

**Collaborative group for Adrenocortical Carcinoma Therapy
- COACT -**

CLINICAL STUDY PROTOCOL

**“First International Randomized trial in locally advanced and
Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT)”**

Etoposide, Doxorubicin, Cisplatin and Mitotane

vs.

Streptozotocin and Mitotane

April 24th 2004

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**First International Randomized trial in locally advanced and Metastatic
Adrenocortical Carcinoma Treatment (FIRM-ACT)
Protocol synopsis**

Sponsor	Collaborative group for Adrenocortical Carcinoma Treatment (COACT)
Objectives	To compare the efficacy of etoposide, doxorubicin and cisplatin plus mitotane (EDP/M) as first line treatment versus streptozotocin plus mitotane (Sz/M) as first line treatment
Study design	Randomized, prospective, controlled, open -label multicenter, parallel-group study
Sample size	300 patients (150 per regimen)
Inclusion criteria	<ul style="list-style-type: none"> • Histologically confirmed diagnosis of adrenocortical carcinoma • Locally advanced or metastatic disease not amenable to radical surgery resection (Stage III-IV) • Radiologically monitorable disease • ECOG performance status 0-2 • Life expectancy > 3 months • Age ≥18 years • Adequate bone marrow reserve (neutrophils ≥1500/mm³ and platelets ≥100.000/mm³) • Effective contraception in pre-menopausal female and male patients • Patient's written informed consent • Ability to comply with the protocol procedures (including availability for follow-up visits) • Previous palliative surgery, radiotherapy or radiofrequency ablation is acceptable as long as radiologically monitorable disease is verifiably afterwards.
Exclusion criteria	<ul style="list-style-type: none"> • History of prior malignancy, except for cured non-melanoma skin cancer, curatively <i>in situ</i> cervical carcinoma, or other cancers treated with no evidence of disease for at least five years. • Previous cytotoxic chemotherapy for adrenocortical carcinoma • Renal insufficiency (serum creatinine ≥2 mg/dl or creatinine clearance ≤ 50 ml/min) • Hepatic insufficiency (serum bilirubin ≥2 x the institutional upper limit of normal range and/or serum transaminases ≥ 3 x the institutional upper limit of normal range; exception: in patients on mitotane transaminase levels up to 5 x the institutional upper limit of normal range are acceptable) • Pregnancy or breast feeding • Known hypersensitivity to any drug included in the treatment protocol • Presence of active infection • Any other severe clinical condition that in the judgment of the local investigator would place the patient at undue risk or interfere with the study completion • Decompensated heart failure (ejection fraction <50%), myocardial infarction or revascularization procedure during the last 6 months, unstable angina pectoris, and uncontrolled cardiac arrhythmia • Current treatment with other experimental drugs and/or previous participation in clinical trials with other experimental agents for adrenocortical carcinoma • Prisoners

Endpoints	<p>Primary endpoint: to compare overall survival</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • To compare quality of life • To compare time to progression, best overall response rate, duration of response, and number of disease-free patients • To assess the impact of mitotane blood levels between 14-20 mg/l in both regimens on survival and response • To assess the effects of both schemes as a second line treatment in case of failure of the other regimen (measured by best overall response)
Treatment schedule	<p>Patients will be randomly assigned to receive:</p> <p>I) Etoposide, Doxorubicin and Cisplatin (EDP) plus Mitotane (EDP/M) on day 1 40mg/m² D, day 2 100mg/m² E, day 3+4 100mg/m² E + 40mg/m² P; every 28 days plus oral mitotane aiming at a blood level between 14-20mg/l</p> <p>II) Streptozotocin plus Mitotane (Sz/M) Induction day 1-5 1g Sz/d. Afterwards 2g/d Sz every 21 days plus oral mitotane aiming at a blood level between 14-20mg/l</p> <p>Evaluation of response is scheduled every 8 weeks in the first 6 months after beginning first line and second line treatment, respectively, and afterwards every 12 weeks. In case of documented disease progression or unacceptable toxicity, subjects will be switched to the alternative regimen.</p>
Statistical analysis	<p>The main statistical analysis of the primary endpoint will be based on the intention-to-treat (ITT) population. For each treatment group the overall survival distribution and the median survival time will be estimated using the Kaplan-Meier method. The two-sided logrank test at a 0.05 significance level will be used to test the survival time null hypothesis assuming proportional hazards. For the hazard ratio a point estimate and a 95% confidence interval will be provided. One interim analysis without alpha spending and two interim analyses with alpha spending are planned. The final analysis will be conducted after 200 observed events (deaths).</p>
Trial duration	<p>7 years (Recruitment period: 60 months. Follow-up period: 18 months. Data base validation prior to data base lock and final analysis: 6 months)</p>

1. INTRODUCTION

1.1 Background about advanced Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare disease with an extremely poor prognosis (Scheingart & Homan 2001; Allolio *et al.* 2004). The incidence is approximately 1-2 per million population per year (National Cancer Institute 1975; Dackiw *et al.* 2001) leading to 0.2% of cancer deaths according to data from the United States (Wajchenberg *et al.* 2000).

MacFarlane has reported that patients with untreated ACC have a median survival of 3 months (MacFarlane 1958). In treated ACC, overall 5 year survival ranged between 23% and 60% in different series (Nader *et al.* 1983; Venkatesh *et al.* 1989; Haak *et al.* 1990; Luton *et al.* 1990; Icard *et al.* 1992; Haak *et al.* 1993; Vassilopoulou-Sellin & Schultz 2001). In a recent series including 253 patients from France, the 5 year survival rates were 60% for stage I, 58% for stage II, 24% for stage III and 0% for stage IV. The median survival in stage IV was 25 weeks (Icard *et al.* 2001).

Due to poor survival and low incidence of ACC, single centers or even single countries have been unable to collect sufficient number of patients to conduct a reliable evaluation of treatment options. Thus, treatment of patients with advanced ACC has never been adequately standardized, and the choice of therapy is based on personal experience and data from uncontrolled trials. In two large multi-center European series, it was reported that approximately 20% of patients have stage IV disease at the time of presentation (Bellantone *et al.* 1997; Icard *et al.* 2001). Similar studies carried out in the U.S. have demonstrated an even higher percentage of advanced disease (Schulick & Brennan 1999). Analysis of the surgical outcomes of patients with ACC has suggested that about one in four patients is left with residual disease after operation, furthermore, in half of the patients subjected to a radical surgical procedure the disease relapsed, often with distant metastases (Bellantone *et al.* 1997; Icard *et al.* 2001). It is, indeed, well known that patients with stage III-IV ACC have a devastating prognosis when surgical removal of local relapse and distant metastases, or both, is not feasible (Pommier & Brennan 1992; Bellantone *et al.* 1997; Schulick & Brennan 1999; Icard *et al.* 2001).

1.2 Previous therapy trials in ACC

Mitotane (o.p'DDD)

Mitotane has been widely employed in the medical treatment of advanced ACC, but it is difficult to critically appraise the evidence of its efficacy, particularly in early studies that were performed before the era of modern imaging techniques. Moreover, mitotane was combined with other cytotoxic agents in some series. Because of the additional variability of the response criteria for these studies, a statistical comparison of the results of these studies is not feasible (Vassilopoulou-Sellin *et al.* 1993; Wooten & King 1993; Dackiw *et al.* 2001). Additionally, because some of the

studies included hormonal amelioration as an indicator of a clinical response, it has been difficult to document a survival advantage in some series reporting a high percentage of remissions (Vassilopoulou-Sellin *et al.* 1993; Wajchenberg *et al.* 2000).

Another confounding factor is the fact that most of these studies were retrospective and employed variable dosages of mitotane, ranging from 3 to 20 grams daily (using two different formulations Lysodren® (o,p'DDD alone) and the so called "French mitotane" (o,p'DDD mixed with enteric gastroresistant coated granules of cellulose acetylphthalate), respectively). In the study of Williamson *et al.* (Williamson *et al.* 2000), mitotane was prospectively used as a second-line treatment at disease progression after treatment with cisplatin and etoposide and the response rate was only 13 %. In only two studies was the monitoring of serum mitotane concentration performed; objective responses were observed only among patients whose serum mitotane concentrations were higher than 14 mg/L (Haak *et al.* 1994; Baudin *et al.* 2001).

Notwithstanding the great heterogeneity of these studies, mitotane appears to have some activity in inducing objective tumor regressions of variable duration (2-190 months); overall, the median response rate was 24% (range, 13-33%). Mitotane treatment is also able to control hormone secretion in most patients with functioning ACC (Vassilopoulou-Sellin *et al.* 1993). The drawback of this agent is its toxicity, and the fact that it appears to have only a narrow therapeutic index (Pommier & Brennan 1992; Dackiw *et al.* 2001). The experience with monitoring serum mitotane concentrations is limited but appears promising, especially in regard to avoiding the severe toxicity associated with high concentrations. Although the threshold mitotane concentration of 14 mg/l was defined arbitrarily and retrospectively by van Slooten *et al.* (van Slooten *et al.* 1984), the therapeutic impact of such concentrations has been confirmed in a further prospective study (Baudin *et al.* 2001). However, therapeutic concentrations of mitotane are reached in only about 50% of patients, and this usually takes months of treatment. In this study the "French mitotane" was used. This time lag may pose a problem when treating patients with rapidly progressive disease. However, in an Italian series (using Lysodren®) 100% of the patients reached the therapeutic levels after 3-5 months (Terzolo *et al.* 2000). Therefore, in this trial Lysodren® will be used.

Cytotoxic chemotherapy

Classic cytotoxic chemotherapy was first tested in single cases or small case series. Cisplatin has been the most widely used drug, either alone or in combination with other agents (Haq *et al.* 1980; Tattersall *et al.* 1980; Chun *et al.* 1983; Johnson & Greco 1986; Hesketh *et al.* 1987).

In Table 1, the prospective chemotherapeutic studies that employed standardized criteria of response encompassing more than ten patients with unresectable ACC (either metastatic or locally advanced) are listed. Only one of these studies presents data on single-agent chemotherapy experience (Decker *et al.* 1991), while in the other studies multiple-agent regimens were employed. In the various multiple-agent regimens cisplatin was most commonly used followed by etoposide

and doxorubicin. Mitotane was combined with conventional cytotoxic agents in about half of the studies listed in table 1. The rationale for combining mitotane with classic cytotoxic chemotherapy is based on the finding that mitotane is able to reverse multidrug resistance mediated by P-glycoprotein expression *in vitro*, thus enhancing the effects of doxorubicin, vincristine and etoposide (Bates *et al.* 1991). This effect could not be shown *in vivo* (Abraham *et al.* 2002). Although, the combination clearly increases gastrointestinal and neurological toxicity (Bukowski *et al.* 1993; Berruti *et al.* 1998; Abraham *et al.* 2002), mitotane-containing regimens have consistently provided the overall best results, objective responses in at least 30% of patients, with the exception of one study (Abraham *et al.* 2002). This latter study was, however, not designed to establish the best chemotherapeutic response, but rather to define the optimal time to proceed with surgery. Whether the seemingly beneficial effect of combining mitotane with conventional chemotherapy simply reflects the exceedingly limited number of patients included in trials so far remains to be established.

Due to the limited number of patients enrolled in each of the studies described in Table 1, the confidence intervals of response are wide and overlapping across the different studies. Thus, it is difficult to determine which regimen is most active. Cisplatin and doxorubicin with addition of cyclophosphamide or 5-fluoruracil was evaluated in 2 studies with an observed response rate of about 20% (van Slooten & van Oosterom 1983; Schlumberger *et al.* 1991). The problem in assessing results obtained in small series is exemplified by the comparison of two reports of the cisplatin and etoposide regimen. The satisfactory results obtained by Burgess & Legha (Burgess *et al.* 1993), who reported a response rate of 46% (range, 18-74) in 13 patients, were not replicated by Williamson *et al.* (Williamson *et al.* 2000), who obtained only a 11% of response (range, 4-24) in 45 patients.

Table 1 – Results of chemotherapy obtained in prospective studies including more than 10 patients with advanced adrenocortical cancer (Allolio *et al.* 2004).

Cytotoxic agent	Mitotane	n	response			Reference
			CR (n)	PR(n)	total	
D, V, E	+	36	1	4	14%	Abraham <i>et al.</i> 2002
S	+	22	1	7	36%	Khan <i>et al.</i> 2000
P, E	-	45	-	5	11%	Williamson <i>et al.</i> 2000
E, D, P	+	28	2	13	54%	Berruti <i>et al.</i> 1998
P, E	+	18	3	3	33%	Bonacci <i>et al.</i> 1998
P, E	-	13	-	6	46%	Burgess <i>et al.</i> 1993
P	+	37	1	10	30%	Bukowski <i>et al.</i> 1993
D	-	16	1	2	19%	Decker <i>et al.</i> 1991
D, P, 5-FU	-	13	1	2	23%	Schlumberger <i>et al.</i> 1991
C, D, P	-	11	-	2	18%	van Slooten & van Oosterom 1983
		239	10	54	27%	

D: doxorubicin, E etoposid, 5-FU 5-fluorouracil, C cyclophosphamide, V vincristin, S streptozocin, P cisplatin

CR complete response

PR partial response

Recently, Khan *et al.* (Khan *et al.* 2000) evaluated the efficacy of streptozotocin plus mitotane. Oral mitotane (1-4 g/d) was given together with intravenous streptozotocin (1/g for 5 days, thereafter 2 g once every 3 weeks). Complete and partial responses were obtained in 36.4% (8 out of 22) patients with measurable advanced disease. Survival was determined as secondary endpoint and the treatment with streptozotocin plus mitotane led to a median survival of 16 months.

The most encouraging results to date were observed by Berruti *et al.* (1998) using the combination regiment of low-dose mitotane with etoposide, doxorubicin and cisplatin (EDP). Mitotane was started at a dose of 1 gram daily and escalated to either 4 grams daily, or the maximum tolerated dose. The EDP schedule (etoposide 100 mg/m² on days 5, 6, 7; doxorubicin 20 mg/m² on days 1, 8; cisplatin 40 mg/m² on days 2, 9) was repeated every 4 weeks and planned for a maximum of 6 cycles. These authors treated 28 patients with advanced ACC, and reported a 53% response rate; the median time to disease progression in the responding patients was 24 months. There were no treatment-related deaths and only 11% of patients had to discontinue treatment. The same group has recently updated these results in abstract form to include the outcome of a total of 66 patients treated according to this scheme. The overall response rate was 48.5% with a median survival time of 28 months (Berruti *et al.* 2003).

1.3 Rationale for performing the study

Due to the poor survival and the low incidence of ACC, a prospective randomized treatment trial for this disease is still missing. The relative efficacy of the regimens described in the above-mentioned 10 trials is difficult to judge, and, therefore, there is no worldwide consensus about the optimal treatment of advanced ACC. Despite this lack of clear evidence, the International Consensus Conference on Adrenal Cancer, held in Ann Arbor, USA, in September 2003 recommended the etoposide, doxorubicin, cisplatin plus mitotane regimen and the streptozotocin plus mitotane regimen as best choices until better data arise. Although the results of the EDP/M protocol suggest a higher response rate, the EDP/M regimen may be more toxic than Sz/M, which is relatively well tolerated. The FIRM-ACT study will address the question if EDP/M as first line treatment (followed by Sz/M as second line treatment) prolongs survival in comparison to Sz/M as first line treatment and EDP/M as second line treatment. The study also aims at providing information on whether any of these two regimens are useful as a second line treatment at all. The main goal of this study is to establish an accepted standard therapy in advanced ACC, thereby putting an end to the current dissatisfying situation.

2 STUDY OBJECTIVES

The aim of this phase III trial is to compare the efficacy of treatment with Etoposide, Doxorubicin and Cisplatin plus Mitotane (EDP/M) versus Streptozotocin plus Mitotane (Sz/M) in patients with locally advanced or metastatic adrenocortical carcinoma.

2.1 Primary Objectives

Primary objective of this trial is to investigate whether Etoposide, Doxorubicin, Cisplatin plus Mitotane (EDP/M) as first line treatment will prolong survival as compared to Streptozocin plus Mitotane (Sz/M) as first line treatment.

2.2 Secondary Objectives

- To compare quality of life
- To compare time to progression
- To compare best overall response rate and duration of response
- To compare number of disease-free patients
- To assess the impact of mitotane blood levels between 14-20 mg/l in both regimens on survival and response
- To assess the effects of both schemes as a second line treatment in case of failure of the other regimen (measured by best overall response rate)

3 STUDY POPULATION

3.1 Number of Patients

A minimum number of 135 patients per group will be required for a total number of 270 evaluable patients (excluding dropouts). Adjusting for a potential 10 % dropout rate, a randomization of 300 patients (150 per group) is planned. See also section 14.5, page 56.

3.2 Inclusion criteria

Clinical inclusion criteria

- Histologically confirmed diagnosis of adrenocortical carcinoma
- Locally advanced or metastatic disease not amenable to radical surgery resection (Stage III-IV)

Other inclusion criteria

- Radiologically monitorable disease
- ECOG performance status 0-2 (see appendix 2)
- Life expectancy > 3 months
- Age \geq 18 years
- Adequate bone marrow reserve (neutrophils \geq 1500/mm³ and platelets \geq 100.000/mm³)
- Effective contraception in pre-menopausal female and male patients
- Patient's written informed consent
- Ability to comply with the protocol procedures (including availability for follow-up visits)
- Previous palliative surgery, radiotherapy or radiofrequency ablation is acceptable as long as radiologically monitorable disease is verifiably afterwards.

3.3 Exclusion criteria

- History of prior malignancy, except for cured non-melanoma skin cancer, cured *in situ* cervical carcinoma, or other cancers treated with no evidence of disease for at least five years.
- Previous cytotoxic chemotherapy (prior therapy with mitotane is allowed) for adrenocortical carcinoma
- Renal insufficiency (serum creatinine ≥ 2 mg/dl or creatinine clearance ≤ 50 ml/min).
- Hepatic insufficiency (serum bilirubin ≥ 2 x the institutional upper limit of normal range and/or serum transaminases ≥ 3 x the institutional upper limit of normal range; exception: in patients on mitotane transaminase levels up to 5 x the institutional upper limit of normal range are acceptable)
- Pregnancy or breast feeding
- Known hypersensitivity to any drug included in the treatment protocol
- Presence of active infection
- Any other severe clinical condition that in the judgment of the local investigator would place the patient at undue risk or interfere with the study completion
- Decompensated heart failure (ejection fraction $< 50\%$), myocardial infarction or revascularization procedure during the last 6 months, unstable angina pectoris, and uncontrolled cardiac arrhythmia
- Current treatment with other experimental drugs and/or previous participation in clinical trials with other experimental agents for adrenocortical carcinoma
- Prisoners

3.4 Patient Informed Consent

A consent document including patient information upon the nature, scope and possible consequence of the trial must have been approved by the Institutional Review Board. Patients amenable for inclusion in the trial will be given sufficient time to study the written information, as well as possibility to ask questions before signing the consent document.

3.5 Patient Registration and Randomization

All centers participating in the study will receive a password to the internet-based database. After registering the patient by means of day of birth, participating center, and name of the local investigator responsible for the patient, size and number of tumors (according to the RECIST criteria, see section 7.3.4, page 40) and checking/marking inclusion and exclusion criteria the patient will automatically be randomized to either EPD/M or Sz/M. The computer will immediately tell the results of the randomization and this page should be printed and stored.

Randomization

The time between randomization and day 1 of administration of the chemotherapy should not extend 7 days.

The sample size and power consideration suggest 300 patients, 150 per regimen (see section 14.5, page 56). About 350 (including about 50 in reserve) entries (records) for treatment allocation will be held by a table, the allocation table, in the database, half of the entries (about 175) with EDP/M and Sz/M each. The webmaster will take care of the concealment of the allocation list. Since interim analysis will be performed during the course of the study, the allocation ratio for EDP/M : Sz/M should constantly be approximately 1 : 1 at every time during recruitment. The table will, therefore, consist of 50 random permuted balanced blocks with short block length, block length 6 (random permutation of 3 EDP/M and 3 Sz/M) and 8 (random permutation of 4 EDP/M and 4 Sz/M). Prediction of allocation results will be avoided by simple 1 : 1 randomization of the block length (6 and 8).

The allocation table will be integrated into the database, the empty database including the allocation table will be stored (backup copy), and the file name and date of integration will be documented together with the VB-script (Microsoft Visual Basic script) of the generation procedure. When a patient is submitted for registration a SQL statement will be executed asking the database of the next free (not taken) record in the allocation table. All records in the allocation table contain a unique ID number, this ID number together with all the other registration parameters will be inserted in to the database and the patient gets a patient ID number. A new SQL statement updates the allocation table guaranteeing that this record is set to "taken".

Documentation of evaluation and follow up

At each evaluation the local investigator responsible for administering the treatment must complete the CRF directly into the internet-based database. After discontinuation of administration of study drugs, survival status should be reported at least every 3 months to the data management center. The quality of life forms must be printed out and given to the patient for answering before the treatment at each evaluation. The answered questionnaire should be faxed to the data management center in Uppsala, Sweden (Fax +46-18 55 39 43).

A webmaster responsible for creating the homepage, database and randomization procedures will be available for support and questions concerning registration and data submission weekdays 9 am to 4 pm European time by e-mail or telephone, throughout the study.

The study concept, appendices, and tutorial examples of how to handle the database will be available on the web for all centers with a password.

Data from individual cases can only be assessed by the center that have registered the patient and by the administrator.

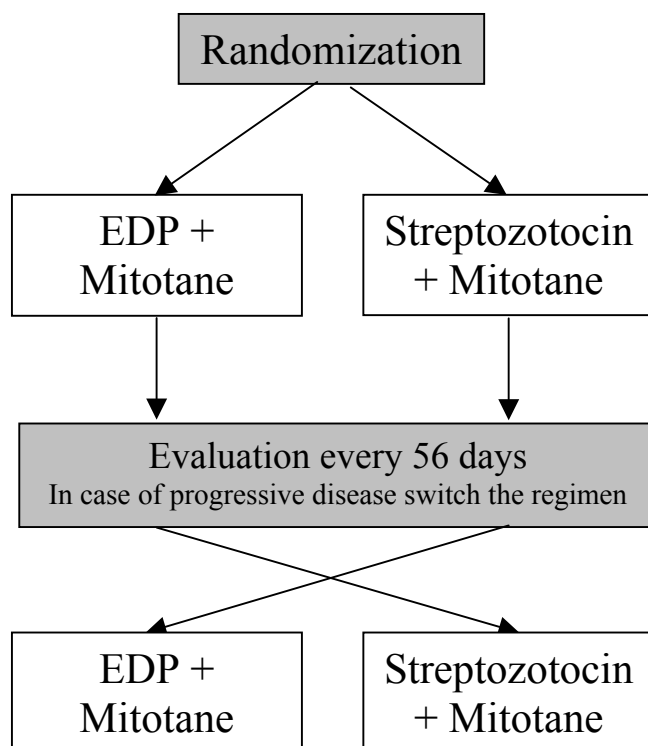
4 STUDY DESIGN

The study is designed as a Phase III, randomized, open-label, multi-national trial in which patients with locally advanced or metastatic adrenocortical carcinoma not amenable to complete surgical resection will be randomized to receive either therapy with Etoposide, Doxorubicin, Cisplatin plus Mitotane (EDP/M) or Streptozotocin plus Mitotane (Sz/M) as first line treatment.

Patients who fulfill the inclusion criteria and in whom no exclusion criteria are met will be randomized by a web-based hotel procedure (see section 3.5 page 18).

Evaluation of response is scheduled every 56 ± 5 days (8 weeks) for the first 6 months after beginning first line and second line treatment, respectively, and afterwards every 12 weeks.

In case of documented disease progression or in case of unacceptable toxicity, subjects will be switched to the alternative regimen.



5 TREATMENT SCHEDULE

5.1 Chemotherapy

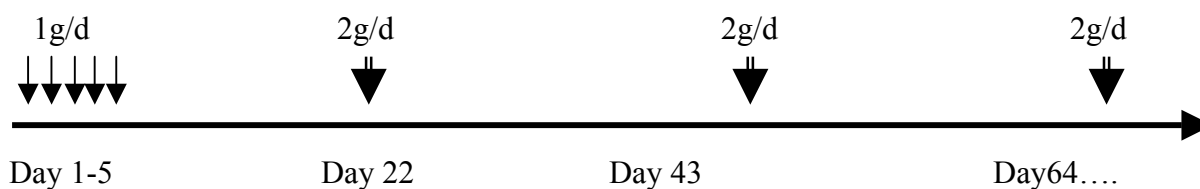
5.1.1 EDP

DRUG	DAY			
	1	2	3	4
DOXORUBICIN 40 mg/m ²	*			
ETOPOSIDE 100 mg/ m ²		*	*	*
CISPLATIN 40 mg/ m ²			*	*

every 28 days

This regimen represents a shortening of the original EDP treatment described by Berruti *et al.* (1998). However, the doses are unchanged, leading to an expectation of equal therapeutic efficiency and toxicity. Shortening of the treatment schedule from 9 to 4 days is expected to increase compliance with the chemotherapeutic scheme. The local investigator may administer EDP according to the original 9-day long scheme but he must inform the study coordinator.

5.1.2 Streptozotocin



5.1.3 Route of administration of chemotherapeutic drugs

The local investigator is responsible for the exact procedures of administration the chemotherapeutic drugs (including supportive drugs and timing).

Extravasation precautions should be maintained at all times, especially for doxorubicin, and if burning or stinging occurs or extravasation is suspected, the infusion should be immediately terminated and restarted in another vein. The suspected extravasation area should be cooled and topical steroids and dimethyl sulfoxide can be used. Close observation and plastic surgery consultation are recommended. Local erythematous streaking along the vein or facial flushing are indicative of too rapid rate of administration.

The following recommendations may be used as a feasible way of administration:

Etoposide is administered IV diluted I 500 ml of isotonic NaCl or 5% dextrose over 60 minutes.

Doxorubicin is administered by intravenous push into the tubing inserted into a large vein, in parallel with a freely running intravenous infusion of isotonic NaCl or 5 % dextrose in water. The speed of the doxorubicin administration is dependent on the size of the vein, but must not be injected over less than 3 to 5 minutes. Doxorubicin can also be administered as a continuous infusion. It is incompatible with heparin.

Cisplatin will be administered IV, diluted in 500 ml of isotonic NaCl, over 60 minutes. **Before** cisplatin, 1000 ml isotonic NaCl with addition of 20 mmol potassium is given during 2 h. Cisplatin infusion is administered over 60 minutes. After cisplatin, 500 ml mannitol IV should be administered at a concentration of 150 mg/ml during 1 hour. Afterwards, on day 3/4 Etoposide is given followed by 1000 ml isotonic NaCl with addition of 5 mmol Magnesium and 20 mmol potassium during 1 hour. During day 3 and 4 body mass has to be measured 3 times daily and injections of small doses of diuretics (e.g. furosemide 10-20 mg) should be given IV to ensure diuresis and avoid retention of fluids.

Before administration of **streptozotocin**, start an IV infusion of 1000 ml isotonic NaCl and run over 3 hours. After the first half of the infusion has run in (500 ml) inject streptozotocin over a 10 minute period. Complete the infusion.

5.2 Mitotane

Mitotane will be administered orally aiming at a blood level of 14-20 mg/l (or the maximum tolerated dose). Analysis of circulating mitotane levels will be performed by one of the reference laboratories (see Appendix 6). The first 6 months after beginning mitotane therapy blood levels of mitotane will be assessed at least once every four weeks and after 6 months analysis will be done at least every 8 weeks.

The daily dose of the drug should be increased if serum levels of the mitotane are below 14 mg/l. The dosage should be decreased if serum levels are over 20 mg/l. In the event of high levels in combination with side effects it might be necessary to temporarily discontinue the treatment.

Mitotane administration should start at least two weeks before the initiation of chemotherapy.

All patients will receive concomitant glucocorticoid replacement. For more details see section 6.4.

The detailed dosage scheme is the responsibility of the local investigator. Two variants of administration are outlined below.

Low starting dose approach: Mitotane will be administered at a starting dose of 1 g/day and increased in case of good gastrointestinal tolerance every 3 days week by 0.5 g up to a total dose of 4.0 g and then adjusted according to blood concentrations and tolerability.

High starting dose approach: Mitotane will be administered at a starting dose of 1.5 g / day and increased in case of good gastrointestinal tolerance on day 2 to 3 g/ day, on day 3 to 4.5 g/d, and on day 4 to 6 g/d. 6g/d will be administered until first mitotane blood level is assessed. In this high dose regimen, it is strongly recommended to measure mitotane blood levels 14 days after initiation of therapy. Afterwards dosage will be adjusted according to blood concentrations and tolerability.

6 DRUG INFORMATION

6.1 Cytotoxic Drugs

6.1.1 Etoposide (VP-16) (Vepesid)

6.1.1.1 Biochemistry:

VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, and has antineoplastic properties in experimental animals and in man. It is a lipophilic agent and the empiric formula $C_{29}H_{32}O_{13}$ has a molecular weight of 588. Etoposide is a topoisomerase II inhibitor. It acts at the premitotic stage of cell division to inhibit DNA synthesis. It is cell-cycle dependent and phase specific, with maximum effect on the S and G2 phases of cell division.

6.1.1.2 Pharmacokinetics

After IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4-11 hours. After intravenous infusion of 100 milligrams/meter squared over 30-60 minutes, a plasma concentration of 21 milligrams/liter five minutes was reported after infusion ended. The volume of distribution after a single dose is 9.7 liters/meter squared and 8.3 liters/meter squared at steady state. This can be as high as 17 liters/meter squared. Drug does not accumulate in plasma following daily administration of 100 mg/m² for 4-5 days. Drug crosses blood-brain barrier poorly. Recovery after IV administration of radio-labeled etoposide in the urine ranges from 42-67% and feces from 0-16%. Etoposide is metabolized by the liver. Renal excretion accounts for 44% to 60% (67% of this is unchanged). Mean renal clearance is 7 to 10 milliliter/minute/meter squared (about 35% of total clearance in adults); in children approximately 55% of the dose is excreted unchanged. Fecal excretion accounts for up to 16%, biliary excretion accounts for 6% or less. Elimination half-life ranges from 4 to 11 hours and is independent of dose. Oral etoposide has variable bioavailability, mean 50% absorbed with a range of 25 to 75%. Bioavailability of oral solution is 67% ± 17%. Product information reports that the oral bioavailability is linear up to doses of 250 milligrams/meter squared but in another study, the authors report that bioavailability is decreased at single doses greater than 200 mg. Etoposide is highly protein bound (97%).

6.1.1.3 Pharmaceutical Data

Oral etoposide is available in 50 mg soft gelatin capsules in the U.S. and 50 and 100 mg capsules in Canada. Parenteral etoposide is available in multiple dose vials as follows: 100 mg/5 mL, 150 mg/7.5 mL, 500 mg/25mL, and 1 g/50mL. Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in sterile Multiple dose Vials for injection. The pH of the yellow clear solution is 3-4. Each ml contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. VP-16 must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before

precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/ml it is stable for 48 hours.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose Injection and precipitation is reported.

6.1.1.4 Human Toxicology

The maximum tolerated dose of etoposide given chronically was found to be 50 milligrams/meter squared/day for 21 days. The primary toxicity was hematologic. Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect and is the dose-limiting toxicity. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12-16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Severe thrombocytopenia (less than 50,000 cells/mm³) is reported in 1% to 20% of patients. Leukopenia (less than 4000 WBC/mm³) develops in 60% to 91% of all patients and is severe (less than 1000 WBC/mm³) in 3% to 17% of all patients. Gastrointestinal toxicities including transient modest nausea, vomiting and diarrhea, are common. Liver toxicity has been reported in approximately 3% of patients. In general transient elevation of alkaline phosphatase, serum bilirubin, and SGOT have been reported. Severe hepatocellular necrosis has been reported in 3 case following high doses. Diarrhea has been reported in 1% to 13% of patients. Abdominal pain is reported in 2% of patients. Other reactions could include aftertaste, rash, pigmentation, pruritis, abdominal pain, constipation and dysphagia. Reversible alopecia, possibly progressing to total baldness, may occur in up to 66% of patients. VP-16 does not produce phlebitis, or nephrotoxicity. Rarely it's has been observed dyspnea, acute bronchospasm, apnea and cyanosis. Fatal pulmonary toxicity fibrosis of the lung has been reported after oral use. Peripheral neuropathies and paralytic ileus have been reported. Fatal cerebral edema is very rare. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of VP-16 administration. Erythema and desquamation, alopecia, onycholysis, and Stevens-Johnson syndrome have occurred following therapeutic use of etoposide. Hypersensitivity and anaphylactic-like reactions may occur in 1% to 2% of patients during the initial parenteral or oral administration of etoposide, and hypotension as well. Transient hypotension has been reported in 1% to 2% of patients following rapid intravenous administration. Hypotension can be managed by infusing the drug over at least a 30 minutes period. It is not associated with cardiac toxicity or ECG changes. A case of angina due to coronary vasospasm has been reported in 1 patient treated with etoposide, cisplatin and bleomycin and a case of a non-Q-wave myocardial infarction has been reported after bleomycin and etoposide treatment. Etoposide may be carcinogenic by causing

secondary leukemia. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other antineoplastic agents.

Pregnancy and Lactation: Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. In these studies, etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity. Fetal abnormalities included decrease weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. For humans, it is rated as FDA pregnancy category D. There have been no reports of teratogenicity in pregnant women; however there may be potential toxicity to the fetus. A preterm infant, whose mother received etoposide, cytosine arabinoside, and daunorubicin during pregnancy, was delivered with severe anemia and neutropenia. Etoposide is distributed into breast milk and breast-feeding is not recommended. No information is available on excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued. Etoposide has been reported to cause DNA repair, DNA damage, DNA inhibition, mutations, sex chromosome loss and nondisjunction, sister chromatid exchange, gene conversion, and mitotic recombination in various bacterial or human cell models
Safety and efficacy in children has not been established.

6.1.1.5 Supplier

VP-16 is commercially available for purchase by third party.

6.1.2 Doxorubicin

6.1.2.1 Biochemistry

Anthracycline antibiotics have antineoplastic actions that are isolated from certain strains of *Streptomyces* (i.e., *S. peucetius*). This group includes doxorubicin and several other agents that are structural analogues (e.g., aclarubicin, daunorubicin, epirubicin, idarubicin, pirarubicin) of doxorubicin. Doxorubicin appears to form a complex with DNA and thereby interfere with nucleic acid synthesis. Doxorubicin has immunosuppressive properties. Doxorubicin accumulates in cardiac tissue. Cardiac toxicity may be an oxidative mechanism. Cardiac tissue is not adequately equipped to handle the quantity of free radical produced. Antioxidant (vitamin E) or sulfhydryl donors (cysteamine or N-acetylcysteine) may be effective in attenuating the acute lethality and preventing the cardiac lesions produced by doxorubicin in experimental animals. Cardiotoxicity is the dose-limiting toxicity associated with a total lifetime cumulative dose approaching 550 mg/m² or greater. Other data indicated that doses of 450 mg/m² or less have caused cardiotoxicity. Sixty to 75 milligrams/square meter given intravenously or 1.2 to 2.4 milligrams per kilogram body-weight, as a single dose every 21 days Alternatively, 20 to 30 milligrams/square meter can be given intravenously daily for 3 days, every 3 to 4 weeks. This schedule, however, may cause an increased incidence of mucositis. Maximum cumulative dose is 550 milligrams/square meter. This is reduced

to 450 milligrams/square meter in patients over 70 years, and to 400 milligrams/square meter in patients with previous cardiac irradiation or previous cardiotoxic medications.

6.1.2.2 Pharmacokinetics

Doxorubicin is rapidly and widely distributed. Detectable doxorubicin was not found in the cerebrospinal fluid nor brain following intravenous injection. Doxorubicin may penetrate the blood-brain barrier when administered in combination with a hyperosmotic agent, such as mannitol. From 50 to 80% doxorubicin is bound to plasma protein. The liposomal formulation acts slightly different; the use of macrogols in the surface layer of the liposomes (pegylation) reduces removal of liposomes by macrophages. This allows for prolonged circulation in the plasma, with little tissue distribution. Tumor neovasculature is able to allow penetration of liposomes into tumor tissue. Plasma half life represents distribution and is about 30 minutes. Doxorubicin undergoes rapid metabolism in the liver. The "first-pass" phenomenon may occur with extensive liver extraction and subsequent release of metabolites and drug back into the systemic circulation. Doxorubicin has a large volume of distribution and only about 5 percent is cleared renally. Based on these facts, hemodialysis is unlikely to be effective. Approximately 5% of the administered dose of doxorubicin is recovered in the urine within 5 days. Approximately 40% to 50% of the administered dose of doxorubicin is recovered in bile or feces within 7 days and approximately 40% of the administered dose of doxorubicin is recovered in bile or feces within 7 days.

6.1.2.3 Pharmaceutical Data

Availability and storage: conventional doxorubicin is supplied as a sterile red-orange lyophilized powder in several single dose vial sizes and a 150 mg multidose vial and as a sterile red orange solution of 2mg/mL. Unconstituted powder vials should be stored at controlled room temperature, at 15 C to 30 C in the original carton to protect from light. The solution should be store refrigerated, at 2 C To 8 C in the original carton to protect from light.

Preparation and stability: the lyophilized powder is reconstituted with preservative free 0.9% NaCl to yield a final concentration of 2 mg/ml. The reconstituted solution is then stable for 7 days at room temperature and 15 days refrigerated. The stock solution may be further diluted with 0.9% NaCl.

6.1.2.4 Human Toxicology

Alopecia is frequently reported with therapeutic doses of doxorubicin. Nausea and vomiting may occur. Diarrhea is frequently reported with therapeutic doses. Anal fissures or proctitis may occur with high doses of doxorubicin. Hepatitis and non-specific hepatocellular damage has been reported in patients receiving therapeutic doses of doxorubicin along with combination therapy. Fatal hepatotoxicity has occurred following doxorubicin therapy in one case and may be related to an idiosyncratic reaction. Bone marrow suppression is the dose-limiting toxicity for a single acute dose

of doxorubicin. Leukopenia, thrombocytopenia, and anemia may occur. The nadir is about 10 to 14 days and resolution usually occurs over about 1 week.

Doxorubicin has irritant properties. Conjunctivitis and excessive tearing may occur. Corneal infiltrate and iritis has been described. Severe ulceration and necrosis may occur from extravasation of doxorubicin. Check vein patency prior to administration. ECG changes, dysrhythmias, pericarditis, and perimyocarditis may occur 1 to 24 hours after administration of doxorubicin. In chronic administration, congestive heart failure that may or may not respond to digoxin, diuretics and ACE inhibitors appears. The likelihood of cardiac failure is related to the cumulative total dose administered. Incidence of cardiac failure with doxorubicin has been estimated to be 3-4% with a cumulative dose of 450 mg/m² and up to 18% following a cumulative dose of 700 mg/m². Peak incidence occurs 1 to 3 months after the last dose, and has occurred as late as 20 years after treatment. Risk factors that contribute to an increased risk for development of cardiomyopathy are previous mediastinal irradiation, age (the young and old are more vulnerable), and concurrent use of other cytotoxic agents (cyclophosphamide and vinca alkaloids), mediastinal radiotherapy, cumulative anthracycline dose greater than 450 mg/m² with pre-existing cardiac disease. Other risk factors include hypertension, liver disease, and previous cardiac disease. Established heart failure has a poor prognosis. Over 50% of patients with doxorubicin-induced cardiomyopathy die. Liposome encapsulation of doxorubicin, may significantly decrease its cardiac toxicity. Doxorubicin has been reported to be embryotoxic and teratogenic in rats, and embryotoxic and abortifacient in rabbits. Acute cardiac failure has been reported in a neonate after her mother received idarubicin for acute lymphoblastic leukemia. Due to potential risk to the infant, breast-feeding is not recommended.

6.1.2.5 Supplier

Doxorubicin is commercially available and should be purchased by a third party. Doxorubicin is available in the United States as 2 milligrams per mL (5-, 10-, 25-, and 37.5 mL single dose vials, and 100 mL multidose vial) vials. In Canada, it is available in 2 milligrams per mL (5- and 25- mL single dose vials, and 200-mL multidose vial). The liposomal doxorubicin formula is available in 2 milligrams per mL).

6.1.3 Cisplatin

6.1.3.1 Biochemistry

Cis (II) platinum diamminedichloride (cis-DDP) is a heavy metal compound which a divalent platinum molecule binds two potential leaving groups, the chloride ions. Two NH₃ groups are bound in a firm covalent linkage in transposition to the chloride moieties. Both chloride ions

undergo a slow displacement by water, generating a positively charged aquated complex, which is capable of interacting with a nucleophilic site on DNA, RNA, or protein.

6.1.3.2 Pharmacokinetics

The dominant action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25-49 minutes, and a secondary phase ranging from 58-73 hours. This prolonged phase is due to protein binding, which exceeds 90% of the activity in the second phase. Urinary excretion is incomplete with only 27-45% excreted in the first five days. Largely unchanged drugs are the initial fraction excreted. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

6.1.3.3 Pharmaceutical Data

Formulation: Cisplatin (Platinol) is available as an aqueous solution in a concentration of 1 mg/ml.

Storage and Stability: The aqueous solution is stored at room temperature protected from light. Cisplatin is stable in mannitol/NS/ D5W mixtures for 48 to 72 hours at room temperature and up to 72 hours when refrigerated (per Trissel's Handbook on Injectable Drugs, 11th edition). Cisplatin should be given immediately after preparation over one hour.

6.1.3.4 Human Toxicology

Human toxicity from cisplatin includes: nausea, vomiting, anorexia, loss of taste, renal toxicity (with an elevation of BUN/Urea, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss, which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy, allergic reactions, and uricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white blood cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy.

6.1.3.5 Supplier

Cisplatin is commercially available, and should therefore be purchased by the third party.

6.1.4 Streptozotocin

6.1.4.1 Biochemistry

Streptozotocin is a naturally occurring, water soluble, glucose-based nitrosurea with a molecular weight of 265.2. Its antiproliferative activity is dependent on the *in vivo* spontaneous decomposition into reactive moieties which are actively involved in DNA cross-linking. Cell proliferation is inhibited at a substantially lower concentration than that required to inhibit precursor incorporation into DNA or to inhibit several of the enzymes involved in DNA synthesis. RNA or protein synthesis appear not to be substantially involved in the cytotoxic effect of streptozotocin. Although streptozotocin is commonly considered a phase non-specific drug, some data show block of progression into mitosis from G2 to M phase. Like other nitrosureas, streptozotocin has also the ability to carbamoylate various macromolecules, but these actions appear to play only a secondary role compared with the alkylation of DNA. The degree of streptozotocin carbamoylation activity appears also independent from the reduced myelosuppressive activity of the drug.

6.1.4.2 Pharmacokinetics

Absorption: The drug is poorly absorbed when given orally, therefore the drug must be administered intravenously. Following IV injections over minutes of single 200 and 400mg /m² doses, serum streptozotocin concentrations one minute after injection were 32 and 39 microgram/ml, respectively; one hour after injection serum streptozotocin concentration dropped to 1 and 6 microgram/ml, respectively. Following IV infusion over 40 minutes of a 1.6 g/m² dose, the serum streptozotocin concentration one minute after completion of the infusion is 41 microgram/ml, decreasing to 12 microgram/ml one hour after completion of infusion.

Distribution: Distribution of streptozotocin into human body tissues and fluids has not been extensively studied. In a limited number of adults with normal renal function, the apparent volume of distribution following a single IV dose reportedly averaged 43.8L. High concentrations of the drug and its metabolites (at levels consistently higher than those detectable in plasma) are found in the liver, kidney, intestine and pancreas, with lower concentrations being found in skeletal muscle, spleen, lungs, heart and thymus. Streptozotocin does not appear to cross the blood-brain barrier in animals or humans; however, metabolites readily distribute into CSF. ¹⁴C labeled metabolites (containing the nitrosurea moiety) were equivalent to those detected in plasma two hours after IV administration, and were detectable in CSF for at least 24 hours after administration. ³H labeled metabolites could not be detected in CSF during the first two hours.

It is not known whether streptozotocin crosses the placenta in humans, but the drug readily crosses the placenta in monkeys. No data are available about the drug distribution into the milk.

Metabolism: Although no clear information is available on exact metabolic fate of streptozotocin, the drug is known to be extensively metabolized, probably in the liver and kidneys. Several metabolites have been detected, but their exact structures have not been completely elucidated.

¹⁴C-labelled metabolites containing the nitrosurea moiety showed a substantially longer half-life than ³H-labelled metabolites containing the d-glucopyranose moiety.

Excretion: Following IV administration, plasma disappearance is biphasic, with an initial half-life in the 5 minutes range and a terminal half-life in the 35-40 minutes range. Plasma clearance of a 1.5 g/m² dose given by a rapid IV injection averaged 478 microgram/min in patients with normal renal and hepatic function.

Excretion is mainly through the kidneys. Up to 70% of an IV dose is excreted in the urine within 24 hours from drug administration, mainly in the form of metabolites; approximately 10% of a dose is however excreted unchanged. Streptozotocin and/or its metabolites may also be eliminated in expired air (approximately 5% of the IV dose, within 24 hours). Less than 1% of an administered dose is excreted in feces.

6.1.4.3 Pharmaceutical data

Formulation: Streptozotocin is commercially available as freeze-dried powder (marketing authorization holder Pfizer, Zanosar^R) contained in a colourless glass vial, each containing 1 g of the active ingredient streptozocin 2-deoxy-2[[[(methylnitrosamino)carbonyl]amino]-a(and b)-D-glucopyranose, and 220 mg citric acid anhydrous. The pH has been adjusted with sodium hydroxide. When reconstituted as directed (below) the pH of the solution will be between 3.5 and 4.5. Zanosar is available as a sterile pale yellow, freeze dried preparation for intravenous administration.

Storage and Stability: Streptozotocin freeze-dried powder for injection has a shelf life of 24 months stored under refrigeration (2-8° C) and protected from light. Once the drug has been reconstituted, the solution has to be used within 48 hours if stored under refrigeration, and within 24 hours if stored at room temperature (below 25 °C). However, since the product contains no preservatives and is not intended as a multiple-dose vial and in order to avoid the risk of microbial contamination, it is recommended that the solution be used as soon as possible and within 12 hours from reconstitution.

6.1.4.4 Route of administration

Streptozotocin powder for injection (1 g vial) has to be reconstituted with 9.5 ml of dextrose for injection USP, sterile water for injection USP, or sodium chloride for injection USP. The resulting pale-gold solution will contain 100 mg of streptozotocin per ml. Where more dilute infusion solutions are desirable, further dilution in the above vehicles is recommended. Procedures for proper handling and disposal of anticancer drugs should be considered. Caution in the preparation of the powder and solution should be exercised, and the use of gloves, masks and protective goggles is recommended.

Before administration of streptozotocin infusion of 1000 ml of isotonic NaCl is started and given during 3 hours. After approximately half of the sodium chloride infusion (1.5 hours) streptozotocin is given as an injection during 10 minutes.

Induction encompasses 1 g streptozotocin daily for 5 consecutive days. The drug is then given as a single dose of 2 g once every three weeks.

6.1.4.5 Human Toxicology

Streptozotocin produces a dose-related and cumulative renal toxicity, which may be severe and fatal. Renal function may be monitored before each course of therapy. Mild proteinuria is one of the first signs of renal toxicity and may herald further deterioration of renal function. Reduction of the dose or discontinuation of treatment is suggested in the presence of significant renal toxicity. Adequate hydration is mandatory and may help reduce the risk of nephrotoxicity to renal tubular epithelium by decreasing renal and urinary concentration of the drug and its metabolites. Use of streptozotocin in patients with preexisting renal disease requires a judgment of the physician. The drug should not be used in combination with or concomitantly with other potential nephrotoxins.

Streptozotocin will cause nausea and vomiting in most of the patients, but could be managed sufficiently in about 90% of cases by giving effective antiemetic drugs. Nausea and vomiting usually begin within 1-4 hours following administration of streptozotocin and may persist for 24 hours or longer.

Diarrhea as occurred in patients receiving streptozotocin.

Transient increases in serum concentrations of transaminases and/or alkaline phosphatases have been reported to occur in 25% of patients receiving streptozotocin. Increases in serum bilirubin concentrations and hypoalbuminemia have also been reported. Severe and fatal hepatic effects have occurred rarely.

Mild to moderate reversible abnormalities of glucose tolerance have been noted in some patients.

Severe necrosis has been reported following extravasation of the drug. A burning sensation, extending from the site of injection up the arm, has been reported in some patients following IV push administration.

Other reactions related to the use of streptozotocin include confusion, lethargy and depression, all reported in a limited number of patients receiving continuous IV infusion for 5 days. Fever has occurred rarely.

Hematological toxicity has been rare, most often involving mild decreases of hematocrit values. However, fatal hematological toxicity with substantial reduction in leukocyte and platelet count has been observed.

No antidote is known. A single dose of 1500mg/m² should not be exceeded.

6.1.4.6 Supplier

Streptozotocin is commercially available (marketing authorization holder Pfizer, Zanosar^R), and should therefore be purchased by the third party.

6.2 Mitotane (o,p'-DDD)

6.2.1.1 Biochemistry

Mitotane (1,1 dichloro-2(o-chlorophenyl)-2-(p-chloro-phenyl)ethane) is an isomer of the insecticide p,p'-DDD and a chemical congener of the insecticide DDT.

6.2.1.2 Pharmacokinetics:

The oral bioavailability after oral intake is about 40 %. It is mainly metabolized in the liver. Mitotane is hydroxylated in the mitochondria at the β -carbon and further transformed into an acyl-chloride. It has been reported that the active metabolites cause toxicity by oxygen activation with superoxide formation or by covalent binding to specific proteins. The elimination half-life of the parent compounds ranges between 18 and 159 days. There is a significant distribution of mitotane and its metabolites to fatty tissue. The renal excretion is about 10 %.

6.2.1.3 Pharmaceutical Data:

Formulation: Mitotane is available as a 500 mg tablet.

Storage and Stability: The tablets may be stored at room temperature. Mitotane is insoluble in water and approximately 10 % soluble in oil or fat.

6.2.1.4 Human Toxicology

Human toxicity from mitotane mainly includes gastrointestinal (nausea, vomiting, diarrhea, anorexia) and neurological adverse effects (depression, lethargy, somnolence, ataxia, dizziness, confusion, vertigo). Theoretically every patient will develop adrenal insufficiency requiring a high dose glucocorticoid replacement due to increased metabolic clearance of glucocorticoids. In addition, mitotane strongly increases hormone binding globulins (e.g. cortisol-binding globulin, sex hormone binding globulin) leading to impaired bioavailability of the free hormones. Total thyroxine levels may be reduced as mitotane competes with endogenous thyroxin for thyroxine-binding globulin binding sites. In some patients also free thyroid hormone concentrations decrease and thyroxin replacement may become necessary. Gynecomastia was observed in some patients.

Increases in hepatic gamma glutamyl transaminase levels are frequent and in most cases do not require withdrawal of the drug. However, serious hepatotoxicity has also been described. Mitotane increases serum cholesterol mainly by increasing LDL-cholesterol. Leukopenia and prolonged bleeding times may occur. Therefore, the bleeding time should be analyzed when surgery is

scheduled. Orthostatic hypotension and hypertension have been reported as infrequent adverse effect.

The combination of mitotane to chemotherapy can increase the treatment-related toxicity, particularly in terms of gastro-intestinal and neurologic side effects.

6.2.1.5 Supplier

Mitotane (Lysodren®) is commercially available (Bristol Myers Squibb and HRA Pharma, respectively), and should therefore be purchased by the third party.

6.3 Typical adverse effects of the study drugs

Study drug	Typical adverse effects
Etoposide	<ul style="list-style-type: none"> • Reversible myelotoxicity (mainly granulocytopenia, with thrombocytopenia and anemia to a lesser extent) are common • Transient modest nausea, vomiting and diarrhea are common • Liver toxicity with elevation of alkaline phosphatase, bilirubin, and transaminases • Reversible alopecia (up to 66 % of patients) • Hypersensitivity and anaphylactic-like reactions (1-2 % of patients) • Other reactions could include aftertaste, rash, pigmentation, pruritis, abdominal pain, constipation and dysphagia
Doxorubicin	<ul style="list-style-type: none"> • Reversible myelotoxicity • Alopecia • Nausea, vomiting, diarrhea • Congestive heart failure
Cisplatin	<ul style="list-style-type: none"> • Renal toxicity • Nausea, vomiting, anorexia • Reversible myelotoxicity • Ototoxicity • Peripheral neuropathy • Allergic reactions, uricaemia, loss of taste
Streptozotocin	<ul style="list-style-type: none"> • Renal toxicity • Nausea, vomiting, diarrhea • Transient increases in serum transaminases and/or alkaline phosphatases
Mitotane	<ul style="list-style-type: none"> • Nausea, vomiting, diarrhea, anorexia • Depression, lethargy, dizziness, somnolence, ataxia • Adrenal insufficiency • Other endocrine abnormalities (partly due to the increase of hormone binding globulines) including changes in thyroid and sex hormone concentrations

6.4 Concomitant Medication

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patients are allowed. Only those drugs that are specifically listed in the protocol/CRF should be entered in the appropriate CRF. All other drugs required for the patient's medical care should be documented in the patient's medical record. The administration of any other anticancer agents including chemotherapy and active biologic agents is NOT permitted. Similarly, the use of other concurrent investigational drugs (except of mitotane) is not allowed.

Since ketoconazole potentiates the risk of toxicity by cytotoxic agents, ketoconazole must be withdrawn for at least 24 hours before chemotherapy, but may be restarted 24 hours after completion of the cycle.

Steroid replacement therapy

Due to the adrenolytic activity of mitotane, all patients will receive concomitant administration of glucocorticoids to cover adrenal insufficiency. Due to an increased metabolic clearance rate of glucocorticoids by mitotane therapy, high-dose glucocorticoid replacement is typically required. Hydrocortisone or cortisone acetate are the steroids of choice and glucocorticoid replacement is monitored best with careful clinical assessment. A total daily dose of 50 mg hydrocortisone (divided as 20-20-10mg) or 75 mg cortisone acetate and more may be needed. Fludrocortisone may be added depending on blood pressure, serum potassium levels and plasma renin activity.

7 TREATMENT EVALUATION

7.1 Diagnostic Tools

The primary diagnosis made by the local pathologist will be confirmed by one of the reference pathologists (see Appendix 5). However, the process of pathological review should not delay registration and randomization of the patient.

Contrast-enhanced **spiral CT-scan** of the abdomen and chest is the method of choice to determine staging of the disease (If CT scans are not available, imaging of the chest and abdomen by **MRI** is also acceptable).

Definition of measurable and non-measurable lesions (Therasse *et al.* 2000)

Measurable lesions include all the lesions detected by spiral CT scan or MRI that can be accurately measured in at least one dimension ≥ 1 cm. All measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repetitive measurement. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as **nontarget lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Non-measurable disease includes all the lesions which are not included in the category above, but should be considered in the overall assessment of response. They include the following:

- bone lesions
- leptomeningeal disease
- ascites
- pleural/pericardial effusion
- lymphangitis cutis/pulmonis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- ACC induced hormone excess

These lesions must be considered in the overall assessment of response.

7.2 Initial Clinical Evaluation

All baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of chemotherapy.

- Complete history and physical exam
- CBC with differential and platelet count
- Serum chemistry profile to include: comprehensive panel (Na, K, Mg, Creatinine, Glucose, AST/SGOT, ALT/SGPT, gamma Glutamyl Transpeptidase, Alkaline Phosphates, Total Bilirubin, Albumin).
- Pregnancy test in women of childbearing potential
- Radiologic imaging studies (CT/MRI) of chest and abdomen
- Quality of life questionnaire (EORTC-QLQ-C30)
- Baseline ECG
- Measurement of cardiac ejection fraction (e.g., by echocardiogram or MUGA scan)
- Bone scan if presence of bone lesions is clinically suspected
- ENT examination with audiogram in patients with known hearing problems or when clinically indicated

The same evaluation has to be performed within 4 weeks before starting the second line treatment (including definition of potentially new target lesions (see section 7.1, page 38)).

7.3 Definition of the endpoint criteria

7.3.1 Overall survival

Overall survival (= primary endpoint) is defined as the time interval between the date of randomization and the date of death from any cause (= target event) or the last known alive date (i.e., patients who are alive at the time of an analysis will be censored for survival at the time of their last contact).

7.3.2 Quality of life

Quality of life will be measured by the standardized EORTC-QLQ-C30 (see Appendix 3) questionnaires. The EORTC-QLQ-C30 is a standardized questionnaire developed to assess the quality of life of cancer patients, which has been translated and validated in 38 languages and has been used in more than 1500 studies worldwide. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue,

pain, nausea and vomiting); and a global health and quality-of-life scale. The average time required to complete the questionnaire was approximately 11 minutes (Aronson *et al.* 1993).

7.3.3 Time to progression

In the first part of the study (before cross-over) time to progression is defined as the time between the date of randomization until documentation of progressive disease or the last date of follow-up. In the second part of the study (after cross-over) time to progression is defined as the time between the first day of administration of the second line regimen until documentation of progressive disease or the last date of follow-up. For definition of progressive disease see section 7.3.4.

7.3.4 Evaluation of Response Rate

Response evaluation will be performed according to the RECIST criteria (Therasse *et al.* 2000). The same methods of measurement and the same technique should be used to characterize each identified and reported lesion at baseline and during study.

Evaluation of target lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions.
- **Partial response (PR)** requires at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
- **Progressive disease (PD)** is defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.
- **Stable disease** is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter recorded since the treatment started

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

For CR ACC induced hormone excess has to be disappeared.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessment performed no less than 4 weeks after the criteria for response are first met.

7.3.4.1 Best overall response

The best overall response is defined by the best response recorded from the start of treatment until disease progression/recurrence. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Table 2 provides overall response for all possible combinations of tumor response in target and non-target lesions with or without the appearance of new lesions.

Table 2: Overall response for all possible combinations of tumor responses (Therasse *et al.* 2000)

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.4.2 Duration of response

Duration of overall response is defined as the interval between first documentation of CR or PR and documentation of recurrent or progressive disease.

Duration of stable disease is measured from the start of the treatment until the criteria for disease progression is met.

7.3.4.3 Number of disease-free patients

Number of disease-free patients includes all patients with documented and confirmed complete response as well as the patients with partial response, who are subsequently rendered disease-free after surgery/ radiofrequency ablation therapy at any time during the study for at least 8 weeks.

7.3.5 Assessment of impact of mitotane blood levels

To assess the importance of mitotane treatment, the blood levels will be correlated to clinical response. Therefore, mitotane plasma/serum levels will be measured at least every four weeks in the first 6 months of administration and later every 8 weeks in one of the reference laboratories (see Appendix 6, page 81). Blood has to be drawn in the morning at least 12 hours after administration the last tablet. The best overall response rate in patients reaching serum levels above 14 mg/l (and 10 mg/l, respectively) will be compared with patients reaching levels below 14 mg/l (and 10 mg/l, respectively).

7.3.6 Assessment of both schemes as second line treatment

To assess the effects of both regimens as second line treatment, the same criteria used to assess Overall Response Rate will be used. To determine the baseline, the status of measurable and non-measurable lesions at the time of crossover will be used.

8 SAFETY ASSESSMENT / Reporting of Adverse Events

The collection of information on safety in clinical studies must be carried out efficiently and consistently so that analysis within and across studies is possible. Serious adverse events must be identified and reported rapidly so that potential hazards to patients can be identified and regulatory reporting requirements can be met. When an adverse event occurs it should be graded according to the NCI-CTG criteria (version 2.0) (see Appendix 4).

8.1 Adverse Events

8.1.1 Definition of Adverse Event

Any unfavorable symptom, sign, illness, or experience which develops or worsens in severity during the course of the study whether or not considered related to the medical treatment. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures including abnormal laboratory findings are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is considered by the investigator to be of clinical significance

Worsening of the disease under study will normally be measured by efficacy parameters, and should only be recorded as an AE if the outcome is serious or if specified in the protocol.

8.1.2 Definition of a Serious Adverse Events (SAE)

A SAE is any event that is:

- fatal
- life-threatening
- results in persistent or significant disability or incapacity
- requires or prolongs hospitalization
- a congenital anomaly or birth defect
- an important medical event

Death as a consequence of worsening of the disease will not be recorded as SAE.

Life-threatening means that the patient was at immediate risk of death from event as it occurred. It does not include an event that, had it occurred in more serious form, might have been life threatening (i.e. asymptomatic febrile neutropenia, anemia or thrombocytopenia, laboratory findings of impaired liver or kidney function resulting in a dose modification or delay of therapy less than four weeks).

Requires inpatient hospitalisation or prolongation of existing hospitalisation should be defined as hospital admission required for treatment of the AE or occurred as a consequence of the event. Hospital admission required for treatment of bone marrow suppression as a result of the study drugs (transfusions with blood products, prophylaxis against infections by means of isolation and antibiotics) represents well known complications to the therapeutic regimens included in the study and will not be reported as SAE, unless the seriousness calls upon the investigator to withdraw the patient from the study, or embark on the second phase and cross over. Hospitalisation due to nausea and vomiting resulting in need of parenteral infusion for nutrition and hydration will be graded according to the NCI-CTG criteria, but not recorded as SAE. Hospital admission for scheduled elective surgery would not be a SAE.

Important medical events are those which may not result in death or be immediately life threatening or result in hospitalisation, but may jeopardize patients and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment for allergic bronchospasm, development of drug dependency, occurrence of a second malignancy.

Peripheral neuropathy is commonly seen in patients treated with the included study drugs. This symptom may increase over time and will not be considered a SAE unless it results in drug withdrawal.

Impaired kidney function is frequently seen over time in patients treated with the study drugs. This expected side effect results in dose modification specified under chapter 10. Unless the impairment warrants cross-over or complete withdrawal from the study this adverse event will not be recognized as SAE, and not reported in the CRF as an adverse event. Degree of, and reason for dose modification of given study drug will be recorded in the CRF.

Impaired liver function is frequently seen over time in patients treated with the study drugs. This expected side effect may result in dose modification specified under chapter 10. Unless the impairment warrants cross-over or complete withdrawal from the study this adverse event will not be recognized as SAE, and not reported in the CRF as an adverse event. Degree of, and reason for dose modification of given study drug will be recorded in the CRF.

All AE which do not meet any of the criteria for serious should be regarded as **non-serious AE**.

All SAE occurring from the registration until 30 days following the last infusion of chemotherapy must be reported according to the procedure described below. Any late SAE (occurring after this 30-day period) possibly or probably related to the study chemotherapy should follow the same reporting procedure.

8.2 Laboratory Tests

The following laboratory procedures should be regarded as a minimum of safety procedures and oncological routine testing before embarking on treatment with the study drugs.

Basic panel (every cycle): CBC with differential and platelet count, Na, K, Creatinine, AST/SGOT, ALT/SGPT, Total Bilirubin, Albumin

Comprehensive panel (every evaluation): CBC with differential and platelet count, Serum chemistry profile to include: comprehensive panel (Na, K, Mg, Creatinine, Glucose, AST/SGOT, ALT/SGPT, gamma Glutamyl Transpeptidase, Alkaline Phosphates, Total Bilirubin, Albumin)

In addition, CBC with differential and platelet count on day 12 and 14 (nadir) of every EDP cycle.

Laboratory test results listed above will only be included in the CRF at the first evaluation, before cross-over, at final evaluation and when relevant for the decision of giving a modified dose of the study drug. Laboratory test results gathered before each administration of chemotherapy are to be regarded as clinical routine and safety procedures and not target variables for this study. Thus, extensive recording of laboratory test data will not be included in the CRF.

8.3 Special Investigations

The following investigations will be performed **prior to enrollment** in the trial, in case of drop out due to toxicity and during the trial as indicated.

- Echocardiography/MUGA scan: in all patients during ongoing EDP administration on every second evaluation
- ENT examination (in patients with hearing problems): during the trial in patients receiving the EDP regimen and suffer hearing problems

8.4 Documentation and reporting of adverse events by investigator

The study drugs are toxic and side effects such as nausea, vomiting, asymptomatic impaired renal function, asymptomatic impaired liver function, bone marrow inhibition, alopecia, infertility, and symptoms of peripheral neuropathy are well known and must be expected. These frequently recognized and expected side effects need not be recorded in the CRF unless they result, upon clinical judgment of the physician responsible for administering the drug, in dose modification other than those listed in the recommendations of dose modification (see section 10, page 49), or if

they result in cross-over or complete withdrawal from the study. These above listed side effects need however to be recorded in the medical journal as a clinical routine.

Concerning adverse events (other than the side effects listed above), at each contact with the patient, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded promptly in the adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures should be grouped together and recorded as a single diagnosis in the CRFs. The component parts of the diagnosis may be listed for verification.

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause. For SAEs, the Serious Adverse Event Report Form (SAERF) must also be completed. SAEs which are still ongoing at the end of the study period must be followed up to determine the final outcome.

Any SAE which occurs after the study period and is considered to be possibly or probably related to study treatment or study participation should be recorded and reported immediately.

The following definitions will be used to assess causality:

Code	Descriptor	Definition
5	Definite	The adverse event is <i>clearly related</i> to the investigational agent(s)
4	Probable	The adverse event is <i>likely related</i> to the investigational agent(s)
3	Possible	The adverse event <i>may be related</i> to the investigational agent(s)
2	Unlikely	The adverse event is <i>doubtfully related</i> to the investigational agent(s)
1	Unrelated	The adverse event is <i>clearly not related</i> to the investigational agent(s)

Toxicities will be recorded as they occur and graded according to the Common Toxicity Criteria (CTC) (see Appendix 4) at the end of every cycle. Toxicities that can not be graded using the NCIC-CTG Common Toxicity Criteria will be graded as mild (asymptomatic), moderate (symptomatic but not interfering significantly with function) or severe (causing significant interference with function).

8.5 Immediate reporting by investigators to the Principal Investigator

Any adverse event that is considered SERIOUS (for definition see 8.1) must be reported immediately (within 48 hours or, at the latest, on the following working day) by the investigator to the Study Chair:

Prof. Britt Skogseid
Fax: + 46-18-55 39 43
Tel. + 46-18 611 00 00 or +46-733 70 69 93
e-mail: Britt.Skogseid@medsci.uu.se

In addition, Serious Adverse Events that are considered *unexpected* and for which a *relation with any of the study drugs* cannot be ruled out shall be reported in writing to the local regulatory authorities by the investigator within pre-defined time limits;

Relevant information about unexpected serious adverse events that are *fatal* or *life threatening* shall be recorded and reported as soon as possible but not later than *7 days* after first knowledge by the investigator. Relevant follow-up information is subsequently communicated within an additional 8 days.

All other unexpected serious adverse events shall be reported to the regulatory authorities and the ethical committee as soon as possible but not later than *15 days* after first knowledge by the investigator.

It is the responsibility of the Study Chair to inform all National Study Coordinators of Unexpected Serious Adverse Events that might have relevance for the conduct of the study and it is the responsibility of the National Study Coordinators to forward this information to the local investigators and to notify the local regulatory authorities and ethical committees.

9 THERAPEUTICAL PROCEDURES IN PATIENTS WITH CLINICAL RESPONSE

9.1 Patients with complete response

Patients achieving a complete response will receive two additional treatment cycles after documented complete response (a maximum of 6 cycles EDP is recommended), and, afterwards, will undergo regular follow-up (every 3 months). Surgical re-evaluation in dubious cases (i.e. persistence of fibrotic tissue in sites of disease) is left to the judgment of the local investigator.

Mitotane should be administered at least up to two years after documentation of complete response or until progression or unacceptable toxicity. During this time regular staging (every 3 months) is recommended.

9.2 Patients with partial response or stable disease

Patients achieving partial response (PR) or disease stabilization (SD) should be evaluated for surgery with radical intent or radiofrequency ablation with radical intent; otherwise, the patients will receive treatment for at least two more cycles (a maximum of 6 cycles of EDP is recommended) or until progressive disease is documented or adverse effects necessitate withdrawal from therapy. Mitotane should be administered at least up to two years after documentation of response until progression or unacceptable toxicity. Regular staging (every 3 months) and submitting to surgical re-evaluation is recommended.

If a patient is stable on EDP/M but the maximal cumulative dose of doxorubicin is reached, EDP should be withdrawn and mitotane continued. In case of progression the patient will switch to Sz/M (when EDP was first line treatment).

10 DOSE MODIFICATION

10.1 Cytotoxic drugs

Doxorubicin

Care should be taken not to exceed the maximum cumulative dose of doxorubicin (550 milligrams/m²). This is reduced to 450 milligrams/m² in patients over 70 years.

Hematologic toxicity:

Blood counts with differential will be performed on day 1, 12 and 14 of every cycle (before start of cycle and at nadir).

Table 3 Dose modifications due to hematologic toxicity

Neutrophil count / mm ³	Platelet count / mm ³	E, D, P dosed
> 1500	> 100 000	100%
1000 – 1500	50 000 - 100 000	Delay for 1 week, if persist 50 %
< 1000	< 50 000	Hold until return to baseline, then 75%

Streptozotocin usually has no hematologic toxicity.

If severe neutropenia (neutrophil count <500/mm³) and/or severe thrombocytopenia (platelet count <30000/mm³) is observed in the interval (nadir) between two cycles, the next dose of E and D will be administered at 80% of the total dose; P dose will not be modified.

Chemotherapy will be delayed by 1 week in patients showing neutrophil and platelet counts of 1000 to 1500/mm³ and/or 50.000 to 100.000/mm³, respectively, on day 1 of each cycle.

If neutrophil and platelet counts do not return to normality after four weeks of chemotherapy delay, the treatment will be withdrawn.

In patients showing more severe neutropenia (<1000/mm³) and/or thrombocytopenia (<50000/mm³) on day 1 of each cycle, chemotherapy will be held until resolution of hematological abnormalities; afterwards, the doses will be administered at 75% of the total doses.

Administration of colony stimulating factors at nadir is recommended in the event of severe neutropenia (neutrophil count <1000 mm³) in order to reduce the risk of infection.

Renal toxicity

In the event of renal toxicity the following drugs dose will be adjusted according to table 4.

Table 4 Dose modifications due to renal toxicity

S-Creat / BCC	P	D	E	Strepto
≤1.2 / ≥75ml/min	100%	100%	100%	100%
1.2-2.1 / 60-75	50%	100%	100	1g for 2 days
>2 / 50-60	Stop	Delay*	Delay*	1g one day
<50	Stop	Delay*	Delay*	Delay*

* until recovery

Neurologic Toxicity

Table 5 provides guidelines for subsequent dosing following the neurologic toxicity demonstrated in the previous cycle.

Table 5 Dose modifications due to neurologic toxicity

CTC grade	P	D	E
0-1	100%	100%	100%
2	50%	100%	50%
3	Delay*	Delay*	Delay*
4	Stop	Stop	Stop

* until recovery

Streptozotocin usually has no neurologic toxicity.

Liver Toxicity

Liver toxicity is rare but can be seen early in patients receiving streptozotocin, including patients in their first cycle. If serum transaminases increase more than 3 times of the individual baseline level and do not return to baseline before next cycle the streptozotocin regimen should be stopped.

Patients will be eligible to switch to EDP or discontinue study treatment.

If albumin is below 32 g/l, the dose of etoposide will be reduced by 50%. If it is below 25 g/l etoposide will be not delivered until albumin is again above 25 g/l.

10.2 Mitotane

Dose modification should be performed according to circulating drug level aiming at a blood level between 14 and 20 mg/l.

In case of grade 2 neurologic toxicity or grade 3 and 4 non-hematological toxicity (with exception of alopecia), mitotane administration will be stopped until recovery occurs and restarted with a lower dose (50-75% of the most recent dose).

In case of nausea and vomiting, partial adrenal insufficiency has to be considered and treated with higher doses of glucocorticoids. However, a permanent potent antiemetic treatment (e.g. 5-HT-antagonists) is strongly recommended.

Chemotherapy and mitotane administration must be temporarily discontinued if the patients experienced grade 3 non-hematological toxicities, with the exception of alopecia.

Increases in hepatic gamma glutamyl transpeptidase levels (< 5 x of patient's baseline) are frequent and in most case not require withdrawal of the drug. In case of an increase of AST/SGOT, ALT/SGPT > 5 x the institutional upper limit of normal range, mitotane administration should be stopped until recovery and restarted with a lower dose (50-75% of the most recent dose).

11 FLOW CHART OF EXAMINATION

	At baseline	every cycle	every evaluation	every second evaluation (in addition)
Physical Examination	*	*	*	
Laboratory Tests	‡	†	‡	
ECG	*			* ¹
Echocardiogram/MUGA	*			* ¹
Side effects		*	*	
Abdominal CT scan	*		*	
Chest CT scan	*		*	
Quality of Life	*		*	

‡ comprehensive and † basic laboratory panel (definition see 8.2 page 45)

¹ in case of EDP regimen

12 CRITERIA FOR DISCONTINUATION OF ADMINISTRATION OF STUDY DRUGS

Subjects may withdraw from the study treatment at any time and for any reason, without affecting their right to treatment by the investigator.

Administration of study drugs should be stopped if one or more of the following events occur:

- disease progression (after switch to the alternative regimen)
- NCI CTC grade 4 non-hematological toxicities due to the cytotoxic chemotherapeutic drugs, with exception of alopecia and gastrointestinal toxicity
- a treatment delay greater than four weeks for any toxicity
- occurrence of cardiotoxicity
- refusal of the patient to continue treatment
- unsatisfactory compliance with study procedures.

The investigator must make every effort to contact subjects lost to follow-up.

13 STUDY MONITORING AND AUDITING

Standard monitoring and auditing procedures will be followed.

13.1 Study monitoring

The study will be monitored centrally by the Data Management Center in Uppsala, Sweden. The responsible Data Manager is not involved in patient care and will function as independent Monitor. He will review all e-CRF within 4 weeks. By frequent communications (letter, telephone, e-mail), the monitor will ensure that the investigations is conducted according to the protocol design and regulatory requirements. In addition, monitoring will be done by personal visits from independent persons (site monitor), which are not involved in patient care of the study patients. The site monitor will review the patient's informed consent, the case report forms, and source documents. The site monitoring will be organized by the National Coordinators according to the national rules.

13.2 Source data verification and on-site audits

The Data Monitor, the Site Monitor, the members of the Independent Data Monitoring Committee, regulatory authorities, and the Institutional Review Board may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Study Chair, the Study Coordinators and the local Investigators, who must provide support at all time for these activities.

14 STATISTICAL CONSIDERATIONS

14.1 Objective

The primary purpose of this trial is to investigate whether EDP/M will prolong survival as compared to Sz/M.

14.2 Study design

The study is designed as a Phase III, randomized, open-label, multi-national trial in which patients with adrenocortical carcinoma and advanced/metastatic disease not amenable to surgical resection will be randomized to receive either therapy with Etoposide, Doxorubicin, Cisplatin plus Mitotane (EDP/M) or Streptozocin plus Mitotane (S/M). Overall survival (= primary endpoint) is defined as the time interval between the date of randomization and the date of death from any cause (= target event) or the last known alive date (i.e., patients who are alive at the time of an analysis will be censored for survival at the time of their last contact).

14.3 Statistical hypotheses

The problem will be formulated statistically as a test of the null hypothesis $H_0: \theta = 1$ versus the alternative hypothesis $H_1: \theta \neq 1$, where the hazard ratio (θ) is the risk of death in the Sz/M group, divided by the risk of death in the EDP/M group. A hazard ratio greater than 1 indicates that therapy with EDP/M is superior.

14.4 Statistical Analysis

The primary analysis on survival will be conducted as follows: For each treatment group, the overall survival distribution and the median survival time will be estimated using the Kaplan-Meier method. The two-sided logrank test will be used to test the survival time null hypothesis assuming proportional hazard rates (i.e., a hazard ratio independent of the time). For the hazard ratio a point estimate and a 95% confidence interval will be provided. The final analysis will be conducted after 200 observed events.

The primary analysis will be based on the intention-to-treat (ITT) analysis set. However, a sensitivity analysis will be conducted on a per protocol analysis set. The latter only serves to confirm the robustness of the results.

Further analyses of the secondary endpoints are sensitivity analyses, or they are descriptive or explorative.

Evaluation of Second-Line Therapies

The second-line therapy for a patient will start immediately after progression is observed in a follow-up assessment of the patient. Depending on the allocated first-line treatment, the second line

therapies of choice until proven failure are defined to be the first-line therapies in the way of a cross-over.

Every second-line therapy of the study will be evaluated as a separate phase II sub-study with observation of success or failure in a patient as primary endpoint. Success is defined as response or stable disease in the next follow-up visit after 8 weeks.

The aim of the statistical analysis is the estimation of the success rate with 95% confidence interval. An exact confidence interval will be calculated similar to the Clopper-Pearson interval, only similar because an interim analysis will be taken into account. However, for anticipated success rates of about 15% (between 10% and 20%), the precision of the 95% confidence intervals remains low with an interval width of more than 10% even if all patients per treatment arm (max. 150) could be evaluated for second-line treatment. Thus evaluation should include all available second-line treatment courses. On the other hand, failure of a second-line therapy should be detected as early as possible. In the case of proven failure, the second-line therapy should be rejected. The first time where a success rate of less than 15% can be proven statistically is after assessment of the first 23 patients. At this time a simple interim analysis will be performed. If none of these 23 patients will have a success, the result will be regarded as early failure and the respective second-line therapy will be rejected. As a consequence, the upper confidence limit of the 95% confidence interval will at least be 14,82%, either if the Clopper-Pearson interval based on the final results may have a lower upper limit.

14.5 Sample size and power considerations

The sample size was calculated using the primary endpoint, overall survival. Based on the results from the Swedish ACC study (Khan *et al.* 2000) a median survival time of 18 months in patients treated with Streptozocin plus Mitotane (Sz/M) is expected. Taking into account the results from the Italian ACC trial (Berruti *et al.* 2003) an increase to 27 months due to Etoposide, Doxorubicin, Cisplatin plus Mitotane (EDP/M) assuming proportional hazards and exponential distributions of survival time is expected. The improvement of 9 months corresponds to a hazard ratio of 1.5 and is considered as clinically relevant.

The survival time distributions of the two treatment groups will be compared using a two-sided logrank test at a 0.05 significance level. To detect a hazard ratio of 1.5 with a power of $1-\beta = 80\%$, 193 observed events (deaths) are needed. Note that the median survival time estimates of the cited trials were 16 and 28 months, respectively, and that the estimated survival curves are approximately exponential. These results promise a slightly higher hazard ratio of about 1.75.

An interim analysis plan would increase the required number of events by about 4%, hence observation of 200 deaths would be required. Assuming an accrual period of 60 months and an observation period of at least 18 months from the last patient recruited, a minimum number of 270 patients (135 per regimen) will be required. With a lost-to-follow-up rate of maximal 10%, a total of 300 patients (150 per regimen) will be needed. However, the participating investigators are optimistic to keep the lost-to-follow-up rate below 5%.

14.6 Interim analyses with regard to effectiveness

Studies with an accrual period of many years require interim analyses for ethical and practical reasons. The ethical obligation is the need to minimize the number of patients receiving a clearly inferior treatment, the practical obligation is to conclude the study as soon as possible. The confirmatory analysis of the primary endpoint should therefore be carried out using a group sequential analysis plan, based on the number of observed events (Pocock 1977; Lan & DeMets 1983; DeMets 1989).

A first interim analysis without alpha spending is planned after approximately 2½ years. This interim analysis serves to assess the assumptions of the design. Two interim analyses and the final analysis using alpha-spending will follow after 79, 122, and 200 events are observed. The cumulative alpha-spending amounts to 0.00982, 0.01704, and 0.05, respectively. The nominal alpha levels of interim analyses can be calculated unambiguously from the specified values. The selected three stage group sequential plan increases the maximum number of events by 4% compared with the fixed sample design, but reduces the expected number of events by 17.2%. The plan has the quality that a power of 80% will be achieved to detect a hazard ratio of 13/6, 11/6, and 1.5 at the first, second, and final analysis where part of alpha is spent. (Schäfer & Müller 2004: Construction of group sequential designs in clinical trials on the basis of detectable treatment differences. *Statistics in Medicine*: in press.)

If, at a specific interim analysis, the number of observed events differs from the planned number of deaths, corrections will be made employing a use function (Lan & DeMets 1983; DeMets 1989; DeMets & Lan 1994). The use function is specified by linear interpolation where, in addition to the above specifications, the use function is set to a value of 0.05 if at least 180 events are observed. The corrections will be made without knowledge of grouped data.

If necessary, the design will be modified using the CRP-principle by Müller & Schäfer. A detailed description for application to survival analysis is given by Schäfer & Müller (Schäfer & Müller 2001). According to this method, interim analyses can be performed at any time during the conduct of a trial. Design elements can be checked and redesigned. All design modifications require an amendment to the study protocol.

14.7 Time schedule

A first interim analysis without alpha-spending is planned after 30 months (= 2½ years). The following first interim analysis with alpha-spending is planned after approximately 42 months (= 3½ years). The second interim analysis with alpha-spending is planned before recruitment is complete after approximately 54 months (4½ years). The final analysis will be conducted after 78 months (= 6½ years). A delay of six months due to recall intervals, documentation, monitoring, and reporting of results is expected. The whole study period will be, therefore, 7 years.

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APPENDICES

Appendix 1 Adrenocortical cancer staging criteria (according to MacFarlane/Sullivan 1978)

Stage	Sullivan et al. 1978
I	T ₁ , N ₀ , M ₀
II	T ₂ , N ₀ , M ₀
III	T ₃ , N ₀ , M ₀ or T ₁₋₂ , N ₁ , M ₀
IV	T ₄ , N ₀ , M ₀ or T ₃ , N ₁ , M ₀ or T ₁₋₄ , N ₀₋₁ , M ₁

T₁: tumour < 5cm

T₂: tumour > 5cm

T₃: tumour infiltration locally reaching neighbouring organs

T₄: tumour invasion of neighbouring organs

N₁: positive lymph nodes

M₁: distant metastasis

Appendix 2. ECOG index for Performance Status

Eastern Cooperative Oncology Group (Zubrod-ECOG) ^{1,2}	
Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.	1
Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	4

¹ Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man.*

² *Journal of Chronic Diseases*, 11:7-33, 1960.

³ Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* *Am J Clin Oncol (CCT)* 5: 649-655, 1982

Appendix 3 Quality of Life questionnaire



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

Appendix 4 NCI Common Toxicity Criteria (CTC) Version 2.0 1999

Toxicity	Grade				
	0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immunosuppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify,)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years) 90% cellularity average younger adults (19-59) 60-70% cellularity average older adults (≥ 60 years) 50% cellularity average					
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm ³	200 - < 500/mm ³	50 - < 200/mm ³	< 50/mm ³
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L

Toxicity	Grade				
	0	1	2	3	4
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs [®]) schistocytes]	evidence of red cell destruction and ≥ 2 gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hgb.					
Leukocytes (total WBC)	WNL	$< \text{LLN} - 3.0 \times 10^9 / \text{L}$ $< \text{LLN} - 3000 / \text{mm}^3$	$\geq 2.0 - < 3.0 \times 10^9 / \text{L}$ $\geq 2000 - < 3000 / \text{mm}^3$	$\geq 1.0 - < 2.0 \times 10^9 / \text{L}$ $\geq 1000 - < 2000 / \text{mm}^3$	$< 1.0 \times 10^9 / \text{L}$ $< 1000 / \text{mm}^3$
Lymphopenia	WNL	$< \text{LLN} - 1.0 \times 10^9 / \text{L}$ $< \text{LLN} - 1000 / \text{mm}^3$	$\geq 0.5 - < 1.0 \times 10^9 / \text{L}$ $\geq 500 - < 1000 / \text{mm}^3$	$< 0.5 \times 10^9 / \text{L}$ $< 500 / \text{mm}^3$	-
Neutrophils/granulocytes (ANC/AGC)	WNL	$\geq 1.5 - < 2.0 \times 10^9 / \text{L}$ $\geq 1500 - < 2000 / \text{mm}^3$	$\geq 1.0 - < 1.5 \times 10^9 / \text{L}$ $\geq 1000 - < 1500 / \text{mm}^3$	$\geq 0.5 - < 1.0 \times 10^9 / \text{L}$ $\geq 500 - < 1000 / \text{mm}^3$	$< 0.5 \times 10^9 / \text{L}$ $< 500 / \text{mm}^3$
Platelets	WNL	$< \text{LLN} - < 75.0 \times 10^9 / \text{L}$ $< \text{LLN} - 75000 / \text{mm}^3$	$\geq 50.0 - < 75.0 \times 10^9 / \text{L}$ $\geq 50000 - < 75000 / \text{mm}^3$	$\geq 10.0 - < 50.0 \times 10^9 / \text{L}$ $\geq 10000 - < 50000 / \text{mm}^3$	$< 10.0 \times 10^9 / \text{L}$ $< 10000 / \text{mm}^3$
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs Also consider Hemoglobin.	none	-	-	Yes	-
Blood/Bone Marrow-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations Note: Grade palpitations <u>only</u> in the absence of a documented arrhythmia.	none	present	-	-	-
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-

Toxicity	Grade				
	0	1	2	3	4
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T-wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of $\geq 10\%$ but $< 20\%$ of baseline value; shortening fraction $\geq 24\%$ but $< 30\%$	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction $\geq 20\%$ of baseline value; $< 24\%$ shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to $> 150/100^*$ if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to $> 150/100^*$ if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
<i>*Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.</i>					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. <i>For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.</i>					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade				
	0	1	2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with <u>no</u> bleeding	laboratory findings <u>and</u> bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/bleeding or thrombosis/embolism or renal failure) requiring therapeutic intervention
Coagulation-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level <u>or</u> 20% Karnofsky or <i>Lansky</i>) <u>or</u> causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels <u>or</u> 40% Karnofsky or <i>Lansky</i>) <u>or</u> loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10 ⁹ /L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia) Note: Bruising <u>resulting from grade 3 or 4 thrombocytopenia</u> is graded as Petechiae/purpura <u>and</u> Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, <u>not</u> in the DERMATOLOGY/SKIN category.	none	localized or in dependent area	generalized	-	-

Grade					
Toxicity	0	1	2	3	4
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic, TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences

Toxicity	Grade				
	0	1	2	3	4
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients without colostomy:					
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis					
Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension.					
Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation.					
Note: Fistula is graded separately as Fistula- rectal/anal.					
Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					

Toxicity	Grade				
	0	1	2	3	4
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion-pRBCs, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as a toxicity.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

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

Grade					
Toxicity	0	1	2	3	4
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema with ulceration
Lymphatics-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl > 10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Hypocalcemia	WNL	< LLN - 8.0 mg/dl < LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	< 6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	< LLN - 55 mg/dl < LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	< LLN - 3.0 mmol/L	-	2.5 - < 3.0 mmol/L	< 2.5 mmol/L
Hypomagnesemia	WNL	< LLN - 1.2 mg/dl < LLN - 0.5 mmol/L	0.9 - < 1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	< LLN - 130 mmol/L	-	120 - < 130 mmol/L	< 120 mmol/L
Hypophosphatemia	WNL	< LLN - 2.5 mg/dl < LLN - 0.8 mmol/L	≥ 2.0 - < 2.5 mg/dl ≥ 0.6 - < 0.8 mmol/L	≥ 1.0 - < 2.0 mg/dl ≥ 0.3 - < 0.6 mmol/L	< 1.0 mg/dl < 0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle)	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).					
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					

Toxicity	Grade				
	0	1	2	3	4
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/radiculitis	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Also consider Headache, Vomiting, Fever.					
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/involuntary movement/restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision.					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis

Grade					
Toxicity	0	1	2	3	4
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade				
	0	1	2	3	4
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify,)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL _{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV ₁	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O ₂ saturation with exercise	decreased O ₂ saturation at rest, requiring supplemental oxygen	decreased O ₂ saturation, requiring pressure support (CPAP) or assisted ventilation

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

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

Appendix 5 List of reference pathologists

To be completed

Australia	
Argentina	
Canada	
France	Dr Bernard Caillou Dept. d'anatomopathologie Institut Gustave-Roussy Villejuif France
Germany	Prof. Dr. Wolfgang Saeger Institute for Pathology Kath. Marienkrankenhaus gGmbH Alfredstr. 9 22087 Hamburg Germany
Italy	Prof. Papotti University of Turin Regione Gonzole, 10 10043 Orbassano Italy
Scandinavia	Prof. Dr. Lars Grimelius Dept. of Pathology Uppsala University Hospital SE 75185 Uppsala Sweden
UK	Dr Anne Marie McNicol University Department of Pathology, Royal Infirmary, Castle Street Glasgow G4 0SF Scotland, United Kingdom
United States	
The Netherlands	

Appendix 6 List of reference laboratories for mitotane measurement

To be completed

Australia	
Argentina	
Canada	
France	HRA Pharma, Paris
Germany	HRA Pharma, Paris
Italy	University of Turin Regione Gonzole, 10 10043 Orbassano Italy
Scandinavia	Department of Clinical Chemistry at Sahlgrenska University Hospital, in Gothenburg Sweden
United States/Canada	
The Netherlands	Klinische Farmacie en Toxicologie Leids Universitair Medisch Centrum The Netherlands