UNLOCK Herzuma®

A guide to the landscape of biosimilars and the key to the evidence of Herzuma

HEALTHCARE CELLTRION

Herzuma® Trastuzumab

The Approval Pathway of Biosimilars

Biosimilars are approved according to the same standards of pharmaceutical quality, safety, and efficacy set up by regulatory agencies such as the European Medicines Agency (EMA), and Therapeutic Goods Administration (TGA), that apply to all biologic medicines. Like any other biologics, biosimilars must demonstrate a positive benefit-risk balance based on the pharmaceutical quality, safety, and efficacy in order to be approved.

The only noticeable difference in the biosimilar approval pathway is that for a biosimilar, this positive benefit-risk balance is determined by demonstration of biosimilarity to the reference medicinal product, achieved by all scientific evidence generated in extensive comparability studies assessing quality, non-clinical, and clinical aspects (Figure 1).[1]

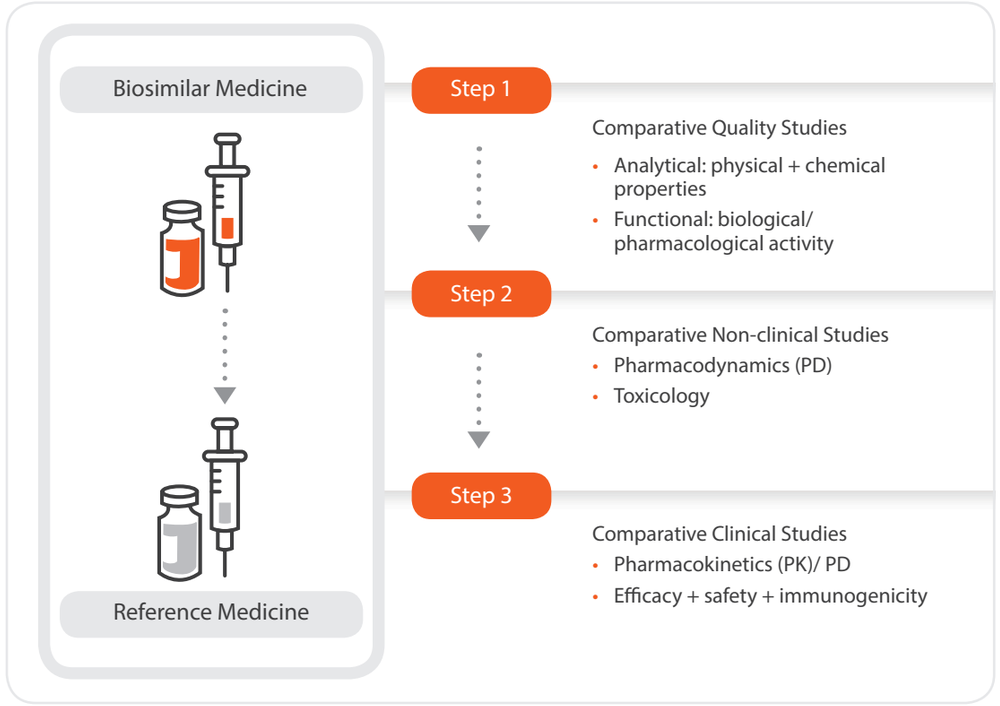


Figure 1. Comparability studies conducted for the demonstration of biosimilarity

By demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicinal product, avoiding unnecessary repetition of clinical trials. Consequently, the non-clinical and clinical data needed to approve a biosimilar are different from those required in the approval process of a biologic with a new active ingredient (Figure 2).[1]

This does not mean in any way that the approval pathway for biosimilars does not conform to the strict regulatory requirements for approving biologics. The robust regulatory framework regarding biosimilars has evolved to keep pace with rapid advances in biotechnology and analytical sciences.[1]

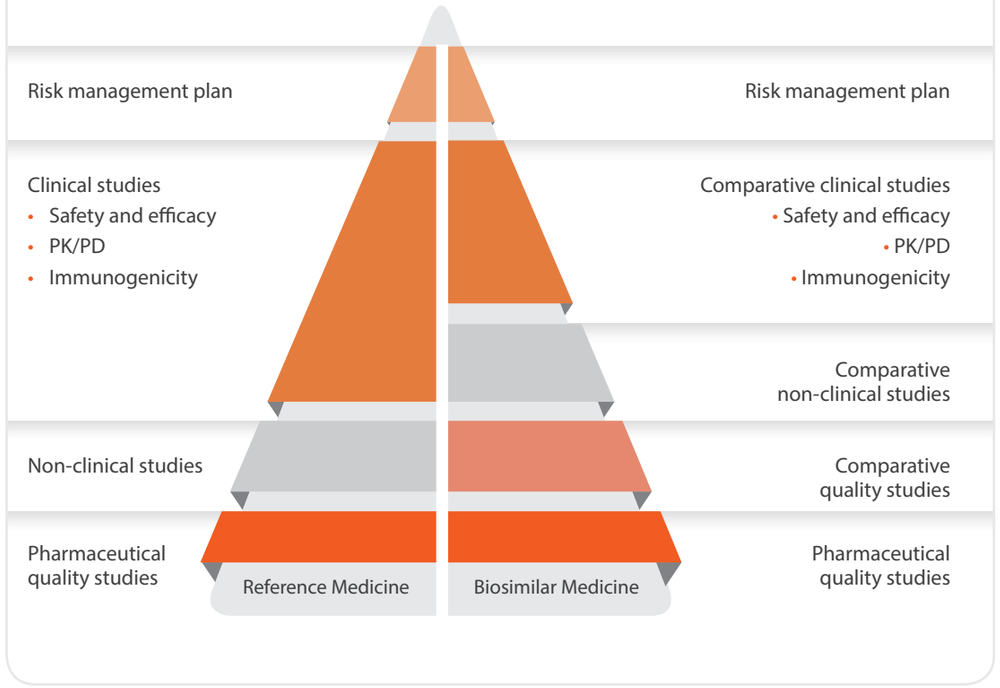


Figure 2. Comparison of data requirements for approval of a biosimilar versus the reference biologic

The Value of Biosimilars

Biosimilars are bringing about changes to the landscape of biological therapy and are emerging as cost-saving alternatives to highly priced reference biologics that pose a significant burden for patients.

The potential economic impact and value of biosimilars have been highlighted, as the introduction of biosimilars has led to both increase in patient access to essential biological therapeutic products and significant reduction in treatment costs.

Furthermore, biosimilars are expected to reduce pressure on healthcare budgets, and increase access to promising new combination regimens, biologics, or other expensive drugs (Figure 3).[2,3]

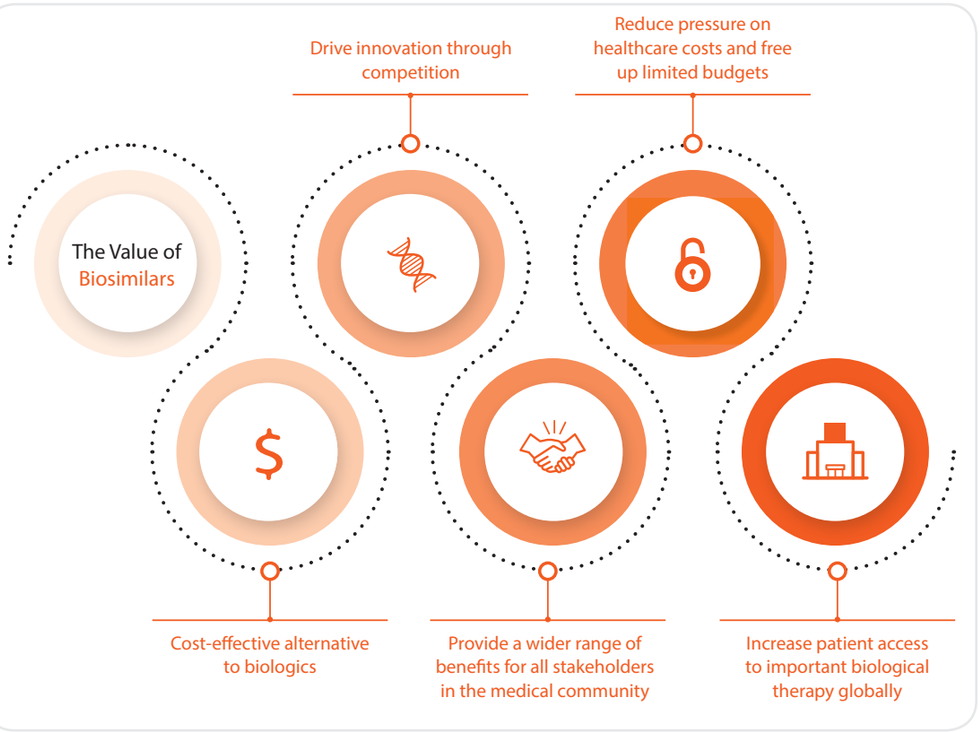


Figure 3. The potential economic impact and benefits of biosimilars

Indications of Herzuma

Herzuma is indicated for the treatment of adult patients with early breast cancer, locally advanced breast cancer, metastatic breast cancer and advanced gastric cancer.[4]

Early Breast Cancer

Herzuma is indicated for the treatment of patients with:

- HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy, followed by adjuvant Herzuma; or
- HER2-positive early breast cancer following surgery, sequentially or concurrently with chemotherapy and, if applicable, radiotherapy.

Herzuma should only be used in early breast cancer patients with a normal left ventricular ejection fraction.

Metastatic Breast Cancer

Herzuma is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease; or
- in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
- in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Advanced Gastric Cancer

Herzuma is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herzuma Phase I Study[5]

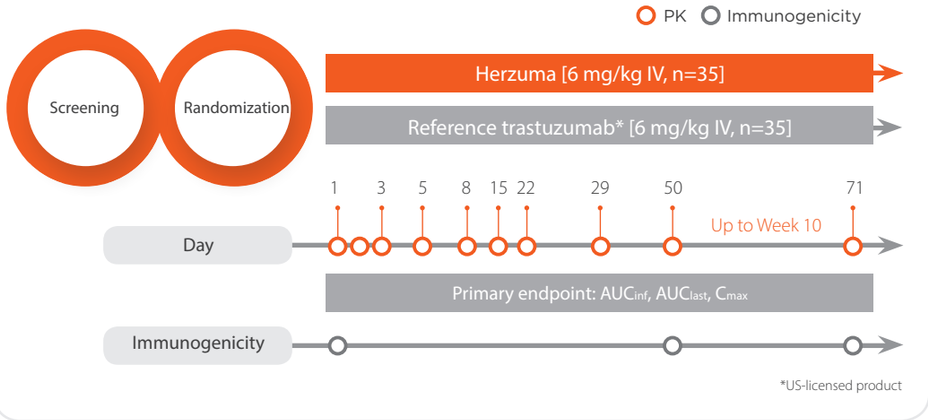
Objective

1) To demonstrate equivalence of pharmacokinetic (PK) profiles between Herzuma and reference trastuzumab in healthy male subjects.

2) To assess the safety of Herzuma and reference trastuzumab in healthy male subjects.

Study Design

- 70 healthy male subjects were randomized 1:1 to receive a single dose (6mg/kg) of either Herzuma or US-licensed reference trastuzumab by intravenous (IV) infusion for 10 weeks.
- A total of 14 serum samples were obtained from each subject for PK analysis.
- The immunogenicity was assessed at baseline and after treatment using serum samples measured by anti-Herzuma and reference trastuzumab antibodies in an immunoassay.
- qPrimary endpoints: AUC_{inf}, AUC_{last}, and C_{max}.

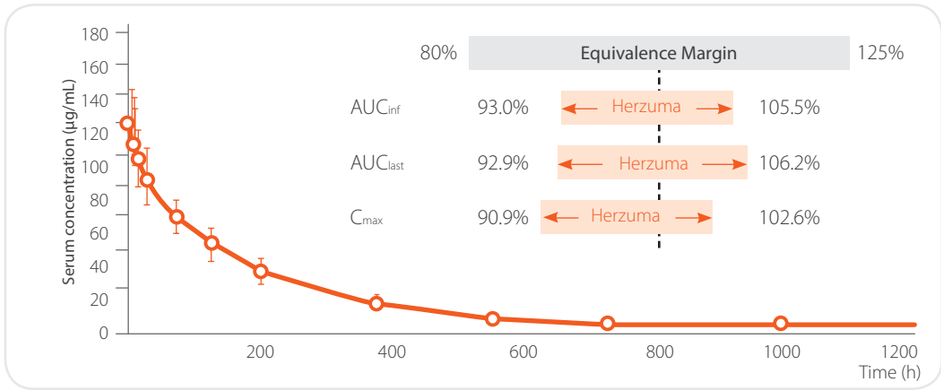


AUC_{inf}; area under the concentration-time curve from time zero to infinity, **AUC_{last};** area under the concentration-time curve from time zero to the last quantifiable concentration, **C_{max};** maximum serum concentration, **LS;** least squares.

PK similarity was demonstrated in terms of AUC_{inf}, AUC_{last}, and C_{max} between Herzuma and reference trastuzumab group in healthy male subjects.

Pharmacokinetic Profiles

- The 90% CIs for the geometric Least Squares (LS) means ratios of AUCinf, AUClast, and Cmax were entirely within in the predefined margin of 80% to 125%, indicating bioequivalence between Herzuma and reference trastuzumab.



Primary PK Endpoints

Parameter	Treatment	N	Geometric LS Mean	Ratio (%) of geometric LS means	90% CI of the ratio (%)
AUCinf (h*μg/mL)	Herzuma	35	19523.05	99.05	93.00-105.51
	Reference trastuzumab	35	19709.36		
AUClast (h*μg/mL)	Herzuma	35	18183.73	99.30	92.85-106.20
	Reference trastuzumab	35	18312.53		
Cmax (μg/mL)	Herzuma	35	127.95	96.58	90.93-102.59
	Reference trastuzumab	35	132.48		

Herzuma Phase I Study[5]

Secondary PK endpoints were also comparable for Herzuma and reference trastuzumab.

Secondary PK Endpoints

- Secondary PK endpoints of Herzuma were comparable to those of the reference trastuzumab treatment groups.

Parameter (Unit)	Herzuma (n=35)	Reference trastuzumab (n=35)
AUCext (%)	6.81 (1.17)	7.00 (2.52)
t½ (h)	189.31 (36.03)	183.68 (37.53)
Tmax (h)1	1.55	1.52
λz (1/h)	0.0038 (0.0007)	0.0039 (0.0007)
Vz (L)	6.38 (1.42)	6.09 (1.71)
CL (L/h)	0.0236 (0.0043)	0.0230 (0.0048)

[1]Median (min, max) for Tmax

λz; terminal elimination rate constant, **AUC_{ext};** area extrapolated for calculation of **AUC_{inf}**, CL; total body clearance, **PK;** pharmacokinetic, **$t_{1/2}$;** terminal elimination half-life, **T_{max};** time to observed maximum measured serum concentration, **Vz;** volume of distribution during the terminal phase.

Herzuma was well-tolerated and exhibited a comparable safety profile including immunogenicity to that of reference trastuzumab with no serious adverse events.

Safety

- There were no notable changes in LVEF on Day 71 in Herzuma and reference trastuzumab treatment groups.
- Premedication with 650mg of oral acetaminophen was administered to all 70 subjects; infusion-related reactions were reported by a small number of subjects.
- No ≥ Grade 3 TEAE, SAE, death, or discontinuation due to TEAE.

Events	Herzuma (n=35)		Reference trastuzumab (n=35)	
	Total, n(%)	Related, n (%)	Total, n(%)	Related, n (%)
AE	10 (28.6)	5 (14.3)	11 (31.4)	5 (14.3)
Grade 3 ≥AEs	0	0	0	0
SAE	0	0	0	0
Infusion-related reaction*	1 (2.86)	1 (2.86)	2 (5.7)	2 (5.7)
Discontinuation due to AEs	0	0	0	0
Death	0	0	0	0

* Seven TEAEs relating to IRRs: nausea, vomiting, chills, feeling of body temperature change, myalgia, dizziness, and headache.

Immunogenicity

- None of the subjects developed anti-drug antibodies (ADA) at assessment time points after infusion.

LVEF; left ventricular ejection fraction, **SAE;** serious adverse events, **SD;** standard deviation, **TEAE;** treatment-emergent adverse events.

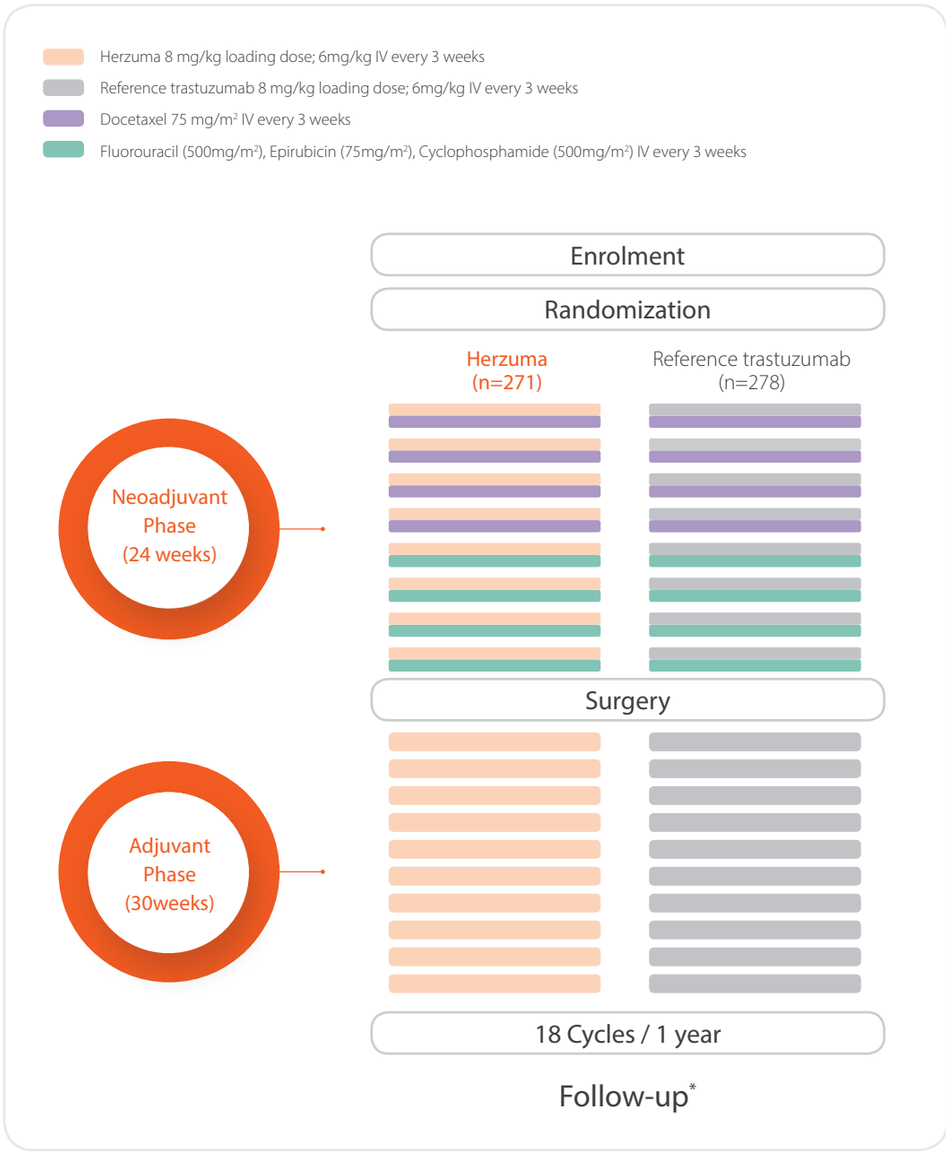
Herzuma Phase III Study[6]

Objective

- To establish the equivalence of Herzuma to reference trastuzumab in terms of efficacy in patients with HER2-positive, operable, and early-stage breast cancer treated in the neoadjuvant setting.

Study Design

- 549 women aged 18 years or older with stage I–IIIa operable HER2-positive breast cancer were randomized 1:1 to receive either neoadjuvant Herzuma or reference trastuzumab intravenously for 24 weeks at 3-week intervals. (8 mg/kg at cycle 1 and 6 mg/kg at cycles 2–8).
- Additionally, docetaxel (75 mg/m^2 at cycles 1–4) and FEC (fluorouracil [500 mg/m^2], epirubicin [75 mg/m^2], and cyclophosphamide [500 mg/m^2]; at cycles 5–8) therapy were also administered.
- Surgery was conducted within 3–6 weeks of the final neoadjuvant cycle, followed by an adjuvant treatment period of up to 1 year.
- Stratification factors: clinical stage, receptor status, country, and used permuted blocks.
- Long-term safety and efficacy were monitored for 3 years.
- Primary endpoints: pathologic complete response (pCR) rate (ypT0/is, ypN0) at the time of definitive surgery.



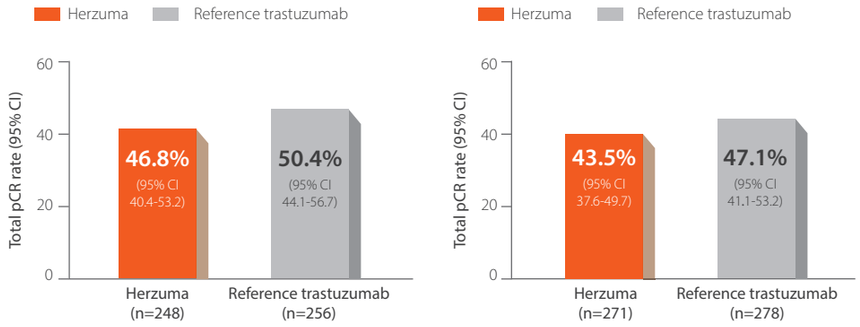
*Follow-up : Up to 3 years from the last enrolled date

Herzuma Phase III Study[6]

Therapeutic equivalence in terms of pCR was demonstrated between Herzuma and reference trastuzumab group.

Efficacy Profiles

- A similar proportion of patients achieved pathological complete response with Herzuma and reference trastuzumab.
- The 95% CI of the estimated treatment outcome difference (–0.04 [95% CI –0.12 to 0.05]) was within the equivalence margin.
- The result of secondary endpoints in terms of breast pCR, pCR without DCIS, and overall response rates in both per-protocol and intent-to-treat analysis were also similar.



Per-Protocol Analysis

Difference (95% CI)	-0.0362 (-0.1238 to 0.0516)
Risk Ratio (95% CI)	0.9282 (0.7753 to 1.1113)

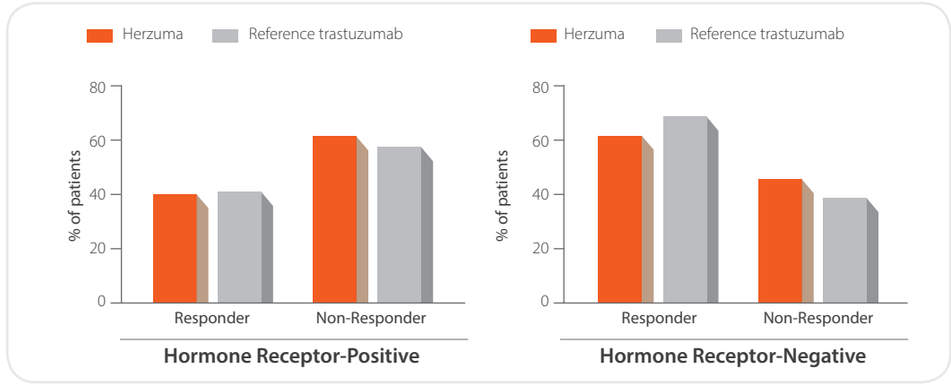
Intent-to-Treat Analysis

Difference (95% CI)	-0.0358 (-0.1198 to 0.0480)
Risk Ratio (95% CI)	0.9240 (0.7687 to 1.1108)

TEAE; treatment-emergent adverse events, **DCIS;** ductal carcinoma in situ, **SAE;** serious adverse events.

Secondary Efficacy Endpoints	Herzuma	Reference trastuzumab
PP	n=248	n=256
Breast pCR (ypTO/is)	51.6% (45.2–58.0)	55.1% (48.8–61.3)
pCR without DCIS (ypT0, ypN0)	39.9% (33.8–46.3)	41.4% (35.3–47.7)
Overall response	87.1% (82.3–91.0)	86.3% (81.5–90.3)
ITT	n=271	n=278
Breast pCR (ypTO/is)	49.1% (43.0–55.2)	52.2% (46.1–58.2)
pCR without DCIS (ypT0, ypN0)	37.3% (31.5–43.3)	38.8% (33.1–44.9)
Overall response	84.9% (80.0–88.9)	84.2% (79.3–88.3)

- Regardless of hormone receptor status, there were no notable differences in proportion of pCR responder and non-responder between the two treatment groups.
- The response was better in the hormone receptor-negative group.



CI; confidence interval, **ITT;** intention-to-treat, **pCR;** pathological complete response, **PP;** per-protocol, **ypT0/is ypN0;** absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma in situ.

Herzuma Phase III Study[6]

Herzuma was well-tolerated and the safety profiles of Herzuma during neoadjuvant and adjuvant periods were similar to that of reference trastuzumab.

Disease Recurrence Rate[7]

- In terms of disease recurrence during treatment and follow-up period, the numbers were small, and the majority of patients responded well to the treatment.

Period, n(%)	Per-Protocol		Intent-to-Treat	
	Herzuma n=248	Reference Trastuzumab n=256	Herzuma n=271	Reference Trastuzumab n=278
Overall	6 (2.4)	5 (2.0)	9 (3.3)	6 (2.2)
Neoadjuvant period	1 (0.4)	2 (0.8)	3 (1.1)	2 (0.7)
Adjuvant period	5 (2.0)	3 (1.2)	5 (1.8)	3 (1.1)
Follow-up period*	0	0	1 (0.4)	1 (0.4)

* Follow-up period data up to 1 year from the first study drug administration of neoadjuvant period in patients who discontinued early or discontinued during the neoadjuvant or adjuvant period.

Safety Profiles[6,7]

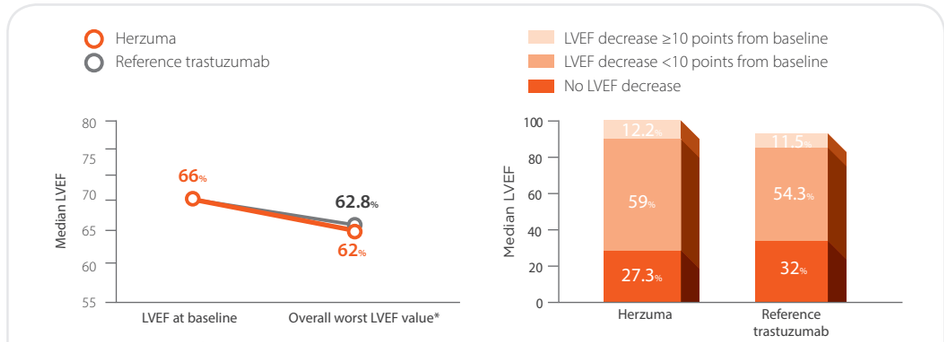
- The safety profile of Herzuma during neoadjuvant/adjuvant period was similar to that of reference trastuzumab.

n (%) of patients	Herzuma (n=271)	Reference trastuzumab (n=278)
Treatment-emergent AEs	263 (97.0)	265 (95.3)
Hematological TEAEs		
Neutropenia	111 (41.0)	129 (46.4)
Anaemia	60 (22.1)	67 (24.1)
Leukopenia	29 (10.7)	40 (14.4)
Febrile neutropenia	17 (6.3)	19 (6.8)
Non-hematological TEAEs		
Alopecia	195 (72.0)	213 (76.6)
Fatigue	100 (36.9)	100 (36.0)
Nausea	99 (36.5)	94 (33.8)
Treatment-emergent SAEs	**20 (7.4)**	**33 (11.9)**
Treatment-related	5 (1.8)	8 (2.9)
Death	**2 (0.7)**	**2 (0.7)**
Infusion-related reactions	31 (11.4)	29 (10.4)

TEAE; treatment-emergent adverse events, **SAE;** serious adverse events.

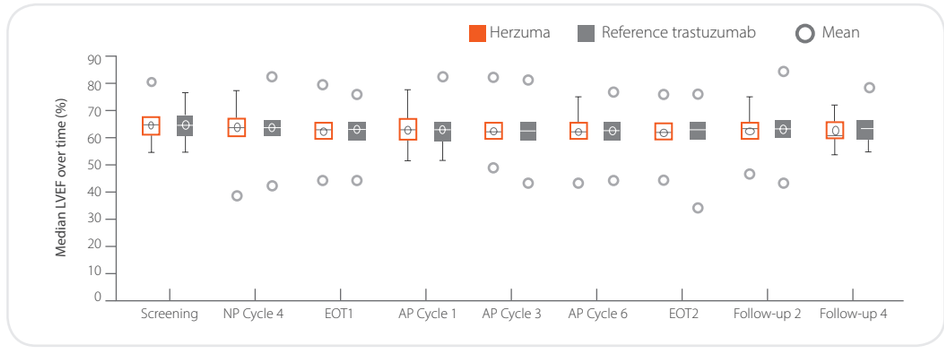
LVEF Changes Over Time[8]

- Overall worst LVEF value was similar between two treatment groups. Majority of patients showed a decrease of <10 points from baseline.



* The overall worst LVEF value for a patient was the lowest post-baseline LVEF value.

- For LVEF, there were no notable differences between the two treatment groups throughout the study period. The mean LVEF value was maintained over 60% during 1-year treatment and follow-up period.



AP; adjuvant period, **EOT1;** end of treatment visit during neoadjuvant period, **EOT2;** end of treatment visit during adjuvant period, **LVEF;** left ventricular ejection fraction, **NP;** neoadjuvant period

IMPORTANT INFORMATION ABOUT HERZUMA (TRASTUZUMAB)

PHARMAC Pharmaceutical Schedule: Herzuma (trastuzumab) is a funded medicine - Special Authority Criteria Apply (SA2277)

Before prescribing, please refer to the data sheet available on the Medsafe website at www.medsafe.govt.nz

Herzuma (trastuzumab) is a Prescription Medicine containing 150mg or 440mg trastuzumab powder for intravenous infusion.*

INDICATIONS: Treatment of HER2 overexpressing metastatic breast cancer; as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease; in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer. Treatment of early breast cancer in HER2-positive locally advanced disease in combination with neoadjuvant chemotherapy, followed by adjuvant Herzuma; HER2-positive early breast cancer following surgery, sequentially or concurrently with chemotherapy and, if applicable, radiotherapy. Herzuma should only be used in early breast cancer patients with a normal left ventricular ejection fraction. Treatment of advanced gastric cancer in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. **CONTRAINDICATIONS:** Herzuma is contraindicated in patients with known hypersensitivity to trastuzumab or to any of its excipients. **PRECAUTIONS:** Not for IV push, bolus admin, SC inj; advanced malignancy, comorbidity associated dyspnoea at rest (should not use); pretreatment physical (especially cardiac) exam, HER2 testing (See full data sheet); monitor cardiac function including LVEF (pretreatment, every 3 months during treatment, then every 6 mths until 24 mths (yearly for ≥ 5 yrs if anthracycline therapy) after last dose), for infusion related reaction (IRR); IRRs are known to occur with the administration of trastuzumab; asymptomatic cardiac dysfunction (monitor 6-8 weekly); cardiac risk for example hypertension (poorly controlled, history), CAD, CHF (or history), diastolic dysfunction, low baseline and declining LVEF (< 55%), prior, concurrent antihypertensives; treatment induced symptomatic heart failure, LVEF reduction by 10% to < 50% withhold therapy; high risk uncontrollable arrhythmia, angina requiring medication, clinically significant valvular disease, MI history, other cardiomyopathy, haemodynamically significant pericardial effusion; prior anthracycline, cyclophosphamide, taxane, gemcitabine, vinorelbine, radiation exposure; use in renal, hepatic impairment was not studied; high cumulative anthracycline dose, BMI > 25 kg/m2 (after adjuvant chemo); age > 50 yrs; women of childbearing potential (ensure adequate contraception), pregnancy, lactation (avoid incl ≥ 7 months after last dose); safety and efficacy of trastuzumab in patients under the age of 18 years have not been established. I**NTERACTIONS:** If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab; do not admix with dextrose 5%, other medicines. **ADVERSE EFFECTS:** Most common: Infections and infestations (incl. Nasopharyngitis, UTI, URTI, Neutropenic sepsis, Skin infections), Febrile neutropenia, Anaemia, Thrombocytopenia, White blood cell count decreased leukopenia, Neutropenia, Hypersensitivity reactions, Change in Body Weight, Decreased appetite, Anorexia, Psychiatric disorders (incl. Insomnia, Depression, Anxiety), Nervous system disorders (incl. Tremor, Paraesthesia, Hypoaesthesia, Peripheral neuropathy, Hypertonia, Ataxia), Conjunctivitis, Cardiac disorders (incl. Change in Blood Pressure, Heart beat irregular, Palpitation, Cardiac flutter, Ejection fraction decreased, Cardiac failure (congestive), Supraventricularartachyarrhythmia, Cardiomyopathy), Lymphoedema, Respiratory Disorders (incl. Dyspnoea, Epistaxis, Rhinorrhoea, Asthma, Pneumonia, Pleural Effusion), Gastrointestinal disorders (incl. Pancreatitis and other), Hepatocellular Injury, Hepatitis, Skin and subcutaneous disorders (incl. Erythema, Rash, Palmar-plantar erythrodysaesthesia syndrome and other), Musculoskeletal and connective tissue disorders (incl. Arthralgia, Myalgia, Arthritis), Renal disorder, General disorders and administration site conditions (incl. Influenza-like symptoms, Infusion related reaction, Pyrexia, Peripheral oedema, Mucosal inflammation). For others, see full Data Sheet. **DOSAGE AND ADMINISTRATION:** Confirm HER2 status pretreatment. Check vial label to ensure the medicine being used is trastuzumab and not trastuzumab emtansine. Reconstitute with sterile water for injection (7.2 mL for 150 mg vial; 20mL for 440mg vial) then add required dose to 250 mL NaCl 0.9% infusion solution. Admin by IV infusion: loading dose over approx. 90 min, maintenance doses over 30 min if well tolerated. Early breast cancer, locally advanced breast cancer or metastatic breast cancer: for 3 weekly regimen, loading dose: 8 mg/kg followed by maintenance dose 6 mg/kg; for Weekly regimen: loading dose 4 mg/kg followed by maintenance dose of 2 mg/kg. Advanced gastric cancer: for 3 weekly regimen: loading dose 8 mg/kg followed by maintenance dose of 6 mg/kg. Missed dose: admin maintenance dose (if less than or equal to 1 week late) or re-loading dose (if > 1 week late) as soon as possible then maintenance doses 7 or 21 days later according to weekly or 3 weekly regimen. Dose modification for IRR: may slow infusion rate or interrupt. Treatment duration: Early or locally advanced breast cancer: maximum 1 yr or until disease recurrence or unmanageable toxicity (whichever occurs first); metastatic breast and advanced gastric cancer: until disease progression or unmanageable toxicity.

*not all dosage forms might be available at the same time.

Date of preparation: July-2020 (based on Data Sheet last updated 7-Nov-2019). Material last updated 8-Nov-2023, TAPS BG3473, November 2023.

References: 1. European Medicines Agency. Biosimilars in the EU. Information guide for healthcare professionals. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdfAccessed Jan 2018. **2.** Declerck PJ, et al. Biosimilars 2012;2:33-40. **3.** Henry D, et al. Semin Oncol. 2014;41:S13-S20. **4.** Herzuma® prescribing information. **5.** Esteva FJ, et al. Cancer Chemother Pharmacol. 2018. https://doi.org/10.1007/s00280-017-3510-7. **6.** Stebbing J, et al. Lancet Oncol. 2017;18:917-928. **7.** Esteva FJ, et al. Annals of Oncology. 2017;28(suppl. 5):v43-v67. **8.** Esteva FJ, et al. Cancer Res. 2018;78(suppl. 4):P5-22-22.

To allow for quick identification of new safety information, kindly report any side effects you may observe at the following contact channels. Phone: 0800 838 899 or Email: medinfo-nz@celltrionhc.com

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