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**Clinical Study Protocol**

Drug Substance	ZD1839
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Final version 02

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**AN OPEN RANDOMISED PHASE II STUDY OF GEMCITABINE  
PLUS CISPLATIN +/- CONCOMITANT OR SEQUENTIAL ZD1839  
IN PATIENTS WITH ADVANCED OR METASTATIC  
TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

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**In co-operation with the study groups:**

- **Central European Society for Anticancer Drug Research (CESAR-EWIV)**
- **Arbeitsgemeinschaft Urologische Onkologie (AUO)  
der Deutschen Krebsgesellschaft (DKG)**
- **Arbeitskreis Urologische Onkologie (AUO)  
der Österreichischen Gesellschaft für Urologie (ÖGU)**

**The following amendment(s) have been made to this protocol since the date of preparation:**

<b>Amendment No.</b>	<b>Date of amendment</b>
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For further clarifications regarding:

- Procedures in case of medical emergency see Section 9.2
- Procedures in case of overdose see Section 9.3.

## PROTOCOL SYNOPSIS

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### AN OPEN RANDOMISED PHASE II STUDY OF GEMCITABINE PLUS CISPLATIN +/- CONCOMITANT OR SEQUENTIAL ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM

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#### Study centres and number of patients planned

It is planned to enrol 125 patients in approx. 20 study centres

#### Study period

#### Phase of development

Estimated date of first patient  
enrolled

July 2003

Phase II

Estimated date of last patient  
completed

March 2005

completed

## **Objectives**

### **Primary**

The primary objective of the study is to assess the activity of ZD1839 250 mg once daily administered continuously in addition to the standard chemotherapy gemcitabine and cisplatin or sequentially after completion of standard chemotherapy in patients with advanced or metastatic transitional cell carcinoma of the urothelium by estimating the time to progression (TTP).

### **Secondary**

The secondary efficacy objectives of the study are:

1. To estimate the response rate for each treatment arm
2. To estimate the overall survival time for each treatment arm
3. To estimate the time to treatment failure for each treatment arm
4. To estimate the disease control rate for each treatment arm
5. To estimate the duration of response for each treatment arm

The safety objective of the study is:

To investigate the safety and tolerability for each treatment arm

### **Exploratory**

The exploratory endpoint of the study is to estimate the efficacy and safety profile of patients in the extension arm.

## **Study design**

This is a multicentre, multinational, randomised phase II study of gemcitabine and cisplatin +/- ZD1839 given concomitantly or sequentially.

Patients will be randomised (1:1:1) into one of 3 arms:

Arm A: 6 cycles of gemcitabine and cisplatin in combination with ZD1839 250 mg daily followed by ZD1839 250 mg daily as maintenance therapy until objective disease progression

Arm B: 6 cycles of gemcitabine and cisplatin followed by ZD1839 250 mg once daily until objective disease progression

Arm C: 6 cycles of gemcitabine and cisplatin followed by observation until objective disease progression

Extension: Patients in Arm B and Arm C who cannot complete 6 cycles of chemotherapy either due to toxicity or objective disease progression, can be treated with ZD1839 250 mg once daily until further objective disease progression

### **Target patient population**

Chemotherapy-naïve male and female patients aged 18 years or older with histologically- or cytologically-confirmed, measurable, advanced or metastatic transitional cell carcinoma of the urothelium.

### **Investigational product, dosage and mode of administration**

ZD1839 250 mg (one tablet) orally once daily, administered continuously.

### **Standard therapy, dosage and mode of administration:**

All patients:

Gemcitabine 1250 mg/m<sup>2</sup> as a 30 minute intravenous (iv) infusion on day 1 and day 8 of every 21-day cycle.

Cisplatin 70 mg/m<sup>2</sup> as an iv infusion on day 1 of every 21-day cycle. The infusion rate should be 1 mg/min.

### **Duration of treatment**

All patients will receive standard therapy with gemcitabine and cisplatin for 6 cycles. ZD1839 (250 mg) will be administered in parallel (Arm A) or sequentially (Arm B). Patients in Arm B and C who cannot complete 6 cycles of chemotherapy either due to toxicity or objective disease progression may be treated with ZD1839 250 mg daily monotherapy until further disease progression.

Treatment will be discontinued at any time if disease progression, unacceptable toxicity or withdrawal of consent occurs. Patients who experienced progression or toxicity will be followed-up for survival until withdrawal of study medication of the last patient (study closure).

### **Efficacy Endpoints**

#### **Primary**

- Time to progression based on the Response Evaluation Criteria in Solid Tumours (RECIST)

#### **Secondary**

- Objective tumour response (complete response [CR] and partial response [PR]) after cycle 3 (visit 7) and cycle 6 (visit 13), 6 months after the start of treatment (visit 14) and every 12 weeks thereafter based on the RECIST criteria
- Time to treatment failure
- Overall survival time
- Incidence of controlled disease (CR, PR and stable disease [SD]) after cycle 3 (visit 7) and cycle 6 (visit 13), 6 months after the start of treatment (visit 14) and every 12 weeks thereafter
- Duration of response

### **Safety Endpoints**

- Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of and reasons for dose interruptions, reductions (chemotherapy only) and withdrawals due to AEs
- Laboratory assessments, physical examinations

### **Statistical methods**

All patients that are enrolled and receive at least one dose of study drug will be considered the all-subjects-treated population (AST). All patients that are enrolled and receive at least one dose of study drug and have at least one tumour assessment or die before the first tumour assessment takes place will be considered the ITT population. For efficacy endpoints the ITT population will be used and for safety endpoints the analysis population will be the AST population.

The standard summary statistics for continuous variables are: mean, standard deviation, median, quartiles, minimum and maximum. The standard summary statistics for discrete variables are: count and proportion. Response rates and controlled disease rates will be summarised by proportions together with exact two-sided 95% confidence intervals. Durations (time to progression, overall survival time, and duration of response) will be summarised by Kaplan-Meier methods.

Because of the use of a selection design the trial is non-comparative in the statistical sense. The goal of the study is to select the most efficient of the three treatment arms, which should be used in a following study.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and specialist terms are used in this study protocol. Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse event (see definition in Section 0).
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (statistic)	All subjects treated
AST (lab value)	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BUN	Blood urea nitrogen
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRA	Clinical Research Associate
CRF	Case report form
CT	Computerised tomography
CTC	Common toxicity criteria
DCF	Data clarification form
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
EGFR	Epidermal growth factor receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HRPC	Hormone-refractory prostate cancer
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
ITT	Intention-to-treat
Iv	Intravenous
Kg	Kilogram
L	Litre
LLT	Low level term

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<b>Abbreviation or specialist term</b>	<b>Explanation</b>
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
ML	Millilitre
MRI	Magnetic resonance imaging
M-VAC	Cisplatin, methotrexate, vinblastine, and doxorubicin
NCI	National Cancer Institute
NCR	No carbon required
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse event (i.e. an adverse event of special interest in this clinical development; see definition in Section 0). The classification of OAEs will be performed by AstraZeneca drug safety physicians after the study is complete
Principal investigator	The investigator who leads the study conduct at an individual study centre. Every study centre has a principal investigator.
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen
PT	Preferred term
QA	Quality assurance
QC	Quality control
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 0).
SAP	Statistical Analysis Plan
SD	Stable disease
SI	Standard international
TGF-alpha	Transforming growth factor-alpha
TTP	Time to progression
ULRR	Upper limit of reference range
WBC	White blood cell
WHO	World Health Organisation

---

## 1 INTRODUCTION

### 1.1 Background

Investigators should be familiar with the latest version of the Investigator's Brochure (IB).

ZD1839 is a potent and selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. Activation of the tyrosine kinase catalyses autophosphorylation and subsequent phosphorylation of protein tyrosine residues, which then initiates a cellular signal transduction cascade. Selective ZD1839 inhibition of the EGFR tyrosine kinase results in interruption of mitogenic and anti-apoptotic signals responsible for cellular cancer processes such as proliferation, growth, metastases, angiogenesis, and responsiveness to chemotherapy or radiotherapy.

There is now considerable evidence of expression and over-expression of EGFR in an extensive range of human cancers, e.g., non-small cell lung cancer (NSCLC) as well as prostate, colorectal, head and neck, bladder, breast and gastric cancers.

In Phase I studies, ZD1839 has shown anti-tumour effects in subjects with various solid tumours which were refractory to standard therapies or where no appropriate treatment was available, suggesting that ZD1839 may be useful in the treatment of various cancers. In Phase II studies, ZD1839 has demonstrated clinically significant anti-tumour activity in subjects with locally advanced or metastatic NSCLC who have previously received chemotherapy. In addition, ZD1839 palliated disease-related symptoms in these subjects. Two large randomised phase III studies (the INTACT studies) of ZD1839 in combination with platinum based doublet chemotherapy regimen as first line treatment in advanced NSCLC failed to show a survival benefit over the doublet chemotherapy regimen alone. The two chemotherapy regimens used were cisplatin and gemcitabine in one of the studies whilst carboplatin and paclitaxel was used in the other study. The safety profile of ZD1839 in the two trials was as expected from the monotherapy experience with no new major safety findings.

As of December 2002 ZD1839 has been administered in clinical trials, compassionate use and as a marketed drug to over 50,000 people worldwide.

The majority of drug-related adverse events in patients receiving ZD1839 monotherapy are mild and non-cumulative, and rarely lead to withdrawal of ZD1839 therapy.

Subjects receiving ZD1839 frequently experience drug-related gastrointestinal disturbances (mainly diarrhea, sometimes associated with dehydration) and skin reactions (rash, acne, dry skin, and pruritus). The majority of these side effects are low grade and infrequently require management.

The frequency of adverse drug reactions and the system/organ involved is shown in Section 3.4.10.

The most commonly reported adverse drug reactions (ADRs), occurring in more than 20% of the patients, are diarrhoea, rash, pruritus, dry skin and acne. ADRs usually occur within the first month of therapy and are generally reversible. Approximately 8% of patients had a severe ADR (Common Toxicity Criteria, (CTC) grade 3 or 4). However only 1 % of patients stopped therapy due to an ADR.

Interstitial lung disease has been reported in patients treated with ZD1839 but is uncommon, with a world-wide frequency of less than 1%. This is lower than the frequency reported for other lung cancer therapies. As of December 2002 Interstitial lung disease had a fatal outcome, whether deemed ZD1839-related or not, in approximately 0.24% in this medically complex group of over 50,000 patients receiving ZD1839. The occurrence of pulmonary toxicity and interstitial lung disease was similar across all treatment arms in the placebo-controlled INTACT trials.

Two small early phase studies investigating the combination of ZD1839 given concurrently with intravenous vinorelbine in chemo-naïve patients with advanced NSCLC indicated a higher incidence and severity of neutropenia with the combination treatment than would have been expected with single agent vinorelbine alone.

## **1.2 Bladder cancer**

Bladder cancer is the fourth most common cancer in men and the fifth most common cause of cancer death in most western countries. The frequency of bladder cancer is much higher in men than in women (Landis 1999). The risk factors in Europe include smoking and other occupational exposures. The incidence of bladder cancer worldwide continues to rise by 5-10% every 5 years, which may be related to the increase in tobacco use (Herr et al 2001).

Patients with metastatic urothelial tumours die from their disease if left untreated. Before the development of effective chemotherapy, median survival rarely exceeded 3-6 months (von der Maase 2000). Even with the most aggressive chemotherapy regimens, the overall median survival rarely exceeds 13 months and there is considerable treatment-related toxicity and morbidity, although long-term survival is achieved in a few patients (Herr et al 2001).

### **1.2.1 Gemcitabine and cisplatin in bladder cancer**

Until recently, the combination of cisplatin, methotrexate, vinblastine and doxorubicin (M-VAC) has been considered standard treatment for advanced bladder cancer. Complete response rates of 13-35% and overall response rates of 39-65%, which translate into a median survival of 12.5-12.6 months, have been reported in randomised studies comparing this combination with cisplatin alone and with the combination of cisplatin, cyclophosphamide and doxorubicin (Loehrer 1992 and Logothetis 1990). Treatment with M-VAC is associated with substantial toxicity, including febrile neutropenia, significant mucositis, nausea and vomiting, and alopecia.

Single-agent studies with gemcitabine have shown this agent to be active and safe in advanced bladder cancer (Stadler 1997 and Moore 1997). In vitro and in vivo studies have shown synergistic activity of gemcitabine and cisplatin (Peters 1995). Three phase II studies have indicated that the combination of gemcitabine and cisplatin has activity comparable with M-VAC but it has a better toxicity profile (von der Maase 1999; Moore 1999 and Kaufman 2000). A recently published, randomised, multinational, multicentre, phase III study comparing M-VAC with the combination gemcitabine and cisplatin has shown comparable survival for the two combinations; however, cisplatin and gemcitabine had a better safety profile and better tolerability (von der Maase 2000), which shows advantages for gemcitabine and cisplatin regarding patient weight, performance status and the incidence of neutropenic complications, stomatitis and alopecia. Gemcitabine and

cisplatin can therefore be considered the new standard in the treatment of advanced bladder cancer.

### **1.3 Rationale for this study**

Patients with advanced or metastatic transitional cell carcinoma of the urothelium continue to have a poor prognosis. Rigorous clinical investigation is needed for innovative, biology-based, non-cytotoxic therapies without marrow toxicity and with a potential synergistic effect when administered in parallel or sequentially with conventional chemotherapeutic drugs.

ZD1839 has been developed to be a potent and specific inhibitor of EGFR. Transitional cell carcinomas of the urothelium use the EGFR signal pathway. Therefore the use of ZD1839 in epithelially-derived transitional cell carcinoma of the urothelium is thoroughly grounded on a strong biological rationale. Phase I studies have confirmed antitumour activity of ZD1839 when used as monotherapy with predictable and reversible mild toxicity. Also, in a Phase I trial, the combination of ZD1839 with gemcitabine and cisplatin in patients with advanced solid tumours appeared to be highly active and well tolerated (Giaccone et al 2001).

## **2 STUDY OBJECTIVES**

### **2.1 Primary objective**

The primary objective of the study is to assess the activity of ZD1839 250 mg once daily administered continuously in addition to the standard chemotherapy gemcitabine and cisplatin or sequentially after completion of standard chemotherapy in patients with advanced or metastatic transitional cell carcinoma of the urothelium by estimating the time to progression (TTP).

### **2.2 Secondary objectives**

The secondary efficacy objectives of the study are:

1. To estimate the response rate for each treatment arm
2. To estimate the overall survival time for each treatment arm
3. To estimate the time to treatment failure for each treatment arm
4. To estimate the disease control rate for each treatment arm
5. To estimate the duration of response for each treatment arm

The safety objective of the study is:

To investigate the safety and tolerability for each treatment arm

### **2.3 Exploratory**

The exploratory endpoint of the study is to estimate the efficacy and safety profile of patients in the extension arm.

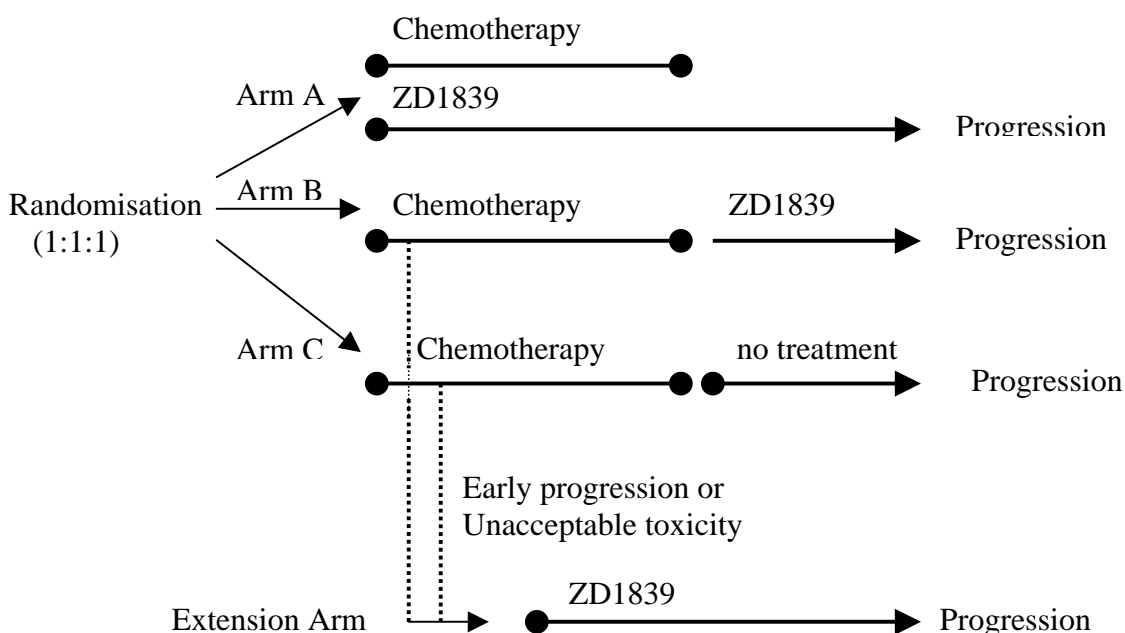
### 3 STUDY PLAN AND PROCEDURES

#### 3.1 Overall study design and flow chart

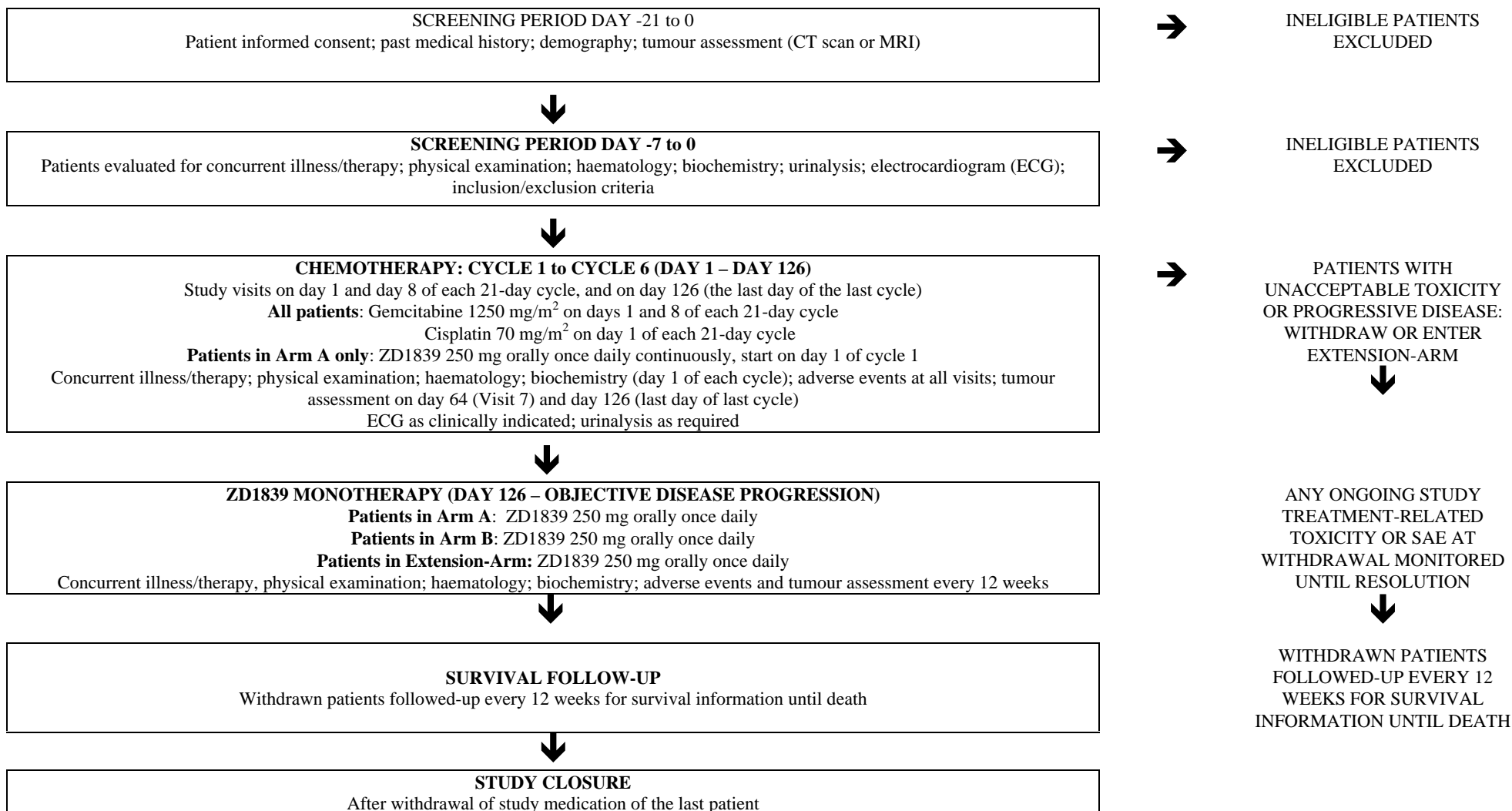
This is a multicentre, open-label, randomised, non-comparative phase II study in chemotherapy-naïve patients with histologically- or cytologically-confirmed, measurable, advanced or metastatic transitional cell carcinoma of the urothelium. Patients who fulfil the inclusion criteria and do not meet any of the exclusion criteria will be randomised (1:1:1) into one of 3 arms:

- Arm A: 6 cycles of gemcitabine and cisplatin in combination with ZD1839 250 mg daily followed by ZD1839 250 mg daily as maintenance therapy until objective disease progression
- Arm B: 6 cycles of gemcitabine and cisplatin followed by ZD1839 250 mg once daily until objective disease progression
- Arm C: 6 cycles of gemcitabine and cisplatin followed by observation until objective disease progression
- Extension: Patients in Arm B and Arm C who cannot complete 6 cycles of chemotherapy either due to toxicity or objective disease progression, can be treated with ZD1839 250 mg once daily until further objective disease progression

Treatment will be discontinued at any time if disease progression, unacceptable toxicity or withdrawal of consent occurs. Patients who experienced progression or toxicity will be followed-up for survival until withdrawal of study medication of the last patient (study closure).



**Figure 1 Study flow chart**



**Table 1 Study plan**

	SCREENING		ARMS A, B AND C: CHEMOTHERAPY CYCLES 1 to 6 (± 1 day after visit 2)		ARM C: POST CHEMOTHERAPY (± 14 days)	ARM A, ARM B, EXTENSION-ARM <sup>H</sup> : ZD1839 MONO THERAPY (± 14 days)	ALL: WITHDRAWAL	ALL: SURVIVAL FOLLOW-UP
<b>Day</b>	-21 to 0	-7 to 0	1, 22, 43, 64, 85, 106	8, 29, 50, 71, 92, 113	126, 185 then every 12 weeks	126, 185 then every 12 weeks	disease progression, unacceptable toxicity or withdrawal of consent	Every 12 weeks after withdrawal
<b>Visit</b>	Screening		1, 3, 5, 7, 9, 11	2, 4, 6, 8, 10, 12	Visit 13, 14, 15 until withdrawal	Visit 13, 14, 15 until withdrawal		
Informed consent	✓							
Past medical history	✓							
Demography	✓							
Concurrent illness/therapy		✓	✓ <sup>a</sup>	✓	✓	✓	✓	
Physical examination (performance status, weight, vital signs <sup>b</sup> )		✓	✓ <sup>a</sup>		✓	✓	✓	
Pregnancy test, if appropriate		✓ <sup>c</sup>						
Tumour assessment (CT scan or MRI) <sup>d</sup>	✓		Visit 7 only		✓	✓	✓	
Haematology <sup>b</sup>		✓	✓ <sup>a</sup>	✓	✓	✓	✓	
Biochemistry <sup>b</sup>		✓	✓ <sup>a</sup>		✓	✓	✓	
Urinalysis <sup>b</sup>		✓	As required					
Electrocardiogram (ECG)		✓	As clinically indicated					
Adverse events <sup>f</sup>			✓	✓	✓	✓	✓ <sup>e</sup>	
Dispense ZD1839 study medication			Arm A only Visits 1+9			✓		
Gemcitabine infusion			✓	✓				
Cisplatin infusion			✓					
Survival								✓ <sup>g</sup>

CT – computerised tomography; MRI – magnetic resonance imaging

## Notes to study plan

- a If assessed within 7 days before enrolment and meets the stated eligibility criteria, these assessments need not be repeated on Day 1.
- b Laboratory/vital signs abnormalities should **not** be reported as AEs unless any criterion for a serious adverse event (SAE) is fulfilled, the laboratory/vital signs abnormality causes the patient to discontinue from the trial, or the investigator insists the abnormality should be reported as an AE.
- c Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7 days before Day 1 of treatment. In the event of suspected pregnancy during the study, the test should be repeated. If the results are positive, AstraZeneca must be notified immediately.
- d Upon clinical suspicion tumour assessment may be performed more frequently
- e Any ongoing study treatment-related toxicity or serious adverse event (SAE) at withdrawal must be monitored until resolution.
- f In the event of any subjective eye symptoms, or new or worsening respiratory symptoms (e.g. cough, breathlessness), appropriate medical advice should be sought promptly. Any symptoms should be treated as clinically indicated and reported as an adverse event.
- g After withdrawal from the study for reasons other than withdrawal of consent, patient's family or the patient's current physician must be contacted every 12 weeks where possible for survival information until death.
- h For patients who enter the extension arm, day 1 of treatment with ZD1839 corresponds to day 126 for patients in arm A or B.

## 3.2 Rationale for study design, doses and control groups

A randomised phase II design has been chosen to assess the impact on efficacy and tolerability of ZD1839 given additionally or sequentially to standard chemotherapy (gemcitabine and cisplatin) in patients with transitional cell carcinoma of the urothelium.

The combination chemotherapy of cisplatin and gemcitabine has shown comparable survival to treatment with M-VAC; however, cisplatin and gemcitabine had a better safety profile and better tolerability (von der Maase 2000), which shows advantages regarding patient weight, performance status and the incidence of neutropenic complications, stomatitis and alopecia. Gemcitabine and cisplatin can therefore be considered the new standard in the treatment of advanced bladder cancer.

The combination of ZD1839 in the dosage of 250 mg with gemcitabine and cisplatin in patients with advanced solid tumours appeared to be highly active and well tolerated in a Phase I study (Giaccone et al 2001) and is therefore investigated further in the present indication.

### **3.3 Selection of study population**

#### **3.3.1 Inclusion criteria**

For inclusion in the study, patients must fulfil all the following criteria:

1. Provision of written informed consent
2. Male or female, aged 18 years or older
3. Histologically- or cytologically-confirmed transitional cell carcinoma of the urothelium
4. Locally advanced or metastatic disease
5. At least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) (see Appendix G)
6. Chemotherapy-naïve
7. WHO performance status (PS) of 0 to 1
8. Life expectancy of at least 3 months
9. Willing and able to comply with the treatment and survival follow-up

#### **3.3.2 Exclusion criteria**

Any of the following is regarded as a criterion for exclusion from the study:

1. Previous chemotherapy or other systemic antitumour therapy (e.g. monoclonal antibody therapy)
2. Less than 4 weeks since completion of previous radiotherapy
3. Any evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who are asymptomatic need not be excluded).
4. Clinically significant cardiac disease (New York Heart Association Class III or IV; symptomatic coronary artery disease; cardiac arrhythmia not well controlled with medication; myocardial infarction within the last 12 months)
5. Brain metastasis or spinal cord compression that is newly diagnosed and/or has not yet been definitively treated with surgery and/or radiation OR previously diagnosed and treated central nervous system (CNS) metastases or spinal cord compression without evidence of clinically stable disease
6. Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or cervical cancer in situ
7. Pre-existing neurotoxicity greater than CTC grade 1
8. Incomplete healing from previous oncologic or other surgery
9. Absolute neutrophil count (ANC) less than  $1500/\text{mm}^3$ , white blood cells (WBC) less than centre-specific normal value, or platelets less than  $100\,000/\text{mm}^3$
10. Serum bilirubin greater than 1.25 times the centre-specific upper limit of reference range (ULRR)
11. In the opinion of the investigator, any evidence of severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, hepatic or renal disease)

12. Estimated creatinine clearance (COCKROFT) <60 ml/min
13. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2.5 times the centre-specific ULRR if no demonstrable liver metastases, or greater than 5 times the ULRR in the presence of liver metastases
14. Evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study
15. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampicin or St.John's Wort
16. Hypersensitivity to mannitol, corticosteroids, H2-antagonists and antihistamines
17. Pregnancy or breastfeeding
18. Known ongoing drug or alcohol abuse
19. Known hepatitis B and/or human immunodeficiency virus (HIV) positive blood tests
20. Participation in another study with an investigational drug within 30 days prior to study entry
21. Previous enrolment into this study or another trial with ZD1839
22. Known, severe hypersensitivity to ZD1839 or any of the excipients of this product
23. Known severe hypersensitivity to gemcitabine or cisplatin or any of the excipients of these products

### **3.3.3 Restrictions**

Women of child-bearing potential must be willing to practice acceptable methods of birth control to prevent pregnancy.

In female patients only recruited in Austria a monthly pregnancy test has to be conducted according to the Austrian drug law.

Males taking ZD1839 must also practice acceptable methods of birth control while taking the drug to avoid pregnancy of a partner.

### **3.3.4 Discontinuation of patients from treatment**

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Safety reasons as judged by the investigator and/or AstraZeneca.
- Incorrect enrolment of the subject. Incorrectly enrolled subjects will be discussed by the investigator and the AstraZeneca study physician on a case-by-case basis taking into account tolerability and the clinical benefit to the subject.
- Death
- Subject lost to follow-up

If the reason for withdrawal from the study is death of the patient, the two options for categorising withdrawal are either progressive disease or an adverse event (AE; more than one AE may be documented as causing withdrawal). Please note death is an outcome and not an AE.

### **Voluntary discontinuation by a patient**

Patients are free to discontinue their participation in the study at any time, without prejudice to further treatment. Patients who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any AEs. If possible, they should be seen and assessed by an investigator. Adverse events should be followed up and investigational products should be returned by the patient.

### **Incorrectly enrolled patients**

Incorrectly enrolled patients will be discussed by the investigator and the AstraZeneca study physician on a case-by-case basis, taking into account tolerability and the clinical benefit to the patient.

### **Procedures for discontinuation**

Subjects who discontinue should, if possible, be seen and assessed by an investigator. The reason for withdrawal and the date of withdrawal must be documented on the case report form (CRF). If possible investigational products should be returned by the subject.

All subjects who have new or worsening CTC grade 3 or 4 laboratory values at the time of withdrawal must have further tests performed and the results recorded on the appropriate CRF until the laboratory values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions on the CRFs and in the subject's medical records. Laboratory abnormalities should **not** be reported as adverse events unless any criterion for an SAE is fulfilled, the laboratory abnormality causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

At withdrawal all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

After withdrawal from treatment, subjects must be followed up for all existing and new AEs for 4 weeks. All new AEs occurring during that period must be reported to AstraZeneca and all study-related toxicities and SAEs must be followed up for resolution where possible.

After withdrawal the long-term follow up information for survival should be collected at least every 12 weeks until study closure by telephone contact with the subject, subject's family, or by contact with the subject's current physician.

## 3.4 Treatments

### Investigational products

#### Identity of investigational product and comparators

##### 3.4.1 ZD1839

ZD1839 will be supplied to the investigator by AstraZeneca as film-coated tablets.

	<b>Strength (mg)</b>	<b>Formulation number</b>	<b>Colour</b>	<b>Description</b>
ZD1839	250 mg tablet	F12653	Brown	Plain-faced

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Descriptive information for ZD1839 can be found in the IB.

Tablets are provided in high-density polyethylene (HDPE) bottles containing 100 tablets. Each bottle of investigational product includes a 3-panel investigational-use label containing two tear-off portions for investigational site records.

Additional packaging details for this clinical study material are described in the Clinical Supply Action Plan on file with the AstraZeneca Investigational Products Section.

### Presentation of chemotherapy

For Germany and Austria only, gemcitabine and cisplatin will be supplied by AstraZeneca and administered as study therapy.

##### 3.4.2 Gemcitabine

Gemcitabine will be presented as a sterile lyophilised white powder in 10 mL sterile single-dose vials containing 200 mg or in 50 mL sterile single dose vials containing 1000 mg of the compound.

The contents of the vial should be reconstituted in 0.9% sodium chloride without preservatives so that the maximum concentration on reconstitution is 40 mg/mL. The appropriate amount of gemcitabine may be administered as prepared or further diluted to concentrations as low as 0.1 mg/mL. When prepared as directed, the solution is stable for 24 hours at controlled room temperature (20-25°C).

##### 3.4.3 Cisplatin

Cisplatin will be presented as a sterile lyophilised white powder in single-dose amber vials containing 10 mg or 50 mg of the compound or as aqueous solutions (20ml, 50ml or 100ml) containing 0.5mg Cisplatin pro ml.

The contents of the vial should be reconstituted with 10 mL (10 mg vial) or 50 mL (50 mg vial) of sterile water for injection. The reconstituted solution is stable for 20 hours at room temperature (27°C). The solution should not be refrigerated because a precipitate will form. Solution removed from the amber vial should be protected from light if it is not used within 6 hours. The total dose is dissolved in 500 mL saline or 5% dextrose and infused using a programme of forced diuresis.

### **3.4.4 Labelling**

Study medication will be labelled including the following information:

- Study Code
- Study medication to be used only for investigational purposes
- Keep out of the reach of children
- Name and address of local AstraZeneca company
- Name of drug, strength and dose(s)
- Batch number and expiry date
- The labelling of ZD1839 includes instructions stating that the tablets should be taken as a single dose orally at the same time in the morning

There are blank information areas on the label for insertion of the patient number, dose to be administered, date of dispensing and centre number; this information is to be completed at the time of dispensing. One tear-off portion of the label of the investigational product provides batch and tablet strength information. All dispensing and study medication management activities will be the responsibility of investigational site personnel.

### **3.4.5 Storage**

All investigational products must be kept in a secure place under appropriate storage conditions. ZD1839 must be stored below 30°C .

Vials of gemcitabine and cisplatin are to be stored unopened according to the manufacturer's instructions (at controlled room temperature: 20-25°C). For storage of reconstituted solution, see section 3.4.2 and 3.4.3.

### **3.4.6 Accountability**

It is the investigator's/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (e.g. a pharmacist)
- Deliveries are recorded
- Study treatments are handled and stored safely and properly
- Study treatments are dispensed only to study patients in accordance with the protocol
- Patients return all unused medication and empty containers to the investigator

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist.

Study medication may be disposed of at the centres according to local guidelines. Disposals of unused study drugs must be documented.

### **3.4.7 Prescription record cards**

At the time the drug is dispensed to the patient, the tear-off portion of the carton label should be removed and attached to the patient's prescription record card.

Each time ZD1839 is dispensed to the patient, the dispenser should add the patient number and date to the tear-off portion of the label, attach the label to the prescription record card, and initial and date the relevant box on the prescription record card.

Prescription record cards will be checked by the clinical research associate (CRA) at each monitoring visit.

Each dose of gemcitabine and cisplatin administered to the patient will be recorded in the CRF.

### **3.4.8 Doses and treatment regimens**

#### **ZD1839**

The ZD1839 dose level for this study is 250 mg. Study treatment will be dispensed to patients on day 1 (Arm A) or day 126 (Arm B) or upon entering the Extension-Arm and every 12 weeks thereafter until the patient withdraws. One 250 mg tablet will be taken at each dose administration.

ZD1839 treatment will be taken once a day, every day at about the same time. It can be taken with or without food. If the patient forgets to take a dose, they should take the last missed dose as soon as they remember, provided it is at least 12 hours before the next dose is due.

Patients will receive ZD1839 daily until disease progression, unacceptable toxicity or withdrawal of consent. Afterwards patients will be followed-up for survival.

#### **ZD1839 dose interruption/reduction**

Dose interruptions should be used as the first approach to managing toxicity. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. No dose reduction is allowed.

In all cases where the patient has been withdrawn because of unusual or unusually severe toxicity that is considered to be related to ZD1839, the investigator must contact the Study Team Physician (see 9.1 AstraZeneca emergency contact procedure). The investigator should also report the event immediately as an SAE to the monitoring CRA (see 4.4.2.3).

#### **Guideline for dispersing whole ZD1839 tablets**

ZD1839 tablets cannot be crushed. Experimentation has shown that ZD1839 tablets will break up into a fine dispersion within 5 to 7 minutes when they are dropped whole into lukewarm water. There are felt to be no risks to the chemical stability of ZD1839 providing this process occurs immediately prior to administration to or by the subject. The only risk is felt to be concerned with ensuring delivery of the whole dose, as a certain amount of deposition of powder on the surfaces of the container will occur while the container is being emptied.

Although bio-equivalence has not yet been formally tested in clinical trials the following procedure is recommended for administering dispersed whole tablets to subjects who are unable to swallow the tablets:

Drop one tablet of ZD1839 into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 1-2 ounces (or 50 mls) of lukewarm water. Stir the liquid occasionally to ensure complete break-up of the tablet(s).

When the tablet has broken up into a fine dispersion (approximately 5 minutes) it can be administered to or by the subject. Administration should occur immediately after dispersion is complete.

Rinse the container with a similar amount of water to ensure removal of any material adhering to the walls of the container and administer the additional water to the subject.

### **Gemcitabine and cisplatin**

All patients will receive gemcitabine 1250 mg/m<sup>2</sup> administered as a 30-minute intravenous (iv) infusion on Day 1 and Day 8 of each 21-day cycle.

All patients will receive cisplatin 70 mg/m<sup>2</sup> administered as an iv infusion at a rate of 1 mg/min. The total dose will be dissolved in 500 mL of 5% dextrose and is administered using a programme of forced diuresis. It is recommended that the infusion programme contains at least 3 L of fluids over a minimum of 6 hours. Cisplatin administration will follow gemcitabine administration on Day 1 of each 21-day cycle.

Patients will receive chemotherapy for 6 cycles, or until disease progression, unacceptable toxicity or withdrawal of consent.

#### **3.4.9 Method of assigning subjects to treatment groups**

This is an open-label, centrally randomised study. Patients first undergo a screening period in which their eligibility for participation in this trial is confirmed. Each centre is required to keep a screening log in their investigator's file. This screening log must list all patients who signed the informed consent form, irrespective of whether or not they are subsequently randomised to receive study treatment. It is imperative that the exact reason is given in the screening log for all patients who were not randomised after giving their informed consent. Subject eligibility will be established before treatment randomisation. Subjects will be randomised strictly sequentially, as subjects are eligible for randomisation, and the subject will not be allowed to re-enter the study. Randomisation will be stratified according to centre.

Once a subject's eligibility has been confirmed, the investigator (or nominated assistant) should send the completed randomisation request form including the complete baseline documentation via Fax (+49 611 2678992) to the central randomisation centre at CRS Creative-Research-Solutions GmbH. Subjects will be identified to CRS using subject number, subject initials, and date of birth. The investigator will receive a confirmatory fax detailing the allocated treatment group within one workday. If during randomisation questions arise concerning the eligibility of the patient or the completeness of the baseline documentation CRS will phone the investigator to clarify these points.

Subjects must begin their study drug within 72 hours following the date of randomisation (to allow for weekends).

If a subject discontinues from the study, the subject number will not be reused.

### 3.4.10 Management of toxicity

#### ZD1839 expected adverse events

**Table 3 Adverse Drug Reactions by frequency and system/organ:**

<b>Very common</b> (>10%)	<i>Digestive:</i>	<ul style="list-style-type: none"> <li>- Diarrhoea, mainly mild in nature (CTC grade 1) and, less commonly, moderate (CTC grade 2), there have been isolated reports of severe (CTC grade 3) diarrhoea with dehydration.</li> <li>- Nausea, mainly mild in nature (CTC grade 1).</li> </ul>
	<i>Skin and appendages:</i>	<ul style="list-style-type: none"> <li>- Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash or acne, sometimes itchy with dry skin, on an erythematous base.</li> </ul>
<b>Common</b> (>1 - ≤10%)	<i>Digestive:</i>	<ul style="list-style-type: none"> <li>- Vomiting, mainly mild or moderate in nature (CTC grade 1 or 2).</li> <li>- Anorexia, mild or moderate in nature (CTC grade 1 or 2).</li> <li>- Stomatitis, predominantly mild in nature (CTC grade 1).</li> </ul>
	<i>Metabolic and nutritional:</i>	<ul style="list-style-type: none"> <li>- Liver function abnormalities, consisting mainly of asymptomatic mild or moderate elevations in transaminases (CTC grade 1 or 2).</li> </ul>
	<i>Skin and appendages:</i>	<ul style="list-style-type: none"> <li>- Nail disorder</li> <li>- Alopecia</li> </ul>
	<i>Whole body:</i>	<ul style="list-style-type: none"> <li>- Asthenia, predominantly mild in nature (CTC grade 1).</li> </ul>
	<i>Ophthalmological:</i>	<ul style="list-style-type: none"> <li>- Conjunctivitis and blepharitis, mainly mild in nature (CTC grade 1).</li> </ul>
<b>Uncommon</b> (>0.1 - ≤1%)	<i>Haematologic and lymphatic:</i>	<ul style="list-style-type: none"> <li>- INR elevations and/or bleeding events in some patients taking warfarin</li> </ul>
	<i>Ophthalmological:</i>	<ul style="list-style-type: none"> <li>- Corneal erosion, reversible and sometimes in association with aberrant eyelash growth</li> </ul>
	<i>Respiratory:</i>	<ul style="list-style-type: none"> <li>- Interstitial lung disease, often severe (CTC grade 3-4). Fatal outcomes have been reported.</li> </ul>
<b>Rare</b> (>0.01 - ≤0.1%)	<i>Skin and appendages:</i>	<ul style="list-style-type: none"> <li>- Isolated reports of toxic epidermal necrolysis and erythema multiforme</li> </ul>

### **ZD1839 non-haematopoietic toxicity**

If any of the following conditions occur, administration of ZD1839 may be interrupted for a maximum of 14 days to allow the AE to resolve or decrease in severity:

- CTC grade 3 or 4 or unacceptable toxicity, e.g. cosmetic effect of grade 2 rash
- There is no consideration and/or corroborative evidence that the AE is because of progressive disease
- The AE is consistent with previously described ZD1839 toxicity

Toxicity should be reassessed at least twice weekly and more frequently if clinically indicated. Once the AE decreases in severity to CTC grade 1, the patient may continue to take the assigned dose.

Every attempt should be made to manage possible drug-related toxicity so that a patient remains evaluable for efficacy.

### **ZD1839 skin toxicity**

Subjects with poorly tolerated skin toxicity may be successfully managed by providing a brief (up to 14 days) interruption of ZD1839; the daily dose of ZD1839 should then be reinstated (see Section 3.4.2.2). However, the rash may improve without the need for interrupting therapy with ZD1839.

A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

### **ZD1839 nausea and/or vomiting**

In subjects who have emesis and are unable to retain ZD1839, every attempt should be made to obtain control of nausea and vomiting. The dose of ZD1839 may be repeated if emesis occurs within 30 minutes of taking the tablet.

### **ZD1839 diarrhoea**

If GI toxicity is not appropriately managed this may be associated with a development of dehydration.

Diarrhoea has been successfully managed with anti-diarrhoeal agents such as loperamide.

**CTC grade 1-2 diarrhoea.** No specific supportive care is usually needed or indicated.

**CTC grade 3 or 4 diarrhoea.** If this occurs immediate supportive care measures should be instigated, ZD1839 should be interrupted for up to a maximum of 14 days until resolution, or the diarrhoea has decreased in severity to CTC grade 1. If CTC grade 3 or 4 diarrhoea recurs, and in the investigators opinion cannot be controlled by further drug interruptions and optimal symptomatic management, then ZD1839 should be discontinued..

**CTC grade 2, 3, or 4 diarrhoea with rapidly or precipitously declining absolute neutrophil count (ANC), or at same time as neutropenia CTC grade 3 or 4.** ZD1839 should be discontinued for up to a maximum of 14 days until the ANC is  $\geq 1.0 \times 10^9/L$ , or resolution of the diarrhoea, or the diarrhoea has decreased in severity to CTC grade 1..

If a **grade 4 diarrhoea** is associated with hemodynamic collapse, the investigator should notify the AstraZeneca Study Team Physician to discuss further participation in the trial, and report as an SAE.

In all cases where the subject has been withdrawn due to unusual or unusually severe toxicity considered related to ZD1839, the investigator must contact the AstraZeneca Study Team Physician.

### **ZD1839 interstitial lung disease**

Interstitial lung disease (ILD), including interstitial pneumonitis, is a common complication of lung diseases including advanced lung cancer, regardless of treatment. It has been widely observed in clinical trials in which chemotherapy and/or radiotherapy has been used for the treatment of advanced lung cancer.

Interstitial Lung Disease, which may be acute in onset, has been observed uncommonly in patients treated with ZD1839. These patients usually present with a fairly acute onset of dyspnoea sometimes associated with cough or low grade fever. This may become quite severe within a short period of time and usually results in hospitalisation. Radiological investigations, often including CT scan, frequently show pulmonary infiltrates or interstitial shadowing with ground glass appearance. There is often respiratory distress with arterial oxygen desaturation. Cultures are frequently negative for bacterial growth. In a number of cases, the event has responded to steroid therapy but this is not always so and a significant number of cases have had a fatal outcome.

If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnoea, cough and fever, ZD1839 should be interrupted and the patient promptly investigated for Interstitial Lung Disease. If Interstitial Lung Disease is confirmed, ZD1839 should be discontinued and the patient treated appropriately.

### **ZD1839 hypersensitivity**

One case of hypersensitivity with hives following the first dose of ZD1839 occurred in phase I studies. This was successfully managed over several months with low dose daily oral antihistamines while treatment with ZD1839 continued.

### **Cisplatin renal toxicity**

Serum creatinine must be evaluated on day 1 of each cycle and creatinine clearance calculated (Cockroft formula). Cisplatin dose adjustments will be performed according to the criteria indicated in Table 4.

**Table 4 Renal based dose modification**

<b>Creatinine clearance</b>	<b>Gemcitabine dose</b>	<b>Cisplatin dose</b>
≥60 ml/min	100%	100%
45 - <60 ml/min	100%	50%
<45 ml/min	Withhold dose	Withhold dose

### Gemcitabine and cisplatin neurological toxicity

Gemcitabine and cisplatin doses should be modified for neurological toxicity, see Table 5. No dose reductions in ZD1839 will be made for neurological toxicity.

**Table 5 Neurological-based dose modification**

Neurological	CTC grade, gemcitabine and cisplatin doses			
	1	2	3	4
Ototoxicity	No dose reduction	50% cisplatin	withhold cisplatin	withhold cisplatin
Neuropathy - sensory	No dose reduction	75% cisplatin	50% cisplatin	withhold cisplatin
Neuropathy - motor	No dose reduction	Hold cisplatin and gemcitabine treatment until patient recovers to CTC grade 1 toxicity, then resume treatment with both at 75%	Hold cisplatin and gemcitabine treatment until patient recovers to CTC grade 1 toxicity, then resume treatment with both at 50%	withhold cisplatin and gemcitabine

Gemcitabine and cisplatin can be withheld for a maximum of 14 days. If the toxicity has not resolved or reverted to CTC grade 1 in this time, withdraw the patient from the trial or offer treatment with ZD1839 in the extension arm of the study.

### Gemcitabine hematological toxicity

The absolute neutrophil count must be greater than or equal to 1,000/mm<sup>3</sup> and platelet count must be greater than or equal to 100,000/mm<sup>3</sup> to receive chemotherapy on Day 1 of each cycle.

Treatment with gemcitabine should be delayed for up to 2 weeks until the absolute neutrophils on day 1 of each cycle are ≥1,000 and the platelet count is ≥100,000.

Note: granulocyte colony-stimulating factor [filigastim] [G-CSF] may be used in accordance with the American Society of Clinical Oncology (ASCO) guidelines 1997.

Dose modifications of gemcitabine on day 8 must be made according to the criteria specified in Table 6 below.

**Table 6 Neutrophil and/or platelet-based dose modification for gemcitabine**

Neutrophil count mm <sup>3</sup>	Platelet mm <sup>3</sup>	Gemcitabine dose
>1000	and >100000	100%
500 - 1000	50000 - 100000	75%
<500 or febrile neutropenia	<50000	Withhold dose

No dose reductions will be made for anemia. Patients may be supported at the investigators' discretion.

In the event of febrile neutropenia requiring antibiotic therapy, or thrombocytopenia requiring platelet transfusions, subsequent cycles of gemcitabine will be permanently reduced by 25%.

If chemotherapy must be withheld due to hematological toxicity, a complete blood count (hemoglobin, white cell count, absolute neutrophil count and platelets) should be obtained at least weekly until the white cell and platelet counts reach the lower limits for treatment as outlined.

### **Gemcitabine and cisplatin other toxicity**

For any unanticipated, clinically or potentially clinically significant drug-related CTC grade 3 or 4 toxicity not mentioned above, treatment with gemcitabine/cisplatin should be withheld for a maximum of 14 days until the patient recovers completely, or the toxicity reverts to CTC grade 1. Treatment may be resumed at original doses or an individual agent may be reduced by 50% as clinically determined per investigator discretion (gemcitabine, cisplatin). For CTC grade 1 and 2 toxicities, no dose reduction should be made.

### **3.4.11 Pre-study, concomitant and post-study treatment(s)**

#### **Treatment for cancer**

Except for ZD1839, and gemcitabine and cisplatin administered according to the protocol, no systemic treatment or radiotherapy known to have an effect on transitional cell carcinoma may be used during the study.

#### **Other concomitant treatment during ZD1839 therapy**

No concomitant use of the following drugs is allowed: phenytoin, carbamazepine, rifampicin, barbiturates or St John's Wort, as these drugs induce CYP3A4 and may decrease levels of ZD1839.

Concomitant use of CYP3A4 inhibitors, e.g., itraconazole, may result in increased levels of ZD1839. This exposure may be clinically relevant since adverse experiences are related to dose and exposure, therefore caution should be exercised.

Co-administration of drugs that cause significant sustained elevations in gastric pH  $\geq 5$  may reduce plasma concentrations of ZD1839 and therefore may reduce efficacy.

International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some subjects taking warfarin. Subjects taking warfarin or coumadin should be monitored regularly for changes in their prothrombin time or INR.

For subjects on steroids at the start of the study, the dose of steroids can be changed during the study.

Other medication that is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF.

### **3.4.12 Treatment compliance**

ZD1839 compliance will be monitored by pill count. All doses of gemcitabine and cisplatin will be administered under supervision and recorded in the CRF.

## 4 STUDY MEASUREMENTS AND ENDPOINTS

See Table 1 for details of when each assessment should be conducted.

### 4.1 Primary endpoint

The primary endpoint in this study is the time to progression based on the RECIST criteria.

### 4.2 Screening and demographic measurements

The data listed below will be collected on the relevant CRFs:

- Date of birth, sex, race\*
- Height\*, weight\*
- Full physical examination, including performance status\*, heart rate\* and blood pressure\*
- Significant medical and surgical history
- ECG will be evaluated locally
- Serum or urine pregnancy test\* (in women of child-bearing potential only)
- Concurrent illnesses and therapies at the time of entry to the study
- Haematology, biochemistry and urinalysis

\* for these data, entries on CRFs may be considered as source data

### 4.3 Efficacy measurements and endpoints

#### 4.3.1 Summary of efficacy objectives and endpoints

Table 7 shows how the efficacy endpoints of this study relate to the study objectives.

Table 7 Efficacy objectives and endpoints relating to each objective

Objective	Endpoint(s)	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
<b>Primary</b>				
To evaluate the activity of ZD1839 in combination with standard therapy gemcitabine and cisplatin by estimating the time to progression	Time to progression based on the RECIST	Kaplan-Meier estimation after 18 month  Mean and median time to progression  ITT population	Calculation of pair-wise log-rank statistic for difference between treatment groups  95% CI on mean and median time and difference in median between treatment groups	Only exploratory

**Table 7 Efficacy objectives and endpoints relating to each objective**

<b>Objective</b>	<b>Endpoint(s)</b>	<b>Summary statistic for analysis (including timepoint and population)</b>	<b>Planned analysis</b>	<b>Significance of results</b>
<b>Secondary</b>				
To estimate the response rate for each treatment arm	Objective tumour response (CR and PR) based on the RECIST	Proportion of patients responding at any visit ITT population	Fisher-Freemann-Halton Test Pair-wise exact 95% CI on difference in proportion between treatment groups	Only exploratory
To estimate the overall survival time for each treatment arm	Overall survival time	Kaplan-Meier estimation after 18 month Mean and median time to progression ITT population	Calculation of pair-wise log-rank statistic for difference between treatment groups 95% CI on mean and median time and difference in median between treatment groups	Only exploratory
The estimate the time to treatment failure for each treatment arm	Time to treatment failure	Kaplan-Meier estimation after 18 month Mean and median time to progression ITT population	Calculation of pair-wise log-rank statistic for difference between treatment groups 95% CI on mean and median time and difference in median between treatment groups	Only exploratory
To estimate the disease control rate for each treatment arm	Incidence of controlled disease (CR, PR and SD)	Proportion of patients with disease controlled at any visit ITT population	Fisher-Freemann-Halton Test Pair-wise exact 95% CI on difference in proportion between treatment groups	Only exploratory
To estimate the duration of response for each treatment arm	Duration of response	Kaplan-Meier estimation after 18 month Mean and median duration of response ITT population (subjects with response only)	Calculation of pair-wise log-rank statistic for difference between treatment groups 95% CI on mean and median time and difference in median between treatment groups	Only exploratory

CI – confidence interval; CR – complete response; N/A – not applicable; PR – partial response; RECIST – Response Evaluation Criteria in Solid Tumours; SD – stable disease

The methods for collecting efficacy data are presented below. The timings of the efficacy assessments are presented in the study plan in Table 1.

### **4.3.2 Objective tumour assessments**

#### **Methods of assessment**

The RECIST will be used for this study for objective tumour response assessment; details are given in Appendix D, also see the study plan for timing of the assessments, which will be performed in accordance with the guidelines of the German Cancer Society and the German Society for Urology. Only computerised tomography (CT) scans or magnetic resonance imaging (MRI) will be accepted as methods of radiological tumour evaluation.

The date on which response is first observed is to be considered the date of response. The tumour response assessment will be performed by each investigator. An evaluation by independent experts may be conducted at the end of the study.

#### **Derivation of tumour endpoints**

##### **Time to progression**

The time to progression for each patient is the number of days from the day of randomisation to the earlier of death (from any cause) or progression. If the patient discontinues the study (e.g. because of toxicity or premature discontinuation of study) and no progression is observed, then the time to progression is treated as right censored at last tumour assessment.

##### **Objective tumour response (CR and PR) based on the RECIST**

A patient is deemed to be a responder if the RECIST for complete or partial response are satisfied at any time of tumour assessment. All treated patients who do not satisfy the conditions to be a responder are deemed to be a non-responder.

##### **Overall survival time**

The overall survival time for each patient is the number of days from the day of randomisation to death (from any cause). If the survival time does not correspond to the patient's death then it is treated as right censored.

##### **Time to treatment failure**

Time to treatment failure is the number of days from the day of randomisation to the earlier of death (from any cause), progression, or withdrawal of study medication (from any reason). If the time to treatment failure does not correspond to the analysis time-point then it is treated as right censored.

##### **Incidence of controlled disease (CR, PR and SD)**

A patient is deemed to have controlled disease if the patient is alive and all tumour assessments at any visit satisfied the RECIST for CR, PR or SD. All treated patients who do not satisfy the conditions for controlled disease are deemed not to have controlled disease.

## Duration of response

Duration of response will be derived for each patient with a best objective tumour response of CR or PR at any time of tumour assessment. The duration of response is the number of days from the date of first documented response to the earlier of death (from any cause) or progression. If the duration does not correspond to the patient's death or progression then it is treated as right censored at last tumour assessment.

## 4.4 Safety measurements and endpoints

### 4.4.1 Summary of safety objectives and endpoints

Table 8 shows how the safety endpoints of this study relate to the study objectives.

**Table 8 Safety objectives and endpoints relating to each objective**

Objective	Endpoints	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
To investigate the safety and tolerability for each treatment arm	Nature, incidence and severity of adverse events and serious adverse events	Counts and proportions AST population	None	
	Incidence of and reasons for study drug dose interruptions, study drug dose reductions and withdrawals due to Aes	Counts and proportions AST population		
	Laboratory assessments, physical examinations	Standard summary statistics AST population		

The methods for collecting safety data are described below. The timings of the safety assessments are presented in the study plan in Table 1.

### 4.4.2 Adverse events

#### Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is extremely important that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

## Adverse event

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. **Any events that are unequivocally because of progression of disease need not be reported as an AE.**

## Serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (i.e. run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (i.e. their relationship to study treatment) will be assessed by the investigators, who in completing the relevant CRF must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?” **Any events or hospitalisations that are unequivocally because of progression of disease need not be reported as an SAE.** For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix C.

## Other significant adverse event

The AstraZeneca Drug Safety Group will identify other significant adverse events (OAEs) during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

## Recording of adverse events

For the purpose of this study, any detrimental change in a patient’s condition, subsequent to their entering the study and during the 30-day follow-up period after the final treatment, should be considered an AE. The development of a new cancer should be regarded as an

AE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this clinical study. All AEs will be recorded on the CRFs provided. A description of the event, including its severity, duration, any action taken (e.g. treatment and follow-up tests) and the outcome, should be provided, along with the investigator's assessment of the relationship to the study treatment. AEs and laboratory values will be graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) and recorded on the appropriate CRF page.

Any CTC grade 3 or 4, or any clinically significant CTC grade 1 or 2, haematology or biochemistry laboratory values that are not considered to be because of tumour progression should be recorded as an AE. Abnormal laboratory tests and other objective measures that meet the criteria for an SAE or result in discontinuation of the study drug should be recorded and reported as SAEs or AEs, respectively.

All patients who have CTC grade 3 or 4 laboratory values at the time of withdrawal must be followed up until the laboratory values have returned to CTC grade 1 or 2, or until 30 days after the date of withdrawal (whichever comes first), unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions on the CRFs and in the patients' medical records.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study medicinal product and the AE (see Appendix C for guidelines on interpretation of causality).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria mentioned under 'Serious adverse event'. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

### **Lack of efficacy**

When there is deterioration in the condition for which the medicine is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the medicine contributed to the deterioration, or local regulations state to the contrary, **the deterioration should be considered to be a lack of efficacy and not an AE.**

### **Handling unresolved SAEs/AEs at completion/withdrawal**

All study treatment-related toxicities and SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve because of the patient's underlying disease.

### **Pregnancy**

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

## Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e. immediately but no later than the end of the next business day) or when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the CRF. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

### 4.4.3 Laboratory safety measurements and variables

#### Methods of assessment

Routine haematology and biochemistry assessments will be performed at the laboratory local to the study centre and preferably documented in SI units.

The following laboratory parameters will be investigated. See Table 9 for the total volume of blood samples to be collected:

#### Biochemistry

ALT and AST	ALP
Albumin	Total protein
Blood urea nitrogen (BUN) or urea	Creatinine
Calcium	Magnesium
Total bilirubin	Sodium
Inorganic Phosphate	Potassium

#### Haematology

Absolute neutrophil count	With blood cell count (total)
Haemoglobin	Platelet count

#### Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient from screening until the 6-months visit is as follows (blood drawn during the ZD1839 monotherapy is not included in this table):

**Table 9** Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Biochemistry	6	9	54

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Haematology	3	15	45
Total		24	99

### Calculation or derivation of endpoints

Section 4.4.2 provides details on how AEs based on laboratory tests will be recorded and reported.

#### 4.4.4 ECG

ECG will be evaluated locally at screening and thereafter as clinically indicated. Any clinically significant abnormal findings observed and recorded during the treatment period will be recorded as AEs. The same method of assessment should be used throughout.

#### 4.4.5 Physical examination and performance status

Full physical examination will be performed and will include performance status, weight, heart rate and blood pressure.

Performance status will be scored according to WHO criteria as follows:

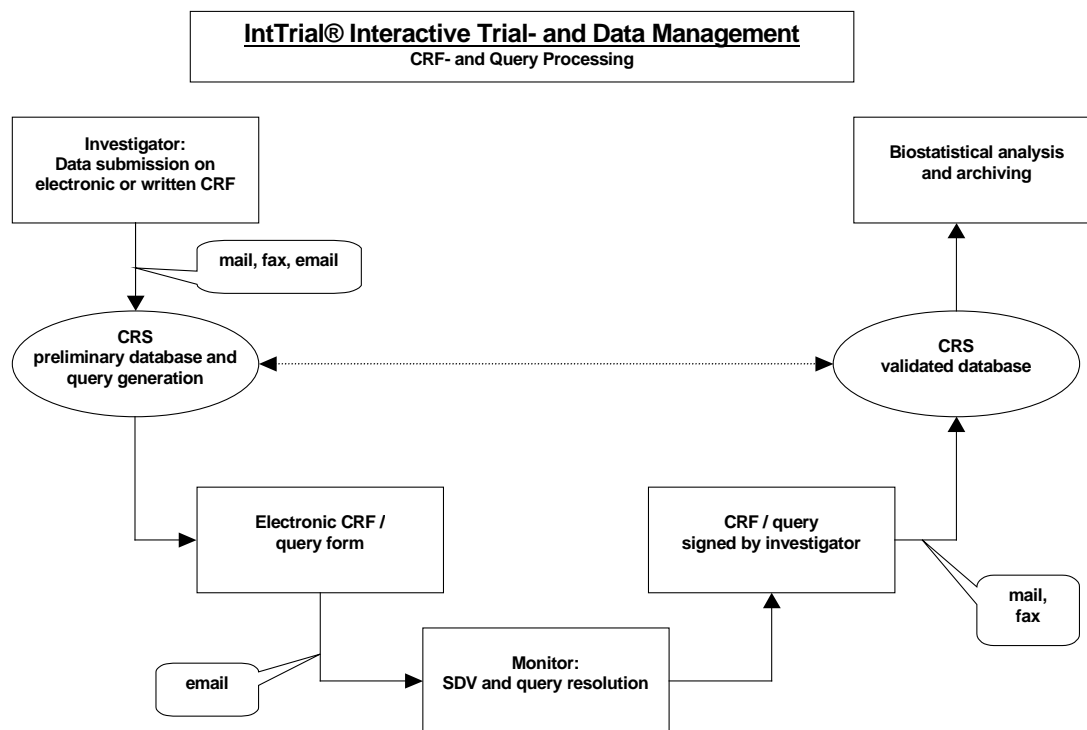
- 0 = Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia
- 1 = Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in Grade 0, but only with the aid of analgesics
- 2 = Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled, unable to carry out any self-care and confined totally to bed or chair

Any new conditions reported during the study will be recorded on the AE forms. Only those findings that are in addition to the condition being treated will be recorded as AEs. Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

## 5 DATA MANAGEMENT

Data management will be performed by CRS Creative Research Solutions GmbH using IntTrial®, which is a modular system based on the universal PDF format for creation, recording and archiving of CRFs.

The following scheme illustrates the data-flow of IntTrial®.



Using an IntTrial®-CRF the investigator can choose whether to perform the documentation in electronic (“on screen”; e-CRF) or paper form (paper-CRF). The CRF for the trial will be provided on a CD-Rom, containing all CRF-pages as PDF-files, which can be completed electronically or printed out and completed in hand writing.

Upon “on screen”-completion the CRF can subsequently be sent to data management either by secure email or printed out and sent by mail or fax. For conventional documentation a print-out of the CRF will be used, which will be sent to data management after documentation either by mail or fax. Data should be recorded directly and legibly onto the CRFs in black ball-point pen. A copy of each CRF page sent will be kept at the site and will be filed at the end of the trial together with a copy of the fully validated CRF-page signed by the investigator.

Upon receipt by CRS the CRF will be electronically evaluated by the IntTrial® System, manually validated and entered into the preliminary database. Manual validation includes performing obvious corrections and generating “simple queries” (e.g. missing values, illegible data). From the preliminary database a CRF will be re-generated which includes the original entries, obvious corrections and “simple queries”. This CRF will be forwarded to the monitor, who in turn will perform SDV at the centre using the printed out CRF. After SDV the CRF will be signed by the investigator, and sent to CRS. A copy of the

signed CRF will remain at the centre. The signed CRF will again be evaluated by the IntTrial®-System, manually checked and entered into the second, validated database.

Data in the second database will undergo extensive electronic validation plausibility- and cross-checks. Queries raised during this process will be resolved by using Data Query Sheets. These will be sent as a single copy via the CRA to the investigator. The original copy of the DQS/response is returned to data management, a copy of the DQS/response is placed with the CRF in the CRA files, and a copy of the DQS/Response remains at the investigator site.

After resolving any occurring queries by conventional data query sheets the cleaned database will be locked. The data will be evaluated and statistically analysed using SAS® (Statistical Analysis Software).

## **6 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE**

### **6.1 Statistical methods**

Due to the open-label study design a comprehensive Statistical Analysis Plan (SAP) will be prepared within three months after the start of the study. The analysis of the data will be done by CRS Creative Research Solutions GmbH.

#### **6.1.1 Statistical review**

The statistical and analytical methods section will be reviewed and updated, if necessary, immediately before the database will be locked and the statistical analysis will be performed. If changes in the plan are necessary, there will be a description of the changes in the clinical trial report in the corresponding subsection. A careful explanation will be provided for deviations from the planned analysis.

#### **6.1.2 Presentation of data**

All individual data (including relevant derived variables) will be presented by parameter in listings in the statistical appendix of the clinical trial report. Results of statistical analysis, descriptive summary statistics and supportive listings/figures will also be presented in the statistical appendix of the clinical trial report.

### **6.2 Determination of sample size**

The assumed time to progression of a therapy with gemcitabine and cisplatin alone in patients with advanced or metastatic transitional cell carcinoma of the urothelium is 7.4 month (von der Maase 2000). Assuming an exponential survival function, this time to progression corresponds to a progression-free rate of 18.5% after 18 month. The estimated maximum benefit of the additional use of ZD1839 (either together with gemcitabine and cisplatin or following the gemcitabine and cisplatin therapy) is relative 30%. This results in a time to progression of 9.6 month (equal to 27.3% progression-free subjects) in the best treatment arm.

Assuming this is true, the goal is to have a probability of 75% of concluding that further evaluation of ZD1839 in combination with gemcitabine and cisplatin on the improvement of time to progression in patients with advanced or metastatic transitional cell carcinoma of the urothelium is warranted.

This conclusion will be based on the observed difference in the response rates between the treatment arms using a selection design with three arms (Sargent 2001). Based on these considerations, 102 subjects (34 per treatment group) will be required for the intent-to-treat population. Assuming a drop-out rate of approximately 20%, 125 patients have to be enrolled.

Because of the use of a selection design the trial is non-comparative in the statistical sense. The goal of the study is to select the most efficient of the three treatment arms, which should be used in a following study.

## **6.3 Statistical evaluation**

### **6.3.1 Trial population**

#### **Disposition of patients**

The number of patients who were screened, selected at baseline to participate in the scheduled treatment period, treated, discontinued prematurely and who completed the treatment period will be tabulated by treatment group and centre (including overall). A disposition graph of patients by treatment group will also be provided.

#### **Patient discontinuations**

All treated patients who discontinued prematurely from the trial (according to the corresponding End-of-Trial form) will be listed by treatment group and centre; at least the time point of discontinuation, the main reason for discontinuation and relevant data of exposure will be presented.

Non-treated patients will be excluded from all efficacy and safety analyses.

#### **Blind broken during the study**

Not applicable (this is an open-label study).

#### **Patient data sets**

The number of patients within the various patient data sets as defined in the following sections will be tabulated by treatment group and centre (including overall).

Data from the AST population will be used to assess the safety profile, whereas data from the ITT population will be used to assess efficacy.

##### **a) All-patients-screened population**

The all-patients-screened population will consist of all patients who were screened.

##### **b) All-subject-treated population**

The AST population will consist of all patients who received at least one dose of trial medication (e.g., chemotherapy and/or ZD1839). In cases where all dispensed trial medication is returned (per investigator's record), the patient will be considered non-treated and will not be included in the AST population.

##### **c) Intention-to-treat population**

The ITT population will consist of all patients from the AST group who had at least one tumour assessment or who died before the first tumour assessment took place.

### **6.3.2 Demographics and other patient characteristics**

Relevant data of important baseline characteristics (demographics, vital signs [blood pressure, heart rate, height, weight, body mass index], medical history, physical examination, pregnancy test, inclusion and exclusion criteria) and important clinical measurements at baseline (overall tumour burden) will be tabulated by treatment group and centre (including overall) for both the AST and the ITT population, using appropriate descriptive statistics (number of missing data, number of non-missing data, mean, standard deviation, median, lower and upper quartile, minimum and maximum) or frequency distributions (absolute and percentage number of patients).

### **6.3.3 Extent of exposure**

For all treated patients, the duration of exposure to trial drug (total number of days) will be determined, calculated as the date of the last trial medication intake within the scheduled treatment period (according to the Termination form) minus the date of the first intake (according to the drug accountability form) plus 1. In cases where the necessary information cannot be derived from the CRFs mentioned above, relevant information from other CRFs will be used to calculate the duration of exposure as accurately as possible.

All parameters related to the extent of exposure will be presented in a listing. Appropriate descriptive statistics and frequency tables of the duration of exposure will be presented by treatment group and centre (including overall) for both the AST and the ITT population.

### **6.3.4 Dosing compliance**

Based on information from the Drug Accountability Form, the difference between the total number of tablets dispensed and the total number of tablets returned will be used to calculate the total number of tablets taken. Relevant information from other CRFs will be taken into account, if necessary.

The overall compliance (in %) will be defined as [total number of tablets taken divided by the total number of tablets to be taken] multiplied by 100. The total number of tablets to be taken will be calculated per patient, taking into account the prescription information and the actual length of the treatment period. Based on all available information in the CRFs, the overall compliance (in %) will be assessed on an individual level. In case of missing data on returned trial medication, it will be assumed for the compliance check(s) that the patient took the prescribed dose as dispensed.

The mean daily dose will be determined per patient. This calculation will be based on the total number of tablets, the strength of the tablets, and the actual length of the treatment period.

All parameters related to the dosing compliance will be presented in a listing. Appropriate descriptive statistics of the number of tablets taken, overall compliance and mean daily dose will be presented by treatment group and centre (including overall) for both the AST and the ITT population.

### **6.3.5 Concomitant medications**

All patients will be checked by the responsible study personnel for the use of pre-study and concomitant medication that might interfere with the study outcome.

All medications as documented by the investigator will be coded using the latest installed version of the WHO Drug Dictionary.

A combined listing will be made of the pre-study and/or concomitant medication(s) used by each patient consisting of the medication, the daily dose, the unit, the time-period of administration and the indication. The indication, based on the one given by the investigator, will be represented by the dictionary term (LLT and PT) according to dictionary MedDRA (Version 5.1 or higher).

Frequency tables of patients with specific indications coded according to preferred terms, related to concomitant medication, will be given for the AST population presented by treatment group. If a patient had taken more than one drug for the same indication, the patient will be counted in that indication class only once. The time-frame for the analysis on concomitant medications is equal to the time-frame of the efficacy analysis.

### 6.3.6 Efficacy

The efficacy analysis will be based on the ITT population.

For all efficacy parameters, appropriate descriptive statistics will be presented by treatment group and centre (including overall). All statistical tests will be performed two-sided and considered statistically significant if  $p \leq 0.05$ . Due to the exploratory character of this trial, all p-values should be interpreted in a purely exploratory way. No adjustments for multiplicity will be made due to the exploratory nature of the trial.

The following time-frame will be used for the analysis of all efficacy parameters.

Table 10 Time frame to be used in the efficacy analysis

Visit (scheduled day)	Time-frame for analysis	Visit numbering for analysis
1 ( $\leq 0$ )	$\leq 0$	1
7 (63 – 65)	57 – 68	7
13 (115 – 140)	115 – 155	13
14 (171 – 199)	156 – 227	14
every 12 weeks: (255 – 283)	228 – 311	15
(339 – 367)	312 – 395	16
(423 – 451)	396 – 479	17

#### Primary efficacy parameter

To evaluate the activity of ZD1839 in combination with gemcitabine and cisplatin, the TTP will be used as primary efficacy parameter.

The TTP for each patient is defined as the number of days from the day of randomisation to the earlier of death (from any cause) or progression. If the time to progression does not correspond to the patient's death or progression then it is treated as right censored at last tumour assessment.

For the analysis of the primary efficacy parameter the Kaplan-Meier estimation after 18 months will be used, calculated by treatment group. Appropriate figures will be presented. The pair-wise log-rank test will be used to point out differences between the groups. For each group, frequency tables containing estimates of the mean and median time together with their 95% CIs will be provided. Ninety-five percent CIs on the pair-wise differences in median survival time between the treatment groups will be calculated.

#### Secondary efficacy parameters

The analysis of the secondary parameters will be supportive to the main (exploratory) conclusions based on the primary efficacy variable and descriptive in nature. The following variables will be considered as secondary efficacy parameters:

- a) response rate, defined by the proportion of patients responding at visits 7, 13, 14, 15, and every 12 weeks thereafter
- b) overall survival time, defined by the number of days from the day of randomisation to death (from any cause) (If the survival time does not correspond to the patient's death then it is treated as right censored).

- c) Time to treatment failure, defined by the number of days from the day of randomisation to the earlier of death (from any cause), progression, or withdrawal of study medication (from any reason) (if the time to treatment failure does not correspond to the analysis time-point then it is treated as right censored).
- d) disease control rate, defined by the proportion with disease controlled at visits 7, 13, 14, 15 and every 12 weeks thereafter.
- e) duration of response, defined by the number of days from the date of first documented response to the earlier of death (from any cause) or progression. (If the duration does not correspond to the patient's death or progression then it is treated as right censored at the last tumour assessment).

The Variables (b), (c) and (e) will be analysed in a similar way as described for the primary efficacy parameter.

For the analysis of variables (a) and (d), the Fisher-Freemant-Halton test will be used to point out differences between the treatment groups. Additionally, pair-wise exact two-sided 95% CIs will be calculated on the difference in proportions between the groups. For each group, frequency tables containing the proportions by visit and treatment group will be prepared.

### **6.3.7 Explorative Endpoint**

The analysis of the extension arm will be performed by using the methods described for the analysis of the primary and secondary endpoint (except comparisons with the three treatment groups). The patients may enter the extension arm either due to objective disease progression during the chemotherapy or toxicity. The observations are left censored at the time point of patient's change from treatment arm B or C to the extension arm.

Additionally, the analysis of the extension arm will be performed for both causes, disease progression and toxicity, individually.

### **6.3.8 Safety**

The safety analysis will be based on the AST population.

Safety data from the scheduled treatment period will be used in the statistical analysis. The time-frame that will be used for the safety analysis of AEs will be the same as described in the efficacy section.

Listings of safety data not included in the analyses will be presented in the statistical appendix of the clinical trial report.

Any statistical comparison on changes from baseline on any of the safety parameters should be interpreted in a purely explorative sense. All tests will be performed two-sided and considered statistically significant if  $p \leq 0.05$ .

### **Adverse events**

All adverse events (AE and SAE) as described by the investigator(s) will be coded according to dictionary MedDRA (Version 5.1 or higher).

For any AE as described by the investigator(s) a dictionary low level term (LLT) will be chosen that best matches or approximates the investigator's actual description. These LLTs will be translated into more general terms (so-called preferred terms), which will be classified into system organ classes. The primary system organ class (related to the preferred terms) will be used unless there is a convention to use an alternate path.

If a patient has more than one AE and at least one of the AEs was considered drug-related, the patient will be counted as having a drug-related AE. If a patient has more than one AE and at least one of the AEs was considered severe, the patient will be counted as having a severe AE. The same AE (i.e., the same preferred term) reported more than once for a single patient will be counted as one AE. If an AE occurs more than once for a single patient, the AE with the highest reported relation to trial drug (worst case) will be used in the AE analysis.

An overview table will be presented with the number (and percentage) of patients with at least one AE, with at least one SAE, with AEs causing premature discontinuation, with AEs of known severe intensity, with drug-related AEs (according to the investigator) as well as the number of patients who died during the trial. The number (and percentage) of patients with at least one AE will be presented in a frequency table by body system and per dictionary preferred term within the various body systems by treatment group and relationship to trial drug.

### **Laboratory parameters**

The measurements of each laboratory parameter will be converted to Standard International (SI) units before the statistical analysis. For each laboratory parameter (including the absolute changes from baseline), descriptive statistics will be calculated by visit. The same calculations will be performed for the “minimal” and “maximal” change from baseline. In addition, the number and/or percentage of patients with at least one clinically significant value will be presented for each parameter.

### **Physical examination**

A physical examination will be performed at screening and at each following visit. For all time-points, the number of patients with at least one abnormal finding will be presented. In addition, the number of patients with abnormal findings will be presented by body system (according to dictionary MedDRA (version 5.1 or higher)) and visit.

### **Vital signs and body weight**

For each parameter (including the absolute changes from baseline), descriptive statistics will be calculated by visit. The same calculations will be performed for the “minimal” and “maximal” change from baseline. In addition, the number and/or percentage of patients with at least one clinically significant value will be presented for each parameter.

### **Additional measures of safety**

At screening and when clinically indicated, ECGs are to be performed.

Details about the analysis of the ECG parameters will be added. For both safety measurements, at least the number of patients with abnormal findings will be presented.

### **Special safety considerations**

Not applicable.

### **6.3.9 Interim analysis**

No interim analysis is planned.

## **7 STUDY MANAGEMENT**

### **7.1 Monitoring**

Before the initiation of the study, a representative of AstraZeneca or a company representing AstraZeneca will visit the investigational site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives

During the study, a CRA from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patients' records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (e.g. clinic charts)

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

### **7.2 Audits and inspections**

Authorised representatives of AstraZeneca, a regulatory authority, an IEC or an IRB may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and whether data were recorded, analysed and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if they are contacted by a regulatory agency about an inspection at their centre.

### **7.3 Training of staff**

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all these staff, and that they will receive any new information of relevance to the performance of this study.

### **7.4 Changes to the protocol**

Study procedures will not be changed without the mutual agreement of the international principal investigator(s) and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be notified to or approved by each IEC or IRB, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Written Informed Consent Form, AstraZeneca and the centre's IEC or IRB must be notified. Approval of the revised Written Informed Consent Form by AstraZeneca and by the IEC or IRB is required before the revised form can be used.

AstraZeneca will distribute amendments to the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IEC or IRB, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

## **7.5 Study agreements**

The principal investigator at each centre must comply with all the terms, conditions and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, the study protocol shall prevail.

## **7.6 Study timetable and termination**

The expected start date for this study is July 2003. Enrolment is expected to be completed by the end of May 2003 and the study is expected to be completed by the end of March 2005.

## **8 ETHICS REVIEW**

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favourable opinion in writing by an IEC or IRB as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The principal investigator(s) is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit patients for the study.

### **8.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

### **8.2 Patient information and consent**

The principal investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and should be allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study; see Sections 3 and 4 for study-specific procedures and measurements.

The principal investigator(s) must store the original, signed Written Informed Consent Form. A copy of the Written Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

### **8.3 Patient data protection**

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Patients in this database will be identified by initials or patient number only. The Written Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital or practice records relevant to the study, including patient medical history.

## 9 EMERGENCY PROCEDURES

### 9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the local Project Leader. If the local Project Leader is not available, contact the Study Team Physician or the local Drug Safety representative.

Role in the study	Name	Address and Telephone Number
Study Team Physician responsible for the Protocol	Dr. med. Madeleine Billeter	Tel: +41 41 725 76 00 AstraZeneca AG Grafenau 10 CH-6301 Zug
Project Leader responsible for the protocol at the MC	<p><b>Switzerland:</b> Verena Renggli AstraZeneca AG, Zug</p> <p><b>Germany:</b> Dr. med. Alexander Tolle AstraZeneca GmbH, Wedel</p> <p><b>Austria:</b> Herr Magister Andreas Baumgartner, AstraZeneca GmbH, Wien</p>	<p>Tel: +41 41 725 76 14 Fax: +41 41 725 71 57 Mobile + 41 79 214 43 24</p> <p>Tel: +49 4103 708 3508 Fax: +49 4103 708 7 3508 Mobile: +49 173 967 2254</p> <p>Tel: +43 171 131 360 Fax: +43 171 131 292 Mobile: +43 676 403 17 33</p>
Drug Safety representatives at the MC	<p><b>Switzerland:</b> Dr. med. Madeleine Billeter, AstraZeneca AG, Zug</p> <p><b>Germany:</b> Prof. Dr. med. Helmut Brasch, AstraZeneca GmbH, Wedel</p> <p><b>Austria:</b> Dr. Helmut Pauliny,, AstraZeneca GmbH, Wien</p>	<p>Tel: +41 41 725 76 00 Fax: +41 41 725 71 57 Mobile: +41 79 214 43 25</p> <p>Tel: +49 4103 708 3453 Fax: +49 4103 708 73453 Mobile: +49 173 967 2238</p> <p>Tel: +43 171 131 203 Fax: +43 171 131 292 Mobile: +43 676 681 60 02</p>

### 9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

### 9.3 Procedures in case of overdose

There is currently no known antidote for ZD1839. The treatment of AEs associated with overdose should be supportive and for the underlying adverse symptoms. To date, no patient has experienced an overdose with ZD1839.

Information on overdoses that do not result in AEs should be forwarded to the responsible CRA. This will then be reported to the AstraZeneca Drug Safety Group in accordance with procedures defined for non-SAEs.

### 9.4 Procedures in case of pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) however, must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

## 10 REFERENCES

1. American Society of Clinical Oncology (ASCO). Clinical Practice guidelines for the treatment of unresectable NSCLC. *Journal of Clinical Oncology* 1997; 15(8): 2996-3018.
2. Giaccone G, Gonzalez Larriba JL, Smit EF, Alfonso R, Van Oosterom AT, Martens M, Peters GJ, Van der Vijgh WJ, Smith R, Fandi I, Averbuch S. Combination therapy with ZD1839 (Iressa), an orally active, selective, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), gemcitabine and cisplatin, in patients with advanced solid tumours. *Clinical Cancer Research* 2001; 7 (11) (Suppl S): 3765S, Abs 553.
3. Herr HW, Shipley WU, Bajorin DF: Cancer of the bladder, in De Vita VT, Hellman S, Rosenberg SA (eds): *Cancer: Principles & Practice of Oncology* (6th Edition). Philadelphia, Lippincott Williams & Wilkins, 2001, pp1396-1418.
4. Investigator's Brochure, ZD1839.
5. Kaufman D, Raghavan D, Carducci M, Levine EG, Murphy B, Aisner J et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. *Journal Clinical Oncology* 2000; 18(9): 1921-7.
6. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics 1999. *CA Cancer Journal for Clinicians* 1999; 49(1): 8-31.
7. Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I et al. A randomized comparison of cisplatin alone or in combination with methotrexate,

- vinblastine and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *Journal Clinical Oncology* 1992; 10(7): 1066-73.
8. Logothesis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG et al. A prospective randomised trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumours. *Journal Clinical Oncology* 1990; 8(6): 1050-5.
  9. Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *Journal Clinical Oncology* 1997; 15(12): 3441-5.
  10. Moore MJ, Winquist EW, Murray N, Tannock IF, Huan S, Bennet K et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *Journal Clinical Oncology* 1999; 17(9): 2876-81.
  11. National Cancer Institute Common Toxicity Criteria version 2.0.
  12. Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *The EMBO Journal* 2000; 19 (13): 3159-167.
  13. Peters GJ, Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Braakhuis BJ. Interaction between cisplatin and gemcitabine in vitro and in vivo. *Seminars in Oncology* 1995; 22(suppl 11): 72-9.
  14. Sargent D, Goldberg R: A flexible design for multiple armed screening trials. *Statistics in Medicine* 20: 1051-1060, 2001.
  15. Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *Journal Clinical Oncology* 1997; 15(11): 3394-8.
  16. von der Maase H, Andersen L, Crino L, Weinknecht S, Dogliotti L. Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium: a phase II clinical trial. *Annals Oncology* 1999; 10(12): 1461-5.
  17. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomised, multinational, multicentre phase III study. *Journal Clinical Oncology* 2000; 18(17): 3068-77.
  18. Wadler S, Benson AB, Engelking C, Catalano R, Field M, Komblau SM, et al. Recommended guidelines for the treatment of chemotherapy-induced diarrhoea. *Journal Clinical Oncology* 1998; 16: 3169-78.

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**Clinical Study Protocol: Appendix A**

Study Code 1839IL/0063

Appendix Date 17 June 2003

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Final version 02

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**Appendix A**  
**Signatures**

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**ASTRAZENECA SIGNATURE(S) GERMANY**

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**AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

---

I agree to the terms of this study protocol

**AstraZeneca Study Team Physician  
responsible for the  
Protocol**

.....

Dr. med. Madeleine Billeter

Date

**AstraZeneca Marketing Company  
representative**

.....

Date

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**ASTRAZENECA SIGNATURE(S) AUSTRIA**

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**AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

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Dr. med. Madeleine Billeter

Date

**AstraZeneca Marketing Company  
representative**

.....

Date

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## **ASTRAZENECA SIGNATURE(S) SWITZERLAND**

---

### **AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

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**AstraZeneca Study Team Physician  
responsible for the  
Protocol**

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Dr. med. Madeleine Billeter

Date

**AstraZeneca Marketing Company  
representative**

.....

Date

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## SIGNATURE OF INTERNATIONAL PRINCIPAL INVESTIGATORS

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### AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM

---

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

**Centre No.:**

Dr. med. Rudolf Morant, Zentrum für Tumordiagnostik und Prävention (ZeTuP),  
9006 St. Gallen, Switzerland

**Signature:**

.....  
Date

**Centre No.:**

Prof. Dr. med. Manfred Wirth, Department of Urology,  
Universitätsklinikum Carl-Gustav-Carus der Technischen  
Universität Dresden, Fetscherstr. 74, 01307 Dresden,  
Germany

**Signature:**

.....  
Date

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## **SIGNATURE OF NATIONAL COORDINATING INVESTIGATOR**

---

### **AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

---

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

**Centre No.:**

**Signature:**

.....  
Prof. Dr.med.Kurt Miller  
Universitätsklinikum Benjamin Franklin  
Urologische Klinik  
Hindenburgdamm 30  
D-12200 Berlin

.....  
Date

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## **SIGNATURE OF NATIONAL COORDINATING INVESTIGATOR**

---

### **AN OPEN-LABEL, RANDOMISED, PARALLEL GROUP, NON-COMPARATIVE PHASE II STUDY OF GEMCITABINE, CISPLATIN AND TWO DOSES OF ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM**

---

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

**Centre No.:**

**Signature:**

.....  
Dr. med. Rudolf Morant  
Zentrum für Tumordiagnostik  
und Prävention (ZeTuP),

.....  
Date

CH- 9006 St.Gallen

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**Clinical Study Protocol: Appendix B**

Study Code 1839IL/0063

Appendix date 17 June 2003

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Final version 02

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**Appendix B**  
**Study administrative structure**

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## ASTRAZENECA STUDY PERSONNEL

<b>Address</b>	<b>Name (First name, Last name)</b>	<b>Qualifications</b>	<b>Position</b>	<b>Role in the study</b>
AstraZeneca AG, 6301 Zug, Switzerland	Madeleine Billeter	MD	Medical Director, AZ Switzerland	Responsible for the protocol
AstraZeneca AG, 6301 Zug, Switzerland	Verena Renggli	dipl. pharm.	Medical Services Manager, Oncology AZ Switzerland	Overall Study Co-ordinator
AstraZeneca GmbH, Wedel, Germany	Alexander Tolle	MD	Project Leader Oncology, AZ Germany	Study Co-ordinator, Germany
AstraZeneca AG, 6301 Zug, Switzerland	Madeleine Billeter	MD	Drug Safety Physician	Drug Safety, Switzerland
AstraZeneca GmbH, Wedel, Germany	Helmut Brasch	MD	Drug Safety Physician	Drug Safety, Germany
AstraZeneca, Wien, Austria	Helmut Pauliny	PhD	Medical Director, AZ Austria	Drug Safety, Austria
AstraZeneca, Wien, Austria	Andreas Baumgartner	Mag.	Project Leader, AZ Austria	Study Co-ordinator, Austria
AstraZeneca, Germany	Kai Vogtländer		Project Statistician	Biostatistician

## **OTHER PARTICIPANTS**

---

<b>Organization and address</b>	<b>Name (First name, Last name)</b>	<b>Qualifications/Position</b>	<b>Role in study</b>
SKM Oncology Research GmbH, D-65183 Wiesbaden, Germany	Renate Walter-Kirst		CRO

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**Clinical Study protocol: Appendix C**

Study Code 1839/0063

Appendix date 17 June 2003

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Final Version 02

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**Appendix C**  
**Additional safety information**

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## **FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)**

### **Life threatening**

‘Life-threatening’ means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. ‘Life-threatening’ does not mean that had an adverse event occurred in a more severe form it might have caused death (i.e. hepatitis that resolved without hepatic failure).

### **Hospitalisation**

Out-patient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

### **Important medical event or medical intervention**

Medical and scientific judgement should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity, but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Examples of such events are:

- Angio-oedema not severe enough to require intubation but requiring iv. hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g. neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

## FURTHER GUIDANCE ON THE ASSESSMENT OF CAUSALITY

The following factors should be considered when deciding if there is a “reasonable possibility” that an adverse event (AE) may have been caused by the investigational product.

- **Time course of events and exposure to suspect drug.** Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- **Consistency with known drug profile.** Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- **Dechallenge experience.** Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- **No alternative cause.** The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- **Rechallenge experience.** Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- **Laboratory tests.** Has a specific laboratory investigation confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this.

**Any events that are unequivocally because of progression of disease need not be reported as an adverse event**

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**Clinical Study protocol: Appendix D**

Study Code 1839IL/0063

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Final Version 02

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**Appendix D**  
**Objective tumour response criteria (RECIST)**

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## 1. INTRODUCTION

The introduction explores the definitions, assumptions, and purposes of tumour response criteria. Below, guidelines that are offered may lead to more uniform reporting of outcomes of clinical trials. Note that although single investigational agents are discussed, the principles are the same for drug combinations, non-investigational agents, or approaches that do not involve drugs.

Tumour response associated with the administration of anticancer agents can be evaluated for at least three important purposes that are conceptually distinct:

- Tumour response as a prospective end point in early clinical trials. In this situation, objective tumour response is employed to determine whether the agent/regimen demonstrates sufficiently encouraging results to warrant further testing. These trials are typically phase II trials of investigational agents/regimens (*see* section 1.2), and it is for use in this precise context that these guidelines have been developed.
- Tumour response as a prospective end point in more definitive clinical trials designed to provide an estimate of benefit for a specific cohort of patients. These trials are often randomised comparative trials or single-arm comparisons of combinations of agents with historical control subjects. In this setting, objective tumour response is used as a surrogate end point for other measures of clinical benefit, including time to event (death or disease progression) and symptom control (*see* section 1.3).
- Tumour response as a guide for the clinician and patient or study subject in decisions about continuation of current therapy. This purpose is applicable both to clinical trials and to routine practice (*see* section 1.1), but use in the context of decisions regarding continuation of therapy is not the primary focus of this document.

However, in day-to-day usage, the distinction among these uses of the term "tumour **response**" can easily be missed, unless an effort is made to be explicit. When these differences are ignored, inappropriate methodology may be used and incorrect conclusions may result.

### 1.1. Response outcomes in daily clinical practice of oncology

The evaluation of tumour response in the daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgement that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined criteria developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to make a distinction between "clinical improvement" and "objective tumour response" in routine patient management outside the context of a clinical trial.

### 1.2. Response outcomes in uncontrolled trials as a guide to further testing of a new therapy

"Observed response rate" is often employed in single-arm studies as a "screen" for new anticancer agents that warrant further testing. Related outcomes, such as response duration or proportion of patients with complete responses, are sometimes employed in a similar fashion. The utilisation of a response rate in this way is not encumbered by an implied assumption about the therapeutic benefit of such responses, but rather implies some degree of biologic antitumour activity of the investigated agent.

For certain types of agents (i.e. cytotoxic drugs and hormones), experience has demonstrated that objective antitumour responses observed at a rate higher than would have been expected to occur spontaneously can be useful in selecting anticancer agents for further study. Some agents selected in this way have eventually proven to be clinically useful. Furthermore, criteria for "screening" new agents in this way can be modified by accumulated experience and eventually validated in terms of the efficiency by which agents so screened are shown to be of clinical value by later, more definitive, trials.

In most circumstances, however, a new agent achieving a response rate determined *a priori* to be sufficiently interesting to warrant further testing may not prove to be an effective treatment for the studied disease in subsequent randomised phase III trials. Random variables and selection biases, both known and unknown, can have an overwhelming effect in small, uncontrolled trials. These trials are an efficient and economic step for initial evaluation of the activity of a new agent or combination in a given disease setting. However, many such trials are performed, and the proportion that will provide false-positive results is necessarily substantial. In many circumstances, it would be appropriate to perform a second small confirmatory trial before initiating large resource-intensive phase III trials.

Sometimes, several new therapeutic approaches are studied in a randomised phase II trial. The purpose of randomisation in this setting, as in phase III studies, is to minimise the impact of random imbalances in prognostic variables. However, randomised phase II studies are, by definition, not intended to provide an adequately powered comparison between arms (regimens). Rather, the goal is simply to identify one or more arms for further testing, and the sample size is chosen so to provide reasonable confidence that a truly inferior arm is not likely to be selected. Therefore, reporting the results of such randomised phase II trials should not imply statistical comparisons between treatment arms.

### **1.3. Response outcomes in clinical trials as a surrogate for palliative effect**

#### **1.3.1 Use in nonrandomised clinical trials.**

The only circumstance in which objective responses in a nonrandomised trial can permit a tentative assumption of a palliative effect (i.e. beyond a purely clinical measure of benefit) is when there is an actual or implied comparison with historical series of similar patients. This assumption is strongest when the prospectively determined statistical analysis plan provides for matching of relevant prognostic variables between case subjects and a defined series of control subjects. Otherwise, there must be, at the very least, prospectively determined statistical criteria that provide a very strong justification for assumptions about the response rate that would have been expected in the appropriate "control" population (untreated or treated with conventional therapy, as fits the clinical setting). However, even under these circumstances, a high rate of observed objective response does not constitute proof or confirmation of clinical therapeutic benefit. Because of unavoidable and nonquantifiable biases inherent in nonrandomised trials, proof of benefit still requires eventual confirmation in a prospectively randomised, controlled trial of adequate size. The appropriate end points of therapeutic benefit for such a trial are survival, progression-free survival, or symptom control (including quality of life).

#### **1.3.2. Use in randomised trials.**

Even in the context of prospectively randomised phase III comparative trials, "observed response rate" should not be the sole, or major, end point. The trial should be large enough that differences in response rate can be validated by association with more definitive end points reflecting therapeutic

benefit, such as survival, progression-free survival, reduction in symptoms, or improvement (or maintenance) of quality of life.

## **2. MEASURABILITY OF TUMOUR LESIONS AT BASELINE**

### **2.1. Definitions**

At baseline, tumour lesions will be categorised as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as 20 mm with conventional techniques or as 10 mm with spiral CT scan [*see* section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(*Note:* Tumour lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

### **2.2. Specifications by methods of measurements**

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

#### **2.2.1 Clinical examination**

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography—including a ruler to estimate the size of the lesion—is recommended.

#### **2.2.2 Chest x-ray**

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

#### **2.2.3 CT and MRI**

CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-

mm contiguous reconstruction algorithm; this specification applies to the tumours of the chest, abdomen, and pelvis, while head and neck tumours and those of the extremities usually require specific protocols.

#### **2.2.4 Ultrasound**

When the primary end point of the study is objective response evaluation, ultrasound should not be used to measure tumour lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Justifications for not using ultrasound to measure tumour lesions for objective response evaluation are provided in Appendix C.

#### **2.2.5 Endoscopy and laparoscopy**

The utilisation of these techniques for objective tumour evaluation has not yet been fully or widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may be available only in some centres. Therefore, utilisation of such techniques for objective tumour response should be restricted to validation purposes in specialised centres. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

#### **2.2.6 Tumour markers**

Tumour markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumour lesions have disappeared. Specific additional criteria for standardised usage of prostate-specific antigen and CA (cancer antigen) 125 response in support of clinical trials are being validated.

#### **2.2.7 Cytology and histology**

Cytologic and histologic techniques can be used to differentiate between partial response and complete response in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumour response will be integrated into these criteria when they are fully validated to be used in the context of tumour response evaluation.

### **3. TUMOUR RESPONSE EVALUATION**

#### **3.1. Baseline evaluation**

##### **3.1.1 Assessment of overall tumour burden and measurable disease**

To assess objective response, it is necessary to estimate the overall tumour burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in

section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

### **3.1.2 Baseline documentation of "target" and "nontarget" lesions**

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

## **3.2. Response criteria**

### **3.2.1 Evaluation of target lesions**

This section provides the definitions of the criteria used to determine objective tumour response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

### **3.2.2 Evaluation of nontarget lesions**

This section provides the definitions of the criteria used to determine the objective tumour response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalisation of tumour marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumour marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

(*Note:* Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair]).

### **3.2.3 Evaluation of best overall response**

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (*see* section 3.3.1). Table provides overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions.

(*Notes:*

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.
- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.)

### 3.2.4 Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e. 6-8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the phase II trial has, as a goal, the response rate or the time to an event (disease progression/death). If time to an event is the main end point of the study, then routine re-evaluation is warranted of those patients who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

**Table 1.** Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions\*

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

\* CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

### 3.3. Confirmatory measurement/duration of response

### 3.3.1 Confirmation

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomised trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol (*see* section 3.3.3).

(*Note:* Repeat studies to confirm changes in tumour size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, patients will not have "confirmed response." This distinction should be made clear when reporting the outcome of such studies.)

### 3.3.2 Duration of overall response

The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

### 3.3.3 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

(*Note:* The duration of response or stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency that should take into account many parameters, including disease types and stages, treatment periodicity, and standard practice. However, these limitations to the precision of the measured end point should be taken into account if comparisons among trials are to be made.)

## 3.4 Progression-free survival/time to progression

This document focuses primarily on the use of objective **response** end points. In some circumstances (e.g. brain tumours or investigation of noncytoreductive anticancer agents), response evaluation may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, progression-free survival/time to progression can be considered valuable alternatives to provide an initial estimate of biologic effect of new agents that may work by a noncytotoxic mechanism. It is clear though that, in an uncontrolled trial proposing to utilise

progression-free survival/time to progression, it will be necessary to document with care the basis for estimating what magnitude of progression-free survival/time to progression would be expected in the absence of a treatment effect. It is also recommended that the analysis be quite conservative in recognition of the likelihood of confounding biases, e.g. with regard to selection and ascertainment. Uncontrolled trials using progression-free survival or time to progression as a primary end point should be considered on a case-by-case basis, and the methodology to be applied should be thoroughly described in the protocol.

#### 4. RESPONSE REVIEW

For trials where the response rate is the primary end point, it is strongly recommended that all responses be reviewed by an expert or experts independent of the study at the study's completion. Simultaneous review of the patients' files and radiologic images is the best approach.

(*Note:* When a review of the radiologic images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer[s]).

#### 5. REPORTING OF RESULTS

All patients included in the study must be assessed for **response** to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete **response**, 2) partial **response**, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note:* By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility **criteria** should be included in the main analysis of the **response** rate. Patients in **response** categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the **response** rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g. early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

#### 6. RESPONSE EVALUATION IN RANDOMISED PHASE III TRIALS

Response evaluation in phase III trials may be an indicator of the relative antitumour activity of the treatments evaluated but may usually not solely predict the real therapeutic benefit for the population studied. If objective response is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumour response and a real therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applicable to phase II trials (RECIST guidelines) should be used.

On the other hand, some of the guidelines presented in this special article might not be required in trials, such as phase III trials, in which objective response is *not* the primary end point. For example, in such trials, it might not be necessary to measure as many as 10 target lesions or to confirm response with a follow-up assessment after 4 weeks or more. Protocols should be written clearly with respect to planned response evaluation and whether confirmation is required so as to avoid *post-hoc* decisions affecting patient evaluability.

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**Clinical Study protocol: Appendix E**

Study Code 1839IL/0063

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Final Version 02

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**Appendix E**  
**Cockcroft formula for calculating creatinine clearance**

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## **Cockroft formula to calculate the estimated creatinine clearance**

**Warning :** in obesity patients Cockroft formula can provide an overestimation of creatinine clearance.

### **For serum creatinine values in mg/dl:**

Men:  $\text{CrCl (ml/min)} = [(140 - \text{age}) \times \text{weight (kg)}] / [72 \times \text{serum creatinine (mg/dl)}]$

Women:  $\text{CrCl (ml/min)} = [(140 - \text{age}) \times \text{weight (kg)} \times 0.85] / [72 \times \text{serum creatinine (mg/dl)}]$

### **For serum creatinine values in $\mu\text{mol/l}$ :**

Men:  $\text{CrCl (ml/min)} = [1.23 \times (140 - \text{age}) \times \text{weight (kg)}] / [\text{serum creatinine } (\mu\text{mol /l)}]$

Women:  $\text{CrCl (ml/min)} = [1.04 \times (140 - \text{age}) \times \text{weight (kg)} \times 0.85] / [\text{serum creatinine } (\mu\text{mol /l)}]$

### **Reference:**

Cockroft DW, Gault HM. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976 (16): 31-41.

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