European Journal of Cancer 64 (2016) 12–21

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer – The Phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29)

G. von Minckwitz [a,*], M. Rezai [b], H. Tesch [c], J. Huober [d], B. Gerber [e], D.M. Zahm [f], J. Hilfrich [g], S.D. Costa [h], P. Dubsky [i], J.U. Blohmer [j], C. Denkert [j], C. Hanusch [k], C. Jackisch [l], S. Kümmel [m], P.A. Fasching [n], A. Schneeweiss [o], S. Paepke [p], M. Untch [q], N. Burchardi [a], K. Mehta [a], S. Loibl [a] for the German Breast Group and Austrian Breast and Colon Cancer Study Group Investigators[1]

[a] *German Breast Group, Martin Behaim Strasse 12, 63263 Neu-Isenburg, Germany*
[b] *Luisenkrankenhaus Düsseldorf, Hans-Günther-Sohl-Straße 6-10, 40235 Düsseldorf, Germany*
[c] *Hämatologisch-Onkologische Gemeinschaftspraxis Bethanien, Im Prüfling 17-19, 60389 Frankfurt/Main, Germany*
[d] *Universitäts-Frauenklinik Ulm, Prittwitzstraße 43, 89081 Ulm, Germany*
[e] *Universitäts-Frauenklinik Rostock, Südring 81, 18059 Rostock, Germany*
[f] *SRH Wald-Klinikum Gera GmbH, Straße des Friedens 122, 07548 Gera, Germany*
[g] *Eilenriede Krankenhaus, Uhlemeyerstraße 16, 30175 Hannover, Germany*
[h] *Universitäts-Frauenklinik Magdeburg, Gerhart-Hauptmann-Straße 35, 39108 Magdeburg, Germany*
[i] *Medizinische Universität Wien, Währinger Gürtel 18-20, 1090 Wien, Austria*
[j] *Charité-Universitätsmedizin, Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany*
[k] *Rotkreuzklinikum München, Taxisstr. 3, 80637 München, Germany*
[l] *Klinikum Offenbach, Starkenburgring 66, 63069 Offenbach, Germany*
[m] *Brustzentrum, Kliniken Essen-Mitte, Henricistr. 92, 45136 Essen, Germany*
[n] *Universitätsfrauenklinik Erlangen, Universitätsstr. 21-23, 91054 Erlangen, Germany*
[o] *Nationales Centrum für Tumorerkrankungen (NCT), Heidelberg, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany*
[p] *Universitäts-Frauenklinik rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany*
[q] *Helios Klinikum Berlin-Buch, Schwanebecker Chaussee 50, 13125 Berlin, Germany*

Received 10 March 2016; received in revised form 27 April 2016; accepted 14 May 2016

* *Corresponding author*: German Breast Group, c/o GBG Forschungs GmbH, Martin-Behaim-Strasse 12, 63263 Neu-Isenburg, Germany. Tel.: +49 69 6102 798740; fax: +49 69 6102 7987440.

*E-mail addresses:* gunter.vonminckwitz@gbg.de (G. von Minckwitz), dr.mahdi.rezai@luisenkrankenhaus.de (M. Rezai), Hans.Tesch@chop-studien.de (H. Tesch), jens.huober@uniklinik-ulm.de (J. Huober), bernd.gerber@med.uni-rostock.de (B. Gerber), dirk-michael.zahm@wkg.srh.de (D.M. Zahm), j.hilfrich@eilenriedeklinik.de (J. Hilfrich), serban-dan.costa@med.ovgu.de (S.D. Costa), peter.dubsky@meduniwien.ac.at (P. Dubsky), jens.blohmer@charite.de (J.U. Blohmer), carsten.denkert@charite.de (C. Denkert), claus.hanusch@swmbrk.de (C. Hanusch), christian.jackisch@sana.de (C. Jackisch), s.kuemmel@kliniken-essen-mitte.de (S. Kümmel), Peter.Fasching@uk-erlangen.de (P.A. Fasching), Andreas.Schneeweiss@med.uni-heidelberg.de (A. Schneeweiss), stefan.paepke@lrz.tu-muenchen.de (S. Paepke), michael.untch@helios-kliniken.de (M. Untch), nicole.burchardi@gbg.de (N. Burchardi), Keyur.mehta@gbg.de (K. Mehta), Sibylle.loibl@gbg.de (S. Loibl).

[1] See list of investigators in acknowledgements.

http://dx.doi.org/10.1016/j.ejca.2016.05.015

**KEYWORDS**
Adjuvant treatment;
Postneoadjuvant;
Zoledronate;
Early breast cancer

**Abstract** ***Background:*** Patients with invasive residual disease after neoadjuvant chemotherapy (NACT) are considered to have chemo-resistant breast cancer. Bisphosphonates are an established treatment for bone metastases and are of potential benefit as adjuvant treatment in early breast cancer.
***Patients and methods:*** Patients who had invasive tumour residuals (ypT1-4 and/or ypN+) after a minimum of four cycles of anthracycline-taxane-containing NACT were eligible for the NeoAdjuvant Trial Add-oN study. Patients were randomised within 3 years after surgery to receive zoledronate 4 mg i.v. for 5 years versus observation. Zoledronate was given every 4 weeks for the first 6 months, every 3 months for the following 2 years, and every 6 months for the last 2.5 years. Primary objective was disease-free survival.
***Results:*** After a median time of 54.7 months no difference in disease-free survival was observed between the zoledronate and observation groups (hazard ratio [HR] 0.960, 95% confidence interval [CI] 0.709–1.30, log rank $P = 0.789$). Various subgroups were examined without identifying a treatment effect of zoledronate. Patients over 55 years of age showed a HR of 0.832 in favour of zoledronate, but the result was not significant ($P = 0.480$). A similar result was obtained for overall survival with a HR of 1.19 (95% CI 0.79–1.79; log rank $P = 0.408$). Zoledronate was well tolerated and no new toxicity signal was identified.
***Conclusion:*** Postneoadjuvant treatment with zoledronate does not improve outcome in patients without pathological complete response after neoadjuvant anthracycline-taxane-based chemotherapy for early breast cancer.


## 1. Introduction

Neoadjuvant chemotherapy (NACT) is routinely used in patients with operable or locally advanced breast cancer to down-stage the breast tumour and to improve surgical options [1]. If a pathological complete response (pCR) is obtained, prognosis is usually highly favourable, whereas outcome of patients without pCR is largely dependent on the biological subtype of disease. In patients with an aggressive tumour subtype both the risk of relapse and the prognostic information obtained from pCR assessment are greater [2]. At the time, the NeoAdjuvant Trial Add-oN (NaTaN) study was designed, prognosis of patients without a pCR was in general considered to be unfavourable [3]. Neoadjuvant systemic treatment was therefore considered as a tool for identifying patients requiring further adjuvant systemic treatment beyond endocrine therapy or trastuzumab.

Bisphosphonates have a distinct mechanism of action and have demonstrated efficacy both in the treatment of breast cancer with metastasis to the bone [4] and in several adjuvant studies after surgery for early breast cancer [5,6]. As a 3rd generation bisphosphonate, zoledronate also showed a favourable toxicity profile, this compound was considered to be an ideal candidate for exploring the concept of postneoadjuvant treatment.

## 2. Patients and methods

### 2.1. Objectives

The NaTaN study (NCT00512993) was an open label, uncontrolled, randomised phase III study investigating disease-free survival (DFS) after zoledronate administered for 5 years versus no postoperative bisphosphonate treatment in patients with invasive residual breast cancer (ypT1-4 and/or ypN1-3) after preoperative anthracycline/taxane-containing chemotherapy. Secondary objectives were to determine DFS in subgroups including subgroups with respect to time interval between surgery and randomisation and response to NACT, as well as overall and bone-metastasis-free survival, and the toxicity of zoledronate.

### 2.2. Selection of patients

Female patients previously treated with NACT for at least four cycles, of which at least two cycles had to contain a taxane and an anthracycline and with completely resected (R0) unilateral or bilateral primary carcinoma of the breast with histologically detectable tumour residuals (ypT1–4) and/or histology confirmed involvement of axillary nodes (ypN1–3) represent the trial population. A maximum interval of 3 years from the date of axillary surgery (axillary dissection mandatory in node-positive cases, sentinel-node-biopsy optionally in node-negative cases) prior to entering the trial was allowed. Patients had to be older than 18 years and of adequate general health status. Current active dental problems including infection of the teeth or jawbone, dental or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw, of exposed bone in the mouth, or of slow healing after dental procedures, or recent or planned dental or jaw surgery were, among others, the exclusion criteria.