



RHÔNE-POULENC RORER

CLINICAL TRIAL PROTOCOL

STUDY RP56976V - 327

**A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING
DOCETAXEL ADMINISTERED EITHER WEEKLY OR EVERY THREE WEEKS
IN COMBINATION WITH PREDNISONE
VERSUS MITOXANTRONE IN COMBINATION WITH PREDNISONE
FOR METASTATIC HORMONE REFRACTORY PROSTATE CANCER.**

Compound Number: RP56976
I.N.N. / Trade Name: docetaxel / Taxotere®
Protocol Number: Study RP56976V - 327
Phase of Study: III
IND Number:

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Author(s):

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study Chair :

[REDACTED]

[REDACTED]

[REDACTED]

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LOCAL STUDY CONTACTS

COUNTRIES	PRIMARY CONTACT	
SOUTH AFRICA	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

CENTRAL STUDY CONTACTS

PROTOCOL CONTRIBUTORS

A horizontal bar chart illustrating the distribution of clinical trial roles across various study phases. The y-axis lists the roles: Statistician, Study Managers, Physicians, Pharmacokineticist, Quality of Life and Socio-economics, Clinical supplies contributor, and Study Chair. Each role is represented by a black bar of a specific length, indicating its prevalence or duration across the phases.

Role	Approximate Bar Length (Relative Scale)
Statistician	Very Short
Study Managers	Very Long
Physicians	Medium-Long
Pharmacokineticist	Medium
Quality of Life and Socio-economics	Medium
Clinical supplies contributor	Short
Study Chair	Medium-Long

CONTACTS FOR SERIOUS ADVERSE EVENT REPORTING

Any serious adverse event should be reported within 24 hours by telephone or fax, or, at the latest, on the following working day. Contact should be made with study monitors listed previously (see local study contacts) or with :

[REDACTED]

If contact cannot be made with the above, then contact Rhône-Poulenc Rorer Worldwide Pharmacovigilance and Pharmacoepidemiology (WPVP) Department :

France

20 avenue Raymond Aron
92165 Antony Cedex
FRANCE
Telephone (33) 1 5571 6965
Fax (33) 1 5571 7433

US

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Telephone (1) 610-454-5321
Fax (1) 610-454-2258

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AL(A)T	Alanine aminotransferase
ANC	Absolute neutrophil count
AS	Analgesics Score
AS(A)T	Aspartate aminotransferase
AP	Anteroposterior
bid	Twice daily
°C	Degrees Celsius
CBC	Complete blood count
C.I.	Confidence interval
CNS	Central Nervous System
CR	Complete response
CRF	Case report form
CT scan	Computerized tomography scan
dL	Deciliter(s)
ECG	Electrocardiogram
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factors
HGB	Hemoglobin
HRPC	Hormone Refractory Prostate Cancer
HSR	Hypersensitivity reaction
ITT	Intention To Treat
IV (iv.)	Intravenous
K(I)PS	Karnofsky (Index) Performance Status
L	Liter(s)
LHRH	Luteinizing Hormone-Releasing Hormone
LVEF	Left Ventricular Ejection Fraction
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
µL	Microliter(s)
mm	Millimeter(s)
MRI	Magnetic Resonance Imaging
NC	No change
NCI-CTC	National Cancer Institute Common Toxicity Criteria
ng	Nanogram(s)
NS	Not Significant
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PF	Physical Functioning
PK	Pharmacokinetics
PLT	Platelets
PO	Per os (by mouth)
PPI	Present Pain Intensity
PR	Partial response
PSA	Prostate-Specific Antigen
pt(s)	Patient(s)

QoL	Quality of life
qw	Every week
q3w	Every three weeks
RBC	Red Blood Cells
RDI	Relative dose intensity
R-PR RD	Rhône-Poulenc Rorer - Research and Development
RR	Response rate
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (software)
SD	Stable disease
SGOT	Serum Glutanic Oxalacetic Transaminase
SGPT	Serum Glutanic Pyruvic Transaminase
tid	three times per day
TTP	Time to progression
UNL	Upper Normal Limit
WBC	White blood cell(s)
wk(s)	Week(s)
WHO	World Health Organization

SYNOPSIS

Study RP56976V - 327

Title of the study:

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL ADMINISTERED EITHER WEEKLY OR EVERY THREE WEEKS IN COMBINATION WITH PREDNISONE VERSUS MITOXANTRONE IN COMBINATION WITH PREDNISONE IN METASTATIC HORMONE REFRACTORY PROSTATE CANCER

Investigators:

Investigative sites will be recruited in the following countries : Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, The Netherlands, New Zealand, Norway, Poland, Russia, Slovakia, Spain, South Africa, Sweden, United Kingdom, USA.

Study Center(s):

100 investigative sites will be recruited for this trial.

Study period (years):	Jan 2000 to Dec 2002	Clinical Phase:	III
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Objectives:**Primary objective :**

To compare the overall survival (OS) after mitoxantrone and prednisone (arm A), and docetaxel and prednisone (arm B: docetaxel q. 3weeks combined with arm C: weekly docetaxel) in patients with metastatic hormone refractory prostate cancer.

Secondary objectives

To compare :-

- Time to progression,
- Pain improvement (incidence and duration)
- PSA response (incidence and duration)
- Quality of life
- Response rate in patients with measurable disease
- Safety
- Pharmacokinetics of docetaxel in combination with prednisone

An independent socio-economic evaluation will be conducted in parallel of the clinical study.

Methodology:

Prospective, non blinded randomized phase III trial. Randomization will be centralized and stratified for center, pain level (PPI >2 and/or AS ≥10), and KPS (≥ 80 vs. ≤ 70).

Arm A : Mitoxantrone 12 mg/m² intravenously every 21 days, plus prednisone 10 mg orally given daily

Arm B : Docetaxel 75 mg/m² intravenously (day 1) every 21 days, plus prednisone 10 mg orally given daily

Arm C : Docetaxel 30 mg/m² intravenously on days 1, 8, 15, 22, 29, every 6 weeks, plus prednisone 10 mg orally given daily.

Dose reduction and/or treatment delay and/or treatment discontinuation are planned for the 3 arms in case of severe hematological and/or non hematological toxicities.

Number of Patients (total and for each treatment):

804 Patients (268 per arm) will be enrolled into this trial.

Diagnosis & criteria for inclusion:

Inclusion criteria

- (1) Signed informed consent prior to beginning protocol specific procedures.
- (2) Histologically proven prostate adenocarcinoma.
- (3) All patients must have metastatic prostate adenocarcinoma that is unresponsive or refractory to hormone therapy.
- (4) Patients must have received prior hormonal therapy as defined below:
Castration by orchietomy and/or LHRH agonists with or without
 - i) Antiandrogens
 - ii) Antiandrogen withdrawal
 - iii) Monotherapy with oral estramustine
 - iv) Other hormonal agents (e.g., ketoconazole, ...)

-If the patient has been treated with LHRH agonists (i.e. without orchietomy), this therapy should be continued
- the testosterone level should be <50ng/dl in all patients.
-If the patient has been treated with antiandrogens, they must have been stopped at least 4 weeks prior to enrollment for flutamide or nilutamide or cyproterone acetate and at least 6 weeks prior to enrollment for bicalutamide and the patient must have demonstrated progression despite cessation of antiandrogen therapy.
-In case of prior treatment with estramustine i.e. monotherapy and by oral route, at least 4 weeks must have elapsed since completion of estramustine therapy and the patient must have recovered from side effects.
- (5) Patients should have documented progression detected by PSA increase, physical examination and/or imaging:
- Rising PSA. Patients whose only evidence of progressive disease is a rising PSA, must have a value of at least 5 ng/ml in addition to increasing PSA to be eligible.
Rising PSA is defined as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure
- and/or progression of measurable lesions (bidimensional or unidimensional),
- and/or progression of non-measurable disease, (except bone)
- and/or appearance of new lesions, including those on bone scan.
- (6) Patients must have achieved stable analgesia for a minimum of 7 consecutive days prior to randomization. The patient must keep a pain diary for this 7-day period. Stable analgesia will be defined by both :
- no increase by more than one point in the daily PPI scores recorded over 7 consecutive days with an identical PPI score for the last two days
and
- no variation of the daily analgesic scores (AS) by more than 25% around the mean AS (mean AS = sum of the 7 daily AS divided by 7), i.e., the 7 daily AS should be within the range of values defined below :
- the lowest value should be \geq mean AS - 25% mean AS.
- the highest value should be \leq mean AS + 25% mean AS.
- (7) Prior treatment with corticosteroids is allowed.
- (8) Prior radiation therapy (to less or equal than 25% of the bone marrow only) is allowed. At least 4 weeks must have elapsed since the completion of radiation therapy and the patient must have recovered from side effects.
- (9) Prior surgery is allowed. At least 4 weeks must have elapsed since the completion of surgery.
- (10) Life expectancy \geq 3 months.

- (11) Karnofsky performance status (KPS) ≥ 60 .
- (12) Normal cardiac function must be confirmed by LVEF (MUGA Scan or echocardiography) that should be above the lower normal limit of the institution.
- (13) Laboratory requirements :
 - (a) Hematology :
 - Neutrophils $\geq 1.5 \times 10^9/L$
 - Hemoglobin $\geq 10 \text{ g/dL}$. Erythropoietin use is allowed, but RBC transfusion to upgrade the hemoglobin level is not allowed
 - Platelets $\geq 100 \times 10^9/L$
 - (b) Hepatic function :
 - Total bilirubin < the upper-normal limit of the institution.
 - ALAT (SGPT) and ASAT (SGOT) ≤ 1.5 times the upper-normal limit of the institution.
 - (c) Renal function :
 - Creatinine ≤ 1.5 times the upper normal limit (ie NCI grade ≤ 1)
- (14) Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating center. Patients receiving weekly docetaxel who live distal to the center may receive treatments at weeks 2, 3 and 5 of each cycle locally, but under the advice and direction of a trial investigator.

Exclusion criteria

- (1) Prior cytotoxic chemotherapy (except monotherapy with oral estramustine - see inclusion criterion n°4).
- (2) Prior isotope therapy (e.g., strontium, samarium).
- (3) Prior radiotherapy to $>25\%$ of bone marrow (whole pelvic irradiation is not allowed)
- (4) Prior malignancy except the following : adequately treated basal cell or squamous cell skin cancer, or any other cancer from which the patient has been disease-free for ≥ 5 years.
- (5) Known brain or leptomeningeal involvement.
- (6) Symptomatic peripheral neuropathy \geq grade 2 according to the NCI Common Toxicity Criteria.
- (7) Other serious illness or medical condition :
 - (a) Congestive heart failure even if controlled. Previous history of myocardial infarction or angina pectoris within 1 year from study entry, uncontrolled hypertension or uncontrolled arrhythmias.
 - (b) Active uncontrolled infection
 - (c) Peptic ulcer, unstable diabetes mellitus or other contraindications for the use of corticosteroids.
 - (d) Auto-immune disease (lupus, scleroderma, rheumatoid polyarthritis)
- (8) Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational drug within 30 days prior to study screening.
- (9) Concurrent treatment with any other anti-cancer therapy (except LHRH agonists).
- (10) Concomitant treatment with systemic corticosteroids used for reasons other than specified by the protocol.
- (11) Concomitant treatment with bisphosphonates.

Test product, dose and mode of administration

Docetaxel (Taxotere®) given intravenously at 75 mg/m^2 on day 1 every three weeks (Arm B) or at 30 mg/m^2 on days 1, 8, 15, 22, 29 every 6 weeks (Arm C). Both arms in combination with Prednisone given orally at 10 mg daily from day 1.

Duration of treatment:

The patients should receive 10 cycles of treatment in Arms A and B and 5 cycles in Arm C unless the following events occur earlier : adverse events, disease progression, consent withdrawn, start of further anti-tumor therapy.

Reference therapy, dose and mode of administration

Mitoxantrone given intravenously at 12 mg/m² on day 1 every three weeks in combination with Prednisone given orally at 10 mg daily from day 1.

Criteria for evaluation:

Primary endpoint:

Overall Survival is defined as the time between randomization and the date of death (whatever the cause). Patients who are still alive at their last contact or at the cut-off date of the analysis will be censored at their date of last contact for the OS analysis.

Secondary endpoints:

1. Time to progression is defined as the time between randomization and the date of progression (see below).

Progression of the disease will be defined by any of the following:

- 1) Rising PSA: In PSA responders (see below), progression will be defined as a ≥ 50% increase over the nadir and an increase in the absolute value PSA level by at least 5ng/ml, confirmed by a second value. In PSA non-responders, progression will be defined by a ≥ 25% increase over the nadir (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value.
- 2) any increase of ≥ 25% in the product of the largest diameters of any bidimensionally measurable lesion (or ≥ 25% in the size of unidimensionally measurable lesion) in comparison to the nadir level,
- 3) progression in non-measurable lesion according to WHO criteria (excluding bone metastases, see below),
- 4) the appearance of a new lesion including a new lesion on bone scan (i.e., new hot spot).
- 5) Pain progression : increase of ≥1 point in the PPI scale from its nadir noted on two consecutive three-week-apart visits OR ≥25% increase in the daily analgesics score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy.

2. Pain response: Pain response will be defined for the subset of patients with baseline PPI ≥2 and/or AS ≥10. Response criteria will use the Present Pain Intensity scale from the McGill-Melzack questionnaire and will require a 2 point reduction maintained for 2 consecutive evaluations at least 3 weeks apart with no increase in analgesic intake, OR a reduction of at least 50% in analgesic use (from baseline analgesic score) with no increase in pain: the reduced analgesic score must be maintained for 3 weeks. The duration of pain response will be measured from the first to the last assessment at which the above criteria are satisfied.

3. PSA response: PSA response will be evaluated for the subset of patients with raised PSA at baseline and PSA > 20ng/ml. Response requires a PSA decline of ≥ 50% confirmed at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied.

4- Quality of Life: QoL analysis will be evaluated using the FACT-P questionnaire at baseline, every 3 weeks during therapy, every month after completion of therapy and up to the introduction of further antitumor therapy. QoL response for an individual patient will be defined as a 10 point improvement in the FACT-P score maintained for 2 consecutive visits as compared to baseline. Patients not meeting this criterion, including those with inadequate assessments will be regarded as QoL non-responders. An additional analysis will be performed by comparing the distributions of FACT-P scores at months 2, 4, and 6 of study treatment between the randomized treatment groups. QoL data obtained within 2 weeks of the specified time of comparison will be acceptable for this analysis.

5-Responses rates will be reported using the WHO criteria in patients with at least one measurable lesion

6-Safety : Toxicity will be recorded using the NCI-CTC (version 2).

The following tests will be performed prior to and/or on specified days during and following therapy :

- Complete history of malignant and non-malignant diseases including known hypersensitivity reactions and cardiac history.
- Full clinical examination, vital signs, height, weight, assessment of any residual toxicity due to previous therapy, Karnofsky PS.
- Electrocardiogram (ECG), left ventricular ejection fraction (LVEF).
- Chest-X-Ray.
- Adverse events : assessed according to the NCI - CTC (version 2).
- Usual laboratory tests (hematology, renal and liver biochemistry, electrolytes, LDH, calcium) : before and on study.

-Pharmacokinetics

A pharmacokinetic analysis will be performed. It will assess docetaxel PK in combination with prednisone. A limited sampling strategy (6 plasma samples per patient) will be implemented in a limited number of patients (N = 68, i.e. 34 per docetaxel treatment arm) treated in selected centers. Initiation of prednisone will be delayed for 1 day. In arm B, a PK assessment will be performed on day 1 (no concomitant prednisone) and then on day 22 (concomitant prednisone). In arm C, a similar design will be implemented with PK on day 1 and day 22.

Statistical methods:

I. Sample Size Calculation

The primary objective is to detect a statistically significant difference in OS for the combined docetaxel containing arms relative to the control arm using mitoxantrone.

The median survival for patients receiving mitoxantrone + prednisone is expected to be about 12 months (ref: Tannock et al., *J. Clin. Oncol.* 14, 1756, 1996). A total number of 535 events is required to detect with 0.90 power a 33% increase in median OS using a two-sided logrank test at level 0.05 and a 1:2 ratio between the control and the combined docetaxel containing arms. Assuming a median follow-up of 24 months, anticipated from an uniform accrual over 24 months and a minimum follow-up of 12 months, and assuming a maximum of 2% of patients lost to follow-up, 804 patients (i.e., 268 per treatment group) should be randomized into this trial.

II Interim analyses

II-1 Interim Safety Analysis

An interim safety analysis will be conducted among the first 120 randomized patients (40 in each arm) in order to ensure the safety and tolerability of the selected dosing regimens.

II-2 Interim Efficacy and Safety Analysis

An interim analysis will be undertaken when 258 events (disease progression or death whichever occurs first) have been observed. A total number of 258 events would be required to detect with 0.90 power a 50% difference in median TTP using a two-sided logrank test at level 0.05, and a 1:2 ratio between the control and the combined docetaxel containing arms. The median time to progression for mitoxantrone + corticosteroids is expected to be 4 months, (ref :Kantoff et al., *J. Clin. Oncol.* 17, 1999). A total of 258 events will consequently allow detection of a 2-month difference in median TTP for the docetaxel groups compared to the control, with 90% power.

At the time of the interim analysis, and assuming an exponential distribution of the events, 54% of patients are estimated to be recruited and 22% of deaths are estimated to be observed. The interim OS analysis will be conducted at the 0.001 level («Peto's level», ref : Geller et Pocock, *Biometrics*, 43, 1987). Using the fixed nominal significance level of 0.001, this allows the final analysis to be conducted at just under the 0.05 level. Considering that 258 events will ensure adequate power for the TTP endpoint, the interim analysis of TTP will be conducted at 0.05 significance level. Multiplicity is managed for the TTP endpoint by requiring both interim and final analyses to have $p \leq 0.05$.

III. Final Analyses

Primary Efficacy Analysis: The primary analysis will be a comparison of OS using an intent-to-treat analysis between the two combined docetaxel groups versus the control mitoxantrone group based upon the adjusted Logrank test performed at 0.05 level. The final analysis of survival data will be performed provided that at least 535 deaths have been observed overall. This is estimated to occur one year after the recruitment of the last patient.

Secondary Efficacy Analyses

i) **TTP analysis:** A comparison of TTP between the two combined docetaxel groups versus the mitoxantrone control group will be undertaken using an intent-to-treat analysis based upon the adjusted Logrank test performed at 0.05 level. The final analysis of TTP will be undertaken at the end of the study (i.e., when the final OS analysis will be performed). With the total sample size, the power of the final TTP analysis is estimated to be in the range of 98%.

ii) **Pain Response and PSA Response Analyses**

For PSA and Pain response rates, the hypothesis is that they will be both about 35% for the control arm and about 50% for the docetaxel arms. Thus, assuming that about 80% of the patients will be evaluable for PSA response and about 50% for Pain response, the power of the final analysis of these endpoints when analyzed separately will be 94% and 79% respectively (with a type-1 error of 0.05). Response rates will be compared with Chi-square test.

iii) **Exploratory Analyses**

1. For each of the above endpoints where there is significance for the primary analysis (i.e., comparison of the combined docetaxel groups versus the control mitoxantrone group), separate comparisons of docetaxel treatment groups to control and of the two docetaxel groups will be made at the 0.05 level.

With the final sample size of 268 patients per group, the single arm comparisons (i.e., A vs B or A vs C or B vs C) will have approximately a 76% power to detect a 33% increase in median OS, and a 92% power to detect a 35% increase in median TTP. Time to event will be described using Kaplan-Meier curves and life tables by treatment group within the analyzed populations. Multivariate analyses will be performed with logistic regression for tumor response and Cox regression for time-to-event parameters. The goal will be to explore the sensitivity of the magnitude and statistical significance of the treatment effect after adjusting for independent prognostic factors.

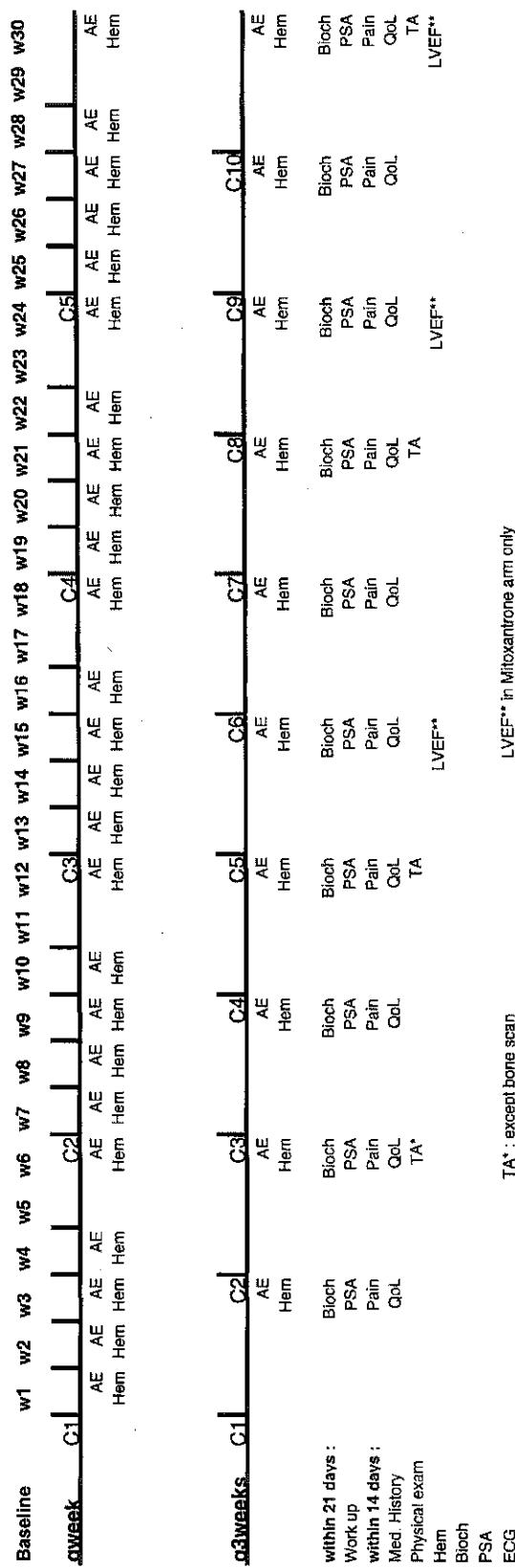
2. Response rates in patients with measurable disease will be compared with Chi-square test.

3. QoL Analysis

4. Toxicity Analysis

FLOW CHART

**Figure 1 : Schedule of assessments in q3w and qw arms
(see section 5.2 Detailed Plan for more details)**



AE : Adverse events
TA : Radiological Tumor assessment
Pain : PPI & Pain Med. Log

22-Dec-99

Rhône-Poulenc Rorer - CONFIDENTIAL

1. INTRODUCTION

1.1 BACKGROUND

Prostate cancer is a major worldwide health problem and is the most frequently diagnosed male malignancy (1).

The initial treatment for metastatic adenocarcinoma of the prostate consists of androgen ablation, either surgically with bilateral orchiectomy, or medically with LHRH receptor agonists (2). Responses are observed in up to 85 % of patients (3). However, this androgen ablation is not curative and the disease will eventually recur in virtually all patients. At this stage, further hormonal manipulations such as treatment with antiandrogens, and subsequent antiandrogen withdrawal (4) can be associated with responses of short duration but without improvement in survival duration (5).

Treatment options for patients with hormone-refractory disease remain limited and include palliation of symptoms (especially pain) and/or systemic cytotoxic chemotherapy (3).

The use of cytotoxic chemotherapy has not been routine practice whereas the role for chemotherapy in symptom palliation and PSA response is established. Even patients with disseminated prostate cancer are commonly managed exclusively by urologists, which likely contributed to the slow development of the cytotoxic paradigm (6).

Single agent chemotherapy has been associated with relevant palliative effects but no single agent has been associated with an objective response rate greater than 30% (6).

Combinations of cytotoxic agents have been tested with evidence of frequent enhanced activity in terms of palliation and PSA decline (3, 5, 6) but the safety profile of these combinations remains problematic, especially in elderly men with concurrent medical problems and limited bone marrow reserve. No survival advantage can be ascribed to any of the treatments tested in these studies. More effective systemic therapies are needed if we are to have an impact on the morbidity and mortality caused by this disease (7).

Palliative effects have been observed in HRPC patients following the administration of corticosteroids (8), mitoxantrone with either prednisone or hydrocortisone (9, 10, 11, 12). Based on results from two phase III randomized trials, the combination of mitoxantrone with corticosteroids is recognized now as the reference treatment in metastatic HRPC (6, 11, 12). There is a strong need for new therapies based on novel methods of inhibiting cancer growth, and docetaxel may represent a suitable therapeutic option in the setting of metastatic HRPC.

There is uniform agreement that responses in advanced prostate cancer are difficult to assess due to the heterogeneity of the disease and the lack of consensus on response criteria complicates the evaluation of new treatments (13). Many patients with metastatic prostate cancer do not have measurable disease but have symptoms dominated by osseous metastases. Prostate-Specific Antigen (PSA) as a measure of disease outcome in metastatic HRPC has emerged as an acceptable surrogate endpoint to evaluate new agents in this clinical setting (13, 14, 15). There is also some evidence of correlation between PSA response and survival based upon retrospective data but a cause and effect relationship remains to be confirmed through prospective investigations. Very recently, eligibility and response guidelines for phase II trials in HRPC have been established by

the PSA Working Group in an attempt to promote common standards for reporting PSA decline and to develop a common approach to outcome analysis (16).

In an attempt to provide an accurate picture of the potential therapeutic benefit of new treatments, it has been recommended that different types of response to therapy should be reported separately : these include changes in PSA, measurable disease, bone-only disease, quality of life, pain control. This method seems preferable to pigeonholing heterogeneous responses into categories of « complete » or « partial » (13).

These progresses in the standardization of outcome analysis and reporting should contribute to the refinement of the assessment of the risk/benefit ratio of new cytotoxic agents in HRPC (5, 13, 16).

Docetaxel in phase I and II trials exhibited a significant activity in various dosing regimen in the range of 40 to 75 mg/m² for the conventional three-weekly schedule and in the range of 20 to 40 mg/m² for the weekly schedule. Evidence of this activity included PSA decline, objective response in bidimensionally measurable lesions and pain control. The safety profile was assessed as acceptable throughout these studies with a good risk/benefit ratio in this clinical setting (17, 18, 19, 20, 21, 22).

On the basis of this preliminary positive clinical experience with docetaxel in HRPC, it is now indicated to assess prospectively the risk/benefit ratio of docetaxel combined with prednisone and to compare it to that of the reference combination of mitoxantrone plus prednisone, with overall survival as the primary endpoint.

1.2 DOCETAXEL

Complete available data on mechanism of action, experimental antitumor activity, preclinical data, safety and efficacy results from clinical trials in several tumor types and pharmacokinetic profile of docetaxel can be found in the updated version of the Investigator Brochure dated September 1, 1999 (23).

Docetaxel (Taxotere®) is a chemical entity of the taxoid class. Docetaxel monotherapy is indicated in the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. It is also indicated in the treatment of non-small cell lung cancer as well as ovarian cancer in some countries.

1.2.1 Docetaxel activity in HRPC: available results

1.2.1.1 Docetaxel monotherapy in HRPC

a) Docetaxel Three-Weekly Schedule in HRPC

The following table summarizes the data available for docetaxel used as a single agent in HRPC patients (17).

A phase II trial has shown evidence of docetaxel activity in HRPC, with the incidence of PSA decline >50% and >80% of 45% and 20%, respectively.

An objective response has been reported in 28% of patients with measurable disease. Responses were maintained for a median of 9 months (range:2-24).

The safety profile was assessed as tolerable. Grade 4 toxicities requiring discontinuation of treatment included stomatitis, small bowel obstruction, and a gluteal abscess. There were 2 deaths on study due to lung toxicity/pneumonia and pulmonary embolus. Six patients stopped the treatment voluntarily due to fatigue or edema. Other common toxicities were neutropenia, anemia, mild edema and hyperglycemia (steroids), anorexia, myalgia and alopecia.

Thus, this study provides evidence that single agent docetaxel given at the dose of 75mg/m² every 3 weeks is feasible, active and assessed as tolerable for the treatment of HRPC patients.

Table 1 : Activity of single agent docetaxel in HRPC

Author	Picus (17)
Regimen	Taxotere® 75 mg/m ² d 1q3 weeks
No Pts (eval/entered)	35 / 35
Prior chemotherapy	None
PSA Decline:	
>50%	45%
>75%	NR
>80%	20%
Objective Response*	
>50%	28% (7/25)
Analgesic requirement ↓	NR
Bone Pain ↓	NR
Median survival	12 months

*Among patients with bidimensionally measurable lesions

NR = Not Reported

b) Docetaxel Weekly Schedule in HRPC

Berry et al.* have performed a phase II trial of single-agent weekly docetaxel in HRPC. The purpose of the study was to determine the response rate and safety in patients treated with weekly docetaxel for hormone-refractory, symptomatic, metastatic prostate cancer. Sixty-one patients were enrolled in this study and 60 were considered to be evaluable. Docetaxel was administered by weekly infusion of 36mg/m² for 6 weeks followed by 2 weeks of rest, for 3 cycles. ECOG performance status (0/1/2) was 15/35/10 and median age was 72 years (41-86). The median serum PSA at baseline was 91.6ng/ml. Sixteen patients received a prior chemotherapy (27%) and 3 (5%) a prior Strontium therapy. Forty-two patients (70%) received a prior radiation therapy. Disease sites were identified in the majority of patients (bone 77%, bone+nodes 7%, bone+visceral lesions 7%, bone+nodes+visceral lesions 5%, nodes 2%, visceral lesions 2%, nodes+visceral 2%).

Eight patients (13%) had a response; one had a complete response and seven had a partial response. The median duration of response was 13 weeks (4-24 weeks), and an additional 24 patients (40%) had stable disease for more than 3 months. Twenty-four patients (41%) had a ≥50% reduction in serum PSA from baseline for at least 2 months. The estimated median time to progression for all patients was 5.1 months (0.9-14.8 months). Estimated median survival for all patients from the start of the treatment was 9.4 months (1.6-14.8 months).

As far as the safety profile is concerned, grade ≥3 toxicities consisted of diarrhea (10%), stomatitis (3%), asthenia (10%), neuropathy (5%), anemia (7%), and neutropenia (3%). One patient had

renal insufficiency, one had a thrombocytopenia, and 2 patients had a grade 3 sepsis. There was no treatment related death.

This trial with weekly docetaxel single agent chemotherapy provides evidence of the favorable risk-benefit ratio of docetaxel in HRPC even in patients at an advanced stage of the disease and who have been heavily pretreated.

In addition and beyond the scope of HRPC, three phase I studies conducted in various tumor types with weekly docetaxel have been published (24, 25, 26). These studies have used different dose levels ranging from 20mg/m²/week to 52mg/m²/week. There was evidence of antitumor activity at the various doses tested. Interestingly, Hainsworth et al. (25) conducted a phase I study to determine the MTD of weekly docetaxel administered as a 30-minute infusion for 6 consecutive weeks followed by 2 weeks without treatment. Premedication consisted of a 3-dose dexamethasone regimen: 8mg PO at 12 hours and 1 hour prior to docetaxel, and then 12 hours after. Dose limiting toxicity of fatigue/asthenia was observed at the 43mg/m²/week and 52mg/m²/week dose levels. No grade 4 leukopenia or grade 3/4 thrombocytopenia was observed at any of the dose levels tested. There were no arthralgias, myalgias and peripheral neuropathy using this schedule. At the 30mg/m²/week dose level, there was no grade 3 or 4 toxicities reported. These studies suggest that weekly docetaxel is a suitable alternative which can result in a higher dose intensity without increased toxicity. This improvement of the therapeutic index is particularly important in the elderly such as HRPC patients.

1.2.1.2 Docetaxel in combination therapy in HRPC

The following tables summarize the data available for docetaxel in combination with estramustine in the treatment of HRPC.

Table 2 : Activity of docetaxel in combination with estramustine in HRPC (I)

Author	Petrylak Phase I (18)	Petrylak* Phase II	Natale Phase I/II (19)
Regimen	Taxotere® 40-70 mg/m ² Every 21-days + Estramustine 280 mg t.i.d. x 5 days	Taxotere® 70 mg/m ² Every 21-days + Estramustine 280 mg t.i.d. x 5 days	Taxotere® 20 to 40 mg/m ² Weekly + Estramustine 280- 420 mg t.i.d. x 3-4 days
No Pts	34	12	18
Status	Closed	Ongoing	Ongoing
PSA Decline: >50%	70%	92%	78%
>75%	40%	58%	50%
>80%	-	-	-
Objective Response >50%	28% (5/18)	75% (3/4)	67% (4/6)
Improved KS or Pain Control	53%	Not Available	86%
Median survival (months)	22.8	NA**	NA**

* personal communication

** NA = Not available

Table 3 : Activity of docetaxel in combination with estramustine in HRPC (II)

Author	Savarese (20)	Sinibaldi (21)	Kreis (22)
Regimen	Taxotere® 70 mg/m ² d1 q3 w Estramustine 10 mg/kg 5 day Hydrocortisone daily	Taxotere® 70 mg/m ² d1 q3 w Estramustine 280 mg q6h x 5	Taxotere® 40,60,70,80 mg/m ² q3w Estramustine 14 mg/kg/daily
Phase	II	II	I
No Pt (eval./entered)	21/40	13/16	17/17
Prior chemotherapy	None	44%	6%
PSA Decline:			
>50%	58%	31%	82%
>75%	64%	NR	NR
>80%	NR	NR	30%
Objective Response*			
>50%	56% (5/9)	29% (2/7)	17% (1/6)
Analgesic requirement ↓	NR	NR	NR
Bone Pain ↓	NR	88%	NR
Survival	NR	NR	NR

* Calculated among patients with bidimensionally measurable lesions

NR = Not Reported

The data demonstrate the activity of docetaxel at various dosing regimen in the range of 40 mg/m² to 70 mg/m² for the three-weekly schedule and at 20 to 40 mg/m² for the weekly schedule, in combination with estramustine at the dose of 280 mg tid for 5 days or 420 mg tid for 3-4 days. Some authors (18) have observed a greater than additive cytotoxicity in vitro when docetaxel is combined with estramustine. However, the respective contribution of the 2 drugs in the clinically observed response rate remains unclear (18). Estramustine 560 to 840 mg/day as single agent given in two or three divided doses, produced objective responses in 19% to 69% of patients and reduced the PSA level in 14% of patients (27).

Evidence of the activity of the docetaxel-estramustine combination includes PSA decline (>50% decline in the range of 31 to 92% of patients), objective response in bidimensionally measurable lesions (17 to 75%), improved Karnofsky performance score or pain/symptom control in the range of 53 to 88%. Survival data are not yet reported except for Petrylak's phase I trial (18) in which the reported median survival was 22.8 months.

The safety of the combination has been assessed as acceptable. In the data published by Petrylak et al. (18), 2 episodes of grade 4 granulocytopenia were observed in patients who received more than 3 cycles of therapy. The incidence of thromboembolic events was 8.8%. No myocardial infarctions or pulmonary emboli were reported on the study. Gastrointestinal toxicity was observed, primarily nausea in 29% and vomiting in 12% of patients. Fluid retention, generally of minimal severity, was reported in 65% of patients.

1.3 RATIONALE

Promising results have been reported with docetaxel in HRPC in terms of i) objective responses in measurable lesions, ii) palliative response (pain relief, analgesic intake, symptom control), iii) PSA decline of more than 50%.

These results which compare favorably with data from other cytotoxic combinations reported thus far should now be confirmed and further prospectively investigated through a multicenter randomized phase III trial.

The combination mitoxantrone-corticosteroids is now considered as the reference combination to treat HRPC patients. Mitoxantrone-prednisone has been approved in the United States by the FDA to treat such patients and is currently under review in the European Union.

Tannock et al. (8), in a study of 37 men with hormone-refractory disease treated with low dose prednisone (7.5 to 10 mg daily), observed a 38 % decrease in pain scores as well as an overall improvement in quality of life as measured by a linear analog self-assessment scale. Moore et al. (9) then added mitoxantrone 12mg/m² every three weeks to prednisone in 27 patients with hormone-refractory prostate cancer and observed a reduction in pain score in 36% and further improvements in quality of life indices. In 25 patients with evaluable disease, one patient had a partial response and 12 had stable disease ; in the nine patients with measurable disease, one partial response was observed. The toxicity of this approach was quite acceptable, with the most serious toxicity being WHO Grade 3 neutropenia in 65% of treatment cycles and Grade 4 neutropenia in 15% of cycles.

Tannock et al. (11) then compared prednisone alone to the combination of prednisone plus mitoxantrone. This study randomized 161 symptomatic hormone-refractory patients to prednisone 10 mg/day or the combination of mitoxantrone (12 mg/m², every three weeks) plus prednisone. Prednisone failures were crossed over to mitoxantrone therapy. Primary endpoint of the trial was palliative response as defined by a two-point reduction on a six-point pain scale, with secondary endpoints being reduction in analgesic use, duration of response, and survival. In this study, palliative response was more common in the chemotherapy arm (29% vs 12%, p = .01), and was more durable (median 43 weeks vs 18 weeks, p < .0001). There was no evidence of survival benefit (median approximately 12 months in both arms). PSA response (as defined by a 50% reduction in baseline PSA maintained in two occasions using an intent to treat analysis) was observed in 34% of chemotherapy patients and 11% of prednisone only patients (p<.001). PSA response correlated with palliative response in both groups (p = .001). Toxicity was comparable to that observed in the phase 2 study, though there were 9 episodes of neutropenic fever, and five cases of cardiac dysfunction with two episodes of clinical congestive heart failure.

Kantoff et al. (12) performed a similar study comparing hydrocortisone 40 mg daily to the same hydrocortisone dose plus mitoxantrone 14 mg/m² every 21 days. Two-hundred forty-two patients were enrolled, with a primary endpoint of survival and secondary endpoints being PSA response, objective response, time to treatment failure and quality of life. Survival duration was not improved with chemotherapy (12.6 months for hydrocortisone vs. 12.3 months for mitoxantrone-hydrocortisone, p= .77). Treatment failure and disease progression occurred at a median time of 2.3 months after hydrocortisone compared with 3.7 months with mitoxantrone-hydrocortisone (log-rank, p=.0254 and p=.0218 respectively). There was an indication that quality of life was better with mitoxantrone-hydrocortisone, in particular with respect to pain control. The overall safety profile of the combination was assessed as acceptable. In particular the use of mitoxantrone 14mg/m² dose was associated with grade 3 and 4 cardiac dysfunction in 5% of cases, with no death related to this specific toxicity.

Taken together, the two phase III randomized studies suggest there is palliative benefit from the addition of mitoxantrone to corticosteroids in the extent and duration of pain control in these hormone-refractory patients. However, there is no evidence of prolongation of survival.

Within the limit of a retrospective comparison and recognizing the heterogeneity in patients and in the criteria used to define antitumor activity, available data for docetaxel compare favorably with what is considered the reference chemotherapy for HRPC.

The design of this study will allow to document the benefit-risk ratio of docetaxel in combination with prednisone and to define the most appropriate dose and schedule for docetaxel in this clinical setting i.e. three-weekly or weekly schedule.

The three-weekly conventional schedule is the currently approved schedule with an extensive clinical experience in solid tumors such as breast cancer, lung cancer, ovarian cancer. The $75\text{mg}/\text{m}^2$ dose has been selected in an attempt to achieve an optimal dose-intensity while providing an acceptable safety profile (17).

There is a growing clinical experience with the docetaxel weekly schedule including HRPC [REDACTED]. The weekly schedule seems to have at least the same activity as the conventional three-weekly schedule but with a better safety profile which can be a significant advantage for this schedule in the elderly (19, 24, 25, 26). In addition, there is a potential benefit for the docetaxel weekly schedule as compared to the three-weekly schedule in terms of safety/tolerability and dose-density with more frequent exposure of tumor cells, favorable anti-angiogenic effects and apoptotic effects (bcl-2 phosphorylation) (28).

The two docetaxel dosing regimen selected for this trial i.e. $30\text{ mg}/\text{m}^2$ on D1, D8, D15, D22, D29 q.6 weeks (five cycles) and the $75\text{ mg}/\text{m}^2$ D1 q. 3 weeks (ten cycles) are characterized by the same dose-intensity ($25\text{ mg}/\text{m}^2/\text{week}$) and the same cumulative dose ($750\text{ mg}/\text{m}^2$). In addition to the daily use of prednisone, a premedication with dexamethasone (8 mg x3 before each docetaxel infusion in the three-weekly schedule, 8 mg x1 before each docetaxel infusion in the weekly schedule) will be used in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. This dosing schedule of dexamethasone has been selected in an attempt to limit the cumulative dose of dexamethasone (240 mg for the three-weekly and 200 mg for the weekly schedule), and to allow for the daily concomitant use of prednisone required by the protocol. This comparable cumulative dose of dexamethasone between the two docetaxel arms will prevent any bias in the evaluation of the treatment effect.

The present TAX 327 phase III trial is therefore conducted to prospectively investigate the risk/benefit ratio of docetaxel to that of the reference chemotherapy in HRPC i.e. the combination of mitoxantrone and prednisone.

2. STUDY OBJECTIVE(S)

2.1 PRIMARY

To compare the overall survival (OS) after mitoxantrone and prednisone (arm A), and docetaxel and prednisone (arm B: docetaxel q. 3 weeks combined with arm C: weekly docetaxel) in patients with metastatic hormone refractory prostate cancer.

2.2 SECONDARY

To compare :

- Time to progression,
- Pain improvement (incidence and duration)
- PSA response (incidence and duration)
- Quality of life
- Response rate in patients with measurable disease
- Safety
- Pharmacokinetics of docetaxel in combination with prednisone

An independent socio-economic evaluation will be conducted in parallel of the clinical study

3. OVERALL STUDY DESIGN

3.1 DESCRIPTION OF THE DESIGN

This study is a prospective, non blinded, randomized 3-arm phase III trial.
Randomization will be centralized and stratified for center, pain level (PPI ≥ 2 and/or AS ≥ 10), and Karnofsky PS (≥ 80 vs. ≤ 70).

- * Arm A : Mitoxantrone 12 mg/m² intravenously every 21 days, plus prednisone 10 mg orally given daily.
- * Arm B : Taxotere® 75 mg/m² intravenously (day 1) every 21 days, plus prednisone 10 mg orally given daily.
- * Arm C : Taxotere® 30 mg/m² intravenously on days 1, 8, 15, 22, 29, every 6 weeks, plus prednisone 10 mg orally given daily.

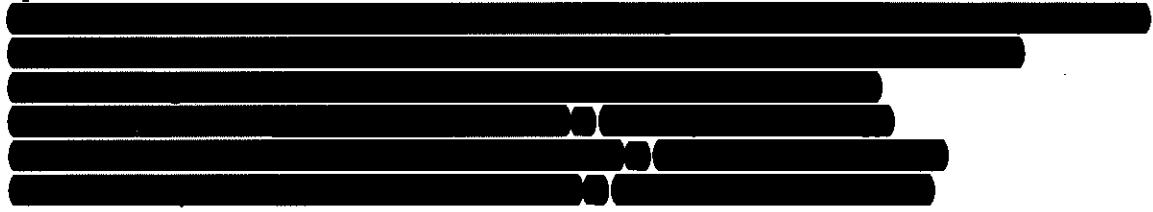
Dose reduction and/or treatment delay and/or treatment discontinuation are planned for the 3 arms in case of severe hematological and/or non hematological toxicities.

3.2 STUDY CENTERS

This study will be conducted in Europe, USA, Canada, South Africa, South America and Australia in around 100 centers which should enroll each 10 patients over a 2-year period.

3.3 REFERENCE COMMITTEES

The Executive Committee will be responsible for coordinating the conduct of this multicenter trial. This Committee will be composed of the Study Chairmen and of representatives of the trial sponsor:



In addition to the Executive Committee, an **Independent Data Monitoring Committee (IDMC)** will assess at intervals the progress of the clinical trial, the safety data, and the critical efficacy endpoints and will recommend to the Executive Committee whether to continue, modify, or stop the trial. This Committee will be composed of independent experts in the field of Clinical Oncology and Prostate Cancer, Urology, Biostatistics, and Quality of Life. These members will be independent of the trial and familiar with the methodology of oncology trials. They must be aware of the dangers of conclusions based on immature data and agree with the design goals of this protocol.

The mission of the IDMC will be detailed in the IDMC Charter which will be issued by the Executive Committee.

4. SELECTION OF STUDY PATIENTS

A total number of 804 HRPC patients (268 patients in each arm) is required for this prospective, non blinded randomized phase III trial.

4.1 INCLUSION CRITERIA

- (1) Signed informed consent prior to beginning protocol specific procedures.
- (2) Histologically proven prostate adenocarcinoma.
- (3) All patients must have metastatic prostate adenocarcinoma that is unresponsive or refractory to hormone therapy.
- (4) Patients must have received prior hormonal therapy as defined below:
Castration by orchectomy and/or LHRH agonists with or without
 - i) Antiandrogens
 - ii) Antiandrogen withdrawal
 - iii) Monotherapy with oral estramustine
 - iv) Other hormonal agents (e.g., ketoconazole, ...)
 - If the patient has been treated with LHRH agonists (i.e. without orchectomy), this therapy should be continued.
 - The testosterone level should be <50ng/dL in all patients.

- If the patient has been treated with antiandrogens, they must have been stopped at least 4 weeks prior to enrollment for flutamide or nilutamide or cyproterone acetate and at least 6 weeks prior to enrollment for bicalutamide and the patient must have demonstrated progression despite cessation of antiandrogen therapy.

- In case of prior treatment with estramustine i.e. monotherapy and by oral route, at least 4 weeks must have elapsed since completion of estramustine therapy and the patient must have recovered from side effects.

(5) Patients should have documented progression detected by PSA increase, physical examination and/or imaging:

- Rising PSA. Patients whose only evidence of progressive disease is a rising PSA, must have a value of at least 5 ng/mL in addition to increasing PSA to be eligible.

Rising PSA is defined as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure

- and/or progression of measurable lesions (bidimensional or unidimensional),
- and/or progression of non-measurable disease, (except bone)
- and/or appearance of new lesions, including those on bone scan.

(6) Patients must have achieved stable analgesia for a minimum of 7 consecutive days prior to randomization. The patient must keep a pain diary for this 7-day period. Stable analgesia will be defined by both :

- no increase by more than one point in the daily PPI scores recorded over 7 consecutive days with an identical PPI score for the last two days

and

- no variation of the daily analgesic scores (AS) by more than 25% around the mean AS (mean AS = sum of the 7 daily AS divided by 7), i.e., the 7 daily AS should be within the range of values defined below :

- the lowest value should be \geq mean AS - 25% mean AS.
- the highest value should be $<$ mean AS + 25% mean AS.

(7) Prior treatment with corticosteroids is allowed.

(8) Prior radiation therapy (to less than 25% of the bone marrow only) is allowed. At least 4 weeks must have elapsed since the completion of radiation therapy and the patient must have recovered from side effects.

(9) Prior surgery is allowed. At least 4 weeks must have elapsed since the completion of surgery.

(10) Life expectancy \geq 3 months.

(11) Karnofsky performance status (KPS) \geq 60.

(12) Normal cardiac function must be confirmed by LVEF (MUGA Scan or echocardiography) that should be above the lower normal limit of the Institution.

(13) Laboratory requirements :

(a) Hematology :

- Neutrophils $\geq 1.5 \times 10^9/L$

- Hemoglobin \geq 10 g/dL. Erythropoietin use is allowed, but RBC transfusion to upgrade the hemoglobin level is not allowed
 - Platelets \geq 100 x 10^9 /L
 - (b) Hepatic function :
 - Total bilirubin < the upper-normal limit of the institution.
 - ALAT (SGPT) and ASAT (SGOT) \leq 1.5 times the upper-normal limit of the institution.
 - (c) Renal function :
 - Creatinine \leq 1.5 times the upper normal limit (i.e., NCI grade \leq 1)
- (14) Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating center. Patients receiving weekly docetaxel who live distal to the center may receive treatments at weeks 2, 3 and 5 of each cycle locally, but under the advice and direction of a trial investigator.

4.2 EXCLUSION CRITERIA

- (1) Prior cytotoxic chemotherapy, except monotherapy with oral estramustine (see inclusion criterion n°4).
- (2) Prior isotope therapy (e.g., strontium, samarium, ...)
- (3) Prior radiotherapy to $>$ 25% of bone marrow (whole pelvic irradiation is not allowed - see appendix 2)
- (4) Prior malignancy except the following : adequately treated basal cell or squamous cell skin cancer, or any other cancer from which the patient has been disease-free for \geq 5 years.
- (5) Known brain or leptomeningeal involvement.
- (6) Symptomatic peripheral neuropathy \geq grade 2 according to the NCI Common Toxicity Criteria.
- (7) Other serious illness or medical condition :
 - (a) Congestive heart failure even if controlled. Previous history of myocardial infarction or angina pectoris within 1 year from study entry, uncontrolled hypertension or uncontrolled arrhythmias.
 - (b) Active uncontrolled infection
 - (c) Peptic ulcer, unstable diabetes mellitus or other contraindications for the use of corticosteroids.
 - (d) Auto-immune disease (lupus, sclerodermia, rheumatoid polyarthritis)
- (8) Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational drug within 30 days prior to study screening.
- (9) Concurrent treatment with any other anti-cancer therapy (except LHRH agonists).
- (10) Concomitant treatment with systemic corticosteroids used for reasons other than specified by the protocol.
- (11) Concomitant treatment with bisphosphonates.

4.3 REMOVAL OF PATIENTS FROM THERAPY

The patients should receive 10 cycles of treatment in Arms A and B and 5 cycles in Arm C (see section 6.1.1) unless the following events occur earlier :

- Development of a life-threatening and/or irreversible toxicity not manageable by symptomatic care, dose reduction, or delay.

- Progression of the disease, defined as follows :

-1) Rising PSA:

In PSA responders (see section 7.1.2.2), progression will be defined as a $\geq 50\%$ increase over the nadir and an increase in the absolute value PSA level by at least 5ng/ml, confirmed by a second value.

In PSA non-responders, progression will be defined by a $\geq 25\%$ increase over the nadir (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value.

-2) any increase of $\geq 25\%$ in the product of the largest diameters of any bidimensionally measurable lesion (or $\geq 25\%$ in the size of unidimensionally measurable lesion) in comparison to the nadir level (see section 7.1.3.1),

-3) progression in non-measurable lesion (see section 7.1.3.2) according to WHO criteria (excluding bone metastases, see below),

-4) the appearance of a new lesion (see section 7.1.3.2) including a new lesion on bone scan (i.e., new hot spot).

-5) Pain progression : increase of ≥ 1 point in the PPI scale from its nadir noted on two consecutive three-week-apart visits OR $\geq 25\%$ increase in the daily analgesics score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy.

- Administration of any other anti-tumor chemotherapy, radiotherapy or experimental drug during the trial.

- Withdrawal of patient consent.

The reason and date of discontinuation for all patients who are discharged from the study will be documented on the case report form (e.g. adverse event, lost to follow-up, completed study, etc.). The investigator must complete all discharge procedures at the time a patient is discontinued from the study.

4.4 PRIOR AND CONCOMITANT TREATMENTS

Patients should receive full supportive care, including antibiotics, antiemetics, etc., when appropriate. The reasons for treatment, dosage, and dates of treatment should be documented.

Allowed :

Ancillary treatments will be given as medically indicated ; they must be specified in the Case Report Form.

The following treatments are permitted : G-CSF (only in case of febrile neutropenia and/or infection), antiemetics (except systemic corticosteroids), anti-allergic measures (section 6.1.3.2).

Not permitted:

- a) Other investigational drugs and anticancer treatment while on study.
- b) Systemic corticosteroids (even as antiemetic prophylaxis)

c) Concomitant treatment with bisphosphonates.

In case of febrile neutropenia and/or documented infection, dose reduction is indicated at subsequent cycles (see section 6.1.3.1) instead of prophylactic G-CSF and/or antibiotics.

5. PLAN OF THE STUDY

5.1 STUDY PERIOD

The planned duration of the enrollment (i.e., first patient screened to last patient randomized) is 24 months. The planned duration of the study (enrollment period + follow-up period) is 36 months.

5.2 DETAILED PLAN

INVESTIGATIONS	TIMING prior to randomization	TIMING on-study	TIMING end of study & follow-up
1. Informed consent	pre registration		
2. History / physical exam (including clinical tumor assessment)	within 14 days	every 3 weeks (day1 before infusion)	end of study Clinical tumor assessment : every 2 months
3. Hematology*	within 14 days	on day1 before infusion. Every 2 days in case of febrile neutropenia or infection up to fever < 38°C and neutrophils $\geq 1.0 \times 10^9/L$	end of study
4. Biochemistry (+)	within 14 days	every 3 weeks (day1 before infusion)	end of study
5. PSA**	within 14 days	every 3 weeks (day1 before infusion)	- end of study - every month until PD or further antitumor therapy
6. Adverse events	within 14 days	day 1 before infusion	- end of study - every month until PD or further antitumor therapy
7. Radiology (#) Tumor assessment (\$)	within 21 days	after weeks 6, 12, 21, 30 and to confirm a response	- end of study - every two months until PD or further antitumor therapy
Bone Scan	within 21 days	after weeks 12, 21, 30 and to confirm a response	- end of study - every two months until PD or further antitumor therapy
8. ECG	within 14 days	as indicated	end of study, then as indicated
9. LVEF (*)	within 14 days	post cycles 5, 8, 10 (arm A) and as indicated	end of study, then as indicated
10. Quality of life (++)	within 3 days	every 3 weeks (day 1 before infusion)	- end of study - every month up to initiation of further anticancer therapy.
11. Pain assessments : PPI + Analgesic Score	within 3 days (\$) averaged over 7 days	every 3 weeks (day 1 before infusion) averaged over 7 days	- end of study - every month up to initiation of further anticancer therapy.
12. Other Investigations	within 14 days	as indicated	as indicated

* WBC, neutrophils, platelet, hemoglobin

** Rising PSA at baseline (see inclusion criteria #5). To ensure comparability, PSA assessments for one patient must be performed in the same laboratory from baseline up to the end of study.

(+) Alkaline phosphatase, LDH, bilirubin, AST (SGOT), ALT (SGPT), serum creatinine, Na+, K+, calcium, protein, albumin and other tests if clinically indicated. Testosterone level at baseline. Alpha-1-acid glycoprotein only in patients with PK samples.

(#) To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ultrasounds/scans to assess response must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

Each lesion must be followed with the same method throughout the study (from baseline until follow-up).

(\\$) To be performed at baseline : chest x-ray/CT scan, abdominal and pelvic CT scan, bone scan; other procedures as indicated.

if initially positive, repeat after weeks 6, 12, 21, 30 and/or end of study. All assessments must be repeated to confirm a response no less than 28 days after the response is observed.

if initially negative, repeat when clinically indicated.

(*) in arm A only : on-study LVEF is required following C5, C8, C10 or earlier if clinically indicated. During follow-up, LVEF will be followed only in patients with LVEF decrease observed on study.

(++) Self administered Fact-P questionnaire, McGill Pain scale and Pain Medication log (diary). QoL questionnaire should be administered before randomization or at randomization, but in any case before the patient is informed of the treatment to which he is assigned

(\\$) Protocol-defined stable analgesia should be observed within 3 days prior to randomization.

5.2.1 Evaluation at End of Study

To be performed no less than 30 days after the last treatment. The same complete work-up as before study entry will be repeated, i.e., physical exam, hematology, biochemistry, ECG, LVEF, record of toxicity, tumor assessment (evaluation of all lesions present at baseline with the same baseline method of measurement), quality of life and pain assessment.

5.2.2 Follow-up after end of therapy

Follow-up will continue thereafter every month until death. During follow-up, any ongoing side effects or tumor related symptoms will be traced until resolution. Any tumor related symptoms will be traced until first progression or further anti-tumor therapy before progression. Fluid retention and cardiac toxicity will be traced until resolution even if the patient received further antitumor therapy. Concomitant medications used for these side effects and/or tumor related symptoms (until further anti-tumor therapy) will be recorded in the CRF. Performance status will also be assessed.

Quality of life questionnaires and pain assessments will be administered every month up to the initiation of further anti-tumor therapy.

If the patient goes off study before disease progression, clinical and radiological assessments of all lesions will be performed every 2 months at the occasion of the follow-up visit until disease progression is documented. **No further antitumor therapy should be administered before disease progression (except prednisone - or equivalent dose of glucocorticosteroids - which can be continued)** unless the patient requests further anti-tumor therapy or the investigator deems it necessary.

6. STUDY MEDICATION

6.1 DESCRIPTION

6.1.1 Study test drug

FOR THE THREE ARMS :

If the calculated body surface area (BSA) of the patient is > 2.2 m², the dose to be given to the patient will be calculated according to BSA = 2.2 m². No ideal body weight should be used for the calculation of BSA.

Docetaxel every 3 weeks in combination with prednisone (Arm B)

Docetaxel

Dose : 75 mg/m², day 1
Route : 1-hour intravenous infusion

Schedule : every 3 weeks.

Prednisone

Dose : 5 mg twice daily (morning and evening), starting on day 1.

Route : per os

Schedule : daily

This is called a cycle of treatment (for administration to patients see section 6.5).

Duration : 10 cycles. Prednisone can be continued after completion of the 10 treatment cycles.

Docetaxel weekly in combination with prednisone (Arm C)

Docetaxel

Dose : 30 mg/m², days 1, 8, 15, 22, 29

Route : 30-minutes intravenous infusion

Schedule : every 6 weeks.

Prednisone

Dose : 5 mg twice daily (morning and evening), starting on day 1.

Route : per os

Schedule : daily

A cycle consists of the following :

Day 1 : Docetaxel 30mg/m² by IV infusion over 30 minutes.

Day 8 : Repeat as above (Day 1)

Day 15 : Repeat as above (Day 1)

Day 22 : Repeat as above (Day 1)

Day 29 : Repeat as above (Day 1)

Day 36 : No infusion

Day 43 : Repeat the cycle. This is Day 1 of the next cycle.

Duration : 5 cycles. Prednisone can be continued after completion of the 5 treatment cycles.

Prophylactic premedication regimen (Arm B and Arm C only)

The following premedication regimen must be administered only for patients treated in docetaxel arms, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Docetaxel every 3 weeks in combination with prednisone (Arm B)

Dexamethasone* 8 mg per Os at 12h, 3h and 1h before docetaxel infusion (ie, starting in the evening Day-1, then in the morning and just prior to the infusion on Day 1).

Docetaxel weekly in combination with prednisone (Arm C)

Dexamethasone* 8 mg per Os 1h before docetaxel infusion.

*Equivalent glucocorticosteroids doses :

<i>Dexamethasone</i>	<i>Methyl-prednisolone and Triamcinolone</i>	<i>Prednisolone and Prednisone</i>	<i>Hydrocortisone</i>	<i>Cortisone</i>
0.75 mg	4 mg	5 mg	20 mg	25 mg

6.1.2 Comparator

Mitoxantrone in combination with prednisone (Arm A)

Mitoxantrone

Dose : 12 mg/m², day 1
Route : 30 minutes intravenous infusion
Schedule : every 3 weeks.

Prednisone

Dose : 5 mg twice daily (morning and evening), starting on day 1
Route : per os
Schedule : daily

This is called a cycle of treatment.

Duration : 10 cycles. Prednisone can be continued after completion of the 10 treatment cycles.

6.1.3 TOXICITY AND DOSE MODIFICATION

General Rules

Every effort will be made to administer the full dose regimen to maximize dose-intensity.
If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics, antihistamines for drug fever.
If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment will be adopted.
No more than 2 dose reductions will be adopted per patient.

Dose reductions

Doses should be adjusted according to the following recommendations (table 4).

Table 4 : Dose levels for dose reduction

DOSE LEVEL	DOCETAXEL Q3 WEEKS	DOCETAXEL WEEKLY	MITOXANTRONE
0	75 mg/m ²	30 mg/m ²	12 mg/m ²
-1	60 mg/m ²	25 mg/m ²	10 mg/m ²
-2	45 mg/m ²	20 mg/m ²	8 mg/m ²

The doses which have been reduced for toxicity must not be re-escalated.

Chemotherapy Delay

A treatment delay \geq 4 days should be justified (i.e., to be reported in the CRF).

Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In case of treatment delay greater than 2 weeks, patient should go off study.

6.1.3.1 Myelosuppression

a) Neutropenia and/or its complications

Adverse event	Action to be taken
- Grade 4 neutropenia* for 7 days or more. - Grade 3-4 neutropenia with oral fever $\geq 38.5^{\circ}\text{C}$ - Infection* (i.e., documented infection with grade 3-4 neutropenia)	If the patient develops one of these adverse events, the next infusion should be given with a one-level dose reduction.

* according to NCI-CTC version 2

ANC on day of infusion (Arm A and B)	Action to be taken
$\geq 1.5 \times 10^9/\text{L}$	Treat on time
$< 1.5 \times 10^9/\text{L}$	Delay maximum 2 weeks Blood counts have to be performed until ANC $\geq 1.5 \times 10^9/\text{L}$. Then treat with a one-level dose reduction. If no recovery (ANC still $< 1.5 \times 10^9/\text{L}$) after 2 week delay : the patient will go off protocol therapy.

In arm C, ANC $\geq 1.0 \times 10^9/\text{L}$ is required on the day prior to each of infusion (on day 8, 15, 22, 29). However, ANC $\geq 1.5 \times 10^9/\text{L}$ is required on day 1 of each cycle.

In case of ANC $< 1.0 \times 10^9/\text{L}$ on day 8, 15, 22, 29 : Delay maximum 2 weeks, blood counts have to be performed until ANC $\geq 1.0 \times 10^9/\text{L}$. Then treat with a one-level dose reduction. If no recovery (ANC still $< 1.0 \times 10^9/\text{L}$) after 2-week delay : the patient will go off protocol therapy.

b) Thrombocytopenia

In case of grade ≥ 3 Platelets (NCI-CTC), delay maximum 2 weeks until Platelets recover to $100 \times 10^9/\text{L}$, then treat with a one-level dose reduction.

6.1.3.2 Allergy (Anaphylactic and Hypersensitivity reactions)

Mitoxantrone in combination with prednisone (Arm A)

No anaphylactic and hypersensitivity reactions are expected. However, if a patient experiences such reactions the same recommendations as for docetaxel arms apply (see table below).

Docetaxel containing arms (Arms B and C)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well being and of blood pressure and heart rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation must be immediately available : antihistamine, corticosteroids, aminophylline, epinephrine.

If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g. epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below :

<ul style="list-style-type: none"> Mild symptoms : localized cutaneous reaction, such as: pruritus, flushing, rash. 	<ul style="list-style-type: none"> - consider decreasing the rate of infusion until recovery of symptoms, stay at bedside - then, complete study drug infusion at the initial planned rate. At subsequent cycles use the premedication outlined in section 6.1.1.
<ul style="list-style-type: none"> Moderate symptoms : generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B.P. > 80 mmHg 	<ul style="list-style-type: none"> - stop study drug infusion - give i.v. antihistamine and i.v. corticosteroids (*) - resume study drug infusion after recovery of symptoms. At subsequent cycles, antihistamines* and steroids* will be given IV, one hour before infusion, in addition to the premedication planned in section 6.1.1.
<ul style="list-style-type: none"> Severe symptoms, such as: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤ 80 mmHg, angioedema, 	<ul style="list-style-type: none"> - stop study drug infusion - give i.v. antihistamine and steroids (*). add epinephrine** or bronchodilators and/or I.V. plasma expanders if indicated. - Once all signs and/or symptoms of hypersensitivity reaction disappear, study drug may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. <p>Premedication regimen as described in section 6.1.1 is only recommended when study drug is reinfused more than 3 hours after the interruption.</p> <p>At the subsequent cycles, dexamethasone will be given at 20 mg orally 24, 18, 13, 7 and 1 hour before study drug infusion.</p> <p>Additionally diphenhydramine (or equivalent) will be given at 50mg IV 1 hour before study drug infusion.</p> <p>If a severe reaction recurs, patient will go off protocol therapy</p>
<u>antihistamines</u> : dexchlorpheniramine <i>or</i> clemastine <i>or</i> diphenhydramine <i>or</i> promethazine	<i>(*) i.v. 5-10 mg</i> <i>(*) i.v. 2 mg</i> <i>(*) i.v. 25-50mg</i> <i>(*) i.m. 50-100 mg</i>
<u>corticosteroids</u> : dexamethasone or equivalent	<i>(*) i.v. 5-10 mg of dexamethasone</i>
<i>** Epinephrine : administered at a 1:1000 dilution (0.01 ml per kilogram with a maximum dose of 0.5 ml subcutaneously repeated every 20 minutes as necessary).</i>	

6.1.3.3 Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients from the first cycle in the three arms. The use of metoclopramide is recommended. More aggressive anti-emetic prophylaxis (i.e., ondansetron, etc.) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle.

If despite the appropriate medication, grade ≥3 nausea/vomiting still occur, reduce the dose of study drug by one dose level. If despite dose reduction, nausea/vomiting still occur at grade ≥3, the patient will go off study.

6.1.3.4 *Diarrhea*

- No prophylactic treatment for diarrhea is recommended from cycle one. However, following the first episode of diarrhea, the patient should receive symptomatic treatment with loperamide : 4 mg following the first episode and then 2 mg following each new episode until recovery of diarrhea (no more than 16 mg daily).
- If despite the use of loperamide, grade ≥ 3 diarrhea still occurs, reduce the dose of study drug by one dose level. If despite dose reduction, diarrhea still occurs at grade ≥ 3 , the patient will go off study.

6.1.3.5 *Stomatitis*

Grade ≤ 2 : No change, study chemotherapy (arms A, B and C) should be withheld until resolution to grade ≤ 1 . In arm C (weekly docetaxel), the dose of docetaxel should be reduced by one dose level for all subsequent infusions.

If grade 3 stomatitis occurs, study drug should be withheld until resolution to grade ≤ 1 . Treatment may then be resumed, but the dose of study drug should be reduced by one dose level for all subsequent doses.

In case of grade 4 stomatitis, the patient will go off study.

6.1.3.6 *Peripheral neuropathy*

In case of symptoms or signs experienced by the patient, dose modification should be performed as follows:

Grade ≤ 1 : no change

Grade 2 : retreat with a one-level dose reduction (no further dose reduction is planned)

Grade 3 : patient will go off protocol therapy

6.1.3.7 *Skin toxicity*

Grade 0, 1, 2 : No change

Grade 3: delay until \leq grade 1, maximum two weeks then reduce dose of study drug by one dose level ; if no recovery to \leq grade 1 within two weeks delay, patient will go off protocol therapy.

6.1.3.8 *Liver toxicity*

In case of increase of SGOT and/or SGPT to $>1.5 \times$ ULN or bilirubin to $>$ ULN, delay study drug treatment for up to 2 weeks until SGOT and/or SGPT returned to $\leq 1.5 \times$ ULN and bilirubin to \leq ULN. Then retreat at one dose level lower.

6.1.3.9 *Docetaxel-induced fluid retention*

In case of fluid retention (peripheral edema and/or effusions) during the treatment with docetaxel, the signs and symptoms should be graded as mild, moderate, severe or life-threatening as recommended in appendix 5.

NO DOSE REDUCTION IS PLANNED.

The patient's body weight will be recorded and followed as frequently as possible to document any weight gain which could be related to edema.

Recommended treatment

Treatment should commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline \geq grade 1 not otherwise explained.

Based on the hypothesis of capillary damage due to docetaxel, the following treatment is recommended in case fluid retention occurs : furosemide 20 mg per os once daily

If the symptoms cannot be controlled adequately i.e. worsening of the fluid retention or spread to another area, the dose of furosemide should be increased to 40 mg. The addition of metolazone p.o. at the recommended dose together with potassium \pm magnesium supplements may be useful.

The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the study drug. It is recommended, however, that patients with fluid retention of grade ≥ 3 severity (appendix 5) should be withdrawn.

In case it is difficult to make a judgment as to whether an effusion is disease-related or study drug-related, the treatment should be continued until progressive disease in other organs is documented, and provided there is no worsening of the effusion during treatment.

6.1.3.10 Docetaxel induced hyperlacrimation

The excessive lacrimation (epiphora) seen in some patients receiving docetaxel (mainly with the weekly regimen) appears to be related to cumulative dose (median~300 mg/m²) and resolves rapidly after treatment discontinuation.

Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with edema) of the lacrimal duct epithelium (producing a reversible lacrimal duct stenosis).

In patients experiencing clinically significant hyperlacrimation, the following approach is recommended :

1. NO DOSE REDUCTION PLANNED
2. Frequent instillation of artificial tears
3. Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate) : 2 drops each eye bid for 3 days starting the day before docetaxel administration in patients **without** history of herpetic eye disease

6.1.3.11 *Mitoxantrone-induced cardiac toxicity*

The total cumulative dose of mitoxantrone is restricted to $\leq 120\text{mg/m}^2$; EKG changes, arrhythmia, tachycardia, and/or chest pain should be managed based on the specific findings. For monitoring the potential cardiotoxicity of mitoxantrone, all the patients randomized to Arm A will be followed by echocardiography or angioscintigraphy to determine the LVEF values according to the following schedule :

- Baseline LVEF at rest before registration.
- LVEF will be repeated after cycle 5, cycle 8 and after cycle 10 and/or the end of study if the treatment is discontinued earlier.
- Once the treatment is completed as per protocol, LVEF will be repeated every month only in patients with LVEF decrease observed on study.

If a patient presents with clinical symptoms suggesting congestive heart failure (i.e., shortness of breath, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, etc...), LVEF should be repeated earlier to confirm this diagnosis and the patient must be removed from protocol treatment.

The patient should also go off study if there is an absolute decrease in LVEF $\geq 10\%$ (EF units) associated with a decline to a level $< 50\%$ (EF units) (29).

6.1.3.12 *OTHER TOXIC EFFECTS:*

- 1- If Grade 2 : manage symptomatically, and retreat without dose reduction.
- 2- If Grade 3 : drugs should be held (except for anemia) until resolution to grade 1, then re-instituted, if medically appropriate, with one level dose reduction.

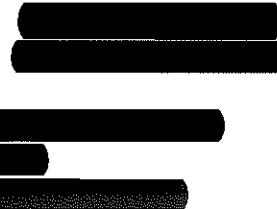
Alopecia and nail changes will not require dose-modification.

6.2 METHODS FOR ASSIGNING PATIENTS TO TREATMENT GROUPS

All patients must be registered by the Rhône-Poulenc Rorer Corporate Clinical Team at [REDACTED] prior to start of treatment.

A patient who has not been registered before the first treatment administration will not be accepted for the study at a later date.

Randomization will be centralized. [REDACTED]



[REDACTED]

The following information will be requested :

- 1/Protocol number
- 2/Institution name
- 3/Caller's name
- 4/Investigator's name
- 5/Patient's identification (first letter of first-, middle- and surname)
- 6/Patient's birth date (day/month/year)
- 7/Date treatment planned (day/month/year)
- 8/Verification of all inclusion and exclusion criteria with values of hematological and biochemical assessments, radiological results and dates of all examination performed.

Randomization will be centralized and stratified for center, pain level (PPI ≥ 2 and/or AS ≥ 10), and Karnofsky PS (≥ 80 vs. ≤ 70).

The RPR Corporate Clinical Team will notify the investigator by fax within 24 hours during working days of the patient's randomization number. In parallel, the treatment group randomly allocated will be notified to the investigator by fax directly by the Interactive Voice Response System within the same timeframe.

6.3 PACKAGING AND LABELING

A) DOCETAXEL (see Appendix 1 for detailed information)

• Packaging

Docetaxel will be provided as a sterile concentrate for infusion (concentration = 40 mg/ml). The appropriate solvent for diluting the docetaxel concentrate for infusion will also be provided. Vials are intended for single administration only.

• Labeling

Products will bear the following information:

- Sponsor's name ;
- Product name ;
- Study code number ;
- Contents ;
- Direction for use ;
- Storage conditions ;
- Batch number and packaging number ;
- Legal requirements.

B) MITOXANTRONE

Mitoxantrone available at the pharmacy of the hospital will be used and will be reimbursed by RPR.

C) PREDNISONE

Prednisone available at the pharmacy of the hospital will be used and will be reimbursed by RPR.

6.4 STORAGE, DISPENSING AND RETURN

All drug supplies must be kept in an appropriate locked room which can be accessed only by the pharmacist, the investigator or a duly designated person.

The person responsible for drug dispensing is required to maintain adequate records of all study drugs. These records (e.g., drug movement form) include the dates the study medications are received from the sponsor, dispensed for the patient and returned to the sponsor.

The person responsible for drug administration to the patient will record precisely the date and the time the drug is administered to the patient. In case the drug infusion has to be stopped, the exact date and time that the infusion has been stopped and restarted will be carefully recorded.

All used and unused medications must be returned to the investigator by the patient. A proper drug accountability will be done by the monitor.

All unused medications must be either returned to the sponsor for destruction or destroyed on site. If drug destruction is possible on site, a written agreement between the sponsor and the site responsible person (e.g., the pharmacist) should be obtained before any destruction.

6.5 ADMINISTRATION OF STUDY MEDICATION

6.5.1 Docetaxel

(see Appendix 1)

Handling precautions

Drug handling precautions for cytostatic drugs should be followed. Avoid contact or inhalation.

For preparation of the docetaxel solution, please refer to Appendix 1.

Dispensing

Docetaxel will be administered to the patient as a one-hour IV infusion in the three-weekly arm (Arm B) and as a 30-minute IV infusion in the weekly arm (Arm C). Use of a peristaltic infusion pump is recommended.

Storage

The vials of docetaxel should be stored as specified in Appendix 1.

6.5.2 Mitoxantrone

Mitoxantrone available at the pharmacy of the hospital will be used. For storage, handling, administration conditions, refer to package insert.

6.5.3 Prednisone

Prednisone available at the pharmacy of the hospital will be used. For storage, handling, administration conditions, refer to package insert.

6.6 VERIFICATION OF COMPLIANCE WITH TREATMENT REGIMEN

There must be an exact counting of the amount of drug dispensed and the amount returned. The batch numbers of all study medications used (ie, docetaxel, mitoxantrone, prednisone) should be reported in the appropriate section of the CRF.

The compliance of the patient is under direct supervision of the investigator and will be checked by the study monitor.

7. STUDY ASSESSMENTS

7.1 EFFICACY ASSESSMENT METHODS

7.1.1 PAIN AND ANALGESICS

7.1.1.1 Schedule

Pain will be assessed prior to registration, every three weeks, at end of study and then every month until further anti-tumor therapy with the Present Pain Intensity scale from the McGill-Melzack questionnaire (30). It will be averaged over the prior week.

The patient will be asked to complete the PPI every day for the one week period prior to each evaluation.

The questionnaire should be administered before any treatment infusion occurs. If treatment is delayed, the assessment schedule should be defined from the actual date of beginning of treatment.

Analgesics consumption will be assessed with the Pain Medication Log prior to registration, every three weeks, at end of study and then every month until further anti-tumor therapy. The patient should record all analgesic use for the one week period prior to each evaluation.

Analgesic Score is calculated as the mean daily score of analgesics, averaged over the prior week, using the following scale (11)

Standard dose of narcotic medication = 2 points

e.g. : Morphine 10mg (5mg if given parenterally)
 Hydromorphone 2mg (1mg if given parenterally)
 Codeine 30mg
 Oxycodone 2.5mg

Fentanyl patch : 25 µg/h over 1 day is equi-analgesic to 90 mg morphine per Os daily

Standard doses of non-narcotic medication = 1 point

e.g. : Aspirin 325mg
Acetaminophen (Paracetamol) 325mg (includes preparations with lower doses of codeine)
Naproxen 250mg

7.1.1.2 Response criteria

Pain response applies only to patients with PPI ≥ 2 on McGill-Melzack scale and/or Analgesics score ≥ 10 points.

Pain response will be defined as a 2-point or greater reduction with no increase in analgesic score, OR a reduction of at least 50% in analgesic use (from baseline analgesic score) with no increase in pain. Either criterion must be maintained for two consecutive evaluations at least 3 weeks apart.

The duration of pain response will be measured from the first to the last assessment at which the above pain response criteria are satisfied.

Pain progression applies to all patients.

Pain progression will be defined as an increase of ≥ 1 point in the PPI scale from its nadir noted on two consecutive three-week-apart visits OR $\geq 25\%$ increase in the daily analgesics score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy.

7.1.2 PSA

7.1.2.1 Schedule

PSA value will be determined within 14 days prior to first infusion (protocol-defined rising PSA), every three weeks on day 1 before infusion, at end of study, and then every month until progression or further anti-tumor therapy. To ensure comparability, PSA assessments for one patient must be performed in the same laboratory from baseline up to the end of the study.

7.1.2.2 Response criteria

-PSA Response (16) :

Applies only to patients with rising PSA at baseline and baseline PSA ≥ 20 ng/ml.

Response requires a PSA decline of $\geq 50\%$ confirmed at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied.

-PSA-Progression (16) :

- in PSA non-responders : progression will be defined as a 25% increase over the nadir value (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value.

- in PSA responders : progression will be defined as a 50% increase over the nadir value (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value.

7.1.3 TUMOR LESION ASSESSMENT

All tumor lesions present at baseline should be followed with the same baseline examination on weeks 6 (except bone scan), 12, 21 and 30 (or earlier if clinically required) during chemotherapy, at end of study and every two months during follow-up until progression or further anti-tumor therapy. Tumor assessment will be performed every three weeks for lesions that are assessable by physical examination.

Confirmation of response (CR or PR) must be performed no less than 28 days after the original declaration of response and requires the assessment of all measurable and non measurable disease. All records and films will be made available for extra-mural review for assessment of antitumor activity.

7.1.3.1 *Measurable lesions*

a) Definition

Bidimensionally measurable lesions

Bidimensionally measurable lesions with clearly defined margins

Examples of such lesions evaluated by clinical examination or imaging tools include :

- a skin nodule or superficial palpable lymph node assessed by physical exam $\geq 20 \text{ mm} \times \geq 10 \text{ mm}$.
- a clearly defined lung lesion surrounded by aerated lung (on chest X Ray or CT scan $\geq 20 \text{ mm} \times \geq 10 \text{ mm}$).
- a liver lesion, soft tissue, lymph node and masses investigated by CT scan or MRI or ultrasound ($\geq 20 \text{ mm} \times \geq 10 \text{ mm}$).

Unidimensionally measurable lesions

These include all the lesions that can be measured with only one diameter $\geq 20 \text{ mm}$ on CT Scan or ultrasound or MRI, on chest X Ray or physical examination.

Examples of these lesions are :

- 1/ Lung lesion not completely surrounded by aerated lung.
- 2/ A palpable abdominal mass or soft tissue mass that can be measured only in one diameter.

b) Response criteria

Complete response (CR) : disappearance of all known disease, determined by 2 observations no less than 4 weeks apart (it means that an intermediate visit with appropriate investigations may be planned 4 weeks ahead from the day when the CR has been assessed).

Partial response (PR) : in case of bidimensionally measurable disease, decrease by at least 50% (i.e., $\geq 50\%$) of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations no less than 4 weeks apart (it means that an intermediate visit with appropriate investigations may be planned 4 weeks ahead from the day when the PR has been assessed). For unidimensionally measurable disease, decrease by at least 50% (i.e., $\geq 50\%$) in the sum of the largest diameters of all lesions as determined by 2 observations no less than 4 weeks apart (see above for assessment time). It is not necessary for all lesions to have regressed to

qualify for partial response, but no lesion should have progressed and no new lesion should appear. Serial evidence of appreciable change documented by radiography or photography must be obtained and must be available for subsequent review.

Progressive disease (PD) : >25% increase in the size of at least one bidimensionally or unidimensionally measurable lesion (in comparison with the measurements at nadir) or appearance of a new lesion. When the progression is observed before 6 weeks after entry into the study, the patient will be considered as an "early progression".

Stable disease (SD) : does not qualify for CR, PR or PD. No lesion should have progressed and no new lesions should appear. Assignment to this category can only be made after at least 6 weeks after the treatment start.

Development of brain metastasis

The development of brain metastasis will be considered as a sign of progression, even if the disease is responding outside the brain. However, the investigator may choose to continue the study drug if the patient is responding elsewhere.

7.1.3.2 Non Measurable lesions

a) Definition

- Lesions below the « cut-off » : lesions with the largest diameter below the protocol-defined cut-off threshold for measurability (see section 7.1.3.1).
- Bone lesions : either blastic or lytic.
- Other lesions :
 - Effusions : ascitis, pleural and pericardial effusions
 - Previously irradiated lesion not in progression
 - Carcinomatous lymphangitis (skin and lung)

b) Response criteria

Complete response : Complete disappearance of all known disease for at least four weeks including normalized bone scan.

Progressive disease :

- **For bone lesions**, PD will be assessed based on the appearance of new lesions on bone scan (ie. new hot spots). An intensity increase of existing hot spots on bone scan does not constitute an evidence of progression. Pathological fracture or collapse of bone are not necessarily evidence of disease progression.

Although the protocol requires that the first bone scan be performed on week 12, it may happen that the investigator decides to perform a bone scan earlier. In case of « flare » phenomenon observed within the first six weeks, progression will not be assigned unless a further bone scan evaluation confirms the progression at least three weeks apart and/or there is additional evidence of progression.

- **For other lesions**, PD will be based on the appearance of any new lesions not previously identified or on the estimated increase of 25% or more in existing lesions (except bone). The

occurrence of effusions is considered as progressive disease if this is substantiated by positive cytology.

Stable disease : applies to lesions that do not satisfy the 2 criteria of CR and PD.
Non measurable lesions either bone or not bone do not qualify for PR.

7.1.3.3 Overall tumor response

Overall tumor response will be determined according to response patterns observed in the various types of lesions, as shown in the table below :

Response in measurable lesions (either bi- or uni dimensional)	Response in non measurable lesions	Overall response
PD or new lesion	Any	PD
Any	PD or new lesion	PD
SD	any except PD	SD
PR	any except PD	PR
CR	any except PD	PR
CR	CR	CR

7.1.4 TIME TO PROGRESSION

Time To Progression will be calculated among all patients. Time To Progression is defined as the time between randomization and the date of progression as previously defined (see section 4.3).

7.2 QUALITY OF LIFE

The quality of life domains covered by the FACT-P (version 4) will be used in the study (31, 32) (appendix 9). It will be assessed in countries where the questionnaire is available in the local language.

Quality of life is to be evaluated in a longitudinal design in all patients entered in the study. Questionnaires will be self-administered.

Baseline assessment should be obtained from all patients. The questionnaire will be administered within 3 days prior to randomization or at randomization, but in any case before the patient is informed of the treatment to which he is assigned. While on treatment, assessments should occur every 3 weeks, before administration of the treatment and at the end of treatment. During follow-up period, assessments will be performed every month until administration of further tumor therapy.

It is recommended that a key person (e.g. research nurse) at each center be responsible for the data collection in order to optimize the compliance of the patient to the quality of life assessment and to ensure the completeness of the data.

7.3 SAFETY ASSESSMENT METHODS

7.3.1 Clinical examination

The following tests will be performed prior to and/or on specified days during and following therapy (see section 5.2) :

- Complete history of malignant and non-malignant diseases including known hypersensitivity reactions and cardiac history.
- Full clinical examination, vital signs, height, weight, assessment of any residual toxicity due to previous therapy, Karnofsky PS.
- Electrocardiogram (ECG), left ventricular ejection fraction (LVEF).
- Chest-X-Ray.
- Adverse events : assessed according to the NCI-CTC version 2 (appendix 4).

7.3.2 Laboratory measurements

The following tests will be performed prior to and on specified days during and following therapy (see section 5.2) :

Hematology : Total White Blood Cell (WBC), neutrophils and platelets count, hemoglobin.

Biochemistry : Total bilirubin, Alkaline Phosphatase, SGOT (AST), SGPT (ALT), LDH, sodium (Na^+), potassium (K^+), creatinine, creatinine clearance (as indicated), total protein, albumin, calcium. Testosterone level at baseline. In addition, in patients with pharmacokinetics samples, alpha-1-acid glycoprotein will be performed before the start of docetaxel infusion on day 1 and on day 22 in arm B and in arm C prior to the first pharmacokinetic blood sample.

7.4 PHARMACOKINETIC ASSESSMENTS

The objective is to assess the pharmacokinetics of docetaxel in combination with prednisone in HRPC patients.

The pharmacokinetic profile of docetaxel will be characterized in 68 study patients (34 patients per docetaxel treatment arm) on day 1 (without prednisone) and day 22 (in combination with prednisone) of treatment. A limited sampling strategy (6 plasma samples per patient) will be implemented.

7.4.1 Biological sample

7.4.1.1 Schedule of biological sampling

Thirty four patients treated in arm B and 34 in arm C, will participate in this study. A six samples optimal sampling strategy will be implemented (33).

In the every-3-week arm (arm B), the blood samples will be collected at first cycle (day 1, docetaxel PK without concomitant prednisone) and then at cycle two (day 22, docetaxel PK with concomitant prednisone). The start of prednisone at first cycle will be delayed by 1 day.

In the weekly arm (arm C) a similar design will be implemented with blood samples collected on day 1 and day 22. The start of prednisone at first cycle will also be delayed by 1 day (Figure 2)

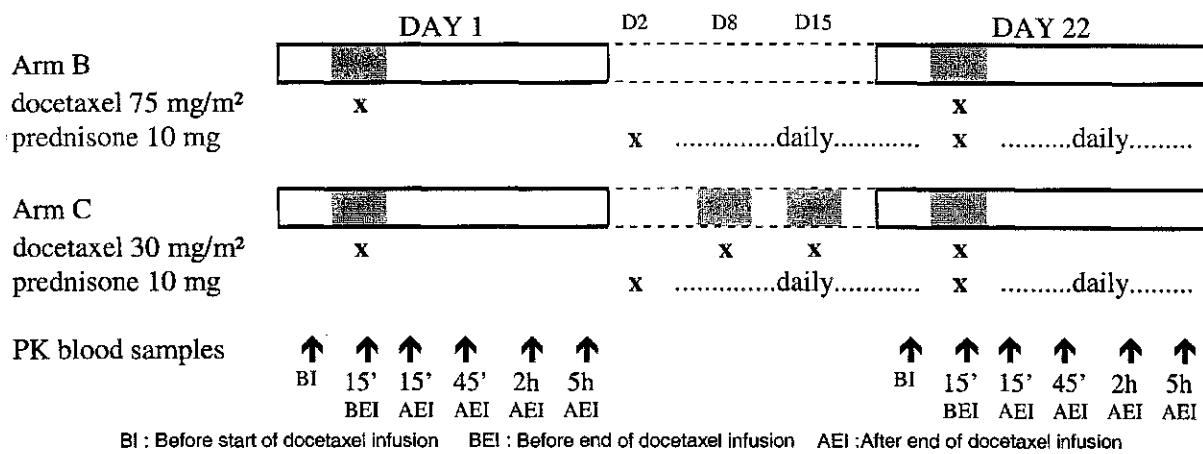
Sampling times will be as follows:

- before the start of docetaxel infusion
- 15 minutes before the end of docetaxel infusion
- 15 min after the end of docetaxel infusion
- 45 min after the end of docetaxel infusion
- 2 hours after the end of docetaxel infusion
- 5 hours after the end of docetaxel infusion

where docetaxel infusion lasts 1 hour in arm B and 30 minutes in arm C.

Actual time of sampling, actual times of beginning and end of docetaxel infusion must be accurately documented using the PK blood collection form (Appendix 10).

Figure 2 : Schedule of blood sampling in patients selected for pharmacokinetic study



7.4.1.2 Collection of biological samples

Blood specimens (7 ml) will be collected in heparinized tubes. The blood samples will be centrifuged within 30 minutes at 3,000 rpm x 15 minutes, plasma removed shared in two equal volumes, labeled, flash frozen within 15 minutes after collection, and stored at -20°C or lower in polypropylene tubes, until shipment.

7.4.2 Handling of biological samples

7.4.2.1 Labeling

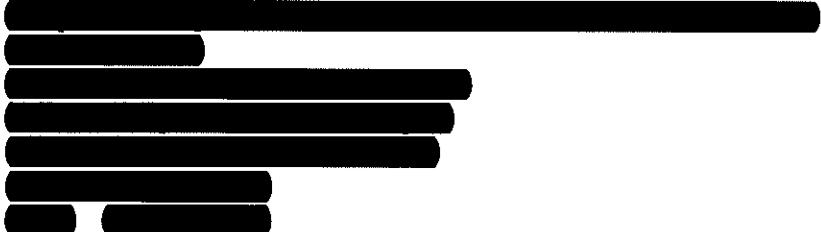
The labels on each plasma tube will contain the following information :

- Study n° : 327

- Patient's initials and identification number in the study
- date of the docetaxel infusion
- date and time (hour, minute) of the sample.

7.4.2.2 Transport of the samples

The transport of samples from investigator's site to RPR will take place in containers of solid C0₂. All tubes for each sampling time are to be shipped.



PACKING

1. One week prior to sample shipment, the investigative site should inform by fax the contact person at Rhône-Poulenc Rorer indicated above by indicating the study number, the planned date of shipment, the airway bill number, number of samples, the name of the courier, the name of the person responsible of the shipment with phone and fax number.
2. For shipment, pack the samples in plastic (preferably zip-seal-able) bags, by patient and treatment period. Do not use paper bags. Use black ball-point pen to label each bag. Add a layer of absorbent paper sufficient to contain any spills.
3. Enclose a copy of each PK Blood Collection Form (enclosed in sealed plastic bag) along with the shipment of samples.

SHIPMENT

1. Ship samples in insulated containers with sufficient dry ice to keep the samples frozen for up to a three-day period.
2. The samples are to be shipped via overnight express using Fedex within North America and World Courier within the other countries (next day delivery is acceptable) in order for them to arrive at Rhône-Poulenc Rorer before Thursday of the shipment week

In addition, the following information should be provided on the outside of the package:

- Description: FROZEN HUMAN PLASMA SAMPLES,
- PERISHABLE (KEEP FROZEN),

- Biohazard sticker,
- Dry ice sticker (with weight of dry ice),
- Correct address label,
- Origin of samples,
- Study (protocol) number,
- Name of person shipping samples.

7.4.3 Bioanalytical methods

Total docetaxel assay will be performed at Rhône-Poulenc Rorer using a LC/MS/MS method.
The bioanalytical analysis will be carried out under the supervision of:

[REDACTED]

8. ADVERSE EVENTS

8.1 DEFINITIONS

An adverse event is any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. 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 associated with clinical signs or symptoms
- 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.

Adverse events are classified as either serious or non-serious. A serious adverse event is any event that is:

- fatal
- life-threatening
- requires or prolongs hospitalization
- results in persistent or significant disability or incapacity
- an important medical event.

Important medical events are those which may not be immediately life-threatening, 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 in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization;

development of drug dependency. New cancer or drug overdosage or abuse will be considered serious by this criterion.

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

The study period for the purpose of adverse event reporting is defined as the period from date of randomization to the end of the follow up period.

8.2 RECORDING OF ADVERSE EVENTS

At each contact with the patient, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly. For serious adverse events, the Serious Adverse Event Form (appendix 8) must be completed. 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 adverse events 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. Serious adverse events which are still ongoing at the end of the study period must be followed up to determine the final outcome.

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

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

All serious adverse events during the study period, whether or not considered to be related to study treatment must be reported to RPR within 24 hours or, at the latest, on the following working day. The report should be made by telephone or fax to one of the individuals listed in the "Local Study Contacts" page.

At the time of the initial report, the following information should be provided if possible: study, center and patient number; the treatment cycle during which the event occurred; a description of the event, date of onset and current status; the start date of treatment, whether treatment has been discontinued; the reason why the event is classified as serious; the investigator's current assessment of the association between the event and study treatment.

Significant new information on ongoing serious adverse events should be provided promptly to RPR.

8.4 PATIENTS REMOVAL FROM STUDY THERAPY DUE TO ADVERSE EVENTS

Any patient who experiences an adverse event may be withdrawn at any time from the study at the discretion of the investigator.

If the adverse event may relate to overdose of study treatment, the Investigator's Brochure should be consulted for details of any specific actions to be taken.

If a patient is withdrawn because of an adverse event, the appropriate Withdrawals section of the CRFs should be fully completed in addition to the Adverse Event module. The monitor should be informed without delay of all patients who are withdrawn for this reason.

9. DATA ANALYSIS

9.1 SAMPLE SIZE DETERMINATION

The primary objective is to detect a statistically significant difference in OS for the combined docetaxel containing arms relative to the control arm using mitoxantrone.

The median survival for patients receiving mitoxantrone + prednisone is expected to be about 12 months (11). A total number of 535 events is required to detect with 0.90 power a 33% increase in median OS using a two-sided logrank test at level 0.05 , and a 1:2 ratio between the control and the combined docetaxel containing arms. Assuming a median follow-up of 24 months, anticipated from a uniform accrual over 24 months and a minimum follow-up of 12 months, and assuming a maximum of 2% of patients lost to follow-up, **804 patients (i.e., 268 per treatment group)** should be randomized into this trial.

9.2 EFFICACY EVALUATION

9.2.1 Efficacy parameters

Primary endpoint: overall survival

Overall Survival is defined as the time between randomization and the date of death (whatever the cause). Patients who are still alive at their last contact or at the cut-off date of the analysis will be censored at their date of last contact for the OS analysis.

Secondary endpoints:

1. Time to progression is defined as the time between the date of randomization and the date of progression (see section 4.3).

2. Pain response: (see section 7.1.1.2)

3. PSA response: (see section 7.1.2.2)

4. Response in measurable disease:

The response rate for each treatment group will be defined as the percentage of patients in the group who achieve either a complete response (CR) or a partial response (PR) among patients with measurable disease. Tumor response will be evaluated according to criteria described in section 7.1.3.

Duration of response will be calculated among patients with measurable disease who achieve either a CR or a PR (see section 7.1.3.4).

9.2.2 Definition of populations

All randomized patients will be included in the **intention-to-treat** analysis, and analyzed in the treatment group they were assigned to.

PSA response will be analyzed in the population of patients who experienced a protocol-defined PSA increase before study entry along with PSA ≥ 20 ng/mL at baseline.

Pain response will be analyzed in the population of patients with PPI ≥ 2 and/or AS ≥ 10 at baseline.

Safety analyses will be conducted in all treated patients.

9.2.3 Statistical methods

Categorical data will be presented in contingency tables along with frequencies and percentages. Continuous data will be summarized with at least the frequency (n), the median and the range. If relevant, the mean and the standard error of the mean will be added. Descriptive analyses will be presented by treatment group, and overall only for the description of baseline characteristics. Treatment group comparison will be based upon the results of the Chi-square test (for 2x2 tables) or the Cochran-Mantel-Haenszel test (for r x c tables, where r or c is greater than 2). Chi-square test will be replaced by Fisher's exact test if the expected frequency in any of the cells of the contingency table is less than 5. The 95% confidence interval for proportion will be calculated using the exact method. All tests of hypothesis will be performed at the 5% significance level.

Time to event variables will be analyzed using the Kaplan-Meier method to account for censored duration. Treatment group comparison will be based upon the results of the stratified logrank test. The variables of adjustment will be the variables of stratification with the exception of center, i.e., the logrank test will be adjusted for pain level and for Karnofsky performance status.

A cut-off date will be defined for all Kaplan-Meier analysis. This date refers as to the deadline for in-house reception of case report forms. This date will be specified in the final version of the statistical analysis plan.

A large number of centers are expected to enrolled a small number of patients. To ensure a minimal sample size to test any center effect, centers will be pooled within country when less than 30 patients have been enrolled in the corresponding center.

Potential effect of covariates (prognostic factors) will be investigated using Cox proportional hazards model for time to event efficacy parameters and using multivariate logistic regression for dichotomic outcome (such as response rates). The objectives of these multivariate analyses will be to explore the sensitivity of the statistical significance after adjusting for main prognostic factors. The first model will include two parameters that are deemed to have a potential prognostic value from a clinical standpoint. These parameters are the two above-mentioned stratification factors (pain level and Karnofsky performance status). The « center » effect (i.e., the « country » effect) will be explored at that step.

The second multivariate modeling will be an exploratory analysis that will be conducted to identify the most significant prognostic factors from a statistical standpoint. A stepwise selection strategy will be applied from a full model including the following covariates: country, age, KPS, pain level, visceral involvement, liver involvement, number of lines of prior hormonal therapy, time between initiation of hormonal therapy and date of randomization, prior estramustine, prior radiation therapy, PSA increase as only sign of progression, hemoglobin level and biochemical

parameters such as ASAT, alkaline phosphatase, LDH, albumin, creatinine (34). The treatment effect will be forced in the covariates selection procedure. The significance level to enter the model or to be removed from the model will be 10%. Treatment x covariate interaction will be tested one by one for the only covariates that are selected in the final model. Interaction will be tested at the 10% level. If significant interactions are detected, further stratified exploratory analyses will be performed. All statistical tests of these exploratory analyses will be interpreted with caution and should be viewed as hypothesis generation.

9.2.4 Efficacy analyses

9.2.4.1 Primary Efficacy Analysis

The primary analysis will be a comparison of overall survival using an intent-to-treat analysis between the two combined docetaxel groups versus the control mitoxantrone group based upon the adjusted Logrank test performed at 0.05 level. The final analysis of survival data will be performed provided that at least 535 deaths have been observed overall. This is estimated to occur one year after the recruitment of the last patient.

9.2.4.2 Secondary Efficacy Analyses

1- TTP analysis:

A comparison of TTP between the two combined docetaxel groups versus the mitoxantrone control group will be undertaken in the intention to treat population based upon the adjusted Logrank test at 0.05 level.

The first TTP analysis will be performed as soon as 258 events have been observed overall (see section 9.2.5.2). This is estimated to occur one year after randomization start. This analysis will have 0.90 power to detect with 0.05 type I error a 50% increase in median TTP. The median TTP in the control group is estimated to be around 4 months (12).

The final analysis of TTP will be undertaken at the end of the study (i.e., when the final OS analysis will be performed). With the total sample size, the power of the final TTP analysis is estimated to be in the range of 98%.

2- Pain Response and PSA Response Analyses

Pain response and PSA response will be compared between combined docetaxel containing groups and Mitoxantrone containing group using the chi-square test in the corresponding evaluable patients population. Duration of pain improvement and duration of PSA response will be analyzed in the same patient populations.

For PSA response, the hypothesis is that there will be about 35% response rate for the control arm and about 50% for the docetaxel arms. Thus, assuming that about 80% of the total patients will be evaluable for this endpoint and using a type I error of 0.05, the power of the final analysis of this endpoint will be of 94%.

For pain response, the hypothesis is that there will be about 35% response rate for the control arm and about 50% for the docetaxel arms. Thus, assuming that about 50% of the total patients will be

evaluable for this endpoint and using a type I error of 0.05, the power of the final analysis of this endpoint will be of 79%.

9.2.4.3 Other secondary analyses

Duration of response will be analyzed using the Kaplan-Meier method. The comparison of duration of response will be done based upon the adjusted logrank test.

Response rate in patients with measurable disease will be compared between docetaxel containing group and mitoxantrone containing group using the chi-square test.

9.2.4.4 EXPLORATORY ANALYSES

For each of the above endpoints where there is significance for the primary analysis (i.e., comparison of the combined docetaxel groups versus the control mitoxantrone group), separate comparisons of docetaxel treatment groups to control and of the two docetaxel groups will be made at the 0.05 level.

With the final sample size of 268 patients per group, the single arm comparisons (ie., A vs B or A vs C or B vs C) will have approximately 76% power to detect a 33% increase in median OS, and 92% power to detect a 35% increase in median TTP.

Statistical tests will be conducted to compare each docetaxel containing regimen to the mitoxantrone containing regimen. If both tests show non significant results then the treatment effect is estimated to be the same in the two docetaxel groups, and is equal to the treatment effect calculated in the primary comparison. If significant results are observed in favor of one docetaxel group only, then conclusion will be based upon the outcome of the test for interaction. If interaction test is significant then treatment effect is estimated to be limited to the docetaxel group where the effect has been observed. If the interaction test is not significant then the treatment effect is estimated to be comparable in the two docetaxel groups and equal to the overall treatment effect as estimated in the primary comparison. If significant result is observed within both docetaxel groups, then a further statistical test will be conducted to compare the two docetaxel groups in order to make a final recommendation as far as the tested efficacy parameter is concerned.

9.2.5 Interim analysis

9.2.5.1 Interim Safety Analysis

An interim safety analysis will be conducted after entry of the first 120 randomized patients (40 in each arm) in order to ensure the safety and tolerability of the selected dosing regimens.

9.2.5.2 Interim Efficacy and Safety Analysis

An interim analysis will be undertaken when 258 events (disease progression or death whichever occurs first) have been observed.

A total number of 258 events would be required to detect with 0.90 power a 50% difference in median TTP using a two-sided logrank test at level 0.05 , and a 1:2 ratio between the control and the combined docetaxel containing arms. The median time to progression for Mitoxantrone + corticosteroids is expected to be 4 months (12). A total of 258 events will consequently allow detection of a 2 month difference in median TTP for the docetaxel groups compared to the control with 90% power.

At the time of the interim analysis, and assuming an exponential distribution of the events, 54% of patients are estimated to have been recruited at that time and 22% of deaths are estimated to have been observed. The interim OS analysis will be conducted at the 0.001 level (35). Using the fixed nominal significance level of 0.001, this allows the final analysis to be conducted at just under the 0.05 level.

Considering that 258 events will ensure adequate power for the TTP endpoint, the interim analysis of TTP will be conducted at 0.05 significance level. Multiplicity is managed for the TTP endpoint by requiring both interim and final to have $p \leq 0.05$.

9.3 SAFETY EVALUATION

All patients will be assessed regularly for potential occurrence of adverse events with severity. The NCI-CTC (version 2) system will be used to classify adverse events whenever possible. In order to analyze all adverse events, including those classified as « Other » by the NCI-CTC system, the COSTART classification will also be utilized.

Hematological toxicities will be assessed from blood count by neutrophils, WBC, platelets and hemoglobin.

Febrile neutropenia is defined as an event with at least one day overlapping between grade 4 neutropenia (as per blood count) and fever $\geq 38^{\circ}\text{C}$ (possibly or probably related to study drugs) in the absence of infection.

Fluid retention is defined as one or more of the following symptoms: edema/peripheral edema/lung edema, effusion (pleural effusion, ascitis, pericardial effusion), with or without weight gain. These symptoms will be recorded with the corresponding COSTART terms.

Cardiotoxicity is defined as an absolute decrease of LVEF $\geq 10\%$ (EF units) associated with a decline to a level less than the lower normal limit of the institution (29). Cardiotoxicity is also defined with respect to the NCI-CTC grading system assessed by the investigators.

Safety analyses will be conducted both on all adverse events (regardless of their relationship to study drugs) and considering only possibly or probably adverse events.

All summary tables will be displayed by treatment group, and by dose level, if appropriate.

The chi-square test, the Fisher's exact test, or the Cochran-Mantel-Haenszel test as appropriate will be used to compare adverse events, toxic deaths, infection, febrile neutropenia, stomatitis, diarrhea, nausea, vomiting, acute hypersensitivity reaction, skin toxicity, cardiotoxicity and fluid retention between treatment groups.

If applicable, the median cumulative dose of mitoxantrone to onset of cardiotoxicity will be estimated using the Kaplan-Meier method with an event defined as either a LVEF decline as per Schwartz criteria or a NCI grade 3 / 4. Likewise, the median cumulative dose of docetaxel to onset of fluid retention will be estimated using the same method.

9.4 QUALITY OF LIFE EVALUATION

Quality of life evaluation will be performed using the FACT-P questionnaire (32).

Changes in total FACT-P score from baseline will be the primary endpoint in the QoL assessment, for this study. Changes of other domain scores of the FACT-G and the PCS (Prostate Cancer-Specific module) will be described from baseline.

The FACT-P scale comprises 5 subscales which are :

- Physical well-being : 7 items
- Social/Family well-being : 7 items
- Emotional well-being : 6 items
- Functional well-being : 7 items
- Additional concerns (= Prostate Cancer Specific): 12 items

Quality of life evaluation will be performed on an exploratory basis on the overall population of randomized patients for whom at least one QoL questionnaire has been considered evaluable for the analysis. Rules for evaluability are the following :

- A baseline QoL questionnaire is considered as evaluable if it is filled in within 14 days prior to randomization, and no later than the day of randomization.
- An on-treatment questionnaire is considered as evaluable if it is filled in after 6 days following the current infusion and no later than next infusion ;
- An end-of-study questionnaire is considered as evaluable if it is filled in after 6 days following the last infusion.
- All other follow-up questionnaires are considered as evaluable for the analysis provided that there is sufficient information to derive the score according to the FACT manual.

QoL response for a patient will be considered as a 10-point improvement in the FACT-P score for 2 consecutive visits as compared to baseline (36, 37).

The comparison of FACT-P scores between treatment groups will be performed at months 2, 4 and 6 of study treatment based upon the least square means as estimated by the mixed modeling.

The Proc Mixed procedure in SAS® will be used with the patient nested in the treatment group as the random effect. The covariance structure will be tested (unstructured versus simple versus compound symmetry versus first order autoregressive). The log-likelihood test will be utilized to compare nested models. Otherwise, the structure that is found to improve the Akaike's criterion will be selected.

The reason for missing data will be first explored descriptively using the specific CRF module, that provides the reason for non-completion of the QoL questionnaire.

The missingness mechanism (i.e., missing at random or not) will be also assessed using different techniques, such as pattern mixture models. In such approach the sensitivity of the results will be assessed using several definitions of pattern (i.e., completers and non-completers). If the time trend for dropouts is different from that for completers, then the missing mechanism could be considered as non-ignorable (i.e., informative).

9.5 PHARMACOKINETIC EVALUATION

9.5.1 Pharmacokinetic parameters

Pharmacokinetic parameters of each subject will be estimated using a Bayesian estimation method and the previously defined population model as prior information (33). This analysis will focus on docetaxel plasma clearance and area under the curve as they are well estimated using the Bayesian approach.

9.5.2 Sample size determination

Docetaxel clearance is expected to be about $24 (\pm 7)$ L/h/m² without prednisone. This estimate was obtained from 31 patients treated at 75 mg/m² in the 640 patient population PK/PD database (38). A total number of 34 patients is required to detect with 0.80 power a 20% difference in median clearance using a two-sample t-test at level 0.05.

Both arms will be assessed independently and therefore 34 patients will be recruited in the every three week arm and 34 patients in the weekly arm.

9.5.3 Statistical methodology

Empirical Bayesian estimates of individual clearance obtained for each treatment day will be compared using the PROC MIXED of SAS software (version 6.12). In the statistical model implemented, inter-individual variability will be considered as a random effect and pathophysiological covariates and treatment day will be considered as fixed effects.

9.6 REVISION OF THE STATISTICAL ANALYSIS PLAN

The above analysis plan will be reviewed before 30% of the study data are entered in the database. During this review, the manner of dealing with irregularities (including spurious data) will be decided and detailed in the final "statistical analysis plan". This document will be filed in the sponsor's Central File.

10. INVESTIGATOR / SPONSOR OBLIGATIONS

This study is to be conducted according to globally accepted standards of Good Clinical Practice (ICH, GCP guidelines, 01 May 1996), and in agreement with the latest revision of the Declaration of Helsinki (Somerset West, October 1996 copy of which is available upon request) and local Regulations.

10.1 ETHICS

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions,

for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of the study.

A list of EC/IRB members and their affiliations should be provided by the Investigator to the Sponsor (according to local regulations).

The investigator is responsible for keeping his/her EC/IRB informed about significant new information about study drug.

10.2 MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by RPR representatives. During site visits, the study monitor should review original patient records, drug accountability records and document retention (study file). Additionally, the monitor should observe study procedures and will discuss any problems with the Investigator. During the course of the study, the Quality Assurance Department of RPR R&D may conduct an onsite audit visit. Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given access to source documents (i.e. hospital or private charts, original laboratory and/or ECG records, appointment books etc....) of the subject which support data entered in the case report forms, as defined in the ICH GCP Guideline, Sections 1.51 and 1.52.

Participation in this study implies acceptance of potential inspection by national or foreign health authorities whose personnel will respect the confidentiality of the information.

10.3 PATIENTS INFORMED CONSENT

Before they agree to participation in this trial, all the patients will be provided with sufficient information in the form of a « Patient Information Sheet » prepared in the local language (appendix 6). This document will be submitted for approval to the EC/IRB along with the protocol. A statement of approval should be provided before commencement of the study.

The formal consent of any patient must be obtained (whether written or witnessed - according to the local regulations) before they are submitted to any study-specific procedures.

10.4 MODIFICATION OF THE PROTOCOL

Any modification to the protocol which may impact on the conduct of the study, or may affect patient safety, including changes of study objectives, study design, patient population, study procedures, significant administrative aspects, will require a formal amendment to the protocol. Such amendments will be agreed upon by the sponsor, the investigator and the EC/IRB prior to implementation.

Administrative changes to the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted. These administrative changes will be agreed upon by the sponsor and the investigator. The EC/IRB may be notified of administrative changes at the discretion of the investigator.

The sponsor has the right to prematurely discontinue the study.

11. RECORDS RETENTION AND PATIENTS IDENTIFICATION

It is the Investigator's responsibility that sufficient information appertaining to the identity of the patients will be retained, so that any Health Authorities or Rhône-Poulenc Rorer may access this information, should the need arise.

Copies of all pertinent information, including patient identity, allocation number and individual patient data records, will be retained in a confidential manner by the Investigator for a minimum period of 15 years from study completion.

11.1 USE OF INFORMATION AND PUBLICATION

Publication of the data arising out of the Study will be the responsibility of the Executive Committee to which shall be submitted a copy of any manuscript, abstracts or oral communications, for review at least 30 days prior to the expected date of submission or presentation. The authorship order will be defined based upon the number of eligible patients entered into the trial by each participating center.

Furthermore, the Sponsor's representatives shall have the right to review and/or delay any publication or presentation to prevent disclosure of Sponsor's confidential information and/or to establish or preserve RPR intellectual property rights. Investigators shall make all changes required and/or delay publication or presentation as necessary to protect Sponsor's confidential information and forfeiture of its intellectual property rights.

It is agreed that consistent with scientific standards, publication of any results shall be made only as part of a publication of the results obtained by all sites performing the protocol.

The Investigator is obliged to provide the Sponsor with complete test results and all data derived from the study. Only the Sponsor may make information obtained during the study available to physicians or regulatory agencies, unless otherwise required by law.

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13. APPENDICES

APPENDIX 1

PREPARATION GUIDE FOR USE WITH TAXOTERE CONCENTRATE FOR INFUSION AND SOLVENT FOR TAXOTERE

1. DRUG SUBSTANCE

- International non-proprietary name : docetaxel
- Code name : RP56976

2. FORMULATIONS

TAXOTERE® concentrate for infusion is a clear viscous, yellow to brown-yellow solution containing 40 mg/ml docetaxel (anhydrous) in polysorbate 80. The Solvent for TAXOTERE® is a 13% w/w solution of ethanol in water for infusion.

3. PRESENTATION

3.1 TAXOTERE® 80 mg vial:

- The TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a red flip-off cap.
- The labeled dosage strength is 80 mg docetaxel per vial.
- The labeled volume of one vial is 2 ml of a 40 mg/ml solution of docetaxel in polysorbate 80.
- Practically, TAXOTERE® 80 mg vial contains 2.36 ml of the 40 mg/ml solution of docetaxel equivalent to 94.4 mg docetaxel. This volume has been established and validated during the development of Taxotere® to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volumes". This overfill ensures that there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labeled amount of 80 mg per vial.

3.2 Solvent for Taxotere® 80 mg vial:

- The Solvent for TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a transparent colorless flip-off cap.
- The Solvent for TAXOTERE® composition is a 13% w/w solution of ethanol in water for infusion
- The theoretical volume of one vial is 6 ml of Solvent for TAXOTERE®.
- Practically, a solvent for TAXOTERE® 80 mg vial contains 7.33 ml ± 5% of Solvent. This volume has been established and validated based on the practical content of the TAXOTERE® 80 mg vial and ensures a premix concentration of 10 mg/ml docetaxel.

STORAGE CONDITIONS :

In a refrigerator, protected from bright light.

4. PREPARATION OF THE PREMIX SOLUTION UNDER ASEPTIC CONDITIONS

- 4.1. Remove the required number of TAXOTERE® 80 mg vials and solvent for TAXOTERE® vials from the refrigerator and allow to stand at room temperature for 5 minutes.
- 4.2. For each TAXOTERE® 80 mg vial, using a syringe fitted with a needle, withdraw THE ENTIRE CONTENTS of the corresponding Solvent for TAXOTERE® 80 mg vial (7.33 ml ± 5% for TAXOTERE® 80mg vial) and inject it into the corresponding TAXOTERE® 80 mg vial.

The addition of **THE ENTIRE CONTENTS** of one Solvent for TAXOTERE® 80 mg vial to one TAXOTERE® 80 mg vial ensures a minimal extractable volume of the premix solution of 8 ml.

- 4.3. Remove the syringe and needle and shake the mixture manually for 15 seconds.
- 4.4. Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation)
The premix solution contains 10 mg/ml docetaxel and is stable for 8 hours in the refrigerator or at room temperature.

5. PREPARATION OF THE INFUSION SOLUTION UNDER ASEPTIC CONDITIONS

- 5.1. More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use graduated syringes fitted with a needle to withdraw the corresponding premix volume containing 10 mg/ml docetaxel from the appropriate number of premix vials. For example, a dose of 140 mg docetaxel would require 14 ml premix solution.
- 5.2. Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution.
If a dose greater than 240 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.9 mg/ml docetaxel is not exceeded.
- 5.3. Mix infusion bag or bottle manually using a rocking motion.
The TAXOTERE® infusion solution should be administered intravenously, as soon as possible after preparation. This should be done as a 1 hour infusion under room temperature and normal lighting conditions.

STORAGE PERIOD :

Premix : 8 hours after reconstitution (at room temperature or in the refrigerator).

Infusion solution : The solution must be used as soon as possible after preparation.

6. VISUAL INSPECTION

As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If TAXOTERE® premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

7. RECOMMENDATIONS FOR THE SAFE HANDLING

TAXOTERE® is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TAXOTERE® solutions. The use of gloves is recommended.

If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

APPENDIX 2

PER CENT OF NORMAL BONE MARROW IRRADIATED USING STANDARD RADIATION PORTS*

MARROW VOLUME AT RISK

Skull (not including mandible)	12%
Upper limb girdle (unilateral) (humeral head, scapulae, clavicle)	4%
Sternum	2%
Ribs (all)	8%
Ribs (hemithorax)	4%
Cervical vertebrae (all)	3%
Thoracic vertebrae (all)	14%
Lumbar vertebrae (all)	11%
Sacrum	14%
Pelvis (including both innomates and both femoral heads and necks)	26%
Mantle (approximate)	25%
Upper para aortic nodes (approximate)	11%
Inverted Y (approximate)	45%

- Based on Ellis RE : *Phys Med Biol* 5 :255, 1961

APPENDIX 3

KARNOFSKY INDEX FOR PERFORMANCE STATUS

- 100 Normal, no complaints, no evidence of disease.
- 90 Able to carry on normal activity ; minor signs or symptoms of disease.
- 80 Normal activity with effort ; some signs or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most of his/her needs.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled, requires special care and assistance.
- 30 Severely disabled, hospitalization indicated. Death not imminent.
- 20 Very sick, hospitalization indicated. Death not imminent.
- 10 Moribund, fatal processes progressing rapidly

APPENDIX 4

NCI COMMON TOXICITY CRITERIA

Version 2.0 (Publish date : April 30, 1999)

Adverse Event	Grade									
	0	1	2	3	4					
AL	ALLERGY/IMMUNOLOGY									
AL LER 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.										
AL RHI Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-					
AL IMM 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 adverse event (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 immuno- suppressive therapy required					
Also consider Hypothyroidism, colitis, hemoglobin, hemolysis										
AL SIC 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.										
AL VAS vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation					
AL OTH Allergy/Immunology-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling					
AU	AUDITORY/HEARING									
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY /HEARING category										
Earache is graded in the PAIN category										
AU EXT 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										
AU INN 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					
AU MID 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					

Adverse Event	Grade				
	0	1	2	3	4
AU OTH Auditory/Hearing-Other (Specify)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
BL CEL 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 to 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 <i>children (< 18 years)</i>	<i>90% cellularity average</i>				
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.					
BL CDC CD4 count	WNL	< LLN - 500/mm ³	200 - < 500/mm ³	50 - < 200/mm ³	< 50/mm ³
BL HAP Haptoglobin	normal	decreased	-	absent	-
BL HGB 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
BL MVE For leukemia studies or bone marrow infiltrative/ myeloproliferative processes, if specified in the protocol	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
BL HEM 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 ≥2gm 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, Hemoglobin.					
BL WBC Leukocytes (total WBC) For BMT studies, if specified in the protocol	WNL	< LLN - 3.0 × 10 ⁹ /L < LLN - 3000/mm ³ ≥2.0 - <3.0 × 10 ⁹ /L ≥2000 - <3000/mm ³	≥2.0 - < 3.0 × 10 ⁹ /L ≥2000 - < 3000/mm ³ ≥1.0 - <2.0 × 10 ⁹ /L ≥1000 - < 2000/mm ³	≥1.0 - < 2.0 × 10 ⁹ /L ≥1000 - < 2000/mm ³ ≥0.5 - <1.0 × 10 ⁹ /L ≥500 - <1000/mm ³	< 1.0 × 10 ⁹ /L < 1000/mm ³ ≥0.5 × 10 ⁹ /L ≥500/mm ³
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol	WNL	≥75 - <100% LLN	≥50 - <75% LLN	≥25 - 50% LLN	<25% LLN
BL LYM Lymphopenia For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol	WNL	<LLN - 1.0 × 10 ⁹ /L <LLN - 1000/mm ³ ≥75 - <100% LLN	≥0.5 - <1.0 × 10 ⁹ /L ≥500 - <1000/mm ³ ≥50 - <75% LLN	<0.5 × 10 ⁹ /L <500/mm ³ ≥25 - 50% LLN	<25% LLN
BL GRA Neutrophils/granulocytes (ANC/AGC) For BMT studies, if specified in the protocol	WNL	≥1.5 - <2.0 × 10 ⁹ /L ≥1500 - <2000/mm ³ ≥1.0 - <1.5 × 10 ⁹ /L ≥1000 - <1500/mm ³	≥1.0 - <1.5 × 10 ⁹ /L ≥1000 - <1500/mm ³ ≥0.5 - <1.0 × 10 ⁹ /L ≥500 - <1000/mm ³	≥0.5 - <1.0 × 10 ⁹ /L ≥500 - <1000/mm ³ ≥0.1 - <0.5 × 10 ⁹ /L ≥100 - <500/mm ³	<0.5 × 10 ⁹ /L <500/mm ³ <0.1 × 10 ⁹ /L <100/mm ³
For leukemia studies or bone marrow infiltrative/ myeloproliferative process, if specified in the protocol	WNL	10 - > 25% decrease from baseline	25 - > 50% decrease from baseline	50 - > 75% decrease from baseline	≥75% decrease from baseline

Adverse Event	Grade				
	0	1	2	3	4
BL PLT Platelets	WNL	<LLN - $75.0 \times 10^9/L$ $<LLN - 75,000/mm^3$	$\geq 50.0 - <75.0 \times 10^9/L$ $\geq 50,000 - <75,000/mm^3$	$\geq 10.0 - <50.0 \times 10^9/L$ $\geq 10,000 - <50,000/mm^3$	$<10.0 \times 10^9/L$ $<10,000/mm^3$
For BMT studies, if specified in the protocol.	WNL	$\geq 50.0 - <75.0 \times 10^9/L$ $\geq 50,000 - <75,000/mm^3$	$\geq 20.0 - <50.0 \times 10^9/L$ $\geq 20,000 - <50,000/mm^3$	$\geq 10.0 - <20.0 \times 10^9/L$ $\geq 10,000 - <20,000/mm^3$	$<10.0 \times 10^9/L$ $<10,000/mm^3$
For leukemia studies of bone marrow infiltrate/myelophthisic process, if specified in the protocol.	WNL	10% - <25% decrease from baseline	25% - <50% decrease from baseline	50% - <75% decrease from baseline	$\geq 75\%$ decrease from baseline
BL TRP 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)
For BMT studies, if specified in the protocol.	None	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	>3 platelet transfusions in 24 hours	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.	-	-	-	-	-
BL TRR Transfusion : pRBCs	none	-	-	Yes	-
For BMT studies, if specified in the protocol.	None	≥ 2 u Prbc in 24 hours elective or planned	≥ 3 u Prbc in 24 hours elective or planned	> 24 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia, medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol.	None	$\leq 15ML/kg$ in 24 hours elective or planned	$>15 - \leq 30ML/kg$ in 24 hours elective or planned	$>30ML/kg$ in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia, medical intervention required to improve hemoglobin
Also consider hemoglobin	-	-	-	-	-
BL OTH Blood/Bone Marrow-Other (Specify _____)	none	mild	moderate	severe	life-threatening or disabling
CR CARDIOVASCULAR (ARRHYTHMIA)					
CR AVB 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)
CR DYS 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)
CR PAL Palpitations	none	present	-	-	-
Note : Grade palpitations only in the absence of a documented arrhythmia					

Adverse Event	Grade				
	0	1	2	3	4
CR QTC 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)
CR BRA 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)
CR TAC Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	
CR SVT 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					
CR VSV Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
CR VAR 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)
CR OTH 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)
CD CARDIOVASCULAR (GENERAL)					
CD LEA 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
CD ISC 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
CD LVF Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥10% but <20% of baseline value ; shortening fraction ≥24% but <30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥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					
CD TNI 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
CD TNT Cardiac troponin T (cTnT)	normal	≥0.03-<0.05 ng/ml	≥0.05-<0.1ng/ml	≥0.1-<0.2ng/ml	≥0.2ng/ml
CD EDE 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)
CD HBP Hypertension	none	asymptomatic, transient increase by >20mmHg (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

*Note : For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.

Adverse Event	Grade				
	0	1	2	3	4
CD LBD 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)					
Notes : Angina or MI is graded as Cardiac-ischemia/infarction in the CARDIOVASCULAR (GENERAL) category					
<i>For pediatric patients, systolic BP 65mmHg 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>					
CD MYO Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
CD INJ 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)
CD PER Pericardial effusion/pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and /or chest pain)	with physiologic consequences	tamponade (drainage or pericardial window required)
CD PIS 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)
CD PHL Phlebitis (superficial)	none	-	present	-	-
Notes : 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					
CD EMB 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					
CD VIS 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)
CD OTH Cardiovascular/ General-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CG COAGULATION					
Note : See the HEMORRHAGE category for grading the severity of bleeding events					
CG DIC DIC (disseminated intravascular coagulation)	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Also consider Platelets.					
Note : Must have increased fibrin split products or D-dimer in order to grade as DIC					
CG FIB Fibrinogen	WNL	$\geq 0.75 - <1.0 \times LLN$	$\geq 0.5 - <0.75 \times LLN$	$\geq 0.25 - <0.5 \times LLN$	$<0.25 \times LLN$
For leukemia studies or bone marrow infiltrative/ myeloproliferative process, if specified in the protocol.	WNL	<20% decrease from pretreatment value or LLN	>20 - <40% decrease from pretreatment value or LLN	>40 - <70% decrease from pretreatment value or LLN	<50 mg pre-treatment value or LLN
CG PTT Partial thromboplastin time (PTT)	WNL	$> ULN - \leq 1.5 \times ULN$	$> 1.5 - \leq 2 \times ULN$	$> 2 \times ULN$	-
Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category					
CG PT Prothrombin time (PT)	WNL	$> ULN - \leq 1.5 \times ULN$	$> 1.5 - \leq 2 \times ULN$	$> 2 \times ULN$	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category					

Adverse Event	Grade				
	0	1	2	3	4
CG TMA Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/ITP or hemolytic uremic syndrome/HUS)	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
For BMT studies, if specified in the protocol	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (<3 x ULN)	evidence of RBC destruction with creatinine >3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy	
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note : Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragment).					
CG OTH Coagulation-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
CS CONSTITUTIONAL SYMPTOMS					
CS FAT 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 or 20% Karnofsky or Lansky) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	bedridden or disabling
Note : See appendix for performance status scales.					
CS FEV Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x $10^9/L$)	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
Also consider Allergic reaction/hypersensitivity. Note : The temperature measurements listed above are oral or tympanic					
Hot flashes/flushes are graded in the ENDOCRINE category.					
CS RIG 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	-
CS SWE Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
CS WGA Weight gain	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
CS WGO Weight gain associated with Veno-Occclusive Disease (VOD) for BMT studies, if specified in the protocol.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
CS WLO Weight loss	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
CS OTH Constitutional Symptoms-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
SK DERMATOLOGY/SKIN					
SK ALO	normal	mild hair loss	pronounced hair loss		
SK BRU	none	localized or in dependent area	generalized	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)					
Note : Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					

Adverse Event	Grade				
	0	1	2	3	4
SK DRY Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
SK ERY 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)
SK FLU Flushing	absent	present	-	-	-
SK HFS 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	-
SK LTO Injection site reaction	none	pain or itching or erythema	pain or swelling, or inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
SK NAI 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.					
SK PHO Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
SK PIG Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
SK PRU 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.					
SK RDE Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥ 1.5 cm diameter not confined to skin folds ; pitting edema	skin necrosis or ulceration of full thickness dermis, may include bleeding not induced by minor trauma or abrasion
Note : Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
SK RRC Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases ; moderate edema	confluent moist desquamation ≥ 1.5 cm diameter not confined to skin folds ; pitting edema	skin necrosis or ulceration of full thickness dermis ; may include bleeding not induced by minor trauma or abrasion
SK RAS Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritis 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 $\geq 50\%$ of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity.					
Note : Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
Rash/dermatitis associated with high dose chemotherapy or BMT studies.	None	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases ; moderate edema	confluent moist desquamation ≥ 1.5 cm diameter not confined to skin folds ; pitting edema	skin necrosis or ulceration of full thickness dermis, may include spontaneous bleeding not induced by minor trauma or abrasion

Adverse Event	Grade				
	0	1	2	3	4
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25% <50% of body surface or localized desquamation or other lesions covering ≥25- >50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note : Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
SK URT 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	-
SK WIN Wound-infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
SK WNI Wound-non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
SK OTH Dermatology/Skin-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
EN ENDOCRINE					
EN CUS Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
EN FEM Feminization of male	absent	-	-	present	-
EN GYN Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
EN FLA Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
EN LTH Hypothyroidism	absent	asymptomatic, TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
EN MAS Masculinization of female	absent	-	-	present	-
EN ADH SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
EN OTH Endocrine-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
GI GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
GI ANO Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
GI ASC Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
GI COL 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.					

Adverse Event	Grade				
	0	1	2	3	4
GI CON Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
GI DEH 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 Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.					
GI DIA Diarrhea Patients without colostomy:	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 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
Diarrhea associated with graft-versus-host disease (GVHD) for BMT studies, if specified in the protocol. For pediatric BMT studies, if specified in the protocol.	none	>500 - ≤1000 ml of diarrhea/day	>1000 - ≤1500 ml of diarrhea/day	>1500 ml of diarrhea/day	severe abdominal pain with or without ileus
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
GI ULD 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
GI DPE Dyspepsia/heartburn	none	mild	moderate	severe	-
GI DPH 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 the adverse event is radiation-related, grade either under Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation.					
GI RDE Dysphagia, esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva), ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation Note: Fistula is graded separately as Fistula-esophageal					
GI RDP Dysphagia, pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva), ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation Note: Fistula is graded separately as Fistula-pharyngeal.					
GI FIE Fistula- esophageal	none	-	-	present	requiring surgery
GI FII Fistula- intestinal	none	-	-	present	requiring surgery
GI FIP Fistula- pharyngeal	none	-	-	present	requiring surgery
GI FIR Fistula- rectal/anal	none	-	-	present	requiring surgery
GI FLA Flatulence	none	mild	moderate	-	-

Adverse Event	Grade				
	0	1	2	3	4
GI ULG 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.					
GI GAS 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.					
GI ILE Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
GI DRY Mouth dryness	normal	mild	moderate	-	-
Mucositis	Notes: Mucositis <u>not due to radiation</u> 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.					
GI RMU Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally < 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally ≥ 1.5 cm in diameter)	necrosis of deep ulceration, may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation.					
Notes: Grade radiation mucositis of the larynx here.					
Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
GI NAU Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
GI PAN Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension					
Note: Amylase is graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
GI PRO 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, Pain due to radiation.					
Notes: 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)					
GI SAL 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
GI SME Sense of smell	normal	slightly altered	markedly altered	-	-
GI STO 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

Adverse Event	Grade									
	0	1	2	3	4					
For BMT studies, if specified in the protocol:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration or requiring prophylactic intubation or resulting in documented aspiration pneumonia					
Note: Radiation-related mucositis is graded as Mucositis due to radiation.										
GI TAS	normal	slightly altered	markedly altered	-	-					
Taste disturbance (dysgeusia)										
GI TYP	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)					
Typhlitis (inflammation of the cecum)										
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile neutropenia.										
GI VOM	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					
Vomiting										
Also consider Dehydration.										
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.										
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.										
GI OTH	none	mild	moderate	severe	life-threatening or disabling					
Gastrointestinal-Other (Specify, _____)										
HE	HEMORRHAGE									
Notes: 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 grading severity by grading 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.										
HE BLT	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia										
Also consider Platelets, Hemoglobin, Transfusion : platelets, Transfusion : pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage - Other (Specify site, _____).										
Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.										
HE BLE	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding requiring major non-elective intervention					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia										
Also consider Platelets, Hemoglobin, Transfusion : platelets, Transfusion : pRBCs, Hemorrhage - Other (Specify site, _____).										
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.										
HE CNS	none	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms						
CNS hemorrhage/bleeding										
HE EPI	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention					
Epistaxis										
HE HMT	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention					
Hematemesis										

Adverse Event	Grade				
	0	1	2	3	4
HE HMU 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
HE HMO Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HE SUR 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 an adverse event.					
HE MEL Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding requiring major non-elective intervention
HE PET 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	-
HE REC 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
HE VAG 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
HE OTH Hemorrhage - Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HP HEPATIC					
HP ALK Alkaline phosphatase	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
HP BIL Bilirubin	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
HP BGH Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
HP 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
HP ENL Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease					
HP LAL Hypoalbuminemia	WNL	<LLN - 3g/dl	≥2 - <3g/dl	<2g/dl	-
HP FAI Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
HP PVF Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
HP AST 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
HP ALT 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

Adverse Event	Grade				
	0	1	2	3	4
HP OTH Hepatic - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
IN LTO 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)
IN FEB Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10 ⁹ /L, fever ≥38.5°C)	none			Present	Life-threatening sepsis (e.g., septic shock)
Also consider Neutrophils. Note : Hypothermia instead of Fever may be associated with neutropenia and is graded here.					
IN NEU Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10 ⁹ /L)	none			Present	Life-threatening sepsis (e.g., septic shock)
Also consider Neutrophils. Notes : Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.					
IN UNK Infection with unknown ANC Note : This adverse event criterion is used in the rare case when ANC is unknown.	none			Present	Life-threatening sepsis (e.g., septic shock)
IN FEC 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)
Also consider Neutrophils. Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
IN OTH Infection/Febrile Neutropenia - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
LYMPHATICS					
LY LYM Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression, lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
LY OTH Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
MT ACI Acidosis (metabolic or respiratory)	normal	pH<normal, but ≥7.3	-	pH<7.3	pH<7.3 with life-threatening physiologic consequences
MT ALK Alkalosis (metabolic or respiratory)	normal	pH>normal, but ≤7.5	-	pH>7.5	pH>7.5 with life-threatening physiologic consequences
MT AMY Amylase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN

Adverse Event	Grade				
	0	1	2	3	4
MT BIC Bicarbonate	WNL	<LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	<8 mEq/dl
MT CPK CPK (creatinine phosphokinase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
MT HCA 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
MT HCH 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
MT HGL 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 acidosis
MT HKA Hyperkalemia	WNL	> ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
MT HMA 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
MT HNA Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
MT HTR Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10 x ULN	>10 x ULN
MT HUR Hyperuricemia	WNL	>ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	>ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	>10 mg/dl >0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Hyperkalemia.					
MT LCA 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
MT LGL 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
MT LKA Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
MT LMA 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
MT LNA Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
MT LPH 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					
MT LIP Lipase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
MT OTH Metabolic/laboratory-Other (Specify _____)	none	mild	moderate	severe	life-threatening or disabling
MS MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
MS ART 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
MS WEA 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 [tenderness or pain in muscles] is graded in the PAIN category.					

Adverse Event	Grade				
	0	1	2	3	4
MS MYO 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)					
MS OST 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
MS OTH Musculoskeletal-Other (Specify)	none	mild	moderate	severe	life-threatening or disabling
NE NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
NE AMR 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.					
NE ATA 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
NE ISC 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.					
NE COG Cognitive disturbance/learning problems	none	cognitive disability, not interfering with work/school performance; preservation of intelligence	cognitive disability, interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones	cognitive disability, resulting in significant impairment of work/school performance; cognitive decline >2 SD	inability to work/frank mental retardation
NE CON 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 of 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					
NE DEL Delusions	normal	-	-	present	toxic psychosis
NE CSC 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.					
NE DIZ 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.					
NE EXT 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
NE HAL Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category					

Adverse Event	Grade				
	0	1	2	3	4
NE INS 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 adverse event is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
NE IRR Irritability (children < 3 years of age)	normal	mild : easy consolable	moderate : requiring increased attention	severe : inconsolable	
NE ENC Leukoencephalopathy associated radiological findings	none	mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	severe increase in SAS; severe ventriculomegaly near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	severe increase in SAS; severe ventriculomegaly diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
NE MEM 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
NE MAN 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
NE MDE 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
NE MEU 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.					
NE CRA Neuropathy-crural	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
NE MOT 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
NE SEN 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
NE NYS Nystagmus Also consider Vision-double vision	absent	present	-	-	-
NE PER 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
NE PYR Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic and interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling ; paralysis
NE SEI 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)

Adverse Event	Grade				
	0	1	2	3	4
NE SPE 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
NE SYN Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-
NE TRE 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	-
NE VER 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
NE OTH Neurology-Other (Specify,)	none	mild	moderate	severe	life-threatening or disabling
OC OCULAR/VISUAL					
OC CAT Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
OC CON Conjunctivitis	none	abnormal ophtalmologic 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	-
OC DRY Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
OC GLA 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)
OC KER Keratitis (corneal inflammation/corneal ulceration)	none	abnormal ophtalmologic 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)
OC TEA 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	-
OC VBL 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	-
OC VDO 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	-
OC VFL Vision-flashing lights/floater	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	-
OC VNB 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	-
OC VPH Vision-photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
OC OTH Ocular/Visual-Other (Specify,)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)

Adverse Event	Grade				
	0	1	2	3	4
PA	PAIN				
PA ABD 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
PA ART 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
Note: Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category					
PA BON 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
PA CHE 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
PA DMR 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
PA DPN 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					
PA EAR 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
PA HEA 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
PA HEP 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
PA MYA 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
PA NEU 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
PA RAD Pain due to radiation	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
PA PEL 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
PA PLE 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

Adverse Event	Grade				
	0	1	2	3	4
PA REC 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
PA TUM 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 flare is graded in the SYNDROME category.					
PA OTH Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
PU PULMONARY					
PU ARD Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
PU APN Apnea	none	-	-	present	requiring intubation
PU CMD 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
PU COU Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
PU DYS Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
PU FEV 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
PU HIC Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
PU HYP 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
PU EFF 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					
PU PNE 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
PU PNT 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.					
PU FIB Pulmonary fibrosis	none	radiographic changes, but 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 section B)					
PU VOI 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
Notes : 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.					
PU OTH Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Adverse Event	Grade				
	0	1	2	3	4
GU	RENAL/GENITOURINARY				
GU BLA Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
GU CRE Creatinine	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
<i>Note : Adjust to age-appropriate levels for pediatric patients</i>					
GU DYS Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
GU FIG Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
GU HGB Hemoglobinuria	-	-	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category					
GU INC Incontinence	none	with coughing, sneezing, etc.	Spontaneous, some control	no control (in the absence of fistula)	-
GU INJ 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
GU PRO 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
<i>Note : If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.</i>					
GU FAI Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
GU OBS Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
GU ELE Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
<i>Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.</i>					
GU FRE 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	-
GU RET 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
GU COL Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
<i>Vaginal bleeding is graded in the HEMORRHAGE category.</i>					
GU VAG 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
GU OTH Renal/Genitourinary-Other (Specify _____)	none	mild	moderate	severe	life-threatening or disabling
SM	SECONDARY MALIGNANCY				

Adverse Event	Grade				
	0	1	2	3	4
SM OTH Secondary Malignancy - Other (Specify type, _____) excludes metastasis from initial primary	none	-	-	-	present
SR SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category					
Dysmenorrhea is graded in the PAIN category					
SR IMP Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
SR STE Female sterility	normal	-	-	sterile	-
Feminization of male is in the ENDOCRINE category					
SR IRM Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
SR LIB Libido	normal	decrease in interest	severe loss of interest	-	-
SR IFT Male infertility	-	-	oligospermia (low sperm count)	azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category					
SR DRY Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
SR OTH Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SD 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					
SD TFL 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					
SD TLY 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.					
SD OTH Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

APPENDIX 5

FLUID RETENTION SEVERITY GRADING

EDEMA	SEVERITY GRADING	EFFUSION
<ul style="list-style-type: none">. Asymptomatic <i>and/or</i>. Very well tolerated <i>and/or</i>. Dependent in evening only	MILD 1	<ul style="list-style-type: none">. Asymptomatic. No intervention required
<ul style="list-style-type: none">. Moderate functional impairment <i>and/or</i>. Pronounced <u>and</u> well tolerated <i>and/or</i>. Dependent throughout day	MODERATE 2	<ul style="list-style-type: none">. Symptomatic :<ul style="list-style-type: none">- exertional dyspnea <i>and/or</i>- chest pain <i>and/or</i>. ECG changes <i>and/or</i>. Abdominal distention. Drainage may be required
Significant impairment of function	SEVERE 3	<p>Symptomatic effusion :</p> <ul style="list-style-type: none">-dyspnea at rest <i>and/or</i>-pronounced abdominal distention
<ul style="list-style-type: none">. Pronounced impairment of function <i>and not well tolerated and/or</i>. Generalized anasarca	LIFE- THREATENING 4	<ul style="list-style-type: none">. Symptomatic effusion :<ul style="list-style-type: none">-tamponnade. Drainage urgently required.



FLUID RETENTION grading
[MILD, MODERATE, SEVERE, LIFE-THREATENING]
Reporting the highest grade of edema or effusion

APPENDIX 6

SAMPLE PATIENT INFORMED CONSENT

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL ADMINISTERED EITHER WEEKLY OR EVERY THREE WEEKS IN COMBINATION WITH PREDNISONE VERSUS MITOXANTRONE IN COMBINATION WITH PREDNISONE FOR METASTATIC HORMONE REFRACTORY PROSTATE CANCER

Drug Name/Project Number docetaxel (RP56976V)

Protocol Number RP 56976-V-327

SPONSOR

RHONE-POULENC RORER

Research & Development

20 avenue Raymond Aron

92165 ANTONY cedex - France

INTRODUCTION

Your doctor has explained that your disease is no longer responding to hormonal treatment. We therefore invite you to take part in a research study with Taxotere® (docetaxel), a drug supplied by Rhône-Poulenc Rorer Research & Development, sponsor of this research study. Docetaxel has been approved for the treatment of breast, lung and ovarian cancer. Preliminary studies suggest that docetaxel is also active for the treatment of your disease. Docetaxel (either weekly or given every 3 weeks) will be combined with prednisone. The effects of docetaxel need now to be compared to those of a treatment in common use i.e. mitoxantrone and prednisone, to assess whether docetaxel is a suitable treatment for patients with your disease.

PURPOSE OF THE STUDY

The aim of this study is to evaluate in your disease the efficacy and side-effects of docetaxel in combination with prednisone, and to compare them to those of the combination of mitoxantrone and prednisone. This clinical study will also determine what is the most effective and safe method for the administration of docetaxel (i.e. docetaxel administered weekly or every 3 weeks).

STUDY DESIGN

An appropriate number of 800 patients will be involved in the trial.

The decision as to which treatment you will receive will be made by chance (« randomization » i.e., like the toss of a coin). You will have an equal chance of being placed in any treatment group. You will be treated either with:

- a) Mitoxantrone 12 mg/m² intravenously every 21 days, plus prednisone 10 mg orally given daily or
- b) Docetaxel 75 mg/ m² intravenously every 21 days, plus prednisone 10 mg orally given daily or
- c) Docetaxel 30 mg/ m² intravenously on day 1, 8, 15, 22, 29, every 6 weeks, plus prednisone 10 mg orally given daily

Mitoxantrone and docetaxel will be administered through a drip into a vein in your arm (an infusion). The duration of the infusion will be of around 30 minutes except for docetaxel given every 3 weeks (1 hour infusion in this case).

You will also take prednisone by mouth twice daily.

If you receive docetaxel (weekly or every three weeks), you will take a steroid medication by mouth before each infusion to decrease the potential side effects of docetaxel (allergic reactions, fluid retention).

TRIAL PROCEDURES

Before receiving the treatment, you will undergo a number of tests to determine if you can enter the study including a blood examination, a physical examination, an evaluation of your heart function and imaging procedures (X-rays, CT scan and bone scan) to check the extent of your disease.

While receiving the chemotherapy treatment, you will have your blood checked at least every 3 weeks and once a week if you receive the treatment weekly. These regular blood tests and other examinations will be performed to check for possible effects of the drugs on your bone marrow, kidneys, and liver. The chemotherapy treatment will last about 7 months. You will undergo x-rays/scans at weeks 6, 12, 21 and 30 to see how your disease is reacting to the treatment.

Procedures may be done even if you do not join the study.

We also want to find out about your quality of life and your level of pain (if you have any). You will be asked to complete quality of life questionnaires before you know which treatment you will receive. The Nurse/Clinical Research Associate at your institution will give you directions for completing these questionnaires. The quality of life questionnaires must be filled out now, every 3 weeks during treatment and once a month after treatment completion.

On the same time schedule, you will be asked about how much pain you are having and the pain medication you took during the past 7 days. You will be asked to keep a daily record of the pain that you have (if any) and the pain medication that you took (if any), and will be given a diary to help you with this.

In addition, if you are treated with docetaxel, you may be asked to give your agreement for extra blood samples in order to determine the quantity of docetaxel in your blood and what happens to docetaxel in your body when combined to prednisone (= « pharmacokinetics study »). In this case, 6 blood samples (each 7 ml) will be required on two times three weeks apart.

You will be followed by your physician for this study. Your doctors may decide to take you off this study if : your disease gets worse despite the treatment ; if the side effects of the treatment are too dangerous for you ; if new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you.

POTENTIAL BENEFITS

Potential benefits of the study drugs may consist of a decrease in pain, improvement in quality of life and delay in the progression of your disease.

The information gathered through this clinical study may also contribute to improvements in treatment for other patients with your disease.

POTENTIAL RISKS

While on the study, you are at risk for some side-effects. You should discuss these with the investigator and/or your regular doctor. The more common side-effects are listed below ; there also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable

With **docetaxel and prednisone**, you may experience nausea and/or vomiting, mouth irritation, diarrhea, fatigue, a pins and needles sensation in your hands or feet, hair loss, changes in your skin and nails, muscular pain, decrease in blood cells counts, fever, infection, and swelling due to fluid retention. Your blood pressure may also fall while the drug is being given, and this will be checked carefully. The infusion of docetaxel may cause temporary local irritation and bruises if it is given into a small vein. All these side-effects have been experienced by some patients during previous studies and most of them are reversible.

With **mitoxantrone and prednisone**, you may also experience decreases in your blood cells counts leading to fever or infection. Rarer side-effects include mouth irritation, nausea and vomiting, irritation of a vein, hair loss, allergic reactions (such as a rash), and green urine. All these side-effects have been experienced by some patients during previous studies and most of them are reversible. The total dose of mitoxantrone will also be limited because at higher doses that will be given to you, it can affect the heart and lead to weakness and shortness of breath. Tests to check your heart function will be undertaken if you receive this drug.

In case of fever or bruising after receiving either drug, you must contact your doctor right away. If you have a fever, your doctor will do some blood work and may prescribe an antibiotic. If your white blood cells (cells responsible for fighting infection) are low, your doctor may also prescribe a medication to stimulate the production of your white blood cells.

For more information about risks and side effects, ask the investigator or contact your regular doctor.

PARTICIPATION

In case of harm caused to you during the study, Rhône-Poulenc Rorer Research & Development has taken out an insurance policy which covers the liability of your doctor during the study. You will be informed of any significant new findings about docetaxel which may occur during the study and which may lead you to change your willingness to participate.

Your doctor can remove you from study if it is harmful to you, if you fail to follow treatment instructions, if it is discovered that you do not meet requirements of the trial or if the study is canceled.

You will be informed in a timely manner if information becomes available that may be relevant to your willingness to continue participation in the trial.

Your participation in this study is voluntary. If you decide to take part but later change your mind, you are free to do so and do not have to give any reason. However, you should advise your doctor of your decision so he can tell you the procedure to be followed for your medical condition to be properly evaluated and then to continue medical care. The level of care you receive from your doctor will not be affected.

CONFIDENTIALITY

All information obtained from this study will be kept strictly confidential and you will not be identified in any report coming from this study.

If you participate, your records may be made available to Rhône-Poulenc Rorer Research & Development, Health Authorities, relevant Regulatory Agencies or may be published for scientific purposes but your identity will remain confidential. Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research or with regard to any research related injury, you should contact:

Dr.....
Tel:.....

PATIENT CONSENT

I have been informed of the purpose, procedures and duration of the study (RP 56976-V-327) with the drug docetaxel plus prednisone or mitoxantrone plus prednisone, of its possible advantages and inconveniences and I agree to participate to this study conducted by Dr.....

In addition, if I am assigned to one of the two docetaxel treatment groups, I agree / do not agree* to participate to the pharmacokinetics part of the study (extra blood samples to determine the quantity of docetaxel in my body), as described in the present patient informed consent.

* Cross out where not applicable

A summary of the information has been given to me.

I know that I am free to refuse to participate and that I can withdraw my consent at any time during the study. I have been given a copy of this consent form to retain.

Name of patient : _____

Signature of patient _____ date : _____

Signature of the person witnessing : _____
the patient's oral consent
(if applicable)

Signature of investigator : _____ date : _____

APPENDIX 8 ADVERSE EVENT REPORT FORM

1. REACTION INFORMATION

PATIENT INITIALS	STUDY CODE PATIENT N°	COUNTRY	DATE OF BIRTH (D.A.MO.YR.)	AGE	SEX	REACTION ONSET (D.A.MO.YR.)	CHECK ALL APPROPRIATE TO ADVERSE REACTIONS
DESCRIBE REACTION(S) (Give signs or symptoms, diagnoses, course, <u>underline the main event</u> . Include relevant lab. data)							

PATIENT DIED
 INVOLVED OR PROLONGED IN PATIENT HOSPITALIZATION
 INVOLVED SEVERE OR
 PERMANENT DISABILITY
 LIFE THREATENING
 NONE OF THE ABOVE

2. SUSPECT RPR DRUG INFORMATION

SUSPECT DRUG (include all information available: Trade name, generic name, form and dosage, batch number. For double blind study, precise if code has been broken.)		DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA*
DAILY DOSE (with unit)	ROUTE OF ADMINISTRATION	DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA*
INDICATION FOR USE		*NA: Not Applicable e.g. only 1 dose or irreversible outcome
THERAPY DATES (D.A.MO.YR.) from _____ to _____	THERAPY DURATION	

3. CONCOMITANT DRUG(S) AND HISTORY

CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (Generic names, exclude those used to treat reaction)	
OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last month of period, etc.)	

4. REPORTER OR INVESTIGATOR INFORMATION

NAME AND ADDRESS	REPORT SENT TO LOCAL AUTHORITY <input type="checkbox"/> Yes <input type="checkbox"/> No DATE (D.A. MO. YR.)	CAUSALITY ASSESSMENT (CONCERNING RPR DRUG) <input type="checkbox"/> NOT RELATED <input type="checkbox"/> REMOTE <input type="checkbox"/> POSSIBLE <input type="checkbox"/> PROBABLE	DATE: (D.A.MO.YR) SIGNED:
------------------	-------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------

5. ADMINISTRATIVE INFORMATION (RESERVED FOR RPR STAFF)

DATE RECEIVED BY MANUFACTURER (D.A.MO.YR.)	TRANSMITTED BY:	AFFILIATE CONTROL NUMBER	CONTROL	M.R.A./PHVIG NUMBER	Y N	
				S <input type="checkbox"/>	<input type="checkbox"/>	
				NR <input type="checkbox"/>	<input type="checkbox"/>	
				U <input type="checkbox"/>	<input type="checkbox"/>	
RPR MANUFACTURER		LOCAL ASSESSMENT (if legally required)				
DATE OF REPORT (D.A.MO.YR.)	REPORT TYPE	REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> HEALTH PROFES. <input type="checkbox"/> LITERATURE <input type="checkbox"/> CONSUMER				
<input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOW-UP						

APPENDIX 9

QUALITY OF LIFE QUESTIONNAIRE Fact P (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea (I feel sick)	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4
SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING		Not at all	A little bit	Somewhat	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Somewhat	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
c2	I am losing weight	0	1	2	3	4
c6	I have a good appetite	0	1	2	3	4
p1	I have aches and pains that bother me.....	0	1	2	3	4
p2	I have certain areas of my body where I experience significant pain	0	1	2	3	4
p3	My pain keeps me from doing things I want to do	0	1	2	3	4
p4	I am satisfied with my current level of physical comfort.....	0	1	2	3	4
p5	I am able to feel like a man.....	0	1	2	3	4
p6	I have trouble moving my bowels	0	1	2	3	4
p7	I have difficulty urinating (passing water)	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
p8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

APPENDIX 10
PHARMACOKINETICS - Blood Collection Form

Investigator name : _____

Investigator n° : |_____|_____|_____|_____|_____|

Patient n° : |_____|_____|_____|

Patient's initials : |_____|

Date of administration (dd/mm/yyyy) : |_____|_____|_____|_____|_____|

Cycle : |____|

Tick appropriate box : Day 1

Day 22

Dose of docetaxel : |_____| mg/m² |_____| mg

Start time for docetaxel : |_____| hour |_____| min

End time for docetaxel : |_____| hour |_____| min

7 mL of whole blood will be drawn in heparinized tubes. Centrifuge within 30 minutes of collection.

TIME	Theoretical time of samples (Hr/min)	Actual time of samples (Hr/min)	Sample number	COMMENTS
Time 0 before infusion				
15 min before the end of infusion				
15 min post infusion				
45 min post infusion				
2 hours post infusion				
5 hours post infusion				

Matrix : Plasma Anticoagulant : Sodium Heparin

Date samples shipped: (dd/mm/yyyy) : |_____|_____|_____|_____|_____|

For Clinical Drug Disposition Department Use Only

Date of samples received: (dd/mm/yyyy) : |_____|_____|_____|_____|_____|

Received by : _____

(Initials)

Comments: _____

Send top copy to RPR with the samples.

14. INVESTIGATOR'S AGREEMENT

I have read the preceding protocol :

**" A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING
DOCETAXEL ADMINISTERED EITHER WEEKLY OR EVERY THREE WEEKS
IN COMBINATION WITH PREDNISONE
VERSUS MITOXANTRONE IN COMBINATION WITH PREDNISONE
FOR METASTATIC HORMONE REFRACTORY PROSTATE CANCER "**

and agree that it contains all necessary details for conducting this study.

I will conduct the study as outlined therein and will attempt to complete the planned enrollment of patients within 24 months of the receipt of clinical supplies. I will provide copies of the protocol and all drug information relating to the preclinical and prior clinical experience, furnished to me by the Sponsor, to all relevant staff/members. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study. I agree to keep accurate records on all patient information (Case Report Forms and patient informed consent statement), drug transportation and return forms, and all other information collected during the study for a minimum period of 15 years.

I agree not to publish all or any part of the results of the study carried out under this protocol, without the prior written consent of RPR.

All parties agree to ensure direct access to examine, analyze, verify and reproduce source data / documents, and reports from all trial related sites for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Investigator Name:

Printed

Signature

Date (dd/mmm/yy)

Rhône-Poulenc Rorer Research and Development
Oncology Department

Name and Title

Signature

Date (dd/mmm/yy)