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Adjuvant tamoxifen and exemestane in postmenopausal early breast cancer: ten-year analysis of the randomised phase III TEAM trial

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Abstract

Background: After five years of median follow-up, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial observed no difference in disease free survival between exemestane monotherapy and a sequential scheme of tamoxifen followed by exemestane in postmenopausal patients with early-stage, hormone receptor positive (HR+) breast cancer. As recurrence risk in HR+ breast cancer remains linear beyond five years after diagnosis, long-term follow-up outcomes of this trial were analysed.

Methods: The TEAM trial, a multicenter open-label phase III randomised controlled trial, included postmenopausal patients with early stage HR+ positive breast cancer from nine countries between 2001 and 2006. Patients were randomly allocated in a 1:1 ratio by a computer-generated random permuted block method to either five years of open-label exemestane monotherapy (25 mg daily) or a sequential scheme of tamoxifen (20 mg daily) followed by exemestane for a total duration of five years. Randomisation was performed centrally in each country. Long-term follow-up data for disease recurrence and survival was collected in six participating countries and analyzed by intention-to-treat. The primary endpoint was disease free survival (DFS) at ten years of follow-up. The trial is registered with ClinicalTrials.gov, NCT00279448, NCT00032136; NTR 267; Ethics Commission Trial 27/2001.

Findings: 6120 patients were included in the current intention-to-treat analysis. Median follow-up was 9·8 years (interquartile range 8·0-10·3). During follow-up, 921 (30%) of 3075 patients in the exemestane arm and 929 (31%) of 3045 patients in the sequential arm experienced a DFS event. DFS at ten years was 67% (95% CI 65-69) for the exemestane arm and 67% (95% CI 65-69) for the sequential arm (hazard ratio (HR) 0·96, 95% CI 0·88-1·05, p=0·39).

Interpretation: The long-term findings of the TEAM trial confirm that both exemestane alone and sequential therapy with upfront tamoxifen are equally effective as adjuvant endocrine therapy in postmenopausal HR+ early breast cancer patients. These results validate the opportunity to

individualize adjuvant endocrine strategy accordingly, based on patient preferences, comorbidities and tolerability.

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Research in context

Evidence before this study

We performed a search in PubMed MEDLINE (OVID-version), Embase (OVID-version), and Cochrane, limited to articles published before March 1st 2017. For the search, we combined the terms 'long-term follow-up', 'aromatase inhibitors', 'tamoxifen', 'sequential therapy', 'postmenopausal women', and 'hormone receptor positive breast cancer', also using various synonyms and related terms. This resulted in 104 papers, of which five were relevant results from randomised clinical trials. The majority of these trials studied long-term follow-up of other adjuvant endocrine therapy regimes, such as five years of tamoxifen versus anastrozole in the ATAC trial, or tamoxifen monotherapy versus sequential therapy in the IES trial. Furthermore, our search strategy identified a recent meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), comparing all major regimes including an aromatase inhibitor (AI) with each other, a sequential scheme or with tamoxifen alone, for the longest follow-up available. In this meta-analysis, the comparison between AI monotherapy and tamoxifen followed by AI was limited to seven years of follow-up; hence, none of the included trials had ten-years data available.

Added value of this study

This study is the first trial to report on ten-year follow-up of randomizing patients between five years of AI monotherapy or sequential therapy with upfront tamoxifen followed by an AI. After ten years, no significant differences in either DFS or OS between both schedules were observed. However, we did observe a small difference in disease recurrence, in favour of patients treated with exemestane monotherapy (20% versus 22% with sequential scheme).

Implications of all the available evidence

For postmenopausal patients with early-stage, HR+ breast cancer five years of tamoxifen monotherapy, AI monotherapy, or sequential treatment with upfront tamoxifen are valid

investigated treatment schedules to prevent relapse after surgery. Earlier, the EBCTCG meta-analysis showed that both the sequential strategy and AI monotherapy are superior to tamoxifen monotherapy after ten years of follow-up. The current analysis of the TEAM trial shows that at ten years of follow-up, both the sequential scheme with upfront tamoxifen and AI monotherapy are equal with regard to DFS and OS. Therefore, both strategies are equally effective treatment options for postmenopausal patients with HR+ early breast cancer.

Introduction

For more than three decades, tamoxifen has been the hallmark for adjuvant treatment in women with hormone receptor positive (HR+) breast cancer, leading to a proportional risk reduction in recurrence of breast cancer and death by 40% and 26% respectively.[1] Over the last ten years, aromatase inhibitors (AI), given either for five years or for two to three years after two to three years of tamoxifen, have shown superior efficacy over tamoxifen alone, further reducing the proportional risk of breast cancer recurrence by approximately 30% over five years of follow-up.[2]

HR+ patients who remain disease free after five years of adjuvant endocrine treatment, still face a substantial risk of recurrence (11% and 20% ten and fifteen years after diagnosis, respectively[3,4]), indicating the importance of long-term follow-up for trials comparing adjuvant endocrine treatment strategies.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) phase III trial compared five years of exemestane with a sequential scheme of 2·5 years of tamoxifen followed by 2·5 years of exemestane. After five years of median follow-up, no significant difference for disease free survival (DFS), overall survival (OS) and relapse free survival (RFS) was observed between the two treatment strategies.[5] The current analysis of the TEAM trial is the first study to present ten-year outcomes of the efficacy of five years of AI (exemestane) versus sequential therapy (tamoxifen followed by exemestane).

Methods

Study design and participants

The TEAM trial is a phase III open-label randomised controlled trial that enrolled postmenopausal women with histologically confirmed breast adenocarcinoma and locally assessed estrogen- (ER) and/or progesterone-receptor-positive (PgR) disease who had completed local treatment with curative intent between 2001 and 2006.[5] There were no age-related restrictions for inclusion. Other eligibility criteria were an ECOG performance status of 0 or 1, adequate hematological parameters (PLT > $100x10^9$/L, WBC > $3x\ 10^9$/L), renal (creatinine <1.5 ULN) and liver function (ASAT or ALAT <2.5 ULN). Exclusion criteria included: earlier adjuvant endocrine therapy or neo-adjuvant chemotherapy, uncontrolled cardiac disease, other malignancies or other serious illnesses interfering with subject compliance, adequate informed consent or study participation.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio centrally in each country by use of a computer-generated random permuted block method with stratification per country. Treatment allocation was not masked to participants, those prescribing the medication, those assessing outcomes and analysing the data. Patients were enrolled by the local clinicians in the participating hospitals.

Procedures

Endocrine treatment was started within ten weeks after completion of surgery and end of chemotherapy if indicated, and was administered orally daily for five years in both treatment arms. Patients were initially assigned either to exemestane (25 mg once a day) for a duration of five years or tamoxifen (20 mg once a day, orally) for a duration of five years. After the publication of the IES trial,[6] the protocol was amended. Patients assigned to tamoxifen were switched after 2·5 to three years to exemestane therapy for a total duration of five years of treatment. Dose reductions were not allowed. Patient visits were required every 3 months during the first year, and every 6 months

during the remaining active treatment period. Study endpoints and adverse events were recorded during each visit during active treatment. Mammography was performed yearly, laboratory tests and other radiological evaluations were performed as determined by local guidelines.

The original study was conducted in 566 hospitals in nine countries. For the current pre-planned long term follow-up analysis, we only included patients who were enrolled in countries where follow-up was collected for at least two additional years after the five years of endocrine therapy in the context of the study. For this reason, patients from Japan (n=184), France (n=1,230), and the United States (n=2,232) were excluded from analyses (Figure 1). Data were collected in the different countries and sent as a batch per country to Leiden, and thereafter merged into one database. Information on cause of death was gathered on the case report form and thereafter categorized into ten pre-specified groups. Classification of cause of death was verified by the TEAM central datacenter. Late side effects after five years of endocrine therapy in this current analysis were not recorded. Database cutoff was set at February 19, 2016.

Outcomes

The primary endpoint was disease free survival (DFS), defined as the time from randomisation to disease recurrence or death from any cause. Disease recurrence was defined as disease recurrence (locoregional or distant) or a new primary breast cancer. Ductal carcinoma in situ was not considered as recurrent disease. Secondary outcomes were overall survival (OS) defined as time from randomization to time of death due to any cause, recurrence free interval (RFI) defined as time from randomisation to recurrence or time of death due to breast cancer if no recurrence was reported before death and distant recurrence free interval (DRFI) defined as time from randomisation to distant recurrence or time of death due to breast cancer if no recurrence was reported before death. Patients with distant metastases at time of death were categorized as death due to breast cancer.

Statistical analysis

All patients who were randomly assigned to treatment, except those who withdrew consent before start of treatment, were included in the intent-to-treat population. All analyses were performed in the intent-to-treat population. A power calculation was performed before study initiation for analyses after five years of follow-up, and has been described previously.[5] All tests were two-sided and a p-value of less than or equal to 0·05 was considered statistically significant. Kaplan-Meier estimates of DFS and OS were calculated for each treatment group. DFS and OS were compared between treatment groups using log-rank tests and stratified by country and additional stratification factors within countries (nodal status (positive versus negative), PgR status (positive versus negative), adjuvant chemotherapy (yes versus no)). All hazard ratios (HRs) were calculated with a Cox regression analysis using the same stratification factors as the log-rank tests. Cumulative incidence of recurrence and subdistribution hazard ratios (sHRs) for RFI and DRFI were calculated using the Fine and Gray model for competing risks, taking other causes of death into account as competing events.[7] Proportional differences were tested using Pearson's χ^2 test. All time-to-event curves were truncated after ten years of follow-up, while HRs and sHRs include all events until database cutoff.

Additional analyses

Predefined subgroup analyses were performed for DFS. Interaction between treatment and prognostic factors was tested for effect modification using the Cox proportional hazard model. A post-hoc analysis was performed to study the relation between treatment and breast cancer specific mortality (BCSM) and other cause mortality (OCM). Cumulative incidence of recurrence and sHRs were calculated using the Fine and Gray model for competing risks.

An additional five year conditional survival analysis for DFS using the Cox proportional hazard model was performed as a post-hoc analysis to compare treatment groups for late disease recurrences, and subgroup analyses were performed to test interaction between treatment and prognostic factors for late recurrences. Furthermore, to estimate the influence of HER2 positive patients included in this

study population, analyses were repeated post-hoc after exclusion of the HER2 positive patients. Kaplan Meier estimates were calculated for ten year DFS for each treatment arm in the remaining population.

For this long-term follow up analysis, patients from countries that did not collect long-term follow-up data were excluded. To assess whether findings from this study could be generalized to the original population various additional post-hoc analyses were performed. First, baseline clinicopathological factors between the in- and excluded patients were compared. Second, DFS at five years after randomisation was compared between the in-and excluded patients. Third, treatment effect between the in- and excluded patients at five years was tested for interaction. Last, a sensitivity analysis was performed to compare treatment arms for DFS with complete follow up time for the original TEAM population. Patients from countries that did not collect outcomes after five years were censored.

Statistical analyses were performed using R 3.3.0 version using the *survival*, *prodlim* and *cmprsk* packages.

The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice. Appropriate approvals from the ethical committee were obtained. All patients provided written informed consent. This study is registered in France with ClinicalTrials.gov, NCT00279448; the Netherlands and Belgium with Netherlands Trial Register, NTR 267; the UK and Ireland with ClinicalTrials.gov, NCT00032136; and Germany with Ethics Commission Trial, 27/2001. *Role of the funding source*

The TEAM trial was initially funded by an unrestricted grant from Pfizer. Collection of long term follow-up was funded by the Dutch Cancer Foundation (UL 2010-4674). Funding sources had no role in the study design, data collection, analysis, interpretation of the data, writing of the manuscript, or the decision to publish. Study investigators listed as authors were involved in data interpretation

writing the report and the decision to submit. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors had access to the raw data.

Results

In the original TEAM trial, 9766 patients were included in the intention-to-treat population between January 16th 2001 and January 31st 2006.[5] Overall, 6120 (63%) patients from six countries were included in the current intention-to-treat population and analyzed for the primary and secondary outcomes (Figure 1). Median follow-up was 9·8 years (IQR 8·0-10·3) and median age at diagnosis was 63·8 years (IQR 57·8-70·8). Baseline characteristics were similar between both treatment arms (Table 1).

During the ten year study period, 921 (30%) of 3075 patients in the exemestane group and 929 (31%) of 3045 patients in the sequential group experienced a DFS event (Table 2). The Kaplan-Meier-estimated ten year DFS percentage was 67% (95% CI 65-69) for the exemestane arm and 67% (95% CI 65-69) for the sequential arm (HR 0·96, 95% CI 0·88-1·05, p=0·39, Figure 2A). Treatment effect was consistent between all subgroups and no significant interaction was observed between treatment and clinicopathological factors (Figure 3). Overall, hazard ratios were similar to those of the previous report after five years of median follow-up.[5]

During follow-up, 733 (24%) of 3075 patients in the exemestane arm and 727 (24%) of 3045 patients in the sequential arm died (Table 3). Overall survival after ten years was 74% (95% CI 72-75)in the exemestane group and 73% (95% CI 72-75) in the sequential group (HR 0·98, 95% CI 0·89-1·09, p=0·74, Figure 2B). BC recurrence occurred in 567 (18%) of 3075 patients in the exemestane arm and 623 (20%) of 3045 patients in the sequential arm during follow-up. Cumulative incidence for BC recurrences after ten years of follow up was slightly lower in the exemestane group (20%, 95% CI 19-22) than in the sequential group (22%, 95% CI 20-24) (sHR for RFI 0·88, 95% CI 0·79-0·99, p=0·03, Figure 4A). Distant recurrences occurred in 468 (15%) of 3075 patients in the exemestane arm and 497 (16%) of 3045 patients in the sequential arm. No difference in cumulative incidence for distant recurrence was observed for exemestane alone versus sequential therapy (16% (95% CI 15-18)

versus 18% (95% CI 16-19) respectively, sHR for DRFI 0·91, 95% CI 0·80-1·03, p=0·15, Figure 4B).

Additional analyses

In the exemestane arm, 377 (12%) of 3075 patients died due to breast cancer and in the sequential arm 419 (14%) of 3045 patients died due to breast cancer (Table 3). Cumulative incidence for BCSM after ten years of follow-up was 13·5% (95% CI 12·3-14·9) in the exemestane arm and 15·4% (95% CI 13·0-16·9) in the sequential arm (sHR 0·88, 95% CI 0·77-1·01, p=0·07, Figure 5). Death due to other causes than BC occurred in 356 (12%) of 3075 patients in the exemestane arm and 308 (10%) of 3045 patients in the sequential arm (Table 3). Cumulative incidence for OCM was 12·8% (95% CI 11·5-14·2) in the exemestane arm and 11·3% (95% CI 10·0-12·6) in the sequential arm (sHR 1·14, 95% CI 1·00-1·31, p=0·08, Figure 5). No significant differences for cause of death were observed between the treatment arms. The number and types of new primary non-breast cancers are shown in Table 4. Endometrial cancer occurred more frequently in the sequential arm than in the exemestane arm (23 (0·8%) of 3045 patients versus 7 (0·2%) of 3075 patients, respectively). Other second, non-breast cancers were not different between both treatment arms (Table 4).

Five years after randomization, 2470 (80%) of 3075 patients in the exemestane arm and 2385 (78%) of 3045 patients in the sequential arm were alive and disease free. 431 (17%) of 2470 patients in the exemestane arm and 423 (18%) of 2385 patients in the sequential arm experienced a DFS event in the remaining follow up period. DFS at ten years was 80% (95% CI 78-82) in the exemestane arm and 81% (95% 79-82) in the sequential arm (HR 0·98, 95% CI 0·86-1·13, p=0·82). This effect was consistent among all subgroups and no significant interaction was observed between treatment and clinicopathological factors (webappendix, page 1).

For the repeated analysis excluding the HER2 positive patients, 560 HER2 positive patients (9 %) were excluded from the original trial population. In the remaining HER2 negative or HER2 unknown population, 812 (29%) of 2819 patients assigned to the exemestane arm and 814 (30%) of 2741 patients assigned to the sequential arm experienced a DFS event. DFS at ten years was 68% (95% CI

66-70) for patients in the exemestane arm and 67% (95% CI 66-69) for patients in the sequential arm. This was not significantly different compared to the results of the total study population.

Patients from countries that did not collect long-term follow-up had more favourable tumour characteristics at baseline (webappendix, page 2). DFS at five years for patients included in the long-term follow-up analysis was lower than that of excluded patients (DFS 84%, 95% CI 83-84 and DFS 90%, 95% CI 89-91, respectively). Treatment effect for DFS at five years was comparable between patients included in the long-term follow-up analysis and patients that were excluded (HR 0·96 (95% CI 0·88-1·06) and HR 1·01 (95% CI 0·84-1·22), respectively, p-value for interaction = 0·66). Treatment effect for the original TEAM population was comparable to the results of the long-term follow-up study (HR 0·97, 95% CI 0·90-1·06).

Discussion

To our knowledge, this is the first trial reporting ten year outcomes of five years of AI monotherapy compared to five years sequential therapy with upfront tamoxifen, showing that after ten years of median follow-up both exemestane monotherapy and the sequential scheme are equally effective treatment strategies for postmenopausal patients with HR+ early breast cancer. No significant differences between the treatment arms were observed for DFS and OS, although a small benefit was observed for exemestane monotherapy with regard to cumulative incidence of recurrences. An additional analysis looking into cause of death suggests a lower breast cancer specific mortality but a higher other cause mortality for exemestane monotherapy compared to sequential therapy.

The results from this ten year analysis of the TEAM trial are consistent with the long-term analysis of the BIG 1-98 trial. After a median follow-up of 8·0 years, this study reported no differences between letrozole and sequential therapy (tamoxifen followed by letrozole) for DFS (HR 1·07, 0·92-1·25) and OS (HR 1·10, 0·90-1·33).[8] The TEAM results reported in this study represent a much larger patient cohort and a longer follow-up period, thereby strengthening the results reported from the BIG 1-98 trial. Furthermore, our results are in line with findings from the EBCTCG meta-analysis, including all trials investigating the value of AI versus tamoxifen regimens in postmenopausal HR+ breast cancer patients. They observed a very small benefit regarding recurrences rates of AI monotherapy over the sequential scheme with upfront tamoxifen after a median follow-up period of seven years (recurrence rate 14·5% versus 13·8%), but observed no benefit with respect to OS in this same time period.[2] In view of the current ten year results of the TEAM trial and data from the BIG 1-98 trial and EBCTCG meta-analysis, both the sequential scheme with upfront tamoxifen and AI monotherapy are equally effective strategies.

When considering cause of death, results of the current analyses suggest that there might be a small benefit of exemestane therapy on breast cancer-specific mortality, although the percentage of distant metastasis was not significantly different (Figure 4B). Interestingly, this beneficial effect of

exemestane on breast cancer-specific mortality seems to be counterbalanced by an increase in non-breast cancer related mortality leading to similar overall survival rates. In the TEAM trial report after five years of median follow-up, significantly more cardiovascular adverse events were observed in the patients receiving exemestane alone.[5] After ten years of follow-up, death due to cardiac cause or vascular cause was higher in the exemestane arm (n=65) than in the sequential arm (n=47). In addition, more patients died due to a thromboembolic cause in the exemestane arm (n=11) than in the sequential arm (n=5) (Table 3). Unfortunately, this trial was not designed to show a significant difference in cause of death. A recently published meta-analysis showed a significantly higher risk for cardiovascular events for patients treated with AI monotherapy compared to upfront tamoxifen followed by an AI (RR 1·16, 95% CI 1·03-1·31). It has been suggested that the occurrence of more cardiovascular events in patients receiving an AI compared to patients receiving tamoxifen is most likely explained by the protective effect of tamoxifen on cardiovascular outcomes.[9,10] The increased risk of death with an AI has also been observed in the ABCSG-12 trial, investigating zoledronic acid versus no zoledronic acid with adjuvant tamoxifen or anastrozol (in combination with LHRH analogues) in premenopausal BC patients. Anastrozol and tamoxifen (in combination with LHRH analogues) were equally effective for disease free survival after eight years of follow-up but a significantly worse overall survival for anastrozol was observed.[11] Overall, these findings suggest that although AI might be more favorable for breast cancer related outcomes, it lacks the cardioprotective effect of tamoxifen, which might be preferred for patients with a relatively low risk breast cancer and high risk cardiovascular profile. Further long-term research is necessary to confirm these observations and to better define subgroups with high risk for cardiovascular diseases that might benefit from upfront tamoxifen.

An important remaining question is whether it is possible to select some subgroups for which there is a more clear benefit for either upfront tamoxifen or AI use. In the BIG 1-98 trial, patients with a poor prognosis (using ER and PgR status, HER2 status, Ki-67 index and clinical prognostic factors) appeared to have more benefit regarding DFS from letrozole monotherapy compared to any other

treatment strategy.[12] A meta-analysis, comparing tamoxifen and AI monotherapy (either for five or two to three years), suggested that HER2-negative tumors would benefit more from AI monotherapy.[13] However, this study evaluated only the period in which the active treatment was different between both arms. Our analysis, covering 10 years of follow-up and comparing the sequential scheme with AI monotherapy in a large cohort, failed to identify any clinicopathological subgroup that would benefit more from either the sequential treatment or AI monotherapy. Therefore, the identification of a subgroup for which there is a more clear benefit of either therapy remains challenging. In the context of the TEAM pathology study, we plan to combine clinicopathological factors with biomarkers. This will hopefully identify biomarkers that will allow for better stratification.

With no evident improvement in disease related outcomes and overall survival nor a clear benefit for a specific subgroup for either AI monotherapy or sequential therapy, the choice of therapy might depend on safety and tolerability not only during but also after completion of treatment. The TEAM five-year analysis showed that the use of tamoxifen is associated with an increase in gynaecological- and thromboembolic side effects, whereas exemestane was more often associated with musculoskeletal disorders like arthralgia, osteoporosis and subsequent fractures.[5] In the current analyses, after ten years of median follow-up and five years after treatment completion, more endometrial cancers were still observed in the sequential than in the exemestane arm, although absolute numbers were low (23 versus 7, Table 4). Further analysis showed that median time to diagnosis of endometrial cancer was 7·0 years after randomization in this study for patients who received the sequential therapy. This suggests a long-term carry-over effect of tamoxifen use. Reassuringly, deaths due to endometrial cancer did not occur more frequently in one of the groups (Table 3). Unfortunately, no other long-term adverse events on the abovementioned items were collected in the context of the TEAM study. In the ATAC trial, fractures were more common during treatment in the anastrozole arm compared to the tamoxifen arm, but were similar after treatment completion at ten years of follow-up, suggesting no carry-over effect after treatment completion.[14]

Although some evidence from side studies of the TEAM trial and the BIG 1-98 trial suggest poorer cognitive functioning in patients receiving tamoxifen compared to patients using an AI,[15,16] it remains unclear whether tamoxifen also affects long term cognitive functioning. Quality of life did not appear to be different between AIs and tamoxifen in several trials.[17-19] However, no quality of life data from these trials are available after completion of therapy. It would be worthwhile to develop a cardiovascular risk and potentially other risk profiles, enabling to select the appropriate therapy regimen for a particular patient.

Another relevant unanswered question is the optimal length of adjuvant endocrine therapy, which is currently being studied in several trials.[20] Of note, 435 (16%) of the 2,753 Dutch patients in this analysis continued with letrozole beyond five years in the context of the prospective phase-III Investigation on the Duration of Extended Adjuvant Letrozole treatment (IDEAL) trial (randomization between 2·5 or five years of extended therapy with letrozole).[21] TEAM trial patients that continued in the IDEAL trial were equally distributed among both treatment arms of the TEAM trial and were equally randomised for either 2·5 or five years of extended therapy in the IDEAL trial. Differences between the two treatment arms in the TEAM trial are therefore not likely explained by the extended therapy. However, extended therapy could have affected the ten year results at a similar rate for both arms and possibly have led to an underestimation of recurrence rates. Given the equivalence of sequential therapy (tamoxifen followed by AI) compared with AI therapy for the first five years of adjuvant endocrine therapy, it will be highly interesting whether upfront tamoxifen or AI monotherapy during five years has a differential benefit in patients who will receive extended endocrine therapy.

During the inclusion period of the TEAM trial (study closure January 31, 2006), adjuvant trastuzumab was not yet administered as the first reports on the efficacy of adjuvant trastuzumab therapy only became available mid-2005.[22,23] In the current patient cohort, only a minority of patients had HER2 positive breast cancer (n=560, 9%). Our subgroup analysis did not show any difference in treatment

effect between patients with HER2-negative, HER2-positive or unknown HER2 status, and no significant interaction between subgroups was observed (Figure 3). Further, repeated analyses excluding the HER2 positive patients were consistent with the findings in the total cohort. Given these results, the findings of the total study cohort may be considered reliable estimates of outcome for HER2 negative/HR+ patients.

Some countries that did not collect long-term follow-up (such as the United States and Japan) included relatively more low-risk patients in the TEAM trial (wepappendix, page 2). As a result, these patients had a significantly higher DFS at five years after randomization compared to patients included in the current long-term follow-up analysis. However, as subgroup analysis in this study showed that prognostic factors did not influence treatment effect (Figure 2), it is not expected to affect the findings of the current analyses. Moreover, no significant interaction for treatment was found between patients included in this long-term follow-up analysis and excluded patients . Therefore, we expect that results for treatment comparison in the current study cohort are representative for the original TEAM population. Furthermore, a sensitivity analysis that included both the included patients and excluded patients (with five years of follow-up) yielded consistent results. Despite the decreased number of patients included in the current analyses, the power to detect differences between treatment arms for the primary endpoint was sufficient as the number of events due to longer follow-up time increased compared to the five year evaluation of this study (current analysis: n=1850, Table 2; previous report: n=1428,[5] respectively).

There are some other limitations that we are aware of. Firstly, we did not collect long-term adverse events for the current analyses. Secondly, as mentioned previously, extended adjuvant therapy either inside or outside a study protocol could have possibly led to an underestimation of disease recurrence. Finally, we collected data on cause of death and although cause of death classification is more reliable in clinical trial settings, it could have been subject to misclassification.

In conclusion, both the sequential scheme with upfront tamoxifen and exemestane monotherapy for five years are equally effective adjuvant treatment options for postmenopausal, hormone-receptor-positive breast cancer patients, with comparable survival rates after ten years of median follow-up. This allows the possibility for shared decision making between the clinician and patient, balancing individual patient characteristics and preferences, side effect profiles, and tolerability. Future studies will hopefully show which subgroup, if any, benefits more from either strategy, and whether extension of any of these strategies is worthwhile.

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Declaration of interests

Prof. Paridaens reports grants from TEAM compensation for data management of the trial, to the academic hospital, during the conduct of the study; personal fees from Pfizer advisory board - consulting fees, outside the submitted work. The other authors declared no conflicts of interest.

Author contributions

MD and EB contributed to current study design, data preparation, data analysis and interpretation, prepared the first draft of the report, contributed to subsequent versions and the final report. CS, JN, DR, AH, CM, JS and CvdV initiated the study, contributed to study design, data collection, data interpretation, reviewed the first draft of the report, subsequent versions and the final version. EM contributed to data collection, data preparation and data interpretation reviewed the first draft of the report, subsequent versions and the final version. HP contributed to study design, data preparation and data analysis and interpretation, reviewed the first draft of the report, subsequent versions and the final version. RP initiated the study, contributed to study design, data collection, data interpretation and reviewed the final version of the report. GL and JK contributed to data interpretation, reviewed the first draft of the report, subsequent versions and the final version. LD contributed to data interpretation, datacollection and reviewed the final version of the manuscript. Contributions are guaranteed by the corresponding author (CvdV)**.**

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Tables

Table 1. Baseline characteristics of patients in the intention to treat population

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Age (years)				
< 50	102	3·3	109	3·5
50-59	948	31·1	926	30·1
60-69	1193	39·2	1180	38·4
≥ 70	802	26·3	860	28·0
Histological grade				
G1 (well)	301	9·9	315	10·2
G2 (moderate)	1569	51·5	1599	52·0
G3-G4 (poor)	930	30·5	905	29·4
Unknown	245	8·0	256	8·3
Tumour (T) stage				
T0,Tis	1	0·0	1	0·0
T1	1500	49·3	1526	49·6
T2	1321	43·4	1363	44·3
T3, T4	216	7·1	175	5·7
Tx, unknown	7	0·2	10	0·3
Nodal (N) stage				
N0	1295	42·5	1308	42·5
N1	1538	50·5	1562	50·8
N2-3	201	6·6	195	6·3
Unknown	11	0·4	10	0·3
Metastasis (M) stage				
M0 (no distant metastasis)	3041	99·9	3069	99·8
M1 (distant metastasis)	2	0·1	5	0·2
Not assessed	2	0·1	1	0·0
Estrogen-receptor status				
Positive	2970	97·5	3014	98·0
Negative	75	2·5	58	1·9
Unknown	0	0·0	3	0·1
Progesterone-receptor status				
Positive	2163	71·0	2215	72·0
Negative	535	17·6	535	17·4
Unknown	347	11·4	325	10·6
Most extensive surgery				
Mastectomy	1464	48·1	1409	45·8
Wide local excision	1577	51·8	1663	54·1
No resection	0	0·0	1	0·0
Unknown	4	0·1	2	0·1
Time from surgery to initiation of hormone treatment (months)				
< 3	1882	62·5	1886	61·8
3 to 6	628	20·8	694	22·7
≥ 6	502	16·7	472	15·5
Unknown	33	1·1	23	0·7
Adjuvant radiotherapy				
Yes	2053	67·4	2114	68·7
No	984	32·3	950	30·9

Unknown	8	0·3	11	0·4
Adjuvant chemotherapy				
Yes	1112	36·5	1141	37·1
No	1933	63·5	1934	62·9
Unknown	0	0	0	0
Country				
Netherlands	1379	45·3	1374	44·7
Germany	723	23·7	748	24·3
United Kingdom and Ireland	639	21·0	636	20·7
Greece	100	3·3	107	3·5
Belgium	204	6·7	210	6·8

Table 2. Disease-free survival events*

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Total	929	30·5	921	30·0
Locoregional recurrence only**	71	2·3	52	1·7
Distant metastases	502	16·5	470	15·3
New primary breast cancer***	50	1·6	45	1·5
Intercurrent deaths	306	10·0	354	11·5

* only first events for DFS were recorded **Includes ipsilateral breast cancer. ***Without distant metastasis.

Table 3. Causes of death

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Death due to breast cancer*	419	13·8	377	12·3
Death due to other causes	308	10·1	356	11·6
Second malignant disease	72	2·4	85	2·8
Endometrial cancer	2	0·1	1	0·0
Cardiac related	45	1·5	61	2·0
Thromboembolism	5	0·2	11	0·4
Pulmonary related	18	0·6	20	0·7
Cerebral related	16	0·5	23	0·7
Vascular related	2	0·1	4	0·1
Other	91	3·0	95	3·1
Unknown reason	57	1·9	57	1·9

*Death due to breast cancer was defined as death due to breast cancer as recorded or if distant metastasis were present at time of death

Table 4. Non-breast cancers

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Non-breast cancers				
Colorectal	40	1·3	52	1·7
Lung	32	1·1	37	1·2
Endometrial	23	0·8	7	0·2
Other	132	4·3	140	4·6

One patient in the sequential arm developed two colorectal tumours; five patients in the sequential arm and six patients in the exemestane arm developed more than one non-breast cancer tumour.

Figures

Figure 1

Caption: trial profile

Figure 2

Caption: Disease free survival (A) and overall survival (B)**Figure 3:**

Caption: Subgroup analysis of disease free survival

Legend: Numbers are number of events by numbers at risk at time of randomization (n/N(%)). The gray line represents a hazard ratio of 1·00, the black line is the overall hazard ratio of 0·96

Figure 4:

Caption: Cumulative incidence of recurrences (A) and distant recurrences (B)

Figure 5:

Caption: Stacked cumulative incidence of breast cancer specific mortality (BCSM) and other cause mortality (OCM) by treatment arm

Legend: Cumulative incidence function for cause of death stacked on top of each other by the two treatment arms. Sum of the two functions represents all-cause mortality.

Supplementary Tables (provided as webappendix)

Supplementary Table 1. Subgroup analysis of disease free survival for patients who remained disease free at five years after randomization

	n	N	HR (95% CI)
Histological grade			
G1 (well)	96	525	1·14 (0·76-1·71)
G2 (moderate)	415	2594	0·98 (0·81-1·19)
G3-G4 (poor)	278	1398	0·90 (0·72-1·15)
Gx/unknown	65	383	0·99 (0·72-1·92)
Tumour size			
T ≤2cm	347	2537	1·09 (0·88-1·34)
T >2cm	504	2273	0·93 (0·81-1·27)
Nodal status			
negative	304	2167	1·01 (0·81-1·27)
positive	548	2676	0·96 (0·81-1·14)
Progesterone receptor status			
positive	611	3564	0·97 (0·83-1·14)
negative	153	764	1·17 (0·85-1·61)
not performed	90	527	0·81 (0·53-1·24)
HER2			
positive	87	408	1·01 (0·67-1·55)
negative	617	3087	0·96 (0·82-1·12)
not performed	150	1360	1·09 (0·79-1·50)
Most extensive surgery			
mastectomy	479	2128	0·91 (0·76-1·09)
wide local excision	375	2724	1·12 (0·91-1·37)
Radiotherapy			
yes	542	3377	1·06 (0·90-1·26)
no	311	1467	0·87 (0·70-1·10)
Chemotherapy			
yes	261	1797	1·10 (0·86-1·40)
no	593	3058	0·93 (0·80-1·10)
Age (years)			
<50	19	166	0·91 (0·37-2·25)
50-59	200	1560	0·88 (0·67-1·17)
60-69	278	1942	0·88 (0·67-1·17)
≥70	357	1187	1·12 (0·69-1·11)
Overall estimate	**854**	**4855**	**0·98 (0·86-1·13)**

n: number of events, N: numbers at risk at time of randomization, hazard ratio (HR) and corresponding 95% confidence intervals (95% CI) for sequential therapy (reference) and exemestane monotherapy.

Supplementary Table 2. Baseline characteristics of patients in the original TEAM population, patients included for the current analysis and patients excluded for the current analysis

	Original TEAM population (n=9766)		Included for ten year analysis (n=6120)		Excluded for ten year analysis (n=3646)		
	N	%	N	%	N	%	P value*
Age (years)							
< 50	331	3·4	211	3·4	120	3·3	0·44
50-59	3017	30·9	1874	30·6	1143	31·3	
60-69	3731	38·2	2373	38·8	1358	37·2	
≥ 70	2687	27·5	1662	27·2	1025	28·1	
Histological grade							
G1 (well)	1677	17·2	616	10·1	1061	29·1	<0·001
G2 (moderate)	4797	49·1	3168	51·8	1629	44·7	
G3-G4 (poor)	2438	25·0	1835	30·0	603	16·5	
Unknown	854	8·7	501	8·2	353	9·7	
Tumour (T) stage							
T0,Tis	6	0·1	2	0·0	4	0·1	<0·001
T1	5690	58·3	3026	49·4	2664	73·1	
T2	3592	36·8	2684	43·9	908	24·9	
T3, T4	457	4·7	391	6·4	66	1·8	
Tx, unknown	21	0·2	17	0·3	4	0·1	
Nodal (N) stage							
N0	5112	52·3	2603	42·5	2509	68·8	<0·001
N1	4110	42·1	3100	50·7	1010	27·7	
N2-3	478	4·9	396	6·5	82	2·2	
Unknown	66	0·7	21	0·3	45	1·2	
Metastasis (M) stage							
M0 (no distant metastasis)	9725	99·6	6110	99·8	3615	99·1	<0·001
M1 (distant metastasis)	8	0·1	7	0·1	1	0·0	
Not assessed	33	0·3	3	0·0	30	0·8	
Estrogen-receptor status							
Positive	9586	98·2	5984	97·8	3602	98·8	0·001
Negative	176	1·8	133	2·2	43	1·2	
Unknown	4	0·0	3	0·0	1	0·0	
Progesterone-receptor status							
Positive	7300	74·7	4378	71·5	2922	80·1	<0·001
Negative	1725	17·7	1070	17·5	655	18·0	
Unknown	741	7·6	672	11·0	69	1·9	
Most extensive surgery							
Mastectomy	4333	44·4	2873	46·9	1460	40·0	<0·001
Wide local excision	5423	55·5	3240	52·9	2183	59·9	
No resection	3	0·0	1	0·0	2	0·1	
Unknown	7	0·1	6	0·1	1	0·0	
Time from surgery to initiation of hormone treatment (months)							
< 3	5100	52·2	3768	61·6	1332	36·5	<0·001
3 to 6	2661	27·2	1322	21·6	1339	36·7	
≥ 6	1912	19·6	974	15·9	938	25·7	
Unknown	93	1·0	56	0·9	37	1·0	
Adjuvant radiotherapy							
Yes	6697	68·6	4167	68·1	2530	69·4	<0·001
No	2976	30·5	1934	31·6	1042	28·6	

Unknown	93	1·0	19	0·3	74	2·0	
Adjuvant chemotherapy							
Yes	3514	36·0	2253	36·8	1261	34·6	<0·001
No	6252	64·0	3867	63·2	2385	65·4	
Unknown	0		0		0		

* P value corresponds to proportional distribution of patients included in the current analysis versus patient excluded in the current analysis

Figure 1

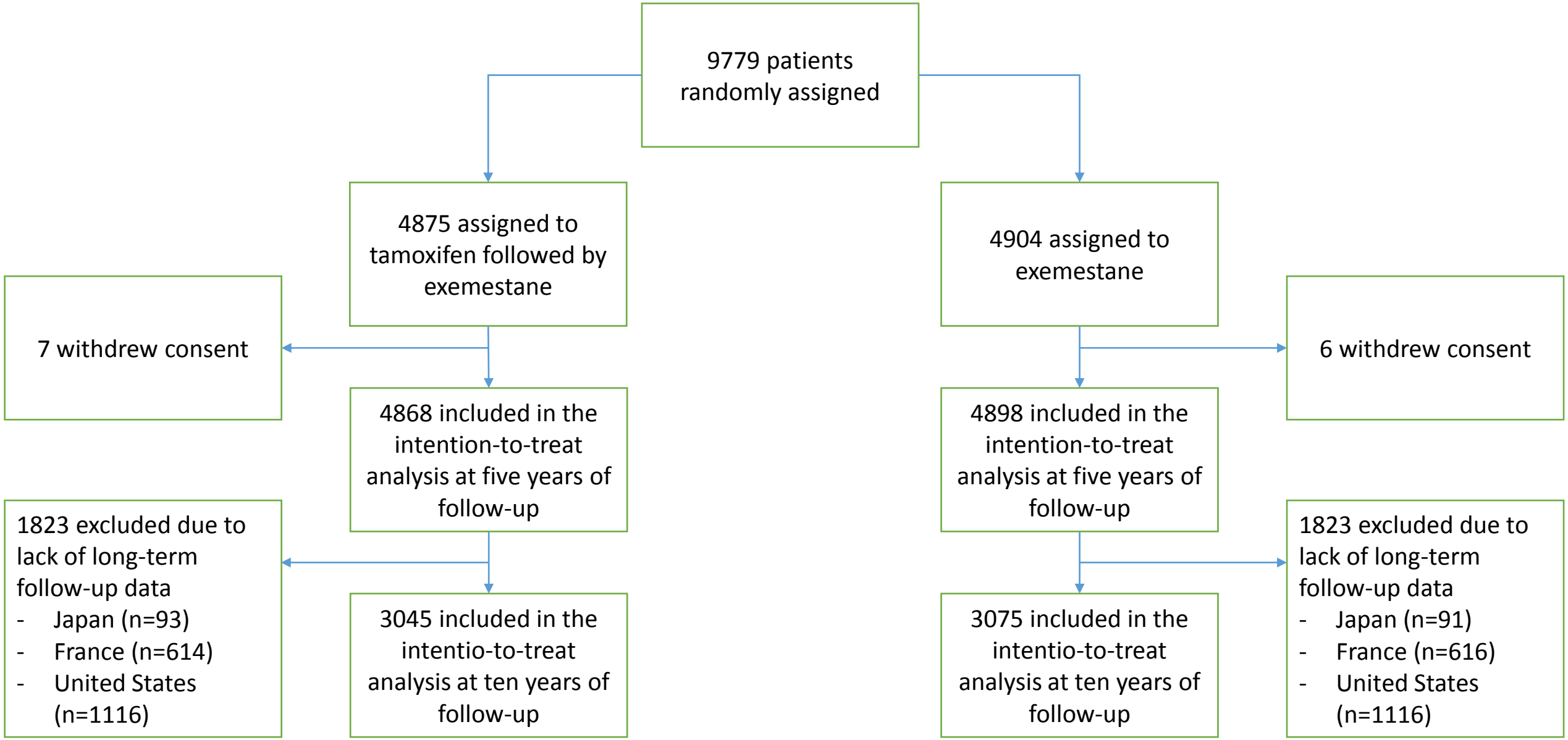

9779 patients randomly assigned
4875 assigned to tamoxifen followed by exemestane
4904 assigned to exemestane
7 withdrew consent
6 withdrew consent
4868 included in the intention-to-treat analysis at five years of follow-up
4898 included in the intention-to-treat analysis at five years of follow-up
1823 excluded due to lack of long-term follow-up data
- Japan (n=93)
- France (n=614)
- United States (n=1116)
3045 included in the intentio-to-treat analysis at ten years of follow-up
3075 included in the intentio-to-treat analysis at ten years of follow-up
1823 excluded due to lack of long-term follow-up data
- Japan (n=91)
- France (n=616)
- United States (n=1116)

Figure 2

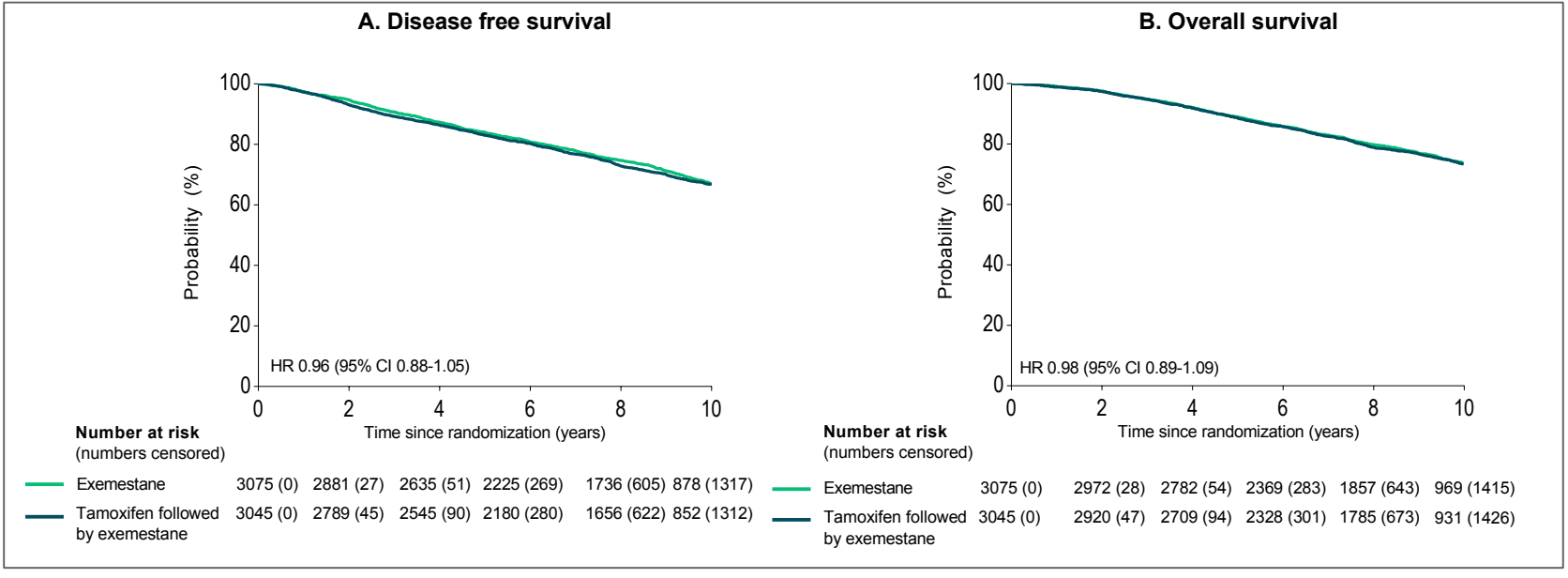

A. Disease free survival
Probability (%)
100
80
60
40
20
0
HR 0.96 (95% CI 0.88-1.05)
0
2
4
6
8
10
Time since randomization (years)
Number at risk
(numbers censored)
Exemestane 3075 (0) 2881 (27) 2635 (51) 2225 (269) 1736 (605) 878 (1317)
Tamoxifen followed by exemestane 3045 (0) 2789 (45) 2545 (90) 2180 (280) 1656 (622) 852 (1312)
B. Overall survival
Probability (%)
100
80
60
40
20
0
HR 0.98 (95% CI 0.89-1.09)
0
2
4
6
8
10
Time since randomization (years)
Number at risk
(numbers censored)
Exemestane 3075 (0) 2972 (28) 2782 (54) 2369 (283) 1857 (643) 969 (1415)
Tamoxifen followed by exemestane 3045 (0) 2920 (47) 2709 (94) 2328 (301) 1785 (673) 931 (1426)

Figure 3

	Tamoxifen followed by exemestane	Exemestane	HR (95% CI)
Histological grade			
G1 (well)	80/292 (27%)	87/309 (28%)	1.03 (0.77-1.41)
G2 (moderate)	437/1566 (28%)	446/1597 (28%)	0.97 (0.85-1.11)
G3-G4 (poor)	344/930 (37%)	309/901 (34%)	0.90 (0.78-1.06)
Gx/unknown	68/244 (28%)	79/248 (32%)	1.16 (0.83-1.60)
Tumour size			
T ≤ 2cm	322/1487(22%)	339/1525 (22%)	1.01 (0.87-1.18)
T > 2cm	602/1536 (39%)	580/1534 (38%)	0.95 (0.85-1.06)
Nodal status			
N negative	300/1288 (23%)	310/1304 (24%)	1.03 (0.88-1.20)
N positive	627/1737 (36%)	607/1754 (38%)	0.93 (0.83-1.04)
Progesterone receptor status			
positive	617/2156 (29%)	612/2210 (28%)	0.95 (0.85-1.06)
negative	205/534 (38%)	206/535 (39%)	0.98 (0.81-1.19)
not performed	107/347 (31%)	103/324 (32%)	1.08 (0.82-1.42)
HER2			
positive	115/302 (38%)	109/256 (43%)	1.15 (0.89-1.50)
negative	628/1887 (33%)	616/1933 (32%)	0.94 (0.84-1.05)
not performed	186/846 (22%)	196/882 (22%)	0.98 (0.80-1.20)
Most extensive surgery			
mastectomy	565/1463 (39%)	535/1405 (38%)	0.97 (0.86-1.09)
wide local excision	362/1569 (23%)	385/1662 (23%)	0.99 (0.86-1.14)
Radiotherapy			
yes	567/2051 (28%)	590/2111 (28%)	0.99 (0.88-1.11)
no	359/979 (37%)	328/945 (35%)	0.93 (0.80-1.08)
Chemotherapy			
yes	303/1111 (27%)	307/1139 (27%)	0.97 (0.83-1.14)
no	626/1926 (33%)	614/1929 (32%)	0.96 (0.86-1.07)
Age (years)			
< 50	22/101 (22%)	24/104 (23%)	1.02 (0.57-1.83)
50-59	236/946 (25%)	203/925 (22%)	0.84 (0.70-1.01)
60-69	315/1187 (27%)	295/1178 (25%)	0.95 (0.81-1.11)
≥ 70	315/801 (44%)	399/856 (47%)	1.04 (0.90-1.20)
Overall estimate	**881/3045 (29%)**	**880/3075 (29%)**	**0.96 (0.88-1.05)**

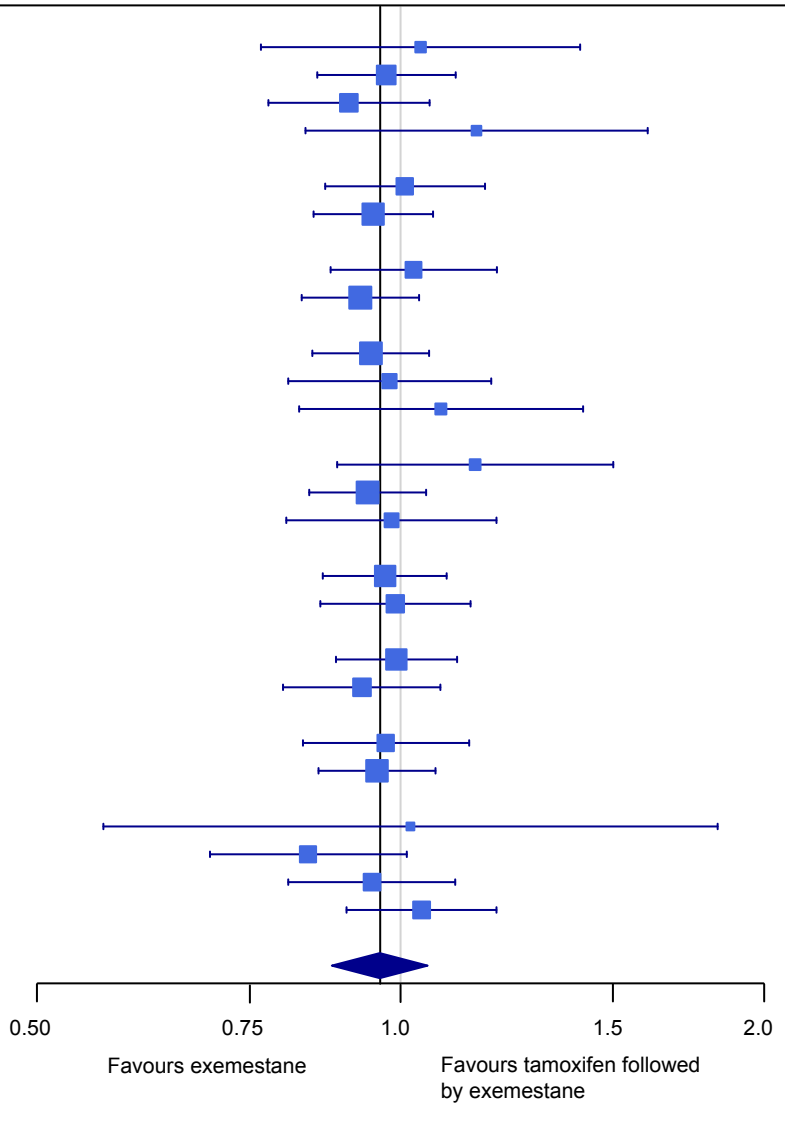


Figure 4

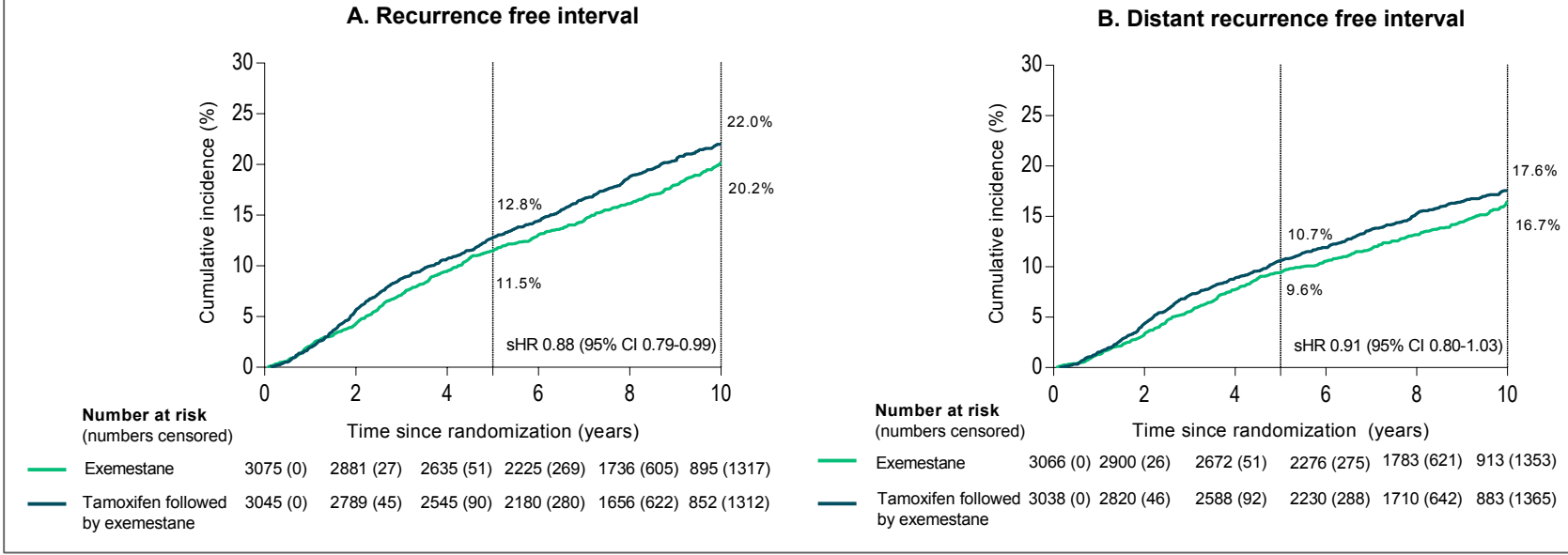
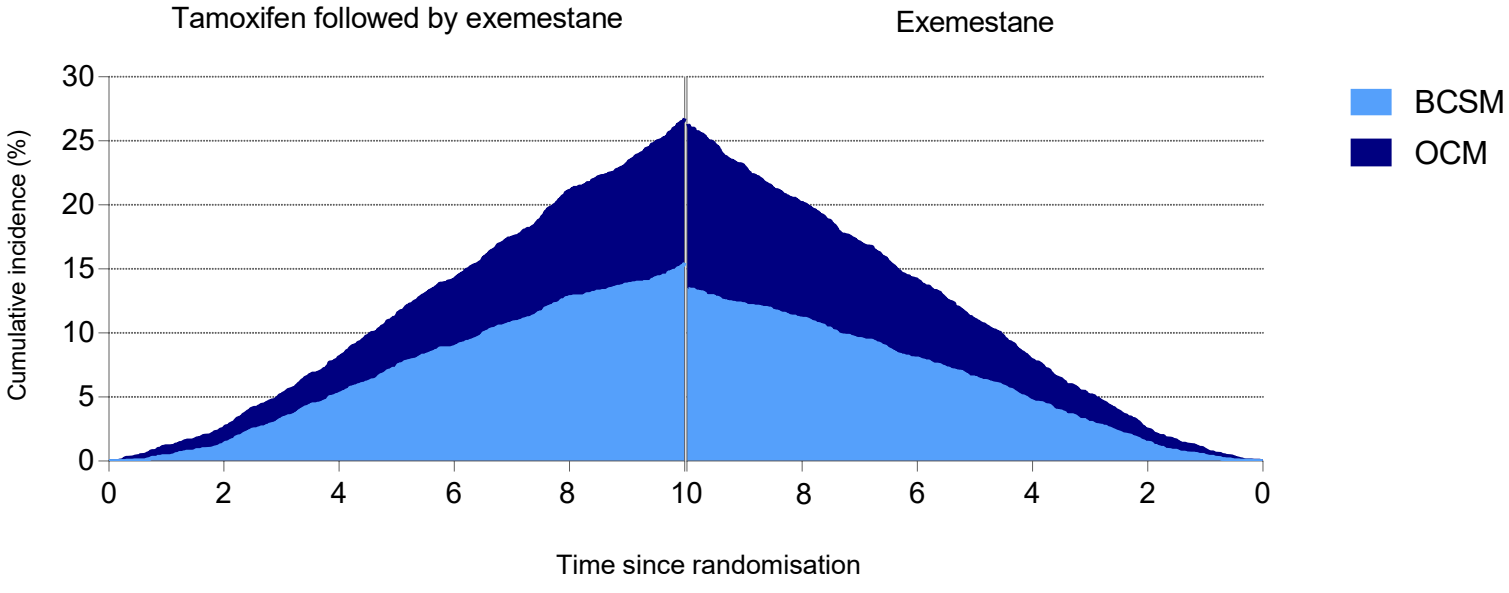

A. Recurrence free interval
Cumulative incidence (%)
30
25
20
15
10
5
0
0
2
4
6
8
10
Time since randomization (years)
22.0%
20.2%
12.8%
11.5%
sHR 0.88 (95% CI 0.79-0.99)
Number at risk
(numbers censored)
Exemestane 3075 (0) 2881 (27) 2635 (51) 2225 (269) 1736 (605) 895 (1317)
Tamoxifen followed by exemestane 3045 (0) 2789 (45) 2545 (90) 2180 (280) 1656 (622) 852 (1312)
B. Distant recurrence free interval
Cumulative incidence (%)
30
25
20
15
10
5
0
0
2
4
6
8
10
Time since randomization (years)
17.6%
16.7%
10.7%
9.6%
sHR 0.91 (95% CI 0.80-1.03)
Number at risk
(numbers censored)
Exemestane 3066 (0) 2900 (26) 2672 (51) 2276 (275) 1783 (621) 913 (1353)
Tamoxifen followed by exemestane 3038 (0) 2820 (46) 2588 (92) 2230 (288) 1710 (642) 883 (1365)

Figure 5


Tamoxifen followed by exemestane
Exemestane
BCSM
OCM
Cumulative incidence (%)
30
25
20
15
10
5
0
0
2
4
6
8
10
8
6
4
2
0
Time since randomisation

Webappendix

Click here to download Necessary Additional Data: Webappendix.pdf

Tamoxifen and **E**xemestane **A**djuvant **M**ulticenter Trial

TEAM trial

An open label, randomized multicenter comparative trial of 5 years adjuvant Exemestane treatment versus Tamoxifen for 2½-3 years followed by 2½-2 years of Exemestane, for a total of 5 years as adjuvant treatment in Postmenopausal Women with Early Breast Cancer

By the Dutch TEAM Study Group

Including amendment 1 & 2

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2 PROTOCOL SUMMARY

Title

Tamoxifen and Exemestane Adjuvant Multicenter trial

TEAM trial

Subtitle

An open label, randomized comparative Trial of 5 years adjuvant Exemestane treatment versus Tamoxifen for 2½-3 years followed by 2½-2 years of Exemestane, for a total of 5 years as adjuvant treatment in Postmenopausal Women with Early Breast Cancer

Study Design

Open label, randomized multicenter study, forming a part of a number of identical studies performed all over the world of which the results in terms of primary endpoints will be presented centrally. Subjects will be randomized 1:1 to receive either exemestane (25 mg once daily) for 5 years or tamoxifen (20 mg once daily) for 2½-3 years followed by 2½-2 years of exemestane (25 mg once daily).

Subjects

Globally, the study will include approximately 8700 evaluable subjects from multiple multinational study sites.
Women with histologically or cytologically confirmed primary adenocarcinoma of the breast which have undergone curative intended surgery (R_0) and who meet the following criteria will be enrolled in the study:

- Postmenopausal status (as defined in the protocol)
- Estrogen Receptor (ER) and/or Progesteron Receptor (PgR) positive tumor
- Any Tumor with a size > 3 cm, **or**

  Any N^+ **or**

  Tumor size 1-3 cm, N_0 and one of the following factors:

  - MAI > 10
  - Tumor gradation according to Bloom-Richardson: grade 3
  - Any TNM stage Breast Cancer (BC) considered to receive adjuvant hormonal therapy, as agreed by NABON and NVMO (49, appendix VI)

- Adequate hematological-, renal- and hepatic function (defined as PLT > $100x10^9$/L, WBC > $3x\ 10^9$/L, Creatinine< 1.5 UNL and SGOT (ASAT) or SGPT (ALAT) < 2.5 UNL
- Accessible for follow-up for the duration of the trial
- ECOG performance status 0 or 1 (appendix II)
- Written informed consent (according to ICH/GCP and local IRB guidelines)

Treatment

Patients will be randomized to receive exemestane 25 mg/day p.o. for 5 years or tamoxifen 20 mg/day p.o. for 2½-3 years followed by 2½-2 years of exemestane 25 mg/day.

Primary Endpoint	Relapse Free Survival (RFS) at 2¾ years	
Key secondary endpoint	RFS at 5 years	
Other secondary Endpoints	Overall survival (OS) Incidence of second breast cancer (in contralateral breast) Safety and long-term tolerability of the regimens	
Follow-up	According to center policy, but minimally:	
	Year 1:	every 3 months
	Year 2, 3, 4, and 5:	every 6 months
	Year 6+:	annually
Data to be recorded	Tumor Events:	local or distant relapse, contralateral breast cancer, deaths (breast cancer related and others)
	Second malignancies	
	Adverse events	
	Co-medication	
Participating Centers	75 Dutch centers and other (inter)national Cooperative Groups (i.e. US Oncology)	

3 ABBREVIATIONS AND DEFINITIONS OF TERMS

ALAT	Alanineaminotransferase
ASAT	Gutamaatoxaalacetaattransaminase
BC	Breast Cancer
BOOG	BOrstkanker Onderzoeks Groep Nederland (Dutch Breast Cancer Trialists' Group)
CRF	Case Report Form
DHT	Dihydroxytestosterone
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen Receptor
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
Hb	Hemoglobin
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethical Committee
IRB	Institutional Review Board
MAI	Mitotic Activity Index
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NABON	NAtionaal BOrstkankeroverleg Nederland
NVMO	Nederlandse Vereniging voor Medische Oncologie
OS	Overall Survival
PgR	Progesteron Receptor
PLT	Platelets
RBA	Relative Binding Affinity
RFS	Relapse (Recurrence) Free Survival
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TTP	Time To Progression
UNL	Upper Normal Limit
WBC	White Blood Cell Count

4 BACKGROUND AND INTRODUCTION

4.1 Background Tamoxifen

At the present time tamoxifen is still the standard hormonal treatment for post-menopausal women following curative intended surgery (R_0) for primary ER positive breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has summarized the available randomized trials, in women of all ages, as showing a 25% relative reduction in annual odds of relapse and 16% relative reduction in the annual odds of dying after a median follow-up of about 10 years (1).

The issue of the optimal duration of tamoxifen still remains to be solved. The results from the 1995 EBCTCG overview show that 2 years of treatment was beneficial and that there was an additional benefit for continuing treatment to a total of 5 years, suggesting that in women with ER+ve/ER-unknown tumors the proportional average relative recurrence reductions (after about 10 years of follow-up) compared with patients who received no tamoxifen were 21% for 1 year of tamoxifen, 29% for 2 years of tamoxifen and 47% for 5 years of tamoxifen. The corresponding average relative reductions for mortality were 12%, 17%, and 26%, respectively (1). However, the interpretation of indirect evidence such as this must be done with caution, as comparison between trials may be confounded by factors like concomitant chemotherapy, patient selection and duration of follow-up.

Several trials have been initiated to establish the tamoxifen duration question directly. Results from the first of these studies have been published. Early results from both the Swedish Breast Cancer Co-operative Group and the Cancer Research Campaign (CRC) Breast Cancer Trials Group, comparing 2 versus 5 years of tamoxifen, appear to suggest that patients treated for 5 years have a better disease-free survival than those allocated to receive 2 years (2,3). For patients treated with 5 compared with 2 years of tamoxifen, the CRC trial reports a relative risk (hazard ratio) of recurrence/death of 0.81 (95%CI 0.69-0.98) [all ER unknown] and the Swedish trial similarly estimates the hazard ratio of recurrence/death as 0.82 (95%CI 0.71-0.96). Both trials suggest a relative reduction in the risk of recurrence/death of approximately 18% for 5 years compared with 2 years of tamoxifen, remarkably similar to that estimated indirectly from the overview. This translates to approximately a 4% difference in recurrence-free survival (RFS) 5 years after randomization, although the size of the confidence intervals for each trial confirms that further information is needed before this estimate can be considered statistically reliable. Longer follow-up is also needed to provide a reliable analysis of overall survival. The results of both trials are, however, consistent with a modest reduction in risk of death following 5 years compared with 2 years of tamoxifen.

Four trials that were designed to investigate duration of tamoxifen beyond 5 years have now reported early results (4,5,6,7). However, the results thus far are controversial and do not support prolongation of tamoxifen beyond 5 years. The NSABP B14 trial (5) shows a significant better relapse free survival and overall survival for the 5 years treatment in node-negative patients. The Scottish trial also claims better outcome for the 5 years treatment in a population of node-positive and node-negative patients (4). Finally, in contrast to both studies previously mentioned, the only randomized study that shows benefit for 10 years tamoxifen is a relatively small ECOG trial (6). Longer follow-up in a larger patient group is necessary to provide a reliable answer as to whether to continue tamoxifen treatment for more than 5 years (8). Further trials are still ongoing which will, in due course, provide definitive information as to the optimal duration of tamoxifen. At that time the balance between therapeutic effect and increase in risk of endometrial cancer will be determined. Therefore, based on the current evidence, 5 years of tamoxifen is considered as the best standard adjuvant endocrine treatment for postmenopausal patients.

In order to achieve improved results, several groups have initiated studies to determine the effect of the addition of cytotoxic chemotherapy in the setting of postmenopausal patients. Two trials seem representative to summarize the results: (a) The IBCSG randomized patients to receive chemotherapy plus tamoxifen compared with tamoxifen alone; this trial resulted in a marginal benefit for those women receiving cytotoxic chemotherapy (an average of an extra 6 months free from recurrence), but this appeared to be outweighed by the decrease in quality of life as estimated by TWIST (9). (b) The ICCG have compared the use of epirubicin in addition to tamoxifen with tamoxifen alone; this resulted in a significant improvement in RFS (p=0.023) (10). In both studies survival was not significantly improved by the addition of chemotherapy. However, based on these results, chemotherapy combined with tamoxifen has been incorporated in the Dutch National Guidelines (49, appendix VI). Therefore, (planned) chemotherapy will not be an exclusion criterion for this trial. Patients will be stratified for (planned) chemotherapy and type of chemotherapy (if applicable).

4.2 Background Exemestane

Another form of endocrine therapy, with similar tolerability compared to tamoxifen, has been developed which appears to benefit patients with advanced breast cancer who have responded and/or stabilized to tamoxifen and who developed progression later on. This class of compounds is called aromatase inhibitors.

Aromatase inhibitors act systemically to inhibit estrogen synthesis in tissues. These compounds prevent estrogen biosynthesis by inhibiting the enzyme aromatase, which catalyses the conversion of adrenal- and ovarian androgens to estrogens. There has therefore been interest in developing these compounds as potential therapies for hormone responsive breast cancer in postmenopausal women.

Aminoglutethimide was the first generation aromatase inhibitor. Although effective as an adjuvant therapy in breast cancer (11), it was poorly tolerated and was replaced by the well-tolerated second-generation aromatase inhibitor 4-OH-androstenedione (formestane). This compound, however, only suppresses plasma estradiol to 1/3 of baseline levels and requires parenteral administration (12,13).

Some years later, third generation aromatase inhibitors were developed. They fall into two principal categories, i.e.: (a) non-steroidal, exemplified by fadrozole, vorozole, letrozole and anastrozole and (b) steroidal, exemplified by exemestane (14-23).

Exemestane is a very potent, orally active, selective and long lasting steroidal, irreversible inactivator of aromatase. In *in vitro* studies exemestane appeared to be 2.8 and 156 times more potent than the steroidal formestane and the non-steroidal aminoglutethimide (AG), respectively, in inhibiting human placental aromatase. *In vivo* studies of aromatase inactivation indicate that exemestane, by the oral route, is several times more potent than formestane (24,25).

Exemestane has no noteworthy binding to estrogen-, progesterone-, glucocorticoid- or mineralocorticoid receptors and only a very low binding to the androgen receptor (relative binding affinity, RBA, 0.2% from that of dihydrotestosterone, DHT) (26). However, its metabolite FCE 25071 (17-hydro-exemestane) was found to have a binding affinity to the androgen receptor (100-fold higher than that of exemestane (RBA 27% from and 0.28% that of DHT, respectively) (P&U, data on file).

Early hormonal studies in breast cancer patients using an estrogen assay, later on found to suffer from non-specific interactions of exemestane metabolites (Celite-RIA), indicated for exemestane a maximal inhibition of estrogens up to 30% of baseline levels starting from doses of 2.5-5 mg daily (19-21). However, more recent results obtained, using a very specific and sensitive

analytical method (HPLC - RIA), indicate that exemestane suppresses plasma estrogens down to 6-11% of pre-treatment levels (18, 22), thus showing an activity comparable to that observed with non steroidal aromatase inhibitors of third generation such as letrozole, and significantly more pronounced than that of formestane.

Recent *in vitro* and clinical data on intratumoral and peripheral aromatase inhibition indicate that the drug is a potent inhibitor of the enzyme. *In vitro*, exemestane inhibits the aromatase enzyme in human placenta, in adipose breast tissue and in tumor tissue, at concentrations of 1000nM, to 5%, 13% and 15% of the baseline values, respectively. In patients, the drug inhibits peripheral aromatisation down to 2.2% of the baseline, after 8 weeks of treatment with 25mg daily (P&U, data on file), which is considered to be the standard dose. These results are in line or superior to the ones obtained with other, non-steroidal, aromatase inhibitors, such as anastrozole or letrozole, and are consistent with the efficacy data so far obtained in phase I and phase II studies.

4.2.1 Exemestane trial results

Phase I studies

In total 137 patients have been treated with exemestane at various daily doses (up to 600 mg), and no MTD was determined, whereas 25 objective responses have been observed (18%).

Phase II studies

Four multicenter, multinational phase II trials in second- (tamoxifen failures) or third line treatment (tamoxifen- and megestrol acetate or tamoxifen- and AG failures) have been completed enrolling 437 patients (P&U, data on file).

In total 265 patients were accrued in the two studies (US and European) carried out at the standard dose of 25 mg daily in patients with advanced breast cancer, primarily refractory to tamoxifen or progressing after initial response to tamoxifen, and in patients relapsing during or within 12 months of discontinuing adjuvant tamoxifen. Of these, 262 are currently available for response evaluation. Overall, the objective response rate (CR plus PR) was 23%; including patients with long term stabilization of disease (>24 weeks), 45% of the patients benefited from therapy (P&U, data on file). In the European study, the median duration of objective response was 68 weeks, of overall response (CR, PR or disease stabilization > 24 weeks) 59 weeks and the median time to progression (TTP) was 29 weeks; the corresponding figures in the US study were 49, 43 and 24 weeks, respectively (P&U, data on file).

Considering the response rate to exemestane observed in patients failing tamoxifen (21%), this is in the same range as reported in the recent phase III studies for letrozole (29) or vorozole (30), but higher than that recorded with anastrozole 1 mg daily (27), or formestane (28).

In a US study assessing the efficacy of exemestane (25 mg daily) as 3rd-line treatment after failure of both tamoxifen and megestrol acetate, 91 patients were evaluable for response assessment (50). Response to treatment was observed in 13% of patients with an additional 18% obtaining stable disease >24 weeks. The median duration of objective response, overall response and TTP are currently 27, 34, and 9 weeks, respectively (50).

In total 78 patients were treated in a study assessing the efficacy of exemestane (200 mg daily dose) as 3rd-line treatment of patients progressing on AG given at a daily dose of >500 mg for at least 8 weeks (22,23) and all of them are currently available for response evaluation. They include 33 patients unresponsive to AG, 39 patients who had progressed after an initial response to AG, and 6 patients for whom response to prior therapy was either not available or not evaluable. Overall, the objective response rate was 26% (12% in patients refractory to AG and 33% in the responsive ones). Disease stabilization (>24 weeks) was achieved in an additional 13% of patients (15% of those refractory to AG and 13% of those responsive percentage of patients benefiting from therapy thus being 39% in this study. The median duration of objective response (CR+PR), overall response (CR, PR or disease stabilization >24 weeks) and time to progression (TTP) were 59, 48, and 21 weeks, respectively. These results are very promising considering the fact that the patient population consisted of patients previously treated with at least two hormonal agents and that 55% of them had received in addition at least one line of chemotherapy. Furthermore, this study confirms previous observations of lack of cross-resistance when steroidal aromatase inhibitors are given after non-steroidal aromatase inhibitors (27, 28, 51).

Randomized Phase II and III studies

Exemestane (25 mg daily) was evaluated in a phase III, randomized, double-blind, multicenter, multinational comparative study of postmenopausal women with advanced breast cancer who had disease progression after hormonal treatment with antiestrogens (primarily TAM) for metastatic disease or as adjuvant therapy. Subjects were required to have measurable metastases or lytic bone disease due to breast cancer, reasonable performance, ER/PgR receptor status positive or unknown, and near-normal organ function. Subjects may also have received prior cytotoxic therapy, either as adjuvant treatment or for metastatic disease. In this study (94 OEXE 018), 769 subjects were randomized to receive exemestane 25 mg once daily (N = 366) or megestrol acetate 40 mg four times daily (N = 403). Intent-to-treat results for randomized subjects from the study are summarized in Table 1 (46).

Table 1. Efficacy Results from a Phase III Study of Postmenopausal Women with Advanced Breast Cancer Whose Disease Had Progressed after Antiestrogen Therapy

Response Characteristics	Exemestane (N=366)	Megestrol acetate (N=403)	p-value
Objective Response Rate = CR + PR (%)	15.0	12.4	
95% Confidence Interval	(11.5-19.1)	(9.4-16.0)	
Overall Success = CR + PR + SD ≥ 24 Weeks (%)	37.4	34.6	
95% Confidence Interval	(32.3-42.6)	(29.9-39.6)	
CR (%)	2.2	1.2	
PR (%)	12.8	11.2	
SD (%)	40.7	41.9	
SD ≥ 24 Weeks (%)	21.3	21.1	
PD (%)	35.0	36.2	
Other (%)*	9.3	9.4	
Median Duration of Response (weeks)	76.1	71.0	
Median Duration of Overall Success (weeks)	60.1	49.1	0.025
Median Duration of SD ≥ 24 Weeks (weeks)	48.0	46.6	
Median TTP (weeks)	20.3	16.6	0.037
Hazard Ratio (Exemestane-MA) 0.84			
Median TTF (weeks)	16.3	15.7	0.042
Median Overall Survival (weeks)	Not reached	123.4	0.039
75% Survival (weeks)†	74.6	55.0	
95% Confidence Interval	(59.1-91.0)	(46.1-70.3)	

*****Includes subjects who were not treated or not evaluable
†25th percentile
Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease (no change), TTP = time to tumor progression, TTF = time to treatment failure

Comparison of exemestane vs. tamoxifen as 1st-line hormonal therapy in advanced breast cancer therapy is ongoing. Results from a randomized phase II trial comparing exemestane versus tamoxifen are promising and show high activity and low toxicity for exemestane (48). Recently, superior results were reported of exemestane compared with tamoxifen as first line hormonal treatment in a phase III trial of the EORTC Breast Group (52). This superiority consisted of a significant higher response rate, time to progression and less thrombo embolic events.

A large adjuvant study has recently been completed comparing 5 years treatment with tamoxifen with sequential treatment of tamoxifen and exemestane for 5 years (53). The published data demonstrated that there is a significant clinical benefit produced by switching patients to exemestane after 2–3 years of tamoxifen therapy, compared to keeping patients on 5 years of tamoxifen (3). Switching to exemestane significantly improved disease-free survival and resulted in significantly fewer second breast cancers (P=0.04) with a more favorable safety profile. At three years there was an absolute difference in disease-free survival of 4.7% with a 32% reduction in risk of recurrence for women switched to exemestane. However at a median follow-up of 30.6 months, overall survival was not different in patients switched to exemestane, compared to those patients who remained on tamoxifen for a total of 5 years.

4.3 Safety

4.3.1 Exemestane

An overall safety analysis has been performed on 744 postmenopausal breast cancer patients treated in the exemestane clinical program (phase I and II studies) with fixed doses ranging from 0.5 to 600mg daily, for a median time of 4 months. Approximately 20% of them received the drug for 1 year or longer (up to 3.5 years). In total 555 patients received the dose of 25 mg, which is considered the standard dose.

When events are considered in this safety analysis, that either are drug-related or from indeterminate cause, the overall frequency at the standard dose of 25mg was 49%. Reported events were mainly mild to moderate in severity using the CTC criteria. The most frequent adverse events reported were hot flushes (16%), nausea (12%), fatigue (7%) and dizziness (6%). More detailed data are shown below:

Table 2. Adverse events, either drug-related or of indeterminate cause, in postmenopausal breast cancer patients treated with exemestane in a daily dose of 25 mg.

Adverse Event	**25mg(555 pts)**	
	%	n
Any Event	49	274
Hot flushes	16	88
Nausea	12	65
Dizziness	6	36
Increased Sweating	5	30
Fatigue	7	37
Headache	5	29
Asthenia	1	6
Insomnia	3	18
Alopecia	2	14
Pain	3	15
Skin Rash	3	18
Anorexia	3	15
Edema-peripheral/leg	2	9
Abdominal Pain	2	14
Vomiting	2	13
Constipation	2	9
Dyspepsia	2	9
Hypertricosis	1	5
Paresthesia	<1	4
Dysphonia	<1	2
Acne	<1	4

Severe adverse events that were drug-related or from indeterminate cause were reported in only 3% of the overall patient population considered, but increased to 7% in patients treated with the 200mg dose.

Treatment discontinuation due to adverse drug reactions occurred in 1.5% of the patients. Of the 555 patients treated with the 25mg daily dose, 1% discontinued treatment for drug-related adverse reactions and only in two cases for grade 3 adverse reactions (allergic skin reaction in one case and grade 3 nausea in another). The other 4 patients discontinued treatment for grade 2 nausea (two cases, with concurrent grade 2 depression in one of them), grade 2 dizziness and weakness in one case and elevated liver function test in the last one.

Laboratory tests performed during clinical trials in patients with advanced disease did not indicate major side effects, apart from liver test alterations and decrease in lymphocyte count. Grade 2-3 liver function tests abnormalities led to drug discontinuation in one case (0.2%).

When compared to other treatments in comparative trials, the toxicity of exemestane seems to be mild. When compared to megestrol acetate, side effects appear to be comparable or favorable for exemestane. Preliminary results indicate the same when compared with tamoxifen. (48).

4.3.2 Tamoxifen

Secondary cancers:

The effect of tamoxifen on endometrial tissue has been investigated for many years. Results and conclusions however, remain controversial. Effects that appear to be associated with tamoxifen treatment are: uterine fibroids, endometrial polyps, endometriosis and endometrial hyperplasia (36-41).

Besides this, several reports associate tamoxifen treatment with increased risk for endometrial cancer (42-44). Moreover, in a very recent article from the Dutch Comprehensive Cancer Centres' Alert Group, published in The Lancet (45), it has been reported that the risk of endometrial cancer increased with longer duration of tamoxifen use ($p< 0.001$), with relative risks of 2.0 (1.2 – 3.2) for 2-5 years and 6.9 (2.4 – 19.4) for at least 5 years compared to non-users. Moreover, long-term tamoxifen users have a worse prognosis of endometrial cancers, which seems to be due to less favorable histology and higher stage. However, the benefit of tamoxifen on breast cancer survival far outweighs the increased mortality from endometrial cancer.

Other adverse events:

In ***table 3*** the adverse events are shown that were reported in the placebo-controlled NSABP B-14 trial. In this study, pre- and postmenopausal patients with primary breast cancer and histologically negative axillary nodes whose tumor estrogen receptors were positive (≥ 10 fmol) were re-randomized (in case they were still free of breast cancer recurrence after 5 years of tamoxifen adjuvant treatment) to either an additional 5 years of tamoxifen or 5 years placebo in a double-blind fashion. Hot flashes, vaginal discharge, and irregular menses were more frequent in women who were treated with tamoxifen, whereas fluid retention and weight gain were similar in the placebo and tamoxifen–treated groups. Thromboembolic phenomena were higher in the tamoxifen-treated group (1.2% vs. 0.4%), and 2 patients in the tamoxifen-treated group died of pulmonary emboli. A minority of patients may suffer severe symptoms, but these will diminish with time. Finally, less than 5% of women stop tamoxifen because of side effects (5).

Table 3. Percentage of Women Who Reported an Adverse Side Effect in the NSABP-14 5-Year Tamoxifen Trial (20 mg Daily) Vs Placebo

Both pre- and postmenopausal women participated in the study. These are the only side effects noted by the nearly 3,000 women involved in the trial. It should be recognized that all side effects were not experienced by all women.

Adverse Effects	**Tamoxifen (n = 1424)**	**Placebo (n = 1420)**
Hot flashes	63,9%	47,6%
Weight gain (> 5%)	38,1%	40,1%
Fluid retention	32,4%	29,7%
Vaginal discharge	29,6%	15,2%
Nausea	25,7%	23,9%
Irregular menses	24,6%	18,8%
Weight loss (> 5%)	22,6%	18,0%
Skin changes	18,7%	15,3%
Increased blood urea nitrogen (BUN)	18,1%	20,2%
Diarrhea	11,2%	14,0%
Increased serum glutamic-oxaloacetic transaminase (SGOT)	4,8%	2,8%
Increased alkaline phosphatase	3,0%	4,6%
Vomiting	2,1%	1,7%
Increased bilirubin	1,8%	1,2%
Increased creatinine	1,7%	1,0%
Thrombocytopenia*	1,5%	1,2%
Leukopenia**	0,4%	1,1%
Thrombotic events		
Deep vein thrombosis	0,8%	0,3%
Pulmonary embolism	0,4%	0,1%
Superficial phlebitis	0,3%	0.0%

* Defined as a platelet count of < 100,000/mm^3

** Defined as a white blood cell count of < 3,000/mm^3

4.3.3 Exemestane versus Tamoxifen

The only information about adverse events in a randomized study comparing exemestane and tamoxifen comes from a randomized phase II trial conducted by the EORTC Breast Cancer Cooperative Group (EORTC protocol 10951) in postmenopausal patients with metastatic breast cancer who received exemestane or tamoxifen as first line hormonal treatment. ***Table 4*** shows the results.

Table 4. Percentage of women who reported grade 2 and 3 NCIC-CTC toxicities in EORTC protocol 10951

Grade 2 and 3 NCI-CTC Toxicities		
	% of Patients	
	Exemestane (n=37)	**Tamoxifen (n=39)**
Anorexia	**_**	**5.1**
Dyspnea / Cough	**16.2**	**12.8**
Edema	**2.7**	**7.7**
Fatigue	**5.4**	**12.8**
Diarrhea / Constipation	**5.4**	**5.1**
Hot Flashes	**2.7**	**15.4**
Infection	**5.4**	**5.1**
Nausea	**2.7**	**7.7**
Pain, bone	**5.4**	**15.3**
Sweating	**_**	**10.3**
Skin	**8.1**	**_**
Weight gain / loss	**5.4 / 2.7**	**5.1 / 0**

The results have been presented at ASCO, 2000 by Paridaens (48). The phase II study will be extended to a phase III study.

5 STUDY RATIONALE

The good antitumor activity and safety profile of exemestane, as demonstrated in the phase II and III studies in postmenopausal women with metastatic breast cancer (discussed in chapter 4) provide a good rationale to investigate the efficacy and safety of adjuvant exemestane in a prospective, randomized study versus the current standard tamoxifen, in postmenopausal women with ER positive early breast cancer. Besides efficacy end-points (RFS, OS), safety and long-term tolerability (second malignancies) are important research objectives in such a trial.

6 TRIAL OBJECTIVES AND ENDPOINTS

6.1 Primary objective

To determine whether up-front adjuvant treatment with exemestane compared with adjuvant tamoxifen improves the relapse-free survival (RFS) of postmenopausal, receptor positive, early breast cancer patients following 2¾ (2½ -3) years of treatment.

6.2 Key secondary objective

5-years RFS as a point estimate obtained from the Kaplan-Meier survival estimates of the two treatment arms. The difference in 5-years RFS between the treatment arms will be reported, along with its standard error (SE) and an associated 95%-confidence interval.

6.3 Other secondary objectives

Overall survival, the relative safety profiles, and the incidence of new primary breast cancers of the postmenopausal women treated with 5 years of exemestane versus tamoxifen therapy for 2½ -3 years followed by 2½ -2 years of exemestane (a total of 5 years).

6.4 Endpoints

Primary endpoint of this study will be relapse-free survival (RFS) at 2¾. Key secondary endpoint will be relapse-free survival (RFS at 5 years. Other secondary endpoints will determine overall survival, the incidence of contralateral breast cancer, safety and long-term tolerability of both hormonal regimens.

Relapse is defined as the appearance of loco-regional recurrence or distant metastases at any site. Time to first locoregional recurrence, contralateral breast cancer and time to first distant recurrence will be recorded on separate parts of the CRF. In the event of relapse, all patients will be followed for progression and survival, irrespective whether their recurrence is loco-regional, consists of a second (breast) primary, or is in a distant site. These above sites will be registered, whereas recurrence in a supraclavicular node will be registered as a separate item. Date of suspicion of relapse, as confirmed by the investigator, as well as action taken to confirm relapse, will be recorded on the CRF.

Events that should be recorded are:

1. Ipsilateral breast-, chest wall-, or axillary nodal relapse (loco-regional)
2. Contralateral breast cancer
3. Supraclavicular nodal relapse
4. Distant relapse
5. Death and cause of death (breast cancer / other)
6. Other second malignancies
7. (Serious) Adverse Events

7 STUDY DESIGN

This is a multi-center open-label, randomized, parallel group, comparative clinical trial. The trial is conducted by the Dutch TEAM Study Group under the auspices of NABON-BOOG (Dutch Breast Cancer Trialists' Group). A Steering Committee has been appointed, consisting of one medical oncologist and one surgical oncologist from each of the 9 Dutch Comprehensive Cancer Centres, acting as regional study coordinators. This Steering Committee is responsible for a good conduct of the trial.

Treatment

Eligible subjects must be randomized and started on adjuvant hormonal treatment within ten weeks after completion of surgery, and/or chemotherapy (primary treatment).

Subjects will be randomized 1:1 to receive either exemestane, 25 mg once daily for 5 years or tamoxifen 20 mg once daily for 2½-3 years followed by 2½ -2 years of exemestane 25 mg once daily, for a total of 5 years. Both study drugs are registered for breast cancer and will be prescribed by the investigator.

Evaluation schedule

After randomization, patients will visit the hospital every 3 months during the first year. Thereafter, during year 2, 3, 4 and 5 after randomization, patients will be seen by the physician every 6 months.

At each visit, complaints and adverse effects will be recorded, physical examination will be performed, and concomitant medication will be registered. Yearly, a mammography will be performed. Furthermore, blood chemistry and hematology will be assessed according to local policy. For an exact overview of the follow-up schedule, please see the trial flowchart on page 27.

For patients who relapse during the 5 years adjuvant treatment and who are still considered to be suitable for hormonal therapy, it is strongly recommended to switch to the medication of the other trial arm. Results of this "cross-over" (response rate, duration of response and time to progression) will be registered.

Registration of relapse

In case of any relapse, the adjuvant treatment has to be stopped, and this is registered as an event. Any malignant contralateral breast cancer will be registered as a second primary, and relapse with supraclavicular disease will be registered as distant relapse, unless otherwise specifically indicated.

'Breast cancer' deaths will be all deaths with breast cancer specified as a cause of death and deaths from any cause following a distant relapse.

All patients will be evaluated for endpoints in the treatment arm to which they were randomized, irrespective of the treatment they actually received. No patient will be removed from the analyses, irrespective of whether she is found to have violated an eligibility criterion after randomization or to have been withdrawn from trial medication prematurely. Thus, analysis will be by "intention to treat" including all patients randomized.

Premature discontinuation

Patients will be withdrawn from the trial if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document the patient's outcome. Particularly, if a patient requests withdrawal from the trial, the patient must be asked whether she accepts that her clinical data will continue to be used for trial purposes (particularly details of disease-related events and follow-up).

Patients will discontinue study treatment in the case of any relapse. Treatment after relapse is at the discretion of the investigator, taking into consideration the recommendation under "Evaluation Schedule" concerning the crossover design. Other reasons for a patient to discontinue treatment will be the occurrence of a serious adverse event (SAE), withdrawal of consent or experience of unacceptable toxicity. There will be no dose modification and the patient will be discontinued from treatment should any unacceptable event occur. An 'Off Treatment' form must be completed, and the Central Data Center must be informed if treatment is discontinued prematurely for any reason. **All patients will continue to be followed-up, irrespective of whether they have discontinued treatment prematurely or not.**

8 SELECTION OF SUBJECTS

8.1 Inclusion criteria

The study population consists of postmenopausal women diagnosed with resectable breast cancer, meeting all of the following eligibility criteria:

- Histologically/cytologically confirmed adenocarcinoma of the breast, followed by intended curative surgery (R_0) and if indicated, also radiotherapy
- Any Tumor with a size > 3 cm, **or**
  Any N^+ **or**
  Tumor size 1-3 cm, N_0 and one of the following factors:
  - MAI > 10
  - Tumor grading according to Bloom-Richardson: grade 3
  - Any TNM stage BC considered to receive adjuvant hormonal therapy, as agreed by NABON-NVMO (49, appendix VI)

- ER and/or PgR receptor status positive (as defined by local hospital criteria)

- Post-menopausal defined as:
  - Age ≥ 50 and amenorrhea for > 1 year
  - Bilateral surgical oophorectomy (and no HRT) (any age is acceptable)
  - Age < 50 with natural amenorrhea > 1 year at breast cancer diagnosis (and uterus in situ)

  In case of doubt about subject's menopausal status, FSH assessments have to be performed to define the menopausal status (FSH should be in the postmenopausal range according to values of the local institution)

- Adequate hematological-, renal- and hepatic function (defined as PLT > $100x10^9$/L, WBC > $3x\ 10^9$/L, Creatinine< 1.5 UNL and SGOT (ASAT) or SGPT (ALAT) < 2.5 UNL)
- Accessible for follow-up for the duration of the trial

- ECOG performance status 0 or1 (appendix II)

- Written informed consent (according to ICH/GCP and local IRB guidelines)

- Baseline clinical laboratory tests are done within 4 weeks prior to randomization

- Adjuvant hormonal treatment is started within 10 weeks after completion of surgery (date of tumor removal or re-excision) or date of last adjuvant chemotherapy

8.2 Exclusion criteria

Those patients who did not undergo intended curative primary treatment or who fulfilled one of the following criteria:

- Inflammatory breast cancer
- Positive supraclavicular nodes
- Ulceration/infiltration of local skin metastasis

- Both ER negative and PgR negative primary tumor

- Evidence of distant metastases (M1)

- Patients who have received previous hormonal treatment as adjuvant treatment for breast cancer

- Uncontrolled cardiac disease including unstable angina, CHF or arrhythmia requiring medical therapy or with a history of myocardial infarction within the past 3 months or any other serious concomitant disease.

- Psychiatric disorders preventing proper informed consent

- Tumor with a size < 1cm and N_0

- Tumor size 1-3 cm, N_0 without additional risk factors

- Concomitant malignancies except for adequately treated carcinoma in situ of the uterine cervix or basal squamous cell carcinoma of the skin, unless agreed by the Steering Committee. Subjects with other malignancies must be disease-free for at least 5 years. Patients with a history of breast cancer should be excluded.

- Concurrent participation in another clinical study that may interfere with the results of the trial involving investigational agents within thirty days of treatment from this study, unless this is agreed by both the Steering Committee and the Coordinating Investigator of the study involved.

- Other serious illnesses that may interfere with subject compliance, adequate informed consent or determination of causality of adverse events.

- Hormone replacement therapy for treatment of menopausal symptoms that was not stopped at least 4 weeks prior to randomization

- Patients who were treated with neo-adjuvant chemotherapy

- Patients with a bilateral tumor

9 TRIAL ADMINISTRATION, DATA MANAGEMENT & MONITORING

9.1 Data Management

The Data Center Heelkunde from the department of Surgery of the Leids Universitair Medisch Centrum (LUMC) in Leiden will be the Central Data Center for the Dutch Team Study Group. The Central Data Center will be responsible for randomization of patients, supply of Case Record Forms (CRF's), receipt of CRF pages, generation of edits/queries, creation of Clean File and submission of clean CRF data to the Central Data Base in Canada.

Also, the Central Data Center can perform audits in participating institutions, whenever the Steering Committee considers this to be necessary.

Randomization

Randomization can be done by telephone or by fax. During the randomization procedure all eligibility criteria will be checked. At the end of the procedure the treatment will be randomly allocated to the patients. A sequential identification number will also be given. This number and the allocated medication have to be recorded on the randomization form, along with the randomization date. The randomization form must be signed by the investigator (in case of faxed randomization, the confirmation of the data manager will also have to be signed by the investigator) and be filed with the Case Report Forms.

Data Flow

The CRF's must be completed and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available. CRF's will contain common information, but this information will be kept to a minimum. The time between the patient's visit and completion/shipment of CRF pages should be kept to a reasonable minimum. In all cases it remains the responsibility of the investigator to check that original case report forms are sent to the Central Data Center and to verify that they are completed and filled out correctly.

The CRF will have the form of a booklet that can be kept in the patient's records and can serve as source document. After completion (within 1 month after the visit), the pages must be sent by mail to the Central Data Center. Afterwards, the CRF must be restored in the patients' records. All sections are to be completed on the forms before faxing it to the Central Data Center. If information is not known, this must be clearly indicated.

To enable peer review, and/or audits from Health Authorities/NABON-BOOG, the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRF's and hospital records), all original signed Informed Consent Forms, copies of all CRF's and detailed records of drug disposition. To comply with international regulations, the records should be retained by the Investigator for 15 years, including assessments like CT scans.

9.2 Monitoring

A pre-study and/or site initiation visit to determine the qualifications of the Investigator(s), to inspect the clinical laboratory facilities, and to fully inform the Investigator of his/her

responsibilities and the procedures for assuring adequate and correct documentation may be conducted on behalf of the Dutch Team Study Group, if deemed necessary.

Monitoring of the individual centers will take place on a regular pre-determined basis, but monitoring will be confined to a minimum. The decision to perform monitoring visits lies with the Steering Committee of the Dutch TEAM Study Group, who may also decide who will perform the monitoring visits.

Data to be verified will include informed consent, eligibility adverse events and outcome. Any major problems identified during monitoring will be reported to the Steering Committee.

All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

The Investigator must assure that the subjects' anonymity will be maintained on all documents submitted to the Dutch TEAM Study Group. Each subject will be identified in the Case Report Form (CRF) by a subject identification number, initials and date of birth. The subject identification number will consist of site number and randomization number.

A case report form (CRF) is required and should be completed for each included subject. The completed original CRF's are the sole property of the Dutch Team Study Group and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the Dutch TEAM Study Group.

10 ASSESSMENTS AND FOLLOW UP SCHEDULE

10.1 Pre-randomization (within 4 weeks of randomization and start of hormonal therapy)

To be recorded:

- Medical history
- Metastatic screen: Additional tests/investigations, if clinically indicated, are at the investigator's discretion.
- Hematology (Hb, WBC, platelets) & Biochemistry (Creatinine, ASAT or ALAT, Calcium, Protein, Alkaline Phosphatase and Glucose)
- Demography (date of birth)
- Concomitant medication (description of other medication prescribed for more than 7 days and taken within one month of randomization).
- Type of menopause (see eligibility criteria)
- Clinical examination
- Mammography (pre-surgery)

10.2 On Study

To be recorded:

- Trial Events (End-points): see Chapter 6
- Concomitant medication

Evaluation schedule

After randomization, patients will visit the center every 3 months for the first year. Thereafter, during year 2, 3, 4 and 5 after randomization, patients will visit the center every 6 months.

During the visits, physical examination will be performed, concomitant medication will be registered and adverse events (if any) will be recorded. Yearly, a mammography will be performed. Furthermore, blood chemistry and hematology will be assessed, according to local policy.

TRIAL FLOWCHART

Year	**1**					**2**		**3**		**4**		**5**		**Follow-up** [5]
Visit	0	1	2	3	4	5	6	7	8	9	10	11	12	
Month	0	3	6	9	12	18	24	30	36	42	48	54	60	
Medical History	X													
Initial Data 1	X													
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/Biochem 2	X													
Events (if present)		X	X	X	X	X	X	X	X	X	X	X	X	X
Co-medication 3	X	X	X	X	X	X	X	X	X	X	X	X	X	X 6
Adverse events 4	X	X	X	X	X	X	X	X	X	X	X	X	X	X 7
Mammography	X				X		X		X		X		X	X

Notes:

1. Type of primary surgery, tumor pathology and characteristics, pre- existing medical conditions

2. Hb, WBC, PLT, ASAT/ALAT, creatinine, Alkaline Phosphatase, Calcium, Protein and Glucose

3. Any medication **prescribed** and used for more than 7 consecutive days

4. As described in the chapter "Adverse Events"

5. Yearly, according to the Dutch National Guidelines

6. Not mandatory

7. Only if they occur within 30 days after last dose of study drug (see also 11.2)

10.3 Follow-up

Follow-up after relapse should be according to the schedule in the Trial Flowchart, unless otherwise clinically indicated.

All patients should have long-term follow-up, irrespective of whether they have been withdrawn from treatment prematurely. The anticipated follow-up frequency is once every year, unless otherwise clinically indicated.

To be recorded:

- Trial Events (End-points): see Chapter 6

11 ADVERSE EVENTS

11.1 Adverse Event Definition

11.1.1. An adverse event is defined as any untoward medical occurrence in a subject to whom a drug has been administered; the event does not need to have a causal relationship to the study drug(s). All such medical occurrences from the first dose of study medication to 30 days after the last dose of study drug(s) are reported as adverse events and must be recorded on the CRF.

In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the Investigator assesses as possibly related to the study drug(s) should also be considered an adverse event.

11.1.2 A pre-existing condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

11.1.3 Symptoms of the targeted cancer should not be reported as adverse events.

11.1.4 A serious adverse event (SAE) is one that is fatal or life- threatening (i.e., results in an immediate risk of death); is permanently or substantially disabling; requires or prolongs hospitalization (only if related to an unexpected complication); or is a congenital anomaly, a new cancer or medication overdose. This category also includes any other event the Investigator judges to be serious or which would suggest a significant hazard, contra-indication, side effect or precaution.

11.1.5 An unexpected event is one that is not listed as a known toxicity of the investigational drug in the protocol, the consent form, the package insert, or the Investigator's brochure.

11.2 Adverse Event Recording

Toxicity's will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC version 2.0) (Appendix I). Any toxicity's incurred but not categorized by the NCI CTC should be graded by the physician and be recorded using a scale of (1) mild, (2) moderate, or (3) severe, on the Case Report Form (CRF), as defined in Appendix IV.

All adverse events will be recorded on the CRF through 30 days following last treatment dose on study or until the start of other anti-cancer treatment, whichever occurs first. Additionally, all adverse events deemed possibly related to the study products (exemestane or tamoxifen) will be followed until resolution (or the Investigator assesses them to be chronic or stable) or initiation of other anti-cancer therapy, whichever occurs first.

11.3 Serious Adverse Event Recording

All serious adverse events occurring during the treatment period and within 30 days of the last treatment dose on study must be reported. Any SAE possibly or probably related to the study treatment should be reported by **fax to the Central Data Center in The Netherlands within 24 hours of the initial observation of the event.** Details should be documented on a specified Serious Adverse Event Form.

The Serious Adverse Event Form must be completed and returned to the Central Data Center within 5 calendar days of the initial observation of the event. The SAE form should be signed by the investigator

PLEASE SEND THE ORIGINAL REPORT TO:

Central Data Center Dutch Team Study Group

Leids Universitair Medisch Centrum (LUMC)

Department of Surgery K-6-R

P.O. Box 9600

2300 RC LEIDEN

The Netherlands

12 DETERMINATION OF EFFICACY

Patients on both treatment arms are followed at specified intervals and evaluated for evidence of relapse. Required evaluations at each time point are specified in this protocol (Section 10.2).

12.1 Relapse Free Survival

Relapse free survival is defined as the time from first drug administration to the earliest recorded documentation of relapse, or death due to any cause in the absence of previous documentation of relapse. Patients without relapse may be withdrawn from treatment for a variety of reasons (page 21), and their relapse time will be censored. Where available, patients withdrawn because of a specific event will be censored at the date of the specific event or the date of recorded confirmation of event. If such a date is not appropriate or available, the patient will be censored at date of last follow-up.

12.2 Overall Survival

Overall survival is defined as the time from first drug administration to date of death. In the absence of confirmation of death, survival time will be censored to last date of follow-up.

13 STATISTICAL CONSIDERATIONS

13.1 Organization of the TEAM Trial

The TEAM Trial is organized as a single trial consisting of 8 separate managed country specific trials with 10 participating countries. Each country has its own protocol, CRF, and database. The trials are very similar to each other in design, with efforts made to ensure that data are compatible. The countries have their own side studies that they are running with questions, which they will be able to answer with their own patients. For the primary analysis of RFS, the overall results will be pooled. Each country specific trial has a Principal Investigator and a Country Trial Committee.

The overall trial is managed by a Steering Committee consisting of all of the Principal Investigators, a statistician from the Central Data Centre, and representatives from the sponsoring company. There is an Independent Data Monitoring Committee consisting of a biostatistician and 4 oncologists, 2 each from Europe and North America who meet regularly to evaluate the progress of the trial and make recommendations on whether to continue. There is also a sub-committee of the Steering Committee called the Data Management Committee, which consists of 4 of the Principal Investigators, the biostatistician from the Central Data Center and representatives of the sponsoring company.

The Central Data Center is located at the Leiden University Medical Center in the Netherlands. Data from all the countries are collected in the central database regularly to prepare for DMC meetings and to monitor the progress of the trial.

13.2 Hypothesis

13.2.1 Hypothesis and Sample Size calculation for 3 years analysis

Patients in the tamoxifen arm switch to exemestane after 2¾ years (range from 2½ -3 years) of treatment with tamoxifen. Analysis of the comparison between tamoxifen and exemestane in RFS will be the first primary analysis of this protocol. For this analysis, patients in the switch arm will be censored at the time of switch; patients in the upfront exemestane arm will be censored at 2¾ years, halfway between 2½ and 3 years.
The ATAC paper (by Aman U. Buzdar) provided updated information comparing tamoxifen and anastrozole (Clinical Cancer research, Vol. 10, 2004). The 3-yr DFS rate was estimated approximately 0.9 for the tamoxifen arm. If we still assume the HR of RFS to be 1.28 between the two treatment groups (tamoxifen arm / exemestane arm), at least 720 events are required to detect the statistical significance in RFS with the significant level of 0.05 (2-sided) and 90% of power. Assume that patients were uniformly entered into the study in 3 years and 3-yr RFS rate is 0.9 for the tamoxifen arm, **8740 evaluable patients are required in order to observe 720 events.** It is estimated that 720 events will be observed at 2¾ years after the last patient is randomized.

Timing of the first primary analysis on RFS: approximately 2¾ years after the last patient has been enrolled.

Based on this, the following hypotheses are stated:

A: under the null-hypothesis (H_0) if there is no difference between the two treatments, assuming the 3 years RFS is 90%, then: treatment arm A (tamoxifen) and treatment arm B (exemestane) will show a 3 years RFS of 90%.

B: under the alternative hypothesis (H_1) that the HR is 1.28 for the first 2¾ years
Based on these assumptions and considering a significance level (α) of 0.05, a power (1-β) of 0.90 and a two-sided test, approximately 8740 randomized patients will be required.

The Data Management Committee for the trial will monitor the event rate and may consider whether there is a need to use a tighter hazard ratio. Any decision to work with a smaller hazard ratio will mean more events will need to be observed and the trial duration will be longer.

13.2.2 Rationale for 5 years analysis

It is expected that the hazard ratio (HR) of the switch-arm with respect to the exemestane arm is considerably different before (HR=1.28) and after switch (lower). This makes the Cox proportional hazards assumption (namely, a constant HR over the whole five years) a priori unlikely to be true and hence standard survival analysis like the Cox regression model and the log-rank test, and standard sample size calculations, based on a single hazard ratio, invalid. Moreover, it is very hard to pose hypotheses concerning the anticipated difference in RFS between the two treatment arms at 5 years. Given these two considerations, we choose a non-hypothesis driven analysis at 5 years, with the second primary endpoint being 5-years RFS as a point estimate obtained from the Kaplan-Meier survival estimates of the two treatment arms. The difference in 5-years RFS between the treatment arms will be reported, along with its standard error (SE) and an associated 95%-confidence interval.
At the first primary analysis at 2½ -3 years, it will be computed (given the accrual of the already included patients) how much additional follow-up (with a maximum of 5 years after the last patient has been enrolled) is required to be able to estimate the difference in 5-years RFS between the treatment arms with a pre-specified precision, a standard error of at most 0.01. As the standard error of 3-years RFS at the first primary analysis, given the hypothesized hazard rates, is approximately 0.006, this should be feasible.

13.3 Patient enrolment

The trial will remain open to accrual in all countries until 8700 core patients are accrued. After this target has been reached, some countries may continue accrual until side studies have reached their accrual targets. Patients enrolled after the core accrual is completed will be included in the final analysis.

13.4 Stratification

At randomization, patients will be stratified by center and by treatment with chemotherapy (yes/no) and time period between surgery and start of hormonal therapy, if applicable.

13.5 Rationale for Type of Analysis and Trial Organization

This country specific study is designed to be a part of a larger group of studies that will be pooled in order to test RFS and OS. A total of 720 events are needed in order to test for a reduction in the RFS between the two treatment arms when the true hazard ratio is 1.28 (3 years relapse free survival of 90%)

The rationale for testing using multiple studies and testing using a pooled analysis as opposed to conducting one large multi-national study is that many additional questions of interest that do not require such a large sample size can be answered. The reporting of one study's main objective will not be delayed while waiting for the other studies to finish and therefore, not delaying the release of important clinical results. In addition, the CRF's will be more manageable and data clean up will be simplified.

The data from all the trials will be collected in a central database located at the Leiden University Medical Center, Netherlands periodically throughout the trial. Interim analyses and the final analysis for the combined trial will be conducted in this central location.
There are six major areas in which a meta-analysis might lead to misinterpretation: study design, combinability, heterogeneity of studies, statistical analysis, sensitivity analysis, and control of bias. The confidence one places in the results of any such meta-analysis is limited by the combinability of the studies; that is inherent differences in design, sample, and endpoints. Thus, the greater the similarity of the studies with regard to those points, the greater the confidence one may have in the results of a meta-analysis.
The TEAM Trial, of which this trial is a part, is different from trials usually analyzed with meta-analytic methods. The data in this trial can be pooled because the studies will all be similar in patient population, design, duration, endpoints, and will use similar forms for data collection. Care will be taken to test for heterogeneity of studies and to incorporate any such heterogeneity into the statistical analysis. As this is a pre-specified pooling it will not be subject to the usual issues facing a meta-analysis such as publication bias (the phenomenon in which studies with positive results are more likely to be published than studies with negative results), which is often the largest bias of meta-analysis results.

13.6 Efficacy Analysis

13.6.1 Primary Efficacy Analysis

The primary efficacy endpoint will be the cumulative probability of being relapse-free at 2¾ years post-treatment start (before tamoxifen arm switching to exemestane), as estimated from the Kaplan-Meier curves for each treatment arm. The difference in RFS will be assessed using the log-rank test at the 0.05 significance level.

13.6.2 Key Secondary Efficacy Analysis

The key secondary efficacy endpoint will be relapse-free survival at 5 years post-treatment start as a point estimate obtained from the Kaplan-Meier survival estimates of the two treatment arms. The difference in 5-years RFS between the treatment arms will be reported, along with its standard error (SE) and an associated 95%-confidence interval.

The difference in this cumulative probability will be assessed using the log-rank test for Kaplan-Meier curves at the p = 0,05 significance level. Ninety-five percent confidence intervals on the treatment estimates and the hazard ratio will be computered. Cox regression models will be used to explore the influence of stratification and prognostic factors on relapse-free survival. Each factor will be evaluated for inclusion in the multivariate model, and only factors significant at the 10% level will be considered.

13.6.3 Other Secondary Efficacy Analyses

Other secondary efficacy endpoints will be assessed as above.

13.6.4 Safety Analysis

Safety analyses will include all randomized subjects who received at least one dose of study medication. Adverse events will be recorded and graded according to the CTC classification system.

The frequency and percentage of patients experiencing a specific adverse event will be tabulated by treatment group. Adverse events will be summarized by worst CTC grade and reported relationship with study group. In the case that the adverse events or event frequencies are judged to be clinically important, a Chi-square test will be used to analyze the difference between the treatment groups.

14 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established which will be independent of the trial organizers.
Interim analysis of side effects, tolerability, relapse -free and overall survival for all randomized patients will be performed at 2 years after the start of the study. All these analyses will be supplied in strict confidence by the trial organization to the IDMC together with any other analyses that the IDMC may request.

The IDMC reserves the right to release any data on outcome or side-effects through the chairman of the Steering Committee to participating investigators if it determines at any stage that the combined evidence from this and other studies justifies it. This includes the circulation of the toxicity data if the IDMC believes that this may lead to an improvement in patient care.

15 STOPPING RULES / DISCONTINUATION CRITERIA

The Dutch TEAM Study Group reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating subjects within four weeks. Study materials must be collected and case report forms completed to the extent possible.

16 ETHICAL REQUIREMENTS

16.1 Ethical Conduct of the Study

The Investigator will ensure that the study is performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions (see Appendix III) or the laws and regulations of the country, whichever provide greater protection for the subject.
It is the responsibility of the investigator to obtain approval of the trial protocol and any subsequent amendment from the IRB/IEC. All correspondence with the IRB/IEC should be filed by the Investigator. Copies of the IRB/IEC approval should be forwarded to the Central Data Center of the Dutch Team Study Group.

It is the responsibility of the investigator to give each patient (or the patient's legally authorized representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patients must be informed about their right to withdraw from the trial and the possible risk involved. Written patient information (included as appendix to the protocol) must be given to each patient before enrolment. The written patient information enclosed is a sample, but may only be changed on request of the Medical Ethical Committee. I it is the responsibility of the investigator to obtain signed informed consent from all patients prior to inclusion in the trial.

A copy of the patient information sheet is included in Appendix V. All amendments and translations to the patient information sheet must be agreed by the TEAM Study Group, prior to trial commencement.

Patient identification data (initials and hospital number) will be required at randomization to assist with long-term follow-up. TEAM Study Group will preserve the confidentiality of patients taking part in this study.

16.2 Changes to the Final Study Protocol

Any variation in procedure from that specified in the final Study Protocol may lead to the results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be discussed with and approved by the TEAM Study Group and is submitted for Ethics Committee/Institutional Review Board and Health Authority (when applicable) approval or notification, in accordance with local regulatory requirements. Any protocol change should be documented in a Protocol Amendment. Changes not pre-approved by the Team Study Group may be considered as protocol deviations.

17 PUBLICATION POLICY

The results of the pooled analysis will be published in the name of the TEAM Trial in a peer-reviewed journal on behalf of all collaborators. All presentations and publications, including abstracts, relating to the main trial must be authorized by the TEAM Steering Committee. The individual countries will be allowed to publish their efficacy results, however, the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the Steering Committee decides otherwise.

Individual countries will be encouraged to publish the results of their side studies as soon as the data are mature. The Principal Investigator and Country Trial Committee will have the responsibility to make decisions about publications of these results and authorship.

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APPENDIX I Common Toxicity Criteria (CTC, version 2.0)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	None	transient rash, drug fever < 38°C (<100.4°F)	Urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	Anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	None	mild, not requiring treatment	Moderate, requiring treatment	-	-
Autoimmune reaction	None	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	None	-	-	Present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	None	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	Normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	Normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	Normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	Normal	Mild	moderate	Severe	life-threatening or disabling
BLOOD/BONE MARROW					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years) younger adults (19-59) older adults (≥ 60 years)	90% cellularity average 60-70% cellularity average 50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	Normal	Decreased	-	Absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	None	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hgb.					
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	None	-	-	Yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT:	None	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	None	-	-	Yes	-
For BMT:	None	≤2 u pRBC (*≤15cc/kg*) in 24 hours elective or planned	3 u pRBC (*>15 ≤30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (*>30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
			CARDIOVASCULAR (ARRHYTHMIA)		
Conduction abnormality/ Atrioventricular heart block	None	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations Note: Grade palpitations only in the absence of a documented arrhythmia.	None	Present	-	-	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Prolonged QTc interval (QTc > 0.48 seconds)	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	None	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	None	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	Absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	None	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	Normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	Normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Cardiac troponin T (cTnT)	Normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	None	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	None	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	None	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	None	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	None	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	None	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	None	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	None	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	None	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	None	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	Absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	Absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	None	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	None	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	None	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	Normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	Normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	None	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	None	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	Normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	Absent	Present	-	-	-
Hand-foot skin reaction	None	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	None	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	Normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	None	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	None	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	None	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	None	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	None	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	None	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	None	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	None	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	None	Cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	None	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify, _____)	None	Mild	moderate	Severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	Absent	-	present	-	-
Feminization of male	Absent	-	-	Present	-
Gynecomastia	None	Mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	None	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	Present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	Present	-
Endocrine-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	Asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	Mild	moderate	Severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	Present	requiring surgery
Fistula- intestinal	none	-	-	Present	requiring surgery
Fistula- pharyngeal	none	-	-	Present	requiring surgery
Fistula- rectal/anal	none	-	-	Present	requiring surgery
Flatulence	none	Mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	Mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse

Toxicity	Grade 0	1	2	3	4
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion.					
For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
			HEPATIC		
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	Present	-
Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	Asterixis	encephalopathy or coma
Note: Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
			INFECTION/FEBRILE NEUTROPENIA		
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.	none	-	-	Present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	Present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Infection/Febrile Neutropenia-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	Present	toxic psychosis

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	Present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration- anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	Present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	Present	-
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
			OCULAR/VISUAL		
Cataract	none	Asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	Mild	moderate	Severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	Mild	moderate	Severe	disabling
			PULMONARY		
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	Present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	Present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	Sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	Mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	Mild	moderate	Severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	Present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	Mild	moderate	Severe	life-threatening or disabling

APPENDIX II Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

ECOG (Zubrod)	KARNOFSKY	DEFINITIONS
0	100	Asymptomatic
1	80-90	Symptomatic, fully ambulatory
2	60-70	Symptomatic, in bed less than 50% of the day
3	40-50	Symptomatic, in bed more than 50% of the day, but not bedridden
4	20-30	Bedridden

APPENDIX III Declaration of Helsinki

World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the

human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient – including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-

Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX IV Classifications of Severity and Relationship to Therapy for Adverse Events

Relatedness

A determination of relatedness (yes/no) to Pharmacia Corporation investigational or trial medication, concomitant trial specific and other medication is required for all SAEs reported in clinical trials.

The criteria applied is a determination of whether there is a reasonable possibility that the event is related to the investigational product. Note that a "reasonable possibility" does not include cases where there is only a remote or unlikely possibility that the SAE may have been caused by the product.

All SAEs should be reviewed by a Local Pharmacia Corporation Office (MC) physician before sending to GDS and the CPL. The MC physician is encouraged to comment on the SAE in order to assist the CPL/GDS in reaching the final corporate determination of relatedness although the MC physician is not required to provide her/his own personal relatedness determination. When a MC physician is not available during the required timeframe the SAE report should be immediately sent to CPL/GDS by designated MC personnel.

Severity

Adverse events will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC) (Appendix I). Any adverse events incurred but not categorized by the NCI CTC should be graded by the physician and be recorded using a scale of (1) mild, (2) moderate, (3) severe, or (4) life threatening on the case report form, as defined below:

MILD	Does not interfere with subject's usual function
MODERATE	Interferes to some extent with subject's usual function
SEVERE	Interferes significantly with subject's usual function
LIFE THREATENING	Resulting in risk of death, organ damage or disability

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria that define serious events.

APPENDIX V Sample Informed Consent Form

PATIËNTENINFORMATIE behorend bij het vergelijkend onderzoek naar het effect van een aanvullende behandeling met 2½-3 jaar Tamoxifen gevolgd door 2½-2 jaar Exemestaan of met 5 jaar Exemestaan bij vrouwen na de overgang die geopereerd zijn voor borstkanker

Geachte mevrouw,
Uw behandelend arts heeft u voorgesteld aan het hierboven genoemde onderzoek deel te nemen en heeft u al het een en ander uitgelegd. Uw toestemming of weigering om deel te nemen moet u kunnen baseren op goede voorlichting onzerzijds en zorgvuldig overwegen van uw kant. Daarom ontvangt u deze schriftelijke informatie die u rustig kunt (her)lezen en in eigen kring bespreken. Ook daarna kunt u altijd nog vragen voorleggen aan uw arts of aan de artsen die aan het einde van deze informatie genoemd staan.

Uw medische situatie en behandelingsmogelijkheden
U bent recent geopereerd wegens borstkanker. Op grond van bepaalde tumorkenmerken, het feit dat u na de overgang bent en er sprake is van een hormoongevoelige borstkanker, komt u in aanmerking voor een aanvullende behandeling met een anti-hormonaal medicament om de kans te verkleinen dat de ziekte terugkeert.
De behandeling van vrouwen met borstkanker die na de overgang zijn bestaat uit een operatie en eventueel bestraling en/of chemotherapie. Als aanvullende behandeling hierop was het gebruikelijk om Tamoxifen (Nolvadex) te geven gedurende een periode van 5 jaar. **Tamoxifen** is een anti-oestrogeen medicijn dat belemmert dat oestrogenen (= vrouwelijke geslachtshormonen) de groei van tumorcellen stimuleren. Recent heeft onderzoek uitgewezen dat een behandeling met Tamoxifen gedurende 2½-3 jaar gevolgd door 2½-2 jaar **Exemestaan** de kans op terugkeer van de ziekte verder vermindert t.o.v. een behandeling met Tamoxifen gedurende 5 jaar.
Exemestaan (Aromasin) is een nieuw medicijn voor de behandeling van borstkanker dat werkt door remming van het enzym aromatase. Blokkering van het aromatase enzym zorgt ervoor dat er minder oestrogeen bij een vrouw na de overgang wordt aangemaakt, waardoor de stimulering van tumorcelgroei verhinderd wordt.
Op grond van de hogere effectiviteit van de sequentiele behandeling van tamoxifen, gevolgd door exemestane, is in de Nederlandse richtlijngroep afgesproken dat de sequentie van tamoxifen, gevolgd door een aromataseremmer, beschouwd wordt als de standaardbehandeling bij hormoongevoelige postmenopauzale borstkanker. Vooralsnog is het niet bekend hoe het effect is van de sequentiebehandeling van tamoxifen gevolgd door exemestane in vergelijking met exemestaan gedurende 5 jaren.

Doel van het onderzoek
In dit onderzoek willen we nagaan wat het effect is van de behandeling met 2½-3 jaar **Tamoxifen** gevolgd door 2½-2 jaar **Exemestaan** in vergelijking met 5 jaar **Exemestaan** als aanvullende behandeling van hormoongevoelige borstkanker bij postmenopauzale vrouwen. Voorts wordt onderzocht welke bijwerkingen optreden bij de behandelingen.

Dit onderzoek vindt plaats in het kader van een vergelijkende studie, die uitgevoerd wordt door onderzoekers uit verschillende landen. In totaal zullen wereldwijd ongeveer 8700 vrouwen aan deze studie deelnemen. Algemene informatie over klinisch onderzoek kunt u nalezen in de folder “Wetenschappelijk onderzoek bij patiënten met kanker”.

Wijze van onderzoek en behandelingsplan

Om het antwoord op de onderzoeksvraag te krijgen worden de patiënten in 2 volledig vergelijkbare groepen verdeeld. De ene groep krijgt de behandeling met 2½-3 jaar **Tamoxifen** (1X per dag 1 tablet van 20 mg) gevolgd door 2½-2 jaar **Exemestaan (**1x per dag 1 tablet van 25 mg**)** De andere groep krijgt de behandeling met 1x per dag 1 tablet **Exemestaan** (25 mg) gedurende 5 jaar. De medicatie kan het beste op een vast tijdstip van de dag ingenomen worden. **Exemestaan** dient bij voorkeur na het eten ingenomen te worden. Beide groepen patiënten worden behandeld gedurende een totale periode van 5 jaar.

Een dergelijke objectieve vergelijking van effect en bijwerkingen tussen 2 behandelingen noemen we een vergelijkend onderzoek. De verdeling van de patiënten in de verschillende behandelingsgroepen gebeurt door loting (randomisatie) zodat niemand - d.w.z. noch de patiënt, noch de arts - hierop invloed kan uitoefenen (zie folder “Wetenschappelijk onderzoek bij patiënten met kanker”).

Bij de start van de behandeling wordt orienterend onderzoek gedaan, bestaand uit: algemeen lichamelijk onderzoek, bloedonderzoek, mammografie (borstfoto) en eventueel aanvullend onderzoek als uw arts dat nodig acht.

Het eerste jaar wordt u eens in de 3 maanden gecontroleerd, daarna vindt de controle plaats om de 6 maanden. Na 5 jaar wordt u jaarlijks gecontroleerd. Naast het lichamelijk onderzoek bij de controles, wordt er jaarlijks een mammografie (borstfoto) verricht. Deze controles verschillen niet van de gebruikelijke controles bij een patiënte met borstkanker.

Bijwerkingen, risico’s en ongemakken
De bijwerkingen van **Exemestaan** en **Tamoxifen** zoals die in eerdere onderzoeken werden waargenomen zijn meestal mild en redelijk te verdragen.
Bij **Tamoxifen** kunnen optreden: opvliegers, transpireren, milde misselijkheid (tijdelijk), geringe gewichtstoename, vaginale afscheiding, jeuk of droog gevoel ter hoogte van de vagina. Zeldzaam optredende bijwerkingen zijn: trombose, vocht vasthouden, veranderingen vanhet oog (lens [=staar], netvlies, hoornvlies), veranderingen in het baarmoederslijmvlies (verdikking, poliepvorming, kanker bij langdurig gebruik).
De bijwerkingen die bij de behandeling met **Exemestaan** kunnen optreden zijn: opvliegers, enige misselijkheid, transpireren, tijdelijk enige duizeligheid, moeheid en hoofdpijn. Zeldzaam optredende bijwerkingen zijn: slapeloosheid, huiduitslag, vocht vasthouden, enige buikpijn.

Door het afnemen van bloed kan wat irritatie ontstaan op de plaats van de prik.
Als er tijdens het onderzoek nieuwe informatie beschikbaar komt die uw deelname kan beinvloeden, wordt u hiervan tijdig op de hoogte gesteld zodat u de gelegenheid krijgt te overwegen of u met het onderzoek wilt doorgaan.
In geval van (onverwachte) klachten van de behandeling dient u te overleggen met uw behandelend specalist, zodat hieraan op adequate wijze aandacht kan worden besteed.
Voorts vragen wij van u de voorschriften van uw behandelend arts goed op te volgen en u niet, zonder diens medeweten, elders te laten behandelen.

Voordelen en nadelen
De informatie die uit dit onderzoek verkregen wordt, kan nuttig zijn voor de wetenschap en kan daarmee mogelijk andere vrouwen helpen.

Privacy
Uw medisch dossier kan slechts door daartoe geautoriseerde en gekwalificeerde medewerkers van het onderzoeksteam, medewerkers van de Inspectie voor de Gezondheidszorg of bevoegde inspecteurs van een buitenlandse overheid, leden van de Medisch Ethische Toetsings Commissie

Erasmus MC worden ingezien met als doel de onderzoeksprocedures en de betrouwbaarheid van de verzamelde gegevens te controleren. Onderzoeksgegevens zullen vertrouwelijk worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens en het privacyreglement van het [naam ziekenhuis]. Alle medische gegevens die tijdens deze studie worden verzameld zullen worden voorzien van een codenummer. De persoonsgegevens zullen niet gebruikt worden op studiedocumentatie, in rapporten of publicaties van dit onderzoek. De onderzoeksgegevens worden gedurende 15 jaar bewaard. Uw huisarts zal, zoals gebruikelijk in Nederland, in kennis worden gesteld van uw behandeling en dus ook van uw deelname aan dit onderzoek. U dient hiervoor echter wel toestemming te geven.
Voor dit onderzoek is goedkeuring verkregen van de Raad van Bestuur van uw ziekenhuis na een positief oordeel van de Medisch Ethische Toetsings Commissie van het Erasmus MC. De voor dit onderzoek geldende internationale richtlijnen zullen nauwkeurig in acht worden genomen.

Schade
Voor de uitvoering van het onderzoek is een schade verzekering afgesloten (zie bijlage).

Weigeren voor en tijdens het onderzoek
Als u besluit deel te nemen, kunt u te allen tijde op dit besluit terugkomen en met het onderzoek stoppen zonder opgave van redenen. Uw deelname aan dit onderzoek is dus geheel vrijwillig.
Mocht u besluiten niet aan het onderzoek mee te doen, of met het onderzoek te willen stoppen, dan zal dit de houding van uw arts ten aanzien van uw behandeling niet beinvloeden. In overleg met uw behandelend arts zal dan uw behandeling worden bepaald.

Nadere informatie
Mocht u nog aanvullende vragen hebben, dan kunt u die voorleggen aan uw behandelend specialist of aan een van de verantwoordelijke onderzoekers of onderzoeksverpleegkundigen:

Dit zijn:
Erasmus MC, lokatie Daniel den Hoed: dr. C. Seynaeve, internist-oncoloog (bereikbaar via het secretariaat Interne Oncologie, tel. 010-4391754), of dr. M. Bontenbal, internist-oncoloog (bereikbaar via het secretariaat Interne Oncologie, tel. 010-4391505)

Mocht U besluiten tot deelname aan dit onderzoek dan vragen wij u het toestemming-formulier te ondertekenen. U ontvangt dan een kopie van het getekende formulier.

Indien u twijfelt over deelname kunt u een onafhankelijk arts raadplegen, die zelf niet is betrokken bij dit onderzoek, maar wel deskundig is op het gebied van geneesmiddelen onderzoek: Dr. J. Raemakers, Universitair Medisch Centrum St. Radboud te Nijmegen, afdeling hematologie, tel. 024-3614762. Ook als u voor of tijdens de studie vragen heeft, die u liever niet aan uw behandelend arts stelt, kunt u contact opnemen met de onafhankelijk arts.

Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de onafhankelijke klachtencommissie van het Erasmus MC. De klachtencommissie is te bereiken op telefoonnummer 010-4633198.

Bijgesloten:
- folder Wetenschappelijk Onderzoek bij patiënten met kanker

Bijlage: Informatie betreffende de verzekering

In geval van schade kunt u contact op nemen met de verzekeraar*:*
De verzekeraar van het onderzoek is:

Naam:	AIG Europe (Nederland) NV
Adres:	Postbus 8606
	3009 AP Rotterdam
Telefoonnummer:	010-4535455
Fax nummer:	010-4528502

De volgende passage met betrekking tot de verzekering van het onderzoek is ontleend aan de wet 'Medisch-wetenschappelijk onderzoek met mensen' (WMO):
Voor de uitvoering van het onderzoek is een verzekering afgesloten. Deze verzekering dekt de eventuele schade door letsel als gevolg van uw deelname aan het onderzoek en die zich openbaart gedurende deelname aan dit onderzoek of binnen vijf jaar ná deelname aan dit onderzoek. Voor aan het onderzoek gerelateerd letsel zal u kosteloze medische behandeling ter beschikking worden gesteld. De verzekering biedt dekking voor een schade tot een maximumbedrag van 450.000 euro per proefpersoon, met een maximumbedrag van 3.500.000 euro per verzekeringsjaar per onderzoek. Indien de opdrachtgever van dit onderzoek meerdere onderzoeken tegelijk verricht, geldt een maximumbedrag van 5.000.000 euro per verzekeringsjaar voor álle onderzoeken. Als u van mening bent dat u door of tijdens het onderzoek schade hebt opgelopen, adviseren wij u zo snel mogelijk contact op te nemen met de hieronder genoemde verzekeraar. U dient in dit geval de verzekeraar alle benodigde informatie te verschaffen. Het niet nakomen van deze verplichtingen kan leiden tot het niet vergoeden van de schade.
Wij willen u erop wijzen dat de verzekering geen dekking biedt voor schade:

- die zich bij nakomelingen openbaart als gevolg van een nadelige inwerking van het onderzoek op het genetisch (=erfelijk) materiaal van de proefpersoon;
- door aantasting van uw gezondheid, die zich ook zou hebben geopenbaard wanneer u niet aan het onderzoek had deelgenomen;
- waarvan op grond van de aard van het onderzoek (nagenoeg) zeker was dat deze zich zou voordoen (zoals bijvoorbeeld de bijwerkingen die in dit informatieformulier beschreven worden);
- die het gevolg is van het niet of niet volledig opvolgen van aanwijzingen en instructies van de behandelend arts.

Verzekeraar:	AIG Europe (Nederland) NV Postbus 8606 3009 AP Rotterdam tel: 010-4535455	Schaderegelaar:	AON Nederland Postbus 518 3000 AM Rotterdam tel: 010-4488911

TOESTEMMING VOOR DEELNAME AAN WETENSCHAPPELIJK ONDERZOEK

Betreft :
vergelijkend onderzoek naar het effect van een aanvullende behandeling met 2½-3 jaar Tamoxifen gevolgd door 2½-2 jaar Exemestaan of met 5 jaar Exemestaan bij vrouwen na de overgang die geopereerd zijn voor borstkanker.

Ondergetekende verklaart als volgt:

- ik heb uitvoerig mondelinge en schriftelijke informatie ontvangen inzake opzet, doel en eventuele ongemakken van bovengenoemd onderzoek en heb dit volledig begrepen;
- ik heb voldoende gelegenheid gehad tot nadenken, overleg en het stellen van vragen aan de onderzoeker(s);
- ik stem geheel vrijwillig in met deelname aan bovengenoemd onderzoek, zolang ik deze toestemming niet herroep;
- ik weet dat de resultaten van het onderzoek, met inbegrip van gegevens betreffende familie, geslacht, leeftijd, geboortedatum, screening, diagnose en identificatienummer onder codenummer ter beschikking gesteld kunnen worden aan gekwalificeerde mede-onderzoekers. De inzage in mijn dossier gebeurt slechts na goedkeuring van mijn arts.
- Ik weet dat, indien aan de orde, uitwisseling van gegevens plaatsvindt met mijn huisarts, en andere betrokken specialisten.
- ik kan mij op ieder moment uit het onderzoek terugtrekken zonder nadelig effect op de verdere controle, behandeling, verzorging en/of begeleiding van mijzelf of mijn verwanten.

Naam patiënt:
Handtekening : Datum: ___ /___ /200.

Naam onderzoeker :
Handtekening : Datum: ___ /___ /200.

(ter informatie arts: patiënt dient een kopie te krijgen van het getekende toestemmingsformulier)
goedgekeurd Medisch Ethische Toetsingscommissie d.d. [datum]

APPENDIX VI NABON / NVMO guidelines for treatment of primary breast cancer 2000 (ref. 49)

Guideline for adjuvant systemic therapy in patients with a resectable breast carcinoma, divided in the presence or lack of metastases in the axillary lymphnodes			
metastases in the axillary lymphnodes (N+ patients)			
receptor	menopausal status/age		
	premenopausal	postmenopausal	
		< 70 years	≥ 70 years
ER+ and/or PgR+	chemotherapy and endocrine therapy*	tamoxifen (possibly with chemotherapy)B	tamoxifen
ER- and PgR-	chemotherapy	chemotherapy	no therapyX
no metastases in the axillary lymphnodes (N_0 patients)			
tumor size	differentiation grade § or mitotic activity index ‖¶		
	BR I/II or MAI < 10	BR III or MAI ≥ 10	
< 1 cm	no therapy	no therapy	
1-3 cm	no therapy	as in N+ patients	
> 3 cm	as in N+ patients	as in N+ patients	

ER = estrogen receptor; PgR = progesteron receptor.
* Endocrine therapy after chemotherapy (sequential approach).
B Gives limited therapeutic gain in combination with tamoxifen; to be considered in young patients with a poor prognosis.
X The data are insufficient for an advice.
§ The differentiation grade is expressed in the modified Bloom-Richardson (BR)-grading: 'moderately to well differentiated' (respectively BR I and BR II); 'poorly differentiated' (BR III).
‖ The mitotic activity index (MAI) expresses the number of mitoses visible in the tumor tissue in every 10 microscopy fields with strong magnification.
¶ For each institution the choice has to be made which of the two risk factors will be used.

APPENDIX VII NABON / NVMO richtlijnen behandeling primair mammacarinoom 2000 (ref. 49)

Richtlijn voor adjuvante systemische therapie bij patiënten met een resectabel mammacarcinoom, uitgesplitst naar het al of niet aanwezig zijn van metastasen in de okselklieren			
lymfkliermetastasen in de oksel (N+ patiënten)			
receptor	menopauzale status/leeftijd		
	premenopauzaal	postmenopauzaal	
		< 70 jaar	≥ 70 jaar
ER+ en/of PgR+	chemotherapie met endocriene therapie*	tamoxifen (eventueel met chemotherapie)B	tamoxifen
ER- en PgR-	chemotherapie	chemotherapie	geen therapieX
geen lymfkliermetastasen in de oksel (N_0 patiënten)			
tumorgrootte	differentiatiegraad § of mitoseactiviteitsindex ‖¶		
	BR I/II of MAI < 10	BR III of MAI ≥ 10	
< 1 cm	geen therapie	geen therapie	
1-3 cm	geen therapie	zoals bij N+ patiënten	
> 3 cm	zoals bij N+ patiënten	zoals bij N+ patiënten	

ER = oestrogeenreceptor; PgR = progesteronreceptor.
* Endocriene therapie na de chemotherapie toepassen.
B Geeft beperkte therapeutische winst in combinatie met tamoxifen; te overwegen bij jonge patiënten met een slechte prognose.
X Hierover zijn onvoldoende gegevens voor een advies.
§ De differentiatiegraad wordt uitgedrukt met de gemodificeerde Bloom-Richardson (BR)-gradering: 'matig tot goed gedifferentieerd' (respectievelijk BR I en BR II); 'slecht gedifferentieerd' (BR III).
‖ De mitoseactiviteitsindex (MAI) geeft het aantal mitosen zichtbaar in het tumorweefsel per 10 microscoopvelden met sterke vergroting.
¶ Per instituut moet men vaststellen welke van beide risicofactoren gebruikt wordt.

Tamoxifen and **E**xemestane **A**djuvant **M**ulticenter Trial

TEAM trial

An open label, randomized multicenter comparative trial of 5 years adjuvant Exemestane treatment versus 2½-3 years adjuvant Tamoxifen treatment followed by 2½-2 years of adjuvant Exemestane treatment, for a total of 5 years, in postmenopausal women with early breast cancer

Protocol amendment 3

By the Dutch TEAM Study Group

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MEC approval: Protocol: 4 July 2001
Amendment 1: 12 August 2003
Amendment 2: 13 December 2004
Amendment 3: 8 February 2007

Initiation date: 16 July 2001
Closure date: 16 February 2006

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1. REASONS FOR CHANGING THE PROTOCOL

The Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) study is an open label, randomized, multicenter, comparative trial. The trial was originally designed to compare the efficacy and tolerability of 5 years adjuvant exemestane versus 5 years adjuvant tamoxifen in post-menopausal women with estrogen receptor (ER) and/or progesterone receptor (PgR) positive early breast cancer. In amendment 2 (approved December13, 2004), the design was changed to randomization for tamoxifen 2½-3 years followed by exemestane for 2-2 ½ years vs 5 years of adjuvant exemestane. Subsequently the study objectives and sample size were changed accordingly.

In this amendment, the primary objective is clarified in addition to amendment 2 and standardized according to the definitions used in other adjuvant hormone therapy trials. The efficacy analysis variable will change from relapse free survival (RFS) to disease free survival (DFS). Furthermore, primary endpoints and timing of interim analysis has changed

2. PRIMARY OBJECTIVE

2.1. Old version primary objective

The primary objective of this study is to determine whether up-front adjuvant treatment with exemestane compared with adjuvant tamoxifen improves the relapse-free survival (RFS) of postmenopausal, receptor positive, early breast cancer patients following 2½ -3 years of treatment. RFS will be measured as the time from start of treatment to the date of relapse. Relapse is defined as local or distant recurrence of disease, secondary invasive breast cancer, or death of any cause. Patients who have not had any such event at the time of data analysis will be censored at the last date they were known to be event-free. RFS analysis will be based on tumour assessments and survival follow-up assessments.

2.2. New version primary objective

There are 2 co- primary objectives in this study:

1. To determine whether adjuvant treatment with exemestane 25 mg once daily improves the disease free survival (DFS) of postmenopausal, receptor positive, node negative or node positive breast cancer patients at 2¾ years compared with adjuvant tamoxifen 20 mg once daily for 2½ – 3 years, followed by exemestane, 25 mg once daily for 2 – 2½ years. DFS is defined as the time from randomization to the earliest recorded documentation of local/regional or distant recurrence of breast cancer, new 2nd primary (contra lateral) invasive breast cancer or death from any cause

2. To determine whether adjuvant treatment with exemestane 25 mg once daily improves the disease free survival (DFS) of postmenopausal, receptor positive, node negative or node positive breast cancer patients at 5 years compared with adjuvant tamoxifen 20 mg once daily for 2½ – 3 years, followed by exemestane, 25 mg once daily for 2 – 2½ years.

3. SECONDARY OBJECTIVES

3.1. Old version secondary objectives

3.1.1 Key secondary objective

The key secondary objective of this study will be 5-years RFS as a point estimate obtained from the Kaplan-Meier survival estimates of the two treatment arms. The difference in 5-years RFS between the treatment arms will be reported, along with its standard error (SE) and an associated 95%-confidence interval.

3.1.2. Other secondary objectives

Other secondary objectives of this study will include analysis of overall survival, the relative safety profiles, and the incidence of new primary breast cancers of the postmenopausal women treated with 5 years of exemestane versus tamoxifen therapy for 2½ -3 years followed by 2½ -2 years of exemestane (a total of 5 years).

3.2. New version secondary objectives

Secondary objectives of this study are DFS, overall survival, the relative safety profiles, and time from randomization to new primary breast cancer in postmenopausal women treated with 5 years of exemestane versus tamoxifen therapy for 2½- 3 years followed by 2½- 2 years of exemestane.

3.3. Reasons for change secondary objectives

The primary objective will be clarified and standardized according to the definitions used in other adjuvant hormone therapy trials. The efficacy analysis variable will change from relapse free survival (RFS) to disease free survival (DFS), and a universal changes will be made within the protocol from RFS to DFS. As a co-primary endpoint, DFS will be analyzed after 5 years of treatment.

4. DETERMINATION OF EFFICACY

4.1. Old version endpoints

4.1.1. Relapse Free Survival (RFS)

Relapse free survival is defined as the time *from first drug administration* to the earliest recorded documentation of relapse, or death due to any cause in the absence of previous documentation of relapse. Patients without relapse may be withdrawn from treatment for a variety of reasons (page 21), and their relapse time will be censored. Where available, patients withdrawn because of a specific event will be censored at the date of the specific event or the date of recorded confirmation of event. If such a date is not appropriate or available, the patient will be censored at date of last follow-up.

4.1.2. Overall Survival

Overall survival (OS) is defined as the *time from first drug administration* to date of death. In the absence of confirmation of death, survival time will be censored to last date of follow-up.

4.2. New version endpoints

4.2.1. Disease Free Survival (DFS)

Disease free survival (DFS) is defined as the *time from randomization* to the earliest recorded documentation of local/regional or distant recurrence of breast cancer, new 2nd primary (contralateral) invasive breast cancer or death from any cause. Patients who have not had any such event (relapse or death) at the time of data analysis will be censored at 2¾ years for the first co-primary endpoint and at the last date they were known to be event-free for the 2nd co-primary endpoint and the secondary endpoints. Kaplan-Meier estimates of the survival curves for each treatment arm (including medians and 95% confidence intervals) as well as the result of the log-rank test will be presented.

4.2.2. Overall Survival

Overall survival (OS), from the *time of randomization* to death due to any cause, and time from randomization to new primary breast cancer are secondary efficacy endpoints

4.3. Reasons for change endpoints

The efficacy analysis variable will change from relapse free survival (RFS) to disease free survival (DFS), and a universal changes will be made within the protocol from RFS to DFS. DFS will be analyzed at 2¾ years from randomization, with censoring at 2¾ years of all subjects in either treatment arm who have not experienced a DFS event at that time. As a co-primary endpoint, DFS will be analyzed after 5 years of treatment.

5. STATISTICAL CONSIDERATIONS

5.1. Addition of section Interim Analysis

The entire TEAM trial will accrue a total of 9300 patients in order to observe 723 DFS events in the first co-primary endpoint at 2¾ years. Safety analyses will be reported to the Independent Data Monitoring Committee (IDMC) every 6 months without evaluation of efficacy. The number of efficacy events will be monitored centrally every 3 months and reported to the IDMB. One interim efficacy analysis is planned for the first co-primary endpoint, to be reviewed by the IDMC. As part of their evaluation of the progress of the trial, they will review an interim analysis of the combined TEAM trial at the time 50% of the events are reported for the first co-primary endpoint, at or before 2¾ years form the time of randomization when half of the required number of DFS events for the first co-primary endpoint have occurred. These unblinded data will only be reviewed by IDMC members. The primary objective of the interim analysis is the early detection of either alarming side effects, intolerability to the treatment regimens, or of large differences in treatment effects.

The overall alpha-level for the first co-primary analysis will be maintained at 0.0302 using an O'Brien-Fleming-type alpha-spending function. The levels of significance at the interim analysis and at the final analysis for the first co-primary endpoint are 0.0012 and 0.0298, respectively.

6. HYPOTHESIS AND SAMPLE SIZE

6.1. Old version hypothesis and sample size

The study will evaluate primarily the relapse-free survival among women who receive either tamoxifen or exemestane daily for 30 – 36 months , and secondarily the relapse free and overall survival for patients who received tamoxifen for 20-26 months followed by 24 – 30 months of exemestane vs. exemestane for 5 years. The safety of adjuvant tamoxifen followed by exemestane or exemestane for 5 years will also be assessed in these postmenopausal, receptor positive, node negative or node positive breast cancer patients.

Sample size calculation for the therapy switch from exemestane after tamoxifen treatment

Sample size calculation for 3-yr analysis before patients in tamoxifen group switching to Aromasin

As per amendment 7, patients in tamoxifen arm are switched to exemestane after 33 months (range from 30 to 36 months) of treatment with tamoxifen. Analysis of comparison tamoxifen and exemestane in RFS will be the primary analysis of this protocol. In this analysis, only data from patients in both 2 arms prior to 33 months of treatment will be included. Rules of what data should be included in this analysis will be described in SAP in detail.

ATAC (by Aman U. Buzdar) paper provided updated information comparing tamoxifen and Anastrozole (53). The 3-yr DFS rate was estimated approximately 0.9 for tamoxifen arm. If we still assume the HR of RFS to be 1.28 between the two treatment groups (tamoxifen arm/exemestane arm). At least 720 events are required to detect the statistical significance in RFS with the significant level of 0.05 (2-sided) and 90% of power. Assume that patients were uniformly entered the study in 3 years and 3-yr RFS rate is 0.9 for the tamoxifen arm, 8740 patients are required in order to observe 720 events. It is estimated that 720 events will be observed at 33 months after the last patient is randomized.
This country specific study is designed to be a part of a larger group of studies that will be pooled in order to test RFS and OS. The data from all the trials will be collected in a central database located at the Leiden University Medical Center, Netherlands periodically throughout the trial. Interim analyses and the final analysis for the combined trial will be conducted in this central location. The German protocol will accrue 500 additional patients to permit th entire TEAM study to reach its accrual goals.

Timing of the primary analysis on RFS: approximately 33 months after the last patient has been enrolled.

Based on this, the following hypotheses are stated:

A: under the null-hypothesis (H_0) if no difference between the two treatments, assuming the 3 years RFS is 90%, then: treatment arm A (tamoxifen) and treatment arm B (Aromasin) will show a 3 years RFS of 90%.

B: under the alternative hypothesis (H_1) that the HR is 1.28 for the first 33 months and the HR is 1.20 after treatment switch to Aromasin for patients in the tamoxifen arm favouring Aromasin but the further conditions remain the same.

This difference in HR of recurrence/death of 1.28 for the first 33 months and 1.20 for the next 27 months between treatment groups is considered to be clinically relevant.

Based on these assumptions and considering a significance level (α) of 0.05, a power (1-β) of 0.90 and a two-sided test, approximately 8740 randomised patients will be required.

Sample size calculation for 5-yr analysis

5-yr analysis on RFS becomes a secondary analysis in the amended protocol. It needs to be confirmed that there will be no regulatory (EU and US) impact due to this change. Assume the HR is still 1.28 for the first 33 months of the RFS curves, the HR will be smaller between the two arms after the time of patients switching from tamoxifen to Aromasin. A paper by R. Charles Coombes et al provided information on DFS rate for patients on Aromasin after being on tamoxifen for 2-3 years (NEJM Vol. 350 No 11, March 2004). It was estimated in this paper that 3-yr DFS rate was 91.5% after switching from tamoxifen to Aromasin. Assume patients switched to Aromasin after 2½ years of treatment on tamoxifen, it can be calculated that 5-yr (a 2½-year treatment of tamoxifen followed by a 2½-year treatment of Aromasin) DFS rate is 83.76%. It can be estimated that the HR of the two arms after switch is approximately 1.3. It is even larger than the one assumed in the sample size calculation for the 3-yr analysis before the time of switch. To be conservative, we assume HR=1.2 after switch. 878 events are required to detect the statistical significance at the significance level of 0.05 (2-sided) with 90% of power. With a total of 8740 patients, it is estimated that 878 events will be observed at 1.92 years after the last patient is randomized.

To demonstrate the 'switch' effect, we need to follow patients long enough after switch. Therefore, the required number of DFS events was calculated in order to demonstrate the 'switch' effect. The number of DFS events needed after 'switch' for the 5-yr analysis was calculated as if there was a pseudo hypothesis test to detect the statistical significance (significance level of 0.05, 2-sided) between the two treatment groups with power of 80%, assuming that the hazard ratio was 1.20. In the calculation we also assumed that only the data after 'switch' would be included in the analysis of this pseudo test. 952 DFS events after 'switch' were required. Therefore, the 5-yr analysis will be performed when 1672 DFS events (720 events from the data before 'switch', 952 events from the data after 'switch') are observed. It is estimated that 1672 DFS events will be observed at 5.46 years after the last patient is randomized.

Timing of the primary analysis on RFS: approximately 33 months after the last patient has been enrolled.

Based on this, the following hypotheses are stated:

A: under the null-hypothesis (H_0) if no difference between the two treatments, assuming the 3 years RFS is 90%, then: treatment arm A (tamoxifen) and treatment arm B (Aromasin) will show a 3 years RFS of 90%.

B: under the alternative hypothesis (H_1) that the HR is 1.28 for the first 33 months and the HR is 1.20 after treatment switch to Aromasin for patients in the tamoxifen arm favouring Aromasin but the further conditions remain the same.

This difference in HR of recurrence/death of 1.28 for the first 33 months and 1.20 for the next 27 months between treatment groups is considered to be clinically relevant.

Based on these assumptions and considering a significance level (α) of 0.05, a power (1-β) of 0.90 and a two-sided test, approximately 8740 randomised patients will be required.

6.2. New version hypothesis and sample size

In the amended protocol (3rd revised protocol, 2005-02-21), patients in the tamoxifen arm will be switched to exemestane after 2½- 3 years of treatment with tamoxifen. The primary analysis will compare DFS between the treatment arms after patients have received 2¾ years of treatment. The 3-yrs DFS probability was estimated to be approximately 0.90 for the Tamoxifen Arm (i.e., Arm B before switch). If the hazard ratio of DFS is assumed to be 1.28 between the two treatment arms (Arm B / Arm A), **723 events** will achieve 87% power to detect the corresponding difference in DFS with a two-sided significance level of 0.0298. Assuming constant exponential rates in both groups with a hazard ratio of 1.28), **9300 patients (4650 in each group) are sufficient in order to observe these 723 events after each subject is followed for 2¾ years.** A maximum of 1550 patients will be enrolled into this study in Germany.

The second co-primary endpoint is DFS after 5 years of treatment. Because of the switch from tamoxifen to exemestane after 2½ – 3 years for patients in arm B (switch arm), the assumption of proportional hazards is unlikely to be true. Therefore, two distinct hazard ratios, one for the first 2¾ years (before-switch HR), and one for the subsequent years (post-switch HR) are hypothesized.

Based on a pre-switch tamoxifen 3-yrs DFS rate of 0.90, the pre-switch hazard rate is 0.03512 per year assuming DFS follows an exponential distribution. Assuming the pre-switch HR is 1.28, it can be calculated that the 3-yrs DFS rate for Exemestane Arm is 92.1% and the hazard rate of the Exemestane Arm is thus 0.0274 per year. Coombes et al. (2004) estimated 3-yrs DFS of 91.5% after switching from tamoxifen to exemestane. This amounts to a post-switch hazard rate of 0.02986 per year for the Switch Arm (receiving exemestane after switch). Assuming that pre-switch and post-switch hazard rates of the Exemestane Arm remain equal, then compared to the post-switch rate of the Switch Arm, this would imply a post-switch HR of 1.08 (0.02986/0.0274). Aiming at detecting a post-switch HR of 1.11. Using a sample size calculation procedure due to Shih (1995) allowing for piecewise-proportional hazards, 1285 events achieve 88 % power to detect a statistically significant difference in DFS with a HR of 1.28 for the first 2¾ years and a HR of 1.11 thereafter, at a two-sided nominal significance level of 0.0298. With 9300 patients enrolled uniformly in 3 years, it is estimated that 1285 events will be observed 3.5 years after the last patient was enrolled.

The correlation between the two primary endpoints has been assumed to be 0.75 based on the number of events for the two endpoint [(723/1285)1/2 =0.75].

6.3. Reason for change hypothesis and sample size

Sample size has been re-calculated on the basis of the ATAC study (Buzdar 2004) provided updated information comparing tamoxifen and anastrozole.

7. RATIONALE FOR TYPE OF ANALYSIS AND TRIAL ORGANIZATION

7.1. Old version rationale for type of analysis and trial organization

This country specific study is designed to be a part of a larger group of studies that will be pooled in order to test RFS and OS. A total of 720 events are needed in order to test for a reduction in the RFS between the two treatment arms (tamoxifen vs. exemestane) for the first 2¾ years of treatment when the true hazard ratio is 1.28.

7.2. New version rationale for type of analysis and trial organization

This country specific study is designed to be a part of a larger group of studies that will be pooled in order to test DFS and OS. The 3-yrs DFS probability was estimated to be approximately 0.90 for the Tamoxifen Arm (i.e., Arm B before switch). If the hazard ratio of DFS is assumed to be 1.28 between the two treatment arms (Arm B / Arm A), **723 events** will achieve 87% power to detect the corresponding difference in DFS with a two-sided significance level of 0.0298. Assuming constant exponential rates in both groups with a hazard ratio of 1.28), **9300 patients (4650 in each group) are sufficient in order to observe these 723 events after each subject is followed for 2¾ years.**

7.3. Reason for change rationale for type of analysis and trial organization

Sample size has been re-calculated on the basis of the ATAC study (Buzdar 2004)

8. PRIMARY EFFICACY ANALYSIS

8.1. Old version primary efficacy analysis

The primary efficacy endpoint will be the relapse-free survival at 33 months post-treatment start (before tamoxifen arm switching to exemestane), as estimated from the Kaplan-Meier curves for each treatment arm.
The difference in RFS will be assessed using the log-rank test at the 0.05 significance level. Ninety-five percent CI on the treatment estimates and the HR will be computed. Cox regression models will be used to explore the influence of stratification and prognostic factors on RFS. Each factor will be evaluated for inclusion in the multivariate model, and only factors significant at the 10% level will be considered.

8.2. New version primary efficacy analysis

The primary efficacy endpoint will be disease free survival (DFS). DFS is defined as the time from randomization to the earliest recorded documentation of local/regional or distant recurrence of breast cancer, new 2nd primary (contralateral) invasive breast cancer or death from any cause. DFS will be analyzed at 2¾ years from randomization, with censoring at 2¾ years of all subjects in either treatment arm who have not experienced a DFS event at that time. As a co-primary endpoint, DFS will be analyzed after 5 years of treatment.

8.3. Reason for change primary efficacy analysis

The primary objective is standarized according to the definitions used in other adjuvant hormone therapy trials.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	9 and reference to previous report
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 7

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 7
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 2 and throughout the result section for each analysis
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12,13,14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12,13,14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	13,14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19, 20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15,16,17,18
Other information			
Registration	23	Registration number and name of trial registry	10
Protocol	24	Where the full trial protocol can be accessed, if available	Provided as

			webappendix
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.