PROTOCOL

TITLE:	A Phase 2, Randomized, Proof-of-Concept Study of Nab-Paclitaxel/Gemcitabine Alone and in Combination with ACP-196 in Subjects with Previously Untreated Metastatic Pancreatic Cancer
PROTOCOL NUMBER:	ACE-ST-004
STUDY DRUG:	ACP-196 (acalabrutinib)
IND NUMBER:	124612
EUDRACT NUMBER:	2015-003428-30
SPONSOR MEDICAL MONITOR:	[redacted]
SPONSOR:	Acerta Pharma BV Kloosterstraat 9 5349 AB Oss The Netherlands
STUDY CENTERS AND PRINCIPAL INVESTIGATORS:	[redacted]
PROTOCOL DATE:	Version 0.0 – 01 March 2015
AMENDMENT 1 DATE:	Version 1.0 – 18 May 2015
AMENDMENT 1.1 DATE:	Version 1.1 – 30 September 2015
AMENDMENT 2.0 DATE:	Version 2.0 – 18 November 2015
AMENDMENT 3.0 DATE:	Version 3.0 – 01 February 2016

Confidentiality Statement

PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-ST-004 entitled "A Phase 2, Randomized, Proof-of-Concept Study of Nab-Paclitaxel/Gemcitabine Alone and in Combination with ACP-196 in Subjects with Previously Untreated Metastatic Pancreatic Cancer." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Acerta Pharma representative is authorized to sign the protocol and any amendments:

[redacted]

SUMMARY OF AMENDMENT 3.0

This protocol is being amended to add hepatitis serology testing at screening. For subjects who test positive for latent hepatitis B infection at screening (or who have a known history of hepatitis B infection), this protocol will now require monthly monitoring for potential hepatitis B reactivation. The reason for this amendment is hepatitis B virus (HBV) reactivation has occurred in patients treated with Btk inhibitors (Ngoma 2015), including 1 subject on ACP-196 treatment.

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment:

Change	Rationale
In various parts of the protocol, the nonproprietary name for ACP-196 was introduced.	The nonproprietary name of acalabrutinib was recently approved for use.
Title page: On 01 January 2016, Sponsor address changed to Acerta Pharma BV, Kloosterstraat 9, 5349 AB Oss, The Netherlands	Administrative change.
Synopsis	Updated to reflect changes made throughout the protocol.
Section 3.3.2 Exclusion Criteria Revised exclusion criterion as follows (**bold** is new text): 15. Known history of HIV **or serologic status indicating** active ~~infection with~~ HCV or HBV infection or any **uncontrolled** active **systemic** infection~~ requiring systemic therapy with 14 days of randomization~~. **Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.**	Revised to provide greater detail on screening for active HBV and HCV infections.
Section 3.10 PRECAUTIONS New section and corresponding language was added: **Section 3.10.1 Hepatitis B Virus Reactivation** **Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with ACP-196. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of HBV infection, should be monitored monthly with a**	As HBV reactivation has occurred in 1 subject on acalabrutinib treatment this language is being added to ensure adequate monitoring of patients with a history of HBV.

quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming ACP-196 in subjects who develop HBV reactivation.	
Section 4.1.8 Electrocardiogram Added the following text: **In addition, a single ECG will also be performed 1 hour after ACP-196 administration at Cycle 1 Day -1 for the first 6 subjects enrolled to Arm 1.**	Revised to clarify a discrepancy in the protocol.
Section 4.1.9 Urine or Serum Pregnancy Test Revised as follows (**bold** is new text): Pregnancy tests will be required only for women of childbearing potential. Testing will be done by a central **or local** laboratory as listed on the investigator's Form FDA 1572.	Clarifying edit.
Section 4.1 DESCRIPTION OF PROCEDURES New section and corresponding language was added: **Section 4.1.14 Hepatitis B and C Testing** **Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix 7 and exclusion criterion #15). Testing will be done by local or central laboratory.** **Refer to Section 3.10.1 and Appendix 7 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.**	Adds hepatitis serology at screening and monitoring for potential of HBV reaction in subjects with latent HBV infections.
Section 4.3 SAFETY FOLLOW-UP VISIT The following text was deleted: Each subject should be followed for 30 (+ 7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.5) and to document the occurrence of any new events~~; unless, the subject receives a new anticancer therapy within this timeframe.~~	Updated for consistency with other ACP-196 protocols.
Section 6.1.1 Adverse Events The definition of adverse event was revised as follows:	This change was made align the protocol with the ICH definition of "adverse

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product ~~or other protocol imposed intervention,~~ regardless of attribution. This includes the following: • AEs not previously observed in the subject that emerge during the protocol specified AE reporting period, including signs or symptoms associated with pancreatic cancer that were not present before the AE reporting period (see Section 6.2.1). • ~~Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).~~ • Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.	events".
Section 6.2.1 Adverse Event Reporting Period The following sentences were deleted from this section: The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the safety follow-up visit~~. If a subject received a new anticancer therapy before the safety follow-up visit then the AE reporting period ends with initiation of the new anticancer therapy. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure.~~	Updated for consistency with other ACP-196 protocols.
Section 6.2.3 Pregnancy The following correction was made (**bold** is new text): All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to ~~30~~ **90** days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.	Correction.
Section 6.2.4 Expedited Reporting Requirements for Serious Adverse Events New language was added to this section as follows: <u>Other Safety Issues Requiring Expedited Reporting</u> For studies being conducted in Europe expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational	This language was added as this is a global study.

medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006" available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.	
Section 6.2.5 Type and Duration of Follow-up of Subjects after Adverse Events All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable~~, a new anticancer therapy is initiated~~, or the subject is lost to follow-up or withdraws consent.	Updated for consistency with other ACP-196 protocols.
Section 7.6 Investigational Study Drug Accountability The following language was revised as follows (**bold** is new text): ACP-196 capsules must be kept in a locked limited access cabinet or space. ~~The study drug~~ **ACP-196** must not be used outside the context of the protocol. Study drug accountability records, **for ACP-196 and, when applicable, for nab-paclitaxel and gemcitabine,** must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.	Clarifying edits.
Section 8.0 References Reference list updated.	Updated to reflect changes made throughout the protocol.
Appendix 7 Schedule of Assessments Added tumor assessment at follow-up phase.	Added to correct an omission in the schedule of events.
Revised footnote "f" as follows (**bold** is new text): f. At Cycle 1 Day 1 and Cycle 1 Day 15, a single ECG will be done 1 hour after ACP-196 administration. **In addition, a single ECG will also be performed 1 hour after ACP 196 administration at Cycle 1 Day -1 for the first 6 subjects enrolled to Arm 1.**	Revised to clarify a discrepancy in the protocol.
Revised footnote "s" as follows (**bold** is new text):	Revised for clarification.

~~s. This urine or serum pregnancy test is to be performed on Cycle 1 Day 1 (- 3 days).~~ **The pregnancy test can be performed any day from -3 days prior to Cycle 1 Day 1 or on the same day as Cycle 1 Day 1.**	
Added the following footnote "t": **t. Per protocol, the first 6 subjects randomized to Arm 1 (ACP-196 + nab paclitaxel/gemcitabine) are dosed with ACP-196 first at Cycle 1 Day -1. For these 6 subjects, hematology, serum chemistry/CA 19-9, and coagulation panel must be performed and analyzed within 7 days before this first dose of ACP-196. Additionally, a urine pregnancy test must be performed and analyzed within 1 day of the Cycle 1 Day -1 first dose of ACP-196. These 4 labs may be performed either locally, or using the central laboratory.**	Revised to add these lab assessments at Cycle 1 Day -1.
Added hepatitis serology at screening and HBV PCR testing monthly, and added the following associated footnotes "u" and "v": **u. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #15).** **v. Subjects who are anti-HBc positive (or have a known history of HBV infection) should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.**	As HBV reactivation has occurred in 1 subject on acalabrutinib treatment hepatitis serology at screening and monthly HBV PCR testing are being added to ensure adequate monitoring of patients with a history of HBV.

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IN–TEXT FIGURES

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ABBREVIATIONS

5-FU	5-fluorouracil
AE	adverse event
Akt	protein kinase b
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BID	twice per day (dosing)
BOR	best overall response
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CA19-9	cancer antigen 19-9 (carbohydrate antigen 19-9)
CD	cluster of differentiation (cell surface marker)
cGMP	current Good Manufacturing Practice
CI	confidence interval
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response (remission)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
CTLA-4	cytotoxic t-lymphocyte-associated protein 4
CYP	cytochrome p450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food And Drug Administration
FOLFIRINOX	leucovorin, irinotecan, and oxaliplatin
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
HABP	hyaluronic-acid binding protein
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	Informed Consent Form
IEC	independent ethics committee
IND	investigational new drug application
IRB	institutional review board
IRR	Independent Radiology Review
ITT	intent-to-treat (analysis set)
IV	intravenous or intravenously
IXRS	Interactive Voice/Web Response System
Jak	Janus kinase
λ_z	terminal elimination rate constant
LDH	lactate dehydrogenase
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NE	nonevaluable
NK	natural killer (cells)
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OCT	organic cationic transporter
ORR	overall response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease or pharmacodynamics
PD-1	programmed death-1 (receptor)
PD-L1	programmed death ligand-1
PDX-1	Pancreatic and duodenal homeobox 1
PE	physical exam

PFS	progression-free survival
P-gp	p-glycoprotein 1 (transporter)
PI3K	phosphatidylinositol-3 kinase
PK	pharmacokinetic or pharmacokinetics
PO	per os (oral)
PP	per-protocol (analysis set)
PR	partial response (remission)
PR+L	partial response with lymphocytosis
PT	prothrombin time
Q3W	every three weeks
Q12W	every 12 weeks
QD	once per day (dosing)
QM	every month
QT	cardiac QT interval
QTc	corrected cardiac QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease or standard deviation
SLL	small lymphocytic leukemia
SMA	smooth muscle actin
SUSAR	suspected unexpected serious adverse reaction
Syk	spleen tyrosine kinase
$t_{½}$	terminal elimination half-life
TAM	tumor-associated macrophage
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
T_{reg}	regulatory T cell (lymphocyte)
ULN	upper limit of normal
V_z	volume of distribution
V_z/F	oral volume of distribution
WHODRUG	World Health Organization Drug Dictionary

STUDY SYNOPSIS

Protocol Number:	ACE-ST-004
Study Drug:	ACP-196 (acalabrutinib)
Comparator Drugs:	Nab-paclitaxel: paclitaxel protein-bound particles for injectable suspension Gemcitabine for injection
Protocol Title:	A Phase 2, Randomized, Proof-of-Concept Study of Nab-Paclitaxel/Gemcitabine Alone and in Combination With ACP-196 in Subjects with Previously Untreated Metastatic Pancreatic Cancer
Phase:	Phase 2
Study Centers:	Subjects will be enrolled at up to 30 centers globally.
Background and Rationale for Study	Pancreatic ductal adenocarcinoma exists in a complex desmoplastic microenvironment that provides stromal support for tumor growth and conceals the tumor from immune surveillance. Tumor-associated stroma comprises a mix of fibroblasts and an abundance of mast cells, immunosuppressive regulatory T cells (T_{regs}), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) that promote tumor growth and restrain immunologically mediated tumor cell killing. Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed in B cells, myeloid cells, and mast cells, where it regulates cellular proliferation, differentiation, apoptosis, and cell migration. Btk inhibition leads to preferential differentiation of macrophages into M1 instead of immunosuppressive M2 macrophages; Btk inhibition thus decreases the tumor-associated macrophages that promote tumor invasion and metastasis. Acerta Pharma BV is developing ACP-196, an orally bioavailable, small-molecule inhibitor of Btk. A Phase 1 study of ACP-196 in 31 subjects with relapsed/refractory chronic lymphocytic leukemia showed an overall response rate of 94%. ACP-196 monotherapy has shown robust antitumor activity in murine solid tumor models, including models of pancreatic cancer. Treatment with single-agent ACP-196 substantially slowed tumor growth and increased animal survival in a murine pancreatic cancer model. Further, the combination of ACP-196 and gemcitabine resulted in a greater reduction in tumor growth when compared to each single agent. The antitumor effect observed with ACP-196 correlates with biomarkers of response similar to those reported for other immunomodulating agents such as inhibitors of cytotoxic t-lymphocyte-associated protein 4

	(CTLA-4), programed cell death receptor (PD-1) and its ligand (PD1-L). The combination of nab-paclitaxel and gemcitabine has demonstrated statistically significant improvement in overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) as compared with gemcitabine alone in first-line treatment of metastatic adenocarcinoma of the pancreas. This proof-of-concept study will assess the clinical potential of ACP-196 in combination with nab-paclitaxel and gemcitabine by evaluating the safety, pharmacodynamics (PD), pharmacokinetics (PK), and efficacy of the ACP-196 combination in subjects with previously untreated metastatic pancreatic cancer.
Study Design:	This clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating ACP-196 plus nab-paclitaxel/gemcitabine compared with nab-paclitaxel/gemcitabine in subjects who have previously untreated metastatic pancreatic cancer. Subjects meeting the eligibility criteria for the study will be randomized 1:1 using an Interactive Voice/Web Response System (IXRS) to one of the following arms: Arm 1: ACP-196 100 mg administered orally (PO) twice per day (BID) on Days 1-28 and nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on Days 1, 8, and 15; cycles are repeated every 28 days. Arm 2: Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on Days 1, 8, and 15; cycles are repeated every 28 days. Although ACP-196 has not demonstrated any dose-limiting toxicities (DLTs) to date, the safety of ACP-196 in combination with nab-paclitaxel/gemcitabine in this patient population needs to be assessed and standard DLT criteria will be applied to Arm 1 of the study. Therefore an interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 1 cycle (1 cycle = 28 days). Enrollment will be paused while the safety interim analysis occurs. If ≤ 1 DLT is observed in Arm 1, then randomization will continue to evaluate the safety and efficacy of the ACP-196 combination (ie, up to 60 subjects per arm). If ≥ 2 DLTs are observed in Arm 1, then enrollment will continue until an additional 6 subjects are randomized to Arm 1, but with a reduced dose level for ACP-196 (Level -1). If the DLT review is cleared in those additional 6 subjects in Arm 1 then continued enrollment will occur at Level -1 for the ACP-196 combination arm. If ≥ 2 DLTs are observed in Arm 1 at Level -1, then an additional 6 subjects will be randomized at Level -2 and assessed for DLTs. If the DLT review is cleared, continued enrollment will occur at Level -2 for the ACP-196 combination arm. If the DLT review is not cleared, enrollment

	will be halted. In addition, analyses for toxicity will also be done as outlined in Section 5.5. Treatment can continue until the end of trial, defined as 52 weeks (13 cycles) after the last subject is randomized to the study, for subjects who are tolerating therapy and not progressing. Subjects who have **confirmed** progressive disease will discontinue study treatment. The primary efficacy analysis will be based on Investigator assessment. Independent radiology review (IRR) of the efficacy data will also be performed in accordance with the independent radiology review (IRR) charter. Refer to Appendix 7 for a comprehensive list of study assessments and their timing. A study schema is provided in Figure 3-1.
Definition of Dose-limiting Toxicity:	A DLT will be defined as the occurrence of any of the following ACP-196-related adverse events (AEs) (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs): 1. Grade 4 vomiting or diarrhea 2. Grade 3 nausea, vomiting, or diarrhea lasting for > 72 hours 3. Other Grade ≥ 3 toxicities (Note: Transient Grade 3/4 laboratory abnormalities, including chemotherapy induced myelosuppression, that are not clinically significant will not be considered DLTs) 4. Dosing delay due to toxicity for > 21 consecutive days.
Study Objectives:	**Primary Objective:** To evaluate the efficacy of ACP-196 and nab-paclitaxel/gemcitabine based on ORR in subjects with metastatic pancreatic cancer using standard response criteria. **Secondary Objective:** To characterize the safety profile of ACP-196 and nab-paclitaxel/gemcitabine in subjects with metastatic pancreatic cancer. **Exploratory Objectives:** • [redacted]

	• [redacted]
Safety Endpoints:	Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), DLTs or AEs leading to discontinuation of study treatment.
Pharmacodynamic, Pharmacokinetic and Biomarker Parameters:	The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 and nab-paclitaxel/gemcitabine on B cells, T cells, and MDSCs will also be evaluated. Tumor tissue will be evaluated for various tumor markers, including but not limited to: • hyaluronic-acid binding protein (HABP) • smooth muscle actin (SMA) • Ki67 proliferation • cleaved-caspase 3 • PD-1 and its ligand PD1-L ACP-196 will be measured in blood plasma.
Efficacy Endpoints:	• ORR defined as partial response (PR) or complete response (CR) based on modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Change in serum cancer antigen 19-9 (CA19-9)
Sample Size:	[redacted]
Inclusion Criteria:	1. Men and women ≥ 18 years of age. 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 3. Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas.

	4. Presence of radiographically measurable disease per RECIST 1.1. 5. No previous radiotherapy, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatment with 5-fluorouracil (5-FU) or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present. 6. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Highly effective forms of contraception are defined in Section 3.10.5. 7. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Highly effective forms of contraception are defined in Section 3.10.5. 8. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. 9. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. 10. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)
Exclusion Criteria:	1. Prior malignancy (other than pancreatic cancer), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years. Note: These cases must be discussed with the medical monitor. 2. Known central nervous system (CNS) metastases and/or carcinomatous meningitis. 3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening.

	4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. Note: Subjects with prior pancreatoduodenectomy are not excluded. 5. Biliary obstruction or presence of a percutaneous biliary drain. Note: Subjects with endobiliary stents may participate as long the enrollment criterion relating to serum bilirubin concentration is met. 6. Prior therapy with any inhibitor of Btk, protein kinase B (Akt), Janus kinase (Jak), mammalian target of rapamycin (mTOR), phosphatidylinositol-3 kinase (PI3K), or spleen tyrosine kinase (Syk). 7. History of interstitial lung disease or active non-infectious pneumonitis. 8. History of bleeding diathesis (eg, hemophilia or von Willebrand disease). 9. Major surgical procedure within 28 days of first dose of study drug. 10. Known hypersensitivity to gemcitabine or nab-paclitaxel. 11. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). 12. Requires treatment with a strong cytochrome P450 (CYP) 3A or CYP2C8 inhibitor/inducer. 13. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug. 14. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids. Note: At screening and during study participation, subjects may use topical or inhaled corticosteroids or systemic corticosteroids at dosages equivalent to prednisone ≤ 10 mg/day as therapy for comorbid conditions. 15. Known history of human immunodeficiency virus (HIV) or serologic status indicating active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.

	16. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug. 17. Absolute neutrophil count (ANC) < 1.5 x 10^9/L or platelet count < 100 x 10^9/L or hemoglobin < 9.0 g/dL. 18. Total bilirubin > upper limit of normal (ULN); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN. 19. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) > 1.2 x the ULN. 20. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female]. 21. Breastfeeding or pregnant. 22. Concurrent participation in another therapeutic clinical trial. 23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
Dose Regimen/Route of Administration:	ACP-196 is provided as hard gelatin capsules for oral administration. Nab-paclitaxel is supplied as lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution. It is administered as an IV infusion over 30 to 40 minutes. Gemcitabine is supplied in 200-mg and 1000-mg vials as a sterile lyophilized powder for reconstitution. It is administered as an IV infusion over 30 to 40 minutes immediately after nab-paclitaxel. **Arm 1 (ACP-196 plus nab-paclitaxel/gemcitabine):**

ACP-196 Dose Level	ACP-196 Dosing Regimen	Nab-paclitaxel/gemcitabine
Starting Dose	100 mg BID PO	See Arm 2
Level -1	100 mg QD PO	See Arm 2
Level -2	50 mg BID PO	See Arm 2

Abbreviations: BID = twice per day; PO = oral; QD = once per day
Note: 1 cycle of ACP-196 treatment is 28 days.

Arm 2 (nab-paclitaxel/gemcitabine):

Nab-paclitaxel 125 mg/m^2 intravenous (IV) infusion on Day 1, 8 and 15 of every 28-day cycle.

<table>
<tr><td></td><td>Gemcitabine 1000 mg/m^2 IV infusion on Day 1, 8 and 15 of every 28-day cycle.
<table>
<tr><th>Dose Level</th><th>Nab-paclitaxel (mg/m^2)</th><th>Gemcitabine (mg/m^2)</th></tr>
<tr><td>Starting Dose</td><td>125</td><td>1000</td></tr>
<tr><td>Level -1</td><td>100</td><td>800</td></tr>
<tr><td>Level -2</td><td>75</td><td>600</td></tr>
<tr><td>If additional dose reduction required</td><td>Discontinue</td><td>Discontinue</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications:</td><td>The concomitant use of strong inhibitors/inducers of CYP3A with ACP-196 should be avoided when possible. The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on ACP-196 absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors (eg, dexlansoprazole, rabeprazole, or pantoprazole) while taking ACP-196 is not recommended due to a potential decrease in study drug exposure. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A.</td></tr>
<tr><td>Statistical Methods:</td><td>Analysis Methods

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate.

Statistical Basis for the Sample Size

For the safety interim analysis (DLT review), enrollment of 6 subjects in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in ≤ 17% of subjects). Provided the study is not stopped early due to toxicity in the ACP-196 combination arm, then a total of 60 subjects will be randomized per arm.

The sample size for this 2-arm trial was determined by a Z-test for normal approximation of binomial distribution, based on one-sided α = 0.10, 80% power, with projected response rates of 42% in the ACP-196 combination arm and 23% in</td></tr>
</table>

	nab-paclitaxel/gemcitabine arm. Accounting for 10% drop-out rate (6 in each arm), final sample size is 60 in each arm.

1.0 BACKGROUND INFORMATION

1.1 PANCREATIC CANCER

In 2014, ~46,420 people in the United States will be diagnosed with pancreatic cancer (Siegel 2014). Because of the aggressive nature of this cancer, the annual mortality rates almost matches the incidence rate, and it is expected that ~39,590 will die from this disease in the same year. For the 20% of patients with disease involving only the pancreas, surgical resection is the primary therapy. In the ~80% of patients with regional disease extension or metastases at presentation, chemotherapy is the primary treatment (Tempero 2014). Among the therapeutic options, polychemotherapy with infusional 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) are commonly employed (Tempero 2014). Erlotinib in combination with gemcitabine has also been approved for front-line treatment of pancreatic cancer (TARCEVA prescribing information).

In the Phase 3 study, nab-paclitaxel + gemcitabine was tolerable and demonstrated superiority to gemcitabine alone for all efficacy endpoints in patients with metastatic pancreatic cancer. This trial met the study's primary endpoint by demonstrating a significant improvement in OS (median 8.5 vs 6.7 months; hazard ratio [HR] 0.72; 95% CI, 0.617 to 0.835; $P < 0.001$) and the secondary endpoints of PFS (median 5.5 vs 3.7 months; HR 0.69; 95% CI, 0.581 to 0.821; $P < 0.001$) and ORR (23% vs 7%; $P < 0.001$) (Von Hoff 2013).

However, because of the inherent chemoresistance of pancreatic cancer, median PFS with currently available regimens is ≤ 6 months (Conroy 2011, Von Hoff 2013). Moreover, while antitumor benefit has been observed with such regimens, toxicity is substantial. Novel, less toxic approaches are desperately needed for this lethal cancer.

1.2 THE ROLE OF STROMA IN PANCREATIC CANCER

The importance of pancreatic cancer stroma in the biology of pancreatic cancer has been increasingly recognized (Feig 2012, Rucki 2014, Wilson 2014). Pancreatic ductal adenocarcinoma exists in a complex desmoplastic microenvironment that provides stromal support for tumor growth and conceals the tumor from immune surveillance. Tumor-associated stroma comprises a mix of fibroblasts (pancreatic stellate cells) and an abundance of mast cells, immunosuppressive T_{regs}, MDSCs, and

TAMs that promote tumor growth and restrain immunologically mediated tumor cell killing (Shibuya 2014). Pancreatic cancers secrete chemokines that recruit immune cells to the tumor site. These immune cells are then activated either by direct contact or by cancer cell–derived triggers to selectively release “procancer” mediators (Feig 2012, Ma 2014). These mediators induce angiogenesis, promote tumor proliferation, inhibit antitumor responses, and alter the surrounding stroma to permit metastases. Treatment of tumor-bearing mice with agents that block immunocyte migration and function has been shown to decrease the growth of pancreatic cancer (Ma 2014, Shibuya 2014).

1.3 BRUTON TYROSINE KINASE INHIBITION IN CANCER

Btk is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Khan 2001, Mohamed 2009, Bradshaw 2010). In addition, Btk-dependent activation of mast cells, myeloid cells and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance (Soucek 2011, Ponader 2012, de Rooij 2012). Taken together, these findings suggest inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.

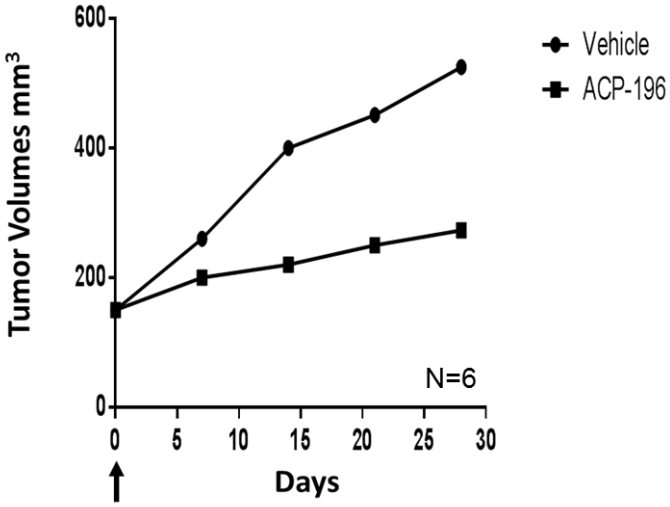
In model systems, ex vivo analyses demonstrated Btk inhibition results in macrophages that polarize into M1 macrophages, instead of showing enhanced induction of immunosuppressive M2 macrophages (Ni Gabhann 2014). These data suggest inhibition of Btk may impair the capacity of tumor-associated macrophages critical for promotion of tumor invasion and metastasis (Mouchemore 2013). Several lines of evidence demonstrate Btk inhibition interferes with cross-talk between malignant cells and their microenvironment, suggesting disruption of intrinsic and extrinsic survival signals may be a critical mechanism for the clinical activity of Btk inhibitors (Ponader 2012, Herman 2013). Furthermore, epithelial derived tumors contain large numbers of TAMs, which are the dominant innate immune cell in mammary cancers of humans (Pollard 2009). Therefore, the clinical usefulness of Btk inhibitors may extend to the treatment of invasive solid tumors.

Btk is also a signaling hub in immature myeloid cells known as MDSCs (Schmidt 2004). Recent evidence suggests MDSCs play an important part in suppression of host immune responses through several mechanisms such as production of arginase 1, release of reactive oxygen species, nitric oxide and secretion of immune-suppressive cytokines. This leads to an immunosuppressive environment necessary for the growth of malignant cells (Wesolowski 2013).

Immune evasion is one of the multiple characteristics of cancer. Monoclonal antibodies that block negative regulators of T cells, such as PD-1, amplify immune responses. Antibodies against PD-1 are showing impressive results in advanced hematologic and solid malignancies (Hamid 2013, Westin 2014, Berger 2008, Topalian 2014). Interestingly, studies examining circulating MDSCs in anti-CTL4 and anti-PD-1/PD-L1-treated patients have shown alterations in the myeloid cell compartment correlate with clinical outcome. Specifically, solid tumor progressors had proportionally higher circulating MDSC levels and a high myeloid gene signature (Powles 2014, Heery 2014, Weide 2014, Meyer 2014). Recent preclinical results show elevated MDSC levels are responsible for this lack of response and elimination of MDSCs may lead to increased efficacy with immune checkpoint blockade (Highfill 2014, Kim 2014).

Given the potential for Btk inhibition to affect TAMs and MDSCs, single-agent ACP-196 was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic and duodenal homeobox 1 differentiation promoter PDX-1 (KPC mice). The KPC mouse model recapitulates many of the molecular, histopathologic, and clinical features of human disease (Westphalen 2012). Mice were enrolled after identification of spontaneously appearing tumors in the pancreas that were ≥ 100 mm^3 (as assessed by high-resolution ultrasonography). Mice were treated with vehicle (N=6) or ACP-196 administered orally at a dosage of 15 mg/kg/dose BID (N=6). As shown in Figure 1-1, treatment with single-agent ACP-196 substantially slowed pancreatic cancer growth and increased animal survival.

Figure 1-1. Efficacy of ACP-196 Monotherapy in a Genetic Model of Pancreatic Cancer



Tumor volumes

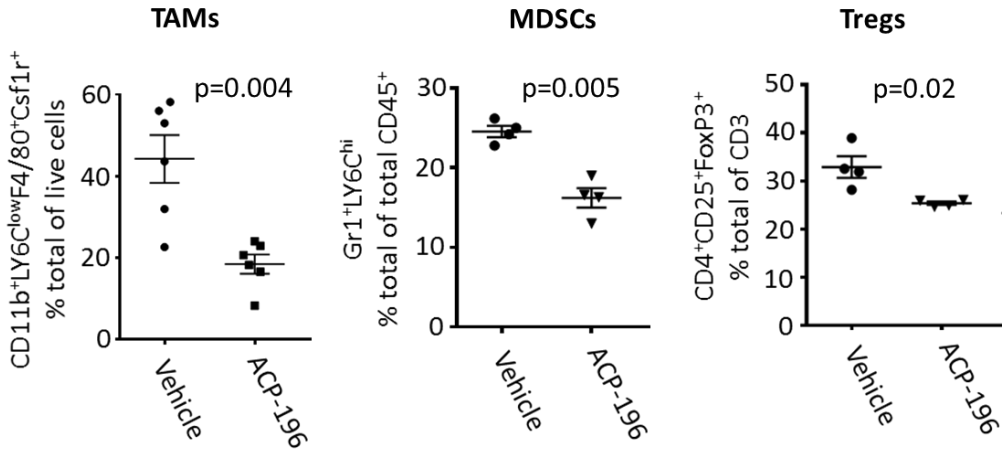
	Predose	Day 28
Control	152 mm³	525 mm³
ACP-196	165 mm³	272 mm³

Survival

	Day 14	Day 28
Control	5/6	0/6
ACP-196	6/6	5/6

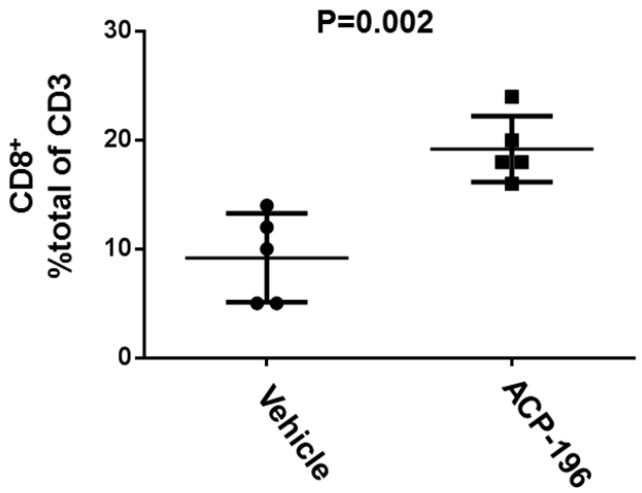
Analysis of tumor tissues showed that immunosuppressive TAMs ($CD11b^+Ly6C^{low}F4/80^+Csf1r^+$), MDSCs ($Gr1^+Ly6C^{Hi}$), and T_{reg} ($CD4^+CD25^+FoxP3^+$) were significantly reduced with ACP-196 treatment by 47%, 30%, and 20%, respectively (Figure 1-2). As expected the decrease in these immunosuppressive cell subsets correlated with a significant increase in CD8+ cells (Figure 1-3).

Figure 1-2. Effects of ACP-196 on Tumor-Associated Immunosuppressive Cells in a Genetic Model of Pancreatic Cancer



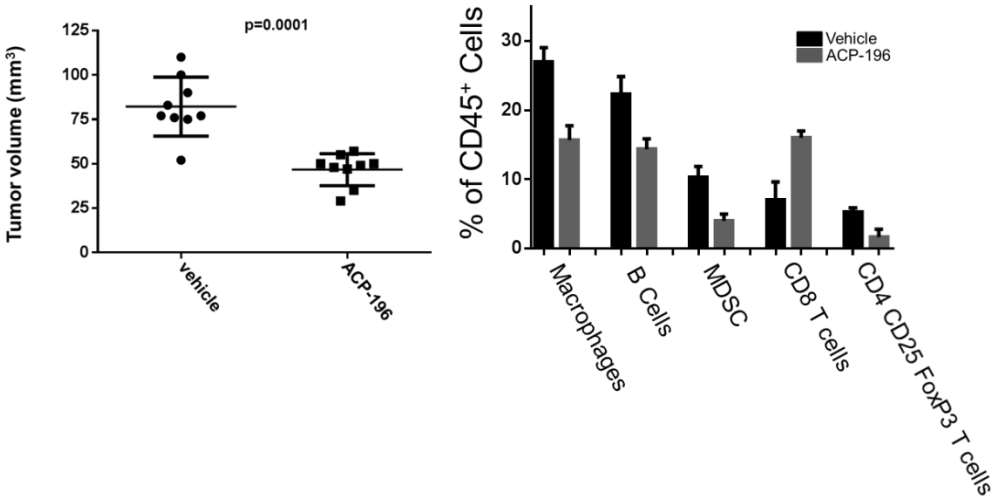
Abbreviations: MDSC = myeloid-derived suppressor cell; TAM = tumor-associated macrophage, T_{reg} = regulatory T cell.

Figure 1-3. Effects of ACP-196 on Cytolytic T Cells in a Genetic Model of Pancreatic Cancer



Similar single-agent activity was also observed with ACP-196 (15 mg/kg BID) in the ID8 syngeneic orthotopic ovarian model. Figure 1-4 shows a substantial decrease of tumor growth in this model with ACP-196 monotherapy compared with vehicle. This antitumor effect correlated with a significant decrease in immunosuppressor cells and an increase in cytolytic T cells similar to the KPC pancreatic model.

Figure 1-4. ACP-196 Impairs ID8 Ovarian Cancer Growth and Decreased Immunosuppressive Cellular Subsets in Syngeneic Murine Model

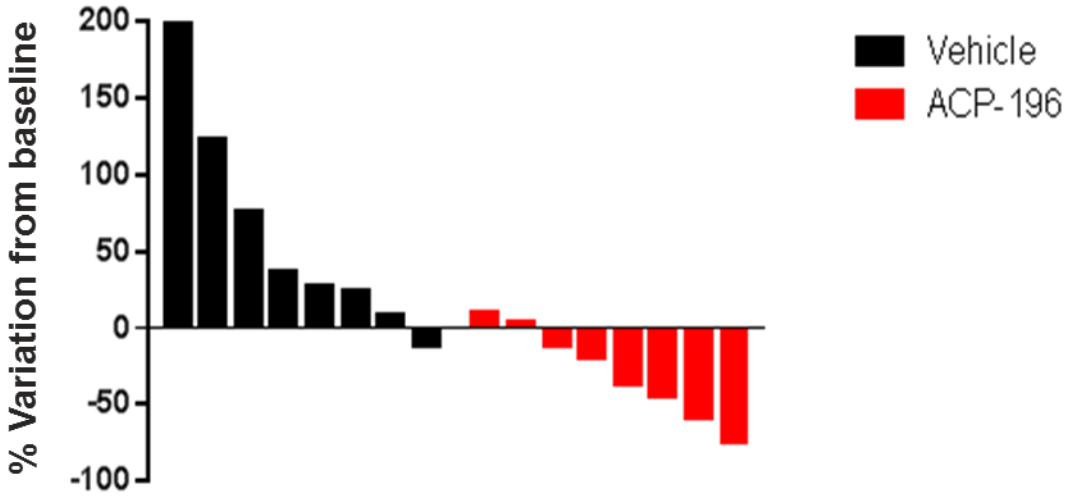


Abbreviation: MDSC = myeloid-derived suppressor cell.

Single-agent ACP-196 also was evaluated in mice with non-small cell lung carcinoma arising as the result of G12D mutant Kras triggered by spontaneous

intrachromosomal recombination (KrasLA2 mice). This model has several advantages over traditional transgenic strategies, including that it more closely recapitulates spontaneous oncogene activation as seen in human cancers (Johnson 2001). Mice were enrolled after identification of spontaneously appearing tumors in the lung by micro-computed tomography (CT) scanning (~ 10 to 12 weeks of age). Mice were treated with vehicle (N=8) or ACP-196 administered orally at a dosage of 15 mg/kg/dose BID (N=8) for 3 weeks. As shown in Figure 1-5, treatment with single-agent ACP-196 produced tumor regressions, as measured by micro-CT scanning, of ≥ 25% in 5 of 8 mice (63%) compared with a single mouse in the vehicle group that had a reduction of 12%.

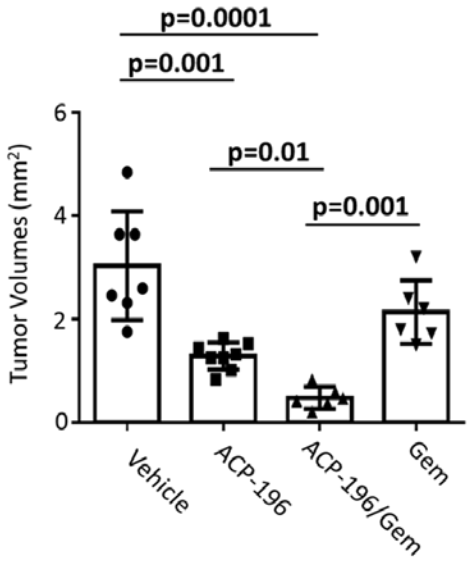
Figure 1-5. Efficacy of ACP-196 Monotherapy in a Genetic Model of Lung Cancer



Lastly, the activity of ACP-196 was confirmed in an orthotopic mouse model evaluating both single-agent and combination efficacy. In this study, 10,000 KPC mouse pancreatic cancer cells were injected into the pancreases of 24 female mice. After one week of expansion, drug treatment was started in mice developing pancreatic tumors. Animals were treated with vehicle (N=6); ACP-196, 15 mg/kg/BID given orally (N=6); gemcitabine 50 mg/kg IV administered every 4 days for 3 injections (N=6); or ACP-196, 15 mg/kg/BID given orally together with gemcitabine, 50 mg/kg IV administered every 4 days for 3 injections (N=6). At 2 weeks after initiation of treatment, mice in the vehicle group showed signs of deteriorating health and all groups were euthanized. Tumors were collected and measured (Figure 1-6);

relative to the vehicle treatment, ACP-196 monotherapy resulted in a 2-fold reduction in tumor growth, results which compared favorably with gemcitabine alone. The combination of ACP-196 and gemcitabine resulted in a further reduction in tumor growth when compared to each single agent.

Figure 1-6. Efficacy of ACP-196 Monotherapy and Combination Therapy with Gemcitabine in an Orthotopic Model of Pancreatic Cancer



Abbreviation: Gem = gemcitabine.

In summary, ACP-196 alone and in combination with gemcitabine produces robust antitumor effects in established solid tumor models. The antitumor effect observed with ACP-196 correlates with biomarkers of response similar to those reported for other immunomodulating agents such as inhibitors of CTLA-4, PD-1 and PD-L1.

This proof-of-concept study will assess the clinical potential of combined Btk inhibition and chemotherapy by evaluating the safety, PD, PK and efficacy of ACP-196 and nab-paclitaxel/gemcitabine in subjects with previously untreated metastatic pancreatic cancer.

Summaries of preclinical and clinical studies for ACP-196 are provided below. For more detailed information please refer to the Investigator Brochure for ACP-196. For detailed information on nab-paclitaxel/gemcitabine refer to the nab-paclitaxel prescribing information provided in Appendix 2.

1.4 ACP-196

ACP-196 (also known as acalabrutinib) is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and

ACP-196 is the S-enantiomer. ACP-196 is orally bioavailable and is suitable for formulating in capsules. For clinical testing, ACP-196 has been manufactured and formulated according to current Good Manufacturing Practice (cGMP).

ACP-196 is an investigational product and has not been approved for marketing in any country.

1.4.1 Mechanism of Action

ACP-196 is a potent covalent inhibitor of Btk with a half maximal inhibitory concentration (IC_{50}) of 3.1 nM in a biochemical kinase assay for Btk. ACP-196 was specifically designed to be a more potent and selective inhibitor of Btk to avoid off-target side effects as seen with ibrutinib, a first generation covalent Btk inhibitor. When profiled against 282 human kinases, ACP-196 was more selective than ibrutinib.

ACP-196 is a covalent inhibitor of Btk, forming a covalent interaction with Cys481 in the front position of the ATP-binding pocket of Btk. In addition to Btk there are 9 kinases with a cysteine in the same position as Btk: Tec, Bmx, Itk, Txk, epidermal growth factor receptor (EGFR), ErbB2, ErbB4, Blk and Janus kinase (Jak) 3. Due to the position of the cysteine in the ATP pocket, these kinases are referred as the group of 3F-Cys kinases (Barf 2012).

In Table 1-1 the group of 3F-Cys kinases are listed with the IC_{50} for ACP-196 and ibrutinib. For ACP-196, the strongest inhibition was observed for Btk with less activity against Tec, Bmx and ErbB4. However, ibrutinib showed inhibition of all 10 kinases. One kinases potently inhibited by ibrutinib is EGFR, which may explain the ibrutinib-related incidence of diarrhea, rash and hemorrhaging events reported for ibrutinib in clinical trials of hematologic malignancies (IMBRUVICA prescribing information).

Table 1-1. Potency of ACP-196 and Ibrutinib on Group of 3F-Cys Kinases

	IC_{50} (nM)	
	ACP-196[1]	**Ibrutinib[2]**
Btk	3.1	0.5
Tec	29	78
Bmx	39	0.80
Itk	>1000	10.7
Txk	291	2.0[1]
EGFR	>1000	5.6
ErbB2	912	9.4
ErbB4	13.2	2.7[1]
Blk	>1000	0.5
Jak3	>1000	16.1

Abbreviation: IC_{50} = inhibitory concentration causing half-maximal inhibition.
1. Profiling at Life Technology
2. Honigberg 2010; ibrutinib data for Txk and ErbB4 profiled at Life Technology

1.4.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 showed significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated an IC_{50} of 2.7 µM, suggesting a low clinical risk of off-target effects.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. ACP-196 inhibited hERG channel activity by 25% at 10 µM, suggesting a low clinical risk that ACP-196 would induce clinical cardiac QT interval (QT) prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practice (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses through 300 mg/kg (the highest dose level) revealed no adverse effects on

neurobehavioral effects or body temperature. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP-196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (including QT interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.4.3 Drug-drug Interaction Potential

The in vitro studies suggest CYP-mediated metabolism of ACP-196 appears to be catalyzed predominantly by CYP3A. However, in elimination studies in preclinical species, the metabolic fate of ACP-196 is dominated by direct conjugation of ACP-196 with glutathione, providing evidence for a significant non-CYP mechanism of elimination. In a healthy volunteer study (ACE-HV-001), the effect of coadministration of a potent CYP3A and p-glycoprotein 1 (P-gp) inhibitor, itraconazole, on the plasma levels of ACP-196 was evaluated. The mean plasma ACP-196 maximum concentration (C_{max}) and area under the curve ($AUC_{0\text{-last}}$) values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment. In vitro studies also show that ACP-196 is a substrate for P-gp.

ACP-196 is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms.

Results from drug transporter studies suggest that ACP-196 is not anticipated to alter the PK of other therapeutic agents that are substrates for MDR1, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2.

Please refer to Section 3.10.3 for guidance on drugs that may cause drug-drug interactions.

1.5 IN VIVO GENERAL TOXICOLOGY – ACP-196

The systemic toxicity of ACP-196 has been investigated in six repeat-dose general toxicology studies, three with recovery periods, in the rat and the dog. The pivotal GLP studies were two 28-day repeat dose studies in Sprague Dawley rats with 32- and 28-day recovery periods, and a 28-day study in Beagle dogs with a 28-day recovery period.

The no observable adverse effect level (NOAEL) in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest non-severely toxic dose. The pancreatic findings were investigated in subsequent rat toxicology studies and found to be treatment related, non-adverse at lower doses, and not associated with systemic toxicity or changes in biomarkers of pancreatic function. The islet cell changes resemble a spontaneous pancreatic lesion that is described as an age-related finding in male rats of this strain. In dogs at 30 mg/kg/day, there were no microscopic findings in the pancreas, and all clinical biomarkers of pancreatic function were normal.

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg dose group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

1.6 CLINICAL EXPERIENCE – ACP-196

For more detailed information on the clinical experience for ACP-196 please refer to the Investigator Brochure.

1.6.1 Pharmacokinetics and Pharmacodynamics of ACP-196

ACE-HV-001 was a PK/pharmacodynamic, dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 or 2 days in healthy volunteers. This study evaluated the PK and pharmacodynamics of ACP-196 at various dose levels and regimens. The starting dose for ACP-196 was 2.5 mg BID. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to study drug were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

In Part 1, PK properties of ACP-196 were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects

evaluated, all observed systemic concentrations of ACP-196. ACP-196 plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean C_{max} values was greater than dose proportional based on the increases of C_{max} from the first dose administered. When evaluating AUC_{0-12}, AUC_{0-12} or AUC_{0-inf}, the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

ACP-196 was not detected in the urine of subjects receiving the 2.5- or 5.0-mg BID doses of ACP-196. ACP-196 was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose-dependent manner.

In Part 2, the effect of food on the PK of ACP-196 (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median ACP-196 plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma ACP-196 C_{max} fed values decreased to 27.3% of the C_{max} values observed in the fasted state. In contrast, the relative AUC exposure of ACP-196 remained mostly unchanged in both states.

In Part 3, the effect of itraconazole on the PK of ACP-196 (50 mg) after a single oral administration was evaluated in 17 subjects. No difference in ACP-196 T_{max} values was observed in the presence or absence of itraconazole.

Mean ACP-196 exposures (as assessed by C_{max}, AUC_{0-last}, AUC_{0-12}, and AUC_{0-inf}) increased in the presence of itraconazole. The mean plasma ACP-196 C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma AUC_{0-last}, AUC_{0-12}, and AUC_{0-inf} values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole (CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The pharmacodynamics of ACP-196 was evaluated using a Btk occupancy assay and correlated with a functional assay that determines the level of Btk inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in Btk occupancy and corresponding decrease in CD69/86 expression was observed in

this study. Full Btk occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred at the 75- and 100-mg single dosed cohorts 1 to 3 hours after administration. However, only the 100-mg cohort maintained high Btk occupancy (91.5%) and high B-cell receptor (BCR) functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects receiving a second dose of ACP-196 12 hours after the first administration, full Btk target occupancy was observed 3 hours after the second dose for the 50-mg dosed cohort (Btk occupancy 97 ± 4%).

1.6.2 ACP-196 in CLL

ACE-CL-001 (NCT02029443), an ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, has a sequential, dose-escalation design. As of 22 January 2015, 125 subjects have received ACP-196 at dosages from 100 to 400 mg QD or 100 to 200 mg BID for up to 11 cycles (1 cycle = 28 days).

To date, ACP-196 has been well tolerated at all dose levels evaluated. No DLTs have occurred at any dose level. The MTD was not reached in this study; however, per the protocol, dose escalation was stopped once a plateau in PK was observed (ie, between 250 and 400 mg).

Preliminary pharmacodynamics data show that Btk occupancy with ACP-196 QD dosing, in peripheral blood cells, is > 95% at 4 hours after dosing but decreases to < 95% at 24 hours, while with BID dosing complete Btk occupancy (97% to 100%) is maintained over 24 hours at steady state (Table 1-2). These data suggest that synthesis of de novo Btk may occur within 24 hours.

Table 1-2. Btk Occupancy in Peripheral Blood of Subjects from ACE-CL-001

		Sample					
Cohort	**Metric**	**Day 1 4hr post**	**Day 2 pre**	**Day 8 pre**	**Day 8 4hr post**	**Day 28 pre**	**Day 28 4hr post**
100 mg QD	% Btk Occupancy	96.1	84.4	87.6	98.0		
	Std. dev.	3.2	9.8	5.1	1.8		
	N	8	8	8	8		
175 mg QD	% Btk Occupancy	97.1	79.2	84.0	96.9		
	Std. dev.	2.3	11.2	12.9	4.8		
	N	8	8	8	8		
200 mg QD (Naive)	% Btk Occupancy	97.4	86.2	91.3	99.8	92.3	99.0
	Std. dev.	4.4	7.5	7.8	1.1	0.9	0.9
	N	9	9	9	9	3	3
200 mg QD (Ibrutinib intolerant)	% Btk Occupancy	96.7	94.4	99.7	96.2	93.3	99.9
	Std. dev.						
	N	1	1	1	1	1	1
100 mg BID	% Btk Occupancy	97.0	94.8	**97.8**	**99.3**	**97.3**	**99.6**
	Std. dev.	2.7	2.7	**2.0**	**0.6**	**1.3**	**0.3**
	N	10.00	10.00	**10.00**	**10.00**	**6.00**	**6.00**
250 mg QD	% Btk Occupancy	94.4	82.4	93.1	100.1		
	Std. dev.	12.4	10.6	2.7	0.4		
	N	6	6	6	6		
400 mg QD	% Btk Occupancy	98.8	89.9	94.7	99.4	93.6	99.8
	Std. dev.	1.1	10.5	2.5	0.6	4.5	0.2
	N	6	6	6	6	6	6
200 mg BID (Richter's)	% Btk Occupancy	99.7	92.7	98.6	99.8	99.0	100.0
	Std. dev.						
	N	1	1	1	1	1	1

BID = twice per day; Btk = Bruton tyrosine kinase; QD = once per day

Preliminary PK data from Day 8 show dose linearity from 100 to 250 mg and no accumulation with repeat dosing (Table 1-3).

Table 1-3. Preliminary Day 8 PK Results from ACE-CL-001 (December 2014)

Cohort	Mean C_{max} ± SD (ng/mL)	Mean AUC_{0-6} ± SD (ng•h/mL)
100 mg QD (N=8)	529 ± 286	634 ± 197
175 mg QD (N=7)	800 ± 692	1240 ± 788
250 mg QD (N=7)	1350 ± 933	2170 ± 1180
400 mg QD (N=6)	932 ± 576	1870 ± 1040
100 mg BID (N=22)	716 ± 658	837 ± 485*

Timepoints: Predose, 0.25, 0.50, 0.75, 1.0, 2.0, 4.0, and 6.0 postdose.
BID regimens were not sampled during the second daily dose interval; 0-24 hour exposures are expected to be approximately 2-fold the AUC_{0-6} values shown.
AUC = area under the curve; BID = twice per day; C_{max} = maximum concentration; QD = once per day; SD = standard deviation

To date, 31 subject have been evaluated for tumor response based on International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include partial response with treatment-induced lymphocytosis. Based on preliminary, unaudited data an ORR of 94% (29 of 31 subjects) has been observed (Table 1-4).

Table 1-4. Best Response by Cohort from ACE-CL-001 (December 2014)

n (%)	All Cohorts (N = 31)	100 mg QD (N = 8)	175 mg QD (N = 8)	250 mg QD (N = 7)	100 mg BID (N = 3)	400 mg QD (N = 5)
PR	22 (71)	7 (88)	5 (63)	5 (71)	3 (100)	2 (40)
PR+L	7 (23)	0 (0)	3 (37)	2 (29)	0 (0)	2 (40)
SD	2 (6)	1 (12)	0 (0)	0 (0)	0 (0)	1 (20)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (range)						
	7.3 (3.0-10.8)	10.0 (9.0-10.8)	8.6 (3.0-8.8)	7.0 (7.0-7.3)	5.2 (4.7-5.5)	5.0 (4.8-5.5)

BID = twice per day; PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease; QD = once per day

1.7 NAB-PACLITAXEL/GEMCITABINE

Nab-paclitaxel/gemcitabine is approved for first-line treatment of patients with metastatic pancreatic cancer. For complete information on nab-paclitaxel/gemcitabine, including contraindications and warnings and precautions refer to the nab-paclitaxel prescribing information (Appendix 2).

Nab-paclitaxel/gemcitabine treatment is associated with:

- myelosuppression
- sensory neuropathy

- sepsis (with or without neutropenia)
- pneumonitis
- severe hypersensitivity reactions with fatal outcome

Management of these specific adverse reactions is described in the prescribing information (Appendix 2).

Additional AEs reported in ≥ 20% of patients with metastatic pancreatic cancer treated with nab-paclitaxel/gemcitabine included neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration.

1.8 BENEFIT/RISK

ACP-196 is a potent, orally available small-molecule inhibitor of Btk. In the Phase 1/2 study of ACP-196 in subjects with CLL or Richter's syndrome, no DLTs have been identified at dosages of ≤ 400 mg QD or 100 to 200 mg BID. The ORR in the evaluable subjects for this study is currently 94% with some subjects obtaining PRs after only 2 cycles of therapy. In summary, the preliminary data suggest that ACP-196 is well tolerated and has robust activity as a single agent in the treatment of subjects with CLL/small lymphocytic leukemia (SLL).

Based on the currently known toxicity profiles of ACP-196 and nab-paclitaxel/gemcitabine, overlapping toxicities are expected to be limited. At the dosage of ACP-196 administered in this study, no drug-drug interactions are anticipated between ACP-196 and nab-paclitaxel/gemcitabine.

In nonclinical studies, ACP-196 monotherapy has shown robust antitumor activity in murine solid tumor models of pancreatic, lung and ovarian cancer. Preliminary results from a murine pancreatic cancer model suggest a synergistic anti-tumor effect of ACP-196 in combination with gemcitabine. These results support evaluating ACP-196 in combination with nab-paclitaxel/gemcitabine in this protocol.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the efficacy of ACP-196 and nab-paclitaxel/gemcitabine based on ORR in subjects with metastatic pancreatic cancer using standard response criteria

2.2 SECONDARY OBJECTIVES

To characterize the safety profile of ACP-196 and nab-paclitaxel/gemcitabine in subjects with metastatic pancreatic cancer

2.3 EXPLORATORY OBJECTIVES

- [redacted]

3.0 STUDY DESIGN

This clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating ACP-196 plus nab-paclitaxel/gemcitabine compared with nab-paclitaxel/gemcitabine in subjects who have previously untreated metastatic pancreatic cancer.

Subjects meeting the eligibility criteria for the study will be randomized 1:1 using an IXRS to one of the following arms:

Arm 1: ACP-196 100 mg administered orally BID on Days 1-28 with nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 administered IV on Days 1, 8, and 15; cycles are repeated every 28 days.

Arm 2: Nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 are administered IV on Days 1, 8, and 15; cycles are repeated every 28 days.

Although ACP-196 has not demonstrated any DLTs to date, the safety of ACP-196 in combination with nab-paclitaxel/gemcitabine in this patient population needs to be assessed and standard DLT criteria will be applied to Arm 1 of the study. Therefore an interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 1 cycle (1 cycle = 28 days). Enrollment will be paused while the safety interim analysis occurs.

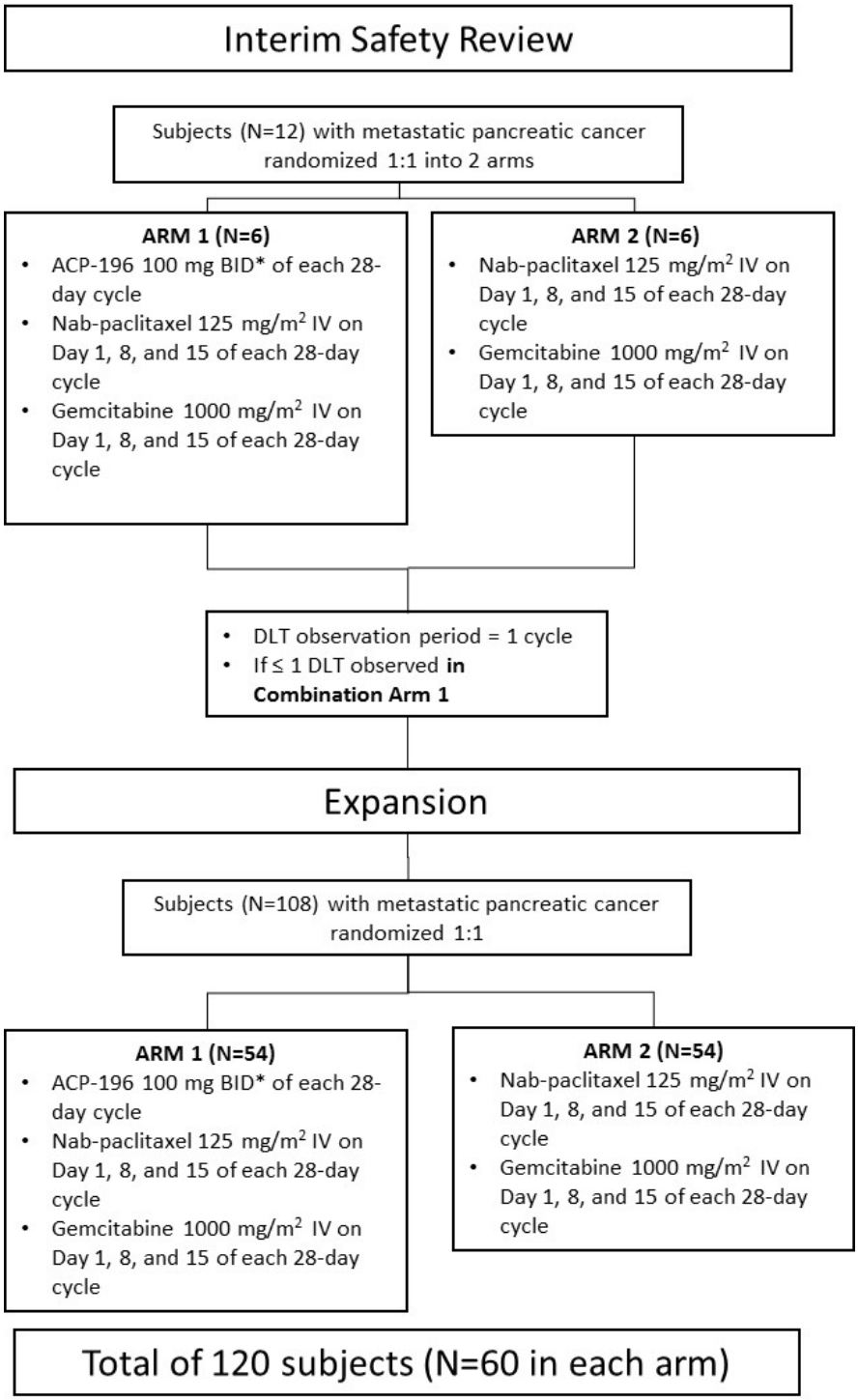
If ≤ 1 DLT is observed in Arm 1, then randomization will continue to evaluate the safety and efficacy of the ACP-196 combination (ie, up to 60 subjects per arm). If ≥ 2 DLTs are observed in Arm 1, then enrollment will continue until an additional 6 subjects are randomized to Arm 1, but with a reduced dose level for ACP-196 (Level -1). If the DLT review is cleared in those additional 6 subjects in Arm 1 then continued enrollment will occur at Level -1 for the ACP-196 combination arm. If ≥ 2 DLTs are observed in Arm 1 at Level -1, then an additional 6 subjects will be randomized at Level -2 and assessed for DLTs. If the DLT review is cleared, continued enrollment will occur at Level -2 for the ACP-196 combination arm. If the DLT review is not cleared, enrollment will be halted. In addition, analyses for toxicity will also be done as outlined in Section 5.5.

Treatment can continue until the end of trial, defined as 52 weeks (13 cycles) after the last subject is randomized to the study, for subjects who are tolerating therapy and not progressing. Subjects who have **confirmed** progressive disease will discontinue study treatment. Subjects who discontinue study drug for any reason other than disease progression, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until disease progression or initiation of any other anticancer therapies, whichever comes first.

All subjects will have hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, serum amylase and lipase, and hematology. PD (subjects in both arms) and PK testing (only the first 20 subjects enrolled in Arm 1) will be performed during the first few months of treatment. Radiologic tumor assessments will be completed at baseline and at approximately 8-week intervals during the trial. The primary efficacy analysis will be based on investigator assessment. Independent radiology review (IRR) of the efficacy data will also be performed in accordance with an IRR charter.

Refer to Appendix 7 for a comprehensive list of study assessments and their timing. A study schema is provided in Figure 3-1.

Figure 3-1. Study Schema



Abbreviations: BID = twice per day; IV = intravenous.
*ACP-196 and nab-paclitaxel/gemcitabine administration begins on the same day except for the first 6 subjects enrolled due to pharmacokinetic sampling. In the first 6 subjects, ACP-196 will be administered on Cycle 1 Day -1. On Cycle 1 Day 1, the first nab-paclitaxel/gemcitabine infusion will occur. When ACP-196 and nab-paclitaxel/gemcitabine are administered on the same day, ACP-196 is administered first followed by the nab-paclitaxel and then gemcitabine infusions.

3.1 STUDY PARAMETERS

3.1.1 Safety Parameters

The safety of ACP-196 and nab-paclitaxel/gemcitabine will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment emergent AEs or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 6.1).

3.1.2 Pharmacodynamic, Pharmacokinetic, and Biomarker Parameters

The occupancy of Btk by ACP-196 will be measured in PBMCs with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 and nab-paclitaxel/gemcitabine on B cells, T cells and MDSCs and cytokines may also be evaluated. Tissue sections from either an archived or newly obtained tumor sample (most recent biopsy) are to be provided at screening. Tumor tissue from archival tumor biopsies and/or any newly obtained biopsies performed during the study will be evaluated for various tumor markers, including but not limited to:

- HABP
- SMA
- Ki67 proliferation
- cleaved-caspase 3
- PD-1 and its ligand, PD1-L

Additional exploratory correlative studies of tumor tissue, when available, may include characterization of tumor subtypes by immunohistochemistry.

The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196:

- $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration.
- $AUC_{0\text{-}12}$: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.

- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- $AUC_{0\text{-}24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-}12}$.
- C_{max}: Maximum observed plasma concentration
- T_{max}: Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$: Terminal elimination half-life (whenever possible)
- λ_z: Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance
- Vz/F: Oral volume of distribution

Leftover plasma may be analyzed for ACP-196 metabolites.

3.1.3 Efficacy Parameters

Efficacy will be evaluated based on assessments of tumor response and progression using the standardized Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer 2009, Appendix 1).

Efficacy endpoints will include:

- ORR, defined as PR or CR based on modified RECIST 1.1 criteria
- DOR
- OS
- PFS
- Change in CA19-9

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.6.2, ACP-196 is currently being evaluated in a Phase 1/2 study in subjects with CLL or Richter's syndrome (ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD and 100 to 200 mg BID of ACP-196. All tested dose levels have been well tolerated and, to date, no drug-related toxicities have been observed in ACE-CL-001.

Robust clinical responses have been observed with dosages as low as 100 mg QD. Preliminary PK data from ACE-CL-001 suggests a plateauing of exposure after 250 mg QD (Table 1-3). Pharmacodynamic results from this study also show 100 and 200 mg BID have the highest Btk occupancy at 24 hours of all the regimens evaluated (Table 1-2).

The nab-paclitaxel/gemcitabine dose regimen being evaluated in this study is consistent with the prescribing information of these drugs for the treatment of metastatic pancreatic cancer (nab-paclitaxel prescribing information).

As described in Section 1.4 and Section 1.5, Acerta Pharma has conducted nonclinical solid tumor studies of ACP-196 monotherapy and ACP-196 in combination with chemotherapy (ie, gemcitabine). The robust results observed for ACP-196 monotherapy and in combination with chemotherapy warrant testing these regimens on this protocol.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. ECOG performance status of 0 or 1.
3. Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas.
4. Presence of radiographically measurable disease per RECIST 1.1.
5. No previous radiotherapy, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present.
6. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Highly effective forms of contraception are defined in Section 3.10.5.
7. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Highly effective forms of contraception are defined in Section 3.10.5.

8. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer.
9. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
10. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Prior malignancy (other than pancreatic cancer), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years. Note: These cases must be discussed with the medical monitor.
2. Known CNS metastases and/or carcinomatous meningitis.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec at screening.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. Note: Subjects with prior pancreatoduodenectomy are not excluded.
5. Biliary obstruction or presence of a percutaneous biliary drain. Note: Subjects with endobiliary stents may participate as long the enrollment criterion relating to serum bilirubin concentration is met.
6. Prior therapy with any inhibitor of Btk, Akt, Jak, mTOR, PI3K, or Syk.
7. History of interstitial lung disease or active non-infectious pneumonitis.
8. History of bleeding diathesis (eg, hemophilia or von Willebrand disease).
9. Major surgical procedure within 28 days of first dose of study drug.
10. Known hypersensitivity to gemcitabine or nab-paclitaxel.
11. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
12. Requires treatment with a strong CYP3A or CYP2C8 inhibitor/inducer.
13. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
14. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids. Note: At screening and during study participation, subjects may use topical or inhaled corticosteroids or systemic corticosteroids at dosages equivalent to prednisone ≤ 10 mg/day as therapy for comorbid conditions.
15. Known history of HIV or serologic status indicating active HCV or HBV infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are

hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.

16. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
17. ANC < 1.5 x 10^9/L or platelet count < 100 x 10^9/L or hemoglobin < 9.0 g/dL.
18. Total bilirubin > ULN; and AST or ALT > 3.0 x ULN.
19. PT and aPTT > 1.2 x the ULN.
20. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].
21. Breastfeeding or pregnant.
22. Concurrent participation in another therapeutic clinical trial.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.

3.3.3 Replacement of Subjects

Any subject who does not complete study therapy through Cycle 1 for reasons other than the occurrence of a DLT may be replaced at the discretion of the study investigators and sponsor.

3.3.4 Enrollment Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the sponsor confirms enrollment.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours.
- Screening and treatment assignment will occur through the use of an IXRS. As subjects qualify for enrollment, designated study center personnel will contact the IXRS, which will assign a treatment arm to each eligible subject.

Treatment must begin within the screening window (see Appendix 7) and after the site has received the treatment-arm allocation per IXRS.

3.4 STUDY DRUGS

3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with ACP-196 or nab-paclitaxel/gemcitabine administration.

3.4.2 Formulation, Packaging, and Storage

ACP-196

ACP-196 is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. ACP-196 should be stored according to the instructions on the label that is affixed to the package of the drug product. ACP-196 will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative. Refer to the ACP-196 Investigator Brochure for additional information regarding the drug product to be used in this trial.

Nab-paclitaxel/gemcitabine

Commercially available nab-paclitaxel and gemcitabine will be used in this study. The provisioning of these drugs for use in this study will be detailed in the clinical trial agreement with each site.

Nab-paclitaxel (100 mg/vial) is provided as lyophilized powder in single-use vials for reconstitution.

Gemcitabine (200 mg or 1 g/vial) is provided as lyophilized powder in single-use vials for reconstitution.

Information on the formulation, packaging and storage of nab-paclitaxel is provided in the prescribing information (Appendix 2). Information on the formulation, packaging and storage of gemcitabine is provided in the prescribing information (Appendix 3).

3.4.3 Administration of Study Drug

Investigators are prohibited from supplying ACP-196 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that subjects receive ACP-196 or nab-paclitaxel/gemcitabine

only from personnel who fully understand the procedures for administering the drugs.

ACP-196 100 mg is intended to be administered orally twice daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice or Seville orange juice due to potential CYP3A inhibition). Doses should be administered 12 hours apart (a window of ± 1 hour is allowed). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Guidance on co-administration of ACP-196 with agents that affect gastric pH is provided in Section 3.10.3.

Nab-paclitaxel (125 mg/m^2) will be administered as an IV infusion over 30 to 40 minutes on Day 1, 8 and 15 of every 28-day cycle. Detailed information on preparation of nab-paclitaxel for infusion is provided in Appendix 2.

Gemcitabine (1000 mg/m^2) will be administered immediately after nab-paclitaxel as an IV over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day cycle. Do not increase infusion time > 60 minutes as increased toxicity may occur. Detailed information on preparation of gemcitabine for infusion is provided in Appendix 3.

When ACP-196 and nab-paclitaxel/gemcitabine are administered on the same day, ACP-196 should be administered first, followed by nab-paclitaxel and then immediately by gemcitabine. When PK sampling is done, the nab-paclitaxel/gemcitabine infusion should begin within 10 minutes of ingesting ACP-196. However, for the first 6 subject enrolled on the ACP-196 combination arm (Arm 1), ACP-196 will be administered alone on Day -1 and then concomitantly with nab-paclitaxel/gemcitabine on Day 1 as described above.

3.4.4 Assuring Subject Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other ACP-196 treatments

will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Nab-paclitaxel/gemcitabine infusions will be administered only at the clinics per the study schedule **and must be administered by study personnel experienced with this regimen.**

Subject compliance with ACP-196 dosing will be assessed on Day 1 of every cycle. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to another subject.

3.5 STUDY TREATMENT SCHEDULE

3.5.1 Arm 1 – ACP-196 + Nab-paclitaxel/Gemcitabine

The ACP-196 100 mg BID will be administered orally every day of the 28-day cycle. Nab-paclitaxel/gemcitabine will be administered as described in Section 3.4.3. ACP-196 and nab-paclitaxel/gemcitabine dosing will begin on the same day (Cycle 1 Day 1) except for the first 6 subjects enrolled due to PK sampling. The first 6 subjects enrolled will receive ACP-196 on Cycle 1 Day -1. Then on Cycle 1 Day 1, the first nab-paclitaxel/gemcitabine infusion will be administered.

3.5.2 Arm 2 – Nab-paclitaxel/Gemcitabine

For complete information on dosing and dose modifications refer to the respective prescribing information for each drug (Appendix 2 and Appendix 3); a summary of this information is shown in Table 3-3 in Section 3.8.2.

3.6 DURATION OF THERAPY

Treatment can continue until the end of trial, defined as 52 weeks (13 cycles) after the last subject is randomized to the study, for subjects who are tolerating therapy and not progressing. Subjects who have confirmed progressive disease will discontinue study treatment.

3.7 ASSESSMENT OF DOSE-LIMITING TOXICITY (DLT)

An interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 1 cycle. Enrollment will be paused while the safety interim analysis occurs.

A DLT will be defined as the occurrence of any of the following ACP-196-related AEs (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs):

1. Grade 4 vomiting or diarrhea
2. Grade 3 nausea, vomiting, or diarrhea lasting for > 72 hours
3. Other Grade ≥ 3 toxicities (Note: transient Grade 3/4 laboratory abnormalities, including chemotherapy induced myelosuppression, that are not clinically significant will not be considered DLTs)
4. Dosing delay due to toxicity for > 21 consecutive days.

For any DLT related to ACP-196, the dose of ACP-196 will be withheld until the toxicity is Grade 1 or lower. Thereafter, ACP-196 will be resumed at one lower dose level (Table 3-1). The minimum dose of ACP-196 is 50 mg PO BID.

Table 3-1. Dose Reductions for Arm 1

ACP-196 Dose Level	ACP-196 Dosing Regimen	Nab-paclitaxel/Gemcitabine
Starting Dose	100 mg BID PO	See Arm 2
Level -1	100 mg QD PO	See Arm 2
Level -2	50 mg BID PO	See Arm 2

Abbreviations: BID = twice per day; IV = intravenous, PO = oral.

3.8 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate ACP-196- or nab-paclitaxel/gemcitabine-related toxicity. If a subject experiences a treatment-related AE or other intolerable AE during the course of therapy, then ACP-196, nab-paclitaxel/gemcitabine, or both drugs should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. For Arm 1, ACP-196 treatment should continue when nab-paclitaxel/gemcitabine treatment is held or dose reduced for expected AEs associated with chemotherapy. Similarly, gemcitabine and nab-paclitaxel may be continued if ACP-196 is held.

3.8.1 Dose Modification and Discontinuation of ACP-196

After the DLT review is cleared, the actions in Table 3-2 should be followed for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2006] and use must be recorded on the case report form [CRF]).
- Grade 3 platelets in presence of significant bleeding.
- Grade 4 platelets.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 3-2. Drug Discontinuation Actions for ACP-196

Occurrence	Action
1st – 2nd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; may restart at original dose level
3rd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (100 mg QD)
4th	Discontinue ACP-196

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade ≤ 1. If ACP-196 is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of ACP-196 for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of ACP-196 is 100 mg BID for this protocol.

Treatment with ACP-196 should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the medical monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be

discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of ACP-196 for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.11 for more information on assessing disease progression under these circumstances.

3.8.2 Dose Modification and Discontinuation of Nab-paclitaxel/Gemcitabine

The dose levels for nab-paclitaxel and gemcitabine are summarized below in Table 3-3.

Table 3-3. Dose Reductions for Arm 2

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Starting Dose	125	1000
Level -1	100	800
Level -2	75	600
If additional dose reduction required	Discontinue	Discontinue

Dose reductions/modifications for nab-paclitaxel/gemcitabine in response to neutropenia, thrombocytopenia, febrile neutropenia, peripheral neuropathy, cutaneous toxicity, and gastrointestinal toxicity are summarized below (Table 3-4 and Table 3-5). For any toxicities not listed in these tables, the nab-paclitaxel prescribing information (Appendix 2) will be referred to after discussion with study monitor. As mentioned previously, for subjects in Arm 1, ACP-196 treatment should be continued when nab-paclitaxel/gemcitabine are held or dose reduced for AEs expected with this chemotherapy regimen. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the medical monitor.

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Subjects who experience a severe hypersensitivity reaction to nab-paclitaxel/gemcitabine should not be re-challenged and will be discontinued from the study.

Table 3-4. Dose Modifications of Nab-paclitaxel/Gemcitabine for Neutropenia and/or Thrombocytopenia

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Nab-paclitaxel/Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Abbreviation: ANC = absolute neutrophil count.

Table 3-5. Dose Modifications of Nab-paclitaxel/Gemcitabine for Other Adverse Drug Reactions

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity Grade 3 or higher mucositis or diarrhea	Withhold until resolved to Grade 1 and lower by 1 dose level	

Abbreviation: ANC = absolute neutrophil count.

3.9 CONCOMITANT THERAPY

3.9.1 Permitted Concomitant Therapy

Standard supportive care medications, including growth factor support, antiemetic and antidiarrheal medications, are permitted as per institutional standards.

3.9.2 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 10 mg/day), warfarin or equivalent vitamin K antagonists (eg, phenprocoumon), experimental therapy, and radiotherapy (other than palliative radiation for symptom management) are prohibited.

The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 5) should be avoided when possible (see Section 3.10.3). If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. Conversely, concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of ACP-196 and could reduce efficacy. For additional information on drugs with potential drug-drug interactions, refer to Section 3.10.3.

3.10 PRECAUTIONS

3.10.1 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with ACP-196. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of HBV infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming ACP-196 in subjects who develop HBV reactivation.

3.10.2 Dietary Restrictions

ACP-196 can be taken with or without food. Because ACP-196 may be metabolized by CYP3A, subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

3.10.3 Drug-drug Interactions

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.4.3, concomitant administration of ACP-196 with a strong CYP3A inhibitor increased exposure by

approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 5) should be avoided when possible.

Based on these considerations, subjects who require therapy with drugs listed in Appendix 5 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A inhibitor while on study, the ACP-196 dose should be reduced by one level (refer to Table 3-1 for dose reductions). Conversely, concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of ACP-196 and could reduce efficacy.

The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on ACP-196 absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing-drugs or supplements (eg, antacids and calcium supplements) and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors (eg, dexlansoprazole, rabeprazole, or pantoprazole) while taking ACP-196 is not recommended due to a potential decrease in study drug exposure.

The metabolism of nab-paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A (nab-paclitaxel prescribing information). No formal drug interaction studies have been reported for gemcitabine (gemcitabine prescribing information).

3.10.4 Surgery

Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib (IMBRUVICA prescribing information). As a precaution, it is suggested that ACP-196 be held for 3 days before and after any major surgical procedure.

3.10.5 Reproductive Toxicity

Pilot reproductive toxicity studies have been performed that evaluate the effects of ACP-196 on embyrofetal development. Definitive studies of ACP-196 on embryofetal development are pending.

Nab-paclitaxel/gemcitabine is Pregnancy Category D. Women who are sexually active and can bear children must use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Men who are sexually active and can beget children must use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer. Examples of highly effective methods of contraception include combined or progesterone-only hormonal contraceptives associated with inhibition of ovulation (implants, injectables or oral), intrauterine devices, intrauterine hormone releasing system, true sexual abstinence, bilateral tubal occlusion or vasectomized partner. . Note that barrier methods with and without spermaticide, progesterone-only hormonal contraceptives where inhibition of ovulation is not the primary mode of action, periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) or withdrawal are not acceptable methods of contraception. Men must refrain from sperm donation during the study and for 90 days after the last dose of ACP-196 or 4 months after the last dose of nab-paclitaxel/gemcitabine, whichever is longer.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a woman becomes pregnant during the treatment period, she must discontinue ACP-196 and nab-paclitaxel/gemcitabine immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.2.3.

3.10.6 Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥ 1000 mg of ACP-196 at once), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If

the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

There is no known antidote for nab-paclitaxel or gemcitabine overdosage. The primary anticipated complications of overdosage for nab-paclitaxel would consist of bone marrow suppression, sensory neurotoxicity, and mucositis (nab-paclitaxel prescribing information). Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose of gemcitabine as high as 5700 mg/m^2 was administered by IV infusion over 30 minutes every 2 weeks to several patients in a dose-escalation study (gemcitabine prescribing information).

The medical monitor must be contacted if a study drug overdose occurs.

3.11 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Any subject has the right to withdraw from the study at any time.

- Any subject who has confirmed objective evidence of cancer progression while receiving ACP-196 and/or nab-paclitaxel/gemcitabine should be withdrawn from the study treatment. If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 3- to 6-week intervals) pending confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn

from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.

- The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety (Section 4.3) and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate CRF.

3.12 REASONS FOR STUDY EXIT

Reasons for study exit are:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

3.13 DATA AND SAFETY MONITORING

This trial will be conducted in accordance with the sponsor's Pharmacovigilance Committee procedures. AEs and SAEs will be reviewed by the sponsor on an ongoing basis to identify safety concerns. Conference calls among the sponsor and the investigators will be conducted periodically to discuss study progress, obtain investigator feedback and exchange of study information, review safety events (in particular: DLTs; SAEs; AEs leading to dose interruption, dose reduction, or therapy discontinuation), determine transitions between dose regimens, or discuss potential amendments to the protocol.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 7. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the IRB/IEC-approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug. Eligibility must be confirmed by the medical monitor before randomization.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 4.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.8 Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs. ECGs will be done at screening (3 ECGs taken at least 1 minute apart), on Cycle 1 Day 1 (1 ECG taken 1 hour [± 10 minutes] after taking ACP-196 on Day 1), Cycle 1 Day 15 (1 ECG taken 1 hour [± 10 minutes] after taking ACP-196), and at the treatment termination and/or safety follow-up visit (1 ECG at any time during the visit). In addition, a single ECG will also be performed 1 hour after ACP-196 administration at Cycle 1 Day -1 for the first 6 subjects enrolled to Arm 1.

4.1.9 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. Testing will be done by a central or local laboratory as listed on the investigator's Form FDA 1572.

4.1.10 Hematology

Hematology studies must include complete blood count with differential and platelet counts. Testing will be done by a central laboratory as listed on the investigator's Form FDA 1572.

4.1.11 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, C-reactive protein, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium,

phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a central laboratory as listed on the investigator's Form FDA 1572.

4.1.12 Amylase and Lipase

Serum amylase and serum lipase testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.13 Coagulation

Coagulation studies must include PT and aPTT. Testing will be done by a central laboratory as listed on the investigator's Form FDA 1572.

4.1.14 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix 7 and exclusion criterion #15). Testing will be done by local or central laboratory.

Refer to Section 3.10.1 and Appendix 7 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.

4.1.15 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be done by a central laboratory as listed on the investigator's Form FDA 1572.

4.1.16 T/B/NK/Monocyte Cell Count

Flow cytometry testing for CD3+, CD4+, CD8+, CD14+, CD19+, and CD16/56+ cells. Testing will be done by a central laboratory as listed on the investigator's Form FDA 1572.

4.1.17 Disease Markers

Serum samples will be used for the determination of CA19-9.

4.1.18 Pharmacodynamics/Pharmacokinetics and Biomarker Studies

Blood samples will be used for pharmacodynamic testing (Section 3.1.2).

Tissue sections from archival tumor biopsies and/or any newly obtained biopsies performed during the study will be used for exploratory biomarker studies (Section 3.1.2). Tissue sections from either an archived or newly obtained tumor sample (most recent biopsy) are to be provided at screening, if allowed by regional authorities. If available, de-identified pathology reports from the most recent diagnostic work-up, including immunohistochemistry and cytogenetic analyses of tumor tissue, may be requested by the sponsor.

Refer to the laboratory manual for instructions on collection and shipment of the pharmacodynamic and biomarker samples. All testing will be done by the sponsor or designee.

For Arm 1 (for the first 20 subjects enrolled only), the following PK sampling will be done for the measurement of ACP-196 levels: 0 (predose), 0.5, 1, 2, and 4 hours after ACP-196 administration on Cycle 1 Day -1 (for the first 6 subjects enrolled only), Cycle 1 Day 1, and Cycle 2 Day 15. The predose sample can be taken up to 30 minutes before dosing. The window for other timepoints is ± 5 minutes. Leftover plasma samples may be used for ACP-196 metabolite analyses. Testing will be done by a central laboratory. Refer to the laboratory manual for instructions on collection and shipment of PK samples.

4.1.19 Tumor Assessments

A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. Magnetic resonance imaging (MRI) may be used for subjects allergic to CT contrast media.

On treatment CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) will be done for tumor assessments on Cycle 3 Day 1 then on Day 1 every other cycle (± 7 days) thereafter or more frequently at investigator discretion. At all other visits, tumor assessments will be done by physical exam and laboratory results.

RECIST 1.1 guidelines (Eisenhauer 2009) will be followed for selection of measurable and nonmeasurable lesions and also with regard to the number of lesions to be assessed (refer to Appendix 1 for more details on RECIST 1.1).

De-identified copies of all radiology results may be requested by the sponsor.

4.1.20 Treatment Termination Visit

A treatment termination visit is required for safety assessments as outlined in the Schedule of Assessments (Appendix 7). The treatment termination visit will occur within 7 days of the last dose of study drug and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit. If the treatment termination visit and the safety follow-up visit coincide, then these can be combined into 1 visit.

4.1.21 Study Drug Accountability

See Section 7.6.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Responses will be categorized as CR, PR, SD, or PD. The definitions of response in target lesions are provided in Table 4-1. The definitions of response in nontarget lesions are provided in Table 4-2.

Table 4-1. Evaluation of Target Lesions (RECIST)

Response Category	Definition
CR	Disappearance of all target and nontarget lesions including normalization of an elevated tumor marker level. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
PR	A ≥ 30% decrease in the sum of the diameters of target lesions taking as a reference the baseline sum of the diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.
PD[a]	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

a. Transient apparent worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. If there is uncertainty regarding whether there is true cancer progression, the subject may continue or resume study treatment and remain under close observation (eg, evaluated at 3- to 6-week intervals) pending confirmation of progression.

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response, SD = stable disease.

Evaluation of nontarget lesions: while some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the Schedule of Assessments.

Table 4-2. Evaluation of Nontarget Lesions (RECIST)

Response Category	Definition
CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
PD[a]	Unequivocal progression[b] of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

a. Transient apparent worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity or intercurrent illness) may not indicate true cancer progression. If there is uncertainty regarding whether there is true cancer progression, the subject may continue or resume study treatment and remain under close observation (eg, evaluated at 3- to 6-week intervals) pending confirmation of progression

b. Refer to RECIST 1.1 criteria for detailed explanation of "unequivocal progression".

Abbreviations: CR = complete response; PD = progressive disease.

4.2.1 Determination of Response at Each Timepoint (RECIST)

The tumor response at each timepoint will be determined. Table 4-3 provides a summary of the overall response status calculation at each timepoint.

Table 4-3. Timepoint Response (RECIST)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; NE = nonevaluable..

4.2.2 Confirmation of Tumor Status and Determination of Best Overall Response (RECIST)

The best overall response (BOR) recorded from the start of treatment until tumor progression will be determined. Adjudication of BOR is based on evaluation of each successive set of 2 scans as indicated in Table 4-4.

Table 4-4. Best Overall Response Assessment and Requirements for Confirmation (RECIST)

Response Category at First Timepoint	Response Category at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met otherwise PD
CR	PD	SD provided minimum criteria for SD duration met otherwise PD
CR	NE	SD provided minimum criteria for SD duration met otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met otherwise PD
PR	NE	SD provided minimum criteria for SD duration met otherwise NE
NE	NE	NE

Abbreviations: BOR = best overall response; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; NE = nonevaluable

a. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 SAFETY FOLLOW-UP VISIT

Each subject should be followed for 30 (+ 7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.5) and to document the occurrence of any new events. Subjects who withdraw consent for study treatment should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedule of Assessments (Appendix 7) describes the procedures required for safety follow-up.

4.4 SURVIVAL

After discontinuing study therapy, subjects will be contacted approximately every 12 weeks until death, withdrawal by subject, lost to follow up, or study terminated by the sponsor, whichever comes first.

4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the Statistical Analysis Plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. Should the SAP and this protocol differ, the methods in the SAP prevail. The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate.

For the safety interim analysis (DLT review), enrollment of 6 subjects in the ACP-196 combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of MTD. The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in ≤ 17% of subjects). Provided the ACP-196 combination arm is not stopped early for toxicity (Section 5.5), then up to a total of 60 subjects will be enrolled per arm.

The sample size for this 2-arm trial was determined by a Z-test for normal approximation of binomial distribution, based on one-sided $\alpha = 0.10$, 80% power, with projected response rates of 42% in the ACP-196 combination arm and 23% in the nab-paclitaxel/gemcitabine arm (based on the 23% response rate observed in the Phase 3 study [nab-paclitaxel prescribing information]). Accounting for 10% drop-out rate (6 in each arm), final sample size is 60 in each arm.

Independent Radiology Review

The IRR will be performed by independent central radiologists in accordance with the IRR charter.

5.2 DEFINITION OF ANALYSIS SETS

The following definitions will be used for the efficacy and safety analysis sets.

- **Intent-to-treat (ITT) analysis set:** All enrolled subjects. The ITT analysis set will be used to summarize demographics, as well as baseline and disease characteristics.
- **Safety analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug. The safety analysis set will be used for both safety and efficacy endpoints. Subjects will be analyzed as treated.
- **Per-protocol (PP) analysis set:** A subset of subjects from the ITT analysis set who received ≥ 1 dose of study drug and do not have any important protocol deviations. This analysis set may be used for sensitivity analysis relating to the efficacy endpoints.
- **Response evaluable analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug, and undergo ≥ 1 tumor assessment after treatment. This analysis set may be used for sensitivity analysis relating to the efficacy endpoints.
- **PK/PD analysis set:** A subset of subjects from the ITT analysis set who received ≥ 1 dose of study drug, have sufficient baseline measurements, and undergo ≥ 1 PK/PD assessment after treatment. This analysis set will be used for PK/PD parameters.

5.3 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

5.4 ENDPOINT DATA ANALYSIS

5.4.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term.

Summaries will also be presented by the severity of the AE (per CTCAE, v4.03) and by relationship to study drug (eg, either ACP-196, nab-paclitaxel/gemcitabine, or both).

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

5.4.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded and tabulated according to the World Health Organization WHO Drug Dictionary (WHODRUG).

5.4.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of ACP-196 and nab-paclitaxel/gemcitabine doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

For each subject, ACP-196 and nab-paclitaxel/gemcitabine compliance will be described in terms of the proportion of study drug actually taken.

5.4.4 Analysis of Efficacy Parameters

Response Rate

The individual and composite endpoints of response and progression will be determined. Tumor control will be documented at each assessment by response category (see Section 4.2) as defined for each response parameter, date that response is first documented, and date of disease progression. ORR will be defined as the proportion of subjects who achieve a PR or CR (see Section 4.2).

ORR will be calculated and the corresponding 2-sided 95% CI will be derived.

Duration of Response

The duration of response defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored and detailed censoring rules will be specified in the statistical analysis plan (SAP).

Progression-free Survival

Progression-free survival is defined as the interval from the date of first dose of study drug to the earlier of the first documentation of objective disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored and detailed censoring rules will be specified in the SAP.

Overall Survival

OS is defined as the time from date of first dose of study drug until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who are completely lost to follow-up for survival will be censored at date of randomization. The analysis methods for OS will be similar to those described for progression-free survival.

Serum cancer antigen 19-9 (CA19-9)

Changes in CA19-9 will be evaluated using descriptive statistics evaluating the absolute and the percent change from baseline in serum CA19-9 levels.

In addition, several exploratory endpoints will be evaluated.

5.4.5 Pharmacodynamic or Biomarker Analyses

Additional PD, PK and biomarker analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques.

5.5 FUTILITY AND TOXICITY MONITORING

The futility and toxicity monitoring will be analyzed for Arm 1 only. The primary efficacy endpoint in Arm 1 is response, which is defined as ORR by RECIST 1.1 (ie, CR and PR). An ORR of at least 23% is clinically meaningful in this population (Von Hoff 2013). The response outcome within 12 weeks will be used in the primary analysis. A Bayesian method (Thall 1995) will be used for futility and toxicity monitoring of ACP-196 in combination with nab-paclitaxel/gemcitabine. The stopping rules are as follows:

$Pr(\theta_E < 0.23 \mid data) > 0.95$

$Pr(T_E > 0.30 \mid data) > 0.90$

Enrollment will be stopped early if there is > 95% probability that the ORR is < 23% or there is > 90% probability that the toxicity rate is higher than 30%. Where θ_E denotes the marginal response rate, assuming that θ_E follows a prior distribution of beta (a,b), where a and b represent nonresponse and response rates (0.23, 0.77), and T_E denotes the toxicity rate, assuming that T_E has a prior distribution of beta (0.30, 0.70). The definition of toxicity of ACP-196 in Arm 1 will follow the same definition used for assessing DLTs (see Section 3.7) including the DLT assessment window.

The above futility and toxicity monitoring rules will be implemented once the first 10 subjects have been evaluated in Arm 1 and will be applied through the first 40 subjects enrolled. The corresponding stopping boundaries for the futility monitoring are: enrollment will be stopped early due to futility if (number of subjects with ORR/number of subjects evaluated) ≤ 0/(10-13), 1/(14-20), 2/(21-26), 3/(27-32), 4/(33-38), 5/(39-40). The corresponding stopping boundaries for toxicity monitoring are listed in Table 5-1. The operating characteristics of the design are presented in Table 5-2. Multc Lean software v2.1 was used for the design.

Table 5-1. Stopping Boundaries for ACP-196 Toxicity Monitoring (Applies to Arm 1 Only)

	Stop enrolling if there are this many DLTs total:
No. Subjects (inclusive)	# Toxicities (inclusive)
1-9	Never stop with this many subjects
10-12	6-12
13-14	7-14
15-17	8-17
18-20	9-20
21-23	10-23
24-25	11-25
26-28	12-28
29-31	13-31
32-34	14-34
35-37	15-37
38-39	16-39

Table 5-2. Operating Characteristics of the Design

ORR	Toxicity rate	Probability of early stop	Average # of subjects treated
0.23	0.1	0.23	34.8
0.23	0.3	0.42	30.3
0.23	0.5	0.96	15.0
0.33	0.1	0.05	38.8
0.33	0.3	0.28	33.5
0.33	0.5	0.95	15.7

6.0 ASSESSMENT OF SAFETY

All randomized subjects will be evaluated clinically and using standard laboratory testing during their participation in this study. Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pancreatic cancer that were not present before the AE reporting period (see Section 6.2.1).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as AEs; however, any clinically significant laboratory value (ie, requiring medical intervention, reduction or withholding of ACP-196 and/or nab-paclitaxel/gemcitabine dose, or leading to study discontinuation) will be reported as adverse events.

6.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject’s ability to conduct normal life functions).

- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs must be reported on the SAE/Product Compliant form or clinical database.

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the safety follow-up visit. If a fatal AE occurs beyond 30 days after the last dose of ACP-196 and/or nab-paclitaxel/gemcitabine ***AND*** it is assessed by the investigator as related to ACP-196 and/or nab-paclitaxel/gemcitabine, it must be reported as an SAE.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drugs (see following guidance), and any actions taken. The causality of AEs to the study drugs will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

See Appendix 6 for more detail on assessing causality.

6.2.3 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (Section 6.2.4).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 90 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital

abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any women receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to DrugSafety@acerta-pharma.com.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE reports and follow-up information will be reported on an SAE/Product Complaint form using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE/Product Complaint forms may be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

Drug Safety Contact Information	
Fax:	[redacted]
[redacted]	[redacted]

Other Safety Issues Requiring Expedited Reporting

For studies being conducted in Europe expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006" available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.

6.2.5 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records

- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Form FDA 1572 (Investigator Obligation Form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be

shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the CRFs are never obliterated or destroyed.

7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of

verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

ACP-196 capsules must be kept in a locked limited access cabinet or space. ACP-196 must not be used outside the context of the protocol.

Study drug accountability records, for ACP-196 and, when applicable, for nab-paclitaxel and gemcitabine, must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. Additionally a Drug Re-order Form for requesting more study drug is provided in the pharmacy binder. If it is used, then the Drug Re-order Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. The designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-ST-004)
2. subject identification number
3. lot number(s) of ACP-196 and nab-paclitaxel/gemcitabine dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma

or its designee, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the

subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.

10. CRF pages are completed promptly.
11. All Investigational New Drug (IND) Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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9.0 APPENDICES

Appendix 1. RECIST 1.1 Guidelines

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed*: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a *short* axis of $\geqslant$15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment *or* to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ⩾15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. *Specifications by methods of measurements*

3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

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

4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist *is* able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

4.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. *Best overall response: all time points*

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
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, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. *Special notes on response assessment*

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

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

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval*.

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

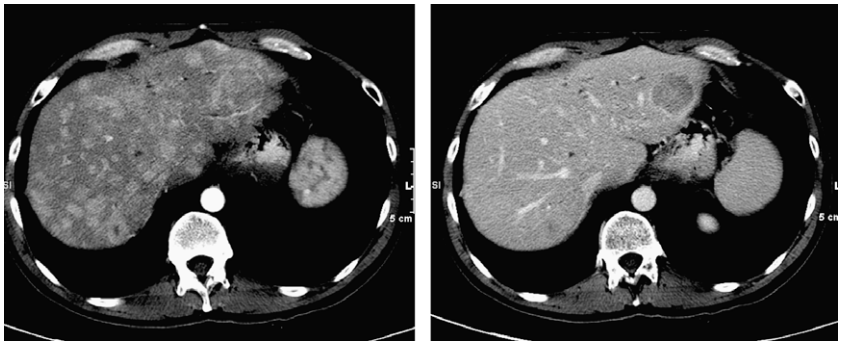

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

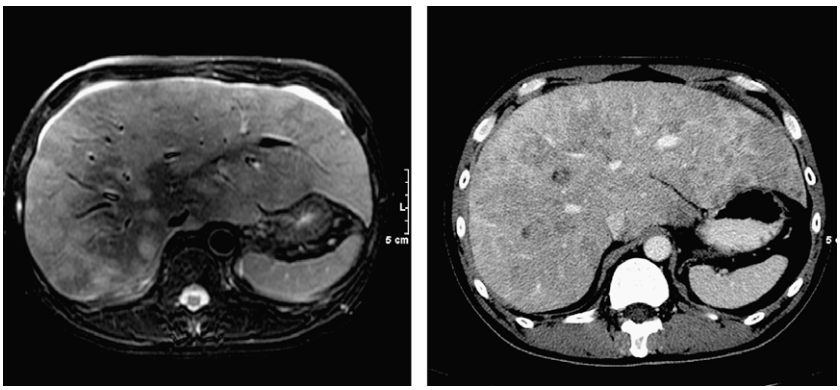

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

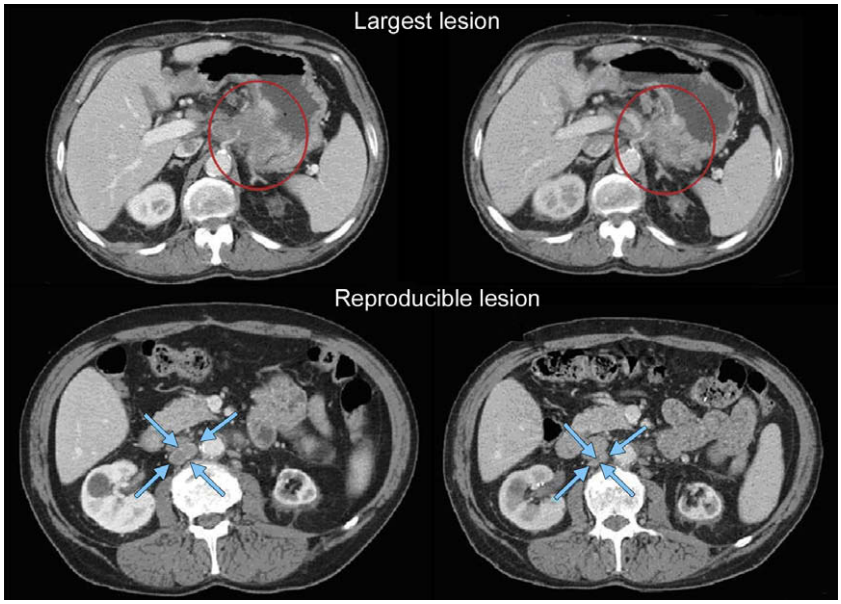

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

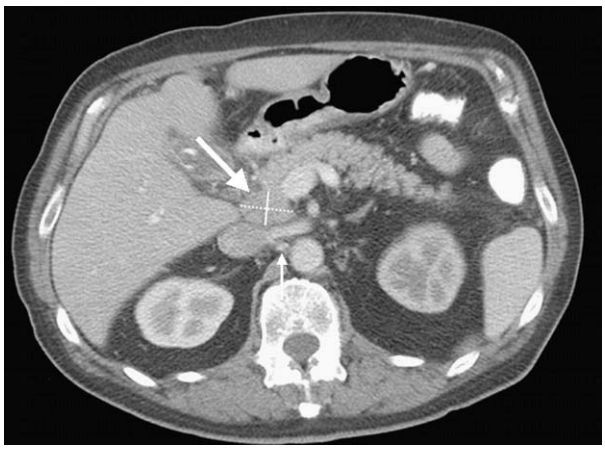

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

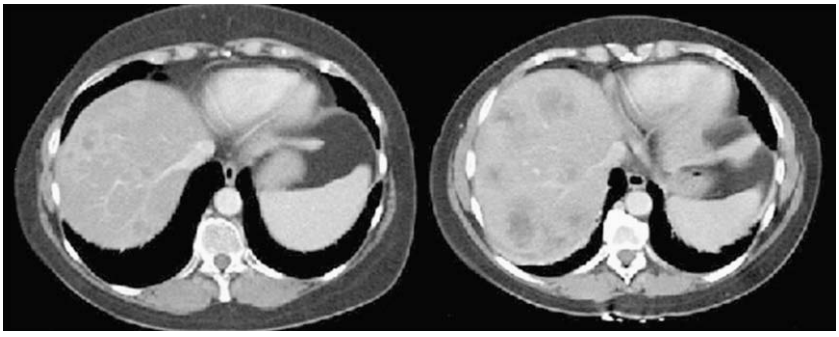

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

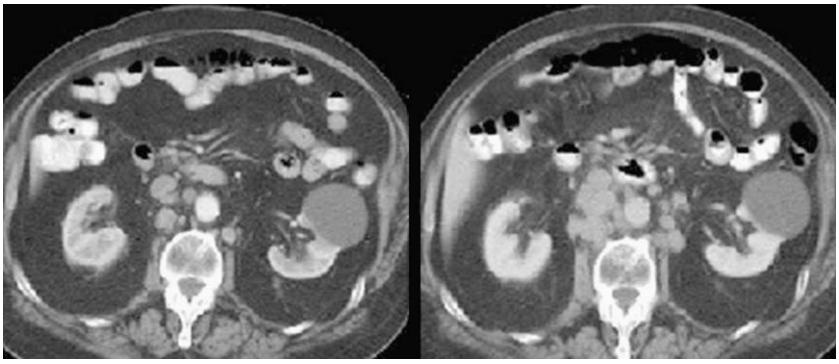

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients…in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(*continued on next page*)

Appendix III – *continued*

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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Appendix 2. Nab-paclitaxel Prescribing Information

ABRAXANE- paclitaxel injection, powder, lyophilized, for suspension
Abraxis BioScience, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE.

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Initial U.S. Approval: 2005

WARNING: NEUTROPENIA

See full prescribing information for complete boxed warning.

- **Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. (4)**
- **It is recommended that frequent peripheral blood cell counts be performed to monitor the occurrence of bone marrow suppression. (4, 5.1, 6.1, 6.2, 6.3)**

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

RECENT MAJOR CHANGES

• Dosage and Administration (2.4, 2.8)	12/2014
• Dosage and Administration (2.7)	07/2015
• Warnings and Precautions, Hepatic Impairment (5.6)	12/2014

INDICATIONS AND USAGE

ABRAXANE is a microtubule inhibitor indicated for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. (1.1)
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. (1.3)

DOSAGE AND ADMINISTRATION

- Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m^2 intravenously over 30 minutes every 3 weeks. (2.1)
- Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE. (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after ABRAXANE. (2.3)
- Do not administer ABRAXANE to any patient with AST > 10 x ULN or bilirubin > 5 x ULN. Do not administer ABRAXANE to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment. For diseases other than metastatic adenocarcinoma of the pancreas, reduce starting dose in patients with moderate to severe hepatic impairment. (2.4)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.5)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

DOSAGE FORMS AND STRENGTHS

- For injectable suspension: lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution. (3)

CONTRAINDICATIONS

- Neutrophil counts of < 1,500 cells/mm^3. (4)
- Severe hypersensitivity reaction to ABRAXANE. (4)

WARNINGS AND PRECAUTIONS

- ABRAXANE causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed. (5.1)
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.6)
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving ABRAXANE. (5.8)
- Advise men not to father a child while on ABRAXANE. (5.9)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)
- The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

WARNING: NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2, 6.3)]*.**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer

ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

1.2 Non-Small Cell Lung Cancer

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer

The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21 day cycle immediately after ABRAXANE *[see Clinical Studies (14.2)]*.

2.3 Adenocarcinoma of the Pancreas

The recommended dose of ABRAXANE is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8 and 15 of each 28-day cycle *[see Clinical Studies (14.3)]*.

2.4 Dosage in Patients with Hepatic Impairment

For patients with mild hepatic impairment (total bilirubin greater than ULN and less than or equal to 1.5 x ULN and aspartate aminotransferase [AST] less than or equal to 10 x ULN), no dose adjustments are required, regardless of indication.

Do not administer ABRAXANE to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.

Do not administer ABRAXANE to patients with total bilirubin greater than 5 x ULN or AST greater than 10 x ULN regardless of indication as these patients have not been studied.

Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	NSCLC [c]	Pancreatic [c] Adenocarcinoma
Mild	< 10 x ULN	AND	> ULN to ≤ 1.5 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	>1.5 to ≤ 3 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.

[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

[b] A dose increase to 260 mg/m^2 for patients with metastatic breast cancer or 100 mg/m^2 for patients with non-small cell lung cancer in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.

[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophils less than 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

Non-Small Cell Lung Cancer

- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 *[see Contraindications (4),Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5

Platelet count less than 50,000/mm³	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas
Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	ABRAXANE	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.6 Preparation and Administration Precautions

ABRAXANE is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions *[see Adverse Reactions (6.4)]*.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration

of ABRAXANE. Premedication may be needed in patients who have had prior hypersensitivity reactions to ABRAXANE. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug *[see Warnings and Precautions (5.5)]*.

2.7 Preparation for Intravenous Administration

ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient and slowly withdraw the dosing volume of the reconstituted suspension from the vial(s) into a syringe: Dosing volume (mL)=Total dose (mg)/5 (mg/mL).

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of medical devices containing silicone oil as a lubricant (ie, syringes and intravenous bags) to reconstitute and administer ABRAXANE may result in the formation of proteinaceous strands.

Visually inspect the reconstituted ABRAXANE suspension in the intravenous bag prior to administration. Discard the reconstituted suspension if proteinaceous strands, particulate matter or discoloration are observed.

2.8 Stability

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial
Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag
The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted ABRAXANE in the vial and in the

infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension: lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution.

4 CONTRAINDICATIONS

- ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Effects

Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

In patients with NSCLC, resume treatment if recommended (see Dosage and Administration, Table 2) at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle *[see Dosage and Administration (2.5)]*.

In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended *[see Dosage and Administration (2.5)]*.

5.2 Nervous System

Sensory neuropathy is dose- and schedule-dependent *[see Adverse Reactions (6.1, 6.2, 6.3)]*. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE *[see Dosage and Administration (2.5)]*.

5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels *[see Dosage and Administration (2.5)]*.

5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine.

5.5 Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with this drug.

5.6 Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression. ABRAXANE is not recommended in patients who have total bilirubin >5 x ULN or AST >10 x ULN. In addition, ABRAXANE is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN). The starting dose should be reduced for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.7 Albumin (Human)

ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

5.8 Use in Pregnancy

ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

There are no adequate and well-controlled studies in pregnant women receiving ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE *[see Use in Specific Populations (8.1)]*.

5.9 Use in Men

Men should be advised not to father a child while receiving ABRAXANE *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 20%) with single-agent use of ABRAXANE in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea *[see Adverse Reactions (6.1)]*.

The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue *[see Adverse Reactions (6.2)]*. The most common serious adverse reactions of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of ABRAXANE in combination with gemcitabine for pancreatic adenocarcinoma *[see Clinical Studies (14.3)]*, the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of ABRAXANE are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of ABRAXANE (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are peripheral neuropathy (8%), fatigue (4%)

and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

6.1 Clinical Trials Experience in Metastatic Breast Cancer

Table 6 shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260 mg/m^2 over 30 min (n=229)	**Paclitaxel Injection 175 mg/m^2 over 3 h[b] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction[c]		
All	4	12
Severe[d]	0	2
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[d]	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[d]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[d]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[d]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[d]	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms[d]	3	<1
Vomiting		

Any Symptoms	18	10
Severe Symptoms[d]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[d]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[d]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 2.

[b] Paclitaxel injection patients received premedication.

[c] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

[d] Severe events are defined as at least grade 3 toxicity.

Adverse Event Experiences by Body System

Hematologic Disorders
Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections
Infectious episodes were reported in 24% of the patients treated with ABRAXANE. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)
Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with ABRAXANE.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE and 1%

were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events
Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

6.2 Clinical Trials Experience in Non-Small Cell Lung Cancer

Adverse reactions were assessed in 514 ABRAXANE/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion.
The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 7 provides the frequency and severity of laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities With a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m^2 weekly) plus carboplatin		**Paclitaxel Injection (200 mg/m^2 every 3 weeks) plus carboplatin**	
	Grades 1-4 (%)	**Grade 3-4 (%)**	**Grades 1-4 (%)**	**Grade 3-4 (%)**
Anemia[1,2]	98	28	91	7
Neutropenia[1,3]	85	47	83	58
Thrombocytopenia[1,3]	68	18	55	9

[1] 508 patients assessed in ABRAXANE/carboplatin-treated group
[2] 514 patients assessed in paclitaxel injection/carboplatin-treated group
[3] 513 patients assessed in paclitaxel injection/carboplatin-treated group

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

		ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=514)	**Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=524)**

System Organ Class	MedDRA v 12.1 Preferred Term	Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy[a]	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and mediastinal disorders	Epistaxis	7	0	2	0
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

[a] Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

6.3 Clinical Trials Experience in Adenocarcinoma of the Pancreas

Adverse reactions were assessed in 421 patients who received ABRAXANE plus gemcitabine and 402 patients who received gemcitabine for the first-line systemic treatment of metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1-4 (≥ 5%) or for Grade 3-4 (≥ 2%) toxicity in ABRAXANE plus gemcitabine-treated patients.

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the ABRAXANE/Gemcitabine Arm

	ABRAXANE(125 mg/m^2)/ Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group

[b] 388 patients assessed in gemcitabine-treated group

[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group

[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the ABRAXANE plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)

	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections [b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

[a] Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).

[b] Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of ABRAXANE-treated patients with Grade 3 peripheral neuropathy, 44% resumed ABRAXANE at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received ABRAXANE/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the ABRAXANE arm with pneumonitis died.

6.4 Postmarketing Experience with ABRAXANE and other Paclitaxel Formulations

Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of pneumonitis, interstitial pneumonia and pulmonary embolism in patients receiving ABRAXANE and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety and may also be observed with ABRAXANE.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with ABRAXANE.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with ABRAXANE as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

Hepatic
Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABRAXANE treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., “recall”, has been reported.

Other Clinical Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with ABRAXANE. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.5 Accidental Exposure

No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

7 DRUG INTERACTIONS

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]*.

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a

pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE.

Administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the 229 patients in the randomized study who received ABRAXANE for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received ABRAXANE.

A subsequent pooled analysis was conducted in 981 patients receiving ABRAXANE monotherapy for metastatic breast cancer, of which 15% were 65 years of age or older and 2% were 75 years of age or older. A higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema was found in patients 65 years of age or older.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received ABRAXANE and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of ABRAXANE did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

8.6 Patients with Hepatic Impairment

The exposure to paclitaxel may be higher in patients with hepatic impairment than in patients with normal hepatic function. Reduce ABRAXANE starting dose in patients with moderate to severe hepatic impairment. Do not administer ABRAXANE to patients with total bilirubin > 5 x ULN or AST > 10 x ULN *[see Dosage and Administration (2.4), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*. Do not administer to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment *[see Dosage and Administration (2.4)]*.

8.7 Patients with Renal Impairment

Adjustment of the starting ABRAXANE dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 mL/min) *[see Clinical Pharmacology (12.3)]*. There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min).

10 OVERDOSAGE

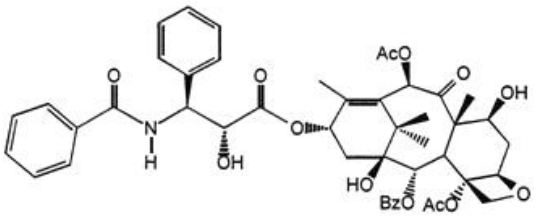
There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

11 DESCRIPTION

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel formulated as albumin-bound particles. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ABRAXANE is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

12.3 Pharmacokinetics

Absorption
The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of intravenous administration.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for ABRAXANE than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution
Following ABRAXANE administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized

primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4 *[see Drug Interactions (7)]*.

Elimination
At the clinical dose range of 80 to 300 mg/m^2, the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m^2, and the mean terminal half-life ranges from 13 to 27 hours.

After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel.

Fecal excretion was approximately 20% of the total dose administered.

Specific Populations

Pharmacokinetics in Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of paclitaxel following ABRAXANE administration was studied in patients with advanced solid tumors. The results showed that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN, AST ≤10 x ULN, n=8) had no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤ 3 x ULN, AST ≤10 x ULN, n=7) or severe (total bilirubin >3 to ≤5 x ULN, n=5) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ULN, AST ≤ULN, n=130). *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for ABRAXANE exposure. Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic adenocarcinoma of the pancreas *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Pharmacokinetics in Renal Impairment
The effect of pre-existing mild (creatinine clearance ≥60 to <90 mL/min, n=61) or moderate (creatinine clearance ≥30 to <60 mL/min, n=23) renal impairment on the pharmacokinetics of paclitaxel following ABRAXANE administration was studied in patients with advanced solid tumors. Mild to moderate renal impairment had no clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel *[see Use in Specific Populations (8.7)]*.

Other Intrinsic Factors
Population pharmacokinetic analyses for ABRAXANE show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m^2), gender, race (Asian vs. White), age (24 to 85 years) and type of solid tumors do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel.

Pharmacokinetic Interactions between ABRAXANE and Carboplatin
Administration of carboplatin immediately after the completion of the ABRAXANE infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

Pharmacokinetic Interactions between ABRAXANE and Gemcitabine
Pharmacokinetic interactions between ABRAXANE and gemcitabine have not been studied in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel was clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel formulated as albumin-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area

basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration was observed in single-dose toxicology studies in rodents administered paclitaxel formulated as albumin-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies
In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3-week intervals. Objective responses were observed in both studies.

Randomized Comparative Study
This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 11. There was no statistically significant difference in overall survival between the two study arms.

Table 11: Efficacy Results from Randomized Metastatic Breast Cancer Trial

		ABRAXANE 260 mg/m^2	**Paclitaxel Injection 175 mg/m^2**
Reconciled Target Lesion Response Rate (primary endpoint)[a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	p-value[b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.
[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.
[c] Prior therapy included an anthracycline unless clinically contraindicated.

14.2 Non-Small Cell Lung Cancer

A multicenter, randomized, open-label study was conducted in 1052 chemonaive patients with Stage IIIb/IV non-small cell lung cancer to compare ABRAXANE in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The major efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST

guidelines (Version 1.0).

In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms.

Patients in the ABRAXANE/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%) see Table 12]. There was no statistically significant difference in overall survival between the two study arms.

Table 12: Efficacy Results from Randomized Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

	ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=521)	**Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=531)**
Overall Response Rate (ORR)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
P-value (Chi-Square test)	0.005	
Median DoR in months (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

CI = confidence interval; DoR= Duration of response

14.3 Adenocarcinoma of the Pancreas

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing ABRAXANE plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the ABRAXANE/gemcitabine arm (N=431) or to the gemcitabine arm (N=430). Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to ABRAXANE/gemcitabine received ABRAXANE 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8 and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

In the intent to treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Results for overall survival, progression-free survival, and overall response rate are shown in Table 13.

Table 13: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

	ABRAXANE (125 mg/m^2) and gemcitabine	**Gemcitabine (N = 430)**

	(N = 431)	(N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
95% CI	7.9, 9.5	6.0, 7.2
HR (95% CI) [a]	0.72 (0.62, 0.83)	
P-value[b]	<0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI) [a]	0.69 (0.58, 0.82)	
P-value[b]	<0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1, 27.2	5.0, 10.1
P-value [d]	<0.0001	

CI = confidence interval, HR = hazard ratio of ABRAXANE plus gemcitabine / gemcitabine, ITT = intent-to-treat population.

[a] Stratified Cox proportional hazard model.

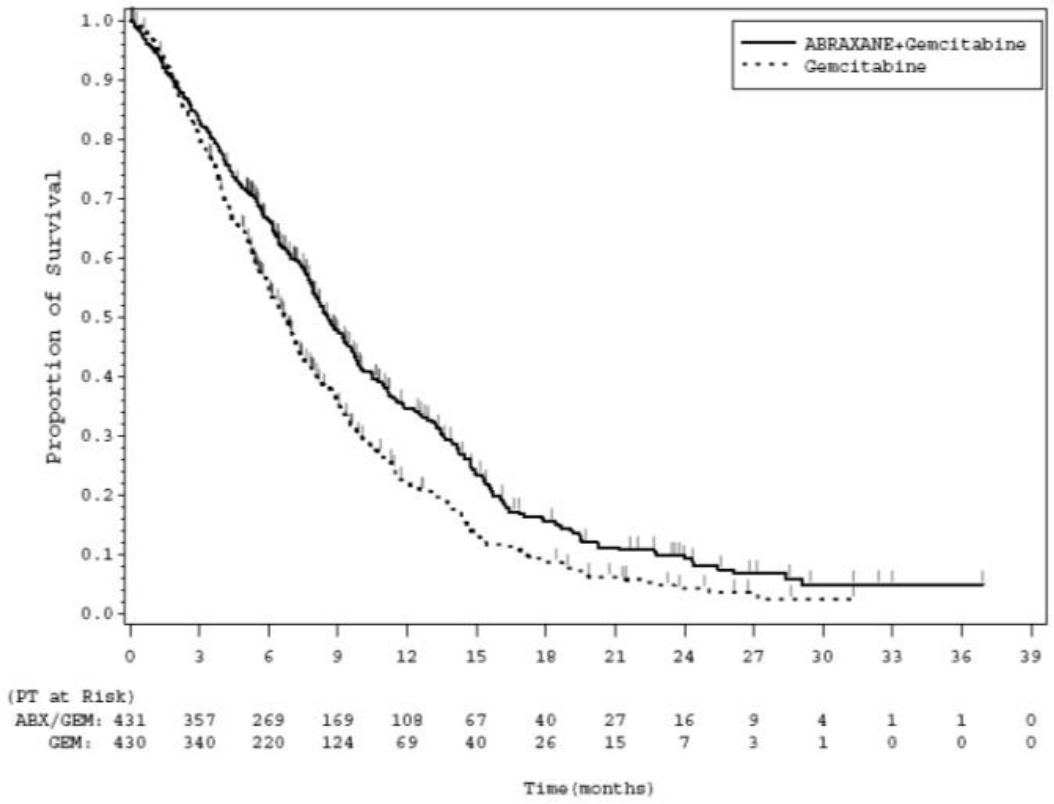
[b] Stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

[c] Based on Independent Radiological Reviewer Assessment.

[d] Chi-square test.

In exploratory analyses conducted in clinically relevant subgroups with a sufficient number of subjects, the treatment effects on overall survival were similar to that observed in the overall study population.

Figure 1: Kaplan-Meier Curve of Overall Survival (Intent-to-treat Population)



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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Product No.: 103450
NDC No.: 68817-134-50 100 mg of paclitaxel in a single-use vial, individually packaged in a carton.

16.2 Storage

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling

- ABRAXANE injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives while receiving ABRAXANE *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*.
- Advise men not to father a child while receiving ABRAXANE *[see Warnings and Precautions (5.9)]*.
- Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their physician immediately for fever or evidence of infection. *[see Warnings and Precautions (5.1), (5.3)]*.
- Patients should be instructed to contact their physician for persistent vomiting, diarrhea, or signs of dehydration.
- Patients must be informed that sensory neuropathy occurs frequently with ABRAXANE and patients should advise their physicians of numbness, tingling, pain or weakness involving the extremities *[see Warnings and Precautions (5.2)]*.
- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with ABRAXANE
- Instruct patients to contact their physician for signs of an allergic reaction, which could be severe and sometimes fatal. *[see Warnings and Precautions (5.5)]*.
- Instruct patients to contact their physician immediately for sudden onset of dry persistent cough, or shortness of breath *[see Warnings and Precautions (5.4)]*.

Manufactured for: Celgene Corporation
Summit, NJ 07901

U.S. Patent Numbers: See www.celgene.com.

ABRPI.009/PPI.009 07/15

Patient Information

ABRAXANE® (ah-BRAKS-ane)
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Read this Patient Information before you start receiving ABRAXANE and before each infusion. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is ABRAXANE?

ABRAXANE is a prescription medicine used to treat:

- advanced breast cancer in people who have already received certain other medicines for their cancer.
- advanced non-small cell lung cancer, in combination with carboplatin in people who cannot be treated with surgery or radiation.
- and advanced pancreatic cancer, when used in combination with gemcitabine as the first medicine for advanced pancreatic cancer.

It is not known if ABRAXANE is safe or effective in children.

Who should not receive ABRAXANE?

Do not receive ABRAXANE if:

- your white blood cell count is below 1,500 cells/ mm^3.
- you have had a severe allergic reaction to ABRAXANE.

What should I tell my doctor before receiving ABRAXANE?

Before you receive ABRAXANE, tell your doctor if you:

- have liver or kidney problems.
- have any other medical conditions.
- are a man planning to father a child. You should not father a child during your treatment with ABRAXANE. ABRAXANE can harm the unborn baby of your partner. Talk to your doctor if this is a concern to you.
- are pregnant or plan to become pregnant. ABRAXANE can harm your unborn baby. You should not become pregnant while receiving ABRAXANE. Women who may become pregnant should use effective birth control (contraception). Talk to your doctor about the best way to prevent pregnancy while receiving ABRAXANE.
- are breastfeeding or plan to breastfeed. It is not known if ABRAXANE passes into your breast milk. You and your doctor should decide if you will receive ABRAXANE or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your doctor and pharmacist when you get a new medicine.

How will I receive ABRAXANE?

- Your doctor will prescribe ABRAXANE in an amount that is right for you.
- Premedication to prevent allergic reactions is generally not needed to receive ABRAXANE. Premedication may be needed if you have had an allergic reaction to ABRAXANE. In case of severe allergic reaction, ABRAXANE should not be used again.
- ABRAXANE will be given to you by intravenous infusion into your vein.
- Your doctor should do regular blood tests while you receive ABRAXANE.

What are the possible side effects of ABRAXANE?

ABRAXANE may cause serious side effects, including:

- decreased blood cell counts. ABRAXANE can cause a severe decrease in neutrophils (a type of white blood cells important in fighting against bacterial infections) and platelets (important for clotting and to control bleeding). Your doctor will check your blood cell count during your treatment with ABRAXANE and after you have stopped your treatment.
- numbness, tingling, pain, or weakness in your hands or feet (neuropathy).
- severe infection (sepsis). If you receive ABRAXANE in combination with gemcitabine, infections can be severe and lead to death. Tell your doctor right away if you have a fever (temperature of greater than 100.4° F) or develop signs of infection.
- lung or breathing problems. If you receive ABRAXANE in combination with gemcitabine, lung or breathing problems may be severe and can lead to death. Tell your doctor right away if you have a sudden onset of persistent dry cough or shortness of breath.
- allergic reactions. Allergic reactions to ABRAXANE may be severe and can lead to death.

The most common side effects of ABRAXANE include:

- hair loss
- numbness, tingling, pain, or weakness in the hands or feet
- abnormal heart beat
- tiredness
- joint and muscle pain
- changes in your liver function tests

- rash
- low red blood cell count (anemia). Red blood cells carry oxygen to your body tissues. Tell your doctor if you feel weak, tired or short of breath.
- nausea and vomiting
- infections. If you have a fever (temperature of greater than 100.4° F) or other signs of infection, tell your doctor right away.
- Diarrhea
- Loss of body fluid (dehydration)
- Swelling in the hands or feet

These are not all the possible side effects of ABRAXANE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ABRAXANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

This Patient Information leaflet summarizes the important information about ABRAXANE. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about ABRAXANE that is written for health professionals.

For more information, call 1-888-423-5436.

What are the ingredients in ABRAXANE?

Active ingredient: paclitaxel (bound to human albumin).

Other ingredient: human albumin (containing sodium caprylate and sodium acetyltryptophanate)

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: July 2015

Manufactured for: Celgene Corporation
Summit, NJ 07901

U.S. Patent Numbers: See www.celgene.com.

ABRPPI.009 07/15

PRINCIPAL DISPLAY PANEL - 100 mg Vial

NDC 68817-134-50
103450

Abraxane®
for Injectable Suspension

(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

100 mg per vial
Single Use Vial

Discard any unused portion.

For Intravenous Use Only
Rx only

Functional properties differ from other paclitaxel products. DO NOT SUBSTITUTE.

Appendix 3. Gemcitabine Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gemzar safely and effectively. See full prescribing information for Gemzar.

GEMZAR (gemcitabine for injection), for intravenous use

Initial U.S. Approval: 1996

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration:
Dose Modifications for Non-Hematologic Adverse Reactions (2.5) 6/2014

Warnings and Precautions:
Posterior Reversible Encephalopathy Syndrome (5.9) 6/2014

---------- INDICATIONS AND USAGE ----------

Gemzar® is a nucleoside metabolic inhibitor indicated:
- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum- based therapy. (1.1)
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. (1.2)
- in combination with cisplatin for the treatment of non-small cell lung cancer. (1.3)
- as a single agent for the treatment of pancreatic cancer. (1.4)

----------DOSAGE AND ADMINISTRATION----------

Gemzar is for intravenous use only.
- Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.1)
- Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.2)
- Non-Small Cell Lung Cancer: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.3)
- Pancreatic Cancer: 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg/single-use vial (3)
- 1 g/single-use vial (3)

---------- CONTRAINDICATIONS ----------

Patients with a known hypersensitivity to gemcitabine. (4)

----------WARNINGS AND PRECAUTIONS----------

- Schedule-dependent toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly. (5.1)
- Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression. (5.2, 5.7)
- Pulmonary Toxicity and Respiratory Failure: Discontinue Gemzar immediately for unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity. (5.3)
- Hemolytic-Uremic Syndrome (HUS): Monitor renal function prior to initiation and during therapy. Discontinue Gemzar for HUS or severe renal impairment. (5.4)
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during therapy. Discontinue Gemzar for severe hepatic toxicity. (5.5)
- Embryofetal Toxicity: Can cause fetal harm. Advise women of potential risk to the fetus. (5.6, 8.1)
- Exacerbation of Radiation Therapy Toxicity: May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy. (5.7)
- Capillary Leak Syndrome: Discontinue Gemzar. (5.8)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue Gemzar. (5.9)

----------ADVERSE REACTIONS----------

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

Gemzar in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

1.2 Breast Cancer

Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

1.3 Non-Small Cell Lung Cancer

Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

1.4 Pancreatic Cancer

Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1000 mg/m^2 as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after Gemzar administration on Day 1 of each 21-day cycle. Refer to carboplatin prescribing information for additional information.

Dose Modifications

Recommended Gemzar dose modifications for myelosuppression are described in Table 1 and Table 2 *[see Warnings and Precautions (5.2)].* Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 1: Dosage Reduction Guidelines for Gemzar for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
Day 1	≥1500	and	≥100,000	100%
	<1500	or	<100,000	Delay Treatment Cycle
Day 8	≥1500	and	≥100,000	100%
	1000-1499	or	75,000-99,999	50%
	<1000	or	<75,000	Hold

Table 2: Gemzar Dose Modification for Myelosuppression in Previous Cycle In Ovarian Cancer

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial Occurrence	Absolute granulocyte count less than 500 x 10^6/L for more than 5 days Absolute granulocyte count less than 100 x 10^6/L for more than 3 days Febrile neutropenia Platelets less than 25,000x10^6/L Cycle delay of more than one week due to toxicity	Permanently reduce Gemzar to 800 mg/m^2 on Days 1 and 8
Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction	Permanently reduce Gemzar dose to 800 mg/m^2 on Day 1 only

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3 hour intravenous infusion before Gemzar administration.

Dose Modifications

Recommended dose modifications for Gemzar for myelosuppression are described in Table 3 *[see Warnings and Precautions (5.2)].* Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 3: Recommended Dose Reductions for Gemzar for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
Day 1	≥1500	and	≥100,000	100%
	less than 1500	or	less than 100,000	Hold
Day 8	≥1200	and	>75,000	100%
	1000-1199	or	50,000-75,000	75%
	700-999	and	≥50,000	50%
	<700	or	<50,000	Hold

2.3 Non-Small Cell Lung Cancer

Recommended Dose and Schedule

Every 4-week schedule

The recommended dose of Gemzar is 1000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar.

Every 3-week schedule

The recommended dose of Gemzar is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar.

Dose Modifications

Recommended dose modifications for Gemzar myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)].* Refer to Dosage and Administration (2.5) for Gemzar recommendations for non-hematologic adverse reactions.

2.4 Pancreatic Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1000 mg/m^2 over 30 minutes intravenously. The recommended treatment schedule is as follows:

- Weeks 1-8: weekly dosing for the first 7 weeks followed by one week rest.
- After week 8: weekly dosing on Days 1, 8, and 15 of 28-day cycles.

Dose Modifications

Recommended dose modifications for Gemzar for myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)].* Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 4.

Table 4: Recommended Dose Reductions for Gemzar for Myelosuppression in Pancreatic Cancer and Non-Small Cell Lung Cancer

Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
≥1000	And	≥100,000	100%
500-999	Or	50,000-99,999	75%
<500	Or	<50,000	Hold

2.5 Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemzar for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold Gemzar or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

2.6 Preparation and Administration Precautions

Exercise caution and wear gloves when preparing Gemzar solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemzar contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption. For further guidance on handling Gemzar go to "OSHA Hazardous Drugs" (refer to antineoplastic weblinks including OSHA Technical Manual) at OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

2.7 Preparation for Intravenous Infusion Administration

Reconstitute the vials with 0.9% Sodium Chloride Injection without preservatives.

Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a Gemzar concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemzar. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration. Gemzar solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur.

No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS

Gemzar (gemcitabine for injection USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

4 CONTRAINDICATIONS

Gemzar is contraindicated in patients with a known hypersensitivity to gemcitabine.

5 WARNINGS AND PRECAUTIONS

5.1 Schedule-dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of Gemzar, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of Gemzar is influenced by the length of the infusion *[see Clinical Pharmacology (12.3)]*.

5.2 Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemzar as a single agent and the risks are increased when Gemzar is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent Gemzar. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving Gemzar in combination with another drug.

5.3 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of Gemzar. Discontinue Gemzar in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity *[see Adverse Reactions (6.1 and 6.2)]*.

5.4 Hemolytic Uremic Syndrome

Hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis, can occur in patients treated with Gemzar. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS *[see Adverse Reactions (6.1 and 6.2)]*. Assess renal function prior to initiation of Gemzar and periodically during treatment. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN) *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*. Permanently discontinue Gemzar in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.

5.5 Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs *[see Adverse Reactions (6.1 and 6.2)]*. Administration of Gemzar in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency *[see Use in Specific Populations (8.7)]*. Assess hepatic function prior to initiation of Gemzar and periodically during treatment. Discontinue Gemzar in patients that develop severe liver injury.

5.6 Embryofetal Toxicity

Gemzar can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a

woman becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

5.7 Exacerbation of Radiation Therapy Toxicity

Gemzar is not indicated for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which Gemzar was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart) — Excessive toxicity has not been observed when Gemzar is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive Gemzar after prior radiation.

5.8 Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemzar as a single agent or in combination with other chemotherapeutic agents. Discontinue Gemzar if CLS develops during therapy.

5.9 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemzar as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI) and discontinue Gemzar if PRES develops during therapy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label

- Schedule-dependent Toxicity *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Pulmonary Toxicity and Respiratory Failure *[see Warnings and Precautions (5.3)]*
- Hemolytic Uremic Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*
- Embryofetal Toxicity *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1), and Nonclinical Toxicology (13.1)]*
- Exacerbation of Radiation Toxicity *[see Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.8)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Single-Agent Use:

The data described below reflect exposure to Gemzar as a single agent administered at doses between 800 mg/m^2 to 1250 mg/m^2 over 30 minutes intravenously, once weekly, in 979 patients with a variety of malignancies. The most common (≥20%) adverse reactions of single-agent Gemzar are nausea/vomiting, anemia, increased ALT, increased AST, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema. The most common (≥5%) Grade 3 or 4 adverse reactions were neutropenia, nausea/vomiting; increased ALT, increase alkaline phosphatase, anemia, increased AST, and thrombocytopenia. Approximately 10% of the 979 patients discontinued Gemzar due to adverse reactions. Adverse reactions resulting in discontinuation of Gemzar in 2% of 979 patients were cardiovascular adverse events (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of Gemzar in less than 1% of the 979 patients were anemia, thrombocytopenia, hepatic dysfunction, renal dysfunction, nausea/vomiting, fever, rash, dyspnea, hemorrhage, infection, stomatitis, somnolence, flu-like syndrome, and edema.

Table 5 presents the incidence of adverse reactions reported in 979 patients with various malignancies receiving single-agent Gemzar across 5 clinical trials. Table 5 includes all clinical adverse reactions, reported in at least 10% of patients. A listing of clinically significant adverse reactions is provided following the table.

Table 5: Selected Per-Patient Incidence of Adverse Events in Patients Receiving Single-Agent Gemzar[a]

	All Patients[b]		
	All Grades	Grade 3	Grade 4
Laboratory[c]			
Hematologic			
Anemia	68	7	1
Neutropenia	63	19	6
Thrombocytopenia	24	4	1
Hepatic			

Increased ALT	68	8	2
Increased AST	67	6	2
Increased Alkaline Phosphatase	55	7	2
Hyperbilirubinemia	13	2	<1
Renal			
Proteinuria	45	<1	0
Hematuria	35	<1	0
Increased BUN	16	0	0
Increased Creatinine	8	<1	0
Non-laboratory[d]			
Nausea and Vomiting	69	13	1
Fever	41	2	0
Rash	30	<1	0
Dyspnea	23	3	<1
Diarrhea	19	1	0
Hemorrhage	17	<1	<1
Infection	16	1	<1
Alopecia	15	<1	0
Stomatitis	11	<1	0
Somnolence	11	<1	<1
Paresthesias	10	<1	0

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=699-974; all patients with laboratory or non-laboratory data.
[c] Regardless of causality.
[d] For approximately 60% of patients, non-laboratory adverse events were graded only if assessed to be possibly drug-related.

- Transfusion requirements — Red blood cell transfusions (19%); platelet transfusions (<1%)
- Fever — Fever occurred in the absence of clinical infection and frequently in combination with other flu-like symptoms.
- Pulmonary — Dyspnea unrelated to underlying disease and sometimes accompanied by bronchospasm.
- Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%); <1% of patients. discontinued Gemzar due to edema.
- Flu-like Symptoms — Characterized by fever, asthenia, anorexia, headache, cough, chills, myalgia, asthenia insomnia, rhinitis, sweating, and/or malaise (19%); <1% of patients discontinued Gemzar due to flu-like symptoms
- Infection — Sepsis (<1%)
- Extravasation — Injection-site reactions (4%)
- Allergic — Bronchospasm (<2%); anaphylactoid reactions *[see Contraindications (4)]*.

Non-Small Cell Lung Cancer:

Table 6 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus cisplatin arm, reported in a randomized trial of Gemzar plus cisplatin (n=262) administered in 28-day cycles as compared to cisplatin alone (n=260) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*.

Patients randomized to Gemzar plus cisplatin received a median of 4 cycles of treatment and those randomized to cisplatin received a median of 2 cycles of treatment. In this trial, the requirement for dose adjustments (>90% versus 16%), discontinuation of treatment for adverse reactions (15% versus 8%), and the proportion of patients hospitalized (36% versus 23%) were all higher for patients receiving Gemzar plus cisplatin arm compared to those receiving cisplatin alone. The incidence of febrile neutropenia (9/262 versus 2/260), sepsis (4% versus 1%), Grade 3 cardiac dysrhythmias (3% versus <1%) were all higher in the Gemzar plus cisplatin arm compared to the cisplatin alone arm. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm.

Table 6: Per-Patient Incidence of Selected Adverse Reactions from Randomized Trial of Gemzar plus Cisplatin versus Single-Agent Cisplatin in Patients with NSCLC Occurring at Higher Incidence in Gemzar-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)][a]

	Gemzar plus Cisplatin[b]			**Cisplatin**[c]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						

Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion[e]	39			13		
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions[e]	21			<1		
Lymphopenia	75	25	18	51	12	5
Hepatic						
Increased Transaminases	22	2	1	10	1	0
Increased Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Elevated creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[f]						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

[a] National Cancer Institute Common Toxicity Criteria (CTC) for severity grading.

[b] N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data Gemzar at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[c] N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[d] Regardless of causality.

[e] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

[f] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 7 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus cisplatin arm, reported in a randomized trial of Gemzar plus cisplatin (n=69) administered in 21-day cycles as compared to etoposide plus cisplatin alone (n=66) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*. A listing of clinically significant adverse reactions is provided following the table.

Patients in the Gemzar cisplatin (GC) arm received a median of 5 cycles and those in the etoposide/cisplatin (EC) arm received a median of 4 cycles. The majority of patients receiving more than one cycle of treatment required dose adjustments; 81% in the (GC) arm and 68% in the (EC) arm. The incidence of hospitalizations for treatment-related adverse events was 22% (GC) and 27% in the (EC) arm. The proportion of discontinuation of treatment for treatment-related adverse reactions was higher for patients in the (GC) arm (14% versus 8%). The proportion of patients hospitalized for febrile neutropenia was lower in the (GC) arm (7% versus 12%). There was one death attributed to treatment, a patient with febrile neutropenia and renal failure, which occurred in the Gemzar/cisplatin arm.

Table 7: Per-Patient Incidence of Selected Adverse Reactions in Randomized Trial of Gemzar plus Cisplatin versus Etoposide plus Cisplatin in Patients with NSCLC[a]

	Gemzar plus Cisplatin[b]			Etoposide plus Cisplatin[c]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[e]	29	-	-	21	-	-
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions[e]	3	-	-	8	-	-
Hepatic						
Increased ALT	6	0	0	12	0	0
Increased AST	3	0	0	11	0	0
Increased Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory[f]						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0
Flu-like syndrome[g]	3	-	-	0	-	-
Edema[g]	12	-	-	2	-	-

[a] Grade based on criteria from the World Health Organization (WHO).

[b] N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.

[c] N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 and intravenous etoposide at 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[d] Regardless of causality.

[e] WHO grading scale not applicable to proportion of patients with transfusions.

[f] Non-laboratory events were graded only if assessed to be possibly drug-related. Pain data were not collected.

[g] Flu-like syndrome and edema were not graded.

Breast Cancer

Table 8 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus paclitaxel arm, reported in a randomized trial of Gemzar plus paclitaxel (n=262) compared to paclitaxel alone (n=259) for the first-line treatment of metastatic breast cancer (MBC) in women who received anthracycline-containing chemotherapy in the adjuvant/neo-adjuvant setting or for whom anthracyclines were contraindicated *[see Clinical Studies (14.2)]*.

The requirement for dose reduction of paclitaxel were higher for patients in the Gemzar/paclitaxel arm (5% versus 2%). The number of paclitaxel doses omitted (<1%), the proportion of patients discontinuing treatment for treatment-related adverse reactions (7% versus 5%), and the number of treatment-related deaths (1 patient in each arm) were similar between the two arms.

Table 8: Per-Patient Incidence of Selected Adverse Reactions from Comparative Trial of Gemzar plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer[a] Occurring at Higher Incidence in Gemzar-Treated Patients

[Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemzar plus Paclitaxel	Paclitaxel

	(N=262)			(N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Hepatobiliary						
Increased ALT	18	5	<1	6	<1	0
Increased AST	16	2	0	5	<1	0
Non-laboratory[c]						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Vomiting	29	2	0	15	2	0
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Rash/desquamation	11	<1	<1	5	0	0
Febrile neutropenia	6	5	<1	2	1	0

[a] Severity grade based on National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0.
[b] Regardless of causality.
[c] Non-laboratory events were graded only if assessed to be possibly drug-related.

Clinically relevant Grade 3 or 4 dyspnea occurred with a higher incidence in the Gemzar plus paclitaxel arm compared with the paclitaxel arm (1.9% versus 0).

Ovarian Cancer

Table 9 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the Gemzar plus carboplatin arm, reported in a randomized trial of Gemzar plus carboplatin (n=175) compared to carboplatin alone (n=174) for the second-line treatment of ovarian cancer in women with disease that had relapsed more than 6 months following first-line platinum-based chemotherapy *[see Clinical Studies (14.1)]*. Additional clinically significant adverse reactions, occurring in less than 10% of patients, are provided following Table 9.

The proportion of patients with dose adjustments for carboplatin (1.8% versus 3.8%), doses of carboplatin omitted (0.2% versus 0), and discontinuing treatment for treatment-related adverse reactions (10.9% versus 9.8%), were similar between arms. Dose adjustment for Gemzar occurred in 10.4% of patients and Gemzar dose was omitted in 13.7% of patients in the Gemzar /carboplatin arm.

Table 9: Per-Patient Incidence of Adverse Reactions in Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer[a] Occurring at Higher Incidence in Gemzar-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemzar plus Carboplatin (N=175)			Carboplatin (N=174)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusions[c]	38			15		
Platelet Transfusions[c]	9			3		
Non-laboratory[b]						
Nausea	69	6	0	61	3	0
Alopecia	49	0	0	17	0	0
Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Diarrhea	25	3	0	14	<1	0

Stomatitis/pharyngitis	22	<1	0	13	0	0

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0.
[b] Regardless of causality.
[c] Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red blood cells and whole blood.

Hematopoietic growth factors were administered more frequently in the Gemzar-containing arm: granulocyte growth factors (23.6% and 10.1%) and erythropoietic agents (7.3% and 3.9%).

The following clinically relevant, Grade 3 and 4 adverse reactions occurred more frequently in the Gemzar plus carboplatin arm: dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1 %), motor neuropathy (1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Gemzar. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular — Congestive heart failure, myocardial infarction, arrhythmias, supraventricular arrhythmias

Vascular Disorders — Peripheral vasculitis, gangrene, and capillary leak syndrome *[see Warnings and Precautions (5.8)]*

Skin — Cellulitis, severe skin reactions, including desquamation and bullous skin eruptions

Hepatic — Hepatic failure, hepatic veno-occlusive disease

Pulmonary — Interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS)

Nervous System — Posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.9)]*

7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. *[See Warnings and Precautions (5.6)]*.

Risk Summary

Gemzar can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Gemzar is expected to result in adverse reproductive effects. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (approximately 0.005 times the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 0.002 times the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. *[See Warnings and Precautions (5.6)]*.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemzar, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Gemzar have not been established in pediatric patients. The safety and pharmacokinetics of gemcitabine were evaluated in a trial in pediatric patients with refractory leukemia. The maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one-week rest period. The safety and activity of Gemzar were evaluated in a trial of pediatric patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) at a dose of 10 mg/m^2/min administered over 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation. No meaningful clinical activity was observed in this trial.

8.5 Geriatric Use

In clinical studies of GEMZAR, enrolling 979 patients with various cancers who received GEMZAR as a single agent, no overall differences in safety were observed between patients aged 65 and older and younger patients, with the exception of a higher rate of Grade 3-4 thrombocytopenia in older patients as compared to younger patients. In a randomized trial in women with ovarian cancer, 175 women received GEMZAR plus carboplatin, of which 29% were age

65 years or older. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older.

GEMZAR clearance is affected by age, however there are no recommended dose adjustments based on patients' age *[see Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased renal function.

8.7 Hepatic Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased hepatic function.

8.8 Gender

Gemzar clearance is affected by gender *[see Clinical Pharmacology (12.3)]*. In single-agent studies of Gemzar, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

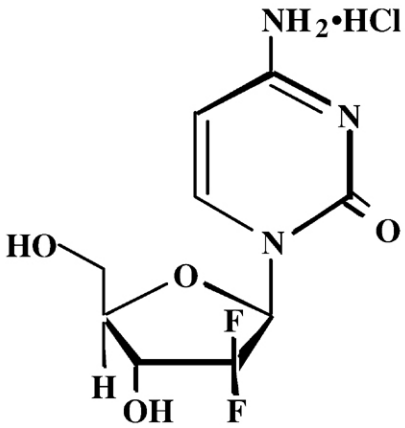
10 OVERDOSAGE

Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a dose-escalation study.

11 DESCRIPTION

Gemzar (gemcitabine for injection, USP) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemzar is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

12.3 Pharmacokinetics

Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest

weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m^2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2´-deoxy-2´,2´-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Elimination

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 10 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 10: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving <70 minute infusion.

Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

Drug Interactions

When Gemzar (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. Analysis of data from metastatic breast cancer patients shows that, on average, Gemzar has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine. Data from NSCLC patients demonstrate that Gemzar and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of Gemzar have not been conducted. Gemcitabine was mutagenic in an *in vitro* mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day administered intravenously (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

The safety and efficacy of Gemzar was studied in a randomized trial of 356 women with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either Gemzar 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemzar infusion on Day 1 of each cycle (n=178) or to carboplatin AUC 5 administered on Day 1 of each 21-day cycle (n=178). The primary efficacy outcome measure was progression free survival (PFS).

Patient characteristics are shown in Table 11. The addition of Gemzar to carboplatin resulted in statistically significant improvements in PFS and overall response rate as shown in Table 12 and Figure 1. Approximately 75% of patients in each arm received additional chemotherapy for disease progression; 13 of 120 patients in the carboplatin alone arm received Gemzar for treatment of disease progression. There was no significant difference in overall survival between the treatment arms.

Table 11: Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer - Baseline Demographics and Clinical Characteristics

	Gemzar/Carboplatin	Carboplatin
Number of randomized patients	178	178
Median age, years Range	59 36 to 78	58 21 to 81
Baseline ECOG performance status 0-1[a]	94%	95%
Disease Status Evaluable Bidimensionally measurable	 8% 92%	 3% 96%
Platinum-free interval[b] 6-12 months >12 months	 40% 59%	 40% 60%
First-line therapy Platinum-taxane combination Platinum-non-taxane combination Platinum monotherapy	 70% 29% 1%	 71% 28% 1%

[a] 5 patients on Gemzar plus carboplatin arm and 4 patients on carboplatin arm with no baseline Eastern Cooperative Oncology Group (ECOG) performance status.

[b] 2 on Gemzar plus carboplatin arm and 1 on carboplatin arm had platinum-free interval <6 months.

Table 12: Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer - Efficacy Outcomes

	Gemzar/Carboplatin (N=178)	Carboplatin (N=178)
Progression-free Survival Median (95% CI[a]) months	8.6 (8.0, 9.7)	5.8 (5.2, 7.1)
Hazard Ratio (95% CI)	0.72 (0.57, 0.90)	
p-value[b]	p=0.0038	
Overall Survival Median (95% CI) months	18.0 (16.2, 20.3)	17.3 (15.2, 19.3)
Hazard Ratio (95% CI)	0.98 (0.78, 1.24)	
p-value[b]	p=0.8977	
Investigator Reviewed Overall Response Rate	47.2%	30.9%
p-value[c]	p=0.0016	
CR[d] PR plus PRNM[e]	14.6% 32.6%	6.2% 24.7%
Independently Reviewed Overall Response Rate[f]	46.3%	35.6%
p-value[c]	p=0.11	
CR[d] PR plus PRNM[e]	9.1% 37.2%	4.0% 31.7%

[a] CI=confidence interval.

[b] Log rank, unadjusted.

[c] Chi square.

[d] CR=Complete response.

[e] PR plus PRNM=Partial response plus partial response, non-measurable disease.

[f] Independently reviewed cohort - Gemzar/carboplatin (n=121), carboplatin (n=101); independent reviewers unable to measure disease detected by sonography or physical exam.

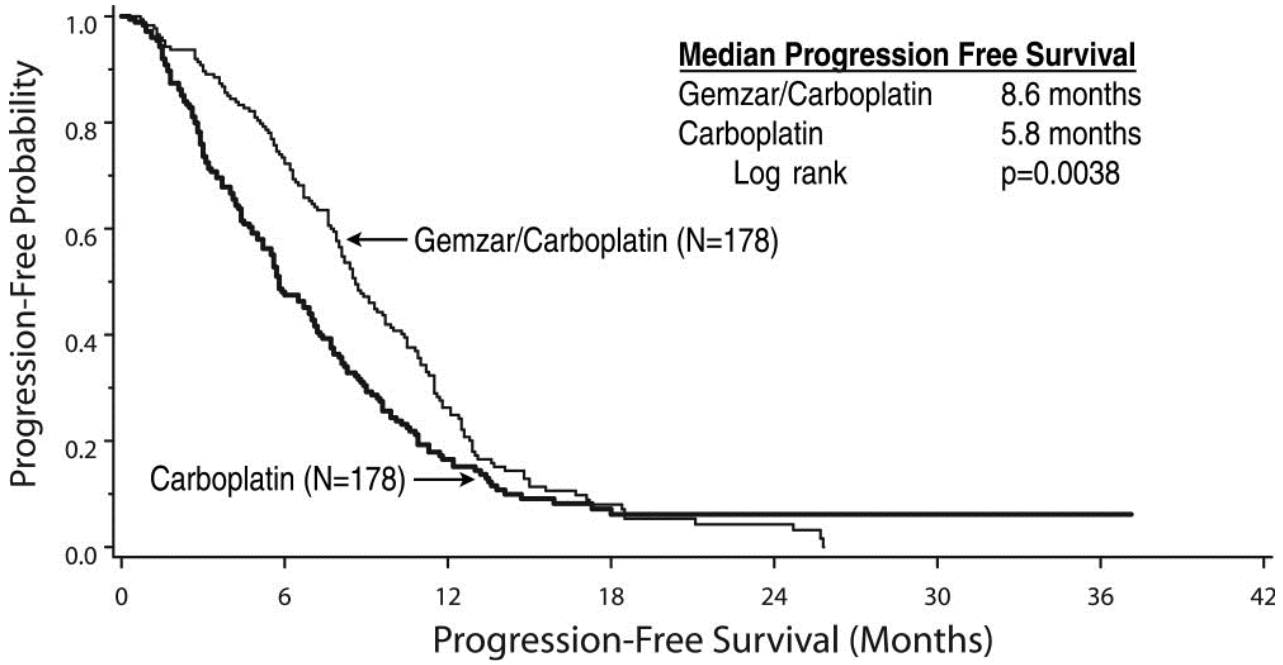


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer (N=356).

14.2 Breast Cancer

The safety and efficacy of Gemzar were evaluated in a multi-national, randomized, open-label trial conducted in women receiving initial treatment for metastatic breast cancer in women who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Patients were randomized to receive Gemzar 1250 mg/m^2 on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m^2 administered prior to Gemzar on Day 1 of each cycle (n=267) or to receive paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle (n=262). The primary efficacy outcome measure was time to documented disease progression.

A total of 529 patients were enrolled; 267 were randomized to Gemzar and paclitaxel and 262 to paclitaxel alone. Demographic and baseline characteristics were similar between treatment arms (see Table 13). Efficacy results are presented in Table 13 and Figure 2. The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to paclitaxel alone. There was no significant difference in overall survival.

Table 13: Randomized Trial of Gemzar plus Paclitaxel versus Paclitaxel in Breast Cancer

	Gemzar/Paclitaxel	Paclitaxel
Number of patients	267	262
Demographic/Entry Characteristics		
Median age (years) Range	53 26 to 83	52 26 to 75
Metastatic disease	97%	97%
Baseline KPS[a] ≥90	70%	74%
Number of tumor sites 1-2 ≥3	 57% 43%	 59% 41%
Visceral disease	73%	73%
Prior anthracycline	97%	96%
Efficacy Outcomes		
Time to Documented Disease Progression[b]		
Median in months (95% CI)	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)
Hazard Ratio (95% CI)	0.650 (0.524, 0.805)	
p-value	p<0.0001	
Overall Survival[c]		
Median Survival in months (95% CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)

Hazard Ratio (95% CI)	0.86 (0.71, 1.04)	
p-value	Not Significant	
Overall Response Rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)
p-value	p<0.0001	

[a] Karnofsky Performance Status.

[b] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

[c] Based on the ITT population.

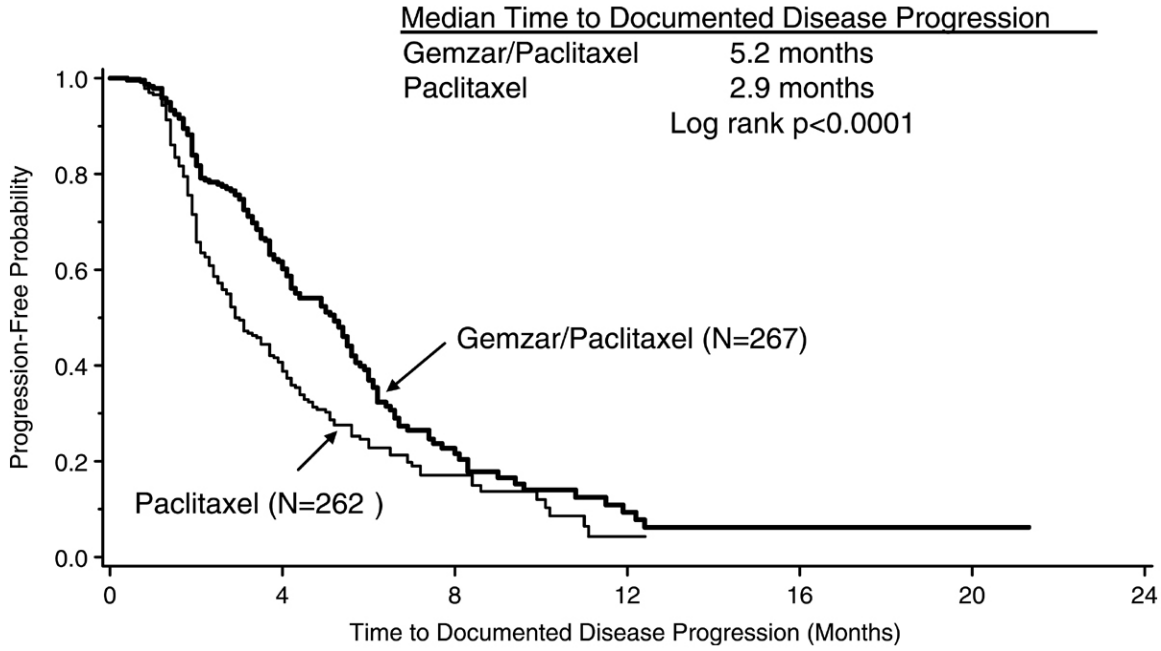


Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemzar plus Paclitaxel versus Paclitaxel Breast Cancer Study (N=529).

14.3 Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of Gemzar was evaluated in two randomized, multicenter trials.

28-Day Schedule

A multinational, randomized trial compared Gemzar plus cisplatin to cisplatin alone in the treatment of patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Patients were randomized to receive Gemzar 1000 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle or to receive cisplatin 100 mg/m^2 on Day 1 of each 28-day cycle. The primary efficacy outcome measure was overall survival. A total of 522 patients were enrolled at clinical centers in Europe, the US, and Canada. Patient demographics and baseline characteristics (shown in Table 14) were similar between arms with the exception of histologic subtype of NSCLC, with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm having adenocarcinoma. Efficacy results are presented in Table 14 and Figure 3 for overall survival.

21-Day Schedule

A randomized (1:1), multicenter trial was conducted in 135 patients with Stage IIIB or IV NSCLC. Patients were randomized to receive Gemzar 1250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to receive etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 and cisplatin 100 mg/m^2 on Day 1 of a 21 -day cycle.

There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two- sided, see Table 14). The median survival was 8.7 months for the Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the Gemzar plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

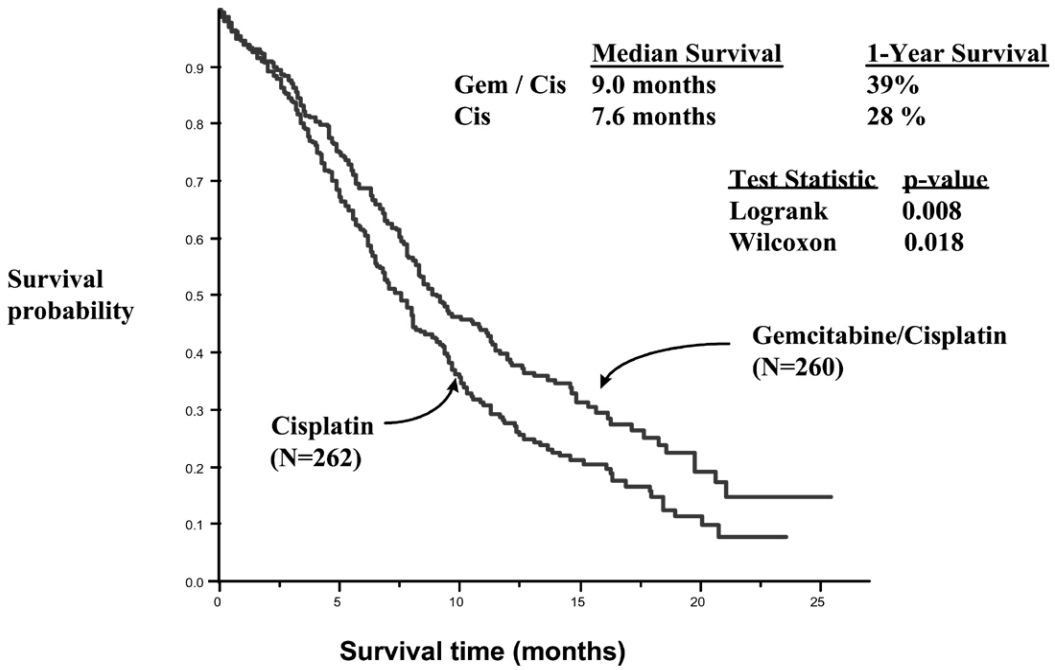


Figure 3: Kaplan-Meier Survival Curve in Gemzar plus Cisplatin versus Cisplatin in Patients with NSCLC Study (N=522).

Table 14: Randomized Trials of Gemzar plus Cisplatin in Patients with NSCLC

Trial	28-day Schedule[a]		21-day Schedule[b]	
Treatment Arm	Gemzar plus Cisplatin	Cisplatin	Gemzar plus Cisplatin	Etoposide plus Cisplatin
Number of patients	260	262	69	66
Demographic/Entry Characteristics				
Male	70%	71%	93%	92%
Median age, years	62	63	58	60
Range	36 to 88	35 to 79	33 to 76	35 to 75
Stage IIIA	7%	7%	N/A[c]	N/A[c]
Stage IIIB	26%	23%	48%	52%
Stage IV	67%	70%	52%	49%
Baseline KPS[d] 70 to 80	41%	44%	45%	52%
Baseline KPS[d] 90 to 100	57%	55%	55%	49%
Efficacy Outcomes				
Survival				
Median in months	9.0	7.6	8.7	7.0
(95% CI[e]) months	8.2, 11.0	6.6, 8.8	7.8, 10.1	6.0, 9.7
p-value[f]	p=0.008		p=0.18	
Time to Disease Progression				
Median in months	5.2	3.7	5.0	4.1
(95% CI[e]) months	4.2, 5.7	3.0, 4.3	4.2, 6.4	2.4, 4.5
p-value[f]	p=0.009		p=0.015	
Tumor Response	26%	10%	33%	14%
p-value[f]	p<0.0001		p=0.01	

[a] 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.

[b] 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and intravenous etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c] N/A Not applicable.

[d] Karnofsky Performance Status.
[e] CI=confidence intervals.
[f] p-value two-sided Fisher's Exact test for difference in binomial proportions; log rank test for time-to-event analyses.

14.4 Pancreatic Cancer

The safety and efficacy of Gemzar was evaluated in two trials, a randomized, single-blind, two-arm, active-controlled trial conducted in patients with locally advanced or metastatic pancreatic cancer who had received no prior chemotherapy and in a single-arm, open-label, multicenter trial conducted in patients with locally advanced or metastatic pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The first trial randomized patients to receive Gemzar 1000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles (n=63) or to 5-fluorouracil (5-FU) 600 mg/m^2 intravenously over 30 minutes once weekly (n=63). In the second trial, all patients received Gemzar 1000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles.

The primary efficacy outcome measure in both trials was "clinical benefit response". A patient was considered to have had a clinical benefit response if either of the following occurred:

- The patient achieved a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Status) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR

- The patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The randomized trial enrolled 126 patients across 17 sites in the US and Canada. The demographic and entry characteristics were similar between the arms (Table 15). The efficacy outcome results are shown in Table 15 and for overall survival in Figure 4. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to those randomized to receive 5-FU. No confirmed objective tumor responses were observed in either treatment arm.

Table 15: Randomized Trial of Gemzar versus 5-Fluorouracil in Pancreatic Cancer

	Gemzar	5-FU
Number of patients	63	63
Demographic/Entry Characteristics		
Male	54%	54%
Median age	62 years	61 years
Range	37 to 79	36 to 77
Stage IV disease	71%	76%
Baseline KPS[a] ≤70	70%	68%
Efficacy Outcomes		
Clinical benefit response	22.2%	4.8%
p-value[b]	p=0.004	
Survival		
Median	5.7 months	4.2 months
(95% CI)	(4.7, 6.9)	(3.1, 5.1)
p-value[b]	p=0.0009	
Time to Disease Progression		
Median	2.1 months	0.9 months
(95% CI)	(1.9, 3.4)	(0.9, 1.1)
p-value[b]	p=0.0013	

[a] Karnofsky Performance Status.
[b] p-value for clinical benefit response calculated using the two-sided test for difference in binomial proportions. All other p-values are calculated using log rank test.

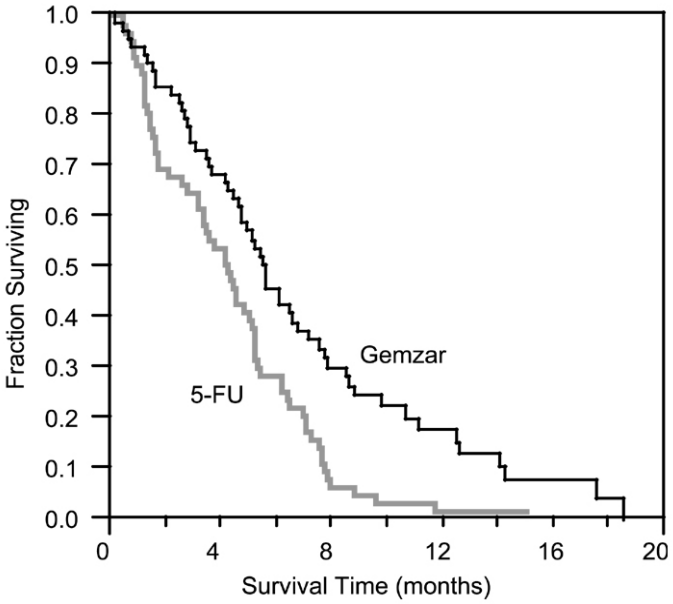


Figure 4: Kaplan-Meier Survival Curve.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemzar (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing:

200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial – NDC 0002-7501-01 (No. 7501)

1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial – NDC 0002-7502-01 (No. 7502)

16.2 Storage and Handling

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] *[see Dosage and Administration (2.6 and 2.7)]*.

17 PATIENT COUNSELING INFORMATION

- Advise patients of the risks of low blood cell counts and the potential need for blood transfusions and increased susceptibility to infections. Instruct patients to immediately contact their healthcare provided for development of signs or symptoms of infection, fever, prolonged or unexpected bleeding, bruising, or shortness of breath *[see Warnings and Precautions (5.2)]*.
- Advise patients of the risks of pulmonary toxicity including respiratory failure and death. Instruct patients to immediately contact their healthcare provider for development of shortness of breath, wheezing, or cough *[see Warnings and Precautions (5.3)]*.
- Advise patients of the risks of hemolytic-uremic syndrome and associated renal failure. Instruct patients to immediately contact their healthcare provider for changes in the color or volume of urine output or for increased bruising or bleeding *[see Warnings and Precautions (5.4)]*.
- Advise patients of the risks of hepatic toxicity including liver failure and death. Instruct patients to immediately contact their healthcare provider for signs of jaundice or for pain/tenderness in the right upper abdominal quadrant *[see Warnings and Precautions (5.5)]*.

Marketed by: Lilly USA, LLC

Indianapolis, IN 46285, USA

GEM-0001-USPI-20140610

Appendix 4. Performance Status Scores

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 5. Known Strong In Vivo Inhibitors or Inducers of CYP3A or CYP2C8

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	
Strong Inhibitors of CYP2C8[a]	**Strong Inducers of CYP2C8[e]**
gemfibrozil	

a. A strong inhibitor for is defined as an inhibitor that increases the AUC of a substrate for by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 6. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drugs? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drugs.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 7. Schedule of Assessments

		Treatment Phase														Safety Follow-up Visit[b]	Follow-up Phase[c]
Cycles		**Cycle 1**					**Cycle 2**				**Cycles 3+**						
Study Days	**Screening [a]**	**-1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**TT**	**+ 30 days after last dose**	**Q12W**
Study Window	**-21 days**			**± 3 days**			**± 3 days**				**± 3 days**				**+ 7 days**	**+ 7 days**	**± 10 days**
Informed consent	x																
Confirm eligibility	x																
Medical history	x																
PE[d]/Vital signs[e]/Weight	x	x[n]	x	x	x	x	x		x		x				x	x	
ECOG status	x	x[n]	x	x	x	x	x		x		x						
ECG[f]	x	x[n]	x		x										x	x	
Lab assessments:																	
Urine or serum pregnancy test[g]	x	x[n,t]	x[p,s]				x				x				x	x	
Hematology[h]	x	x[n,t]	x[p]	x	x	x	x	x	x	x	x	x	x		x	x	
Serum chemistry/ CA19-9[i]	x	x[n,t]	x[p]				x				x				x	x	
Serum lipase/amylase	x	x[n]	x[p]	x	x	x	x		x		x				x	x	
Coagulation panel[j]	x	x[n,t]	x	x	x	x	x		x		x						
Hepatitis serology[u]	x																
HBV PCR[v]							x				x						QM
Urinalysis[k]	x	x[n]	x	x	x	x	x		x		x						
T/B/NK/monocyte cell count[l]		x[n]	x[p]						x		Day 1 every 3 cycles						
Pharmacokinetics[m] (Arm 1 only)		x[n]	x						x								
PD/Biomarkers	Tumor sample[o]	x[n]	x[p]	x[p]	x[p]	x[p]			x[p]		Cycle 3 Day 8 and Cycle 4 Day 1 only[p]				x[q]		
ACP-196 100 mg BID		x[n]	Continuous Twice Daily Dosing														
Nab-paclitaxel/gemcitabine IV			x	x	x		x	x	x		x	x	x				
Study drug compliance			x				x				x						
Tumor assessment[r]	x										Day 1 every other cycle (eg, Cycle 3 Day 1, Cycle 5 Day 1)						x

Concomitant medications	x	x^n	x	x	x	x	x	x	x	x	x				x	x	
Adverse events		x^n	x	x	x	x	x	x	x	x	x				x	x	
Survival																x	x

Abbreviations: BID = twice per day; CA 19-9 = cancer antigen 19-9; CR = complete remission; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; IV = intravenous; MRI = magnetic resonance imaging; NK = natural killer; PCR = polymerase chain reaction; PD = pharmacodynamics; PE = physical exam; Q12W = every 12 weeks; QM = every month; TT = treatment termination.

Footnotes for ACE-ST-004 Schedule of Study Activities:

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. A 30-day (+ 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
c. Subjects who discontinue study therapy will continue on study for time-to-next therapy and survival unless they withdraw consent or are lost to follow up or the sponsor ends the study. Subjects who discontinue study drug for any reason other than disease progression, death, lost to follow-up, or withdrawal of consent will also be followed for tumor assessment until disease progression or initiation of any other anticancer therapies, whichever comes first.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams, including tumor assessments by palpation, are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs. The screening ECGs will be done in triplicate taken ≥ 1 minute apart. At Cycle 1 Day 1 and Cycle 1 Day 15, a single ECG will be done 1 hour after ACP-196 administration. In addition, a single ECG will also be performed 1 hour after ACP-196 administration at Cycle 1 Day -1 for the first 6 subjects enrolled to Arm 1. The window is ± 10 minutes for the ECGs at the Cycle 1 Day 1 and Cycle 1 Day 15 visits. At the treatment termination and/or safety follow-up visit, a single ECG will be done at any time during the visit.
g. Women of childbearing potential only.
h. Hematology includes complete blood count with differential and platelet counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was done within 7 days. For subjects in Arm 1 who discontinue nab-paclitaxel/gemcitabine but who are still receiving ACP-196, hematology assessment is to occur only on Day 1 of each cycle for Cycles 3+.
i. Serum chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, C-reactive protein, CA 19-9, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 7 days.
j. Prothrombin time and partial thromboplastin time.
k. Urinalysis: pH, ketones, specific gravity, bilirubin, blood, and glucose.
l. T/B/NK/monocyte cell count (ie, CD3, CD4, CD8, CD14, CD19, CD16/56).
m. For the first 20 subjects enrolled in Arm 1: Blood samples will be drawn at 0 (predose), 0.5, 1, 2, and 4 hours after ACP-196 administration on the visits indicated. The predose sample can be taken up to 30 minutes before dosing. The window for other timepoints is ± 5 minutes. Refer to the protocol for more detailed information.
n. Cycle 1 Day -1 dosing of ACP-196, assessments, and PK sample collection in Arm 1 only applies to the first 6 subjects enrolled to this treatment arm.
o. Provide tissue sections from either an archived or newly obtained tumor sample (most recent biopsy) for biomarker analysis, if allowed by regional authorities.
p. The indicated samples at this timepoint must be drawn predose.
q. This peripheral blood sample will be collected if treatment termination is due to disease progression.
r. A pretreatment computed tomography (CT) scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. CT scans will be done for tumor assessments on Cycle 3 Day 1 and then on Day 1 of every other cycle (± 7 days) or more frequently at the investigator's discretion. Magnetic resonance imaging (MRI) may be used for subjects allergic to CT contrast media.
s. The pregnancy test can be performed any day from -3 days prior to Cycle 1 Day 1 or on the same day as Cycle 1 Day 1.
t. Per protocol, the first 6 subjects randomized to Arm 1 (ACP-196 + nab-paclitaxel/gemcitabine) are dosed with ACP-196 first at Cycle 1 Day -1. For these 6 subjects, hematology, serum chemistry/CA 19-9, and coagulation panel must be performed and analyzed within 7 days before this first dose of ACP-196. Additionally, a urine

pregnancy test must be performed and analyzed within 1 day of the Cycle 1 Day -1 first dose of ACP-196. These 4 labs may be performed either locally, or using the central laboratory.

u. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #15).

v. Subjects who are anti-HBc positive (or have a known history of HBV infection) should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.