Supplement

Friedl TWP, Fehm T, Müeller V, et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online June 24, 2021. doi:10.1001/jamaoncol.2021.1854

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methods

Randomization procedures

The randomization was a stratified block randomization, performed by fax or electronically via internet by the appointed clinical research organization. The randomization allocation ratio was 1:1 for both the first randomization (three cycles of FEC followed by three cycles of either docetaxel or docetaxel plus gemcitabine) and the second randomization (two vs five years of zoledronate treatment). Stratification factors were lymph node status (pN0/pN1/pN2/pN3), hormone-receptor status (negative/positive), histological grading (G1/G2–G3), menopausal status (pre-/postmenopausal), and HER2 status (negative/positive/unknown). Both randomizations were performed before the start of the first treatment period.

Endocrine treatment

All patients with a positive hormone receptor status of the primary tumor received tamoxifen treatment 20 mg p.o. per day for 2 years, after the end of chemotherapy. Postmenopausal patients with positive hormone receptor status were subsequently treated with anastrozole (Arimidex®) 1 mg p.o. for additional 3 years, while premenopausal patients continued tamoxifen treatment for additional 3 years. In case of contraindications against tamoxifen or severe adverse effect during the treatment with tamoxifen, anastrozole was given before the end of the initial 2 years. In addition to tamoxifen, all patients with positive hormone receptor status of the primary tumor and under the age of 40 or with a restart of menstrual bleeding within 6 months after the completion of cytostatic treatment or with premenopausal hormone levels received goserelin (Zoladex®) 3.6 mg subcutaneously every 4 weeks over a period of 2 years.

CTC detection

For patients that provided informed consent for the translational part of the SUCCESS A study, 30 ml of peripheral blood were collected for CTC enumeration at four different time points (before chemotherapy, immediately after chemotherapy, two years after chemotherapy, and five years after chemotherapy), pooled and concentrated to a final volume of 7.5 ml. CTC detection was performed using the FDA-approved CellSearch® system (Menarini-Silicon Biosystems, Bologna, Italy), as described in detail elsewhere [1]. All positive samples automatically preselected by the CellSearch® system were reviewed by two independent investigators for final assessment of CTC status. A blood sample was defined as CTC positive if at least one CTC was detected.

eReference

[1] Riethdorf S, Fritsche H, Müller V, et al. Detection of circulating tumor cells in peripheral blood of patients with metastatic breast cancer: A validation study of the CellSearch system. Clin Cancer Res. 2007;13(3):920-928. doi:10.1158/1078-0432.CCR-06-1695

Power analysis and sample size calculations

“The Success A study was designed as an open-label, multi-center, 2x2 factorial design, randomized controlled, Phase III trial. The first primary objective of this study was to compare disease-free survival in patients treated with 3 cycles of Epirubicin-Fluorouracil-Cyclophosphamide(FEC)-chemotherapy, followed by either 3 cycles of Docetaxel or 3 cycles of Gemcitabine-Docetaxel-chemotherapy. The second primary objective of this study was to compare disease free survival in patients receiving 2 years versus 5 years of zoledronate treatment (i.e. the subject of this paper).

The original sample size calculation as stated in the study protocol was based on the following assumptions:

- The DFS at 5 years of patients receiving FEC followed by Docetaxel (Arm A1) is 78,3%.
- There will be an absolute of 4% improvement in 5-year DFS (i.e. an increase from 78.3% to 82.3%) for patients receiving FEC followed by Docetaxel plus Gemcitabine (Arm A2).
- There will be the same improvement in 5-year DFS for patients receiving 5 years of zoledronate treatment (Arm B1) in relation to patients receiving 2 years of zoledronate treatment (Arm B2).
- The error rate for a false positive outcome (α) is set to 5% (two-sided) and the power of the trial is set to 80%.
- The accrual period during which patients enter the study is 60 months (5 years) and the follow-up period from the end of accrual until the analysis of the data is 36 months (3 years).

The resulting original sample size calculation can be summarized as follows:
To confirm the absolute increase of DFS-rates at 5 years by 4% from 78.3% to 82.3% for patients from therapy arms A1/A2 by a two-sided log rank tests, a total of N = 743 events are needed. The total number of patients to be included into the trial is equal to N = 3658 (i.e. 1829 patients per arm, assuming both 1:1 randomization and a common exponential drop-out rate over whole duration of the study of 10%).

The Success A study was conducted with the recruitment aim of enrolling N = 3658 patients, and the study recruitment indeed exceeded all expectations with a total of 3754 patients enrolled within only 30 months.

Importantly, it has to be noted that the original sample size calculation was not specifically powered for the landmark-approach-based analysis for the second primary objective, i.e. the comparison of DFS in patients receiving 5 years versus 2 years of zoledronate treatment, as presented in this paper.
Notwithstanding to what was stated in the original statistical analysis plan, we have decided to use a landmark approach for this analysis, as this is in our view the best statistical approach to analyze and evaluate this second primary objective. However, due to using the landmark approach, both the sample size available for the analysis and median follow up duration were reduced as compared to an analysis using the full data set of randomized patients with survival times measured as from randomization, leading to a reduced statistical power.

A retrospective power analysis to assess the statistical power of this modified statistical approach using the landmark method accounting for the reduced sample size (N = 2987) and the shorter follow-up duration (about 36 months) yielded a power of 80% to detect an absolute increase of DFS-rates at 5 years by 4.8% from 78.3% to 83.1% by a two-sided log rank tests (as compared to a difference of 4% obtained in the original power calculation).

Definitions of survival endpoints

Two-year landmark disease-free survival (DFS) was defined as the time from two years after the start of zoledronate treatment to the earliest date of disease progression (any invasive ipsilateral, regional, contralateral, and distant disease recurrence, second primary tumors, or death from any cause; non-invasive, in-situ cancer events were excluded) or the date of censoring. Patients that were lost to follow-up before the maximal observation time were censored at the last date they were known to be disease-free and patients with no disease progression after four years were censored at the maximal observation time. Overall survival (OS) was defined accordingly with death from any cause as an event, and for the calculation of distant disease-free survival (DDFS) only distant recurrence (metastasis and second primary tumors) and death from any cause were regarded as events.

In a similar way, we furthermore assessed bone-recurrence-free survival as an additional survival endpoint particularly relevant for bisphosphonate treatments. First distant recurrences were defined as an event if bone metastases were found (with or without concurrent other recurrence); in case of distant disease without bone metastases, the patients were censored at the date of distant disease recurrence.

Potential bias and sensitivity analysis

Probably due to the open-label, non-placebo-controlled study design, there was a slight bias with regard to loss of follow up, as a higher number of patients was lost to follow up during the first 200 days of the follow-up period in the 2-year zoledronate arm (54 patients vs. 16 patients). Of note, 47 out of these 70 patients had a hormone receptor positive primary tumor, and the proportion of hormone receptor positive patients lost-to-follow-up during the first 200 days were similar between the two treatments arms (36 out of 54 patients, i.e. 67%, in the 2-year zoledronate treatment arm; 11 out of 16 patients, i.e. 69%, in the 5-year zoledronate treatment arm).

As a consequence of the slight bias with regard to loss of follow up, median follow-up time in lost-to-follow up patients was numerically longer in the 5-year zoledronate arm compared to the 2-year zoledronate arm (1088 vs 1051 days); however, this difference was not significant (Mann-Whitney U-test, $P = .15$). To further evaluate whether this bias affected the results regarding DFS and OS, we performed a sensitivity analysis with survival times measured as from 200 days after the end of the 2-year zoledronate study treatment, thereby excluding the time period in which patients in the 2-year zoledronate arm seem to be more likely to drop out. However, this sensitivity analyses also showed no significant difference between the two zoledronate treatment arms with regard to 2-year landmark DFS (HR 1.01, 95%CI 0.76 – 1.33, $P = .96$) and 2-year landmark OS (HR 0.89, 95%CI 0.61 – 1.28, $P = .52$).

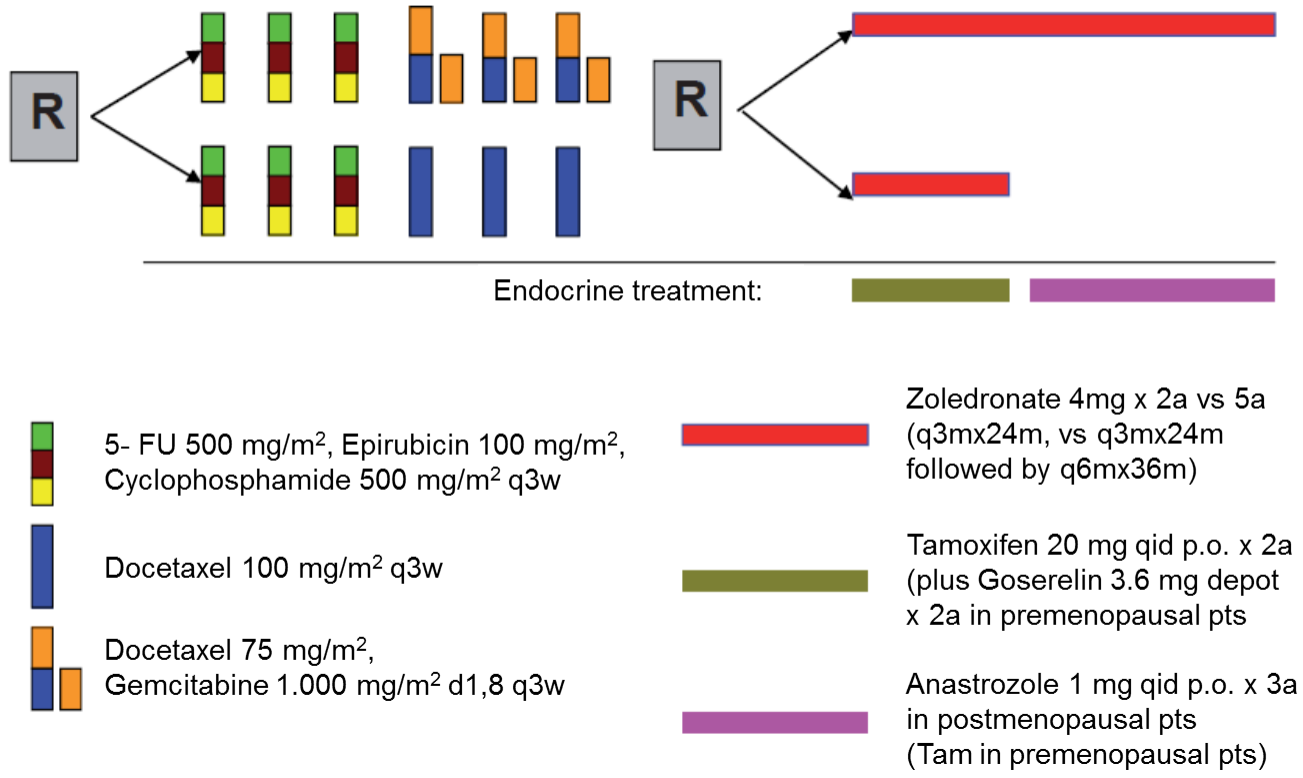
eTable. Observed Frequencies of the Ten Most Common Adverse Events

Adverse event	No. (%)			
	5 y of zoledronate (n = 1540)		2 y of zoledronate (n = 1447)	
	All grades	Grade 3/4	All grades	Grade 3/4
Bone pain	158 (8.3)	9 (0.6)	57 (3.7)	5 (0.3)
Arthralgia	96 (5.1)	1 (0.1)	50 (3.1)	1 (0.1)
Fatigue	78 (4.4)	5 (0.3)	34 (2.1)	0 (0.0)
Anemia	84 (4.4)	1 (0.1)	7 (0.5)	1 (0.1)
Neuropathy	47 (2.3)	0 (0.0)	32 (1.9)	2 (0.1)
Leukopenia	63 (3.6)	0 (0.0)	8 (0.6)	3 (0.2)
Hot flashes	41 (2.2)	0 (0.0)	25 (1.5)	0 (0.0)
Myalgia	39 (2.1)	4 (0.3)	17 (1.1)	0 (0.0)
SGPT elevation	42 (2.5)	1 (0.1)	12 (0.7)	0 (0.0)
Headache	33 (1.8)	4 (0.3)	21 (1.2)	0 (0.0)

Abbreviation: SGPT, serum glutamic pyruvic transaminase.

eFigure 1

Study design of the SUCCESS A trial.



eFigure 2

Forest plot showing results of explorative subgroup analyses in terms of the comparison of overall survival between patients with five or two years of zoledronate treatment duration according to different patient and tumor characteristic subgroups. The diamonds indicate the hazard ratios (five vs. two years of zoledronate treatment), and diamond size is proportional to the number of patients per subgroup. The horizontal lines indicate the corresponding 95% confidence intervals for the hazard ratios. The solid vertical line represents a hazard ratio of 1.0 (i.e., no difference in survival between five or two years of zoledronate treatment), and the dashed vertical line represents the hazard ratio for the overall analysis with all 2987 patients.