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

A randomized phase III study comparing paclitaxel (Taxol) – BEP (T-BEP) to standard BEP with in intermediate prognosis germ cell cancer (GCC); An intergroup study of EORTC, German TCSG/AUO , MRC/UK NCRI and Spanish GCC Group (EORTC 30983).

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EORTC GENITO-URINARY CANCER COOPERATIVE GROUP
EORTC PROTOCOL 30983 RANDOMIZED PHASE II/III STUDY OF TAXOL-BEP VERSUS BEP IN PATIENTS WITH INTERMEDIATE PROGNOSIS GERM CELL CANCER

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1. BACKGROUND AND INTRODUCTION

2. OBJECTIVES OF THE TRIAL

2.1. Phase II

2.1.1. To determine the CR rates obtained with T-BEP and BEP in patients with intermediate prognosis germ cell cancer

2.1.2. To further define the toxicity profile of T-BEP

2.2. Phase III

2.2.1. Primary endpoint

2.2.1.1. To compare disease-free survival between the 2 treatment arms

2.2.2. Secondary endpoints

2.2.2.1.To compare the CR rates and overall survival between the 2 treatment arms

2.2.2.2.To document symptoms and aspects of quality of life at baseline and after treatment, and acute and intermediate (1-2 years) side effects of treatment

3. PATIENT SELECTION CRITERIA

3.1. Eligibility criteria

3.1.1. Histologically proven germ cell cancer. Both seminoma and non-seminoma are allowed. Note: patients with histologically pure seminoma but with an elevated level of AFP should be regarded combined seminoma / non-seminoma and must be reported as such upon registration.

3.1.2. Fulfilling the criteria of the intermediate prognosis group according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification.

Intermediate prognosis :

3.1.2.1.Non-seminoma :

- Testis/ retroperitonal primary **and**
- Intermediate markers* **and**
- No non-pulmonary visceral metastases

* intermediate markers:	AFP $\geq$ 1,000 and $\leq$ 10,000 iu/l or
(nadir value after primary surgery)	HCG $\geq$ 5,000 and $\leq$ 50,000 iu/L or
	LDH $\geq$ 1,5 x N and $\leq$ 10 x N*
	none of them above upper limit

* denotes upper normal value

3.1.2.2. Seminoma

- Any primary site
- Any LDH and any HCG
- Non-pulmonary visceral metastases present
- AFP within normal range

3.1.2.3. Age ≥ 16 years and ≤ 50 years, male sex

3.1.2.4. WHO Performance Status 0, 1 or 2.

3.1.2.5. Creatinine clearance ≥ 40 ml/min.

3.1.2.6. WBC ≥ 3.0 x 10^9/l, and platelets ≥ 100 x 10^9/l.

3.1.2.7. No previous chemotherapy

3.1.2.8. Before patient registration/randomization, informed consent must be given according to ICH/EU GCP, and national/local regulations.

<u>3.2. Exclusion criteria</u>

3.2.1. Patients with <u>all</u> of the characteristics of the good prognosis group

3.2.2. Patients with <u>any</u> of the characteristics of the poor prognosis group

3.2.3. Previous chemotherapy

3.2.4. Patients with a second malignancy except basal cell skin cancer

3.2.5. Age < 16 years, or > 50 years

3.2.6. Female sex

3.2.7. WHO-PS 3 or 4.

3.2.8. Patients with a renal function impairment; creatinin clearance < 40 ml/min, <u>unless</u> this is due to obstructive uropathy that can be relieved by nephrostomy

3.2.9. Patients with liver function impairment; bilirubin > 1.25 x N and/or ASAT > 2xN

3.2.10. Patients with pre-existing neuropathy.

3.2.11. Patients with other serious illness or medical conditions incompatible with the protocol

<u>4. TRIAL DESIGN AND SCHEME</u>

A randomized phase II that will extend into a phase III study of 4 cycles of Taxol-BEP versus 4 cycles of BEP in intermediate prognosis germ cell cancer.

Treatment scheme

Patient groups		Treatment arms
Non-seminoma All of the following - Testis or retroperitonal primary and - No non-pulmonary visceral metastases and - AFP ≥ 1.000 and ≤ 10.000 iu/l or HCG ≥ 5.000 and ≤ 50.000 iu/l or LDH ≥ 1.5 x N and ≤10 x N None of them above upper limit *Seminoma* All of the following - Any primary site - Any LDH, any HCG and - Non-pulmonary visceral metastases present	R A N D O M I Z A T I O N	T-BEP 4 cycles BEP 4 cycles

T-BEP

Taxol	175 mg/m^2 in a 3 hours infusion day 1		q 3 weeks
Cisplatin	20 mg/m^2	i.v. days 1-5	q 3 weeks
Etoposide	100 mg/m^2	i.v. days 1-5	q 3 weeks
Bleomycin	30 mg	i.v. days 2,8,15	q 3 weeks

G-CSF (filgrastim) 5 µg/kg s.c. days 6-15

BEP

Cisplatin	20 mg/m^2	i.v. days 1-5	q 3 weeks
Etoposide	100 mg/m^2	i.v. days 1-5	q 3 weeks
Bleomycin	30 mg	i.v. days 2,8,15	q 3 weeks

G-CSF (filgrastim) as secondary prophylaxis only

5. THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATIONS

5.1. DRUG ADMINISTRATION

5.1.1. BEP will consist of:

Cisplatin	20 mg/m^2	i.v. days 1-5
Etoposide	100 mg/m^2	i.v. days 1-5
Bleomycin	30 mg	i.v. days 2,8,15

Secondary prophylaxis with G-CSF (Filgrastim) 5 µg/kg s.c, days 6-15, according to the guidelines depicted in paragraph 5.1.7.

Every 3 weeks for a total of 4 cycles.

T-BEP will consist of:

Taxol 175 mg/m^2 in a 3-hour infusion on day 1, followed by

Cisplatin	20 mg/m^2	i.v. days 1-5
Etoposide	100mg/m^2	i.v. days 1-5
Bleomycin	30 mg	i.v. days 2,8,15

G-CSF (Filgrastim), 5 µg/kg s.c., days 6-15, will be used in T-BEP treated patients during all cycles, according to paragraph 5.1.7.

Every 3 weeks for a total of 4 cycles.

5.1.2. Cis-diammine-dichloro-platinum

For chemotherapy with DDP we use a daily times five regimen, the second cycle starting on day 22. During each cycle the patient will have an i.v. line until 24 hours after the completion of the last DDP administration. On the first treatment day prehydration with saline will be given as depicted in the table. DDP 20 mg/m^2, daily for 5 days will be administered in 1000cc saline in a 4 hour period. An additional 2 litres of saline will be infused over the next 16 hours. Suppletion with 40 mmol KCl and 8 grams $MgSO_4$ daily is mandatory in all patients (both BEP and T-BEP) in all cycles (see paragraph 5.3.2.a). This procedure will be repeated daily up to the end of the treatment cycle to maintain optimal diuresis. On day 6 another 2 litres of saline will be infused. If urine output is insufficient (less than 600 ml/6 hours) 10 mg of furosemide (Lasix^R) should be given by i.v. bolus since this low dose is safe and yet effective. The use of higher doses of furosemide should be avoided, because of the hazard of additional toxicity to the renal tubule when DDP is given.

5.1.3. VP 16-123, etoposide

VP-16 will be given in 500 ml of saline over a period of 1 hour of each treatment cycle at a dose of 100 mg/m^2 daily on days 1-5. If the VP-16 solution is prepared between 2 and 12 hours before the planned infusion, a maximum concentration of 0.5 mg/ml is advised which may thus require the use of 1000 ml of saline. VP-16 solutions should not be prepared more than 12 hours before administration.

5.1.4. Bleomycin

Bleomycin 30 I.U. will be given in 100 ml saline over a minimum of 30 minutes on day 2 of the first treatment cycle and every week thereafter times 12.

5.1.5. Taxol administration

Taxol (Paclitaxel) is supplied as a concentrated sterile solution, 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol USP 50%. The contents of the vial **must be diluted as required before use.**

Shelf life surveillance of the vial product is ongoing. Concentrations of 0.6 mg/ml in 5% dextrose or normal saline solution have demonstrated chemical and physical stability for at least 24 hours at room temperature.

The intact vial should be stored under refrigeration at 2 - 8 degrees Celsius.

Solution preparation

Taxol is administered as a continuous infusion in 500 cc normal saline (NS) over 3 hours. (**Note**: Infusions should be mixed as closely as possible to the start of each infusion period).

NOTE:

A small number of fibers within acceptable limits of USP Particulate Matter Test for LVP have been observed; hence **IN-LINE FILTRATION** is necessary with all Taxol infusions. Cellulose acetate filters, with 0.22 microns pore size (such as IVEX II) can be used for this purpose. Filtration could be performed during reconstitution. Solutions exhibiting excessive particulate formation should not be used. **POLYVINYLCHLORIDE (PVC) BAGS AND SETS SHOULD BE AVOIDED** since cremophor may leach plasticizer from such products. This consideration applies also to the material (such as syringes) used during reconstitution.

Infusion schedule

All patients receiving Taxol receive premedication according to the schedule, half an hour before the start of the Taxol infusion.

TAXOL: premedication		
Dexamethasone	10 mg iv	0.5 hour prior to Taxol
Clemastine (Tavegil)	2 mg iv	0.5 hour prior to Taxol
Ranitidine (Zantac)	50 mg iv	0.5 hour prior to Taxol

5.1.6. Time table of T-BEP drug administration and electrolyte (KCl and $MgSO_4$) suppletion.

TAXOL/CISPLATIN day 1		**CISPLATIN** days 2-5	
-030 HRS START PREMEDICATION		NO PREMEDICATION	
-00.30 hrs	Premedication		
00.00 hrs	Taxol in NaCl 0,9% 500 cc	00.00 hrs	NaCl 0,9% 500 cc
	Zofran 8 mg in 100 cc NaCl 0.9%		Zofran 8 mg + Dexamethason 10 mg in 100 cc NaCl 0,9%
03.00 hrs	Etoposide in 500 cc Nacl 0.9%	03.00 hrs	Etoposide in 500 cc Nacl 0.9%
04.00 hrs	Cisplatin in 1000 cc NaCl 0,9%	04.00 hrs	Cisplatin in 1000 cc NaCl 0,9%
08.00 hrs	NaCl/Gluc 1000 cc + 20 mmol KCl + 4 gr $MgSO_4$	08.00 hrs	NaCl/Gluc 1000 cc + 20 mmol KCl + 4 gr $MgSO_4$
16.00 hrs	NaCl/Gluc 1000 cc + 20 mmol KCl + 4 gr $MgSO_4$	16.00 hrs	NaCl/Gluc 1000 cc + 20 mmol KCl + 4 gr $MgSO_4$
	Bleomycine 30 mg in 100 cc NaCl on day 2		

5.1.7. G-CSF Filgastrim administration

BEP

In the BEP arm filgrastim (Amgen) will be used for secondary prophylaxis <u>only</u>. Filgrastim is commercially available. <u>Secondary prophylaxis</u> with G-CSF will consist of 5 µg/kg per day, s.c., days 6-15. G-CSF will be continued after day 15 if WBC have not recovered to $\geq 2.0 \times 10^9$/l. If G-CSF is continued after day 19, the next cycle of BEP should be postponed until a minimum of 96 hours following the last dose of G-CSF.

T-BEP

Patients on T-BEP will be administered G-CSF, filgrastim (Amgen), in <u>all</u> cycles. Filgrastim is commercially available.

G-CSF 5 µg/kg per day will be given from days 6-15.

G-CSF will be stopped before day 15 only if following the nadir value WBC have recovered to $> 10 \times 10^9$/l.

G-CSF will be continued after day 15 if WBC have not recovered to $\geq 2 \times 10^9$/l.

If G-CSF is continued after day 19, the next cycle of T-BEP is postponed until a minimum of 96 hours following the last administration of G-CSF.

5.2. DRUG TOXICITY

5.2.1. Cis-diammine-dichloro-platinum (DDP)

The most important toxicity is nausea and vomiting, that can largely be prevented with the administration of a $5HT_3$ receptor antagonist plus dexamethasone prior to the DPP infusion. Renal function impairment can be largely prevented by forced diuresis. High-pitch hearing loss may occur. Myelosuppression reaching its nadir at day 10-14 is often seen, but is not severe. Anaphylactic reactions are rare. In case of infectious complications following treatment, aminoglycosides should be avoided because of potential additional toxicity to the kidney [7].

5.2.2. VP 16-213 (Vepesid^R)

Nausea and vomiting have been experienced by 25% of patients. Myelosuppression is the major side effect. Infrequent side effects include stomatitis, phlebitis, fever, chills, and allergic reactions. Etoposide causes alopecia.

5.2.3. Bleomycin.

Pneumonitis and lung fibrosis are the most important side effects of bleomycin. Fever, rigors, and skin toxicity may occur as well. The risk of these complications increases with the total dose employed. Dyspnea on exertion and the development of fine rales at auscultation may precede chest X-ray abnormalities. In these cases, and if infectious lung complications, except bronchitis, occur, bleomycin should be stopped. In case of surgical procedures or respiratory insufficiency oxygen therapy should be carried out with caution because of the increased risk of oxygen toxicity to the lung in bleomycin treated patients.

5.2.4. Taxol

Myelosuppression is the major side effect. With the use of anti-allergic premedication hypersensitivity (allergic) reactions are rarely observed. **Guidelines for management of allergic reactions are specified in paragraph 5.3.2.6.** Occasionally paraesthesias or numbness of fingers and toes is seen, which is usually tempory. Occasionally slowing of the heart rate is observed, which is usually asymptomatic. Mucositis, diarrhea, nausea and vomiting are mild. Taxol causes total body hair loss, which is reversible. Side effects are in general reversible when treatment is stopped.

5.3. DOSE MODIFICATIONS

In this protocol the toxicity (both acute and intermediate) will be measured using the NCI-CTC version 2.0. scale.

5.3.1. Hematologic toxicity

5.3.1.1. BEP: Dose modifications for VP-16 and CDDP

If at the start of a treatment cycle WBC has not recovered to ≥ 1.5 x 10^9/l, nor was such recovery observed in patients treated with secondary prophylaxis with G-CSF, treatment is delayed for 4 days. The same applies if at the start of a treatment cycle platelets are < 50 x 10^9/l. If WBC have recovered to between 1.5 x 10^9/l and 2.0 x 10^9/l and platelets are between 50 x 10^9/l and 100 x 10^9/l, use the following scheme for dose modifications in this cycle.

BEP dose modifications: % of starting dose

Platelets x 10^9/l	≥ 100		75-99		50-74		< 50	
WBC x 10^9/l	VP-16	DDP	VP-16	DDP	VP-16	DDP	VP-16	DDP
≥ 2.0	100	100	75	100	50	100	delay 4 days	
1.5-1.99	75	100	50	100	50	75	delay 4 days	
< 1.5	delay 4 days		delay 4 days		delay 4 days		delay 4 days	

Decisions for dose modifications in a given cycle should be made on the values obtained at retreatment day, i.e. dose modifications made in previous cycles should not be maintained. In the treatment of complicated neutropenia and/or to avoid dose-delay and/or dose reductions in subsequent cycles the use of G-CSF is strongly advised (paragraph 5.1.7.).

However, in case of complicated neutropenia i.e. grade 3 and 4 infections despite secondary G-CSF prophylaxis, or neutropenia grade 4 lasting for more than 7 days despite G-CSF, or grade 4 thrombocytopenia lasting for more than 3 days or requiring platelet transfusions, the dose modifications should be maintained in all remaining cycles. No dose reduction should be made for myelosuppression during a given treatment cycle. In addition, no dose modification should be made based on the nadir of a previous cycle.

5.3.1.3 . T-BEP dose modifications of taxol, etoposide and cisplatin

If at the start of a treatment cycle WBC has not recovered to ≥ 1.5 x 10^9/l, nor was such recovery observed at the time of cessation of G-CSF, treatment if delayed for 4 days. The same applies if the start of a treatment cycle platelets are < 50.

If WBC have recovered to between 1.5 x 10^9/l and 2.0 x 10^9/l at any time during the past week, and platelets are between 50 x 10^9/l and 100 x 10^9/l, use the following scheme for dose modifications in this cycle.

T-BEP dose modifications: % of starting dose

Platelets x 10^9/l	≥ 100	75-99	50-74	< 50

WBC x 10^9/l	Tax	VP-16	DDP	Tax	VP-16	DDP	Tax	VP-16	DDP	Tax	VP-16	DDP
≥ 2.0	100	100	100	75	75	100	0	50	100	delay 4 days		
1.5-1.99	50	75	100	50	50	100	0	50	75	delay 4 days		
< 1.5	delay 4 days			delay 4 days			delay 4 days			delay 4 days		

Decisions for dose modifications in a given cycle should be made on the values obtained at that occasion, i.e. dose modifications made in previous cycles should not be maintained.

However, in case of complicated neutropenia i.e. grade 3 and 4 infections, or neutropenia grade 4 lasting for more than 7 days, or grade 4 thrombocytopenia lasting for more than 3 days or requiring platelet transfusions, the dose modifications should be maintained in all remaining cycles.

5.3.2. Dose Modifications for Non-Hematological Toxicity

5.3.2.1 Renal function impairment (both arms)

DDP should not be reduced unless the creatinine clearance falls below 40 ml/min. Then DDP will be stopped. If renal function recovers DDP should be resumed at 75% of prior dose.

BLM should be stopped if the creatinine clearance falls below 40 ml/min, as accumulation may then occur.

VP-16 has a low renal clearance: dose modification according to renal function is not advised.

For **T-BEP** only:

Taxol has a low renal clearance: dose modification according to renal function is not advised.

5.3.2.2 Mucosal toxicity (both arms)

Following the development of severe (grade 3 or 4) mucosal toxicity, the next cycle of chemotherapy will be delayed until recovery of this toxicity.

For **T-BEP** only:

Following grade 3 or 4 diarrhea, the dose of Taxol in subsequent cycles must be reduced by 25%.

5.3.2.3 Diarrhea (both arms)

Following the development of severe (grade 3 or 4) diarrhea, the next cycle of chemotherapy will be delayed until recovery of this toxicity.

For **T-BEP** only:

Following grade 3 or 4 diarrhea, the dose of Taxol in subsequent cycles must be reduced by 25%.

5.3.2.4 Skin toxicity (both arms)

The development of severe skin toxicity (e.g. peeling) is a reason for termination of BLM until the skin has recovered. BLM should be reinstituted thereafter.

5.3.2.5 Pulmonary toxicity (both arms)

Following the development of dyspnea on exertion, fine rales, chest X-ray abnormalities or significant decrease in pulmonary function thought to be due to BLM lung toxicity discontinue BLM permanently. A dropin vital capacity (VC) below 80% of the value measured at the beginning of therapy, or reductions of more than 20% of the carbomonoxide diffusion (DLCO) capacity also require the cessation of BLM. Patients who have received BLM are at increased risk of oxygen to the lung. If they subsequently require surgery or develop respiratory insufficiency, oxygen therapy must be used with great caution. Oxygen flow rate (FiO_2) during and after anaesthesia should not exceed 25%.

5.3.2.6 Allergic reactions (both arms)

Allergic reactions to DDP have been observed including wheezing, facial flush, skin eruptions and anaphylactic shock. If patients develop allergic reactions DDP should be given under the protection of anti-histamines and steroids. If anaphylaxis occurs DDP should be stopped permanently. Hypotensive reactions to VP-16 rarely is an allergic reaction. Most often it is a toxic reaction to the transport vehicle for i.v. administration. Slow infusion will prevent this side effect.

Allergic (hypersensitivity) reactions to Taxol:

For significant hypersensitivity reactions (hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria), ® **discontinue Taxol infusion.**

For other hypersensitivity reactions, the Taxol infusion may be discontinued at the investigator's discretion.

The following management of hypersensitivity reactions is recommended:

Administer clemastine (Tavegil) 2 mg iv. Administer epinephrine 0.35 - 0.5 cc s.c. every 15 - 20 minutes until the reaction subsides or a total of six doses is given.

If hypotension is present that does not respond to epinephrine, administer IV fluids.

If wheezing is present that is not responsive to epinephrine, administration of 0.35 cc of nebulized salbuterol solution is recommended. Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent), may be administered to prevent recurrent or ongoing allergy manifestations.

Guidelines for rechallenge after a hypersensitivity reaction:

a. Following an interruption of Taxol due to a hypersensitivity reaction, patients may be retreated if the investigator judges it to be appropriate.
   If the investigator evaluates that rechallenge is not appropriate the patient will be taken off study.
b. **ALL PATIENTS WILL RECEIVE A PROLONGED (24 hour) INFUSION of TAXOL.**
   As will be seen below, the retreatment procedure will actually cause the Taxol infusion to be slightly longer than 24 hours.
c. If less than 75% of the Taxol dose was infused prior to the hypersensitivity reaction, retreatment should take place as soon as can be arranged within 72 hours. The amount of Taxol to use at time of retreatment should be the total Taxol dose less the amount infused before the Taxol infusion was stopped for the hypersensitivity reaction.
d. **Retreatment procedure:**
   i. Dexamethasone 8 mg **intravenously** 24,18, 12, 6 hours prior to Taxol.
   ii. Clemastine (Tavegil) 2 mg iv 30 minutes prior to Taxol.
   iii. Ranitidine 50 mg iv 30 minutes prior to Taxol.
   iv. Give Taxol in usual volume but at **ONE QUARTER OF THE PLANNED RATE OF A 24 HOUR IV INFUSION OVER THE FIRST SIX HOURS.** Patient should be carefully observed for this period. Thereafter, if no reaction has been seen, the rate may be increased to the normal infusion speed. The entire infusion time will be somewhat longer than 24 hours because the first 6 hours were given at a slower rate. The total infusion time will be approximately 28.5 hours.

e. **Subsequent cycles:**
   i. If hypersensitivity reactions requiring discontinuation of the Taxol infusion **RECURS** using the above-mentioned described procedure, the patient should **GO OFF PROTOCOL THERAPY AND NOT RECEIVE TAXOL AGAIN.**
   ii. If the patient is succesfully retreated using this procedure without the recurrence of a reaction requiring discontinuation of the infusion, **THIS RETREATMENT PROCEDURE MUST BE USED IN ALL SUBSEQUENT TAXOL ADMINISTRATIONS.**

5.3.2.7 Ototoxicity (both arms)

T-BEP:

In the T-BEP dose-finding study, several patients had tinnitus during treatment, that appeared not to worsen during the course of treatment and was reversible in all cases.

The dose of cisplatin and/or taxol should therefore not routinely be reduced for tinnitus in between cycles. However, should there be increasing tinnitus in patients on T-BEP, taxol should be withheld until recovery, and treatment should continue with BEP. If tinnitus recovers, in subsequent cycles taxol could be resumed at 75% of prior dose.

Both arms:

Following development of clinically significant hearing loss (either on T-BEP or BEP), patients may be taken off study and treated according to the investigator's discretion.

5.3.2.8 Neurotoxicity -

T-BEP:

Neuropathy may develop after cisplatin and taxol. Taxol should be stopped in case of CTC grade 2 neurosensory and/or neuromotor toxicity. In case of grade ≥ 3 neurotoxicity, both taxol and cisplatin should be stopped, and patients may be taken off study and treated according to the investigator's discretion.

BEP:

In case of grade ≥ 3 neurotoxicity, cisplatin should be stopped, and patients may be taken off study and treated according to the investigator's discretion.

5.3.2.9 Hypomagnesemia (both arms)

In the **T-BEP** dose-finding study several patients had Mg values of < 0.40 mmol/l despite standard administration of 6 grams $MgSO_4$ per day during the days of chemotherapy. Following increase of $MgSO_4$ suppletion no additional cases of severe hypomagnesimia were observed. After completion of the chemotherapy there were no cases of sustained hypomagnesemia.

Based on this observation <u>suppletion of 8 grams $MgSO_4$ i.v. per day will be given in all patients, both on T-BEP and on BEP.</u>

<u>6. CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP</u>

<u>6.1. Examinations before treatment start</u>

6.1.1. Physical examination with special reference to supraclavicular lymph nodes, hepatomegaly, palpable abdominal mass and pathologic inguinal lymph nodes.

6.1.2. Whole blood count, serum creatinine, creatinine clearance, Na, K, Ca, P, Mg, bilirubin Alkaline Phosphatase, ASAT.

6.1.3. AFP, HCG and LDH samples should be taken at day 1 of the start of treatment. AFP, HCG, LDH entry values should never be more than 1 week old at the start of treatment.

6.1.4. Chest X-ray.

6.1.5. CT-scanning at ≥ 1 cm intervals of the abdomen and the chest are mandatory. Tumour diameters must be measured in cross-sectional diameters. CT Scans must be repeated if the start of treatment is delayed for ≥ 3 weeks.

6.1.6. Audiometry (obligatory) and pulmonary vital capacity and/or DLCO capacity (optional). The minimal requirements for audiometry will consist of measurements in the 4000 Hz area.

6.1.7. Fertility examination; sperm quality and sperm count.

6.2. Examinations during remission induction treatment

6.2.1. Before each treatment cycle: physical examination, whole blood cell count, serum creatinine, creatinine clearance, Na, K, Ca, P, Mg, bilirubin, Alkaline Phosphatase, ASAT, LDH, HCG, AFP, chest X-ray.

6.2.2. During the out-clinic period: weekly physical examination, whole blood cell count, serum creatinine, Na, K, Ca, P, Mg, LDH, HCG, AFP.

Summary table of examinations before and during treatment

	Before treatment starts	**During treatment**		**Within 6 weeks of end of treatment**
		Before each period (weekly)	**During Out clinic cycle**	
Physical examination	**x**	**x**	**x**	**x**
Blood cell count	**x**	**x**	**x**	
Creatinine, Na, K, Ca, P, Mg	**x**	**x**	**x**	**x**
Creatinine clearance	**x**	**x**		**x**
Alkaline phosphatase, bilirubin, ASAT	**x**	**x**		
b-HCG, AFP and LDH	**x**	**x**	**x**	**x**
Chest X-ray	**x**	**x**		
CT-Scan	**x**			**x**
Audiometry	**x**			**x**[1]
Pulmonary capacity: FVC and/or DLCO	**x**			**x**[1]
Fertility examination	**x**			

1: earlier in case of symptoms, within 6 weeks of the end of chemotherapy otherwise

<u>6.3. Examinations at the end of the induction treatment.</u>

6.3.1. Within 3-6 weeks after the start of the last cycle of chemotherapy, and earlier at the occurrence of symptoms: audiometry (obligatory) and pulmonary vital capacity and/or DLCO capacity (optional). The minimal requirements for audiometry will consist of measurements in the 4000 Hz area.

6.3.2. Assessment of presence of residual masses

To determine whether there is evidence of a residual mass after chemotherapy, all previous tumour sites should be evaluated upon completion of induction chemotherapy, which should be performed between 3 and 6 weeks after the starting day of the last scheduled cycle. This evaluation should include physical examination, HCG. AFP, LDH, CT-scanning of previous lung lesions, CT-scanning of previous abdominal lesions and any other radiological examination necessary to evaluate previous tumour sites.

<u>6.4. Follow-up studies after the end of treatment</u>

6.4.1.Follow-up studies after the completion of chemotherapy are given in the table. All patients need to be followed for long-term survival.

Schedule of assessments after the end of the treatment

	1st year	2nd	3rd	4th	≥ 5th
Physical examination (blood pressure once a year)	monthly	every 2 months	every 3 months	every 6 months	once a year
Blood cell count	every 6 months	every 6 months	every 6 months	every 6 months	once a year
Biochemistry: Creatinine, Na, K, Ca, P, Mg	monthly	every 6 months	every 6 months	every 6 months	once a year
Alkaline phosphatase, bilirubin, ASAT	every 6 months	every 6 months	every 6 months	every 6 months	once a year
b-HCG, AFP and LDH	monthly	every 2 months	every 3 months	every 6 months	once a year
Chest X-ray	monthly	every 2 months	every 3 months	every 6 months	once a year
Fertility examination		once			

CT-Scans:

Patients who enter complete remission on chemotherapy alone should have follow-up CT-scans at 6 months, 1 year, 2 years, and 3 years after the completion of chemotherapy.

CT-scans should also be performed 1 month following explorative surgery for residual masses of non-seminomatous tumour.

Residual masses following chemotherapy for pure seminoma are followed by CT scanning at 3 monthly intervals for the first year, unless regression occurs. Masses that do not regress over the first year should be followed by further CT scans at 6 monthly intervals for 3 years after the completion of chemotherapy.

7. CRITERIA FOR THE EVALUATION OF ENDPOINTS

7.1. Evaluation of response-Guidelines for explorative surgery

7.1.1. Non-seminoma/Seminoma (all patients). Complete response with chemotherapy: every patient will receive 4 cycles of induction chemotherapy. Thereafter, patients with negative tumour markers and no clinical or radiological evidence of residual masses (abdominal lesions ≤ 1 cm and pulmonary lesions ≤ 0,5 cm on CT-scan), are classified as complete responders and will be followed without further therapy.

7.1.2. Non-seminoma (including combined Non-seminoma and Seminoma)

7.1.2.1. Explorative/debulking surgery for residual masses.

Physical and roentgenographic examinations are less reliable in the assessment of the response to chemotherapy because shrinkage of tumour may stop as a result of the development of fibrosis. Therefore, every patient with non-seminomatous tumour who becomes marker-negative during induction chemotherapy, but who has apparent evidence of residual disease defined as abdominal lesions greater than 1 cm or pulmonary lesions greater than 0,5 cm, should have explorative surgery within 6 weeks after the completion of the chemotherapy to remove the residual tumour for histological examination. Complete resection of residual masses should always be attempted. In case of residual retroperitoneal lymph node enlargements combined with residual lung lesions, the retroperitoneal masses have a higher priority for resection. Complete resection should also be attempted in case of mature teratoma to prevent the "growing mature teratoma syndrome" or the possible dedifferentiation to malignant teratoma [8].

7.1.2.2. Definitions of response at explorative/debulking surgery.

- Patients will be classified as complete responders if no viable cancer cells are detected in these specimens.
- Patients with mature teratoma that is completely resected are classified as complete responders.
- Patients with residual viable cancer that is completely resected are classified as No evidence of disease (NED after chemotherapy plus surgery).
- Patients with residual viable tumour that is not/cannot be completely resected are classified as Treatment Failures.

7.1.2.3. Treatment failure

Patients who have persistently elevated tumour markers after the completion of scheduled chemotherapy and those who have viable cancer cells in the resected specimens that is not completely resected, are classified as treatment failures and go off study, their further treatment being left at the discretion of the investigator. Patients who have persistently elevated tumour markers after 4 cycles are also classified as Treatment Failures and go off study, their further treatment being left at the discretion of the investigator. However, these patients will be followed for survival. It should be noted that tumour markers may not have normalized yet, despite a satisfactory half-life. If the (further) marker decline is considered appropriate by the investigator, patients must not be given further chemotherapy, and treatment decisions and final response classification postponed until either normalization or persistently elevated values have been obtained.

Patients with markers rising within 8 weeks from the start of the last chemotherapy cycle are also classified as Treatment Failures.

7.1.2.4. Inevaluable for Response:

Patients with residual non-seminoma who will not undergo explorative surgery and resection of the remants will be regarded Inevaluable for Response, but included in disease-free survival and survival analysis.

7.1.2.5. Guidelines for management of patients with residual viable cancer that is completely resected (NED after chemotherapy plus surgery): disease-free survival in patients who have residual viable cancer that is completely resected appears not to be influenced by additional chemotherapy (13). If there is concern about the completeness of the surgery (at the discretion of the investigator), 2 additional cycles of Vinblastine, Ifosfamide, Cisplatin (VeIP) are advised (14). Since there are no data on toxicity of T-BEP/EP if continued for more than 4 cycles, particularly cumulative neurotoxicity, it is strongly advised not to continue with T-EP.

7.1.3. Seminoma

7.1.3.1. Following the policy in non-seminoma, some centres have routinely performed resection of the residual tumour masses of seminoma. Residual vital seminoma has been found in < 10% of the operated specimens and this is mainly observed in residual lesions greater than 3 cm. Pronounced fibrosis significantly increases the risk of peri- and post-operative complications. Post-operative death is reported more frequently in the seminoma patients than in non-seminoma patients [17,19]. The masses, present immediately after chemotherapy usually shrink gradually during the first post-chemotherapy year.

The presence of fibrotic masses after chemotherapy, visible on CT makes the definition of complete response difficult in advanced seminoma. Therefore, patients with pure seminoma and residual lesions of greater than 1 cm in the abdomen or greater than 0.5 cm in the chest upon response evaluation, and from whom no post-chemotherapy histology is available are classified Inevaluable for Response. These patients are included in the rate and duration of disease-free survival.

7.1.3.2. Patients with residual masses following chemotherapy for pure seminoma are followed by CT scanning at 3 monthly intervals for the first year, unless regression occurs. If there is no regression after 6 months then biopsy should be considered. Biopsy documentation of residual seminoma is scored as Treatment Failure and management left at the discretion of the investigator.

7.2. Disease progression

Rising tumour markers above the upper limit of normal will be considered as an end-point indicating progression of disease. Values should be checked to exclude laboratory error. Clinical or radiological evidence of an increase in the size of residual lesion(s) or the occurrence of new lesions will also be considered as an end-point indicating progression of disease, with the exception of growing mature teratoma, documented at explorative surgery and histologic examination and that is completely resected.

7.3. Overall survival

Overall survival is computed as the time between the randomization of a patient at the date of his death. Deaths due to any cause are considered as events. Patients still alive at the time of the analysis are censored at the date of the most recent follow-up.

7.4. Disease-free survival

For patients with a complete response, a partial response, those not evaluable for response and the patients classified under ‘no evidence of disease’, the disease-free survival is calculated as the time from randomization to either the first progression of the disease or the date of death, whichever occurs first. Patients classified under ‘treatment failure’ are considered an event at the date of treatment failure. Patients still alive with no evidence of disease at the time of their last visit are censored at the time of the most recent information.

7.5. Assessment of toxicity

In this protocol the toxicity (both acute and intermediate) will be measured using the NCI-CTC version 2.0. scale. In grading the toxicity per cycle the worst grade observed is to be reported.

8. PATIENT REGISTRATION AND RANDOMIZATION

Patient registration/randomization will only be accepted from authorized investigators.
A patient can be randomized after verification of all eligibilty criteria. This must be done before the treatment starts. The procedure for randomizing the patients is as follows, depending on the affiliation of the institution (EORTC, German Testicular Cancer Study Group, French Group).
Randomization must be done **before the start of the treatment.**

Patients will be stratified at randomisation by histology (seminoma and non-seminoma) and by hospital. They will be randomised to either of

1. BEP, 4 cycles
2. T-BEP, 4 cycles

9. FORMS AND PROCEDURES FOR COLLECTING DATA

10. REPORTING OF ADVERSE EVENTS

11. STATISTICAL CONSIDERATIONS

11.1. Sample size calculation and statistical design

11.1.1. Phase II

The main endpoint of the phase II part of the trial will be the rate of complete response achieved on each treatment arm. The expected CR rate with the use of standard BEP in patients with intermediate prognosis germ cell cancer is 65% (P_0). It is aimed to achieve a CR rate with T-BEP of 80% (P_1). With the Optimum 2-stage Simon design (α=0.10, β=0.05), the first step will require 42 eligible patients in each arm. If less than 29 patients on T-BEP obtain CR, the trial is stopped after the first step of the phase II. If at least 29 of the 42 patients on T-BEP obtain a CR then the accrual is continued in phase II until 82 eligible patients are entered on each arm. At that time , if less then 59 patients achieve a CR on T-BEP, the trial is stopped and not continued into a phase III. If at least 59 of the 82 respond (72%), the trial will be continued in a phase III trial. With this design, there is 65% probability of stopping the trial early if the response rates with T-BEP were 65% and the maximum overall sample size for the phase II is 164 patients.

11.1.2. Phase III

The primary endpoint of the phase III part of the study will be Disease-Free Survival. Secondary endpoints include overall survival and response rate.

It is aimed to achieve an improvement in DFS at 3 years of 10%, from 75 to 85% which corresponds to a hazard ratio of 1.77. A total of 498 patients (249 in each arm) and 98 events are needed to ensure 80% power of detecting such a difference with a two-sided Logrank test at the 5% significance level.

Based on the expected patient numbers with intermediate prognosis germ cell cancer eligible for this trial which would be accrued by the groups (EORTC 60 patients per year, French Group and German group, 40 each) the trial should be completed in 4 years at the maximum. If the accrual is completed over a period of 4 years, the final analysis of the trial is expected to be performed one year after the entry of the last patient.

<u>11.2. Indepent Data Monitoring Committee</u>

The Independent Data Monitoring Committee will review the data at the end of the phase II part of the trial and will advise the PRC on the possibility of continuing the trial in the setting of a phase III. The PRC will then take the final decision to continue the trial into a phase III or to stop the trial. In order to prevent closing the trial between the phase II and the phase III stages, the trial may remain open for a maximum of 3 months after the number of patients required for the phase II has been accrued to enable the analysis of the phase II part to be performed and the meetings of the IDMC and the PRC to take place.

<u>11.3. Method of analysis</u>

<u>Phase II</u>

The rate of complete response will be calculated on eligible patients only. For the interim report only eligible patients will be used: tables of the toxicity will be provided by treatment arm, according to the treatment actually received by the patient and the survival status and the disease-free survival status will also be described, as well as the causes of death. Any reported serious adverse event will be described in detail. No formal comparison of the two treatment arms will be performed.

Phase III

The time-to-event endpoints will be analyzed on the intent-to-treat population (all randomized patients in the arm they assigned by randomization). Kaplan-Meier curves of the disease-free survival and overall survival will be computed by treatment arm and compared using a the logrank test (two-sided, 5% significance level).

The analysis will not be stratified for the stratification factors used at randomization (histology and institution). In case large imbalances in baseline patient characteristics are observed, the distribution will be compared using the Chi-square test (Fisher exact test if cells contain less than 5% of the patients) for dichotomous and categorical variables, the Chi-square test for linear trend for ordinal variables and the Wilcoxon-rank sum test for continuous variables. If significant ($P<0.05$) imbalances are found, the analysis will be repeated using the Cox proportional hazards regression model with appropriate covariates. This model will also be used for prognostic factor analyses. The complete response rates will be computed on all eligible patients and compared using the chi-square test. In case of imbalances or for prognostic factors analyses, the logistic regression model will be used. Rates of grade 3-4 toxicity will be calculated on all eligible patients in the treatment arm actually received. Suspected significant differences will be tested using the chi-square test.

12. QUALITY OF LIFE ASSESSMENT

Since quality of life is an endpoint of the phase III part of the trial it will also be assessed in all patients randomized into the phase II part of the trial.

QoL would be important since the continuation of taxol and cisplatin will induce grade 1 sensory neuropathy in a considerablenumber of the patients. Although grade 1 is not considered serious toxicity, we should not disregard its possible effects on the well-being of the patients. Also taxol results in severe hair loss (including pubic hair, axilla and sometimes eyebrows and eyelashes), which is not that extensive with BEP alone.

14. INDEPENDENT DATA MONITORING COMMITTEE

An independent Data Monitoring Committee will be formed. Toxicity data will be discussed at each meeting of the cooperative group, but efficacy results will not be presented at groups meetings before the trial is closed to recruitment. The role of the IDMC will be to review the results of the phase II part of the trial and to advise the Cooperative Group and the EORTC PRC on the decision to continue the trial into phase III. In the instance it is decided to pursue the trial into a phase III, the results of the phase II will remain confidential and will not be divulgated to either the EORTC GU Group or the medical community before the phase III is terminated and analysed.

15. QUALITY ASSURANCE

15.1. Control of data consistency

Data forms will be entered in the database of the EORTC Data Center by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies.

15.2. On site quality control

This trial will not be monitored by means of on-site visits.

16. ETHICAL CONSIDERATIONS

- **For the EORTC, see chapters 16.1, 16.2 and 16.3**
- **For the other participating Groups, see corresponding appendix**

16.1. Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice.

The protocol will by approved by the Local, Regional or National Ethics Committees.

16.2. Subject identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

16.3. Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol (appendix no. 5).

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

17. INVESTIGATOR COMMITMENT STATEMENT

addressed to the EORTC Data Center.

EORTC DATA CENTER
83, avenue Emmanuel Mounier, Bte 11
B - 1200 BRUSSELS, BELGIUM
Fax: 32-2-772.35.45

19. PROTOCOL SPONSORSHIP AND FINANCING

The sponsor of the study for the investigators belonging to the EORTC is the EORTCis the EORTC.

The Director General of the EORTC is:
Professor Françoise Meunier
EORTC Central Office
Avenue E. Mounier 83, Bte 11
1200 Brussels
Belgium
Tel.   0032-2-774 1641
Fax.   0032-2-771 2004

Taxol will be provided free of charge by Bristol Myers Squibb. All other medication, including G-CSF, will be commercially available. Since Amgen is lending support for the Datamanagement of this trial at the EORTC Data Center, filgrastim (Neupogen), Amgen/Roche is to be used in this trial. This applies both for patients on T-BEP and for patients on BEP who need secondary G-CSF prophylaxis.

20. TRIAL INSURANCE

21. PUBLICATION POLICY

- **For the EORTC:**

The final publication of the trial results will be written by the Study Coordinator on the basis of the statistical analysis performed at the EORTC Data Center. A draft manuscript will be submitted by the study coordinator to the Data Center for review no later than six months after receiving the Data Center report. After revision by the Data Center and other co-authors the manuscript will be sent to a major scientific journal. Authors of the manuscript will include at least the Study Coordinator and Study Co-coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and the Data Center data manager and statistician in charge of the trial.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the EORTC Data Center prior to submission.

Any publication, abstract or presentation based on patients included in this study must be approved by the Group Chairman, the Study Coordinator and the Study Co-coordinators. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published by the Study Coordinator.

The data of the phase II part of the trial will not be published or presented before the final results of the phase III are available in case the trial continues into phase III.

The title of all manuscripts will include “EORTC” and the names of the other participating Groups, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial.