AstraZeneca

Amended Clinical Study Protocol

Drug Substance	AZD8931
Study Code	D0102C00002
Edition Number	3
Date	

A Phase I, Open-label, Multiple-dose, Dose-escalation Study To Assess the Safety, Tolerability and Pharmacokinetics of AZD8931 in Patients with Advanced Solid Malignancies

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment
1	
2	
3	

Administrative Change No.	Date of Administrative Change

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency you should contact the Medical Monitor. If the Medical Monitor is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	**Name**	**Address and Telephone number**
(Contract Research Organisation [CRO])		
Medical Monitor		
AstraZeneca Medical Contact		
24-hour emergency cover at central R&D site.		
AstraZeneca and/or CRO personnel are available for guidance and discussion of study-specific implications of the emergency. The responsibility of managing any emergency is the sole responsibility of the investigator/ investigator teams.		

For further clarifications regarding:

- Procedures in case of medical emergency, see Section 8.2.
- Procedures in case of overdose, see Section 8.3.
- Procedures in case of pregnancy, see Section 8.4.

For details of serious adverse event (SAE) reporting, refer to Section 4.7.1.3.

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PROTOCOL SYNOPSIS

A Phase I, Open-label, Multiple-dose, Dose-escalation Study To Assess the Safety, Tolerability and Pharmacokinetics of AZD8931 in Patients with Advanced Solid Malignancies

Investigator

The principal investigator is

The Leiter der Klinischen Prüfung (LKP) for this study is

Details of all sites, investigators and related study personnel are documented in the study files.

Study centre(s), type and number of subjects planned

The AZD8931 study will be conducted in approximately 30 patients with advanced solid malignancies, in approximately 5 dose groups of 3 to 6 evaluable patients, recruited from approximately 4 to 6 centres in Russia and Germany during a recruitment period of approximately 10 months. It is planned to recruit approximately 5 to 8 evaluable patients at each centre.

Optional blood samples will be collected for pharmacogenetic research. No planned number of patients is required for this genetic research. The samples will be stored and may be analysed for future research. Patients from all centres are eligible to participate in the pharmacogenetic research.

Study period

Estimated date of first patient enrolled

Estimated date of last patient completed March 2009

Objectives

The primary objective of this study is:

- To explore the safety and tolerability of multiple ascending doses (MAD) of AZD8931 in patients with advanced solid malignancies, by evaluation of adverse events (AEs), laboratory findings, physical examinations, vital signs, cardiac monitoring, and ophthalmological assessments.

The secondary objectives of this study are:

- To identify the maximum tolerated dose (MTD) of AZD8931 following repeated twice daily administration, by assessment of dose-limiting toxicities (DLT)
- To explore the pharmacokinetics (PK) of single doses of AZD8931 in patients with advanced solid malignancies
- To explore the PK of multiple doses of AZD8931 in patients with advanced solid malignancies

Exploratory objectives of this study are:

- To measure cell death biomarkers from blood samples to examine the relationship to treatment with AZD8931 (optional).
- To obtain a blood sample for host pharmacogenetics for deoxyribonucleic acid (DNA) extraction and archiving (optional).
- To obtain preliminary assessments of the efficacy of AZD8931 (including Response Evaluation Criteria In Solid Tumours [RECIST] criteria and change in tumour length).

Study design

This study is an open-label, multiple ascending dose (MAD) study to explore the safety and tolerability of AZD8931. In each dose group each patient will receive initial treatment with a single dose of AZD8931, followed by a 4-day observation period then a 21 day treatment period with twice daily dosing starting between Day 5 and Day 7.

Patients will be evaluable for the dose escalation set if they have experienced a DLT, or received at least 80% of planned doses of AZD8931 and who had all safety assessments completed during the DLT evaluation period.

A minimum of 3 and a maximum of 6 eligible patients will be dosed initially. At the discretion of the SMC, or if a patient within a dose cohort experiences a DLT additional patients will be enrolled to ensure that the cohort includes a maximum of 6 evaluable patients. The dose may be escalated in the next cohort if the SMC declares the dose level in the current

cohort as tolerable. The dose level in the current cohort is defined as intolerable according to the algorithm in Section 3.1.2.

The dose of AZD8931 will initially be escalated by dose doubling, up to a level where the SMC decides that smaller escalation steps are warranted. Based on emerging data including PK and/or safety data and/or pre-clinical data, the SMC can consider alternative schedules including once-daily dosing and intermediate dose levels. There will be adequate time between dose groups to allow review of relevant safety and PK data by the SMC.

Target patient population

Adult patients with advanced solid malignancies will be eligible for enrolment into this study.

Investigational product, dosage and mode of administration

AZD8931 is available as four strengths of plain, round, biconvex, white film coated tablets containing 2.5 mg, 10 mg, 40 mg and 100 mg of AZD8931 (expressed as free base). Tablets to be taken orally.

The starting dose will be 40 mg, based on the results of the single ascending dose (SAD) study, D0102C00001.

Dosing will be once only on Day 1, followed by a 4-day observation period. Multiple dosing can start between Day 5 and Day 7, and will be twice daily for 21 days (days R1 to R21). For example, if the dose level is 40 mg, the patient will receive 40 mg on Day 1 (D1), then 40 mg twice daily (total 80 mg per day) on Days R1 to R21.

AZD8931 should continue to be administered beyond the DLT evaluation period if, in the investigators opinion, the patient is experiencing or may receive some benefit from therapy, is free from intolerable toxicity and has not met a discontinuation criterion.

Safety Monitoring Committee

When the last patient in a dose level cohort has completed the DLT evaluation period the SMC will evaluate available safety and PK data from that cohort. Dose escalation will proceed only if the SMC confirms that it is safe to do so.

Variables

- **Safety**
  - AEs
  - Laboratory findings (refer to Sections 4.4.1 and 4.7.1.2)
  - Physical examination
  - Vital signs

- Cardiac monitoring (including 12-lead electrocardiograms [ECGs] and echocardiography)

- Dermatological examinations

- Ophthalmological examinations (including visual acuity, Schirmer's test, slit-lamp examination, pupil dilation and intraocular pressure measurements [if considered appropriate by investigator]).

For definition of DLT, refer to Section 3.1.5.

- Pharmacokinetics

PK of AZD8931 will be investigated after both single and multiple doses

- Single dose plasma PK, including area under the plasma concentration-time curve from time zero to 12 hours (AUC_{0-12}), 24 hours (AUC_{0-24}), time t (AUC_{0-t}) and infinity (AUC) after dosing, maximum plasma drug concentration (C_{max}), time to reach the maximum plasma drug concentration (t_{max}), terminal elimination half-life ($t_{1/2}$), total apparent drug clearance (CL/F), and apparent volume of distribution (V/F)

- Multiple dose plasma PK, time to ss and assessment of any accumulation of AZD8931, including $AUCss_{0-12}$, Css_{max}, tss_{max}, CLss/F, minimum plasma concentration at ss (Css_{min}), accumulation ratio (R_{AC}) and linearity factor

Other PK parameters may be determined if deemed appropriate.

- Exploratory

- Correlation of cell death (proapoptotic) biomarkers with AZD8931 therapy (optional)

- Optional pharmacogenetic sampling (blood sample) for DNA extraction and archiving

- Objective Response Rate (ORR) and Best Overall Response (based on RECIST) for patients with measurable disease, or other measures of efficacy in patients with non-measurable disease.

Statistical methods

Outcome variables will be listed and summarised using descriptive statistics, as appropriate. No formal hypotheses will be associated with these variables.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACE	Angiotensin-converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under plasma concentration-time curve from time zero to infinity
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to 12 hours
$AUCss_{0-12}$	Area under the plasma concentration-time curve from time zero to 12 hours at steady state
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{0-t}	Area under plasma concentration-time curve from time zero to the last quantifiable concentration
BP	Blood pressure
CL/F	Total apparent drug clearance
CLss/F	Total apparent drug clearance at steady state
C_{max}	Maximum plasma concentration
Css_{max}	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
Css_{min}	Minimum plasma concentration at steady state
CR	Complete response
CRF	Case report form
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediamine-tetra-acetic acid

Abbreviation or special term	Explanation
ELISA	Enzyme-linked immunosorbent assay
ErbB2	Human epidermal growth factor receptor type 2 (also known as HER2)
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
EGFR	Epidermal growth factor receptor type 1 (also known as ErbB1)
GCP	Good Clinical Practice
H&N	Head and neck
HIV	Human immunodeficiency virus
IB	Investigator brochure
IC_{50}	Concentration for 50% inhibition
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IUD	Intrauterine device
λ_z.	Terminal elimination rate constant
LIMS	Laboratory Information Management System
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OAE	Other significant adverse event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1).
ORR	Objective Response Rate
pCRF	Paper case report form
PD	Progression of disease
PK	Pharmacokinetic(s)
PR	Partial response

Abbreviation or special term	Explanation
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study centre has a principal investigator.
QRS	QRS complex is a structure on the ECG that corresponds to the depolarisation of the ventricles
QT	Interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	QT-interval corrected for heart rate according to the Bazett method
QTcF	QT-interval corrected for heart rate according to the Fridericia method
R#	Repeat dosing day (number)
R_{AC}	Accumulation ratio
RECIST	Response Evaluation Criteria In Solid Tumours
RR	Interval from the onset of one QRS complex to the onset of the next QRS complex.
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SLE	Systemic lupus erythematosus
SMC	Safety Monitoring Committee
SPF	Sun protection factor
ss	Steady state
$t_{1/2}$	Terminal elimination half-life
TBUT	Tear break-up time test
t_{max}	Time to reach maximum plasma concentration
tss_{max}	Time to reach maximum plasma concentration at steady state
TNM	Tumour, node, metastases
ULN	Upper limit of normal
Vss/F	Apparent volume of distribution at steady state
WHO	World Health Organization

1. INTRODUCTION

AZD8931 is a selective, oral, adenosine triphosphate (ATP) competitive inhibitor of the tyrosine kinase domain of epidermal growth factor receptor type 1 (EGFR; also known as ErbB1) and human epidermal growth factor receptor type 2 (ErbB2; also known as HER2), in development for the treatment of solid tumours.

The broad clinical objectives of AZD8931 in early clinical development will include determination of safety, tolerability and initial pharmacokinetics (PK) of AZD8931 administered as an oral formulation, as well as identification of early signals of clinical activity. It is also planned to perform a similar phase I study in Japan.

1.1 Background

The EGFR family has been identified as a promising target for anti-cancer therapy. The family includes four members; EGFR/ErbB1, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4. All members have an extra-cellular ligand-binding domain, a single membrane-spanning domain and a cytoplasmic-tyrosine kinase domain.

The ErbB family is bound by the epidermal growth factor (EGF) family of ligands which can be divided into three groups: the first includes EGF, transforming growth factor-α and amphiregulin, which bind specifically to EGFR; and the second includes betacellulin, heparin-binding EGF (HB-EGF) and epiregulin, which show dual specificity, binding both EGFR and ErbB4. The third group is composed of the neuregulins or heregulins (NRGs or HRG) and forms two subgroups based on their capacity to bind ErbB3 and ErbB4 (NRG1 and NRG2) or only ErbB4 (NRG3 and NRG4). EGFR is primarily activated via heterodimerisation, induced following ligand binding (Hynes and Lane 2005). ErbB2 is peculiar in that it lacks any ligand binding capacity, whereas ErbB3 is intrinsically kinase inactive and becomes activated only following heterodimerisation and cross-phosphorylation by another ErbB receptor. In the case of ErbB2, activation may arise via a) overexpression (gene amplification) inducing homodimerisation and b) heterodimerisation with another family member, from which ErbB3 is considered to be the preferable and most oncogenic partner. ErbB2 receptor heterodimerisation is induced by ligands such as HRG, which specifically binds to ErbB3, exposing its heterodimerisation domain (arm), which then interacts with that of ErbB2. ErbB2 itself maintains a constantly extended heterodimerisation arm.

Ligand binding to the ErbB receptors induces receptor homo- and hetero-dimerisation, leading to phosphorylation of critical sites in the tyrosine kinase domain, and subsequent activation of downstream pathways involved in cellular proliferation and survival (Olayioye et al 2000).

ErbB2 is the preferred dimerisation partner, as ErbB2-containing dimers exert the most potent mitogenic signal (Giuliani et al 2007, Graus Porta et al 1997). ErbB2 is expressed in a variety of epithelial cell types in the gastrointestinal tract, respiratory, reproductive and urinary tracts, skin and breast. In general, expression levels are higher in foetal tissues than in adult tissues (Press et al 1990). There is also evidence of a role for ErbB2 in cardiac development

(Hudelist et al 2006, Hynes and Lane 2005, Lee et al 1995). In contrast EGFR is expressed in all epithelial and stromal cells as well as in some glial cells and smooth muscle cells, but it is not found in haematopoietic cells. Growth factor-induced EGFR signalling is important in many normal cellular processes in adult tissues, with effects including cell proliferation, cell migration and cell differentiation.

Aberrant EGFR and ErbB2 activity has been identified in a number of human malignancies and is notable for its association with a more aggressive disease course and poor clinical outcome (Sjogren et al 1998; Nicholson et al 2001). In human tumours, activation occurs through receptor over-expression, autocrine growth factor loops, or the presence of activating mutations in the kinase domain (Voldborg et al 1997).

EGFR activation is seen in tumour types such as non-small cell lung cancer (NSCLC), breast, colorectal, and head and neck (H&N) cancer. Over-expression of ErbB2 is seen in a proportion of breast, ovarian, bladder, and gastric malignancies.

Therapeutic approaches to EGFR/ErbB2 signalling pathways include the use of monoclonal antibodies targeting the extra-cellular domain (eg, trastuzumab [Herceptin®, Roche] and cetuximab [Erbitux®, Merck]) and small molecule EGFR tyrosine kinase inhibitors (eg, gefitinib [Iressa™ [1]] and erlotinib (Tarceva®, Genentech Incorporated, OSI Pharmaceuticals, Incorporated). More recently, dual tyrosine kinase inhibitors, with the ability to inhibit the tyrosine kinase domain of both EGFR and ErbB2, have been generated. The reversible dual tyrosine kinase inhibitor, lapatinib (Tykerb, GlaxoSmithKline) has shown activity in pre-treated patients (Arteaga 2007, DiGiovanna et al 2005, El-Rehim et al 2004, Geyer et al 2006), and has been approved for use in combination with capecitabine (Xeloda™, Roche) for advanced metastatic breast cancer that is ErbB2 positive.

The role of EGFR, ErbB2 and ErbB3 in cancer is well documented. The significance of ErbB4 in carcinogenesis is still very unclear. In breast cancer, expression of the individual receptors has been shown to correlate with poor prognosis which worsens when more than one ErbB receptor is expressed (Slamon et al 1987; Slamon et al 1989; Thor et al 2000; El-Rehim et al 2004; DiGiovanna et al 2005). In addition, pre-clinical and clinical evidence indicate that blocking all family members may be necessary in order to effectively block signalling via these receptors. Even if individual EGFR (eg, by Iressa) or ErbB2 (eg, by Herceptin) activation is inhibited, signalling and activation is rescued by the presence of another ErbB receptor or ligands (Olayioye et al 2000; Giuliani et al 2007; Smith et al 2004; Tovey et al 2006; Arteaga 2007; Hudelist et al 2006). None of the ErbB targeted agents currently undergoing clinical evaluation has conclusively demonstrated that they can effectively and simultaneously inhibit EGFR, ErbB2 and ErbB3 receptor activation in relevant clinical settings. Our pre-clinical work has demonstrated that AZD8931 is able to potently inhibit the activation of these receptors whether constitutively or ligand-induced.

[1] IRESSA™ is a trademark of the AstraZeneca group of companies.

Pre-clinical evidence indicates that in tumours the ErbB3 receptor is the ErbB family member coupled to the PI3K/Akt survival pathway, inhibition of which leads to apoptosis. The drug exposure required to induce apoptosis through this pathway in tumours has not been identified (Hsieh and Moasser 2007, Sergina et al 2007).

In vitro studies to clarify the pharmacology of AZD8931 and, more specifically, how the mechanism of action of this dual EGFR/ErbB2 inhibitor differs from that of agents that are selective inhibitors of either EGFR or ErbB2, have indicated that AZD8931 is much more potent in inhibiting activated ErbB2/ErbB3 heterodimers, formed in the presence of ligand, than any of the other agents. Effects on cellular proliferation mirrored the effects on phosphorylation by AZD8931, gefitinib and a selective ErbB2 inhibitor, with AZD8931 always being more potent.

AZD8931 is being developed with the expectation that, as an inhibitor of both EGFR and ErbB2 receptor kinases, it will provide superior efficacy compared to currently available inhibitors of either target alone by specifically inhibiting the signals through the more potent heterodimers.

Relevant preclinical data for AZD8931 are presented in the current investigator brochure (IB).

1.1.1 Non-clinical studies

1.1.1.1 Pharmacology

AZD8931 inhibited the activity of ErbB2 and EGFR kinase in in-vitro isolated enzyme assays and in screening kinase panels, and inhibited auto-phosphorylation in cellular assays, with an activity in the nM range. AZD8931 demonstrated at least 100-fold selectivity towards ErbB2 and EGFR over other kinase enzymes in a screening panel of >200 protein kinases.

AZD8931 inhibited the growth of a wide range of tumour cell lines that depend on ErbB2 and EGFR signalling. Treatment of mice and rats bearing a variety of xenografted tumours, including breast, lung, gastric and prostate carcinomas, with AZD8931 resulted in dose-dependent inhibition of tumour growth at well tolerated doses, and produced regressions in some models. AZD8931 at 105 and 53 μmol/kg (50 and 25 mg/kg) produced dose-dependent inhibition of EGFR (88% and 67%) and ErbB2 (90% and 59%) phosphorylation in BT474C tumour xenografts.

1.1.1.2 Pharmacokinetics

Following intravenous administration to male and female rats, the volume of distribution and clearance of AZD8931 were moderate, resulting in a half-life of 0.7 hours to 2.3 hours. Oral bioavailability was low to moderate, ranging from 21% to 41%. The oral half-life of parent compound was approximately 2 hours. Female exposure tended to be greater than males, the result of lower clearance. The protein binding of [^{14}C]AZD8931 was in the range 93.7% to 98.2% in all species. In a rat quantitative whole-body autoradiography study, radioactivity was widely distributed to all tissues with the exception of the brain. At 3 hours post-dose in male rats, the highest concentrations of radioactivity were associated with the uveal tract,

kidney, liver, spleen, Harderian gland, mesenteric lymph gland, pituitary, preputial gland and intestine wall of pigmented animals. The elimination of radioactivity was generally rapid. However, in pigmented tissues (uveal tract, skin, meninges) radioactivity was only slowly eliminated; in the uveal tract concentrations decreased by less than 25% over the course of 14 days.

In hepatocytes from rat, dog and human, metabolism was primarily to hydroxylated and dealkylated products with conjugation to a range of glucuronide and sulphate conjugates. In vivo in the rat, the main circulating components in addition to parent compound were a de-methylated metabolite and its corresponding sulphate conjugate. The de-methylated metabolite was also the major metabolite observed in excreta. The excretion of radioactivity following intravenous and oral administration of [^{14}C]AZD8931 has been investigated in the male and female rat. The vast majority of radioactivity was recovered principally within the first 24 hours of dosing. The majority of the radioactivity was recovered in faeces.

AZD8931 did not show a marked potential for clinically relevant inhibition of any major cytochrome P (CYP) isoform. There was some evidence for time-dependent inhibition of CYP3A4 but this was equivocal. In a 14-day toxicity study in rats and a 1-month toxicity study in dogs, there was no evidence of induction of CYPs measured ex vivo by enzyme-linked immunosorbent assay (ELISA). In contrast, in the dog, there was a reduction in CYP2B11 and 3A12 protein levels in the high dose group animals.

1.1.1.3 Toxicology

A core battery of safety pharmacology and genetic toxicology studies, in addition to toxicology studies in rats and dogs, have been conducted with AZD8931. A brief summary of the key findings is outlined below.

AZD8931 was not mutagenic in the Ames test or in the mouse lymphoma assay, and was not clastogenic in an in vivo micronucleus assay in the rat. Carcinogenicity studies have not been conducted.

In rats, repeated administration of AZD8931 was associated with dose-related widespread degenerative and atrophic changes, particularly in epithelial tissues, consistent with the pharmacology of the compound. These included changes in skin, stomach, intestine, oesophagus, salivary gland, kidney, female reproductive tract and eye. Gastrointestinal toxicity was dose limiting. Reactive responses to these changes were seen in the haematopoietic and lymphoreticular systems. A no observed adverse effect level (NOAEL) in rats after dosing for 1 month was 10 μmol/kg/day (4.74 mg/kg/day).

In dogs, the dose-limiting toxicity (DLT) following repeated administration of AZD8931 was corneal epithelial ulceration. Pharmacologically-related histopathology changes were seen in the eye, lacrimal gland, the digestive tract (salivary glands, tongue, oesophagus, stomach and small intestine), skin and/or eyelids and urinary bladder. The NOAEL in dogs after dosing for 1 month was 3 μmol/kg/day (1.4 mg/kg/day), which was also a no effect dose level for ophthalmology changes and corneal epithelial ulceration. At the high dose in the 1-month dog

study, corneal translucencies were observed from Day 3 onwards with corneal ulceration observed from Day 7. One animal was terminated for humane reasons on Day 7 showing severe ulceration. For remaining animals there was recovery of ulceration despite continued treatment with AZD8931. It is not possible to assess reversibility of a severe ulcer. At the mid-dose on the 1-month dog study, faint corneal translucencies were observed from Day 13 with translucencies observed from Day 24. One animal at this dose level showed corneal ulceration at examination on Day 28.

In dogs, the DLT following single escalating oral doses of AZD8931 was gastrointestinal toxicity (fluid faeces) and decreased activity. Corneal translucencies were observed by ophthalmology examination. On completion of the dose escalation pharmacologically-related histopathology changes were seen in the eye (mild corneal epithelial ulceration), stomach and duodenum. The NOAEL in the dog after single escalating oral doses was 15 μmol/kg (7.1 mg/kg).

In the 1-month rat and dog studies, there was evidence of reversibility of findings following a 4-week recovery period. In the rat there were residual effects remaining in the skin and on the pattern of the female oestrus cycle.

In vitro assays indicate a potential for QT prolongation (prolongation of Interval from the beginning of the QRS complex to the end of the T wave) and arrhythmia with AZD8931. The compound was active in the human ether-a-go-go-related gene (hERG) assay with an 50% inhibitory concentration of 3.6 μM and caused significant prolongation of action potential duration in dog Purkinje fibres at concentrations of 10 μM and above. In the rabbit Langendorff model AZD8931 caused a concentration-related increase in pro-arrhythmic risk starting at 3 μM, with overt signs of pro-arrhythmia seen at 30 μM. There was no evidence of QT interval corrected for heart rate (QTc) prolongation during in vivo cardiovascular studies. However, the plasma concentrations which could be investigated in vivo were limited by tolerability.

AZD8931 caused dose-related hypotension in dogs following oral or intravenous dosing. In a dog single ascending dose (SAD) toxicity study, administration of single oral doses of AZD8931 produced reductions in blood pressure (BP) at dose levels of 15 μmol/kg and above. Daily oral dosing at 30 μmol/kg/day to dogs produced a reduction in BP, which was evident post-dose from week 1 of the study, but did not increase in magnitude with further daily dosing to 28 days. In an anaesthetised haemodynamic dose study, intravenous infusion at dose levels of 17 μmol/kg and above resulted in reductions in BP.

In an anaesthetised haemodynamic dose study, intravenous infusion at dose levels of 17 μmol/kg and above resulted in elevations in plasma potassium. At a dose level of 63 μmol/kg, the increases resulted in electrocardiogram (ECG) waveform changes. This finding has not been observed following oral dosing to conscious dogs.

Dose-related increases in plasma glucose have been observed following administration of oral doses to dogs. Increases were reversed by 24 hours post-dose and were generally associated

with increases in plasma cortisol. The insulin response to the glucose elevation appeared to be attenuated/absent especially at high plasma levels of AZD8931.

AZD8931 was shown to be positive in an in vitro 3T3 Neutral Red Uptake phototoxicity test. Radioactivity was detected in both the skin and uveal tract in a rat quantitative whole-body autoradiography study with AZD8931. These data indicate a potential phototoxicity risk of AZD8931.

Reproductive and developmental toxicity studies, and local tolerance studies, have not been conducted.

1.1.2 Clinical studies

The tolerability and initial PK of AZD8931 was investigated in a phase I study (D0102C00001) in healthy male volunteers. D0102C00001 was the first administration of AZD8931 to humans and consisted of 2 parts. Part A was a randomised, double-blind, placebo-controlled, SAD design. Part B was a randomised, double-blind, placebo-controlled crossover design. Part A was designed to allow a gradual escalation of doses with intensive clinical monitoring to ensure the safety of the volunteers. In Part B, volunteers were dosed at the maximum tolerated dose (MTD). Volunteers were randomised to receive AZD8931 followed by placebo, or placebo followed by AZD8931, in a 2-period, randomised crossover design with a minimum of 7 days washout between treatments.

The results from Part A of the SAD study were used to determine the starting dose of AZD8931 to be used in the current study:

Preliminary non-validated pharmacokinetic and blinded safety data from Part A of the study indicate that single doses of 2.5 mg, 10 mg, 40 mg, 80 mg, 160 mg and 200 mg were well tolerated. No subject experienced a clinically relevant change in safety parameters such as physical examinations (including ophthalmological assessments), BP, pulse, ECG parameters, urinalysis, faecal occult blood, clinical chemistry or haematological assessments. Asymptomatic corneal epithelial changes, detected by fluorescence staining, were noted in 1/5 healthy volunteers treated at 200 mg in this study. These findings were suggestive of superficial desquamation, and an external ophthalmology expert confirmed that normal environmental factors (eg, swimming in chlorinated water) could result in similar observations. These findings were seen on day 5 only and began resolving within a few hours of being noticed, complete resolution being documented 3 days later. The external ophthalmologist providing corneal evaluation expertise to the AZD8931 clinical studies and involved in the ophthalmic clinical evaluations has deemed these findings as highly unlikely to be a drug-related event.

The non-validated PK results showed that AZD8931 is orally bioavailable over the dose range 2.5 mg to 200 mg. Absorption was moderately rapid with time to reach maximum plasma concentration (t_{max}) occurring in most subjects at 1.5 or 2 hours after the dose (range 0.5 to 4 hours). After reaching the maximum plasma concentration (C_{max}), plasma concentrations declined biphasically. A terminal phase became apparent from about 24 hours after the dose,

when the plasma concentrations had fallen to around 6% of the peak values. The mean terminal elimination half-life ($t_{1/2}$) across the dose range was 12.1 hours (range 7.6 to 16.6 hours).

Based on the above data, it was determined that twice-daily administration should be employed in the current study to avoid excessive fluctuations between steady state (ss) C_{max} (Css_{max}) and minimum plasma concentration (Css_{min}). It is predicted that twice-daily dosing will lead to accumulation of study drug at about 30%, with a 5-fold fluctuation between Css_{min} and Css_{max}.

1.2 Rationale

The key aim of this study is to generate data that may support the opportunity for AZD8931 in the treatment of patients with solid malignancies.

1.2.1 Rationale for safety and pharmacokinetics

AZD8931 is a new investigational medicinal product intended for the treatment of solid malignancies. Non-clinical studies have demonstrated the potential for AZD8931 to produce various toxicities in addition to its anti-cancer effect, possibly secondary to its pharmacological action (see Section 1.1.1). It is therefore imperative to determine the safety and tolerability of AZD8931 in the intended patient population before further studies of its potential efficacy can be done. It is also necessary to determine the PK profile of AZD8931 in this patient population to assess whether the intended dosing schedule will provide adequate exposure to the investigational product.

This study is therefore intended to assess the safety, tolerability, MTD and PK of AZD8931 in patients with advanced solid malignancies.

1.2.2 Rationale for planned biomarker research

As an exploratory objective, it is planned to investigate the correlation between cell death (pro-apoptosis) biomarkers and AZD8931 therapy. This may provide preliminary evidence that AZD8931 induces apoptosis and tumour necrosis in EGFR- and Erb-driven tumours.

1.2.3 Rationale for pharmacogenetic research

As an exploratory objective, it is planned to take blood samples for future pharmacogenetic analysis, with the intention to determine any potential ability to identify individuals who may respond optimally to AZD8931 or a specific dose of AZD8931, or to identify factors that may affect the absorption, distribution, metabolism or excretion or tolerability of AZD8931 or its comparators.

1.2.4 Rationale for efficacy assessments

As an exploratory objective, the anti-tumour activity of AZD8931 will be investigated. Patients who complete the DLT evaluation period and who do not meet any discontinuation criteria are permitted to continue on the study. Efficacy will be assessed by means of Response Evaluation Criteria In Solid Tumours (RECIST) evaluations, and by changes in

tumour length, every 6 weeks (relative to the first day of AZD8931 dosing). Results will be preliminary only, but will be used to aid design of future studies.

This study will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to explore the safety and tolerability of multiple ascending doses (MAD) of AZD8931 in patients with advanced solid malignancies, by evaluation of AEs, laboratory findings, physical examinations, vital signs, cardiac monitoring, and ophthalmological assessments.

2.2 Secondary objectives

The secondary objectives of this study are:

1. To identify the MTD of AZD8931 following repeated twice daily administration, by assessment of DLT

2. To explore the PK of single doses of AZD8931 in patients with advanced solid malignancies

3. To explore the PK of multiple doses of AZD8931 in patients with advanced solid malignancies

Exploratory objectives of this study are:

4. To measure cell death biomarkers from blood samples to examine the relationship to treatment with AZD8931 (optional)

5. To obtain a blood sample for host pharmacogenetics for deoxyribonucleic acid (DNA) extraction and archiving (optional)

6. To obtain preliminary assessments of the efficacy of AZD8931 (including RECIST criteria and change in tumour length).

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca ( ) standard procedures.

3.1.1 Overall design

This study is an open-label, MAD, phase 1 study to explore the safety and tolerability of AZD8931.

Adult patients with advanced solid malignancies will be eligible for enrolment into this study. Written informed consent for participation in the study is required from the patient before any study specific procedures are conducted.

A minimum of 3 and a maximum of 6 eligible patients will be dosed initially. At the discretion of SMC or, if 1 patient within a dose cohort experiences a DLT, additional patients can be enrolled to ensure the cohort includes a maximum of 6 evaluable patients. Dose escalation may occur if the SMC declares the dose level as tolerable (as detailed in Section 3.1.2 for dose escalation and recruitment procedures). The dose will initially be escalated by dose doubling, up to a level where the SMC decide that smaller escalation steps are warranted. Based on emerging data, including PK and/or safety data and/or pre-clinical data, the SMC can consider alternative schedules, including once-daily dosing of AZD8931, in consultation with AstraZeneca and There will be adequate time between dose groups to allow review of relevant safety and PK data by the SMC.

Hospitalisation of patients (for safety monitoring or convenience) is at the discretion of the investigator, although the patients should remain at the clinic until completion of the 12 hour post-dose assessments.

Each of the cohorts may remain open until a maximum of 6 patients within the cohort have been defined as evaluable for the dose escalation set (see Table 4), and thereafter further recruitment into that cohort may be closed pending a decision about dose escalation. At the discretion of the SMC, in order to explore any safety concerns in the absence of DLT, each dose level cohort may be expanded to include a maximum of 6 patients who are evaluable for the dose escalation set.

The study design is presented in Figure 2 and the study plan is presented in Table 1.

Patients will have the option to provide a blood sample for genotyping after confirmation of eligibility. Patients who agree to take part in this genetic research will be asked to sign a separate informed consent form to confirm their willingness to have this sample taken. The samples will be stored and may be analysed in future research. See Appendix G for further details on the pharmacogenetics research planned in this study.

AZD8931 tablets will be taken orally. The starting dose level is 40 mg. In each dose group, each patient will receive initial treatment with a single dose of AZD8931, followed by a 4-day observation period then, starting between Day 5 and Day 7, a 21 day repeat dosing (twice daily) treatment period (Days R1 to R21). The 21 days of twice daily dosing with AZD8931 shall constitute a treatment cycle. Hospitalisation of the patients (for safety monitoring or convenience) is at the discretion of the investigator, although the patients should remain at the clinic until completion of the 12 hour post-dose assessments on Days D1 and R14. Patients

should continue treatment after day R21 if, in the investigator's opinion, the patient is receiving or may receive some benefit from therapy, is free from intolerable toxicity and has not met a discontinuation criterion (see Section 3.3.5.1).

Up to approximately 30 evaluable patients with advanced solid malignancies will be included, in approximately 5 dose groups of 3 to 6 evaluable patients, recruited from approximately 4 to 6 centres in Russia and Germany during a recruitment period of approximately 6 months. It is planned to recruit between 5 and 8 evaluable patients at each centre.

AZD8931 dose escalation decisions will be based on a minimum of 3 and a maximum of 6 evaluable patients per dose cohort (for further information see Table 4, dose escalation evaluable set).

3.1.2 Criteria to conduct dose escalation

The DLT evaluation period starts from the first administration of AZD8931 and continues until the completion of all assessments prior to cycle 2. For patients who continue beyond cycle 1, the DLT evaluation period ends following the completion of pre-dose assessments on the first day of cycle 2 (ie R1 cycle 2). For those patients who do not proceed beyond cycle 1 the DLT evaluation period ends following the completion of all assessments on the last day of cycle 1. Following cycle 1, subsequent treatment cycles are continuous. Dose reductions are not permitted during the DLT evaluation period, except following a DLT. If dosing of AZD8931 needs to be interrupted due to intolerable toxicities, then the DLT evaluation period may extend by the appropriate duration. Dose omissions for any other reason must not extend the DLT evaluation period. Evaluability of such patients will depend on meeting the description of analysis sets as described in Table 4 (Section 6.4.3). The cohorts may remain open until a maximum of 6 patients within the cohort have been defined as evaluable and thereafter further recruitment into that cohort will be closed pending a decision from the SMC.

Prior to each dose escalation, the SMC (see Section 6.6) will meet to review the available safety, tolerability (including AEs, laboratory assessments, ophthalmic assessments, physical examinations, vital signs, cardiac monitoring parameters) and PK data. The dose escalation decision will be documented and the minutes will be distributed to each site.

Throughout the study, dose escalation decisions will be based on a minimum of 3 and a maximum of 6 evaluable patients per dose cohort (see 'dose escalation evaluable set' described in Table 4). If a patient has received less than 80% of the defined dose and this is due to toxicity, a discussion will take place between AstraZeneca and the investigator to determine if this is a DLT. Replacement patients will enrol until the minimum required number of evaluable patients is available for assessments – see Section 3.4.4 for information on replacement of patients. Reasons for patient withdrawal will be given due consideration when enrolling replacement patients.

The SMC will review the data from each of the patients who completed the DLT evaluation period and decide if dose escalation is appropriate according to the following criteria:

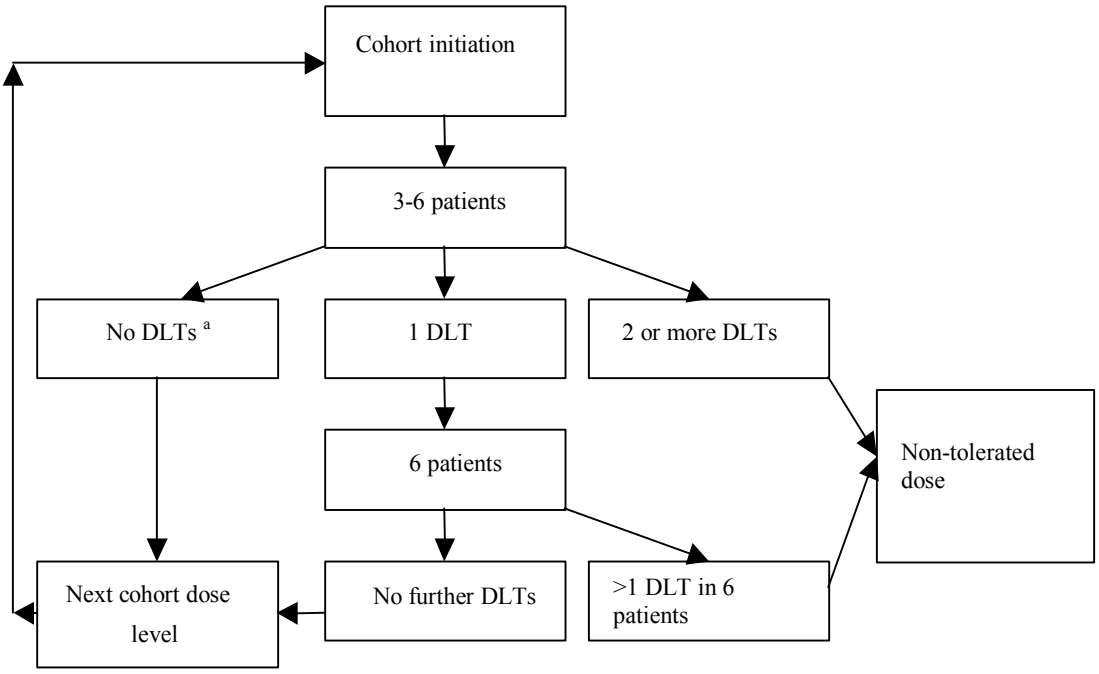
- If DLT is observed in ≥ 2 patients within the DLT evaluation period then this dose will be declared as non-tolerated and dose escalation will stop. A lower dose may be investigated at the discretion of the SMC (Section 6.6).

- If during the DLT evaluation period a DLT is observed in 1 patient within a dose level cohort consisting of less than 6 evaluable patients, additional patients will be recruited, to maintain a maximum of 6 evaluable patients in the cohort

- If during the DLT evaluation period there are no DLTs observed within a dose level cohort, containing 3 to 6 patients evaluable for the presence of DLT, then the dose will be defined as tolerable and dose escalation will continue with an incremented increase in a new group of at 3-6 patients.

Figure 1 summarises the rules to be applied.

Figure 1 Phase I dose escalation decision tree



Footnotes:
Patients in the above schematic refer to evaluable patients (dose escalation set).
[a] At the discretion of the SMC, in order to explore any safety concerns in the absence of DLT, each dose level cohort may be expanded to include a maximum of 6 patients who are evaluable for the dose escalation set.

Abbreviations: DLT: dose-limiting toxicity, MTD: maximum tolerated dose

The dose will initially be escalated by dose doubling, up to a level where the SMC decide that smaller escalation steps are warranted, based on PK and/or safety data. If the exposure in patients is more than 10% to 15% greater than predicted based on data obtained in healthy subjects, the dose escalation may proceed in a more conservative manner. The SMC will determine the dose escalation based on the above criteria at the end of each dose group.

Based on emerging data, including PK and/or safety data and/or pre-clinical data, the SMC can consider alternative schedules, including once-daily dosing of AZD8931, in consultation with AstraZeneca and .

When a non-tolerated dose is defined, dose escalation will be stopped and the MTD will be confirmed (see Section 3.1.4).

Following each dose decision, the patients already receiving study medication may remain on treatment at their original dose if, in the opinion of the investigator, the patient is receiving some benefit from therapy, is free from intolerable toxicity and does not meet one of the discontinuation criterion listed in Section 3.3.5.1.

Intra-patient dose escalation is not permitted.

If the patient experiences an AZD8931-related toxicity, their dose may be withheld or reduced (see Section 3.4.3).

3.1.3 Definition of non-tolerated dose

A dose will be considered non-tolerated, and dose escalation will cease, if ≥2 DLTs occur within a dose group (see Section 3.1.2).

3.1.4 Definition of maximum tolerated dose

When a non-tolerated dose is defined, dose escalation will be stopped and the MTD will be confirmed at the previous dose level below the non-tolerated dose, or a dose between the non-tolerated dose and last tolerated dose assessed may be investigated.

- If a dose between the non-tolerated dose and the last tolerated dose assessed is selected for investigation, then the dose escalation criteria detailed in Section 3.1.2 will apply

- When the non-tolerated dose is defined and the data on the dose below is based on data from <6 evaluable patients, then additional patients will be recruited at this lower dose to confirm that <2 DLTs have occurred in 6 evaluable patients treated at the MTD. If 5 evaluable patients in a given cohort have not experienced any DLTs, then further cohort expansion to confirm MTD is not required.

3.1.5 Definition of dose limiting toxicity

A DLT is defined as an AE or laboratory abnormality considered to be related to AZD8931, that commences anytime during the DLT evaluation period and meets any of the following criteria:

- Ophthalmological toxicity:
  - Symptomatic ocular surface lesion (epitheliopathy or erosion) with the following clinically significant criteria: >1 mm in diameter, <1 mm in diameter and clustered in a group of 10 or more, appearance of filaments or multiple (>2) small (<1 mm) areas or a large (>1 mm) area of negative fluorescein staining which cannot be attributed to another cause and which does not recover over a period of 3 days following detection of these findings.

- Haematological toxicity:
  - Any Common Terminology Criteria for AEs (CTCAE) grade 4 haematological toxicity of any duration
  - Febrile neutropenia (CTCAE grade ≥ 3 with temperature ≥38.5°C which is unresponsive to antipyretics)
  - CTCAE grade ≥ 3 neutropenia requiring hospitalisation
  - CTCAE grade ≥ 3 thrombocytopenia associated with non-traumatic bleeding (but not applicable to patients on therapeutic anticoagulation)

- Clinical chemistry toxicity:
  - CTCAE ≥ grade 3 hyperkalemia (ie, ≥6.0 mmol/L) which has been confirmed (by repeat sampling) and is considered to be drug related
  - CTCAE ≥ grade 3 hyperglycemia (ie, ≥13.9 mmol/L), from fasting glucose, which has been confirmed (by repeat sampling) and is considered to be drug related

- Cardiovascular toxicity:
  - QTcF (Fridericia's correction) interval > 500 msec on two ECGs at least 30 minutes apart, that cannot be attributed to another cause
  - Symptomatic congestive cardiac failure (New York Heart Association [NYHA] class III/IV) and a drop in left ventricular ejection fraction (LVEF) which cannot be attributed to another cause[2]
  - A decrease in LVEF of ≥20% to a level below the institution's lower limit of normal range
  - CTCAE ≥ 3 hypotension which cannot be attributed to another cause

- Other toxicities:

[2] Concomitant use of vasotonic drugs, adrenergic blockers, negative inotropic agents and anti hypertensives should be taken into consideration when assigning causality.

  - Clinically significant rash that despite optimal treatment remains CTCAE grade ≥3 for 5 days or longer and that cannot be attributed to another cause.
  - CTCAE grade ≥ 3 urological toxicity which cannot be attributed to another cause
  - CTCAE grade ≥3 interstitial lung disease or pneumonitis which cannot be attributed to another cause
  - CTCAE grade ≥ 3 nausea, vomiting or diarrhoea, despite optimal anti-emetic or anti-diarrhoeal therapy, and which cannot be attributed to another cause

- Any other CTCAE grade ≥ 3 toxicity which, in the opinion of the investigator, is clinically significant and related to the study drug, with the exception of sub-optimally treated nausea, vomiting or diarrhoea

The National Cancer Institute (NCI) CTCAE version 3.0 will be used whenever applicable to characterise DLTs. However, pre defined stopping criteria will supersede the CTCAE criteria.

If patients present with a potential DLT, the patient should be promptly investigated to define the aetiology of the symptoms. The use of appropriate (ie non restricted) medications in prophylactic or therapeutic management of toxicities are permitted. In the case of suspected interstitial lung disease, specialist pulmonary consultation is strongly recommended.

The decision to interrupt dosing or to stop a patient from receiving further dosing will be taken by the principal investigator, in consultation with the study team, based on the clinical significance of the observed toxicity. If the toxicity is subsequently determined by the SMC to not be a DLT, this patient will be replaced.

The principal investigator, in consultation with the study physician, may request replacement of patients who develop DLTs which are attributed to confounding factors and concomitant medications started during the DLT assessment period. Confounding medications for the specific DLT will be prohibited for the new patient(s) recruited to that dose group.

3.1.6 Study flow chart and study plan

Figure 2 Study flow chart

3 to 6 patients	**Single dose**	**4-day observa-tion period**	**Twice daily dosing for 21 days**	**Data collection /review**	**SMC review**	**Single dose**	**4-day observ ation period**	**Twice daily dosing for 21 days…**
Day Repeat dosing day	D1		D5 to 7 R1……..R21			(1)		

(1) New dose group (increased dose, same dose, decreased dose) depending on result of SMC meeting to discuss previous dose cohort of 3 to 6 evaluable patients (see Section 6.6).
Abbreviations: SMC: Safety Monitoring Committee. Shading: AZD8931 treatment.

Table 1 Study plan

Assessments	**Screening**	**DLT Evaluation Period[q]**									**Premature discontinuation**	**Continuation beyond R21[a]**	**Post-study follow-up**
		Single dose											
Day (h = hours)	**D–21 to D0**	***D1***	***D2*** (24 h)	***D3*** (48 h)	***D4*** (72 h)	**D5 to D7**						**Every 3 weeks**	**7 days after last dose**
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	≤2d	±3d	±1d
Informed consent (main study, genetics [optional], proapoptotic biomarkers [optional])	x												
Inclusion/exclusion criteria	x												
Tumour TNM stage at diagnosis and at study entry (and ErbB2 status, if available)	x												
Tumour assessment (RECIST)	x[b]										x[c]	x[d]	
Chest X-ray	x												
Demographics	x												
Medical/surgical history	x												
Previous anticancer therapy, including surgery	x												
Urine pregnancy test	x												
Administer AZD8931		Single dose [e]				Twice daily for 21 days [e]						Twice daily [e]	
Physical examination	x										x		x
Dermatological examinations[f]	x									x	x		x[g]

Table 1 Study plan

Assessments	**Screening**	**DLT Evaluation Period[q]**									**Premature discontinuation**	**Continuation beyond R21[a]**	**Post-study follow-up**
		Single dose											
Day (h = hours)	**D–21 to D0**	***D1***	***D2*** (24 h)	***D3*** (48 h)	***D4*** (72 h)	**D5 to D7**						**Every 3 weeks**	**7 days after last dose**
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	≤2d	±3d	±1d
Ophthalmological assessments	x									x	x	x[h]	x[g]
Echocardiography	x									x	x	x[i]	x[g]
12-lead Electrocardiogram [j]	x	x[k]	x	x	x	x	x[l]	x[l]	x[k]	x	x	x	x
Vital signs (heart rate, blood pressure)	x	x[k]	x	x	x	x	x[l]	x[l]	x[k]	x	x	x	x
Blood sample for AZD8931 pharmacokinetic (PK) analysis		x[k]	x	x	x		x[l]	x[l]	x[k]				
Blood sample for clinical chemistry, haematology, coagulation parameters	x	x[l,m]	x	x	x	x[l]	x[l]	x[l]	x[l,m]	x[l]	x	x	x
Blood samples for proapoptotic biomarkers (optional)		x[l, n]					x[l]	x[l]	x[l]	x[l]	x	x[l]	x[g]
Blood sample for pharmacogenetics (optional)		x[o]											
Urine sample for urinalysis	x	x[l]	x	x	x	x	x	x	x	x	x	x	x
Patient diary (including times study drug taken on PK days, and survey of ophthalmological [weekly] and other symptoms)						x[p]	x[p]	x[p]	x[p]	x[p]		x[p]	

Table 1 Study plan

Assessments	**Screening**	**DLT Evaluation Period[q]**									**Premature discontinuation**	**Continuation beyond R21[a]**	**Post-study follow-up**
		Single dose											
Day (h = hours)	**D–21 to D0**	***D1***	***D2*** (24 h)	***D3*** (48 h)	***D4*** (72 h)	**D5 to D7**						**Every 3 weeks**	**7 days after last dose**
Repeat dosing (R) day (d=day)						**R1**	**R3**	**R7** ±1d	**R14** ±1d	**R21** ±1d	≤2d	±3d	±1d
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x

TNM = Tumour, Node, Metastases; RECIST = Response Evaluation Criteria In Solid Tumours; HbA1c = glycosylated haemoglobin

Notes to study plan

[a] Treatment should extended beyond day R21 if, in the investigator's opinion, the patient is receiving or may receive some benefit from therapy is free from intolerable toxicity and has not met a discontinuation criterion (see Section 3.3.5.1).

[b] Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment.

[c] Where possible and appropriate.

[d] Every 6 weeks (±7 days), relative to day R1, until objective disease progression, study drug discontinuation, withdrawal of informed consent or death (whichever is soonest).

[e] No food is allowed from 2 hours before to 2 hours after study drug dosing.

[f] Full examination at screening (see Section 4.4.4). Full examination at other visits only if clinically significant abnormalities are observed. Brief symptom-directed examinations, or follow-up of existing abnormalities, should be performed at study visits, as appropriate.

[g] Only if not performed at day R21 (or premature discontinuation visit).

[h] Full ophthalmological assessment will be done at screening. Thereafter it will be done at premature discontinuation or day R21, whichever is earliest. Beyond day R21, questionnaire survey will be done every cycle or at discontinuation, with full examination only if indicated in accordance with the protocol.

[i] Every 9 weeks for 3 times, then every 18 weeks.

[j] 12-lead electrocardiogram (ECG) after 10 minutes rest in the supine position. The patient should be examined using the same machine throughout the study. Digital ECGs for QTc interval analysis (days D1 and R14) must be in triplicate (one after another). Paper read-outs are sufficient for other assessments.

[k] At pre-dose and at 1, 2, 4, 6, 8 and 12 hours post-dose (days D1 and R14).

[l] Pre-dose.

[m] Glucose and potassium only at 6 hours post-dose (days D1 and R14).
[n] At 8 hours post-dose.
[o] After confirmation of eligibility.
[p] Daily.
[q] The DLT evaluation period starts from the first administration of AZD8931 and continues until the completion of all assessments prior to cycle 2 see Section 3.1.2 for further information

3.2 Rationale and risk/benefit assessment

AZD8931 is in development for the treatment of patients with solid malignancies. Modulation of the EGF and ErbB2 receptors has been shown to provide clinical benefit for other agents. Non-clinical testing has indicated that patients with Erb family-driven solid tumours may benefit from treatment with AZD8931. However, at present there are no data available from exposure of patients to AZD8931, consequently there are no clinical benefit data available yet.

The proposed initial dose (ie, 40 mg twice daily) is considered unlikely to elicit significant target related pharmacological or clinical effects. Whilst patients are unlikely to gain therapeutic benefit, participation in the study will provide information on the safety and tolerability profile of AZD8931, together with PK and pharmacodynamic data, which will support the future clinical development of AZD8931 for the treatment of cancer and potentially meeting the unmet medical need in future cancer patient populations.

In order to provide a risk/benefit assessment for this study, detailed rationales for the choice of patient population, doses and design (including inclusion/exclusion, and stopping criteria) of this study are provided below.

3.2.1 Rationale for patient population, doses and design

This study will be conducted in patients with advanced solid malignancies. This population has been chosen to obtain safety, tolerability and PK data in a patient population relevant to further studies and future use of this compound.

This is the first study of AZD8931 in cancer patients and as such follows a conventional sequential dose escalation design. The number of evaluable patients to be enrolled is based on the desire to gain adequate information whilst exposing as few patients as possible to the study medication and procedures.

There are no data to indicate that the safety and tolerability of AZD8931 will differ significantly in patients with different types of tumour. An “all comers” population of patients with advanced solid malignancies are therefore eligible to enter this part of the study.

The design of this study takes into account the anticipated patient population to be enrolled and the emerging toxicity profile of AZD8931.

The starting dose of AZD8931 proposed for this study is 40 mg twice daily. Experience with AZD8931 and other EGFR inhibitors suggests that the parameter that predicts for corneal toxicity (the DLT in dog studies) is cumulative drug exposure (area under plasma concentration-time curve [AUC]) rather than dose. Thus selection of a starting dose for the study took into consideration a comparison between the predicted exposure in humans and the exposure observed in the toxicity studies in the dog. The starting dose for this study was determined to be 40 mg twice daily, which is predicted to produce a cumulative AUC that is 2 to 8-fold lower in patients than observed at the no effect level in the dog 1-month study. At 40 mg twice daily, approximately 40% of individuals would be predicted to have plasma

concentrations maintained continuously above the AZD8931 IC_{50} (concentration for 50% inhibition) for EGFR, about 10% above the value for phosphorylated ErbB3 and none above the IC_{50} of ErbB2. However, 10% of individuals would be predicted to exceed the ErbB2 IC_{50} for 8 hours in every 12-hour dosing interval. Thus 40 mg twice daily could be considered sub-therapeutic in respect of all of the key targets of AZD8931, but possibly still capable of eliciting some pharmacological action. On the assumption that the IC50 values used in these predictions are valid, it would be predicted that a therapeutic dose should be achieved for a significant proportion of patients after one or two dose escalations.

The escalation will be by dose doubling unless the SMC decide, on the basis of observations in the patients, that an alternative (eg, a smaller escalation) is warranted. The rationale for the proposed starting dose is provided in Section 1.1.2. The study is designed to gain safety and tolerability data whilst exposing as few patients as possible at each dose level.

Administration of a single dose of AZD8931 followed by an observation period (of 4 to 6 days) will allow single dose PK data to be collected. PK samples will also be collected after 14 days of twice daily dosing to allow investigation of the PK after multiple dosing. The 21-day repeat dosing period should permit adequate assessment of safety and tolerability data.

A dose doubling strategy will be employed as this prioritises the safety and well being of the patients by escalating the dose in a relatively cautious manner but reaching a non-tolerated dose level in the minimum possible number of dose increments. Dose escalation will take into account emerging safety, tolerability and PK data but will not exceed a doubling in dose at any dose increment.

Based on emerging data, including PK and/or safety data and/or pre-clinical data, the SMC can consider alternative schedules, including once-daily dosing, in consultation with AstraZeneca and .

There will be an adequate period between dose groups to allow collection and review of relevant safety and PK data by the SMC prior to dose decisions.

3.2.2 Rationale for inclusion, exclusion criteria, stopping criteria and monitoring

As stated in Section 1.1.1, dosing with AZD8931 to non-clinical species has raised the following as potential safety concerns: corneal epithelial ulceration, arrhythmia, hyperkalemia, hyperglycemia, hypotension, epithelial degeneration, and phototoxicity. The relevance of some of these findings to humans is not clear and these will be carefully monitored during the study and specific stopping criteria have been defined in the protocol.

Specific ophthalmologic exclusion criteria have been incorporated into the study design to limit confounding morbidity. A robust ophthalmologic monitoring will be considered, including a schedule of ophthalmic examinations with frequent symptomatic follow-up with additional corneal examinations if indicated.

QT prolongation (prolongation of interval from the beginning of the QRS complex to the end of the T wave) and arrhythmia were not considered to be a risk in study D0102C00001, as the

free AUC exposure limit for this study is more than 30-fold below the level at which pro-arrhythmia was identified in non-clinical studies. No clinically significant QT or cardiac arrhythmia related safety concerns were noted up to a single dose of 200 mg in healthy volunteers. However, any potential effects of AZD8931 on the QT interval in man will be closely monitored in this patient study. Patients with a baseline QTc interval in excess of 460 msec will be excluded from participation in the study. Digital ECG monitoring will be performed during the study, particularly around time points where C_{max} is anticipated to occur on the first day and at steady state. The ECGs will be reviewed on site for the SMC decision making. In addition ECGs will be reviewed centrally for formal analysis of QT liability.

Based on non-clinical data, blood pressure, potassium and glucose were monitored intensively in study D0102C00001. No significant findings were noted up to 200 mg. Patients in the MAD study will be monitored for BP changes through frequent measurement of blood pressure, particularly around the time of C_{max} after dosing on the first day and at steady state, and will be monitored for potassium and glucose particularly at time points around where C_{max} is anticipated to occur.

Patients with random blood glucose above 11.1 mmol/L at screening will be excluded from the study. Those with impaired glucose tolerance would be included only if their fasting blood glucose levels are recorded within non-diabetic ranges. Blood glucose levels will be monitored during the study. In the event of a patient developing significant hyperglycemia (fasting glucose >13.9 mmol/L), that cannot be attributed to any other cause, this will be deemed as a DLT. The evaluation of post-prandial glucose as an assessment of a patient's glycemic state in this study population may be confounded by disease burden, concomitant medications (steroids), study conditions (food restrictions, disturbed circadian activity, mobility etc). The clinical picture of day-to-day glycemic state obtained from random pre- and post-dose glucose samples may not reflect the true glycemic state.

Patients with history or evidence of cardiac dysfunction will be excluded from the study and a baseline echocardiogram and digital ECG will be used to reference any symptomatic or non-symptomatic deterioration in cardiac function that may happen during the study.

Patients with history or evidence of interstitial lung disease will be excluded from the study and baseline radiology will be used to compare the findings associated with any respiratory symptoms later in the study.

Patients in this study will be advised of the need for sun protection measures such as avoidance of sun beds, the application of sun-cream (sun protection factor [SPF] minimum 15) to body parts exposed to the sun, and the use of sunglasses in sunny conditions. Patients will be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD8931.

No reproductive toxicology studies have been conducted to assess safety to the human foetus. AZD8931 has not shown any genotoxic potential. It is not known whether AZD8931 or its metabolites are secreted in human milk or semen. Therefore, until further data is available, AZD8931 is not suitable for administration to pregnant or nursing women, and conception

while on treatment must be avoided. For AZD8931 studies, male subjects will be required to abstain from unprotected sex and sperm donation for 4 months following dosing, and will be advised to use condoms in addition to a second reliable form of contraception for a specified period.

Finally, all safety data will be collected on a regular basis and reviewed by the principal investigator.

3.2.3 Summary of risk/benefit assessment

In conclusion, the risk/benefit assessment for the conduct of this study of AZD8931 in patients with advanced solid malignancy is considered acceptable.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but never enrolled, eg, patient screening log, according to local procedures. This information is necessary to establish that the patient population was selected without bias.

Patients will be recruited from specialist clinics and from referral from primary care. Advertising may be used as an aid to recruitment in accordance with local regulations.

3.3.2 Inclusion criteria

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

1. Provision of written informed consent

2. Male or female aged ≥18 years

3. Cancer which is refractory to standard therapies, or for which no standard therapies exist. Inclusion is irrespective of stage of disease or extent of prior therapy

4. Histologically or cytologically confirmed solid, malignant tumour

5. World Health Organization (WHO) performance status 0 to 2 (those with performance status 2 must have been stable with no deterioration over the previous 2 weeks) (see Appendix D)

6. Adequate haematology, liver function and biochemistry tests:
   Absolute neutrophils count >1.5 x 10^9/L, platelets >100 x 10^9/L, haemoglobin ≥9 g/dL (5.59 mmol/L) (blood transfusion, iron and/or erythropoietin therapy are permitted at the discretion of the investigator, and must be recorded in the concomitant medications page of the case report form [CRF])
   Serum bilirubin ≤1.5 x upper limit of normal (ULN), and alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, except in patients with liver or bone metastases [ALT, AST and alkaline

phosphatase ≤5 x ULN]
International normalisation ratio and activated partial thromboplastin time <1.2 x ULN

7. Adequate cardiac function (baseline LVEF higher than the institution's lower limit of normal range, determined by echocardiography)

8. Negative screens for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV)

9. Likely ability to complete 3 weeks continuous treatment

10. Female patients with evidence of post-menopausal status or pre-menopausal patients must use acceptable (to AstraZeneca) contraception and follow the study restrictions (see Section 3.3.4). There must be a negative urinary pregnancy test for female pre-menopausal patients.
Post-menopausal females are defined as follows: Natural menopause with last menses at least 1 year ago; radiation induced oophorectomy with last menses >1 year ago; chemotherapy induced menopause with last menses >1 year ago; serum follicle stimulating hormone and luteinising hormone and plasma oestradiol levels in post-menopausal range for the institution; bilateral oophorectomy or hysterectomy

For inclusion in the **exploratory biomarker component** of the study (optional), patients must fulfil the following criterion:

11. Provision of informed consent to take additional blood samples for use in exploratory biomarker research

If a patient declines to participate in the biomarker component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

For inclusion in the optional **pharmacogenetic component** of the study (optional), patients must fulfil the following criterion:

12. Provision of informed consent for genetic research

If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

3.3.3 Exclusion criteria

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

1. Receipt of any of the following treatments within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormone therapy (except for androgen-deprivation therapy for patients with prostate cancer), immunotherapy and any other anti-cancer therapies

2. Unresolved toxicity ≥CTCAE grade 2 from previous anti-cancer therapy, except alopecia

3. Prior cumulative doxorubicin dose of >360 mg/m^2, or the equivalent

4. History of other malignancies with the exception of basal cell carcinoma of the skin or cervical cancer in situ, within the previous 5 years

5. History of documented cardiac failure, angina pectoris requiring antianginal medication, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic >180 mmHg or diastolic >100 mmHg), significant valvular disease or history of high risk dysrrhythmia (such as ventricular fibrillation or ventricular tachycardia [includes ventricular triplets])

6. Resting ECG with measurable QTc interval of >460 msec at 2 or more time-points within a 24-hour time period, or history of prolonged QTc syndrome

7. Currently receiving agents designated as Class I Arizona risk for QT prolongation (see Section 3.4.6 and Appendix F). Agents designated as Class II Arizona risk for QT are allowed provided the patient has received these agents for at least 5 half-lives of the drug with no change in dose

8. The presence of any ocular disease or condition that is active or is likely to flare up during the course of the study or any systemic disease/condition that is affecting or has affected the eye in the past and may flare up, or the treatment of which may have an adverse effect on the eye. Eye conditions that are stable and of long standing, such as scars from trauma, pinguecula, atrophic pterygia etc, should not be considered as reasons to exclude the patient

9. Wearing contact lens (patients should discontinue wearing contact lens from at least 1 week prior to entering the study to 1 week following discontinuation of AZD8931)

10. Recent acute changes in patient's vision, or ongoing symptoms of ocular pain, discomfort or irritation

11. History of radiotherapy where the eye orbits was included in the treatment field

12. History of Collagen vascular disease with eye involvement (eg, rheumatoid, Sjögren syndrome, systemic lupus erythematosus [SLE]) or of ocular surface disease

(including Steven-Johnson syndrome, ocular cicatricial pemphigoid or chemical burns)

13. History of Herpes simplex virus or Herpes Zoster virus eye disease, or chronic or recurrent intraocular inflammation

14. History of corneal surgery, including laser refractive surgery, within the past 3 years

15. Evidence of 'dry eye': persistent symptoms of ocular surface irritation, Schirmer's test without anaesthesia of less than 5 mm in 5 minutes and tear break-up time [TBUT] test of less than 10 seconds (if one of these is satisfactory, the patient may be included – both of these parameters should be normal if the patient is receiving anti-cholinergic medication [see Section 3.4.6])

16. Evidence of 'sticky eyes' with discharge, symptomatic blepharitis or of active macular degenerative processes, dry or wet

17. Medical diagnosis of acne rosacea, psoriasis, or severe atopic eczema (common acne Vulgaris is acceptable for this study)

18. A history of brain metastases or with clinical signs and/or symptoms attributable to active intra-cerebral metastases and/or oedema or progressive growth demonstrated by brain imaging or use of concomitant anti-seizure medication or corticosteroids

19. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease

20. Current infection, or history of untreated spinal cord compression, uncontrolled hypercalcaemia or any other severe or uncontrolled systemic condition likely to increase the risk of treatment complications

21. Uncontrolled diabetes mellitus (glycosylated haemoglobin [HbA1c] ≥9%)

22. Elevated glucose levels at screening (random blood glucose >11.1 mmol/L). Patients with random glucose 7 to 11 mmol/L may be included ONLY if fasting glucose is <7 mmol/L

23. Elevated potassium levels at screening (>5.5 mmol/L)

24. Impaired renal function defined as creatinine ≥1.5 x ULN or creatinine clearance of ≤50 mL/minute, determined by Cockroft-Gault formula or through measurement of glomerular filtration rate

25. Clinically abnormal urinalysis at screening, as judged from the current clinical condition of the patient

26. Currently receiving, or recently taken, drugs (eg, prescribed and non-prescription) with known significant CYP3A4 or CYP2D6 inhibitor or inducer effects (see Section 3.4.6 and Appendix F). Where half-life data are not available, the patient should not have received the therapy within the last 4 weeks

27. Known hypersensitivity reaction or prior anaphylaxis attributed to previous therapy with oral tyrosine kinase inhibitors.

28. Current disease or condition known to interfere with absorption, distribution, metabolism or excretion of drugs

29. Personal history of repeated unexplained episodes of syncope and/or dizziness

30. If participation in the study would result in the patient donating more than 1350 mL of blood in the 12 months before the end of the study or 500 mL of blood in the 3 months before the end of the study

31. Female patients who are breast feeding, or patients of reproductive potential not employing reliable methods of birth control

32. History of use of an investigational agent within the 30 days prior to entry or who have not recovered from side effects of an investigational study drug

33. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

34. Clinical judgment by the investigator that the patient should not participate in the study

The following criterion will require exclusion from the optional **pharmacogenetic component** part of the study:

35. Receipt of a whole blood transfusion in the preceding 90 days, or a previous bone marrow transplant

3.3.4 Restrictions

The following restrictions will apply:

1. Female patients of child bearing potential will be required to use 2 reliable methods of contraception (or abstain from heterosexual intercourse) from Screening, for the duration of the study, and for at least 28 days after the last dose of study drug. The 2 methods of reliable contraception must include 1 highly effective method (ie, intrauterine device [IUD], tubal ligation, partner's vasectomy) and 1 additional effective (barrier) method (ie, condom, diaphragm, cervical cap) or non-pharmacologic contraception measures. The female patient must be referred to a qualified provider of contraceptive methods, if needed

2. Male patients will be required to use reliable methods of contraception (condom) during any sexual contact with a female of childbearing potential for the duration of the study and until 16 weeks after the last dose of AZD8931 (even if he has undergone successful vasectomy).

3. Male patients will be advised to abstain from sperm donation from first dose until 16 weeks following receipt of the last dose of AZD8931

4. All patients will be counselled on the potential risks of foetal exposure to the study drug at the start of the study

5. No food is allowed from 2 hours before to 2 hours after taking study drug

6. Patients must not receive any concomitant anti-cancer agents or any other investigational agents while receiving AZD8931

7. Abstain from taking drugs with known significant CYP3A4 and CYP2D6 inducer/inhibitory affects (see Appendix F)

8. Abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, eg, grapefruit juice or marmalade) during the study. Amounts should not exceed more than a small glass of grapefruit juice (120 mL), or half a grapefruit, or 1-2 teaspoons (15 g) of Seville orange marmalade daily

9. Refrain from driving for 4 hours following ophthalmic examination if pupillary dilatation performed

10. Refrain from wearing contact lenses from at least 1 week prior to starting AZD8931 to 1 week after discontinuation of AZD8931

11. Avoid use of sun beds or tanning booths (including dye-based tanning booths) during the course of the study and for 3 months after the last dose. Use sunglasses and sun cream (with SPF minimum 15), if exposed to sunlight during this period of time

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

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

- Voluntary discontinuation by the patient, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment

- Safety reasons as judged by the investigator and/or AstraZeneca (including positive pregnancy test)

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrolment, ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Patient is considered to have clear evidence of clinical progression of disease (PD), based on investigator's opinion
- Patient has objective evidence of radiological PD, based on RECIST evaluation (refer to Appendix C)

Specific reasons for discontinuing a patient from the biomarker research component of the study are:

- Withdrawal of consent for biomarker research. A patient may withdraw from this component at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

Specific reasons for discontinuing a patient from the genetic research component of the study are:

- Withdrawal of consent for genetic research. A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment

For patients who discontinue from the study for any reason, further therapy will be at the discretion of the investigator and patient.

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s) (see Table 1 for assessments to be performed). Ongoing Serious Adverse Events (SAEs) and AEs should be followed up to resolution or stabilisation, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigator must record his/her opinion in the patient's medical records), or the patient is lost to follow-up. Any investigational products should be returned by the patient.

3.3.5.3 Procedures for discontinuation from genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for the optional genetic research. See details in Appendix G.

3.3.5.4 Procedures for handling incorrect enrolled subjects

Patients not meeting the inclusion/exclusion criteria for a study should, under no circumstances, be enrolled into the study. No waivers for inclusion/exclusion criteria will be granted.

Patients who have been entered into the study in error, in violation of inclusion or exclusion criteria, will be evaluated on an individual basis to determine the likely benefits and risks to the patient if they remain in the study; such patients may remain in the study if considered appropriate by the investigator, Medical Monitor and AstraZeneca (the decision must be documented). These patients are non-evaluable for evaluation of MTD and PK and should be replaced.

3.4 Treatment(s)

3.4.1 Investigational product(s)

3.4.1.1 Identity of investigational product

AstraZeneca Investigational Product Section (UK) Macclesfield will supply investigational product to the investigator as plain, white film-coated, biconvex round tablets as follows:

Table 2 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number
AZD8931	2.5 mg	AstraZeneca	F013432
AZD8931	10 mg	AstraZeneca	F013433
AZD8931	40 mg	AstraZeneca	F013394
AZD8931	100 mg	AstraZeneca	F013574

3.4.1.2 Labelling

Study drug will be packed, labelled and supplied by AstraZeneca Investigational Products, Macclesfield, UK as open-labelled supply packed into high-density polyethylene bottles with desiccant. Study drug will be supplied in bottles containing a quantity of tablets sufficient for each dispensing visit, plus an overage to allow for permitted visit windows.

The tear-off section of the label will be affixed to a drug accountability sheet, and appropriate information will be transcribed onto the drug accountability section of the CRF at the time of administration/dispensation.

The label will comply with Annex 13 of the Clinical Trials Directive and local regulations and state that the drug is for clinical trial use only and should be kept out of reach of children.

3.4.1.3 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the bottle label.

3.4.1.4 Accountability

The study drug provided for this study is for use only as directed in the protocol. All unused drugs will be accounted for by study site personnel and should be destroyed at site. If this is not possible, the clinical team should be contacted for confirmation of the place for destruction. The study site personnel will account for all drugs dispensed and returned prior to destruction. Certificates of delivery, destruction and return must be signed and dated by study site personnel.

Study drug and label accountability records will be maintained by the study site personnel. These will be used in conjunction with the handling and preparation worksheets for recording all drug and label use. All dispensing operations will be second checked and the record sheets signed by both dispenser and checker.

On study completion all original documents will be stored in the investigator study file.

3.4.2 Doses and treatment regimens

3.4.2.1 AZD8931 dosing

AZD8931 tablets will be taken orally twice daily (except for the single dose on D1), with the doses being taken approximately 12 hours apart. The AZD8931 tablets should be taken with a glass of water (approximately 150 mL) at approximately the same time each day. The effect of food on the absorption of AZD8931 has not been established. Therefore it is requested that AZD8931 be taken at least 2 hours after a meal and that no food is consumed until 2 hours after the tablets are taken. There is no restriction on the consumption of water.

The initial dose level will be 40 mg. See also Section 3.1.2 for more details on dose escalation.

Day 1 of a subsequent cycle is the day after the last day of the previous cycle (R21) i.e. AZD8931 dosing is continuous twice daily (except if there is a dose interruption due to toxicity).

3.4.2.2 During the DLT evaluation period

The DLT evaluation period is described in Section 3.1.2. Each patient will receive initial treatment with a single dose of AZD8931, followed by a 4 day observation period then, starting between Day 5 and Day 7, a 21 day twice daily treatment period (Days R1 to R21). On study days when patients are required to return to the clinic for pre-dose blood samples to be collected, patients will be instructed not to take their study drug medication until after a

pre-dose sample has been provided. On Day R14, the 12h blood samples should be collected prior to administration of AZD8931.

3.4.2.3 Dosing beyond the DLT evaluation period

Following each dose escalation decision (see Section 3.1.2), the patients already receiving study medication may remain on twice daily treatment at their original dose if, in the opinion of the investigator, the patient is receiving or may receive some benefit from therapy, is free from intolerable toxicity and has not met a discontinuation criterion listed in Section 3.3.5.1.

3.4.3 Dose adjustment of AZD8931

Intra-patient dose adjustment of AZD8931 may be permitted according to the criteria detailed below and only after discussion and agreement of individual patient situations between the investigator, the medical monitor and the sponsor. During the study, the dose of AZD8931 may only be reduced by one dose level for an individual patient if required.

- For all patients who experience a DLT or an unacceptable toxicity, if the toxicity does not resolve to CTCAE ≤grade 1 or baseline (pre-study) after 21 days of onset, then the patients must be discontinued from the study

- If a DLT or unacceptable toxicity resolves or reverts to CTCAE ≤grade 1 or baseline levels within 21 days of onset and the patient is showing or, in the investigators opinion may show clinical benefit, treatment with AZD8931 may be restarted at a preceding, lower dose level that has been defined as tolerated

The dose of AZD8931 may only be reduced by 1 dose level in any given patient. If this dose reduction occurs during the DLT evaluation period the patient will no longer be defined as evaluable for the presence of DLT, unless they have already experienced a DLT (see Section 3.1.2).

All dose modifications and interruptions (including any missed doses due to AEs), and the reasons for the dose modifications/interruptions are to be recorded in the CRF.

3.4.4 Method of assigning subjects to treatment groups

Informed consent will be obtained at screening and each patient will be identified with a unique screening number starting with E# (incorporating centre identification). This number will be retained regardless of whether they subsequently fulfil the eligibility criteria.

Patients will be assigned patient numbers strictly sequentially as patients become eligible for inclusion. If a patient discontinues from the study the patient number will not be re-used and the patient will not be allowed to re-enter the study.

Patients may be replaced if they are withdrawn without meeting all the criteria for a DLT (see Section 3.1.2), or withdrawn due to a DLT that is attributed to taking confounding medications (see Section 3.1.5), or if they are enrolled in error (see Section 3.3.5.4), or if they are non-evaluable (see Section 6.4.3).

3.4.5 Blinding and procedures for unblinding the study (Not applicable)

3.4.6 Concomitant medication

Patients are not eligible to enter the study if they have taken any of the following within the specified timeframe:

- Within 4 weeks prior to study entry: chemotherapy (within 6 weeks for nitrosurea or mitomycin C), radiotherapy, hormone therapy (except for androgen-deprivation therapy for patients with prostate cancer), immunotherapy and any other anti-cancer therapies

- Currently receiving, or taken within 7 half-lives of the drug: drugs (eg, prescribed and non-prescription) with known significant CYP3A4 and CYP2D6 inhibitor and inducer effects (see Appendix F for details). Where drug half-life information is not available, the patient should not have received the therapy within the last 4 weeks

- Currently receiving, or taken within 7 half-lives of the drug: drugs designated as Class I Arizona risk for QT prolongation (see Appendix F for details). Agents designated as Class II Arizona risk for QT are allowed provided the patient has received these agents for at least 5 half-lives of the drug with no change in dose

- Currently receiving anti-seizure medication.

Ongoing treatment with anti-cholinergic medication, oral steroids, angiotensin converting enzyme (ACE) inhibitors, potassium-sparing diuretics or potassium supplements is allowed, provided the patient has been on therapy for at least 4 weeks with no changes in dose in that time.

All medications and aspects of medical management that are standard in the treatment of advanced solid malignancies, as well as any treatment for inter-current diseases, will be allowed during the treatment period, with the exception of the following:

- Concomitant anti-cancer agents or any other investigational agents

- Agents designated as Class I Arizona risk for QT prolongation (refer to Appendix F). If agents designated as Class II Arizona risk for QT prolongation are started during the DLT assessment period, they may influence the QT interval (refer to Appendix F)

- Drugs with known significant CYP3A4 and CYP2D6 inducer/inhibitory effects (refer to Appendix F)

- Systemic steroids. (Systemic steroids may be administered at the discretion of the investigator).

Patients who receive any of the above concomitant medications during the period of DLT assessment (up to Day R21) could be considered non-evaluable and may be replaced.

Additional monitoring of potassium should be undertaken if the patient receives drugs that may cause hyperkalemia.

Additional monitoring of glucose should be undertaken if the patient receives drugs that may affect glucose metabolism.

If a patient requires elective surgery with anaesthesia during the study, it is recommended that study drug therapy should be discontinued for 3 days beforehand. If urgent anaesthesia/ muscle relaxants are required, the anaesthetist should be informed that hyperkalemia has been seen in dogs anaesthetised with propofol and alfentanil and who received high doses of AZD8931. The decision to restart study drug will be taken in consultation with the Medical Monitor and AstraZeneca physician.

Any medication, which is considered necessary for the patient'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.

3.4.7 Treatment compliance

When patients are at the clinic, compliance will be assured by supervised administration of AZD8931 by the investigator or his/her delegate.

When patients are not at the clinic, patients will be asked to return all unused study drug at each visit (if treatment is continuing). Compliance will be assessed by means of tablet counts of returned unused study drug at each clinic visit, and by monitoring of patient diary cards. Compliance will be calculated at the end of the study.

4. MEASUREMENT OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (Table 1). The following 'priority order' will be in effect when more than one assessment is required at a particular time point:

- AEs
- Echocardiography
- 12-lead ECG (recordings will start 5 minutes prior to PK sampling when triplicate recordings are acquired)
- Heart rate and BP
- Safety blood sampling

- PK sampling (planned for the exact time of assessment)
- Ophthalmological examination
- Dermatological examination
- Urine sampling.

NB: The order of assessments will not be explored in the data reporting.

4.1 Medical examination and demographic measurements

4.1.1 Enrolment medical examination and demographic measurements

The following screening and demographic data will be collected in the paper CRF (pCRF) in the 21 days prior to the first treatment visit (see Table 1 for the timing of these assessments).

- Provision of written informed consent
  - Provision of written informed consent must be obtained at screening for all patients. Additional written informed consent for participation in the genotyping component and biomarker analysis is optional
- Date of birth, sex, height, weight and race
- Relevant medical and surgical history, including menstrual status, concurrent illness and recent and current medications
- Urine pregnancy test
- Previous anti-cancer therapy, including surgery (concomitant medications will be recorded from Screening until the Study Completion Visit)
- Echocardiography and ECG
- Chest X-ray
- Physical examination, including but not limited to the following body systems: general appearance, skin, head and neck, lymph node, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological
- Safety blood sampling and urine sampling
- Dermatological examination (observational and symptom-directed)
- Ophthalmological examination (see Section 4.4.5)

- Vital signs (resting BP and heart rate, measured with the patient in a sitting position)

- Type of tumour, TNM (tumour, node, metastases) stage at diagnosis and at study entry, and ErbB2 status (if available)

- Tumour assessment according to local standards to define all areas of disease (eg, bone, liver and lung). Document measurable disease according to RECIST criteria (see Appendix C), using Computer tomography (CT) or magnetic resonance imaging (MRI) scan. The baseline tumour assessment must be within 4 weeks prior to the start of treatment. This does not need to be repeated prior to starting treatment unless the investigator believes that there has been a change in tumour burden. If imaging is repeated before study entry, the most recent assessment should be recorded as the screening assessment. For patients with prior first line chemotherapy the screening imaging tests must have been performed at least 4 weeks after the last cycle of prior chemotherapy.

For assessment of patient eligibility for study entry, blood samples for haematology (platelet count) and clinical chemistry analysis (total bilirubin, ALT, and AST) will be collected according to standard local practice and analysed at the local laboratory of each study centre using standard procedures. Confirmation that the values meet the inclusion or exclusion criteria must be recorded in the pCRF.

Histological or cytological confirmation of advanced solid malignancy is required for inclusion in the study.

Patients must fulfil all inclusion and exclusion criteria before being entered into the study and allocated to treatment.

4.1.2 Treatment period medical examinations

Refer to Table 1 for details of examinations to be performed during the treatment period. Ophthalmological and dermatological assessments are detailed in Sections 4.4.4 and 4.4.5, respectively.

4.1.3 Medical examinations after completion of the DLT evaluation period

Refer to Table 1 for details of examinations to be performed for patients who continue repeat dosing beyond the DLT evaluation period.

Patients who continue treatment with AZD8931after the DLT evaluation period should have their safety parameters monitored and clinically assessed at least once during each cycle in accordance to the protocol schedule. From the second cycle onwards, periodic clinic visits are according to Table 1. Where appropriate a visit window of ±7 days is permitted for the scheduled study procedures to be combined.

4.1.4 Post-study medical examination

A post-study medical examination will be conducted approximately 7 days after last dose of AZD8931, as specified in Table 1. Patients will be asked to contact their doctor (general practitioner) should they develop any eye symptoms in the 3 months after their post-study medical examination.

4.2 Pharmacokinetic measurements

For timing of individual samples refer to the study plan (Table 1).

4.2.1 Determination of drug concentration in biological samples

Analysis of plasma samples for the determination of AZD8931 will be the responsibility of the Clinical Pharmacology & DMPK Department, AstraZeneca, UK. If warranted, the samples may also be used for investigation/analysis of circulating metabolites and/or exploratory biomarkers.

4.2.2 Collection of biological samples

PK samples will be collected at the following time points for determination of AZD8931 plasma concentrations:

Days D1 and R14: pre-dose, 1, 2, 4, 6, 8, 12 (prior to AZD8931 administration on Day R14), 24 (D1 only), 48 (D1 only) and 72 (D1 only) hours post dose Days R3 and R7: pre-dose (see Table 1).

Depending on emerging data/information, the timings and number of PK samples may be altered, but the maximum blood volumes from scheduled samples given in Table 3 will not be exceeded. The actual sample time and date of all PK samples must be recorded in the CRF.

All biological samples will be collected, processed, labelled and shipped to a central laboratory ( ), as per the laboratory study manual. At appropriate time intervals, the central holding laboratory will arrange to have the samples transported on dry ice to the appropriate laboratory(ies) for analysis. Samples should be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable.

Samples will be disposed of after the Clinical Study Report has been finalised.

Venous blood samples (3 mL) for determination of AZD8931 in plasma will be taken at the timepoints detailed in the study plan (see Table 1).

4.3 Efficacy and pharmacodynamic measurement and variables

4.3.1 Pharmacodynamic/exploratory measurements

4.3.1.1 Plasma samples for measurement of biomarkers

Optional blood samples (3 mL) will be taken to include (but not limited to) markers of cell death, invasion and angiogenesis. For timing of individual samples refer to the study plan (Table 1).

All biological samples will be collected, processed, labelled and shipped to a central laboratory, as per the laboratory study manual.

The biomarkers planned to be measured will include (but not limited to) M30 and M65. Measurements of M30 and M65 are by ELISA and will be analysed at the . Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD8931 studies.

4.3.2 Efficacy measurements

Patients with non-measurable disease only are not excluded from this study.

4.3.2.1 Tumour assessment for patients with measurable disease

Tumour assessment will be performed using RECIST criteria for patients with measurable disease. The RECIST guidelines for measurable, non-measurable, target and non-target lesions, and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD] or PD) are presented in Appendix C. The RECIST criteria will be used to programmatically determine Objective Response Rate (ORR) and Best Overall Response.

Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment. After the start of repeat dosing (day R1), efficacy for all patients with measurable disease will be assessed by objective tumour response every 6 weeks (relative to day R1). Assessments may be performed ±7 days relative to the specified visit date.

Baseline CT examination will be performed on anatomical coverage to adequately define all areas of disease. Post-baseline imaging should follow and evaluate all previous identified lesions. MRI should only be used where CT is not feasible or if it is medically contra-indicated.

All measurable lesions confirmed and assessed by radiological methods (CT or MRI scans) up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at baseline, and at the time points specified above.

Lesions that have been previously irradiated should not be considered measurable lesions.

Non-target lesions will also be monitored throughout the study, and an assessment of non-target lesions will be made and recorded as "present", "present with progression" or "absent".

Details of any new lesions will also be collected.

It is important to follow the assessment schedule as closely as possible. If an unscheduled radiological and clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan, Table 1).

Tumour assessment will be performed in accordance with the protocol schedule until evidence of one of the following:

- Objective PD
- Death
- Withdrawal of informed consent
- Withdrawal from study therapy.

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions.

Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (eg, CT, MRI or plain X-ray), prompted by symptoms is considered disease progression and should be recorded as new lesions. If progression is uncertain, patients should continue on treatment until the next scheduled assessment (ie, 6 weeks later ±7 days) or may have an unscheduled assessment earlier than this if considered appropriate by the investigator.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the CRF page in the same order as they were recorded at screening.

Details of any new lesions will also be collected. Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum. Overall visit response will be recorded on the CRF.

Categorisation of overall visit response will be based on RECIST using the following response categories: CR, PR, SD, and PD (see Appendix C). To be assigned a best overall response of PR or CR, changes in tumour assessments must be confirmed no less than 4 weeks after the criteria for response were met. For a best overall response of SD, measurements must have met the SD criteria at least once after start of study treatment for a minimum interval of 6 weeks.

Measurable lesions will also be used to monitor the change in tumour length, which will also be used as a preliminary assessment of efficacy.

4.3.2.2 Tumour assessment by imaging techniques for patients with non-measurable disease only at baseline

For patients with non-measurable disease only at baseline, other measures of efficacy for patients can be used at investigator discretion. In these cases, the investigator will decide the imaging methods used and the schedule of the tumour assessments.

4.4 Safety measurements

4.4.1 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the study plan (see Table 1). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of blood and urine sample collection will be recorded on the appropriate CRF.

Blood samples should be collected for all clinical chemistry and haematology parameters. Fasting samples are not required for this study (except if random blood glucose is >13.9 mmol/L then a fasting blood glucose [minimum 8 hours fast without sugar-containing drinks] is recommended to confirm hyperglycemia).

The laboratory assessments will be performed locally at each centre's laboratory by means of their established methods.

Glucose and potassium monitoring: On Days D1 and R14 a blood sample should be taken at 6 hours post-dose for measurement of potassium and glucose levels only. Additional monitoring of potassium should be undertaken if the patient receives drugs that may cause hyperkalemia. Hyperkalemia should be managed according to local standards. Hyperglycemia should be managed according to local standards.

Females of child bearing potential must give a sample of the first urine passed during the day (see Table 1) for a pregnancy test to be performed.

All laboratory safety analyses will be performed by a local laboratory.

The following laboratory variables will be measured:

Clinical chemistry	**Haematology**
P – Urea	B – Haemoglobin
P – Creatinine	B – Erythrocyte count
P – Glucose (fasting [b])	B – Haematocrit
P – Sodium	B – Platelet count
P – Potassium	B – Total leukocyte count
P – Calcium	B – Mean cell haemoglobin concentration
P – Albumin	B – Mean cell volume
P – Total bilirubin	B – Mean cell haemoglobin
P – Alkaline phosphatase	B – Monocytes (absolute)
P – AST	B – Eosinophils (absolute)
P – ALT	B – Basophils (absolute)
P – Gamma glutamyltransferase	B – Neutrophils (absolute)
P – Lactate dehydrogenase	B – Lymphocytes (absolute)
P – Unconjugated bilirubin (if total bilirubin elevated)	**Urinalysis**
Additional analyses at screening only	U – Glucose
P – Activated partial thromboplastin time	U – Protein [a]
P – International normalisation ratio	U – Blood [a]
B – HbA1c	U – Urine sediment microscopy (Crystals, Casts, Epithelial Cells, Leucocytes and Erythrocytes)

[a] If blood or protein are present at ≥ +, urine sediment microscopy will be performed on the sample.
[b] Fasting glucose only if random blood glucose is >13.9 mmol/L.
B – Blood, P – Plasma, U – Urine

4.4.2 Electrocardiographic measurements

For timing of individual measurements, refer to the study plan (Table 1).

4.4.2.1 Echocardiography

Echocardiography and Doppler measurements should be done at the times specified in Table 1. Echocardiography will also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in left ventricular function.

Echocardiography should include assessment of left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and LVEF. Doppler measurements should include peak velocity E point, peak velocity A point, and E/A ratio. It is strongly encouraged that the same

laboratory and operator perform the procedure for each individual patient. Other alternative methods of cardiac assessment may be used instead of echocardiography if they are a part of the local standard of care, or if the investigator considers them necessary for the therapeutic management of the patient.

Important cardiac symptoms should be reported as AEs. If necessary to safeguard the patient's safety, the patient should be withdrawn from the study.

Congestive cardiac failure should be treated and followed according to standard medical practice.

4.4.2.2 Resting 12-lead ECG

ECG measurements should be done at the times specified in Table 1. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study. 12-lead ECGs will be recorded at 25 mm/sec after the patient has been resting in a supine position for 10 minutes in each case.

Digital 12-lead ECGs (in triplicate for central review) are required on Days D1 and R14 (full PK sampling days) for analysis of QTc interval, and should be repeated 3 times (one after another) at each sampling time. Paper read-outs of all ECG time points are sufficient for on site safety assessments.

The QTc interval should be the mean of the 3 digital 12-lead ECG recordings, taken from the lead in which the T-wave is highest.

The investigator or designated physician will review the paper copies of each of the ECGs. Decisions on dose escalation will be based on the local reading of the ECGs. Also, ECGs with evidence of increased QTc intervals should be collected. If any clinically significant finding is observed on the ECG, the investigator will record this as an AE.

Digital ECG recordings will be collected and reviewed by a central ECG vendor to allow direct pooling of the data.

4.4.3 Vital signs

4.4.3.1 Blood pressure and heart rate

For timing of individual measurements, refer to the study plan (Table 1).

BP and heart rate will be measured (single measurement) using a semi-automatic BP recording device with an appropriate cuff size after the patient has been sitting down for 10 minutes.

4.4.4 Dermatological examination

For timing of full dermatological examinations, refer to the study plan (Table 1). Brief symptom-directed examinations or follow-up of existing skin lesions should be performed at study visits, as appropriate.

Patients will be examined for signs of dermatological toxicity. In case of clinically relevant dermatological abnormalities, a symptom-directed examination should be performed. Important symptoms should be reported using CTCAE version 3.0 criteria.

4.4.5 Ophthalmic assessments

Ophthalmic assessment will be performed on each occasion by the same ophthalmic expert where possible. For timing of individual assessments, refer to the study plan (Table 1).

The following assessments will be performed in the order stated:

- Visual acuity (best corrected) using both distance and near vision charts and Amsler grid test
- Schirmer's test without anaesthesia – read after 5 minutes (this test should be done before instillation of stains or dilatory agents)
- Slit lamp examination:
  - Evert lid and assess for presence of tarsal, fornicial, bulbar and circumcorneal hyperaemia. Before staining, photograph any abnormalities to be captured.
  - Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
  - Photograph any abnormalities
- Fundoscopy following pupil dilatation, Schirmer's test without anaesthesia (read after 5 minutes) and intraocular pressure measurement will be performed at pre-study examination only but may be repeated at the ophthalmologist's discretion. Fundoscopy may be the last appropriate test.

Any corneal changes must be monitored frequently, with therapeutic intervention as appropriate until resolution. Any abnormalities elicited will be recorded as an AE.

In addition, patients will provide responses to the questions below at weekly intervals, by diary card. Patients will be advised to call the designated trial contact if they answer 'yes' to any of the following questions:

- Are you experiencing any symptoms with regard to your eyes? (grittiness, dryness, irritation, discomfort, burning, pain)
- Have you noted any change in vision in either eye, for distance or near (reading)?
- Are your eyes light sensitive (photophobia)?
- Do you get excessive watering from the eyes (lacrimation or epiphora)?

If the answer to any one of the above is 'Yes', the patient should be questioned about any confounding factors and should be examined by the study ophthalmologist as soon as possible, preferably on the same day.

At all visits, patients should be examined briefly for presence of ophthalmological abnormalities. In case of clinically relevant ophthalmological abnormalities, a full examination (as detailed above) must be performed. Important symptoms should be reported as AEs (or DLT, if appropriate; see Section 3.1.5). Clinical photographs with the slit-lamp camera should be taken, with and without fluorescein (please note images without fluorescein should be obtained first where possible). The patient should be managed under the care of a competent ophthalmologist with appropriate medication and followed up until the condition has resolved.

4.5 Genetic measurements and co-variables

An optional blood sample for genotyping will be collected on Day 1 from all patients who provide written informed consent to confirm their willingness to take part in genetic research. As genotype is a stable parameter, if for any reason the blood sample is not drawn on Day 1, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

See Appendix G for details.

Genetic data will be reported separately to the Clinical Study Report.

4.6 Volume of blood sampling

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 3 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	Number of samples per patient	Total volume per patient (mL)
Pharmacokinetics	3.0	19	57.0
Safety [a]	[c]		144.0 [d]
Pharmacogenetics [b]	9.0	1	9.0
Cell death (proapoptotic) biomarkers [b]	3.0	6	18.0
Total (with optional samples)			**228** [d]
Total (without optional samples)			**201** [d]

INR = International Normalized Ratio

a Including clinical chemistry and haematology (11 samples each per patient), glucose and potassium (6 hours post-dose on days D1 and R14) (2 samples per patient), and screening tests (INR etc.).

b Optional sample.

c Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The blood volumes are therefore subject to site-specific change.

d Approximate maximum volume.

For patients who continue dosing beyond the DLT evaluation period, a blood sample for laboratory safety analyses and an optional blood sample (3 mL) for proapoptotic biomarkers may be collected at each visit.

Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment, but will be not greater than 10% more of the planned volume.

4.7 Adverse Events

The methods for collecting AEs are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of AEs, SAEs and other significant AEs (OAEs) are given below. It is of the utmost importance 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 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or observation periods, even if no study treatment has been administered.

Any events that are unequivocally due to PD must not be reported as an AE. Signs and symptoms clearly associated with the disease under study should not be reported as AEs unless they are newly emergent (ie, not previously observed in the patient) judged by the investigator to be unusually severe or accelerated, or if the investigator considers deterioration of disease related signs and symptoms to be caused directly by the drug.

Serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, observation, 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.

If a patient is hospitalised purely for convenience, to enable easier performance of study assessments, the hospitalisation does NOT qualify as an SAE.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form 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 any of the following – study medication – other medication?”. For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B.

Any events that are unequivocally due to PD must not be reported as an SAE.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs 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.

4.7.1.2 Recording of adverse events

Time period for collection of AE/SAEs

Non-serious AEs and SAEs will be collected from the time informed consent is given and throughout the treatment period until 30 days after the last dose of study drug.

Method for detecting AE/SAEs

The method of detecting AE and SAEs in this study will be by:

- Information volunteered by the patient, or carer
- Open-ended and non-leading verbal questioning of the patient at every visit, such as the following: "How are you feeling? Have you had any (other) medical problems since your last visit?"
- Observation by the investigational team, other care providers or relatives

Collection of AE data

All AEs will be recorded on the pCRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (eg, changes to study treatment, other treatment given, follow-up tests) and outcome, should be provided along with the investigator's assessment of causality (the relationship to the study treatment[s]). AEs will also be graded according to the NCI CTCAE, version 3 (Appendix E). The maximum CTCAE grade must be recorded on the CRF.

AEs will be coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Causality

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 B for guidelines on interpretation of causality).

Deaths

All deaths that occur during the study, or within 30 days after the administration of the last dose of study treatment, must be reported as follows:

- Death that is clearly the result of PD should be reported to the study monitor at the next monitoring visit and should be documented in the pCRF but should not be reported as a SAE
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death
- Deaths with an unknown cause should always be reported as a SAE. A post mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post mortem results should be forwarded to Medical Services within the usual timeframes

A statement of death form should be submitted at any point during the study (to Medical Services) when a patient has died.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be PD.

Abnormal laboratory findings

Laboratory abnormalities should not be reported as an AE unless any criterion for a SAE is fulfilled, the laboratory abnormalities cause the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE. If an abnormal laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated abnormal laboratory result should be considered additional information. The reporting of laboratory abnormalities as both laboratory findings and AEs should be avoided.

An isolated grade 4 NCI CTCAE laboratory abnormality should be only reported as an SAE when meeting standard ICH SAE criteria (see Section 4.7.1.1) as evaluated by the investigator. Any grade 4 laboratory abnormalities that are part of the disease profile should not be reported as an SAE before start of study treatment. In case of any uncertainty whether a specific grade 4 laboratory abnormality should be reported as a SAE or not, the Medical Monitor should be contacted to further discuss the finding.

Follow up of AEs/SAEs

After the initial AE/SAE report, the investigator is required to follow up proactively each patient and provide further information to Medical Services on the patient's condition. During the study, all AE/SAEs should be followed up to resolution or until the condition stabilises, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigators must record their opinions in the patient's medical records), or the patient is lost to follow-up. AEs/SAEs should be followed up after the final safety assessment (see Table 1), as deemed necessary by the investigator and/or AstraZeneca.

AstraZeneca reserves the right to ask for further information on any AE which may be considered of interest.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 8.3 regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.4. 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.

4.7.1.3 Reporting of serious adverse events

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

For SAE reporting:

will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report within 24 hours (one business day) for all fatal and life-threatening cases and by day five 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 Drug Safety Department (via Medical Services) within 1 day as described above. For a non-serious AE that becomes serious but which is not

fatal or life-threatening a report should be received by the AstraZeneca Drug Safety Department (via Medical Services) within 5 days.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF.

The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the European (EU) Clinical Trials Directive, this will be taken care of by AstraZeneca (see Section 7.1).

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of GCP as laid out in the ICH document "Good Clinical Practice: Consolidated Guideline".

The specific requirements of the genetic part of the study will be discussed with the investigator(s) (and other personnel involved with the study).

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the patient's medical notes (permission from the patient will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

Source verification of the genetic consent of participating patients will be performed and make sure that the investigational team is adhering to the specific requirements of the genetics aspects of the study.

5.1.3 Archiving of study documentation

will transfer all study documentation to AstraZeneca at the end of the study. AstraZeneca will retain all documentation pertaining to this study in the Clinical Document Management Centre in accordance with ICH-GCP requirements.

The investigator will retain all paper documentation pertaining to this study in a Data depot, until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in a ICH region (or until at

least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product).

5.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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 data were recorded, analysed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

5.3 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 of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first patient is entered into the study, the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic testing with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

5.4 Changes to the protocol

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

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

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the Ethics Committee must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

Amendments and new versions of the protocol will be distributed to each principal investigator(s) who in turn is responsible for the distribution of these documents to his or her Ethics Committee, 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.

5.5 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, this protocol shall prevail.

Specific reference to genetics should be included in the agreement. The contractual obligations should not include any additional payment for collecting the samples, unless special processing is required.

5.6 Study timetable and end of study

The study is expected to start in February 2008 (first patient in) and to be completed by March 2009 (last patient out). However, patients will have the option to continue treatment after the DLT evaluation period if, in the opinion of the investigator, the patient is receiving some benefit from therapy is free from intolerable toxicity and has not met a withdrawal criterion (see Section 3.3.5)

The results of the study (up to the end of the DLT evaluation period) will be presented in a Clinical Study Report. Any data collected from patients who continue treatment beyond the DLT evaluation period will be summarised in an addendum to the Clinical Study Report. End of study is defined as final database lock, which is the time point after which no subject will be exposed to study related activities.

5.6.1 Premature termination of the study

If the investigator, AstraZeneca, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study (or part of the study) may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- Decision of the SMC (see Section 6.6)
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enrol patients at an acceptable rate
- A decision on the part of AstraZeneca to suspend or discontinue development of AZD8931.

5.7 Data management

5.7.1 Case report forms

pCRFs will be used to record all data except for results of blood sample evaluations collected by the central laboratory. Raw laboratory and PK data will be electronically transferred to Data Management for inclusion in the study database. The transfer of derived data will be described in the statistical analysis plan (SAP).

Data should be recorded legibly in English onto the pCRFs in black ballpoint pen. Corrections should be made legibly and initialled and dated by approved personnel; the reasons for significant changes must be provided. Correction fluid or covering labels must not be used.

The study monitor will check data at the monitoring visits to the study site. The investigator will ensure that the data in the pCRFs are accurate, complete and legible.

pCRFs will be printed in at least triplicate on carbonless paper. The white copy of the pCRFs will be sent to Data Management, the green copy will be retained by the investigator in the site files, and the pink copy will be retained in the monitor's file.

Data from the completed pCRFs will be entered onto the study database by Data Management using double-data entry, and validated under the direction of the Data Manager. Any missing, invalid or inconsistent recordings in the pCRFs will be referred back to the investigator using a data query form and be documented for each individual patient before clean file status is declared.

The patient diary is primarily used to assess patient dosing compliance. Data from the patient diary will only be transcribed into the pCRF if appropriate. Any text must be translated into English before transcribing.

5.7.2 Genetic data

In the case of genotyping data, only the date and time the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the pCRF and database.

The genotyping data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the datasets from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

However, some or all of the clinical study dataset may be duplicated within the AstraZeneca LIMS database or other appropriate system for exploratory analysis.

5.8 Reporting of genotyping results

See Appendix G.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic / pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed by Clinical Pharmacology and DMPK AstraZeneca.

PK parameters to be calculated are:-

- Single dose plasma PK
  - AUC from time zero to 12 hours (AUC_{0-12}), 24 hours (AUC_{0-24}), time t (AUC_{0-t}) and infinity (AUC) after dosing, C_{max}, t_{max}, $t_{1/2}$, total apparent drug clearance (CL/F), apparent volume of distribution at (V/F)
- Multiple dose plasma PK
  - time to ss and assessment of any accumulation of AZD8931, including $AUCss_{0-12}$, Css_{max}, time to reach maximum plasma concentration at steady state (tss_{max}), CLss/F, Css_{min}, accumulation ratio (R_{AC}) and linearity factor

Other PK parameters may be determined if deemed appropriate.

Minimum plasma concentration (C_{min}), C_{max} and t_{max} (and Css_{min}, Css_{max} and tss_{max}) will be determined by visual inspection of the plasma concentration time profile. The area under the plasma concentration time curve from time zero to 12 and 24 hours after dosing, AUC_{0-12} and AUC_{0-24}, respectively, and from zero to the time of the last quantifiable plasma concentration, AUC_{0-t}, will be calculated using the linear trapezoidal rule (linear/log interpolation). The $t_{1/2}$ will be calculated from the equation $\ln(2)/ \lambda_z$ (where the rate constant of the slowest disposition phase [λ_z] will be calculated by log linear regression of the terminal portion of the concentration time profile where there are sufficient data [ie, the terminal phase is followed for at least 3 x $t_{1/2}$]). The AUC will be derived by using λ_z to extrapolate AUC_{0-t} to infinity. CL/F and Vss/F will be estimated by dividing the dose by the AUC and multiplying mean residence time by CL/F, respectively. Linearity factor will be determined by dividing $AUCss_{0-12}$ by AUC after the single dose and R_{AC} will be determined by dividing $AUCss_{0-12}$ by AUC_{0-12} after the single dose.

6.1.2 Population analyses

PK and safety data from this study and other future studies may be subjected to exploratory population PK-pharmacodynamic analyses. If appropriate, a detailed analysis plan will be

produced prior to any such investigations and will be reported separately. The output of these analyses may be used to influence the design of future studies.

6.1.3 Calculation or derivation of pharmacodynamic/exploratory variables (Not applicable)

6.1.4 Calculation or derivation of efficacy variables

Best overall response will be calculated as the best response recorded from date of start of study drug (taking as reference for PD the smallest measurements recorded since the treatment started) for each patient, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST criteria.

ORR is defined as the proportion of patients who have a best response of either CR or PR.

6.2 Safety evaluation

6.2.1 Calculation or derivation of safety variables

The following heart rate corrected QT intervals will be calculated: Fridericia (QTcF) and Bazett (QTcB).

The corrected QTc are calculated using:

$$QTc = \frac{QT}{RR^b}$$

(where b is 0.33 for the Fridericia correction and 0.5 for the Bazett correction).

RR = interval from the onset of one QRS complex to the onset of the next QRS complex.

6.3 Genetics as a co-variate

See Appendix G.

6.4 Statistical methods and determination of sample size

6.4.1 Statistical evaluation

Full details of all data summaries and listings will be documented in a SAP, which will be prepared and finalised before clean file and datalock of the data. will produce the SAP and perform all statistical analyses. Any deviations from those analyses presented here and/or in the SAP will be detailed in the Clinical Study Report. All outputs will be produced using SAS® software version 9 or later.

6.4.2 Description of variables in relation to hypotheses

6.4.2.1 Primary variables

The primary objective of the study is to investigate the safety and tolerability of AZD8931. This will be done through review of:

- AEs
- Physical examination results
- Dermatological examinations
- Ophthalmological assessments
- Vital signs (BP and heart rate)
- ECG parameters
- Echocardiographic parameters
- Clinical chemistry, haematology and urinalysis.

No formal hypotheses will be associated with these variables.

6.4.2.2 Secondary variables

Pharmacokinetics

The pharmacokinetic variables to be investigated are described in Section 6.1.1. No formal hypotheses will be associated with these variables.

ECG parameters

QT, QTcB and QTcF will be reported descriptively.

6.4.2.3 Exploratory variables

Pharmacodynamic/exploratory parameters

Analysis of data for exploratory biomarkers may be carried out. Any data will be reported separately from the main study data.

Efficacy parameters

The ORR, best overall RECIST response and/or other measures of efficacy will be presented descriptively. This will include graphical presentations of the percentage change from baseline in the sum of the lengths of the RECIST target lesions for individual subjects. More details will be given in the SAP.

6.4.3 Description of analysis sets

Three patient analysis sets will be used as defined in Table 4; the safety set, the dose escalation evaluable set and the PK evaluable set. The primary analysis set will be the dose escalation evaluable set.

Table 4 Definition of analysis sets

Analysis set	Definition
Safety set	This population comprises all patients entered into the study who received at least one dose of AZD8931
Dose escalation evaluable set*	All patients in the safety set who have either experienced a DLT, or received at least 80% of planned doses of AZD8931 and who had all safety assessments completed during the DLT evaluation period
PK evaluable set	All patients in the safety set who have Day D1 PK data and/or have Day R14 PK data (and have received all doses during the day before Day R14)

*The SMC decide evaluability in the absence of appropriate assessments

Rules for identification of significant protocol violations will be given in the SAP. If a substantial number of patients are deemed to be protocol violators a separate 'per-protocol' analysis set will be determined, prior to analysis, which will exclude these patients.

6.4.4 Methods of statistical analyses

6.4.4.1 Pharmacokinetic data

The PK analysis is described in Section 6.1.1. The PK endpoints will be listed for individual subjects and summarised by dose level.

6.4.5 Determination of sample size

No formal sample size calculations were performed since the study follows a 3+3 dose group dose escalation design (see Section 3.1.2).

6.5 Interim analyses (Not applicable)

No interim analyses are planned.

6.6 Data monitoring committee

Working rules of the SMC are described in the SMC charter.

The SMC will comprise:

- The principal investigators of all sites
- The AstraZeneca physician
- The Medical Monitor.

In each case at least one deputy may be nominated.

On a case-by-case basis, the SMC may seek advice from further experts, including qualified representatives of AstraZeneca/

Following completion of the DLT period by ≥3 evaluable patients, the SMC will review all available data and decide upon dose progression. Further 'ad-hoc' meetings of the SMC may be convened, if required.

The safety review of data from each dose group will lead to one of 4 possible outcomes:

- Escalate to a higher dose
- Repeat dose level in further patients to obtain 6 evaluable patients at that dose level
- Stop escalation and investigate lower dose(s) – the lower dose may be intermediate between the previous dose level and current dose level
- End study.

A consensus decision must be made. The SMC may seek advice from further experts, including qualified representatives of AstraZeneca, in order to reach a consensus decision. All decisions will be documented, and distributed to all SMC members.

No formal statistical analyses will be performed in the safety review.

Based on emerging data, including PK and/or safety data and/or pre-clinical data, the SMC can consider alternative schedules, including once-daily dosing, in consultation with AstraZeneca and

7. ETHICS

7.1 Ethics review

AstraZeneca will provide Central Ethics Committees and Regulatory Authorities with safety updates/reports according to local requirements. Investigators and local Ethics Committees will receive this information from

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

The principal investigator is responsible for informing the local Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The annual report must be submitted to the Ethics Committee annually, as local regulations require.

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must receive written approval before any patient participates in this genetic research.

7.2 Ethical conduct of the study

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

7.3 Informed consent

The principal investigator 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 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.

The principal investigator must store the original, signed Informed Consent Form. A copy of the 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.

The exploratory biomarker analysis is optional and the patient may participate in the main study without participating in this component. To participate in this component of the study the patient must sign and date the consent forms for both the main study and the biomarker component of the study. Copies of signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue this aspect of the study at any time.

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date the consent forms for both the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

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

7.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by patient number.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research. Reference to participation in this genetic research should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records. Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

8. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel as found on page 2 in this protocol, 'Procedures in case of Emergency'.

8.2 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. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.3.**

8.3 Procedures in case of overdose

There is no known antidote for AZD8931, and there are no definitions regarding what constitutes an overdose. Investigators will be advised that any patient who inadvertently receives a higher dose than stated in the protocol should be treated with appropriate symptomatic, supportive care as required. All details should be recorded within the AE (if appropriate) and concomitant medication CRFs.

- Use of study drug in doses in excess of that specified in the protocol should not be recorded in the CRFs as an AE of 'Overdose' unless there are associated symptoms or signs

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRFs

- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRFs. In addition, the overdose should be reported on the separate "Clinical Study Overdose Report Form"

- An overdose without associated symptoms should not be recorded as an AE in the CRFs. The overdose should be reported on the separate "Clinical Study Overdose Report Form"

8.4 Procedures in case of pregnancy

Pregnancy itself (in either a patient or the patient's partner) 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. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

If pregnancy or a positive pregnancy test occurs in a patient or in the partner of a patient during study participation, study drug must be immediately discontinued.

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 on the pregnancy outcomes report form.

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Clinical Study Protocol: Appendix B

Drug Substance	AZD8931
Study Code	D0102C00002
Appendix Edition Number	1
Appendix Date	

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject 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 situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema 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 (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the 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. A specific laboratory investigation (if performed) has 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. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Amended Clinical Study Protocol: Appendix C	
Drug Substance	AZD8931
Study Code	D0102C00002
Appendix Edition Number	2
Appendix Date	

Appendix C
Definitions of Measurable, Non-measurable, Target and Non-target Lesions and Treatment Evaluation Response Based on the RECIST (Response Evaluation Criteria in Solid Tumours) Criteria*

* Therasse et al 2000.

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1. INTRODUCTION

This appendix details the implementation of RECIST for study D0102C00002 in regards to the investigator site review, including modifications specific for this study.

2. SCHEDULE OF EVALUATION

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. Baseline assessment must be able to adequately define all areas of disease. Any other sites at which new disease is suspected should also be properly imaged at follow-up.

The same method of assessment and the same technique should be used at baseline and follow-up.

All imaging should be performed according to the study plan (see protocol Table 1)

DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

Measurable:

- Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20mm with conventional techniques or as ≥10 mm with spiral CT scan

Non-measurable:

- All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan)
- Truly non-measurable lesions 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; cystic lesions
- Lesions that have been previous irradiated should not be considered measurable lesion.

3. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

All measurements should be recorded in metric notation by use of a ruler, callipers or electronic callipers etc.

Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

A summary of the methods of assessment originally reviewed for RECIST is provided below and those excluded from tumour assessments for this study are highlighted with the rationale provided.

3.1 Clinical examination

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, 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.

In study D0102C00002 clinical assessment will not be used for measuring target lesion selected for response assessment. Clinical examination will however be used to assess non-target and new lesions.

3.2 Chest x-ray

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

In study D0102C00002 chest X-ray assessment will not be used as part of RECIST assessment for measurable lesions, as CT or MRI examinations are being performed, which provide a more precise measurement. Chest radiograph will however be used to assess non-target and new lesions.

Note: Plain X-ray may be principally used for confirmation of bone lesions visible on bone scans, assessed as non-target and new lesions.

3.3 CT and MRI (target and non target lesions)

CT and MRI are generally considered to be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head and neck and extremities usually require specific protocols.

It is recommended that baseline CT examination to be performed to adequately define all areas of disease. Post-baseline imaging should follow and evaluate all previous identified lesions. CT examination with intravenous (iv) contrast media administration is the preferred method. If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study than the recommended methods are: CT chest examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without iv contrast is an option for the chest, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

3.4 Ultrasound

Ultrasound (US) should not be used to measure tumour lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

In study D0102C00002 ultrasound examination will not be used as part of RECIST assessment for measurable lesions as it is not a reproducible method and does not provide an accurate assessment of tumour size. If new or worsening clinical symptoms occur and an ultrasound is performed then new lesions or progression of the existing lesions needs to be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

The utilization of these techniques for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

These methods will not be used as part of the RECIST assessment in this study.

In study D0102C00002 these methods will not be used as part of the RECIST assessment as they are not validated in the context of tumour assessments.

3.6 Tumour markers

According to RECIST criteria, tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Tumour markers will not contribute to the response assessment in study D0102C00002.

3.7 Cytology and histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

In study D0102C00002 these methods will not be used as part of the RECIST assessment.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

Where cytology findings are not available, pleural effusion that worsens or appears will be considered to be progression of non-target lesions, or disease progression due to new lesions.

3.8 Note: Radioisotope bone scans will not be used to assess bone lesions as non-target or new lesions as it is not an accepted method of assessment for RECIST. Bone lesions identified on an isotopic bone scan and confirmed by CT, MRI or X-ray at baseline should be recorded as non-target lesions and followed by the same method as per study schedule. If new bone lesions or worsening bone symptoms occur and a bone scan is performed then worsening of disease needs to be confirmed by X-ray, CT or MRI and recorded as a new lesion.

4. TUMOUR RESPONSE EVALUATION

4.1 Assessment of overall tumour burden and measurable disease

To assess the objective response during the study, it is necessary to estimate the overall tumour burden at baseline to which subsequent measurements will be compared.

Patients with non-measurable disease only are not excluded from this study.

Tumour assessment will be performed using RECIST criteria for patients with measurable disease.

Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

4.2 Target lesions

4.2.1 Documentation of target lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

The longest diameter will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

If a lesion splits into 2 or more parts, then the sum of the LDs of those parts is recorded.

If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion.

If a lesion becomes too small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD.

If a lesion cannot be measured accurately due to progression, then the maximum measurable LD should be used in the sum LD and response assessment.

If a lesion cannot be measured accurately due to it being too large, and was measurable previously, then the maximum measurable size should be recorded as the LD and should be used in the sum LD and response assessment.

4.2.2 Evaluation of target lesions:

This section provides the definitions of the criteria used to determine objective tumour response for target lesions:

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded (either at baseline or at previous assessment since treatment began)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions

4.3 Non-target lesions

4.3.1 Documentation of non- target lesions

All other lesions (or sites of disease) not recorded as target lesions should be identified as non-target lesions and should also be recorded at baseline.

Measurements are not required for these lesions, but these should be followed as “present”, “absent” or “present with progression” at subsequent visits.

4.3.2 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine objective tumour response for non- target lesions:

Complete Response (CR)	Disappearance of all non-target lesions
Incomplete response / Stable Disease	Persistence of one or more non-target lesion
Progression (PD)	Unequivocal progression of existing non-target lesions.

In study D0102C00002 non-target lesions will be recorded and assessed as a group.

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.

4.3.3 Evaluation of Overall Visit Response and Best Overall Response

Overall visit response will be derived by the Investigator at site and recorded on the CRF. Overall visit response will be derived from assessment of target, non-target and new lesions as part of the analysis for this study.

Overall Visit Response Table

Target lesions	Non-target lesions	New lesions	Overall visit 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; PD = progressive disease

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).

Best overall response will be derived as part of the study analysis by the sponsor.

5. CONFIRMATORY MEASUREMENT

5.1 Confirmation

The main goal of confirmation of objective response is to minimise the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomised trials where response is the primary endpoint.

In study D0102C00002, to be assigned a status of PR or CR, changes in tumour assessment must be confirmed at the next visit assessment (no less than 4 weeks after the criteria of response were met).

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies and as such these protocols for computed tomography (CT) and magnetic resonance imaging (MRI) scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest. The type of CT scanner is important regarding the slice thickness and minimum sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm.

Other body parts, where CT scans are of different slice thickness, (such as the neck, which are typically of 5 mm thickness) or in the young paediatric population, where the slice thickness may be different, the minimum sized lesion allowable will be different.

In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses.

Intra-venous (iv) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. The method of administration of iv contrast agents is variable. It is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject.

All images from each examination should be included and not “selected” images of the apparent lesion.

All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination, then on soft tissue settings on the next. In the lung, it does not really matter whether lung or soft tissue windows are used for intra-parenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate using the same window settings for repeated examinations throughout the study.

MRI

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be

measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Wherever possible, the same scanner should be used. Moreover many subjects with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is at this point in time the imaging modality of choice.

Same method

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

7. REFERENCES

Therasse et al 2000
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumours. Journal of the National Cancer Institute. 2000;92(3):205-216.

AstraZeneca

Clinical Study Protocol: Appendix D	
Drug Substance	AZD8931
Study Code	D0102C00002
Appendix Edition Number	1
Appendix Date	

Appendix D
World Health Organization Performance Status*

* Miller AB, Hoostraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214.

WORLD HEALTH ORGANIZATION PERFORMANCE STATUS

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

Clinical Study Protocol: Appendix E	
Drug Substance	AZD8931
Study Code	D0102C00002
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Appendix Date	

Appendix E
Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

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ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*:	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome						
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*:	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia						
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin. ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- – External ear
- – Middle ear

CARDIOVASCULAR
- – Cardiac/heart
- – Pericardium

DERMATOLOGY/SKIN
- – Face
- – Lip
- – Oral-gums
- – Scalp
- – Skin

GASTROINTESTINAL
- – Abdomen NOS
- – Anus
- – Dental/teeth/peridontal
- – Esophagus
- – Oral cavity
- – Peritoneum
- – Rectum
- – Stomach

GENERAL
- – Pain NOS
- – Tumor pain

HEPATOBILIARY/PANCREAS
- – Gallbladder
- – Liver

LYMPHATIC
- – Lymph node

MUSCULOSKELETAL
- – Back
- – Bone
- – Buttock
- – Extremity-limb
- – Intestine
- – Joint
- – Muscle
- – Neck
- – Phantom (pain associated with missing limb)

NEUROLOGY
- – Head/headache
- – Neuralgia/peripheral nerve

OCULAR
- – Eye

PULMONARY/UPPER RESPIRATORY
- – Chest wall
- – Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- – Larynx
- – Pleura
- – Sinus
- – Throat/pharynx/larynx

RENAL/GENITOURINARY
- – Bladder
- – Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- – Breast
- – Ovulatory
- – Pelvis
- – Penis
- – Perineum
- – Prostate
- – Scrotum
- – Testicle
- – Urethra
- – Uterus
- – Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

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Appendix F
List of Medications to be Avoided or Used with Caution in Combination with AZD8931

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GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

NB. This list is not exhaustive and the absence of a drug from the list does not imply that its combination with AZD8931 is safe. Please contact the Medical Monitor or AstraZeneca physician if further clarification is required.

Drugs, which are permitted at steady state on a stable dose, may be used at investigator's discretion for acute indications. (eg, ondansetron for vomiting).

1. DRUGS AFFECTING CYTOCHROME P450

1.1 Potent inhibitors: May increase exposure to AZD8931 by more than 3-fold

The following drugs should not be combined with AZD8931.

Contra-indicated		
Drug	**Inhibits**	**Minimum washout period prior to AZD8931 administration**
Ketoconazole	CYP3A4	2 days
Ritonavir	CYP3A4	
Saquinavir	CYP3A4	
Indanavir	CYP3A4	
Nefazodone	CYP3A4	
Itraconazole	CYP3A4	7 days
Clarithromycin (250 mg bd or 500 mg bd)	CYP3A4	
Erythromycin	CYP3A4	
Fluconazole 400 mg	CYP3A4	
Diltiazam	CYP3A4	2 Weeks
Quinidine	CYP2D6	7 days
Paroxetine	CYP2D6	2 weeks
Fluoxetine	CYP2D6	5 weeks

1.2 Potent Inducers of CYP3A4: May reduce exposure to AZD8931 by more than 3-fold

The following drugs should not be combined with AZD8931.

Contra-indicated	
Barbiturates	**Minimum of 2 Weeks Washout prior to AZD8931 administration**
Carbamazepine	
Phenytoin	
Rifampicin, Rifabutin	
St John's Wort	

1.3 Moderate Inhibitors of Cytochrome P450: May increase exposure to AZD8931

Caution should be exercised in combining the following drugs with AZD8931.

Warning of possible interaction		
Drug	**Inhibits**	
Verapamil	CYP3A4	These drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD8931.
Nelfinavir	CYP3A4	
Grapefruit juice	CYP3A4	Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study. Please do not have more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily.
Seville oranges (and other products containing Seville oranges)	CYP3A4	
Duloxetine	CYP2D6	These drugs are permitted but caution should be

Warning of possible interaction		
Drug	**Inhibits**	
Terbinafine	CYP2D6	exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD8931.

2. DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by
and
.

Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

2.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD8931. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Contraindicated drug	**Withdrawal period**
Clarithromycin	2 days
Droperidol	
Erythromycin	
Procainamide	
Cisapride	7days
Disopyramide	
Dofetilide	
Domperidone*	
Ibutilide	
Quinidine	
Sotalol	
Sparfloxacin	
Thioridazine	
Bepridil	14 days

Contraindicated drug	Withdrawal period
Chlorpromazine	
Halofantrine	
Haloperidol	
Mesoridazine	
Levomethadyl	4 weeks
Methadone	
Pimozide	
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone	1 year
Chloroquine	

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

2.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Warning of possible interaction	
Drug	**Minimum treatment period**
Alfuzosin	2 days
Chloral hydrate	
Ciprofloxacin	
Dolasetron	
Foscarnet	
Galantamine	
Gemifloxacin	
Isradipine	
Ketoconazole	
Levofloxacin	
Mexiletine	
Nicardipine	
Octreotide	
Ofloxacin	

Warning of possible interaction	
Drug	**Minimum treatment period**
Ondansetron	2 days
Quetiapine	
Ranolazine	
Telithromycin	
Tizanidine	
Vardenafil	
Venlafaxine	
Ziprasidone	
Amantadine	7 days
Amitriptyline	
Amoxapine	
Clozapine	
Doxepin	
Felbamate	
Flecainide	
Fluconazole	
Fosphenytoin	
Gatifloxacin	
Granisetron	
Imipramine	
Indapamide	
Lithium	
Moexipril/HCTZ	
Moxifloxacin	
Risperidone	
Roxithromycin	
Sertraline	
Trimethoprim-Sulfa	
Trimipramine	
Voriconazole	

Warning of possible interaction	
Drug	**Minimum treatment period**
Azithromycin	14 days
Citalopram	
Clomipramine	
Itraconazole	
Nortriptyline	
Paroxetine	
Solifenacin	
Tacrolimus	
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

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Appendix G
Details of Exploratory Genetic Research

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1. GENETIC COMPONENT

As an exploratory objective, it is planned to take blood samples for future pharmacogenetic analysis, with the intention to determine any potential ability to identify individuals who may respond optimally to AZD8931 or a specific dose of AZD8931, or to identify factors that may affect the absorption, distribution, metabolism or excretion or tolerability of AZD8931 or its comparators.

Optional blood samples will be collected for pharmacogenetic research. Patients who agree to take part in this genetic research will be asked to sign a separate informed consent form to confirm their willingness to have this sample taken. The patient may participate in the main study without participating in the genetic component. The samples will be stored and analysed for future research. Patients from all centres are eligible to participate in the pharmacogenetic research. No planned number of patients is required for this genetic research.

1.1 Procedures for discontinuation from genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this linked genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any deoxyribonucleic acid (DNA) extracted from the sample being kept for genetic analyses in the future.

- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to the Clinical Genotyping Group (CGG) at AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator site file. Requests by the patient to withdraw from the genetic research should be made through the principal investigator, who will inform the CGG and the study monitor to that effect. The address of the CGG group is:

2. GENETIC MEASUREMENTS AND CO-VARIABLES

2.1 Collection of samples for genetic research

An optional blood sample for genotyping will be collected on Day 1 from patients who provide written informed consent to confirm their willingness to take part in genetic research. As genotype is a stable parameter, if for any reason the blood sample is not drawn on Day 1, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

A single venous blood sample (9 mL) will be collected into a polypropylene tube containing ethylenediamine-tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date and time of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the case report form (CRF).

2.2 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within 1 month of collection and must remain frozen at all times.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment number and/or patient number and date of sample collection, should accompany the shipment.

2.3 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labelled with the study number and patient number. Only the investigator will be able to link the blood sample to the individual patient. The sample and data will not be labelled with a personal identifier. The link between the patient enrolment/patient code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the CGG Laboratory Information Management System (LIMS) at AstraZeneca, The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotyping results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

2.4 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to AZD8931 or its comparators and/or susceptibility to or prognosis of advanced solid malignancies under investigation in this protocol. The results of the genetic research will not form part of the Clinical Study Report for this study. The results may be pooled with genetic data from other studies on AZD8931 to generate hypotheses to be tested in future studies.

2.5 Derivation or calculation of genetic parameters

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan (SAP) will be prepared where appropriate.

3. REPORTING OF GENOTYPING RESULTS

Results from any genetic research performed will be reported separately from the Clinical Study Report. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

4. GENETIC METHODOLOGY

4.1 Genetics as a co-variate

4.1.1 Calculation or derivation of genetic variables

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP will be prepared where appropriate.

Amended Clinical Study Protocol: Appendix I

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Appendix I
GUIDANCE TO INVESTIGATORS REGARDING OPTIMAL THERAPY OF RASH

1. GUIDANCE TO INVESTIGATORS REGARDING OPTIMAL THERAPY OF RASH

Investigators are recommended to institute appropriate management of AZD8931 rash-related adverse events in line with published recommendations, established practices, and investigator discretion relating to the management of rash associated with EGFR inhibitors. The D0102C00002 study protocol allows for the use of appropriate measures and protocol permitted medications in prophylactic or therapeutic management of toxicities in the study.

Systemic and topical therapies at or before the occurrence of rash of CTCAE Grade 3 severity (according to Version 3 Common Terminology Criteria for Adverse Events) are recommended. Appropriate systemic therapy may include permitted antibiotics, antihistamines and anti-inflammatory agents. AZD8931 treatment should be temporarily suspended if the rash progresses to CTCAE grade 3 severity.