

## **The SWENOTECA ABC-study**

### **A Randomized Phase III Study Comparing One Course of Adjuvant Bleomycin, Etoposide and Cisplatin (BEP) and One Course of Carboplatin AUC7 in Clinical Stage I Seminomatous Testicular Cancer**

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A study by the Swedish Norwegian Testicular Cancer Group

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## 1 Abbreviations

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|           |  |
|-----------|--|
| AFP       | Alpha-fetoprotein  |
| ALT       | Serum alanine transaminase                                 |
| ANC       | Absolute neutrophil count                                  |
| AUC       | Area under the curve                                       |
| BEP       | Bleomycin, etoposide and cisplatin                         |
| CRF       | Case report form   |
| CS        | Clinical stage   |
| ECOG      | Eastern cooperative oncology group                         |
| eGFR      | Estimated glomerular filtration rate                       |
| EORTC     | European Organisation for Research and Treatment of Cancer |
| FSH       | Follicle-stimulating hormone                               |
| G-CSF     | Granulocyte colony stimulating factor                      |
| GFR       | Glomerular filtration rate                                 |
| hCG       | human chorionic gonadotropin                               |
| HDL       | High-density lipoprotein                                   |
| HRQoL     | Health related quality of life                             |
| LDH       | Lactate dehydrogenase                                      |
| LDL       | Low-density lipoprotein                                    |
| LH        | Luteinizing hormone  |
| MRI       | Magnetic resonance imaging                                 |
| NSGCT     | Nonseminomatous germ cell testicular cancer                |
| PS        | Pathological stage   |
| QLQ       | Quality of life questionnaire                              |
| RPLND     | Retroperitoneal lymph-node dissections                     |
| SCIN      | Scale for chemotherapy-induced long-term neurotoxicity     |
| SGCT      | Seminomatous germ cell testicular cancer                   |
| SHBG      | Sex hormone-binding globuline                              |
| SWENOTECA | The Swedish and Norwegian Testicular Cancer Group          |
| ULN       | Upper limit of normal range                                |

## 2 Background

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### 2.1 Testicular Cancer

In the last 30 years, testicular germ-cell cancer has been a model for a curable neoplasm(1). Although a relatively rare tumour, it is the most predominant malignancy in males between 15-49 years of age. Today most patients are cured, regardless of the presenting stage. Due to the young age at onset, the late toxicity of treatment is of major importance as patients have an almost normal life expectancy following treatment(2). Thus, the choice of treatment strategies impacts the long-term morbidity and mortality. The focus in the treatment today is to maintain, or if possible to improve, the excellent results of treatment while at the same time reducing the risk of morbidity and mortality associated with treatment.

As recently as the 1960s testicular cancer was the most frequent single cause of death from disease in young Norwegian males. The improved survival has been most pronounced in the Nordic and the western European countries, while survival in some Eastern-European countries have not improved as satisfactory(3). The relative survival in testicular cancer in Norway and Sweden is now over 97%, with over 99% survival in patients with localized disease(4, 5).

In 2012 325 Norwegian males and 346 Swedish males were diagnosed with testicular cancer, giving an age-adjusted incidence rate of 11.6/100 000 and 7.3/100 000(6, 7). The incidence rates in Norway and Denmark are the highest reported in the world(8). Approximately 1% of Norwegian males are expected to be diagnosed with testicular cancer by the age of 75(4). The reason why the incidence in these neighbouring countries differs so much given the similar populations is still unknown. The incidence of testicular cancer has been increasing steadily in Norway, and most western countries, since registration of cancers commenced, while mortality has decreased(8) (Figure 2).

### 2.2 Treatment of Seminoma Clinical Stage I Testicular Cancer

This group of patients is by far the most frequent in testicular cancer, constituting over 40% of all cases of testicular cancer. It is also a group with close to 100% cancer specific survival, and the issues of long-term survivorship therefore become paramount.

#### 2.2.1 Adjuvant radiotherapy

Seminomatous germ cell testicular cancer (SGCT) is exceedingly radiosensitive and radiotherapy has for decades been the mainstay of treatment in CS I SGCT. With a low rate of relapse and manageable acute toxicity it has been an attractive treatment option. Randomized, controlled trials have been performed in an effort to minimize both dose and volume of radiation(9-11). Consequently, the standard modality of radiotherapy for CS I SGCT is now 20 Gy delivered in ten fractions to a para-aortic field. The main concern of this treatment modality is the possibility of radiation induced secondary cancers(12).

#### 2.2.2 Surveillance

Data from studies with retroperitoneal lymph-node dissections (RPLND) done in the late 1960's, showed that under 10% of CS I SGCT had PS II disease in the retroperitoneum(13). The excellent survival in early stage SGCT, and early experiences on the use of surveillance in CS I NSGCT rendered surveillance a tempting new modality of treatment of CS I SGCT. Early reports on surveillance came from the UK and Canada in the late 1980's, with the first report with adequate follow-up by the Royal Marsden Hospital in 1992(14). Large studies on the use of surveillance have been reported, but no randomized study comparing surveillance and adjuvant treatment has been performed. Using the surveillance strategy, 15-20% of patients will receive salvage radiotherapy or chemotherapy(15). As in CS I NSGCT surveillance requires compliant patients and abdominal imaging over many years. Due to the more indolent nature of SGCT, relapses following surveillance occurs later than in NSGCT, although the incidence of late relapses in total is lower(16).

### 2.2.3 Adjuvant chemotherapy

In addition to being extremely radiosensitive, SGCT is very chemosensitive. Trials on the use of one or two adjuvant courses of carboplatin started in 1982(17, 18). A large randomized non-inferiority trial between one course of adjuvant carboplatin and radiotherapy was published in 2005(11). Relapses following carboplatin and radiotherapy were reported to be 5.3% and 4%, respectively. Although adjuvant chemotherapy prevents the majority of relapses, abdominal imaging requirements are the same as with surveillance. Patients have to be compliant to follow up, as the aim is to diagnose relapses before symptomatic and advanced disease manifests itself.

### 2.3 Toxicity of treatment

As most patients present with early stage disease and disease-specific survival is high, treatment-related toxicity has received increasing attention in the last decades. The main concern is the growing evidence of treatment-related late toxicity, which may manifest itself decades after treatment. The most serious culprits are secondary malignancies and cardiovascular disease, but also neurological and renal impairment, decreased fertility and endocrine toxicities may impair the cancer survivors well-being(2, 12, 19-32). Due to an almost exclusively public health care and good quality national registries, both on cancer and causes of death, Norway and Sweden have an advantage when conducting studies on late toxicities, and many of the reported studies on late toxicity have been performed in Norway. Common features of the studies is that the risk of late toxicity is closely correlated to the total dose of chemotherapy given, and it seems that the combination of chemotherapy and radiotherapy act synergistic in inflicting late toxicity(23, 33). Radiotherapy, including adjuvant radiotherapy given only under the diaphragm, increases the frequencies of secondary malignancies(34, 35). There is also a growing concern, and evidence, of radiation induced secondary malignancies due to the multiple CT scans many testicular cancer patients are subjected to(36, 37).

### 2.4 Adjuvant Carboplatin

Adjuvant carboplatin, dosed at AUC7, is an international standard adjuvant treatment option in CS I seminoma(38, 39). The treatment is given as a single dose of carboplatin, with minimal short-term toxicity.

### 2.5 Bleomycin, Etoposide and Cisplatin

Cisplatin-based chemotherapy has been the standard chemotherapy given to metastatic seminomatous germ cell tumours the last 3 decades. Today treatment of metastatic disease usually entails three or four cycles of chemotherapy with a cycle length of three weeks. In CS I nonseminoma two cycles of adjuvant BEP chemotherapy have been used. SWENOTECA pioneered the implementation of one adjuvant cycle of BEP chemotherapy, resulting in a very low rate of relapse (40). With over 500 patients treated with one course of adjuvant BEP in CS I nonseminoma, there have not been any reported treatment-related deaths.

### 2.6 Salvage treatment

Salvage treatment is given according to current SWENOTECA guidelines in SWENOTECA IX, or later appendix/protocol if present.

## 3 Rationale for the study

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One course of adjuvant carboplatin AUC7 is considered internationally to be a standard treatment option in clinical stage I seminoma, regardless of risk factors. Treatment is based on a large, randomized phase III study comparing adjuvant carboplatin with adjuvant radiotherapy. This study was done without registering data on possible risk factor for relapse. The relapse rate following carboplatin was in this study estimated to be 5.3 %(41). Data from a prospective, risk-adapted Spanish study showed that patients without risk factors had a very low risk of relapse, even without adjuvant treatment(42). This result is also confirmed by a recent analysis of SWENOTECA VII data, showing that this group of patients has a risk of relapse of less than 5 % without adjuvant treatment(43). The same data estimated a relapse-rate in patients with one or two risk factors followed by surveillance of about 20 %.

Combined data from SWENOTECA V and VII indicate a high risk of relapse in patients with one or two risk factors (tumor > 4 cm, stromal invasion of rete testis) treated with one course of adjuvant carboplatin. The relapse rate in this group of patients was 9.4 %, indicating a very modest effect of one

course of adjuvant carboplatin. If adjuvant chemotherapy is the preferred treatment strategy, more potent chemotherapy regimens should be explored in this patient group. The results from SWENOTECA III/VI with one course of cisplatin-based adjuvant chemotherapy in clinical stage I nonseminoma, show a very low rate of relapse. As seminoma is even more chemosensitive than nonseminoma we expect the relapse rate following one course of adjuvant BEP to be very low, close to 1 %.

## 4 Aims of the study

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The overall aim is to investigate whether one course of adjuvant BEP have a lower relapse rate compared to one course of adjuvant carboplatin AUC7. Furthermore, we will investigate if there is a difference in health related quality of life as well as acute and long-term toxicities from treatment.

### Primary endpoint:

- Relapse rate

### Secondary endpoints:

- Short-term toxicity
- Long-term toxicity
- Health related quality of life
- Overall survival
- Health economy analysis

## 5 Statistical considerations and enrolment plan

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### 5.1 Sample size calculation

Based on the SWENOTECA experience with one course of adjuvant carboplatin AUC7 we estimate the relapse rate in patients with one or two risk factors to be 9 %. We consider a reduction in relapse free survival of 7 % to be the minimum difference that will lead to routine use of one course of adjuvant BEP. To demonstrate an improvement in relapse rate from 9 to 2 % with an  $\alpha = 0.05$  and  $\beta = 0.80$ , 332 evaluable patients are required. We expect a dropout rate of maximum 5 %, and therefore intend to randomize a total of 348 patients.

### 5.2 Statistical analysis

Descriptive characteristics will to be presented as means (standard deviation) for normally distributed continuous variables, median (interquartile range) for skewed continuous variables, and percent (number) for categorical variables. The log rank test will be used to compare relapse rates between the treatment groups and relapse curves will be presented using Kaplan-Meier's method. Cox proportional hazard regression model will be used to estimate hazard ratio of adverse event between the treatment groups.

### 5.3 Adjustment of sample size

Short term overall survival is, regardless of treatment allocation, expected to be very close to 100 %. The primary outcome is relapse rate. The power of the study depends on the number of observed relapses. If the relapse rate in the adjuvant carboplatin group, the reference group, is lower than the anticipated 9 %, we need to include more people in the study. Based on all previous published material on adjuvant treatment in clinical stage I seminoma it is not possible to precisely estimate the correct relapse rate until the median follow-up is four years. Consequently, we will estimate the relapse rate in the reference group close to the end of accrual. If the estimated relapse rate, and thus the number of relapses, is lower than the anticipated we will increase the sample size to make sure that the study meets the minimum required number of relapses in the reference group. A possible inclusion of more study participants does not compromise the Type I error rate of the study.

### 5.4 Enrolment plan

We assume that 80 patients will be included, and randomized every year. As a binational multicentre trial, all hospital managing testicular cancer in Sweden and Norway will be recruiting patients. We aim at completing randomization in 54 months. The first patient will be enrolled in Q2 2015. The last patient should be randomized by Q3 2019. All patients will be followed for 120 months.

## 6 Eligibility criteria for inclusion

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### 6.1 Inclusion criteria

1. Histological diagnosis of unilateral seminoma testicular cancer, evaluating both size of tumor and stromal invasion of the rete testis. NB: intratubular or pagetoid spread to rete testis is **not** considered to be rete testis invasion.
2. Clinical stage I
3. Tumor size over 4 cm and/or stromal invasion of the rete testis by tumor cells
4. Normal value of AFP before orchiectomy. A stable, slightly elevated AFP as a normal value may be permitted.
5. Age  $\geq$  18 years and  $<$  60 years
6. ECOG performance status 0, 1 or 2.
7. Adequate organ function defined as:
  - a. Serum alanine transaminase (ALT)  $\leq$  1.5 x upper limit of normal (ULN).
  - b. Total serum bilirubin  $\leq$  1.5 x ULN
  - c. Absolute neutrophil count (ANC)  $\geq$   $1.5 \times 10^9/L$
  - d. Platelets  $\geq$   $100 \times 10^9/L$
  - e. GFR  $>$  50 ml/min (see below for allowed methods of analysis)
8. All fertile patients should use safe contraception 6 months following adjuvant treatment (Patient: Condom (Sweden only) or sterilisation or Partner: combination hormonal contraceptive, sterilisation or intrauterine device)
9. Written informed consent

### 6.2 Exclusion criteria

1. Signs of metastatic disease evaluated by CT thorax, abdomen and pelvis.
2. Prior diagnosis of testicular cancer
3. Chronic pulmonary disorders giving a high risk of bleomycin induced toxicity (for example chronic obstructive pulmonary disease or lung fibrosis)
4. Prior history of any cancer the last 5 years excluding basal cell carcinoma
5. Known hypersensitivity or contraindications for the study drugs
6. Serious concomitant systemic disorders (for example active infection, unstable cardiovascular disease) that in the opinion of the investigator would compromise the patient's ability to complete the study or interfere with the evaluation of the efficacy and safety of the study treatment
7. Conditions – medical, social, psychological – which could prevent adequate information and follow-up
8. Medication interacting with the study drugs

## 7 Assessments before inclusion

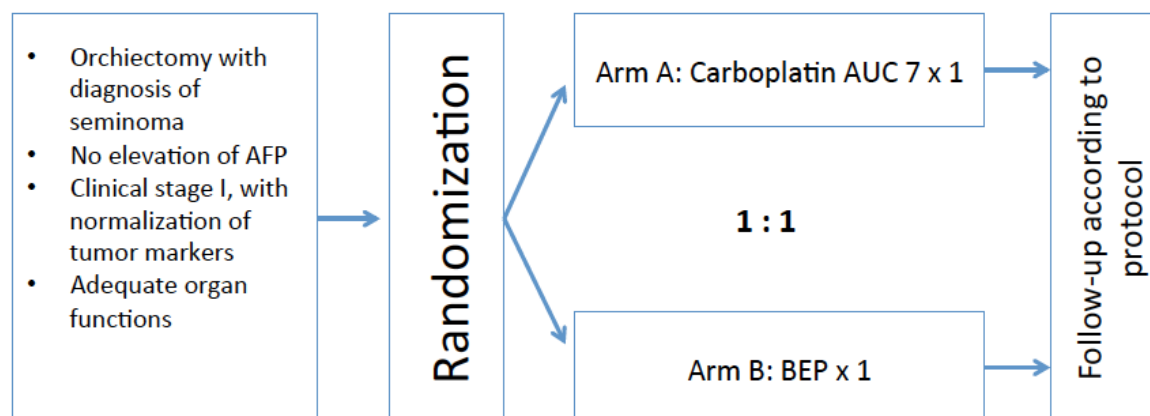
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- Medical history, comorbidity
- Medication
- ECOG performance status
- Clinical examination including blood pressure
- Weight and height
- CT scan (thorax, abdomen and thorax) within 7 weeks of start of adjuvant chemotherapy
- GFR evaluation by either Cr-EDTA, Tc-DTPA, Iohexol, 24 hour urinary collection or eGFR with Cystatin C. The Cockcroft-Gault (CG) formula using only height/weight/age and creatinine is **not** allowed as primary screening.
- Blood samples within one week of start of adjuvant chemotherapy: Haemoglobin, Leucocytes, Absolute Neutrophils, Thrombocytes, AFP, hCG, testosterone, LH, FSH, SHBG, ALT, Bilirubin Albumin, Creatinine, CRP, fasting lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), fasting glucose and HbA1c.
- HRQoL reported on the EORTC QLQ-C30 + TC26 + Fatigue questionnaire.



## 8 Trial design

Open, multicentre, randomized phase III study. Patients with CS I unilateral seminoma, with stromal invasion of the rete testis and/or tumor size over 4 cm. Randomised to adjuvant carboplatin (Arm A) or one course of BEP (Arm B):



**Figure 1. Flow chart – Trial design**

## 9 Eligibility criteria for randomization

In addition to the eligibility criteria for inclusion patients must have a histology report with details regarding stromal invasion of rete testis and tumor size.

At randomization, the treatment groups will be *stratified according to*:

1. Tumour size, > 4 cm / ≤ 4 cm
2. Stromal invasion of the rete testis, present or not

Randomization will be performed by each investigator using a website specially designed for this trial. The website also contains an electronic CRF for registration of data.

## 10 Study treatment

### 10.1 Adjuvant chemotherapy

After inclusion the patients will receive one course of BEP (bleomycin, etoposide and cisplatin) or one course of carboplatin according to randomization.

The doses of adjuvant BEP and carboplatin given in this study are based in the international standard doses of these chemotherapy regimen used in the adjuvant setting of CS I nonseminoma and seminoma(39).

### 10.2 Formulas

The Calvert's formula AUC 7 is used to calculate the carboplatin dose: **7 x (GFR +25)**.

**The GFR should always be an uncorrected value estimated by iohexol or Cr-EDTA clearance.**

BEP is dosed based on body surface, estimated by height and weight (Du Bois formula).

### 10.3 Preparation and labelling

The study drugs will be provided, prepared and packed by a pharmacy unit specialised in the use of chemotherapy at the hospital administering the adjuvant treatment. The study drug will be labelled according to national and international guidelines.

### 10.4 Accountability

Before treatment is administered identity and dosage of study drugs is checked by health personal. Administered treatment is recorded, either in a separated system for chemotherapy (e.g. Cytodose®) or in a electronic patient journal.

### 10.5 Dosing schedule Carboplatin

- Day 1: Carboplatin AUC 7 (Calvert's formula) IV dissolved in 250-500 ml glucose 50 mg/ml and infused over 30 minutes.

### 10.6 Dosing schedule Bleomycin, Etoposide and Cisplatin (BEP)

- Days 1-5: Etoposide 100 mg/m<sup>2</sup>, cisplatin 20 mg/m<sup>2</sup> dissolved in 1000 ml sodium-chloride 9 mg/ml and infused in 1,5-2 hours. Prehydration of 1000 ml sodium-chloride 9 mg/ml and infused in one hour. Additional 2000 ml of fluids should be administered every 24 hours oral or IV days 1-6. Day 1, 5 and 15: IV Bleomycin 30 mg dissolved in 250 ml sodium-chloride 9 mg/ml and infused in 30 minutes or IM Bleomycin 30 mg dissolved in 5 ml sodium-chloride 9 mg/ml

### 10.7 Antiemetic medication

Adjuvant antiemetic medication is to be given with adjuvant chemotherapy. The regimens should be based on guidelines at the individual sites based on the emetic risk of the adjuvant treatment.

**Carboplatin AUC7: Moderate emetogenic risk**

**Bleomycin, Etoposide and Cisplatin: High emetogenic risk**

### 10.8 Dose modifications

**There should be no dose modification, as patients requiring dose modification should not be included in the study.**

### 10.9 Granulocyte colony stimulating factor

The use of G-CSF is allowed in patients receiving adjuvant BEP. If G-CSF is used it must be registered in the CRF at the time of adjuvant chemotherapy is given

### 10.10 Emergency plan

All patients will receive the study drugs at outpatient clinics or wards specialised in administering chemotherapy. Appropriate emergency equipment/procedures for complications during or shortly after study drug administration are ensured. All patients will be given the possibility to directly contact the investigator (or delegate) at all times following treatment for medical guidance.

### 10.11 Concomitant medication

Some medications may interact with the study drugs, mostly resulting in unpredictable serum concentration of the study drugs. This includes valproate, carbamazepine, barbiturates, phenytoin, rifampicin, cyclosporine, methotrexate, hypericum and tuberculostatica. Patients using these drugs should either change medication where appropriate or should not be included in the study.

## 11 Post-study therapy

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In case of relapse patients will be treated according the SWENOTECA management program for seminomatous testicular cancer.

## 12 Evaluation and follow-up

### Visits

- Clinical examination at 4 weeks, 3, 12, 18, 24, 36, 48, 60, 72, 96 and 120 months.

### Imaging following adjuvant chemotherapy

- MRI scans of the abdomen/pelvis 3, 12, 18, 24, 36, 48, 60, 72, 96 and 120 months. If MRI is not feasible or is contraindicated, CT abdomen should be done instead.

### Blood samples

Tumor markers AFP, hCG and LDH at 3, 6, 12, 18, 24, 30, 36, 42, 48, 60, 72, 96 and 120 months.

- Fasting lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), fasting glucose, HbA1c and fasting sex hormones (testosterone, LH, FSH and SHBG) at 12, 36, 60, and 120 months. GFR at 12 months using the same method as initial inclusion screening.

### Suspicion of relapse

- If relapse is suspected, patients are staged according to the SWENOTECA IX protocol, or new addendum if present.

## 13 Trial plan

### Inclusion, adjuvant chemotherapy and evaluation

|  |              | Inclusion | Adjuvant chemotherapy | Evaluation adjuvant chemotherapy |
|--|--------------|-----------|-----------------------|----------------------------------|
| Visit                                    |              | I         | II (Day 1)            | III (Day 28 - 35)                |
| Week                                     | 0            | 0-8       | 1-8                   | 4 weeks following II             |
| Orchiectomy                              | 0            |           |                       |                                  |
| CT thorax/abdomen/pelvis                 | 0 ± 1 week   |           |                       |                                  |
| Tumormarkers <sup>a</sup>                | 0 – 0-1 days |           | X                     | X                                |
| Informed consent                         |              | X         |                       |                                  |
| Randomization                            |              | X         |                       |                                  |
| Medical history                          |              | X         |                       | X                                |
| Physical exam                            |              | X         |                       | X                                |
| Weight, height                           |              | X         |                       |                                  |
| Haematology <sup>b</sup>                 |              | X         | X                     | X                                |
| Biochemistry <sup>c</sup>                |              | X         |                       | X                                |
| Sex hormones <sup>d</sup>                |              | X         |                       |                                  |
| Cardiovascular risk profile <sup>e</sup> |              | X         |                       |                                  |
| Sperm count <sup>f</sup>                 | X            |           |                       |                                  |
| HRQoL-questionnaire <sup>g</sup>         |              | X         |                       | X                                |
| Chemotherapy                             |              |           | X                     |                                  |
| GFR evaluation <sup>h</sup>              |              | X         |                       |                                  |
| GFR for Carboplatin dosage <sup>i</sup>  |              |           | X                     |                                  |

**Follow-up**

| Visit                                    | IV | V | VI | VII | VIII | IX | X  | XI | XII | XIII | XIV | XV | XVI |
|--|----|---|----|-----|------|----|----|----|-----|------|-----|----|-----|
| Months after III                         | 3  | 6 | 12 | 18  | 24   | 30 | 36 | 42 | 48  | 60   | 72  | 96 | 120 |
| Physical exam                            | X  |   | X  | X   | X    |    | X  |    | X   | X    | X   | X  | X   |
| Tumormarkers                             | X  | X | X  | X   | X    | X  | X  | X  | X   | X    | X   | X  | X   |
| Creatinine                               | X  |   |    |     |      |    |    |    |     | X    |     |    | X   |
| Sex hormones <sup>d</sup>                |    |   | X  |     |      |    | X  |    |     | X    |     |    | X   |
| Cardiovascular risk profile <sup>e</sup> |    |   | X  |     |      |    | X  |    |     | X    |     |    | X   |
| MRI abdomen/pelvis                       | X  |   | X  | X   | X    |    | X  |    | X   | X    | X   | X  | X   |
| HRQoL questionnaires <sup>g</sup>        | X  |   | X  |     |      |    | X  |    |     | X    |     |    | X   |
| GFR evaluation <sup>h</sup>              |    |   | X  |     |      |    |    |    |     |      |     |    |     |

- AFP, hCG, LDH
- Haemoglobin, Leucocytes, Absolute Neutrophils, Thrombocytes
- ALT, bilirubin, albumin, creatinine.
- Testosterone, LH, FSH and SHBG (Fasting).
- Blood pressure, weight, fasting glucose, HbA1c and fasting lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides).
- Sperm count should be offered prior to orchiectomy, or at least prior to chemotherapy.
- EORTC QLQ-C30, TC26 and fatigue questionnaire.
- GFR evaluation prior to inclusion and at 12 months, using the same method at both occasions. Allowed methods are Cr-EDTA, Tc-DTPA, Iohexol, Cystatin C or 24 hour urinary collection.
- Only for patients randomized to Carboplatin, if Iohexol or Cr-EDTA clearance has not been performed prior to inclusion (see h.).

**14 Discontinuation**

The criteria for enrolment must be followed explicitly. If a patient who does not meet enrolment criteria is enrolled, that patient should be discontinued from the study, but included in the analysis. Other reasons for discontinuation:

- The patient decides to discontinue
- Safety reasons

**15 Adverse Events**

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product regardless of its causal relationship to the study treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and

interviews of a study participant, or upon review by a study monitor. All AEs occurring up to 4 weeks after end of study treatment must be documented appropriately regardless of relationship.

Information to be collected includes event description, time of onset, clinician's assessment of grade, relationship to study product (assessed only by those with the training and authority to make a diagnosis), seriousness, action taken with study drug, outcome, and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE. Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Serious adverse events (SAE) occurring at any time after study initiation or within 30 days after end of study treatment should be reported by the PI to the Sponsor within 24 hours after the investigator is notified about the event.

SAE is defined as an event leading to:

- Death
- Hospitalization – or prolonged hospital stay (unless hospitalization is unrelated to study therapy or study procedures)
- A life-threatening experience
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Suspected unexpected serious adverse reactions (SUSARs) will then be further reported by the Sponsor to the Norwegian or Swedish Medicines Agency and Ethics Committee within 15 days according to current regulations or within 7 days if fatal or life threatening.

An annual safety report will be sent by the sponsor to the national Medicines Agency listing all suspected SAE over this period and report the subject's safety.

## 16 Evaluations

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### 16.1 Relapse rate and Survival

**RR (Relapse rate)** is measured from the date of randomization to the first date of objective relapse of disease. RR will be censored at the date of the patient's last tumor assessment prior to the cut-off date. Statistical survival analyses will be done with Kaplan Meier. Log rank test will be used for comparing groups.

**OS (Overall survival)** is measured from the date of randomization to the date of death from any cause (or last prior contact/observation).

### 16.2 Health related quality of life

HRQoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the testicular cancer specific module TC26. The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients in general, the TC26 measures symptoms commonly associated with testicular cancer and its treatment. The patients will report HRQoL at the following time points:

- Before inclusion
- At evaluation after adjuvant chemotherapy
- 3, 12, 36, 60 and 120 months after adjuvant treatment

All HRQoL scores will be transformed to a scale from 0 to 100 according to the EORTC scoring manual. A difference in mean scores of >10 is considered clinically relevant. The calculated sample size will have enough power to detect a significant difference of at least 11 points between the two arms. For group comparisons of baseline scores during and after chemotherapy, and changes in scores from baseline, the Mann–Whitney test will be used. Time to change of > 10 points will be assessed. Primary HRQoL-endpoints are Global QoL, physical function and fatigue. Other exploratory HRQoL-analyses will be conducted.

Fatigue will be evaluated using the fatigue questionnaire at same time points as EORTC HRQoL.

### 16.3 Short-term toxicity

Short-term toxicity will be assessed at visit III, four weeks after adjuvant treatment. Short-term toxicities are defined from reported blood values, and reported adverse event. Toxicity will be classified and graded according to CTCAE 4.0.

### 16.4 Long-term toxicity

The long-term toxicity will be assessed by changes in the cardiovascular risk profile, sex hormones at 12, 36, 60 and 120 months after adjuvant treatment, and GFR after 12 months.

### 16.5 Radiological evaluation of relapse

Almost all relapses occur in the abdomen and MRI will be the modality by which most relapses are detected. If a marker negative relapse is suspected additional imaging with PET-CT should be performed. Only in case of unequivocal progression or rising markers should treatment of relapse start without obtaining histological verification.

As relapse is to be confirmed morphologically there is no need for a central radiological evaluation.

## 17 Organization of the study

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The study will be conducted by the Swedish and Norwegian testicular cancer group (SWENOTECA) ([www.swenoteca.org](http://www.swenoteca.org)) – which is a collaborative group of physicians from disciplines involved in diagnosis, staging, treatment and follow-up of testicular cancer in Sweden and Norway. The group develop binational guidelines for treatment of testicular cancer, as well as conducting clinical research on testicular cancer. All hospital treating testicular cancer in Sweden and Norway take part in the SWENOTECA collaboration. The SWENOTECA group has published several publications on the treatment on all groups of testicular cancer patients (40, 44, 45). The study has been discussed in the working group of SWENOTECA and all members agree to conduct this study.

The principal investigators will be Torgrim Tandstad, MD, PhD and Olof Ståhl, MD, PhD. Tandstad is a specialist in oncology at the Cancer Clinic at St. Olavs University Hospital in Trondheim, Norway, and he is the chairman of the SWENOTECA. Ståhl is a specialist in oncology at the Department of Oncology at Skåne University Hospital in Lund, Sweden, and a member of the SWENOTECA study group.

The study management will consists of personnel at the office of clinical cancer research at St. Olavs Hospital. St. Olavs Hospital, represented by The Cancer Clinic will be sponsor and the responsible research institution for the study.

### 17.1 Data handling and archiving

Data will be collected electronically and archived at St. Olavs University Hospital in Trondheim, Norway for a minimum of 15 years after the end of the study. The sponsor will provide each site with a CD containing site specific data, to be stored for a minimum of 15 years after the end of the study.

### 17.2 Quality control and monitoring

All participating institutions must agree to trial-related monitoring, audits, IRB/IEC reviews and regulatory inspections providing direct access to source data/documents. The study has a detailed monitoring plan as an addendum to the study protocol.

## 18 Risk benefit analysis

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Adjuvant chemotherapy in the form of adjuvant carboplatin is in international guidelines considered a standard treatment option in clinical stage I seminoma(39). One course of adjuvant cisplatin-based chemotherapy is on the other hand a standard treatment option in CS I nonseminoma(46). Both treatment arms therefore represent standard treatment options in CS I testicular cancer.

However, adjuvant BEP represents an increased treatment burden compared to adjuvant carboplatin. The duration of treatment is five days for BEP ACT versus one day in carboplatin ACT. The short-term toxicity also favours adjuvant carboplatin, with less haematological toxicity and no loss of hair. Within two large SWENOTECA publications we found no treatment related deaths from adjuvant chemotherapy, 573 patients were treated with adjuvant carboplatin and 517 patients with adjuvant BEP(43, 46).

The potential long-term consequences of a single cycle of BEP are likely to be few. The extensive data on long term sequelae such as hypogonadism, neurotoxicity, reduced fertility, paternity and cognition all suggest that the risk is increasing with the burden of treatment, although data regarding secondary cancers and cardiovascular disease after 1-2 cycles of chemotherapy are still lacking (31, 47-49).

In the case of relapse patients are in need of a minimum of three courses of BEP chemotherapy, with a minimum treatment duration of 9 weeks and an increased risk of Secondary cancers and cardiovascular disease constitute the most serious late effects, while other late and long-term effects include pulmonary toxicity, nephrotoxicity, neurotoxicity, ototoxicity, infertility, hypogonadism as well as several psychosocial sequelae(50).

We consider the possibility of reducing the risk of relapse, and thereby the consequent risk of salvage therapy to outweigh the increased treatment burden of adjuvant BEP chemotherapy compared to adjuvant carboplatin.

## 19 Ethical considerations

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This study will be conducted in compliance with the protocol and in accordance with the ethical principles put forward in the Declaration of Helsinki and in accordance with GCP rules.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. The investigators will submit the study protocol and any accompanying material (such as patient information sheets) provided to the patient to an Independent Ethics Committee, IEC,

Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigators specifying the date on which the committee met and granted the approval.

The investigators must also submit any modifications made to the protocol after receipt of the IEC approval in accordance with established procedures and regulatory requirements.

## 20 Publication

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The results will be submitted for publication in international peer-reviewed medical journals, and abstracts presenting preliminary results will be submitted for presentation at international meetings. Authorship will be defined according to the Vancouver Rules.



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