The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease – Results from International Breast Cancer Study Group Trials VIII and IX

Metzger-Filho, et al

DOI: 10.1200/JCO.2012.46.1574

International Breast Cancer Study Group

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- Data - Management Center (USA)
- Scientific Committee
- Foundation Council

September 28, 1999

RE: CLOSURE OF IBCSG TRIAL

Dear colleagues,

Please note that study :

VIII

Will be closed as per 1 October 1999.
Congratulations to all !
Thanks to everyone's efforts we were able to complete yet another IBCSG trial.

Our ongoing projects are:

- trials 10-93, 15-95, 16-98, 17-98,18-98 and 20-98

Best regards,

Dr. M. Laura Nasi
IBCSG Studies Coordinator

Vis. PD Dr.M. Castiglione
IBCSG Chief Executive Officer

International Breast Cancer Study Group

Trial VIII

Addendum 7

Reason for Addendum:

- To limit entry to patients with estrogen receptor-positive tumors.

Rationale for Change:

Substantial data exist from the most recent Overview that patients with ER-negative tumors obtain little or no benefit from endocrine therapy. Therefore, there is evidence that one of the treatment arms may be inferior for this subgroup.

Summary of Changes:

1) Patients with tumors ER-negative or ER-unknown are not eligible for Trial VIII.

2) Patients with tumors ER-positive remain eligible for Trial VIII.

Specifically:

- Patient Population: Delete "ER- or ER unknown."
- Add Section 3.3.12, under "Criteria for Patient Ineligibility":
  3.3.12 Patients who have estrogen receptor-negative tumors or who are estrogen receptor status unknown.

Activation Date:

1 August 1998

International Breast Cancer Study Group

Trial VIII

Addendum 6

Reasons for Addendum:

- To simplify the logistics of obtaining quality of life assessments following treatment failure.

Summary of Changes:

1) All patients, REGARDLESS OF DISEASE STATUS are to be assessed on the same schedule. Patients whose tumors have recurred are to be followed on the same schedule as those whose tumors have not recurred. QL assessments are required for all patients for 6 years.

2) The requirements for QL assessments within 1 month of and at 6 months after treatment failure have been dropped.

Specifically:

- Amend your current versions of Table of Study Parameters (Table 7.6, June 1995 revision) by crossing out the footnote on QL assessments:
  ~~[Until treatment failure. Also required within 1 month and at 6 months after treatment failure.]~~
- Amend Section 12, Form QL by crossing out the second sentence:
  ~~[A QL Form should also be completed one month and again at 6 months after relapse of any type.]~~
- Amend Appendix III (Psychosocial Assessment), Section 3b (Methods: Timing of measurements) by crossing out the second sentence:
  ~~[A QL form should be filled in one month and 6 months after recurrence of any type.]~~

Activation Date:

1 December 1996

International Breast Cancer Study Group

Trial VIII

Addendum 5
Parts A and B

A: Reason for Addendum

This addendum simplifies the dose modification schedule and ensures a higher dose will be administered.

Summary of Changes:

Section 5.2.1 has been revised extensively. Please cross out section 5.2.1 (page 14) and insert the attached page into your protocol document.

B: Reason for Addendum

The Coordinating Center's address, phone and fax numbers have changed.

Summary of Changes:

On September 15, 1996, the Coordinating Center moved to a new location in Bern. Please note the change of address, telephone, and fax numbers. Please update the telephone and fax number on the first page of all protocols and the address in the "Records to be Kept" section 12.1.

IBCSG Coordinating Center
Effingerstrasse 40
CH-3008 Bern
Phone: +41 31 389 91 91
Fax: +41 31 389 92 00

Activation Date:

1 December 1996

5.2 DOSE MODIFICATIONS: (CMF Regimen only)

5.2.1 Hematological toxicity: Standard International Breast Cancer Study Group modifications of CMF will be used. Doses of cyclophosphamide, methotrexate, and 5-fluorouracil will be administered according to the following guidelines, based on blood counts performed on the day of treatment administration:

Percentage of full dosage to be given:

Platelets	**WBC >3 x 10^9/l**	**WBC 2.0-3.0 x 10^9/l**	**WBC <2.0 x 10^9/l**
≥ 75,000	100%	75%	Delay one week then treat according to scale. If WBC still below 2.0, omit treatment for that week.
< 75,000	75%	Delay one week then treat according to scale. If WBC still below 2.0, omit treatment for that week	

Do not reduce dose for grade 3 nadir hematologic toxicity not associated with morbidity. For grade 3 toxicity associated with morbidity or grade 4 toxicity, dose may be reduced in the next cycle by 25%.

Patients should be closely monitored while on treatment.

A re-escalation of drug dosage should be performed only in cases where close monitoring of the patient is possible.

Reduce subsequent doses by 25% for lowest WBC< 1.0 x 10^9/l without toxicity or WBC 1.0 x 10^9/l - 1.5 x 10^9/l

INTERNATIONAL BREAST CANCER STUDY GROUP

Trial VIII

Addendum 4

June 1, 1995

- The follow-up schedule for this trial has been modified. Please replace Table 7.6 with the attached modified version.
- CA 15-3 is optional, but strongly encouraged at yearly intervals.
- Chest x-ray is optional, as clinically indicated after randomization.
- A Follow-up Form (E) is required every six months years 3-5 and yearly starting year 6. (Modification of Section 12 of the protocol.)
- Quality of Life forms <u>are required</u> at year 3, 4, 5, and 6. (Modification of Section 10 of the protocol and Section 3b of Appendix III.)
- A Follow-up Questionnaire may be used instead of a clinic visit after 10 years of follow-up for patients without overt metastases. Two samples are enclosed. You may adapt one of these to your local language or prepare a more detailed form. If you use the Follow-up Questionnaire you must submit it, along with a Follow-up Form (E), yearly.
- Breast recurrence in the ipsilateral conserved breast is considered a local failure for the purpose of reporting disease-free survival. There are no longer any protocol requirements for treatment following such recurrences.
  - Section 6b, second sentence. "Disease-free survival is defined as the time from randomization to relapse (**<u>including</u>** isolated breast recurrence, after breast conservation), appearance of a second tumor, or death from any cause, whichever occurs first."
  - Section 6.1.0 should be removed.
  - Section 6.2.0 should be removed.
  - Section 6.2.1 should include "tumor within the conserved breast" in the description of local recurrence.

7.6 TABLE OF STUDY PARAMETERS (Trial VIII)
REVISED JUNE, 1995

REQUIRED	Prior to Rand.	Day 1 of each HT cycle	During each CMF Cycle Day 1 & 8	During each CMF Cycle Days 9-21	First 3 Yrs every month	First 2 Yrs. q 3 mos.	Yrs 3-5 q 6 mos	Yrs 6-10 Yearly	> 10 Year Yearly
History & Physical Examination	X	X	X	X					
Menstrual History	X	X				X	X	X	
Follow-up Questionnaire[1]					X		X	X	
Hematology:									X
Hgb or Hct	X	Z	X	X					
WBC	X	Z	X	X		X	X	X	
Platelet Count	X	Z	X	X		X	X	X	
Chemistries:						X	X	X	
Serum Creatinine & BUN	X	Z							
Bilirubin	X	Z				X	X	X	
Alkaline Phosphatase	X	Z				X	X	X	
SGOT	X	Z				X	X	X	
Gamma-GT	X	Z				X	X	X	
Serum Calcium	X	Z				X	X	X	
Cholesterol	X	Z				X	X	X	
Glycemia	X	Z				X	X	X	
CA 15-3	X[5]	X[5]				X[5]	X[5]	X[5]	
X-Rays / Scans:									
Chest (PA and Lateral)	X, then 1x yearly[3]								
Xeromammogram or Mammogram	X[3], then 1x yearly[3]						X[3]	X[3]	X[3]
Liver CAT scan or ultrasound	X[3], then 1x yearly[3]								
Bone Scan (Bone X-Ray)[2,3]	- within 1 month of surgery and once yearly thereafter.[3]							X[3]	X[3]
Quality of Life Evaluation	X[6] (day 1 of cycles 1,3,6)					X[6]	X[4,6]	X[6](through 6 yr)	
Hormone Receptors: must be determined on primary tumor, if at all possible, at recurrent disease.									

X = For all patients.
Z = Before Cycle 1,2,3, and 4. Then once every 3 months.
1 = For disease-free patients only.
2 = If hot spots: X-Ray of suspicious areas should be performed. If bone scan without demonstrable disease, repeat scan within 3 months.
3 = Optional, as clinically indicated.
4 = Once a year.
5 = Optional, but strongly encouraged.
6 = Until treatment failure. Also required within 1 month and at 6 months after treatment failure.

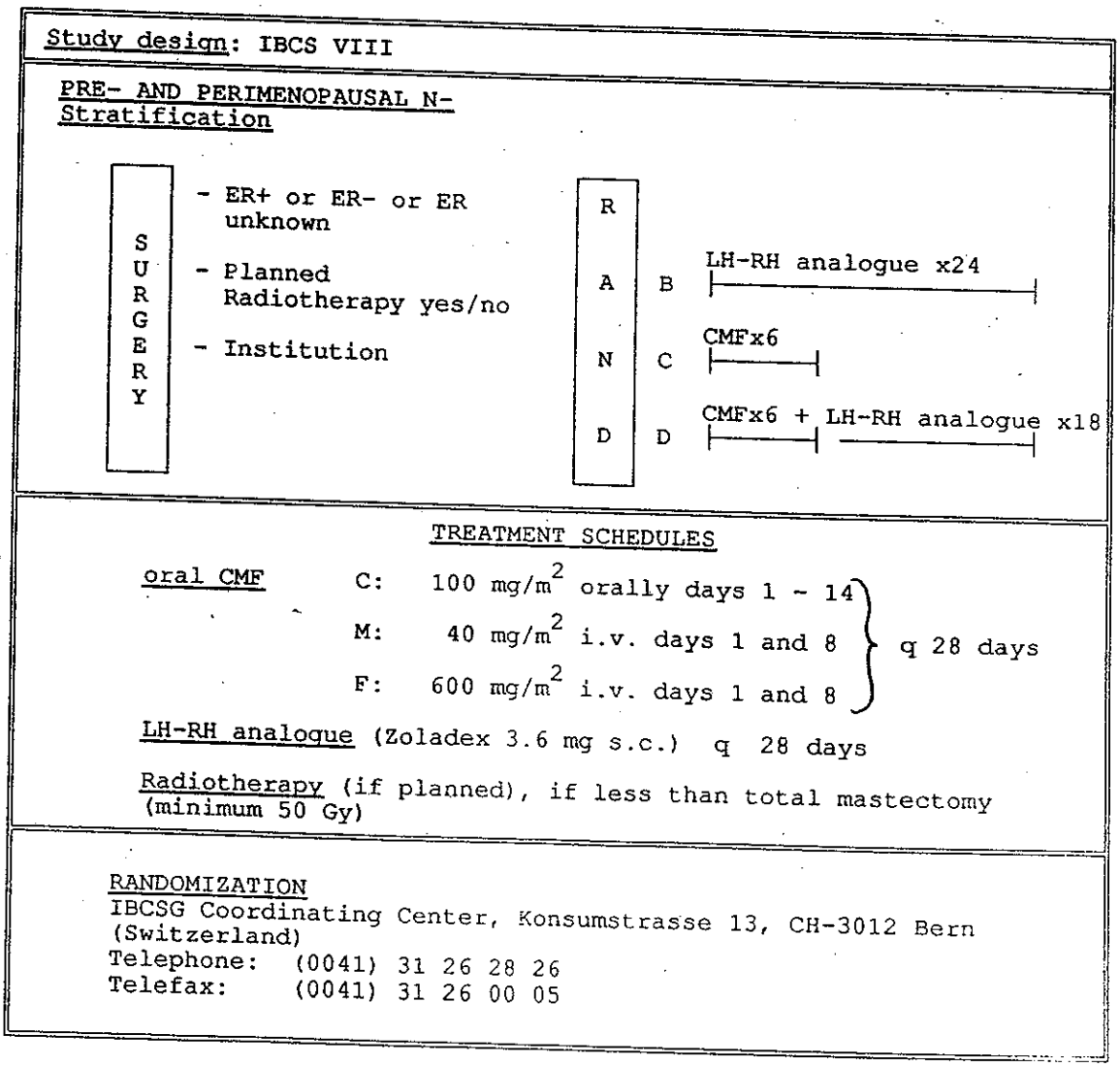
INTERNATIONAL BREAST CANCER STUDY VIII
ADJUVANT THERAPY IN PRE- AND PERIMENOPAUSAL PATIENTS WITH NODE-NEGATIVE BREAST CANCER

Patient population

Pre- and perimenopausal patients with histologically proven breast cancer, who have had either a total mastectomy with axillary clearance, or a lesser procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection (+/- planned radiotherapy), and who are classified as T1a,b,c, T2, T3, pN0, M0 (UICC 1987), ER+, ER- or ER unknown.

Patient entry

Patients will be randomized after surgery but before the end of the 6th week post-operatively.



NEW VERSION!
ACTIVATED APRIL 2, 1992

STATISTICAL CONSIDERATIONS

For changing Trial VIII to a Three-arm Trial (without the no adjuvant treatment control arm)

PREMISES

The accrual to Trial VIII was insufficient for reaching its objectives. The main reason was that "good-risk" node-negative patients are at too good a risk to participate in a trial which contains three treatment arms, and "average" to "high-risk" patients are likely to benefit from treatment and could not be randomized to no adjuvant therapy. It was felt that only "average-risk" and high-risk" patients should be included in a trial in which all patients receive some adjuvant therapy.

CALCULATIONS

The baseline prognosis for node-negative patients at "average-risk" or "high-risk" who receive CMF x 6 is estimated to be 80% 5-year DFS%.

Question # 1: Will the combined CMF x 6 followed by Zoladex x 18 improve the result to 88% 5-year DFS% (a 43% reduction in the risk of an event)?

Answer # 1: Entry of 340 evaluable patients into each of these two treatment groups (108 events) will provide an 80% statistical power to detect the prescribed effect.

Questions # 2: Will the treatment with Zoladex x 24 be comparable with the CMF x 6 alone? To be precise, we will want to have an 80% statistical power to declare Zoladex alone to be worse than CMF alone if the true difference in 5-year DFS% is 72% compared with 80% (a 47% increased risk for Zoladex compared with CMF).

Answer # 2: Entry of 355 evaluable patients into each of these two treatment groups (170 events) will provide an 80% statistical power to detect the prescribed effect.

Summary: Entry of **1,065 evaluable patients** followed for an average of five years will satisfy the objectives for the tree-arm trial. Allowing for a 10% rate of non-compliance and ineligibility, total accrual should exceed **1170 patients.**

Boston, March 11, 1992

2. OBJECTIVES

2.1 To determine whether the use of an LH-RH analogue following 6 months of CMF chemotherapy reduces relapse and prolongs survival as comparison to the use of either a 2 years administration of a LH-RH analogue alone or the use of 6 months of CMF alone.

2.2 To investigate the patients' perceptions on well-being and coping during adjuvant treatment, after therapy but before relapse, and after relapse.

International Breast Cancer Study Group

Trial VIII

Addendum 3

Reason for Addendum:

A new Quality of Life (QL) assessment form was developed for the new generation of trials. This one-page form no longer has the Bf-S item checklist (page 2 of the old form) and has the previous LASA scales, plus six new scales. In order to simplify data collection, the new form replaces the old form for all trials, including Trials VI through IX.

Summary of Changes:

1. The new version of the Quality of Life assessment form should be used. The timing of the QL assessments has not changed. See Appendix V to any one of Protocols 10-93 through 14-93 for a description of the new LASA scales.

2. The noncompliance form has been modified, and only needs to be completed once per patient for those patients who refuse or are unable to continue participation. This simplifies the past requirement that this form be submitted every time a QL form was missed.

Activation Date:

1 May 1993

Considerations for the Interim Monitoring of IBCSG Trial VIII
Prepared by Rich Gelber - December 31, 1993

Trial VIII was modified on April 2, 1992, to include randomization of patients among three treatment groups (discontinuing entry for the "no adjuvant therapy" control group). This modification removed the possibility to evaluate the trial as a 2 x 2 factorial design. The original accrual goal was 1200 patients and the accrual rate was assumed to be 300 per year. The actual accrual rate is 130 per year, and 46 patients were randomized to the "no adjuvant therapy" arm before the protocol amendment. The revised statistical considerations call for enrollment of 1,170 patients (1,065 evaluable), 390 to each of the remaining three treatments. Approximately 6 more years of entry will be required to complete entry to this protocol. Due to the relatively low event rate anticipated for this node-negative patient population and the long accrual period (typical of trials evaluating the role of ovarian ablation), careful consideration for interim monitoring is required.

The baseline prognosis for node-negative patients at "average-risk" or "high-risk" who receive CMF x 6 is estimated to be 80% 5-year DFS%. Two separate pairwise questions will be addressed by this revised study design (we will not adjust for multiple comparisons, but will conduct each one individually at the alpha = 0.05 level).

1. Will the combined CMF x 6 followed by Zoladex x 18 improve the result to 88% 5-year DFS% (a 43% reduction in the risk of an event)? Entry of 340 evaluable patients into each of these two treatment groups (108 events) will provide an 80% statistical power to detect the prescribed effect using a two-sided, alpha = 0.05 significance test.

2. Will the treatment with Zoladex x 24 be comparable with the CMF x 6 alone? To be precise, we will want to have an 80% statistical power to declare Zoladex alone to be worse than CMF alone if the true difference in 5-year DFS% is 72% compared with 80% (a 47% increased risk for Zoladex compared with CMF). Entry of 355 evaluable patient into each of these two treatment groups (170 events) will provide an 80% statistical power to detect the prescribed effect using a one-sided, alpha = 0.05 significance test.

A total of 1065 evaluable patients, 355 per each of the three treatment arms, will be entered. Interim analyses for possible early stopping will be based on systemic-disease-free survival (SDFS) for which relapses in the mastectomy scar are not counted as events. At 5 years median follow-up, we anticipate systemic failure in approximately 20% of the patients for a total of 210 events. Two interim analyses and one final analysis are planned. Therefore, the study will be monitored for the two efficacy comparisons when the total number of events is 70, 140, and 210. The stopping boundaries for each of the two pairwise comparisons based on the O'Brien-Fleming criterion are p-values equal to 0.00019, 0.012, and 0.046, respectively. For the first comparison of CMF x 6 versus CMF x 6 plus Zoladex x 18 two-sided p-values will be used. For the second comparison of CMF x 6 versus Zoladex x 24 one-sided p-values will be used.

INTERNATIONAL BREAST CANCER STUDY GROUP

STUDY VIII

ADDENDUM II

SUMMARY OF CHANGES:

— **Drop the "NO ADJUVANT THERAPY" option "A"**

From the date of activation, patients will be randomized to receive one of the following 3 treatment options:

- **B: LH-RH ANALOGUE every 28 days for 24 times**

- **C: CMF x 6, 28-day cycles**

- **D: CMF x 6, 28-day cycles followed on Day 28 of cycle 6 by LH-RH ANALOGUE every 28 days for 18 times.**

The OBJECTIVES of the Study (paragraph 2 of protocol document page 9) will therefore be: **(See enclosed separate new protocol page 9!)**

The new statistical considerations are enclosed too!

ACTIVATION DATE: APRIL 2, 1992

INTERNATIONAL BREAST CANCER STUDY GROUP

STUDY VIII

ADDENDUM I

Please add the following to Section 3.3.

Criteria for patient Ineligibility:

Not eligible are:

3.3.12. PATIENTS OLDER THAN 45 YEARS WHO HAVE HAD A HYSTERECTOMY, UNLESS THERE IS CHEMICAL PROOF OF OVARIAN FUNCTION BY ALL OF THE FOLLOWING TESTS:

- **LH**
- **FSH**
- **E_2**

Please attach a copy of the results of these three tests to Clinical Form B.

BERN. NOV. 1, 1991

ACTIVATED VERSION

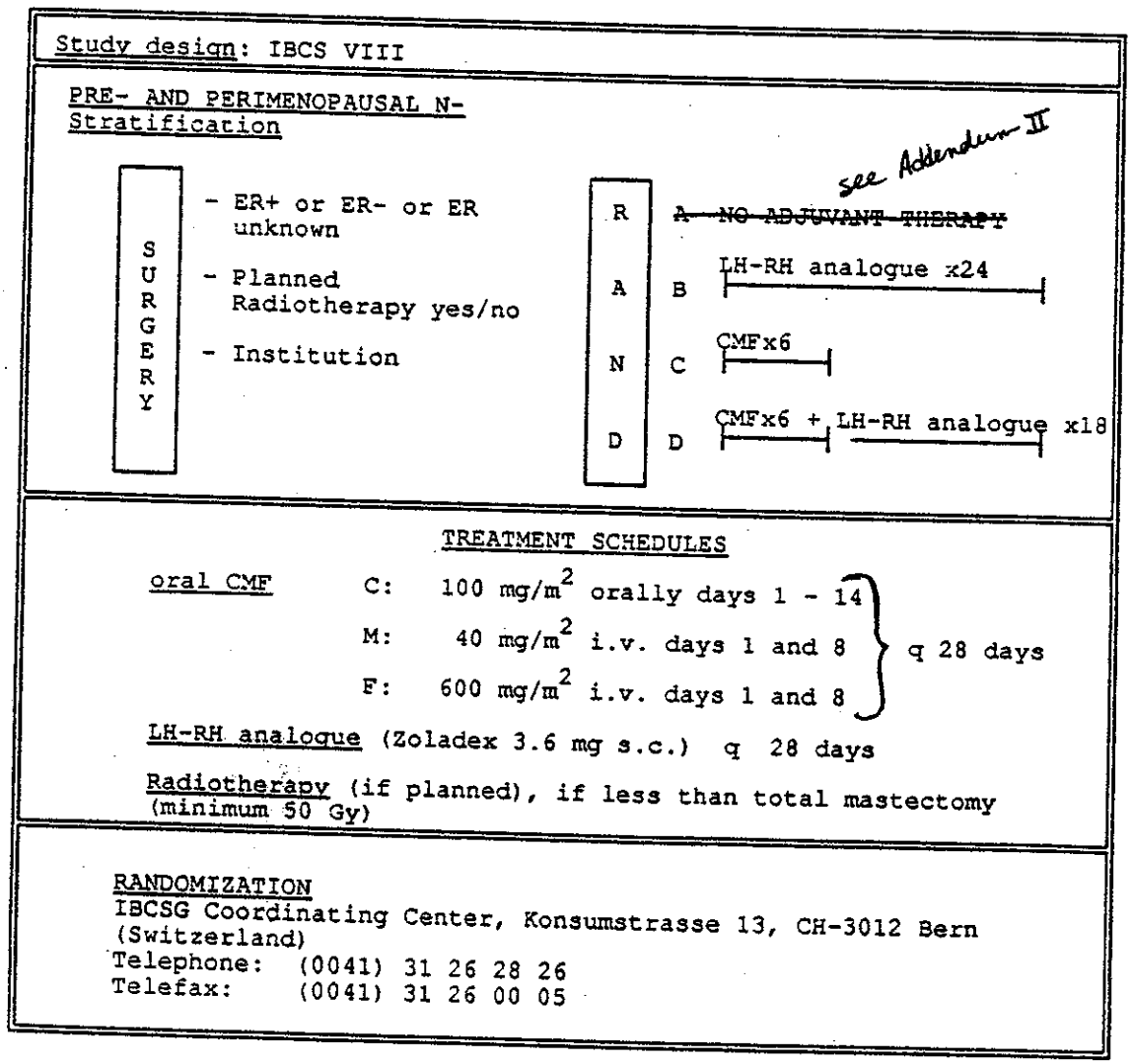
INTERNATIONAL BREAST CANCER STUDY VIII
ADJUVANT THERAPY IN PRE- AND PERIMENOPAUSAL PATIENTS WITH NODE-NEGATIVE BREAST CANCER

Patient population

Pre- and perimenopausal patients with histologically proven breast cancer, who have had either a total mastectomy with axillary clearance, or a lesser procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection (+/- planned radiotherapy), and who are classified as $T1_{a,b,c}$, T2, T3, pN0, M0 (UICC 1987), ER+, ER- or ER unknown.

Patient entry

Patients will be randomized after surgery but before the end of the 6th week post-operatively.



ACTIVATION DATE: 1.3.90

INDEX

1. INTRODUCTION

The following information has emerged from previous trials of patients receiving adjuvant systemic treatment for breast cancer:

1.1 Combination chemotherapy delayed relapse and improved survival in premenopausal patients (1). The addition of prednisone to the combination chemotherapy (CMF) significantly increased tolerance to the treatment but did not improve outcome (2).

1.2 The optimal duration of adjuvant chemotherapy in premenopausal patients is unknown, but could be six months or less. A single cycle of i.v. CMF was inadequate when compared to six cycles for N+ breast cancer patients (3).

1.3 Premenopausal node-negative (N-) patients in Ludwig V have a 4-year DFS percentage of 72% if not receiving adjuvant therapy (4). Similarly, an overview of randomized clinical trials in early breast cancer showed that the 5-year recurrence-free survivals for patients in tamoxifen studies and chemotherapy studies were 75% and 72%, respectively (1). Patients with tumours containing low levels of or no hormone receptors (ER- and, if available, PR-) have been identified as being at high risk for relapse (5). Patients with higher levels of ER included in Ludwig V had a similar 4-year DFS rate as patients with low or no ERs in their primaries (71% for both). The accrual of patients into this trial was performed without knowledge of any pathologically determined prognostic factor. Selection might have occurred based upon clinical signs which remain unknown. All premenopausal patients with N- disease may therefore be considered suitable candidates for clinical trials with systemic adjuvant therapy.

1.4 Adjuvant endocrine therapy for premenopausal patients is controversial. Table 1 summarizes adjuvant oophorectomy trials which have yielded overall an advantage for the treated patients.

Table 1. Adjuvant oophorectomy or ovarian irradiation (*) ± low-dose prednisone (**) vs. local therapy alone in randomized trials [6]

Trial [ref]	Yrs of accrual	No. pts.	Years of follow-up reported	Survival difference (%) in report	Survival difference significant?
Christie* [7]	'48-'55	598	15	5	No
Norwegian* [8]	'57-'63	169	30	16	Yes
NSABP [9]	'61	357	5	2	No
Boston [10]	-	143	5	-	No
Saskatchewan [11]	'64-'73	359	10	11	Yes
Toronto** [12]	'65-'72	308	15	28	Yes
Toronto* [13]	'65-'72	137	10	4	No

The following conclusions emerge from these trials:

1. The differences in favour of the adjuvant therapy group as compared to surgical controls appeared later during follow-up (7,8,11,12,13).
2. The effects of treatment were more evident in patients with lower risk (N-) than in those at high risk for relapse.
3. In the single trial which tested the use of combined ovarian radiation and low-dose continuous prednisone for 5 years (in premenopausal patients 45 years old or older), the combined endocrine approach yielded significantly better results than local treatment with or without ovarian irradiation alone (12). This has been attributed to additional suppression of steroid hormones in the adrenals. The fact that all these trials demonstrated some degree of prevention of relapses and some reduction of mortality from breast cancer in premenopausal patients provided evidence that suppression of ovarian function was beneficial. In view of this, the issue of the role of endocrine approaches in the adjuvant treatment of premenopausal breast cancer patients has retained its clinical relevance.

Another aspect which reflects the importance of endocrine mechanisms and tumour progression in this age group is represented by the relationship between cytotoxic-induced amenorrhea and outcome. Cytotoxic agents, especially alkylating agents, cause suppression of the endocrine function of the ovaries, probably due to a direct effect of the drugs upon hormone-producing cells (14,15). Table 2 summarizes the results of studies in which this aspect has been investigated.

Table 2. Trials in which the effect of amenorrhea on outcome has been analyzed (disease-free survival = DFS, overall survival = OS)

Trial [Ref]	Regimen	No. pts. analyzed	% to achieve amenorrhea	Years of follow-up reported	Amenorrhea vs. no amen.: sig. differences? DFS	OS
NSBAP* B-05 [16]	L-PAM &	76	57%	4	NA	NA
	L-PAM + 5FU	20	40%			
Milan* [17]	CMF	78	73%	10	No	No
Guy's/ Manchester [18]	CMF	87	61%	3	Yes	Yes
ECOG [19]	CMF		40%			
	CMFP	506	46%	3.2	Yes	NA
	CMFPT		51%			
Denmark* [20]	CMF	423	84%	3.5	No	NA
	C	424	80%		Yes	NA
Ludwig I [2]	CMF	203	87%	4	Yes	Yes
	CMFp	196	83%		No	No

*Trials with surgical controls

In our Group's own experience (Ludwig Trial I), 399 of the 491 pre- and perimenopausal patients with N+ breast cancer were evaluable for the effects on treatment outcome of chemotherapy-induced amenorrhea. In this trial premenopausal patients with operable breast cancer and 1 to 3 involved axillary nodes were randomized to receive CMF or CMF plus low-dose continuous prednisone (CMFp) for 1 year. The results at 4 years have been extensively reported [2]. Induced amenorrhea was associated with a longer disease-free survival for younger patients (<40 years old), patients who received lower CMF doses (<80% of the average dose specified by the protocol) and patients with ER+ tumours.

Adjuvant tamoxifen has also been tested in premenopausal women (Table 3). In two trials the effect of the drug has been compared to that of local therapy alone, in the third trial to x-ray castration, and in the fourth trial to a CMF combination chemotherapy. Interpretation of the results is difficult since the number of patients included in the comparisons of tamoxifen vs. local treatment alone for this age group is small. The only trial (Heidelberg) with a direct comparison of tamoxifen with 6 months of an i.v. CMF regimen (C = 500 mg/m^2, M = 40 mg/m^2, F = 600 mg/m^2, all on days 1 and 8 of each courses) showed a significant benefit in favour of the chemotherapy-treated premenopausal patients [24].

Table 3. Randomized trials comparing adjuvant tamoxifen (TAM) versus local therapy alone (Copenhagen and NATO), versus ovarian irradiation (Christie) or versus CMF (Heidelberg) in premenopausal women

Trial [ref]	Yrs. of accrual	No. of pts.	Yrs. of follow-up reported	Benefit for TAM	
				DFS	OS
Copenhagen [21]	'75-'78	213	6.5	Yes (n.s.)	Yes (n.s.)
Christie [22]	'76-'82	373	7	Yes (n.s.)	No (n.s.)
NATO [23]	'77-'81	128	6	Yes (n.s.)	Yes (n.s.)
Heidelberg [24]	'81-	not given	5	No*	No

*Favours the CMF group: includes only patients with both ER+ tumours and 1-3 axillary nodes involved

The only conclusions which may be based upon this set of trials are:

i) the vast majority of trials investigating the effects of ovarian suppression showed some difference in outcome (statistically significant or not) favouring the patients who had oophorectomy or another form of induced amenorrhea.
ii) the tamoxifen trials are not conclusive for premenopausal patients, but chemotherapy appears to be superior to adjuvant tamoxifen in a single direct comparison. Recent information from trials in N- disease indicates significant benefit also for premenopausal patients treated with tamoxifen as compared to placebo (25).

The combination of adjuvant chemotherapy with concomitant endocrine treatment has been studied in many trials. These studies were motivated by observations in advanced disease [26] and by the hypothesis that the endocrine component might

eradicate a small proportion of cells and prevent subsequent development of chemotherapy resistance. On the other hand, there are theoretical reasons why endocrine therapy and chemotherapy might be antagonistic [6]: tumour cells responding to endocrine treatments rapidly enter a resting or Go phase shortly after administration of this treatment. Relative resistance to chemotherapeutic agents would thus result if the two modalities act upon the same cell population [27].

Experiments conducted in vitro on MCF-7 cells show that the cell kill of the combination of either melphalan or 5-fluorouracil with tamoxifen is inferior not only to what is expected if the effect of the drugs would have been additive, but even to the effect of each drug used alone (28).

Table 4 lists data derived from seven trials in which premenopausal patients were treated with chemo-endocrine therapy as compared with chemotherapy alone. Only one of the trials (31) has shown a significant advantage for the chemotherapy plus tamoxifen combination as compared to chemotherapy alone. In the largest trial (30) a retrospective subgroup analysis by receptor content of the primary revealed a difference in favour of the chemotherapy alone treatment group in all patients with either ER- or PR- tumours. The experiments which show a negative effect of tamoxifen upon the cytotoxicity of melphalan and 5-fluorouracil (28) may explain these results to some extent.

Table 4. Randomized trials comparing chemo-endocrine therapy (CT+HT) including oophorectomy (Ox) or tamoxifen (TAM) with chemotherapy (CT) in premenopausal women

Trial [ref.] Endocrine Rx	CT	Accrual years	No. pts.	Yrs. follow-up reported	Benefit for CT+HT DFS	Benefit for CT+HT OS
Case Western [29] - TAM	CMF	'74-'79	108	9	NS	NA
NSABP [30] - TAM	PAM/F	'77-'80	779	5	No	No
ECOG [19] - TAM	CMF/P	'78-'82	369 (2 arms)	4	No	NS
Mayo/NCCTG [31] - TAM	CFP	NA	370	NA	Yes	No
Heidelberg [24] - TAM	AC	'81-	NA	5	NS	No
Ludwig II [32]* - Ox	CMFp	'78-'81	327	4	NS	NS
SWOG [33] - Ox	CMFVP	'79-	179+	NA	NS	NA

*for 8-year results see text. Abbrev.: NA = not available; NS = not significant

The only available mature results of the combination of chemotherapy and oophorectomy are those from Ludwig Trial II. Differences in terms of DFS or OS observed at eight years of median follow-up are presented in Table 5. These differences began to emerge only after six years of median follow-up. It is important to note that the patients selected for this trial had four or more involved axillary nodes and were thus

at very high risk for relapse. It is hypothesized that a patient population at lower risk for relapse might gain a greater benefit even earlier in the course of follow-up.

Table 5. Ludwig Study II: DFS and OS at 8-Year Median Follow-up

		No. pts.	5-year	8-year	p-value
DFS					
	CMFp	161	43 ± 4	30 ± 4	.17
	Ox+CMFp	166	48 ± 4	37 ± 4	
ER+					
	CMFp	45	40 ± 7	26 ± 7	.09
	Ox+CMFp	62	55 ± 6	41 ± 7	
ER-					
	CMFp	42	40 ± 8	29 ± 7	.92
	Ox+CMFp	51	39 ± 7	25 ± 7	
ER unknown					
	CMFp	74	47 ± 6	33 ± 6	.39
	Ox+CMFp	53	47 ± 7	42 ± 7	
OS					
	CMFp		61 ± 4	41 ± 4	.20
	Ox+CMFp		65 ± 4	50 ± 4	
ER+					
	CMFp		64 ± 7	47 ± 8	.23
	Ox+CMFp		73 ± 6	61 ± 7	
ER-					
	CMFp		50 ± 8	33 ± 8	.51
	Ox+CMFp		57 ± 7	34 ± 7	
ER unknown					
	CMFp		66 ± 6	43 ± 6	.63
	Ox+CMFp		64 ± 7	52 ± 7	

A retrospective analysis of outcome by estrogen receptor content in the primary tumour revealed that the difference in favour of oophorectomy is confined to patients with ER+ tumours.

1.5 LH-RH analogues cause a "partial hypophysectomy" with decreased gonadotropin and prolactin secretion as well as a chemical castration with a fall in plasma sex steroids, and inhibition of enzymes involved in steroidogenesis. Furthermore, a direct inhibitory effect of the LH-RH analogues has been described for experimental mammary,

prostate, pituitary, bone and pancreatic tumours (34). LH-RH-like receptors have been found in an experimental prostatic tumour and in human breast cancer cells (35,36, 37).

In premenopausal women with advanced breast cancer LH-RH analogues have been reported to yield an objective response rate of 37% (34/92 patients) (38,39,40,41,42) which was not altered by an update of the series. The number of patients with advanced breast cancer who were treated for periods of >1 year is small. Some patients were treated for a duration of 2 years without notable side effects. Side effects due to the chronic use of LH-RH-analogue include castration (hot flashes) and occasional nausea. Menses ceases by two months after start of drug administration (in some patients there is slight spotting beyond this period), and, preceded by ovulation, resumes within approximately 80 days after the final depot administration (43).

While LH-RH agonists are achieving widespread acceptance for short-term administration, questions related to their theoretical effects upon lipid and bone metabolism remain open with respect to their long-term use. A limited period of its administration, with careful monitoring of changes in lipid profiles and bone metabolism might be one of the endpoints of a trial with adjuvant LH-RH analogues.

1.6. Results from the NSABP Trial B-06 indicate that lumpectomy and local radiotherapy provided equivalent control of disease as compared with total mastectomy (44,45). The Milan National Cancer Institute Trial, which compared quadrantectomy with axillary clearance and radiotherapy to radical mastectomy, resulted in equivalent outcomes for the two treatments in patients with T_1 tumours (46,47). Furthermore, similar results have emerged recently from an EORTC study (48). Thus, the combination of segmental mastectomy, axillary clearance and radiotherapy is considered to be acceptable local management. Some ongoing trials evaluate the relevance of local management without radiation therapy because of the question of possible overtreatment for patients with very small tumours.

1.7 The side effects of the therapies to be tested vary considerably, and may have an impact on the quality of life of patients treated. It is important that this be measured as an outcome variable, and that any prognostic value of the patients quality of life status should be assessed. Instruments introduced by the Group in earlier studies will be used (Appendix III).

2. OBJECTIVES

2.1 To evaluate the efficacy of six months of adjuvant CMF chemotherapy compared with no adjuvant chemotherapy in reducing relapse and prolonging survival.

2.2 To determine whether the monthly administration of an LH-RH analogue for the duration of two years reduces relapse and prolongs survival as compared to no endocrine therapy.

2.3 A pairwise evaluation of the study has the objective of determining whether the use of an LH-RH analogue following six months of adjuvant CMF chemotherapy reduces relapse and prolongs survival as compared to no adjuvant therapy, or to the use of either of the above modalities alone.

2.4 To investigate the patients' perceptions on well-being and coping during adjuvant treatment, after therapy but before relapse, and after relapse.

see Addendum II

3. PATIENT SELECTION

3.1 General Criteria for Patient Eligibility

3.1.1 Node negative disease (without metastases detected at pathologic examination in at least 8 ipsilateral axillary nodes).

3.1.2 Patients must have had

a. either total mastectomy or, optionally if the tumour was <5 cm, a breast-conserving procedure (lumpectomy or quadrantectomy). In the latter case there should be pathological verification of clear margins.
Radiation therapy to the breast is optional for patients with breast-conserving surgery.

b. Axillary clearance (not sampling) with at least eight lymph nodes for pathological examination.

c. The surgical procedure within 6 weeks prior to randomization.

3.1.3 At least eight lymph nodes histo-pathologically examined.

3.1.4 Tumour confined to the breast with no detected metastases.

3.1.5 Adequate marrow function (WBC $\geq$ 4000/mm^3 and platelets $\geq$ 100,000/mm^3).

3.1.6 Documented evidence of adequate renal (creatinine < 120 µmol/l) and hepatic (bilirubin < 20 µmol/l, SGOT < 60 IU/l) function.

3.1.7 Informed consent according to the criteria established within the individual countries. The Helsinki declaration of human rights must be the basis for inclusion and information of patients in the trial.

3.2 Study-Specific Criteria for Patient Entry

3.2.1 Pre- and perimenopausal patients.
This group will include patients who are:

a. >52 years, and have had the LNMP (last normal menstrual period) within 1 year; or

b. ≤52 years, and have had the LNMP within 3 years, or are currently menstruating; or

c. ≤55 years, and who have had a hysterectomy without a bilateral oophorectomy;

d. or have had biochemical confirmation of continuing ovarian function (in questionable cases).

3.3 Criteria for Patient Ineligibility

Not eligible are:

3.3.1 Patients with any axillary node involvement;

3.3.2 Patients who have malignant breast tumours other than carcinoma;

3.3.3 Patients who have T4 tumours with ulceration or infiltration (complete fixation) of the skin, with peau d' orange, or who have metastatic disease. Any suspicious manifestation requires additional investigation to rule out metastases.

3.3.4 Patients who have bilateral malignancies, or a mass in the opposite breast, unless the mass is proven by biopsy to be non-malignant.

3.3.5 Patients who have had less than total mastectomy procedure in which the margins of resection contained tumour cells, after which they did not subsequently undergo a total mastectomy (within 4 weeks of the first surgery).

3.3.6 Patients who are pregnant at diagnosis or lactating (including those who have stopped lactating within the past six months).

3.3.7 Patients with a previous or concurrent malignancy, EXCEPT patients with squamous or basal cell carcinoma of the skin, or adequately treated in-situ carcinoma of the cervix.

3.3.8 Patients who have received prior therapy for breast cancer, including prior irradiation, surgery, or chemo- and/or hormonal therapy.

3.3.9 Patients with other non-malignant systemic diseases (cardiovascular, renal, hepatic, etc.) which prevent them from being subject to any of the treatment options or to prolonged follow-up (attention also to lipid metabolism disorders).

3.3.10 Patients with psychiatric or addictive disorders which prevent them from giving informed consent or being subject to any of the treatment options.

3.3.11 Patients who, prior to randomization, have had bone scan showing hot spots which cannot be confirmed as benign disease upon subsequent X-ray examination, or patients with skeletal pain of unknown cause.

4. STRATIFICATION AND RANDOMIZATION

Patients must be randomized within 6 weeks after the definitive breast cancer surgery, so that the adjuvant treatment can be started within the same period of time.

All of the information listed on the confirmation form must be known at the time of randomization. This includes:

4.1 List of eligibility criteria including MENOPAUSAL STATUS (see section 3.2.1 for definition).

4.2 STRATIFICATION

i) **ESTROGEN RECEPTOR STATUS**
ER+ = ≥ 10 fmol/mg cytosol protein*
ER- = < 10 fmol/mg cytosol protein*
ER unknown: no determination possible

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* If only immunochemistry is available then ER+ = ≥+ and ER- = <+

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ii) For patients with breast-conserving surgery:
RADIATION THERAPY TO THE BREAST: PLANNED OR NOT

Radiation therapy is optional for patients who have undergone less than total mastectomy procedures with axillary clearance, where the margins of resection of the primary tumour were found to be pathologically free of malignant tissue.

Radiation therapy should be started within 3 months after randomization for patients who do not receive CMF treatment, and within 2 weeks after the end of the last cycle of adjuvant CMF for all other patients (see Treatment Regimens in Sections 4.4 and 5).

iii) **INSTITUTION**

4.3 Additional information required at randomisation includes:

i) Method of initial diagnosis:
(Was initial tumor detected only by mammography?)

ii) Type of definitive surgical procedure (Total mastectomy + axillary node clearance vs segmental mastectomy or lumpectomy + axillary node clearance).

iii) If less than total mastectomy: Were margins of excision histologically free of cancer?

iv) Date of definitive surgery?

4.4 RANDOMIZATION

Patients will be randomized to receive one of the following 4 treatment options:

- A : NO ADJUVANT THERAPY
- B : LH-RH ANALOGUE every 28 days for 24 times
- C : CMF x 6, 28-day cycles
- D : CMF x 6, 28-day cycles followed on Day 28 of cycle 6 by LH-RH ANALOGUE every 28 days for 18 times.

Randomized assignments are provided by telephone call or telefax to the Coordinating Center after stratification and eligibility information is given. The treatment assignment is confirmed by mailing **Form A** - Confirmation Form from the Coordinating Center to the participating institution.

5. TREATMENT REGIMENS

5.1 Doses and schedules

5.1.1 CMF treatment, with dosages administered as follows:

Cyclophosphamide	100 mg/m² orally days 1-14
Methotrexate	40 mg/m² i.v. days 1 and 8
5-Fluorouracil	600 mg/m² i.v. days 1 and 8

Repeat every 28 days for 6 cycles.

The treatment schedules for the arms B and D are the following:

5.1.2 LH-RH Analogue (Zoladex) 1 subcutaneous injection of 3.6 mg once every 28 days given 24 times for patients who receive Zoladex only (arm B), and 18 times for patients who receive adjuvant CMF before Zoladex (arm D).

5.1.3 Radiation therapy will be planned and performed as described in Appendix I.

Radiation therapy is optional for patients who have undergone less than total mastectomy procedures with axillary clearance, where the margins of resection of the primary tumour were found to be pathologically free of malignant tissue.

Radiation therapy should be started within 3 months after randomization for patients who do not receive CMF treatment, and within 2 weeks after the end of the last cycle of adjuvant CMF for all other patients.

5.2 DOSE MODIFICATIONS (CMF regimen only)

5.2.1 Hematologic Toxicity

Dosages of cyclophosphamide, methotrexate and 5-fluorouracil will be administered according to the following guideline, based on blood counts performed on the day of treatment administration:

	Percentage of Full Dosage to be Given		
Platelets	WBC ≥ 4,000	WBC 3,999-2,500	WBC < 2,500
≥100,000	100%	50%	0%
99,999-50,000	50%	50%	0%
<50,000	0%	0%	0%

WBC = Total white blood cell count

Dosage of the three drugs can be modified according to neutrophil count on the day of treatment administration according to the following guideline:

	Percentage of Full Dosage to be Given		
Platelets	Neutro ≥ 1,900	Neutro 1,899-1,500	Neutro<1,500
≥100,000	100%	50%	0%
99,999-50,000	50%	50%	0%
<50,000	0%	0%	0%

Any grade 3 hematologic toxicity noted during the course of treatment should be managed by a 25% dose reduction in the total amount of drug administered in each cycle after hematological recovery.

A re-escalation of drug dosage should be performed only in cases where close monitoring of the patient is possible.

5.2.2 Renal dysfunction at the time of drug administration:

Methotrexate should be administered only in the presence of normal renal function. **The monitoring of creatinine should be carried out routinely every two months,** and also in cases where impairment of renal function is suspected. **SPECIAL CAUTION** should be used in order to ensure that patients who receive methotrexate are not concomitantly receiving drugs such as **salicylates, sulphonamides, etc.,** which might increase the toxic effect of methotrexate.

Early onset of toxicities (within 2-3 days of drug administration), such as stomatitis, diarrhea and/or blood count fall, must be considered as premonitory signs for severe methotrexate toxicity. These should be treated as emergencies, for example through correction of renal function or administration of leucovorin rescue factor.

5.2.3 Hemorrhagic Cystitis: All patients should be instructed on the importance of high fluid intake during cyclophosphamide therapy. If hemorrhagic cystitis occurs in spite of vigorous hydration, cyclophosphamide treatment should be stopped.

5.2.4 Gastrointestinal Toxicity: In the event of severe anorexia, nausea, vomiting, diarrhea, stomatitis, dryness of the mouth or epigastric pain, all therapy should be postponed until the symptoms subside. In the event of debilitating vomiting or diarrhea, a 25% dosage reduction of CMF is recommended for the next cycle, with subsequent escalation to tolerance. If mucosal ulceration occurs, no 5-FU or methotrexate should be given for the remainder of the cycle. If mucosal ulceration has occurred with a prior treatment, a 50% reduction in 5-FU and methotrexate with subsequent escalation in each cycle by 25% of the original dosage of each drug to tolerance is required.

5.2.5 Neurotoxicity: If ataxia develops, omit 5-FU until resolution. After that, 5-FU may be re-introduced at 50% of full calculated dose with a 25% escalation in each subsequent cycle to tolerance to full dosage.

5.2.6 Other toxicities: If any other toxicities indicate the need to decrease drug dosages, this is allowed; however, the toxicities as well as the changes in dosages must be recorded. Patients will not be excluded from evaluation because of either partial or total drug intolerance.

5.2.7 Any grade 4 toxicity, other than hematologic, noted during the course of treatment should be handled through a 50% reduction in the total dosage administered in the next cycle after full recovery and reported immediately to the study coordinator.

5.3 Toxicities of LH-RH Analogue Depot (Zoladex)

5.3.1 Local toxicity: Prior to administration the skin should be anaesthetized. This way of administration is comfortable and painless. Local reaction has been described as rare (about 1%).

5.3.2 Effects of chemical castration: Hot flashes, rare nausea, and obligatory amenorrhea with some spotting were described in premenopausal patients. These effects are reversible once administration of the drug is stopped. Patients should be informed about these patterns, also in relationship with anti-conception. Hormonal contraceptive should be avoided in patients included in the trial.

5.3.3 Long-term effects on lipid and bone metabolism are unknown. Hypercalcemia has not been reported.

5.3.4 Every uncommon (i.e., not mentioned above) side effect should be extensively reported to the Coordinating Center in a special letter.

All severe or life-threatening adverse drug reactions thought to be associated with "Zoladex" must be promptly (within 24 hours) reported to the Coordinating Center (fax or telephone call).

(For details of reporting toxicities see also section 11).

6. END POINTS AND DEFINITIONS OF TREATMENT FAILURE

The end points of this trial are:

a. first confirmation of recurrence or metastatic disease, and/or
b. death. Autopsy must be performed on all patients entered in the study if at all possible.
Disease-free survival is defined as the time from randomization to relapse (excluding isolated breast recurrence, after breast conservation, treated with a simple mastectomy), appearance of a second primary tumour, or death from any cause, whichever occurs first. Overall survival is defined as the time from randomization to death from any cause.
c. Systemic relapse is defined as any recurrent disease in sites other than local (mastectomy scar or homolateral breast in case of less than mastectomy) or contralateral breast only. Systemic disease-free survival will be used as surrogate for overall survival for the purpose of possible early stopping of some or all treatment options.
d. Sites of first metastatic disease or recurrence (see 6.1 for definition) as well as incidence of second malignancies (not breast) and causes of deaths without breast cancer relapse.
e. Side effects of treatment.
f. Incidence of amenorrhea. For this purpose a special emphasis will be placed upon documentation of menses in relation to each treatment option (including no-adjuvant treatment and chemotherapy-alone).

In addition to these end points, other information recorded on the various forms will be collected regularly and analyzed by appropriate statistical procedures. It is important that all failures, local or distant, continue to be registered after first relapse.

6.1 Diagnosis of treatment failure

The diagnosis of first treatment failure depends on the presence of recurrent disease which can be classified as either suspicious or acceptable. In each case, this should be specified and reported. Any events which are not included in the following guideline as acceptable or suspicious would be considered as unacceptable for positive evidence of disease. The time of recurrence will be designated as when a suspicious lesion, subsequently proven to be a definitive recurrence/metastasis, is first seen. Hormone receptor assays must be performed on recurrent disease whenever possible.

6.1.0 Reappearance of cancer in the ipsilateral conserved breast.

This should be diagnosed by cytological and histological means. Treatment should preferably be total mastectomy. Protocol-assigned adjuvant treatment should continue afterwards to completion. Follow-up should be continued as in patients free of any event. The incidence of such events will be recorded as a separate endpoint (breast-recurrence-free survival).

6.1.1 Local and regional failure

Loco-regional failure is defined as a tumour recurrence in any soft tissues of the ipsilateral sites, such as the chest wall (local), internal mammary, supraclavicular and/or ipsilateral axillary nodes and/or soft tissue of the axilla (regional).
Specific site should be recorded on follow-up forms.

A tumour in the other breast is not considered a loco-regional treatment failure.

ATTENTION: according to UICC guidelines 1987 supraclavicular lymph node metastases are considered distant failures, however for consistency to our previous protocols we will continue to consider these as regional metastases.

Criteria:

acceptable: positive cytology or histology or progression of disease (UICC criteria) if only indirect methods were used (e.g., x-ray)

suspicious: a visible or palpable lesion

6.1.2 Distant failures

Tumours in all areas other than those mentioned above (6.1.0 and 6.1.1) are considered distant metastases.

Criteria

Contralateral breast, contralateral axilla and contralateral supraclavicular nodes

acceptable: positive cytology or histology

suspicious: a visible or palpable lesion

Bone marrow

acceptable: positive cytology, aspiration or drill biopsy

suspicious: unexplained depression of peripheral counts and/or erythroblastic blood picture

Lung and/or pleura

(should be distinctly specified)

acceptable: positive cytology or histology or presence of progressive lesion(s) on two successive X-rays or CT scans in the absence of constitutional symptoms

suspicious: a new lesion on an X-ray

Bone

acceptable: positive cytology or histology or a positive X-ray, or two bone scans performed at least 3 months apart, which show progressive changes

suspicious: skeletal symptoms or positive scan and bone X-ray excluding benign lesions as possible cause

Liver

acceptable: positive cytology or histology or progressive changes in liver ultrasound, or CT scan

suspicious: any two of the following: hepatomegaly by physical examination, abnormal liver scan, abnormal liver function test (especially increase of gamma-GT), pathological ultrasound or CT scan

Central nervous system

acceptable: positive biopsy or cytology or symptoms plus a diagnostic brain scan, or positive CT scan

suspicious: any other clinical findings suggestive of this diagnosis

Distant soft tissue (e.g., skin, other than local) and other organs
acceptable: positive biopsy or cytology or progressive manifestations (UICC criteria) if only indirect methods were used (e.g., X-ray)
suspicious: clinical and radiological evidence of a tumour

6.2 Treatment Failure

6.2.0 Breast Recurrence in Less than Total Mastectomy
Evidence of tumor within the conserved breast. Assigned protocol treatment should continue to its completion following local management of the breast recurrence.

Criteria
acceptable: positive cytology or histology
suspicious: a visible or palpable lesion

Special consideration should be given to the **documentation of breast recurrence after less than mastectomy procedures.**

The following information should be submitted:
a. the extension of relapse
b. the treatment procedure
c. a histology report in cases of biopsy or surgical removal of recurrence, along with a description of any tumour tissue not surgically removed; and
d. results of the hormone receptor assay performed on the recurrence (submitted on Form F).

6.2.1 Local Treatment Failure
Acceptable evidence of tumour in any soft tissues of the ipsilateral chest wall, operative scar. This includes the area bounded by the midline of the sternum, superiorly by the clavicle, along the lateral edge of latissimus dorsi and inferiorly by the costal margin. A soft tissue recurrence in this area extending into the bony chest wall or across the midline will still be considered as evidence of local treatment failure.

The following information should be submitted:
a. the extension of relapse
b. the treatment procedure
c. a histology report in cases of biopsy or surgical removal of recurrence, along with a description of any tumour tissue not surgically removed; and
d. results of the hormone receptor assay performed on the recurrence (submitted on Form F).

6.2.2 Regional Treatment Failure
Evidence of tumour in the ipsilateral internal mammary, supraclavicular and/or axillary nodes and/or in the soft tissue of the axilla.

6.2.3 Distant Treatment Failure
Evidence of tumour in all areas except those described above (6.2.0, 6.2.1 and 6.2.2).

6.3 Survival

Survival will be measured from the date of randomization.

6.4 Morbidity

Information will be recorded relative to any complications.

7. STUDY PARAMETERS (See Table 7.6)

It is essential that follow-up be regular, accurate and disciplined, if meaningful and worthwhile information is to be obtained.

7.1 The aim of the follow-up is to determine the time of tumour recurrence and the duration of patient survival.

7.2 **Information will be recorded at regular intervals.**

7.3 The day of randomization is considered Day 0 for the purpose of follow-up. All patients will be followed-up in each clinic after every CMF and LH-RH analogue administration. Follow-up is required every third month during the first two years, every six months for the next three years, and yearly thereafter. The follow-up form (Form E) is filled out at the time of each scheduled visit (see Section 10. for the timing of submission of the forms) and sent to the Operations Office.

7.4 All patients will be followed and evaluated at the same intervals, regardless of treatment assignment.

7.5 Morbidity of treatments

Toxicity must be recorded on Form D+M according to the grades defined in Appendix II. The Form C must include all complications occurring in the postoperative period. Form D+M is to be used for accurate reporting of menstrual history for all patients.

7.6 Required investigations

See Table 7.6 on next page.

7.6 TABLE OF STUDY PARAMETERS

REQUIRED	Prior to Rand.	Day 1 of each HT Cycle	Day 1 & 8 of Cycle During Cytotoxic CT	Days 9 - 21 of Cycle During CT	Every Month for 36 Months	Every 3 Months First 2 Years	Every 6 Months Years 3 - 5	Every 12 Months After Year 5
History & Physical Examination	X	X	X	X		Y	Y	Y
Menstrual History	X	X			Y		Y	Y
Hematology:								
HGB or HCT	X	Z	X	X		Y	Y	Y
WBC	X	Z	X	X		Y	Y	Y
Platelet Count	X	Z	X	X		Y	Y	Y
Chemistries:								
Serum Creatinine & BUN	X	Z				Y	Y	Y
Bilirubin	X	Z				Y	Y	Y
Alkaline Phosphatase	X	Z				Y	Y	Y
SGOT or SGPT	X	Z				Y	Y	Y
Gamma-GT	X	Z				Y	Y	Y
Serum Calcium	X	Z				Y	Y	Y
Cholesterol	X	Z				Y	Y	Y
Glycemia	X	Z				Y	Y	Y
X-Rays / Scans:								
Chest (PA and Lateral)	X							
Xeromammogram or Mammogram	X[3] and then 1x yearly[3]					Y[4]	Y[5]	
CAT Scan or Ultrasound of the liver	X[3]							
Bone Scan (Bone X-Ray)[2,3]	- within 1 month of mastectomy and once yearly thereafter						Y[3]	Y[3]
Quality-of Life Evaluation	X (day 1 of therapy)					X (as per Quality-of-Life protocol)		
Hormone Receptors: must be determined on primary tumor, if at all possible, at recurrent disease.								

X = For all patients prior to and during treatment time.
Y = All patients.
Z = Before Cycle 1, 2, 3, and 4. Then once every 3 months.
[2] = If hot spots: X-Ray of suspicious areas must be performed. If bone scan without demonstrable disease, repeat scan within 3 months.
[3] = Optional
[4] = Only every 6 months.
[5] = Once a year.

8. PATHOLOGY (Prof. Torhorst/Prof. Gusterson)

The responsible pathologist in each centre must be identified. The inclusion of each patient into the trial is dependent upon accurate assessment of the status of axillary lymph nodes. All negative lymph nodes must be examined from each patient. A minimum of 8 lymph nodes are to be examined for each patient.

The work of the pathologist is basic to the success of this study and includes the diagnosis, classification and grading of the primary tumour and of local spread as found in the biopsy and/or mastectomy specimen, including precise documentation of the total number of examined lymph nodes.

For the pathology study of the mastectomy specimen a standardized procedure is suggested, including the preparation for forwarding of a set of slides (one hematoxilin eosin stained, 4 unstained) and a copy of the clinic/hospital pathology report, and pathology form (Form P) to the Coordinating Center.

The intent of this paragraph is to describe what should be performed and which items should be submitted for a central review. Ludwig V will hopefully provide indications regarding the extent of pathological work-up of the axillary nodes. We should therefore not attempt to repeat the review performed in Ludwig V but rather plan for a tumour-biology oriented research program.

Special studies will be done according to a protocol prepared by Prof. Gusterson, the review Pathologist.

Guidelines are presented below.

8.1 Preparation of Specimen

Tissue for hormone receptor determination is removed and prepared (if not already performed).

8.1.1 The location of the tumour by breast quadrant and its relationship to the skin and fascia must be recorded.

8.1.2 The greatest two dimensions of the tumour should be measured (unfixed or fixed specimen). Record it on your report.

8.2 Fixative

As routinely done in your institution. Whenever possible a sample of primary tumour (0,5 g) and a sample of non-tumorous breast should be snap frozen without prior fixation and stored at -70°.

8.3 Sampling

8.3.1 Primary tumour

One hematoxilin eosin stained and 4 unstained slides of primary tumour should be submitted.

8.3.2 Lymph nodes

Dissection of the nodes can be undertaken before or after fixation of the specimen. Whenever possible the axillary fat should be divided into upper and lower parts, utilizing the sutures placed by the surgeon.

Remarks:

Care should be taken during excision and handling of lymph nodes, as compression of tissue during the procedure can result in distortion. Forceps should be applied only to the surrounding tissue and not to the node. The node should be removed intact rather than in fragments.

8.4 Embedding and Sectioning

Embed in paraffin or paraplast.

8.5 Staining and Mounting

Routine staining using hematoxilin eosin method is the accepted standard. Routine mounting on glass slides covered with glass slips is the accepted standard.

8.6 Central Pathology Review

Goal: To verify and establish uniform diagnoses in all cases. To correlate pathological and biological findings with clinical course of the disease.

8.7 Objectives

a. To receive:
   aa. A copy of the hospital/clinic pathology report.
   ab. A summary of the hospital/clinic pathology findings as provided on Form P.
   ac. A set of slides (1 stained and 4 unstained) from the primary tumour.
b. To classify all carcinomas using WHO classification.
c. To use the material for innovative studies to be defined.
d. To submit findings to the Statistical Center on a Form CPR (Central Pathology Review Form) which will also be sent to the contributing local Pathologist as a documentation of the Central Review of each case.
e. To report the results of all studies back to the contributing pathologist on a regular basis.
f. To be available for discussion and consultation with reference to any questions about the pathology of any case.
g. To present the pathology data at the Group's meeting.
h. To publish the results of the findings in the name of the Group.

9. STATISTICAL CONSIDERATIONS

See addendum II

This study is designed to test simultaneously the following two questions concerning adjuvant systemic therapy for pre- and perimenopausal patients with operable breast cancer and negative axillary nodes: i) Does the use of 6 cycles of CMF improve disease-free survival and overall survival? and ii) Does the use of Zoladex for a limited period of time reduce relapse and prolong survival?

Patients are randomized to receive one of four treatment programs as specified in Section 4.4.

Combining the evidence from the two comparisons C vs. A and D vs. B uses results from all randomized patients to provide information about the effect of CMF chemotherapy. Combining the evidence from the two comparisons B vs. A and D vs. C also uses results from all randomized patients to provide information about the effect of Zoladex. In addition, a sufficient number of patients should be treated in each of the four options to provide acceptable statistical power for separate pairwise comparisons between individual treatment programs.

The primary end point for evaluation of therapeutic effect will be disease-free survival (DFS) where all relapses (with special consideration of breast recurrence after breast conserving procedures), second primary tumours, and deaths without recurrence are counted as failures. Overall survival, patterns of relapse, and treatment-related side effects will also be assessed. Systemic disease-free survival will be monitored throughout the trial for possible early termination of patient entry.

For the purpose of sample size calculation, the baseline five-years DFS percentage for patients who enter this study and receive no adjuvant treatment is assumed to be approximately 70% (based on Ludwig V). The table below shows the total number of patients and total number of failures (all 4 treatment arms) required to detect specified differences in 5-year DFS with 80% power using a two-sided alpha=0.05 logrank test of main treatment effects assuming the no interaction model. It is assumed that the analyses are performed at a time when about 25% of the patients in the trial have failed.

Number of Patients* Required for the 2x2 Design** to Achieve 80% Power Using a Two-Sided Alpha=0.05 Logrank Test to Detect Specified Differences in 5-Year DFS Percentage Relative to a Baseline Percentage of 70%

Differences in 5-Year DFS %	Total Number of Patients (all 4 arms)	Patients Per Treatment Arm	Total Number of Failures
70% - 76%	1711	428	462
70% - 77%	1246	312	330
70% - 78%	946	237	246
70% - 79%	738	185	188
70% - 80%	592	148	148
70% - 81%	486	122	119
70% - 82%	404	101	97
70% - 83%	340	85	80
70% - 84%	292	73	67
70% - 85%	250	63	56

* Based on Freedman, L.S. Tables of the number of patients required in clinical trials using the logrank test. Statistics in Medicine I:121-129, 1982.

** Pairwise comparisons use 1/2 the total number of patients

The yearly accrual rate for node-negative premenopausal patients in Ludwig V was 165/year. Ludwig V, however, required randomization of patients within 36 hours of mastectomy. Furthermore, screening programs are identifying an increasing number of node-negative patients. Therefore, a total of 300 node-negative pre- and perimenopausal patients are anticipated to enter Trial VIII each year.

The table below shows the relationship between patient entry, accrual and follow-up periods, and differences in 5-year DFS percentage that can be detected with 80% power. Entry of 1200 patients will provide precise estimates of treatment effects within the separate subpopulations defined by estrogen receptor status (% ER+ vs. %ER- based on Ludwig V) and will strengthen the statistical power for separate pairwise comparisons. An accrual period of 4 years should be anticipated with additional follow-up of at least 5 years after the last entry. Longer follow-up will be required to determine if any early treatment differences are maintained.

Number of Patients, Accrual and Follow-up Times (Assuming 300/year) and 5-Year DFS Percentage Differences for the Treatment Comparison Detectable with 80% Power.

	1200 Patients (4 years of Accrual) (+ 5 Years of Follow-up)	
Overall Analysis 2 x 2 No Interaction	Total Number of Patients	DFS Percentage Differences
All patients	1200	7%
ER Positive	700	9%
ER Negative	500	11%
Separate Pairwise Treatment Comparisons (1/2 of Patients in each Analysis)		
All Patients	600	10%
ER Positive	350	13%
ER Negative	250	15%

9.1 Early Stopping Criteria for Treatment Option Regarding Patient Subgroups for Whom Therapy Might be Ineffective

During the discussion concerning this trial, the following concerns were expressed:

a. That LH-RH analogue might not affect the relapse rate for patients with ER-negative primaries.
b. That evidence exists demonstrating benefit from i.v. CMF therapy for N-negative patients with ER-negative primaries.

At yearly intervals (starting at the end of the second year of accrual) the systemic disease-free survival (SDFS) will be evaluated in a coded fashion and patient entry to the inferior treatment group will be suspended in case a difference of $p \leq 0.01$ (Pocock boundaries: Pocock, S.J. Group sequential methods in the design and analysis of clinical trials. Biometrika 64:191-199, 1977) is observed within any subgroup defined by estrogen receptor status.

Two pairwise comparisons are planned for each evaluation: for concern a) the analysis will be performed between LH-RH alone compared with no adjuvant therapy; for concern b) the analysis will be performed between CMF and no CMF treatments (2 x 2 factorial analysis).

Considering three interim analyses of the data, for 2 specific questions the overall chance of declaring SDFS differences significant when no differences exist is 6%.

10. ETHICS COMMITTEE REVIEW AND PATIENT INFORMED CONSENT

10.1 The protocol must be submitted to the relevant local ethics committee and approval must be obtained from the said committee before commencing local participation in the study.

10.2 A letter confirming the said approval of an ethics committee must be sent to the Coordinating Center.

10.3 Informed consent must be obtained from all patients taking part in the study in accordance with the principles set out in the Declaration of Helsinki (as amended) or the laws and conventions prevailing in the country where the patient is being treated whichever represents the greater requirements as regards the protection of the patient.

10.4 **Documentation recording the obtaining of informed consent in accordance with section 10.3 must be sent to the Coordinating Center.**

11. ADVERSE DRUG REACTION REPORTING

11.1 All severe or life-threatening adverse drug reactions thought to be associated with "Zoladex" must be promptly (within 24 hours) reported to the Coordinating Center (FAX or telephone call).

11.2 In addition, all severe or life threatening adverse drug reactions thought to be due to the combination of chemotherapy and "Zoladex" must be reported.

11.3 Furthermore, all side effects of treatment regardless of cause are to be recorded on the Menstrual Status, Treatment and Morbidity Form (Form D+M), including those already recorded on other forms (4.1, 4.2).

12. RECORDS TO BE KEPT

The keeping of accurate and consistent records is essential to a cooperative study.

The following forms are to be submitted at the indicated times by the participating Institutions for each patient:

Form IC	Informed Consent Form	To be sent to the Coordinating Center within 1 month after randomization (see Appendix IV)
Form B	Clinical Form	Submitted within one month of resection
Form C	Surgery Form	After complete postoperative recovery. Document all postoperative complications giving etiology, treatment and outcome
Form F	Hormone Receptor Analysis Form	At surgery and at each recurrence of disease (whenever a hormone receptor analysis is performed)
Form P	Pathology Form	Completed by pathologist and submitted to the Coordinating Center with a copy of the hospital/clinical pathology report and a set of five slides (1 stained and 4 unstained) from the primary tumour within 3 months after randomization
Form D+M	Menstrual Status, Treatment and Morbidity Form	One column completed monthly for all patients (for 36 months) and submitted every 3 months. THE MENSTRUAL STATUS INFORMATION MUST BE COMPLETELY FILLED IN EACH MONTH FOR EVERY PATIENT.
Form R	Radiotherapy	To be completed at the end of radiotherapy
Form E	Follow-up Form	Approximately every 3 months with adjustment according to the treatment schedules during the first 2 years, every 6 months during the next 3 years, and yearly thereafter

Form QL	Quality-of-Life Form	To be completed on day 1 of therapy, on day 1 of the third cycle of CMF or on day 1 of 3rd LH-RH application, then every 3 months for the next 2 years. A QL Form should also be completed one month and again at six months after relapse of any type.
Form NC	Non-Compliance Form	To be completed when QL Form will not be submitted. Once the Coordinating Center has been notified that the patient has refused to participate in any future assessments, subsequent NC-Forms are not required.

Two additional forms are initiated at the central offices and sent to the participating institutions:

The **Form A** (Confirmation Form) is completed by the Coordinating Center and mailed to the Statistical Center and to the Participating Institution to confirm the randomization and treatment assignment.

The **Form CPR** (Central Pathology Review Form) is completed by the Central Review Pathologist and returned to the Coordinting Center for distribution to the Statiscial Center and to the local pathologist.

12.1 Submission of Forms

After completion of each form, the bottom (pink) copy should be removed and kept on file at the participating institution. The two remaining copies (the top white and the middle yellow copies) should be sent to

International Breast Cancer Studies
Coordinating Center
Konsumstrasse 13
CH-3007 Bern, Switzerland.

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RADIATION THERAPY FOLLOWING SEGMENTAL MASTECTOMY

Since the local therapy is not the prime question of these studies, details will be left to the discretion of participating institutions provided that (i) timing follows outlines given in the protocol, and (ii) therapy is NOT directed to axilla or supraclavicular nodes and only to the parasternal nodes as required to cover the breast. Radiation following segmental mastectomy is intended to be delivered in a cancericidal dose to all remaining ipsilateral breast tissue. The dose is chosen to produce sterilization of occult tumor foci which may possibly be present in the residual breast tissue following segmental mastectomy and in order to avoid distortion or fibrosis of the breast as a result of radiation. The following guidelines are offered as a suggestion. Radiotherapists are encouraged to contact Professor Arne Wallgren concerning details of their own techniques.

1. Area to be treated and technique

It is the intent of radiation therapy to treat the skin, breast tissue, and entire scar of the breast. No attempt will be made to include axillary, supraclavicular, interpectoral and internal mammary lymph nodes. The latter lie at the medial edge of the treatment field and may sometimes either partially or wholly be included. No special attempt should be made to exclude these since this would interfere with irradiation of the entirety of the breast.

When segmental mastectomy and axillary dissection are performed through separate incisions, if the scar of the axillary dissection is extrinsic to the breast, no irradiation will be specifically directed to that scar.

If the axillary dissection scar is in continuity with that of the segmental mastectomy, no special attempt will be made to irradiate that portion of the scar which is beyond the breast tissue.

A. Position of the Patient. Patient lies supine, straight (no pillows are used unless dorsal convexity of patient is extreme), upper arm abducted 90° with forearm supported in upright position by vertical arm board. If CT-scans are used for individual planning purpose, the arm may have to be abducted 180° and rest above the head for this investigation. The same position should then be used during the treatment.

B. Description of Radiation Field. The breast (and the chest wall) are treated through opposing tangential fields to avoid direct irradiation of the lung. Beam splitting devises or an outward tilting of the fields of approximately 5° may be recommended to reduce the dose in the lung.

If no individual planning of doses is performed the following guide-lines should apply:

The medial border lies along the midsternal line.

The lateral border lies along the mid-axillary line. If the scar extends beyond this line, the lateral border may, within limits, be moved posteriorly to include the entire scar. The extent to which this line may be moved posteriorly should be guided by the amount of lung tissue which would be irradiated if this border is parallel-opposed to the medial border. If the irradiated slice of lung tissue exceeds a width of 5 cm, the lateral portal should be left along the mid-axillary line and the end of the surgical scar treated by superficial irradiation.

The inferior border of the tangential field is drawn horizontally across the hemithorax at a level about 2 cm, below the inframammary fold. This line can be drawn by extension from the contralateral fold if the ipsilateral breast is distorted.

The superior border is located along a horizontal line which bisects the sternomanubrial junction (angle of Louis). If necessary, this border may be moved superiorly to be sure that the entire breast and the tail of the breast are included. If the scar extends above this boundary, the line should be moved superiorly so as to include it entirely.

C. Breast Target and Field Boundaries. If individual planning of the fields is performed the boundaries of the target area have to be determined individually using all available information. What was above described about including the scar is also applicable in the individual dose planning.

D. Angle of Tangential Fields. The angle of the tangential treatment fields can be determined with a rolling ball, inclinometer bridge, or by rotating the head of the machine until the back pointer and the front pointer lie respectively on the lateral or medial field boundaries. Beam splitting devises or tilting of the fields about 5° according to an individual plan may decrease the dose in the lung. It is also essential to rotate the collimator in order to include all breast tissue and remove as far as possible lung tissue from the irradiated volume. The fields should be wide enough to irradiate at least 1 cm of air outside the breast.

E. Verification of Irradiated Volume. Preferably the field setup should be done on a radiation simulator. Verification films should also be taken in treatment position with a treatment beam. If more than 5 cm of lung tissue is includes in the beam the lateral field boundary is probably located too far posteriorly.

F. SSD: 80 cm or more.

2. Dosage and Time of Onset

A. Time of Onset of Therapy. The study concerns differences in the scheduling of chemo-, hormonal therapy, or combination of both. In order not to interfere with this study and make these patients comparable to those treated by a total mastectomy, irradiation should be started 2 weeks after the last chemotherapy course, or within 3 months for control (no adjuvant therapy patients) and for patients receiving LH-RH analogue alone.

B. Dose. A minimum dose of 50 Gy should be given. This dose is calculated at a specification point at a depth of two-thirds distance between the skin overlying the breast and the base of the tangential fields at mid-separation. This point should not be located in lung tissue. This depth generally ranges from 3 - 7 cm.

C. Dose Fractionation. The dose is given at a rate of 10 Gy per week (daily increments of 2 Gy per day, 5 days per week with no split) calculated at the minimum dose point. Both tangential fields will be treated daily, 1 Gy, T.D. given to each.

TOXICITY GRADING (Trial VIII)

Please use the following table when reporting complications. Any life-threatening toxicity attributable to treatment should be reported to the study coordinator immediatly.
For any toxicity not specifically described, grades correspond to the following terms:
1: mild; 2: moderate; 3: severe; 4: life-threatening

Codes*		0	1	2	3	4
WBC	Leukopenia	≥ 4000	2500 - 3999	1000 - 2499	< 1000	
Plate-	Thrombocytopenia	≥ 100000	75000 - 99999	50000 - 74999	< 50000	
N	Nausea & Vomiting		Nausea	N & V controllable	Vomiting intractable	
D	Diarrhea		No dehydration	Dehydration	Grossly bloody	
S/M	Stomatitis/ Mucositis		Soreness	Ulcers - can eat	Ulcers - cannot eat	
11	Anemia	Hb > 11	Asymptomatic Hb 10 - 11	Slight symptoms Hb 8 - 10	Symptoms - transfusion required	
12	Neutropenia	> 1900	1500 - 1900	750 - 1499	< 750	
13	Hemorrhage (non-vaginal)		Minimal	Moderate; not debilitating	Debilitating	Life-threatening
14	Vaginal Bleeding		Mild	Moderate	Severe	Life-threatening
15	Infection (local systemic)		No active treatment	Active treatment required	Major intervention required	Life-threatening septic shock
16	Anorexia		Partial food aversion	Complete food aversion		
17	Epigastric pain		Occasional - no treatment required	Controlled with treatment		
18	Pulmonary		Mild symptoms	Moderate symptoms	Severe symptoms intermittent O2	Assisted vent. or continuous O2
	Pneumonia is considered an infection and should not be graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment					

Codes*		0	1	2	3	4
19	Neurological: CNS PN		Mild anxiety, mild headache insomnia, fatigue, malaise Decreased deep tendon reflexes mild paresthesia, mild constipation	Mild hyperactivity, severe anxiety, moderate headache, somnolence, tremor Absent deep tendon reflexes, mild weekness, severe paresthesia, severe constipation	Confused or manic, severe headache, cord dysfunction, confined to bed due to CNS dysfunction Disabling sensory loss, constipation severe weekness, bladder dysfunction, severe PN pain	Seizures, suicidal, coma Respiratory dysfunction, 2° weekness, constipation requiring surgery, paralysis confining patient to bed, wheelchair
20	Depression		Occasional	Conrolled by treatment	Uncontrollable	Suicidal
21	Skin (Allergic)		Transient erythema	Vesiculation	Ulceration	
22	Alopecia		Partial	Complete		
23	Renal: BUN mg% Creatinine	 ≤ 20 < 1.2	 21 - 40 1.3 - 2.0	 41 - 60 2.1 - 4.0	 > 60 > 4.0	 Symptomatic Uremia
24	Cystitis		Mild	Moderate	Severe (hemorrhagic)	Life-threatening
	(Urinary tract infection should be graded under Infection (Code 15). Hematuria resulting from throbocytopenia is graded under Hemorrhage (Code 13)).					
25	Hepatic: SGOT Alkaline phos. Bilirubin	 <1.5 x nl <1.5 x nl <1.5 x nl	 1.5-2 x normal 1.5-2 x normal 1.5-2 x normal	 2.1 - 5 x normal 2.1 - 5 x normal 2.1 - 5 x normal	 > 5 x normal > 5 x normal > 5 x normal	
	(Viral hepatitis should be recorded as Infection (15) rather than liver toxicity)					
26	Headache		Occasional, mild	Constant, mild	Severe	
27	Muscle weakness		Slight	Moderate	Severe, debilitating	

* FORM D+M only

Codes*		0	1	2	3	4
28	Hyperglycemia: Non-diabetic		Glycemia 140 - 180 mg%	Glycemia >180 mg%, contol-lable with diet	Requiring insulin	Keto-acidosis
	Diabetic		Adjustable with diet	Requiring <25% increase in insulin dosage	Requiring >25% increase in insuline dosage	Keto-acidosis
29	Hypercalcemia		<2.6 mmol/l	2.6-3.0 mmol/l without symptoms	< 3.0 mmol/l with symptoms	≥3.0 mmol/l, with or without sympt.
30	Hypertension: Pre-existing		Hypertension controlled by occasional treatment	Hypertension contolled by chronic oral medication	Requiring hospit-alisation, treat-ment with i.v. drugs	Uncontollable
31	Hot flashes		Occasional - not requiring treatment	Frequent - requiring treat-ment		
32	Euphoria		Slight	Moderate	Severe	
33	Thrombosis, Phle-bitis, Embolism		Local, oligo-symptomatic	Painful, with or without edema	Severe edema, dyspnea (no O2)	Pulmonary emboli-sm, requiring O2
34	Edema		Notdebilitating	Debilitating		
35	Lymphedema		Notdebilitating	Debilitating		
36	Weight gain (not edema)		<5% body weight	5-10% body weight	> 10% body weight	
37	Eye disorders		Tearing	Tearing and pain	Objective lesion (e.g. punctate keratitis)	
38	Joint pain		Slight	Moderate	Severe	
39	Wound healing		Delayed less than 4 weeks	Delayed more than 4 weeks	Major interven-tion required	
40	Amenorrhea (treatment ind.)		No period			
41	Other treatment problems, specify		Mild	Moderate	Severe	Life-threatening
ZOLA-DEX Sec-tion	Local reaction to ZOLADEX (cutaneous)		Erythema	Vesiculation	Ulceration	Necrosis requi-ring surgical intervention

* FORM D+M only

INTERNATIONAL BREAST CANCER STUDY VIII
Psychosocial Assessment (Quality of life)

1. Introduction

Preliminary findings of recent prospective studies suggest that the initial psychosocial reaction of breast cancer patients at diagnosis may be a prognostic indicator of outcome (1,2,3,4). Patients showing a strong emotional coping reaction seem to do better than patients who deny having any difficulties. On the other hand patients with initial helplessness/hopelessness (low level of well-being) seem to do worse. As there are contradictory results (5), further studies may clarify the controversy (6).

In addition to the traditional measures of outcome (disease- free survival, overall survival) the assessment of different aspects of quality of life is considered in clinical trials. The goal is to improve quantity and quality of survival. This is of special importance in the adjuvant situation.

2. Objectives

There are two hypotheses to evaluate:

1. The level of early coping/well-being of the patient at diagnosis can be used as a prognostic indicator of outcome.

2. The coping/wellbeing of the patients is different for different treatment arms. The first hypothesis is tested in a longitudinal design for all patients, independent of the differing treatment arms, with one measurement of coping/wellbeing within the first 6 weeks after definitive surgery. In addition, this hypothesis will be refined, using also the assessments at month 3,6 and possibly 9 and 12. Thereby the intra-individual differences of coping/wellbeing at the different points in time will be used to classify the patients into several groups of distinct coping/wellbeing pattern, e.g. initial crises and consecutive improvement / stable crises, no improvement / no initial difficulties and consecutive worsening / no initial and later difficulties (7). So far an eventual prognostic psychosocial factor has never been tested in such a large sample with biologically well-defined subgroups. The second hypothesis is evaluated by comparison of different groups with serial measurements of coping/wellbeing over time. The longitudinal assessments of global coping/well- being is considered as a new endpoint in the evaluation of clinical trials with breast cancer patients. The questionnaire does not evaluate observer-selected criteria such as disease symptoms, but rather the patients' subjective appraisal of their well-being and amount of adjustment needed to cope with their illness - a central issue absent in most other studies. The evaluation of the two hypotheses separately for each study may clarify how the subtle differences of the biological subgroups may influence psychosocial factors.

3. Methods

a. Measurement instruments:
To assess coping, the SLCU (Subjective Life Change Unit Score), a simple self-assessment scale developed by Rahe (8), is used. This scale has been used under different names and is now called PACIS (Personally Perceived Adjustment to Chronic Illness Scale, 7). The patient is asked to rate the amount of adjustment

needed to cope with her illness on a scale from 0 to 100. The scale has been used with good compliance in the Swiss subset of patients in Ludwig Study V and in several other studies with cancer patients (5,9,10,11). Rogentine et al. (9) found in a prospective study of melanoma patients that the amount of adjustment needed to cope with this illness (SLCU) is a valid prognostic factor in predicting one-year disease-free survival post-operatively.

Well-being is assessed by the Bf-S, a short, self- administered adjective checklist with well-documented psychometric properties developed by v. Zerssen (12,13). Our experience with this scale in a lung cancer protocol of the Swiss Cooperative Group (SAKK 15/84) gave us the opportunity to simplify the design of the form for better patient understanding. In a current Swiss study of coping processes in breast cancer patients using this scale, the items numbered 2,9,15,18 and 28 provoked negative reactions in some patients. For this reason we have exchanged these items with generally acceptable items from the parallel version of the scale (Bf-S'). These modifications have been done in consultation with the author of the scale. We are convinced that the changes will contribute to a good compliance. In addition to the Bf-S, important aspects of well-being are assessed by three LASA scales, "Physical well-being", "Mood", and "Appetite". These scales were used by the Australian and the New Zealand Breast Cancer Trial Group, and were proven to be sensitive, feasible and valid (14,15,16).

A general problem in self-assessment of subjective appraisal is the patients' tendency to give socially desirable answers. This has to be considered carefully in a psychosocial study of cancer patients (17). According to the empirical experience with the SLCU (5,9,10,11), the Bf-S (18-21), and the three LASA scales (14,15), no considerable bias is expected. The use of different languages has considerably reduced the choice of adequate instruments. An important aspect of international quality of life research is the possibility of cross-cultural differences in patient responses.

b. Timing of measurements: Patients are asked to fill in the questionnaire within six weeks of surgery (e.g. day 1 of treatment), 2 months later (e.g. day 1 of therapy cycle 3,) or eight weeks after Zoladex start) and every three months thereafter for a period of two years. A QL form should be filled in one month and 6 months after recurrence of any type. Filling in the questionnaire required an average of ten minutes per patient in a comparable study in Switzerland (SAKK 15/84).

4. Feasibility

A comprehensive assessment of quality of life would imply high expenses in research staff and patient time. Because of limitations in an international protocol, the interest has to be focused on only a few aspects of quality of life. This protocol is tailored to the limited possibilities of an international trial. The feasibility is granted by minimal expense in data collection, a questionnaire easily understandable for the patient and available in all 11 languages of the participating centers.

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INFORMED CONSENT DOCUMENT

Trial:

Patient: *Rand. No.:* *Ident.-No.:*

1) I have explained the procedures to be followed.

2) I have explained the risks of the adjuvant treatment program.

3) I have explained the benefits of the adjuvant treatment program.

4) I have discussed alternative treatments.

5) I have explained the right to withdraw from the participation in the program.

Physician's Signature: ..... Date: .....

Witness' Signature: .....