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

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

July 29, 1999

RE: - CLOSURE OF IBCSG TRIALS

Dear colleagues

Please note that study :

- IX
- 12-93
- 13-93
- 14-93

will be closed per 01. August 1999. Our ongoing projects are:

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

BEST REGARDS

Castiglione

PD DR. MONICA CASTIGLIONE
STUDY COORDINATOR

International Breast Cancer Study Group

Trial IX

Addendum 12

Reasons 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 IX.

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

Specifically:

- Patient Population: Delete "ER- or ER unknown."
- Add Section 3.2.12, under "Criteria for Patient Ineligibility":
  3.2.12 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 IX

Addendum 11

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:

- Delete Addendum 4.
- Amend your current version 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 10, Form QL by crossing out the second sentence:
  [~~A QL Form should also be completed one month after relapse 6 months thereafter (+ 1 month).~~]
- 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 after recurrence of any type and 6 months later.~~]

Activation Date:

1 December 1996

International Breast Cancer Study Group

Trial IX

Addendum 10
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 10 and 11) 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 10.1.

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 IX

Addendum 9

This addendum includes two protocol modifications:

1. The target sample size will increase from 1200 to 1600 patients to enable more precise estimation of treatment effect size.

2. Interim analysis monitoring plans will be modified to accomodate the increased target sample size.and allow early termination of accrual.

Activation Date:

June 1, 1995

Addendum 9, June 1, 1995
Revised Statistical Considerations for IBCSG Trial IX - Recommended by the Scientific Committee on March 4, 1995

The following two changes will be made to the statistical considerations:

1. The total sample size will be increased from 1200 to 1600 patients.

2. Formal statistical rules will be applied for potential early stopping.

Rationale:
Ten-year follow-up data for the 496 postmenopausal, node-negative patients in Trial V with known estrogen receptor values suggested an interaction between estrogen receptor status of the primary tumor and the effectiveness of a single cycle (days 1 and 8) of i.v. CMF perioperative chemotherapy (p= 0.004 for DFS; p=0.04 for OS). Postmenopausal patients with ER-negative tumors benefitted significantly from the single perioperative cycle of adjuvant chemotherapy compared with surgical controls (10-year DFS percents: 71% (n= 102) versus 48% (n= 58), p= 0.0006; 10-year OS percents: 77% versus 62%, p= 0.01). In contrast, the results for patients with ER-positive tumors were the same regardless of treatment group (10-year DFS percents: 57% (n= 231) versus 57% (n= 105), p= 0.91; 10-year OS percents: 73% versus 75%, p= 0.84). Therefore, a sufficient number of patients should be enrolled in Trial IX to allow separate analyses to be conducted according to estrogen-receptor status of the primary tumor.

Revised Sample Size:
The original sample size for Trial IX was 900 patients, 600 with ER-positive tumors and 300 with ER-negative tumors. This was increased to 1200 patients according to addendum 5 issued in June, 1993, to obtain 300 patients with ER-negative tumors (given that 25% rather than 33% of the entries were ER-negative). As of December 31, 1994, 1026 eligible patients had been enrolled, 688 (67%) ER-positive, 260 (25%) ER-negative, and 78 (8%) ER-unknown. The overall sample size of 1200 provides an 80% power to detect a disease-free survival difference of 7.5% (75% to 82.5% 5-year DFS) corresponding to a 33 percent reduction in the risk of an event. By increasing the sample size to 1600 patients, the trial will have an 80% power to detect a disease-free survival difference of 6.0% (75% to 81%) overall corresponding to a 26.8 percent reduction in the risk of an event. This increase will also enable an analysis for ER-positive tumors to detect a 7.5% difference (33% relative risk reduction) and an analysis for ER-negative tumors to detect an 11.6% difference (50% relative risk reduction). The total sample size should be increased to **1600 patients**. At the current rate of 168 patients enrolled annually, this objective will be achieved in June, 1998.

Interim Monitoring:
Interim monitoring will be performed to allow early termination of accrual to the study. Two interim analyses are planned prior to reaching five years of median follow-up. The main analysis will be conducted in coded fashion to determine if sufficient evidence exists to modify the protocol on the basis of observed differences in systemic disease-free survival (SDFS). With the increased total sample size of 1600 patients, the target number of total events for disease-free survival comparisons is 350. As of December 31, 97 patients experienced events and 77 of these were systemic events. Thus, about 80 percent of all events are systemic events and the target number of systemic events for the study is anticipated to be 280. Two interim analyses and one final analysis will be planned after 100, 195 and 280 systemic events, respectively. The sequential boundary used is based on an O'Brien-Fleming type use function, as described by Kim and Tsiatis. The p-values to be used at the 3 analysis times for the two-sided logrank tests are 0.0003, 0.015, and 0.045. We anticipate that 30 more systemic failures will be observed during 1995. Therefore, the first interim analysis of Trial IX will be conducted in early 1996 for review by the Scientific Committee.

INTERNATIONAL BREAST CANCER STUDY GROUP

Trial IX

Addendum 8

June 1, 1995

- The follow-up schedule for this trial has been modified. Please replace Table 7.6 with the attached modified version. Please review the reduced number required tests and frequency of follow-up visits.
- CA 15-3 is optional, but strongly encouraged.
- A Follow-up Form (E) is required yearly starting year 3. (Modification of Section 12 of the protocol.)
- Quality of Life forms <u>are no longer required</u> at months 15 and 21.
  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.

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

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

X = For all patients.
1 = For disease-free patients only.
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, as clinically indicated.
4 = Optional, but strongly encouraged.
5 = Until treatment failure. Also required within 1 month and at 6 months after treatment failure.

International Breast Cancer Study Group

Trial IX

Addendum 7

Reason for Addendum:

Information from NSABP protocol B-14 has shown that tamoxifen increases the risk of uterine cancer. After an average of eight years of follow-up, the annual risk observed in this large-scale trial of breast cancer patients taking 20 mg of tamoxifen daily is about two per 1,000 women. This level of risk is approximately three times greater than that of a similar group of women in the general population in the United States. (1)

Reference

(1) Fisher B, Costantino JB, Redmond CK, Fisher ER, Wickerham DL, Cronin WM, Other NSABP Contributors. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the national surgical adjuvant breast and bowel project (NSABP) B-14. JNCI 7: 527-537, 1994.

Summary of Changes:
Section 5.3 has been changed. Please replace section 5.3 with the following:

5.3 **Side effects of tamoxifen**
Hot flashes, nausea, vaginal discharge or abnormal vaginal bleeding have been reported. Hypercalcemia, bone pain, and retinopathy are rare. Beneficial effects upon lipid and bone metabolism have been reported. Because of the increased risk of uterine cancer, patients receiving tamoxifen should be promptly evaluated in the event of a pelvic complaint. Investigators should remain aware of current recommendations for the gynecological monitoring of asymptomatic women during and after tamoxifen therapy. Any case of endometrial cancer should be promptly reported to the Coordinating Center with extensive clinical therapeutic details. Modification of tamoxifen dosage is rarely indicated. No standard dosage modifications are prescribed.
Side effects are graded in protocol Appendix II.

Activation Date:

1 September 1994

International Breast Cancer Study Group

Trial IX

Addendum 6

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

INTERNATIONAL BREAST CANCER STUDY GROUP

STUDY IX

ADDENDUM 5

This addendum includes two protocol modifications:

1. **The target sample size will increase from 900 to 1200 patients to enable more precise estimation of treatment effect size.**

2. **Interim analysis monitoring plans will be implemented to allow early termination of accrual.**

Addendum 5, June 1, 1993
Revised Statistical Considerations for IBCSG Study IX
Recommended by the Scientific Committee on May 25, 1993

The following two changes will be made to the statistical considerations:
1. The total sample size will be increased from 900 to 1200 patients.
2. Formal statistical rules will be applied for potential early stopping.

Rationale:
Eight-year follow-up data for the 469 postmenopausal, node-negative patients in Trial V with known estrogen receptor values suggested an interaction between estrogen receptor status of the primary tumor and the effectiveness of a single cycle (days 1 and 8) of i.v. CMF perioperative chemotherapy (p= 0.002). Postmenopausal patients with ER-negative tumors benefitted significantly from the single perioperative cycle of adjuvant chemotherapy compared with surgical controls (8-year DFS percents: 77% (n= 102) versus 47% (n= 58), p= 0.0001; 8-year OS percents: 82% versus 65%, p= 0.006). In contrast, the results for patients with ER-positive tumors were the same regardless of treatment group (8-year DFS percents: 61% (n= 231) versus 58% (n= 105), p= 0.93; 8-year OS percents: 82% versus 83%, p= 0.88). Therefore, a sufficient number of patients should be enrolled in Trial IX to allow separate analyses to be conducted according to estrogen-receptor status of the primary tumor.

Revised Sample Size:
The original sample size for Trial IX was 900 patients, 600 with ER-positive tumors and 300 with ER-negative tumors. As of November 26, 1992, 689 eligible patients had been enrolled, 445 (65%) ER-positive, 168 (24%) ER-negative, and 76 (11%) ER-unknown. To achieve the goal of 300 patients with ER-negative tumors (80% power to detect an improvement in 5-year DFS from 75% to 87.5%), the total sample size should be increased to 1200 patients.

Interim Monitoring:
Interim monitoring will be performed to allow early termination of accrual to the study. Two interim analyses are planned prior to reaching five years of median follow-up. The target number of events for the study is 260, so interim analyses will be planned after 90 events and after 180 events have been observed. The main analysis will be conducted in coded fashion to determine if sufficient evidence exists to modify the protocol on the basis of observed differences in systemic disease-free survival (SDFS). The sequential boundary used is based on an O'Brien-Fleming type use function, as described by Kim and Tsiatis. The p-values to be used at the 3 analysis times for the two-sided logrank tests are 0.0003, 0.015, and 0.045.

INTERNATIONAL BREAST CANCER STUDY GROUP

STUDY IX

ADDENDUM 4

One Quality of Life Form should be completed one month after relapse of any type and 6 months thereafter (± 1 month).

IBCSG Operations Office, Bern
MC, 27.2.90

INTERNATIONAL BREAST CANCER STUDY GROUP

STUDY IX

ADDENDUM 3

Tamoxifen treatment has to be administered for the duration of

5 years

IBCSG Operations Office, Bern
MC 27.2.1990

INTERNATIONAL BREAST CANCER STUDY IX

ADDENDUM II

TAMOXIFEN has to be given for the duration of **4 years** (instead of 3 years).

Bern, May 1, 1989

INTERNATIONAL BREAST CANCER STUDY IX

ADDENDUM I

Chest X-ray during follow-up for N- patients is required only **once a year.**

Bern, May 1, 1989

INTERNATIONAL BREAST CANCER STUDY IX
ADJUVANT THERAPY IN N- POSTMENOPAUSAL PATIENTS WITH OPERABLE BREAST CANCER

Patient population

Postmenopausal 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 (+/- radiotherapy), and who are classified as T1a,b,c, T2, T3, N0 (pathologically negative), M0 (UICC 1987), ER+, ER- or ER unknown.

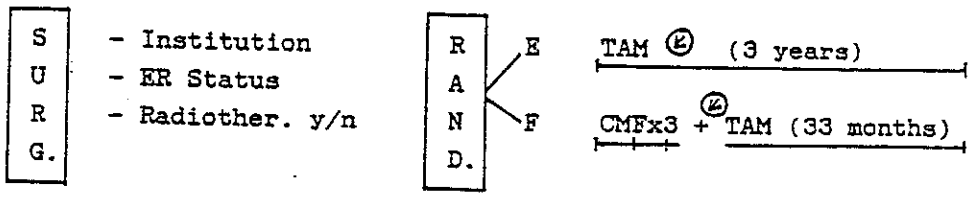
Patient entry

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

Study design: IBCS IX

POSTMENOPAUSAL N-

Stratification



TREATMENT SCHEDULES

oral CMF
C: 100 mg/m² orally days 1-14
M: 40 mg/m² i.v. days 1 and 8 q 28 days
F: 600 mg/m² i.v. days 1 and 8

TAM: Tamoxifen 20 mg daily for 3 years (Arm E) and 33 ms. (Arm F)

(K) radiotherapy (if planned), if less than total mastectomy

RANDOMIZATION
IBCSG-Operations Office, Seidenweg 63, CH-3012 Bern (Switzerland)
Telephone: (0041) 31 24 41 01
Telefax: (0041) 31 24 41 03
Telex: SAKK CH 912 539

INDEX

1. INTRODUCTION

The use of tamoxifen has provided a reduction in deaths due to breast cancer in postmenopausal node-positive and node-negative (N+ and N-) patients (1), but the benefit of tamoxifen treatment may be restricted to patients with ER+ tumors (2,3,4,5).

1.1 A "standard" adjuvant treatment for all postmenopausal patients classified as N+ and ER- has not yet been defined. For the entire postmenopausal patient population, however, the combination of CMFp + TAM (chemo-endocrine therapy) improved disease-free survival as compared with CMFp or surgery alone (6), or with p + TAM or surgery alone (2). In a retrospective analysis of the data from these two trials, patients with ER- tumors were also found to have benefited significantly (7) from the combined regimen. Thus, a prospective evaluation of alternative chemo-endocrine vs. endocrine treatments in this sub-population should be given high priority. In IBCSG Study VII the schedule of concurrent CMF (3 cycles) and continuous tamoxifen for three years is being evaluated in node-positive patients. In Study IX, a sequential combined modality schedule (i.e., 3 cycles of CMF followed by continuous tamoxifen for three years after completion of the cytotoxic treatment) will be compared to tamoxifen alone.

1.2 The optimal duration of treatment with tamoxifen in postmenopausal patients has not yet been established, but an ongoing ECOG randomized trial comparing two vs. five years' treatment with tamoxifen may ultimately provide an answer to this question. A minimum of three years of tamoxifen will be considered standard until additional evidence favoring a longer duration becomes available.

1.3 Results from the NSABP trial B-06 indicate that lumpectomy and local radiotherapy provided equivalent control of disease as compared with total mastectomy (8,9). 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 T1 tumors (10,11). Furthermore, similar results have emerged recently from an EORTC study (12). 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 tumors.

2. OBJECTIVES

2.1 Trial IX (postmenopausal N- patients)

a. To compare the combination of three cycles of chemotherapy (CMF) followed by tamoxifen versus tamoxifen alone in terms of disease-free survival, patterns of relapse and overall survival.

b. Quality of life Study: see Appendix III

3. PATIENT SELECTION

3.1 Criteria for Patient Eligibility

3.1.1 Postmenopausal patients

This group will include patients who are:

a. > 52 years, with at least 1 year of amenorrhea; or
b. ≤ 52 years, with 3 or more years of amenorrhea; or
c. > 55 years, and who have had a hysterectomy, without bilateral oophorectomy or
d. have biochemical evidence of cessation of ovarian function (in questionable cases).

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

3.1.3 Patients must have had

a. either total mastectomy or, optionally if the tumor 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.

3.1.4 Eight lymph nodes histo-pathologically examined.

3.1.5 Tumor confined to the breast with no detected metastases.

3.1.6 Adequate marrow function (WBC > 4000/mm3 and platelets > 100,000/mm3).

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

3.1.8 Informed consent according to the criteria established within the individual countries.

3.2 Criteria for Patient Ineligibility

Not eligible are:

3.2.1 Patients with any axillary node involvement;

3.2.2 Patients who have malignant breast tumors other than carcinoma;

3.2.3 Patients who have T4 tumors 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.

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

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

3.2.6 Premenopausal patients (see 3.1.1)

3.2.7 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.

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

3.2.9 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.

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

3.2.11 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 surgery, so that the adjuvant treatment can be started within the same period of time.

4.1 The following information is required at time of randomization:

4.1.1 MENOPAUSAL STATUS (see Section 3.1.1 for definition)

4.1.2 ESTROGEN RECEPTOR STATUS

ER+ = ≥ 10 fmol/mg cytosol protein*
ER- = < 10 fmol/mg cytosol protein*
ER unknown: no determination possible

---

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

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

4.1.4 INSTITUTION

4.1.5 METHOD OF INITIAL DIAGNOSIS
- mammography alone as only evidence
- other

4.2 Stratification

The randomization will be stratified by INSTITUTION, ESTROGEN RECEPTOR STATUS, AND RADIATION THERAPY TO THE BREAST PLANNED OR NOT.

4.3 Randomization

4.3.1 patients will be randomized to receive one of the following two treatment options:

- E : TAMOXIFEN 20 MG DAILY FOR 36 MONTHS
- F : CMF X three 28-DAY CYCLES FOLLOWED BY TAMOXIFEN 20 MG DAILY FOR 33 MONTHS.

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 3 cycles.

5.1.2 Tamoxifen 20 mg orally daily continuously for patients receiving either tamoxifen alone or tamoxifen after 3 cycles of CMF. Patients who received three cycles of CMF should start Tamoxifen treatment on Day 15 of Cycle 3.

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 tumor 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 1,500-1,900	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.

5.3 Side effects of tamoxifen

Hot flashes, nausea, occasional vomiting and other rare side effects such as hypercalcemia, have been reported in patients treated with tamoxifen.

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 tumor, 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.

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.

6.1.1 Local and regional failure

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

A tumor 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

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

Criteria

Opposite breast or 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 tumor

6.2 Treatment Failure

6.2.1 Local Treatment Failure

Acceptable evidence of tumor in any soft tissues of the ipsilateral chest wall, operative scar or breast, if a less than total mastectomy procedure was performed. This includes the area bounded by the midline of the sternum, superiorly by the clavicle, along the lateral edge of latissimus dorsi and inferiorly, 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.

Special consideration should be given to the documentation of local 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 tumor 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 tumor 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 tumor in all areas except those described above (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 vital 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 tumor 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 administration or every three months during tamoxifen 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 according to the grades defined in Appendix II. The Form C must include all complications occurring in the postoperative period.

7.6 Required investigations

See Table 7.6 on next page.

8. PATHOLOGY (tentative)

The responsible pathologist in each center must be identified. The inclusion of each patient into the trial is dependent upon accurate assessment of the status of axillary lymph nodes. All grossly negative lymph nodes must be examined from each patient.

The work of the pathologist is basic to the success of this study and includes the diagnosis, classification and

7.6 TABLE OF STUDY PARAMETERS

REQUIRED	Prior to Rand.	Days 1 & 8 of Cycle During Cytotoxic CT	Days 9 - 21 of Cycle During CT	Every 3 Mos. First 2 Years	Every 6 Mos. Years 3-5	Every 12 Mos. After Year 5
History & Physical Examination	X	X	X	Y	Y	Y
Hematology:						
HGB or HCT	X	X	X	Y	Y	X
WBC	X	X	X	Y	Y	Y
Platelet Count	X	X	X	Y	Y	Y
Serum (see 8.6.2)		X (day 1)		Y (after therapy)		
Chemistries:						
Serum Creatinine & BUN	X			Y	Y	Y
Bilirubin	X			Y	Y	Y
Alkaline Phosphatase	X			Y	Y	Y
SGOT or SGPT	X			Y	Y	Y
Gamma-GT	X			Y	Y	Y
Serum Calcium	X			Y	Y	Y
X-Rays / Scans:						
Chest (PA and Lateral)	X			Y[4]		
Xeromammogram or Mammogram	X[3]	and then 1x yearly[3]			Y	Y
CAT Scan or Ultrasound of the liver	X[3]					
Bone Scan (Bone X-Ray)[2,3]					Y[3]	Y[3]
Quality-of-Life Evaluation	- within 1 month of mastectomy and once yearly thereafter	X (day 1 of therapy)		X (as per Quality-of-Life protocol)		

Hormone Receptors: must be determined on primary tumor; and when possible, at recurrent disease.

X = For all patients prior to and during treatment time.

Y = All patients.

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

grading of the primary tumor, evaluation of the non-tumor breast tissue and 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, blocks and a copy of the clinic/hospital pathology report, and pathology form (Form P) and the Pathology Transmittal Form (Form PTF) to the Operations Office.

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 tumor-biology oriented research program.

Special studies will be done according to protocol prepared by pathologists.

A block or 5 unstained slides containing some of the primary tumor and 2 or 3 blocks (or 5 unstained slides per block) containing representative negative nodes should be submitted together with one representative slide of the primary tumor to the Operations Office (accompanied by a PTF-Form).

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 tumor by breast quadrant and its relationship to the skin and fascia must be recorded.

8.1.2 The greatest three dimensions of the tumor should be measured (unfixed specimen). Record it on your report.

8.2 Fixative

As routinely done in your institution. For special studies: see respective protocol.
Whenever possible a sample of primary tumor (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 tumor

One block (or 5 unstained slides) of primary tumor should be submitted. One stained slide of the primary should be submitted.

8.3.2 Other tissue from mastectomy specimen

A non-tumor tissue block submission is warranted (optional).

8.3.3 Lymph nodes

Representative lymph nodes (at least 2) should be submitted as a block to central review. Five unstained slides per block may be submitted instead of the blocks.

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 H & E 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 from tumor (and non-tumor) tissue.
   ad. Representative blocks (or unstained slides) of each of the following:
      1. tumor
      2. non-cancerous breast (optional)
      3. negative lymph nodes.
b. To classify all carcinomas using WHO classification.
c. To use the material for innovative studies to be defined.
d. To submit finding to Statistical Center.
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

Trial IX

This study is designed to test the following questions concerning the role of adjuvant systemic therapy for postmenopausal patients with operable breast cancer and negative axillary lymph nodes: Is the addition of 3 initial cycles of oral CMF administered prior to continous adjuvant tamoxifen more effective than continuous tamoxifen alone?

Patients are randomized to receive one of two treatment programs as described in paragraph 4.3.2. The pairwise comparison of F vs. E will be evaluated.

The primary endpoint for evaluation of therapeutic impact will be disease-free survival (DFS) where all relapses (with special consideration of breast recurrence after breast conserving procedures), second primary tumors, 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 adjuvant tamoxifen therapy is assumed to be approximately 75% (based on the NATO trial). The table below shows the total number of patients and total number of failures required to detect specified differences in 5-year DFS with 80% power using a two-sided alpha=0.05 logrank test. It is assumed that the analyses are performed at a time when about 20% of the patients in the trial have faile.

Number of patients* Required 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 75%.

Differences in 5-Year DFS %	Total number of Patients in the Trial	Total Number of Failures
75%-80%	2190	492
75%-81%	1495	329
75%-82%	1084	233
75%-83%	819	172
75%-84%	640	131
75%-85%	510	102
75%-86%	416	81
75%-87%	343	65
75%-88%	285	53

* 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.

The yearly accrual of node-negative, postmenopausal patients in Ludwig V was 140/year. Because patients can enter Trial IX up to 6 weeks following local treatment, we anticipate the accrual rate to be 225 per 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. Nine hundred patients will be accrued over a period of 4 years (as anticipated from Ludwig V) with an additional follow-up of at least 5 years after the last entry.

Number of Patients, Accrual and Follow-up Times (Assuming 225/year) and 5-Year DFS Percentage Differences for the Treatment Comparison Detectable with 80% Power.

	900 Patients (4 years of Accrual) (+ 5 Years of Follow-up)	
	Total Number of Patients	DFS Percentage Differences
All patients	900	7.5 %
ER Positive	600	9.0 %
ER Negative	300	12.5 %

10. 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 B	Clinical and Preoperative Form	- Submitted within one month of resection
Form C	Surgery form	- After complete post-operative recovery. Document all post-operative complications giving etiology, treatment and outcome.

Form P	Pathology Form	- Completed by pathologists and submitted with a copy of the clinic pathology report within 3 months after randomization.
Form PTF	Pathology Transmittal Form	- To be sent within 3 months of randomization with slides, blocks, clinic pathology report, and P Form
Form D	Treatment and Morbidity Form	- At the completion of every 3 cycles (or 3 months) of adjuvant therapy.
Form E	Follow-up Form	- Commencing at 3 months post-randomization, then submitted every 3 months during the first 2 years, every 6 months during the next 3 years, and yearly thereafter.
Form F	Hormone receptor Analysis Form	- At surgery and at each recurrence of disease (whenever a hormone receptor analysis is performed).
Form QL	Quality of life Form	- To be completed on day 1 of therapy, on day 1 of the third cycle of CMF or eighth week of tamoxifen alone, then every 3 months for the next 2 years. A QL

Form should also be completed one month after relapse of any type.

Form NC	Non-Compliance Form	- To be completed when QL Form will not be submitted.
Form R	Radiotherapy	- To be completed at the end of radiotherapy.

10.1 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
Operations Office
Seidenweg 63
CH-3012 Bern, Switzerland.

11. REFERENCES

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Proceedings of the 4th European Conference on Clinical Oncology and Cancer Nursing, ECCO 4, Abstr, 394, Madrid, 1-4 Nov, 1987.

RADIATION THERAPY FOLLOWING SEGMENTAL MASTECTOMY Appendix I

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 lymphnodes. 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 irraditation 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 sterno-manubrial 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 tisue 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 set-up 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 chemotherapy. 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 from the start of tamoxifen therapy for patients receiving tamoxifen 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

Appendix II

Please use the following table when reporting complications. Any life-threatening toxicity attributable to treatment should be reported to the study coordinator immediately.
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	
Platelets	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 - transfusions 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		

* FORM D only

CODES*		0	1	2	3	4
18	Pulmonary		Mild symptoms	Moderate symptoms	Severe symptoms intermittent O_2	Assisted vent or continuous O_2
		(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				
19	Neurological: CNS		Mild anxiety, mild headache insomnia, fatigue, malaise	Mild hyperactivity, severe anxiety, moderate headache, somnolence, tremor	Confused or manic, severe headache, cord dysfunction, confined to bed due to CNS dysfunction.	Seizures, suicidal, coma
	PN		Decreased deep tendon reflexes, mild paresthesia, mild constipation	Absent deep tendon reflexes, mild weakness, severe paresthesia, severe constipation	Disabling sensory loss, constipation, severe weakness, bladder dysfunction, severe PN pain	Respiratory dysfunction, 2° weakness, constipation requiring surgery, paralysis confining patient to bed, wheelchair
20	Depression		Occasional	Controlled 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 thrombocytopenia is graded under Hemorrhage (Code 13)).				

* FORM D only

CODES*		0	1	2	3	4
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	
28	Hyperglycemia: Non-diabetic		Glycemia 140 - 180 mg%	Glycemia >180 mg%, controllable with diet	Requiring insulin	Keto-acidosis
	Diabetic		Adjustable with diet	Requiring <25% increase in insulin dosage	Requiring > 25% increase in insulin 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 symptoms
30	Hypertension: Pre-existing		Hypertension controlled by occasional treatment	Hypertension controlled by chronic oral medication	Requiring hospitalisation, treatment with i.v. drugs	Uncontrollable
31	Hot flashes		Occasional - not requiring treatment	Frequent - requiring treatment		
32	Euphoria		Slight	Moderate	Severe	
33	Thrombosis, Phlebitis, Embolism		Local, oligo-symptomatic	Painful, with or without edema	Severe edema, dyspnea (no 0_2)	Pulmonary embolism, requiring 0_2

* FORM O only

CODES *		0	1	2	3	4
34	Edema		Not debilitating	Debilitating		
35	Lymphedema		Not debilitating	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 4 weeks	Major intervention required	
40	Amenorrhea (treatment-induced)		No period			

* FORM D only

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

Appendix III

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/well-being 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/well-being within the first 6 weeks after definitive surgery. 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/well-being 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 (7), is used. 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 (5,8,9,10). Rogentine et al. (8) 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 (11,12). 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 Trail Group, and were proven to be sensitive, feasible and valid (13,14,15).

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 (16). According to the empirical experience with the SLCU (5,8,9,10), the Bf-S (17-20), and the three LASA scales (13,14), 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 chemotherapy cycle 3, or eight weeks after tamoxifen start) and every three months thereafter for a period of two years. A QL form should be filled in one month after recurrence of any type and 6 months later. 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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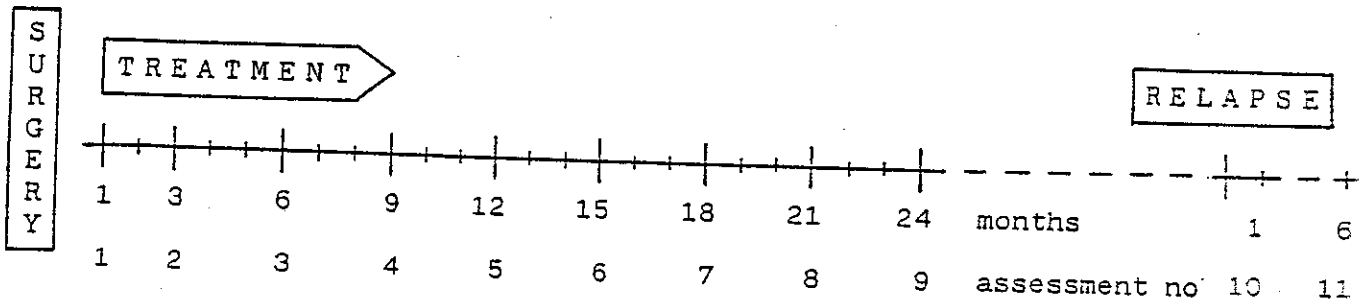
INTERNATIONAL BREAST CANCER STUDIES VI, VII, VIII & IX

QUALITY OF LIFE FORM

1) This is not a three-part form. The laminated set of 2 pages should be the only set used for copying. DO NOT MAKE COPIES FROM OTHER COPIES, as the length of the line used for assessment would eventually be distorted by multiple copying. Copies should be sent to affiliated clinics for their use.

2) This form is to be completed by the patient herself: ON DAY 1 OF TREATMENT (within 6 weeks of surgery), TWO MONTHS LATER FOR TAMOXIFEN TREATED PATIENTS OR DAY 1 OF CYCLE 3 FOR CMF TREATED PATIENTS AND EVERY 3 MONTHS THEREAFTER FOR THE FIRST 2 YEARS (months 6/9/12/15/18/21/24). For methological reasons, this schedule has to be followed exactly, neither more nor less assessments:

TIMING:



If unavoidable the first assessment may be within 6 weeks of surgery. Subsequent assessments may be ± 1 month of the 3 month requirement.

Quality of life evaluation has to be performed additionaly WITHIN ONE MONTH OF RELAPSE AND 6 MONTHS THEREAFTER (± 1 month).

3) If chemotherapy is given, the form has to be filled in BEFORE administration of chemotherapy.

4) EVERY STUDY PATIENT has to fill in the form, do not select patients for the quality of life study.

5) The patient should be instructed to SEEK HELP ONLY IF SHE HAS PROBLEMS in understanding any of the items in the form.

6) Page one simply requires an X TO BE MARKED at the place on the line which respresents the patient's response to the questions. Leave the left hand column blank.

7) Page two requires an X ON EACH LINE in one of the 3 columns. No line should have more than one X! Again this represents the patient's feelings at the present time.

8) On both pages ALL QUESTIONS SHOULD BE RESPONDED TO: Check the form after completion and if necessary ask the patient to fill in missing answers.

9) If the patient is being followed elsewhere make ARRANGEMENTS WITH THE CLINIC OR PHYSICIAN to have the patient fill in the form as required and send it to you.

10) Fill in the header information on each page. If completed elsewhere, please verify the information, especially RANDOMIZATION NUMBER AND DATE OF COMPLETION, before forwarding.

11) When completed make a copy for your files and send THE ORIGINAL FORM to the Operations Office in Bern. It will be scored there and forwarded to the Statistical office for data entry.

12) If the patient refuses to fill in the form or the form is not filled in for any other reasons ask the patient why and fill in the NONCOMPLIANCE FORM (form NC for investigators).

21.02.87 Hürny, Bernhard
Quality of Life Office
Revised 9/88

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APPENDIX V

Tables for Determination of Surface Area (m^2) as a Function of Height (cm) and Weight (kg) *

Height (cm)	Weight (kg)																							
	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	44	48	52	56	60
50	0.25	0.31	0.36	0.40	0.44	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.68	0.71	0.73	0.75	0.78	0.80	0.82	0.86	0.90	0.94	0.97	1.01
55	0.26	0.32	0.37	0.42	0.46	0.50	0.53	0.57	0.60	0.63	0.66	0.68	0.71	0.74	0.76	0.78	0.81	0.83	0.85	0.90	0.94	0.98	1.01	1.05
60	0.27	0.33	0.39	0.43	0.48	0.52	0.55	0.59	0.62	0.65	0.68	0.71	0.74	0.76	0.79	0.81	0.84	0.86	0.88	0.93	0.97	1.01	1.05	1.09
65	0.28	0.34	0.40	0.45	0.49	0.53	0.57	0.61	0.64	0.67	0.70	0.73	0.76	0.79	0.82	0.84	0.87	0.89	0.91	0.96	1.00	1.05	1.09	1.13
70	0.29	0.36	0.41	0.46	0.51	0.55	0.59	0.63	0.66	0.69	0.73	0.76	0.79	0.81	0.84	0.87	0.89	0.92	0.94	0.99	1.04	1.08	1.12	1.16
75	0.30	0.37	0.42	0.48	0.52	0.57	0.61	0.64	0.68	0.71	0.75	0.78	0.81	0.84	0.87	0.89	0.92	0.95	0.97	1.02	1.07	1.11	1.16	1.20
80	0.31	0.38	0.44	0.49	0.54	0.58	0.62	0.66	0.70	0.73	0.77	0.80	0.83	0.86	0.89	0.92	0.95	0.97	1.00	1.05	1.10	1.14	1.19	1.23
85	0.31	0.39	0.45	0.50	0.55	0.60	0.64	0.68	0.72	0.75	0.79	0.82	0.85	0.88	0.91	0.94	0.97	1.00	1.02	1.08	1.13	1.17	1.22	1.26
90	0.32	0.40	0.46	0.51	0.56	0.61	0.65	0.70	0.73	0.77	0.81	0.84	0.87	0.91	0.93	0.97	0.99	1.02	1.05	1.10	1.15	1.20	1.25	1.29
95	0.33	0.40	0.47	0.53	0.58	0.63	0.67	0.71	0.75	0.79	0.83	0.86	0.89	0.93	0.96	0.99	1.02	1.05	1.07	1.13	1.18	1.23	1.28	1.32
	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	48	52	56	60	64	68	72
100	0.59	0.64	0.68	0.73	0.77	0.81	0.84	0.88	0.91	0.95	0.98	1.01	1.04	1.07	1.10	1.13	1.15	1.21	1.26	1.30	1.35	1.40	1.44	1.48
105	0.60	0.65	0.70	0.74	0.78	0.82	0.86	0.90	0.93	0.97	1.00	1.03	1.06	1.09	1.12	1.15	1.18	1.23	1.28	1.33	1.38	1.43	1.47	1.52
110	0.61	0.67	0.71	0.76	0.80	0.84	0.88	0.92	0.95	0.99	1.02	1.05	1.08	1.11	1.14	1.17	1.20	1.25	1.31	1.36	1.41	1.45	1.50	1.55
115	0.63	0.68	0.73	0.77	0.81	0.86	0.89	0.93	0.97	1.00	1.04	1.07	1.10	1.13	1.16	1.19	1.22	1.28	1.33	1.38	1.43	1.48	1.53	1.58
120	0.64	0.69	0.74	0.79	0.83	0.87	0.91	0.95	0.99	1.02	1.06	1.09	1.12	1.15	1.19	1.22	1.24	1.30	1.36	1.41	1.46	1.51	1.56	1.60
125	0.65	0.70	0.75	0.80	0.84	0.89	0.93	0.97	1.00	1.04	1.07	1.11	1.14	1.17	1.21	1.24	1.27	1.32	1.38	1.43	1.49	1.54	1.58	1.63
130	0.66	0.71	0.77	0.81	0.86	0.90	0.94	0.98	1.02	1.06	1.09	1.13	1.16	1.19	1.23	1.26	1.29	1.35	1.40	1.46	1.51	1.56	1.61	1.66
135	0.67	0.73	0.78	0.83	0.87	0.92	0.96	1.00	1.04	1.07	1.11	1.15	1.18	1.21	1.25	1.28	1.31	1.37	1.43	1.48	1.53	1.59	1.64	1.69
140	0.68	0.74	0.79	0.84	0.89	0.93	0.97	1.01	1.05	1.09	1.13	1.16	1.20	1.23	1.26	1.30	1.33	1.39	1.45	1.50	1.56	1.61	1.66	1.71
145	0.69	0.75	0.80	0.85	0.90	0.94	0.99	1.03	1.07	1.11	1.14	1.18	1.22	1.25	1.28	1.32	1.35	1.41	1.47	1.53	1.58	1.64	1.69	1.74
	30	34	38	42	46	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114	118	122
150	1.12	1.20	1.27	1.34	1.40	1.46	1.52	1.58	1.63	1.69	1.74	1.79	1.84	1.88	1.93	1.98	2.02	2.07	2.11	2.15	2.19	2.23	2.27	2.31
155	1.14	1.21	1.29	1.35	1.42	1.48	1.54	1.60	1.65	1.71	1.76	1.81	1.86	1.91	1.96	2.00	2.05	2.09	2.14	2.18	2.22	2.26	2.30	2.34
160	1.15	1.23	1.30	1.37	1.44	1.50	1.56	1.62	1.68	1.73	1.78	1.84	1.89	1.94	1.98	2.03	2.08	2.12	2.17	2.21	2.25	2.29	2.34	2.38
165	1.17	1.25	1.32	1.39	1.46	1.52	1.58	1.64	1.70	1.75	1.81	1.86	1.91	1.96	2.01	2.06	2.10	2.15	2.19	2.24	2.28	2.32	2.37	2.41
170	1.18	1.26	1.34	1.41	1.48	1.54	1.60	1.66	1.72	1.78	1.83	1.88	1.94	1.99	2.04	2.08	2.13	2.18	2.22	2.27	2.31	2.35	2.40	2.44
175	1.20	1.28	1.35	1.43	1.49	1.56	1.62	1.68	1.74	1.80	1.85	1.91	1.96	2.01	2.06	2.11	2.16	2.20	2.25	2.30	2.34	2.38	2.43	2.47
180	1.21	1.29	1.37	1.44	1.51	1.58	1.64	1.70	1.76	1.82	1.88	1.93	1.98	2.03	2.09	2.13	2.18	2.23	2.28	2.32	2.37	2.41	2.45	2.50
	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	132
185	1.42	1.49	1.56	1.63	1.69	1.75	1.81	1.87	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.28	2.33	2.37	2.42	2.46	2.50	2.55	2.59	2.63
190	1.44	1.51	1.58	1.65	1.71	1.77	1.83	1.89	1.95	2.00	2.06	2.11	2.16	2.21	2.26	2.31	2.35	2.40	2.44	2.49	2.53	2.58	2.62	2.66
195	1.45	1.53	1.60	1.67	1.73	1.79	1.85	1.91	1.97	2.02	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43	2.47	2.52	2.56	2.60	2.65	2.69
200	1.47	1.54	1.62	1.68	1.75	1.81	1.87	1.93	1.99	2.05	2.10	2.15	2.21	2.26	2.31	2.36	2.40	2.45	2.50	2.54	2.59	2.63	2.68	2.72
205	1.49	1.56	1.63	1.70	1.77	1.83	1.89	1.95	2.01	2.07	2.12	2.18	2.23	2.28	2.33	2.38	2.43	2.48	2.52	2.57	2.62	2.66	2.70	2.75
210	1.50	1.58	1.65	1.72	1.79	1.85	1.91	1.97	2.03	2.09	2.14	2.20	2.25	2.30	2.36	2.41	2.45	2.50	2.55	2.60	2.64	2.69	2.73	2.77
215	1.52	1.59	1.67	1.74	1.80	1.87	1.93	1.99	2.05	2.11	2.17	2.22	2.27	2.33	2.38	2.43	2.48	2.53	2.58	2.62	2.67	2.71	2.76	2.80
220	1.53	1.61	1.68	1.75	1.82	1.89	1.95	2.01	2.07	2.13	2.19	2.24	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65	2.69	2.74	2.79	2.83

*K. Stanley, J. Stjernswärd, H. Isley. The Conduct of a Cooperative Clinical Trial. (Monograph series: Recent Results in Cancer Research: No. 77) Springer-Verlag, 1981, p. 36.

APPENDIX V

TABLE FOR DETERMINING IDEAL SURFACE AREA BY HEIGHT AND AGE CATEGORIES
(Used for Dose Calculations if Less Than Actual Surface Area)

HEIGHT			AGE						
cm	Ft.	Ins.	25-29	30-34	35-39	40-44	45-49	50-54	55 UP
149	4	11	1.5	1.5	1.5	1.6	1.6	1.6	1.6
152	5	0	1.5	1.6	1.6	1.6	1.6	1.6	1.6
155	4	1	1.5	1.6	1.6	1.6	1.6	1.7	1.7
157	5	2	1.6	1.6	1.6	1.6	1.7	1.7	1.7
160	5	3	1.6	1.6	1.7	1.7	1.7	1.7	1.7
162	5	4	1.6	1.7	1.7	1.7	1.7	1.7	1.8
165	5	5	1.7	1.7	1.7	1.7	1.8	1.8	1.8
167	5	6	1.7	1.7	1.8	1.8	1.8	1.8	1.8
170	5	7	1.7	1.8	1.8	1.8	1.8	1.8	1.8
172	5	8	1.8	1.8	1.8	1.8	1.9	1.9	1.9
175	5	9	1.8	1.8	1.9	1.9	1.9	1.9	1.9
177	5	10	1.9	1.9	1.9	1.9	1.9	2.0	2.0
180	5	11	1.9	1.9	1.9	1.9	2.0	2.0	2.0
183	6	0	1.9	1.9	2.0	2.0	2.0	2.0	2.0