Methods and Materials: Between 1996 and 2004, 4004 patients were accrued into the trial. Most important inclusion criteria were: informed consent, age $\leqslant 75$ years, unilateral and operable breast cancer, tumour site at the medial or central quadrants irrespective of the axillary status or any location with axillary node invasion. Patients were randomised between no radiotherapy (RT) and 50 Gy RT of the IM-MS nodes.
Results: Ineligibility rate was <0.75%. The median age at randomisation was 55 years (range 19–75), with 59% post-menopausal women. Of the 4004 patients, 15% presented with a primary tumour <10 mm, 44% between 11–20 mm, 37% between 21–50 mm and 4% *51 mm. Axillary nodal invasion was absent in 44% and present in 56% (43% one to three nodes; 10% four to nine nodes and 3% had $\geqslant 10$ positive nodes). Using the current TNM classification UICC 6th Ed., 33.5% of the patients had st I, 32% st IIA, 19% st IIB and only 12% st IIIA beast cancer and 1.5% unknown. 73% of the patients had positive oestrogen receptors and 58% had positive progesterone receptors. The surgery consisted of breast conserving technique (BCT) in 76% and mastectomy in 24%. RT has been given in all but 7% of the patients. A boost has been added in 66.7% of the overall patients respectively 85% after BCT. The median total dose to the breast after the BCT was 64 Gy (20–76) including the boost and to the chest wall after mastectomy was 50 Gy(16–84 Gy). The adjuvant systemic treatment consisted of chemotherapy in 25%, hormonal therapy in 29% and both in 29% of the patients respectively. Overall, we found a major deviation from the protocol guidelines in 2.5% of the cases, including 1.1% refusal of the assigned treatment and 1.1% not treated according to the randomisation. In the IM-MS treatment arm an under-treatment (IM-MS dose <45 Gy) occurred in 0.7%. Minor treatment deviations were found in 44.4% of the patients, consisting of a slight under-treatment (IM-MS dose 45–47.5 Gy) in 3.3%, an extended delay between RT and surgery in 3.8%, modifications in technique (ratio and energy of photons and electrons) in 37.3% of patients.
Conclusions: In this study, the actual patient population has a lower risk and better overall survival than anticipated more than 10 years ago, when the protocol was written. This was timely recognised and led to a modification of the statistics of the trial, resulting in a recalculation of the necessary number of patients based on the corrected assumptions. This will result in a more accurate and representative final analysis of the primary endpoint.

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Letrozole is cost-effective versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer: BIG-1–98

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Background: The BIG 1–98 study is an ongoing, independent, phase 3, double-blind, randomised clinical trial comparing tamoxifen with letrozole – both as monotherapy and in sequence – in 8,010 postmenopausal women with endocrine responsive breast cancers following complete tumour resection. Results from the primary core analysis comparing tamoxifen and letrozole monotherapies were reported at ASCO 2005. Median age at enrolment was 61 yrs and median follow-up at time of primary core analysis was 26 months. Compared to tamoxifen, letrozole significantly improved disease-free survival (hazard ratio [HR] = 0.81, p = 0.003), especially reducing time to distant recurrence (HR = 0.73, p = 0.001). This analysis incorporates the effects of letrozole on breast cancer events and adverse events as observed in BIG 1–98, and extrapolates the cost, quality of life, and mortality effects of these events to estimate the cost-effectiveness of letrozole versus tamoxifen in this setting.
Methods: A published economic model (Karnon 2002) is adapted to calculate the cost per life year (LY) and cost of quality-adjusted life year (QALY) saved of 5 years of initial adjuvant therapy with letrozole versus tomoxifen in postmenopausal women with early breast cancer. The model describes life time incidence of breast cancer events (contralateral tumours, locoregional, and distant recurrences) and treatment-related adverse events (endometrial cancer, bone fractures, coronary heart disease, stroke, venous thromboembolism, and hypercholesteremia). HRs (lerozole versus tamoxifen) for each event were estimated form the BIG-1–98 trial. Mortality rates for each specified adverse event, for other causes, and extrapolated breast cancer event rates are estimated from other published sources, as are health-care costs and utility values, which are both discounted at 3.5% annually. Probabilistic sensitivity analyses are undertaken to calculate 95% confidence interval for cost-effectiveness.
Results: The baseline results show that the additional costs associated with adverse events are similar to the cost savings as a result of fewer breast cancer events. The additional lifetime cost of letrozole per patient is £4,546 (£9,568 letrozole vs. £5,022 tamoxifen). Letrozole leads to a gain of 0.29 LYs (13.34 vs. 13.05) and 0.33 QALYs (12.67a vs. 12.34). The incremental cost per LY gained is £15,549 and per QALY is £14,001. In probabilistic sensitivity analyses, the 95% confidence interval for cost-effectiveness is £11,341 to £29,406 per LY saved, and £10,067 to £26,068 per QALY saved.
Discussion: Letrozole is a cost-effective use of healthcare resources and should be considered as a new option for the adjuvant treatment of patients with early breast cancer, based on preliminary analysis of published results of the primary core analysis of the BIG-1–98 study.

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No differences in quality of life for letrozole relative to placebo in post-menopausal women with early breast cancer regardless of age: results from the MA-17 study

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Introduction: MA-17 was a randomized placebo-controlled trial that compared the efficacy and safety of 5 years of letrozole (Femara®) 2.5 mg/d versus placebo and related QoL impact on postmenopausal women with early breast cancer, after 5 years of tamoxifen. Due to significant lowering in risk of disease recurrence and distant metasteses observed with letrozole, the trial was unblinded early after 2.4 years mean follow-up. Earlier studies have reported that letrozole did not worsen patient's QoL relative to placebo in this population. However, evaluation of QoL impact may vary by age, thus the objectives were to describe QoL scores by treatment group and age (<65; $\geqslant 65$ years) in MA-17.
Methods: The generic validated QoL scale (SF-36 Health Survey) and the validated patient bother scale (MENQOL) were administered. The SF-36 yielded 2 summary scores providing a global indicator of patients' physical and mental QoL and 8 specific domains providing insight on specific QoL aspects. Symptom impact associated with estrogen suppression was assessed using 4 domains of the MENQOL. Due to the early unblinding of MA17, differences in SF-36 and MENQOL scores between treatment groups are reported only for the first 3 years of the study (6, 12, 24, 36 months), using non-parametric testing.
Results: Across all timepoints for both age groups, no statistically significant differences between letrozole and placebo were observed for MENQOL psychosocial and physical domains and SF-36 mental QoL summary score and physical functioning, role-physical, general health, social functioning, role-emotional, and mental health sub-domains. In both age groups, statistically significant differences in favour of placebo were observed for SF-36 Bodily Pain (months 6, 12, 24 for <65 and month 6 for $\geqslant 65$) and MenQoL vasomotor symptoms (months 6, 12 for <65 and months 12 and 24 for $\geqslant 65$). In the younger age group, differences in MENQOL sexual functioning were observed at month 24 in favour of letrozole, For the older group, physical summary score at month 24 and vitality at month 6 were impacted in favour of placebo. No further differences were observed. Although statistically significant these differences were not considered clinically relevant based on current methodology.
Conclusions: Extended adjuvant treatment with letrozole after standard adjuvant tamoxifen in postmenopausal women provides improved efficacy while not worsening QoL relative to placebo, regardless of women's age.

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Comparison of cardiovascular (CV) safety profiles of aromatase inhibitors (AIs)

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Background: The recent ASCO Technology Assessment recommended that adjuvant endocrine treatment should include an AI to lower the risk of recurrence in postmenopausal women with hormone-receptor positive early breast cancer. It is uncertain, however, if the AIs are interchangeable in clinical practice. Emerging data suggest that the distinct molecular structures of the AIs may result in different safety profiles. We report here an indirect comparison of available data on the CV events of letrozole, exemestane and anastrozole.
Methods: Safety data from the BIG 1–98 trial, evaluating letrozole versus tamoxifen (n = 8028), and the IES study, evaluating exemestane versus tamoxifen (n = 4742), were compared with safety data from the monotherapy arms of the ATAC trial, which evaluated anastrozole versus tamoxifen (n = 6186).
Results: Data from BIG 1–98 at 26 months' median follow-up demonstrated a significantly greater incidence of moderate to severe (grade 3–5) cardiac events with letrozole versus tamoxifen (2.1% vs 1.1%, respectively; p = 0.0003). There were 7 cerebrovascular deaths on letrozole compared with 1 on tamoxifen, and double the number of cardiac

deaths with letrozole versus tamoxifen treatment (13 vs 6, respectively). Data from IES at 37.4 months' median follow-up showed a significantly greater incidence of myocardial infarction (MI) with exemestane versus tamoxifen (20 vs 8, respectively; p = 0.02). However, more mature data from ATAC at 68 months' median follow-up showed the incidence of stroke was significantly reduced with anastrozole versus tamoxifen (62 vs 88, respectively; p = 0.03). There was a difference, although not significant, between anastrozole and tamoxifen in the number of ischaemic CV events (127 vs 104, respectively; p = 0.1). The majority of these events, however, continued to be mild to moderate in severity and there was no difference in the incidence of MI (1.2% vs 1.1%, respectively). Also, the numbers of CV deaths remained low and similar for the two groups (anastrozole 49, tamoxifen 46), with the majority of these deaths occurring after completion or discontinuation of study treatment.
Conclusions: The differences in CV safety profiles between the AIs confirm that AIs are not interchangeable in clinical practice. At present, anastrozole is the only AI in the adjuvant setting with a detailed benefit risk profile from over 5 years' follow-up, from which no CV safety concerns have emerged.

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Skeletal protective effect of clodronate in primary breast cancer-bone mass, bone turnover, and skeletal-related events (SRE's)

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Breast cancer treatments that suppress ovarian function – such as hormone therapy and chemotherapy – accelerate the loss of bone mass, yet hormonal osteoporosis prophylaxis is contraindicated. Thus, anti-osteolytic agents such as bisphosphonates have been suggested to maintain bone integrity.
In a randomized, double-blind, placebo-controlled study in 1069 patients, oral clodronate (BONEFOS®, Schering AG, Berlin, Germany) 1600 mg was given daily for 2 years (medication period) followed by a 3-year follow-up period (5 years total). There was a significant reduction in the occurrence of bone metastases and improved overall survival with clodronate.
In a predefined subgroup of 498 patients, it was also shown that oral clodronate had a protective effect with regard to bone mineral content of the spine and hip. While on treatment, patients in the clodronate group either had an increase in mean bone mineral density (BMD) or maintained their baseline BMD in contrast with the placebo group, where a significant decrease in mean BMD was seen at all sites but one. During the 3-year follow-up period, the mean BMD decreased significantly for both treatment groups at all sites studied and there was no difference in the changes between the treatment groups. Therefore, clodronate had a protective effect on the loss of bone mineral content during the medication period as compared with placebo, but this effect was not maintained during the follow-up. Similar patterns of change are observed using biochemical markers of bone formation, such as serum PINP, or bone resorption such as urinary NTx excretion. Thus, the temporal courses of BMD and biochemical marker changes are similar to the effects of clodronate on the occurrence of bone metastases during treatment, with a reduction in effect when treatment is discontinued.
Over the 5-year study period, a total of 124 patients developed bone metastases: 51 patients treated with clodronate and 73 treated with placebo. In these patients, adjuvant oral clodronate treatment decreased the overall occurrence of SREs for both the 5-year study period (5.5% vs 9.8% with placebo; $P < 0.01$), with the most notable differences seen in the need for radiation (4.5% vs 8.7% with placebo) or incidence of skeletal fractures (2.3% vs 5.6% with placebo). Thus, adding clodronate to standard adjuvant therapy in primary breast cancer protects the skeleton from metastases and SREs, but the optimum duration of treatment with clodronate remains to be determined.

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Nomograms to predict outcome after preoperative chemotherapy for breast cancer

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Background: The aim of this study was to develop and validate nomograms to predict residual breast and axillary tumor, breast conservation and disease-free survival (DFS) after preoperative chemotherapy (PC) for breast cancer.
Patients and Methods: Data from 496 patients treated with anthracycline PC at the Institut Gustave Roussy was used to develop and calibrate the nomograms. These nomograms were tested on 2 independent cohorts of patients treated at MD Anderson Cancer Center. The first cohort received anthracycline (n = 337), the second a combination of paclitaxel and anthracycline (n = 237) PC.
Results: A nomogram to predict breast and axillary residual tumor had good discrimination and calibration in the training and the anthracycline-treated validation sets ($P < 0.01$). Application of the nomogram to patients treated with combination of paclitaxel and anthracycline indicated that patients with intermediate chemotherapy sensitivity benefit the most from an optimized schedule of paclitaxel whereas patients who are unlikely to achieve pCR to anthracylines remain at low probability for pCR even after inclusion of paclitaxel. The nomogram for breast conservation had a good discrimination but a poor calibration because of difference in terms of attitude toward breast conservation across countries. The nomogram for DFS had a concordance index of 0.72 ($P < 0.01$) in the validation set and outperformed commonly used prediction tools ($P = 0.02$).
Conclusions: We developed and validated several nomograms that predict outcome after preoperative chemotherapy for breast cancer. These tools will be available online.

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Taxanes as adjuvant chemotherapy for early breast cancer: pooled-analysis of 15,000 patients enrolled in 8 randomized clinical trials

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Background: The benefit of taxanes as part of adjuvant chemotherapy for early breast cancer undergone surgery is still unclear. We performed a pooled analysis of published phase III trials, to look if adjuvant chemotherapy with taxanes can add some advantage over standard chemotherapy.
Methods: All phase III trials published or presented at major meetings were considered eligible. A pooled analysis was accomplished, and event-based relative risk ratios (RR) with 95% confidence interval (CI) were derived. Both analyses were performed to look at significant differences in: disease-free survival (DFS), and overall survival (OS). The combined effect estimation was computed with both fixed- and random-effect model. For both analyses, Cochran Q heterogeneity test was applied as well. To increase the clinical meaning of that approach, a subgroup analysis considering only those trials enrolling patients with node-positive disease (9670 patients) was performed as well.
Results: Eight trials (15003 patients) were gathered; they were designed to look if chemotherapy with taxanes (paclitaxel or docetaxel) improves survival. Two out of 8 trials did not report OS results. When data were pooled and plotted, significant differences in favor of taxanes were seen in DFS in the overall population (RR = 0.84, 95%CI: 0.79–0.88, p < 0.00001, heterogeneity p = 0.55) and in node-positive group (RR = 0.84, 95%CI: 0.79–0.89, p < 0.0001, heterogeneity p = 0.57). Moreover, a significant differences in favor of taxanes were seen in OS in the overall population (13,575 patients, RR = 0.85, 95%CI: 0.78–0.92, p < 0.0001, heterogeneity p = 0.33) and in node-positive group (RR = 0.84, 95%CI: 0.77–0.91, p < 0.0001, heterogeneity p = 0.15), as well.
Conclusions: Considered the available phase III trials, taxanes-based adjuvant chemotherapy for early breast cancer seems to add a significant benefit in both disease-free and overall survival over standard chemotherapy. The lack of significant heterogeneity in both the overall population and in the node-positive group does underscore the homogenous effect through al trials.