Updated long-term overall survival of older adjuvant ibandronate-treated patients with intermediate- or high-risk early breast cancer compared with additional adjuvant capecitabine treatment – The ICE Randomized Clinical Trial

Marcus Schmidt[1], Ulrike Nitz[2], Toralf Reimer[3], Sabine Schmatloch[4], Heiko Graf[5], Marianne Just[6], Georg Heinrich[7], Elmar Stickeler[8], Michael Untch[9], Jens Huober[10], Christian Jackisch[11], Valentina Nekljudova[12], Sibylle Loibl[12]

109P

[1]Universitätsklinikum Mainz, Germany, [2]West German Study Group, Mönchengladbach, [3]Klinikum Südstadt, Universitäts-Frauenklinik, Rostock, [4]Elisabeth Krankenhaus, Kassel, [5]Helios Klinikum Meiningen GmbH, Meiningen, [6]Onkologische Schwerpunktpraxis, Bielefeld
[7]Schwerpunktpraxis der Gynäkologie und Onkologie, Fürstenwalde/Spree, [8]Uniklinik RWTH Aachen, [9]Helios Kliniken Berlin-Buch, [10]Kantonspital St. Gallen, Brustzentrum, Department Interdisziplinäre medizinische Dienste, St. Gallen, Schweiz, [11]Sana Klinikum Offenbach, [12]German Breast Group, Neu-Isenburg

Background

The phase III ICE study (GBG 32, BIG 4-04) compared adjuvant ibandronate with or without capecitabine in elderly patients with moderate or high-risk early breast cancer.

The majority of breast cancers occur in women over the age of 65, but older breast cancer patients are largely underrepresented in clinical trials.[1-3] Based on the increasing rate of hormone receptor (HR)-positive tumors and sensitivity to endocrine therapy with increasing age, the importance of endocrine therapy as a mainstay in HR-positive elderly breast cancer patients is underlined.[4,5] A large meta-analysis with only a few women over 70 years of age, demonstrated that adjuvant chemotherapy improves long-term outcome regardless of patient or tumor characteristics.[6] Therefore, we investigated the effect of adding capecitabine to adjuvant treatment with ibandronate in patients ≥65 years with node-positive and high-risk node-negative breast cancer.

We present here an update on long-term follow-up for the secondary endpoint of overall survival (OS). Primary analysis was presented in San Antonio Breast Cancer Symposium 2014.

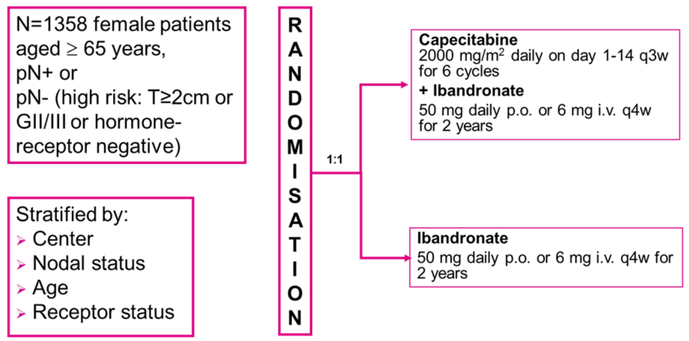
Patients and Methods

Study design: The prospective, multicentric, controlled, randomized and open-labeled phase III ICE trial enrolled women ≥65 years with early node-positive/high-risk node-negative breast cancer and a Charlson Comorbidity Index (CCI) ≤2. Patients were randomized to capecitabine 2000 mg/m² day 1-14 q3w for 6 cycles plus ibandronate (50 mg p.o. daily, or 6 mg i.v. q4w), or ibandronate alone for 2 years (**Figure 1**).

Endpoints: Primary endpoint was invasive disease-free survival (iDFS). Main secondary endpoint was OS. Further endpoints were bone-related events (e.g., fractures, surgery, new osteoporosis), evaluation of preference to oral or intravenous application of ibandronate, compliance, and safety.

Statistical considerations: OS is presented graphically by Kaplan-Meier curves and compared between arms by stratified log-rank test. Estimates of 3-, 5-. 7- and 10-year probability of survival are reported with 95% CI. A univariate Cox model for OS according to treatment group was fit to estimate the hazard ratio of OS between treatment groups and its 95% confidential interval. Multivariable and subgroup analyses were also performed for OS.

Figure 1: Study Design



➢If ER and/or PR ⊕ : Anastrozol 1mg p.o. daily 5 yrs (in sequence to Capecitabine)
➢In Amendment 2 any endocrine treatment was allowed, not only Anastrozol.

Note that for the time period assessed in the chemotherapy safety analysis the patients of „ibandronate alone" arm also received endocrine therapy and the patients of ibandronate plus capecitabine arm received no endocrine therapy.

Results

1358 (96.4%) from 1409 randomized patients started treatment. 564 (83.4%) completed 6 cycles of capecitabine. 513 (77.7%) and 516 (78.8%) completed ibandronate in the capecitabine/ibandronate and ibandronate arm, respectively (**Figure 2**). Median age was 71 (range 64-88) years, 1099 (81%) were hormone receptor (HR)-positive, 705 (51.9%) node-negative, 794 (58.5%) had a CCI of 0 (**Table 1**). HR-positive patients received additional adjuvant endocrine treatment. After an updated median follow-up time of 74 (IQR 56-126) months for OS in the entire cohort (**Figure 3**), 7-year OS was 83.5% for capecitabine/ibandronate versus 80.9% for ibandronate, and 10-year OS was 73.1% for capecitabine/ibandronate versus 70.8% for ibandronate (P=0.413), (**Table 2**). Lack of effect was independent from age, nodal and HR status (**Figure 4**). Addition of capecitabine caused significantly higher skin and gastrointestinal toxicities.

Figure 2: Consort diagram

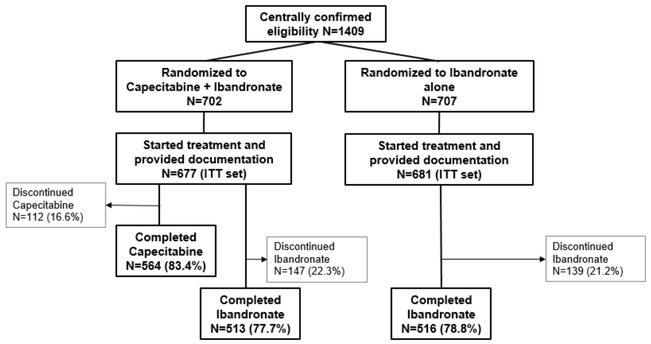


Table 1: Baseline Characteristics

Parameter	Category	Capecitabine + Ibandronate N=677 N (%)	Ibandronate N=681 N (%)	Overall N=1358 N (%)
Age, years	Median (range)	71 (64-85)	71 (64-88)	71 (64-88)
	65-69	252 (37.2)	241 (35.4)	493 (36.3)
	70-74	259 (38.3)	271 (39.8)	530 (39.0)
	75-79	134 (19.8)	133 (19.5)	267 (19.7)
	80+	32 (4.7)	36 (5.3)	68 (5.0)
Charlson comorbidity index	0	412 (60.9)	382 (56.1)	794 (58.5)
	1	198 (29.2)	230 (33.8)	428 (31.5)
	2	66 (9.7)	68 (10.0)	134 (9.9)
pT	1	254 (37.5)	258 (37.9)	512 (37.7)
	2	346 (51.1)	364 (53.5)	710 (52.3)
	3	44 (6.5)	32 (4.7)	76 (5.6)
	4	33 (4.9)	27 (4.0)	60 (4.4)
pN	0	353 (52.1)	352 (51.7)	705 (51.9)
	1	226 (33.4)	236 (34.7)	462 (34.0)
	2	66 (9.7)	59 (8.7)	125 (9.2)
	3	32 (4.7)	34 (5.0)	66 (4.9)
Grading	3	242 (35.8)	231 (33.9)	473 (34.9)
Biological subtype	HR positive	548 (80.9)	551 (81.0)	1099 (81.0)
	HER2 positive*	88 (17.9)	95 (19.7)	183 (18.8)
	Triple negative	72 (14.6)	65 (13.5)	137 (14.1)

*Missing in 383 patients.
HR: hormone receptor

Figure 3: Overall survival in two randomized treatment groups, Kaplan-Meier (ITT set)

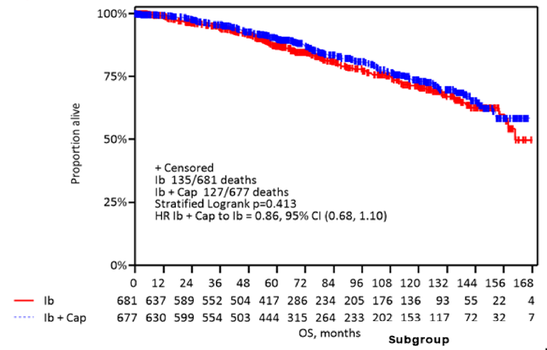


Figure 4: Treatment effect on overall survival by randomized arms overall and in predefined subgroups after a median follow-up of 74 months

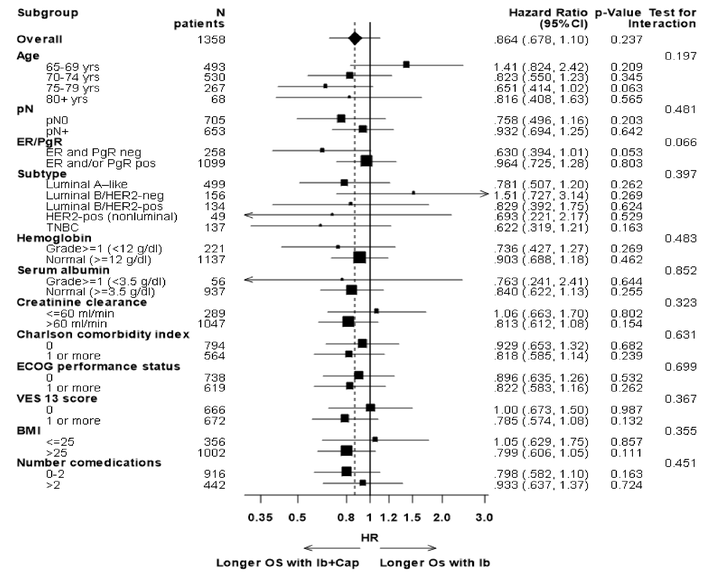


Table 2: Overall survival for 3, 5, 7 and 10 years in two randomized treatment groups

	Capecitabine + Ibandronate N=677	Ibandronate N=681	*Stratified log-rank-test*
Number of deaths	127	135	0.413
3 years OS (95% CI)	95.6% (93.6%, 97.0%)	94.2% (92.0%, 95.8%)	
5 years OS (95% CI)	90.0% (87.3%, 92.2%)	87.1% (84.0%, 89.6%)	
7 years OS (95% CI)	83.5% (79.7%, 86.6%)	80.9% (76.9%, 84.2%)	
10 years OS (95% CI)	73.1% (68.1%, 77.5%)	70.8% (65.6%, 75.4%)	

Conclusions

ICE I is still the largest ever conducted randomize phase III trial in elderly breast cancer patients. The adjuvant combination of capecitabine and ibandronate resulted in a numerically improved OS by 2.9% at 5 years compared to ibandronate alone in elderly breast cancer patients. The improvement did not reach statistical significance due to the relative small sample size and OS not being the primary endpoint. The improvement of OS by the addition of capecitabine in the HR-negative subgroup is more pronounced and reaches almost statistical significance.
Overall, mono-chemotherapy added to a bone modifying agent is a well tolerated treatment option and might be an alternative to standard chemotherapy in elderly patients in need for chemotherapy.

References

1. Freedman et al. *J Clin Oncol*. 2017; 2. Hutchins et al. *The New England journal of medicine*. 1999; 3. Lewis et al. *J Clin Oncol*. 2003; 4. Gluz et al. *Annals of Oncology*. 2022; 5. Nitz et al. *J Clin Oncol*. 2022; 6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *The Lancet*. 2012

Presented at: ESMO Breast Cancer Congress 2023 (May 11-13), Berlin, Germany

V. Nekljudova declares to be GBG Forschungs GmbH employee. GBG Forschungs GmbH received funding for research grants from Abbvie, AstraZeneca, BMS, Daiichi-Sankyo, Gilead, Novartis, Pfizer and Roche (paid to the institution); other (non-financial/medical writing) from Daiichi-Sankyo, Gilead, Novartis, Pfizer, Roche and Seagen (paid to the institution). GBG Forschungs GmbH has following royalties/patents: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8 and VM Scope GmbH.

This presentation is the intellectual property of the author/presenter.
Contact them at publications@gbg.de for permission to reprint and/or distribute.