CLINICAL STUDY PROTOCOL

Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of CF102 in the Second-Line Treatment of Advanced Hepatocellular Carcinoma in Subjects with Child-Pugh Class B Cirrhosis
Test Drug:	CF102
Protocol Identification:	CF102-201HCC
Sponsor:	Can-Fite BioPharma, Ltd. 10 Bareket Street, Petach Tikva, Israel +972 3 924 1114
Compliance Statement:	The trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable national and local regulations.
Date of Protocol:	07 January 2014
Date of Amendments	Amendment #1, 16 June 2014 Amendment #2, 3 October 2014 Amendment #3, 21 October 2015 Amendment #4, 21 September 2018 Amendment #5, 6 November 2018

Michael H. Silverman, MD **Medical Monitor**	6 November 2018 Signature Date
Prof. Pnina Fishman, PhD **Chief Executive Officer**	6 November 2018 Signature Date

Confidentiality Statement

INVESTIGATOR AGREEMENT

Protocol Title:

CF102-201HCC: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of CF102 in the Second-Line Treatment of Advanced Hepatocellular Carcinoma in Subjects with Child-Pugh Class B Cirrhosis

Investigator Statement:

I have received and completely reviewed the above-named protocol, including all appendices and amendments. As Investigator, I agree to conduct the trial in accordance with all stipulations of the protocol and in accordance with 21 CFR Part 50, ICH Guidelines for Good Clinical Practices (GCP), and the Declaration of Helsinki.

Investigator Signature: _____

Investigator Name (print): _____ Date: _____

Investigator Address: _____

Institution Telephone No.: _____

Institution Fax No.: _____

Signature on this page assures Can-Fite BioPharma, Ltd. that, to the best of the Investigator's knowledge, the affiliated IRB/EC operates in accordance with applicable local and national regulations, and that the Investigator understands and agrees to abide by all regulatory obligations and ICH GCP guidelines while conducting this clinical investigation.

Once signed, the original of this form should be detached from the protocol and returned to the Sponsor.
(Please retain a copy for your files)

TRIAL CONTACT INFORMATION

Serious and Unexpected Adverse Events

Any death, serious adverse event (SAE), or suspected unexpected serious adverse reaction (SUSAR) occurring in a subject while receiving study drug or within 30 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone, fax, or e-mail to the Sponsor (or designee).

Unless otherwise instructed, SAE and SUSAR reports are to be submitted by fax to:

Medical Monitor:
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For urgent medically-related questions, contact the Medical Monitor. On weekends, holidays, and after business hours, you may also call 781-639-1349 and leave a message.

1.0 SYNOPSIS

Sponsor: Can-Fite BioPharma, Ltd.

Product: CF102

Study Title:

CF102-201HCC: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of CF102 in the Second-Line Treatment of Advanced Hepatocellular Carcinoma in Subjects with Child-Pugh Class B Cirrhosis

Estimated Number of Trial Centers:

Multicenter, up to 22-24 sites in 5 countries

Phase of Development: 2

Objectives:

The primary objective of this trial is to:

- Evaluate the efficacy of orally administered CF102 25 mg twice daily (BID) as compared to placebo, as determined by Overall Survival (OS), when used as second-line therapy in subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh Class B (CPB) cirrhosis.

The secondary objectives of this trial are to:

- Evaluate other indicators of efficacy of CF102 as compared to placebo, including time to progression (TTP), progression-free survival (PFS), objective response (OR) rate, and disease control (DC) rate in this population;
- Explore exposure-response relationships using sparse pharmacokinetic (PK) sampling;
- Characterize the safety profile of CF102 in subjects with advanced HCC and CPB cirrhosis;
- Characterize the effects of CF102 on laboratory parameters associated with viral hepatitis, hepatic dysfunction, and cirrhosis; and
- Explore the relationship between white blood cell (WBC) adenosine A3 receptor (A3AR) expression and clinical response.

Methods:

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial in subjects with advanced HCC and CPB cirrhosis who did not tolerate prior sorafenib therapy or experienced disease progression on prior sorafenib therapy. The trial will evaluate the efficacy and safety of CF102 as compared to placebo. Subjects will be randomly assigned in a 2:1 ratio to treatment with oral doses of either CF102 25 mg or matching placebo administered BID for consecutive, 28-day cycles. Subjects will be evaluated regularly for safety, and will undergo sparse PK

sampling to assess the PK profile of CF102 and to explore exposure-response relationships. Tumor imaging will be performed every 8 weeks. Treatment will continue until the subject experiences unacceptable drug-related intolerability (Section 8.2). Subjects will return for a follow-up visit 28 days after completion of the last dose of study drug, and every attempt will be made to obtain survival data on all randomized subjects. Subjects who discontinue will be followed indefinitely for survival status.

Once the requisite number of events has occurred and the blind is opened for analysis of the trial results, any surviving subjects who remain on blinded drug will be offered the opportunity to continue dosing with open-label CF102 25 mg BID indefinitely, following the protocol-specified schedule of events (Table 1–2).

Number of Subjects Planned:

Approximately 78 subjects will be enrolled and randomized in a 2:1 ratio to receive either CF102 or matching placebo.

Diagnosis and Main Criteria for Inclusion:

DB Portion of the Trial

Inclusion Criteria:

1. Males and females at least 18 years of age.
2. Diagnosis of HCC:
   - For subjects without underlying cirrhosis at the time of diagnosis, diagnosis of HCC documented by cytology and/or histology.
   - For subjects with underlying cirrhosis at the time of diagnosis, diagnosis of HCC established according to the American Association for the Study of Liver Diseases Practice Guideline algorithm (Appendix E).
3. HCC is advanced, i.e., treatment-refractory or metastatic, and no standard therapies are expected to be curative.
4. Receipt of prior sorafenib therapy for at least 3 weeks and withdrawal from treatment due either to intolerability or to radiographic evidence of disease progression. If treatment was withdrawn due to intolerability manifested as a Grade 3 or 4 event by National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE v4.0), less than 3 weeks of continuous prior administration prior to withdrawal is acceptable (see also Exclusion Criterion #3).
5. Prior sorafenib treatment was discontinued for at least 2 weeks prior to the Baseline Visit.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 (Appendix B).
7. Cirrhosis classified as Child-Pugh Class B (Appendix C).

8. The following laboratory values must be documented within 3 days prior to the first dose of study drug:
   - □ Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   - □ Platelet count ≥ 75×10^9/L
   - □ Serum creatinine ≤ 2.0 mg/dL
   - □ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × the upper limit of normal (ULN)
   - □ Total bilirubin ≤ 3.0 mg/dL
   - □ Serum albumin ≥ 2.8 g/dL
   - □ Prothrombin time (PT) no greater than 6 seconds longer than control.
9. Life expectancy of ≥ 6 weeks.
10. For women of childbearing potential, negative serum pregnancy test result.
11. Provide written informed consent to participate.
12. Willing to comply with scheduled visits, treatment plans, laboratory assessments, and other trial-related procedures.

Exclusion Criteria:

1. Receipt of no, or of > 1, prior systemic drug therapies for HCC.
2. Receipt of systemic cancer therapy, immunomodulatory drug therapy, immunosuppressive therapy, or corticosteroids > 20 mg/day prednisone or equivalent within 14 days prior to the Baseline Visit or concurrently during the trial.
3. Presence of an acute or chronic toxicity of prior chemotherapy that has not resolved to ≤ Grade 1, as determined by CTCAE v 4.0.
4. Locoregional treatment within 4 weeks prior to the Baseline Visit.
5. Major surgery or radiation therapy within 4 weeks prior to the Baseline Visit.
6. Use of any investigational agent within 4 weeks prior to the Baseline Visit.
7. Child-Pugh Class A or C cirrhosis, or hepatic encephalopathy.
8. Occurrence of esophageal or other gastrointestinal hemorrhage requiring transfusion within 4 weeks prior to the Baseline Visit.
9. Uncontrolled or clinically unstable thyroid disease, per judgment of the Principal Investigator.
10. Active bacterial, viral, or fungal infection requiring systemic therapy or operative or radiological intervention.
11. Known human immunodeficiency virus- or acquired immunodeficiency syndrome-related illness.

12. Liver transplant.
13. Active malignancy other than HCC.
14. Uncontrolled arterial hypertension or congestive heart failure (New York Heart Association Classification 3 or 4) (Appendix B).
15. Angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass graft surgery, transient ischemic attack, or pulmonary embolism within 3 months prior to initiation of study drug.
16. History of or ongoing cardiac dysrhythmias requiring treatment, atrial fibrillation of any grade, or persistent prolongation of the QTc (Fridericia) interval to > 450 msec for males or > 470 msec for females.
17. Pregnant or lactating female.
18. Women of childbearing potential, unless they agree to use dual contraceptive methods which, in the opinion of the Investigator, are effective and adequate for the subject's circumstances while on study drug.
19. Men who partner with a woman of childbearing potential, unless they agree to use effective, dual contraceptive methods (i.e., a condom, with female partner using oral, injectable, or barrier method) while on study drug and for 3 months afterward.
20. Any severe, acute, or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with trial participation or study drug administration; may interfere with the informed consent process and/or with compliance with the requirements of the trial; or may interfere with the interpretation of trial results and, in the Investigator's opinion, would make the subject inappropriate for entry into this trial.

Eligibility Criteria for Open Label

- The subject signed the ICF for the Open Label treatment.
- The subject received double blind treatment with CF102/placebo and is still taking the investigational medication when Amendment 5 is approved.

Test Product, Dose, and Mode of Administration:

CF102 is a small molecule agonist of the A_3AR. Study drug will be supplied in child- and tamper-resistant bottles as hard capsules containing either 25 mg of CF102 or matching placebo. CF102 or placebo will be self-administered orally BID on an empty stomach (1 hour before or 2 hours after meals) beginning on Day 1 of the trial and thereafter at approximately the same times each day of the 28-day cycle.

Dosing Interruptions and Reductions:

In the case of any Grade 3 toxicity by CTCAE v4.0 judged by the Principal Investigator to be at least "possibly" drug-related, the dose of study drug will be interrupted for up to 7 days. If

toxicity does not resolve to Grade ≤ 1 within 7 days, the subject will be discontinued from treatment. If toxicity does resolve to Grade ≤ 1 within 7 days, dosing will be resumed at the decreased dose of 1 capsule per day. In the case of any Grade 4 toxicity by CTCAE v4.0 judged by the Principal Investigator to be at least "possibly" drug-related, the dose of study drug will be withdrawn permanently.

Only 1 dose reduction will be allowed. If a Grade 3 or 4 toxicity judged by the Principal Investigator to be at least "possibly" drug-related occurs upon re-challenge at the reduced dose, study drug dosing will be withdrawn permanently.

Duration of Treatment:

Each treatment cycle will be 28 days of twice daily dosing. Treatment will continue until the subject experiences unacceptable drug-related intolerability.

Once the requisite number of events has occurred and the blind is opened for analysis of the trial results, any surviving subjects who remain on blinded drug will be offered the opportunity to continue dosing with open-label CF102 25 mg BID indefinitely, following the protocol-specified schedule of events (Table 1–2).

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint will be OS, defined as the number of days from first dose to death due to any cause. Secondary endpoints to be evaluated are TTP, PFS, OR rate consisting of Complete Response (CR) or Partial Response (PR) for subjects who enter the trial with measurable disease by RECIST v1.1, and DC rate which includes both subjects who experience OR as well as those who experience Stable Disease (SD). Survival status will be assessed continuously. Tumor status will be assessed at the Pre-Study Visit and every 8 weeks thereafter (i.e., at the end of even-numbered cycles) by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to RECIST v1.1 (Appendix A, [Eisenhauer 2009 as modified by Santoro 2013]).

Alpha-fetoprotein (AFP) levels will be assessed at baseline and every 4 weeks thereafter on Day 1 of each subsequent cycle.

Laboratory parameters associated with hepatic dysfunction and cirrhosis, such as serum ALT, AST, bilirubin, and albumin levels, prothrombin time (PT), and International Normalized Ratio (INR), will be assessed every cycle. Where applicable, viral load measurements will be performed every odd-numbered cycle. WBC A_3AR expression will be assessed at baseline and, unless waived by the Sponsor, every odd-numbered cycle (at selected sites only).

Safety:

Assessments of adverse events (AEs) will include characterization of the type, incidence, severity (graded by CTCAE v 4.0), seriousness, and relationship to treatment. Changes in vital signs, laboratory parameters including thyroid functions, electrocardiograms (ECG), physical examinations, and ECOG PS from baseline will be assessed.

Pharmacokinetics:

CF102 concentrations will be determined from EDTA plasma samples obtained on Day 1 of Cycles 1 and 2, as well as from trough samples on Days 8 and 15 of Cycle 1. A composite PK profile following the morning dose of the BID regimen will be generated for subjects receiving CF102 treatment.

Statistical Analysis:

Sample Size:

Approximately 78 subjects will be enrolled during an accrual period estimated to be approximately 78 weeks (18 months) in duration and randomized to either CF102 or placebo using a 2:1 randomization. Assuming a hazard ratio of 0.5, 75 events will provide 80% power for the logrank test at level 0.05.

General Considerations:

Time to event variables will be summarized using the number observed, number censored, median, and 25^{th} and 75^{th} percentiles from Kaplan-Meier curves. Continuous variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

Efficacy Analyses:

Between-treatment comparisons with respect to OS, TTP, and PFS will be performed using logrank tests, with Cox's proportional hazards regression model used for secondary analyses to assess the impact of covariates. Tumor lesion measurements and changes from baseline will be summarized by cycle and treatment. Objective response rates and DC rates will be presented and between-treatment comparisons will be performed using the normal approximation to the binomial distribution by treatment for each even-numbered cycle. Between-treatment comparisons with respect to AFP will be performed using Analysis of Covariance (ANCOVA) with the baseline value used as a covariate and frequencies of subjects with AFP levels <20, 20-200, or >200 ng/mL will be presented by treatment for each cycle.

Pharmacokinetic Analyses:

PK analysis will include population PK analysis based on sparse sampling, and the estimation of C_{max}, C_{min} and $AUC_{(0\text{-}12h)}$ on Day 1 of Cycles 1 and 2; and trough plasma levels on Days 8 and 15

of Cycle 1. Exploratory analyses will be performed to evaluate the relationship between these PK parameters and WBC A_3 receptor expression and clinical responses to CF102.

Safety Analyses:

Safety data analysis will be conducted on all subjects receiving at least 1 dose of CF102 or matching placebo. The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment group, relationship to study drug, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA™) terminology. Listings of subjects who experienced dosing interruptions and dose reductions, withdrawal due to an AE, serious AEs and/or death will be presented. Laboratory parameters, other than Liver Chemistry Tests (see below), INR, and viral load, will be summarized using descriptive statistics and data listings of clinically significant abnormalities. Liver Chemistry Tests, INR, and viral load will be presented as exploratory efficacy variables. Vital signs, ECOG PS, physical examination, and ECG data will be summarized by changes from baseline values for each treatment group using descriptive statistics.

Exploratory Analyses:

Certain laboratory parameters associated with hepatic dysfunction and cirrhosis will be examined. These include: Chemistry (bilirubin [direct and total], ALT, AST, and albumin, referred to collectively as "Liver Chemistry Tests"); INR; and viral load. These parameters will be summarized using descriptive statistics and clinically significant abnormalities will be listed. Additionally, between-treatment comparisons will be performed using ANCOVA with the baseline value used as a covariate. The relationship between WBC A_3AR expression and clinical response will be assessed by providing the counts and percentages for Overall Response by Change from Baseline (CFB) in A_3AR expression categorized as less than or at least the median by treatment at each visit.

Table 1–1: Schedule of Events for Double Blind Portion of the Trial

Trial Procedures	Pre-Study (-28 Days)	Cycle 1		Subsequent Cycle		End of Study/End of Dosing (EOS)[1]	Follow-up (28 ± 3 Days Post EOS)
		Day 1 Baseline	Days 8 and 15 ±2 Days	Day 1 ±2 Days	Day 15 ±2 Days	Day 1 ± 2 Days	
Medical and disease history	X						
Physical examination	X[a]	X[a,c]	X[b]	X[b]	X[b]	X[a]	X[b]
Inclusion/exclusion criteria	X	X					
Informed consent	X						
Body weight	X	X[c]		X		X	X
Vital signs[d]	X	X	X	X	X	X	X
Clinical laboratory testing[e]	X	X[c]	X	X	X	X	X
T3. T4, TSH	X	X		X		X	X
ECG [f]	X	X	X[f]	X	X	X	X
Pregnancy test (serum)[g]	X	X[c]		X		X	X
ECOG PS[g]	X	X[c]		X		X	
α-fetoprotein (AFP)		X		X		X	X
WBC A_3AR sample		X		X[h]			
PK samples		X[k]	X[k]	X[k]			
Hepatitis B/C virus serology	X						
Hepatitis B/C viral load (if seropositive)		X		X[i]		X[i]	
Tumor imaging for RECIST	X[j]			X[j]		X	
Concomitant medications	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Dispense study drug supplies		X		X			
Review treatment compliance		X	X	X	X	X	

Trial Procedures	Pre-Study (-28 Days)	Cycle 1		Subsequent Cycle		End of Study/End of Dosing (EOS)[1]	Follow-up (28 ± 3 Days Post EOS)
		Day 1 Baseline	Days 8 and 15 ±2 Days	Day 1 ±2 Days	Day 15 ±2 Days	Day 1 ± 2 Days	

a. Complete PE performed at the Pre-Study (and/or the Baseline Visit if performed > 3 days prior to first dose) and End of Study/End of Dosing (EOS) visits.

b. Symptom-directed examination.

c. If Pre-Study assessment was performed ≤ 3 days prior to the Baseline Visit, assessments do not need to be repeated.

d. Temperature, pulse, respiration, blood pressure at: Pre-Study; pre-dose at all visits; at 1, 2, 3, 4h (± 5 min), 6 and 8h (± 10 min) post-dose on Cycle 1 Day 1 and at Follow-up.

e. See list of parameters in Section 9.2.8 and Appendix D.

f. ECG at Pre-Study; pre-dose at all visits; and at 2, 4, and 6h (± 10 min) post-dose on Cycle 1 Days 1 and 8; and at Follow-up.

g. Performed at Pre-Study, prior to the first dose, Day 1 of each cycle, and at Follow-up.

h. Day 1 of odd-numbered cycles, unless waived by the Sponsor (selected sites only).

i. For subjects with measurable viral load at the Baseline Visit; on Day 1 of odd-numbered cycles only and at EOS.

j. CT scan or MRI at Pre-Study, the end of Cycle 2, and at the end of subsequent even-numbered cycles. For trial eligibility purposes, a scan performed ≤ 21 days prior to the Pre-Study Visit may be used (allowed time window is of -7days/+1 day with respect to day 28 of each even numbered cycles; if performed at +1 day after day 28, CT/MRI scan must be performed before administration of the morning dose of that day).

k. Sparse sampling on Day 1 of Cycles 1 and 2 only. Pre-dose trough sample on Cycle 1 Days 8 and 15 only. See Table 10–1 for PK sampling time points.

l. End of Study visit timeframe is of 2 days since the last administered dose of IMP/matching Placebo.

Table 1–2: Schedule of Events for Open Label (OL) Treatment

Trial Procedures	OL Cycle 1		Subsequent OL Cycle		OL End of Study/End of Dosing (EOS) [j]	OL Follow-up (28 ± 3 Days Post EOS)
	Day 1 Baseline	Days 8 and 15 ± 2 Days	Day 1 ± 2 Days	Day 15 ± 2 Days	Day 1 ± 2 Days	
Physical examination	X[b]	X[b]	X[b]	X[b]	X[a]	X[b]
Eligibility criteria for OL	X					
Informed consent for OL	X					
Body weight	X		X		X	X
Vital signs [c]	X	X	X	X	X	X
Clinical laboratory testing [d]	X	X	X	X	X	X
T3, T4, TSH	X		X		X	X
ECG [e]	X	X	X	X	X	X
Pregnancy test (serum) [f]	X		X		X	X
ECOG PS [f]	X		X		X	
α-fetoprotein (AFP)	X		X		X	X
WBC A_3AR sample	X		X[g]			
Hepatitis B/C viral load (if seropositive)	X		X [h]		X [h]	
Tumor imaging for RECIST			X [i]		X	
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Dispense study drug supplies	X		X			
Review treatment compliance	X	X	X	X	X	

a. Complete PE performed at Open Label (OL) End of Study/OL End of Dosing (EOS) visits.

b. Symptom-directed physical examination.

c. Temperature, pulse, respiration, blood pressure performed at the following times: pre-dose at all visits; at 1, 2, 3, 4h (± 5 min), 6 and 8h (± 10 min) post-dose on OL Cycle 1 Day 1 and at OL Follow-up.

d. See list of parameters in Section 9.2.8 and Appendix D.

e. ECG at pre-dose at all visits; and at 2, 4, and 6h (± 10 min) post-dose on OL Cycle 1 Days 1 and 8; and at OL Follow-up.

f. Performed pre-dose on Day 1 of each OL cycle, and at OL Follow-up.

g. Day 1 of odd-numbered cycles, unless waived by the Sponsor (selected sites only).

h. For subjects with measurable viral load at the Baseline Visit; on Day 1 of OL odd-numbered cycles only and at OL EOS.

i. CT scan or MRI at the end of OL even-numbered cycles. If performed at +1 day after day 28, CT/MRI scan must be performed before administration of the morning dose of that day).

j. End of Study OL visit timeframe is of 2 days since the last administered dose of IMP.

2.0 TABLE OF CONTENTS

LIST OF TABLES

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
A_1AR	subtype A1 of adenosine receptor
A_2AR	subtype A2 of adenosine receptor
A_3AR	subtype A3 of adenosine receptor
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-hCG	beta human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CPB	Child-Pugh Class B cirrhosis
CR	complete response
CRF	case report form (which may refer to either paper or electronic versions)
CRO	Contract Research Organization
CT	computed tomography
CTCAE	National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
DC	disease control rate (CR + PR + SD)
EC	Ethics Committee
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EOS	end of study (end of dosing)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high density polyethylene
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
ID	identification
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent to treat
LD	longest diameter
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NYHA	New York Heart Association
OL	Open label
OR	overall response rate (CR + PR)
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os; oral(ly)
PP	Per Protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
RH	relative humidity
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SD	stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	time to C_{max}
TSH	Thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
WBC	white blood cell
Wnt	group of signal transduction pathways

4.0 INTRODUCTION

4.1 Overview of CF102

CF102 is a synthetic ribose-based purine nucleoside with adenosine A3 receptor (A_3AR) selectivity. CF102 selectivity for the A_3AR is 4750-fold over A_1AR and 1770-fold over A_2AR. The A_3AR is overexpressed in the tumor and in the peripheral blood mononuclear cells (PBMC) of patients with hepatocellular carcinoma (HCC). CF102, an A_3AR agonist, inhibits tumor cell growth by inducing apoptosis of HCC cells via deregulation of the NF-κB and the Wnt signaling pathways (Olah, 1995; Bar-Yehuda, 2008; Fishman, 2002a; Fishman, 2002b; Fishman, 2003; Fishman, 2004; Madi, 2003; Ohana, 2003). A_3AR agonists also stimulate natural killer cells in vivo, which further potentiates the antitumor activity of this class of compounds (Fishman 2000; Fishman 2002a; Fishman 2002b; Madi 2003; Bar-Yehuda, 2002; Bar-Yehuda, 2007).

A_3AR expression is also elevated in PBMC isolated from patients with hepatitis C viral (HCV) infections. HCV infection is associated with elevated and persistent NF-κB levels that inhibit apoptosis of the infected cells and lead to chronic HCV infection. The observation that CF102 inhibits the replication of HCV in a culture system assay using human hepatoma Huh-7 cells transfected with HCV plasmid (JFH-1wt HCV) suggests that CF102 and other A_3AR agonists may provide new therapies to treat HCV infections. In addition, CF102 acts as a protective agent against liver damage in acute hepatitis, ischemia and partial hepatectomy. These findings suggest a role for CF102 in preventing liver tissue damage associated with HCV infections and hepatitis.

CF102 is a relatively low clearance compound in nonclinical species suggesting that there is little first pass effect and that absorption is the major limiting factor that dictates bioavailability. Plasma protein binding of CF102 is high, greater than 99% in all species. Studies with human hepatic microsomes indicate that drug-drug interactions related to CF102 inhibition of cytochrome p450 metabolism are unlikely to occur.

CF102, given orally, induced a marked inhibitory effect on the growth of N1S1 HCC in an orthotopic model in rats. The drug was also efficacious in inhibiting the development of xenografted Hep-3B tumors inoculated subcutaneously in nude mice.

CF102 has a favorable safety profile in nonclinical toxicology testing. In safety pharmacology studies, there were no adverse effects on respiratory or central nervous system parameters in monkeys. In monkeys, 60 mg/kg was associated with increased heart rate and 300 mg/kg caused increased heart weight in rats, likely secondary to increased heart rate. No toxicity was identified at 1000 or 300 mg/kg in 14-day toxicity studies in rats and monkeys, respectively. Higher doses

in monkeys were not tolerated and were associated with decreased food consumption and vomiting.

CF102 was not genotoxic in the Ames, mouse lymphoma, and mouse micronucleus assays.

4.2 Previous Human Experience with CF102

4.2.1 Phase 1 Trial in Normal Volunteers (CF102-101)

A Phase 1 randomized, dose-escalation trial was conducted in 25 male normal volunteers. Single doses of CF102 as high as 40 mg were not associated with intolerability, clinically important AEs, or changes in electrocardiograms (ECG) or laboratory assessments [data on file]. Absorption of CF102 following oral administration of 1, 3, 10, 20 or 40 mg CF102 was fairly slow, with C_{max} observed at 2 to 6 hours after dosing. The median t_{max} ranged from 4 to 6 hours for the first 4 cohorts, and 2 hours for the last cohort (40 mg). CF102 showed good oral bioavailability and linear pharmacokinetics (PK) behavior. Single- and repeated-dose plasma concentrations of the drug were dose-proportionate. Decline of CF102 plasma concentration was at a moderate rate, with mean half-life estimates consistently ranging between ~11 and ~12 hours at all doses.

Increases in C_{max} and AUC values were dose-related up to a 20 mg dose. However, the mean C_{max} and mean $AUC_{(0-t)}$ with the 40 mg dose were similar to those at the 20 mg dose level, suggesting exposure to CF102 might have reached a plateau between 20 mg and 40 mg. Pharmacokinetics parameters are summarized in Table 4-1 below.

Table 4–1: Human Pharmacokinetic Parameters for CF102

Mean (Std. Dev.) plasma CF102 pharmacokinetic parameters following single oral dose of CF102 in healthy male subjects (N=4 active per cohort)						
Dose (mg)	**C_{max} (ng/mL)**	**t_{max} [a] (h)**	**$AUC_{(0-t)}$ [b] (ng•h/mL)**	**$AUC_{(inf)}$ (ng•h/mL)**	**$t_{1/2}$ (h)**	**CL/F (mL/h)**
1	4.49±1.52	4 (2-4)	64.03±24.59	68.91±24.45	11.84±0.84	16124±6302
3	21.91±8.52	4 (2-4)	330.7±112.1	350.9±122	11.47±1.49	9571±4030
10	45.73±8.64	4 (2-4)	747.3±210.9	796.2±251.1	11.01±3.11	13694±4949
20	104.9±15.8	6 (6-6)	1911±400.1	2060±461.6	11.84±2.39	10128±2529
40	134.6±37.6	2 (2-6)	2052±894.7	2239±1053	12.25±2.05	20809±8670

a. Median (range)

b. $AUC_{(0-48h)}$

4.2.2 Phase 1/2 Trial in Subjects with HCC (Study CF102-102HCC)

An open-label trial was conducted in 19 subjects with advanced unresectable HCC to evaluate the safety and PK profile of CF102 given orally (1, 5, and 25 mg BID) in 28-day cycles (Stemmer, 2013). Evaluation of the antitumor effects and the utilization of A_3AR as a biological predictive marker of response to CF102 were secondary objectives.

CF102 demonstrated good oral bioavailability and linear PK behavior in subjects with Child-Pugh A and B hepatic dysfunction. The best response by RECIST criteria was SD in 5/17 subjects (29.4%). Median overall survival (OS) was 8.2 months for all subjects, 8.3 months for subjects with no prior sorafenib use, and 7.2 months for subjects with prior sorafenib and for Child-Pugh class A hepatic dysfunction subjects. Median OS in Child-Pugh class B hepatic dysfunction subjects was 9.5 months.

These results are encouraging in light of the fact that 63% of the subject population had disease progression on sorafenib and that, for these subjects, CF102 treatment was second-line therapy.

The most common adverse events (all causalities combined) were decreased appetite (52.6%); fatigue (42.1%); abdominal pain, constipation, and diarrhea (31.6% each); ascites and pyrexia (26.3% each); and nausea, asthenia, back pain, and pain in extremity (21.1% each). CF102-related AEs included fatigue (26.3%), asthenia and decreased appetite (21.1% each), and pyrexia and constipation (15.8% each). Grade 3 drug-related AEs included: cerebral hemorrhage, headache, hyponatraemia, fatigue, asthenia, and back pain. One death (5.3%) due to cerebral hemorrhage was judged possibly related to CF102 by the Investigator. SAEs with fatal outcomes in 5 subjects were judged as not related to CF102.

CF102 had no adverse effect on routine measures of liver function over a 6-month period in 12 subjects treated for at least that duration. No dose-limiting toxicities were observed during the trial and the MTD was not reached.

These findings corroborate clinical CF102 data published earlier that show a protective effect on normal liver tissue in an experimental model of liver inflammation (Cohen, 2011), and suggest that CF102 could be used in patients with cirrhosis and/or hepatic impairment. The highest dose tested of 25 mg BID, being well tolerated and showing a potentially favorable therapeutic index in subjects with HCC, was recommended for further clinical study. Please refer to the Investigational Brochure for additional information.

4.3 Rationale for the Trial

Liver cancer is the fifth most frequently diagnosed cancer in men worldwide, and is the second leading cause of cancer-related death in the world (Jemal, 2011). In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer deaths. In the United States, liver cancer is the ninth leading cause of cancer death (Altekruse, 2009). The number of deaths per year in HCC is virtually identical to the incidence throughout the world (between 250,000 and 1 million cases annually), underscoring the high case fatality rate of this aggressive disease (Jemal, 2011). Almost 80 percent of cases are due to underlying chronic hepatitis B and C virus infection (Perz, 2006).

Treatments for HCC can be divided into those delivered with the intention to cure and those that are palliative and/or delay disease progression. Surgery and transplantation have the potential to cure the disease, but they are generally offered to only 30-40% of patients at early stages of the disease. There is no accepted standard treatment for advanced HCC. Palliative therapies include radiofrequency ablation, transarterial chemoembolization, and chemotherapy. None of these treatments have been shown to improve survival.

The Child-Pugh classification system is used to assess the severity of liver disease, the prognosis, and the appropriate treatment. A Child- Pugh score of 5-6 is considered Class A (well-compensated disease); a score of 7-9 is Class B (significant functional compromise); and a score of 10-15 is Class C (decompensated disease).

Sorafenib (Nexavar®) is a new oral drug indicated for advanced HCC in patients with unresectable liver cancer. A randomized controlled trial comparing sorafenib to placebo in patients with advanced HCC and Child-Pugh Class A disease found that median survival and time to progression were nearly 3 months longer for patients treated with sorafenib compared to placebo (SHARP trial (Llovet, 2008). The median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group. There are no published, randomized controlled studies of the efficacy of sorafenib in patients with advanced HCC who have Child-Pugh Class B (CPB) or Child-Pugh Class C cirrhosis.

4.4 Rationale for Amendment 5

Amendment 5 implements the transition to open-label (OL) dosing for patients who are surviving and remain on drug at the time of analysis; and establishes the assessments and schedule of visits for the OL dosing aspect of the trial. This includes defining the OL eligibility

criteria; detailing the visit and assessment schedule; and specifying that the only patients still on treatment in this trial at the time of this amendment are in Romania.

An ancillary change has been made to remove reference to the Modified Intent to Treat (MITT) Population, as such an analysis is deemed to be non-contributory to trial objectives.

4.5 Potential Risks and Benefits of Therapy

4.5.1 Risks

Adverse events observed during CF102 therapy in the CF102-102HCC trial included the following:

- Most common AEs (4 or more occurrences, all causalities combined): abdominal pain, ascites, diarrhea, edema, fatigue, fever, lack of appetite, pain, and weakness.
- AEs considered possibly or probably related to CF102: pain in various bodily locations, fatigue, diarrhea, lack of appetite, weakness, and fever.
- Of the 25 serious adverse events reported, ascites, cellulitis, cerebral hemorrhage, headache, hyponatremia, and leg thrombus were considered at least possibly related to CF102.

For additional information, please refer to the Investigator Brochure.

4.5.2 Potential Benefits

Previous experience has shown that the OS for Child-Pugh Class B patients with HCC is in the range of 3.5–5.5 months (Pinter, 2009; Pinter, 2011; Hollebecque, 2011). More importantly, data emerging from a number of recent trials have indicated that the median OS for patients with CPB and HCC who have failed treatment with sorafenib is generally no more than 2 months (Pinter, 2009; Wörns, 2009; Kim, 2011; Hollebecque, 2011; Abou-Alfa, 2011; Chiu, 2012; Køstner, 2013; Pressiani, 2013; Zugazagoitia, 2013).

Considering that Child-Pugh Class B patients with HCC have few available treatment options, and that these patients when treated with sorafenib generally have poor outcomes with very limited OS due to underlying liver dysfunction, CF102 may offer a therapeutic option for this sub-population of patients. CF102 has the further advantage of lacking, to date, any evidence of hepatotoxicity, making it highly suitable for use in patients with CPB cirrhosis.

5.0 TRIAL OBJECTIVES

The primary objective of this trial is to:

- Evaluate the efficacy of orally administered CF102 25 mg BID as compared to placebo, as determined by Overall Survival (OS), when used as second-line therapy in subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh Class B (CPB) cirrhosis.

The secondary objectives of this trial are to:

- Evaluate other indicators of efficacy of CF102 as compared to placebo, including time to progression (TTP), progression-free survival (PFS), objective response (OR) rate, and disease control (DC) rate in this population;
- Explore the exposure-response relationships of oral CF102 using sparse PK sampling;
- Characterize the safety profile of CF102 in subjects with advanced HCC and CPB cirrhosis;
- Characterize the effects of CF102 on laboratory parameters associated with viral hepatitis, hepatic dysfunction, and cirrhosis; and
- Explore the relationship between white blood cell (WBC) adenosine A_3 receptor (A_3AR) expression and clinical response.

6.0 INVESTIGATIONAL PLAN

6.1 Overall Trial Design and Plan Description

This is a multicenter, randomized, double-blind, placebo-controlled trial in subjects with advanced HCC and CPB cirrhosis who did not tolerate prior sorafenib therapy or experienced disease progression on prior sorafenib therapy.

The trial will evaluate the efficacy and safety of CF102 as compared to placebo. Subjects will be randomly assigned in a 2:1 ratio to treatment with oral doses of either CF102 25 mg capsules or matching placebo capsules administered twice daily (BID) for consecutive, 28-day cycles. Treatment will continue until the subject experiences unacceptable drug-related intolerability. Subjects who discontinue will be followed indefinitely for survival status.

The primary efficacy endpoint will be OS, defined as the number of days from first dose to death due to any cause. Secondary endpoints to be evaluated are TTP, PFS, OR rate (consisting of Complete Response (CR) or Partial Response (PR) in subjects who enter with measurable disease by RECIST v1.1), and DC rate which includes subjects with OR as well as those with Stable Disease (SD). Survival status will be assessed continuously. Tumor status will be assessed at baseline and every 8 weeks thereafter (i.e., at the end of even-numbered cycles) by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to RECIST v1.1 criteria

as modified by Santoro (2013) (Appendix A). Alpha-fetoprotein (AFP) levels will be assessed at baseline and every 4 weeks thereafter on Day 1 of each subsequent cycle. Laboratory parameters associated with hepatic dysfunction and cirrhosis, such as serum ALT, AST, bilirubin, and albumin levels; PT; and INR, will be assessed every cycle where applicable. Hepatitis B and/or C viral load measurements will be performed every odd-numbered cycle. White blood cell A_3AR expression will be assessed at baseline and, unless waived by the Sponsor, every odd-numbered cycle (at selected sites only). Sparse PK blood samples on Day 1 of Cycles 1 and 2 as well as trough samples collected on Days 8 and 15 of Cycle 1 will be used to generate a composite PK profile for subjects receiving CF102, and allow an exploratory analysis of exposure-response relationships for this trial.

Subjects will be evaluated regularly for safety including changes in laboratory parameters including thyroid functions, vital signs, physical examination, ECOG PS, and ECG assessments compared to baseline findings. Subjects will return for a follow-up visit 28 days after completion of the last dose of study drug, and every attempt will be made to obtain subject survival data.

Once the requisite number of events has occurred and the blind is opened for analysis of the trial results, any surviving subjects who remain on blinded drug will be offered the opportunity to continue dosing with open-label CF102 25 mg BID indefinitely, following the protocol-specified schedule of events (Table 1–2).

6.2 Discussion of Trial Design Including the Choice of Control Group

The use of a placebo control group in this trial reflects clinical equipoise since subjects with advanced HCC and CPB cirrhosis who had failed one prior therapy for locally advanced or metastatic disease would otherwise have received best supportive care, because there are no proven or approved therapies for this patient population. Randomized, controlled trials are currently considered to be the clinical and scientific standard for Phase 2 trials of new drug treatments for HCC (Llovet, 2008; Thomas, 2010).

Randomizing subjects in a 2:1 ratio ensures that 67% of subjects will receive the active agent, thus decreasing the number of subjects receiving placebo from that for a balanced randomization.

Because overall survival is the primary endpoint of the trial, the potential impact of unintentional unblinding is considered to be minimal.

6.3 Number of Subjects

Approximately 78 subjects will be enrolled and randomized in a 2:1 ratio to receive treatment with either CF102 or matching placebo.

6.4 Duration of Trial

The subject accrual period is estimated to be approximately 102 weeks (~24 months) in duration. Each treatment cycle will be 28 days of daily dosing. Study drug treatment may continue until the subject experiences unacceptable drug-related intolerability (Section 8.2).

The post-accrual treatment period will continue until a total of 75 subjects have died.

Once the requisite number of events has occurred and the blind is opened for analysis of the trial results, any surviving subjects who remain on blinded drug will be offered the opportunity to continue dosing with open-label CF102 25 mg BID indefinitely, following the protocol-specified schedule of events (Table 1–2).

7.0 SELECTION OF SUBJECTS

7.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for the trial:

1. Males and females at least 18 years of age.
2. Diagnosis of HCC:
   - □ For subjects without underlying cirrhosis at the time of diagnosis, diagnosis of HCC documented by cytology and/or histology.
   - □ For subjects with underlying cirrhosis at the time of diagnosis, diagnosis of HCC established according to the American Association for the Study of Liver Diseases Practice Guideline algorithm (Appendix E).
3. HCC is advanced, i.e., treatment-refractory or metastatic, and no standard therapies are expected to be curative.
4. Receipt of prior sorafenib therapy for at least 3 weeks and withdrawal from treatment due either to intolerability or to radiographic evidence of disease progression. If treatment was withdrawn due to intolerability manifested as a Grade 3 or 4 event by National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE v4.0), less than 3 weeks of continuous prior administration prior to withdrawal is acceptable (see also Exclusion Criterion #3).
5. Prior sorafenib treatment was discontinued for at least 2 weeks prior to the Baseline Visit.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 (Appendix B).

7. Cirrhosis classified as Child-Pugh Class B (Appendix C).
8. The following laboratory values must be documented ≤ 3 days prior to the first dose of study drug:
   - □ Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   - □ Platelet count ≥ 75×10^9/L
   - □ Serum creatinine ≤ 2.0 mg/dL
   - □ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × the upper limit of normal (ULN)
   - □ Total bilirubin ≤ 3.0 mg/dL
   - □ Serum albumin ≥ 2.8 g/dL
   - □ Prothrombin time (PT) no greater than 6 seconds longer than control.
9. Life expectancy of ≥ 6 weeks.
10. For women of childbearing potential, negative serum pregnancy test result.
11. Provide written informed consent to participate.
12. Willing to comply with scheduled visits, treatment plans, laboratory assessments, and other trial-related procedures.

7.2 Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for the trial:

1. Receipt of no, or of > 1, prior systemic drug therapies for HCC.
2. Receipt of systemic cancer therapy, immunomodulatory drug therapy, immunosuppressive therapy, or corticosteroids > 20 mg/day prednisone or equivalent within 14 days prior to the Baseline Visit or concurrently during the trial.
3. Presence of an acute or chronic toxicity of prior chemotherapy that has not resolved to ≤ Grade 1, as determined by CTCAE v 4.0.
4. Locoregional treatment within 4 weeks prior to the Baseline Visit.
5. Major surgery or radiation therapy within 4 weeks prior to the Baseline Visit.
6. Use of any investigational agent within 4 weeks prior to the Baseline Visit.
7. Child-Pugh Class A or C cirrhosis, or hepatic encephalopathy.
8. Occurrence of esophageal or other gastrointestinal hemorrhage requiring transfusion within 4 weeks prior to the Baseline Visit.
9. Uncontrolled or clinically unstable thyroid disease, per judgment of the Principal Investigator.
10. Active bacterial, viral, or fungal infection requiring systemic therapy, or operative or radiological intervention.

11. Known human immunodeficiency virus- or acquired immunodeficiency syndrome-related illness.
12. Liver transplant.
13. Active malignancy other than HCC.
14. Uncontrolled arterial hypertension or congestive heart failure (New York Heart Association Classification 3 or 4) (Appendix B).
15. Angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass graft surgery, transient ischemic attack, or pulmonary embolism within 3 months prior to initiation of study drug.
16. History of or ongoing cardiac dysrhythmias requiring treatment, atrial fibrillation of any grade, or persistent prolongation of the QTc (Fridericia) interval to > 450 msec for males or > 470 msec for females.
17. Pregnant or lactating female.
18. Women of childbearing potential, unless they agree to use dual contraceptive methods which, in the Investigator's opinion, are effective and adequate for the subject's circumstances while on study drug.
19. Men who partner with a woman of childbearing potential, unless they agree to use effective, dual contraceptive methods (i.e., a condom, with female partner using oral, injectable, or barrier method) while on study drug and for 3 months afterward.
20. Any severe, acute, or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with trial participation or study drug administration; may interfere with the informed consent process and/or with compliance with the requirements of the trial; or may interfere with the interpretation of trial results and, in the Investigator's opinion, would make the subject inappropriate for entry into this trial.

7.3 Randomization and Blinding

On Day 1, each subject will be randomly assigned in a 2:1 ratio to receive either CF102 25 mg BID or placebo BID. A randomization schedule will be prepared for treatment group assignment of each subject. The subject's randomization number will be unique. This number is not the same as the subject identification (ID) number which is assigned at the time of informed consent. The subject ID number identifies the subject and consists of the site number plus subject number for that site. The randomization number identifies the treatment; the randomization schedule provides the correspondence between the subject ID number and the randomization number.

The trial will be double-blind, meaning the subject and Investigator/staff will not have access to or knowledge of the subject's treatment assignment.

Additional details regarding randomization and procedures for unblinding the treatment assignment for individual subjects will be provided in the Pharmacy Manual or other separate documentation.

7.4 Discontinuation from Dosing

Discontinuation from dosing means that upon the subject's decision to terminate dosing early, the End of Study visit is to be performed and indefinite monthly survival follow up will be performed.

Subjects should be discontinued from dosing for the following reasons:

- Grade 3 toxicity considered by the Investigator to be at least "possibly" drug-related that does not resolve to Grade ≤ 1 within 7 days following interruption of treatment.
- Need for > 1 dose reduction.
- Grade 4 toxicity considered by the Investigator to be at least "possibly" drug-related.
- Treatment interruption or delay for more than 14 days after the next scheduled dose due to an event unrelated to toxicity (e.g., intercurrent illness, scheduled surgery, etc).
- Subject withdrawal of consent for trial participation at any time, for any reason, and without prejudice.
- Withdrawal of a subject by the Investigator, at his/her discretion, for any reason that the Investigator believes continuation of study drug therapy would not be in the subject's best interest. The reason for the subject's discontinuation must be recorded on the case report form (CRF).
- An intercurrent illness which, in the Investigator's opinion, would prevent completion of trial-related evaluations.
- Pregnancy.
- Subject noncompliance with trial or follow-up procedures.
- Termination of the trial by the Sponsor.

If a subject is withdrawn from treatment, the Investigator will make every effort to complete all final evaluations and laboratory tests required by the protocol. The reason(s) for discontinuation of dosing must be clearly documented on the CRF. Subjects who discontinue will be followed indefinitely for survival status.

7.5 Withdrawal from the Trial

A subject will be considered to be withdrawn from the trial for the following reasons:

- Withdrawal of consent (in which every effort will be made to follow the subject for survival information).
- Lost to Follow-up (subject does not return for trial visits and contact cannot be reestablished).
- Termination of the trial by the Sponsor.

7.6 Replacement of Subjects

No replacement of subjects is planned in this trial.

7.7 Eligibility Criteria for Open Label

- The subject signed the ICF for the Open Label treatment.
- The subject received double blind treatment with CF102/placebo and is still taking the investigational medication when Amendment 5 is approved.

8.0 TREATMENTS

Study drug is to be administered only to subjects who have provided informed consent and have met the criteria outlined in 7.1 Inclusion Criteria and 7.2 Exclusion Criteria.

Open-label CF102 is to be administrated only to subjects who have provided informed consent for the open label treatment and met the criteria outlined in 7.7 Eligibility Criteria for Open Label.

8.1 Treatments Administered

CF102 or matching placebo will be administered in continuous 28-day cycles beginning on Day 1 of Cycle 1.

During OL the CF102 will be administrated in continuous 28-days cycles beginning on Day 1 of Cycle 1 of OL period.

Subjects will self-administer CF102 or placebo twice daily (BID) beginning on Day 1 of the trial. Study drug should be taken on an empty stomach (1 hour before or 2 hours after meals) at approximately the same times each day of the 28-day cycle. On days of a scheduled clinic visit, the dose of CF102 or placebo should be taken at the clinic after visit procedures have been completed. Missed or vomited doses will not be “made up.”

8.2 Dose Modification

Any safety-related modification of study drug dosing (i.e., dose reduction or interruption of scheduled dosing) and the reason for such action must be clearly noted on the Adverse Events page of the CRF, and the Medical Monitor informed.

In the case of any Grade 3 toxicity by CTCAE v4.0 judged by the Principal Investigator to be at least "possibly" drug-related, the dose of study drug will be interrupted for up to 7 days. If toxicity does not resolve to Grade ≤ 1 within 7 days, the subject will be discontinued from treatment. If toxicity does resolve to Grade ≤ 1 within 7 days, dosing will be resumed at the decreased dose of 1 capsule per day.

In the case of any Grade 4 toxicity judged by the Principal Investigator to be at least "possibly" drug-related, the dose of study drug will be withdrawn permanently.

Only 1 dose reduction will be allowed. If a Grade 3 or 4 toxicity judged by the Principal Investigator to be at least "possibly" drug-related occurs upon rechallenge at the reduced dose, study drug dosing will be withdrawn permanently.

All changes in dosing will be recorded on the CRF.

8.3 Study Drug Identification

All study drug product is intended for oral administration. CF102 is formulated as opaque, white, size 3, Coni-Snap hard gelatin capsules containing 25 mg of CF102 active pharmaceutical ingredient. Matching placebo is formulated as opaque, white, size 3, Coni-Snap hard gelatin capsules containing inactive ingredients (microcrystalline cellulose, maltodextrin, sodium lauryl sulfate, and imperial talc 500).

CF102 and placebo capsules are stable under long-term storage conditions (25°C/60% RH). Excursions to elevated temperatures (40°C/75% RH) are permitted.

8.4 Packaging and Labeling

CF102 and matching placebo capsules are packaged in 75cc white, high-density polyethylene (HDPE) wide-mouth oblong bottles capped with 33 mm white, HDPE ribbed caps (child resistant) with a heat seal inner foil liner.

Study drug supplies will be shipped to the investigational site and /or investigational site pharmacy by CSM (Fargo, ND). The pharmacist will prepare individual bottles of study drug to

dispense to subjects based on their randomized treatment assignment. The labels on the subject bottles will include the following:

- Number and strength of capsules; route of administration
- Directions for use
- Storage conditions
- Product ID code
- Protocol number
- Sponsor's name
- The statement: "Caution: New drug-limited by Federal Law to Investigational Use. Keep out of reach of children."
- Subject randomization number

8.5 Study Drug Handling and Accountability

The Investigator (or designee, i.e., investigational site pharmacist) at the site will be responsible for handling study drug and maintaining required documentation. The Investigator must maintain complete and current inventory and dispensing records supplied by the Sponsor.

The Investigator (or designee) will:

- Ensure study drug supplies are stored at stable room temperature (20-25°C) in an appropriately controlled limited-access room in a secure location.
- Dispense the appropriate study drug according to the subject's randomized treatment assignment.
- Record pertinent information regarding the dose of study drug dispensed (e.g., subject ID number, date, number of doses/bottles dispensed, etc.) on the Drug Dispensing Log, or other appropriate inventory form. This inventory will be maintained throughout the trial and will be reviewed periodically by a Sponsor representative.
- Inform subjects that at each clinic visit and at the end of their participation in the trial, all partially used and empty pill bottles must be returned to the Investigator so that a final inventory may be conducted. Once returned to the Investigator, capsules from partially-used bottles will not be re-dispensed to another subject.

8.6 Treatment Compliance

Bottles of study drug dispensed to subjects at the start of each treatment cycle will contain a sufficient supply of CF102 or matching placebo for 28 days of continuous dosing (1 cycle). Treatment compliance will be monitored by the investigative site staff at each clinic visit.

Bottles of study drug dispensed to subjects at the start of each treatment OL cycle will contain a sufficient supply of CF102 for 28 days of continuous dosing (1 cycle). Treatment compliance will be monitored by the investigative site staff at each clinic visit.

The Investigator will instruct subjects to bring all partially used and empty pill bottles to each clinic visit. Any dosing error will be reported to the Investigator and Sponsor's monitor.

8.7 Study Drug Disposal

Throughout the trial, the Investigator will maintain a careful inventory of all partially used and empty bottles of study drug.

Periodically throughout and at the conclusion of the trial, an inventory of **unused** bottles of study drug will be conducted by a Sponsor representative. At the completion of the trial, all **partially used** as well as all **unused** study drug materials must be returned to the Sponsor or destroyed on site, with appropriate documentation.

At the termination of the trial, a final drug accountability review and reconciliation must be completed and any discrepancies must be investigated and their resolution documented.

8.8 Concomitant Medications and Supportive Care

All prior anti-neoplastic medications, medications taken within 1 month prior to the Baseline Visit, and concomitant medications will be collected from the time the subject signs the consent form and throughout the trial, including the Follow-Up Visit, and recorded on the appropriate Case Report Form. Medications/treatments that affect trial eligibility are listed in the Inclusion and Exclusion criteria in Sections 7.1 and 7.2.

During the trial, all medications considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of the study drug may be administered at the Investigator's discretion. If site personnel have any questions regarding the suitability of a particular concomitant medication, the Medical Monitor should be contacted.

There is no requirement for premedication with CF102. Any medications administered for either prophylaxis or treatment of symptoms associated with study drug should be documented on the Concomitant Medication page of the CRF.

The following are prohibited from concomitant administration with CF102:

1. Systemic cancer therapy, immunomodulatory drug therapy, immunosuppressive therapy, or radiotherapy

2. Corticosteroids > 20 mg/day prednisone or equivalent
3. Hematopoietic growth factors may not be given prophylactically but may be administered to treat toxicity.

9.0 EFFICACY AND SAFETY VARIABLES ASSESSED

9.1 Trial Visits

All subjects will be assessed by scheduled clinical, laboratory, and other diagnostic assessments throughout the trial. See the flow chart (Table 1–1 and Table 1–2) for the timing of trial procedures and assessments to be performed at each clinic visit.

Pre-Study (i.e., Screening) assessments are to be performed within 28 days prior to first study drug dose, unless otherwise specified.

*The first day of study drug dosing will be considered Day 1 (**Baseline**) of the trial.*

Clinic Visits will take place within ± 2 working days of the scheduled time unless a waiver is approved by the Sponsor. Trial assessments will be performed prior to administration of the study drug dose for that day.

If significant changes from baseline are noted during the trial, additional unscheduled clinic visits may be performed in order to determine the relevance of findings and/or the duration of events.

End of Dosing assessments are to be performed within 2 working days after the last dose of study drug.

A **Follow-Up** visit is to be scheduled 28 ± 3 days after the **End of Dosing** visit to perform all final safety assessments and collect information on any adverse events.

The subjects who are still on blinded treatment when the Amendment 5 is approved will be switched to open label treatment at their next scheduled visit. During this visit, the Cycle 1 Day 1 for OL procedures will be performed (Table 1-2). In OL period, Clinic Visits will take place within ± 2 working days of the scheduled day unless a waiver is approved by the Sponsor. Trial assessments will be performed prior to administration of the study drug dose for that day.

*The first day of open label study drug dosing will be considered Day 1 (**OL**) of the trial.*

9.2 Trial Assessments

9.2.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol specific procedures, including Pre-Study screening procedures, are to be performed until the subject has signed and dated an IRB/EC-approved informed consent form (ICF). The ICF can be signed outside of the Pre-Study period; however, no protocol-related procedures can be performed until the consent has been signed. Documentation of the informed consent process must be noted in the subject's source documents. The subject ID number will be assigned after the ICF is signed.

The subjects will receive CF102 in open label portion of the trial only after the subject signs and dates the IRB/EC-approved informed consent form (ICF) for the OL.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be collected at the Pre-Study (Screening) Visit. Baseline characteristics consist of a complete medical history and detailed disease history. Medical history includes prior and ongoing medical diagnoses and conditions, surgical procedures not related to the primary diagnosis, and medications taken within the previous 30 days.

Disease history is a history of the primary diagnosis and should include the date of initial HCC diagnosis and staging; date of most recent relapse and/or re-staging; histologic or cytologic diagnosis; prior treatments (e.g., chemotherapy, surgery, radiation), dates of treatments, numbers of cycles, and best response to such treatments; duration of prior sorafenib therapy; reason(s) for discontinuation of sorafenib, and if applicable, nature of intolerability to sorafenib; current signs and symptoms related to the primary diagnosis; and location and measurement of target and non-target sites of disease.

9.2.3 Concomitant Medications

All prior and concomitant medications will be collected from the time of the Pre-Study Visit throughout the trial, including the OL period and OL Follow-Up Visit 28 days after the last dose of study drug. The information will include: the name of the drug (including generic when known), the indication for which it was used, total daily dosage, and duration of treatment. Any diagnostic, therapeutic, or surgical procedures performed during the trial (e.g., blood transfusion) should be recorded on this form, including the date, indication, description, and findings, if any.

9.2.4 Adverse Event Assessments

Information regarding the occurrence of adverse events will be collected from the Cycle 1 Day 1 visit (i.e., the Baseline Visit) throughout the trial, including the OL period and OL Follow-Up Visit 28 days after the last dose of study drug. If AEs related to study drug are ongoing at the OL Follow-Up Visit, safety data will be collected until the adverse event resolves or stabilizes.

9.2.5 ECOG Performance Status

Performance status will be assessed using ECOG PS criteria (Appendix B).

9.2.6 Vital Signs

Vital signs will be measured after the subject has been seated for 5 minutes. Vital signs will include blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (degrees Celsius).

9.2.7 Physical Examination (PE)

A complete physical examination (PE) will be performed by the Investigator or Sub-Investigator at the Pre-Study, Day 1 (the Baseline Visit if not performed within 3 days prior), and End of Study/End of Dosing (EOS) visits/OL End of Study/OL End of Dosing (EOS) visits. The complete PE will include a thorough review of all body systems as well as measurement of weight (kg) and height (cm).

At all other visits, a symptom-directed PE, including weight (kg), will be performed covering targeted body systems.

9.2.8 Laboratory Assessments

Laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis) will be performed at the Pre-Study Visit; Days 1 (i.e., the Baseline Visit if not performed within 3 days prior), 8, and 15 of Cycle 1; Days 1 and 15 of subsequent cycles; EOS; and Follow-up/ Days 1, 8, and 15 of Cycle 1 OL; Days 1 and 15 of subsequent OL cycles; OL EOS; and OL Follow-up. Thyroid function tests (T3, T4, thyroid stimulating hormone [TSH]) will be performed at Pre-Study; Baseline; Day 1 of subsequent cycles; EOS; and Follow-up/ Baseline OL; Day 1 of subsequent OL cycles; OL EOS; and OL Follow-up. A serum β-hCG pregnancy test should be performed within 3 days prior to first study drug dose for all females of childbearing potential (defined as women ≤ 50 years of age or history of amenorrhea for ≤ 12 months prior to entering the trial). Where applicable, hepatitis B and/or C viral load measurements will be performed (for subjects with measurable viral load at baseline).

A complete list of laboratory tests is provided in Appendix D.

9.2.9 WBC A_3AR Expression

At selected sites, a blood sample will be obtained at the Cycle 1 Day 1 (Baseline) visit, prior to dosing. 2.5 mL of blood are to be collected. The complete procedure is detailed in the laboratory manual provided by the central laboratory.

Sampling will be repeated at the beginning of every odd-numbered cycle, unless waived by the Sponsor.

9.2.10 Electrocardiogram (ECG)

A 12-lead ECG will be performed at the following times after the subject has been supine for 5 minutes: Pre-Study; pre-dose at all visits/pre-dose at all OL visits; Cycle 1 Days 1 and 8 at 2, 4, and 6h (± 10 min) post-dose/OL Cycle 1 Days 1 and 8 at 2, 4, and 6h (± 10 min) post-dose; and at Follow-up/OL Follow-up.

9.2.11 Tumor Assessment

At the Pre-Study visit, an assessment of disease status will be determined using RECIST V1.1 criteria as modified by Santoro (2013) (Appendix A). For the purposes of trial eligibility, a scan obtained within 14 days prior to the Pre-Study visit may be used. The location and dimensions of target lesions will be documented on the CRF.

9.2.12 Response Assessment

Response assessments will be performed and documented throughout the trial using RECIST v1.1 (Appendix A).

The same method/technique for assessing response, either CT scan or MRI, should be used for any individual subject throughout the trial. If progressive disease (PD) is documented at any time, the patient will not be discontinued from the trial. Further imaging or target lesion measurements will not be required and all other trial visits and procedures will continue. Diagnostic studies documenting disease response must be available for review by the Sponsor, if requested.

In the event of an objective response, the duration of the response will be determined from the day the initial response is observed (using the Pre-Study Visit images for comparison) to the day that progression is observed. Duration of stable disease will also be assessed (see Appendix A).

9.2.13 Pharmacokinetics Sampling

Blood samples will be collected from all subjects enrolled at sites with the requisite technical capabilities during Cycle 1 on Days 1, 8, and 15 and on Day 1 of Cycle 2 to determine plasma concentrations of CF102. The sampling time points are shown in Table 10–1. Pharmacokinetic (PK) analyses will include area under the curve (AUC_{0-12h}), maximum plasma concentration (C_{max}), trough plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}) following the morning dose on Day 1 of Cycles 1 and 2 and C_{min} on Days 8 and 15 of Cycle 1.

9.3 Timing of Assessments

9.3.1 Pre-Study (Screening) Visit (-28 Days)

The following assessments are to be performed Pre-Study within 28 days prior to the first dose of study drug, unless otherwise specified.

- Medical history
- Complete physical examination
- Inclusion/exclusion criteria
- Informed consent
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8). If performed ≤ 3 days prior to first dose of study drug, need not be repeated at the Baseline Visit (Section 9.3.2)
- ECG (Section 9.2.10)
- ECOG PS (Section 9.2.5)
- Hepatitis B and/or C virus serology
- Tumor imaging for RECIST (need not be repeated if performed within the previous 21 days)
- Concomitant medications (taken within the previous 30 days)

9.3.2 Cycle 1 Day 1 (Baseline) Visit

The following assessments will be performed at the Cycle 1 Day 1 (Baseline) Visit prior to the first dose of study drug, and at other times as specified:

- Complete physical examination unless performed ≤ 3 days prior to first dose
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8) unless performed ≤ 3 days prior
- Serum β-hCG pregnancy test (Section 9.2.8) unless performed ≤ 3 days prior

- ECG pre-dose and at 2, 4, and 6h (± 10 min) post-dose (Section 9.2.10)
- ECOG PS (Section 9.2.5) unless performed ≤ 3 days prior
- AFP
- WBC A_3AR sample (selected sites only) (Section 9.2.9)
- PK sampling (selected sites; Table 10–1)
- Hepatitis B and/or C viral load (if seropositive)
- Concomitant medications
- Administer the first dose of study drug and record the time of administration
- Adverse events (post-dosing)
- Dispense the balance of Cycle 1 study drug supplies
- Instruct the subject regarding treatment compliance, and (at selected sites) not to take the dose prior to PK sampling on the morning of Days 8 and 15

9.3.3 Cycle 1 Day 8 and Day 15 Visits (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments (Section 9.2.8)
- ECG pre-dose (Days 8 and 15); and at 2, 4, and 6h (± 10 min) post-dose (Day 8 only) (Section 9.2.10)
- Trough PK sample pre-AM dose)
- Concomitant medications
- Adverse events
- Review treatment compliance
- Instruct the subject not to take the dose prior to PK sampling on the morning of Cycle 2 Day 1 (selected sites)

9.3.4 Subsequent Cycles Day 1 Visit (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG pre-dose (Section 9.2.10)
- ECOG PS (Section 9.2.5)

- AFP
- WBC A_3AR sample (selected sites only; beginning of odd-numbered cycles only, unless waived by the Sponsor) (Section 9.2.9)
- PK sampling (Table 10–1) (Note: Day 1 of Cycle 2 only; selected sites)
- Tumor imaging for RECIST (at **end** of Cycle 2 and **end** of subsequent even-numbered cycles, with a time window of up to 7 days prior or 1 day after; if 1 day after, scan is to be done prior to the AM dose) (Appendix A)
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit) (beginning of odd-numbered cycles only)
- Concomitant medications
- Adverse events
- Collect used study drug supplies
- Dispense study drug supplies
- Review treatment compliance

9.3.5 Subsequent Cycles Day 15 Visit (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments (Section 9.2.8)
- ECG pre-dose (Section 9.2.10)
- Concomitant medications
- Adverse events
- Review treatment compliance

9.3.6 End of Study/End of Dosing (EOS) Visit (within 2 days of last dose)

- Physical examination (complete examination)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG (Section 9.2.10)
- ECOG PS (Section 9.2.5)
- AFP
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit)
- Tumor imaging for RECIST (Appendix A)
- Concomitant medications

- Adverse events
- Review treatment compliance and collect all used study drug supplies

9.3.7 Follow-Up Visit (28 ± 3 days Post End of Dosing)

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG (Section 9.2.10)
- AFP
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit)
- Concomitant medications
- Adverse events

9.3.8 Cycle 1 Day 1 OL Visit

The following assessments will be performed at the Cycle 1 Day 1 (OL) Visit prior to the first dose of study drug in OL, and at other times as specified:

- Complete physical examination
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8)
- ECG pre-dose and at 2, 4, and 6h (± 10 min) post-dose (Section 9.2.10)
- ECOG PS (Section 9.2.5)
- AFP
- WBC A_3AR sample (selected sites only) (Section 9.2.9)
- Hepatitis B and/or C viral load (if seropositive)
- Concomitant medications
- Administer the first dose of study drug in OL and record the time of administration
- Adverse events (post-dosing)
- Dispense the balance of Cycle 1 OL study drug supplies

9.3.9 Cycle 1 Day 8 OL and Day 15 OL Visits (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)

- Laboratory assessments (Section 9.2.8)
- ECG pre-dose (Days 8 OL and 15 OL); and at 2, 4, and 6h (± 10 min) post-dose (Day 8 OL only) (Section 9.2.10)
- Concomitant medications
- Adverse events
- Review treatment compliance

9.3.10 Subsequent Cycles Day 1 OL Visit (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG pre-dose (Section 9.2.10)
- ECOG PS (Section 9.2.5)
- AFP
- WBC A_3AR sample (selected sites only; beginning of odd-numbered cycles only, unless waived by the Sponsor) (Section 9.2.9)
- Tumor imaging for RECIST (at **end** of Cycle 2 and **end** of subsequent even-numbered cycles, with a time window of up to 7 days prior or 1 day after; if 1 day after, scan is to be done prior to the AM dose) (Appendix A)
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit) (beginning of OL odd-numbered cycles only)
- Concomitant medications
- Adverse events
- Collect used study drug supplies
- Dispense study drug supplies
- Review treatment compliance

9.3.11 Subsequent Cycles Day 15 OL Visit (± 2 days)

The following assessments will be performed prior to the daily dose of study drug:

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments (Section 9.2.8)
- ECG pre-dose (Section 9.2.10)
- Concomitant medications

- Adverse events
- Review treatment compliance

9.3.12 End of Study/End of Dosing (EOS) OL Visit (within 2 days of last dose)

- Physical examination (complete examination)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG (Section 9.2.10)
- ECOG PS (Section 9.2.5)
- AFP
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit)
- Tumor imaging for RECIST (Appendix A)
- Concomitant medications
- Adverse events
- Review treatment compliance and collect all unused study drug supplies

9.3.13 Follow-Up OL Visit (28 ± 3 days Post OL End of Dosing)

- Physical examination (symptom-directed)
- Vital signs (Section 9.2.6)
- Laboratory assessments including thyroid functions (Section 9.2.8)
- Serum β-hCG pregnancy test (Section 9.2.8) if indicated
- ECG (Section 9.2.10)
- AFP
- Hepatitis B and/or C viral load (for subjects with measurable viral load at the Baseline Visit)
- Concomitant medications
- Adverse events

10.0 EFFICACY AND PHARMACOKINETICS ASSESSMENTS

10.1 Response Assessments

Data on primary disease, response, and the duration of any OR or SD, as well as the TTP, PFS, and OS will be collected for all subjects. Subjects will undergo disease assessment at Pre-Study (within 28 days prior to first dose of study drug), at the end of Cycle 2, and at the end of even-numbered cycles thereafter. Response will be determined by RECIST version 1.1 as modified by Santoro (2013) (Appendix A).

Disease parameters to be assessed:

- Diagnostic imaging/measurement of target lesions
- Response assessment

10.1.1 Disease Classification

Details of the primary diagnosis should be documented at the Pre-Study Visit. The histological/ cytological type (if known) and stage of disease should be noted on the CRF.

10.1.2 Diagnostic Imaging/Measurement of Target Lesions

Subjects should be followed with the same imaging procedure (CT scan or MRI) throughout this trial. If PD is documented at any time, no further imaging or lesion measurements will be required. Diagnostic studies documenting response must be available for Sponsor review.

10.1.3 Response Assessment

Response will be assessed as detailed in Appendix A. Efficacy will be assessed for the Intent-to-Treat (ITT) Population (Section 12.3.2).

10.2 Time to Event

The time to event assessments include OS, TTP, and PFS. Overall Survival (OS) is the number of days from Day 1 of Cycle 1 to the day of death+1, where a death can be due to any cause. Subjects who discontinue will be followed indefinitely to obtain survival status. Time to Progression (TTP) is the number of days from Day 1 of Cycle 1 to the day of PD+1. Progression-Free Survival is the number of days from Day 1 of Cycle 1 to the day of death or PD+1.

10.3 Laboratory Assessments for Exploratory Efficacy

Certain laboratory parameters associated with hepatic dysfunction and cirrhosis will be examined, as will WBC A_3AR expression.

10.3.1 Liver Chemistry Tests

Bilirubin (direct and total), ALT, AST, and albumin will be performed along with other laboratory tests assessed for safety at Pre-Study Visit; Days 1 (i.e., the Baseline Visit if not performed within 3 days prior), 8, and 15 of Cycle 1; Days 1 and 15 of subsequent cycles; EOS; and Follow-up/Days 1, 8, and 15 of OL Cycle 1; Days 1 and 15 of subsequent OL cycles; OL EOS; and OL Follow-up.

10.3.2 INR

INR will be assessed along with other laboratory tests assessed for safety at the Pre-Study Visit; Days 1 (i.e., the Baseline Visit if not performed within 3 days prior), 8, and 15 of Cycle 1; Days 1 and 15 of subsequent cycles; EOS; and Follow-up/ Days 1, 8, and 15 of OL Cycle 1; Days 1 and 15 of subsequent OL cycles; OL EOS; and OL Follow-up.

10.3.3 Viral Load

For subjects with measurable viral load at the Baseline Visit, hepatitis B and/or C viral load will be measured on Day 1 of odd-numbered cycles/ Day 1 of OL odd-numbered cycles only.

10.4 Pharmacokinetics Assessment

All subjects enrolled at sites with the requisite technical capabilities will have approximately 8 whole blood samples collected during Cycle 1 and 2 for analysis of plasma concentrations of CF102. Approximately 4 mL of blood will be collected from subjects at each time point (i.e., a total of approximately 32 mL).

The timing of PK sampling is shown in Table 10-1. Sparse PK samples will be collected following the morning dose of CF102 on Cycle 1 Day 1 and Cycle 2 Day 1. In addition, a trough sample will be collected pre-AM dose on Cycle 1 Days 8 and 15. If PK samples are to be drawn at a scheduled safety evaluation visit, the study drug should be held until after the pre-dose PK sample has been drawn and safety assessments have been performed.

Table 10–1: Timing of PK Samples

Timing Relative to Time of AM Dose (T)	Cycle 1			Cycle 2
	Day 1	Day 8	Day 15	Day 1
Pre-dose (AM dose)	X	X	X	X
Post-dose 1, 2, 3, 4, 6, 8, and 12h (prior to the evening dose) [a]	X			X

a. On Day 1 of Cycles 1 and 2, after the morning dose, PK blood samples will be collected at ANY TWO of the specified time points (1, 2, 3, 4, 6, 8, and 12h [prior to evening dose])

Plasma CF102 concentration will be determined using a validated LC-MS/MS method by a Sponsor-designated laboratory.

10.4.1 Sample Storage

Plasma samples will be placed in a storage freezer at -70°C (± 12°C) or on dry ice within 120 minutes of the blood collection. Samples should be placed in a -70°C (± 12°C) freezer until they

are shipped to the bioanalytical laboratory. With prior approval from the Sponsor, sample storage in a -20°C freezer may be permitted.

The complete procedure is detailed in the laboratory manual provided by the central laboratory.

11.0 ASSESSMENT OF SAFETY

11.1 Safety Parameters

Safety parameters assessed throughout the trial include ECOG performance status; vital signs; weight; physical examinations; laboratory parameters; ECG; concomitant medications, and adverse events. Any clinically significant change from baseline in a laboratory parameter will be reported as an AE. Liver Chemistry Tests, INR, and viral load will be presented as exploratory efficacy variables, as will WBC A_3AR expression.

Anticipated toxicities that may occur with CF102 are detailed in Section 4.4 of this protocol as well as in the Investigator Brochure (IB).

11.2 Duration of Follow-Up

Any significant clinical adverse event, whether observed by the Investigator or experienced by the subject, will be reported beginning with the Cycle 1 Day 1 (Baseline) Visit. Final safety evaluations will be performed at the 28-day Follow-Up Visit (28 ± 3 days post End of Dosing)/ OL Follow-Up Visit (28 ± 3 days post OL End of Dosing). If the subject begins an alternative treatment, then the Follow-Up visit will be performed as soon as possible. Every effort will be made to obtain and record survival information for each subject, who will be followed indefinitely for survival with, for example, monthly telephone calls.

If an observed toxicity thought to be at least possibly related to study drug has not resolved by the 28-Day Follow-Up Visit/OL Follow-Up Visit, the subject will continue to be followed until the event has resolved or stabilized.

11.3 Safety Data Review During the Trial

The Medical Monitor will review safety data on an ongoing basis throughout the trial.

- All serious adverse events (SAEs) must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the SAE (Section 11.5).
- Adverse events resulting in a subject's permanent discontinuation from the trial, regardless of seriousness or relationship to study drug, must be promptly reported to the Sponsor.
- The AE pages of each subject's CRF must be completed and submitted to the Sponsor or designee within 2 weeks of each visit.

Availability of these data will also enable the Sponsor to notify other participating trial centers and regulatory authorities of events occurring during the trial.

Safety decisions will be documented and communicated in writing to sites.

11.4 Adverse Event Definitions/Reporting Requirements

11.4.1 Adverse Event

An AE (also known as an "adverse experience") is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (CFR 312.32).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality.

All clinical AEs noted during the trial will be reported on the appropriate AE page of the CRF (paper or electronic).

11.4.2 Suspected Adverse Reaction

A suspected adverse reaction is a subset of all AEs for which there is a reasonable possibility (i.e., evidence to suggest a causal relationship between the drug and the AE) that the drug caused the event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction. Document suspected adverse reactions on the AE page of the CRF.

11.4.3 Adverse Reaction

An adverse reaction is a subset of all suspected adverse reactions, and is defined as any AE caused by a drug. Document any adverse reactions on the AE page of the CRF.

11.4.4 Unexpected Adverse Event/Unexpected Suspected Adverse Reaction

An unexpected AE (or unexpected suspected adverse reaction) is any AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed, if an IB is not required/available, is not consistent with the risk information described in the general investigational plan. This also refers to AEs or suspected adverse reactions mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug.

The Sponsor should be notified within 24 hours of the Investigator becoming aware of the event. Document unexpected AEs on the AE page of the CRF.

11.5 Serious Adverse Event Definitions/Reporting Requirements

11.5.1 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

1. Death. This includes any death that occurs while the subject is enrolled in the trial and/or within 30 days after the last dose of study drug. An autopsy will be requested, and if performed, results will be submitted to the Sponsor.
2. A life-threatening adverse event. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization. In the absence of an AE, hospitalization or prolongation of hospitalization should not be reported as an SAE in the following situations:
    - □ Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
    - □ Hospitalization or prolongation of hospitalization is part of routine procedure followed by trial center.
    - □ Hospitalization for survey visits or annual physicals.
    - □ For a hospitalization planned (and documented) before the start of the trial for a pre-existing condition which has not worsened.
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Sponsor should be notified within 24 hours of the Investigator becoming aware of the event. Document SAEs on the AE/SAE page(s) of the CRF.

11.5.1.1 Pregnancy

For safety reporting purposes, any pregnancy occurring during the trial will be considered an "important medical event" (Section 11.5.1). It is not known whether study drug can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. There have been no studies in pregnant women. Study drug should only be administered to women of childbearing potential when appropriate contraceptive measures have been taken and when pregnancy tests are negative. A negative serum β-hCG pregnancy test must be documented on the CRF prior to the first dose of study drug and periodically throughout the trial.

Studies have not been performed to determine whether CF102 affects reproductive function in males. Men and women with childbearing potential will be informed as to the unknown risks to a pregnancy and will be advised that they must both use effective contraception during the trial and for 3 months afterward. Effective birth control includes (a) IUD plus one barrier method, or (b) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides.

If a trial subject becomes pregnant while participating in the trial, the study drug will be discontinued immediately and the pregnancy will be reported to the Sponsor. The Investigator will then report follow-up information to the Sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of the fact that the subject has discontinued the trial. Once the newborn is determined to be healthy, as defined by and agreed upon by the Sponsor and Investigator, additional follow-up will no longer be required.

11.5.2 Serious and Unexpected Suspected Adverse Reaction

A serious and unexpected suspected adverse reaction (SUSAR) is any SAE related to study drug, the specificity or severity of which is not consistent with those noted in the current protocol and/or IB. This also refers to adverse events or suspected adverse reactions mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug.

The Sponsor should be notified within 24 hours of the Investigator becoming aware of the event. Document SUSARs on the AE/SAE page(s) of the CRF.

11.6 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event/Serious Adverse Event page(s) of the CRF. The Investigator will carefully evaluate the seriousness, severity, duration, and causality of AEs and document the following on the CRF:

- Severity. In most cases the NCI-CTCAE v4.0 criteria will preferably be used to grade severity; however, if an AE is not listed in the CTCAE, the following grading scale may be used: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life-Threatening (Grade 4), or Fatal (Grade 5).
- Duration of the event. The date of onset, duration of the event, method used to treat the AE, and the outcome of the AE should be noted.
- Relationship to study drug: Unrelated, Possibly Related, Probably Related, or Related.

11.7 Determining Relationship of Adverse Events to Study Drug

The following definitions adapted from Karch (1975) will be used to determine the relationship of AEs to study drug.

11.7.1 Unrelated

Category applies to adverse events which are clearly felt to be due to extraneous causes (disease, environment, etc.) that are unrelated to the study drug.

11.7.2 Possibly Related

The relationship to the study drug can be considered possible if (must have first 2):

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known response pattern to the suspected drug.

11.7.3 Probably Related

The relationship to the study drug can be considered probable if (must have first 3):

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases upon cessation of drug or reduction in dose.*
- It follows a known response pattern to the suspected drug.

**There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists, e.g., 1) tardive dyskinesia; 2) fixed drug eruptions.*

11.7.4 Related

The relationship to the study drug can be considered related if (must have first 3):

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases upon cessation of drug or reduction on dose and appears upon rechallenge.*
- It follows a known response pattern to the suspected drug.

  **There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists, e.g., 1) tardive dyskinesia; 2) fixed drug eruptions.*

11.8 Reporting Deaths and Other Serious Adverse Events

11.8.1 Events to Be Reported and Timeframe

Any death or other serious adverse event experienced by the subject during treatment or within 30 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug and is believed to be study drug-related, must be promptly reported to the Sponsor (within 24 hours of the Investigator becoming aware of the event) by telephone, telefax, or e-mail transmission.

11.8.2 Events Excluded from Expedited Reporting to FDA

The Sponsor does not plan to report several types of individual SAEs to FDA in an expedited manner because they are known consequences of the underlying disease and/or anticipated to occur in the trial population at some frequency, independent of drug exposure. These include:

- Progression of the underlying malignancy
- Death due to the underlying malignancy
- Elective hospitalization for transfusion or diagnostic procedure
- Previously scheduled elective surgery

These events will be reported to FDA/other regulatory authorities and all participating Investigators as an IND safety report only if there is evidence, based on an aggregate analysis, to suggest a causal relationship between the study drug and the adverse event.

11.8.3 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the Sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor is required to submit written documentation, in the form of an IND Safety Report, on the following:

- SUSARs.
- Unexpected fatal or life-threatening suspected adverse reactions.
- Findings from other studies that suggest a significant risk to humans exposed to drug.
- Findings from animal or in vitro testing that suggest a significant risk to humans exposed to drug.
- Increased rate of occurrence of serious suspected adverse reactions from what is reported in the Investigator Brochure or the protocol.

Written submission must be made by the Sponsor to the FDA/other regulatory authorities (and by the Investigator to the IRB/EC) as soon as possible, and in no event later than **15 calendar days** after the Sponsor determines that the information qualifies for reporting. The Sponsor shall also inform all Investigators.

In addition, the Sponsor is further required to report, by either telephone or facsimile transmission or in writing to the FDA/other regulatory authorities the occurrence of any unexpected fatal or life-threatening event associated with the use of the drug (SUSARs) no later than **7 calendar days** after notification of the event, followed by a written report **no later than 15 calendar days** after the initial report receipt date. The Sponsor shall also inform all Investigators.

The Sponsor will provide expedited reports of the following SUSARs to Investigators for reporting to their IRB/EC:

- SUSARs that have arisen in the clinical trial that was assessed by the IRB/EC.
- SUSARs that have arisen in other clinical trials of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the IRB/EC.

Investigators are required to promptly report to the IRB/EC all unanticipated problems involving risk to human subjects, including adverse events that should be considered unanticipated problems (21 CFR 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1)).

11.8.4 Initial Information Provided by the Investigator

The Investigator must transmit sufficient initial information to the Sponsor (or designee) should an SAE report meet the criteria for completion of an IND Safety Report. As much of the following information about the subject and the event will be requested:

- Subject identification code, gender, and age or date of birth
- Underlying diagnosis and extent of disease
- Lot number and expiration date of study drug (if available)
- Dose, route, frequency, and duration of study drug administered
- Date of study drug administration
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimens and indications)
- Pertinent laboratory data/diagnostic study (including dates)
- Pertinent medical history
- Study drug status (dose interrupted, discontinued)
- Did event abate after interruption of study drug administration (if applicable)?
- Did event recur after study drug was reintroduced (if applicable)?
- Severity of the AE
- Relationship of the AE to study treatment
- Outcome of the AE

11.8.5 Follow-up Information

Follow-up data concerning the SAE (e.g., diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor as they become available, preferably by telefax or e-mail, as soon as they become available, and until the event resolves or stabilizes.

11.9 SAE and SUSAR Review and Potential Impact on Trial Conduct

The Investigator will review each SAE report and evaluate further the relationship of the SAE to study drug and to the subject’s underlying disease.

Based on the Investigator's and Sponsor's assessment of causality of the adverse event and discussions with the Medical Monitor, a decision will be made by the Sponsor concerning the need for further action with respect to the future conduct of the trial. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical trial. If the discovery of a new AE related to study drug raises concern over the safety of its continued administration to subjects, the Sponsor will take immediate steps to notify FDA, other regulatory authorities, and all Investigators participating in clinical trials with the study drug.

Further action required may include any of the following:

- Alteration of the existing research program by modification of the protocol.
- Discontinuation or suspension of the trial.
- Alteration of the informed consent process by modification of the existing consent form and informing current trial participants of new findings.
- Modification of previously identified expected suspected adverse reaction lists to include adverse events newly identified as study drug-related.

12.0 STATISTICAL METHODS AND PLANNED ANALYSES

12.1 General Considerations

This is a multicenter, randomized, double-blind, placebo-controlled trial in subjects with advanced HCC and CPB cirrhosis whose disease has progressed while taking 1 prior systemic drug therapy for HCC. The trial will evaluate the efficacy and safety of CF102 as compared to placebo. Subjects will be randomly assigned in a 2:1 ratio to treatment with oral doses of either CF102 25 mg or matching placebo administered BID for consecutive, 28-day cycles. Subjects will be evaluated regularly for safety including changes in laboratory parameters, vital signs, physical examination, ECOG PS, and ECG assessments compared to baseline findings. Treatment will continue until the subject experiences unacceptable drug-related intolerability. Subjects will return for a follow-up visit 28 days after completion of the last dose of study drug. Subjects who discontinue will be followed indefinitely for survival status.

The primary efficacy endpoint will be OS, defined as the number of days from first dose to death due to any cause. Secondary endpoints to be evaluated are TTP, PFS, OR consisting of CR or PR for subjects who enter the trial with measurable disease by RECIST v1.1, and DC which includes both subjects with OR as well as those with SD. Survival status will be assessed continuously. Tumor status will be assessed at the Pre-Study Visit and every 8 weeks thereafter (i.e., at the end of even-numbered cycles) by CT scan or MRI according to RECIST v1.1 (Appendix A,

Eisenhauer, 2009 [as modified by Santoro 2013]). Liver Chemistry Tests, INR, and viral load will be presented as exploratory efficacy variables, as will WBC adenosine A_3 receptor expression. PK blood samples collected on Day 1 of Cycles 1 and 2 and trough samples collected on Days 8 and 15 of Cycle 1 will be used to generate a composite PK profile for subjects receiving CF102 treatment, and allow exploratory analysis of exposure-response for this trial.

12.2 Sample Size Determination

Approximately 78 subjects will be enrolled and randomized to either CF102 or placebo using a 2:1 randomization. The post-accrual treatment period was originally planned to continue until a total of 75 deaths have been recorded. Assuming a hazard ratio of 0.5, 75 events will provide 80% power for the logrank test at level 0.05 (two-sided). It is assumed that the 78 subjects will be enrolled in approximately 78 weeks and the trial will continue for a total of 104 weeks (SiZ: Logrank Test with Given Accrual Duration and Study Duration, Version 2.0, Cytel, Inc. 2011). The required number of deaths and the required number of subjects are reasonably stable with respect to the duration of accrual and length of the post-accrual follow-up period, being between 70 and 80, to have power of 80% for an assumed hazard rate of 0.5, especially for studies with a post-accrual follow-up period.

12.3 Trial Populations

12.3.1 Safety Population

The Safety Population will consist of all randomized subjects who received at least 1 dose of CF102 or placebo.

12.3.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will consist of all subjects in the Safety Population who have any post-Baseline efficacy data, including Liver Chemistry Tests and/or INR on Day 8 of Cycle 1, or death or discontinuation due to disease progression at any time.

12.3.3 Per Protocol (PP) Population

The Per Protocol (PP) Population will consist of all subjects in the ITT Population with no major protocol deviations, including major violations of inclusion and exclusion criteria and violation of RECIST requirements regarding the number of target lesions at Screening. Exclusion of subjects from the PP Population will be determined prior to unblinding. Tumor response will be analyzed for the PP Population.

12.3.4 Pharmacokinetic Population

The Pharmacokinetic Population will consist of all subjects with at least 1 on-treatment PK sample for analysis.

12.4 Data Analyses

12.4.1 Subject Accountability, Demographics, and Baseline Characteristics

Subject completion status, dose reductions, and terminations from the trial will be summarized for each of the treatment cycles and for the trial overall. Subjects with major protocol violations will be listed. Demographics will be summarized along with baseline characteristics such as medical history, PE, vital signs, and concomitant medications. Subjects in the Safety Population who are excluded from either the ITT Population or the PP Population will be identified.

12.4.2 Efficacy Data

All efficacy analyses will be performed for the ITT Population. Tumor response will be analyzed for the PP Population, with the analyses for the ITT Population being primary.

Time to event variables will be summarized using the number observed, number censored, median, and 25th and 75th percentiles from Kaplan-Meier curves. Data will be summarized using descriptive statistics (number of subjects (n), mean, median, standard deviation, minimum, and maximum) for continuous variables. Categorical variables will be summarized using frequencies and percentages.

Between-treatment comparisons with respect to OS, TTP, and PFS will be performed using logrank tests, with Cox's proportional hazards regression model used for supportive analyses to assess the impact of covariates. Tumor lesion measurements and changes from baseline will be summarized by cycle and treatment. Objective response rates and DC rates will be presented and between-treatment comparisons will be performed using the normal approximation to the binomial distribution by treatment for each even-numbered cycle. Between-treatment comparisons with respect to AFP will be performed using Analysis of Covariance (ANCOVA) with the value at baseline value used as a covariate and frequencies of subjects with AFP levels <20, 20-200, or >200 ng/mL will be presented by treatment for each cycle.

Liver Chemistry Tests, INR, and viral load will be summarized using descriptive statistics and clinically significant abnormalities will be listed. Additionally, between-treatment comparisons with respect to these laboratory parameters will be performed using ANCOVA with the baseline value used as a covariate.

The relationship between WBC A_3AR expression and clinical response will be assessed by providing the counts and percentages for Overall Response by Change from Baseline (CFB) in A_3AR expression categorized as less than or at least the median by treatment at each visit.

12.4.3 Safety Data

Safety observations and measurements including study drug exposure, adverse events, laboratory data, physical examination findings, vital signs, ECG, and ECOG PS will be summarized and presented in tables and listings.

Laboratory parameters including thyroid functions will be summarized using descriptive statistics and data listings of clinically significant abnormalities. Physical examinations, vital signs, ECOG PS, and ECG data will be summarized by changes from baseline values for each treatment using descriptive statistics. Liver Chemistry Tests, INR, and viral load will be presented as exploratory efficacy variables.

Adverse events will be coded using the MedDRA™ dictionary. The number and percentages of subjects experiencing AEs will be tabulated by system organ class and preferred term. Assessments of AEs will include characterization of the type, incidence, severity, seriousness, and relationship to treatment. Summary subject listings will be provided for subjects with dose interruptions and dose reductions, SAEs, AEs resulting in discontinuation from the trial, and deaths. Adverse events will be graded according to NCI-CTCAE criteria, version 4.0.

12.4.4 Pharmacokinetics Data

A PK and exploratory PK-PD analysis plan will be prepared and finalized prior to database lock.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

Before enrolling any subjects in this trial, a Sponsor representative and the Investigator will review the protocol, Investigator Brochure, CRFs and instructions for their completion, as well as the procedures for obtaining informed consent and for reporting AEs and SAEs. A qualified representative of the Sponsor monitors the conduct of the trial by visiting the site and by contacting the site by telephone and e-mail. During site visits, the trial monitor will assure accurate and reliable data collection by verifying the information recorded on the CRFs (paper or electronic) against source documents and medical records (i.e., source document verification).

All data will be entered into a trial database for analysis and reporting. Upon completion of data entry, the database will receive a quality assurance comprehensive validation check to ensure acceptable accuracy and completeness.

A comprehensive validation check will verify the data and discrepancy reports will be generated for resolution by the Investigator.

A Data Management Plan, which includes an Edit Specifications Document, will be prepared and updated as necessary through the course of the trial.

14.0 DOCUMENTATION AND INSPECTIONS

14.1 Trial Monitoring

The Sponsor has responsibility to governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the trial with respect to trial ethics, protocol adherence, and data integrity and validity.

This trial will be closely monitored by Sponsor representatives throughout its duration. Monitoring will be in the form of personal visits with the Investigator and their staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review progress of the trial, Investigator and subject adherence to protocol requirements, and determine if there are any problems associated with the conduct of the trial. The following may be assessed during site monitoring visits:

- Required regulatory documentation
- Signed informed consent documents
- Subject accrual and follow up
- Study drug inventory records
- Investigator and subject compliance to the trial protocol
- Concomitant therapy use
- Adverse event documentation
- Protocol deviation and violation documentation
- Data is accurate, complete, and verifiable when compared to source documents

The Investigator and site staff are expected to cooperate with monitors during such visits and provide them with all relevant trial documents.

14.2 Audits and Inspections

All documentation pertaining to this clinical trial may be subject to a quality assurance audit by personnel designated by Can-Fite BioPharma, Ltd., the FDA, or other regulatory agencies with similar responsibilities. Upon request, the auditor will have access for inspection, copying, review, and audit of all source documentation, CRFs, medical records, correspondence, and

informed consent documents pertaining to the subjects in the trial. The Investigator agrees to promptly take any reasonable steps that are regulated by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and CRFs. Other documentation subject to quality assurance audit includes the Investigator's IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the trial maintained in any supporting pharmacy facilities. Conditions of storage of study materials are also subject to inspection. Representatives of Can-Fite may observe conduct of any aspect of the clinical trial or its supporting activities both within and outside of the Investigator's institution.

15.0 ETHICAL AND LEGAL ISSUES

15.1 Ethical Conduct/Good Clinical Practice

This trial will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

15.2 Institutional Review Board (IRB) and Ethics Committee (EC)

This trial must be reviewed and approved by the IRB/EC representing each participating institution prior to enrolling subjects. Each IRB/EC must be appropriately constituted and meet all requirements as described in Part 56, Title 21 of the Code of Federal Regulations. The review must include both the protocol and the informed consent document for the trial. A copy of the Letter or Notice of Approval from the IRB/EC must be received by Can-Fite prior to shipment of drug supplies to the Investigator. The IRB/EC membership list must be submitted to Can-Fite with the written IRB/EC approval and updated lists, if applicable.

The Investigator must promptly report all changes in the research activity and all unanticipated problems involving risk to the subjects or others to their IRB/EC. The Investigator will provide progress reports as required by the IRB/EC. The Investigator is responsible for assuring continuing review and approval of the clinical trial on an annual basis and submitting documentation of renewal to the Sponsor. The Investigator will give notice to the IRB/EC when participation in the trial has been completed.

15.3 Written Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the subjects entered into the trial, including obtaining written informed consent prior to performing any trial-related procedures and informing each subject that the study drug is being used for investigational

purposes. A copy of the IRB/EC-approved consent form to be used during the trial must be submitted for Sponsor review prior to initiation of the trial.

Prior to entry into the trial, the purpose and nature of the trial and possible adverse effects must be explained to each subject. All questions about the trial should be answered to the subject's satisfaction or the subject's legal representative. It is the responsibility of the Investigator or designee to obtain written informed consent from each subject, thereby attesting that consent was freely given. An Investigator listed on the Form FDA 1572 will then co-sign the informed consent document. A copy of the signed and dated consent form will be given to the subject. Documentation of the informed consent process must be evident in the subject's clinical files, and the original executed consent form must be available for review by the trial monitor.

15.3.1 Update of Informed Consent

In the event that modifications in the experimental design, dosages, parameters, subject selection, etc., of the protocol are indicated or required, and in the event that such modifications substantially alter the trial design or increase the potential risk to subjects, the Investigator will prepare a revision to the existing informed consent document. Such a revision will be reviewed and approved by the appropriate IRB/EC, and documentation of this approval will be forwarded to the Sponsor for submission to the appropriate regulatory body.

In addition, all current as well as future trial participants will be informed of the trial design modification or increase in potential risk, and written informed consent will be obtained as outlined above (Section 15.3).

15.4 Records and CRFs

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the study drug. Data reported on the CRF (which may be either paper or electronic) that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

The completed CRF must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator or Sub-Investigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

15.5 Modification of the Trial Protocol

The trial is to be conducted as described in this protocol. Under no circumstances should the protocol be modified for any subject without the prior consent of the Sponsor and, if necessary, the IRB/EC responsible at the investigative site.

In the event that modifications in the experimental design, dosages, parameters, subject selection, etc., of the protocol are indicated or required, such changes will only be instituted following consultation between the Sponsor and Investigator and will be accomplished through formal amendment to this protocol and approval by the appropriate IRB/EC, except when necessary to immediately eliminate apparent hazards to subjects. Any amendment prepared by the Sponsor will be submitted to the FDA/other regulatory authorities and to the appropriate IRB/EC, and will be made part of the protocol.

15.6 Termination of the Trial

Should the Sponsor and/or the Investigator(s) discover conditions, during the course of the trial, that indicate that it should be discontinued, an appropriate procedure for termination will be instituted.

15.7 Retention of Records

United States federal law requires that the Investigator retain copies of all files pertaining to the trial (i.e., medical records, laboratory reports, drug inventory/disposition records, signed informed consent forms, CRFs, all correspondence, dates and reports of monitoring visits) for a period of 2 years following the date of marketing application approval of the drug for the indication investigated in the trial, and until there is no pending or contemplated marketing application, or for 2 years following the Sponsor's discontinuing worldwide clinical development of the study drug, as notified by the Sponsor, whichever is longer.

If the Investigator relocates, retires, or withdraws for any reason from the trial, the records may be transferred to an acceptable designee, such as another Investigator within the institution. Prior notice of such transfer will be provided in writing to the Sponsor. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

16.0 PUBLICATION POLICY

The Investigator and the institution understand and agree that participation in a multicenter trial involves a commitment to publish the trial data in a cooperative publication prior to publication or oral presentation of trial results on an individual basis. Upon completion or early termination of the trial and Sponsor evaluation of all data from the trial, the Investigator or institution may publish or disclose the results of the trial, provided a copy of the proposed publication is sent to the Sponsor for review at least 60 days prior to the date of submission for publication or of public disclosure. The Sponsor will complete its review within the 60 days and will have authority to require that the institution and/or the Investigator delete any reference to confidential information (other than the results) from the disclosure.

If during the review period, the Sponsor notifies the institution that it desires patent applications to be filed on any Sponsor's inventions disclosed or contained in the disclosures, the institution and the Investigator will defer publication or other disclosure for a period not to exceed an additional 60 days, sufficient to permit the Sponsor to file any desired patent applications.

No submission for publication or public disclosure by the institution or the Investigator will be made until results from all centers have been received and analyzed by the Sponsor, or the multi-center trial has been terminated or abandoned at all centers. If a publications committee, or a committee of Investigators, is formed for publication of results of the multicenter clinical trial, any separate publication by the institution or the Investigator will be delayed until the initial publication by the committee or a determination has been made by the committee not to make such publication.

17.0 INVESTIGATOR RESPONSIBILITIES

An Investigator conducting a clinical trial with an investigational agent is required to comply with regulations described in the US Code of Federal Regulations, Title 21 CFR Part 312, ICH Good Clinical Practice guidelines, as well as local laws and regulations.

The Investigator:

- Will personally conduct or supervise the conduct of the trial. The Investigator will ensure that all Sub-Investigators and others assisting in the trial are adequately informed about the protocol, the study drug, and their trial-related duties and functions.
- Will make changes to the conduct of the trial only after receiving the Sponsor's approval, except to protect the safety, rights, or welfare of subjects.

- Will not disclose any goods, materials, information (oral or written) and unpublished documentation provided by the Sponsor (including this protocol, the subject CRFs, and the IB) to any unauthorized person without the Sponsor's prior written consent.
- Will maintain a Subject Screening Log listing all subjects entered into the trial, those considered for trial entry and subsequently excluded, and the reason for exclusion.
- Will store study drug in a secure location, under the conditions indicated in Section 8.0, and will maintain a drug inventory form. Will destroy used supplies in an appropriate manner according to institutional policy and document such destruction. At the completion of the trial, the Investigator will return all unused trial materials to the Sponsor, unless otherwise authorized in writing.
- Will record trial data on CRFs (paper or electronic) provided by the contract research organization (CRO) for each subject who receives any amount of study drug, including those who withdraw before completion of the trial. Will ensure the accuracy, completeness, and timeliness of the data reported on the CRF and in required reports. Will review CRFs for completeness and accuracy prior to submission for data entry, and will sign and date the CRF.
- Will maintain adequate and accurate records for each subject dosed with study drug. Will include source documents such as hospital, clinic, or office charts; laboratory reports; trial worksheets; and signed informed consent documents in the Investigator's files along with subject trial records. Will include in the consent form a statement allowing the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data reported on the CRF.
- Will provide the Sponsor with the normal laboratory ranges for the laboratories to be used in the trial as well as the laboratory certification number. Will provide copies of any additional records pertinent to the trial (e.g., radiology reports, chart summaries, autopsy reports) to the Sponsor or regulatory authorities, if requested, with due precaution taken to ensure subject confidentiality.
- Will maintain subject confidentiality at all times during the trial by using coded identifiers when referring to a particular subject (including in any publications).
- Will inform subjects that the study drug is being used for investigational purposes.
- Will report to the Sponsor any AEs that occur during the trial in accordance with ICH, CFR 21 Part 312.64 and local laws.

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APPENDIX A: RECIST RESPONSE CRITERIA (V1.1)

NOTE: RECIST v 1.1 as modified by Santoro [2013]:

Up to **5 target lesions in the liver and 2 target lesions in other organs** are measured.

RATIONALE: Because HCC often presents as a multifocal disease in the liver and the standard RECIST limitation to a maximum of 2 target lesions in the liver was considered too restrictive for a study with time to progression as the primary endpoint.

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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*

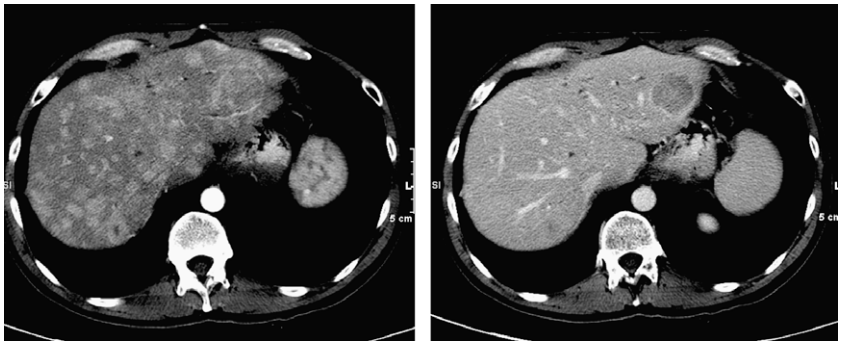

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration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

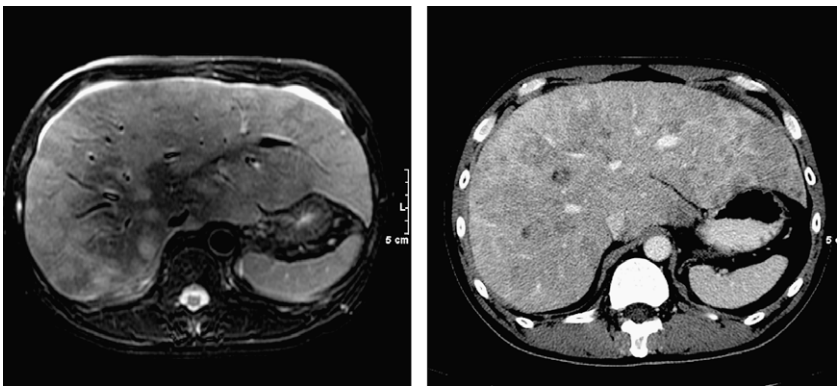

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

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-

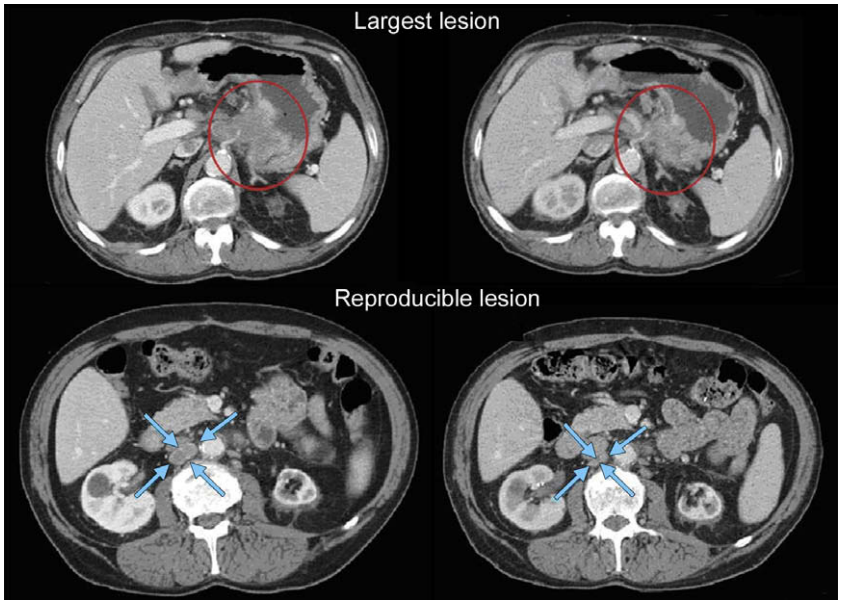

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention 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).

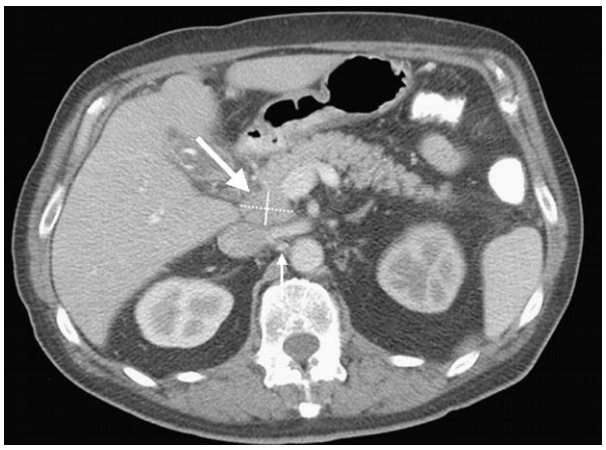

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

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.

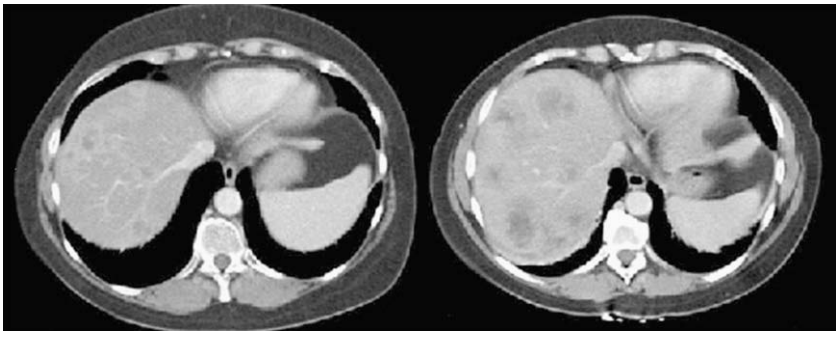

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

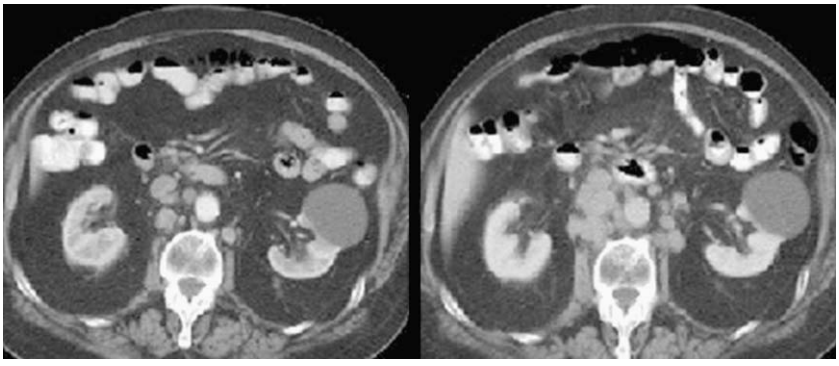

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

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 B: PERFORMANCE STATUS AND CARDIAC FUNCTION SCALES

Level	ECOG Performance Status*
0	Normal activity
1	Symptoms but ambulatory
2	In bed < 50% of time
3	In bed > 50 % of time
4	100 % bedridden

* Oken, 1982

Cardiac Functional Classification	
NYHA Class	**Symptoms**
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

The Criteria Committee of the NYHA, 1994

APPENDIX C: CHILD-PUGH CLASSIFICATION OF SEVERITY OF LIVER DISEASE

Child-Pugh classification of severity of liver disease according to the degree of ascites, plasma concentrations of bilirubin and albumin, prothrombin time, and the degree of encephalopathy.

Class A (well-compensated disease): total score of 5-6.

Class B (significant functional compromise): total score of 7-9.

Class C (decompensated disease): total score of 10-15.

These classes correlate with 1- and 2-year patient survival.

Parameter	Points Assigned		
	1	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	<2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time * Seconds over control * INR	 1-3 <1.7	 4-6 1.7-2.3	 >6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child, 1964; Pugh, 1973

APPENDIX D: CLINICAL LABORATORY TESTS

Except for the "OTHER" category, the following laboratory tests will be performed at Pre-Study Visit; Days 1 (i.e., the Baseline Visit if not performed ≤ 3 days prior), 8, and 15 of Cycle 1; Days 1 and 15 of subsequent cycles; EOS; and Follow-Up.

HEMATOLOGY TESTS	CHEMISTRY TESTS
• hematocrit • hemoglobin • platelet count • red blood cell count • white blood cell count and differential (absolute and percentage); neutrophils, lymphocytes, monocytes, eosinophils, basophils, and reticulocyte count	• alanine aminotransferase (ALT) • albumin • alkaline phosphatase • aspartate aminotransferase (AST) • bicarbonate • bilirubin (direct and total) • blood urea nitrogen (BUN) • calcium • chloride • creatinine • glucose • lactate dehydrogenase (LDH) • phosphorus • potassium • sodium • total protein • uric acid
URINALYSIS	
• glucose • ketones • occult blood • pH • protein • specific gravity • and, when indicated by dipstick abnormality, microscopic sediment evaluation	
COAGULATION PARAMETERS	**OTHER**
• International Normalized Ratio (INR) • partial thromboplastin time (PTT) • prothrombin time (PT)	• alpha-fetoprotein (AFP): at baseline and Day 1 of each subsequent cycle • thyroid functions (T3, T4, TSH) at Pre-Study, Baseline, Day 1 of subsequent cycles, EOS, and Follow-up • serum pregnancy test: females of childbearing potential • hepatitis B and C viral load measurement every odd numbered cycle (where applicable)

APPENDIX E: ALGORITHM FOR THE DIAGNOSIS OF HCC IN PATIENTS WITH UNDERLYING CIRRHOSIS[1]

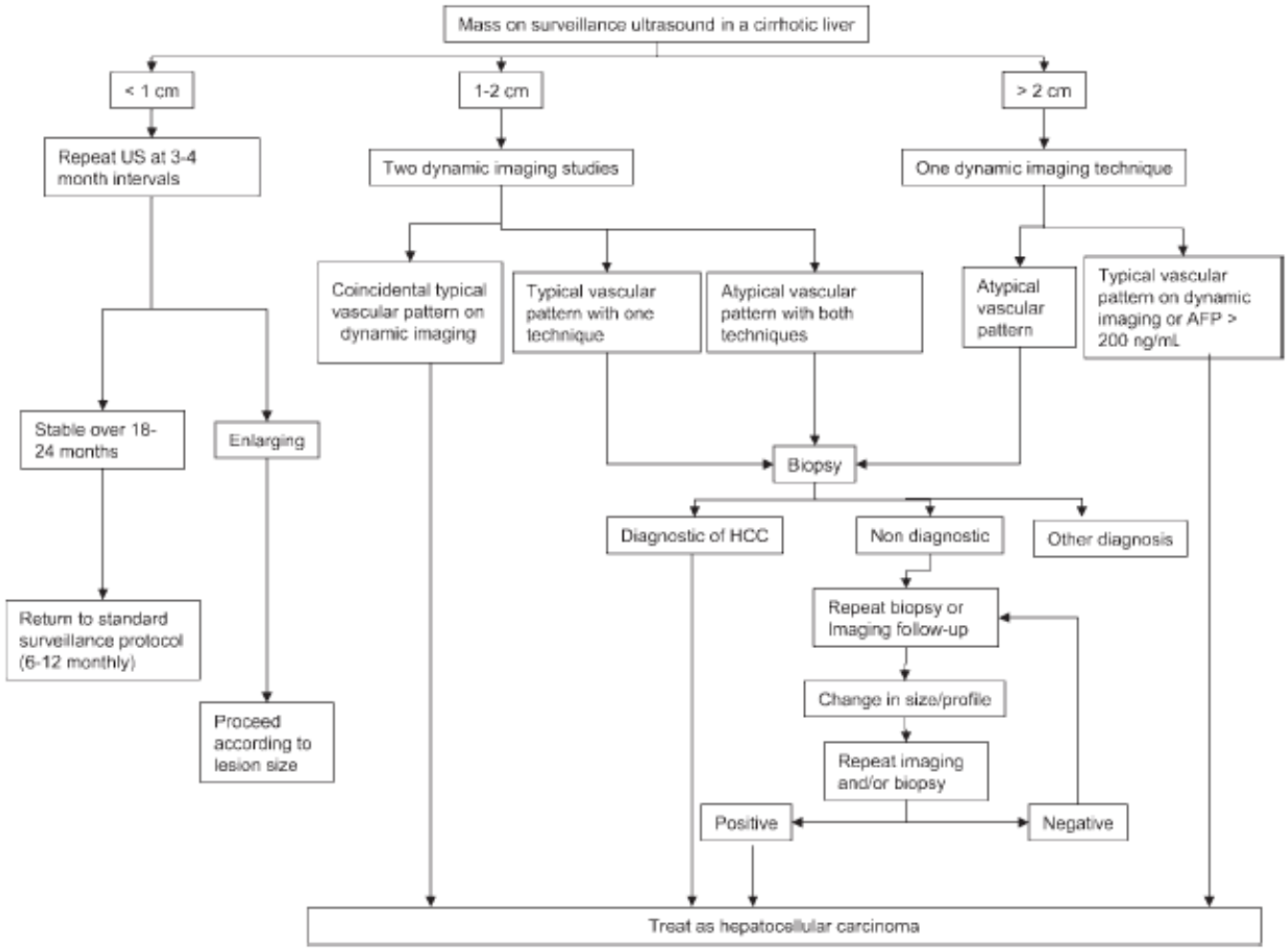

Fig. 1. A suggested algorithm for investigation of a nodule found on ultrasound during screening or surveillance. Note that nodules smaller than 1 cm initially which enlarge over time should be investigated using one of the other two algorithms shown depending on the size of the nodule. The typical vascular pattern referred to means that the lesion is hypervascular in the arterial phase, and washes out in the portal/venous phase. All other patterns are considered atypical.

[1] American Association for the Study of Liver Diseases Practice Guideline (Bruix, 2005)