breast cancer.

Six studies reported on DFS and OS and three studies reported on distant relapse. Compared with 1 year of treatment, shorter trastuzumab treatment (which included all durations of treatment shorter than 12 months) was associated with worse DFS (HR = 1.14, 95% CI ¼ 1.05 to 1.24, P=0.003) and OS (HR = 1.15, 95% CI = 1.02 to 1.29, P=0.02). Studies using trastuzumab for 9–12weeks showed worse DFS than trastuzumab treatment for 6months (HR = 1.28, 95% CI = 1.09 to 1.50 vs HR = 1.09, 95% CI = 0.98 to 1.20), but this did not reach statistical significance ($P_{subgroup\ difference}$ = 0.09). For OS no difference was observed between the two abbreviated trastuzumab durations (P=0.44). After an estimated median follow-up of 71months, shorter treatment with trastuzumab was associated with an absolute increase in DFS events of 2.3% (NNT 43). Similarly, after an estimated median follow-up of 76.8 months, there was a 1.5% higher absolute risk of distant relapse with abbreviated trastuzumab therapy (NNT 67).

Figures 1 and 2 represent the Forest plots for disease free survival and overall survival.

Figure 1: Disease Free Survival (DFS)

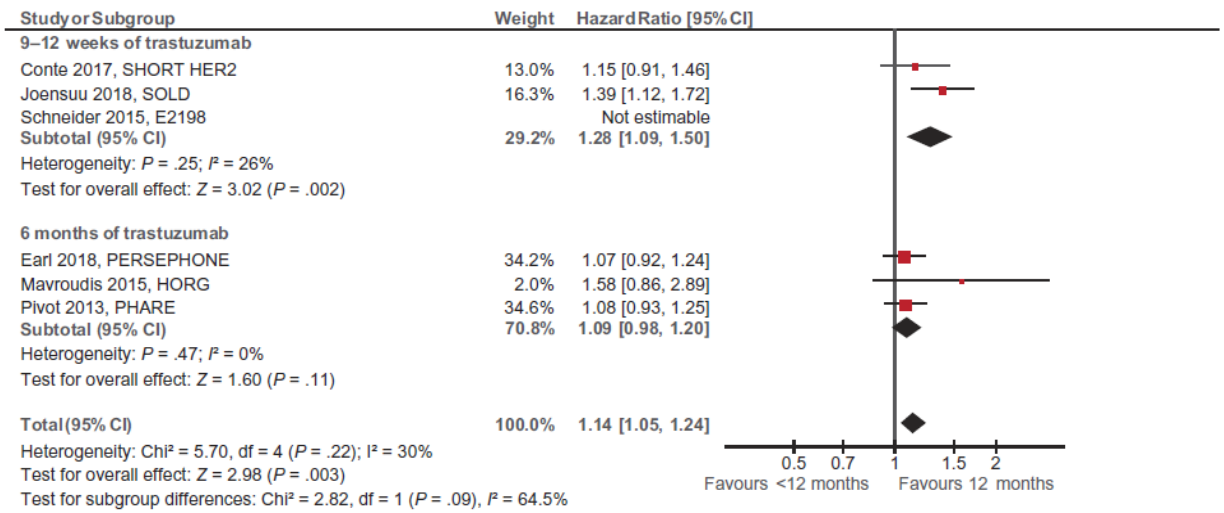
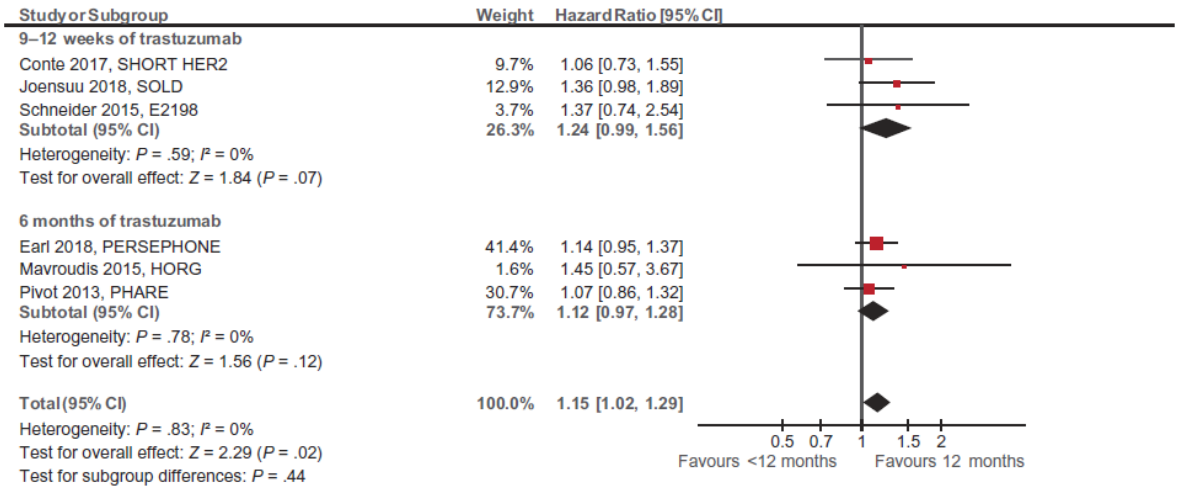


Figure 2: Overall survival



Figures 3 and 4 are the Forest plots for cardiotoxicity.

Figure 3: Cardiac dysfunction

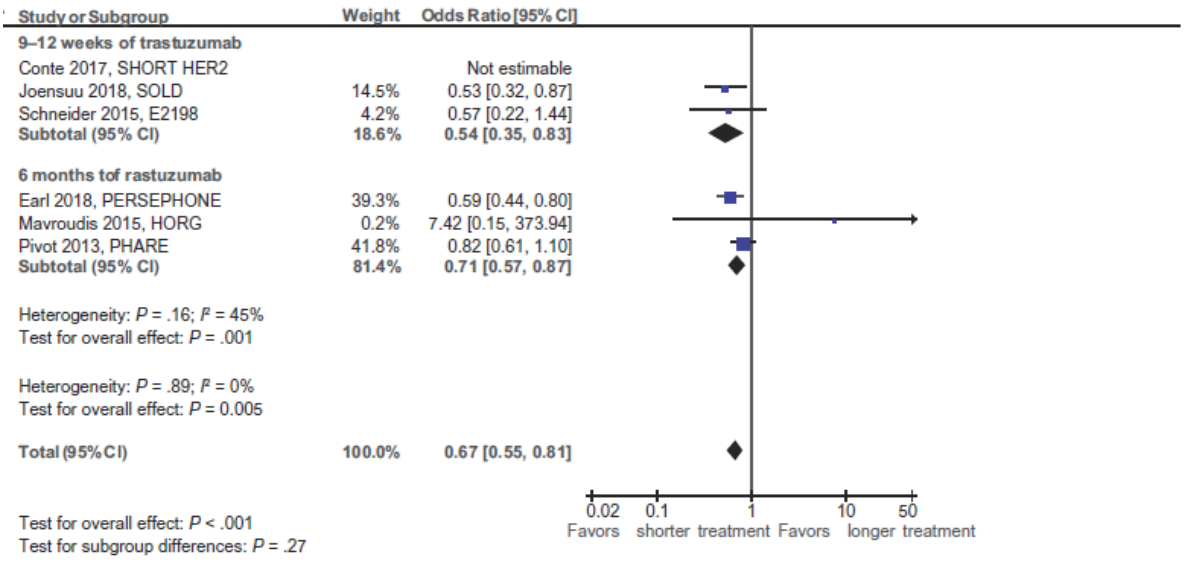
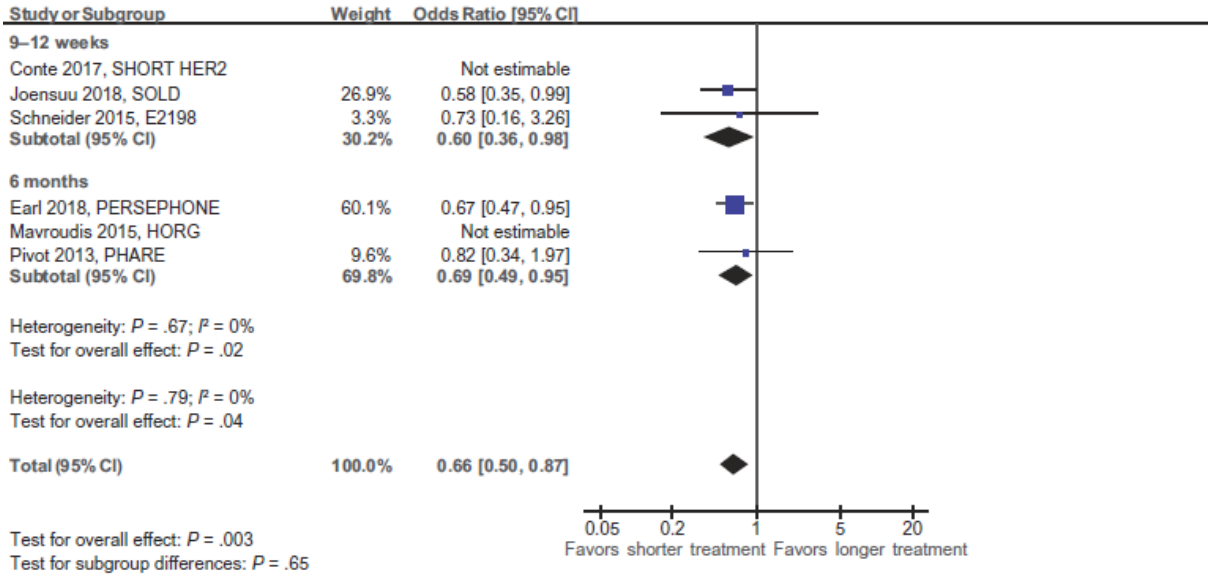


Figure 4: Congestive heart failure



Comment

This meta-analysis reviews and reports only on a comparison of shorter duration therapy (as a whole) versus 12-months. There is a comparison between 9-12 weeks and 6 months, as well as shorter duration (as a whole) versus 12 months but makes no comment on 6 months versus 12-months. There is strong evidence that 12 months is superior to 9-12 weeks therapy, however, grouping all shorter duration therapy together makes for an unfair comparison and provides no assistance in answering the question at hand. The absolute margin of benefit is small thus including the data for an inferior 9-12 week regimen may sway the statistical result in favour of the 12-month regimen. The study, in fact, does not report absolute numbers, making it more difficult to elucidate the absolute benefit of the different durations of therapy and interpret the findings of this study.

This analysis makes no reference to an appraisal of the included studies nor is any consideration given to the findings relative to the quality of these trials.

From a critical appraisal perspective, the authors' conflict of interest statement was noted. Four of 8 authors, including the corresponding author, declare having received honoraria and/or contract grants and/or personal fees from Genentech/Roche for speaking invitations, consulting and expert testimony. It is unclear as to how these conflicts have been managed.

The meta-analyses by Chen et. al. 2019[14] and Inno et. al. 2019[15] were not considered further as a critical appraisal similarly revealed a low quality of methodological rigour. Similarly, the papers by Niraula et. al. 2019[16], Gyawali et. al. 2017[17] and Genuino et. al. 2019[18] were also excluded as they either did not stratify for 9 weeks and 6 months (i.e. results for all short duration therapy were grouped together and compared with 12 months therapy) or they did not include the findings of PERSEPHONE and/or other 6-month data. (See Appendix B for a summary of reasons for excluding these meta-analyses)

10. Conclusion

In the management of early HER2 positive breast cancer:

1. Previous reviews by this Committee have confirmed that the clinical efficacy of 12-months' trastuzumab is superior to observation.
2. This review confirms that the clinical efficacy of 12-months' trastuzumab is superior to that of 9-12 weeks therapy.
3. It is recognised that the 12-month duration of therapy was selected arbitrarily, and that prolonged exposure increases the risk of cardiotoxicity.
4. The PERSEPHONE Study[3] presents new data from a large patient cohort, followed for more than 5 years which demonstrates non-inferiority of 6-months versus 12-months with the shorter duration of therapy being associated with a halving the cardiovascular risk. The Goldvaser et. al. meta-analysis[13] confirms this in their various Forest plots but makes no related comment.
5. The absolute difference in effect size between the 6-month and 12-month treatment regimens is small and is consistent across the various non-inferiority studies.[3, 5]
6. The use of Disease Free Survival, although a surrogate endpoint, was deemed an acceptable outcome measure as it had been used consistently across all relevant studies, including HERA, on which the original decision to include trastuzumab on the EML was based.

11. Recommendation

In the interests of improving access while reducing both cost and toxicity, it is recommended that the duration of trastuzumab therapy be amended to six (6) months when used in the adjuvant management of early HER2 positive breast cancer (as per clinical criteria document).

12. References

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Appendix A: Current EML clinical criteria for access to trastuzumab

CLINICAL CRITERIA FOR ACCESS TO TRASTUZUMAB

Access to be available in line with clinical criteria mentioned below, at authorised sites, prescribed by authorised prescriber (medical and/or radio- oncologist).

Programme facilitating access framework

Indication

- Adjuvant treatment of HER-2 positive early stage breast cancer

Exclusions:

- Patients with locally advanced or metastatic breast cancer
- T1N0M0
- Patients with clinically significant comorbid diseases
- Cardiac ejection fraction < 55%
- Significant hepatic or renal dysfunction
- ECOG Performance Status > 1
- Patients who have only received adjuvant hormonal therapy with no adjuvant chemotherapy
- Pregnancy or lactation

Tests and screening

- Invasive breast cancer diagnosis (Biopsy specimen or histology of surgically resected specimen – segmentectomy or mastectomy)
- HER2 – positive 3+ **OR** HER2 – positive 2+/FISH positive
- Left ventricular ejection fraction (LVEF) evaluation ≥ 55%

Regimen

Medicine		Trastuzumab
Route		Intravenous infusion
Dose	Initial	8mg/kg *(week 1)*
	Maintenance	6mg/kg *(weeks 4-51)*
Dosing cycle		3 weekly
Duration		12 months

Monitoring and Treatment

- 3 weekly follow up for consult and treatment (17 - 18 sessions)
- LVEF tests (4) – every 4 months

Appendix B: Summary of studies

Randomised controlled trials

Author, date	***Study Type***	***Patient numbers***	***Population***	***Intervention***	***Primary outcome***	***Effect sizes***	***Comments***
Earl et. al, 2019[3] *(PERSEPHONE)*	Open-label randomised phase 3 non-inferiority trial	4089 female patients	Invasive early HER2 positive breast cancer	Chemotherapy + trastuzumab 6mg/kg at 3-weekly intervals (8mg/kg loading dose) for 6 months versus chemotherapy + trastuzumab 6mg/kg at 3-weekly intervals (8mg/kg loading dose) for 12 months.	4-year Disease Free Survival	DFS = 89.4% (95% CI 87.9-90.7) in the 6-month group and 89.8% (88.3-91.1) in the 12-month group (hazard ratio 1.07 [90% CI 0.93-1.24], non-inferiority p=0.011). Absolute difference in OS at 4 years was 1% (4-year OS of 94.8% [95% CI 93.7–95.8] in the 12-month group and 93.8% [92.6–94.9] in the 6-month group). Fewer patients terminated the study due to cardiotoxicity (3% vs 8%, p<0.0001).	The prespecified non-inferiority margin for 4-year disease-free survival was set at 3%.
Pivot et. al, 2013[5] *(PHARE)*	Open-label randomised phase 3 non-inferiority trial	3384 female patients	HER2-positive early breast cancer	Patients who had received up to 6-months of trastuzumab were randomised to either discontinue trastuzumab at 6 months or continue trastuzumab for a further 6 months (12	2-year Disease Free Survival	2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; p=0.29). Safety: More patients in the 12-month group experienced a cardiac event than did those in the 6-month group (5·7% of	Despite the large numerical benefit, the pre-specified statistical criteria for non-inferiority were not met. The non-inferiority margin was 1·15, as derived from an estimated absolute difference in 2-year

				months total duration). Trastuzumab was administered at a dose of 6mg/kg at 3-weekly intervals (8mg/kg loading dose) in both groups.		1690 patients vs 1·9%, p<0·0001).	disease-free survival of 2%.
Mavroudis et. al., 2015[4] *(HORG)*	Open-label randomized controlled trial	481 female patients	Women with node-positive or high-risk node-negative HER2-positive early breast cancer	Trastuzumab was administered every 2 weeks (loading dose 6 mg/kg; 4 mg/kg thereafter) in both groups, starting concurrently with docetaxel. Thereafter, trastuzumab 6 mg/kg was administered every 3 weeks until the completion of 12 or 6 months of therapy according to randomization.	3-year Disease Free Survival	3-year DFS was 95.7% for the 12-month group versus 93.3% for the 6-month group (hazard ratio = 1.57; 95% confidence interval 0.86–2.10; P = 0.137).	Inclusion criteria amended to allow women with high risk node-negative disease to participate in the study. Small patient numbers relative to PERSEPHONE and PHARE.

Evidence quality – RCTs

Trial	Method of randomisation	Method of concealment of allocation	Blinding of intervention/ outcome assessors	Were treatment and control groups similar	Intention to treat (ITT) analysis	Limitations
Earl et. al, 2019[3] (PERSEPHONE)	Central computerised minimisation procedure using stratification variables – supplied by telephone	Yes - computerised	Open label	Yes	All analyses done on ITT	
Pivot et. al, 2013[5] (PHARE)	Central randomisation in one-to-one ratio	Yes – central office managed	Open label	Yes	Main analyses done on ITT, safety analysis done on all randomized patients	
Mavroudis et. al., 2015[4] (HORG)	Central randomisation – computer software, in a one-to-one ratio	Yes, centrally managed	Open label	Yes	Not mentioned	- Small enrollment - Relatively large non-inferiority margin set

Meta-analyses and systematic reviews

Goldvaser et. al (2019)[13]:	Systemic Review and Meta-Analysis	11 603 female patients (versus 9-12 weeks = 3 654	Women with HER2- positive early-stage breast cancer	Trastuzumab 6mg/kg at 3-weekly intervals (8mg/kg loading dose) for 12 months compared with shorter duration of therapy (included both	Disease Free Survival	Compared with 1 year of treatment, shorter trastuzumab treatment (a composite of all durations of treatment shorter than 12 months) was associated with a worse DFS (HR = 1.14, 95% CI ¼ 1.05 to 1.24, P=0.003)	Poor study design. No reference to an appraisal of the included studies. No consideration given to the findings relative to

		patients; versus 6-months = 7949)		9-12 week regimens as well as 6-month regimen)		and OS (HR = 1.15, 95% CI = 1.02 to 1.29, P=0.02).	the quality of these trials. Authors demonstrated significant conflict of interest and not adequately dealt with. No conclusion drawn on the 6-month versus 12-month data.

Notwithstanding its low quality, Goldvaser et. al (2019)[13] was summarised in this review as it was the study circulated via the Department of Health to form part of this overall review process and thus warranted the required due diligence.

Excluded studies

Author, date	Type of study	Reason for exclusion
Chen et. al. 2019[14]	Meta-analysis	Low quality review
Inno et. al. 2019[15]	Systematic Review and meta-analysis	Critically low quality review
Niraula 2019	Meta-analysis	No stratification of 6-month and 9-week results
Gyawali 2017	Meta-analysis	Excluded PERSEPHONE results
Genuino 2019	Systematic review and meta-analysis	Excluded PERSEPHONE, PHARE and HORG results

Appendix C: AMSTAR II Critical Appraisal of Systematic Review - Dr Tamra Kredo

Appraisal results: TRASTUZUMAB FOR EARLY STAGE HER 2 POSITIVE BREAST CANCER

	Goldvaser 2019[13]	Chen 2019[14]	Inno 2018[15]
1. Was the question clearly stated (PICO)?	Y	Y	y
2. Were methods pre-specified (a protocol)?	N	Not sure, this is an update	N
3. Did authors explain their choice of study designs	N	N	N
4. Did they conduct a comprehensive search?	N	Y	PARTIAL Y (search terms unusual)
5. Was there duplicate eligibility screening?	N	N	N
6. Was data extraction in duplicate?	Y	Y	Y
7. Did they provide list of excluded studies with reasons?	N	N	N
8. Were included studies clearly described?	PARTIAL Y	PARTIAL Y	PARTIAL Y
9. Did they do appraisal assessment of included studies?	N	Y	PARTIAL YES (whY jadad and rob TABLE 2 CONFUSED)
10. Did they report on funding of included studies?	N	N	N
11. Did they use meta-analysis/ stats appropriately?	Y But not sure about ITT	Y But not sure about ITT	Y But not sure about ITT and why p for heterogeneity 0.05?
12. If meta-analysis done, was bias considered in the analysis?	N	N	N
13. Was potential bias considered in results reporting?	N	N	N
14. Was heterogeneity satisfactorily explained/ explored?	Y	Y	Y
15. Was publication bias explored or considered?	N	Y	Y
16. Were authors competing interests declared and managed?	N	Y	Y
COMMENTS	CRITICALLY LOW-QUALITY REVIEW	LOW QUALITY REVIEW	CRITICALLY LOW-QUALITY REVIEW

- Bolder statements are critical for quality

Box 1: AMSTAR 2 critical domains
• Protocol registered before commencement of the review (item 2) • Adequacy of the literature search (item 4) • Justification for excluding individual studies (item 7) • Risk of bias from individual studies being included in the review (item 9) • Appropriateness of meta-analytical methods (item 11) • Consideration of risk of bias when interpreting the results of the review (item 13) • Assessment of presence and likely impact of publication bias (item 15)

Box 2: 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.

Appraisal of systematic reviews if effects with AMSTAR II.

Citation Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix D: EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Earl et. al. 2019[3] (PERSEPHONE): 4-year disease-free survival for 6-months therapy was non-inferior to 12-months. Absolute difference in overall survival at 4 years was 1% and was also non-inferior. Cardiotoxicity was significantly reduced with shorter duration of therapy (3% vs. 8%, p<0.0001). Magnitude of clinical benefit was consistent in other study. Pivot et. al. 2013[5] (PHARE): 2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; p=0.29). More patients in the 12-month group experienced a cardiac event than did those in the 6-month group (5·7% of 1690 patients vs 1·9%, p<0·0001).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Earl et. al. 2019[3] (PERSEPHONE): For 6-months therapy, 4-year disease-free survival and overall survival were 89.4% and 93.8%, respectively. 6-months therapy was associated with fewer adverse events when compared with 12 months' therapy (19% vs 24%, p=0.0002). Cardiotoxicity was significantly reduced with shorter duration of therapy (3% vs. 8%, p<0.0001). Pivot et. al. 2013[5] (PHARE): 2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; p=0.29). More patients in the 12-month group experienced a cardiac event than did those in the 6-month group (5·7% of 1690 patients vs 1·9%, p<0·0001).
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	Biosimilars now registered by SAHPRA.

VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	Acceptable to patients – shorter duration, decreased toxicity. Acceptable to payers – decreased direct and indirect costs Acceptable to clinicians - lower patient risk
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	**Cost of medicines:** Herclon® = R6 531.61 per 440mg vial **Dose:** 8mg/kg loading dose followed by 6mg/kg 3-weekly **Cost/12 months (70kg adult)** R171 055.87 **Cost/6 months (70kg adult)** R80 496.88
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	Despite the EML inclusion of trastuzumab in 2017, there remains variable access across the country. Affordability remains a concern even when considering both tender prices and a reduced duration of therapy. However, adopting the 6-month treatment schedule offers a pragmatic approach to improving access and equity with the support of the available evidence base.
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	This option is more feasible than the status quo of 12-months therapy. The 6-month regimen is associated with reduced cost, reduced resource requirement, reduced toxicity, similar clinical efficacy.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[ ]	[X]