

ISSUES IN PUBLIC HEALTH

Adjuvant trastuzumab in early HER2-positive breast cancer: Journeying towards the optimal duration of therapy in South Africa

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Trastuzumab was added to the South African *Essential Medicines List* (EML) in 2017 for the adjuvant management of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. However, access has remained inconsistent, as some provinces continue to regard trastuzumab as unaffordable within the contexts of their respective oncology budgets. The intention of providing access to trastuzumab through its inclusion on the EML, therefore, has not been met. The National EML Committee (NEMLC) recently reviewed newly published peer-reviewed information investigating the impact of a shorter trastuzumab treatment period on both clinical efficacy and safety. On account of this review, and with a view to improving access while reducing cost and toxicity, the NEMLC has revised the duration of trastuzumab therapy, i.e. from 12 months to 6 months in the adjuvant management of early HER2-positive breast cancer. This article explores and reports on the data used to make this policy amendment.

S Afr Med J 2020;110(4):271-273. <https://doi.org/10.7196/SAMJ.2020.v110i4.14621>

Trastuzumab was added to the South African (SA) *Essential Medicines List* (EML) in 2017 for the adjuvant management of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer.^[1] In support of this decision, the National Department of Health, via the National EML Committee (NEMLC), developed a clinical criteria document to guide the judicious use of this expensive medicine in eligible patients. To this end, a loading dose of 8 mg/kg, followed by 6 mg/kg, administered 3-weekly for 12 months (17 - 18 cycles), as used in the HERA (HERceptin Adjuvant) trial,^[2] was stipulated. Notwithstanding its inclusion on the EML, access to trastuzumab has remained inconsistent, as some provinces continue to regard it as unaffordable within the contexts of their respective oncology budgets.^[3] Therefore, the intention of providing access to trastuzumab by including it on the EML has not been met.

Duration of therapy and unintended consequences

The optimal duration of trastuzumab therapy in the adjuvant management of early HER2-positive breast cancer has been contentious for many years.^[4-7] The standard of care has been to prescribe therapy over a 12-month period^[8] based on the findings of the pivotal licensing trials, including the HERA trial,^[2] as well as the NSABP B31 and NCCTG N9831 trials.^[9] Importantly, it has since been noted that this treatment duration was selected arbitrarily.^[8,10] Moreover, courses >1 year increase the risk of harm^[8] and offer no advantage in terms of disease-free or overall survival.^[2,11-13]

With breast cancer being the most common cancer in women, comprising 20 - 25% of cancers,^[14,15] and HER2 being overexpressed in ~25% of patients with early breast cancer,^[16] the cost of therapy and the resource implications for managing and monitoring patient response have resulted in the unintended consequence of increasing inequity of access, as there continues to be variable access to trastuzumab among provinces.

Rationale for EML future review

The EML process includes ongoing monitoring and evaluation to ensure the relevance and applicability of policy decisions. The NEMLC terms of reference require expert review committees (ERCs) to review newly published peer-reviewed information within the context of any predefined review indicators. The Tertiary/Quaternary ERC's original review of trastuzumab listed the following review indicators:

- randomised controlled trials (RCTs) investigating the impact of shorter trastuzumab treatment periods on clinical effectiveness and safety
- RCTs investigating the optimal dosing schedule of trastuzumab treatment with different chemotherapy regimens
- pricing changes, including the introduction of generic products and biosimilars.

Several articles^[8,17-22] investigating shorter treatment durations for trastuzumab have been published subsequent to this initial review.

Consequently, the Tertiary/Quaternary ERC's most recent review was commissioned to assess the impact of a shorter trastuzumab treatment period on clinical efficacy and safety.

New data

The PERSEPHONE study^[8] was an open-label randomised phase-3 non-inferiority trial that investigated whether 6-month adjuvant trastuzumab treatment was non-inferior to the standard 12-month treatment regarding disease-free survival. A total of 4 089 female patients aged ≥18 years, with a diagnosis of invasive early HER2-positive breast cancer, were randomised to receive either 12 months (*n*=2 045) or 6 months (*n*=2 044) of trastuzumab treatment. The patient population was considered to be heterogeneous: <5% had a primary tumour >5 cm in size; >60% had a tumour grading of 3 (poorly differentiated); <15% demonstrated ≥N2 nodes (i.e. >4 positive nodes); and ~40% received only anthracyclines.

Both treatment regimens were delivered intravenously every 3 weeks (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 left ventricular ejection fraction (LVEF) during treatment. Patients were followed up for a median of 5.4 years.

The 4-year disease-free survival was 89.4% in the 6-month group and 89.8% in the 12-month group (hazard ratio (HR) 1.07 (90% confidence interval (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% in the 12-month group and 93.8% in the 6-month group). The HR for overall survival was 1.14 (90% CI 0.95 - 1.37; non-inferiority; *p*=0.001, with a prespecified non-inferiority HR of 1.6).

From a safety perspective, there were significantly fewer severe adverse events associated with the 6-month regimen (*n*=373/1 939 (19%) patients v. *n*=459/1 894 (24%) patients; *p*=0.0002). Furthermore, the 6-month regimen was associated with fewer patients terminating the study owing to cardiotoxicity (*n*=61/1 939 (3%) patients v. *n*=146/1 894 (8%) patients; *p*<0.0001).

The PHARE (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure) study,^[23] which was published in 2013, provides a worthwhile reference point for the findings of PERSEPHONE.^[8] Although PHARE failed to meet its prespecified non-inferiority margins, the magnitude of benefit observed in this study lends credence to the extent of benefit observed in PERSEPHONE. PHARE was also an open-label, randomised, phase-3 trial and involved 3 384 female patients with HER2-positive early breast cancer. It compared 6 months with 12 months of trastuzumab therapy (administered by intravenous infusion every 3 weeks; initial loading dose 8 mg/kg; 6 mg/kg thereafter). Patients were followed up for a median duration of 3.5 years. The 2-year disease-free survival was 93.8% in the

12-month group and 91.1% in the 6-month group (HR 1.28; 95% CI 1.05 - 1.56; *p*=0.29). From a safety perspective, more patients in the 12-month group experienced a cardiac event than those in the 6-month group (*n*=96/1 690 (5.7%) patients v. *n*=32/1 690 (1.9%) patients; *p*<0.0001).

Six meta-analyses^[17-22] were considered for this review; however, none met the inclusion requirements. They were either of low quality in terms of methodological rigour and/or failed to include the results from key clinical trials. One study^[21] was published prior to the finalisation of the PERSEPHONE study, while another^[22] excluded the results from the PERSEPHONE, PHARE and HORG (Hellenic Oncology Research Group)^[10] studies. Four studies^[17-20] did not stratify for

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

Indication

- Adjuvant treatment of HER2-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 received only 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
- LVEF evaluation ≥55%

Regimen

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

Monitoring and treatment

- 3-weekly follow-up for consult and treatment
- LVEF tests – baseline and at 6 months

Fig. 1. Updated clinical criteria for access to trastuzumab. (HER2 = human epidermal growth factor receptor 2; TNM = tumour, node, metastasis; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; LVEF = left ventricular ejection fraction.)

9 weeks and 6 months; therefore, the results for all short-duration therapy were consolidated and compared with those for 12 months. In a context where the absolute margins of difference are small, these articles do not assist in answering the question at hand.

Conclusions and updated NEMLC policy stance

The 12-month duration of therapy that became the *de facto* standard of care is recognised as having been selected arbitrarily. Moreover, prolonged exposure to trastuzumab increases the risk of cardiotoxicity. In this context, the PERSEPHONE study^[8] presents important new data from a large patient cohort, demonstrating non-inferiority of 6-month v. 12-month duration. It also confirms that therapy of shorter duration is associated with a halving of the cardiovascular risk. We note that the numerical difference in effect size between the 6-month and 12-month treatment regimens is small and consistently observed across various non-inferiority studies.^[8,23] Therefore, in the interests of improving access while reducing both cost and toxicity, the duration of trastuzumab therapy, as per the NEMLC clinical criteria document, has been amended from 12 months to 6 months. The revised clinical criteria document for access to trastuzumab is shown in Fig. 1. Our hope is that this policy change, combined with substantial cost reductions through the availability of trastuzumab biosimilars, will be welcomed as a further advance for women's health, as more eligible patients are able to access treatment with a reduced risk of harm.

Declaration. None.

Acknowledgements. None.

Author contributions. This article was conceptualised following the NEMLC review of data pertaining to the administration of 6 months of trastuzumab in the adjuvant management of HER2-positive early breast cancer. RJW drafted the article. All authors reviewed the article, provided feedback, and approved the final version.

Funding. None.

Conflicts of interest. All authors are involved in the EML programme convened under the auspices of the SA National Department of Health. RJW is employed by Liberty Health (Pty) Ltd, a private health insurer operating in SA and across the broader African continent. PR declares having presented at the launch of the trastuzumab biosimilar, for which an honorarium was paid to the University of the Witwatersrand, Johannesburg, SA. The remaining authors have no conflicts to declare.

- National Department of Health. Tertiary and Quaternary Level Essential Medicines List: Reviewed Items. Pretoria: NDOH, 2017.
- Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353(16):1659-1672. <https://doi.org/10.1056/NEJMoa052306>
- Kahn T. Provinces race to find money for cancer drug. *Business Day*, 10 August 2018. <https://www.businesslive.co.za/bd/national/health/2018-08-10-provinces-race-to-find-money-for-cancer-drug> (accessed 25 February 2020).
- Metcalfe S, Evans J, Priest G. PHARMAC funding of 9-week concurrent trastuzumab (Herceptin) for HER2-positive early breast cancer. *N Z Med J* 2007;120(1256):U2593.
- Abbratt RP. Short-course adjuvant trastuzumab will increase cure rates in patients with human epidermal growth factor receptor 2-positive breast cancer. *S Afr Med J* 2017;107(8):654-655. <https://doi.org/10.7196/SAMJ.2017.v107i8.12673>
- Jenkins K. Shorter-term Herceptin sufficient? No agreement. *Medscape Intern Med*, 14 June 2019. <https://www.medscape.com/viewarticle/914418> (accessed 25 February 2020).
- Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;354(8):809-820. <https://doi.org/10.1056/NEJMoa053028>
- Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;393(10191):2599-2612. [https://doi.org/10.1016/S0140-6736\(19\)30650-6](https://doi.org/10.1016/S0140-6736(19)30650-6)
- Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;253(16):1673-1684. <https://doi.org/10.1056/NEJMoa052122>
- Mavroudis D, Saloustros E, Malamos N, et al. Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: A multicentre randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015;26(7):1333-1340. <https://doi.org/10.1093/annonc/mdv213>
- Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;18(4):CD006243. <https://doi.org/10.1002/14651858.CD006243.pub2>
- Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 year versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): An open-label, randomised controlled trial. *Lancet* 2013;382(9897):1021-1028. [https://doi.org/10.1016/S0140-6736\(13\)61094-6](https://doi.org/10.1016/S0140-6736(13)61094-6)
- Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomized controlled trial. *Lancet Oncol* 2011;12(3):236-244. [https://doi.org/10.1016/S1470-2045\(11\)70033-X](https://doi.org/10.1016/S1470-2045(11)70033-X)
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer Clin* 2018;68(6):394-424. <https://doi.org/10.3322/caac.21492>
- South African National Cancer Registry. 2014. www.ncrac.za (accessed 31 January 2020).
- Dickens C, Duarte R, Zietsman A, et al. Racial comparison of receptor-defined breast cancer in southern African women: Subtype prevalence and age-incidence analysis of nationwide cancer registry data. *Cancer Epidemiol Biomarkers Prev* 2014;23(11):2311-2321. <https://doi.org/10.1158/1055-9965>
- Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating adjuvant trastuzumab in HER2-positive early-stage breast cancer: A systematic review and meta-analysis. *JNCI Cancer Spect* 2019;3(2):pkz033. <https://doi.org/10.1093/jncics/pkz033>
- Chen L, Zhou W, Hu X, Yi M, Ye C, Yao G. Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer Treat Rev* 2019;75:12-19. <https://doi.org/10.1016/j.ctrv.2019.02.003>
- Inno A, Barni S, Ghidini A, et al. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: A systematic review and meta-analysis. *Breast Cancer Res Treat* 2019;173(2):247-254. <https://doi.org/10.1007/s10549-018-5001-x>
- Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: A meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;173(1):103-109. <https://doi.org/10.1007/s10549-018-4967-8>
- Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer: Overall and disease free survival results from meta-analyses of randomized controlled trials. *Cancer Treat Rev* 2017;60:18-23. <https://doi.org/10.1016/j.ctrv.2017.08.001>
- Genuino AJ, Chaikledkaew U, The DO, Reungwetwattana T, Thakkinian A. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: A systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2019;12(8):815-824. <https://doi.org/10.1080/17512433.2019.1637252>
- Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): A randomised phase 3 trial. *Lancet Oncol* 2013;14(8):741-748. [https://doi.org/10.1016/S1470-2045\(13\)70225-0](https://doi.org/10.1016/S1470-2045(13)70225-0)

Accepted 14 February 2020.