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Original Research

A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results

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KEYWORDS
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Trastuzumab;
HER2;
Early breast cancer;
Event-free survival;
Safety

Abstract ***Background:*** The equivalent efficacy between SB3, a proposed trastuzumab biosimilar, and the trastuzumab reference product (TRZ) in terms of the breast pathologic complete response rate after neoadjuvant therapy in patients with early or locally advanced human epidermal growth factor receptor 2-positive breast cancer was demonstrated in the previous report. Here, we report the final safety, immunogenicity and survival results after neoadjuvant-adjuvant treatment.
Patients and methods: Patients were randomised 1:1 to receive neoadjuvant SB3 or TRZ for 8 cycles concurrently with chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide). Patients then underwent surgery, followed by 10 cycles of adjuvant SB3 or TRZ as randomised. End-points included safety, immunogenicity, event-free survival (EFS) and overall survival through the adjuvant period.
Results: Of 875 patients randomised, 764 (SB3, n = 380; TRZ, n = 384) completed the study. The median follow-up duration was 437 days in the SB3 group and 438 days in the TRZ group. The incidence of treatment-emergent adverse events was comparable between groups (SB3, 97.5%; TRZ, 96.1%) during the overall study period. Up to the end of study, the overall incidence of antidrug antibody was low in both treatment groups (3 patients each). EFS was comparable between groups with a hazard ratio (SB3/TRZ) of 0.94 (95% confidence interval, 0.59–1.51) and EFS rates at 12 months of 93.7% for SB3 and 93.4% for TRZ.
Conclusions: Final safety, immunogenicity and survival results of this study further support the biosimilarity established between SB3 and TRZ.
Trial registration: ClinicalTrials.gov (NCT02149524); EudraCT (2013-004172-35).

1. Introduction

Trastuzumab (Herceptin®; Roche Registration Limited, Welwyn Garden City, UK and Genentech, Inc., South San Francisco, CA, USA) provides benefits in terms of tumour shrinkage, recurrence and survival when administered as neoadjuvant therapy with chemotherapy and continued as adjuvant therapy [1], and when administered as adjuvant therapy [2–7] for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer.

SB3 (Samsung Bioepis Co., Ltd., Incheon, Republic of Korea) is a proposed trastuzumab biosimilar with structural and physicochemical characteristics similar to trastuzumab reference product (TRZ) [8]. A randomised phase I pharmacokinetic study of healthy males demonstrated similarity in terms of pharmacokinetic equivalence [8]. We conducted a phase III trial comparing SB3 and TRZ (EU-sourced) in patients with early or locally advanced HER2-positive breast cancer treated with neoadjuvant-adjuvant therapy. Equivalent efficacy between SB3 and TRZ in terms of the primary end-point, breast pathologic complete response (bpCR) rate, was demonstrated after neoadjuvant therapy. The bpCR rates in the per-protocol set were 51.7% for SB3 and 42.0% for TRZ, with an adjusted ratio (90% confidence interval [CI]) of 1.259 (1.112–1.426) and an adjusted difference (95% CI) of 10.70% (4.13%–17.26%) [9]. Biosimilarity of SB3 and TRZ has been assessed based on the 'totality of evidence' approach, taking structural, functional, nonclinical, pharmacokinetic, clinical immunogenicity and comparative clinical study data into consideration [10,11].

The objective of the current analysis was to compare safety, immunogenicity, and survival with SB3 and TRZ after neoadjuvant-adjuvant therapy in this phase III trial.

2. Materials and methods

The study and clinical protocols were reviewed and approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each study center. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulatory requirements and laws.

2.1. Patients

Inclusion and exclusion criteria were previously described [9], and the key elements follow. Eligible patients were women 18–65 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; with non-metastatic, unilateral, newly diagnosed, histologically confirmed, primary invasive breast adenocarcinoma (clinical stages II–III) including inflammatory breast cancer, with tumour size ≥2 cm and confirmed HER2-positivity (immunohistochemistry 3+ or fluorescence in situ hybridisation +); and with known oestrogen receptor (ER) and progesterone