Document Title:
Clinical Study Protocol
Study Protocol Number: KX-ORAX-007
Title: A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients

NCT Number: 03165955

Document Date: 14 August 2018

REVISION HISTORY

Revisions to KX-ORAX-007 Amendment 05 v6.0_09 Jul 2018

Current Version and Date: Amendment 06 v7.0_14 Aug 2018

Change	Rationale	Affected Protocol Sections
Add a Central Radiology Review Committee to review all radiology images for activity assessment when the patients completed Final Visit.	Further quality assurance of efficacy.	• Protocol summary - Assessments/Activity • Section 8.1.2.2
Add Central Radiology Review for response rate to statistical analyses.	To align with collection of Central Radiology Review result for tumor response.	• Protocol Summary - Activity Analyses • Section 11.5

Revisions to KX-ORAX-007 Amendment 04 v5.0_10 Jul 2017

Current Version and Date: Amendment 05 v6.0_09 Jul 2018

Change	Rationale	Affected Protocol Sections
Added a provision for patients to undergo an optional follow-up contact every 2 months after the study to assess progression-free survival, overall survival, and new anti-cancer therapy treatment.	To obtain long-term progression-free survival, overall survival and new anti-cancer therapy data.	• List of Abbreviations • Protocol Summary - Secondary Objectives - Secondary Endpoints - Study Design - Assessments/Activity • Section 3.2 • Section 3.3.2 • Section 4 • Section 5.3.4 • Section 7.3 • Section 8.1.2.2 • Table 6/footnote b
Added progression-free survival and overall survival to statistical analyses.	To align with collection of long-term progression-free survival and overall survival data.	• Protocol Summary - Activity Analyses • Section 11.5
Revised Clinical Pharmacology and Biostatistics signatories for the Sponsor.	Administrative.	• Sponsor Signature Page

Revisions to KX-ORAX-007 Amendment 03 v4.0_08 May 2017
Current Version and Date: Amendment 04 v5.0_10 Jul 2017

Change	Rationale	Affected Protocol Sections
Revised inclusion for hemoglobin from **≥10 g/dL** to **≥9 g/dL**	As many patients with cancer may have mild anemia, the hemoglobin was lowered to 9 g/dL to facilitate patient enrollment without compromising patient safety.	• Protocol Summary/ Inclusion Criteria #5 • Section 5.1/ Inclusion Criteria #5
Added to inclusion criteria GGT values (<10 x ULN at Screening) to demonstrate adequate liver function.	Preliminary data suggest that subjects who receive Oraxol with screening GGT ≥10 x ULN may be at increased risk for early onset of severe neutropenia or serious adverse events.	• Protocol Summary/ Inclusion Criteria #6 • Section 5.1/ Inclusion Criteria #6

Revisions to KX-ORAX-007 Amendment 02 v3.0_08 Jul 2016

Current Version and Date: Amendment 03 v4.0_08 May 2017

Change	Rationale	Affected Protocol Sections
Changed the frequency of Hematology testing after Week 4 from bi-weekly to weekly; adjusted volumes of blood samples accordingly.	To assure that Hematology parameters are assessed more frequently due to the concern for neutropenia.	• Section 9.2.3 • Table 6, footnote m • Table 6
After Week 1, collection of samples for laboratory assessments is changed from within 72 hours prior to dosing to within 48 hours before dosing. Baseline laboratory tests and urine pregnancy testing will be done within 96 hours before the first dose of drug to allow time for results to become available prior to Week 1 Day 1 dosing.	As a consequence of more frequent Hematology testing, to assure that the most current laboratory results are considered for dosing decisions each week.	• Protocol Summary/ Inclusion Criteria #14 • Section 5.1, #14 • Section 9.2.3 • Table 5, footnote b • Table 6, footnotes f, l, m
Changed the visit window for clinic visits after Week 4 from ±5 days to ±2 days.		• Table 6
Deleted "If significant bone marrow suppression occurs requiring oral paclitaxel dose modification or withholding treatment, weekly hematology tests will be performed until drug is restarted and for an additional 4 weeks."	No longer needed as the frequency of hematology testing after Week 4 has been changed to weekly.	• Section 9.2.3 • Table 6, footnote m
For subjects receiving Oraxol, the definition of an unacceptable toxicity was changed from a Grade 4 ANC of $<0.5x10^{9}$/L to an ANC of $\leq 0.8x10^{9}$/L, which is not Grade 4. Therefore, any subject receiving Oraxol with an ANC $\leq 0.8x10^{9}$/L will have their study treatment delayed until the toxicity improves to Grade 1 or baseline, and then have their dose reduced.	With weekly dosing of Oraxol, the time course of neutropenia development may be longer than the interdose interval, thus a higher threshold for dose unacceptable toxicity is proposed.	• Section 6.3.1

Revisions to KX-ORAX-007 Amendment 02 v3.0_08 Jul 2016

Current Version and Date: Amendment 03 v4.0_08 May 2017

Change	Rationale	Affected Protocol Sections
Inclusion criterion changed to restrict the allowed total bilirubin level at Screening to ≤1.5 mg/dL in all cases. Previously, subjects who had liver metastasis were allowed a total bilirubin of ≤2.0 mg/dL.	IV paclitaxel usage may have an initial dose reduction based on initial bilirubin concentration. Oraxol is bioequivalent or similar to IV paclitaxel.	• Protocol Summary/ Inclusion Criteria #6 • Inclusion Criteria #6 • Section 5.1, #6
Previously, subjects taking Oraxol were not allowed any premedication before the first dose. Now, for subjects receiving Oraxol, anti-emetics should be given on each day of Oraxol administration, with the first dose of anti-emetic given at the same time as HM30181. Specified that steroids or H-1 receptor antagonists are not allowed as anti-emetics for subjects taking Oraxol.	To improve subject comfort. Clarification.	• Section 2.3.2 • Section 6.2.3.2 • Section 6.6
Duration of fasting before and after Oraxol dosing is changed from at least 8 hours before and 4 hours after dosing to at least 6 hours before and 2 hours after dosing.	To facilitate compliance with fasting requirements.	• Protocol Summary/ Inclusion Criteria #10 • Protocol Summary/ Study Treatments • Section 5.1, #10 • Section 6.2.3.1
Designated clinic visits on the Schedule of Procedures and Assessments.	Clarification.	• Table 6
Added a ±1 day visit window to the Week 4 Day 1 clinic visit.	Clarification.	• Table 6

Revisions to KX-ORAX-007 Amendment 01 v2.0_03 Apr 2016
Current Version and Date: Amendment 02 v3.0_08 Jul 2016

Change	Rationale	Affected Protocol Sections
Wording describing how long subjects may be treated is currently as follows: Subjects **may** be treated until disease progression, or unacceptable toxicity requiring more than 2 dose reductions, or a maximum of 16 weeks. Change from: Subjects **will** be treated until disease progression, or **recurrent** unacceptable toxicity requiring more than 2 dose reductions, or a maximum of 16 weeks. Reasons for withdrawal from the study include unacceptable toxicity; NOT as previously stated: recurrent unacceptable toxicity requiring more than 2 dose reductions.	Clarification of terms for continuation of treatment and terms for withdrawal from study.	• Protocol Summary/Treatment • Section 4 • Section 5.3.3
Added Week 3 to frequency of vital signs measurements.	Correction.	• Section 9.2.6
Revised text to reflect subjects who do not complete Week 4 PK assessments will be replaced; qualified language about replacement of subjects who discontinue from the study.	In response to TFDA feedback.	• Protocol Summary/Statistical Methods • Section 5.3.4 • Section 11
Description of prohibited P-gp inhibitors or inducers changed to “strong” from “known”.	Clarification.	• Protocol Summary/Exclusion Criteria • Section 5.2 • Section 6.6
Restructuring of unacceptable toxicity and dose reduction sections so that it is clear when subjects will be discontinued because of unacceptable toxicity including when dose reduction will occur.	Clarification.	• Protocol Summary/Study Treatments • Section 6.3.1

Revisions to KX-ORAX-007 Amendment 01 v2.0_03 Apr 2016

Current Version and Date: Amendment 02 v3.0_08 Jul 2016

Change	Rationale	Affected Protocol Sections
With the potential of oral paclitaxel dose reduction in this study due to unacceptable toxicity, it is noted that the dose of HM30181 will remain the same.	Clarification.	• Protocol Summary/Dose Reductions • Section 6.3.1
Stated that a Pharmacy Manual will be provided to the sites with dosing and dispensing instructions.	Clarification.	• Section 6.2.3
Removal of "IV or sublingual" from the description of ondansetron as an example of an anti-emetic that can be used to manage nausea or vomiting following the first dose or subsequent doses of Oraxol.	Clarification.	• Section 6.2.3.2
Removed timeframe/window associated with Oraxol dosing.	Not needed; clear instruction is already provided.	• Section 6.5
Added text that subjects will be given information cards on which they will record their dosing.	Clarification.	• Section 6.5 • Table 6, footnote k
Results of any assessments performed at unscheduled visits will be entered into the clinical database.	Clarification.	• Section 7.5 • Table 6, footnote c
Results of unscheduled CT and/or MRI scans will be entered into the clinical database.	Clarification.	• Section 8.1.2.1 • Table 6, footnote n
It is noted that CT and/or MRI scans of the chest, abdomen, and pelvis should be conducted at Baseline and repeated at all assessment times to determine the possible change in tumor size at the respective sites.	Additional instructions for CT and/or MRI are provided for clarity.	• Section 8.1.2.1
Deleted reference to imaging acquisition guidelines.	Not needed; scans will be handled according to each site's process.	• Section 8.1.2.1
Deleted reference to a laboratory manual for laboratory parameters.	Correction; the laboratory manual is for PK samples only.	• Section 8.2.1

Revisions to KX-ORAX-007 Amendment 01 v2.0_03 Apr 2016
Current Version and Date: Amendment 02 v3.0_08 Jul 2016

Change	Rationale	Affected Protocol Sections
Specified that AEs will be assessed and recorded at all clinic visits, and that subjects will be instructed to call study personnel if they experience AEs in between clinic visits.	Clarification.	• Section 9.2.1 • Table 6, footnote p
The hematology assessments are weekly assessments for the first 4 weeks of treatment (change is the addition of an assessment at Week 3 to the previously designated assessments at Weeks 1, 2, & 4). After Week 4, hematology testing will be performed every other week. If significant bone marrow suppression occurs requiring oral paclitaxel dose modification or withholding treatment, weekly hematology tests will be performed until drug is restarted and for an additional 4 weeks. Any additional hematology tests may be done at the discretion of the Investigator. All hematology data obtained on subjects during this study will be included in the clinical database.	Additional hematology assessments according to standard safety practices including additional tests if there is bone marrow suppression after Oraxol treatment. Clarification of procedures for additional hematology testing and for the data obtained.	• Section 9.2.3 • Table 6, footnote m
Urinalysis will be conducted at Screening/Baseline and within 72 hours prior to Day 1 dosing at Weeks 1, 4, 8, 12, and 16 instead of at Day 1 of every week up to Week 16 as previously stated. Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator, not for all urinalyses as previously stated.	Change in frequency of urinalysis testing necessary for safety analysis. Correction of stated procedures.	• Section 9.2.3 • Table 5, footnote c • Table 6, footnote l
Notation that depending on laboratory certain hematological parameters may not be collected.	Clarification.	• Table 5, footnote a

Revisions to KX-ORAX-007 Amendment 01 v2.0_03 Apr 2016

Current Version and Date: Amendment 02 v3.0_08 Jul 2016

Change	Rationale	Affected Protocol Sections
Revised description of timing of ECGs.	Clarification.	• Section 9.2.5
Specified that concomitant medications will be assessed and recorded at all clinic visits, and that subjects will be instructed to call study personnel with any AEs they experience in between clinic visits, as well as any associated concomitant medications.	Clarification.	• Section 9.2.8 • Table 6, footnote e
Standard safety language was added for reporting of a pregnancy and subject withdrawal due to pregnancy.	Clarification.	• Section 9.3.3.3
The safety follow-up procedures have been clarified to the following: Subjects with onset of study drug-related AEs will be followed until resolution, resolved with sequelae, or under medical care. Previously the following was stated: Treatment -emergent AEs will be followed through the last subject contact.	Clarification.	• Section 9.4
On the schedule, revised footnote for adverse events to reflect that AEs will be collected from the time the informed consent is signed.	Clarification	• Table 6, footnote p
The Table of Procedures and Assessments was changed to reflect the above changes. Clinic visit days are noted on the table.	Clarification.	• Table 6
Minor formatting, section organization, and editorial changes were made.	Changed for consistency.	• Throughout document

Revisions to KX-ORAX-007 protocol v1.0_20 Jan 2016 (original protocol)
Current Version and Date: v2.0_03 Apr 2016

Change	Rationale	Affected Protocol Sections
Revised PK sampling timepoints.	The 1-hr PK sampling timepoint was added to cover the Oraxol T_{max} 1~1.5 hr observed in a previous study. The 3-hr PK sampling timepoint was added to support PK modeling.	• Protocol Summary/Pharmacokinetic • Section 8.2 • Table 2 • Table 3 • Table 4
Revised text describing the study period.	The study period duration of 8 months is unchanged from original protocol. The planned clinical study start and end dates were removed because the protocol is pending TFDA approval.	• Protocol Summary/Study Period • Section 4
Reorganized information in protocol summary.	Clarification.	• Protocol Summary
Revised text to say all 24 subjects will undergo PK sampling in Week 4, instead of the first 12 subjects.	To provide additional PK information regarding Oraxol chronic dosing.	• Protocol Summary/Pharmacokinetic • Section 4 • Section 7.2 • Section 8.2 • Table 2 • Table 3 • Table 4 • Table 6
Revised text to say that in addition to those who achieve stable disease or partial response, subjects who achieve complete response may also continue treatment in an extension study.	Complete responders should be offered the option of continued Oraxol treatment for the same reasons it is offered to those with stable disease or partial response.	• Protocol Summary/Study Design • Section 4
Added a co-Sponsor for the study.	PharmaEssentia is the local Sponsor for KX-ORAX-007 in Taiwan.	• Title Page • Protocol Summary (added Sponsors) • Section 1
Revised description of study treatments.	Clarification.	• Protocol Summary/Study Treatments

Revisions to KX-ORAX-007 protocol v1.0_20 Jan 2016 (original protocol)
Current Version and Date: v2.0_03 Apr 2016

Change	Rationale	Affected Protocol Sections
Revised background information.	Clarification.	• Protocol Summary/Background • Section 2.1
Added information regarding dose reductions.	Clarification (previously was in Section 6.3.1, but not in the Protocol Summary).	• Protocol Summary/Study Treatments
Stipulated that subjects who do not have Week 4 PK assessments will not be replaced; specified the number of evaluable subjects for analysis.	Clarification.	• Protocol Summary/Statistical Methods • Section 11
Added a 10-minute window to PK sampling times; provided instructions regarding collection times for all PK samples.	Clarification.	• Section 8.2 • Table 3 • Table 4
Revised text pertaining to gastric cancer diagnosis in oncology history.	Correction (study is in breast cancer patients).	• Section 8.1.1.3
Indicated pregnancy testing on Week 1, Day 1 of the schedule of assessments.	Correction.	• Table 6

Clinical Study Protocol

Study Protocol Title:	A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients
Study Protocol Number:	KX-ORAX-007
UTN:	U1111-1176-4228
Investigational Product Name:	Oraxol (Oral paclitaxel + HM30181AK-US)
Sponsor:	Kinex Pharmaceuticals, Inc. 20 Commerce Drive Cranford, New Jersey 07016 USA Tel: (908) 272-0628 PharmaEssentia Inc. 13F, No. 3, YuanQu Street NanKang District, Taipei 115, Taiwan (Nangang Software Park) Tel: +886-2-2655-7688
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Approval Date:	v1.0 20 January 2016 FINAL (original protocol) v2.0 03 April 2016 FINAL (Amendment 01) v3.0 08 July 2016 FINAL (Amendment 02) v4.0 08 May 2017 FINAL (Amendment 03) v5.0 10 Jul 2017 FINAL (Amendment 04) v6.0 09 Jul 2018 FINAL (Amendment 05) v7.0 14 Aug 2018 FINAL (Amendment 06)

STATEMENT OF COMPLIANCE

This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

SIGNATURE PAGES

SPONSOR

Study Protocol Number: KX-ORAX-007

Study Protocol Title: A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients

Investigational Product Name: Oraxol (Oral paclitaxel + HM30181AK-US)

UTN Number: U1111-1176-4228

SIGNATURES

David Cutler, MD, FRCP(C) Study Director Kinex Pharmaceuticals, Inc.	14 AUG 2018 Date
Alissa Verone-Boyle, PhD Scientist, Clinical Pharmacology Kinex Pharmaceuticals, Inc.	Date
Cynthia Chang, MS Biostatistician Kinex Pharmaceuticals, Inc.	Date

SIGNATURE PAGES

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David Cutler, MD, FRCP(C)
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Date

Alissa Verone-Boyle, PhD
Scientist, Clinical Pharmacology
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14 AUG 2018
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Cynthia Chang, MS
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SIGNATURE PAGES

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14 AUG 2018
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INVESTIGATOR

Study Protocol Number:	KX-ORAX-007
Study Protocol Title:	A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients
Investigational Product Name:	Oraxol (Oral paclitaxel + HM30181AK-US)
UTN Number:	U1111-1176-4228

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>		
Investigator	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Terms
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the curve extrapolated to infinity
BSA	body surface area
CI	confidence interval
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRA	contract research associate
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
ICF	informed consent form
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
IP	investigational product

Abbreviation	Terms
IRB	Institutional Review Board
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
NCI	National Cancer Institute
OS	overall survival
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TNM	Tumor, Node, Metastases (Classification of Malignant Tumours)
ULN	upper limit of normal

PROTOCOL SUMMARY

Sponsors

Kinex Pharmaceuticals, Inc., USA and PharmaEssentia, Inc., Taiwan

Study Number

KX-ORAX-007

Name of Active Ingredient

Paclitaxel:

5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13- ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine

HM30181 methanesulfonate monohydrate:

N-(2-(2-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-2H-tetrazol-5-yl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide Methanesulfonate monohydrate

Title of Study

A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients

Phase of Development

This is a pharmacokinetic (PK) study.

Study Sites

Approximately 6 sites in Taiwan

Background

Intravenous (IV) paclitaxel is an approved treatment for breast cancer. Paclitaxel 80 mg/m^2 weekly is the most commonly used regimen for treatment of breast cancer patients. Effective blood concentrations of paclitaxel and duration (AUC) can predict clinical outcomes.

Oraxol is an oral dosage form of the chemotherapeutic agent paclitaxel administered with a novel P-glycoprotein (P-gp) inhibitor, HM30181, to enhance the oral absorption of paclitaxel in cancer patients.

Phase1 and 2 clinical studies with HM30181A and oral paclitaxel (Oraxol) in 111 oncology patients showed that Oraxol was well tolerated. The MTD was not reached, and no anaphylactic reactions were observed. Premedication was not required for Oraxol treatment. The overall safety profile of oral paclitaxel may be better than IV paclitaxel. A Phase 2 clinical trial showed encouraging survival efficacy data in the treatment of gastric cancer.

A clinical PK study showed that HM30181 15 mg plus oral paclitaxel 205 mg/m^2 administered for 3 consecutive days per week can produce a paclitaxel exposure (AUC) similar to that of 80 mg/m^2 IV paclitaxel per week in cancer patients.

Objectives

Primary Objective:

- To investigate the PK (AUC) of orally administered paclitaxel (as Oraxol) in breast cancer patients

Secondary Objectives:

- To determine the safety and activity (response rate, progression-free survival [PFS], overall survival [OS]) of Oraxol in breast cancer patients

Endpoints:

Primary Endpoint:

- Evaluation of PK parameters for oral paclitaxel

Secondary Endpoints:

- Safety
  - Incidence of all AEs, including SAEs
  - Laboratory values
  - Other safety assessments including vital signs, physical exams, electrocardiograms (ECGs)
- Activity
  - Tumor response rate, which is defined as the number of subjects with complete response (CR) or partial response (PR) at any post-baseline assessments expressed as the proportion of the total number of subjects in the Full Analysis Set
  - PFS and OS

Study Design

This is a multicenter, open-label, single-arm PK study in approximately 24 breast cancer patients for whom paclitaxel treatment is indicated. Subjects must have measurable disease as per RECIST v1.1 criteria. The study contains 3 periods: the Screening / Baseline Period, the 16-week Treatment Period, and the 1-week Follow-up Period. A Final Visit will occur within 7 days of the last dose of study treatment. After completion of Final Visit assessments, subjects will be contacted every 2 months to follow progression-free survival and overall survival. New anti-cancer therapy will be collected.

If subjects achieve stable disease (SD), partial response (PR), or complete response (CR) at Week 16, they may continue Oraxol treatment in a separate extension study. The schedule of assessments is presented in Appendix A.

Treatment

Subjects will receive Oraxol 205 mg/m^2 daily x 3 days weekly for up to 16 weeks. Subjects may be treated until disease progression, or unacceptable toxicity requiring more than 2 dose reductions, or a maximum of 16 weeks.

Study Period

Approximately 8 months (first person first visit to last person last visit [FPFV-LPLV]); approximately 21 weeks for each subject (4 weeks Screening/Baseline; 16 weeks for treatment; 1 week follow-up).

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Signed written informed consent
2. Women ≥18 years of age on day of consent
3. Breast cancer in patients for whom treatment with IV paclitaxel at 80 mg/m^2 as monotherapy has been recommended by their oncologist

4. Measurable disease as per RECIST v1.1 criteria
5. Adequate hematological status as demonstrated by not requiring transfusion support or granulocyte-colony stimulating factor (G-CSF) to maintain:
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelet count ≥100 x 10^9/L
    - Hemoglobin (Hgb) ≥9 g/dL
6. Adequate liver function as demonstrated by:
    - Total bilirubin of ≤1.5 mg/dL
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if liver metastasis is present
    - Alkaline phosphatase (ALP) ≤3 x ULN or ≤5 x ULN if bone metastasis is present
    - Gamma glutamyl transferase (GGT) <10 x ULN
7. Adequate renal function as demonstrated by serum creatinine ≤1.5 x ULN
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Life expectancy of at least 3 months
10. Willing to fast for 6 hours before and 2 hours after Oraxol administration on all treatment days
11. Willing to abstain from alcohol consumption for 3 days before the first dose of study drug through the completion of the second inpatient PK sampling period
12. Willing to refrain from caffeine consumption for 12 hours before each inpatient dosing period (Weeks 1 and 4) through the completion of protocol-specified PK sampling for that week
13. Subjects must be postmenopausal (>12 months without menses) or surgically sterile (ie, by hysterectomy and/or bilateral oophorectomy) or must be using effective contraception (ie, oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for 30 days after their last dose of assigned study treatment.
14. Subjects who are of childbearing potential must have a negative serum pregnancy test at Screening and within 96 hours before Week 1 dosing.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Have not recovered to ≤ Grade 1 toxicity from previous anticancer treatments or previous investigational products (IPs)
2. If previously treated with a taxane (paclitaxel or docetaxel) as part of anthracycline-based adjuvant chemotherapy or for metastatic disease, the subject relapsed less than 1 year following treatment
3. Subjects unable to swallow study medication in its intact form or have clinically significant malabsorption syndrome
4. Only site of metastatic disease is unmeasurable according to RECIST v1.1 criteria
5. Known CNS metastasis, including leptomeningeal involvement
6. Received IPs within 14 days or 5 half-lives of the first study dosing day, whichever is longer
7. Are currently receiving other medications intended for the treatment of their malignancy
8. Women who are pregnant or breastfeeding
9. Taking any of the following prohibited medications:
    - Strong inhibitors (eg, ketoconazole) or inducers (eg, rifampin or St. John's Wort) of CYP3A4 (within 2 weeks prior to the start of dosing in the study)
    - Strong inhibitors (eg, gemfibrozil) or inducers (eg, rifampin) of CYP2C8 (within 2 weeks prior to the start of dosing in the study)
    - Strong P-gp inhibitors or inducers. Subjects who are taking such medications but who are otherwise eligible may be enrolled if they discontinue the medication ≥1 week before dosing and remain off that medication through the end of study treatment.
    - An oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to start of dosing in the study
10. Use of warfarin. Subjects receiving warfarin who are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the Investigator, may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.
11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, myocardial infarction within the last 6 months, unstable angina pectoris, cardiac arrhythmia, chronic pulmonary disease requiring oxygen, known bleeding disorders, or any concomitant illness or social situation that would limit compliance with study requirements
12. Known allergic reaction or intolerance to study medication components
13. Known allergic reaction or intolerance to contrast media
14. Subjects who, in the Investigator's opinion, are not suitable for participation in this study

Study Treatments

Test drug: Oraxol (oral HM30181AK-US + oral paclitaxel)

- HM30181 methanesulfonate monohydrate – supplied as 15-mg HM30181AK-US tablets
- Paclitaxel – supplied as 30-mg capsules

Treatment:

- HM30181 15 mg tablet administered orally 1 hour before oral paclitaxel daily x 3 days weekly x 16 weeks
- Oral paclitaxel 205 mg/m^2 daily x 3 days weekly x 16 weeks
- Subjects should fast for 6 hours before and 2 hours after Oraxol administration on all treatment days

Management of Unacceptable Toxicity:

Subjects experiencing unacceptable toxicity who have completed the first week of Oraxol treatment will have their Oraxol treatment delayed until the toxicity improves.

Subjects whose unacceptable toxicity improves to CTCAE Grade 1 or baseline within 2 weeks of their last dose of Oraxol may continue treatment with dose reduction as described below:

Dose Reduction after First Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 165 mg/m^2 per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Dose Reduction after Second Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 130 mg/m^2 per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Once the dose has been reduced, it cannot be increased at a later date.

Discontinuation due to Unacceptability Toxicity:

Oraxol treatment will be permanently discontinued for subjects who are unable to complete the first week of dosing due to unacceptable toxicity.

After 2 dose reductions, subjects whose unacceptable toxicity does not improve to Grade 1 or baseline within 2 weeks of their last dose of Oraxol will have their Oraxol treatment permanently discontinued.

Subjects who continue to experience unacceptable toxicity after 2 dose reductions will be discontinued from the study.

Assessments

Pharmacokinetic: PK sampling times for measurement of plasma concentrations of study drug are shown below.

Treatment	PK Sampling Timepoints[a]
Oraxol (HM30181AK-US tablet + paclitaxel capsule)	**Week 1 (Days 1,2,3):** Predose, and at 1,2, 3, and 4 hours postdose (all 24 subjects) **Week 4 (Days 1,2,3):** Predose, and at 1, 2, 3, and 4 hours postdose (all 24 subjects)

a: For purposes of PK sampling, study weeks will be counted consecutively from Week 1. Week 4 PK sampling may be delayed at the discretion of the Investigator, eg, to allow the subject to recover from unacceptable toxicity. In the event of a treatment delay, Week 4 PK samples should be obtained as soon as possible once the subject resumes treatment.

Safety: Safety will be assessed by evaluating the following parameters:

- determining and recording all AEs including Common Terminology Criteria for Adverse Events (CTCAE) grades (for both increasing and decreasing severity) and SAEs
- laboratory evaluation of hematology, blood chemistry, and urinalyses
- vital sign measurements, physical examinations, and ECGs

Activity: Tumor assessment and response will be evaluated using RECIST v1.1 criteria both by investigator and by independent central radiology review committee.; PFS and OS

Bioanalytical Methods

Plasma concentrations of study drug will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Statistical Methods

A total of 24 evaluable subjects receiving Oraxol will be analyzed. Subjects who do not have Week 4 PK assessments for any reason will be replaced.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the eCRF as well as any derived data will be included in data listings.

Analysis Sets

Safety/Full Analysis Set: The Safety population / Full Analysis Set will include all subjects who receive at least 1 dose of study treatment.

Evaluable Set: The Evaluable population will include all protocol-eligible subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment PK evaluation.

Pharmacokinetic Analyses

Plasma concentrations for paclitaxel only will be analyzed to determine the following PK parameters: C_{max}, C_{min}, C_{avg}, AUC_{0-t}, and AUC_{τ}.

Pharmacokinetic parameters will be summarized using the mean, standard deviation, median, minimum, and maximum. Summaries of PK parameters will also include the geometric mean and the coefficient of variation.

Summary PK and individual timepoints will be tabulated and displayed graphically and listed for all subjects.

Safety Analyses

For AEs, verbatim terms on the eCRF will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0 or higher). The CTCAE criteria v4.03 will be used to grade severity of the AEs. Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized. Adverse events will also be summarized by severity and relationship to study drug. Subject incidence of SAEs will be displayed.

Activity Analyses

Tumor response rate and its 95% confidence interval (CI) will be evaluated based on the number of subjects with any postbaseline CR or PR per RECIST criteria both as evaluated by investigator and by

central radiology review committee. In addition, the incidence of tumor response at each clinical visit will be summarized. Progression-free survival and overall survival will be estimated.
Version and date **v7.0_14 Aug 2018**

Schematic of Study Design:

An overview of the study design is presented in Figure 1.

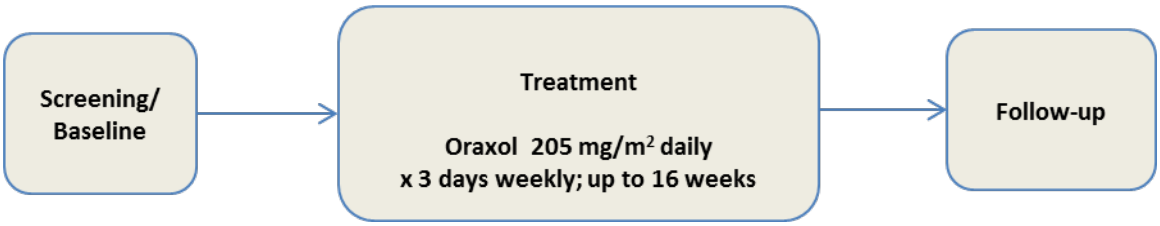

Figure 1 Schematic of Study Design for KX-ORAX-007

1 KEY ROLES

PRINCIPAL INVESTIGATOR

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INVESTIGATORS

This study will be conducted by qualified Investigators under the sponsorship of Kinex Pharmaceuticals, Inc. and PharmaEssentia (Taiwan) (the Sponsors) at approximately 6 sites in Taiwan.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The name of the investigational product (IP) is Oraxol, an oral dosage form of the chemotherapeutic agent paclitaxel administered with a novel P-glycoprotein (P-gp) inhibitor, HM30181 methanesulfonate monohydrate (referred to in this document as HM30181). Experience to date indicates that co-administration of HM30181 allows for clinically relevant blood levels of paclitaxel to be achieved following oral dosing. Oraxol is intended to allow for oral treatment of cancers that would otherwise be treated with intravenous (IV) paclitaxel.

Intravenous paclitaxel is an approved treatment for breast cancer. Paclitaxel 80 mg/m^2 weekly is the most commonly used regimen for treatment of breast cancer patients. Effective blood concentrations of paclitaxel and duration (AUC) can predict clinical outcomes.

Oraxol is an oral dosage form of the chemotherapeutic agent paclitaxel administered with a novel P-glycoprotein (P-gp) inhibitor, HM30181, to enhance the oral absorption of paclitaxel in cancer patients.

Phase1 and 2 clinical studies with HM30181A and oral paclitaxel (Oraxol) in 111 oncology patients showed that Oraxol was well tolerated. The MTD was not reached, and no anaphylactic reactions were observed. Premedication was not required for Oraxol treatment. The overall safety profile of oral paclitaxel may be better than IV paclitaxel. A Phase 2 clinical trial showed encouraging survival efficacy data in the treatment of gastric cancer.

A clinical pharmacokinetic (PK) study showed that HM30181 15 mg plus oral paclitaxel 205 mg/m^2 administered for 3 consecutive days per week can produce a paclitaxel exposure (AUC) similar to that of 80 mg/m^2 IV paclitaxel per week in cancer patients.

Summary of Nonclinical Studies

Results of primary and secondary pharmacodynamic studies confirm that HM30181A is effective in inhibiting P-gp, and when administered with paclitaxel as Oraxol, allows the systemic absorption of paclitaxel to therapeutically effective levels.

In a battery of central nervous system (CNS), respiratory and cardiovascular safety pharmacology studies, HM30181A caused no adverse effects. Oraxol caused minor reductions in body temperature in a CNS safety pharmacology study in rats, and reductions in PR and QRS intervals in cardiovascular safety pharmacology in dogs. No effect doses were achieved for these effects. The effects caused by Oraxol are interpreted as being caused by the paclitaxel component of Oraxol, because of their absence in studies of HM30181A alone.

Pharmacokinetic and metabolism studies showed that HM30181A is poorly absorbed after oral administration, and absorption is less than dose proportional. Absorbed HM30181A is widely distributed in tissues, but is present in low or non-detectable concentrations in the eye and nervous tissue. HM30181A is not an inhibitor of major cytochrome P450 (CYP) enzymes. Protein binding is high. The PK of HM30181A is not affected by co-administration with paclitaxel.

Paclitaxel is readily absorbed in therapeutically relevant concentrations when administered orally in combination with HM30181A. Paclitaxel is widely distributed into tissues after oral administration, in a pattern similar to that seen after IV administration as Taxol. HM30181A may modestly increase the tissue concentrations of paclitaxel after oral administration of both agents in combination.

In oral toxicity studies of HM30181, no toxicity was observed after a single dose of 2000 mg/kg in rats. Administration of HM30181A to rats was characterized by the occurrence of small increases in leucocyte counts and small decreases in lymphocyte counts; these changes were recoverable. Mesenteric lymph nodes were enlarged at doses ≥ 50 mg/kg, and histiocytosis in these lymph nodes was observed at doses ≥ 10 mg/kg (4-week study) or ≥ 50 mg/kg (13-week study). In dogs, increases in total leucocyte and eosinophil counts occurred at doses of ≥50 mg/kg. Enlargement of mesenteric lymph nodes associated with microscopically observed histiocytosis was also observed at these doses. The HM30181A-related effects in dogs were reversible. No other toxic effects of HM30181A occurred in oral toxicity studies of up to 13 weeks duration in rats and dogs. HM30181A is not genotoxic and caused no reproductive or fetal toxicity.

Single and repeat dose administration of Oraxol caused toxicities characteristic of paclitaxel. These included leucopenia related to decreases in circulating neutrophils, lymphocytes and other leucocyte types; anemia associated with bone marrow suppression; hypocellularity/atrophy of lymphoid organs including the thymus; villous stunting and epithelial hyperplasia in the intestinal mucosa in dogs; and hepatic necrosis in dogs. These changes were partially or fully reversible. All of the toxic effects seen in toxicity studies of Oraxol in rats and dogs are typical of the effects of paclitaxel. None of the toxicity of Oraxol appears to be caused by the HM30181A component of the Oraxol. Oraxol was not tested in genotoxicity or reproductive toxicity studies because its effects in such studies can be presumed to be the same as those caused by paclitaxel.

Comprehensive data on the preclinical, toxicology, and clinical experience to date can be found in the Investigator's Brochure.

Summary of Clinical Data

Previous human experience with HM30181 methanesulfonate monohydrate comes from 3 PK studies in healthy male subjects. In these studies, a total of 81 individuals received single oral doses of HM30181 ranging from 1 to 900 mg and 24 individuals received multiple doses ranging from 60 to 360 mg per day for 5 days. In addition to evaluating single- and multiple-dose safety and PK, 2 of these studies evaluated the effect of HM30181 methanesulfonate monohydrate on

the PK of loperamide, a P-gp substrate, and 1 study also compared the effects of HM30181 methanesulfonate monohydrate to quinidine, a known P-gp inhibitor. These data indicate that exposure to HM30181 methanesulfonate monohydrate increases with dose, but not in a dose-proportional manner, and that the effect of HM30181 methanesulfonate monohydrate on P-gp may last for up to 15 days following a single dose of 10 mg or higher but is not as pronounced as that of 600 mg of quinidine.

The HM-OXL-101 study attempted to define the maximum tolerated dose (MTD) for Oraxol in 24 subjects with advanced solid cancer. This was a "3+3" design in which cycles were 28 days and dosing with HM30181A tablets and an oral liquid formulation of paclitaxel was given on Days 1, 8, and 15 of each cycle. Paclitaxel doses evaluated ranged from 60 to 420 mg/m^2. HM30181A doses were half of paclitaxel doses (30 to 210 mg/m^2). The MTD was not reached in this study and dose escalation was stopped because of PK nonlinearity at paclitaxel doses above 300 mg/m^2. The most common nonserious adverse events (AEs) were gastrointestinal (GI), hematologic, and alopecia. Neutropenia was the event that led to either temporary (4 cases) or permanent (1 case) discontinuation of Oraxol. The only serious adverse event (SAE) occurred at the paclitaxel dose of 420 mg/m^2. This subject was hospitalized with cholangio-hepatitis and recovered after treatment with endoscopic retrograde biliary drainage. The event was considered unrelated to the study medication.

HM-OXL-201 is a 2-part study including an initial MTD assessment of Oraxol doses 90, 120, or 150 mg/m^2 paclitaxel per day for 2 days (as liquid-filled capsules), with paclitaxel given concomitantly with a 15-mg HM30181AK tablet on Day 1 in patients with advanced malignant tumors, including advanced gastric cancer. In the second part of this study, the selected dose of Oraxol, 150 mg/m^2 per day, was given for 2 days per week, every 3 weeks out of a 4-week cycle. The Investigators were also given the flexibility of giving an additional 15-mg tablet of HM30181AK on Day 2 of each dosing week. A total of 56 subjects enrolled in this study, 10 subjects with advanced malignant tumors in Part 1 and 46 subjects with advanced gastric cancer in Part 2. The most common AEs were neutropenia, anorexia, diarrhea, nausea, and abdominal pain. In the first part of this study, 1 subject had SAEs of pyrexia and bacteremia (probably not related to study treatment). In the second part of the study, 26 SAEs occurred in 15 subjects. Of these, 3 subjects experienced at least 1 SAE considered at least possibly related to study treatment. These included 1 subject with diarrhea and neutropenia, 1 subject with fatigue, and 1 subject with nausea and vomiting. Among 43 patients with advanced gastric cancer in the Intent-to-Treat (ITT) Population in Part 2 of this study, 4 patients (9.3%) had a partial response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The median overall survival was 10.7 months (95% confidence interval [CI], 7.2-14.2).

Pharmacokinetic results from these 2 studies showed that the paclitaxel maximum concentration (C_{max}) and area under the curve extrapolated to infinity ($AUC_{0-\infty}$) increased with dose up to 300 mg/m^2 following administration of Oraxol. At doses above 300 mg/m^2, both C_{max} and $AUC_{0-\infty}$ plateaued. Half-life ($t_{1/2}$) ranged from 19.9 to 32.1 hours, consistent with published values for

paclitaxel. Metabolic ratios of p-3-hydroxy paclitaxel and 6α-hydroxy paclitaxel metabolites were 0.1 ~ 0.25 and 0.04 ~ 0.13, respectively. Following 2 consecutive daily doses of Oraxol at doses of 60, 90, or 150 mg/m^2, minimal to no accumulation occurred in paclitaxel C_{max} and AUC. The C_{max} and AUC_{0-24} ranged from 202 to 280 (Day 1) and 159 to 315 ng/mL (Day 2), and 611 to 894 (Day 1) and 735 to 1081 ng·h/mL (Day 2), respectively, with minimal increase in C_{max} across the dose levels. Overall exposure on Day 2 was about 20% to 30% higher. These data indicate that Oraxol may represent a clinically useful alternative to IV paclitaxel.

Study ORAX-01-13-US is an ongoing "3+3" MTD study of Oraxol at a fixed dose of 270 mg (approximately 150 mg/m^2 per day for a person with a body surface area [BSA]) of 1.8 m^2) orally given 2 to 5 consecutive days per week for 3 out of 4 weeks. Preliminary data indicate that the most common AEs are gastrointestinal. Ten SAEs have been reported in 7 subjects; 1 case each of neoplasm posterior fossa mass, syncope, right upper quadrant pain, urosepsis, liver dysfunction, nausea, vomiting, abdominal pain, febrile neutropenia, and pain (not otherwise specified [NOS]). Of these, febrile neutropenia, occurring in the 5-day cohort in Cycle 1 is the only SAE considered related to study treatment and is the only dose-limiting toxicity reported to date.

A Phase 1 crossover study (Study ORAX-01-14-NZ) to determine the absolute bioavailability of Oraxol was conducted in New Zealand and is clinically complete. Oraxol doses were 270 mg (approximately 150 mg/m^2) (n=6), 274 mg/m^2 (n=2) and 313 mg/m^2 administered per day for 2 consecutive days (n=2). The reference treatment was paclitaxel 80 mg/m^2 IV, administered over 1 hour as a one-time infusion. Results show that the absolute bioavailability of paclitaxel in Oraxol is approximately 14% but the total drug exposure (AUC) of oral paclitaxel plateaus at a dose of approximately 300 mg/m^2. Therefore, an oral paclitaxel dose of approximately 205 mg/m^2 administered daily for 3 consecutive days per week (ie, a total weekly dose of 615 mg/m^2) is likely to produce a paclitaxel exposure similar to that of 80 mg/m^2 IV paclitaxel per week. The only SAE reported in this study was urosepsis which occurred prior to receiving study treatment.

2.2 Rationale

Intravenous paclitaxel is an approved treatment for breast cancer. Paclitaxel 80 mg/m^2 weekly is the most commonly used regimen for treatment of breast cancer patients. Effective blood concentrations of paclitaxel and duration (AUC) can predict clinical outcomes. Data from Study ORAX-01-14-NZ (described above) showed that the dose used in this current study (KX-ORAX-007) (Oraxol 205 mg/m^2 administered for 3 consecutive days per week) is likely to produce a paclitaxel exposure (AUC) similar to that of 80 mg/m^2 IV paclitaxel per week.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The toxicity caused by Oraxol appears to be caused by the paclitaxel component of the Oraxol, and those effects are predictable from the known toxicity profile of paclitaxel administered by the IV route. It is therefore predicted from nonclinical and clinical studies that the human safety risks from Oraxol will be similar to those known to occur with paclitaxel, and precautions similar to those required when administering paclitaxel should be exercised when administering Oraxol.

Serious AEs commonly occur in patients with cancer even in the absence of study drug exposure. Manifestations typically reflect progression of disease, with the clinical presentation varying depending on the affected organ system.

2.3.2 Known Potential Benefits

Oraxol treatment resulted in encouraging survival results in the Phase 1/2 Study HM-OXL-201, with a median overall survival of 10.7 months (95% CI, 7.2-14.2), in patients with advanced gastric cancer who failed first-line chemotherapy. Oraxol was given at a dose of 150 mg/m^2 per day, taken 2 days per week for 3 weeks out of a 4-week cycle and was well tolerated.

3 OBJECTIVES

3.1 Primary Study Objective

The primary objective of the study is to investigate the PK (AUC) of orally administered paclitaxel (as Oraxol) in breast cancer patients.

3.2 Secondary Study Objectives

The secondary study objectives are to determine the safety and activity (response rate, progression-free survival [PFS], overall survival [OS]) of Oraxol in breast cancer patients.

3.3 Study Outcome Measures

3.3.1 Primary Outcome Measures

Primary Endpoint

- Evaluation of PK parameters for oral paclitaxel

3.3.2 Secondary Outcome Measures

Secondary Endpoints

- Safety
  - Incidence of all AEs, including SAEs
  - Laboratory values
  - Other safety assessments including vital signs, physical exams, electrocardiograms (ECGs)
- Activity
  - Tumor response rate, which is defined as the number of subjects with complete response (CR) or partial response (PR) at any post-baseline assessments expressed as the proportion of the total number of subjects in the Full Analysis Set
  - PFS and OS

4 STUDY DESIGN

This is a multicenter, open-label, single-arm PK study in approximately 24 breast cancer patients for whom paclitaxel treatment is indicated. Subjects will receive Oraxol 205 mg/m^2 daily x 3 days weekly for up to 16 weeks. Subjects must have measurable disease as per RECIST v1.1 criteria 1.

The study will be conducted at approximately 6 sites in Taiwan. The study period will be approximately 8 months (first person first visit to last person last visit [FPFV-LPLV]). The duration of the study for each subject is approximately 21 weeks (up to 4 weeks for Screening/Baseline, 16 weeks for treatment, and 1 week for follow-up).

The study contains 3 periods: the Screening / Baseline Period, the 16-week Treatment Period, and the 1-week Follow-up Period (Section 7). A Final Visit will occur within 7 days of the last dose of study treatment. After completion of Final Visit assessments, subjects will be contacted every 2 months to follow progression-free survival and overall survival. New anti-cancer therapy will be collected.

Subjects may be treated until disease progression, or unacceptable toxicity requiring more than 2 dose reductions, or a maximum of 16 weeks. If subjects achieve stable disease (SD), CR, or PR at Week 16, they may continue Oraxol treatment in a separate extension study.

Pharmacokinetic parameters will be analyzed and various safety assessments (eg, AEs, laboratory tests) will be conducted throughout the study (Table 6), as well as imaging and tumor assessments which will be performed to evaluate tumor response.

For purposes of PK sampling, study weeks will be counted consecutively from Week 1. Week 4 PK sampling may be delayed at the discretion of the Investigator, eg, to allow the subject to recover from unacceptable toxicity. In the event of a treatment delay, Week 4 PK samples should be obtained as soon as possible once the subject resumes treatment.

An overview of the study design is presented in Figure 1.

5 STUDY ENROLLMENT AND WITHDRAWAL

In this study, the PK, safety, and activity of Oraxol (oral paclitaxel dose 205 mg/m^2 daily x 3 days weekly) will be evaluated in adult females with breast cancer patients for whom paclitaxel treatment is indicated. Subjects must have measurable disease as per RECIST v1.1 criteria. Approximately 24 subjects will be treated at approximately 6 sites in Taiwan.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study treatment.

5.1 Subject Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Signed written informed consent
2. Women ≥18 years of age on day of consent
3. Breast cancer in patients for whom treatment with IV paclitaxel at 80 mg/m^2 as monotherapy has been recommended by their oncologist
4. Measurable disease as per RECIST v1.1 criteria
5. Adequate hematological status as demonstrated by not requiring transfusion support or granulocyte-colony stimulating factor (G-CSF) to maintain:
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelet count ≥100 x 10^9/L
    - Hemoglobin (Hgb) ≥9 g/dL
6. Adequate liver function as demonstrated by:
    - Total bilirubin of ≤1.5 mg/dL
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if liver metastasis is present
    - Alkaline phosphatase (ALP) ≤3 x ULN or ≤5 x ULN if bone metastasis is present
    - Gamma glutamyl transferase (GGT) <10 x ULN
7. Adequate renal function as demonstrated by serum creatinine ≤1.5 x ULN
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Life expectancy of at least 3 months
10. Willing to fast for 6 hours before and 2 hours after Oraxol administration on all treatment days
11. Willing to abstain from alcohol consumption for 3 days before the first dose of study drug through the completion of the second inpatient PK sampling period

12. Willing to refrain from caffeine consumption for 12 hours before each inpatient dosing period (Weeks 1 and 4) through the completion of protocol-specified PK sampling for that week
13. Subjects must be postmenopausal (>12 months without menses) or surgically sterile (ie, by hysterectomy and/or bilateral oophorectomy) or must be using effective contraception (ie, oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for 30 days after their last dose of assigned study treatment.
14. Subjects who are of childbearing potential must have a negative serum pregnancy test at Screening and within 96 hours before Week 1 dosing.

5.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Have not recovered to ≤ Grade 1 toxicity from previous anticancer treatments or previous IPs
2. If previously treated with a taxane (paclitaxel or docetaxel) as part of anthracycline-based adjuvant chemotherapy or for metastatic disease, the subject relapsed less than 1 year following treatment
3. Subjects unable to swallow study medication in its intact form or have clinically significant malabsorption syndrome
4. Only site of metastatic disease is unmeasurable according to RECIST v1.1 criteria
5. Known CNS metastasis, including leptomeningeal involvement
6. Received IPs within 14 days or 5 half-lives of the first study dosing day, whichever is longer
7. Are currently receiving other medications intended for the treatment of their malignancy
8. Women who are pregnant or breastfeeding
9. Taking any of the following prohibited medications:
    - Strong inhibitors (eg, ketoconazole) or inducers (eg, rifampin or St. John's Wort) of CYP3A4 (within 2 weeks prior to the start of dosing in the study)
    - Strong inhibitors (eg, gemfibrozil) or inducers (eg, rifampin) of CYP2C8 (within 2 weeks prior to the start of dosing in the study)
    - Strong P-gp inhibitors or inducers. Subjects who are taking such medications but who are otherwise eligible may be enrolled if they discontinue the medication ≥1 week before dosing and remain off that medication through the end of study treatment.
    - An oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to start of dosing in the study
10. Use of warfarin. Subjects receiving warfarin who are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the

Investigator, may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.

11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, myocardial infarction within the last 6 months, unstable angina pectoris, cardiac arrhythmia, chronic pulmonary disease requiring oxygen, known bleeding disorders, or any concomitant illness or social situation that would limit compliance with study requirements
12. Known allergic reaction or intolerance to study medication components
13. Known allergic reaction or intolerance to contrast media
14. Subjects who, in the Investigator's opinion, are not suitable for participation in this study

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Not applicable; this is a nonrandomized, open-label study.

5.3.2 Masking Procedures

Not applicable; this is a nonrandomized, open-label study.

5.3.3 Reasons for Withdrawal

A subject may elect to discontinue from the study at any time for any reason.

The Investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons.

Subjects may continue the study treatment until any of the following primary reasons for discontinuation occurs:

- Death
- Progression of disease
    - computed tomography (CT) or magnetic resonance imaging (MRI) confirmed by RECIST v1.1 criteria and
        - Progression of disease not associated with AE(s) or
        - Progression of disease associated with AE(s)
    - other clinical findings indicating disease progression, eg, pain with bone metastases or seizure with brain metastases
- Unacceptable toxicity
- AEs not associated with progression of disease

- Noncompliance (Investigator needs to describe)
- Withdrawal of consent (subject asked but not required to give a reason)
  - Withdrawal of consent must be qualified as with or without permission to obtain additional assessments after the time of withdrawal
- Termination of the study by the Sponsor
- Other (Investigator must describe)

In addition to the primary reason, the subject may have indicated one or more of the above as secondary reasons for discontinuation. Investigators must document the actual reason(s) why they decided to discontinue subjects or why subjects withdrew consent, as applicable.

Study disposition information will be collected and documented on the electronic case report form (eCRF).

5.3.4 Handling of Withdrawals

If a subject discontinues study treatment, the subject will complete the protocol-specified procedures and assessments for the Final Visit unless the subject withdraws consent. The Investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment procedures and long-term follow-up for progression-free survival, overall survival, and new anti-cancer therapy at the Final Visit (as indicated in Table 6) or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Discontinuation from Treatment eCRF page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded on the eCRF.

Subjects who do not have Week 4 PK assessments for any reason will be replaced.

Subjects who have their Week 4 PK assessments and subsequently discontinue will not be replaced.

5.3.5 Termination of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board (IRB)/Independent

Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

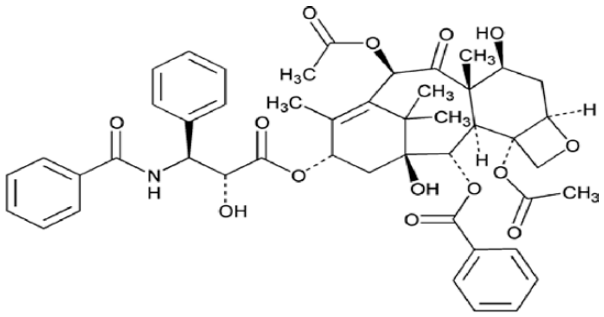
6.1.1 Formulation, Packaging, and Labeling

6.1.1.1 Formulations

Oral paclitaxel will be supplied as 30 mg capsules. HM30181AK-US will be supplied as 15 mg tablets.

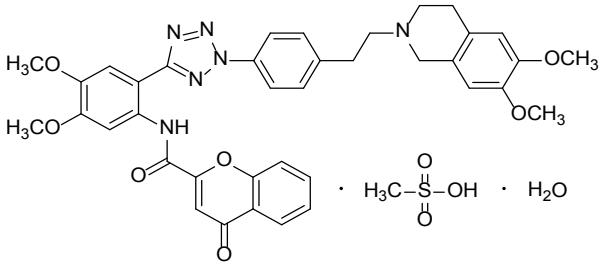
6.1.1.2 Chemical Name, Structural Formula of Paclitaxel

- Study drug code: Paclitaxel
- Chemical name: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13- ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine
- Molecular formula: $C_{47}H_{51}NO_{14}$
- Molecular weight: 853.91
- Structural formula:



6.1.1.3 Chemical Name, Structural Formula of HM30181 Methanesulfonate Monohydrate

- Study drug code: HM30181AK-US
- Chemical name: N-(2-(2-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-2H-tetrazol-5-yl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide Methanesulfonate monohydrate
- Molecular formula: $C_{38}H_{36}N_6O_7 \cdot CH_3SO_3H \cdot H_2O$
- Molecular weight: 802.85 (methanesulfonate monohydrate salt) / 688.72 (free base)
- Structural formula:



6.1.1.4 Packaging and Labeling

Investigational product will be packaged and labeled in a manner consistent with the study and will be designed by:

Kinex Pharmaceuticals, Inc.
1001 Main Street
Suite 600
Buffalo, NY 14203
United States

Lot information, including expiration dates, if necessary, will be recorded for Oraxol (HM3018AK-US tablets and oral paclitaxel capsules).

Labels will be nonremovable in nature. Labels for the IP (Oraxol [oral paclitaxel and HM30181AK-US]) will be in accordance with regional/local regulations and will include (but will not be limited to) the following information:

- For clinical study use only
- Name and address of the Sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

6.1.2 Product Storage and Stability

Study drug will be stored in accordance with labelled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

The IP in the study is Oraxol. Oraxol is an oral dosage form of the chemotherapeutic agent paclitaxel administered with a novel P-gp inhibitor, HM30181. See sections below and Table 1 for a description of treatments administered.

6.2.1 Description and Justification of Dosage Regimen

Previous experience with HM30181 indicates clinically significant P-gp inhibition with an acceptable safety profile. Systemic P-gp inhibition is not observed. Currently, HM30181 is being given at a dose of 15 mg on each dosing day. Absorption of orally administered paclitaxel appears to plateau at doses above 300 mg/m^2 when given with HM30181. The dose of HM30181A of 15 mg daily is being used in current studies of Oraxol based on PK data from healthy volunteer studies that examined the inhibitory effect of HM30181A on gut P-gp (see the Investigator's Brochure).

Intravenous paclitaxel is an approved treatment for breast cancer. Paclitaxel 80 mg/m^2 weekly is the most commonly used regimen for treatment of breast cancer patients. Effective blood concentrations of paclitaxel and duration (AUC) can predict clinical outcomes. As shown in Study ORAX-01-14-NZ (described above), the dose used in this study (Oraxol 205 mg/m^2 administered for 3 consecutive days per week) is likely to produce a paclitaxel exposure (AUC) similar to that of 80 mg/m^2 IV paclitaxel per week.

6.2.2 Treatments Administered

Information regarding study treatment is provided in Table 1.

Table 1 Treatments Administered in KX-ORAX-007

	Strength	Dose Form / Route of Administration	Number Dispensed and Frequency	Study Days Administered
Investigational Product				
HM30181AK-US	15 mg	Tablet taken orally	1 × 15-mg tablet, on designated treatment mornings, 1 hour before oral paclitaxel	Days 1-3, weekly for 16 weeks
Paclitaxel	30 mg	Capsules taken orally	Number dispensed based on calculated doses (205 mg/m^2 once on designated treatment mornings)	Days 1-3, weekly for 16 weeks

6.2.3 Dosing Administration of Study Drugs

Information regarding dosing and dispensing will be included in a Pharmacy Manual provided to the sites.

6.2.3.1 Fasting Requirements

Subjects will be instructed to fast, having nothing to eat or drink (except water) for at least 6 hours before HM30181 dosing on each Oraxol dosing day and to continue to fast for 2 hours after oral paclitaxel dosing. Subjects may take other medications as directed. Subjects may have water 1 hour after completion of Oraxol dosing and as needed with other prescribed medications.

6.2.3.2 Premedication

Anti-emetics should be given on each day of Oraxol administration, with the first dose of anti-emetic given at the same time as HM30181. 5-HT$_3$ or NK-1 antagonists should be used for prophylaxis or initial treatment of nausea or vomiting. Steroids or H-1 receptor antagonists are not allowed as anti-emetics for subjects taking Oraxol.

Steroids or H-1 receptor antagonists should be given only if hypersensitivity-type reactions occur (including dyspnea with or without bronchospasm, urticaria, flushing or rashes, blood pressure changes, or angioedema). For subjects who may experience hypersensitivity type-reactions, premedication with steroids or H-1 antagonists may be given before subsequent doses, if clinically indicated.

6.2.3.3 Oraxol Dosing

The calculated oral paclitaxel dose (based on BSA) for each subject will be rounded up to the closest number of 30-mg paclitaxel capsules to administer Oraxol (oral paclitaxel dose 205 mg/m^2 QD) for 3 consecutive days weekly.

Oraxol will be administered as follows:

- HM30181AK-US tablet will be administered as a single oral dose of 15 mg on each dosing day approximately 1 hour before paclitaxel capsules.
- Paclitaxel capsules will be administered as a single oral dose with water each dosing day.
- Both HM30181 and paclitaxel should be taken with approximately 120 to 240 mL of water.

The amount of water consumed with HM30181AK-US and oral paclitaxel dosing in the clinic must be documented.

On PK sampling days, in the event vomiting occurs within 4 hours postdose of oral paclitaxel, the Investigator should contact Kinex Pharmaceuticals, Inc., Taiwan immediately.

6.3 Modification of Study Intervention/Investigational Product for a Subject

6.3.1 Unacceptable Toxicity, Dose Interruption, and Dose Reduction

Unacceptable toxicity occurs when any of the following events, graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [2] (or later) criteria, are considered at least possibly related to Oraxol:

- ANC ≤0.8 x 10^9/L
- Grade 3 or 4 ANC plus fever or Grade 3 or 4 ANC with bacteremia or sepsis
- Grade 3 thrombocytopenia (<50 x 10^9/L platelets) for more than 7 days, or accompanied by clinically significant bleeding
- Grade 4 thrombocytopenia (<25 x 10^9/L platelets) regardless of duration or clinical manifestations
- Grade ≥3 nausea, vomiting, or diarrhea persisting for more than 48 hours despite optimal medical management
- Grade ≥3 nonhematologic abnormalities not listed above. This does not include:
    - laboratory abnormalities not considered to be SAEs and which resolve back to Grade 1 or baseline within 7 days
    - alopecia
    - anorexia or asthenia which resolves within 7 days
- Nonhematologic toxicities and hematologic toxicities not mentioned above which cause a dose delay of >7 days

Management of Unacceptability Toxicity:

Subjects experiencing unacceptable toxicity who have completed the first week of Oraxol treatment will have their Oraxol treatment delayed until the toxicity improves.

Subjects whose unacceptable toxicity improves to CTCAE Grade 1 or baseline within 2 weeks of their last dose of Oraxol may continue treatment with dose reduction as described below:

Dose Reduction after First Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 165 mg/m^2 per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Dose Reduction after Second Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 130 mg/m^2 per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Once the dose has been reduced, it cannot be increased at a later date.

Discontinuation due to Unacceptability Toxicity:

Oraxol treatment will be permanently discontinued for subjects who are unable to complete the first week of dosing due to unacceptable toxicity.

After 2 dose reductions, subjects whose unacceptable toxicity does not improve to Grade 1 or baseline within 2 weeks of their last dose of Oraxol will have their Oraxol treatment permanently discontinued.

Subjects who continue to experience unacceptable toxicity after 2 dose reductions will be discontinued from the study.

6.4 Accountability Procedures for the Study Intervention / Investigational Products

All study drugs will be supplied to the Principal Investigator (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Designated study personnel will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The Investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the study, the Investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to personnel designated by the Sponsor or, when approval is given by the Sponsor, will destroy supplies and containers at the site.

The Investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the Sponsor's standard operating procedures (SOPs) and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to the site but not dispensed to subjects, and return of reconciled study drugs to the Sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the Sponsor. Any comparable forms that the site wishes to use must be approved by the Sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the Sponsor or a representative of a health authority (eg, United States Food and Drug Administration [FDA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the Investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the Sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the Sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the Sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the Sponsor's personnel, study drugs that are to be returned to the Sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the

central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by Sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the Sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

6.5 Assessment of Subject Compliance with Study Intervention / Investigational Product

Subjects will be assessed for adherence to dosing schedule. At the scheduled clinic visits, subjects should bring all used and unused study drug to the clinical site. These will be checked by site personnel and a capsule and tablet count will be performed before subjects are dispensed a new supply of study drugs.

Study drug should be taken on consecutive days of the week at approximately the same time each morning.

Subjects will be given information cards on which they will record their dosing information. Records of treatment compliance for each subject will be kept during the study. Designated study personnel will review treatment compliance during site visits and at the completion of the study.

6.6 Concomitant Medications/Treatments

All medications (prescription and nonprescription), treatments, and therapies taken from 28 days before the initiation of the study through the final study visit, must be recorded on the eCRF. A complete oncologic treatment history will be recorded on the Oncologic Treatment History eCRF.

Any medication (including nonprescription remedies) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication eCRF. The Investigator will record any AE on the Adverse Events eCRF for which the concomitant medication/therapy was administered.

Subjects are excluded from participation in this study are those who are currently taking:

- strong inhibitors (eg, ketoconazole) or inducers (eg, rifampin or St. John's Wort) of cytochrome P450 (CYP) 3A4 (within 2 weeks prior to the start of dosing in the study)
- strong inhibitors (eg, gemfibrozil) or inducers (eg, rifampin) of CYP2C8 (within 2 weeks prior to the start of dosing in the study)
- strong P-glycoprotein (P-gp) inhibitors or inducers. Subjects who are taking such medications but who are otherwise eligible may be enrolled if they discontinue the

medication ≥1 week before dosing and remain off that medication through the end of study treatment.

- an oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to start of dosing in the study

A list of drugs prohibited due to potential drug-drug interactions will be provided to the sites as part of the Pharmacy Manual.

Subjects should not start prohibited medications while enrolled in this protocol.

Use of warfarin is not permitted (use of low molecular weight heparin is allowed).

Anti-emetics should be given on each day of Oraxol administration, with the first dose of anti-emetic given at the same time as HM30181. 5-HT_3 or NK-1 antagonists should be used for prophylaxis or initial treatment of nausea or vomiting. Steroids or H-1 receptor antagonists are not allowed as anti-emetics for subjects taking Oraxol.

Steroids or H-1 receptor antagonists should be given only if hypersensitivity-type reactions occur (including dyspnea with or without bronchospasm, urticaria, flushing or rashes, blood pressure changes, or angioedema). For subjects who may experience hypersensitivity type-reactions, premedication with steroids or H-1 antagonists may be given before subsequent doses, if clinically indicated.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration.

7 STUDY SCHEDULE

7.1 Screening/Baseline

The Screening/Baseline Period will last no longer than 28 days. Subjects will be screened within 28 days of the first dose of study drug. All screening assessments/evaluations, as detailed in Table 6, will be performed after the subject provides informed consent and eligibility criteria are met.

7.2 Treatment

The Treatment Period will begin on Day 1, Week 1. The dose and timing of administration of study treatments are as follows:

- Oraxol – 15 mg oral HM30181 methanesulfonate monohydrate plus 205 mg/m^2 oral paclitaxel administered once daily for 3 consecutive days, weekly for 16 weeks (HM30181 will be administered 1 hour before oral paclitaxel on all dosing days.)

All subjects will be housed in the clinic from the night before dosing on Week 1, Day 1 through the end of PK sampling on Day 3.

For Week 4 PK sampling, subjects will be housed in the clinic from the night before dosing on Week 4, Day 1 through the end of PK sampling on Day 3.

During PK sampling days, Oraxol will be administered to the subject in the clinic on scheduled dosing days.

Safety and activity assessments evaluations, as detailed in Table 6, will be performed during the Treatment Period.

7.3 Follow-up

Subjects will be requested to participate in long-term follow-up for progression-free survival and overall survival. New anti-cancer therapy will be collected. After completion of this study, subjects or designated family members or physicians may be contacted every 2 months to determine if the patient has had progressive disease or whether the subject remains alive, or if any new anti-cancer therapy has been taken.

If a subject completes the study or discontinues the study at any time, a Final Visit will occur within 7 days after the last dose of study treatment. Safety assessments, as detailed in Table 6, will be performed at the Final Visit. If a subject discontinues the study due to progression of disease,

the Final Visit assessments can be performed at the last on-treatment visit. If possible, this visit should be scheduled before the subject receives additional chemotherapy.

7.4 Early Termination Visit

Subjects may continue treatment until any of the discontinuation criteria occurs as described in Section 5.3.3. If a subject discontinues the study at any time, a Final Visit will occur within 7 days after the last dose. Safety assessments, as detailed in Table 6, will be performed at the Final Visit.

7.5 Unscheduled Visit

Unscheduled visits will occur only at the discretion of the Investigator. Results of any assessments performed at unscheduled visits will be entered into the clinical database.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

All assessments should be performed on the specified weeks/day(s) designated on the Schedule of Procedures and Assessments (Table 6).

8.1.1 Screening/Baseline Assessments

Subjects must be screened within 28 days prior to Week 1 Day 1 dosing.

8.1.1.1 Demography

Subject demographic information will be collected at the Screening/Baseline Visit. Demographic information includes date of birth (or age), sex, race/ethnicity.

8.1.1.2 Body Surface Area

Height (recorded at Screening/Baseline) and weight (with indoor clothing) will be measured to calculate BSA. Sites may use any of the established formula for BSA, but must use the same formula for all subjects at their site, and the method of BSA calculation must be recorded on the eCRF for each subject.

8.1.1.3 Medical/Surgical/Oncology History

Medical history will be obtained at Screening/Baseline and will include:

- a complete medical and surgical history; childhood diseases are not required and common colds are not required unless it is ongoing at Screening/Baseline
- a complete oncology history (including all malignancies, if known, and currently, regardless of diagnosis date or status, eg, skin cancer >5 years). The Tumor, Node, Metastases (TNM) status at time of diagnosis and Screening/Baseline will be recorded. For the subject's qualifying breast cancer diagnosis, estrogen receptor status, progesterone receptor status, and human epidermal growth factor receptor 2 status will be recorded (positive, negative, or unknown).
- complete oncology treatment history including all commercial and IPs, radiation and other prescribed and nonprescription therapies dating back to the initial diagnosis

All medical and surgical history must be noted on the eCRF. A complete oncology history and a complete oncology treatment history will also be recorded on the Oncology History and Oncology Treatment History eCRF.

8.1.1.4 Eastern Cooperative Oncology Group Performance Status

The subject's performance status should be assessed according to ECOG criteria [3] (Appendix B). ECOG will be assessed at Screening/Baseline. Subjects with an ECOG >1 at Screening/Baseline must be excluded from the study.

8.1.1.5 Prior Medications

Prior non-oncologic medications taken within 28 days before Day 1, including nonprescription remedies, vitamins, etc, will be recorded at Screening/Baseline.

8.1.2 Assessment of Activity

8.1.2.1 Computed Tomography/Magnetic Resonance Imaging

To assess tumors, CT and/or MRI scans will be conducted as designated on the Schedule of Procedures and Assessments (Table 6) as follows. During the Screening/Baseline Period, a baseline scan will be conducted before the first dose on Week 1, Day 1 of Oraxol treatment, as close to Day 1 as possible. Subsequent scans will be conducted every 8 weeks (at Weeks 8 and 16) until documented progression. Unscheduled scans should be conducted, if clinically indicated, per the discretion of the Investigator. Results of these unscheduled scans will be entered into the clinical database.

Computed tomography and/or MRI scans of the chest, abdomen, and pelvis will be conducted at Baseline and repeated at all assessment times to determine the possible change in tumor size at the respective sites.

8.1.2.2 RECIST Tumor Assessment

Tumor status will be evaluated using RECIST v1.1 criteria (Appendix C) by the Investigator at each tumor assessment timepoint as discussed above in Section 8.1.2.1.

All radiologic imaging should be sent to the independent central radiology review committee for evaluation when the patients completed Final Visit. Detailed information please refer to the charter for Central Radiology Review Committee.

In addition to using the RECIST criteria, the Investigator must consider all other clinical information as part of tumor status evaluation. The Investigator must record his/her tumor assessment based on each of these factors, including descriptions of nonmeasurable disease and other clinical information. Results and interpretations of all scans or x-rays performed will be recorded on the eCRF.

Long-term follow up for progression-free survival and overall survival:

Subjects will be requested to participate in long-term follow-up for progression-free survival and overall survival. Subjects or designated family members or physicians may be contacted every

2 months to determine if the patient has had progressive disease or whether the subject remains alive or is taking any new anti-cancer therapy.

8.2 Pharmacokinetics

For purposes of PK sampling, study weeks will be counted consecutively from Week 1. Week 4 PK sampling may be delayed at the discretion of the Investigator, eg, to allow the subject to recover from unacceptable toxicity. In the event of a treatment delay, Week 4 PK samples should be obtained as soon as possible once the subject resumes treatment.

All subjects will be housed in the clinic from the night before dosing on Week 1, Day 1 through the end of PK sampling on Day 3.

For Week 4 PK sampling, subjects will be housed in the clinic from the night before dosing on Week 4, Day 1 through the end of PK sampling on Day 3.

During PK sampling days, Oraxol will be administered to the subject in the clinic on scheduled dosing days.

As designated on the Schedule of Procedures/Assessments (Table 6), blood samples (approximately 5 mL per testing timepoint) will be collected for analysis of plasma concentrations of oral paclitaxel starting at Week 1, Days 1-3, and again at Week 4, Days 1-3. PK sampling times are presented in Table 3 (Week 1) and Table 4 (Week 4). A ±10-minute window will be allowed for all PK sampling timepoints. The actual times of PK sampling will be recorded. Reasons must be provided for all samples collected outside of the ±10-minute window. All samples collected early, even within the 10-minute window, must also have reasons provided.

Table 2 presents the amounts of blood (mL) that will be collected over the course of the study for PK analysis.

Table 2 Blood Collection Volumes for Pharmacokinetic Analyses

	Oraxol (paclitaxel and HM30181)	
	Week 1	Week 4
Volume per timepoint (mL)	5	5
Number of timepoints	15	15
Total (mL)	75	75
Total (mL)	150	

Samples will be analyzed for paclitaxel levels using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Table 3 Pharmacokinetic Sampling for Oral Paclitaxel - Week 1: Days 1 to 3

Week 1: Dosing Days	Dosing Days 1[a], 2[b], and 3[c]				
Time after dosing on designated dosing days	0 (predose)	1 h	2 h	3 h	4 h
PK Sample	X	X	X	X	X

h = hours; PK = pharmacokinetic.

Note: A ±10-minute window will be allowed for all PK sampling timepoints. The actual times of PK sampling will be recorded. Reasons must be provided for all samples collected outside of the ±10-minute window. All samples collected early, even within the 10-minute window, must also have reasons provided.

a: Day 1 dosing: predose, and at 1, 2, 3, and 4 h after the first dose (PK sampling times on Day 1).

b: Day 2 dosing: predose, and at 1, 2, 3, and 4 h after the second dose (PK sampling times on Day 2).

c: Day 3 dosing: predose, and at 1, 2, 3, and 4 h after the third dose (PK sampling times on Day 3).

Table 4 Pharmacokinetic Sampling for Oral Paclitaxel - Week 4: Days 1 to 3

Week 4: Dosing Days	Dosing Days 1[a], 2[b], and 3[c]				
Time after dosing on designated dosing days	0 (predose)	1 h	2 h	3 h	4 h
PK Sample	X	X	X	X	X

h = hours; PK = pharmacokinetic.

Note: A ±10-minute window will be allowed for all PK sampling timepoints. The actual times of PK sampling will be recorded. Reasons must be provided for all samples collected outside of the ±10-minute window. All samples collected early, even within the 10-minute window, must also have reasons provided.

a: Day 1 dosing: predose, and at 1, 2, 3, and 4 h after the first dose (PK sampling times on Day 1).

b: Day 2 dosing: predose, and at 1, 2, 3, and 4 h after the second dose (PK sampling times on Day 2).

c: Day 3 dosing: predose, and at 1, 2, 3, and 4 h after the third dose (PK sampling times on Day 3).

8.2.1 Specimen Preparation, Handling, and Shipping

A description of collection, handling, and shipping procedures for PK samples will be provided to the sites in a laboratory manual.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety will be assessed by evaluating the following parameters:

- determining and recording all AEs including CTCAE grades (for both increasing and decreasing severity) and SAEs
- laboratory evaluation of hematology, blood chemistry, and urinalyses (Table 5)
- vital sign measurements, physical examinations, and ECGs

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Adverse events will be assessed and recorded at all clinic visits. In between clinic visits, subjects will be instructed to call designated study personnel if they experience any adverse events.

An AE is any untoward medical occurrence in a patient or clinical investigation subject, and includes events occurring from the time a subject signs the informed consent form (ICF) through the last subject contact. An AE does not necessarily have a causal relationship with the medicinal product.

Treatment-emergent adverse events (TEAEs) are those AEs which occur at any time from the initiation of dosing with the study medication up through the last subject contact. Adverse events occurring at any time following the subject's signing of the ICF up to the time immediately prior to dosing initiation with study medication are, unless associated with performance of a required study procedure, typically considered unrelated a priori to study medication, but are nonetheless reported.

For this study, the study drug is Oraxol.

The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP
- any new disease or exacerbation of an existing disease. This includes any AEs associated with progression of disease. Note, however that in this protocol, progression of disease is captured as a secondary endpoint under RECIST 1.1, and is not itself

considered an AE.

- any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- recurrence of an intermittent medical condition (eg, headache) not present at baseline

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last subject contact. Adverse events will be assessed during clinic visits.

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.

9.2.1.1 Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 as follows:

Grade 1 =	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 =	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3 =	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4 =	Life-threatening consequences; urgent intervention indicated
Grade 5 =	Death related to AE.

Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. The criteria for assessing severity are different from those used for seriousness (see Serious Adverse Events and Other Events of Interest for the definition of an SAE).

9.2.1.2 Assessing Relationship of Adverse Events to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- temporal relationship of the onset of the event to the initiation of the study treatment
- the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable

- whether the event is known to be associated with the study treatment or with other similar treatments
- the presence of risk factors in the study subject known to increase the occurrence of the event
- the presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

9.2.1.3 Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF using the following criteria:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent or underlying disease or other drugs or conditions

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, conditions or concurrent or underlying disease provide plausible explanations.

9.2.2 Serious AEs and Other Events of Interest

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

See Section 9.3.1 for SAE regulatory reporting requirements.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest which include pregnancy, overdose, and treatment-emergent significant laboratory abnormality, are to be captured using the SAE procedures (see Section 9.3.3) but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the eCRF whether or not they meet the criteria for SAEs.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- planned hospitalizations required by the protocol
- hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)

9.2.3 Laboratory Evaluations

The Schedule of Procedures and Assessments (Table 6) show the visits at which blood and urine will be collected for clinical laboratory tests. Collection of both blood and urine may be conducted at a local laboratory or at the clinic site. Approximately 20 mL of blood will be collected for clinical laboratory (hematology and chemistry) testing (or approximately 10 mL for hematology testing alone) at Screening and Baseline within 96 hours prior to Week 1 Day 1 dosing, and within 48 hours prior to Day 1 dosing at each subsequent designated week: Chemistry will be tested at Weeks 1, 2, 4, 8, 12, and 16. Hematology testing will be conducted weekly from Week 1 through Week 16. Any additional hematology tests may be done at the discretion of the Investigator. All hematology data obtained on subjects during this study will be included in the clinical database.

Subjects must be fasted for the Screening/Baseline laboratory assessments. It is recommended but not required, that subjects be fasted for the remaining weekly laboratory assessments. It must be noted if subjects were in a fasted or fed state at the time of blood collection.

Urinalysis will be conducted at Screening and Baseline within 96 hours prior to Week 1 Day 1 dosing, and within 48 hours prior to Day 1 dosing at Weeks 4, 8, 12, and 16. Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator. When conducted, microscopic urinalysis will be recorded on the eCRF.

Laboratory results must be reviewed and acceptable to the Investigator prior to dosing and following any treatment delays for unacceptable toxicity.

Serum pregnancy tests will be obtained in females of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at Screening/Baseline and every 8 weeks (Weeks 8 and 16). A urine pregnancy test will be performed within 96 hours prior to Week 1, Day 1 dosing. Test results must be reviewed prior to dosing. Additional pregnancy testing will be performed as needed per local/country regulatory authority requirement.

The clinical laboratory tests to be measured during the study are provided in Table 5.

Table 5 Clinical Laboratory Parameters

Category	Parameters
Hematology	red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with automated differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW)[a]
Chemistry	
Electrolytes	sodium, potassium, chloride, bicarbonate (HCO_3)
Liver function tests	alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, direct bilirubin
Renal function parameter	blood urea/blood urea nitrogen, creatinine
Other	glucose, calcium, magnesium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, pregnancy test[b]
Urinalysis[c]	hydrogen ion concentration (pH), protein, glucose, ketones, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity, pregnancy test[b]

a. Some of the hematology parameters may not be collected, depending on the laboratory (eg, RDW).
b. Pregnancy tests are performed with serum samples at scheduled assessments (Table 6), except for the timepoint of 96 hours prior to Week 1, Day 1 dosing, when a urine sample will be tested.
c. Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol) or as determined by the Investigator.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Adverse Events and Other Events of Interest) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Serious Adverse Events and Other Events of Interest); the site must fax or send via email the SAE report including the laboratory report (if required by regional regulations) to the Sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.3.1]).

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

An abnormal laboratory test result should be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A treatment-emergent significant abnormal laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study drug
- results in withholding of study drug pending some investigational outcome
- results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- increases in severity compared with baseline by ≥2 CTCAE grades, with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate; for these tests, any change of ≥2 grades will be evaluated by the Investigator to determine if it is of clinical significance and, if so, will be considered an AE
- is otherwise considered by the Investigator to meet serious criteria as defined in Section 9.2.2 (Serious Adverse Events and Other Events of Interest)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- increases in severity compared with baseline by ≥2 CTCAE grades, with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate; for these tests, any change of ≥2 grades will be evaluated by the Investigator to determine if it is of clinical significance and, if so, will be considered an AE
- is otherwise considered by the Investigator to meet serious criteria as defined in Section 9.2.2 (Serious Adverse Events and Other Events of Interest)

9.2.5 Electrocardiograms

A 12-lead ECG is to be completed at Screening/Baseline and on Day 1 at Weeks 4, 8, 12, and 16 (Table 6). The Screening/Baseline ECG may be performed at a convenient time during the visit and 1 hour after Oraxol dosing on dosing days. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. The ECG data recorded on the eCRF must include rate, rhythm, intervals, and QTc/QTcF.

9.2.6 Vital Signs

Vital sign (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) measurements will be taken after the subject has been seated for at least 5 minutes at Screening/Baseline, prior to dosing Day 1 of Weeks 1, 2, 3, 4, 8, 12, and 16, and at the Final Visit (Table 6). All blood pressure measurements should be performed on the same arm, preferably by the same person at the designated visits. Serial vital signs may be obtained to confirm accurate readings.

9.2.7 Physical Examinations

Complete physical examinations will be performed at Screening/Baseline and every 8 weeks, (Weeks 8 and 16) (Table 6).

A complete physical examination will include weight and an assessment of head, eyes, ears, nose, and throat (HEENT), GI, cardiovascular, respiratory, integumentary, muscular-skeleton, and neurological systems. Height will only be measured and recorded at Screening/Baseline.

Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening/baseline physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

9.2.8 Concomitant Medications

The subject's concomitant medications will be assessed and recorded at all clinic visits. In between clinic visits, subjects will be instructed to call designated study personnel if they experience any AEs and/or associated concomitant medications taken (Table 6).

9.3 Reporting Procedures

Adverse events will be reported from the time of consent through the last subject contact.

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.3.1 Serious Adverse Events

Serious AEs will be reported from the time of signing informed consent through the last subject contact; in addition, any SAEs that are reported to the Investigator in the 30 days following the last subject contact are also reported.

Serious AEs reported at any time following the subjects' participation in the study must be reported, if, in the opinion of the Investigator, they are possibly related to study treatment, regardless of the amount of time that may have elapsed since the end of the study.

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE form.

Detailed contact information for reporting of SAEs will be provided in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

9.3.2 Regulatory Reporting

The Sponsor must inform Investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.3.3 Other Adverse Events

9.3.3.1 Reporting of Overdose

Study drug overdose is defined as the accidental or intentional use of the study drug in an amount higher than the dose being studied.

Any study drug overdose during the study should be noted on the Study Medication eCRF.

All AEs associated with an overdose should be entered both on the Adverse Event eCRF and reported using the procedures detailed in reporting of Serious Adverse Events (Section 9.3.1) even if the events do not meet serious criteria. If the AE associated with an overdose does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.3.3.2 Reporting of Significant Laboratory Abnormality

Only treatment-emergent significant laboratory abnormalities are required to be reported. Treatment-emergent significant laboratory abnormalities are those which occur following the first dose of study medication up through 30 days following last subject contact.

A laboratory result should be considered a treatment-emergent significant abnormality if the result meets the criteria described in Section 9.2.4.

Any treatment-emergent significant laboratory abnormality observed during the clinical study should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 9.3.1, even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.3.3.3 Reporting of Pregnancy

Any pregnancy, whether occurring in a subject or in the female partner of a male subject, for which the estimated date of conception falls within either of the following timeframes must be reported:

- anytime from signing informed consent until 30 days after last study treatment, or
- any exposure to study drug through breastfeeding during study treatment or within 30 days after last study treatment

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs (Section 9.3.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy

Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study. If the female partner of a male subject becomes pregnant, that male subject also needs to be withdrawn from the study.

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

Subjects with onset of study drug-related AEs will be followed until resolution, resolved with sequelae, or the subject is under medical care.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

The Sponsor's/ contract research organization's (CRO's) contract research associate (CRA) will maintain contact with the Investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6[4], Section 1.52, source documents include, but are not limited to, the following:

- clinic, office, or hospital charts
- copies or transcribed health care provider notes that have been certified for accuracy after production
- recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, MRIs, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- pain, quality of life, or medical history questionnaires completed by subjects
- records of telephone contacts
- diaries or evaluation checklists
- drug distribution and accountability logs maintained in pharmacies or by research personnel
- laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11 STATISTICAL CONSIDERATIONS

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

A total of 24 evaluable subjects receiving Oraxol will be analyzed. Subjects who do not have Week 4 PK assessments for any reason will be replaced.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the eCRF as well as any derived data will be included in data listings.

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

The definitions of the Analysis Sets which will be used in the study are as follows:

Safety/Full Analysis Set: The Safety population / Full Analysis Set will include all subjects who receive at least 1 dose of study treatment.

Evaluable Set: The Evaluable population will include all protocol-eligible subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment PK evaluation.

11.1 Study Hypotheses

This is a PK study with a single treatment arm. No statistical tests will be applied to the primary endpoints. For the secondary activity endpoint tumor response rate, its 95% CI will be evaluated per a binomial test.

11.2 Planned Interim Analyses

None

11.3 Pharmacokinetic Analyses

11.3.1 Calculation of Noncompartmental Pharmacokinetic Parameters

Plasma concentrations for paclitaxel only will be analyzed to determine the following PK parameters: C_{max}, C_{min}, C_{avg}, AUC_{0-t}, and AUC_{τ}.

Pharmacokinetic parameters will be summarized using the mean, standard deviation, median, minimum, and maximum. Summaries of PK parameters will also include the geometric mean and the coefficient of variation.

Summary PK and individual timepoints will be tabulated and displayed graphically and listed for all subjects.

11.3.2 Population Pharmacokinetic Analysis

Using the PK samples collected at designated timepoints, a population PK analysis will be explored and then used to estimate individual AUCs or clearance (CL) of paclitaxel. The effect of patient factors on paclitaxel PK will be explored that may explain interpatient variability in PK parameters. Both inter- and intra-patient variability in paclitaxel AUC will also be assessed. Paclitaxel AUC, as well as C_{max}, will then be tested for association of changes with toxicity endpoints, such as neutropenia or incidence of neuropathy. If an observable trend exists among changes in any of these AEs, a pharmacokinetic/pharmacodynamic (PK/PD) model will be developed to evaluate the exposure-response relationship between the time course of paclitaxel plasma exposure (eg, AUC, C_{max}) in relation to changes in neutropenia and/or neuropathy. Demographic and clinical data (ie, ethnicity, age, BSA, ECOG performance status, etc) will be utilized to assess interpatient variability in the model.

Time to maximum concentration (T_{max}) and other summary PK and individual timepoints will be tabulated and displayed graphically and listed for all subjects.

11.4 Safety Analyses

11.4.1 Extent of Exposure

The actual number of doses will be summarized by visit.

11.4.2 Adverse Events

For AEs, verbatim terms on the eCRF will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.0 or higher). The CTCAE criteria v4.03 will be used to grade severity of the AEs. Subject incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized. Adverse events will

also be summarized by severity and relationship to study drug. Subject incidence of SAEs will be displayed.

For analysis purposes, a TEAE is defined as an AE that emerges after the first dose of study treatment, having been absent at pretreatment (Baseline) or

- re-emerges after the first dose of study treatment, having been present at Baseline but stopped prior to treatment, or
- worsens in severity after the first dose of study treatment relative to the pretreatment state, when the AE is continuous

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs will be summarized. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. Subjects will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by seriousness, maximum severity (highest CTCAE grade), outcome, action taken with IP, other treatment given, relationship to the IP, and relationship to progression of disease.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

11.4.3 Laboratory Values

Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent time-point. Changes from baseline will also be summarized. Treatment-emergent significant abnormalities (as defined in Section 9.2.4) will be summarized.

11.4.4 Vital Signs

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

11.4.5 Other Special Tests

Eastern Cooperative Oncology Group performance status will be summarized.

11.5 Activity Analyses

Tumor response rate and its 95% CI will be evaluated based on the number of subjects with any postbaseline CR or PR per RECIST criteria both as evaluated by investigator and by central radiology review committee.[5] In addition, the incidence of tumor response at each clinical visit will be summarized.

Progression-free survival and overall survival will be estimated. PFS is defined as the time from the first dose of study drug in study KX-ORAX-007 to the time of documented disease progression or death. OS is defined as the time from the first dose of study drug in study KX-ORAX-007 to date of death.

11.6 Final Analysis Plan

The final analysis plan will be presented in the SAP, including procedures for accounting for missing, unused, and spurious data.

The SAP will be issued prior to database lock and final analyses and will include plans for any exploratory analyses, as well as any changes in the other statistical analyses.

If the prespecified plans need to be revised after the study starts, the Sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

All data to be recorded on the eCRF must reflect the corresponding source documents.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the Sponsor's Clinical Quality Assurance department (or designee) conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the Investigator must inform the Sponsor immediately.

13.2 Database Quality Assurance

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. Validation requirements will be documented in the Data Management Plan.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This study will be conducted in accordance with SOPs of the Sponsor (or designee), which are designed to ensure adherence to the requirements and principles of ICH GCP guidelines (ICH - E6 Guideline for GCP Harmonised Tripartite Guideline)[4], the World Medical Association Declaration of Helsinki 2013, and other applicable national or local regulations. All required study documentation will be archived as required by regulatory authorities.

14.2 Institutional Review Board/Independent Ethics Committee

The protocol, any protocol amendments, and the ICF will be reviewed and approved by an IRB/IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations of the national authority before subjects are screened for entry. Any protocol amendment and/or revision to the ICF will receive appropriate approval prior to implementation. Verification of unconditional approval of the protocol will be transmitted to the Sponsor prior to the shipment of drug supplies to the investigational site. The Investigators or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice.

14.3 Informed Consent Process

The Investigator or the Investigator's staff will obtain written consent directly from subjects prior to the screening examination. After giving informed consent, each subject will be registered and assigned a subject number, which will be recorded. The Investigator or the Investigator's staff will record the subject number (3-digit trial site number + 4-digit sequential serial number) and the date of written informed consent on the medical records and eCRF.

14.4 Subject Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the Investigator, the Investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/Investigator and the Sponsor/CRO.

14.5 Future Use of Stored Specimens

Residual PK samples will be stored until regulatory approval of the IP, at which point the specimens will be destroyed.

14.6 Subject Insurance and Indemnity

The Sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

15 DATA HANDLING AND RECORD KEEPING

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The Investigator must sign each eCRF. The Investigator will provide the eCRFs to the Sponsor and retain a copy of the eCRFs.

15.1 Data Management Responsibilities

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The Investigator or must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

15.2 Data Capture Methods

All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

15.3 Types of Data

Data for this study will include PK, safety, laboratory, and outcome measures.

15.4 Study Records Retention

The circumstances of completion or termination of the study notwithstanding, the Investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the IP.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

15.5 Protocol Deviations

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If the Investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the Sponsor’s medical monitor (or appropriate team member) and the IRB/IEC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations.

16 PUBLICATION POLICY

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the Sponsor/CRO and the institution/Investigator. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each Investigator and the Sponsor or CRO, as appropriate.

17 LITERATURE REFERENCES

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3. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Courtesy of Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. http://ecog-acrin.org/resources/ecog-performance-status. Accessed September 2015.
4. ICH E6: Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance, US Department of Health and Human Services, Food and Drug Administration, April 1996. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf
5. Guidance for Industry; Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007.

SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Table 6 Schedule of Procedures and Assessments in KX-ORAX-007

Period	Screen-ing[a] / Base-line	Treatment														FU[b]
Week		**Week 1**			**Wk 2**	**Wk 3**	**Wk 4**			**Wks 5/6/7**	**Wk 8**	**Wks 9/10/11**	**Wk 12**	**Wks 13/14/15**	**Wk 16**	**Within 7 days**
Day	**-28 to -1**	**1**	**2**	**3**	**1**	**1**	**1**	**2**	**3**	**1**	**1**	**1**	**1**	**1**	**1**	
Visit Window					**±1 day**	**±1 day**	**±1 day**			**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	
Clinic Visit[c]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Informed consent	X															
Inclusion/ exclusion criteria	X															
Demography	X															
Medical/surgical/ oncologic history[d]	X															
Prior/concomitant medications	X[e]	X[e]														
Pregnancy test[f]	X[f]	X									X				X	
ECG[g]	X						X				X		X		X	
ECOG PS	X															
Physical exam[h]	X[i]										X[h]				X[h]	
Vital signs	X	X			X	X	X				X		X		X	X
PK sampling[j]		X	X	X			X	X	X							
Oraxol treatment[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Oraxol					X	X			X		X		X		X	
Lab tests (UA)[l]	X	X					X				X		X		X	
Lab tests (chemistry)[l]	X	X[l]			X		X				X		X		X	
Lab tests (hematology)[l, m]	X	X[l]			X[m]	X[m]	X[m]			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	
Imaging (CT/MRI)[n]	X										X				X	
Tumor assessments[o]	X										X				X	

Table 6 Schedule of Procedures and Assessments in KX-ORAX-007

Period	Screen-ing[a] / Base-line	Treatment														FU[b]
Week		Week 1			Wk 2	Wk 3	Wk 4			Wks 5/6/7	Wk 8	Wks 9/10/11	Wk 12	Wks 13/14/15	Wk 16	Within 7 days
Day	-28 to -1	1	2	3	1	1	1	2	3	1	1	1	1	1	1	
Visit Window					±1 day	±1 day	±1 day			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	
Clinic Visit[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[p]	X	X														

BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FU =follow-up; HEENT = head, eyes, ears, nose, and throat; IP = investigational product; MRI = magnetic resonance imaging; PE = physical examination; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; UA = urinalysis; Wk = Week.

a. Subjects must be screened within 28 days prior to Week 1, Day 1 dosing.

b. Subjects are to be followed-up for safety at a Final Visit, within 7 days after last dose of study treatment. After completion of Final Visit assessments, subjects will be contacted every 2 months to follow progression-free survival and overall survival. New anti-cancer therapy will be collected.

c. Unscheduled visits will occur only at the discretion of the Investigator. Results of any assessments performed at unscheduled visits will be entered into the clinical database.

d. A complete oncology history includes all malignancies prior to Screening, regardless of diagnosis date or status, eg, skin cancer.

e. At Screening/Baseline, includes a complete oncology treatment history which includes all commercial products and IPs, radiation, and other prescribed and over the counter therapies dating back to the initial diagnosis. Concomitant medications will be assessed and recorded at all clinic visits. In between clinic visits, subjects will be instructed to call designated study personnel if they experience any AEs and/or associated concomitant medications taken.

f. Serum pregnancy tests will be obtained at Screening/Baseline and every 8 weeks (Weeks 8 and 16). Urine pregnancy test will be performed within 96 hours prior to Week 1, Day 1 dosing. Test results must be reviewed prior to dosing.

g. ECGs will be performed at Screening/Baseline, and on Day 1 at Weeks 4, 8, 12, 16. ECGs will be performed at a convenient time at Screening/Baseline and 1 hour after Oraxol dosing on dosing days.

h. Physical exam will include body weight and at Screening/Baseline only, height. Complete physical examinations will be performed at Screening/Baseline and every 8 weeks, (Weeks 8 and 16). A complete PE will include an assessment of HEENT, gastrointestinal, cardiovascular, respiratory, integumentary, muscular-skeleton, and neurological systems.

i. BSA will be estimated based on baseline body weight and height and will be calculated at Baseline. Following dose calculation at baseline, BSA will be used to recalculate the dose for dose reduction, if needed, after an unacceptable toxicity.

j. Subjects will be housed in the clinic from the night before dosing on Week 1, Day 1 and Week 4, Day 1 through the end of PK sampling on Day 3. See Table 3 and Table 4 for PK sampling timepoints.

k. Oraxol will be administered on Days 1-3 of each week, up to 16 weeks. During PK sampling days, Oraxol will be administered to the subject in the clinic on scheduled dosing days. Subjects will be given information cards on which they will record their dosing information.

l. Clinical laboratory tests will be conducted at Screening and Baseline within 96 hours prior to Week 1 Day 1 dosing, and within 48 hours prior to Day 1 dosing of each subsequent designated week. See Section 9.2.3 for the frequency of laboratory testing and Table 5 for a listing of the hematology, chemistry, and urine tests to be performed. Subjects must be fasted for the Screening/Baseline laboratory assessments. Fasting is recommended, but not required, at other laboratory assessment times. Collection of both blood and urine may be conducted at a local laboratory or at the clinic site.

Table 6 Schedule of Procedures and Assessments in KX-ORAX-007

Period	Screen-ing[a] / Base-line	Treatment														FU[b]
Week		Week 1			Wk 2	Wk 3	Wk 4			Wks 5/6/7	Wk 8	Wks 9/10/11	Wk 12	Wks 13/14/15	Wk 16	Within 7 days
Day	-28 to -1	1	2	3	1	1	1	2	3	1	1	1	1	1	1	
Visit Window					±1 day	±1 day	±1 day			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	
Clinic Visit[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

m. Clinical hematology laboratory tests will be conducted weekly within 48 hours before Day 1 dosing of Weeks 2 through 16. Additional hematology tests may be done at the discretion of the Investigator. Collection of blood may be conducted at a local laboratory or at the clinic site. All hematology data obtained will be included in the clinical database.

n. During the Screening/Baseline Period, a baseline CT/MRI scan will be conducted before the first dose on Week 1, Day 1 of Oraxol treatment, as close to Day 1 as possible. Subsequent scans will be conducted every 8 weeks (at Weeks 8 and 16) until documented progression. Unscheduled scans should be conducted, if clinically indicated, per the discretion of the Investigator. Results of these unscheduled scans will be entered into the clinical database.

o. Based on RECIST v1.1 criteria.

p. Any adverse events that occur after signing the informed consent. Adverse events will be assessed and recorded at all clinic visits. In between clinic visits, subjects will be instructed to call designated study personnel if they experience any adverse events.

APPENDIX B: ECOG PERFORMANCE STATUS

Grade	Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.
Adapted from Oken MM et al. Am J Clin Oncol. 1982;5:649-5.

APPENDIX C: RECIST CRITERIA

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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 ⩾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.[25]
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.[19]
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.[25]
	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.[19]
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		

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Conflict of interest statement

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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*

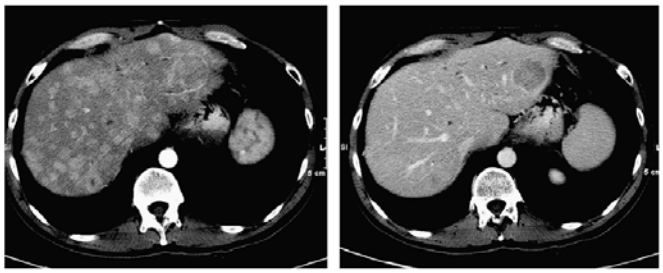

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration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

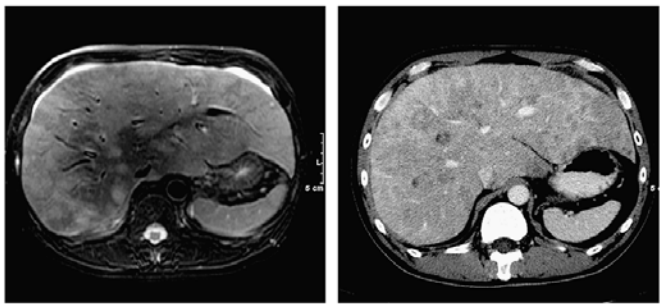

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

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-

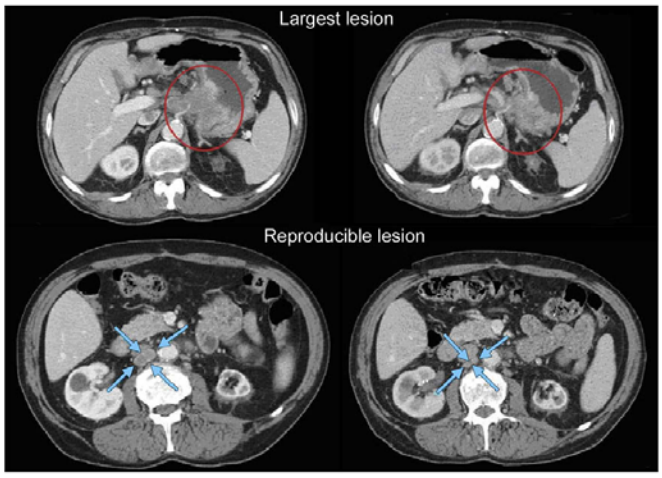

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention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

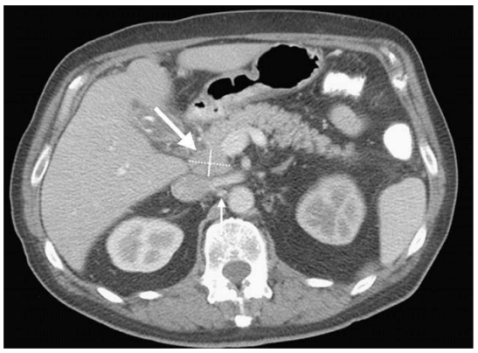

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

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.

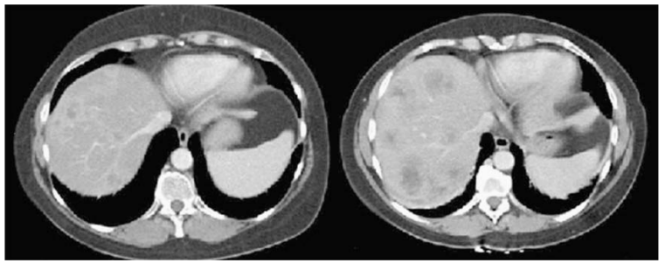

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

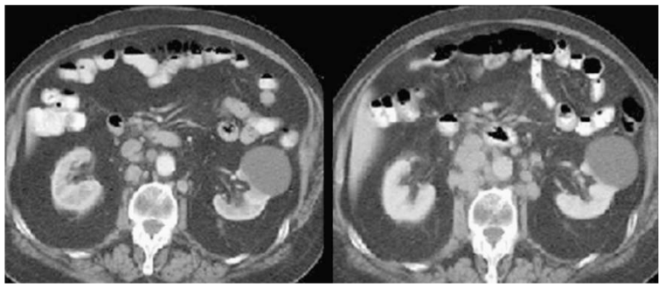

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

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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