A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial

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Background: While extended adjuvant therapy with aromatase inhibitors (AI) after initial tamoxifen has been demonstrated to improve disease-free-survival (DFS) of postmenopausal patients with hormone-receptor positive breast cancer, the optimal duration of extended AI is unknown. Moreover, it remains unclear whether patients after AI in the first 5 years benefit similarly from extended adjuvant AI therapy as patients after Tamoxifen.

Methods: From February 2004 to June 2010, 3484 women with postmenopausal stage I-III hormone-receptor positive early breast cancer were randomized in 71 centers in Austria to receive either 2 years or 5 years of additional Anastrozole (1 mg daily) as extended adjuvant therapy, after initial 5 years of adjuvant endocrine treatment. Eligible patients had to be recurrence-free at 60 months of initial adjuvant therapy with Tamoxifen (Tam) or AI or Tam→AI, and younger than 80 years of age. Stratification factors were tumor stage, nodal status, initial endocrine therapy, adjuvant chemotherapy, and quantitative hormone receptors. Patients were followed-up at least annually. Primary end point of ABCSG-16 was DFS, secondary end points included overall survival (OS), fractures, contralateral breast cancer, and toxicity.

Results: As of June 30, 2016, the median follow-up of the 3468 patients included in the analysis of ABCSG-16 was 105.9 months (IQR 102.2-110.3 months) after randomization (i.e. approx. 14 years after diagnosis). Median patient age was 64 years, 2507 (72%) patients had tumors smaller than 2 cm, 2301 (66%) patients were node-negative, 674 (19%) patients had high-grade tumors, 2683 (77%) patients had tumors both ER and PR positive. 2764 (80%) patients were treated with breast conserving surgery. Before randomization into ABCSG-16, 1000 (29%) patients had undergone (neo)adjuvant chemotherapy, 1774 (51%) patients had received 5 years of Tamoxifen, whereas 1688 (49%) patients had received other (AI containing) regimens in the first five years.

As of June 30, 2016, 757 DFS events have been recorded, 377 (22%) in the 2-year group, and 380 (22%) in the 5-year group. There was no significant difference in DFS (HR 0.997, 95%CI 0.86-1.15, log rank p=0.982), in OS, time to secondary carcinoma and time to contralateral breast cancer. With respect to drug adherence, 81.2% of patients in the 2-year arm were taking the study drug still at 2 years, and 80.1% at 2 years in the 5-year arm. At 5 years, 65.6% of patients in the 5-year arm were still on the assigned medication. Bone fractures were more frequent in the 5-year arm (i.e. years 3 to 5 after randomization: 6% vs 4%, HR=1.405, 95%CI 1.03-1.91, p=0.029).
Conclusion: After 5 years of adjuvant endocrine therapy (Tamoxifen or AI or Sequence), 2 additional years of Anastrozole are sufficient for extended adjuvant therapy – a further extension to 5 additional years did not yield additional outcome benefit but added toxicity.
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