



Trastuzumab (Herceptin) PBS listed for early breast cancer



Trastuzumab (Herceptin) is a monoclonal antibody targeting a specific gene — the human epidermal growth factor receptor 2 (HER2) gene. HER2 is normally involved in the regulation of cell proliferation. Over-expression (excess production of protein) or amplification (an excess number of gene copies) of the HER2 gene is associated with aggressive behaviour in affected cancer cells¹, and occurs in 15-30% of breast cancers.^{2,3}

Who can receive trastuzumab on the PBS?

Trastuzumab is listed on the Pharmaceutical Benefits Scheme (PBS) as an authority prescription for the initial and continuing treatment of HER2-positive early breast cancer, starting concurrently with adjuvant chemotherapy after surgical excision. The Pharmaceutical Benefits Advisory Committee (PBAC) considered accurate diagnosis important for targeting of therapy to those most likely to benefit, while limiting exposure to possible adverse effects in those unlikely to benefit.⁴ Trastuzumab trials used stringent testing protocols to ensure accurate determination of HER2 status.^{5,6} For PBS subsidy, HER2 gene amplification must be demonstrated with an appropriate assay by in situ hybridisation (ISH). Determining HER2 status using immunostaining is associated with high false-positive and false-negative rates.

PBS subsidy for trastuzumab will be provided for a total of 52 weeks, including any non-subsidised treatment (for example, before PBS-listing).⁷ The safety and efficacy of longer treatment is unknown.

What are the treatment benefits?

The primary trial of trastuzumab in early breast cancer is the HERA trial, conducted in 5081 women with cancers showing HER2 amplification or HER2 overexpression.⁶ Trastuzumab therapy for 1-2 years after excision and adjuvant chemotherapy was compared with excision and adjuvant chemotherapy alone. Disease-free survival rates* were improved by 46%, in relative terms, in the trastuzumab group (hazard ratio [HR] 0.54, 95% CI 0.43 to 0.67) with an absolute difference in disease-free survival of 8.4% at 2 years (85.8% with trastuzumab compared with 77.4% without).⁶

A combined analysis of two trials found that trastuzumab with adjuvant chemotherapy (doxorubicin, cyclophosphamide and paclitaxel) improved the relative risk of disease-free survival by 52% (HR 0.48, 95% CI 0.39 to 0.59), compared with multiple control groups receiving different chemotherapy regimens.⁸ The absolute difference in disease-free survival was 11.8% after 3 years (87.1% with trastuzumab compared with 75.4% without).

The relatively short-term nature of the trials and their premature termination because of early differences in outcomes means that there is uncertainty about longer-term survival benefits. The UK authority, NICE, accepted expert advice that decreased early recurrence was an indicator of improved survival; nonetheless, evidence regarding effects on mortality is currently unavailable.⁹

Comparisons between the trials are hampered by differences between them in the chemotherapy regimens used, the types of women included and the characteristics of their cancers. The PBAC concluded that the optimal chemotherapy partner for trastuzumab is unknown but that adjuvant chemotherapy should start concurrently.⁴

Adverse cardiac effects

Trastuzumab has cardiotoxic adverse effects, the exact duration and longer-term implications of which are unknown.

Do not use trastuzumab in women with symptomatic heart failure or with left-ventricular ejection fraction (LVEF) < 45%. LVEF must be monitored 3-monthly during treatment. According to the manufacturer, a decline in LVEF of 10 or more percentage points or to below 50% in patients with normal LVEF at baseline signals the need to withhold therapy. Re-evaluate LVEF after about 3 weeks and consider discontinuing therapy permanently if LVEF has not improved or has further declined.¹⁰

In the HERA trial 1.7% of women treated with trastuzumab developed symptomatic cardiac failure, compared with 0.06% of control patients. There was a decrease in LVEF of 10 percentage points or more from baseline (or to an LVEF of < 50%) for 7.1% of trastuzumab-treated women, compared with 2.2% of control women.⁶ These results occurred after excluding women with LVEF < 55% or with other cardiac conditions (e.g. angina, uncontrolled hypertension, coronary artery disease, chronic heart failure, valvular disease)⁶; trastuzumab is contraindicated in women with symptomatic heart failure or LVEF < 45%.¹⁰ In the HERA trial, 94% of patients received an anthracycline-based chemotherapy regimen, which also has cardiotoxic effects. As trials have been relatively short-term (1-2 years), it is unknown whether cardiac effects are reversible or ongoing.^{1,9}

*In both trials disease-free survival was the primary endpoint and included any of the following: breast cancer recurrence at any site, contralateral breast cancer, second primary cancer, or death.

References

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of clinical circumstances of each patient.